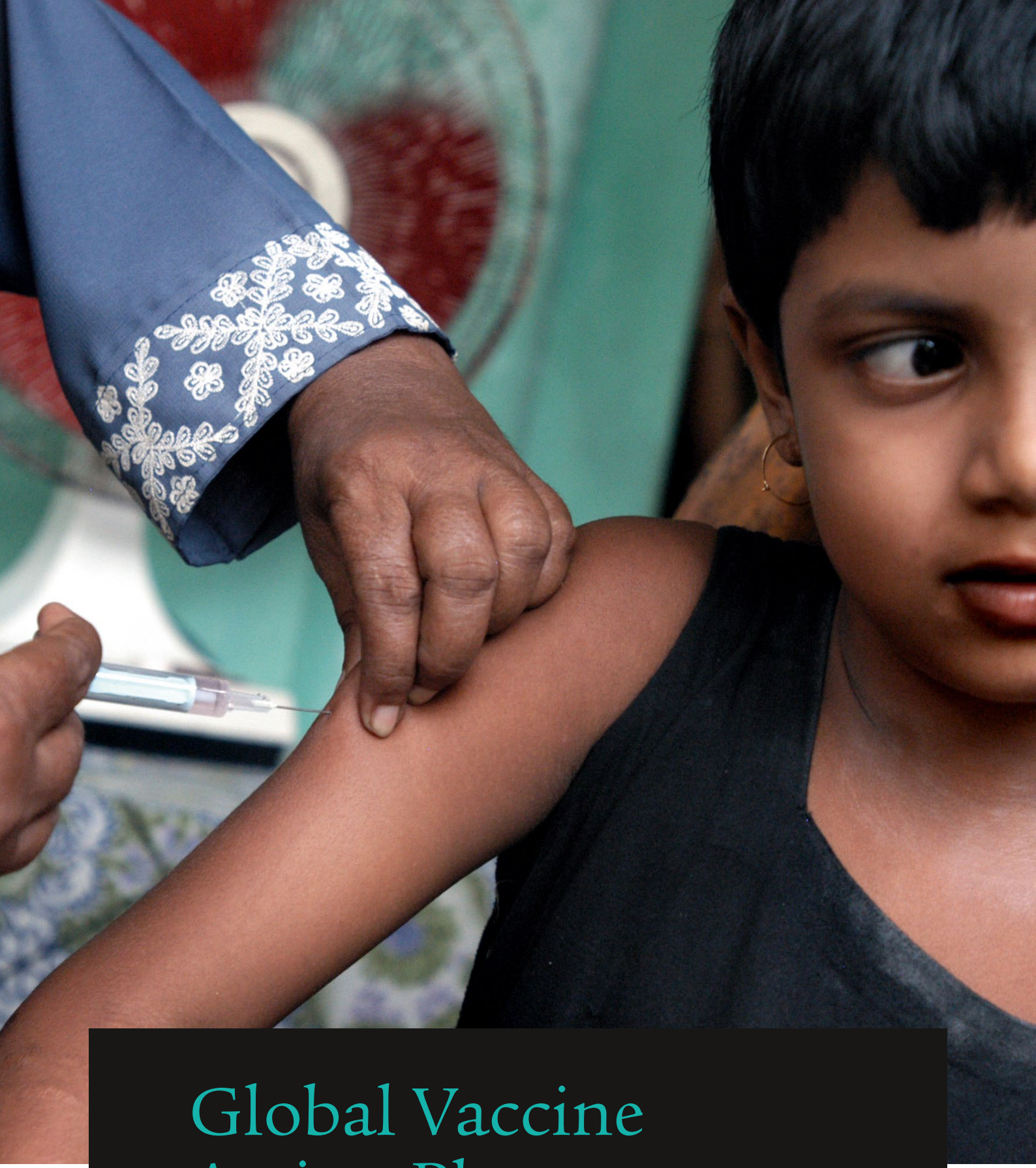

Global Vaccine Action Plan

Monitoring, Evaluation & Accountability

Secretariat Annual Report 2014

BILL & MELINDA GATES foundation
GAVI ALLIANCE
unicef
World Health Organization

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ACRONYMS and ABBREVIATIONS

AVAREF	African Vaccines Regulatory Forum
BCG	Bacille Calmette–Guérin (vaccine)
BMGF	Bill & Melinda Gates Foundation
CFDA	China Food and Drug Administration
CI	Confidence Interval
CMV	Cytomegalovirus
COIA	Commission on Information and Accountability for Women's and Children's Health
CRS	Congenital Rubella Syndrome
CSO	Civil Society Organization
CTC	Controlled Temperature Chain
DHS	Demographic and Health Survey
DoV	Decade of Vaccines
DTP	Diphtheria–Tetanus–Pertussis (vaccine)
EMA	European Medicines Agency
EPI	Expanded Programme on Immunization
EWEC	Every Woman Every Child
FDA	Food and Drug Administration
GPEI	Global Polio Eradication Initiative
GNI	Gross National Income
GVAP	Global Vaccine Action Plan
GVIRF	Global Vaccine and Immunization Research Forum
HA	Haemagglutinin
HepB	Hepatitis B
Hib	*Haemophilus influenzae* type b
HPV	Human Papillomavirus
HQ	Headquarters
iERG	independent Expert Review Group
IAVI	International AIDS Vaccine Initiative
IB-VPD	Invasive Bacterial Vaccine Preventable Diseases
ICTRP	International Clinical Trials Registry Platform
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
IPV	Inactivated Polio Vaccine
IVB	Immunization, Vaccines and Biologicals Department (WHO)
JRF	(WHO-UNICEF) Joint Reporting Form
KANCO	Kenya AIDS NGOs Consortium
LQA-CS	Lot Quality Assurance – Cluster Sampling
M&E/A	Monitoring & Evaluation/Accountability (Framework)
M&RI	Measles & Rubella Initiative
MenAfriVac	Serogroup A meningococcal conjugate vaccine
MCV	Measles-Containing Vaccine
MDG	Millennium Development Goal
MICS	Multiple Indicators Cluster Survey
MR	Measles-Rubella
MMR	Measles, Mumps and Rubella
MNT	Maternal and Neonatal Tetanus
MNTE	Maternal and Neonatal Tetanus Elimination
Mtb	*M. tuberculosis*
NGO	Nongovernmental Organization
NHP	Non-human primate
NIAID	National Institute of Allergy and Infectious Diseases
NITAG	National Immunization Technical Advisory Group
NRA	National Regulatory Authority

NTMR	Neonatal Tetanus Mortality Rate
NVC	National Verification Committee
OECD	Organisation for Economic Co-operation and Development
OPV	Oral Polio Vaccine
ORS	Oral Rehydration Salts
PAB	Protection at Birth
PAHO	Pan American Health Organization
PCV	Pneumococcal Conjugate Vaccine
PMNCH	Partnership for Maternal, Neonatal and Child Health
PQS	Performance, Quality and Safety
RV	Rotavirus Vaccine
RCV	Rubella-Containing Vaccine
RVC	Regional Verification Commission
SAGE	Strategic Advisory Group of Experts (on immunization)
SHA	Systems of Health Accounts
SIA	Supplementary Immunization Activity
SIV	Simian Immunodeficiency Virus
SO	(GVAP) Strategic Objective
TAG	Technical Advisory Group
TPP	Target Product Profile
TT	Tetanus Toxoid
UN	United Nations
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
V3P	Vaccine Product, Price and Procurement
VFC	(United States CDC) Vaccines for Children Fund
VPD	Vaccine-Preventable Diseases
WAP	Weighted Average Prices
WHO	World Health Organization
WPV	Wild Poliovirus
WUENIC	WHO-UNICEF Estimates of National Immunization Coverage

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Introduction

The Global Action Plan and process for monitoring progress

The Global Vaccine Action Plan (GVAP) is a framework adopted at the Sixty-fifth World Health Assembly in May 2012 to achieve the vision of the Decade of Vaccines (DoV) 2011–2020 of "a world in which all individuals and communities enjoy lives free from vaccine-preventable diseases".[1] The GVAP's mission is to "improve health by extending by 2020 and beyond the full benefits of immunization to all people, regardless of where they are born, who they are, or where they live."

The GVAP has articulated five goals and six strategic objectives to achieve this mission, as shown in the Table of Indicators. The Sixty-fifth World Health Assembly requested the World Health Organization (WHO) Director General to monitor progress and report annually, using an accountability framework, in order to guide immunization discussions and future actions.[2] In response, the DoV partners developed a Monitoring & Evaluation/Accountability (M&E/A) Framework that identifies specific indicators to measure progress for each goal and strategic objective. The DoV partners also agreed to a process for an annual independent review of progress.

Table of Indicators: The GVAP Monitoring and Evaluation/Accountability Framework: goals, strategic objectives and indicators to evaluate progress

Goal /Strategic Objective	Indicators
Goals	
1. Achieve a world free of poliomyelitis	1.1 Interrupt wild poliovirus transmission globally
	1.2 Certification of poliomyelitis eradication
2. Meet global and regional elimination targets	2.1 Neonatal tetanus elimination
	2.2 Measles elimination
	2.3 Rubella/Congenital rubella syndrome (CRS) elimination
3. Meet vaccination coverage targets in every region, country and community	3.1 By 2015, reach 90% national coverage and 80% in every district or equivalent administrative unit with three doses of diphtheria-tetanus-pertussis-containing vaccines
	3.2 By 2020, reach 90% national coverage and 80% in every district or equivalent administrative unit for all vaccines in national programmes, unless otherwise recommended
4. Develop and introduce new and improved vaccines and technologies	4.1 Licensure and launch of vaccine or vaccines against one or more major currently non-vaccine preventable diseases
	4.2 Licensure and launch of at least one platform delivery technology
	4.3 Number of low-income and middle-income countries that have introduced one or more new or under-utilized vaccines
5. Exceed the Millennium Development Goal 4 target for reducing child mortality and Integration indicators	5.1 Reduce under-five mortality rate
	5.2 Integration of health care interventions and immunization activities

[1] The GVAP can be found at: http://www.who.int/immunization/global_vaccine_action_plan/en/.
[2] Resolution WHA65.17 (found at: http://apps.who.int/gb/or/e/e_wha65r1.html).

Goal /Strategic Objective	Indicators
Strategic Objectives (SOs)	
1. Ensuring country ownership of immunization	1.1 Increasing domestic expenditures for immunization per person targeted
	1.1 Presence of an independent technical advisory group that meets the defined criteria
2. Demand for immunization	2.1 Percentage of countries that have assessed the level of hesitancy in vaccination at a national or subnational level.
	2.2 Reasons for vaccine hesitancy
3. The benefits of immunization are equitably extended to all people	3.1 Percentage of districts with 80% or greater coverage with three doses of diphtheria-tetanus-pertussis-containing vaccine **Note:** this indicator is included in the narrative of the overall coverage indicator report (under G3.1)
	3.2 Reduction in coverage gaps between wealth quintiles and other appropriate equity indicator(s)
4. Strong immunization systems are an integral part of a well-functioning health system	4.1 Dropout rates between first dose (DTP1) and third dose (DPT3) of diphtheria–tetanus–pertussis-containing vaccines **Note:** this indicator is included in the narrative of the overall coverage indicator report (under G3.1)
	4.2 Sustained coverage of diphtheria-tetanus-pertussis-containing vaccines 90% or greater for three or more years **Note:** this indicator is included in the narrative of the overall coverage indicator report (under G3.1)
	4.3 Immunization coverage data assessed as high quality by WHO and UNICEF To be reported starting from 2015
	4.4 Number of Member States with case-based surveillance for vaccine-preventable diseases: invasive bacterial vaccine-preventable diseases and rotavirus
5. Stock-out and access to sustained supply of vaccines of assured quality	5.1 Percentage of doses of vaccine used worldwide that are of assured quality
	5.2 Number of countries reporting a national-level stock-out of at least 1 vaccine for at least 1 month
6. Country, regional and global research and development innovations maximize the benefits of immunization	6.1 Progress towards development of HIV, TB and malaria vaccines
	6.2 Progress towards a universal influenza vaccine (protecting against drift and shift variants)
	6.3 Progress towards institutional and technical capacity to carry out vaccine clinical trials
	6.4 Number of vaccines that have either been re-licensed or licensed for use in a controlled-temperature chain at temperatures above the traditional 2–8°C range
	6.5 Number of vaccine delivery technologies (devices and equipment) that have received WHO pre-qualification against the 2010 baseline

This report, prepared by the Secretariat for the Decade of Vaccines Global Vaccine Action Plan, serves as the basis for the independent review. As was the case in 2013, this report reviews progress against each of the indicators in the Monitoring and Evaluation/ Accountability Framework of the GVAP. In addition it contains a narrative report on trends in vaccine prices and a report on progress in fulfilling commitments made to immunization efforts.

This report includes a few new features from the 2013 edition, as outlined below.

1. The report does not strictly follow the structure of the GVAP, but rather considers linked indicators relating to specific areas together, even though they reflect different indicators, e.g. all results relating to immunization coverage are compiled into one section of the report, even though they come under separate goals or strategic objectives. Grouping in this way also met the request from the Strategic Advisory Group of Experts (SAGE) on immunization that certain original indicators be considered as part of the overall report on progress with immunization coverage, rather than as independent indicators.
2. This report includes reports on two new indicators, as requested by SAGE in their 2013 review. These include an indicator on national level vaccine stock-out and an indicator that assesses integration of immunization and other interventions aimed at reducing child mortality.
3. The indicator on community demand was revised following the last review and again pilot-tested in one of the WHO regions (the European Region).
4. Progress on several of the research and development indicators, which are meant to be reported biennially, are included in this report. This is the first report on these indicators. As indicated in the previous report, the Global Vaccines and Immunization Research Forum was used as the platform to review progress and report on these indicators.
5. Civil society organizations were specifically invited to submit reports focusing on their efforts to improve community participation and demand for immunization.
6. The report also contains independent submissions by the pharmaceutical industry.

SAGE has been reviewing other indicators, which are still in the process of being developed. It is hoped that the addition of these indicators, and the revisions of others, together with further improvements to the format of the Secretariat report, will lead to a clearer picture of the progress made and challenges remaining to attain the ambitious goals and targets set forth in the Global Vaccine Action Plan.

I

Monitoring results: goals, strategic objectives and indicators

1. DISEASE ELIMINATION

GOAL 1:
Achieve a world free of poliomyelitis (indicators G1.1 & G1.2)

G1.1: INTERUPT WILD POLIOVIRUS TRANSMISSION GLOBALLY

TARGET: 2014

G1.2: CERTIFICATION OF POLIOMYELITIS ERADICATION

TARGET: 2018

For the definition of each indicator, description of data sources, comments on data quality, description of results, narrative and highlights please refer to the following documents.

1. For context, see the *Global Polio Eradication Initiative Annual Report 2012*, available at: http://www.polioeradication.org/Portals/0/Document/AnnualReport/AR2012/GPEI_AR2012_A4_EN.pdf.
2. To review the real-time updates on polio cases worldwide, see: http://www.polioeradication.org/Dataandmonitoring.aspx.
3. To review the May 2014 report of the Independent Monitoring Board of the Global Polio Eradication Initiative (GPEI), see: http://www.polioeradication.org/Portals/0/Document/Aboutus/Governance/IMB/10IMBMeeting/10IMB_Report_EN.pdf.
4. GPEI annual reports 2013 and 2014 can be reviewed here: http://www.polioeradication.org/Resourcelibrary/Strategyandwork/Annualreports.aspx.

Progress towards the achievement of polio eradication goals and interim milestones are intensely monitored, including by the independent monitoring board of the Global Polio Eradication Initiative, which reviews progress on a quarterly basis and issues a report after each meeting. Below are excerpts from WHO documents that summarize progress against this goal and the corrective actions that are being taken, as well as recommendations for future actions.

From the "GPEI Annual Report 2013" and the "2013-2014 Programme of Work – From Plan to Implementation".

In 2013, the three endemic countries restricted the virus to fewer regions than ever before, even as the programme faced serious challenges to reach children. At the same time, outbreaks occurred in five previously polio-free countries. Although these outbreaks were met with effective emergency responses, they reinforced the urgency of ending transmission in these final reservoirs.

In 2013, there were 416 wild poliovirus cases in eight countries (Table 1), compared to 223 cases in five countries in 2012. This increase was largely the result of outbreaks in countries that had previously stopped polio transmission, for example, the international spread of polioviruses from Nigeria into the Horn of Africa,

and from Pakistan into the Middle East (with cases in the Syrian Arab Republic, which in 2014 spread further to Iraq). Wild poliovirus of Pakistani origin was also detected in environmental samples collected in Israel and the West Bank and Gaza Strip. A polio outbreak in Cameroon from 2013 spread further in early 2014, into previously polio-free areas of the country and to neighbouring Equatorial Guinea.

Table 1: Acute flaccid paralysis (AFP)/Polio case count for 2013, by WHO region

WHO region	AFP cases reported	Non-polio AFP rate	AFP cases with adequate specimens (%)	Total confirmed polio cases	Wild-virus confirmed polio cases
African	20 266	5.3	91	93	80*
Americas	1 940	1.1	74	0	0
South-East Asia	59 580	11.0	87	0	0
European	1 608	1.4	88	0	0
Eastern Mediterranean	11 533	5.2	90	386	336*
Western Pacific	6 842	2.0	91	0	0

* The difference between total confirmed polio cases and wild-virus confirmed polio cases is due to circulating vaccine-derived poliovirus.

Source: WHO; data from 16 May 2014.

For the first time in the history of the Global Polio Eradication Initiative, in 2013 all the polio cases caused by a wild virus were due to a single serotype, type 1 (Figure 1). The most recent WPV3 case dates to November 2012, from Nigeria. Cases due to circulating vaccine-derived poliovirus type 2 declined by 10% compared to 2012.

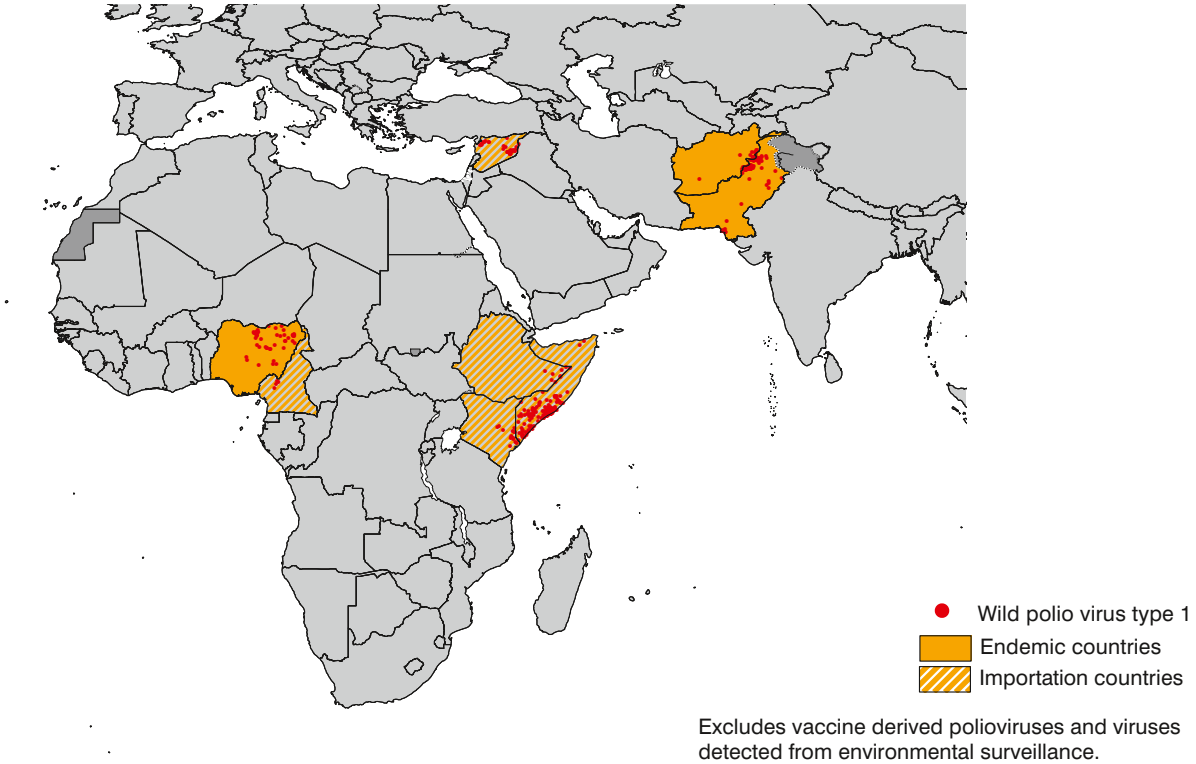
In Nigeria and Afghanistan, cases declined by 57% and 62%, respectively. Of note, only six of Nigeria's 53 cases (Table 2) were reported since September 2013 despite the traditional 'high season' for poliovirus transmission. By contrast, in Pakistan, 60 cases were reported during that same period, 48 of which were from the Federally Administered Tribal Areas and Khyber Pakhtunkhwa province.

Table 2: Case breakdown of confirmed wild poliovirus (WPV) cases in 2013, by country

	WPV1	cVDPV Type 2
Cameroon	4	4
Ethiopia	9	0
Kenya	14	0
Nigeria	53	4
Afghanistan	14	3
Pakistan	93	45
Somalia	194	1
Syrian Arab Republic	35	0

Source: WHO; data from 16 May 2014.

Figure 1: Wild poliovirus cases worldwide in 2013 (01 January - 31 December)



Excludes vaccine derived polioviruses and viruses detected from environmental surveillance.

Source: WHO; data from 06 May 2014.

Endemic countries: progress and challenges

The proportion of children who received polio vaccines in polio endemic countries increased in 2013 compared to 2012. National emergency action plans drove operational improvements in many districts where performance had historically been poor.

- Cases in Afghanistan declined by 62% compared to 2012 (from 37 to 14). Cases overwhelmingly occurred in the eastern region and were linked to cross-border transmission with neighbouring Pakistan.
- Cases in Nigeria declined by 57% (from 122 to 53). Of note, despite the traditional 'high season' for poliovirus transmission, only six of Nigeria's 53 cases were reported since September.
- Pakistan was the only endemic country where cases increased, with cases up 60% compared to 2012 (from 58 to 93). The bulk of cases were from the Federally Administered Tribal Areas and Khyber Pakhtunkhwa province. At the start of 2014 this area of Pakistan represents the only endemic reservoir with uncontrolled poliovirus transmission in the world.

Despite some gains, conducting vaccination campaigns in certain areas has been a fundamental challenge in 2013 and 2014. Insecurity, targeted attacks on health workers and/or a ban by local authorities on polio immunization resulted in difficulties in reaching target populations in several countries (to the Federally Administered Tribal Areas and Khyber Pakhtunkhwa province, in Pakistan; Borno, Nigeria; parts of the Syrian Arab Republic; and parts of south-central Somalia). Chronically poor implementation of activities remained a critical challenge in other priority areas, most notably in Kano, Nigeria. North Waziristan in the Federally Administered Tribal Areas, Pakistan, where immunization activities have been suspended by local leaders since June 2012, was the area with the most children paralysed by poliovirus in the country in 2013 and early 2014.

Effective outbreak response

In 2013, there were three significant outbreaks in countries and regions that were previously polio-free. The virus spread from Nigeria into the Horn of Africa (194 cases in Somalia, 14 in Kenya and 9 in Ethiopia) and from Pakistan into the Middle East, with cases in the Syrian Arab Republic, which spread to Iraq in the early part of 2014. Wild poliovirus of Pakistani origin was also detected in environmental samples collected in Israel and the West Bank and Gaza Strip. An outbreak in Cameroon, due to an imported virus linked to previous transmission from Chad, continued to spread into early 2014, both within Cameroon and internationally to Equatorial Guinea.

The GPEI joint polio programme took swift action to stop these outbreaks. In the Horn of Africa, where the first case was detected in May 2013, an aggressive multi-country response successfully slowed the outbreak, with no new cases reported since July 2013 from Banadir in Somalia – the epicentre of the outbreak. However, efforts to vaccinate more than 500 000 children in parts of south-central Somalia have been unsuccessful due to instability.

Seven countries and territories in the Middle East and Turkey launched a comprehensive, regional outbreak response in October 2013 aiming to vaccinate 22 million children. Health ministers from across the region declared polio a regional public health emergency.

The focus has been, and continues to be, on coordinating all humanitarian and health partners in all areas of the region, in efforts to immunize all children. From reaching approximately 2 million children in Syria during the initial outbreak response campaign in October, more than 3 million children were reached by early 2014. However, there are areas where children continue to be missed, due to a variety of reasons including inaccessibility and conflict.

In Cameroon, an outbreak from 2013 continues to spread in 2014, re-infecting both areas within the country and spreading internationally to Equatorial Guinea. Due to this continued and expanding circulation, gaps in surveillance, and influx of vulnerable refugee populations particularly from neighbouring Central African Republic, in March 2014 WHO elevated the risk assessment of international spread of polio from Cameroon to very high.

Single serotype

In 2013, for the first time in the history of the eradication initiative, all cases of wild poliovirus were due to a single serotype, type 1 (Figure 1). There were zero cases due to wild poliovirus type 3, down from 21 in 2012 (the last case occurred on 10 November 2012 in Nigeria). In addition, cases due to circulating vaccine-derived poliovirus type 2 – which accounts for the vast majority of vaccine-derived cases – declined by 10% compared to 2012, with most cases linked to persistent cVDPV type 2 (cVDPV2) in northern Nigeria (since July 2005) and Pakistan (since August 2012).

Convening in April 2014, the WHO Strategic Advisory Group of Experts (SAGE) expressed grave concern over the persistence of cVDPV2 in northern Nigeria and Pakistan, highlighting that these areas overlapped with some of the last WPV reservoirs in the world. Stopping circulation of both WPV and cVDPV2 requires addressing gaps in the quality of supplementary immunization activities (SIAs), increasing access, and using an appropriate mix of trivalent and bivalent oral polio vaccine (OPV).

The overriding priority in 2014 is to ensure that operations are significantly scaled up to reach those children who have remained inaccessible, and to continue to address chronic quality problems. At the same time, the focus will be on implementing additional measures to limit the renewed international spread of poliovirus. Key to achieving this will be full national ownership of the eradication programme in all infected countries, with deep engagement of all relevant ministries and departments, including holding local authorities accountable for their polio eradication activities. Accessing and vaccinating children in insecure and conflict-affected areas will in addition require the full engagement of relevant international bodies, religious leaders and other actors with influence in such settings. Collaboration with broader humanitarian efforts will be enhanced and area-specific operational plans developed to address local risks and contexts.

IPV introduction

In 2013, SAGE issued its recommendation that all countries introduce at least one dose of inactivated polio vaccine (IPV) into their routine immunization schedule before the end of 2015, ideally to be administered at or after 14 weeks of age (e.g. at the third dose of diphtheria–tetanus–pertussis, DTP, contact), in addition to existing OPV doses. SAGE recommended that by mid-2014 all polio endemic and high-risk countries develop plans for IPV introduction; all other countries that currently use only OPV should have an IPV introduction plan in place by end-2014.

At its November 2013 meeting, the board of the GAVI Alliance approved support to IPV introduction for all 73 GAVI-eligible and -graduating countries. This support includes a streamlined application process, full support for one dose of IPV with no requirement for co-financing and a one-off introduction grant of US$ 0.80 per child (Table 3).

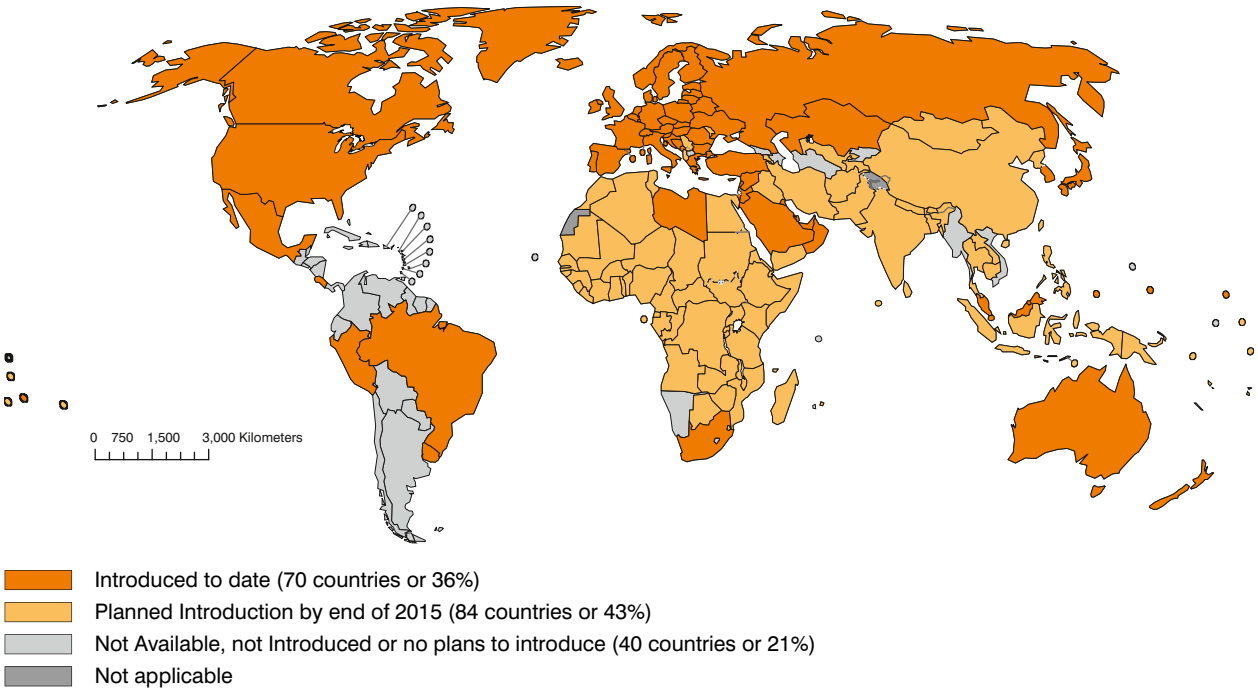
Table 3: IPV pricing as of 28 February 2014

	Ten-dose vials	Five-dose vials	Single-dose vials
GAVI-supported countries	€0.75 per dose (~US$ 1.00 at current exchange rates)	US$ 1.90 per dose	US$ 2.80 per dose
Middle-income countries*	€1.49–2.40 (~US$ 2.04–3.28 at current exchange rates)		

* This is a World Bank income group. For more information about the classification, see: http://data.worldbank.org/news/new-country-classifications.

The Supply Division of the United Nations Children's Fund (UNICEF) issued a tender for the purchase of up to 580 million doses of IPV, covering both the GAVI Alliance and middle-income country market. The tender aimed to achieve affordable prices, appropriate packaging and presentation options, a sustainable supply and a healthy market. In February 2014, UNICEF announced a procurement price of €0.75 per dose in ten-dose vials for GAVI-eligible countries and a price of €1.49–2.40 per dose for middle-income countries. In addition, UNICEF awarded volumes for five-dose vials at a price of US$ 1.90 per dose for both low- and middle-income countries, expected to be available from the fourth quarter of 2014. As of 13 May 2014, 70 countries had already introduced IPV, and 84 countries planned to do so by the end of 2015 (43%) (Figure 2).

Figure 2: Countries using IPV vaccine to date with formal decision or declared intent to introduce by end 2015



Source: WHO; data from 13 May 2014.
Map production: Immunization Vaccines and Biologicals, (IVB), World Health Organization.
194 WHO Member States.

Routine immunization strengthening in focus countries

A joint programme of work was initiated with the GAVI Alliance to support the strengthening of routine immunization systems in the 10 priority countries identified in the Endgame Plan. These countries[3] contain most of the world's under-immunized children and have substantial human resources infrastructures funded by the Global Polio Eradication Initiative. This programme of work capitalizes on the GAVI Alliance's investments in health systems strengthening and the substantial technical assistance deployed through the Global Polio Eradication Initiative. In 2013, the immunization plans in six of these countries were reviewed and revised to align these resources (Chad, Democratic Republic of the Congo, Ethiopia, India, Nigeria and Pakistan).

The Global Polio Eradication Initiative Immunization Systems Management Group continues to work with regional offices to ensure polio resources can be maximized. A framework for measuring polio assets has been developed, and most in-need areas are actively being identified to focus resources within the existing Expanded Programme on Immunization (EPI) plans.

Ensuring the effective use of polio-funded staff time for routine immunization is a key component both of the Endgame Plan and legacy planning. Following a landscaping exercise of existing polio-funded staff in priority countries conducted in 2013, the Immunization Systems Management Group will ascertain the time currently spent by the Global Polio Eradication Initiative on routine immunization in 2014 to help guide future planning.

[3] Afghanistan, Angola, Chad, Democratic Republic of the Congo, Ethiopia, India, Nigeria, Pakistan, Somalia and South Sudan.

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GOAL 2:
Achieve maternal and neonatal tetanus elimination (indicator G2.1)

Highlights

1. The GVAP target for 2013 was not achieved. A total of 34[4] of the 59 priority Member States (58%) had achieved maternal and neonatal tetanus (MNT) elimination as of December 2013 (see Figure 3).
2. Since 2010, 15 of the 22 countries required to meet the GVAP milestone for 2013 had achieved elimination.
3. Maternal and neonatal tetanus (MNT) is still a public health problem in the following 25 Member States: Afghanistan, Angola, Cambodia, Central African Republic, Chad, Democratic Republic of the Congo, Equatorial Guinea, Ethiopia, Guinea, Haiti, India (17 of 35 states), Indonesia, Kenya, Madagascar, Mali, Mauritania, Niger, Nigeria, Pakistan, Papua New Guinea, Philippines, Somalia, Sudan, South Sudan and Yemen.
   Of these 25 countries:
   - Kenya, Niger, a significant part of Nigeria, a significant part of Pakistan, Papua New Guinea and Sudan are really lagging in their efforts to eliminate MNT, despite their relatively stable political situation. The governments in these countries should not only prioritize MNT elimination but also invest domestic funds.
   - Angola, Cambodia, Democratic Republic of the Congo, Equatorial Guinea, Ethiopia, Guinea, Indonesia, Mauritania and Philippines are very close to elimination – strong advocacy to implement the necessary activities and validate elimination in 2015 is urgently required.
   - Afghanistan, Central African Republic, Mali, Somalia, South Sudan and Yemen are countries affected by political instability – lobbying with donors for funding and the use of innovative approaches to reach vulnerable populations including the use of tetanus toxoid (TT) Uniject™ devices are pertinent. More funds are required for operations in these countries.
   - Chad is one of the countries that reports significant number of NT cases each year, with little progress in control efforts. This is partly due to the focus on the country to respond to polio outbreaks. Efforts need to be made to utilize the windows of opportunity within the country's current efforts to improve routine immunization performance through better planning to integrate MNT elimination activities.
4. Even though the number of countries that were validated as attaining MNT elimination was less than the target, it is still significant that five countries and three additional States in India have achieved the goal. This was the result of successful strategies to improve access to TT vaccination and health systems, which increased access to health service delivery in general, including antenatal care and clean delivery practices.
5. All countries have developed their MNT elimination plans of action as part of comprehensive multi-year planning. What is hampering progress, however, is the availability of the required resources to support the implementation of the planned activities that are known to work.
6. Levels of coverage of antenatal care and skilled attendants at birth from the most recent surveys are presented in Annex 1. These very important aspects of MNT elimination rely heavily on the performance of the health systems and often progress slowly unless there is a concerted effort by governments, as seen in China and India.

[4] Bangladesh, Benin, Burkina Faso, Burundi, Cameroon, China, Comoros, Congo, Côte d'Ivoire, Egypt, Eritrea, Gabon, Ghana, Guinea Bissau, Iraq, Lao People's Democratic Republic, Liberia, Malawi, Mozambique, Myanmar, Namibia, Nepal, Rwanda, Senegal, Sierra Leone, South Africa, Timor Leste, Turkey, Togo, Uganda, United Republic of Tanzania, Viet Nam, Zambia and Zimbabwe.

7. Guidelines are being developed to support countries that have attained elimination in sustaining their elimination status using existing routine immunization delivery mechanisms and other cost-effective strategies. The guidelines will also include how countries can assess their status post-elimination through annual district data reviews, and take corrective measures as appropriate.

8. Some of the reported neonatal tetanus (NT) cases are being investigated in countries. However, despite the integrated disease surveillance setup in countries, a significant number of the reported cases are not investigated on account of lack of funds. Investigation of cases is, however, an integral part of pre-validation assessments and validation surveys.

DEFINITION OF INDICATOR	An incidence of <1 case of neonatal tetanus per 1000 live births per year in all districts or similar administrative units of a country (please refer to GVAP Secretariat Report 2013 *(1)* for more information) and the maintenance of elimination; the neonatal tetanus indicator acts as proxy for maternal tetanus
DATA SOURCES	• WHO-UNICEF joint reporting forms (JRF) • Country health management information system (HMIS) reports • Country disease surveillance reports • Immunization coverage survey reports • Multiple indicator cluster sampling (MICS) survey reports, demographic and health survey (DHS) reports and any other reports of immunization and reproductive health programme reviews • Reports of maternal and neonatal tetanus elimination validation surveys
MILESTONES	(From 2010 baseline, with 40 countries still to achieve elimination): • 10 countries eliminated neonatal tetanus (NT) by 2012 • 22 countries eliminated NT by 2013 • 36 countries eliminated NT by 2014 • 40 countries eliminated NT by 2015

Introduction and background

MNT is a marker of inequity, as the disease affects the most vulnerable populations. Almost all cases occur among the poorest segments of the population in low-income countries.[5] Tetanus cannot be eradicated as the bacteria that causes the disease, *Clostridium tetani*, is commonly found in the soil and in the intestinal tracts of animals and humans. About 787 000 deaths were estimated to occur annually from neonatal tetanus in the late 1980s, and in order to eliminate the disease as a public health problem, the Forty-second World Health Assembly in 1989 established a goal to eliminate neonatal tetanus by 1995. This goal was later endorsed by the World Summit for Children in 1990.

In 1999, the Maternal and Neonatal Tetanus Elimination (MNTE) Initiative was launched by UNICEF, WHO and the United Nation's Population Fund (UNFPA), adding the elimination of maternal tetanus to the goal. The Initiative has focused on the 59 priority Member States that were assessed to have more than one case of neonatal tetanus per 1000 live births in some districts in 1999 *(2)*.

[5] Country classifications such as low income and lower-middle income come from the World Bank; for more information, see: http://data.worldbank.org/news/new-country-classifications. See also: GNI per capita, Atlas method (current US$): http://data.worldbank.org/indicator/NY.GNP.PCAP.CD.

Description of the validation process for neonatal tetanus elimination

The MNTE validation process starts with the claim of the attainment of elimination by a country, which may be based on completing supplemental immunization activities to fill immunity gaps in high-risk districts (or when a country's own review of district-level data indicates that there is no need for additional activities) and that neonatal tetanus rates in all districts are less than 1/1000 live births. This is followed by a pre-validation assessment, which assesses whether there is adequate evidence for the claim of elimination.

Once the status of MNT risk in the poorest-performing districts is assessed to be low, a neonatal tetanus lot quality assurance and cluster sampling (LQA-CS) survey is conducted (only in district(s) at highest risk). This assesses whether or not the neonatal tetanus mortality rate (NTMR) in the survey areas probably exceeds 1/1000 live births during the 12-month eligibility period using the pre-determined maximum accepted number of NT deaths that defines whether the district "passes" or "fails" as a reference.

Data availability and quality

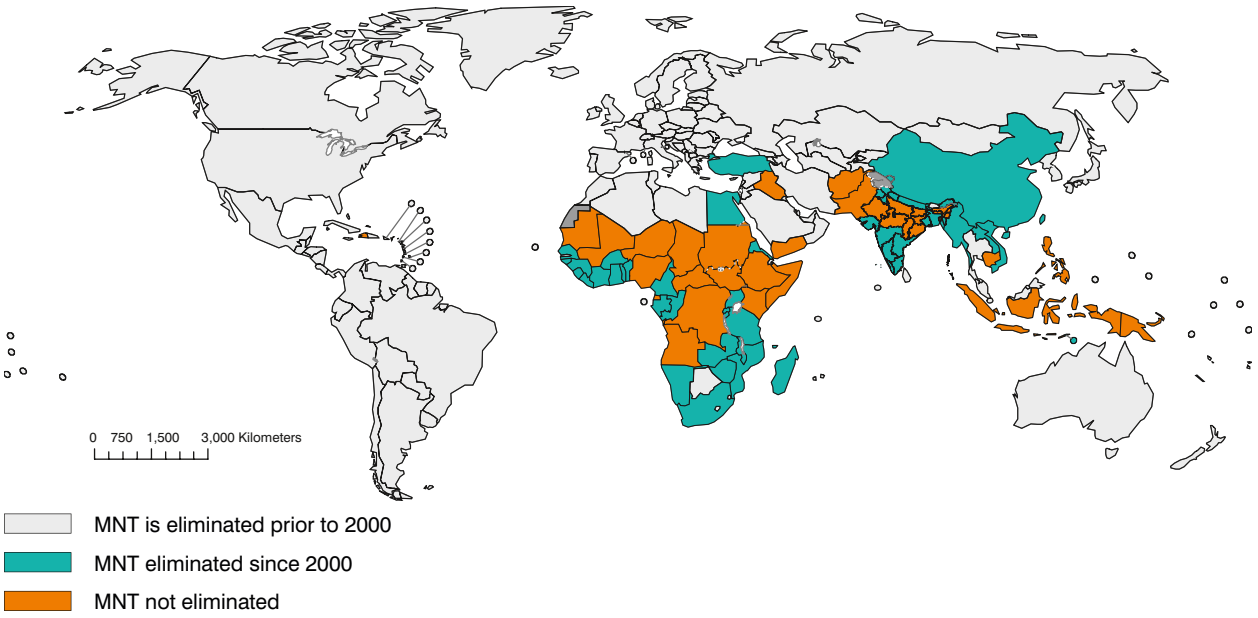
All the limitations of data quality that apply to immunization coverage estimates, also apply to the pre-validation assessment process. The difficulty to correctly identify all births and neonatal deaths and correctly assess whether or not a death may be due to neonatal tetanus are some of the limitations of the LQA-CS. However, a more specific rather than sensitive case definition is used for the survey as each and every case detected has an implication on the outcome of the survey. This is built into the intensive training for the survey.

Results

In 2012, six Member States (Burkina Faso, Cameroon, China, Guinea Bissau, Timor Leste and the United Republic of Tanzania) were validated as having eliminated MNT. With four Member States validated in 2011 (Ghana, Liberia, Senegal and Uganda), the milestone for achieving elimination in ten additional countries between 2010 and 2012 was thus met. In 2013 five additional Member States (Cote d'Ivoire, Gabon, Iraq, Lao People's Democratic Republic and Sierra Leone) and three States in India (New Delhi, Mizoram and Uttarakhand) achieved elimination. As of December 2013, a total of 34[6] out of the 59 priority Member States (58%) have achieved MNT elimination (see Figure 3). Since 2010, the total number of countries that achieved elimination is 15 of the 22 required to meet the GVAP milestone for 2013.

[6] Bangladesh, Benin, Burkina Faso, Burundi, Cameroon, China, Comoros, Congo, Côte d'Ivoire, Egypt, Eritrea, Gabon, Ghana, Guinea Bissau, Iraq, Lao People's Democratic Republic, Liberia, Malawi, Mozambique, Myanmar, Namibia, Nepal, Rwanda, Senegal, Sierra Leone, South Africa, Timor Leste, Togo, Turkey, Uganda, United Republic of Tanzania, Viet Nam, Zambia and Zimbabwe.

Figure 3: Member States with validated elimination of neonatal tetanus (as of 31 December 2013)*



* This includes 18 of 35 states in India, Ethiopia (except Somali Region) and 29 of 33 provinces in Indonesia.

Source: WHO-UNICEF database, May 2014.
194 WHO Member States. Map production: Immunization Vaccines and Biologicals, (IVB). World Health Organization. The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

China's achievement of MNT elimination is a remarkable story because the country did it through massive investments and attention to improving health facility delivery rates and rural maternal and child health outcomes, without any mass supplemental TT vaccination campaigns. India is following a similar course through massive investments in the implementation of strategies to improve clean delivery through the innovative Janani Suraksha Yojana, a conditional cash transfer scheme, to encourage women to give birth in a health facility.

As a result of the Janani Suraksha Yojana scheme, safe deliveries rose from 52.3% (district level household and facility survey - DLHS3) in 2007 to 76.2% coverage evaluation survey in 2009 with the proportion of institutional births increasing in the nine targeted states from a pre-programme average of 20% to 49% during the five-year period (2006-2010). Women delivering in health facilities got further benefits including free drugs, free diagnostics, free blood transfusion (if needed), free diet and free transport under the Janani Shishu Suraksha Karayakaram launched in 2011. Incentives to the 866 000 accredited social health activists were enhanced, which further boosted immunization of mothers and children in 2012.

In 2013, upon completing planned vaccination campaigns (SIAs) and/or improvement in clean delivery practices, pre-validation assessments were conducted in three Member States (Guinea, Lao People's Democratic Republic and Madagascar).

In addition, TT vaccination campaigns targeting women of reproductive age (15–49 years) were conducted in 11 Member States (Afghanistan, Angola, Democratic Republic of the Congo, Ethiopia, Haiti, Kenya, Mali, Niger, Pakistan, Papua New Guinea and South Sudan). Somalia reached target women with TT vaccine during its Mother and Child Health Weeks programme. In all the countries that conducted SIAs in 2013, over 4 million women of reproductive age received at least two doses of TT vaccine.

Protection-at-birth monitoring for TT

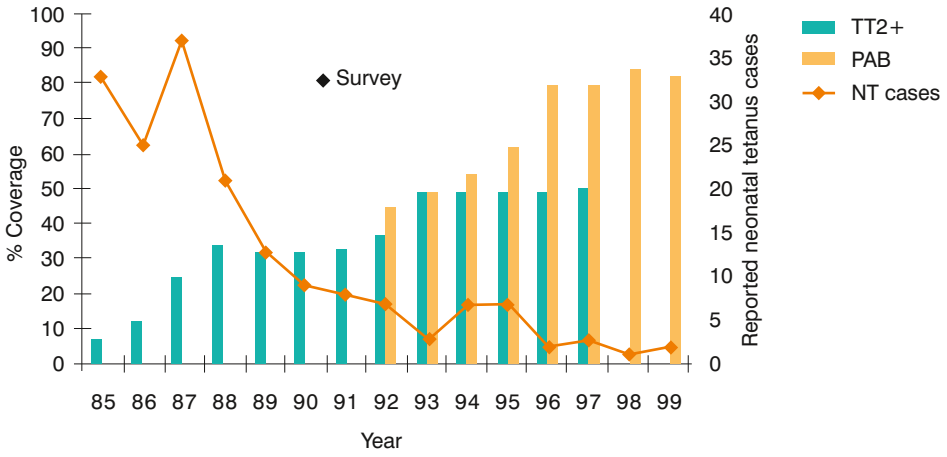
The level of protection against tetanus conferred by vaccination with TT-containing vaccines is monitored at the district level through administratively-reported coverage with at least two doses of the vaccine (TT2+ coverage) or protection-at-birth (PAB) coverage. With the approximate duration of protection after properly-spaced doses of TT-containing vaccines being 3 years after 2 doses, 5 years after 3 doses, 10 years after 4 doses and throughout reproductive years after 5 doses, it becomes imperative to have better estimation of coverage with the vaccine *(3)*.

The TT2+ coverage calculation method uses the cumulative number of pregnant women who received TT2+TT3+TT4+TT5+ but does not include women who have already received their 5 properly spaced doses prior to the current pregnancy and are not eligible for additional doses, though ideally they should have been included. TT2+ coverage monitoring is often problematic in well performing districts.

The PAB method for monitoring TT protection was proposed to overcome the challenges of TT2+ coverage monitoring. The method was recommended by the Global Advisory Group on immunization in 1993 as the prime monitoring method for TT when routine reporting was found inadequate *(4)*, and recommended by the first meeting of SAGE in 1996 for use in every district *(5)*. This method works optimally in countries where DTP1 or Pentavalent 1st dose coverage is very high with 80% being the minimum threshold in the African Region of WHO, and it assesses whether the child brought for its first dose of DTP/Pentavalent was protected at the time of delivery *(6)*. For simplicity, a child is considered protected at birth against NT if the mother has received two doses of TT during the last pregnancy or at least three doses of TT at any time in previous years as evidenced by card or history. The PAB method thus includes protected mothers in the numerator, regardless of whether they received TT in their last pregnancy or not, but leaves out protected mothers whose children do not receive DTP1, which is why high DTP1 coverage was introduced as the criteria for using this method.

Tunisia initiated PAB monitoring in 1992, following consistently low reported TT2+ coverage despite coverage surveys showing the contrary, and the country stopped reporting TT2+ since 1997 as shown in Figure 4.

Figure 4: Protection-at-birth monitoring to address TT coverage underestimation in Tunisia



Source: Ministry of Health, Tunisia (2000); unpublished data.

Discussion

Efforts to sustain MNT elimination in Member States that have achieved it

The Member States that achieved MNT elimination status are focusing on strengthening routine delivery of TT-containing vaccines, introducing school vaccination and expanding networks of community midwives and community health workers to broaden access to clean delivery and aseptic umbilical cord care practices. At the global and regional levels, efforts are being made to provide guidance to Member States on sustaining their achievements. The MNTE Initiative is also following up with Member States on the need for periodic data reviews and implementation of corrective measures based on the findings, to ensure that their elimination status is maintained. There is an on-going review to document the experience of countries that will form the basis for guidelines with a menu of options that countries can adapt based on their local situation.

Efforts to sustain MNT elimination also include:

- a focus on school-based delivery of TT or tetanus-diphtheria (Td) vaccine as part of school health programmes;
- ensuring better linkage between antenatal care attendance and TT/Td vaccination;
- promotion of skilled attendants at birth and discouraging harmful cord care practices;
- supporting integrated disease surveillance that includes neonatal tetanus.

Areas requiring focus in order to keep progress towards the attainment of "MNTE in all countries" on track

1. Need to increase advocacy for MNT elimination

Support for global and country advocacy for MNT elimination: On one hand the programme has made substantial progress in reducing the number of NT deaths since it was re-launched in 1999 (from an estimate of over 200 000 NT deaths in 2000 to 58 000 in 2010 *(7)*) that resulted in a reduction in the burden of the global neonatal deaths contributed by tetanus from 7% to 1%. This declining burden coupled with the fact that neonatal tetanus occurs in very remote parts of countries where service delivery is poor and the vulnerable communities are often politically voiceless, has meant neonatal tetanus elimination is not prioritized during the planning process. There is virtually no media attention on the disease despite the inequity associated with it. Advocacy at all levels is, thus, necessary to bring visibility to the disease with emphasis on resource allocation.

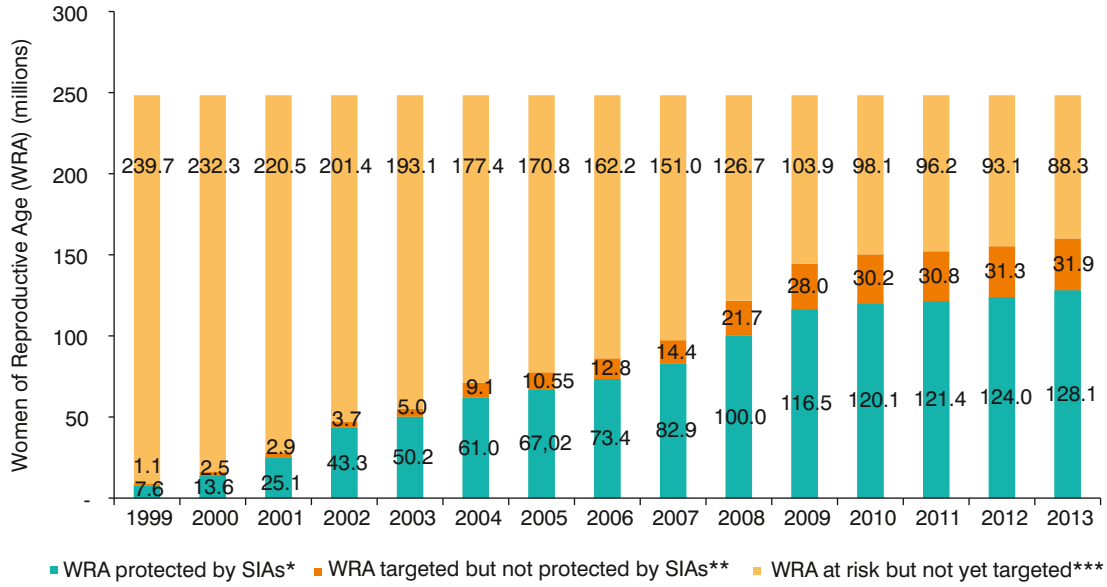
With less than 18 months remaining to achieve MNT elimination goal by 2015, more than one third of the MNT high-risk countries (24 out of 59 countries) have not yet attained MNT elimination (Afghanistan, Angola, Cambodia, Central African Republic, Chad, Democratic Republic of the Congo, Equatorial Guinea, Ethiopia, Guinea, Haiti, India, Indonesia, Kenya, Mali, Mauritania, Niger, Nigeria, Pakistan, Papua New Guinea, Philippines, Somalia, South Sudan, Sudan and Yemen). Of these remaining countries:

- Kenya, Niger, a significant part of Nigeria, a significant part of Pakistan, Papua New Guinea and Sudan are not on track to achieve elimination despite their relatively stable political situation. The governments in these countries should not only prioritize MNT elimination but also invest domestic funds.
- Angola, Cambodia, Democratic Republic of the Congo, Equatorial Guinea, Ethiopia, Guinea, Indonesia, Mauritania and Philippines are very close to elimination – strong advocacy to implement the necessary activities and validate elimination in 2015 is urgently required.
- Afghanistan, Central African Republic, Mali, Somalia, South Sudan, and Yemen are countries affected by political instability. In these countries the need is to lobby donors for funding and the use of innovative approaches to reach vulnerable populations, including the use of TT Uniject™ devices. More funds are required for operations in these countries.
- Chad is one of the countries that reports significant numbers of NT cases each year, with little progress in control efforts. This is partly due to the fact that the primary focus in the country has been to respond to polio outbreaks. Efforts need to be made to utilize the windows of opportunity within the country's current efforts to improve routine immunization performance through better planning to integrate MNT elimination activities.

2. Increase funding for planned TT supplementary immunization activities

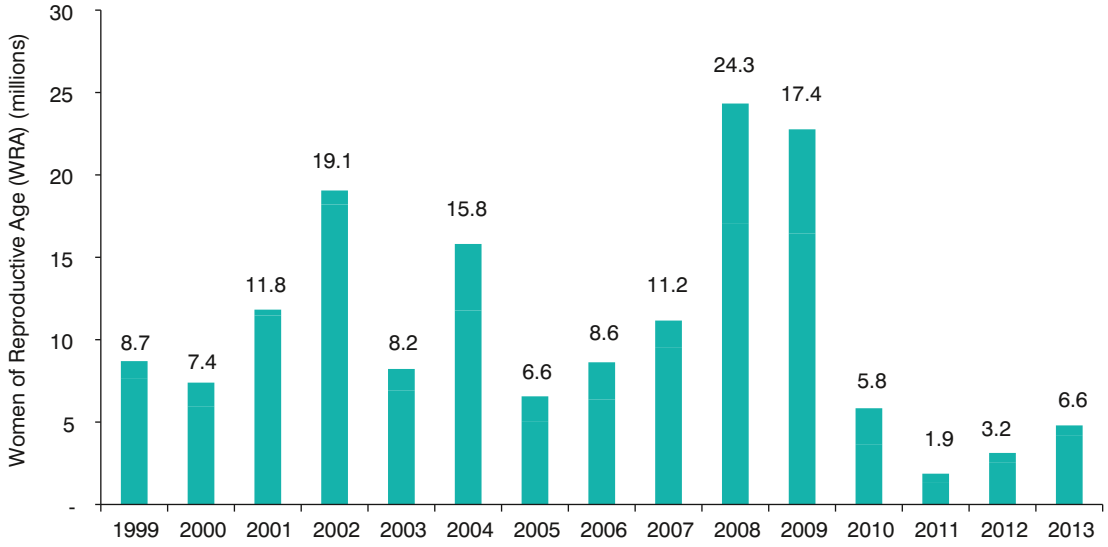
Despite all efforts by priority countries to produce their MNTE plan of action, in recent years the implementation of planned TT SIAs has been faltering. There was initial funding support from UNICEF National Committees, the Bill & Melinda Gates Foundation (BMGF), Ronald McDonald House Charities and Becton Dickinson that enabled reaching and protecting a considerable number of women with at least two doses of TT (Figure 5). The number of women protected peaked in the years following funding from the GAVI Alliance (US$ 62 million) through the International Finance Facility for Immunisation (IFFIm) mechanism from 2006 (Figure 6). Currently the programme receives on an average US$ 10 million per year, which is insufficient to support all the planned activities, resulting in the postponement of most of the planned SIAs. Along with the advocacy for political support, strong lobbying is also required for adequate funding to reach approximately 100 million women of reproductive age in the 24 countries that are yet to achieve MNT elimination. The US$ 91.5 million funding gap is a serious challenge to the global goal for achieving MNTE by 2015.

Figure 5: Cumulative number of women of reproductive age protected with at least 2 doses of TT during SIAs/year



* Protected means receiving at least 2 properly spaced doses of TT.
** Some of the unprotected are likely to have received the 2nd and subsequent doses of TT vaccine during corrective rounds.
*** The number of women of reproductive age at risk but not targeted is added in retrospect following country level data reviews over the years, and includes the fact that by 2014 there are still 88.3 million women of reproductive age to be reached.
Source: WHO/UNICEF MNTE Database; data from 01 May 2014.

Figure 6: Trend in women of reproductive age targeted with TT SIAs



Source: WHO/UNICEF MNTE Database; data from 01 May 2014.

3. Use improved technology (TT-Uniject™)

Improving access to TT vaccine in the most challenging and difficult-to-access locations is of prime importance to the MNTE Initiative. TT vaccine is very stable and does not require refrigeration for weeks, as long as it is not exposed to direct sunlight. TT in monovalent form or as components of combined vaccines is one of the most stable of the vaccines commonly used in national immunization programmes *(8)*. Combining this stability with the use of appropriate technology can significantly improve access to TT vaccine. The TT-Uniject™ device has been used by trained lay health workers in a number of countries, and was evaluated by PATH with no negative effect *(9)*. The use of this device will significantly improve delivery of the vaccine in remote locations where cases of neonatal tetanus often occur, and protect more women and their newborn babies from tetanus. The higher cost (about US$ 0.75/dose) of the vaccine provided through this device is, however, hampering its availability and use. Advocacy with donors, the current sole producer of the device (Becton Dickenson), and especially with the vaccine manufacturers placing the vaccine into the device (most of the cost is for filling the device), will greatly facilitate making this essential device available on a sustained basis and eventually lower cost once there is sustained demand. In the long term there will be additional cost savings as well, since the needs for outreach services, cold chain requirements and the associated operational costs for delivering vaccine to such locations, will lessen.

4. Need to initiate PAB monitoring

To address the challenges of TT2+ monitoring, countries need to initiate the protection-at-birth monitoring so that one of the aspects of poor data quality reported by the GVAP Working Group can start to be practically addressed. WHO and UNICEF are currently working on guidelines that will support countries' efforts in this regard. Opportunities provided by the introduction of new vaccines could be used to revise the tally sheets and other reporting formats to facilitate PAB monitoring as well.

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Annex 1: Reproductive health indicators for MNTE-priority countries

Indicator definition	Reference year for data	Antenatal care – at least one visit (%)	Antenatal care – at least four visits (%)	Skilled attendant at birth (%)
Country or territory	**Time Period**	**Total**	**Total**	**Total**
Afghanistan	2010-2011	48	15	39
Angola	2006-2007	80	-	47
Bangladesh	2011	55	26	32
Benin	2011-2012	86	61	84
Burkina Faso	2010	94	34	66
Burundi	2010	99	33	60
Cambodia	2010	89	59	71
Cameroon	2011	85	-	64
Central African Republic	2010	68	38	54
Chad	2010	53	23	23
China	2010	94		100
Comoros	2004	75		62
Congo	2011-2012	93	-	94
Côte d'Ivoire	2011-2012	91	-	59
Democratic Republic of the Congo	2010	89	45	80
Egypt	2008	74	66	79
Equatorial Guinea	2000	86	-	65
Eritrea	2002	70	41	28
Ethiopia	2011	43	19	10
Gabon	2000	94	63	86
Ghana	2011	96	87	68
Guinea	2007	88	50	46
Guinea-Bissau	2010	93	70	44
Haiti	2005-2006	85	54	26
India	2005-2006	74	37	52
Indonesia	2010	93	82	79
Iraq	2006	84	-	80
Kenya	2008-2009	92	47	44
Lao People's Democratic Republic	2006	35	-	20
Liberia	2007	79	66	46

Indicator definition	Reference year for data	Antenatal care – at least one visit (%)	Antenatal care – at least four visits (%)	Skilled attendant at birth (%)
Country or territory	**Time Period**	**Total**	**Total**	**Total**
Madagascar	2008-2009	86	49	44
Malawi	2010	95	46	71
Mali	2006	70	35	49
Mauritania	2007	75	16	61
Mozambique	2008	92	-	55
Myanmar	2009-2010	83	-	71
Namibia	2006-2007	95	70	81
Nepal	2011	58	50	36
Niger	2006	46	15	18
Nigeria	2008	58	45	39
Pakistan	2006-2007	61	28	43
Papua New Guinea	2006	79	55	53
Philippines	2008	91	78	62
Rwanda	2010	98	35	69
Senegal	2010-2011	93	50	65
Sierra Leone	2010	93	75	63
Somalia	2006	26	6	33
South Africa	2008	97	87	91
South Sudan	2010	40	17	19
Sudan	2010	56	47	23
Timor-Leste	2009-2010	84	55	29
Togo	2010	72	55	59
Turkey	2008	92	74	91
Uganda	2011	93	48	57
United Republic of Tanzania	2010	88	43	49
Viet Nam	2011	94	60	93
Yemen	2006	47	14	36
Zambia	2007	94	60	47
Zimbabwe	2010-2011	90	65	66
Global*	**2007-2012**	**81**	**50**	**66**

* Excludes China, except for the 'total' estimate. Note: Empty cells indicate data not available.

Source: State of the world's children. New York: United Nations Children's Fund; 2013 (http://www.unicef.org/sowc2013/files/SWCR2013_ENG_Lo_res_24_Apr_2013.pdf, accessed 24 November 2014).

GOAL 2:
Achieve measles elimination (indicator G2.2)

Highlights

- The following are highlights from the global level.
  - Worldwide measles morbidity and mortality has been reduced by >90% since the introduction of measles vaccine and 4 out of 5 children are receiving their first dose of measles-containing vaccine (MCV1) through routine services. In addition, each year over 100 million children receive MCV through (SIAs).
  - Because of the highly infectious nature of measles, in order to achieve elimination, the programme target for vaccination coverage is 95% or higher with two doses of measles-containing vaccine delivered through routine and/or SIAs.
  - In 2013, global MCV1 coverage was 84% and global MCV2 coverage was 53% – both short of the programme target.
  - Based on current trends and programme performance, the 2015 global targets for MCV1 coverage, measles incidence and measles mortality reduction will not be achieved on time.
- Six large Member States (Democratic Republic of the Congo, Ethiopia, India, Indonesia, Nigeria, Pakistan) have the most susceptible infants and account for 80% of the measles burden.
  - In these Member States, there is a need to strengthen health systems as a whole to ensure that immunization services are included in national schedules to achieve equitable, high coverage with measles and rubella vaccines (and all other vaccines).
  - Unless the quality of immunization services (both routine and campaign delivery of measles vaccine) can be improved in these Member States, the 2015 global measles incidence and mortality reduction targets will not be met.
  - A strategic cross-cutting approach by all immunization stakeholders is needed in these countries to address the combined challenges of lack of health infrastructure and human resources as well as civil conflict in some areas.
- The following are highlights from the regional level.
  - All six WHO regions now have established measles elimination goals with target dates on or before 2020.
  - The Region of the Americas achieved measles elimination in 2002 but remains under constant threat of spread from importations especially in communities with low vaccination coverage. Experience in the Americas indicates that maintaining elimination is more challenging than achieving it because of complacency and competing public health priorities.
  - There has been little measurable progress towards elimination in four regions over the past 12 months (the African, European, Eastern Mediterranean and Western Pacific Regions).
    - The Western Pacific Region is making progress towards elimination but is being challenged by recent measles outbreaks in China, the Philippines and Viet Nam. Overall, less than 30% of Member States in this region have eliminated Measles.
    - The European Region continued to experience outbreaks in 2013 in Ukraine, Turkey, and Georgia with no decline in overall regional incidence.
    - The Eastern Mediterranean Region experienced large measles outbreaks in 2013 in Pakistan, Lebanon, and the Syrian Arab Republic, which have continued into 2014.
  - SAGE welcomed the establishment of a measles elimination target for 2020 in the South-East Asia Region but noted that with MCV1 coverage still less than 80% in the Region, much work remains to done.
  - In many Member States that are close to interrupting endemic transmission, the reduced threat from measles and rubella and competition from other public health priorities have led to reduced commitment and insufficient human and/or financial resources for achieving the elimination targets.

- Much stronger country ownership and political commitment to measles elimination goals will be needed to get back on track towards elimination in the regions.
- To achieve measles elimination, vaccination coverage needs to be >95% for two doses of MCV administered through routine immunization or routine- and supplementary immunization activities. To prevent measles outbreaks this high level of coverage needs to be achieved uniformly across all districts and very high levels of immunity maintained across all age groups.
- For Member States with routine measles coverage <90% nationally, reaching and sustaining >95% coverage will require substantial additional investments over a sustained period of time.

DEFINITION OF INDICATOR	Framework for verification of measles elimination *(1)* lists the following • Measles eradication: Worldwide interruption of measles virus transmission in the presence of a surveillance system that meets specified performance indicators • Measles elimination: The absence of endemic measles transmission in a defined geographical area (e.g. region or country) for ≥12 months in the presence of a well-performing surveillance system **Note:** Verification of measles elimination takes place after 36 months of interrupted endemic measles virus transmission
DATA SOURCES	• Joint Reporting Forms (JRFs) and WHO-UNICEF estimates of national immunization coverage (WUENIC) data • Progress reports of the regional verification commissions: from the Regions of the Americas, Europe and Western Pacific
COMMENTS ON DATA QUALITY	• JRFs and WUENIC data are subject to the same limitations as all other data submitted via the JRFs, as described in the 2013 GVAP Secretariat report *(2)* • Regional verification commission reports are only available from three regions: European, Western Pacific and Americas (it has to be noted that commissions will only verify elimination if data quality standards are met)
MILESTONES	• Measles elimination goals by WHO region *(3)* · Americas: eliminated in 2002 (2 years after the 2000 goal) · Western Pacific: elimination by 2012 · European: elimination by 2015 · Eastern Mediterranean Region: elimination by 2015 · African: elimination by 2020 · South-East Asia: elimination by 2020

As discussed at the Sixty-third World Health Assembly in 2010, global measles targets for 2015[7] are proposed as milestones towards global eradication of measles. These include achievement of the Global Vaccine Action Plan's goal to increase vaccination coverage as well as targets for reduction of incidence and mortality:

- exceed 90% coverage with the first dose of measles-containing vaccine nationally and exceed 80% vaccination coverage in every district or equivalent administrative unit;
- reduce annual measles incidence to less than five cases per million and maintain that level;
- reduce measles mortality by 95% or more in comparison with 2000 estimates.

[7] Sixty-third World Health Assembly A63/18, Item 11.15, May 2010. http://apps.who.int/gb/ebwha/pdf_files/WHA63/A63_18-en.pdf

Narrative

Last year marked the 50th anniversary of the introduction of the measles vaccine; 2013 also saw the Region of South-East Asia become the final WHO region to commit to measles elimination and rubella control (by 2020). The impact of the measles vaccine on global public health has been tremendous. Before 1963, most of the world's population was infected with measles virus by their 15th birthday, resulting in an estimated 100 million cases and over 2 million deaths annually *(4)*. By 2000, four decades of steadily increasing use of the vaccine saw a dramatic reduction of cases to just over half a million annually. In 2002, the Region of the Americas stopped endemic transmission of measles (i.e., measles was eliminated from the region).

Between 2000 and 2012, routine measles vaccine coverage increased to reach more than eight in 10 children globally, and deaths decreased by 78% to just 122 000 in 2012. During this same time period, the number of Member States providing a second dose of measles vaccine through routine immunization services increased from 96 (50%) to 144 (74%). In 2013, an additional four Member States introduced a second dose of measles vaccine in their routine programme (Burundi, Kenya, Sao Tome and Principe and Zambia) bringing the global total to 148 (76%) Member States. Routine immunization is regularly supplemented with mass immunization campaigns, with approximately 145 million children in 33 Member States vaccinated in 2012 and another 197 million children in 33 additional Member States in 2013.

Despite these efforts, 2013 also saw significant setbacks. Outbreaks continue to threaten elimination goals in at least three regions. In Europe, outbreaks continued into late 2013, affecting primarily Georgia and Turkey but also Italy and the Netherlands. With the disruption of health services in the Syrian Arab Republic due to on-going conflict, reported measles cases rose from 13 in 2012 to over 700 by late 2013, spreading to Lebanon, Jordan, Iraq and Turkey. China is another country that experienced measles resurgence in 2013 following a historic low in 2012, with nearly 27 000 cases reported in 2013. These events illustrate the need for sustained efforts to raise and maintain high levels of immunization coverage even in areas where elimination-level control has previously been attained.

The establishment of Regional Verification Commissions (RVCs) for measles elimination and their corresponding National Verification Committees (NVCs) has helped to sharpen the understanding of the barriers to elimination and build stronger national commitment to achieving elimination goals. The Region of the Americas has the longest standing RVC. At the third Western Pacific Region RVC meeting in March 2014, three Member States were able to document absence of endemic measles (Australia, Mongolia and the Republic of Korea). In the European Region, 50 of 53 Member States have established National Verification Committees and at the Regional Verification Commission meeting in October 2013, 16 (30%) Member States were documented to have interrupted measles transmission. In the Eastern Mediterranean Region, the RVC was established in 2011 with National Verification Committees operating in nine of 21 Member States. However, the RVC has not yet verified elimination in any country of the region. There is no measles RVC in the African Region, and therefore no national verification committees have been established.

In November 2013, SAGE reviewed the status of global measles control and regional elimination and concluded that despite the progress made, based on current trends and programme performance, the 2015 global targets as well as regional elimination targets in the five regions where measles is still endemic, will not be achieved. SAGE welcomed the news that the South-East Asia Region has established a measles elimination target for 2020 and noted that with MCV1 coverage still less than 80% in the region, much work remains to be done.

SAGE emphasized that in order to achieve measles elimination, vaccination coverage needs to be >95% for two doses of MCV administered through routine immunization or routine- and supplementary immunization activities. To prevent measles outbreaks this high level of coverage needs to be achieved uniformly across all districts and across all age groups. For Member States that are now at <90% coverage nationally, reaching >95% coverage will require substantial additional investments over a sustained period of time. SAGE urged Member States and partners to raise the visibility of measles and rubella elimination activities and make the necessary investments of financial and human resources required to strengthen health systems and achieve more equitable access to immunization services. SAGE stressed the importance of building on the work with the polio programme to integrate measles and rubella and other critical services in a way that helps to strengthen the health system and achieve universal health care.

Background data

Tables 4–8 and Figures 7–8 show the progress towards measles elimination in the WHO regions.

Table 4: Progress towards measles elimination, by region

WHO region	Region's elimination target year	RVC established	Regional measles elimination verification report provided in 2014 by RVC for 2013 data	Member States that established NVCs n (% of total)	Established NVCs that submitted Annual Status Reports* n (% of total)	Member States that were verified free of endemic measles n (% of total)****
African	2020	No	No	Unknown	Unknown	Unknown
Americas	2000	Yes	Yes	24	24	34 (97)
Eastern Mediterranean	2015	Yes	No	9 (43)	0	0
European	2015	Yes	Yes	50 *(94)*	47 *(94)*	16 (30)**
South-East Asia	2020	No	No	Unknown	Unknown	Unknown
Western Pacific	2012	Yes	Yes	27*** (100)	14 (82)	3 (11)

* Percentage is expressed out of the total number of established NVCs, not the total number of Member States. Note that a total of 36 reports were submitted to the European RVC, but two of them were submitted by national public health institutions and not NVCs. Thus, they were not considered by the RVC.
** Percentage is based on Member States submitting reports in time for RVC review in October 2013.
*** 13 Pacific Island countries formed one Joint Subregional Verification Committee (they are: Cook Islands, Fiji, Kiribati, Marshall Islands, Micronesia (Federated States of), Nauru, Niue, Palau, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu). Hong Kong, SAR and Macao, SAR established their own Committees in addition to the Chinese NVC. So there are a total of 17 NVCs for 27 Member States in the Western Pacific Region.
**** Percentage is out of the total number of Member States *(27)*, and not the total number of established NVCs.

Table 5: Progress towards measles elimination in the European Region

Status using European Region definitions[a]	Number of Member States n (% of total)	Member States	
Interrupted transmission 2012 (NVC report)	16 (30)	Reduced risk of re-establishment	Armenia, Belarus, Czech Republic, Estonia, Finland, Israel, Kyrgyzstan, Portugal, Slovakia, Slovenia
		At risk of re-establishment	Azerbaijan, Bulgaria, Cyprus, Latvia, Luxembourg, Netherlands
Interrupted transmission 2012 (no NVC report)	1 (2)	Norway	
Endemic transmissions (NVC)	9 (17)	Belgium, France, Greece, Ireland, Kazakhstan, Russian Federation, Spain, Switzerland, United Kingdom of Great Britain and Northern Ireland	
Endemic transmissions (no NVC report)	1 (2)	Poland	
Inconclusive (incomplete data) (NVC report)	9 (17)	Croatia, Germany, Lithuania, Montenegro, Republic of Moldova, Serbia, Tajikistan, Turkmenistan, Uzbekistan	

Status using European Region definitions[a]	Number of Member States n (% of total)	Member States	
Not reviewed	17 (32)	Late submission	Andorra, Austria, Bosnia and Herzegovina, Georgia, Hungary, Iceland, Malta, Monaco, Sweden, The former Yugoslav Republic of Macedonia, Turkey, Ukraine
		No data (no NVC report)	Albania, Denmark, Italy, Romania, San Marino

[a] European Region definitions:
- Interrupted transmission during 2012: Absence of endemic measles transmission in the nation in 2012 in the presence of a well performing surveillance system. Note that data were reviewed for 2010-2012 in the European Regional RVC 2013 report, but elimination was determined based on the absence of endemic measles during 2012 only (different from the definition stated in the WHO Weekly Epidemiological Record, which requires absence of transmission for 36 months or longer).
- Interrupted transmission in 2012 but at risk of re-establishment: Same as "Interrupted transmission 2012" definition above, but for Member States having ≤95% vaccination coverage among infants and young children (different from WHO Weekly Epidemiological Record definition[8]).
- Interrupted transmission 2012, no NVC report: Absence of endemic measles transmission in the nation in 2012 according to a national public health institution report which is not a NVC (different from WHO Weekly Epidemiological Record definition).
- Endemic transmission: The existence of continuous transmission of indigenous or imported measles virus that has persisted in 2012 in the nation (different from WHO Weekly Epidemiological Record definition).
- Endemic transmissions (no NVC report): The existence of continuous transmission of indigenous or imported measles virus that has persisted in 2012 according to a national public health institution that is not a NVC (different from WHO Weekly Epidemiological Record definition).
- Inconclusive (Incomplete data) (NVC report): Data provided by the NVC are not comprehensive enough to classify the country's status on measles elimination conclusively.
- No data (no NVC report): Not available because the country failed to submit the Annual Status Report.

Table 6: Progress towards measles elimination in the Western Pacific Region

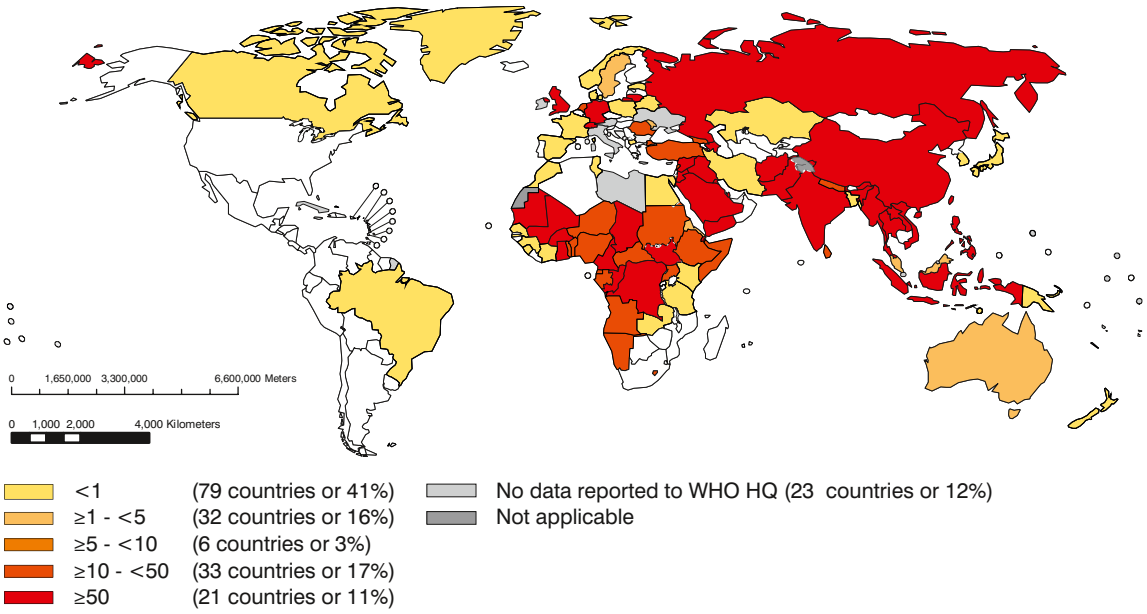
Status according to Western Pacific Region definitions[a]	Number of Countries n (% of total)	Countries
Elimination verified	3 (11)	Australia, Mongolia, Republic of Korea
Possibly ready for verification, but **additional data required**	3 (11)	Brunei Darussalam, Japan, Singapore
Interrupted transmission, <36 months	2 (7)	Cambodia, New Zealand
Period of no or very low transmissions followed by outbreak	16 (59)	Cook Islands, Fiji, Kiribati, Lao People's Democratic Republic, Marshall Islands, Micronesia (Federated States of), Nauru, Niue, Palau, Papua New Guinea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu, Viet Nam
Endemic transmissions	3 (11)	China*, Malaysia, the Philippines

* Data applies for all parts of China excluding Macao, SAR and Hong Kong, SAR. Elimination has been verified for Macao SAR (China). Hong Kong, SAR (China) may be ready for verification of elimination, but additional data are needed.

[a] Western Pacific Region definitions:
- Elimination verified: The interruption of endemic measles virus transmission for ≥36 months in the presence of verification-standard surveillance and genotyping evidence that supports the interruption of endemic measles virus transmission.
- Possibly ready for verification, additional data required: After reviewing the first reports prepared by the NVCs, the RVC determined that interruption may have been achieved, but more detailed epidemiological data was needed to verify measles elimination.
- Interrupted transmission, <36 months: Measles transmission has been interrupted for less than 36 months. There is no endemic transmission, but verification must occur after 36 months. Cambodia will reach 36 months in 2014; New Zealand in 2015.
- Period of no or very low transmissions followed by outbreak: After periods of no or very low transmissions in the country, there are outbreaks that are currently being monitored. An outbreak is defined as a single laboratory-confirmed measles case, whether endemic or imported.
- Endemic transmissions: The existence of continuous transmission of indigenous or imported measles virus that persists for ≥12 months in the nation.

[8] Framework for verifying elimination of measles and rubella, WER, 9, 2013, 88, 89-100

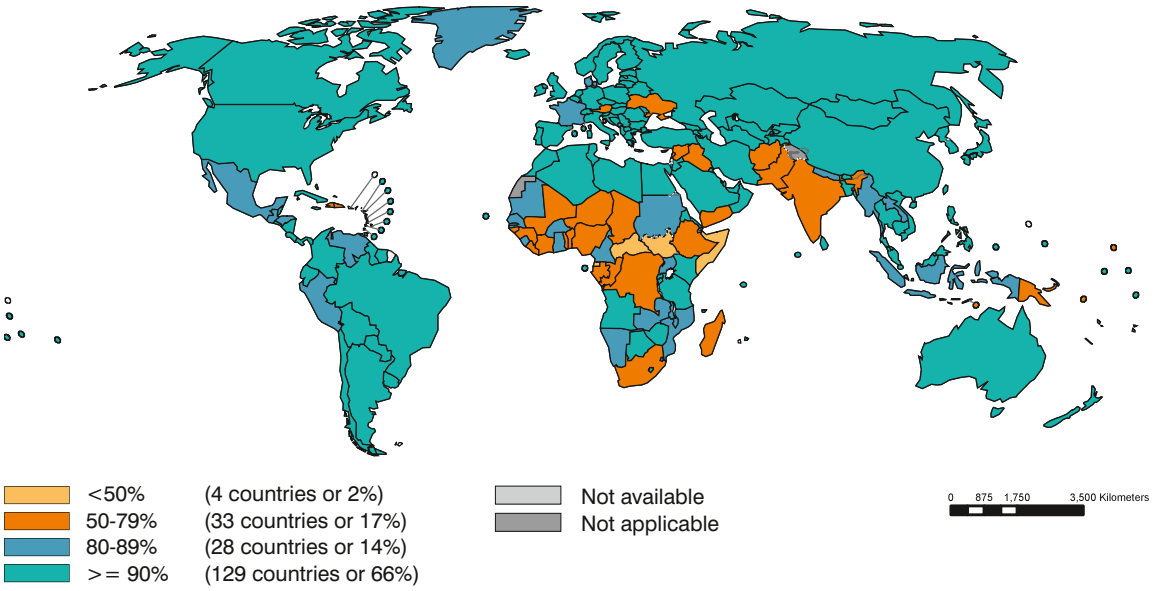
Figure 7: Measles incidence rate per country, 2013*



* Per million population.

Source: WHO/IVB Database as of 28 June 2014. 194 WHO Member States. Map production: Immunization Vaccines and Biologicals, (IVB). World Health Organization. Date of slide: 16 July 2014.

Figure 8: Immunization coverage (%) with measles-containing vaccines (MCV1 cv) in infants per country, 2013



Source: WHO/UNICEF coverage estimates 2013 revision, July 2014. 194 WHO Member States. Map production: Immunization Vaccines and Biologicals, (IVB). World Health Organization
Date of slide: 16 July 2014

Table 7: Number of measles cases and incidence by region, 2011-2012

WHO region	MCV1 national coverage			% of Member States reporting measles in their JRF*			Measles incidence per million population		
	2013	2012	2011	2013	2012	2011	2013	2012	2011
African	74	71	73	100	98	100	90.2	125.6	222.3
Americas	92	94	94	91	100	100	0.3	0.1	1.4
Eastern Mediterranean	78	77	80	86	100	90	35.1	57.4	60.3
European	95	95	94	83	92	94	33.9	34.0	43.1
South-east Asia	78	79	78	100	100	100	16.8	25.6	38.4
Western Pacific	97	97	96	70	100	96	17.2	5.9	11.5
Total	**84**	**83**	**83**	**88**	**97**	**97**	**28.34**	**33.03**	**52.09**

* List of Member States not reporting JRF measles data: Albania; Austria; Bahrain; Barbados; Bosnia and Herzegovina; Brunei Darussalam; Bulgaria; Cook Islands; Cuba; Fiji; Finland; France; Ireland; Italy; Kenya; Libya; Malta; Marshall Islands; Monaco; Nauru; Poland; Samoa; San Marino; Singapore; Trinidad and Tobago; Tuvalu; Ukraine; United Arab Emirates; Uzbekistan.

Source: JRF (as of 28 June 2014) & WHO UNICEF estimates, 1980-2013, revision July 2014.

Table 8: Measles incidence and national coverage of MCV1 for the six Member States with largest number of unimmunized children

	MCV1 national coverage rate			Incidence per million population		
	2013	2012	2011	2013	2012	2011
India	74	74	74	11.0	15.1	27.5
Nigeria	59	37	52	304.4	38.2	114.8
Ethiopia	62	65	68	55.8	47.4	36.4
Indonesia	84	85	80	38.3	62.7	89.8
Pakistan	61	61	63	48.0	44.9	24.9
Democratic Republic of the Congo	73	73	74	12.1*	1096.2	2092.9

* Note that for the Democratic Republic of the Congo, the country officially reports 816 cases in 2013 through the JRF. This total represents the cases confirmed by laboratory and epidemiological link through the case-based system. This system, however, captures less than 4% of cases reported through the aggregate Integrated Disease Surveillance and Response (IDSR) system in the past four years. The IDSR data (reported from the WHO country office) include reports of 89 108 suspect cases. This would represent an incidence of 1319.9 per million for the Democratic Republic of the Congo and 185.4 for the African Region.

Source: JRF (as of 28 June 2014) & WHO UNICEF estimates, 1980-2013, revision July 2014.

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3. Meeting of the Strategic Advisory Group of Experts on immunization, November 2013 – conclusions and recommendations. Wkly Epidemiol Rec. 2014;89*(1)*:1–20 (http://www.who.int/entity/wer/2014/wer8901.pdf?ua=1, accessed 15 December 2014).

GOAL 2:
Achieve rubella and CRS elimination (indicator G2.2)

TARGET

2 WHO REGIONS BY 2015
5 WHO REGIONS BY 2020

Highlights

- As of December 2013, a total of 137 Member States have introduced rubella vaccines; coverage, however, varies from 11% to 94% depending on region.
- As of end 2013, 57 Members States had not introduced rubella-containing vaccine (RCV) in their routine immunization programme. Of those, 45 (79%) have had access to GAVI Alliance support to introduce RCV since 2013.
- The Americas and European Regions have established rubella elimination goals of 2010 and 2015, respectively. Member States in the Region of the Americas achieved their goal in 2009, one year ahead of the target date.
- The South-East Asia Region has established a rubella control goal, linked with their goal to eliminate measles by 2020.
- Three regions (The African, Eastern Mediterranean and Western Pacific) do not have rubella elimination/control targets.
- Rubella and congenital rubella syndrome (CRS) surveillance systems are weak and cases remain underreported, particularly in Member States that have not yet introduced RCV and/or do not have rubella control or elimination goals. Hence, global rubella and CRS surveillance data do not reflect the true burden of these diseases.
- Failure to fully integrate prevention of rubella and CRS with measles elimination activities represents a major missed opportunity for immunization.
- Rubella incidences remain very high in both the African and Western Pacific Regions (14 and 18 per million population, respectively); however, these incidence figures could be even higher due to underreporting of rubella cases. Rubella incidence has declined by >90% in the European Region since 2000 with all the Member States using combined measles, mumps and rubella (MMR) or measles-rubella (MR) vaccines.

DEFINITION OF INDICATOR	• Rubella and CRS elimination: The absence of endemic rubella virus transmission in a defined geographical area (e.g. region or country) for ≥12 months and the absence of CRS cases associated with endemic transmission in the presence of a well-performing surveillance system **Note 1:** There may be a time lag (up to 9 months) in occurrence of CRS cases after interruption of rubella virus transmission has occurred. Evidence of the absence of continuing rubella transmission from CRS cases is needed because CRS cases excrete rubella virus for up to 12 months after birth **Note 2:** Verification of rubella elimination takes place after 36 months of interrupted rubella virus transmission
DATA SOURCES	• JRFs and WUENIC data are subject to the same limitations as all other data submitted via the JRFs, as described in the 2013 GVAP Secretariat report *(1)* • There are no WHO/UNICEF estimates for rubella coverage. MCV1 is used as a proxy in the Member States that have introduced rubella vaccine (as all the Member States use combined vaccines for first dose of rubella except for the Russian Federation)
COMMENTS ON DATA QUALITY	• None
MILESTONES	• Americas: Rubella eliminated in 2009 (one year ahead of 2010 goal) • European: Rubella elimination by 2015 • South-East Asia: Rubella control by 2020 • African: No target • Eastern Mediterranean Region: No target • Western Pacific: No target

Narrative

As of December 2012, a total of 132 (68%) Member States had introduced RCV (Table 9), a 33% increase from 2000. Average coverage globally is low (around 40%) and has remained stable for the past two years. It varies from 11% in the South-East Asia Region to 94% in the European and Americas Regions (Figure 9). In 2013, an additional five Member States introduced rubella vaccine in their routine programme (Cambodia, Ghana, Nepal, Senegal, Solomon Islands) bringing the global total to 137 (70%) Member States.

In 2013, the global incidence of rubella was estimated to be 9.2 per million population (reported by 144 Member States, Figure 10). Note that the total number of Member States reporting rubella incidence to WHO has diminished dramatically in recent years (from 174 in 2012 to 144 Member States in 2013), which explains the appearance that rubella incidence is diminishing.

The same trend can be seen with CRS reporting. In total 101 Members States reported CRS figures in 2013 compared with 129 in 2012. (Table 10) The very low reported incidence probably is more a sign of the almost non-existent CRS surveillance systems outside the Americas and a few other Member States than a reflection of true disease burden.

The Americas Region has achieved its 2010 elimination goal and a significant decline in rubella incidence has been observed in the European Region as well. However, three WHO regions have not yet established elimination goals at all.

A new phase of accelerated rubella control and CRS prevention has begun, marked by the 2011 WHO Position Paper recommending a strategy consistent with rubella and CRS elimination *(2)*, which emphasizes the opportunity to eliminate rubella through its linkage to measles control activities, as described in the M&RI strategic plan, and support eligible Member States to receive support from the GAVI Alliance.

The key challenges are:

a. building support for additional regions to adopt elimination goals. This includes ensuring that all Member States can achieve and maintain the minimum coverage (>80%) through routine services

and/or in SIAs required for introduction of rubella containing vaccine;

b. advocating for resources and a secure vaccine supply needed to meet the European Region's elimination goal;

c. ensuring high routine coverage of RCV (because of the use of combined MR or MMR vaccines, the programmatic target for RCV1 and RCV2 coverage is >95%);

d. ensuring high-quality MR SIAs that reach at least 95% of targeted children, as verified through surveys; and

e. strengthening synergies between rubella and measles surveillance and expanding CRS surveillance – commitment at all levels of government as well as involvement of the private sector is needed to address these challenges.

Financial support from the GAVI Alliance together with the leadership, coordination and technical expertise from M&RI, provide an opportunity for Member States and regions to accelerate rubella control and CRS prevention. However, substantially greater commitment and investment by Member States and the global immunization community will be required to complete the task of rubella elimination in the European Region by 2015 and reach the GVAP target of rubella elimination in five regions by 2020.

Background data

Tables 9 and 10 and Figures 9–11 provide data on cases of rubella and congenital rubella syndrome.

Table 9: Rubella cases and incidence by region, 2011-2013

WHO region	National rubella coverage*			% of Member States reporting rubella cases			Rubella incidence per million population		
	2013	2012	2011	2013	2012	2011	2013	2012	2011
Africa	3.5	0.1	0.1	91	87	85	14.3	13.0	19.2
The Americas	91.5	94.3	93.7	94	100	100	0.0	0.0	0.0
Eastern Mediterranean	40.5	40.6	42.4	86	90	81	6.7	3.0	5.1
Europe	95.2	94.9	94.5	77	89	89	64.1	42.3	13.8
South-East Asia	12.5	11.1	3.1	100	100	91	5.1	3.6	16.6
Western Pacific	91.2	88.3	88.1	63	85	89	18.3	24.1	41.7
Total	**43.9**	**42.9**	**40.7**	**84**	**91**	**89**	**14.71**	**13.94**	**21.02**

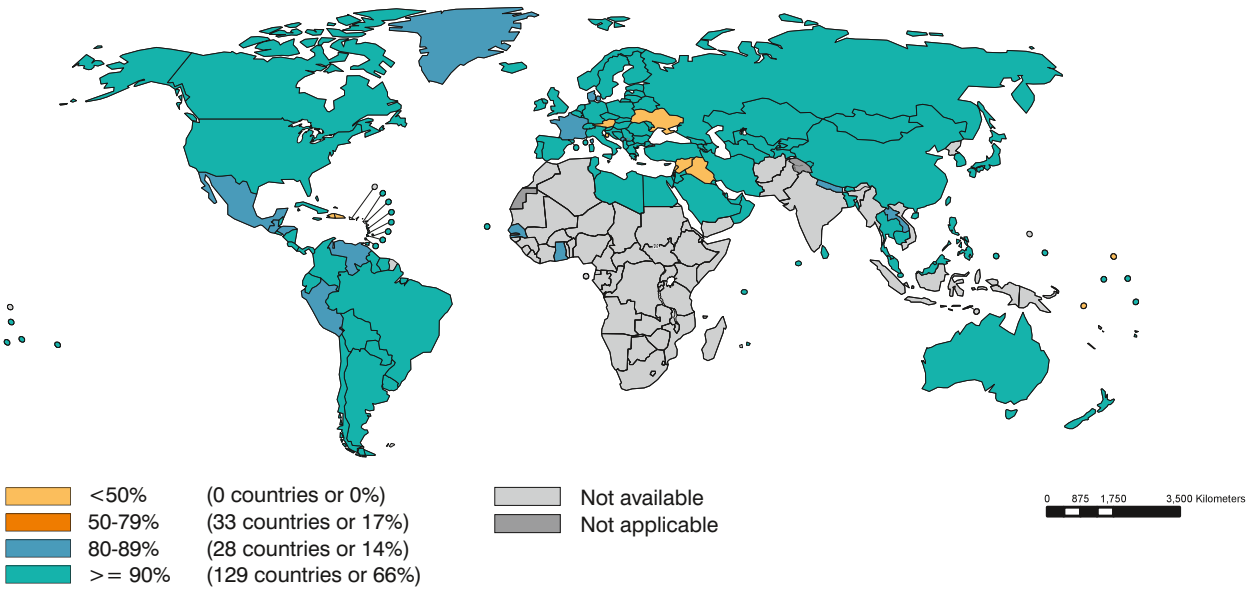
* MCV1 was used as a proxy in the Member States that have introduced rubella vaccine.
Source: JRF (as of 28 June 2014) & WHO UNICEF estimates, 1980-2013, revision July 2014.

Table 10: CRS cases and incidence by region, 2011-2013

WHO region	CRS incidence per million population			% of Member States reporting CRS cases		
	2013	2012	2011	2013	2012	2011
Africa	0	0.3	0	34	43	34
The Americas	0	0	0	94	100	100
Eastern Mediterranean	0.1	0.2	0	52	43	43
Europe	0.1	0.1	0	79	81	89
South-East Asia	0.1	0.1	0.1	55	55	36
Western Pacific	0.1	0.4	0.7	48	63	67
Total	**0.1**	**0.1**	**0.1**	**62**	**67**	**66**

Source: JRF (data as of 6 May 2014).

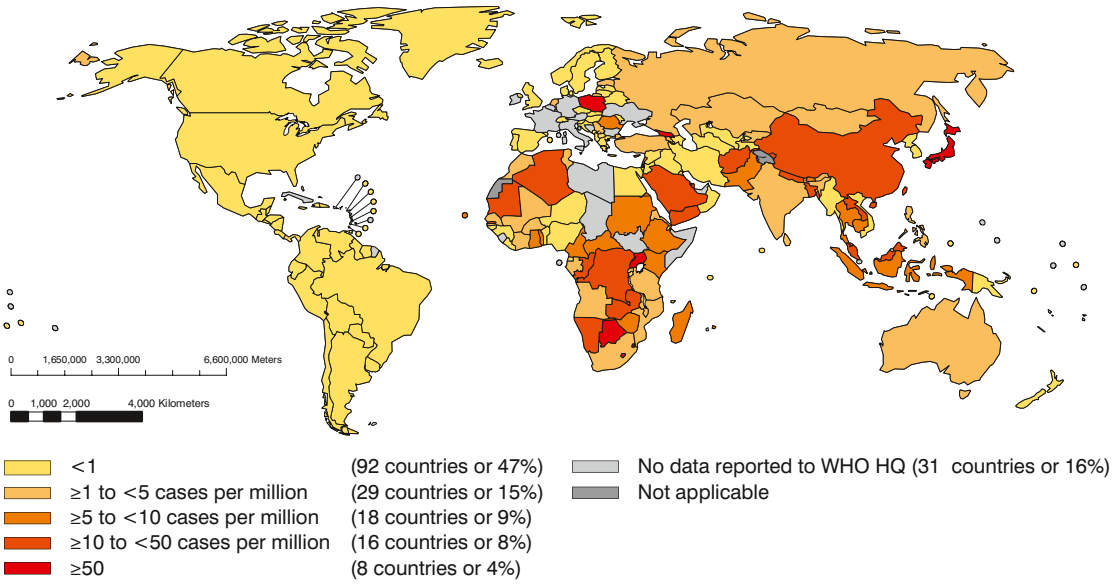
Figure 9: Immunization coverage with rubella containing vaccines* in infants, 2012



* MCV1 was used as a proxy in the Member States that have introduced rubella vaccine.

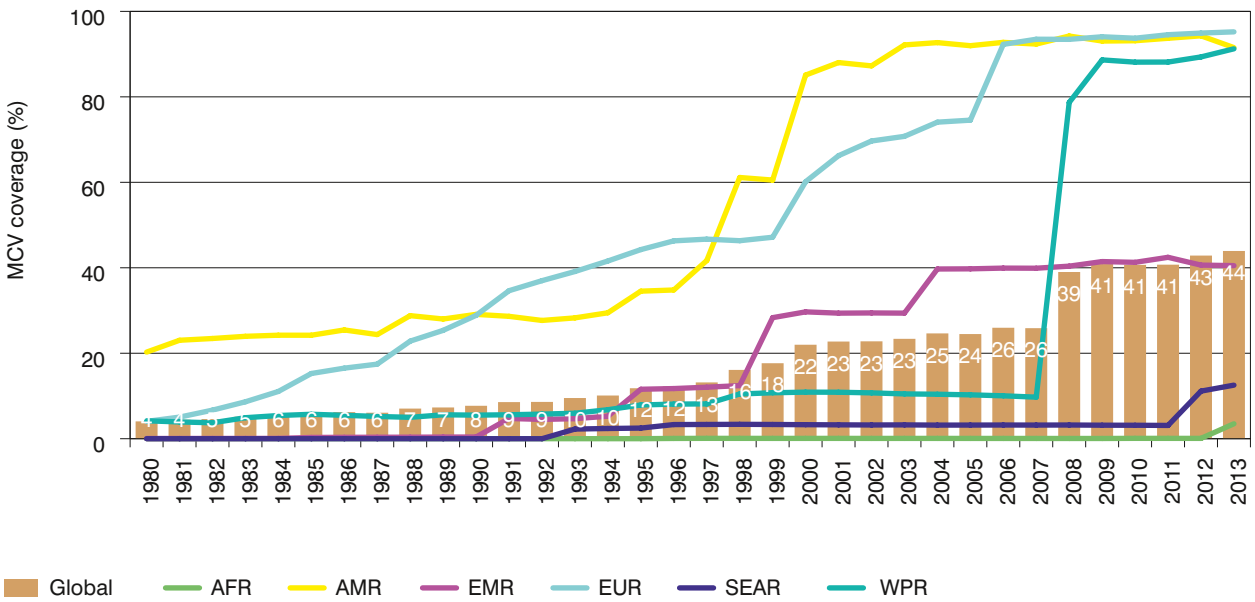
Source: WHO/UNICEF coverage estimates 2013 revision, July 2014. 194 WHO Member States. Map production: Immunization Vaccines and Biologicals, (IVB). World Health Organization
Date of slide: 24 July 2014

Figure 10: Rubella incidence rate per country for 2013



Source: WHO/IVB Database as of 28 June 2014. 194 WHO Member States.
Map production: Immunization Vaccines and Biologicals, (IVB). World Health Organization
Date of slide: 16 July 2014

Figure 11: Rubella-containing vaccine coverage by WHO region, 1980-2013



Source: WHO/UNICEF coverage estimates 2013 revision. July 2014 Immunization Vaccines and Biologicals, (IVB), World Health Organization. 194 WHO Member States. Date of slide: 24 July 2014.

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Coverage-related indicators

The progress against all the GVAP indicators – both goals and strategic objectives – that relate to immunization coverage has been consolidated into this one chapter, since the data are all interrelated.

It has to be noted that, in February 2014, the SAGE GVAP Working Group agreed to include the three following indicators in the narrative of the overall coverage indicator report rather than having them as specific indicators:

- Indicator SO3.1: Percentage of districts (or equivalent administrative units) with ≥80% coverage with three doses of diphtheria–tetanus–pertussis (DTP) vaccine.
- Indicator SO4.2: Number of countries that had sustained DTP3 national coverage ≥90% for 3 or more years.
- Indicator SO3 4.1: Drop-out rate between the 1st and 3rd doses of DTP-containing vaccines at the national level.

The two major sources of data for this report are:

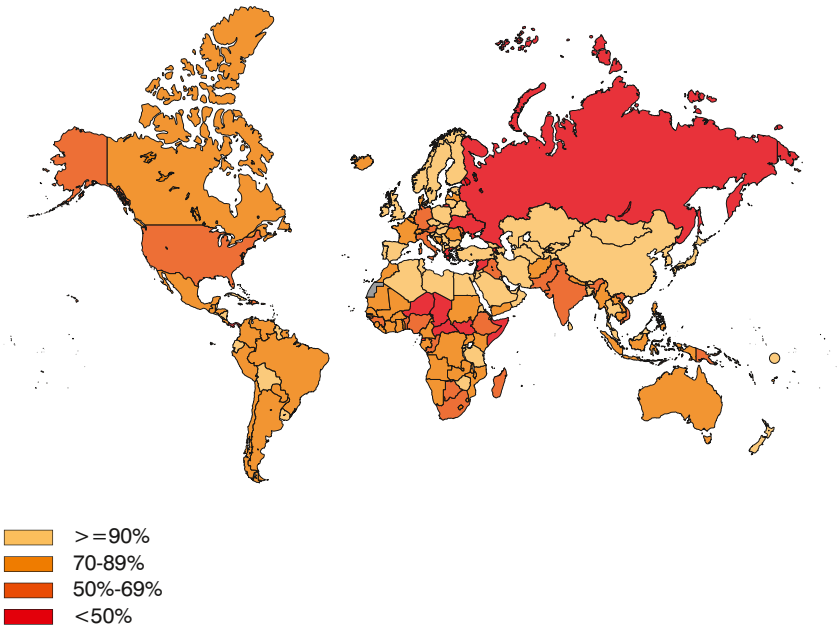
- The WHO-UNICEF Joint Reporting Form on Immunization (JRF), which collects data from WHO Member States on reported cases of selected vaccine preventable diseases; recommended immunization schedules; immunization coverage; vaccine supply; immunization financing; and other information on the structure, policies and performance of national immunization systems; and
- The WHO-UNICEF estimates of national infant immunization coverage (WUENIC), which are derived from various data sources, including coverage data reported in the JRFs.

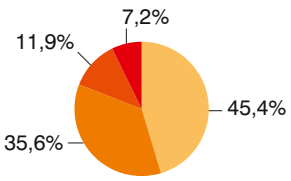
For more information about the JRF and WUENIC coverage data, please refer to the GVAP Secretariat Report 2013, Annex 1.[9]

Please note that for all the coverage indicators, the GVAP Secretariat has provided interactive maps and graphs that will help the reader to better understand and explore of data.

To access these interactive figures/dashboard please use the Technet21 platform: http://www.technet-21.org/resources/gvap-indicators.

National Coverage for All Vaccines in National Programme, 2010-2013





Note:
District coverage data for all vaccines in national programs are currently not available. Thus, only the national coverage rates for all vaccines and their comparison to DTP3 coverage rates are shown here.

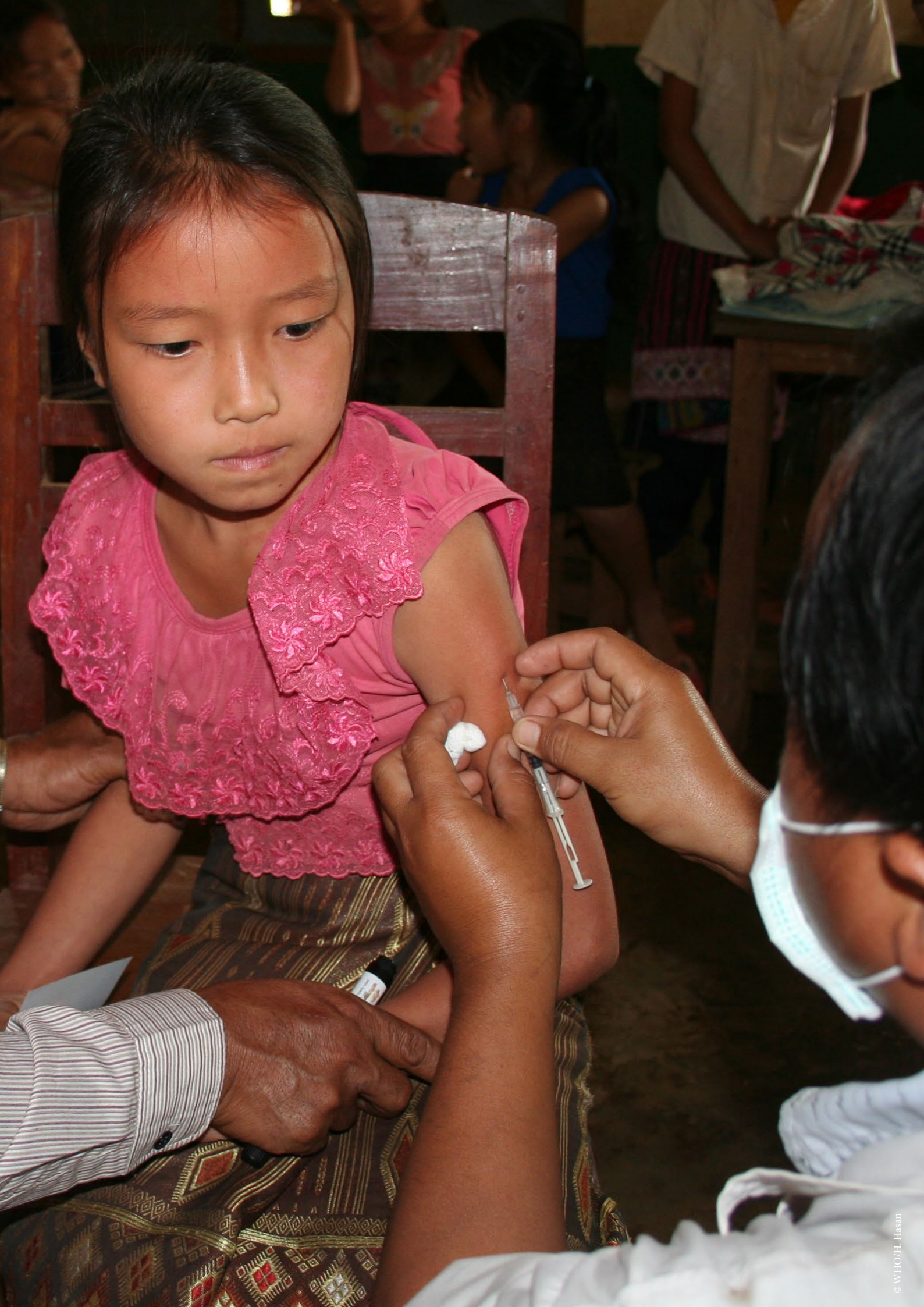
When looking at the data, please hover over the dots, bars and countries; change the year; use the filters; use zoom, etc. to view additional information in the background.

For example, for the graph showing the relationship between DTP1 and DTP3, by filtering by region and then hovering over the circles, one can see which country the circles represent.

[9] Global Vaccine Action Plan monitoring, evaluation & accountability: Secretariat annual report 2013. Geneva: World Health Organization; 2013 (http://www.who.int/entity/immunization/global_vaccine_action_plan/GVAP_secretariat_report_2013.pdf?ua=1, accessed 25 November 2014).

GVAP COVERAGE INDICATORS

Goal/Strategic Objective	Indicators
Goals	
G3 **Meet vaccination coverage targets in every region, country and community**	G3.1 By 2015, reach 90% national coverage and 80% in every district or equivalent administrative unit with three doses of DTP vaccines
	G3.2 By 2020, reach 90% national coverage and 80% in every district or equivalent administrative unit for all vaccines in national programmes, unless otherwise recommended
Strategic Objectives (SOs)	
SO3 **The benefits of immunization are equitably extended to all people**	SO3.1 Percentage of districts with ≥80% coverage with three doses of DTP vaccine **Note:** this indicator is included in the narrative of the overall coverage indicator report (under G3.1)
	SO3.2 Reduction in coverage gaps between wealth quintiles and other appropriate equity indicator(s).
SO4 **Strong immunization systems are an integral part of a well-functioning health system**	SO4.1 Drop-out rates between first dose (DTP1) and third dose (DPT3) of diphtheria-tetanus-pertussis-containing vaccines. **Note:** this indicator is included in the narrative of the overall coverage indicator report (under G3.1)
	SO4.2 Sustained coverage of DTP vaccines ≥90% for three or more years **Note:** this indicator is included in the narrative of the overall coverage indicator report (under G3.1)
	SO4.3 Immunization coverage data assessed as high quality by WHO and UNICEF. To be reported starting from 2015



2. INCREASE VACCINATION COVERAGE

NUMBER OF MEMBER STATES THAT REACH 90% NATIONAL COVERAGE AND 80% IN EVERY DISTRICT OR EQUIVALENT ADMINISTRATIVE UNIT WITH THREE DOSES OF DIPHTHERIA–TETANUS–PERTUSSIS-CONTAINING VACCINES (INDICATOR G3.1)

Highlights

- A total of 129 (66%) Member States had national DTP3 coverage of ≥90% in 2013, six fewer than in 2012.
- In the Region of the Americas the number of Member States with DTP3 ≥90% decreased from 27 in 2012 to 23 in 2013; the change may have been a results of changes in the methods for estimating coverage (e.g. Mexico).
- In 2013, 119 Member States had sustained DTP3 coverage ≥90% for three or more years.
- The global DTP3 coverage was 84% in 2013, with diminishing trends in the Americas (regional coverage of 90% in 2013 vs 94% in 2012), stagnant rates in the South-East Asia Region, the European Region, Western Pacific Region and Eastern Mediterranean Region and an increase in the African Region (75% in 2012 and 82.5% in 2013).
- The total number of unvaccinated children (not receiving three doses of DTP-containing vaccines) diminished globally from an estimated 22.3 million in 2012 to 21.8 million in 2013, mainly due to a diminution of unvaccinated children in Nigeria (4.8 in 2012 and 2.8 in 2013).
- DTP3 coverage in India has not changed for the past several years in the absence of a nationally representative survey to provide data to revise the estimate. However, subnational coverage surveys show increases in coverage in the states that had low coverage in the past.
- Only 53 Member States (27%) reached national DTP3 coverage of ≥90% as well as coverage in all districts of ≥80%. This is 11 (6%) Member States fewer than in 2012. This is primarily due to a higher number of Member States having invalid district-level coverage data in 2013 relative to 2012.

TARGET	2015 in all Member States reach 90% national coverage and 80% in every district or equivalent administrative unit with three doses of diphtheria–tetanus–pertussis-containing vaccines
DEFINITION OF INDICATOR	National coverage data based on WUENIC District-level DTP3 coverage data are considered valid only if the WUENIC and administrative data from the JRF are the same or if the WUENIC for national DTP3 coverage is ≥90%
DATA SOURCES[10]	WUENIC estimates Administrative coverage from country JRFs (for percentage of districts with coverage ≥80%)
DATA AVAILABILITY & QUALITY	112 countries (58%) had valid district-level DTP3 coverage data in 2013 compared to 124 (64%) in 2012, a reflection of the limited improvement in data availability and quality. Forty-seven Member States (24%) did not provide district coverage data and 35 (27%) provided data that were considered invalid

Please note that graphic representations of data for this indicator are available on interactive maps and graphs figures/dashboard for better understanding and exploration of data.

Please visit the Technet21 website to view the interactive content:

http://www.technet-21.org/resources/gvap-indicators

Data availability and quality

By the end of 2013 most countries were using DTP in combination with other vaccines, mainly either DTP-*Haemophilus influenzae* type b (Hib)-hepatitis B (HepB), DTP-Hib-IPV or DTP-Hib-HepB-IPV. Hence, DTP3 in this report refers mainly to coverage with three doses of DTP-containing vaccines.

Though WUENIC data are available every year and can be used to monitor progress against achievement of target coverage at the national level, the full assessment of progress with DTP3 coverage is limited by the availability of valid district-level coverage data. In this assessment, district-level coverage data were considered valid only if WUENIC data were the same as the administrative coverage reported by national authorities on the JRF, or if the WUENIC data were ≥90%.

Using this definition, 112 Member States (58%) had valid DTP3 district-level coverage estimates in 2013 (Table 11). Of the remaining 82 Member States, 55 have WUENIC data that differ from the administrative coverage and have WUENIC data <90% and 27 did not report district-level coverage.

[10] For more information about the JRF and WUENIC coverage data, please refer to the GVAP Secretariat report 2013, Annex 1. http://www.who.int/entity/immunization/global_vaccine_action_plan/GVAP_secretariat_report_2013.pdf?ua=1

Table 11: Distribution of Member States by national and district-level DTP3 coverage achievements and by region, 2013

WHO region	Countries with DTP3 district coverage data available and valid								District DTP3 coverage data not available		District DTP3 coverage data available but considered invalid		Total
	National DTP3 coverage ≥90% & all districts ≥80%		National DTP3 coverage ≥90% but not all districts ≥80%		National DTP3 coverage <90%		Total						
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n
African	5	11%	12	26%	7	15%	24	51%	1	2%	22	47%	47
Americas	7	20%	12	37%	8	23%	27	77%	6	17%	2	6%	35
Eastern Mediterranean	7	33%	2	14%	2	10%	11	52%	4	19%	6	29%	21
European	21	40%	6	32%	0	0%	27	51%	25	47%	1	2%	53
South-East Asia	4	36%	2	27%	2	18%	8	73%	2	18%	1	9%	11
Western Pacific	9	33%	3	22%	3	11%	15	56%	9	33%	3	11%	27
Global	**53**	**27%**	**37**	**19%**	**22**	**11%**	**112**	**58%**	**47**	**24%**	**35**	**18%**	**194**

Relative to the previous year when 124 countries had valid data, there are 12 fewer Member States with valid DTP3 district-level coverage estimates in 2013. The number of countries that did not report district-level coverage increased from 36 in 2012 to 47 (including the 27 that had WUENIC data ≥90%) in 2013.

It is important to note here that the 2012 coverage data used in this comparison is based on the updated time series prepared in 2014 and may differ from those in the last report for some Member States (the coverage time series for Member States is updated each year if and when new data become available, e.g. data from a new survey). For example, at the time of the previous report district level coverage was only available and valid from 114 countries, but subsequently data became available from 10 additional countries. Thus, it is expected that more countries may report district-level coverage data after the data submission deadline, as in the previous year. However, this goes to show the importance of timely and complete reporting by countries, to ensure timely assessment of progress.

The fact that WUENIC data are the same as administrative coverage data from Member States is not by itself a sufficient indicator of the quality of coverage data. This is because administrative reports may be the only source of data for some Member States, and there are no alternate sources of empirical data to question or validate these estimates. For these Member States, the district-level coverage estimates should ideally be validated by conducting a survey in at least a sample of districts.

Results

National DTP3 immunization coverage

In total 129 Member States (66%) had achieved a national DTP3 coverage rate of ≥90% in 2013 (six fewer than the previous year). However, the proportion of Member States reaching this target varied considerably between regions (Table 12), ranging from 38% in the African Region to 92% in the European Region. It has to be noted that 23 Member States achieved the DTP3 ≥90% target in the Region of the Americas compared to 26 last year. While the proportion of countries reaching 90% DTP3 coverage was high in the South-East Asia and Eastern Mediterranean Regions, the most populous Member States in these regions (e.g. India, Indonesia, Pakistan) have yet to achieve this threshold. In India, the country with the largest birth cohort, the coverage estimates have not been revised in the absence of new nationally representative survey estimates; subnational surveys in states that had low coverage in the past have shown impressive increases in coverage rates.

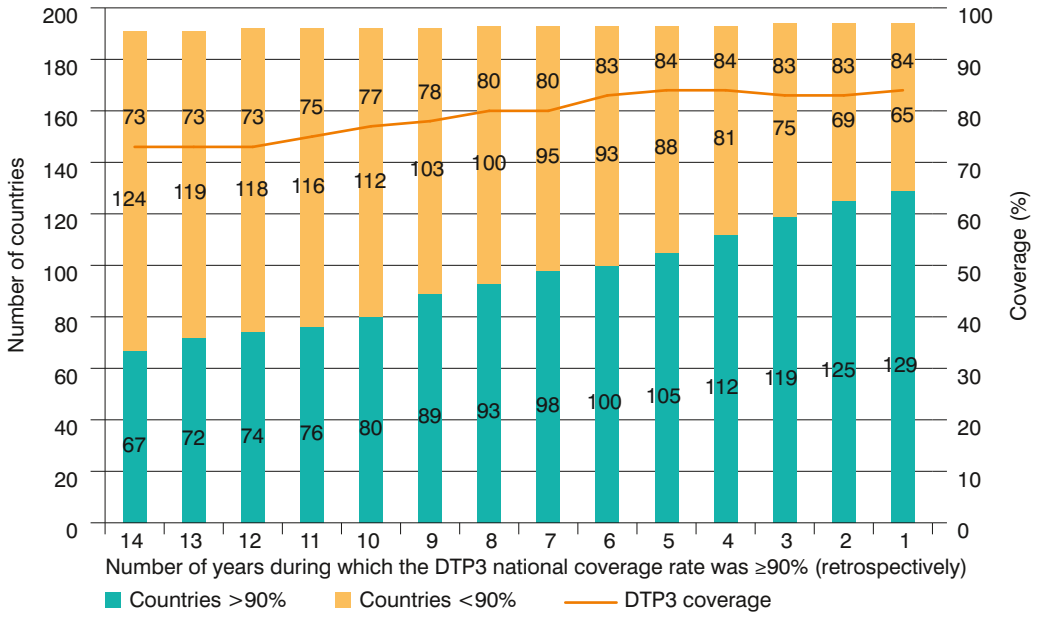
Table 12: Distribution of all 194 Member States by level of national DTP3 coverage rate and region, based on WUENIC estimates for 2013*

WHO region	DTP3 ≥90% in 2012		DTP3 ≥90%		DTP3 of 70–89%		DTP3 of 50–69%		DTP3 <50%		Total
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n
Africa	18	39%	18	38%	20	43%	5	11%	4	9%	47
Americas	26	74%	23	66%	11	31%	1	3%	0	0%	35
Eastern Mediterranean	13	59%	13	62%	5	24%	1	5%	2	10%	21
Europe	48	91%	49	92%	3	6%	1	2%	0	0%	53
South-East Asia	7	64%	7	64%	4	36%	0	0%	0	0%	11
Western Pacific	19	70%	19	70%	4	15%	3	11%	1	4%	27
Global	**131**	**67%**	**129**	**66%**	**47**	**24%**	**11**	**6%**	**7**	**4%**	**194**

* Data from 2012 are shown for comparison.
Source: WHO/UNICEF coverage estimates 2013 revision. July 2014.

In total 119 Member States sustained DTP3 coverage ≥90% for 3 or more consecutive years in 2013. Ten additional countries achieved DTP3 coverage ≥90% in 2013, though they have yet to sustain this coverage rate for 3 or more years (Figure 12).

Figure 12: Number of countries that have sustained ≥90% DTP3 coverage since 2000 and global DTP3 coverage in 2013

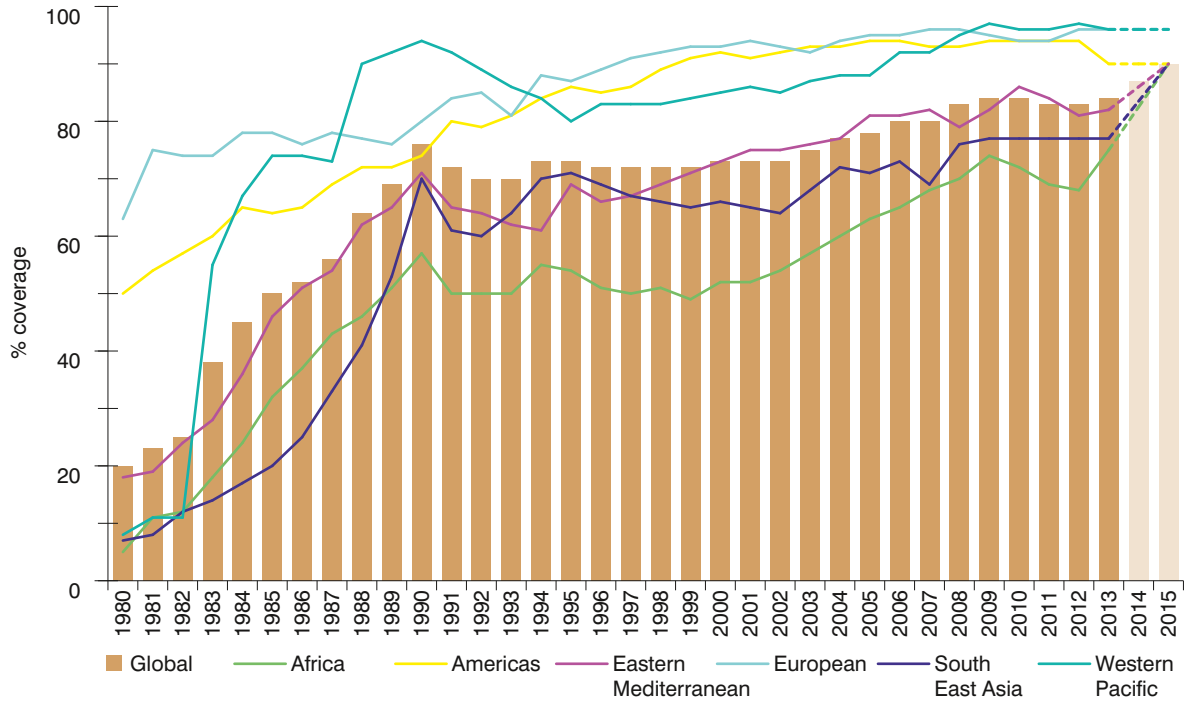


Note: Data in this table should be read as follows: In 2013 (last column), 129 countries have reached and sustained DTP3 coverage ≥90% for 1 year and 67 countries have reached and sustained DTP3 coverage ≥90% for 14 years.

Source: WHO/UNICEF coverage estimates 2013 revision. July 2014.

Global DTP3 coverage was 84% in 2013 (Figure 13). The regional coverage showed a diminishing trend in the Americas (90% in 2013 vs 94% in 2012), stagnant rates in the South-East Asia, European, Western Pacific and Eastern Mediterranean Regions, but an important increase in the African Region (75% in 2012 and 82.5% in 2013).

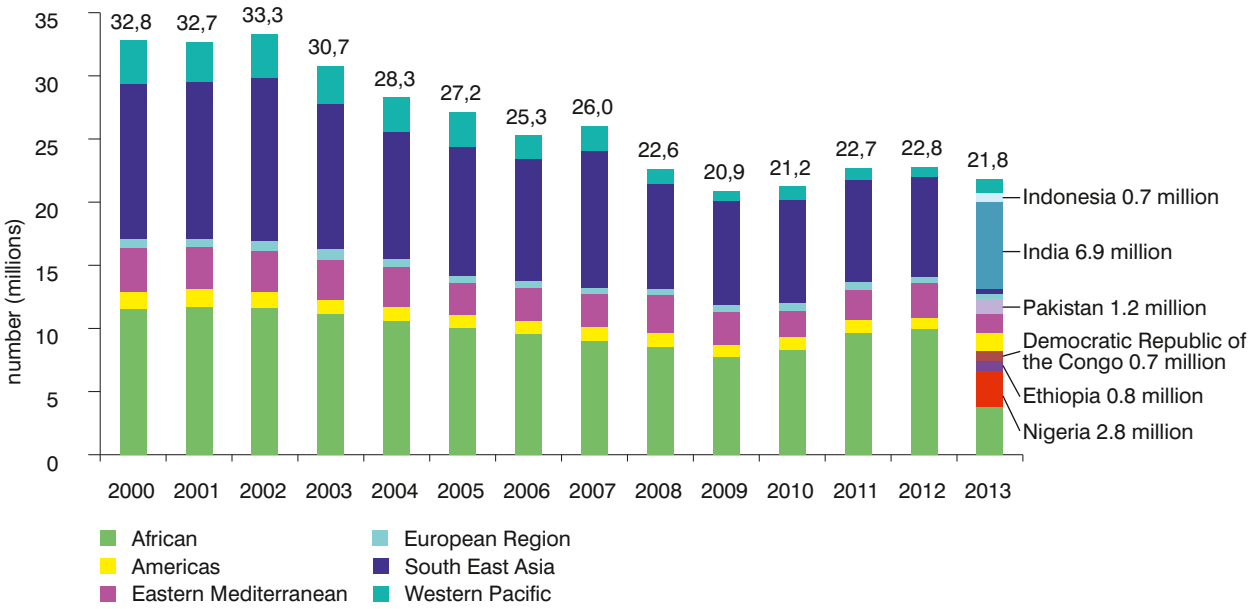
Figure 13: Immunization trends and projections to reach 90% global coverage DTP3 coverage goals in 2015, globally and by WHO region



Source: WHO/UNICEF coverage estimates 2013 revision. July 2014.

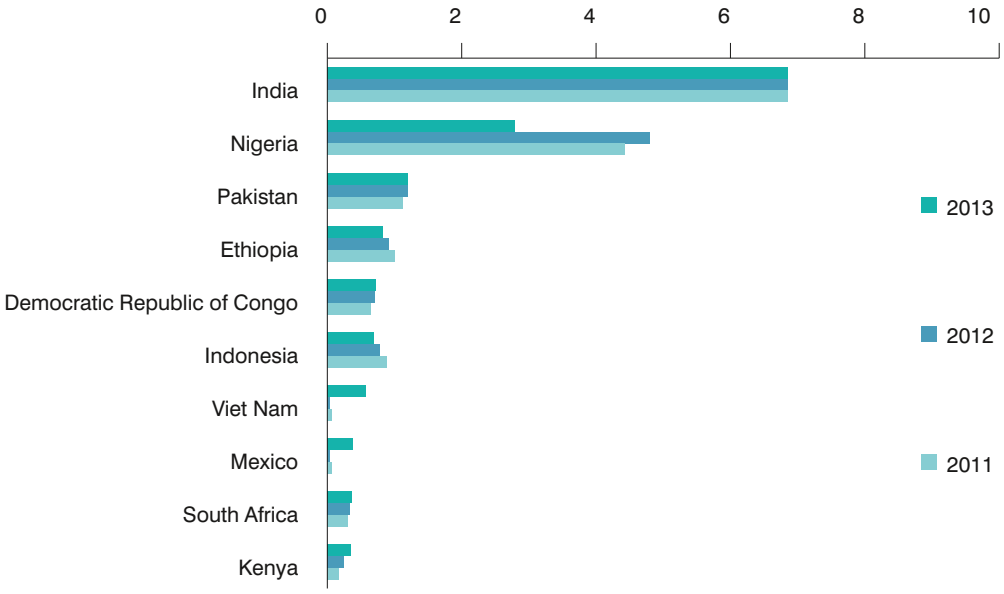
Total number of children who had not received at least three doses of DTP-containing vaccines diminished globally from 22.3 million in 2012 to 21.8 million in 2013 (Figure 14), mainly through the important diminution of un- and under-vaccinated children in Nigeria from 4.8 million in 2012 to 2.8 million in 2013 (Figure 15 and Figure 16). In the other countries that account for the largest number of un- or under-vaccinated children, the numbers have not changed much during the past 3 years, though it should be noted that recent data from India – the country with the highest number of un- or under- vaccinated children – are not available to update their estimates (Figure 15).

Figure 14: Number of unvaccinated children (DTP3) by year and WHO region, 2000-2013



Source: WHO/UNICEF coverage estimates 2013 revision. July 2014 and *(1)*.

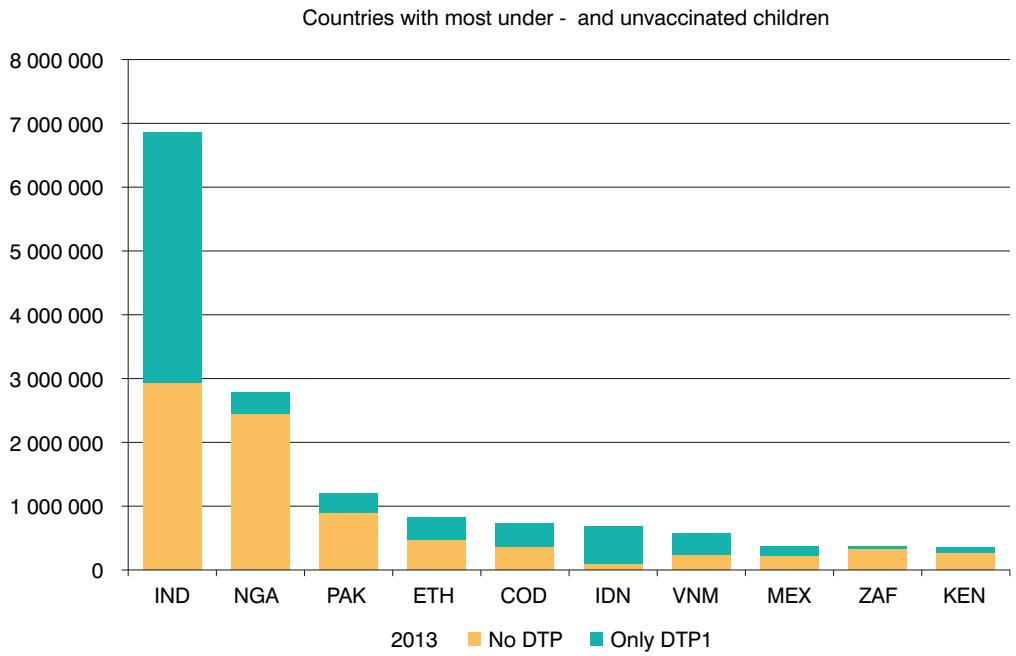
Figure 15: Countries with most unvaccinated infants (DTP3), 2011-2013*



* In millions.

Source: WHO/UNICEF coverage estimates 2013 revision. July 2014.

Figure 16: Top 10 countries with most under- and un-vaccinated children (DTP3)

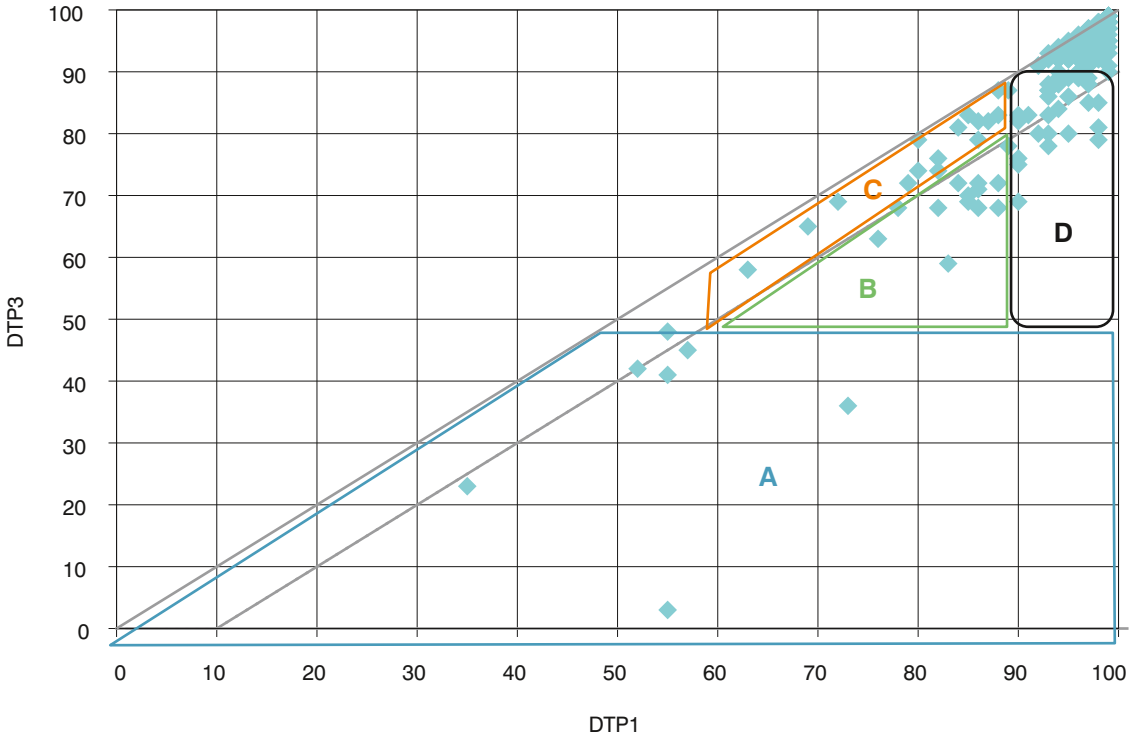


India (IND), Nigeria (NGA), Pakistan (PAK), Ethiopia (ETH), Democratic Republic of the Congo (COD), Indonesia (IDN), Viet Nam (VNM), Mexico (MEX), South Africa (ZAF), Kenya (KEN).

Source: WHO/UNICEF coverage estimates 2013 revision. July 2014.

Countries with DTP3 coverage <90% were classified into four groups based on their DTP1 and DTP3 coverage to allow general, global-level recommendations adapted to their specific situation, as shown in Figure 17 and outlined in Table 13. However, each country must further examine their country level data to achieve a better understanding of the factors impeding the achievement of the coverage targets, and implement strategies to address them.

Figure 17: Classification of those Member States with DTP3 national coverage <90%, by their DTP1 and DTP3 coverage



Note: Data in this table should be read as follows:
- A: Countries with DTP3 coverage <50%
- B: Countries with DTP1 coverage <90% & drop-out ≥10%
- C: Countries with DTP1 coverage <90% but drop-out <10%
- D: Countries DTP1 coverage ≥90% and DTP3 coverage <90%.

Source: WHO/UNICEF coverage estimates 2013 revision. July 2014.

Figure 16 shows the number of un- and under-vaccinated children in the 10 countries that account for the largest number of such children. In countries such as India and Indonesia, which have a substantial number of under-vaccinated children, addressing missed opportunities for vaccination alone has the potential to result in a substantial increase in DTP3 coverage.

Table 13: Classification of those Member States with DTP3 national coverage <90%, by their DTP1 and DTP3 coverage

Group	Definition	Countries	Proposed strategies to increase DTP3 coverage
A	DTP3 <50%	Central African Republic, Chad, Equatorial Guinea, Marshall Islands, Somalia, South Sudan, Syrian Arab Republic	Overall system strengthening
B	DTP1 <90% & drop-out ≥10%	Afghanistan, Benin, Democratic Republic of the Congo, Ethiopia, Guinea, Haiti, India, Iraq, Niger, Papua New Guinea, Uganda, Vanuatu, Viet Nam	Improve access: • Social mobilization & demand generation • Target hard-to-reach populations Address drop out: • Improve quality and predictability of service delivery • Reduce missed opportunities
C	DTP1 <90% but drop-out <10%	Comoros, Djibouti, Gabon, Honduras, Kenya, Lao People's Democratic Republic, Lebanon, Madagascar, Mali, Nigeria, Pakistan, San Marino, Solomon Islands, South Africa, Timor-Leste, Zambia	Improve access
D	DTP1 ≥90% and DTP3 <90%	Argentina, Austria, Barbados, Burkina Faso, Cameroon, Congo, Côte d'Ivoire, Dominican Republic, Guatemala, Guinea-Bissau, Indonesia, Liberia, Malawi, Mauritania, Mexico, Micronesia (Federated States of), Mozambique, Myanmar, Namibia, Nauru, Panama, Paraguay, Peru, Romania, Suriname, Togo, Ukraine, Venezuela (Bolivarian Republic of), Yemen	Address drop-out

District-level DTP3 coverage

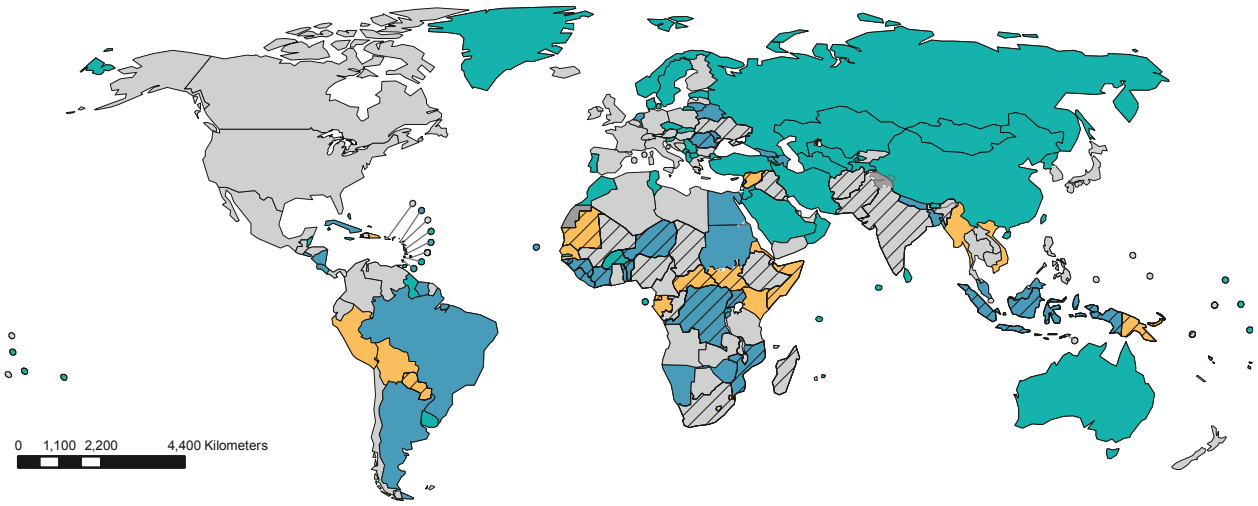
Among the 112 Member States with valid district-level coverage estimates in 2013, only 53 (27%) had achieved national level coverage of ≥90% and coverage of ≥80% in every district (or equivalent administrative level) (GVAP indicator G3.1; Table 11). This was six fewer than in the previous year.

Distribution of Member States by the percentage of districts achieving ≥80% coverage for DTP3 in 2013 (GVAP indicator ex-SO3.1), by WHO region is shown in Figure 18 and Table 14 (one additional Member State (Malawi) also had DTP3 ≥80% in all districts, but had a national coverage of 89%). This is in comparison to 59 Member States which had DTP3 coverage ≥80% in all districts in 2012.

Nineteen (10%) Member States with validated district-level coverage rates had between 50% and 79% of their districts achieving DTP3 coverage of ≥80% in 2013, while 11 countries had <50% of districts achieving coverage of ≥80%.

Forty-seven Member States (24%) did not provide district coverage data and 35 (27%) provided data which were considered invalid.

Figure 18: Member States showing the percentage of districts with DTP3 coverage ≥80%, 2013



< 50% (20 Member States or 10%, 9 of which administrative coverage DTP3 data considered not valid)
50-79% (32 Member States or 16%, 13 of which administrative coverage DTP3 data considered not valid)
80-99% (39 Member States or 20%, 11 of which administrative coverage DTP3 data considered not valid)
All districts (56 Member States or 29%, 2 of which administrative coverage DTP3 data considered not valid)
Not available (47 Member States or 24% with 5 MS having administrative coverage DTP3 data not valid)
Not applicable
WHO-UNICEF (WUENIC) estimate is < 90% or differs from country administrative coverage reported on the JFR and therefore district data are not considered valid (40 Member States or 31%)

Source: WHO-UNICEF joint reporting forms, 2013.

Table 14: Distribution of Member States by the percentage of districts achieving ≥80% coverage for DTP3 in 2013, by WHO region

WHO region	Countries with DTP3 district coverage data available and valid										District DTP3 coverage data not available		District DTP3 coverage data available but invalid		Total
	100% districts with DTP3 ≥80%		80–99% districts with DTP3 coverage ≥80%		50–79% districts with DTP3 coverage ≥80%		0–49% districts with DTP3 coverage ≥80%		Total						
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n
Africa	5	11%	6	13%	7	15%	6	13%	24	51%	1	2%	22	47%	47
Americas	7	20%	11	31%	6	17%	3	9%	27	77%	6	17%	2	6%	35
Eastern Mediterranean	7	33%	2	10%	2	10%	0	0%	11	52%	4	19%	6	29%	21
European	21	40%	6	11%	0	0%	0	0%	27	51%	25	47%	1	2%	53
South-East Asia	4	36%	2	18%	1	9%	1	9%	8	73%	2	18%	1	9%	11
Western Pacific	10	37%	1	4%	3	11%	1	4%	15	56%	9	33%	3	11%	27
Global	**54**	**28%**	**28**	**14%**	**19**	**10%**	**11**	**6%**	**112**	**58%**	**47**	**24%**	**35**	**27%**	**194**

Reference

1. World population prospects: the 2012 revision, key findings and advance tables. New York: United Nations, Department of Economic and Social Affairs, Population Division; 2013. Working Paper No. ESA/P/WP.227.

NUMBER OF MEMBER STATES THAT REACH 90% NATIONAL COVERAGE AND 80% IN EVERY DISTRICT OR EQUIVALENT ADMINISTRATIVE UNIT FOR ALL VACCINES IN NATIONAL PROGRAMMES, UNLESS OTHERWISE RECOMMENDED (INDICATOR G3.2)

Highlights

- District level coverage is currently only monitored for DTP3 and not for all vaccines. Hence, the results in this chapter mainly relate to national level coverage.
- A total of 88 countries (45%) reached the national level target for all vaccines, while 106 did not (55%); this is less than the number achieving the target in 2012, which was 96 (49%).
- Forty-one Member States (21% of all Member States) met DTP3 national coverage goals but failed to meet the ≥90% coverage targets for all vaccines in national programmes, while 65 nations (33.5%) failed to meet the coverage target with both DTP3 and the other vaccines doses included in this indicator.

DEFINITION OF INDICATOR	Indicator covers the following vaccines: • three doses of DTP, polio and the first dose of MCV for all Member States • bacille Calmette–Guérin (BCG) for Member States where included in the schedule (i.e. not limited to high-risk populations) • three doses of HepB, Hib, pneumococcal conjugate vaccine (PCV) and last dose of rotavirus vaccine National coverage data are considered only for vaccines that have been introduced into the immunization schedule for at least one year before the JRF reporting year (e.g. coverage reported for the calendar year 2012 for a vaccine introduced in 2010) and in countries that have reported these data
TARGET	2020 in all Member States
DATA SOURCES[11]	WUENIC estimates and administrative coverage from country JRFs
DATA AVAILABILITY AND QUALITY	It is possible to measure progress against the target only for national-level coverage at this point, since district-level administrative data are currently available only for DTP3 and measles-containing (MCV1) vaccines. For the purposes of this analysis, it should be noted that the lowest coverage rate for any one particular vaccine that is part of the national immunization programme is used to determine whether the country has met the indicator target

Please note that this indicator is available on interactive figures/dashboard for better understanding and exploration of data. Please visit the following website:

http://www.technet-21.org/resources/gvap-indicators

[11] For more information about the JRF and WUENIC coverage data, please refer to the GVAP Secretariat report 2013, Annex 1. http://www.who.int/entity/immunization/global_vaccine_action_plan/GVAP_secretariat_report_2013.pdf?ua=1

Results

The Member States that achieved national coverage of ≥90% for all vaccines in their immunization schedule in 2013 are shown in (Figure 19). Of the 194 Member States, 88 (45%) reached this target for all vaccines, while 106 (55%) did not; this is less than the number that achieved the target in 2012, which was 96 (49%) (Table 15). This could be due to a number of causes, including those that have resulted in a general decline in immunization coverage, or low vaccine-specific coverage as a result of the recent introduction of a new vaccine into the national programme.

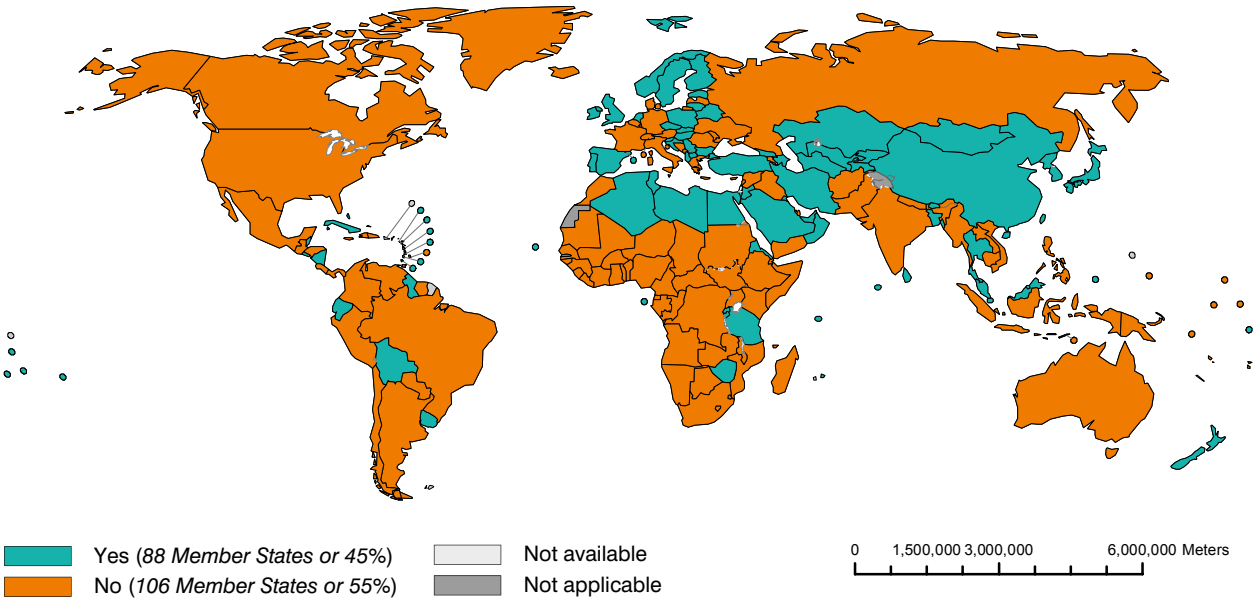
Among the 129 countries that had achieved DTP3 ≥90%, 88 also achieved coverage ≥90% with all other vaccines in their national programmes. On the other hand, 41 Member States (21% of all Member States) met DTP3 national coverage goals but failed to meet the ≥90% coverage targets for all vaccines in national programmes; 65 nations (33.5%) failed to meet both targets. A variety of causes could account for coverage of some vaccines being lower than that of DTP3. These causes are not identifiable by examining data available at the global level. Countries in this category need to examine their own data carefully to understand the underlying causes for lower coverage with one or more vaccines and take the necessary corrective actions.

The global average coverage of different vaccines is shown in Figure 20. Coverage with three doses of hepatitis B has increased to almost reach the DTP3 coverage. With the recommendation that all countries should provide two doses of measles-containing vaccines, the coverage with the second dose is also being monitored. Coverage with MCV2 has increased in the past few years with an increasing number of countries introducing a routine second dose of the vaccine and reporting coverage data, though in many countries MCV2 coverage remains below MCV1 coverage and well short of the 95% coverage required for measles elimination. Coverage for other new vaccines like rotavirus vaccine (RV), PCV and Hib remain low, but their use has been steadily increasing as an increasing number of countries include these vaccines in their national programmes.

Table 15: Number of Member States that achieved ≥90% national coverage for all the vaccines included in their national immunization schedule by region, 2010-2012

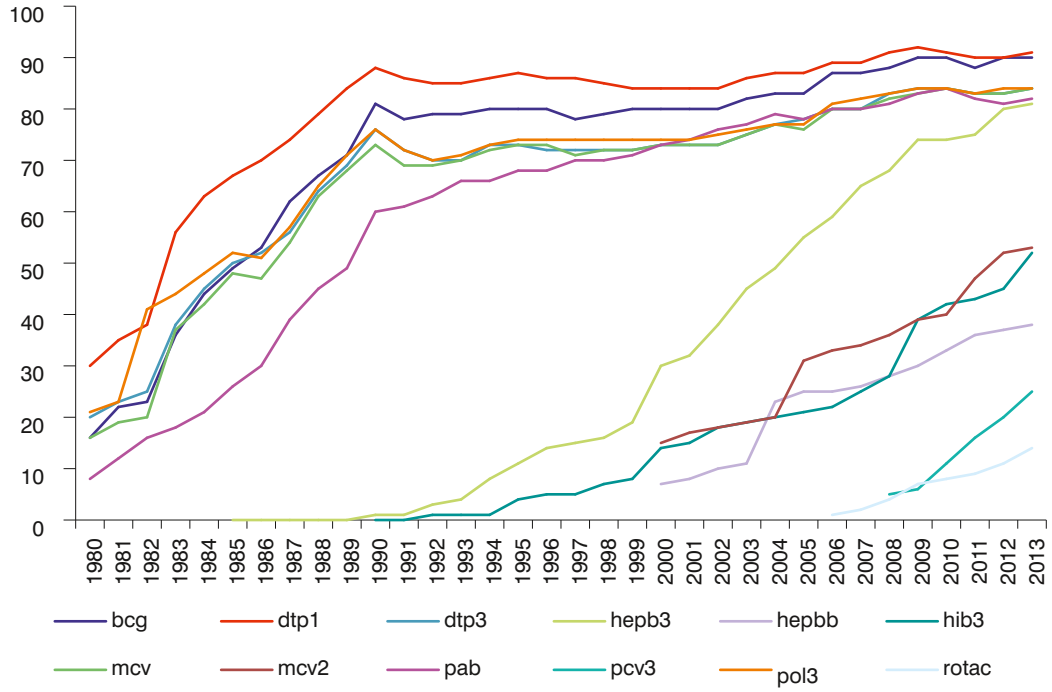
WHO region	2011		2012		2013	
	n	(%)	n	(%)	n	(%)
African	13	28	13	28	11	23
Americas	15	43	17	49	15	43
Eastern Mediterranean	10	48	10	48	10	48
European	33	62	34	64	32	60
South-East Asia	6	55	6	55	6	55
Western Pacific	15	56	16	59	14	52
Global	**92**	**47**	**96**	**49**	**88**	**45**

Figure 19: Member States that have achieved national coverage of ≥90% for all vaccines included in the national infant immunization schedule, 2013



Source: WUENIC coverage estimates, 2014.
Map production: WHO/IVB; 194 WHO Member States. Date of slide: 24 July 2014

Figure 20: Global coverage estimates of various vaccines, 1980-2013



Source: WHO/UNICEF coverage estimates 2013 revision. July 2014.
Immunization Vaccines and Biologicals, (IVB), World Health Organization.

PERCENTAGE OF DISTRICTS (OR EQUIVALENT ADMINISTRATIVE UNITS) WITH 80% OR GREATER COVERAGE WITH THREE DOSES OF DIPHTHERIA–TETANUS–PERTUSSIS-CONTAINING VACCINE (INDICATOR SO3.1)

DEFINITION OF INDICATOR	Meet vaccination coverage targets in every region, country and community District-level DTP3 coverage data are considered valid only if the WUENIC and administrative data from the JRF are the same or if the WUENIC data for national DTP3 coverage is ≥90%
DATA SOURCES	WUENIC administrative data on vaccination coverage from country JRFs (to compare with WUENIC estimates as a check of validity)

In February 2014 the SAGE GVAP Working Group agreed to include the three following indicators in the narrative of the overall coverage indicator report rather than having them as specific indicators:

- Indicator SO3.1: Percentage of districts (or equivalent administrative units) with ≥80% coverage with three doses of DTP vaccine.
- Indicator SO4.2: Sustainability of DTP3 national coverage ≥80% for three years.
- Indicator SO4.1: DTP1–DTP3 drop-out rate for national coverage.

REDUCTION IN COVERAGE GAPS BETWEEN WEALTH QUINTILES AND OTHER APPROPRIATE EQUITY INDICATOR(S) (INDICATOR SO3.2)

Highlights

- Baseline data from DHS or MICS surveys conducted between 2008 and 2012 on national DTP3 coverage rates by wealth quintiles were available for 54 Member States (28%) compared to 25 Member States in the previous year's report; 140 nations still need to conduct surveys to provide a baseline estimate for the decade.
- Coverage was higher in the wealthiest quintile compared to the poorest quintile in most Member States, except eight nations[12] (15%).
- Thirty-seven countries with recent survey data have already reduced the gap between the highest and lowest wealth quintiles for immunization coverage to <20%.
- In 25 Member States DTP3 coverage of the wealthiest quintile was 10% or greater than the coverage in the poorest quintile. In 17 of those Member States, DTP3 coverage was 20% or greater for the wealthiest quintile than the poorest quintile.
- Of the 54 Member States with wealth quintile data, 22 (41%) reached both national DTP3 coverage ≥90% and <20% difference in coverage between the highest and lowest wealth quintiles. Of the 15 countries (28%) that had DTP3 coverage <90% but <20% difference in coverage, seven had a differential ≥10% and eight countries had a differential <10%. Finally, 17 countries (31%) failed to meet both goals – with DTP3 coverage <90% and quintile differential ≥20%.

TARGETS	Increasing trend in equity in immunization coverage Proportion of Member States with <20% difference in DTP3 coverage between the lowest and highest wealth quintile: 60% by 2015 75% by 2020
DEFINITION OF INDICATOR	• DTP3 immunization coverage among 1-year-olds distributed by wealth quintiles for the period 2007-2011 • Determination of wealth index as defined in DHS and the UNICEF MICS • Data are to be measured at least twice (by special study or survey), with an early and late measure
DATA SOURCES	WHO Health Equity Monitor Database of the Global Health Data repository[13], which contains data on 25 reproductive maternal, neonatal and child health indicators disaggregated by child's sex, place of residence (rural vs urban), wealth quintile and educational level. The data come from DHS and MICS conducted in 93 Member States, of which 92 are low- or middle-income countries

Please note that this indicator is available on interactive maps/dashboard for better understanding and exploration of data. Please visit the following website:

http://www.technet-21.org/resources/gvap-indicators

[12] Member States in which the lowest wealth quintile had a higher DTP3 coverage rate than the highest wealth quintile included Albania, Belize, Burundi, Kazakhstan, Maldives, Suriname, Swaziland and Tajikistan.
[13] The database can be found at: http://apps.who.int/gho/data/node.main.HE-1540?lang=en.

Data availability and quality

Data for this analysis was derived from a re-analysis of DHS and MICS micro data, which are publicly available,[14] using the standard indicator definitions for estimating household wealth as published in DHS and UNICEF documents. Health inequality data must be interpreted with caution due to several limitations. Since estimates of household wealth and immunization coverage are only available through DHS and MICS surveys, which are conducted periodically, these data cannot be generated for each country on an annual basis.

In a few cases there may be minor differences between the data reported here and in previous DHS or MICS country reports, due to small discrepancies in the definition and calculation of some indicators. Detailed information about the indicator criteria is available in the WHO Indicator and Measurement Registry (www.who.int/gho/indicator_registry/en/).

At least two measures are required to measure trends. Baseline data were defined as data from DHS or MICS that took place in 2008 or later (which includes the 2007 birth cohort), as was the case in the previous year's report. At the time of this report, 54 countries have data on DTP3 coverage rates by wealth quintiles. The Eastern Mediterranean, European and Western Pacific Regions are in particular need of these data, since at least 80% of the countries in those regions are without data. Relative to last year, when only 25 countries had data on coverage by wealth quintiles, there has been a significant improvement in data availability, though there are still 140 nations from which data are needed.

For those Member States that have not conducted a survey since 2008, the baseline will need to be established once a survey takes place. The United Nations (UN) Secretary General's Global Strategy for Women's and Children's Health recommends household surveys every three years for the 75 'Countdown' Member States (countries with the highest child mortality). Hence, it is expected that at least this subset of Member States will have three sets of data during the decade to monitor reduction in coverage inequities.

Results

Baseline data on DTP3 coverage rates for the highest and lowest wealth quintile from DHS and MICS conducted from 2008 to 2012 in 54 Member States was used to calculate the quintile differential defined as the lowest wealth quintile's coverage rate subtracted from the highest wealth quintile's coverage rate (absolute difference). The quintile differentials for various countries are displayed in Figure 21.

Of the 54 countries with data, 17 countries (31%) had a quintile differential ≥20%, primarily from the African Region and Western Pacific Region. Twenty-five countries (46%) had a quintile differential <20% but ≥10%, highlighting the need to continue the efforts to reduce this gap in those countries. The results are shown in Table 16.

All of the 17 countries (31%) that had a quintile differential of ≥20% had DTP3 national coverage <90%, failing to meet both DTP3 national coverage and wealth quintile coverage gap reduction targets. For these nations, a strategy to increase the overall national coverage – but with a targeted focus on the lower wealth quintiles – will be essential in making progress towards both goals.

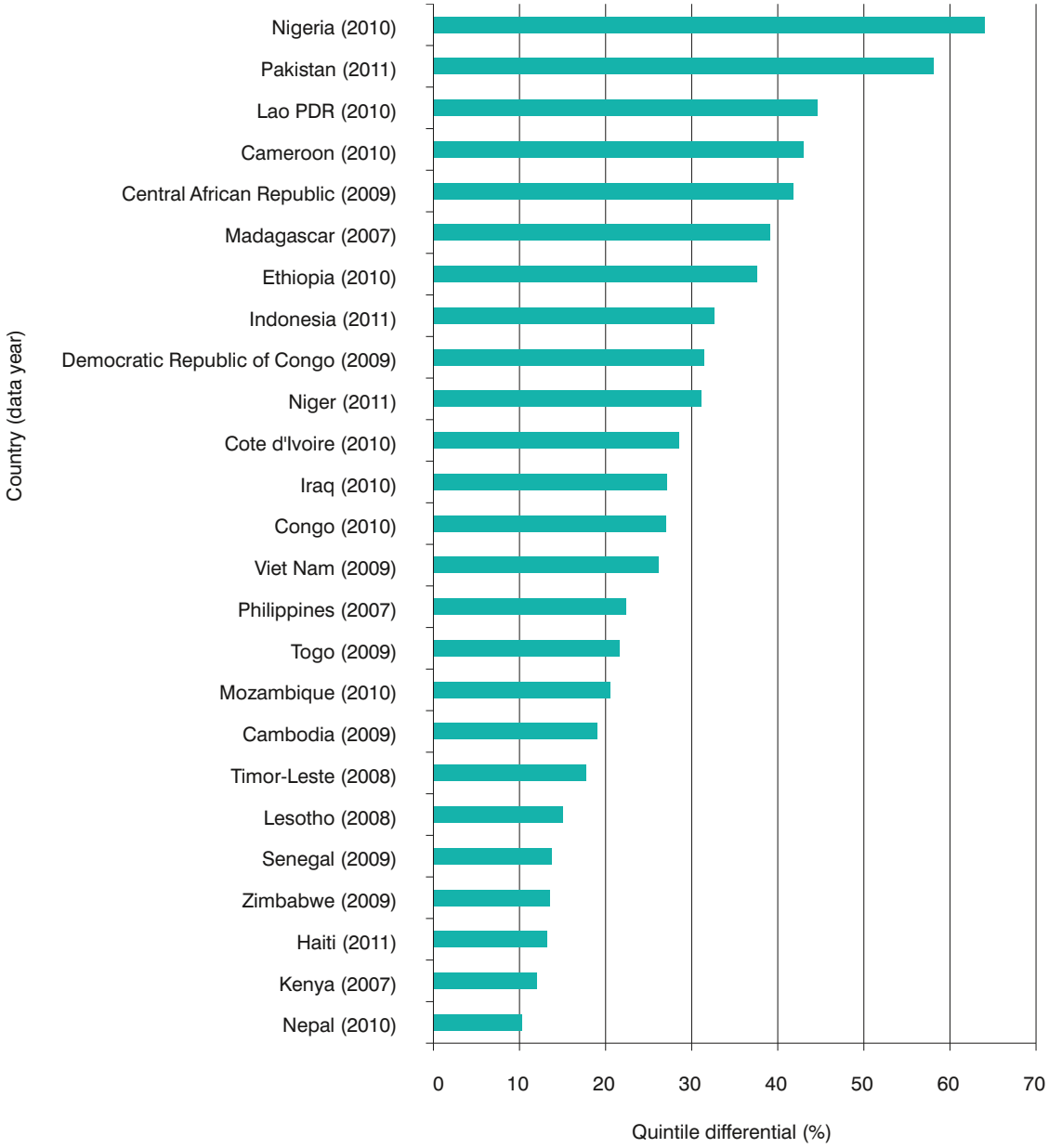
Seven countries (13%) had <90% DTP3 national coverage and a quintile differential ≥10% but <20%. Although these nations have met the goal, additional efforts to lower the quintile differential to <10% is needed in order to meet the coverage target of ≥90%. Only one Member State met the DTP3 coverage target of ≥90% but had a wealth quintile differential ≥10%.

Of the 54 countries with wealth quintile data, 22 (41%) reached ≥90% national DTP3 coverage and the <10% quintile differential (exceeding the <20% quintile differential target by 10%); these Member States are not shown in Figure 21 or Table 16.

In general, Member States with high national coverage were likely to have smaller differences in coverage between wealth quintiles. None of the Member States with national DTP3 coverage rates of ≥90% had a quintile differential ≥20%, and only one had a differential ≥10%. Countries without data are encouraged to conduct a survey to establish a baseline, and countries with a quintile differential ≥10% are encouraged to take urgent measures to address inequities and conduct follow-up surveys to document the impact of these measures.

[14] Immunization: Full, BCG, DTP3, measles, polio: wealth quintile, data by country: http://apps.who.int/gho/data/node.main.HE-1590?lang=en.

Figure 21: DTP3 quintile differential for 32 Member States having a quintile differential of ≥10%*



* Data from DHS or MICS surveys conducted between 2008 and 2012.

Table 16: DTP3 national coverage, DTP3 coverage by wealth quintile, and quintile differential for 32 Member States having a quintile differential of ≥10%*

Category	Country (data year)	DTP3 national coverage	Quintile 1 (poorest)	Quintile 5 (wealthiest)	Quintile differential
DTP3 <90% & quintile differential ≥20% **n = 17 (31%)**	Nigeria (2010)	45	16.4	80.5	64.1
	Pakistan (2011)	80	29.9	88	58.1
	Lao People's Democratic Republic (2010)	74	36.8	81.4	44.6
	Cameroon (2010)	84	44.6	87.6	43
	Central African Republic (2009)	32	17.8	59.6	41.8
	Madagascar (2007)	82	53.6	92.7	39.1
	Ethiopia (2010)	36	26	63.6	37.6
	Indonesia (2011)	72	52.5	85.1	32.6
	Democratic Republic of the Congo (2009)	62	48	79.5	31.5
	Niger (2011)	68	53.3	84.4	31.1
	Cote d'Ivoire (2010)	85	52.1	80.7	28.6
	Iraq (2010)	70	55.2	82.3	27.1
	Congo (2010)	72	54.6	81.6	27
	Viet Nam (2009)	74	59.3	85.5	26.2
	Philippines (2007)	86	71.6	94	22.4
	Togo (2009)	72	62.8	84.4	21.6
	Mozambique (2010)	76	65.4	86	20.6
DTP3 <90% & quintile differential <20% but ≥10% **n = 7 (13%)**	Cambodia (2009)	85	73.5	92.6	19.1
	Timor-Leste (2008)	66	54.8	72.5	17.7
	Lesotho (2008)	84	73.2	88.3	15.1
	Senegal (2009)	86	74.5	88.3	13.8
	Zimbabwe (2009)	73	67.4	80.9	13.5
	Haiti (2011)	62	54.7	67.9	13.2
	Kenya (2007)	86	77.6	89.6	12
DTP3 ≥90% **n = 1 (2%)**	Nepal (2010)	92	88.1	98.4	10.3

* Data from DHS or MICS conducted between 2008 and 2012.

DROP-OUT RATE BETWEEN FIRST DOSE (DTP1) AND THIRD DOSE (DTP3) OF DIPHTHERIA–TETANUS–PERTUSSIS-CONTAINING VACCINES (INDICATOR SO4.1)

TARGET	Decreasing trend in drop-out rates
DEFINITION OF INDICATOR	The indicator is calculated using the formula: (DTP1 – DTP3) / DTP1 × 100
DATA SOURCE	WUENIC (coverage estimates)

SUSTAINED COVERAGE OF DIPHTHERIA–TETANUS–PERTUSSIS-CONTAINING VACCINES 90% FOR THREE OR MORE YEARS (INDICATOR SO4.2)

TARGET	All Member States by 2020
DEFINITION OF INDICATOR	National DTP3 coverage of 90% or greater is sustained for at least three consecutive years (2011, 2012 and 2013 for this report)
DATA SOURCE	WUENIC (coverage estimates)

In February 2014 the SAGE GVAP Working Group agreed to include the three following indicators in the narrative of the overall coverage indicator report rather than having them as specific indicators:

- Indicator SO3.1: Percentage of districts (or equivalent administrative units) with ≥80% coverage with three doses of DTP vaccine.
- Indicator SO4.2: Sustainability of DTP3 national coverage ≥80% for three years.
- Indicator SO4.1: DTP1–DTP3 drop-out rate for national coverage.

3. ESTABLISH STRONG IMMUNIZATION SYSTEMS

IMMUNIZATION COVERAGE DATA ASSESSED AS HIGH QUALITY BY WHO AND UNICEF (INDICATOR SO4.3)

The initial metric used for monitoring this indicator was the Grade of Confidence in the WUENIC data for each Member State. However, after review of the data on using this metric in 2013, SAGE recommended that this indicator be revised to focus on the quality of the reported coverage by Member States.

There was consensus that data quality implied that data of sufficient accuracy, completeness and granularity at all levels to monitor programmes and inform programme planning and corrective actions are what is desired. However, the limitations of currently available data, particularly at subnational levels, were also recognized.

The GVAP Secretariat will include a set of questions in the annual data collection form (JRF) as from 2015 on national activities that assess data quality. A report from the response to these questions will be presented in the 2015 report.

NUMBER OF COUNTRIES WITH CASE-BASED SURVEILLANCE FOR VACCINE PREVENTABLE DISEASES: INVASIVE BACTERIAL VACCINE-PREVENTABLE DISEASES AND ROTAVIRUS (INDICATOR SO4.4)

TARGET	75% of low- and middle-income countries for sentinel site surveillance by 2020
DEFINITION OF INDICATOR	The number of countries that report conducting case-based surveillance, including laboratory confirmation for rotavirus and invasive bacterial vaccine preventable diseases (IB-VPD), at one or more hospital-based sentinel sites, the data from which are included in WHO databases
DATA SOURCES	• Data reported annually through the WHO-UNICEF JRF; and • Data reported by sentinel sites participating in a WHO-coordinated surveillance network

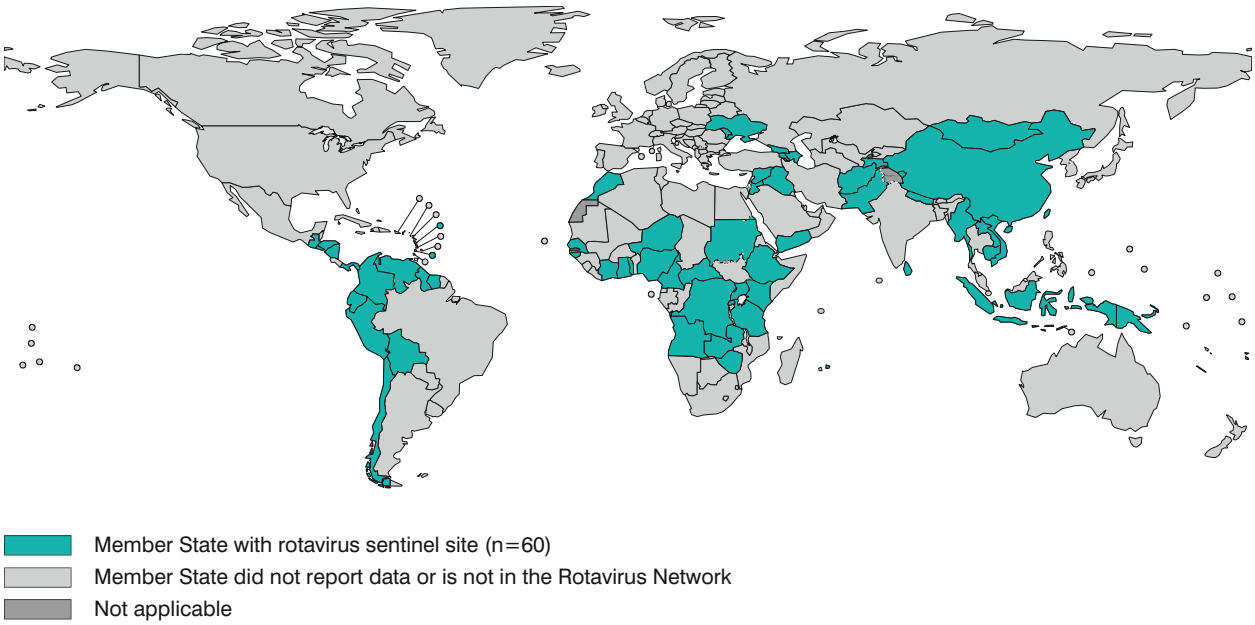
WHO-coordinated sentinel hospital surveillance networks, 2008-2012

In 2008, WHO brought together existing regional surveillance networks to establish standardized global sentinel hospital surveillance networks for rotavirus disease and invasive bacterial vaccine preventable diseases (IB-VPD). The surveillance network includes sentinel surveillance hospitals that report to ministries of health and WHO clinical and laboratory data for children aged under 5 years hospitalized with acute gastroenteritis and/or invasive bacterial diseases (currently targeting cases of meningitis, pneumonia or sepsis). When the network was established, the main objectives of the network were to: 1) provide data for describing disease epidemiology and for estimating disease burden; 2) establish a platform to measure impact after vaccine introduction; and 3) identify circulating serotypes of genotypes of the principal vaccine-preventable pathogens. Since then, the uptake of vaccines targeting the diseases under surveillance has rapidly increased and the surveillance objectives have evolved to include: 1) assessment of disease trends following vaccine introduction; 2) monitoring changes in circulating strains; and 3) increasing use of the platform to conduct studies to document vaccine effectiveness.

From 2008 to 2012, WHO provided managerial oversight, technical assistance and financial support to countries eligible for GAVI Alliance funding for surveillance activities. WHO established networks of sentinel hospitals and national laboratories supported by regional and global reference laboratories. Additionally, WHO launched an annual external quality assessment programme that targeted participating laboratories, developed a standardized protocol for sentinel site assessments, provided technical advice and laboratory supplies to sites, and shared data semi-annually via a global surveillance and information bulletin (http://www.who.int/immunization/monitoring_surveillance/resources/NUVI/en/).

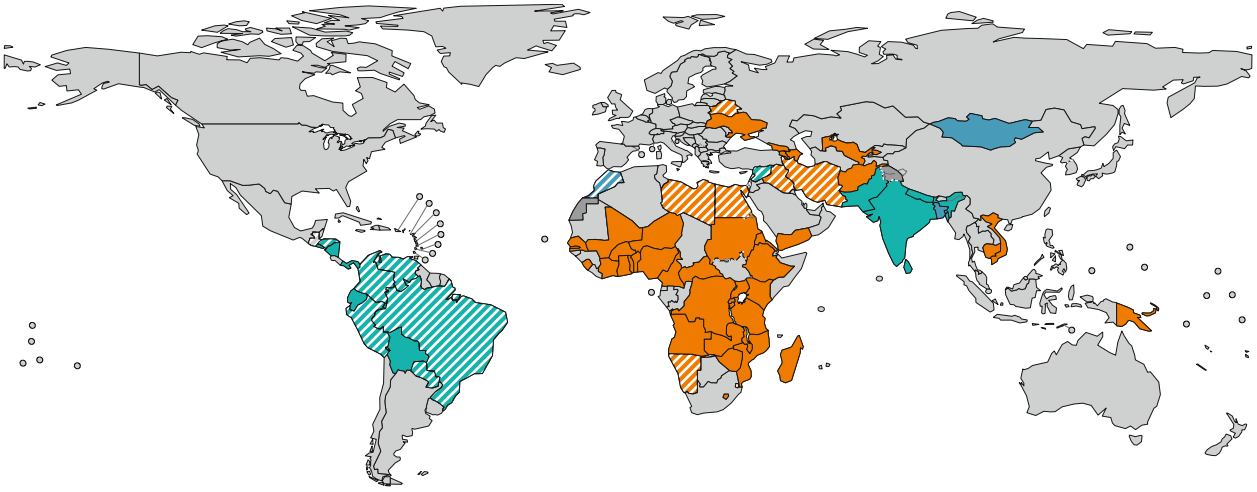
In 2011, WHO established an informal Technical Advisory Group (TAG) of experts and laboratory technical working groups to assess the performance of the surveillance network and provide advice on measures to improve performance. By 2012, the Global Rotavirus Surveillance Network had expanded to 178 sentinel surveillance sites in 60 countries (72% eligible for GAVI Alliance support) from all six WHO regions (Figure 22). The Global Invasive Bacterial Vaccine Preventable Diseases Network had grown to 150 sentinel sites in 58 countries (79% eligible for GAVI Alliance support (Figure 23).

Figure 22: Member States reporting data to the Global Rotavirus Surveillance Network, 2012



Source: WHO/IVB Database as of 28 July 2014.
Map production: Immunization Vaccines and Biologicals, (IVB). World Health Organization.

Figure 23: WHO Member States reporting data to the Global Invasive Bacterial Vaccine Preventable Diseases Surveillance Network, 2012



Note: Non-GAVI-eligible countries are shown with hatching.

Source: WHO/IVB Database as of 28 July 2014.
Map production: Immunization Vaccines and Biologicals, (IVB). World Health Organization.

Strategic Review of the Networks, 2013

In 2013 WHO, under the oversight of the informal Technical Advisory Group of experts, conducted a strategic review of surveillance network performance within the context of the recommendation for high quality case-based disease surveillance in the GVAP. The objectives of the review were to: 1) assess whether and to what extent the 2008 objectives for the network were met; 2) assess health ministries' perspectives on the need and value of the network; 3) assess laboratory network management; 4) review existing data management systems; 5) assess the adequacy of resources available to WHO; and 6) provide recommendations for strengthening the network and assess the network's utility as a platform for other vaccine preventable disease surveillance. Findings and proposed actions to strengthen the surveillance network and further improve surveillance data quality and use were presented to SAGE in November 2013.

Strategic review findings

Briefly, the strategic review[15] concluded that both networks have documented the presence of disease and that the data have contributed to country decisions to introduce rotavirus, Hib and pneumococcal conjugate vaccines. The performance and data provided for rotavirus diarrhoea suggest that the network has the potential to document impact of vaccine following its introduction. The network is successfully monitoring rotavirus genotype distributions in all regions. The IB-VPD surveillance has successfully enhanced the rate of recovery of pneumococcus at many sites and resulted in the detection of illnesses due to other bacterial agents, including the detection of meningococcal meningitis outbreaks. Pneumococcal serotype information has been collected from previously under-represented countries and regions. The ability to monitor impact of

[15] The reports from the strategic review presented to SAGE are available at the WHO/IVB website.

PCV introduction or serve as a platform for specially designed PCV impact projects has been demonstrated in a few sites but the ability of the remaining countries to utilize the platform to document impact remains to be demonstrated.

The strategic review process confirmed that the capacity needed for a site to successfully implement rotavirus surveillance differs substantially from that needed for IB-VPD surveillance. Gastroenteritis is common, easily recognized, and sample collection to test for rotavirus vaccine is non-invasive. Laboratory confirmation of rotavirus is less complex than for invasive bacterial diseases and is sensitive. All IB-VPD sites conduct surveillance for meningitis, an infrequent albeit severe condition, requiring a substantial population to detect more than a small number of cases. Laboratory confirmation requires the collection of cerebrospinal fluid, which is an invasive procedure. Laboratory confirmation is relatively more difficult since the pathogens concerned are fastidious and prior antibiotic treatment or delay in specimen processing can adversely influence assay sensitivity. For the IBD-VPD sites that also conduct surveillance for bacteraemia, sepsis and pneumonia, pathogen-specific confirmation is insensitive, particularly for pneumonia since only a small proportion of cases have associated bacteraemia.

Strategic review recommendations

In November 2013 SAGE endorsed the strategic review findings and agreed that the experience of the network's first 5 years should inform future surveillance needs, including potential use of the network as a platform for other vaccine-preventable disease surveillance.[16] SAGE also noted that surveillance data will be essential to secure long-term national funding for vaccines in some countries and that demonstrating vaccine impact in epidemiologic settings not reflected by existing impact data is important. SAGE endorsed the following strategic review recommendations:

i. revision of the surveillance objectives to align more closely with the current and future vaccine introduction landscape;
ii. further standardization to ensure the generation of credible, well-defined data with linking of clinical and laboratory data at all levels and real-time monitoring of system performance;
iii. sharing of standardized, case-based data at all levels; use of identifiers for linking of clinical and laboratory results; zero/negative reporting to differentiate absence of cases from lack of reporting; and progress on data management including the use of software with editing and verification capability;
iv. development of performance measures and agreements on: 1) sentinel site eligibility for on-going participation in the network; 2) standards for the reference laboratories including site visits, conduct of specialized testing, and testing of a systematic sample of specimens from all sites for laboratory quality control; and 3) WHO roles in support of the network;
v. additional human and financial resources to strengthen the networks through increased access to technical assistance, laboratory quality assurance/control processes, data management systems, exchange of lessons learned, and collaboration;
vi. For the IB-VPD network, management of the programme should focus the limited resources on support for a smaller number of sites to generate better quality data to inform policies.

SAGE noted that both sentinel surveillance networks are aligned with the priorities outlined in the GVAP, which emphasizes the need for low- and middle-income countries to invest resources to establish and/or strengthen sentinel site surveillance systems, including laboratory confirmation of vaccine-preventable diseases. Looking ahead, SAGE urged greater attention to integration of data systems, which would facilitate real-time analysis and performance monitoring. SAGE also noted the opportunities for integration by building upon the enhanced capacity developed by these networks to conduct surveillance for other diseases using a similar case definition (e.g. Japanese encephalitis included in meningitis surveillance; other causes of acute gastroenteritis), laboratory procedures (identification of other bacterial pathogens in laboratories conducting IB-VPD surveillance) and personnel trained in applying and adhering to rigorous surveillance protocols. Both networks should continue to share experiences with the polio surveillance network. Integration efforts must be strategically designed in ways that are logical and synergistic.

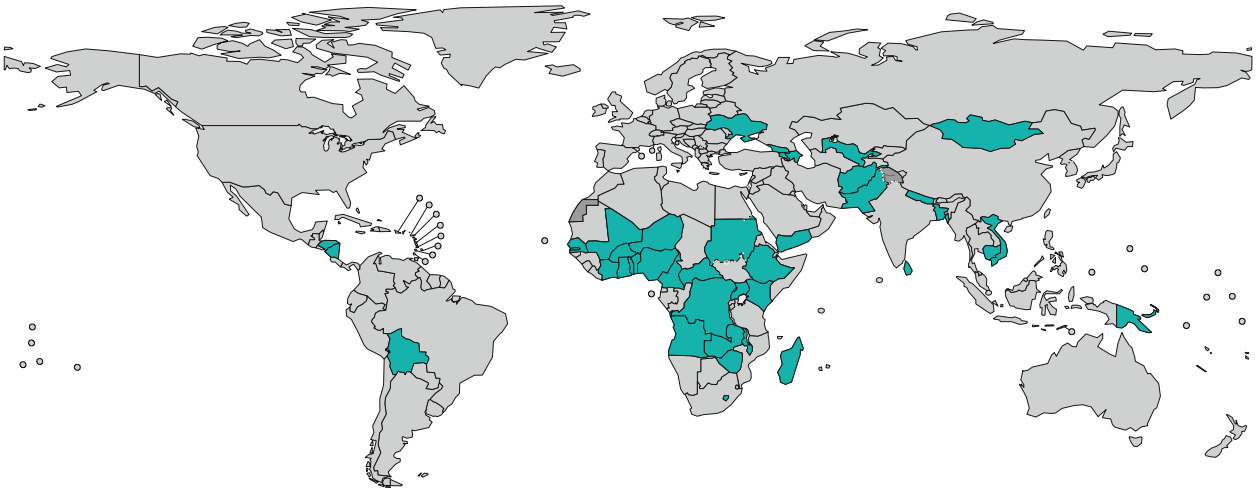
[16] See http://www.who.int/wer/2014/wer8901/en/ for the complete conclusions and recommendations: Meeting of the Strategic Advisory Group of Experts on immunization, November 2013 – conclusions and recommendations. Wkly Epidemiol Rec. 2014;89*(1)*:1–20.

Implementing strategic review recommendations, 2014

In late 2013 WHO developed a performance management framework to guide implementation of 50 strategic review recommendations. The framework groups recommendations by area and summarizes the activities required to achieve each recommendation, the responsible entity, and the targeted quarter of 2014 for completion. In total, 26 (52%) recommendations were targeted for completion by end-June 2014. Of those, 22 (85%) were completed including:

- review and revision of the surveillance objectives to reflect the evolving surveillance environment;
- review and revision of surveillance protocols to facilitate case-based reporting, linking all clinical and laboratory data;
- sharing data quarterly with standardized feedback of agreed process and performance indicators (case-based data are now being shared in five WHO regions, and in two regions that have limited access to case-based data, a web-based, case-based data management system is being piloted);
- development of standardized process and performance for sites and laboratories, which are being monitored on either a quarterly (sites) or twice annual (reference laboratories) basis;
- focus on IB-VPD sites (in accordance with SAGE recommendations, the focus of support will be on only 71 of the 150 sites (47%) located in GAVI-eligible Member States that reported data in 2012); see Figure 24.

Figure 24: Member States with at least one IB-VPD sentinel hospital selected for focused support from WHO, 2013



Source: WHO/IVB Database as of 28 July 2014.
Map production: Immunization Vaccines and Biologicals, (IVB). World Health Organization.

The remaining four of the 26 recommendations in progress include finalization of surveillance performance indicators for both networks and establishment of zero reporting. Collaborations with the proposed Sentinel Etiology and Epidemiology (SEED) surveillance project supported by the Bill & Melinda Gates Foundation are being explored, in order to create synergies, further enhance support for the reference laboratories and sentinel sites, and facilitate bridging of data. In addition, there is likely to be additional technical assistance available through the United States Centers for Disease Control and Prevention (CDC) for select sites in the network through the 2015 GAVI Alliance business plan.

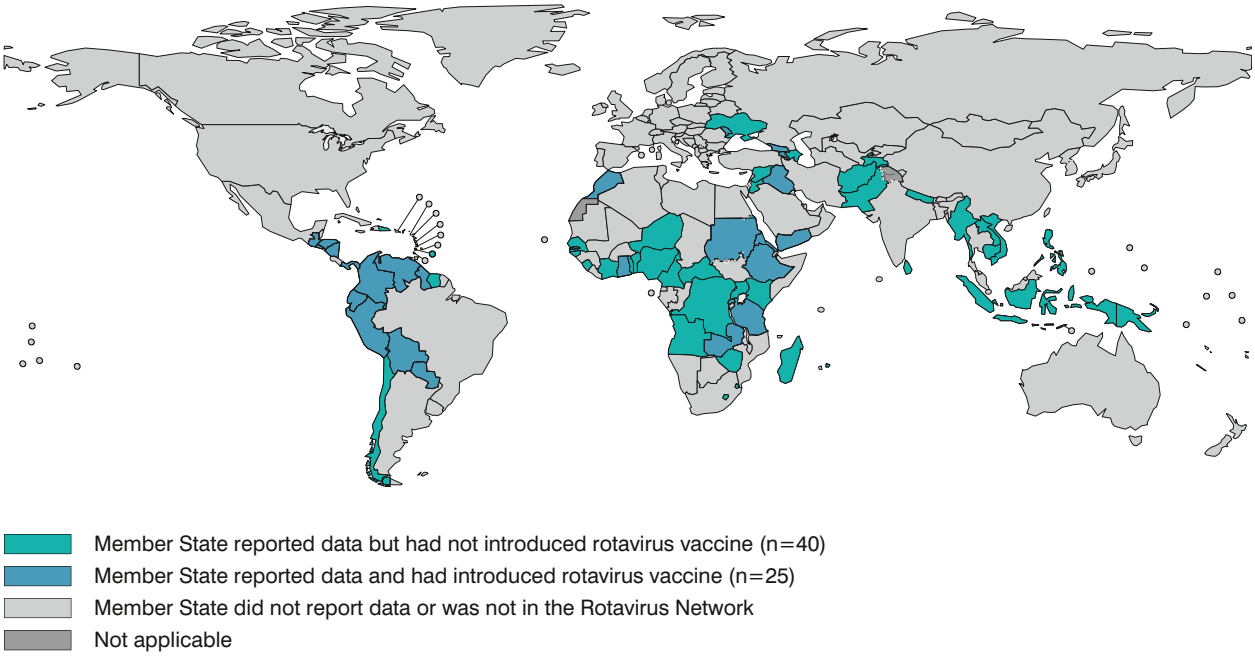
Moving forward, the IB-VPD Network is exploring the option of expanding surveillance in some selected sites to include typhoid (in collaboration with the Coalition against Typhoid) and pertussis. The Global Rotavirus Surveillance Network is strengthening capacity of some reference laboratories to identify other pathogens causing acute gastroenteritis.

Comparison of SO4.4 indicator and target with strategic review recommendations

Indicator SO4.4 is 'number of countries with case-based surveillance for vaccine preventable diseases'. The target is 75% of low- and middle-income countries to have sentinel site surveillance by 2020. Comparison with the strategic review recommendations highlights the following.

- As noted in last year's report, the wording of the indicator does not include 'laboratory-confirmation' of cases and case-based reporting. A strong recommendation of the strategic review was to enhance laboratory testing capacity and to ensure linkage of clinical and laboratory data.
- The strategic review specifically drew attention to the challenges of conducting high-quality sentinel site IB-VPD surveillance and the need to improve bacterial laboratory capacity. The review recommended that WHO should focus on a reduced number of better-performing sentinel sites to improve data quality in the network rather than attempting to institute high-quality IB-VPD surveillance in all countries.
- In 2013 a total of 189 sentinel sites in 65 Member States reported rotavirus surveillance data to WHO from July 2012 to June 2013 (Figure 25). Rotavirus detection is only calculated for sentinel sites that 1) test stool specimens from >100 cases during the 12 month period, and 2) report data for each month of the 12-month period. In total, 84 sites (44%) in 31 Member States met these criteria.

Figure 25: WHO Member States that reported data to the Global Rotavirus Surveillance Network, July 2012 to June 2013



Source: WHO/IVB Database as of 28 July 2014.
Map production: Immunization Vaccines and Biologicals, (IVB). World Health Organization.

Within the above context, it has been proposed to amend indicator SO4.4 to:

- number of countries meeting established surveillance standards with case-based surveillance for vaccine preventable diseases and with viral and bacterial laboratory confirmation of suspect or probable cases; and
- 75% of low- and middle-income countries have sentinel site surveillance for rotavirus diarrhoea that meets surveillance standards.

WHO/Antonio Caballero-Reynolds

4. RESEARCH AND DEVELOPMENT IN IMMUNIZATION

LICENSURE AND LAUNCH OF VACCINE OR VACCINES AGAINST ONE OR MORE MAJOR CURRENTLY NON-VACCINE PREVENTABLE DISEASES (INDICATOR G4.1)

OPERATIONAL DEFINITION OF INDICATOR	Licensure relates to registration by a functional national regulatory authority (NRA). Launch is defined as addition of the vaccine to the national immunization schedule in one or more low- or middle-income countries and sustained for a period of at least 12 months. Excludes use when limited to the private sector only. Includes vaccines in national schedule that may be selectively used in 'at risk' populations
DATA SOURCE/COLLECTION	Subject matter experts; landscape reviews; clinical trial databases
TARGET	Progress towards licensure/launch of one or more such vaccines by 2020
MILESTONES	Incremental progress (i.e. number of products in phase 1, 2 or 3 clinical trials) in development to be reported and assessed by SAGE

Background

Goal 4 of the Monitoring & Evaluation/Accountability Framework in the Global Vaccine Action Plan is to "develop and introduce new and improved vaccines and technologies". Sub-goal 4.1 specifically calls for an assessment of progress towards licensure and launch of vaccine(s) against one or more major diseases, currently not preventable with vaccines. The current status of vaccine development for HIV/AIDS, tuberculosis, malaria and a universal influenza vaccine will be addressed in other reports. A large number of vaccines for other diseases, however, are in research and development globally in both the public and private sectors at the present time. In order to focus efforts in this complex and dynamic area, it was decided to concentrate initially on seven diseases for which vaccines are considered to be highly desirable, candidate vaccines are already in various stages of development, and which represented a broad microbiological spectrum: dengue, hepatitis C, cytomegalovirus (CMV), respiratory syncytial virus, group A streptococcus, leishmaniasis and helminth infections. To that end, WHO consulted with experts, performed a landscape analysis and generated reports for each of the target diseases. The selected candidate vaccines as a group were thus generally considered to provide a representative indication of the changing state of the science.
The information below represents a high level overview and emphasizes cross-cutting themes.

At the present time, there are no vaccines licensed for the target diseases. The goal is to have one or more vaccines licensed or launched for at least one of the target diseases by 2020. Incremental progress, defined as new products entering or moving through clinical development, will be reported on a biennial basis to SAGE and the World Health Assembly. This first report establishes a baseline scenario and presents a forward-looking assessment of potential progress in the Decade of Vaccines and beyond.

Overview of current efforts

Table 17 shows the number of candidate vaccines for the seven target diseases currently in active clinical development. There are substantial basic research and preclinical development efforts in each of the target diseases. Current efforts encompass a variety of diverse technologies and approaches, ranging from live attenuated (dengue, CMV) and inactivated vaccines (dengue) to subunit-based vaccines (all target diseases). In addition, vaccines are being developed for both prophylactic and therapeutic indications (e.g. hepatitis C, schistosomiasis).

Table 17: Number of candidate vaccines against selected diseases currently in active clinical development

Target disease	Phase I	Phase II	Phase III
Dengue	3	2	1
Hepatitis C	3	1	0
Cytomegalovirus	8	2	1
Respiratory syncytial virus	5	2	0
Group A streptococcal disease	2	1	0
Leishmaniasis	2	1	0
Helminth diseases*	2**	0	1***

* Includes schistosomiasis, hookworm, onchocerciasis and lymphatic filariasis.
** Includes 1 candidate vaccine for *Schistosoma mansoni* infection and 1 for hookworm infection.
*** Includes 1 candidate (therapeutic) vaccine for *Schistosoma haematobium*.

Opportunities and challenges

Substantial opportunities for vaccine development for each of the target diseases derive from recent advances inter alia in genomic sequencing, proteomics, systems biology and structural biology, which are facilitating the identification, credentialing and selection of candidate vaccines. In addition, increasing access to manufacturing capacity enhances process development and shortens the interval from preclinical concept to availability of clinical trial material. Furthermore, technology is offering more and more tools for greater depth of analysis for characterization and quality control of vaccines, and for characterization of relevant immune responses.

Interestingly, several common issues present challenges to vaccine development for a number of the target diseases, such as: an incomplete understanding of the pathogenesis (including immune-mediated disease enhancement) and immunologically-mediated protection; the absence of adequate and/or predictive animal models for pathogenesis or protection; and the lack of correlates of protection/pathogenesis to help guide development. The aim of increasingly powerful analytical tools must be to detect and discriminate appropriate signals and identify linkages to relevant biological effects. Defining and measuring crucial analytic characteristics for potency and safety should be an important focus of future efforts. Additional challenges relate to an incomplete understanding of the epidemiology of disease, availability of and access to defined target populations with sufficiently high incidence rates to support efficient and cost-effective clinical trials, and a diversity of clinical manifestations and outcomes depending on the pathogens involved and the target populations. Vaccine hesitancy and perceived safety concerns discourage enrolment and execution of clinical studies; a concerted, evidence-based effort will, therefore, likely also be required to address future delivery and deployment issues. Finally, vaccine affordability should be considered at all stages of the development pathway without compromising quality standards.

Current promising leads, strategies and technologies

As noted above, numerous leads, strategies and technologies are being pursued concurrently. The candidate vaccines in phase III trials, representing the most advanced candidates, are based on recombinant, live attenuated viruses (dengue vaccine), DNA vaccines (human cytomegalovirus vaccine), and adjuvanted recombinant proteins (schistosomiasis vaccine). Candidate vaccines in phase II trials are based on live attenuated vaccines (RSV), recombinant live attenuated viruses (dengue), viral vectored vaccines (hepatitis C), DNA vaccines (hCMV), nanoparticles (RSV), adjuvanted peptide combinations (Group A streptococcus), adjuvanted subunit fusion proteins (*Leishmania*), adjuvanted recombinant proteins (hCMV). Internationally accepted quality standards can be important drivers, especially when identified early in the development cycle, that can support both innovation and subsequent access to affordable, quality products. Finally, investigators working at the basic and preclinical level of research for the targeted vaccines as well as in phase I clinical trials are pursuing a variety of antigens, delivery systems and adjuvants to elicit protective B- and T-cell responses. It is also worth noting that for zoonotic diseases such as leishmaniasis and schistosomiasis, veterinary vaccines are also being pursued that may prove useful in future control programmes and may serve as models for future human vaccines for these diseases. Further details of the various approaches being taken are discussed in the references at the end of this chapter.

Future directions

A. Short-term goals (0-2 years)

In the short-term most efforts in the seven target diseases are focused on maintaining momentum and analysing on-going projects. Of particular note and interest, results from two phase III trials (for the tetravalent, live attenuated vaccines for dengue, and the adjuvanted, subunit vaccine for *Schistosoma haematobium* infection) and a phase II trial of a hepatitis C vaccine are expected to be available and will warrant careful analysis. In addition, research and development efforts will continue to address some of the research challenges identified above, to prioritize standardization needs, and support advancement of promising candidate vaccines for all seven targeted diseases.

B. Medium-term goals (by 2020)

In the medium-term efforts are focused on licensing the first dengue vaccine, post-licensure studies, and delivery strategies. Support of research and development to address unmet research opportunities and gaps identified above remain high priorities as well as identifying promising vaccine candidates, developing and implementing the required standards, and providing appropriate credentials to advance their development as warranted. Assuming encouraging results in phase I trials, a number of candidate vaccines will advance into phase II trials. It is possible that a vaccine to prevent hCMV reactivation will be licensed in the medium-term.

C. Long-term goals (post-2020)

In the long-term the goals are to license safe, effective and affordable vaccines for all of the target diseases as needed to fulfil appropriate medical and public health mandates.

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LICENSURE AND LAUNCH OF AT LEAST ONE PLATFORM DELIVERY TECHNOLOGY (INDICATOR G4.2)

Target	2020: one or more vaccines
Definition of indicator	New platform delivery technology defined as a new mechanism for delivering vaccines to individuals that facilitates coverage, improves performance or reduces the cost of vaccine or delivery (e.g. jet injectors, microneedles, aerosols). Licensure relates to registration by a functional NRA. A launch is defined as the use of the technology in the national immunization programme of one or more low- or middle-income countries
Data sources	Landscape reviews and meeting reports

Background

Innovations in delivery technology have many potential benefits. They can increase access to life-saving vaccines by improving deliverability and accelerating uptake. They can improve the safety of vaccination programmes, for example, by reducing the risk of needle-stick injuries and preventing the re-use of needles and syringes. Indeed, innovations such as auto-disable syringes and vaccine vial monitors are now widely used to improve the safety and efficiency of vaccination programmes. New technologies could lessen the workload of health care workers, which could further improve programme efficiencies and capacity. In addition, new delivery technologies can increase efficacy or reduce the amount of antigen required per dose by delivering antigens directly to immunologically active tissues.

Overview of current efforts

As a result of these potential benefits, this has become an area of active research and development, with many efforts focusing on the needs of low- or middle-income countries. Table 18 describes some technologies currently licensed and in development.

Table 18: Examples of technologies licensed and in development

Technology or delivery method	Key features	Challenges	Status
Prefilled single use syringes (e.g. Uniject™)	Designed to improve ease of use for intramuscular (IM) or subcutaneous (SC) injections, prefilled single use syringes require minimal training and can increase immunization throughput, reduce vaccine wastage, and strengthen outreach.	They may require modification of the fill/finish manufacturing process or conversion to an entirely new fill/finish approach. Certain prefill syringe formats may require more cold chain capacity than multi-dose vials.	Prefilled single use syringes for hepatitis B and tetanus toxoid vaccination are now approved, prequalified and marketed in multiple countries, and a pentavalent product is in development (authorized by a Korean NRA in January 2014, WHO prequalified application in 2014).
Novel primary containers	Lower costs and smaller cold chain footprint. Some containers may offer a cost-effective single dose and preservative-free alternative to multi-dose containers.	Requires new fill/finish equipment.	Alternative prefilled primary containers such as blow-fill-seal technology are being explored for oral vaccine delivery and may be feasible for parenteral delivery. Multi-mono dose concepts are also being evaluated.
Intradermal (ID) adapters and alternative needles	ID adapters and alternative needles ('mini-needles') can be attached to standard syringes or integrated into syringe designs to facilitate consistent ID injections and increase throughput. Re-use prevention features are required for ISO certification and for WHO prequalification to prevent transmission of bloodborne diseases. ID adapters and alternative needles are directly applicable to TB (BCG), influenza and rabies vaccines that are administered intradermally.	Prefilled alternative needle/syringe combinations will be more costly and may require increased cold chain capacity.	Clinical studies indicate that ID administration at reduced dose could be feasible for certain vaccines. Additional studies are being pursued to understand the potential benefits of this approach. Fluzone® ID (Sanofi Pasteur) is approved and available in multiple markets, and it comes in a prefilled, mini-needle device (BD Soluvia®). ID adapters and alternative needles have received clearance by NRAs. None have yet been WHO prequalified.
Disposable syringe jet injectors (DSJI)	Jet injectors deliver a single dose of liquid by ejecting it from a pressurized chamber with sufficient force to penetrate the skin. Typically no formulation changes are necessary for use with jet injectors. Jet injectors have been used to administer hundreds of millions of vaccine doses in mass campaigns against smallpox, measles, meningitis, influenza and other diseases.	Because of the potential for cross-contamination between applications, WHO recommends single-use auto-disabled DSJIs. These DSJIs offer improved safety due to needle-free administration but increase costs as compared to needles and syringes and may not be faster than traditional injections.	Performance specifications for jet injectors have been established by the WHO performance, quality and safety (PQS) programme, and PharmaJet®. Needle-free injector was prequalified in 2013 for delivery of intramuscular and subcutaneous injections. Additional devices have been approved for use in several countries. DSJIs are being evaluated for delivery of influenza, inactivated polio, TB, MMR, and pentavalent vaccines. The US Food and Drug Administration (FDA) currently requires vaccine relabeling for vaccines delivered by jet injection. Currently a modified Biologic License Application (BLA) to allow for jet injection delivery of bioCSL's influenza vaccine (Afluria®) is under review at the FDA and approval is anticipated to allow for DSJI use in the 2014/15 influenza season.

Technology or delivery method	Key features	Challenges	Status
Combined vaccine vial monitor (VVM) plus peak temperature threshold indicators (VVM-plus)	VVM integrated with a peak temperature threshold indicator in one sticker simplifies the monitoring of vaccines used in a controlled temperature chain (CTC) setting. The interpretation of the VVM plus label can be designed to be the same as the current VVM; so additional training would not be required.	Technical development complexities. Global commitment on the appropriate temperature threshold that is broadly representative of all country environments and vaccine products is pending.	Proof of feasibility exists. Multiple products are in various stages of development. WHO is developing prequalification specifications and a threshold temperature (40°C) has been defined by the Vaccine Presentation and Packaging Advisory Group.
Barcodes	Barcoding use may benefit countries in multiple ways as part of their integrated stock management system. Benefits include improved access to vaccines through reduced stock-outs, reduction of closed vial vaccine waste, reduction of emergency trips to remedy stock issues, improving the accuracy of stock data and reducing the time spent by staff on inventory management.	Barcodes will need to be made available on all vaccines in a given country for their benefits to be entirely realized. This requires a labelling change and associated regulatory process for vaccine suppliers. Most importantly, countries will need to develop the systems and hardware and software to reap the benefits of barcodes.	A feasibility study has been conducted in the United Republic of Tanzania with barcoding on secondary and tertiary packaging. A subgroup of the Vaccine Presentation and Packaging Advisory Group has created a consensus recommendation with vaccine suppliers on initial specifications for vaccine barcodes. WHO will signal barcoding as a preferred characteristic in the next version of the Programmatic Suitability of Vaccines for Prequalification document.
Integrated reconstitution devices	Integrated reconstitution devices include prefilled dual-chamber syringes and alternative container-closure systems that facilitate reconstitution and enhance safety by eliminating reconstitution errors. They are directly applicable to lyophilized vaccines, but require process redesign to implement non-standard fill/finish processes and equipment.	Costs and effect on cold chain requirements vary by technology and must be evaluated on a product-by-product basis.	Integrated reconstitution devices have been approved for use with specific drugs and vaccines by NRAs. None are yet WHO-prequalified.
Microneedle arrays	Benefits and limitations vary by technology. In general, microneedles may require lower doses than other technologies and can offer ease of use and reduce needle-stick risks. Immune responses after intradermal delivery as compared to intramuscular delivery will require evaluation.	Costs compared to traditional methods will require further investigation.	Several approaches to intradermal injection with microneedles are being developed, including solid coated, dissolvable, hydrogel and hollow microneedle arrays. Microneedle arrays are being evaluated for delivery of a range of vaccines, such as influenza and inactivated polio vaccines.
Pulmonary administration	Pulmonary administration devices allow inhalation and deposition of solid particles or liquid droplets in the respiratory tract. These approaches could offer improved vaccine stability and safety.	Pulmonary administration will require demonstration of non-inferiority compared to current administration methods. Costs, ease of use, throughput and suitability for infants require further evaluation.	Primarily used for drug delivery, these devices have also been evaluated for administration of measles vaccines.
Sublingual administration	Gels, thin films or tablets that administer vaccine to the sublingual mucosa under the tongue offer ease of use and improved safety, and potentially enhanced mucosal immune responses.	Operational evaluations will be required to understand benefits and limitations.	Some preclinical development is under way. Immunological responses after administration will require evaluation.

Technology or delivery method	Key features	Challenges	Status
Implanted solid dose	Solid doses are implanted using a reusable actuator and dissolve upon contact with interstitial fluid, releasing the active ingredient. When used for vaccination, implanted solid doses may offer greater stability, ease of use, throughput and safety.	Operational evaluations will be required to understand benefits and limitations.	Preclinical studies have been conducted with several vaccines.
Electroporation	Intended to enhance skin permeability or enable immune response.	Operational evaluations will be required to understand benefits and limitations.	This approach is in an early stage of development.

In spite of the many promising options, progress since 2010 in the licensure, prequalification and launch of new technologies has been modest, as shown in Table 19.

Table 19: Technologies licensed and launched in low- or middle-income countries

	Licensed	Prequalified	Launched*
2010 Baseline	• Prefilled single use syringes / Tetanus toxoid vaccine • Prefilled single use syringes / Hepatitis B vaccine • Intranasal spray / Influenza vaccines (Flumist® 2003) • Multi-chamber syringes / Hepatitis A–Typhoid combination vaccine (Viatim® 2001) • Intradermal needles / Influenza vaccines (IDFlu® and Intanza® European Medicines Agency, EMA, 2009)	• Prefilled single use syringes / Tetanus toxoid vaccine • Prefilled single use syringes / Hepatitis B vaccine	• Indonesia: Prefilled single use syringes / Tetanus toxoid vaccine • Indonesia: Prefilled single use syringes / Hepatitis B vaccine
Progress as of 2013	• Prefilled single use syringes / Pentavalent vaccine (Quinvaxem® 2014)	• Disposable syringe jet injector (Stratis® 2013) • *Submitted:* prefilled single use syringes / Pentavalent vaccine (Quinvaxem®)	No new technologies launched since 2010

* Launch refers to use of the technology in the national immunization programme of one or more low- or middle-income countries.

Opportunities and challenges

A next-generation vaccine delivery technologies meeting was convened by WHO and PATH 18–19 February 2014, in Geneva to discuss lessons learned from prior technology development experiences, the landscape of new vaccine delivery, formulation and packaging technologies and current challenges that prevent these technologies from moving forward into programmatic use. A variety of public health global stakeholders participated in the meeting, including representatives from industry and academia, non-profit-making organizations, regulatory authorities, UN agencies and other groups engaged in global health. Challenges identified that hinder technologies from moving through the value chain (concept, research and development, clinical testing, regulatory, manufacturing scale-up, etc.) include public health need identification and consensus, impact quantification, potential requirement for vaccine manufacturer to modify fill/finish process, higher cost when compared to currently available technologies, clarity on purchaser requirements

and meeting evolving or uncertain regulatory requirements. It was acknowledged during the course of the meeting that the public sector must provide greater leadership to set clear policy guidance and communicate preferred product profiles for developers of new technologies.

Many efforts are under way to improve technical guidance and facilitate regulatory review for the licensure and launch of new platform delivery technologies. For example, WHO has developed global standards for assessing the quality, safety and immunogenicity of vaccines, and has provided manufacturers with clear requirements for vaccine prequalification. WHO's Immunization Practices Advisory Committee, has been advising on tools and technologies to strengthen and improve the delivery of immunization, and the Vaccine Presentation and Packaging Advisory Group is providing a forum for public sector and manufacturer representatives to reach consensus on vaccine presentation and packaging attributes that are important to lower-income countries. Donors and policy-makers are clarifying priorities for vaccine research and development and driving the development of target product profiles to provide guidance for manufacturers. Multidose presentations of vaccines remain a cost-efficient strategy to deliver vaccines but have come under scrutiny as they contain preservatives, mostly thiomersal. While thiomersal is safe, public perception issues drive manufacturers to other presentation forms, in particular single-dose devices. Research is needed into the development of alternative preservatives or multi-dose containers that may not need preservatives at all. To cope with the increasing number of vaccines to be administered simultaneously at a given vaccination session, technologies need to be explored that facilitate simultaneous administration of vaccines.

Licensure and uptake of new technologies remains slow for multiple reasons, as experienced by the Uniject™ compact prefilled auto-disable injection system. Such new technologies require significant up-front investments, resulting in more expensive presentations. Even if shown to be cost-effective due to decreasing delivery costs, uptake has been limited as procurement decisions are typically driven by price per dose rather than overall cost-effectiveness.

Current promising leads, strategies and technologies

The interface between alternative presentations for prefill (auto-disable prefill syringes, blow-fill-seal, reconstitution technology, microneedles, etc.) and the impact on fill/finish process and application to one or multiple vaccines is a promising area for future efforts. The benefit of such technologies for improved vaccine delivery and programme efficiencies is promising.

In the area of prefilled syringes there is an important opportunity to broaden the application of the Uniject™ compact prefilled auto-disable injection system and accelerate the uptake of vaccines in Uniject™. For example Uniject™ TT could be invaluable in MNT elimination efforts, particularly in insecure areas. Blow-fill-seal technology might enable lower cost of goods when compared to other prefill technology with compact, volume-efficient designs potentially representing reduced cold chain volume requirements. Blow-fill-seal technology is being considered by several vaccine manufacturers, especially for oral vaccines.

Microneedle patches with an integrated thermostable formulation could allow for storage outside the cold chain and enable improved ease of delivery or even self-administration. Supporting demonstration of feasibility for one or more vaccines (IPV, measles) for the technology class could accelerate potential programmatic introduction and use of this delivery platform. Achieving feasibility will influence the development pipeline for other vaccines in this format.

A VVM combined with a threshold indicator will facilitate implementation of vaccines recommended for CTC environments without causing unnecessary confusion among vaccine administrators. By combining the two technologies into one sticker, there is less risk of health workers perceiving a separate threshold indicator as undermining the effectiveness of the VVM technology that has been trusted to signal vaccine heat exposure status for over a decade.[17]

Barcoding work is advancing with the vaccine industry, international agencies, nongovernmental organizations (NGOs) and GS1 well engaged in collaborative studies and working groups. Given the use of barcodes in industrialized countries, implementation on vaccine packaging should be relatively straightforward. Country preparedness to utilize barcodes will take more time, however.

[17] See for more information: http://www.who.int/immunization/policy/committees/IPAC_2012_October_report.pdf.

Future directions

Addressing these challenges and realizing the potential of new delivery technologies will require that decision-makers assess interventions from a total system cost-effectiveness perspective. Total system cost-effectiveness considers a broader range of factors than just cost, including coverage, safety, and efficacy. Within the cost category, it goes beyond price per dose to evaluate all major costs including product, distribution, storage, wastage and human resource requirements required to achieve effective coverage. A total system cost-effectiveness evaluation would enable a holistic evaluation of trade-offs between price and deliverability, and ideally guide target product profiles and incentive structures that are most representative of what countries need to efficiently achieve maximum immunization coverage. A total system cost-effectiveness framework is currently being developed in collaboration with global health stakeholders to evaluate the trade-offs between various container sizes for WHO/UN prequalified vaccines. Following the initial construction of the framework, methodology and data collection, future assessments will be undertaken to evaluate the trade-offs between new product technologies.

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NUMBER OF LOW-INCOME AND MIDDLE-INCOME COUNTRIES THAT HAVE INTRODUCED ONE OR MORE UNDER-UTILIZED VACCINES (INDICATOR G4.3)

Highlights

- From January 2010 to December 2012, 68 low- and middle-income countries added at least one new vaccine to their national immunization programme and sustained vaccine use for at least 12 months, i.e. until December 2013.
- These 68 low- and middle-income Member States introduced a total of 85 vaccines from January 2010 to 31 December 2012 (16 introduced more than one vaccine during this period).
- These 68 countries represent almost half (48%) of the world's population that live in low- and middle-income countries.
- Lower-middle income countries not eligible for GAVI Alliance assistance (67%) do not appear to be lagging behind in introducing new vaccines, compared to GAVI-eligible (48%) and GAVI-graduating countries (53%).
- The constrained supply of pneumococcal and rotavirus vaccines has eased in 2014; greater quantities of these vaccines in 2015 are expected.

TARGET	2015: At least 90 low- and middle-income Member States 2020: All low- and middle-income Member States
DEFINITION OF INDICATOR	A vaccine is added to the national immunization schedule and used for a sustained period of at least 12 months New and under-utilized vaccines are all vaccines that were not previously in the national immunization schedule
DATA SOURCES	WHO-UNICEF joint reporting forms (JRFs)
DATA AVAILABILITY AND QUALITY	The limitations with JRF and WUENIC coverage data have been discussed in the GVAP Secretariat report 2013[18]

Results

In the first three years of the Decade of Vaccines – January 2010 to December 2012 – 68 low- and middle-income countries added at least one new vaccine to their national immunization programme and sustained vaccine use for at least 12 months, i.e. until December 2013 (Table 20).

[18] For more information about the JRF and WUENIC coverage data, please refer to the GVAP Secretariat report 2013, Annex 1. http://www.who.int/entity/immunization/global_vaccine_action_plan/GVAP_secretariat_report_2013.pdf?ua=1.

Table 20: Number of low- and middle-income Member States that introduced and sustained vaccine use for at least 12 months between January 2010 and December 2012, by vaccine, GAVI Alliance eligibility and World Bank income group

Country classification	Total No. of countries by category	Member States that have introduced at least 1 vaccine	Hib	Pneumo	Rota	HPV	Rubella	No. of countries that could benefit from IPV	IPV*
GAVI-eligible	56	27 (48%)	6	16	5	2	2	73	0
GAVI-graduating	17	9 (53%)	4	3	3	0	0	NA	–
Non-GAVI-eligible lower-middle income	12	8 (67%)	3	4	3	1	1	12	0
Non-GAVI-eligible upper-middle income	54	24 (44%)	8	9	4	6	0	54	8
Total	**139**	**68 (49%)**	**21**	**32**	**15**	**9**	**3**	**139**	**5**

* It is proposed that introduction of a single dose of IPV as part of the polio eradication end-game strategy should not be considered as an inclusion criterion for this indicator. Only countries that replace OPV with IPV or introduce IPV as part of a sequential schedule should be included. Otherwise the target for the decade will be met in 2016.

These vaccines include: Hib-containing vaccine, pneumococcal conjugate vaccine (PCV), rotavirus vaccine, human papillomavirus vaccine, rubella and inactivated polio vaccine.[19] These 68 countries represent almost half (48%) of the world's population that live in low- and middle-income countries.

Fifty-two of these low- and middle-income countries introduced one vaccine during this three-year period, while 16 countries introduced more than one vaccine. A total of 85 vaccine introductions took place in these 68 low- and middle-income countries during this period.

All but five countries[20] had yet to introduce Hib-containing vaccine by the end of 2013. A major increase in new vaccine introductions during the past years was seen with pneumococcal- and Hib-containing vaccines in middle-income countries.

Among the 16 Member States which introduced and sustained more than one vaccine during the period, 7 are upper-middle income countries, 4 are lower-middle income countries, 4 are GAVI-eligible and 1 is a GAVI-graduating country.

When looking at the countries having introduced and sustained use of new vaccines by GAVI Alliance eligibility and income classification (Table 21), non-GAVI-eligible lower-middle income countries (67%) do not appear to be lagging behind in introducing new vaccines, compared to GAVI-graduating (53%) and GAVI-eligible countries (48%).

However, non-GAVI-eligible upper-middle income countries seem to be lagging compared to all other categories as only 44% of upper-middle income countries have introduced a new vaccine during the same period. This is an area that will need to be monitored closely, and additional efforts may be warranted to facilitate access to new vaccines and technologies in these upper-middle income countries.

[19] texte ?

[20] Egypt, Iran (Islamic Republic of) and South Sudan are planning to introduce Hib-containing vaccine in 2014; China and Thailand do not plan to introduce Hib-containing vaccine; Belarus, India and Indonesia already have introduced Hib-containing vaccine but only partially.

Table 21: Number of Member States that have added one or more new vaccines to their national immunization schedule, by year and WHO region

		Number of low-, lower-middle and upper-middle income countries having introduced at least one vaccine			
WHO region	No. of low-, lower-middle and upper-middle income countries* / total Member States in region 2012	2010	2011	2012	2010–2012
African	46/47	3 (6%)	11 (23%)	9 (19%)	20 (43%)
Americas	26/35	9 (26%)	5 (14%)	8 (23%)	16 (62%)
Eastern Mediterranean	15/21	1 (5%)	3 (14%)	4 (19%)	7 (47%)
European	20/53	4 (8%)	3 (6%)	2 (4%)	9 (45%)
South-East Asia	11/11	0 (0%)	2 (18%)	4 (36%)	6 (55%)
Western Pacific	21**/27	5 (19%)	2 (7%)	3 (11%)	10 (48%)
Total	**139/194**	**22 (16%)**	**26 (19%)**	**30 (22%)**	**68 (49%)**

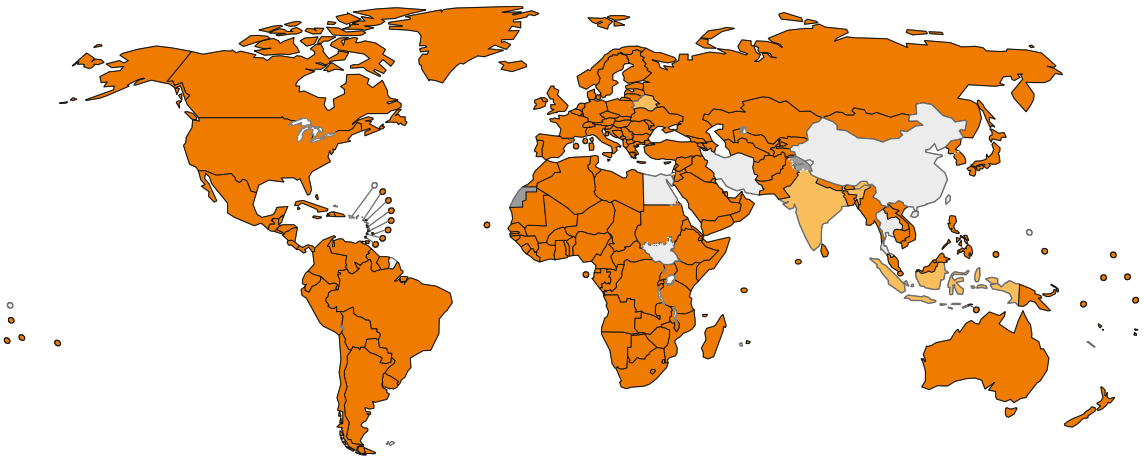
* World Bank classification. It is proposed to keep this reference year for future reports to ensure comparability of data.
** Cook Islands, Niue and Nauru were not classified by the World Bank, but were considered one upper-middle income country for this report.

Progress in adding vaccines to national immunization programmes occurred in all regions. There were constant increases in the proportion of Member States having introduced at least one new vaccine in the reporting period, reaching 62% in the Americas, and 55% and 48%, respectively, in the South-East Asia and Western Pacific Regions. The largest absolute increase in number of countries introducing at least one new vaccine in the past year was seen in the African Region (an additional nine countries).

Continued efforts are required to sustain the use of the new vaccines in national immunization programmes in low- and middle-income countries. This may require increased investments in surveillance and in conducting impact assessments to justify continued domestic investments in these vaccines.

The maps in Figure 26 through Figure 29 show the status of the use of Hib, PCV, rotavirus and human papillomavirus (HPV) vaccines in national immunization programmes worldwide.

Figure 26: Member States with Hib-containing vaccine in their national immunization programme*

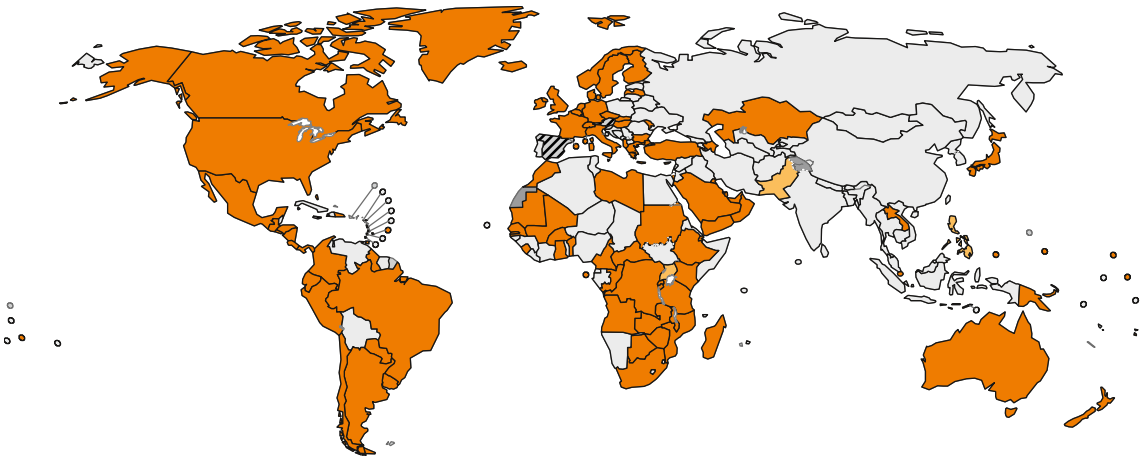


Introduced to date (186 countries or 96%)
Introduced in some parts of the country (3 countries or 2%)
Not introduced (5 countries or 3%)
Not available
Not applicable

* As of 31 December 2013.

Map production: Immunization Vaccines and Biologicals, (IVB). World Health Organization.
Date of slide: 16 July 2014.

Figure 27: Member States with pneumococcal conjugate vaccine in their national immunization programme*

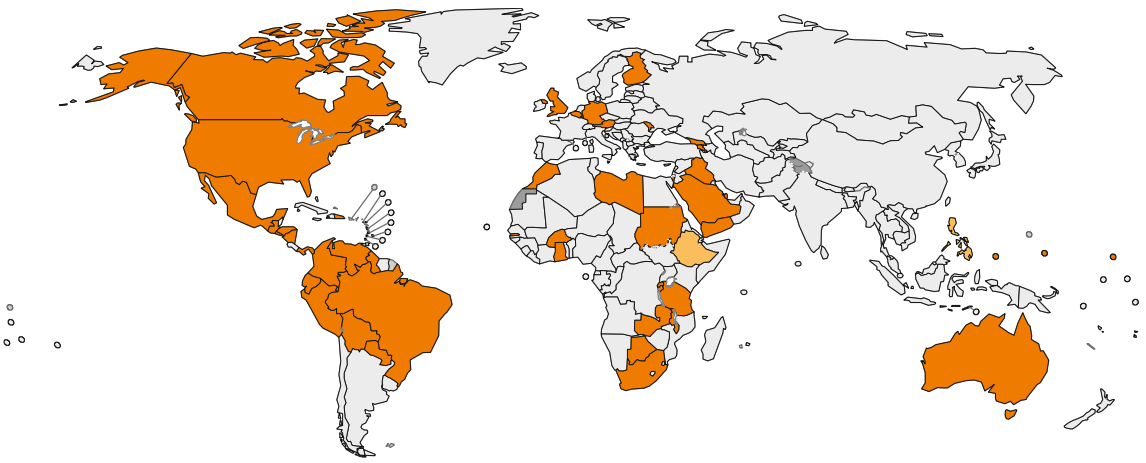


Introduced to date (100 countries or 52%)
Introduced in some parts of the country (3 countries or 2%)
Introduced for risk groups only (4 countries or 2%)
Not introduced (87 countries or 45%)
Not available
Not applicable

* As of 31 December 2013.

Map production: Immunization Vaccines and Biologicals, (IVB). World Health Organization.
Date of slide: 16 July 2014.

Figure 28: Member States with rotavirus vaccine in their national immunization programme*

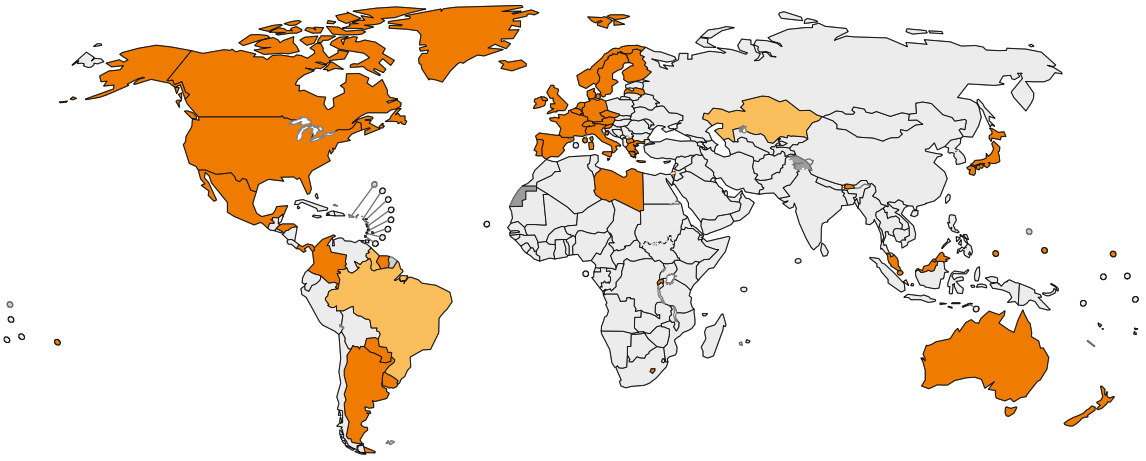


Introduced to date (50 countries or 26%)
Introduced in some parts of the country (2 countries or 1%)
Not introduced (142 countries or 73%)
Not available
Not applicable

* As of 31 December 2013.

Map production: Immunization Vaccines and Biologicals, (IVB). World Health Organization.
Date of slide: 16 July 2014.

Figure 29: Member States with HPV vaccine in the national immunization programme*



Introduced to date (52 countries or 27%)
Introduced in some parts of the country (3 countries or 2%)
Not introduced (139 countries or 71%)
Not available
Not applicable

* As of 31 December 2013.

Map production: Immunization Vaccines and Biologicals, (IVB). World Health Organization.
Date of slide: 16 July 2014.

STRATEGIC OBJECTIVE 6: COUNTRY, REGIONAL AND GLOBAL RESEARCH AND DEVELOPMENT INNOVATIONS MAXIMIZE THE BENEFITS OF IMMUNIZATION

PROGRESS TOWARDS DEVELOPMENT OF TB VACCINES (INDICATOR SO6.1)

Background

In March 1993, WHO designated tuberculosis (TB) a global public health emergency. Currently, *Mycobacterium tuberculosis* disease, also known as TB, is a leading cause of mortality worldwide and a leading cause of death in HIV-infected individuals and women of childbearing age. There are over 1.3 million deaths from TB each year, and TB is the number nine overall cause of mortality worldwide. It is estimated that nearly 1 billion people have died of TB over the past centuries – an astounding number. Ninety-nine per cent of the TB deaths and 95% of the over 8 million new cases each year occur in low- and middle-income countries that comprise 85% of the world's population. The epidemic of TB in sub-Saharan Africa has been fuelled by HIV disease, while the increasing incidence of diabetes in Asia further threatens attempts at TB control.

Consequently, one of the highest priorities of TB research is to develop vaccines that are more efficacious for preventing TB than *Mycobacterium bovis* bacille Calmette–Guérin (BCG), the only vaccine available to protect against TB *(1)*. Better control of TB than that provided by BCG could be achieved by vaccines that protect individuals from initial infection, prevent those infected from progressing to active disease, or decrease the capacity for transmission by those with active disease. Different vaccines may be required to induce immune responses in diverse populations, such as infants versus young adults, those already infected with *M. tuberculosis* (Mtb), and those co-infected with HIV. Experts in TB prevention and control mostly agree that the largest vaccine impact would be to mass vaccinate all adolescents/young adults in high-burden countries, regardless of their infection status, even with a vaccine that is only 60% efficacious. Such a vaccine could prevent an estimated 30–80% of incident TB cases in high-burden settings during the first 35 years after its introduction, depending on the type of protection the vaccine affords *(2)*. This impact would save millions of lives and billions of dollars in treatment and control costs.

Overview of current efforts

BCG is a live, attenuated vaccine that is widely administered to infants in most areas endemic for TB. BCG has been shown to be effective for the prevention of more serious extrapulmonary tuberculosis in young children, such as tuberculous meningitis and miliary tuberculosis *(3)*. A meta-analysis of prospective trials and case–control studies concluded efficacy against pulmonary TB in infants and adolescents at about 50% with a range from a low of 0 to a high of 80% *(4)*. When delivered to newborns, however, BCG is not effective in preventing adult pulmonary TB, which constitutes the bulk of the global morbidity and mortality disease burden.

Most successful, licensed vaccines available today induce neutralizing antibodies that provide protective immunity; however, tuberculosis animal studies suggest that a robust cellular immune response is required for protection against Mtb infection and disease *(5, 6)*. For this reason, the majority of current clinical TB vaccine candidates are based on a variety of vectors, adjuvants and antigens that induce classical TH1 cytokines such as IFN-γ/TNF-α from either CD4+ or CD8+ T cells. Sixteen of these candidates have moved forward into clinical studies in the past 10 years, including a dozen current candidates *(7)*.

These clinical candidates are based on a variety of strategies such as inactivated whole cell or whole cell extracts (Mw, *M. vaccae*, RUTI and *M. smegmatis*) *(8-10)*, viral-vectored candidates (vaccinia-based MVA85A, and adenoviral-based AERAS-402 and AdAg85A) *(11–15)*, fusion protein subunits with TH1-inducing adjuvants (M72/AS01, Hybrid 1/CAF01, Hybrid 1/IC31, H4/IC31, H56/IC31 and ID93/GLA-SE) *(16–19)*, and live recombinant BCG vaccines (VPM 1002, Aeras 422 and rBCG30) *(20–23)*. DNA vaccines are being developed in different countries, notably emerging economies, but have not yet entered into human clinical trials *(24)*. To date, clinical trials characterizing these candidate vaccines have included studies of safety and immunogenicity in diverse populations, including healthy, TB-naive adults and infants, latently infected adolescents and adults, HIV+ adults, as well as patients undergoing drug treatment for TB.

BCG vaccine is the most widely administered neonatal vaccine worldwide, but due to its short-term protective effectiveness, most of the new candidate vaccines are being studied as boosters following a priming immunization with BCG *(25)*. In parallel, however, recombinant BCG vaccines are also being studied as replacements for BCG to improve its safety in HIV-exposed infants and to induce better efficacy as well as better priming. Attenuated live Mtb strains, which have shown acceptable safety in immune suppressed animal models, are also in early clinical development *(22)*.

An initial phase IIb proof-of-concept efficacy trial in 2787 BCG-vaccinated infants boosted with a viral-vectored vaccine containing one antigen (MVA85A) showed no efficacy against TB disease or infection *(26)*. Whether this disappointing outcome was due to the magnitude of the response, the antigen studied, the population vaccinated or an incorrect immunologic hypothesis is not clear. A large, phase IIb trial in HIV-uninfected, latently infected adults in Africa using the GlaxoSmithKline M72 adjuvanted fusion protein vaccine is about to begin.

In addition to these large-scale, proof-of-concept trials, a new set of human studies are under way, based on the use of innovative trial designs intended to show the biologic activity of vaccine candidates using smaller, more focused populations. The first of these new trial designs is testing whether a novel vaccine (H4/IC31) or the use of BCG re-vaccination can prevent infection (as opposed to disease) by Mtb. The trial uses novel blood tests in which BCG vaccination does not interfere with the result – a common obstacle with the long-time, standard diagnostic test, the tuberculin skin test – and requires only 330 subjects per arm rather than the two thousand or more as needed in the classic proof-of-concept trials. The second innovative trial design is to study the ability of a vaccine to prevent the 4–6% relapse and/or reinfection rate typically observed following successful treatment of active TB. These prevention-of-TB recurrence trials, using both the ID93 and H56 candidates, will begin shortly and require approximately 400 subjects per arm.

Opportunities and challenges

Despite recent advances in the field, developing a TB vaccine for any chosen population is fraught with considerable obstacles. First, there is no correlate of protection that can guide vaccine design or animal experiments, or that can be used as a credible end-point in early human studies. Second, without a known efficacious vaccine that effectively prevents pulmonary TB, it is impossible to validate an animal model as a potential surrogate. Third, due to the relatively low regional incidence of TB, despite the high worldwide prevalence, true proof-of-concept trials that use clinical end-points are by necessity very large (1000 to 35 000 subjects) and expensive (US$ 10 to 50 million).

There are no clear models upon which to identify the 'best' vaccine Mtb antigens, as many TB vaccine animal models have a narrow dynamic range of responses that do not allow for easy differentiation among candidates. This limitation is being addressed by refinement of the mouse, guinea pig and macaque models to better approximate natural infection by Mtb and better mimic human disease. The use of low dose challenge, sophisticated imaging techniques and novel vaccine candidates (such as H56, cytomegalovirus approaches and aerosolized adenovirus vaccines) have recently shown that the macaque model may potentially be useful to delineate the true correlates of vaccine-induced protection.

In human biomarker studies, gene expression patterns of inflammatory bio-signatures have correlated with risk for TB disease progression, and with the extent of radiographic involvement in both active and latent TB cases *(27)*. In response to these data, TB vaccine developers are pursuing a systems immunology approach in which gene expression signatures are compared in samples from various time points. These signatures are then correlated to either specific measures of immunogenicity, or to protection in efficacy studies. This method allows for a broader unbiased net to be cast in assessing immune responses.

Current promising leads, strategies and technologies

A rational approach for selection of TB vaccine candidates for future studies is required *(28)*. First, there is a need to ensure that each vaccine carried forward into efficacy studies addresses a new hypothesis, rather than pursuing a vaccine approach that has already failed. It will be critical to then choose only the best vaccine candidate among those that are likely to induce similar magnitude and phenotypes of immune responses. From candidates that have similar target profiles, head to head comparisons of candidates in animal and early human studies would be optimal, and mechanisms and incentives (such as support from funding agencies) to do such comparisons are needed. This approach also implies the need for a diverse and robust pipeline of candidates: not just a set of minor improvements, but truly novel approaches that test different immunologic hypotheses.

To this end, the field of TB vaccines is rapidly changing from one of pure product development based on a single hypothesis to an exploration of multiple immunologic approaches based on novel technologies. The adjuvanted protein approaches, used as a boost during adolescence following infant BCG, have shown promise in non-human primate models and, as mentioned above, are being tested in innovative, fast clinical trial designs that will provide answers over the next few years. If any of these prove promising, then there will be momentum to carry one or more of these into larger disease efficacy studies.

Other leads that will be aggressively pursued over the next five years will be the use of aerosolized adenoviral candidates, either alone or in combination. Of note, the combination of aerosolized adenoviral vectored vaccines followed by modified vaccinia Ankara has been especially promising in both preclinical models and in early human trials. CMV candidates will move forward in both the TB and HIV area, as they induce prolonged and high levels of effector T cells at the mucosal location at which the pathogen first encounters the human host. Other promising leads include intranasal attenuated para-influenza viruses for induction of mucosal immunity, self-replicating RNA candidates, and electroporated DNA vaccines. The value of a number of novel BCG replacement strategies will also become clearer. Systematic study of combinations using common antigen sets is now under way for all of these approaches.

A variety of highly novel candidates are being developed by expert consortia, utilizing a number of approaches such as focusing on prevention of infection through antibody-mediated mechanisms, as well as selecting optimal glycolipid constructs and adjuvants that induce responses via the CD1 system. These are both high-risk/high-reward approaches to expand the immunologic response space being probed by TB vaccine candidates. Testing of these novel candidates is being facilitated by the concurrent development of novel animal models of natural transmission. The models include human-to-guinea pig transmission, as well as novel macaque-to-macaque transmission in a closed setting. While these programmes progress, significant attempts will be undertaken to build a safe bacterial construct that can be used in a TB human challenge model, which would open wide the field of early clinical vaccine assessment. The strain of Mtb used will need some degree of low-level replication, a fail-safe kill switch and a second attenuation mechanism to help ensure safety. The strain must be modified such that the bacterial burden can be easily measured – through the imaging of a luminescent marker or by measuring a soluble, secreted marker in blood or urine.

Future directions

A. Short-term goals (within two years)

- Evaluate vaccine candidates (obtain preliminary results) from 3 types of proof-of-concept clinical trials: prevention of infection in adolescents, prevention of recurrence in recently treated TB patients and prevention of TB disease in latently infected individuals.
- Test aerosol vaccine strategies in humans in phase I/IIa studies.
- Develop improved animal models, specifically a low dose non-human primate (NHP) challenge model, a NHP to NHP transmission model and a natural transmission guinea pig model.
- Choose one to two antibody-based candidates to move into animal challenge studies.
- Identify optimized glycoprotein candidates and adjuvants and design their preclinical and clinical development path.
- Identify most promising combination platforms in preclinical models, using a common antigen set, and test immunogenicity and safety in humans.
- Determine the role of non-tuberculous mycobacteria exposure on TB vaccine responses.

- Build the first prototype human challenge strains and test them in animals for further re-iterations.
- Identify novel protective antigens that are 'unnatural' or not immunodominant during latency or treatment.

B. Mid-term goals (by 2020, end of the Decade of Vaccines; may or may not include licensure)

- Determine whether the M72 vaccine protects against TB in latently-infected adults.
- Determine whether H4 and/or BCG and at least two other candidates protect against Mtb infection in adolescents in a high risk of infection setting.
- Determine whether H56 or ID93 vaccination, in adults who have recently completed successful treatment for drug-sensitive pulmonary TB, protects against recurrent TB disease.
- Have established a reproducible NHP model with a strongly positive control and use it to identify a correlate of protection.
- Have advanced two candidates demonstrating proof of meaningful biological activity (in a NHP model, a prevention of infection trial or a prevention of recurrence trial) into phase IIb prevention of TB disease efficacy trials.
- Have four novel vaccine candidate platforms in clinical development (e.g. electroporated DNA, RNA, antibody-based vaccines such as polysaccharide conjugates, glycolipids, etc.).
- Have established a human challenge model for rapid identification and advancement of the most promising candidates emerging from refined animal models.
- Have a global consortium that influences the overall portfolio and resource allocation.

C. Long-term goals (beyond 2020, if applicable)

- Licensed vaccine by 2027 for prevention of TB disease.
- Longer-term: additional candidates licensed and phase IV studies conducted in multiple populations and geographic areas (HIV, diabetes, prevention of infection; China, India, Asia Pacific, Latin America, etc.).

Discussion

At the 2014 Global Vaccine and Immunization Research Forum (GVIRF), Tom Evans, the CEO of Aeras, an international TB vaccine development partnership, reviewed the status of vaccine research and development for TB. He showed a well-balanced pipeline of TB vaccine candidates, which are in preclinical and clinical evaluation. This represents remarkable progress when compared to the TB vaccine development landscape before ambitious vaccine development goals were first formulated in the Global Plan to Stop TB 2006-2015 *(29)*. Nonetheless, the absence of vaccine efficacy observed during the recent first efficacy trial of a new TB vaccine candidate – an infant trial of TB vaccine candidate MVA85A (Table 22) in South Africa – has significantly curtailed the chances of licensure of a new TB vaccine before 2020. This is unfortunate, as epidemiological modelling clearly demonstrates an urgent need for a new TB vaccine, without which none of the ambitious goals of TB reduction, including elimination of tuberculosis as a public health problem, can be reached.

Just like in the case of development of vaccines for other 'difficult' diseases such as those caused by HIV, dengue or hepatitis C virus, TB vaccine development presents its set of specific bottlenecks. Some of these are illustrated by the shortcomings of the currently available BCG vaccine and may apply to new vaccines as well, e.g. the fact that it needs to be given before infection and very early in life or the fact that it presents a wide range of geographic variation in its efficacy. However, a number of pointers provide encouragement that a new vaccine may do better than BCG. Most importantly, around 90% of immunocompetent individuals infected with *M. tuberculosis* do not develop active TB disease during their entire lifespan. Indications that this remarkable resistance has to do with the human adaptive immune system, and thus can potentially be enhanced by a better vaccine, stem from observations that T-cell deficiencies, including T cell-cytokine/cytokine receptor pathway defects, e.g. IL-12, IFN Gamma, render individuals supremely susceptible to TB disease. Moreover, infectious challenge models of protection against TB in non-human primates have demonstrated superiority of some of the new vaccine candidates over BCG alone.

The fact that there is a TB vaccine, BCG, has been both a blessing and a curse for the prevention of tuberculosis: blessing, as it has allowed us to avert at least part of the burden, and in particular, the most devastating consequences of the disease in children, such as TB meningitis or military TB; and curse, as it has reduced incentives to develop alternative, better products. In addition, the BCG model still imparts a dogmatic element to the current vaccine development debate, exemplified by the focus on prevention of primary and reactivation disease or on certain types

of antigens that are absent from BCG, but not from other mycobacteria. In order to expand the TB vaccine pipeline, we need to move away from these self-imposed limitations and become more ambitious. This includes broadening the choice of antigens tested, developing more relevant animal models, and evaluating different modes of prevention. There are encouraging signs that this is actually starting to happen, thus: (a) the focus on immunodominant T-cell antigens is giving way to a strategy that recognizes the need to 'do better than nature', including consideration of subdominant antigens/epitopes, antigens from different stages of the mycobacterial 'lifecycle' and a renewed look at the role of B cells and non-protein antigens; (b) highly artificial animal models are being brought closer to the natural course of infection and disease in humans, e.g. through innovative transmission models; and finally (c) prevention of primary or reactivation disease is no longer the only mode of prevention targeted, but ambitions are now also set to developing a vaccine to induce sterilizing immunity, block transmission or prevent reinfection and relapse.

Apart from the above scientific improvements, logistics must also improve, in order to avoid wasting precious time as well as valuable human and financial resources by the traditional ways of doing vaccine development. Pre-licensure evaluation could be accelerated by earlier and more stringent candidate up-selection, collection of more relevant data earlier in development, e.g. through 'experimental medicine' trials, and through participation in the debate about new paradigms for the regulation of clinical trial approval and vaccine licensure. Initiatives to synergize the work of the vaccine development community more efficiently, e.g. a 'global TB vaccine initiative', might represent an acceptable vehicle to achieve rationalization of the TB vaccine pipeline. Lastly, the vaccine development 'enterprise' as a whole must become more inclusive, bringing together communities and public health decision-makers from high endemicity countries in all steps of the vaccine development continuum, i.e. from research and development all the way to licensure and manufacture of the new vaccines. One, but by far not the only, means to this end could consist in the creation of a 'global community advisory board', composed of representatives of those whose well-being most critically depends on the appropriateness, accessibility and affordability of much needed new prevention tools against TB.

Table 22: Development status of current vaccine candidates

Candidate name/Identifier	Phase I	Phase IIa	Phase IIb*	Phase III
Ad5 Ag85A [McMaster University, CanSino]	X			
MTBVAC [TBVI, Zaragoza, Biofabri]	X			
ID93 + GLA-SE [IDRI, Aeras]		X		
Crucell Ad35/MVA85A [Crucell, Oxford University, Aeras]	X			
VPM 1002 [Max Planck, VPM, TBVI, Serum Institute of India]		X		
H1 + IC31 [Statens Serum Institut (SSI), TBVI, EDCTP]		X		
RUTI [Archivel Farma, S.L]		X		
H4/Aeras-404 + IC31 [SSI, Sanofi Pasteur, Aeras, Intercell]		X		
H56/Aeras-456 + IC31 [SSI, Aeras, Intercell]		X		
Crucell Ad35/Aeras-402 [Crucell, Aeras]		X		

Candidate name/Identifier	Phase I	Phase IIa	Phase IIb*	Phase III
MVA85A/Aeras-485 [Oxford University, Aeras]			X	
M72 + AS01E [GlaxoSmithKline, Aeras]			X	
M. Vaccae [Anhui Zhifei Longcon, China]				X

* Phase II comprises studies of a candidate vaccine that are intended to result in efficacy data in the target population to whom the vaccine would be administered should it eventually by licensed. A programme of phase II studies usually defines the preferred dose, route and schedule of immunizations that are eventually evaluated for efficacy. Phase II studies also provide an expanded population assessment of the safety of the product.

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PROGRESS TOWARDS DEVELOPMENT OF MALARIA VACCINES (INDICATOR SO6.1)

Background

Malaria is caused by five species of *Plasmodium* that infect humans (*P. falciparum, P. vivax, P. ovale spp., P. malariae* and *P. knowlesi*) and is transmitted by the bite of infected female Anopheline mosquitoes. In 2012, over 3 billion people were at risk of malaria; there were an estimated 207 million cases and 627 000 malaria deaths *(1)*. The vast majority of clinical cases (80%) and deaths (90%) occur in sub-Saharan Africa, with children aged under 5 years and primigravid pregnant women most affected *(1)*. According to the latest WHO estimates, malaria mortality rates were reduced by about 45% globally and by 49% in the WHO African Region between 2000 and 2012. During the same period, malaria incidence rates declined by 29% around the world, and by 31% in the African Region *(1)*. Despite these encouraging gains, associated with the scale-up of preventive, diagnostic and treatment measures, new interventions, including vaccines to prevent clinical disease and transmission, are urgently needed *(2)*.

Overview of current efforts

Vaccines currently available and their limitations

Currently, there are no available malaria vaccines. The Malaria Vaccine Technology Roadmap has guided vaccine development efforts since 2006 *(3)*, and in 2013 was updated to be based on extensive consultations with scientists and public health experts from non-endemic and malaria-endemic countries, industry, NGOs and funding agencies *(4)*. The revised Roadmap includes two new strategic goals to be met by 2030: vaccines to achieve malaria elimination in multiple settings and vaccines that are highly efficacious against malaria disease. The Roadmap also includes an updated set of priority areas in research, vaccine development, key capacities, policy and commercialization, where further funding and activities are likely to be crucial for success *(4)*. The original Roadmap contained a 2015 landmark goal for a partly efficacious malaria vaccine yielding reductions in morbidity and mortality, which remains unchanged, and could be achieved by the RTS,S vaccine currently undergoing phase III testing *(4)*.

General approaches to vaccine development for this disease

Vaccines are needed that target all plasmodia species that cause human disease, but most notably *P. falciparum* and *P. vivax (5)*. Vaccines to prevent clinical disease target pre-erythrocytic and/or asexual blood-stage antigens, and are primarily intended for those enduring the greatest burden of disease; whereas, vaccines interrupting malaria transmission primarily target pre-erythrocytic and/or sexual, sporogonic or mosquito-stage antigens, and are targeted to populations at risk of endemic transmission. While it may be possible to develop vaccines that are highly effective at both preventing clinical disease (i.e. cases averted, towards saving lives and preventing disease) and interrupting the cycle of transmission (i.e. transmission interrupted, to support control and elimination), they are associated with distinct clinical end-points, overlapping but different target populations, discrete target product profiles (TPPs), regulatory approval processes and implementation strategies *(5)*.

There are three general approaches to developing malaria vaccines, each of which is supported by biological evidence that protective immune responses are attainable. Pre-erythrocytic vaccines aim to induce antibodies that block hepatocyte invasion by sporozoites and/or cell-mediated immune responses that target infected hepatocytes. Whole parasite and subunit vaccine approaches, evaluated in controlled human malaria infection and/or field efficacy studies, have proven to successfully induce pre-erythrocytic-stage immunity *(6–8)*. The scientific rationale supporting the development of asexual blood-stage vaccines is rooted in the observations that naturally acquired immunity can be passively transferred to susceptible individuals *(9)*. A specialized asexual blood-stage vaccine approach targeting pregnancy-associated malaria aims to leverage observations that parasite prevalence is highest in first pregnancy and

fall profoundly with each subsequent pregnancy *(10)*. Finally, vaccines to interrupt human to malaria transmission originate from studies in avian and primate models where immunization with extracellular gametes totally suppressed infectivity to the mosquito of a subsequent blood meal *(11, 12)*.

Opportunities and challenges (more specific than phase IIb trials)

Challenges in developing highly effective vaccines against *Plasmodium* sp. can be broadly characterized as being specifically associated with our limited understanding of the parasite, or more broadly as by lack of understanding of key vaccinology principles in humans *(5, 13)*. A selection of the leading challenges and associated opportunities for accelerating malaria vaccine development are summarized below *(5)*.

1. Ensuring vaccines under development have the requisite profile to meet global need, outlined in the 2013 Roadmap, is a critical endeavour. These preferred product characteristics will reduce risk and uncertainty for vaccine developers, clarify the priority applications for future malaria vaccines from WHO's perspective, and reduce the burden of future vaccines on immunization programmes in low-income countries by increasing programmatic suitability for use *(4)*. WHO will publish (by the end of 2014) two preferred product characteristics documents specifying the preferred profiles of malaria vaccines to achieve the new strategic goals laid out in the Roadmap *(4)*.
2. The absence of dual market opportunity for malaria vaccines to help offset the development burdens will persist so long as malaria remains a disease of poverty. To minimize development and implementation costs, the prioritization of cost-efficient delivery and adjuvant platforms for which significant safety databases are available from developed world products is an opportunity.
3. The conduct of pharmacovigilance studies for vaccines developed exclusively for use in developing countries is a near-term challenge for RTS,S, if it is recommended for use, as well as next generation vaccines. The strengthening of the routine pharmacovigilance surveillance systems in developing countries and the establishment of a network of pharmacovigilance sentinel sites, including via the Global Vaccine Safety Initiative, will be important to overcoming this challenge.
4. The absence of a clearly defined regulatory approval pathway for sexual, sporogonic or mosquito-stage-vaccines interrupting malaria transmission is a barrier that needs to be overcome in the coming years to inform development strategies. This can be achieved by vaccine developers and other key stakeholders working closely with regulatory authorities, including in endemic counties, and with WHO, to define a licensure pathway. The full exploration of the direct feeding assay – to demonstrate effective blocking of human-to-mosquito transmission at the level of the individual – as licensure end-point will be important, as will standardization of key functional assays (standard membrane feedings assay, direct membrane feeding assay) towards identification of correlates of transmission-blocking immunity.
5. The absence of biomarkers of protection for RTS,S, irradiated sporozoites/mosquitoes, infection-treatment vaccination, and naturally acquired blood-stage immunity continues to slow development progress. The identification of surrogate markers of protection and an increased understanding of the mechanism of protection are needed, which may be achieved via the increased interrogation from human challenge and field efficacy studies, and via the use of systems biology approaches.
6. In view of the large number of potential vaccine target antigens on *Plasmodium* parasites, there has been a limited evaluation of vaccine target antigens to date, particularly in clinical studies. A more systematic interrogation of sporozoite-, liver-, blood-, sexual-, sporogonic- and mosquito-stage antigens for suitability as vaccine antigens is needed.
7. The limited availability of effective delivery systems to induce strong and durable antibody, Th1 CD4+ and CD8+ T-cell responses, in humans, particularly very young children, continues to challenge the broader, trans-vaccinology, community. The leveraging of data on delivery platform and adjuvants from other disease areas, implementation of clearly defined preclinical go/no-go criteria, and maximal use of a controlled human malaria infection model to test the most promising platforms, all represent important opportunities.

8. The absence of reliable preclinical models and functional assays with established relevance to protection in humans represent on-going challenges. The evaluation of models and assays in the context of a search for correlates (i.e. back validation), including improved assays for measuring biological function (such as sporozoite migration and invasion of hepatocytes) blood-stage growth (GIA and ADCI) sequestration of *P. falciparum*-infected erythrocytes in the placenta, and greater consideration of assays monitoring cytotoxic effects of antibodies represent areas of opportunity.

9. The absence of a reproducible challenge model for *P. vivax* that can be broadly implemented will not be resolved until a reliable continuous culture system is established to ensure the availability of well-characterized challenge strains to support establishment of human challenge models and more reproducible functional assays.

Current promising leads, strategies and technologies

Pre-erythrocytic vaccines

RTS,S, a subunit vaccine based on a single parasite antigen (the circumsporozoite protein), which is genetically fused to hepatitis B surface antigen (HBsAg) and formulated with AS01 adjuvant, is the most clinically advanced malaria vaccine. It is currently undergoing phase III evaluation via collaboration between GlaxoSmithKline Vaccines, the PATH Malaria Vaccine Initiative and 13 clinical sites in eight sub-Saharan African countries *(7, 14)*. The phase III study involves two age groups: children aged 5–17 months and 6–12 weeks at the time of enrolment. Safety and efficacy data (reported as the reduction in incidence of first or only episode of clinical malaria), following 12-month follow-up in both age groups, has been published in recent years *(15, 16)*. In late 2013, the 18-month follow-up data were reported at the Multilateral Initiative on Malaria conference in Durban, South Africa *(17)*. Children aged 5–17 months at first vaccination with RTS,S experienced 46% (95% confidence interval [CI], 42–50%) fewer cases of clinical malaria. Severe malaria cases were reduced by 36% (95% CI, 15–51%) and malaria hospitalizations were reduced by 42% (95% CI, 29–52%). Infants aged 6–12 weeks at first vaccination with RTS,S had 27% (95% CI, 20–32%) fewer cases of clinical malaria. The reduction of severe malaria cases and malaria hospitalizations by 15% (95% CI, 0–39%) and 17% (95% CI, -7–36%), respectively *(17)*.

In late 2014, or early 2015, data from a 32-month follow-up from the phase III trial, including the impact of a fourth 'booster' dose given 18 months after the initial three doses, are expected to become available. Pending a positive scientific opinion from the European Medicines Agency (EMA), and the public health information is satisfactory, including safety and efficacy data from the phase III programme, WHO has indicated that a policy recommendation for the RTS,S malaria vaccine candidate is possible at the end of 2015, paving the way for decisions by African nations regarding large-scale implementation of the vaccine through their national immunization programmes.

Strategies to directly build upon the success of RTS,S via the induction of humoral and cell-mediated immune responses to circumsporozoite proteins and other antigens, have been under way for many years. The scientific rationale for these studies is that a significant proportion of RTS,S-immunized volunteers not protected following controlled challenge display evidence for immunity, as determined by a delay to parasitaemia that correlates with a >90% reduction in parasites exiting the liver *(18)*. Currently, there is a significant focus on translational research studies to evaluate whether vaccine approaches that induce strong cell-mediated immune responses are able to enhance protective efficacy (Table 23, below).

In recent years, two of the most significant advances in the quest to develop highly efficacious pre-erythrocytic vaccines have been: 1) demonstration that radiation attenuated *P. falciparum* sporozoites, administered via direct intravenous inoculation, can confer high levels of protection from infection in controlled human malaria infection studies *(19)*; and 2) vector-based vaccine approaches, targeting multiple antigens, conferred modest levels of protective efficacy in controlled human malaria infection studies *(20, 21)*. In addition to replicating initial findings in larger numbers of volunteers, evidence for sustained protection (via delayed challenge), and for cross-strain protection (via heterologous challenge), will be important next steps. One of these approaches (ChAd63/MVA ME-TRAP), has already advanced to field testing with encouraging initial efficacy data based on an infection end-point using PCR detection *(22)* (Table 23).

Blood-stage vaccines

While immunity to asexual blood-stage antigens is an important mechanism of natural immunity to malaria in endemic regions, defined biomarkers of protection remain elusive. In recent years, preliminary evidence for vaccine-induced clinical efficacy from field studies has been generated using three blood-stage targets, *P. falciparum* AMA1, MSP3 and SERA5 *(23–25)* (Table 23).

However, as with similar preliminary findings for other antigens, such as MSP2, further studies are needed to confirm these initial findings *(26)*. Additional antigens are currently undergoing phase I and II development, with data expected in the coming years *(24, 25)*. Efforts to develop highly effective subunit vaccines targeting asexual blood stages has been buoyed by progress in deciphering the redundant network of merozoite invasion mechanisms for *P. falciparum,* revealing promising new vaccine targets *(27)*.

For *P. vivax*, the challenge of effectively targeting merozoite invasion ligands appears to be less complex, with the Duffy binding protein (DBP) representing the overwhelmingly dominant invasion ligand for ensuring reticulocyte invasion. Protein and vector-based vaccines are expected to enter clinical testing over the coming years. Further, whole blood-stage vaccines for *P. falciparum* (killed and attenuated) are advancing towards clinical development based on promising preclinical data *(28)*. The most advanced pregnancy-associated malaria vaccine approaches, although still at the preclinical stage, target var2CSA, which is preferentially expressed by placental parasites and is the target of acquired immunity over successive pregnancies *(29)*.

Sexual, sporogonic and mosquito-stage vaccines

Clinical studies to evaluate on induction of antibodies to sexual, sporogonic or mosquito-stage antigens, to block human to mosquito transmission, have to-date focused on two antigens (Pfs25 and Pvs25) delivered as either recombinant proteins or via attenuated vaccinia virus; however, high levels of transmission-blocking activity have not been reported *(30–32)*. A promising new Pfs25 construct, whereby the Pfs25 gene is genetically fused to alfalfa mosaic virus capsid protein to produce chimeric virus-like particles (VLPs) in plants, recently entered initial clinical evaluation *(33)*. Additional target antigens, including Pfs48/45, Pfs230, HAP2 and AnAPN1, have been associated with promising preclinical data.

Future directions

A. Short-term goals (within two years)

- Successful achievement of the 2015 Landmark Goal of the 2006 Malaria Vaccine Technology Roadmap[3], and maintained in the 2013 revision of Roadmap *(34)*, would be a pivotal milestone for the malaria vaccine development community. In late 2013 it was reported that GlaxoSmithKline intends to submit a regulatory application to the EMA. WHO has indicated that a policy recommendation for the RTS,S malaria vaccine candidate is possible as early as 2015 if it is granted a positive scientific opinion by EMA.
- To support the malaria vaccine development, WHO intends to publish (by end of 2014) two preferred product characteristics documents specifying the preferred profiles of malaria vaccines to achieve the new strategic goals in the 2013 Roadmap *(4)*.
- According to a recent malaria research and development funding report, "From Pipeline to Product", which estimates the funding needs over the next decade to ensure product development goals in the drug, diagnostic, vector control and vaccine areas, approximately US$ 1.8–2.7bn will be needed for vaccines (US$ 5.5–8.3bn in total) *(35)*. At the present time there is a very notable deficiency in the level of funding to support the development of *P. vivax* vaccines. The community is unlikely to achieve its 2030 goals, outlined in the 2013 Roadmap *(34)*, unless there is significant and sustained investment in this area over the next couple of years.
- Challenges remain in defining the development pathway for vaccine approaches where the end-points are reduced transmission at the level of a community (i.e. sexual, sporogonic or mosquito-stage-vaccines interrupting malaria transmission). Timelines and development costs to reach licensure may be significantly reduced, however, if an analytical end-point (i.e. prevention of infection of mosquitoes in laboratory-based assays) is able to support product licensure with true efficacy and/or effectiveness data collected during post-approval studies. Extensive dialogue with regulatory authorities and national stakeholders in endemic countries will be needed over the coming years to establish an appropriate and practical licensure pathway.

B. Mid-term goals (by 2020, end of the Decade of Vaccines; may or may not include licensure)

- To ensure that the community is on-track to achieve its 2030 goals (outlined below), it will be necessary, by approximately 2020, to have supportive evidence, such as via proof-of-principle controlled human malaria infection studies, that the requisite level of vaccine efficacy, including durability and cross-strain protection, can be achieved. It is likely that initial evidence will be generated via translational research studies, and therefore adaptation of the approach to satisfy the requirements of the preferred product characteristics.

C. Long-term goals (beyond 2020, if applicable)

- The vision and long-term goals of the malaria vaccine development community are described in The Malaria Vaccine Technology Roadmap *(34)*. By 2030, license vaccines targeting *P. falciparum* and *P. vivax* that encompass the following two objectives, for use by the international public health community:

i. Development of malaria vaccines with protective efficacy of at least 75% against clinical malaria suitable for administration to appropriate at-risk groups in malaria endemic areas; and
ii. Development of malaria vaccines that reduce transmission of the parasite and thereby substantially reduce the incidence of human malaria infection. This will enable elimination in multiple settings. Vaccines to reduce transmission should be suitable for administration in mass campaigns *(4, 34)*.

Discussion

While current malaria control methods, including the use of insecticide impregnated bed-nets, insecticide residual spraying and improved diagnostic and treatment methods, have reduced the global burden of malaria significantly over the past decade, there is still a pressing need for effective malaria vaccines, both as tools to accelerate malaria elimination and to enhance malaria control, especially in the face of threats from emerging vector and parasite resistance to existing control tools.

Currently there is one malaria vaccine (RTS,S/AS01) in a phase III trial. The trial is being conducted in 11 centres in seven sub-Saharan African countries, with a wide range of malaria transmission intensities, varying from 0.01 to 2 clinical episodes of malaria per child per year. The trial has two parallel components, the first involving vaccination of children enrolled between the ages of 5 and 17 months, and the second involving children given the RTS,S vaccine with other infant vaccinations as part of the EPI programme *(36)*.

Results from the trial, in each age category, have been published for one year of follow-up after the third vaccine dose *(37, 38)* and recently results have been made available for 18 months of follow-up. After 18 months of follow-up, vaccine efficacy was found to be higher, against all trial end-points, for children vaccinated in the older age category. Efficacies of 46%, 36%, 42% and 19% were observed against the end-points of clinical malaria, severe malaria, malaria hospitalization and all-cause hospitalization, respectively. All of these efficacies were statistically highly significant. In contrast, the corresponding efficacies following vaccination in the younger age category were 27%, 15%, 17% and 6%, respectively, and only the first was statistically significant. Results have been analysed separately for the 11 sites involved in the trial and the efficacies appear broadly similar across sites, despite a wide range of transmission levels. Thus, the cases of malaria prevented, per 1000 children vaccinated, in the 18 months following vaccination, varies substantially across different trial sites – in the older children from 37 to 2365, and in the younger infants from -10 to 1402. It appears, therefore, that the public health value of the vaccine is likely to be greatest in areas with the highest malaria transmission level.

An important feature of the vaccine is that efficacy appears to wane substantially in the 18 months following vaccination. In older children the vaccine efficacy was 68% over the first 6 months, waning to 51% and 46% when considered over the first 12 and 18 months, respectively. As an additional analysis, the reduction in incidence in the same 5–17 month age group, were compared between the RTS,S group and the control group in the three 6-month periods following vaccination. The figures were 68%, 41% and 26% indicating that a degree of protection persists for 18 months, and that protection may not last much beyond 18 months. Half of those in the vaccinated groups were given a booster vaccination at 18 months and the results of one-year follow-up after the booster dose will be available in late 2014. These results will be important for assessing the potential utility and deployment of the vaccine as a malaria control measure. Key questions are: *(1)* Will the booster dose restore

efficacies to the levels seen after primary course? *(2)* Will the decline in efficacy after the booster dose mirror that seen after primary course? *(3)* Will the booster dose to those with primary course with the EPI vaccines bring efficacy up to the level of that seen in those who received primary course as older children?

Decisions on the licensure and recommendations for any initial use of the RTS,S vaccine are likely to be made by the end of 2015 to early 2016. Currently it appears that efficacy is superior in those vaccinated at 5–17 months of age compared to the 6–12 week age category. (There are no data from the trial on administration beyond age 17 months.) Efficacy is waning substantially by 18 months post-vaccination, and hence the booster dose data will be important. While the original target group for vaccination was infants aged 6, 10 and 14 weeks (because of the relative ease of integrating vaccination with other EPI vaccines), the published results raise the question of implementation in children aged 5–17 months.

WHO is commissioning work to model the proportion of malaria hospitalizations 'missed' by different possible vaccination schedules. It is likely that if use is recommended by WHO (in late 2015 or early 2016), this will be in relation to some minimal level of transmission. In the event of licensure of the vaccine, district-scale studies will be desirable to better characterize risk/benefit and to measure impact on mortality when the vaccine is used on a widespread scale.

If RTS,S is licensed for use, some design issues will have to be addressed with respect to trials of second generation malaria vaccines, particularly with respect to the inclusion of placebo groups in trial designs. Ethical issues in the use of placebos in such situations, where a partially efficacious vaccine already exists, were considered in a recent WHO consultation *(39)*.

Table 23: Development status of current vaccine candidates

Candidate name/Identifier	Preclinical	Phase I	Phase II*	Phase III
Pre-erythrocytic projects				
RTS,S/AS01E				X
RTS,S/AS01 delayed fractional third dose		X		
Adenovirus (Ad35) vectored CS and RTS,S-AS01 in heterologous prime-boost regimen		X		
ChAd63/MVA ME-TRAP			X	
ChAd63/MVA ME-TRAP + Matrix M™		X		
PfSPZ		X		
polyepitope DNA EP1300		X		
Adenovirus (Ad35) and adenovirus 26 (Ad26) vectored CS in heterologous prime-boost regimen		X		
PfCelTOS FMP012		X		
CSVAC		X		
ChAd63/MVA (CS; ME-TRAP		X		
ChAd63/MVA (CS; ME-TRAP, AMA-1)		X		
RTS,S/AS01B + ChAd63 and MVA encoding ME-TRAP		X		
Blood-stage projects				
EBA175 RII		X		
FMP2.1/AS01B (AMA-1 3D7 *E.* coli expressed in ASO1B adjuvant)		X		
GMZ2		X		
GMZ2 field			X	

Candidate name/Identifier	Preclinical	Phase I	Phase II*	Phase III
PfAMA1-DiCo		X		
P27A		X		
MSP3 [181-276] field			X	
SE36		X		
ChAd63 AMA1/MVA AMA1		X		
NMRC-M3V-Ad-PfCA		X		
NMRC-M3V-D/Ad- PfCA Prime/Boost		X		
ChAd63/AMA MVA/AMA1 +Alhydrogel®/CPG7909		X		
PfPEBS		X		
ChAd63 MSP1/MVA MSP1		X		
Sexual-stage projects				
Pfs25-EPA		X		
Pfs25 VLP		X		
***P. vivax* project**				
ChAd63/MVA PvDBP		X		

* Phase II comprises studies of a candidate vaccine that are intended to result in efficacy data in the target population to whom the vaccine would be administered should it eventually by licensed. A programme of phase II studies usually defines the preferred dose, route and schedule of immunizations that are eventually evaluated for efficacy. Phase II studies also provide an expanded population assessment of the safety of the product.

Source: WHO/NIAID/BMGF, unpublished data, available at: http://www.who.int/entity/immunization/research/development/Rainbow_Table_Dec2013_Summary_Version.xls?ua=1.

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PROGRESS TOWARDS DEVELOPMENT OF HIV VACCINES (INDICATOR SO6.1)

Background

Since the identification of HIV as the cause of AIDS, the pandemic has caused extensive global morbidity and mortality. In 2012 alone, the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that 35.3 million persons are living with HIV, with 2.3 million new infections and 1.6 million deaths annually *(1)*. HIV remains a major global killer, with sub-Saharan Africa continuing to bear the greatest burden of disease. Transmission of HIV occurs through sexual intercourse, injection of blood or blood-derived products, and from mother-to-child during pregnancy, at delivery or through breastfeeding. Despite significant advances in HIV antiretroviral development and delivery, and new prevention technologies, the development of a safe and effective HIV vaccine for prevention and control of AIDS remains a global public health priority and the best hope for eventually ending the AIDS pandemic.

Overview of current efforts and lessons from human efficacy trials

Multiple HIV vaccine concepts have been developed and tested clinically since 1986 (see Table 24), yet only four concepts have completed efficacy trials, with only one providing evidence for prevention of acquisition of HIV *(2)*. The first HIV vaccine to be assessed in efficacy trials was a monomeric envelope (Env) outer glycoprotein of HIV (gp120; VaxGen) formulated in alum, which aimed to elicit protective antibodies against HIV. However, this candidate failed in human trials to prevent or control HIV infection *(3)*. The next candidate in efficacy trials aimed to control infection by eliciting cellular immune responses to multiple antigens of HIV delivered via an Adenovirus type 5 vector (Ad5-gag-pol-nef; Merck). However, not only did this candidate vaccine fail to control HIV infection when assessed in efficacy trials, it surprisingly led to acquisition of greater numbers of HIV infections in the vaccine versus placebo group, for reasons that to-date remain unclear *(4)*.
The third candidate to advance to efficacy trials aimed to combine cellular and humoral immunity, using a prime-boost regimen of a Canarypox vector + gp120 boost (ALVAC® – Sanofi Pasteur; gp120 – Vaxgen).
In a community-based efficacy trial conducted in Thailand (termed RV-144), this candidate demonstrated for the first time, albeit modestly, that prevention of acquisition of HIV infection with a vaccine was possible, with 31.2% efficacy achieved *(5)*. Extensive efforts have been on-going to determine immune correlates from the RV-144 trial, with binding of IgG antibodies to the variable regions 1 and 2 (V1V2) of Env correlating inversely with the rate of HIV-1 infection *(6)*.
Most recently, another prime-boost regimen, this time using DNA prime + Ad5 vector boost, delivering gag-pol-nef and multiple Env genes (DNA + Ad5 HIV vaccine; National Institute of Allergy and Infectious Diseases', NIAID, Vaccine Research Center), failed to prevent or control HIV infection *(7)*.

Current efforts in HIV vaccine development include building from the RV-144 efficacy trial results, and developing candidate vaccines that elicit broad and long-lived protection against HIV. The preclinical and clinical pipeline is now beginning to be filled with a set of more promising new vaccine candidates. Plans are under way to test the prime-boost regimen ALVAC + gp120 in South Africa, with additional booster immunizations aimed at extending durability of protection, and a more potent adjuvant (MF-59; Novartis), with the aim of increasing the level of protection. If vaccine efficacy of >50% is demonstrated, licensure application in South Africa is possible as early as 2021. In addition, test of concept efficacy trials are now under consideration for prime-boost regimens utilizing next generation pox vectors (NYVAC; Sanofi Pasteur), gp120 boosters, and DNA in adaptive clinical trials. The Pox-Protein Public-Private Partnership, consisting of Sanofi Pasteur, Novartis, NIAID, the Bill & Melinda Gates Foundation, U.S. Military HIV Research Program [MHRP] and the HIV Vaccine Clinical Trials Network are coordinating the planning of these next set of efficacy trials, potentially to include a trial of the RV-144 vaccine regimen in a high-risk population of men who have sex with men in Thailand.

In parallel, vaccine development is on-going with candidates aimed at addressing the hyper-variability of HIV, which is one of the major challenges impeding the development of a safe and effective HIV vaccine

(see below, *Opportunities and challenges*). Two principal approaches to elicit broad cellular immune responses aimed at controlling HIV infection have recently entered phase I clinical trials. The first utilizes conserved regions across the HIV genome expressed in DNA or viral vectors, with the goal of focusing immune responses elicited by the vaccine to those regions of HIV that are highly conserved and therefore may be required for viral replicative fitness *(8)*. The second, termed "mosaic antigens" uses *in silico* methods to design immunogens representing conserved and variable sequences from as many HIV strains as possible in a vaccine, for broad coverage of circulating viruses, expressed in Ad26 vectors *(9)*. Lastly, preclinical studies with genetically modified cytomegalovirus vectors have demonstrated the unique potential to elicit both MHC-class I and MHC-class II CD8+ effector memory cells, target a much greater number of simian immunodeficiency virus (SIV) epitopes than other vectors, and control SIV to undetectable levels in approximately 50% of macaques immunized with CMV-SIV vaccines *(10)*. These studies, along with natural history studies of humans who control HIV infection (termed elite controllers), are providing clues towards understanding how best to elicit cellular immune responses to control and possibly abort HIV infection.

Along with efforts to optimize cell-mediated immune responses for control of HIV infection, there has been significant progress in strategies to elicit broadly neutralizing antibodies (bnAbs) against HIV Env capable of preventing acquisition of HIV infection. Studies in HIV+ subjects have shown that about 5% develop both broad and potent neutralizing antibodies against HIV *(11)*. Recent technological advances in B cell immunology, next generation sequencing and bioinformatics, have now yielded several bnAbs, their binding sites on HIV Env, the structural characteristics of these binding sites with atomic precision, the structure of the HIV Env trimer, which is the target for bnAbs, and insights on the evolution of bnAbs in HIV+ subjects *(12–14)*. Moreover, structure-based vaccine design studies with respiratory syncytial virus *(15)*, coupled with passive protection studies with bnAbs in monkeys *(16)* have together provided proof-of-principle that structure-based HIV vaccine design to elicit bnAbs may be feasible. Designing immunogens to elicit bnAbs remains a major challenge; so in parallel, passive antibody and adeno-associated virus based delivery of bnAbs have recently entered clinical trials *(17, 18)*.

Finally, since the RV-144 trial showed that HIV acquisition could be prevented without bnAbs or robust CD8+ cellular immune responses, studies are on-going to develop vaccines which elicit other antibody effector mechanisms such as Fc mediated antibody dependent cellular cytotoxicity *(19)* or CD4-based cellular immune responses *(20)*.

Opportunities and challenges

HIV presents multiple challenges to vaccine developers. These include: 1) hyper-variability; HIV exhibits a remarkable degree of genetic variability in the individual, and worldwide is characterized by multiple clades and circulating recombinant forms. This variability enables the virus to rapidly escape antibody and cellular immune responses and thus, an effective HIV vaccine will need to protect against the spectrum of globally diverse circulating isolates of HIV; 2) the lack of an ideal animal model for HIV/AIDS, coupled with lack of correlates of protection, makes it difficult to select and prioritize vaccine candidates for further development; 3) natural immunity fails to clear HIV infection, suggesting that vaccine-induced protective immune responses may need to be qualitatively and quantitatively different than natural immune responses; 4) HIV is a retrovirus which integrates into the host genome, thus providing a very short window of opportunity for immune intervention to clear the small foci of infection immediately following transmission, before virus amplification seeds the reservoir of cells which creates a lifelong persistent infection; 5) the vast majority of HIV transmission is sexual, occurring at mucosal sites, which present additional challenges for maintenance of durable protective immune responses; 6) HIV targets cells of the immune system, specifically CD4+ cells which orchestrate vaccine induced immune responses; and, 7) bnAbs against HIV are rare, take years to elicit, and have characteristics such as long CDRH3 regions, high-levels of somatic mutation away from germ-line, and in some cases poly-reactivity, suggesting elicitation of such antibodies by immunization will be quite challenging until more is understood about ways to drive affinity maturation of bnAbs.

Despite these challenges, the outlook is promising for continued advances in HIV vaccine development over the next few years. First of all, feasibility for prevention of acquisition of HIV infection has been demonstrated in humans by the RV-144 regimen and with multiple vaccine regimens in monkeys, using SIV or SHIV challenges. Second, as indicated above, a small percentage of HIV+ subjects ('elite neutralizers')

develop broad and potent neutralizing antibodies against HIV, demonstrating that it should be possible to elicit such neutralizing antibody responses by immunization. Third, a different small percentage of HIV+ subjects ('elite controllers') can control HIV infection without antiretroviral drugs. Control is largely associated with components of the adaptive immune system, suggesting that vaccination may also be able to control HIV infection. Fourth, the recent observations that CMV-based SIV vaccines can elicit immune responses that not only control but, in some cases, clear SIV infection hold promise for comparable HIV vaccines. Lastly, demonstration that passive administration of neutralizing antibodies to macaques, or by adeno-associated virus (AAV) delivery can prevent SHIV and SIV infection respectively, suggest additional avenues for prevention of HIV infection.

Current promising leads, strategies and technologies

Since the HIV vaccine field likely will not see data emerging from the next planned set of efficacy trials until 2019-2020, current promising leads, strategies and technologies are focused on advancing leading candidates through clinical development and improving the next generation of candidates entering clinical development. These include:

- HIV Env trimers: The recent generation of the structure of a stabilized HIV Env trimer *(13)* will lead to the first clinical testing of HIV Env trimers more closely mimicking the native HIV Env trimeric structure in the next 2–3 years.
- HIV epitope-based vaccines: The recent elucidation of at least four major epitopes on HIV Env that are the binding sites for bnAbs will lead to the generation of clinical candidates targeting each of these epitopes *(12)*, including glycopeptides, computationally derived scaffolds and novel immunogens designed to bind to the putative germ-line ancestor of the bnAbs.
- Sequential immunization with different immunogens: The recent elucidation of bnAbs evolution along with virus evolution in the human host *(14)* will lead to the testing of the hypothesis that sequential immunization with different immunogens may be required to drive antibody affinity maturation leading to bnAbs.
- Conserved/Mosaic hybrids: Next generation immunogens to elicit broad cellular immune responses will take advantage of the attributes of both conserved and mosaic antigens, to provide breadth, depth and enhanced coverage of cellular immune responses by immunization.
- Replication competent viral vectors: Several vectors are in preclinical and early clinical development, including vectors providing persistent infection, mucosal delivery and targeting of the gut-associated lymphoid tissues, designed to mimic the efficacy of live attenuated vaccines.
- Antigen presentation systems and novel adjuvants: Several virus-like particle and nanoparticle antigen presentation systems are in development, along with novel adjuvants, building on the recent advances in understanding innate and adaptive immune linkages to optimize vaccine induced immunity.
- Synthetic biology technologies: Novel nucleic acid vaccines, both DNA and RNA, are being explored, in efforts to achieve the efficacy of viral vectors, while mitigating concerns for anti-vector immunity.
- Clinical evaluation of passively administered bnAbs: Passive immunization strategies may provide proof of principle in humans and information regarding the level and specificity of antibodies required for protection.
- Genetic and immune monitoring technologies: New technologies including but not limited to systems biology, next generation sequencing, bioinformatics and single cell assessments with cytometry by time of flight mass spectrometry (CyTOF) collectively are guiding next generation vaccine design by identifying new immune response parameters associated with protective immune responses.
- Glycobiology: Advances in glycobiology are yielding important insights for HIV vaccine research, both in characterization and synthesis of targets recognized by bnAbs, and in strategies to manipulate vaccine induced Fc mediated immune responses such as ADCC.

Future directions

In the near term, clinical development of the leading candidate vaccines will continue to optimize vaccination regimens in order to pursue potential licensure and to gain additional information on correlates of protection. In parallel, there is a rich pipeline of vaccine candidates in or about to enter phase I trials. In addition to clinical development of those candidates that show promise in phase I, a number of small experimental medicine trials are planned to address leading hypotheses about how to elicit protective human immune responses. Preclinical

testing of novel viral vectors, immunogen designs and basic research on key immunology questions are expected to lead to increased knowledge to aid design and development of effective preventative HIV vaccines. In the mid-term, these new approaches will lead to a rich and diverse pipeline of candidate vaccines, with the long-term view of licensing a safe and effective HIV vaccine with at least 50% efficacy in preventing infection, suitable for deployment in regions of the world where the epidemic is most severe.

A. Short-term goals (within two-years)

- Phase IIb/Efficacy trials:
  - Initiate follow-up efficacy trials to determine if the RV-144 efficacy results can be reproduced in high-risk populations and potentially be enhanced by adjuvants and regimen modifications. Continued assessment of samples from RV-144 and HVTN 505 with an aim towards greater understanding of immune correlates.
  - Advance at least one other HIV vaccine candidate to phase IIb trials.

- Phase I clinical trials:
  - If prototype candidates achieve go-no-go milestones, advance passive antibody and AAV delivery of bnAbs to additional phase I trials and initiate development of cocktails of bnAbs (for passive delivery) and/or AAV vectors for gene delivery.
  - If prototype-replicating vectors are successful in on-going clinical trials, initiate development of replicating vectors incorporating the latest concepts in antibody and T-cell immunogens.
  - Advance the first of a series of immunogens mimicking the native HIV trimer to clinical trials.
  - Advance the first of a series of HIV Env-based epitope immunogens to experimental medicine trials.
  - Gain additional clinical data on HIV conserved and mosaic antigens delivered by viral vectors, and if promising, advance to the next phase of clinical development.
  - Advance a prototype human CMV vector to phase I clinical trials.
  - Initiate first in a series of experimental medicine trials aimed at assessing whether germ-line engagement and sequential immunization of related but different immunogens increases potential for driving affinity maturation towards broadly neutralizing antibodies.

- Clinical research:
  - Continue natural history studies of cohorts in developing countries to optimize next generation antigen designs to be included in vaccine candidates.

- Preclinical research:
  - Assess available humanized mouse models to determine if they can be used to prioritize HIV vaccine candidates for clinical testing.
  - Develop additional pathogenic SHIVs from multiple HIV clades for assessing HIV Env-based immunogens in monkeys.

B. Mid-term goals (by 2020, end of the Decade of Vaccines)

- Phase IIb/Efficacy trials:
  - efficacy data from on-going RV-144 follow-on trials and if successful, elucidation of correlates of protection;
  - data from at least one other phase IIb/efficacy trial;
  - feasibility of passive bnAbs to protect against HIV infection;
  - at least two additional candidates combining the most promising platforms and immunogen design strategies advance to phase IIb/efficacy trials.

- Phase I clinical trials:
  - Demonstration in phase I trials that new immunogen designs to elicit cellular immune responses are significantly better than prior candidates and warrant advancement to efficacy trials +/- HIV Env-based immunogens.
  - Advance HIV Env immunogen formulated with a novel adjuvant to clinical trials.

- Clinical research:
  - Increase understanding of mechanisms for protection in 'elite controllers'.
  - Elucidation of immunization strategy to drive antibody affinity maturation.
  - Elucidation of immunization strategy to maintain durable responses against HIV Env.

- Preclinical research:
  - Identification of the first immunogen(s) that elicit bnAbs in preclinical models, leading to definition of characteristics of both immunogen and regimen capable of eliciting bnAbs.
  - Design of vaccine prime-boost regimens to simultaneously optimize both cellular and neutralizing antibody responses.
  - Elucidation of how to elicit CD8+ responses to subdominant, protective epitopes.

C. Long-term goals (beyond 2020)

- Licensure:
  - Contingent on achieving >50% efficacy, licensure of first HIV vaccine for deployment in regions of the world hardest hit by the epidemic.

- Phase IIb/Efficacy trials:
  - Data gathered from mid-term phase IIb efficacy trials.
  - Next set of candidates advance to efficacy trials.
  - First HIV vaccine candidate demonstrates capacity to control HIV infection.
  - First HIV vaccine candidate demonstrates >50% efficacy in prevention of HIV acquisition.
- Phase I clinical trials:
  - First HIV vaccine elicits bnAbs in humans.
  - Improved vaccine candidates emerge from preclinical research and enter phase I trials.

Table 24: HIV vaccines clinical trials – the Rainbow Table

Phase I: HIV vaccines		Phase II: HIV vaccines		
Prime	**Boost**	**Prime**	**Boost**	
Ad26 Env A	Ad26 Env A	Ad 5 Gag-Pol, Env A/B/C	Ad 5 Gag-Pol, Env A/B/C	
Ad35 Env A	Ad5 Env A	DNA (HIVIS) Gag, Rev, RT, Env A/B/C	MVA (CMDR) Gag-Pol, Env E	
Ad5 Env A	Ad48 Env A	Canarypox (ALVAC) Env B/E	Protein (AIDSVAX®) Env gp120 B/E	
Ad26 Env A	Ad35 Env A	DNA (Geovax) Gag, PR, RT, Tat, Rev, Env B	MVA (HIV62) Gag, Pol, Env B	
Ad35 Env A	Ad5 Env A/B	DNA Gag, Pol, Env B'/C	Tiantan Vaccinia Gag, Pol, Env B'/C	
*MVA Mosaic vs natural	Ad26 Mosaic vs natural	*Protein Env gp120 B/E (AIDSVAX®)	Protein Env gp120 B/E (AIDSVAX®)	
*DNA Env Mosaic vs consensus vs natural	MVA Env Mosaic vs consensus vs natural	*DNA Env C	NYVAC Env B	Protein Env gp120/ MF59
MVA (CMDR) Gag-Pol, Env E	MVA (CMDR) Gag-Pol, Env E			
*Canarypox (ALVAC) Env B/E	Protein + MF59 Env gp120 B/E (AIDSVAX®)			
Electroporated DNA (Ichor/ HIVMAG+ GENEVAX®) Gag-Pol, Nef-Tat-Vif, Env B + IL-12	Ad35 Gag-RT-Int-Nef, Env A (GRIN-Env)			
Protein F4Co/AS01b or AS01E	Ad35 Gag-RT-Int-Nef (GRIN)			
DNA Gag, Pol-Nef Env C	NYVAC Gag, Pol-Nef Env C			
DNA (Pennvax) Gag, Env A/C/D	MVA (CMDR) Gag-Pol, Env			
DNA (Geovax) Gag, PR, RT, Tat, Rev, Env B + GMCSF	MVA Gag, Pol, Env B			
DNA (Pennvax) + IL-12 Gag, Pol, Env B	DNA (Pennvax) + IL-12 Gag, Pol, Env B			

KEY:

- Adenovirus
- Poxvirus
- DNA
- Protein
- Replicating vector (adenovirus, poxvirus, VSV, SeV)
- Monoclonal antibody protein or vector

Phase I: HIV vaccines			Phase II: HIV vaccines	
Prime	**Boost**		**Prime**	**Boost**
DNA Env A	Ad35 (VRC) Env A	Ad5 Env A		
DNA HIVconsv	MVA HIVconsv	ChAdV63 HIVconsv		
DNA (SAAVI) Gag, RT, Tat, Nef, Env C	MVA Gag, RT, Tat, Nef, Env C	Protein Env gp120+ MF59		
DNA Gag, Env, Pol-Nef C	NYVAC Gag, Env, Pol-Nef C	Protein Env gp120 B,E (AIDSVAX*)		
DNA Gag, Pol, Nef , Env C	MVA Gag, Pol, Nef	Protein gp140 Env C +GLA-AF		
*DNA HIVconsv	MVA HIVconsv	Ad35 (IAVI) Gag-RT-Int-Nef (GRIN)		
DEC-205-p24gag	DEC-205-p24gag			
gp140 Env C/MF59	gp140 Env C/MF59			
Tat + delta V2 Env	Tat + delta V2 Env			
Env gp41 (FPA2)	Env gp41 (FPA2)			
Env gp41 (UGR7C)	Env gp41 (UGR7C)			
Env C gp140 (CN54)	Env C gp140 (CN54)			
DNA (HIV-MAG) Gag-Pol, Nef-Tat, Vif, Env B	VSV Gag			
Ad4 Gag, Env C	Ad4 Gag, Env C			
SeV Gag	Ad35 Gag-RT-Int-Nef (GRIN)			
VSV Gag	VSV Gag			
AAV1.mAb PG9				
VRC01 mAb				

KEY:

- Adenovirus
- Poxvirus
- DNA
- Protein
- Replicating vector (adenovirus, poxvirus, VSV, SeV)
- Monoclonal antibody protein or vector

* Trial scheduled to start 2014.

Source: WHO/NIAID/BMGF; unpublished data.

Discussion

At the 2014 Global Vaccine and Immunization Research Forum (GVIRF), Koff and Dean, from IAVI, reviewed the status of vaccine research and development for HIV *(21)*. It is clear that despite the availability of multiple behavioural and biomedical preventive interventions the goal of controlling the HIV/AIDS epidemic will depend on the development of a preventive HIV vaccine *(22)*. Recent modelling work suggests that a full scale-up of existing preventing tools will fall short of reaching the goal, and that even a moderately effective vaccine will be critical to the global effort to stop the HIV pandemic *(22)*.

However, the development of an HIV vaccine is confronting a number of unique scientific challenges *(21, 23)*, including the short durability of the vaccine-induced immune responses *(24)*. Despite these difficulties, more than 200 clinical trials have been conducted since 1998 which have sequentially explored three different paradigms: induction of neutralizing antibodies, induction of cell-mediated immunity and exploration of combination approaches and novel concepts *(25)*. Although major progress has been made in understanding the scientific basis for HIV vaccine development, efficacy trials have been critical in moving the field forward. In 2009, the field was reinvigorated with the modest efficacy obtained from the RV-144 trial conducted in Thailand.

Thirty years of HIV vaccine research has taught us a few lessons: a) The development of an HIV vaccine is one of the most difficult challenges that biomedical research is confronting; however, proof of concept that this is an achievable goal has been obtained; b) The temptation of just 'following the fashion', or commonly accepted paradigm, should be avoided; c) Clinical trials are critical, especially large-scale efficacy trials; d) HIV vaccine research requires long-term commitment and funding; and e) Sustainable collaborations from multiple partners, such as those that should be catalysed by the Decade of Vaccines, are needed to accelerate the development of an HIV vaccine *(26)*.

In order to accelerate progress in the development of a much-needed HIV vaccine, a multipronged approach needs to be implemented with the necessary sense of urgency. Things to do include: a) establish and maintain a programme of innovative research with protected funding to explore out-of-the-paradigm approaches, perhaps representing 10% of WHO's total HIV vaccine research and development budget; b) continue supporting the basic research effort, exploring novel opportunities to conduct translational research, including the implementation of small-scale experimental medicine trials; c) assume the ambitious goal of initiating a certain number of well-coordinated efficacy trials in the next five years. That discussion will organize thinking regarding key scientific questions, vaccine manufacturing capacity, access to and preparation of trial populations and, of course, funding issues; d) Design appropriate strategies and trials to answer lingering questions in the field, such as the potential protective efficacy of vaccines against different HIV clades and routes of transmission; e) strengthen the global HIV vaccine architecture, supporting the roles that different national, regional and global organizations play, with the Global HIV Vaccine Enterprise playing a coordinating role *(27)*; and f) bring new partners to the HIV vaccine field and strengthen interactions with other organizations that work in the HIV prevention arena.

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PROGRESS TOWARDS A UNIVERSAL INFLUENZA VACCINE (INDICATOR SO6.2)

Context

Influenza is an acute viral infection caused by the influenza virus. There are three types of human influenza – A, B and C, but infections with type C are uncommon. Type A influenza viruses are further classified into subtypes according to different combinations of the virus surface proteins haemagglutinin (HA) and neuraminidase (NA). While there are 18 different HA subtypes and 11 different NA subtypes found in nature (primarily in wild bird populations) only two influenza A viruses subtypes (H1N1 and H3N2) and two antigenically distinct influenza B virus lineages (Yamagata and Victoria) circulate in human populations.

Influenza epidemics occur yearly during autumn and winter in temperate regions. Worldwide, these annual epidemics result in about 3 to 5 million cases of severe illness, and about 250 000 to 500 000 deaths. Illnesses result in hospitalizations and deaths mainly among high-risk groups (the very young, pregnant women, elderly or chronically ill). Most deaths associated with influenza in industrialized countries occur among people age 65 or older. In some tropical countries, influenza viruses circulate throughout the year with one or two peaks during rainy seasons. There is a paucity of data on influenza transmission patterns in tropical countries.

Influenza pandemics arise when animal influenza viruses adapt to human hosts. In 2009, the reassortment of several human, swine and avian influenza viruses resulted in the emergence of the pandemic influenza A 2009 H1N1 (pdm) virus. In the 20th century, pandemics occurred in 1918 (H1N1), 1957 (H2N2), 1968 (H3N2), and 1977 (reintroduction of H1N1). During the 1918 pandemic, it is estimated that the global death toll exceeded 20–25 million. The sporadic occurrence of human infection with avian influenza subtypes (e.g. H9, H7 and particularly H5) have led to concerns about the possibility of influenza pandemics with increased morbidity and mortality.

The most effective way to prevent the disease or severe outcomes from the illness is vaccination. Safe and effective vaccines have been available and used for more than 60 years. Among healthy adults, influenza vaccine can prevent 70% to 90% of influenza-specific illness. Among the elderly, the vaccine reduces severe illnesses and complications by up to 60%, and deaths by 80%. However, vaccine efficacy varies greatly from year to year, spurring numerous efforts among the scientific and public health communities to develop novel vaccines with increased efficacy.

Influenza vaccination is most effective when circulating viruses are well-matched with vaccine viruses. Influenza viruses are constantly changing, and the WHO Global Influenza Surveillance and Response System (GISRS), a partnership of national influenza centres and WHO collaborating centres around the world, monitors the influenza viruses circulating in humans. WHO annually recommends a vaccine composition that targets the most representative influenza A and B strains in circulation in the northern and southern hemispheres.

Overview of current efforts

Currently approved vaccines and their limitations

There are three broad classes of approved influenza vaccines: a) inactivated virus vaccines which can be whole virion, split virion or subunit vaccines; b) live attenuated influenza vaccines; and c) a third class of vaccines based on recombinant HA. The inactivated and recombinant vaccines function primarily by inducing antibodies to immune-dominant head region of HA, and function by inhibiting virus entry into cells through preventing the HA binding to cell-surface sialic acid. The live attenuated vaccines stimulate an immune response to influenza virus that more closely mimics natural infection.

There are inherent limitations to the effectiveness of current approved vaccines. The greatest weakness of HA-based vaccines is that the most immunogenic regions of the HA protein are the most variable. The virus HA protein evolves rapidly so that circulating viruses may escape the protective effect of a vaccine within a single season; any mismatch between the

vaccine strain and the circulating strain results in significantly decreased efficacy. The rapid evolution of influenza requires global surveillance of influenza viruses and the production of new vaccine every year to match the circulating strains. Moreover, in the event of a sudden emergence of a novel pandemic strain of influenza virus the process of preparing the new seed strains and reagents adds months to the vaccine production, meaning that vaccines could only become available several months after the pandemic has started.

Because these vaccines are composed primarily of HA, they elicit very little response to other influenza viral proteins, such as the surface protein NA, against which antibodies do afford some level of protection. Additionally, most current vaccines do not expose the host to significant quantities of internal components of the virus such as the matrix (M) or nucleoprotein (NP) that do not vary significantly from strain to strain. These more highly conserved viral proteins might induce a useful immune response in the event of a mismatch between the vaccine and circulating HA. Moreover, the HA stem region that is conserved between subtypes does not induce the production of significant amounts of neutralizing antibodies in current vaccines because of the immune-dominant nature of the HA head.

Inactivated vaccines are generally poorly immunogenic in naive individuals – namely infants who have not been exposed to influenza viruses, or the entire population when a new strain with pandemic potential arises. The efficacy of these vaccines in older adults is also not optimal, and in this population eliciting a cellular immune response may increase the efficacy of influenza vaccines.

Live attenuated vaccines have advantages and disadvantages compared to the inactivated or HA vaccines. Because they are nasally administered they induce mucosal immunity, and since there is some viral replication, they also induce cell-mediated responses to conserved proteins, which may offer some limited protection against infection with a new strain. These vaccines are also very efficacious in children and infants, however their efficacy in adults is less than that of inactivated vaccines. As with the inactivated vaccines, new candidate vaccine virus has to be prepared each season, and in the event of a pandemic will not be available for several months.

General approaches to the development of universal influenza vaccines

Numerous avenues are being explored to develop universal influenza vaccines that expand the breadth of the host immune response and the duration of immunity to the virus. The ultimate aim of a universal influenza vaccine is to provide protection against all strains of influenza for many years without the need for annual vaccine strain changes or annual vaccinations.

The main approaches being explored to develop such vaccines are:

1. Vaccines based on the conserved HA stem region. These include prime boost strategies using chimeric proteins and 'headless' stem-based strategies.
2. Vaccine design strategies using bioinformatics approaches to build consensus-based or optimized recombinant HA antigens.
3. Vaccines comprised of nucleic acid coding for HA followed by boosting with HA protein, intended to induce antibody response against the common determinants. DNA-based vaccines also include strategies designed to elicit host response against conserved internal proteins.
4. Live attenuated influenza vaccines that elicit a broadly cross-reactive, longer-lasting host response.
5. Vaccines comprised of conserved internal proteins such as the nucleoprotein or matrix protein, or fragments of these, in formulations destined to induce cell-mediated immunity. These include highly conserved peptide epitopes or expression of these internal proteins in viral vectors or nanoparticles.
6. Vaccines comprised of a plurality of HAs from different strains, intended to provide an antibody response against the common determinants of the HA head.
7. Vaccines that combine multiple strategies bringing together conserved regions from HA and internal proteins into a single vaccine. These multimeric universal vaccines include virus like particles, viral vectors or nanoparticle platforms.

Opportunities and challenges

Opportunities:

- Recent scientific findings on the role of broadly cross-reactive antibodies providing protection to infection with the 2009 pandemic H1N1 demonstrate the potential efficacy of a universal influenza vaccine and provide support for a universal vaccine strategy inducing antibodies to common proteins, and in particular the HA stem.
- Research demonstrating the feasibility of developing monoclonal antibodies with broad cross-reactivity to multiple or all influenza A and B subtypes has provided extensive information on the structure of conserved HA epitopes in the stem, and the receptor binding domain of the globular head domain.
- Promising results from a number of laboratories have stimulated significant interest from pharmaceutical companies interested in developing the next generation of influenza vaccines.
- The urgent public health need for influenza vaccines with improved efficacy and the perception of increased risk of influenza pandemics have spurred increasing government interest in the development of universal influenza vaccines.
- Multiple development strategies can lead to the development of vaccines with enhanced breadth and duration of protection; some approaches may be targeted to enhance the efficacy of current vaccines, or replace seasonal vaccine, whereas others may be useful tools to protect the public against pandemic influenza.

Challenges:

- Though there is a shift in global thinking towards alleviating the need for annual influenza vaccinations, the availability of a relatively effective annual influenza vaccine creates a high barrier for the development and implementation of a universal influenza vaccine.
- In natural infection there is only a limited immune response to the conserved influenza viral epitopes such as the HA stem; and it is not clear how conserved regions will respond to increased immune pressure caused by a universal vaccine.
- It is not fully understood how immunity to one viral antigen can protect against or exacerbate infection with another influenza virus. During the H1N1 pandemic it was observed in several studies that subjects who had been vaccinated with seasonal vaccine just prior to the pandemic were more susceptible to infection with the pandemic strain. This effect has also been replicated in animal studies. Additionally, some studies have indicated that HA stem antibodies may cause enhanced disease in animals and humans.
- Licensure of universal influenza vaccines will require the development and approval of novel assays and correlates of immune protection.
- Potential of a human challenge model for development of universal influenza vaccine needs to be mapped out with the regulatory agencies.
- It is likely that universal influenza strategies will require the use of adjuvants; what are the safety concerns of adjuvants used in coordination with novel antigens?
- Licensure of universal vaccines will require agreement on acceptable outcomes (prevention of infection or severe disease), efficacy of these vaccines and the design of clinical trials and end-points.

Current promising leads, strategies and technologies

Table 25 highlights the status of current vaccine candidates. Some of the most promising strategies and their sponsors (non-exhaustive list) are as follows:

- Chimeric HA proteins designed to focus the immune response (Mt. Sinai School of Medicine/NIAID/BARDA/PATH).
- Computer optimized HA antigens designed to elicit an immune response to a recombinant consensus HA (VGTI/Sanofi Pasteur).
- DNA-based vaccines encoding HA followed by protein boost (NIAID VRC) or coding for a genetic consensus of multiple existing strains of each subtype that is known to cause seasonal (Inovio).
- Immunization with a peptide or protein which combines several conserved regions of influenza proteins into one molecule. Includes synthetic peptide containing small regions of the virus which are highly conserved (SEEK Flu-V) and the M-001 vaccine which contains regions from HA and two internal virus proteins (Biondvax).
- M2e-based vaccines such as M2e fused to TLR-agonists (Vaxinnate).
- Fusion proteins of multiple copies of the M2e region fused to the conserved nucleoprotein and conjugating to these immunostimmulatory oligonucleotides, such as being pursued by Dynavax.

- Expressing conserved internal proteins (NP and M1) in viral vectors such as MVA to induce protective CD8+ T-cell responses (University of Oxford).

Future directions

A. Short-term goals (within two years)

- Consensus on definition, target product profile (interim acceptable and ideal) and roadmap for development of universal influenza vaccines.
- Availability of global platform to coordinate vaccine development efforts.

B. Mid-term goals (by 2020, end of the Decade of Vaccines)

- One or two candidates advanced towards licensure.
- Robust pipeline of vaccine candidates using variety of approaches advanced in preclinical development, ready to move to clinics.

C. Long-term goals (by 2030)

- At least one or two universal influenza candidates licensed.
- Global sustainable support available for roll-out of these vaccines in developing countries.

Table 25: Development status of current vaccine candidates

	Preclinical	Phase I	Phase II	Phase III	Delivery route	Class and target	Company (Funder)
M-001	X	X	X		Intramuscular	Multimeric protein B- & T-cell peptides (HA, M1, NP)	BiondVax
Flunisyn	X	X	X		Intramuscular	Fluoro-conj. T-cell peptides (PA, PB1, PB2, NP, M1)	Immune Targeting Sys.
Flu-v	X	X	X		Intramuscular	6 T-cell peptides	SEEK Group
DNA Prime	X	X			Intramuscular	DNA priming with conventional vaccine boost	NIAID (VRC)
Chimeric	X				Intramuscular	Prime/Boost with denovo-head and conserved stalk	MSSM (DMID, BARDA, GlaxoSmithKline)
Headless	X				Intramuscular	Conserved HA stalk	MSSM, AvatarBiotech
COBRA	X				Intramuscular	Computationally optimized broadly reactive HA antigen	VGTI (DMID, Sanofi Pasteur)
SynCon	X	X			Intramuscular	DNA constructs encoding HA proteins	Inovio
SAVE LAIV	X				Intranasal	Live attenuated vaccine by 'de-optimizing' codon pairs without altering protein sequences	Codagenix (DMID)
REDEE FLU	X				Intranasal	Live, single replication due to partial M2 deletion	Flugen (DMID)
M2 VLP	X				Intramuscular	M2 VLPs (5x M2 VLPs incorporating a tandem repeat of M2e linked to the transmembrane cytoplasmic domain of HA	Emory (DMID)
M2-M2-nanoparticle	X				Intramuscular	Synthetic gold nanoparticle conjugated with different functional M2e peptides	Texas Tech (DMID)

MSSM, Mount Sinai School of Medicine; DMID, Division of Microbiology and Infectious Diseases; BARDA, Biomedical Advanced Research and Development Authority; VGTI, Vaccine & Gene Therapy Institute of Florida.

PROGRESS TOWARDS INSTITUTIONAL AND TECHNICAL CAPACITY TO CARRY OUT VACCINE CLINICAL TRIALS (INDICATOR SO6.3)

Background

Using WHO's International Clinical Registry Platform to assess number of vaccine clinical trials performed by country

WHO's International Clinical Trials Registry Platform (ICTRP) provides a single database collating the clinical trial registry entries from many national and international WHO compliant clinical trial registry databases. It is the single best source of information on clinical trial activity worldwide. The database is available at who.int/ictrp. It was initiated following World Health Assembly resolution WHA58.34, which called for such an international register. While it provides an important source of information for clinical trial activity, there is no built-in and easily accessible quality assurance indicator for clinical trials.

Lack of an appropriate quality indicator for clinical trial capacity

While any clinical trial, which is conducted for product development, must conform to good clinical practice standards, these are assured only variably by sponsors or national regulatory agencies; and good clinical practice inspection reports are not widely available. Therefore, a missing element is a quality assurance indicator for clinical trials. It would be desirable for the global clinical trial community to develop generally-agreed quality indicators for clinical trials, which can be applied to all clinical trials. An existing quality indicator exists for reporting of clinical trials, namely the Consolidated Standards of Reporting Trials (CONSORT) standards. However, these can only be applied once a trial is reported in the literature, which may occur at some time after trial completion.

Methods for reporting on numbers of clinical trials under way by country and region

A search was performed in who.int/ictrp for "vaccine or vaccines or vaccination or immunization".
This generated over 6000 records spanning the time frame from before 2006 to the day of the search (13 May 2014). All records from this search were exported as an .xml file and imported into Microsoft® Excel® where pivot tables were used to produce the outputs found in the annexes to this chapter. The trial ID field (a unique descriptor for each trial) was used to discard duplicate records. The date is the date of registration in a clinical trial registry.

Limitations of this approach

Although multiple literature reports indicate that clinical trial registry is increasing, not all clinical trials will be entered in a clinical trial registry. However, registration is almost universal in many jurisdictions now with good use of clinical trial registries, for example in Africa.
The date universally available in the registries is the date of first registration, not the date of trial start. Manual assessment of each record was not conducted.

Improvements planned for future reports

In future a manual search of each record will be conducted so that the records can be sorted into disease/pathogen categories. If a methodology can be agreed upon, it is also planned to work with partners to derive a database from ICTRP of trial completion dates and proportion of clinical trials with results reported for both numbers of trials and numbers of participants.

Overview of current situation

Please see Annex 1 for results of this search for clinical trials activity. In the last 12-month period (May 2013 to May 2014) at least one clinical trial occurred in between 28% and 45% of Member States in five WHO regions. The outlier is the Eastern Mediterranean Region, where clinical trials occurred in only 14% of Member States (3 of 21). The countries reporting most clinical trials during this reporting year were (in order) the US, Japan, the United Kingdom, China, India, Netherlands, Germany, Australia, France, Republic of Korea, South Africa and Canada.

Extent of reporting of clinical trials

Please see Annex 2 for a detailed description of the extent of clinical trial reporting. In brief, a substantial minority of vaccine randomized clinical trials (RCTs) remain unreported at 48 months post-trial completion (comprising 18% of RCTs of pneumococcal, HPV, rotavirus, influenza and meningococcal vaccines). Failure to report clinical trial results in a timely manner is considered to be a breach of current, widely accepted, international standards (e.g. the Declaration of Helsinki), and is likely to lead to reporting bias, which has major adverse consequences for:

- understanding of innovative science;
- the possibility that regulatory decision-making is subject to reporting bias;
- the possibility that policy recommendation processes are subject to reporting bias in ways that systematic reviews will not necessarily address;
- inefficient research and development resource allocation;
- inefficient allocation of financing for health interventions.

Significant opportunities exist to improve clinical trial reporting and possible options are outlined in Annex 2.

A draft WHO position on vaccine RCT results reporting is under development by the Product Development for Vaccines Advisory Committee, for review by SAGE. This position may outline options for possible corrective actions that could be taken by different stakeholders and constituencies.

Opportunities and challenges for building institutional and technical national capacity to carry out vaccine clinical trials

Inadequate regulatory capacity is known to be a persistent obstacle in the planning, approval and oversight of clinical trials worldwide. With novel vaccine development gaining new momentum in recent years, the need for stronger regulatory oversight is critical, particularly in Africa where many novel vaccine clinical trials will take place. Yet the challenges of understanding vaccine science for novel vaccines and new clinical trials procedures are stretching the capacity of regulators in industrialized countries. Research ethics committees and national regulatory authorities in Africa, as elsewhere, are responsible to protect the health and safety of participants in clinical trials conducted in their countries. Ensuring that trials are approved in an appropriate yet timely manner, and that data generated in novel vaccine trials meet international standards for acceptability, will contribute to the goals of ensuring the safety of subjects, the validity of clinical trial data and strengthening of technical and research capacity.

A regional cooperation mechanism, such as the African Vaccines Regulatory Forum, AVAREF[21], has already been found to be particularly beneficial to build capacity for regulatory oversight of vaccine trials in Africa and provides the opportunity to further strengthen clinical trial oversight so that it is technically adequate and more efficient.

[21] AVAREF member countries include: Botswana, Burkina Faso, Cameroon, Ethiopia, Gabon, Gambia, Ghana, Kenya, Malawi, Mali, Mozambique, Nigeria, Rwanda, Senegal, South Africa, Uganda, United Republic of Tanzania, Zambia and Zimbabwe.

Thus far, AVAREF has been an important resource for countries hosting vaccine clinical trials. As a platform it has achieved the goals of promoting a regional approach to clinical trial regulation while at the same time maintaining national sovereignty and local accountability.

The experience gained through AVAREF of joint reviews of clinical trial approvals *(1)* can potentially be exported to other countries and networks. For example, the AVAREF guidelines could be reviewed by all the stakeholders including sponsors and product developers and offered as a global tool for joint reviews. As a next step for AVAREF, the guidelines could also become the basis of development of tools for evaluation of dossiers for the licensure of products.

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ANNEX 1: Vaccine clinical trial activity from the WHO International Clinical Trials Registry Platform*

WHO region & country	Number of trials 1 May 2012 – 1 May 2013	Number of trials 1 May 2013 – 1 May 2014
The African Region		
Burkina Faso	2	0
Gabon	0	1
Gambia	1	3
Guinea Bissau	1	1
Kenya	3	4
Mali	0	2
Mozambique	2	1
Nigeria	0	1
Rwanda	1	0
Senegal	2	1
South Africa	12	20
Sudan	0	1
Uganda	1	4
United Republic of Tanzania	2	2
Zambia	0	2
Total clinical trials	**27**	**43**
Number of countries in the African Region	10 out of 47 (21%)	13 out of 47 (28%)
Region of the Americas		
Argentina	2	3
Brazil	8	4
Canada	24	19
Chile	1	4
Colombia	3	6
Costa Rica	0	2
Cuba	5	0
Dominican Republic	4	0
Guatemala	1	0
Honduras	1	0
Mexico	6	4
Panama	4	1
Peru	1	1

WHO region & country	Number of trials 1 May 2012 – 1 May 2013	Number of trials 1 May 2013 – 1 May 2014
Puerto Rico	5	1
Venezuela (Bolivarian Republic of)	1	1
United States	147	165
Total clinical trials	**213**	**211**
Number of countries in the Region of the Americas	15 out of 35 (43%)	12 out of 35 (34%)
The Eastern Mediterranean Region		
Egypt	**1**	**1**
Iran (Islamic Republic of)	8	9
Saudi Arabia	3	1
Total clinical trials	**12**	**11**
Number of countries in the Eastern Mediterranean Region	3 out of 21 (14%)	3 out of 21 (14%)
The South-East Asia Region		
Bangladesh	10	2
Democratic People's Republic of Korea	1	1
India	45	33
Indonesia	2	7
Thailand	12	11
Total clinical trials	**70**	**54**
Number of countries in the South-East Asia Region	5 out of 11 (45%)	5 out of 11 (45%)
The European Region		
Austria	8	8
Belgium	11	10
Bulgaria	1	0
Croatia	2	0
Czech Republic	10	8
Denmark	4	4
Estonia	5	1
Finland	11	12
France	13	21
Germany	20	30
Greece	0	1
Hungary	3	3
Israel	2	6
Italy	9	9

WHO region & country	Number of trials 1 May 2012 – 1 May 2013	Number of trials 1 May 2013 – 1 May 2014
Monaco	0	2
Netherlands	15	32
Norway	4	0
Poland	9	8
Portugal	1	0
Russian Federation	10	4
Serbia	1	0
Slovakia	2	0
Spain	20	12
Sweden	10	10
Switzerland	8	7
Turkey	3	2
Ukraine	1	0
United Kingdom	40	40
Total clinical trials	**223**	**230**
Number of countries in the European Region	26 out of 53 (49%)	21 out of 53 (40%)
The Western Pacific Region		
Australia	24	26
China	28	36
Hong Kong, SAR	2	0
Taiwan, China	10	4
Japan	55	72
Korea, Republic of	16	20
Malaysia	2	2
New Zealand	4	3
Papua New Guinea	1	0
Philippines	3	8
Singapore	1	3
Viet Nam	0	2
Total clinical trials	**146**	**176**
Number of countries in the Western Pacific Region	11 out of 27 (41%)	10 out of 27 (37%)

* See chapter on Indicator SO6.3 for search term and methods. More information is available at: www.who.int/ictrp

ANNEX 2:
On extent of non-reporting in vaccine clinical trials: a major concern, and an opportunity to act

The reporting on clinical trial activity is greatly facilitated by the advent of clinical trial registries. While a World Health Assembly resolution in 2006 called for universal use of clinical trial registries for all clinical trials, there is as yet no WHO position on clinical trial results reporting. The gradual adoption of the practice of clinical trial registries has enabled groups to track completion of clinical trial reporting in recent years. A growing amount of literature confirms that clinical trial reporting is incomplete even many years after trial completion. A recent article *(1),* which substantially adds to the literature on reporting of RCTs for vaccines, is briefly summarized below.

Methods: Only RCTs were included in the assessment of reporting. The RCTs were registered in any one of a list of clinical trial registry platforms including WHO's who.int/ictrp and clinicaltrials.gov between 1 Jan 2006 and 31 Dec 2012. The search terms "vaccine or vaccines or vaccination or immunization" and "pneumococcal" or "influenza" or "flu" or "meningococcal" or "meningococcus" or "rotavirus" or "HPV" or "papilloma virus" were used. Thus only pneumococcal, influenza, meningococcal, rotavirus or HPV RCTs were included. Publication was assessed through thorough review of multiple literature database searches. In addition, reporting within clinicaltrials.gov was assessed.

Results: In total 384 RCTs were identified in this way; 355 (92%) had been completed by the end date for analysis: February 2014. The majority of reported trials were published in the literature, but inclusion of searches for clinicaltrials.gov reporting adds a substantial percentage of trials with results in a registry but not in the literature. (In total 176 of 355 (50%) had been published by February 2014, with another 42 (12%) reporting in registry sites only.) Thus, 62% of RCTs had reported through at least one of the two modalities. However, these 62% of RCTs represented only 50% of the total number of enrolled participants. When considering the 355 RCTs, which had reached 48 months from study completion, 45 (18%) had no results reported either in registry sites or in the literature.

There was a low proportion of negative trials identified from those that had reported results, raising the strong possibility of reporting bias. Twenty-four RCTs were identified with no literature reports 6 years after completion. Only five of these reported some outcomes in the registry entry. The 19 trials with no results reported at all included 11 527 participants. The authors attempted to contact authors and sponsors of these 19 trials but received no reply.

Summary and policy implications: This study is an important contribution to the limited literature of vaccine RCT results reporting. It confirms that 1) results are withheld for 18% of RCTs at 48 months from study completion, that 2) reporting of results within clinical trial registries is becoming more widespread and provides an important contribution to the percentage of participants and RCTs reporting, and that 3) further action is required to ensure results of vaccine RCTs are reported in a timely manner.

Rationale for further required action to mandate reporting of clinical trials

There are several ethical, legal, economic and scientific reasons why clinical trial results should be published. This report supports observations by WHO staff members that RCTs are sometimes not reported many years following completion. It is likely that reporting bias exists in the vaccine trials literature as supported by the recent British Medical Journal article and the extensive literature on non-reporting of clinical trials.

The implications of the current incomplete reporting of vaccine trials include the following.

A. It raises major ethical concerns. Both the Declaration of Helsinki and United States Federal Policy for the Protection of Human Subjects acknowledge that investigators and sponsors have an ethical obligation to study participants to publish trial results in a timely manner. Furthermore, failure to report trial results in a timely manner delays or altogether prevents society from reaping the scientific or social benefits of those trials.

B. There is a risk that unnecessary clinical trials are being planned and conducted, as certain vaccine development and policy questions will have previously been tested but not reported. Such questions could include those related to the relative utility of different vaccine platforms, delivery systems, antigens, adjuvants, schedules, strategies, doses and formulations.

C. It jeopardizes scientific state of the art. Vaccine development is based on current scientific understanding, and this state of the art in science is based on reported results. Therefore any non-reported results may affect the current scientific understanding.

D. There is a risk of incorrect policy recommendations and vaccine financing decisions due to reporting bias. Given that RCTs are assessed as higher-quality evidence using GRADE methodology, the non-accessibility of completed RCTs has the potential to substantially skew policy assessments, potentially leading to policy recommendations that would not be supported if all RCTs were available for the assessment. This in turn can lead to financing decisions that are incorrect.

There is an opportunity for WHO to provide leadership by developing a WHO position on clinical trial reporting which would indicate that all vaccine RCTs should be reported by 24 months from study completion. In order to develop the precise wording of such a position, it is planned that a new advisory committee known as the Product Development for Vaccines Advisory Committee, whose scope includes early stage vaccine research and development, will constitute a small working group of scientists familiar with clinical trials to put together a first draft WHO position that will be reviewed by SAGE. This position could also outline options for possible corrective actions that could be taken by different stakeholders and constituencies.

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5. MDG 4 AND INTEGRATION INDICATORS

REDUCE UNDER-FIVE MORTALITY RATE (INDICATOR G5.1)

Highlights

- Substantial progress has been made towards achieving Millennium Development Goal (MDG) 4. The number of deaths of children aged under 5 years worldwide has nearly halved, from 12.6 (12.4–12.9) million in 1990 to 6.6 (6.3–7.0) million in 2012.[22]
- This translates into around 17 000 fewer children dying every day in 2012 than in 1990, but it still implies the deaths of nearly 18 000 children aged under age 5 years every day in 2012.
- Since 1990 the global under-five mortality rate has dropped 47%—from 90 (89–92) deaths per 1000 live births in 1990 to 48 (46–51) in 2012. All regions, except for Sub-Saharan Africa and Oceania, have reduced their under-five mortality rate by 50% or more.

TARGET	2015: two thirds reduction compared to 1990 2020: Exceed 2015 target
DEFINITION OF INDICATOR	Under-5 mortality rate per 1000 live births
DATA SOURCES	United National Interagency Group on Mortality Estimates

Please note that this indicator is available on interactive figures/dashboard for better understanding and exploration of data. Please visit the following website:

http://www.technet-21.org/resources/gvap-indicators

Progress towards the achievement of the MDG 4 goal to reduce child mortality is monitored as part of the Countdown 2015 initiative. Progress is measured by the independent Expert Review Group (iERG), based on the recommendations of the Commission on Information and Accountability of the Global Strategy for Women's and Children's Health. The salient findings in the Countdown 2015 report and other reports are summarized below, with links to details.

- Overall, substantial progress has been made towards achieving MDG 4. The number of deaths of children aged under 5 years worldwide has nearly halved, from 12.6 (12.4–12.9) million in 1990 to 6.6 (6.3–7.0) million in 2012.[23] While this translates into around 17 000 fewer children dying every day in 2012 than in 1990, it still implies the deaths of nearly 18 000 children aged under five years every day in 2012.
- Since 1990 the global under-five mortality rate has dropped 47%—from 90 (89–92) deaths per 1000 live births in 1990 to 48 (46–51) in 2012. All regions, except for Sub-Saharan Africa and Oceania, have reduced their under-five mortality rate by 50% or more.
- The average annual rate of reduction in under-five mortality has accelerated – from 1.2% a year over 1990–1995 to 3.9% over 2005–2012 – but remains

[22] Note that this report was prepared before the release of WHO's 2013 mortality estimates.
[23] Note that this report was prepared before the release of WHO's 2013 mortality estimates.

insufficient to reach MDG 4, particularly in sub-Saharan Africa and south Asia. All regions with the exception of west and central Africa and sub-Saharan Africa as a whole have at least halved their rates of under-five mortality since 1990.

- Since 1990, 216 million children have died before their fifth birthday — more than the current total population of Brazil, the world's fifth most populous country. The highest rates of child mortality are still in sub-Saharan Africa, with an under-five mortality rate of 98 deaths per 1000 live births—more than 15 times the average for developed regions.

- South Asia has made strong progress on reducing preventable child deaths, more than halving its number of deaths among children aged under 5 years since 1990. But nearly one in every three under-five deaths still takes place in this region, and it has not seen a major acceleration in the rate of reduction.

- Sub-Saharan Africa faces a unique and urgent challenge in accelerating progress. By mid-century it will be the region with the single biggest population of children aged under 5 years, accounting for 37% of the global total and close to 40% of all live births. And it is the region with least progress to date in reducing under-five mortality.

- Within sub-Saharan Africa, there is beginning to be a divergence in child survival trends between eastern and southern Africa, and west and central Africa. Eastern and southern Africa have managed to reduce their under-five mortality rate by 53% since 1990. In contrast, west and central Africa have seen a drop of just 39% in their under-5 mortality rate since 1990, the lowest among all regions worldwide.

- About half of deaths in children aged under 5 years occur in only five countries: India, Nigeria, Democratic Republic of the Congo, Pakistan and China. India (22%) and Nigeria (13%) together account for more than a third of all deaths in children aged under 5 years.

- The proportion of deaths in children aged under 5 years that occur within the first month of life (the neonatal period) has increased 19% since 1990, from 37% to 44%, because the neonatal mortality rate is declining more slowly than that for older children.

- The leading causes of death among children aged under five years include pneumonia (17%), preterm birth complications (15%), intrapartum-related complications (10%), diarrhoea (9%) and malaria (7%). Globally, about 45% of deaths in children aged under 5 years are attributable to undernutrition.

- Seven countries with historically high infant mortality rates (Bangladesh, Ethiopia, Liberia, Malawi, Nepal, Timor-Leste and the United Republic of Tanzania) have already reduced their mortality rates of children aged under 5 years by two thirds or more since 1990; six of these countries are low-income, proving that low national income is not a barrier to making gains in child survival. A further 18 countries with historically high infant mortality rates have also managed to at least halve their under-five mortality rates over the same period.

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INTEGRATION OF HEALTH CARE INTERVENTIONS AND IMMUNIZATION ACTIVITIES (INDICATOR G5.2)

TARGET	No target set
DEFINITION OF INDICATOR	Data are presented for the 75 'Countdown' nations[24] with high child mortality rates Integrative interventions include: • Provision of vitamin A with routine or supplementary immunization activities • Comparative rates of health care interventions used against diarrhoea such as use of oral rehydration salts (ORS) and early initiation of breastfeeding with rotavirus vaccine
DATA SOURCES	• WHO-UNICEF Joint Reporting Forms (JRFs) • WUENIC estimates for coverage of rotavirus vaccine final dose and MCV1 • ORS, early initiation of breastfeeding and vitamin A coverage data from Childinfo by UNICEF[25]

Please note that this indicator is available on interactive figures/dashboard for better understanding and exploration of data. Please visit the following websites:

http://www.technet-21.org/resources/gvap-indicators

When reviewing the data, hover over the pie charts and countries to get additional information.

During their review of progress in 2013, SAGE highlighted that more efficient coordination of integrating immunization and child health services is needed in order to achieve greater acceleration in the reduction in child mortality, especially in the regions and countries that are lagging behind *(1)*. They requested the Secretariat to develop one of more indicators to track progress with integrated (or more coordinated) service delivery of interventions to reduce child mortality. In response the Secretariat explored the availability of data to develop indicators to track countries' progress on integration of services for reducing child mortality.

In defining the indicators, the Secretariat considered two facets of integration:

1. delivery of other health interventions along with immunization, for example delivery of vitamin A, anti-helminthic medicines or insecticide treated bed-nets during immunization contact;
2. more coordinated delivery of health interventions by different programmes directed at improving maternal and child health, as exemplified in the Global Action Plan for Pneumonia and Diarrhoea.

In order to minimize the reporting burden on Member States, the Secretariat explored existing sources of data, including the JRFs, the WUENIC estimates, UNICEF Childinfo databases and data from household surveys (DHS and MICS).

Data availability and quality

The JRFs and Childinfo by UNICEF included quality data on several questions that could be used to assess progress in the 75 'Countdown' countries. Member States report whether they provide vitamin A or other interventions along with routine immunization or supplementary immunization activities. These data were used to determine the number of countries among the 75 Countdown nations with high child mortality rates that provided vitamin A with routine immunization or with SIAs; they were also used to estimate the ratio of vitamin A to MCV1 coverage for those nations that provide vitamin A with routine immunization.

The WUENIC estimates and UNICEF Childinfo databases were also used in this analysis to compare the coverage of rotavirus vaccine to coverage of oral rehydration salts (ORS) and early initiation of breastfeeding in the 75 Countdown countries. Countries

[24] The list of Countdown nations can be found here: http://www.countdown2015mnch.org/country-profiles.
[25] Childinfo data on ORS coverage can be found at: http://www.childinfo.org/diarrhoea_ors.php. Childinfo data on early initiation of breastfeeding can be found at: http://www.childinfo.org/breastfeeding_initiation.php. Childinfo data on Vitamin A coverage can be found at: http://data.unicef.org/nutrition/vitamin-a.

with strong integration mechanisms were expected to show similar rates of coverage for prevention, protection and treatment mechanisms such as rotavirus vaccine, early initiation of breastfeeding and ORS, respectively.

Diarrhoea was chosen as the indicator disease as it is part of the WHO & UNICEF's Global Action Plan for Pneumonia and Diarrhoea (GAPPD) *(2)* that addresses diseases in an integrated approach. Furthermore, the data on coverage with ORS and exclusive breastfeeding collected through household surveys were considered to be of better quality than those relating to pneumonia treatment. However, it must be noted that coverage with breastfeeding and ORS use are not available on an annual basis and the current results for coverage are not from the same year as those of rotavirus vaccine. Hence, these may only be considered as a baseline estimate and progress will need to be measured based on changes in coverage in the same countries in subsequent surveys.

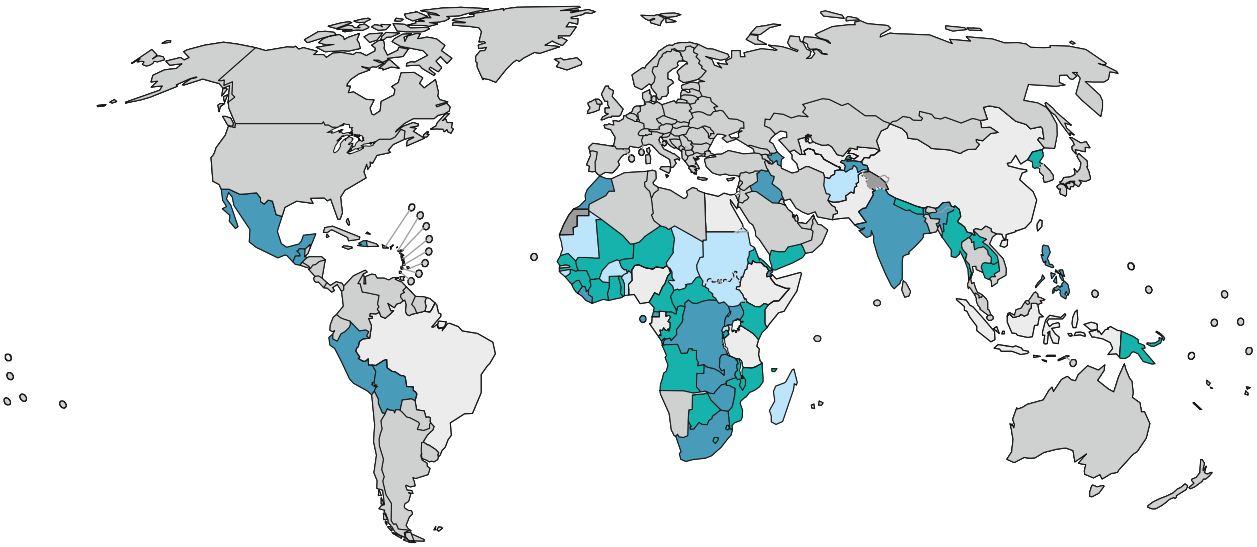
Results

Among the 75 Countdown countries, 28 (37%) provided vitamin A with both routine and supplementary immunization activities (Figure 30); 20 countries (27%) provided vitamin A only with routine immunization activities, while 10 countries (13%) provided vitamin A only with SIAs. In 14 countries (19%) vitamin A was not distributed at all, while in three countries (4%) vitamin A deficiency was not considered a public health problem.

For 48 nations that provided vitamin A with routine immunizations, only 35 countries had vitamin A coverage data from Childinfo by UNICEF (Table 26). Among the 35 countries, the ratio of vitamin A to MCV1 coverage was computed. Fifteen countries (43%) had a vitamin A to MCV1 ratio ≥1, with two nations (Guinea and the Central African Republic) having a ratio of ≥1.5. Twenty countries (57%) had a ratio of less than 1, with 9 of those countries (26%) having a ratio ≥0.5, and 11 countries (31%) having a ratio <0.5.

Data on coverage with last dose of rotavirus vaccine and coverage for ORS or early initiation of breastfeeding showed that the former was higher than both the latter two in countries that fully introduced the rotavirus vaccine, as seen in Figure 31 below. For example, in countries with rotavirus vaccine introduced, there is a coverage differential of 29% and 44% for breastfeeding and ORS, respectively, relative to rotavirus vaccine coverage. However, it must be noted that the coverage estimates are not for the same year and cannot directly be compared. If countries have used the opportunity of rotavirus vaccine introduction to also initiate efforts to scale up the use of other interventions, greater convergence between the coverage of the three interventions in subsequent surveys should be expected.

Figure 30: Countries providing vitamin A supplementation with routine and/or supplementary immunization activities, 2013



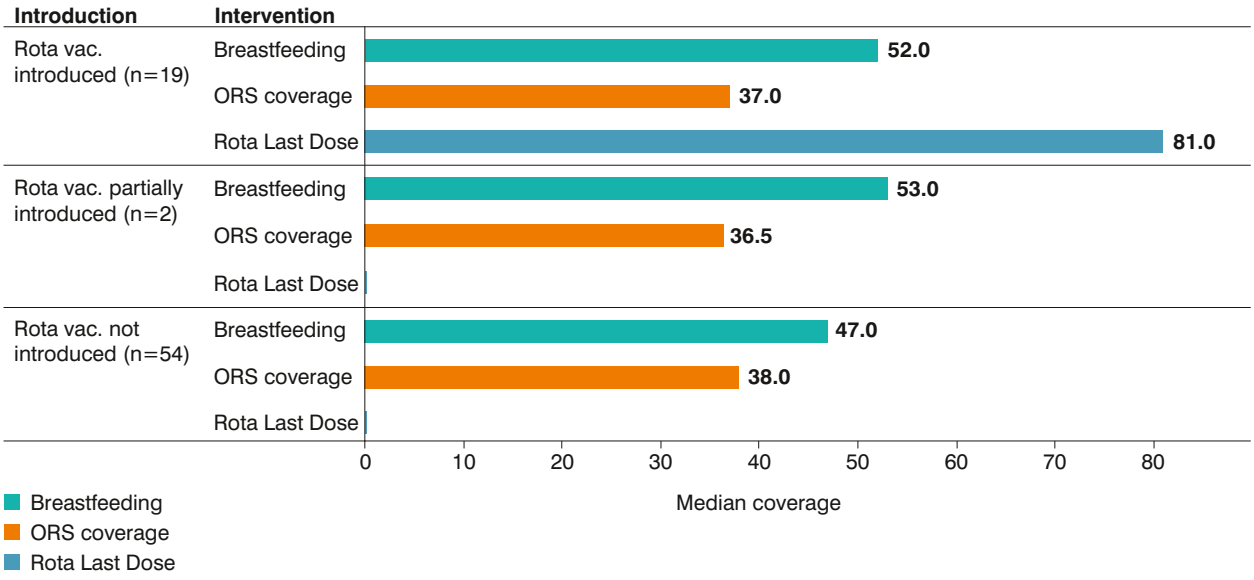
Vitamin A distributed with routine and supplementary immunization activities (28 countries or 37%)
Vitamin A distributed only with routine immunization services (20 countries or 27%)
Vitamin A distributed only with supplementary immunization activities (10 countries or 13%)
No Vitamin A distribution (14 countries or 19%)
Not a Countdown country (119) or Countdown country for which Vitamin A deficiency is not a public health problem (3)

Source: WHO/IVB Database as of 08 June 2014. 194 WHO Member States. Map production: Immunization Vaccines and Biologicals, (IVB). World Health Organization.
Date of slide: 28 July 2014.

Table 26: Ratio of vitamin A to MCV1 coverage for those nations that provide vitamin A with routine immunization, 2012

Vitamin A/MCV1 coverage ratio	Countries
≥1.5	Central African Republic, Guinea
1.5 to 1.0	Cambodia, Cameroon, Democratic Republic of the Congo, Côte d'Ivoire, Djibouti, Democratic People's Republic of Korea, Mali, Myanmar, Nepal, Niger, Philippines, Sierra Leone, Tajikistan
1.0 to 0.5	Azerbaijan, Haiti, India, Kenya, Lao People's Democratic Republic, Malawi, Togo, Uganda, Zimbabwe
≥0.5	Angola, Bolivia (Plurinational State of), Eritrea, Ghana, Guatemala, Liberia, Mozambique, Papua New Guinea, Sao Tome and Principe, Swaziland, Yemen

Figure 31: Median coverage rates for rotavirus vaccine, ORS and early initiation of breastfeeding for countries that have introduced, partially introduced or not introduced the rotavirus vaccine



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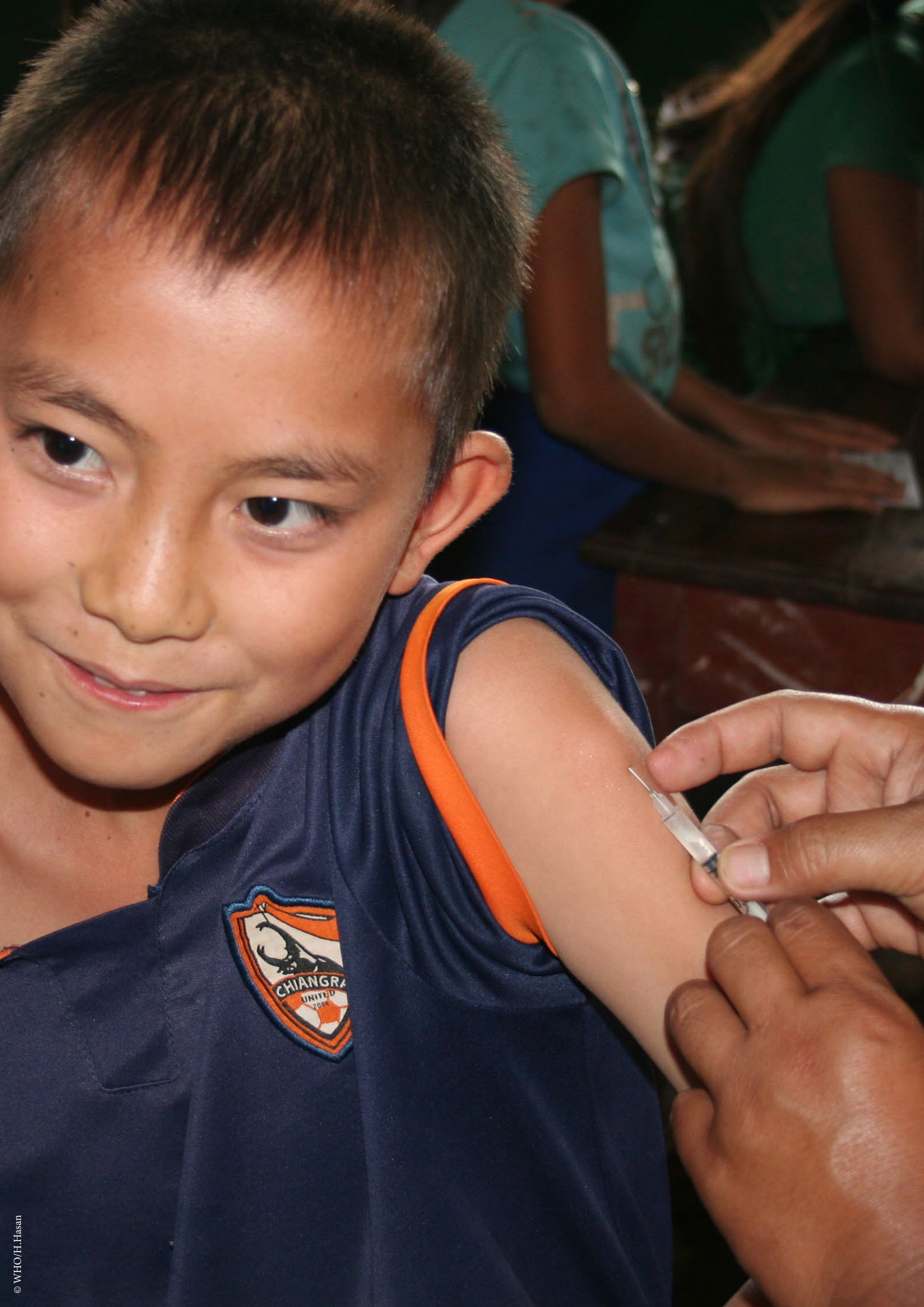
2. WHO/UNICEF. Ending preventable child deaths from pneumonia and diarrhoea by 2025: The integrated Global Action Plan for Pneumonia and Diarrhoea (GAPPD). Geneva: World Health Organization; 2013 (http://www.who.int/maternal_child_adolescent/documents/global_action_plan_pneumonia_diarrhoea/en/, accessed 16 December 2014).



6. ENSURING COUNTRY OWNERSHIP OF IMMUNIZATION

INCREASING DOMESTIC EXPENDITURES FOR IMMUNIZATION PER PERSON TARGETED (INDICATOR SO1.1)

Highlights

- Data quality is variable. Several inconsistencies and missing data are noted.
- Sixty-seven Member States (35%) reported the financing indicator for the last four years and 52 Member States (27%), mainly high-income countries, did not report the financing indicator in the period 2010-2013.
- Among the 67 Member States for which data on domestic expenditure are available for the last four years (2010-2013), 13 Member States have increased their domestic expenditures during the period, and 7 Member States have decreased their expenditures.
- A survey conducted in a sample of countries identified difficulties encountered in reporting financing indicators in the JRFs. Countries' recommendations to UN agencies will be followed by the provision of technical assistance, feedback and capacity building initiatives for collection and reporting financing data.
- The System of Health Accounts (SHA) will be gradually applied in low-income countries and lower-middle income countries to estimate immunization-specific expenditure and improve the reporting of JRF financing indicators.

INDICATOR SO 1.1: DOMESTIC EXPENDITURES FOR IMMUNIZATION PER PERSON TARGETED	
TARGET	Increasing trend in country allocation to national immunization programmes
DEFINITION OF INDICATOR	Domestic expenditures for immunization are all expenditures financed by domestic resources (from national and subnational government budgets) for immunization-specific activities carried out within the routine immunization programme for both vaccine procurement and immunization delivery. Supplemental immunization activities (SIAs) are excluded, as are extra-budgetary expenditures from development partners, and out-of-pocket and private expenditures For persons targeted, the number of live births from UN population data *(1)* was used as a standard denominator that was available for all countries
DATA SOURCES	WHO-UNICEF joint reporting forms (JRFs) (questions concerning immunization financing – see *description of data sources*)

Description of data sources

The JRF template includes the following immunization financing questions:

1. What amount of government funds was spent on vaccines used in routine immunization?
2. What is the total expenditure (from all sources) on vaccines used in routine immunization?
3. If total amounts are not available for the previous questions, please provide an estimated percentage of total expenditure on vaccines financed by government funds.
4. What amount of government funds was spent on routine immunization?
5. What is the total expenditure (from all sources) on routine immunization?
6. If total amounts are not available for the previous question, please provide an estimated percentage of total expenditure on routine immunization financed by government funds.

In 2010, the JRF template was revised to include the indicators total expenditure on vaccines from all sources and total expenditure on routine immunization from all sources, both in absolute values (see questions 2 and 5 above). Instructions were updated to ensure harmonization of Member States' responses. However, some Member States (on average 14% in the period 2010-2013) reported only the estimated percentage of government funding (questions 3 and 6 above) indicating that total amounts are not available.

Question 1, "What amount of government funds was spent on vaccines used in routine immunization?", includes all recurrent, immunization-specific expenditure of routine immunization. Recurrent inputs include vaccines, injection supplies, salaries and per diems of health staff working full-time on immunization, transport, vehicles and cold chain maintenance, training, social mobilization, monitoring and surveillance.

Comments on data quality

The quality of financing data reported through the JRF mechanism is a major concern. The JRF is generally completed by national immunization programme managers or their designees, who appear to have difficulties in securing and reporting reliable immunization expenditure data. From October to December 2013 a survey was conducted in a sample of GAVI-eligible countries to learn about the problems encountered in the process of reporting JRF financing indicators (report to be published). Countries reported difficulties in collecting data, making estimates and addressing inconsistencies of financial data from the several sources of information used. They requested technical support, feedback, and capacity building to guide the collection and reporting of financing data from UN agencies. The Immunization Financing and Sustainability Task Team of the GAVI Alliance is responding to this request through the development of specific guidelines.

The JRF template provides definitions and instructions to report the financing indicator. However, 52 Member States (27%), the majority of which are high-income countries, did not report the financing indicator in absolute values in the last four years (2010-2013). Some of them, as mentioned above, opted to report the estimated percentage of government funding routine immunization.

WHO annually crosschecks the data to identify missing data and potential inconsistencies. These are identified by:

i. analysing time series of financing indicators (e.g. extremely divergent values reported from one year to the other by the same country); and
ii. assessing coherence between reported expenditure for routine immunization and expenditure for vaccines (the former should include and be greater than the latter).

The observed time series are used to fill the missing values by assuming continuation of trends of time series or by averaging available values. For Member States with available comprehensive multiyear plans, data from the costing and financing tools are also used as additional sources to crosscheck and to supply missing or correct inconsistent data.

Apparent mistakes like wrong currency or typing errors are also frequent and are subsequently corrected by WHO. Overall, 39 values in the dataset 2010-2013 have been corrected and replaced by WHO estimates (in italics in the tables below).

Records of inconsistencies and missing values are shared with Member States through the WHO regional offices; however, responses to the feedback in order to revise the data are often lacking. It has to be

noted that some additional checking and correcting inconsistencies for the 2013 data will be done in the next weeks (e.g. internal consistency among the six financing questions; vaccine expenditure greater than routine immunization expenditure). This crosscheck might result in few additional revisions/estimates of the government-financing indicator.

Interpretation of data should be cautious as several inconsistencies remain in the dataset including: Member States reporting high fluctuations of the indicator between years or extremely high values compared to Member States in the same income range.

Response rates have slightly improved since last year's report: 85 Member States (44%) have reported the financing indicator for at least three years, compared to 60 Member States (31%) in last year's report; 38 Member States (20%) have reported for two years, compared to 43 Member States (22%) last year; 19 Member States (10%) have reported only one year, compared to 31 Member States (16%) in last year's report; and 52 Member States (27%) did not report the financing indicator in the period 2010-2013, compared to 60 Member States (31%) that did not report in period 2010-2012.

Ten countries began using the System of Health Accounts (SHA) *(2)* in 2013 to estimate immunization-specific expenditure; this system will be gradually applied in 60 low- and lower-middle income countries by 2015, with the objective of strengthening the quality of reporting JRF financing indicators.

Description of the results

Sixty-seven Member States (35%) reported the indicator on domestic expenditure for the entire time series of four years (2010-2013). Thirteen have increased their domestic expenditures during the period (Table 27), and seven have decreased their expenditures (Table 28). For all other 47 Member States, there is no noticeable trend (Table 29).

Table 27: Member States for which domestic expenditures on routine immunization have been steadily increasing for the past four years (2010-2013)

Country	Income classification*	GNI per capita 2013 (US$)	2010 (US$)	2011 (US$)	2012 (US$)	2013 (US$)
Burundi	1	280	0.7	0.8	1.0	1.3
Cambodia	1	950	0.3	0.4	1.4	2.7
Democratic Republic of the Congo	1	400	0.0	0.7	1.6	1.7
Eritrea	1	490	0.4	1.9	2.0	2.0
Madagascar	1	440	0.6	1.2	1.7	2.7
Mozambique	1	590	3.8	4.3	4.8	6.1
Nepal	1	730	1.7	4.8	6.3	7.8
Congo (the)	2	2 660	0.6	4.7	5.1	5.5
India	2	1 570	3.8	4.2	5.8	7.0
Marshall Islands	3	4 200	18.3	19.2	20.1	21.1
Dominican Republic	3	5 620	14.1	19.6	27.5	83.1
Netherlands	4	47 440	182.0	215.4	255.7	265.0
Republic of Korea	4	25 290	73.1	138.9	286.9	434.0

* 1, low-income country; 2, lower-middle income country; 3, upper-middle income country; 4, high-income country.

Table 28: Member States for which domestic expenditures on routine immunization have been steadily decreasing for the past four years (2010-2013)

Country	Income classification*	GNI per capita 2013 (US$)	2010 (US$)	2011 (US$)	2012 (US$)	2013 (US$)
Bangladesh	1	900	7.9	7.5	6.2	5.3
Chad	1	1 020	7.1	6.5	6.3	5.2
Comoros	1	880	15.8	12.1	8.6	4.1
Lao People's Democratic Republic	2	1 460	1.8	1.6	1.4	1.4
Mauritania	2	1 060	6.9	1.8	1.7	0.4
Azerbaijan	3	7 350	38.3	36.1	34.0	34.0
Cuba	3	Not available	199.5	192.8	171.0	142.5

* 1, low-income country; 2, lower-middle income country; 3, upper-middle income country; 4, high-income country.

Table 29: Member states for which expenditures on routine immunization have been inconsistent over the past four years (2010-2013)

Country	Income classification*	GNI per capita 2013 (US$)	2010 (US$)	2011 (US$)	2012 (US$)	2013 (US$)
Central African Republic	1	320	0.5	1.1	0.4	0.9
Democratic People's Republic of Korea	1	NA	2.3	**13.6**[a]	24.9	23.8
Togo	1	530	18.3	19.7	22.9	21.6
Rwanda	1	620	5.4	**3.8**	2.3	6.2
Burkina Faso	1	670	5.8	6.0	5.3	4.6
Kenya	1	930	4.2	4.3	**4.0**	3.7
Benin	1	790	6.5	5.4	1.7	5.6
Viet Nam	2	1 730	6.0	7.3	7.9	7.8
Côte d'Ivoire	2	1 380	7.9	5.2	14.2	12.2
Swaziland	2	3 080	5.3	36.2	32.5	55.4
Djibouti	2	NA	33.9	29.1	59.6	69.0
Guyana	2	3 750	**69.2**	52.4	94.1	118.7
Sao Tome and Principe	2	1 470	70.4	62.9	98.6	117.8
Georgia	2	3 570	34.7	75.5	18.1	40.1
Sudan	2	1 130	3.3	2.8	0.6	5.5
Timor-Leste	2	3 580	2.0	0.8	1.2	2.0
Pakistan	2	1 380	9.1	**9.6**	10.1	6.8
Papua New Guinea	2	2 010	5.3	8.1	10.1	2.1
Senegal	2	1 070	3.6	**9.5**	15.2	1.6
Indonesia	2	3 580	**11.4**	13.9	**8.8**	3.7
Cameroon	2	1 270	14.1	16.3	7.3	11.2

Country	Income classification*	GNI per capita 2013 (US$)	2010 (US$)	2011 (US$)	2012 (US$)	2013 (US$)
El Salvador	2	3 720	98.5	117.6	79.0	88.2
Honduras	2	2 180	49.8	59.1	40.2	45.4
Yemen	2	1 330	1.7	1.4	1.3	1.5
Nicaragua	2	1 780	77.8	58.4	59.7	75.8
Venezuela (Bolivarian Republic of)	3	12 550	51.5	76.7	79.9	72.7
Iran (Islamic Republic of)	3	5 780	11.9	11.8	17.2	17.2
Lebanon	3	9 870	48.5	42.3	53.7	52.0
Colombia	3	7 560	64.0	109.5	101.7	125.7
Saint Lucia	3	7 090	26.9	19.5	29.6	39.9
Seychelles	3	12 530	29.0	22.3	48.3	81.6
Palau	3	10 970	0.0	0.0	0.0	0.0
Grenada	3	7 460	53.2	38.1	56.6	36.7
Ecuador	3	5 510	153.2	161.9	146.9	96.7
Jamaica	3	5 220	178.3	68.0	69.3	68.2
Peru	3	6 390	224.2	149.7	203.7	100.0
Brazil	3	11 690	218.6	**190.1**	**160.9**	193.5
Costa Rica	3	9 550	**194.2**	81.7	149.0	165.4
Saint Vincent and the Grenadines	3	6 580	26.2	17.5	22.3	24.4
Tonga	3	4 490	14.9	20.8	21.3	18.9
Belize	3	4 660	**55.3**	67.6	38.1	41.9
Finland	4	47 110	373.9	445.6	410.3	387.0
Uruguay	4	15 180	149.7	172.0	**166.5**	160.8
Iceland	4	43 930	153.1	212.0	229.7	179.6
Andorra	4	NA	806.4	869.1	808.0	849.3
Saint Kitts and Nevis	4	13 460	28.2	28.3	24.6	30.3
Chile	4	15 230	203.9	85.9	260.2	125.7

* 1, low-income country; 2, lower-middle income country; 3, upper-middle income country; 4, high-income country. NA, not available.
[a] Figures in bold italics are WHO estimates.

Narrative

As would be expected, the reported domestic expenditure for immunization per person targeted varies considerably across Member States in the various income categories.

In general domestic expenditures on immunization per live birth increase as country income increases (direct relationship). Of the 67 Member States that have reported expenditure data for all four years, 13 report an increase in expenditures in the period 2010-2013. In seven Member States there appears to be a downward trend. In the remaining Member States, no specific trend could be determined over this period. The relatively small number of countries reporting an increasing trend does not show any pattern related to income classification. Among them, seven are low income, two are lower-middle income, two are upper-middle and two are high-income countries.

The quality of reported data remains an impediment to the interpretation and use of these data as markers of country commitment. In future, as country capacity for tracking and reporting data through the SHA is strengthened, this source of data may allow better tracking and use of expenditure data.

References

1. UN, Department of Economic and Social Affairs, Population Division. World population prospects: The 2012 revision [CD-ROM]. New York: United Nations; 2013.

2. OECD/Eurostat/WHO. A system of Health Accounts: 2011 edition. Paris, Organisation for Economic Co-operation and Development; 2011 (http://www.who.int/health-accounts/methodology/sha2011.pdf, accessed 16 December 2014).

PRESENCE OF AN INDEPENDENT TECHNICAL ADVISORY GROUP THAT MEETS THE DEFINED CRITERIA (INDICATOR SO1.2)

Highlights

- By the end of 2013:
  - 75 Member States reported a National Immunization Technical Advisory Group (NITAG) that met six process indicators, representing a 47% increase over the 43 reported in 2010 (including 38 developing countries);
  - 108 (57%) Member States reported the existence of a NITAG with an administrative or legislative basis. These Member States account for 83% of the global population.
- Where there is commitment, progress in the establishment and strengthening of NITAGs is rapid.
- Progress needs to be accelerated to reach the GVAP NITAG target.
- Exploration and formalization of special approaches to allow small Member States to benefit from subregional or other Member States' advisory groups needs to be accelerated.
- Very limited resources are available from partners to support NITAG strengthening, particularly in middle-income countries, and such resources need to be enhanced.
- The existence of a NITAG should be a prerequisite for applications from GAVI-eligible countries in the future, and the possibility of accessing health system strengthening funds for establishing and strengthening NITAGs should be considered.

TARGET	Functional NITAGS in all Member States by 2020
DEFINITION OF INDICATOR	A functional NITAG has been defined as one that meets all of the six following process indicators agreed upon in 2010 by WHO and its partners involved with the strengthening of NITAGs: 1. Legislative or administrative basis for the advisory group 2. Formal written terms of reference 3. At least five different areas of expertise represented among core members 4. At least one meeting per year 5. Circulation of the agenda and background documents at least one week prior to meetings 6. Mandatory disclosure of any conflict of interest These six indicators do not guarantee the functionality of the NITAG but have been agreed upon as a minimum set of indicators that will allow for monitoring of progress at the global level. A more comprehensive set of indicators has been published for use at national level *(1)*
DATA SOURCES	Process indicators related to the establishment of NITAGs have been included in the WHO-UNICEF JRF since 2011 and in that year data were collected for 2010. In this summary information from Member States regarding the existence of a NITAG, the specific criteria are derived from the 2014 JRF and compared with JRF data collected for previous years. For those Member States that did not submit or fully complete the JRF for 2014, information from the previous year's JRF was used to give a more comprehensive picture of the situation The denominator used to calculate the proportion of NITAGs in existence is the number of Member States that completed the NITAG-related section of the JRF. The results are presented by WHO region, World Bank national income status categories and population size. Population figures used are those from the UN Population Division *(2)*

Please note that this indicator is available on interactive maps/dashboard for better understanding and exploration of data. Please visit the following website:

http://www.technet-21.org/resources/gvap-indicators

Data limitations

These results are subject to data limitations. First, some Member States did not provide answers to the NITAG-related questions in the most recent JRF, and there is discrepancy between the answers to the NITAG-related questions for the 2013 JRF and the 2014 JRF by some Member States. In addition, the list of Member States is not stable: for example, the Republic of South Sudan became a new Member State in the Eastern Mediterranean Region in July 2011, and then switched to the African Region in 2013. Second, because the analysis focused on data officially reported by the Member States, without a systematic secondary validation process with national counterparts (although this is done in some regions), it may not reflect the actual situation in the Member States. Data accuracy depends on the knowledge, recollection and interpretation capabilities of the person completing the form. Because the introduction of the NITAG-related questions in the JRF is relatively recent, it is possible that some questions may have been misunderstood or misinterpreted. For example, in some countries an affirmative answer regarding the existence of a NITAG may have actually referred to an Inter-agency Coordinating Committee, a committee whose role is to coordinate and support funding, planning, implementation and advocacy of national immunization programmes and strategies. This confusion was actually documented but has been minimized over time, and several countries have corrected the information provided during previous years.

Overall, 62% of Member States reported the existence of a NITAG with formal terms of reference, and 57% reported the existence of a NITAG with a formal administrative or legislative basis among the Member States that reported data. These data should be less susceptible to reporting bias than the mere reporting of the existence of a NITAG and therefore closest to the number of groups actually formed. The number of Member States reporting the existence of a NITAG which complies with all six JRF indicators is also less susceptible to reporting bias.

Results

As of 28 June 2014, 180 (93%) of 194 Member States had completed the 2014 JRF[26] reporting immunization related data for 2013, and 176 (91%)[27] provided a response to at least one of the NITAG-related JRF questions. Among the Member States that did not submit their JRF or their NITAG-related data for 2014, Antigua and Barbuda, Barbados, Bosnia and Herzegovina, Brunei Darussalam, Bulgaria, Ireland, Italy, Libya, Nauru, Singapore, Trinidad and Tobago, Turkmenistan, Ukraine and the United Arab Emirates had reported NITAG data in last year's JRF (i.e. data for 2012). Data for 2012 were included in the 2013 data set for these Member States. Therefore data for 190 Member States were available for the analysis (Figure 32 and Table 30).

[26] As of 28 June 2014, Member States that have yet to submit 2014 JRF data for 2013 include Austria, Barbados, Bosnia and Herzegovina, Brunei Darussalam, Bulgaria, Ireland, Italy, Libya, Monaco, Nauru, Singapore, Trinidad and Tobago, United Arab Emirates and Ukraine.

[27] Member States that have not completed the NITAG portion of JRF include Antigua and Barbuda, Marshall Islands, Serbia and Turkmenistan.

Figure 32: National Immunization Technical Advisory Groups in 2013

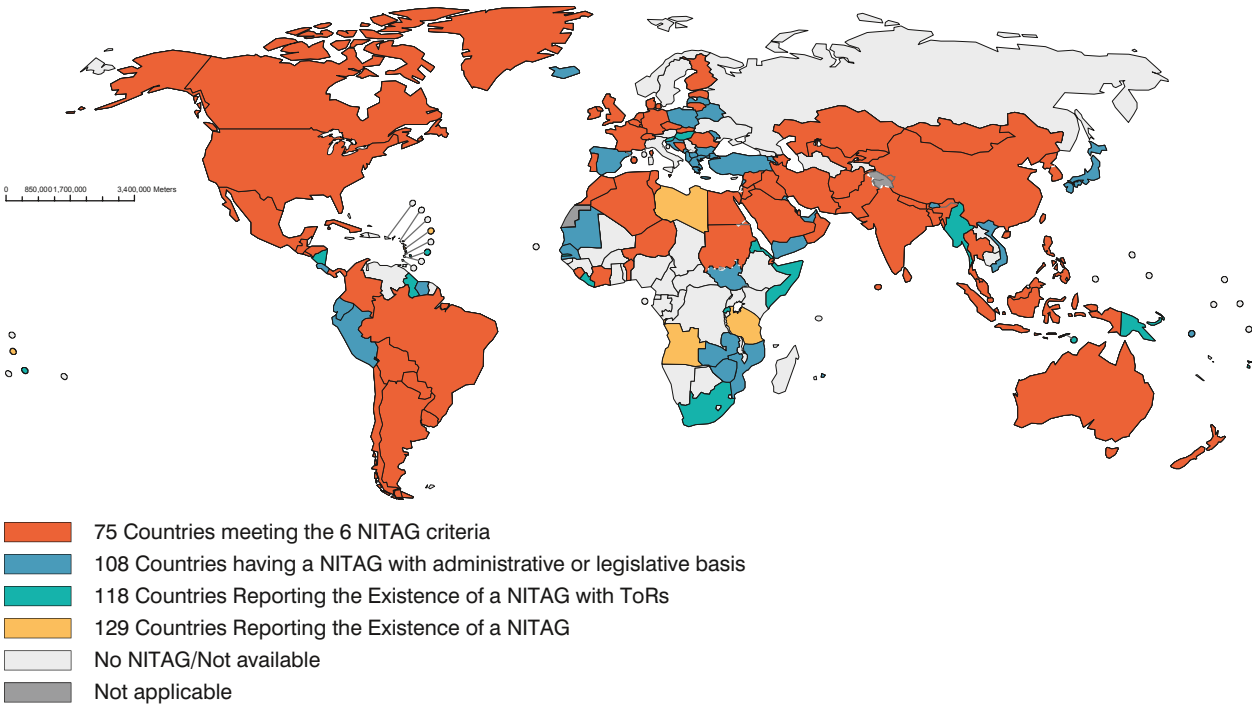


Table 30: Analysis of the NITAG JRF 2013 data at global level and by WHO region

		WHO region						
Indicator		Total	African	Americas	Eastern Mediterra-nean	European	South-East Asia	Western Pacific
	Responding Member States / WHO Member States (%)	190/194 (98)	47/47 (100)	35/35 (100)	21/21 (100)	50/53 (94)	11/11 (100)	26/27 (96)
Existence of a NITAG	No. of Member States responding (%)	129 (68)	19 (40)	23 (66)	21 (100)	40 (80)	11 (100)	15 (58)
	% of population covered	86	35	94	100	67	100	99
NITAG meeting all six process indicators	No. Member States/ No. Member States reporting existence of NITAG (%)	75/129 (58)	5/19 (26)	15/23 (65)	15/21 (71)	24/40 (60)	8/11 (73)	8/15 (53)
	% of responding Member States	39	11	43	71	48	73	31
	% of the entire population covered	74	10	88	90	43	97	86

Notable progress was achieved between 2010 and 2013, and 108 (57%) Member States overall reported the existence of a NITAG with a formal legislative or administrative basis, among the Member States that reported data in the JRF NITAG section. In 2013, there were 75 Member States[28] with a NITAG that met all six process indicators including a total of 48 developing Member States.

In 2013, 22% of low-income countries, 37% of middle-income countries and 55% of high-income countries reported having a NITAG meeting all six

[28] Afghanistan, Algeria, Andorra, Argentina, Australia, Azerbaijan, Bahrain, Bangladesh, Belgium, Benin, Bolivia (Plurinational State of), Bosnia and Herzegovina, Brazil, Canada, Chile, China, Colombia, Côte d'Ivoire, Cuba, Czech Republic, Democratic People's Republic of Korea, Denmark, Djibouti, Egypt, El Salvador, Estonia, Finland, France, Germany, Guatemala, Honduras, India, Indonesia, Iran (Islamic Republic of), Iraq, Ireland, Israel, Jordan, Kazakhstan, Kyrgyzstan, Lithuania, Luxembourg, Malaysia, Maldives, Malta, Mexico, Mongolia, Morocco, Nepal, Netherlands, New Zealand, Niger, Oman, Pakistan, Panama, Paraguay, Philippines, Portugal, Qatar, Republic of Korea, Romania, Saudi Arabia, Sierra Leone, Singapore, Slovakia, Sri Lanka, Sudan, Switzerland, the Syrian Arab Republic, Thailand, Tunisia, the United Kingdom, the United States, Uruguay, Uzbekistan.

process criteria. Overall, 74% live in a country with a NITAG that meets all six process indicators. Forty-one per cent of Member States with smaller populations (less than the median population of all responding Member States) reported the existence of a NITAG that meets all six process indicators compared with 75% of more populated Member States.

The South-East Asia Region had the highest proportion of Member States reporting the existence of a NITAG that met all six process indicators (73%) and the African Region the lowest (26%). The Eastern Mediterranean Region had the greatest percentage (90%) of Member States that had a NITAG based on a formal legislative decree (26% in the African Region, 42% in the Western Pacific Region, 54% in the Region of the Americas (these two latter regions include a substantial number of small Member States), 76% in the European Region, and 82% in the South-East Asia Region). Table 30 presents the 2013 NITAG-related indicators status at global and regional levels.

Narrative

From 2010 to 2013, there was a 75% increase of Member States reporting having a NITAG meeting all six process indicators (75 vs 43). Despite the short period of time and considering that establishing and strengthening NITAGs is a long-term process, there continues to be constant and significant progress in the establishment and strengthening of NITAGs over the past few years. An additional 12 countries met the six process-indicator requirement compared with last year *(3)*.

As already flagged in last year's report, because the proportion of Member States with a NITAG is greater in the more populous Member States than in the less populous ones, the overall proportion of the population supported by a NITAG is substantially greater than the proportion of countries with a NITAG, both at global and regional levels. In areas where regional engagement has been strong and there have been strong regional Technical Advisory Group statements with regard to the need to strengthen NITAGs, rapid progress is being achieved. Of note, NITAG chairpersons participate in immunization and regional technical advisory group meetings in most regions, which has been fostering exchanges between NITAGs and contributing to capacity strengthening by emulation. Country and intercountry NITAG workshops/meetings organized in the past year have been very successful and will further help accelerate progress.

Beyond progress on meeting the indicator, quality improvement in the processes of many NITAGs continues. This, however, remains difficult to quantify at global level. Despite progress, efforts need to be accelerated to reach the GVAP indicator of ensuring that all Member States have the support of a fully functional NITAG. Such progress is particularly necessary in the African Region, which is planning an important NITAG orientation workshop in 2015. Continued concerted advocacy in support of NITAG strengthening from all partners, including staff from partner organizations, is required, including clear communication about the differing responsibilities of NITAGs versus Inter-agency Coordinating Committees. In this context it should be clear that introduction of new vaccines in a country does not in any way diminish the need for the establishment/strengthening of NITAGs but rather just the opposite.

Although falling short of requiring the existence of NITAGs for future funding applications from GAVI-eligible Member States – some applications of which might have been blocked in the short term – strengthening attention to NITAGs and their involvement in proposed vaccine introduction and requiring development plans remains essential to drive progress in GAVI-eligible countries. Enhancing communication on the possibility of accessing GAVI Alliance health system strengthening funds to establish or strengthen NITAGs remains necessary as few if any countries have yet used this opportunity. Global and National level communication should make it clear that the purpose of a NITAG is not only the facilitation of new vaccine introductions, but also to serve as a technical resource to the government and to immunization programme managers. They should use the NITAG's range of expertise to review the strategies and recommendations for use of vaccines in current vaccination programmes as well reviewing and synthesizing evidence to be used for making decisions regarding vaccine introduction.

A special approach has begun to allow Member States with small populations to benefit from subregional or other Member States' advisory groups. It was referred to in last year's report as needs acceleration, giving examples of the Caribbean islands and the small island nations in the Western Pacific Region that do not have a large enough population to justify the establishment of a NITAG and/or adequate resources to support its establishment. Such discussions have been initiated in Region of the Americas for the Caribbean and in the Western Pacific Region for the Pacific Island Member States but not yet brought to fruition.

Current challenges to the establishment of NITAGs continue to include the need to ensure adequate expertise, independence from the government, transparency of the process and quality reviews of the evidence from which recommendations are based. The independence from the government in terms of membership and the implementation of a systematic declaration of interests by core members remain very problematic in some countries due to historical and cultural influences (though this should be easily managed). Systematic declaration of interests is currently the limiting factor for quite a few countries where their NITAGs would otherwise meet all six specific indicators. Meeting these indicators is only a first step, and all committees should continue to be strengthened – a message that must be communicated to countries.

Fostering exchanges between NITAGs is an important way to facilitate support and progress. These exchanges should extend to making evidence available to other groups, such as public posting of systematic reviews orchestrated by or for NITAG review, but this remains limited. A recent publication *(4)* describing the Argentinian NITAG illustrates such useful exchanges and subsequent progress. An international meeting is being planned in Paris, France, 8–9 December 2014 to define the content of the collaboration between NITAGs, such as sharing of experiences and its operational terms.

Very limited resources are available from partners to support NITAG strengthening particularly in middle-income countries. Such resources need to be enhanced. Efforts to establish NITAGs through professional organizations such as academies of paediatrics (as is happening in some African countries) need to be well coordinated with the government to avoid development of parallel groups.

Various NITAG-related tools, including training materials, continue to be developed and are accessible on the NITAG Resource Centre website, which aims to be a central platform for exchange of information on NITAGs. This is maintained by the WHO Collaborating Centre on "evidence-informed policy-making", the Agence de Médecine Préventive and other partners, which represents a resource to help strengthen NITAGs.

Exploring the potential transition from polio or other VPD-specific TAGs (where they exist) to NITAGs has been started and is of particular relevance in the context of the polio Endgame Plan. Emphasis is placed on strengthening routine immunization and integration.

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7. DEMAND FOR IMMUNIZATION

PERCENTAGE OF COUNTRIES THAT HAVE ASSESSED THE LEVEL OF HESITANCY IN VACCINATION AT A NATIONAL OR SUBNATIONAL LEVEL. (INDICATOR SO2.1) & REASONS FOR VACCINE HESITANCY (INDICATOR SO2.2)

Highlights

- Two indicators were pilot tested in the 2012 JRF in the Region of the Americas and European Region. In addition the two indicators were tested within a self-administered questionnaire distributed to the intercountry support teams for regional immunization managers' meetings held in 2013 in the African Region.
- Analysis of the collected data revealed a suboptimal response rate indicating the need for revision of the scope on vaccine confidence as well as the indicators. As a result, the working group on vaccine hesitancy revised the previous indicators broadening the scope from vaccine confidence to vaccine hesitancy and revisited the indicators during its December 2013 face-to-face meeting.
- The European Region volunteered again to pilot test the revised vaccine hesitancy indicators in their 2013 UNICEF/WHO JRF. Forty-five of 53 countries (85%) provided a JRF for 2013 by 26 June 2014.
- Ten of 45 Member States (22%) reported an assessment of vaccine hesitancy and 21 of 45 (47%) reported not having done an assessment. The questions were left blank by 14 countries (31%). More countries indicated some form of vaccine hesitancy assessment in 2013 compared to 2012, 10 of 45 (22%) versus 8 of 48 (17%), respectively. Of the 10 countries that indicated the presence of an assessment, seven provided assessment title(s) and reference(s) to any publication or report on vaccine hesitancy.
- Of the countries that submitted the 2013 JRF form, 16 of 45 (36%) provided at least one reason for vaccine hesitancy while 29 of 45 (64%) did not answer the question. Of the 16 countries that provided reasons, seven based their response on evidence and nine on opinion.

TARGET	Increasing trend in the percentage of Member States having assessed the level of confidence in vaccination at subnational level
DEFINITION OF INDICATOR	• **Indicator 1: Percentage of countries that have assessed the level of hesitancy in vaccination at national or subnational level** · Question 1: Has there been some assessment of vaccine hesitancy or refusal among the public at national or subnational level? · Question 2: If yes, please provide assessment title(s) and reference(s) to any publication/ report. • **Indicator 2: Reasons for vaccine hesitancy** · Question 1: What are the top three reasons for not accepting vaccines according to the national schedule? · Question 2: Is this response based or supported by some type of assessment, or is it an opinion based on your knowledge and expertise?
DATA SOURCES	The European Region volunteered to pilot test the revised vaccine hesitancy indicators in their 2013 UNICEF/WHO JRF

Background

In 2012 SAGE established a working group to address the issue of vaccine hesitancy, which defined vaccine hesitancy and its scope and identified drivers of the phenomenon. In light of the Decade of Vaccines Global Vaccine Action Plan, the working group was asked to develop and pilot test one or several indicator(s) of vaccine confidence that could be used to monitor the issue on a global and national level. As a part of the WHO/UNICEF Joint Reporting Form (JRF) – a questionnaire-based monitoring tool usually completed by national immunization managers designed to examine national immunization coverage, reported cases of vaccine-preventable diseases, immunization schedules and indicators of immunization system performance – the group had developed and pilot tested a set of two indicators on vaccine confidence. Generally, for newly introduced indicators it takes a period of approximately three years to obtain an adequate response rate. Related to the Strategic Objective 2 that individuals and communities understand the value of vaccines and demand immunization both as a right and a responsibility, the working group developed these indicators as a proxy to assess confidence in vaccines. The indicators consisted of the following questions:

- Indicator 1: percentage of countries that have assessed (or measured) the level of confidence in vaccination at subnational level.
- Indicator 2: percentage of un- and under-vaccinated in whom lack of confidence was a fact or that influenced their decision.

The two indicators were pilot tested in the 2012 JRF in the Region of the Americas and the European Region. In addition, the two indicators were tested within a self-administered questionnaire distributed to the intercountry support teams for regional immunization managers' meetings held in 2013 in the African Region.

Analysis of the collected data revealed a suboptimal response rate indicating the need for revision of the scope on vaccine confidence as well as the indicators. As a result, the GVAP working group asked the working group on vaccine hesitancy to revise the previous indicators. The latter broadened the scope from vaccine confidence to vaccine hesitancy and revisited the indicators during its December 2013 face-to-face meeting.

Methods

Sampling frame

The WHO the European Region (53 Member States) volunteered again to pilot test the revised vaccine hesitancy indicators in their 2013 UNICEF/WHO JRF. The 2013 JRF was sent to the countries in the region in January 2014, and countries were asked to return the completed form by 15 April 2014.

Indicators and definition

Given its importance, the working group on vaccine hesitancy decided to keep the previous indicator 1 and only expand to the assessments done on the national level. Indicator 2 was completely revisited to assess the top three reasons for vaccine hesitancy in the country, rather than providing a measured or estimated percentage of un- and under-vaccinated in whom confidence was an influencing factor in their decision (Indicator 2 in 2012).

- **Indicator 1: Percentage of countries that have assessed the level of hesitancy in vaccination at national or subnational level.**
  - Question 1: Has there been some assessment of vaccine hesitancy or refusal among the public at national or subnational level?
  - Question 2: If yes, please provide assessment title(s) and reference(s) to any publication/report.
- **Indicator 2: Reasons for vaccine hesitancy.**
  - Question 1: What are the top three reasons for not accepting vaccines according to the national schedule?
  - Question 2: Is this response based or supported by some type of assessment, or is it an opinion based on your knowledge and expertise?

Results

The JRF form was sent to all 53 Member States in the European Region. Forty-five countries[29] (85%) provided a JRF for 2013 by June 26 2014. Indicator 1 assessed whether a measurement of vaccine hesitancy had been done in the Member States at national or subnational level. The only modification of the indicator to the previous version included in the 2012 JRF was the expansion of the assessments to the subnational and national levels.

Of the countries that submitted the 2013 JRF, 10 (22%) reported an assessment of vaccine hesitancy, and 21 (47%) reported not having done an assessment. The questions were left blank by 14 countries (31%). The response rate for indicator 1 of the JRF increased from 52% (25 of 48) in 2012 to 69% (31 out of 45) in 2013. More countries indicated some form of vaccine hesitancy assessment in 2013 compared to 2012, 22% (10 out of 45) versus 17% (8 out of 48), respectively (Table 31). This decreased non-response by 17% in 2013 (from 48% to 31%). Of the 10 countries[30] that indicated the presence of an assessment, seven provided assessment title(s) and reference(s) to publications or reports on vaccine hesitancy.

Table 31: Number of countries reporting an assessment of vaccine hesitancy at a national/ subnational level

	European Region 2013		European Region 2012	
	Number	Percentage	Number	Percentage
Assessment	n=10	22%	n=8	17%
No assessment	n=21	47%	n=17	35%
Question not completed	n=14	31%	n=23	48%
Total	n=45	100%	n=48	100%

Indicator 2 was modified from the previous version included in the 2012 JRF to assess the top three reasons for not accepting vaccines included in the national schedule. Of the countries that submitted the 2013 JRF form, 16 of 45 countries (36%) provided at least one reason for vaccine hesitancy while 29 (64%) did not answer the question (Table 32).

[29] Countries that did not provide the JRF were: Austria, Bosnia and Herzegovina, Bulgaria, Ireland, Italy, Monaco, Poland and Ukraine. In 2012 countries that did not provide a JRF were: Austria, Finland, Monaco, The Former Yugoslav Republic of Macedonia and Turkey.

[30] Denmark, Estonia, Germany, Luxembourg, Kazakhstan, Kyrgyzstan, Portugal, the Republic of Moldova, Romania, Slovakia.

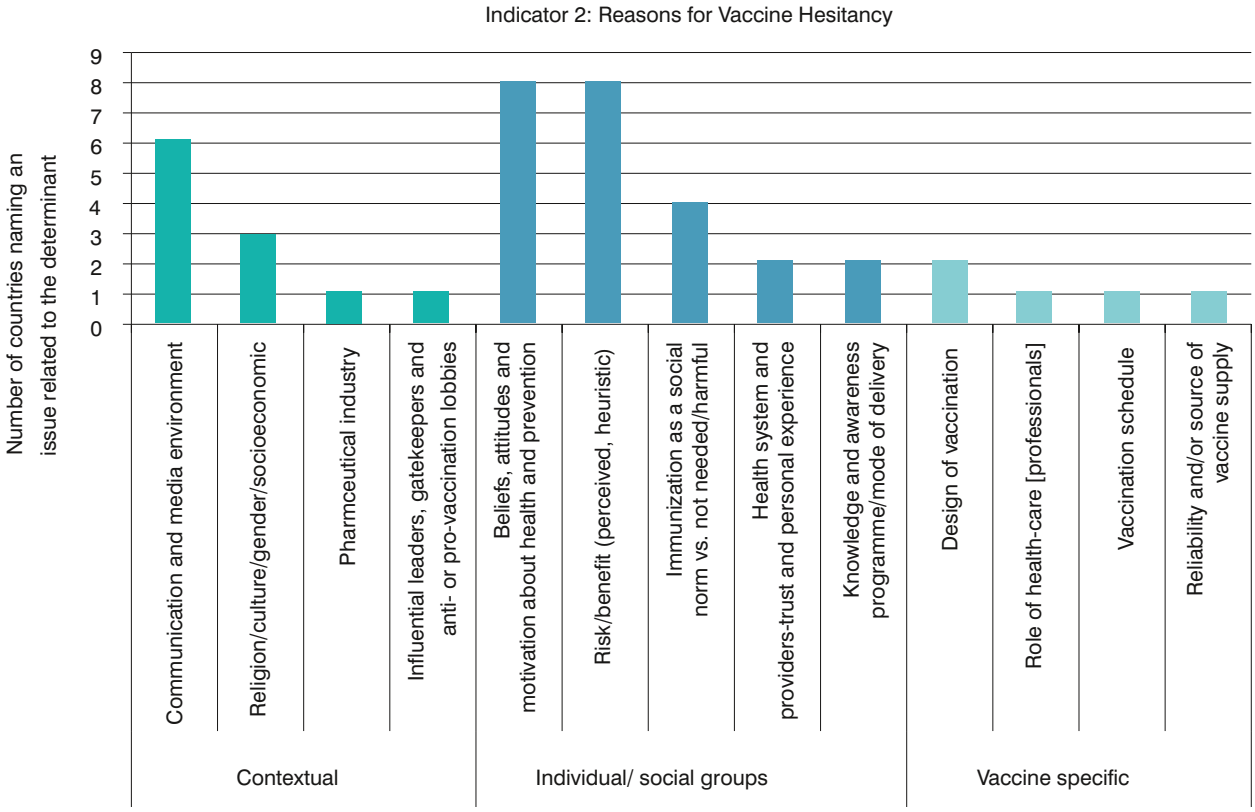
Table 32: Number and percentage of countries that responded to the question on the top three reasons for vaccine hesitancy

	European Region	
	Number	**Percentage**
Reasons provided	n=16	36%
No reasons provided	n=29	64%
Total	n=45	100%

Countries were further asked whether these reasons were evidence-based or opinion-based relying on the expertise of the immunization manager. Of the 16 countries that provided reasons, 7 based their response on evidence and 9 on opinion.

The named reasons were mapped against the matrix of determinants[31] developed by the working group on vaccine hesitancy. The list of reasons is summarized within the matrix of determinants in Figure 33.

Figure 33: Main themes that were indicated as top three reasons for vaccine hesitancy



[31] http://www.who.int/immunization/sage/meetings/2013/april/1_Model_analyze_driversofvaccineConfidence_22_March.pdf?ua=1

Discussion

Modifications to the 2013 JRF were threefold: 1) the scope was widened from the more narrow perspective of vaccine confidence to vaccine hesitancy, which, in addition to vaccine confidence, includes issues related to convenience and complacency; 2) the indicators created to measure vaccine confidence in the JRF 2012 were refined following poor response rates in that questionnaire; and 3) the narrative included in the JRF was adjusted.

More countries responded to the indicator in 2013 than in 2012. This result may be due to an increased number of assessments among the countries in the European Region, better understanding of the question due to the revised narrative, or a result of the inclusion of both national and subnational assessment in the indicator question in comparison to only subnational assessment in 2012. For those countries not responding to indicator 1, it remains unclear if non-response is a proxy for no assessment or lack of understanding or willingness to answer the question.

In regard to indicator 2, 36% of countries (16 of 45) responded to the question and provided reasons for vaccine hesitancy. Response rate to this newly revised indicator was higher compared to the previous indicator used in the 2012 JRF: only 6% (3 out of 48) of the European countries in 2012 had provided a measured or estimated percentage of un- or under-vaccinated in whom a lack of confidence in vaccination was a factor.

The top three reasons for vaccine hesitancy are categorized by the determinants within the matrix developed by the working group on vaccine hesitancy. They are: 1) beliefs, attitudes and motivation about health and prevention, 2) risk/benefit of vaccines (perceived, heuristic), and 3) communication and media environment. Major issues were fear of side-effects of vaccination and distrust in the vaccine, lack of perceived risk by vaccine-preventable disease and the influence of anti-vaccination reports in the media. Interestingly, three countries mentioned unjustified medical contraindications, medical contraindications or the child as being ill the day of the vaccination as reasons for vaccine hesitancy. These were attributed to the category of the role of the health-care professional. The issue of false contraindications should be specified within the matrix of determinants.

A plausible reason for the lower response rate on indicator 2 compared to indicator 1 may be linked to the current structural format of the indicators. Upon analysing the data, it was found that 67% of countries (14 of 21) that answered "No" to indicator 1 failed to continue on and answer indicator 2. Meanwhile, only one country of the 10 that answered "Yes" to indicator 1 did not complete indicator 2. This suggests that countries may have believed that if they answered "No" to indicator 1, they were not required to continue on and complete the remaining questions of the vaccine hesitancy indicator. The JRF questionnaire may require some modification to clarify that indicator 1 and 2 are unrelated and that indicator 2 should be completed regardless of the response in indicator 1.

The overall response rate to both indicators is still suboptimal but not surprising given that, in general, it takes approximately three years to obtain an adequate response rate for newly-introduced indicators of the JRF. There is nothing based on the response rate and pilot testing that would have indicated that this indicator is problematic. Compared to the JRF distributed to Member States in the European Region in 2012, analysis of the 2013 JRF questionnaire certainly indicates an overall increase in response to these two modified indicators.

With further familiarity and adjustment, the vaccine hesitancy indicators of the JRF may prove to be beneficial in identifying key reasons for vaccine hesitancy, examining assessment levels at national and subnational levels and serving as an important advocacy element. Data on vaccine hesitancy, collected on an annual basis, will be a potentiating source of information as well as a monitoring tool to assess possible shifts in the drivers and importance of vaccine hesitancy.

FIVE COUNTRY CASE STUDIES: ROLE OF CIVIL SOCIETY ORGANIZATIONS IN PROMOTING DEMAND OF IMMUNIZATION

Recommended actions for Strategic Objective (SO) 2 outlined in the GVAP include: 1) engage individuals and communities on the benefits of immunization and hear their concerns; 2) create incentives to stimulate demand; and 3) build advocacy capacity. Civil society organizations (CSOs) play a critical role in achieving SO 2 in assisting individuals and communities to understand the value of vaccines, so they demand immunization as both their right and responsibility. The following country snapshots demonstrate CSO actions that contributed to GVAP SO 2 in 2013.

CAMEROON CSO SNAPSHOT

Communication and community partnerships boost demand for vaccines in Cameroon

Western region

Who?	Coalition with key partners, Action pour une Nouvelle Afrique (ANA) and the Child Aid Development Foundation International (CADFIN) Cameroon.
What?	Dual objectives to sensitize the population on the importance of the polio vaccine and advocate to district health leaders to ensure full vaccine coverage of all populations, including those marginalized and/or living in isolated areas.
Where?	Western region.
When?	October–December 2013.
How?	-Educational talks during religious gatherings and community radio programmes. -Animations during organized community meetings. -Informal and formal meetings with religious and traditional health leaders.
Impact?	Partnerships created with religious and traditional leaders on the need for and benefits of the polio vaccine and immunization overall. Activities contributed to the revision of the intervention strategy for vaccine field workers in several health areas of the western region.

Northern region

Who?	Plateforme pour la Promotion de la Vaccination et le Renforcement du Système de Santé au Cameroun (PROVARESSC) with key partner, Union des Organismes d'Appui au Développement Durable (UNOADD).
What?	To better understand community concerns about immunization in order to design targeted interventions.
Where?	Northern region where vaccine coverage is the lowest.
When?	October–December 2013.
How?	Labour-intensive effort to develop trust and understanding between PROVARESSC/ UNOADD workers and communities to enable regular conversations with community members about the health of their children. The work was carried out in the local language.
Impact?	The introduction of community conversations proved to be an effective approach to increasing demand for immunization. PROVARESSC plans to scale up the community conversation model in other provinces of the country with the support of the Cameroon Ministry of Health.

UGANDA CSO SNAPSHOT

UNICEF and Uganda civil society team up to increase capacity and reach of immunization champions

UNICEF saw the huge impact that district immunization 'champions' were having throughout Uganda in linking people at the community level to district health teams for services and supporting teams to organize effective health sensitization, social mobilization and disease surveillance. UNICEF then asked the Malaria and Childhood Illness NGO Secretariat (MACIS) if they could help to strengthen the capacity of the champions and also collaborate with them in their own work. MACIS serves as the secretariat for an extensive network of health-focused CSOs working on malaria control and maternal and child health in Uganda. MACIS also hosts the Uganda Civil Society Immunization Platform supported by the GAVI Alliance CSO Project.

What is a MACIS-supported district immunization champion?

A champion serves as a focal point for platform activities and is primarily responsible for:

- coordinating CSO immunization activities in his/her assigned district;
- maintaining an overview of immunization CSOs active in the district, and motivating and helping new CSOs to join the network;
- fostering and strengthening relationships and collaboration between platform members
- and district health teams, with the aim of CSOs and district health teams working together as a complementary unit for greater impact;
- collecting regular reports from Platform members on immunization progress and challenges in the district and assisting in the analysis and synthesis of the district reports;
- facilitating a range of capacity-building activities for district CSOs in disease surveillance, data collection, analysis and reporting, advocacy and communications and social mobilization.

From November through December 2013, the UNICEF-MACIS partnership supported 111 champions from 88 districts (79% of total districts) to receive training in:

- understanding the broader country context of immunization including the status of immunization in Uganda and an overview of the national Immunization programme;
- utilization of tools for effective and active community disease surveillance and how to train community members in surveillance activities;
- social mobilization and communication;
- creating practical, realistic and detailed community-appropriate solutions to immunization challenges.

As a result, the partnership has achieved a number of successes:

1. increased community demand for immunization services and coverage;
2. greater dialogue between health providers and community members, especially mothers – dialogue that is facilitated by champions serving as a channel of communication between the two;
3. improved disease surveillance, and routine immunization campaigns;
4. stronger links between communities, the Health Ministry and development partners.

The champions' community perspectives and experiences are shared with UNICEF and help ensure that UNICEF's activities are more targeted, appropriate and ultimately more successful. On the other hand, the champions benefit from UNICEF's global, regional and country-level expertise, networks, tools and materials.

MACIS Uganda's model for sensitizing communities on immunization and expanding immunization coverage through district immunization champions is certainly worthy of the attention and support of UNICEF, other development partners and the Ugandan government. The champions model is truly a recipe for success for immunization control in Uganda.

Source: Adapted from UNICEF teams up with immunization champions in Uganda *written by MACIS Uganda for the GAVI Alliance CSO Project Newsletter Volume 1 Issue 3, 2013,* with *additional information provided by Elizabeth Kasujja, Programme and Communications Officer, MACIS Secretariat, Uganda.*

KENYA CSO SNAPSHOT

An effective advocacy model to increase vaccine coverage in a devolved health care system in Kenya

With the new 2010 Constitution of Kenya, health care provision within a devolved system of governance has been re-defined and immunization was no exception. According to the new Constitution (Fourth Schedule), county governments are entrusted with all functions related to health care, *except for* health policy and national referral health facilities. County health services are therefore responsible for the promotion of primary health care, which includes immunization. With the responsibility of immunization delivery divided between national and county governments, Kenya AIDS NGOs Consortium (KANCO), a nationwide coalition of CSOs working in HIV & AIDS and health, identified a need to clarify the legal and institutional arrangements for ensuring progress to increase vaccine coverage across the country.

In collaboration with immunization partners, KANCO embarked in 2013 on a national effort to advocate for increased vaccine coverage at the county level and a new national immunization law that clearly articulates the role of the national versus county governments in immunization delivery and scale up.

Proposing solutions to increasing vaccine coverage in counties

At the subnational level, KANCO realized that information on the current status of vaccine coverage in all 47 counties of Kenya was unavailable. As a first activity, KANCO undertook a mapping of all 47 county governments to determine vaccine coverage.
The mapping revealed that 57% of counties and 24% of districts are below 80% vaccine coverage (and the national average for Kenya of 82%). KANCO then took the information to legislators from the poor performing counties. KANCO discussed with them the findings and sensitized them on the effects of poor immunization to child health. As solutions to increasing coverage, KANCO proposed organizing intensified routine immunization campaigns and SIAs, especially in hard-to-reach areas. KANCO also proposed the inclusion of these activities in the county-level micro-plans, which are still in development in a majority of these counties and supported by UNICEF. KANCO will continue its advocacy focusing on securing funding by county governments for implementation of the micro-plans, including routine and supplementary immunization activities.

Advocating for a national immunization law

At national level, KANCO prepared a policy paper to help increase understanding among parliamentarians on the implications of a devolved health care system, particularly in the delivery of immunization. Titled *Immunization Delivery in Kenya: Devolution and its Implications,* the paper led to a proposal by KANCO to establish a national immunization law that would stipulate the role of national and county government. The law would clarify the various health care functions including funding for and implementation of the Expanded Programme for Immunization (EPI). KANCO organized two parliamentary briefings to share the findings from the report and to engage parliamentarians in a discussion on immunization and the challenges and opportunities of a devolved health care system. As a result, the Parliamentary Health Committee has drafted legislation addressing the role of the state in immunization financing and access as well as clarifying the functions of the national versus county governments in the delivery of EPI services.

While the successful advocacy by KANCO seems simple and straightforward, this was no small feat and took smart strategic advocacy strategizing, planning and persistence. Advocacy is complex, requires time to build relationships, gather data and communicate the information effectively to target audiences. Advocating for a new national immunization law while the country was undergoing a constitutional and governmental change – that included changing Ministry of Health officials and many competing priorities – was not easy. These challenges did not deter KANCO and they swiftly reached out to new Health Ministry officials and sought out partnerships with WHO, UNICEF and the Sabin Vaccine Institute to seek clarity on data and information in order to sharpen their justification for new legislation.

KANCO will continue to work to ensure the content of the immunization law is clear and responds to the needs of all Kenyans. The organization will continue to engage the Ministry of Health, parliamentarians, the media and civil society to ensure passage of the law as well as its funding, implementation and enforcement.

Source: Jackson Ndegwa, Policy and Advocacy Manager, Kenya AIDS NGOs Consortium (KANCO).

GHANA CSO SNAPSHOT

A perfect match: Ghana's civil society-Government partnership to save lives from measles and rubella

Ghana has made significant gains in controlling measles. Over the past decade not a single Ghanaian child has died from the disease. To ensure gains in measles control are sustained, in 2013 the Ghana Government launched a national measles-rubella vaccination campaign that aimed to vaccinate 11 million children from 9 months to 14 years of age.

Recognizing the important immunization control work of the Ghana Coalition of NGOs in Health (GCNH), the Ghana government invited GCNH to work alongside it during the campaign. Specifically, GCNH was responsible for educating and mobilizing communities on the importance of the measles-rubella vaccine in five districts with very low vaccine coverage. The presence of GCNH in all 10 regions of the country and its track record of sensitizing thousands of people in 100 hard-to-reach communities made it an ideal partner.

With funding from the Ghana National Health Service Expanded Programme on Immunization and Lions Club International, GCNH members directly facilitated 145 665 vaccinations in the five focus districts.

They also distributed 5000 leaflets on measles-rubella and educated 200 community volunteers and 500 community members.

GCNH's approach to success in educating communities involves multiple strategies depending on the community context. These include household visits, radio discussions on community FM stations, holding small group discussions in schools, markets, taxi and lorry stations, participating in Ghana National Health Service outreach/patrol immunization teams and supporting nurses to deliver vaccines. This small example demonstrates the importance of civil society and government recognizing each other's strengths and how combining these strengths can achieve greater impact.

Source: Adapted from Ghanaian CSOs go door-to-door against measles and rubella *written by the Ghana Coalition of NGOs in Health for the GAVI Alliance CSO Project Newsletter Volume 1 Issue 3, 2013,* with *additional information provided by Cecilia Senoo, Executive Director,* Hope *for Future Generations, Ghana.*

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PAKISTAN CSO SNAPSHOT

Civil society filling the gap where services are scarce in Pakistan

In Pakistan, CSOs work in hard-to-reach areas and with under-privileged communities – a critical need given that the country suffers from large numbers of displaced people, challenging geographical terrain, extreme climates, lack of adequate infrastructure, high rates of poverty and the world's highest child and maternal mortality rates. In order to strengthen civil society presence in these areas and communities, in 2009 the Pakistan Ministry of Health under its Expanded Programme on Immunization, supported the establishment of a consortium of 15 CSOs working in immunization and health. In 2011 the consortium officially established the Pakistan CSOs Coalition for Health and Immunization (PCCHI) with 48 CSO members covering all five provinces of the country. The PCCHI works at the community level to address deficiencies in the national immunization programme and to improve maternal and child health care.

As a result, CSOs in Pakistan are helping to resolve bottlenecks in the overall health system and delivery of vaccines as well as address challenges due to religious taboos, misinformation or lack of knowledge. These solutions are grounded in the experience of CSOs especially in Sindh province in the south-east part of the country on the border with India. In 2014, PCCHI expanded its work to the Punjab province and added 28 Punjab-based CSOs.

Highlights of activities in the Sindh province by CSO members in 2013 include the following.

Aga Khan Health Services Pakistan (AKHSP): 53 community health workers and 25 health committee members trained on social mobilization; 26 053 people educated about family planning, immunization, nutritional rehabilitation, birth preparedness, safe delivery, antenatal and postnatal care; two EPI centres established in Union Councils of Dad Khan Jarwar and Mirabad; administration of seven national immunization days and 11 471 vaccination doses by community health workers in target communities; administration of five subnational Immunization Days/ Mop-Ups and 5775 vaccination doses.

Aga Khan University (AKU): Capacity building of rural Tehsil Headquarters hospital staff to correctly perform the rotavirus enzyme immunoassay test in target areas; community mobilization sessions about 'rotavirus gastroenteritis'.

Health Education and Literacy Programme (HELP): In the city of Shahdadpur, 5993 vaccine doses given to children and 12 720 doses of tetanus toxoid administered resulting in an increase in vaccine coverage to 74% for women and 80% for children; 400 health education sessions conducted on immunization, breastfeeding and complementary feeding; trainings for doctors and paramedics working in rural areas on immunization, infant and young child feeding and community-based management of acute malnutrition.

Pakistan Village Development Program (PVDP): Created awareness among mothers in two districts on the danger signs of illness in children and pregnant women as well as the benefits of immunization. PVDP's approach to raising awareness involves using pictorial images to guide discussions about each vaccine or health issue.

Aga Khan Health Services and Health And Nutrition Development Society (HANDS): Capacity building of 250 stakeholders, including health-care providers and community health workers from village health committees and health management committees. Sessions focused on empowering stakeholders with knowledge on why routine immunization and maternal, newborn and child health is important.

Through its work, CSOs in Pakistan have become recognized as an essential partner in advancing the immunization control agenda through persistent efforts to reach the most difficult populations. This case study reinforces the absolutely critical role and contribution of CSOs in the most challenging environments.

Source: Adapted from Engaging CSOs in Immunization (Pakistan's Perspective) *written by Dr Alina Akhayar, Pakistan CSO's Coalition for Health and Immunization for the GAVI Alliance CSO Project Newsletter Volume 2 Issue 1, 2014,* with *additional information provided by Professor DS Akram, Honourable Chairperson, Health Education and Literacy Programme (HELP), Pakistan.*

CHAD CSO SNAPSHOT

The simple power of information-sharing to incentivize communities for immunization in Chad

All regions in Chad are hard to reach and have low vaccine coverage. While the latest official estimate (from 2012) of DTP3 coverage is 72%, WHO and UNICEF estimate it to be much lower (at 45%); polio coverage is 56% and MCV is slightly higher at 64%. The country's harsh desert climate, mostly rural population, on-going internal conflict, weak infrastructure and large refugee population have contributed to Chad's ranking as one of the poorest countries in the world.

In this challenging environment, CSOs play a critical role in service delivery of health and immunization services. Responding to the realities of Chad, the Plateforme des Organisations de la Société civile pour le soutien à la Vaccination et à l'Immunisation au Tchad (POSVIT) with support from the GAVI Alliance was established in 2013 to coordinate CSOs working in health system strengthening and immunization.

The platform decided to focus its initial activities on the five regions of the country that are closest to the capital city, N'Djamena – Mayo-Kebbi East, Mayo-Kebbi West, Logone Occidental, N'Djamena and Guéra – and plans to continue reaching out to regions farther out. In Chad in-person visits are the most effective way to communicate with the regions; by focusing on the five closet regions first, the platform can start to build a person-to-person information-sharing network.

As one of its first activities, from November to December 2013, POSVIT successfully organized meetings to educate and train its 86 CSO members in five focus regions to:

- strengthen the capacity of CSO members on the various techniques of social and community mobilization, in order to support immunization;
- convince CSOs and the wider population of the social obligation to get vaccinated;
- promote synergies between CSOs and regional health delegations who are responsible for implementing the national health strategy and plans at the regional level.

The meetings allowed participating CSOs to identify and discuss barriers to immunization, notably the issue of drop-outs and refusal to accept a vaccine. CSOs identified that the recent measles outbreak was due largely to:

- parents' poor understanding of immunization in terms of –
  - their health benefit and value for society
  - vaccine schedule and its importance, especially for children
  - illnesses caused by not being immunized
  - potential side-effects of specific vaccines;
- parents' skewed perceptions of immunization services;
- indifference of religious and cultural leaders towards immunization activities;
- parents' poor knowledge of immunization and related services, resulting in parents' not seeking essential health services for their children or demanding routine immunizations services and campaigns.

The platform and its CSO members have gained valuable community perspectives on immunization and will use the information to develop and implement targeted, evidence-based community-level social behaviour change campaigns. CSOs are also more aware now of the importance of their role in sharing information across remote areas, and communities now are aware that they can engage CSOs as information resources. This simple example from Chad demonstrates the power of knowledge and information as a critical component in ensuring future success in immunization scale up.

Source: Adapted from CSOs in Chad engage in social mobilization *written by POSVIT for the GAVI Alliance CSO Project Newsletter Volume 1 Issue 3, 2013,* with *additional information provided by Brenda Hegarty, Technical Advisor,* GAVI *Alliance CSO Constituency Project, Catholic Relief Services (CRS).*

8. STOCK-OUT AND ACCESS TO SUSTAINED SUPPLY OF VACCINES OF ASSURED QUALITY

PERCENTAGE OF DOSES OF VACCINE USED WORLDWIDE THAT ARE OF ASSURED QUALITY (INDICATOR SO 5.1)

Highlights

- As of July 2014 98.5% of the total vaccine doses used globally in all national immunization programmes is of assured quality.
- The first vaccines prequalified from China in October 2013 and the successful reassessment of the China Food and Drug Administration (CFDA) has opened and sustained the pathway for more vaccines to be prequalified from China in the coming five years.
- All vaccines used by national immunization programmes are produced in 43 Member States, of which 36 have a functional regulatory system, as monitored by WHO.
- New suppliers of vaccines, such as Mexico, are entering the market and may contribute to increasing and securing the global supply of WHO/UN prequalified vaccines.
- Major vaccine suppliers, China and India, have significantly increased their investment to be able to sustain and expand their regulatory oversight for vaccines, medicines, medical devices, blood supplies and traditional medicines.

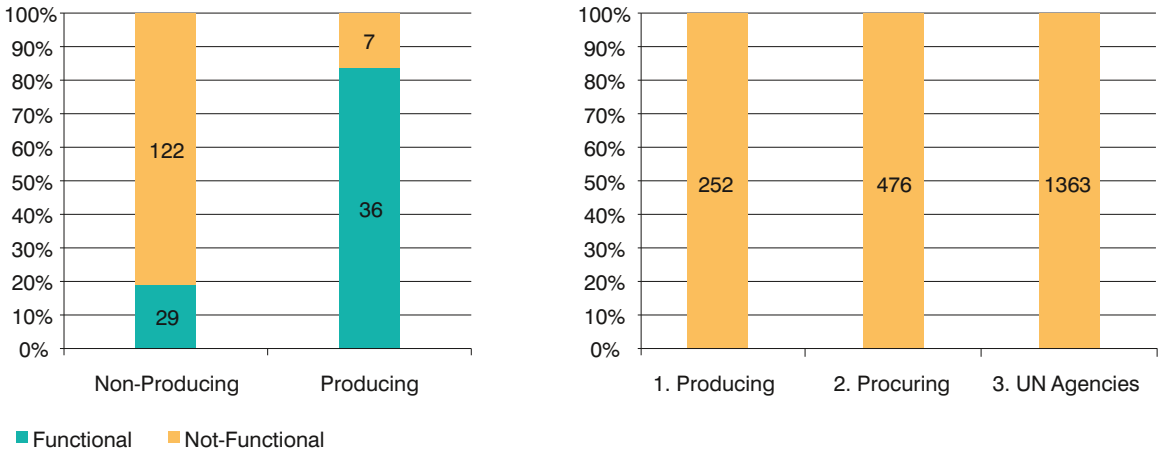
TARGET	100% of vaccine doses by 2020
DEFINITION OF INDICATOR	The proportion of vaccine doses used globally by national immunization programmes that are of assured quality Vaccines of assured quality include vaccines produced in a country with a functional national regulatory authority (NRA), including vaccines prequalified by WHO[32]
DATA SOURCES	• WHO database of prequalified vaccines • WHO-UNICEF joint reporting forms (JRFs) (for number of doses used) • WHO assessments of NRAs • Additional information from vaccine manufacturers, NRAs and national control laboratories, and national immunization programmes

[32] For more information, please refer to the GVAP Secretariat report 2013,p. 80. http://www.who.int/entity/immunization/global_vaccine_action_plan/GVAP_secretariat_report_2013.pdf?ua=1.

Results

WHO has documented that 43 countries are producing human vaccines, of which 36 have functional NRAs (as assessed by WHO) as shown in Figure 34. Twenty-four of these Member States were producing one or more WHO/UN prequalified vaccines by the end of 2013, China being the latest addition, having been able to prequalify Japanese encephalitis vaccines in late 2013. Over 4.8 billion people (about 70%) live in the 65 countries, both vaccine producing and non-producing, where there is direct oversight by a functional NRA. People living in countries without functional NRAs, however, still have access to WHO/UN prequalified vaccines through their national immunization programmes.

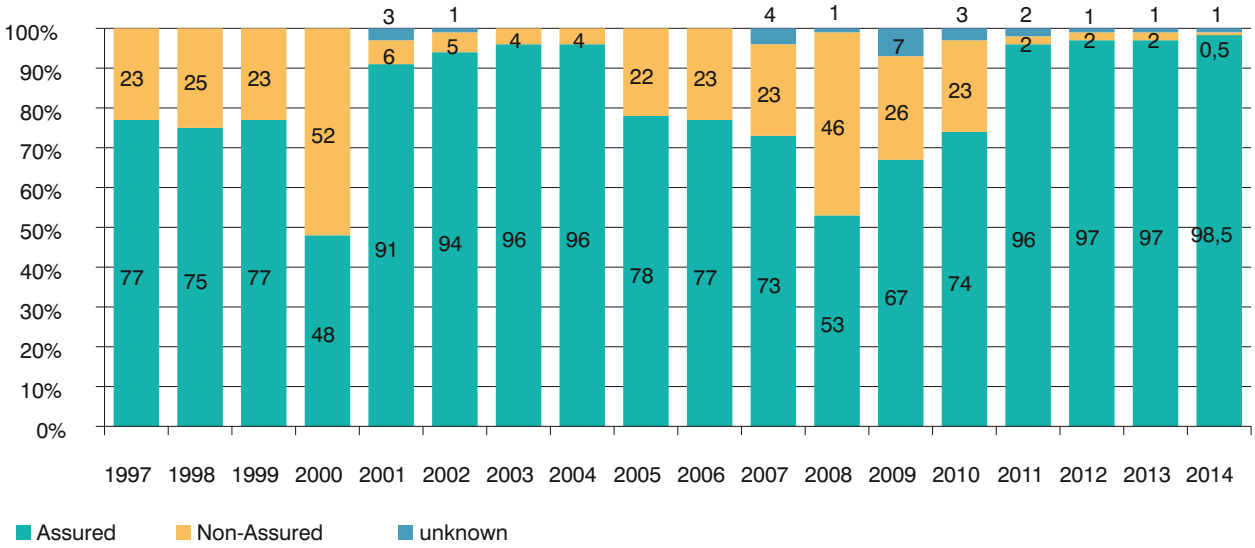
Figure 34: Vaccine producing and non-producing Members States, by the functionality of their NRAs*



* As of July 2014.

Overall, 98.5% of the global doses of vaccines used in national immunization programmes are of assured quality (Figure 35), since Mexico's NRA became functional in 2014. Meeting the target of 100% by 2020 is highly likely.

Figure 35: Percentage of assured vs non-assured quality vaccines used worldwide, 1997-2014



Since 2009, India and China – Member States with large populations and large capacity to produce different types of vaccines – have accelerated their efforts to strengthen their regulatory oversight for vaccines. India – currently one of the world's major suppliers of prequalified vaccines – already had a functional NRA by this time. China's NRA became functional in early 2011 and more recently Mexico in early 2014. However, Mexico's current vaccine production currently does not have a significant impact on the doses of assured quality vaccines. Both China (all types of vaccines) and Mexico (hepatitis B, polio, influenza and quadrivalent or pentavalent vaccines) may contribute to the increased availability of prequalified vaccines. Continuous efforts by these two Member States to meet the highest quality standards have been documented through reassessment conducted in China (April 2014) and Mexico (March 2014) and reflect major commitments by their respective governments and NRAs. This commitment has involved a massive recruitment of regulatory staff in the CFDA and substantially increased budgets (totalling US$ 500 million to US$ 1 billion in each country) between 2008 and 2012. Moreover, through its NRA, COFEPRIS, Mexico has also invested in a risk management approach, including improving its pharmacovigilance system and regulatory inspections. The system is 100% self-funded through a fee system and is autonomous with long-term vision and clear goals to sustain the regulatory system; in future it could serve as a regional reference NRA for the Americas. Both Mexico and China have committed additional support to their NRAs in their national five-year strategic plans. CFDA is now engaged through a declaration of intent with WHO in another long-term expansion of its regulatory functions to medicines, medical devices, blood supplies, traditional medicines and food safety management.

WHO's primary priorities include vaccine-producing countries with non-functional NRAs that may have significant impact on global supply, may have potential to develop their local production, or where major investments have been made by vaccine industry and/or government for specific vaccines such as influenza. These countries are: Argentina, Bangladesh, Islamic Republic of Iran, Romania, Serbia, Viet Nam and Ukraine. Additionally, there are countries potentially at risk for not being able to retain their functional status in future assessments. They include: India, Russia and Senegal. Finally, the last group of countries includes those that are producing vaccines but have difficulties in sustaining production: Bolivarian Republic of Venezuela, Egypt, Islamic Republic of Iran, Myanmar, Pakistan and Tunisia. WHO's secondary priorities are to guide other NRAs through a decentralized approach with WHO regional offices to develop the recommended regulatory functions (four or six functions according the main source of vaccines).

NUMBER OF COUNTRIES REPORTING A NATIONAL-LEVEL STOCK-OUT OF AT LEAST 1 VACCINE FOR AT LEAST 1 MONTH (INDICATOR SO5.2)

Highlights

- Forty-three per cent of countries reported experiencing a national level stock-out in 2013, for at least one vaccine and for at least 1 month. Compared to the situation a year earlier, a slight deterioration was noted (an increase from 37% to 43% of countries).
- A single stock-out event is more the exception than the rule. For countries reporting national-level stock-outs, almost two stock-out events per year are reported on average and with a duration lasting between 28 to 45 days on average.
- The incidence of national stock-out of vaccines is concentrated in countries in sub-Saharan Africa and in the Western Pacific Region. Of all countries reporting national-level stock-outs in 2013, a quarter (26%) of them are in west Africa.
- National level stock-outs of vaccine occur in countries of all income groups – 20 lower-middle income countries and 3 upper-middle income countries represent 59% of all countries reporting national level stock-outs in 2013.
- Close to 70% of countries reporting national level stock-out have medium to large birth cohorts.

TARGET	Two thirds reduction in countries reporting national level stock-outs by 2020 (from the 2010 level)
DEFINITION OF INDICATOR	Number of countries reporting a national level stock-out of at least 1 vaccine for at least 1 month
DATA SOURCES	WHO-UNICEF joint reporting forms (JRFs)

Please note that this indicator is available on interactive figures/dashboard for better understanding and exploration of data. Please visit the following website:

http://www.technet-21.org/resources/gvap-indicators

When reviewing the data, hover over the pie charts and countries to get additional information

Defining vaccine availability

National vaccine supply chain systems are considered the backbone of any routine immunization programme. Their role is to provide uninterrupted availability of potent vaccines at service delivery levels in the most efficient manner possible. If vaccine availability is interrupted, vaccination cannot take place, putting a country at risk for not reaching its immunization coverage goals and targets, and its citizens at risk of disease.

The most common metric of availability is the incidence and duration of a vaccine stock-out. Ideally, this metric should be measured at the lowest distribution level of the vaccine supply chain given its potential impact on service delivery and, ultimately, on vaccination coverage. Unfortunately, in-country data systems are seldom strong enough to collect and report this information back up the chain. Until investments in strengthened logistics management information systems occur, an alternative (though imperfect) is to measure vaccine stock-outs occurring at the national vaccine store – the central warehouse at national level. Given the global consensus to maintain a 3-month buffer stock of vaccines at national level at all times, a vaccine shortage at national level would indicate that the safety stock has been depleted and vaccine availability for lower levels of the system could be compromised.

That being said, any interpretation of this indicator needs to be made giving consideration to its limitations. Firstly, a national level stock-out could be the result of exogenous factors outside the control of the national immunization programme (e.g. global vaccine supply shortages, procurement or international transport delays, limited competition/parallel monopoly, transition to new formulations (i.e. from DTP/DTP-HepB to DTP-HepB-Hib, bringing risks on both supply and demand side), and other factors. Thus, national level stock-outs can occur for a host of different reasons beyond poor national forecasting of needs or inefficient in-country stock management. Secondly, a national-level shortage of vaccine does not necessarily translate into shortages at subnational levels or an interrupted availability of vaccines for service delivery. The reverse is equally true in that vaccine shortages at subnational level could be occurring without a national level stock-out occurring. If subnational level shortages do occur, other causes could be at the root of it – a breakdown of the distribution system or poor stock management at lower levels of the supply chain. Furthermore, there could be enough stock of vaccines subnationally to ensure vaccine availability at the service level even if shortages occur at national level.

These reasons encapsulate the limitations of using national-level vaccine stock-outs as a metric of vaccine availability. Until investments in logistics management information system strengthening allow countries to report better-quality subnational information, the national indicator is a measure of a stressed system – a shortage of vaccines at national level is not a desirable situation and national level stock-outs of vaccines do highlight that recommended safety stocks have been used up, putting the performance of the national immunization programme at risk.

Data sources availability and quality

The unique source of information for this indicator is the WHO-UNICEF Joint Reporting Form (JRF). To align with the GVAP period, this analysis reports on the information collected between 2010 and 2013 – the last reporting year available. Among the JRF routine immunization indicators are several questions relating to vaccine availability. For each vaccine in the national immunization schedule, Member States respond to a yes/no question about whether a stock-out occurred at the national level. In the case of a reported stock-out for a particular vaccine, the duration of the stock-out in months is reported in a separate field. A stock-out event is defined when a stock-out of a vaccine occurred for at least one month. For example, if a stock-out (of at least one month) in a country were reported for two vaccines, these would be considered as two stock-out events for that country.

To improve cross-country comparisons, the analysis focused on select vaccines common to all national immunization schedules. These include: BCG, DTP and measles-containing vaccines (e.g. DTP-HepB-Hib or MMR), and polio (OPV or IPV). On the basis of these vaccines, the reporting completeness for this indicator (as measured by the proportion of Member States responding) ranged from 85% to 88% depending on the reporting year. The quality of the data was improved by following up with WHO regional and country office focal points to clarify and resolve data inconsistencies.

Lastly, this analysis was undertaken for the 91 countries that were prioritized as part of the Global Vaccine Action Plan (GVAP) costing and financing estimates. The full list of countries is available in Annex 3, Table 9 of the Global vaccine action plan 2011-2020 *(1)*. In subsequent analyses, the data availability will cover all 194 WHO Member States as well as new vaccines like pneumococcal and rotavirus.

Results

Of the 91 Member States included in this analysis, 39 (43%) reported experiencing a national level stock-out in 2013 for at least one vaccine and for at least 1 month. This represents a slight improvement in the situation since 2010 where 43 (or 47% of countries) had reported national level stock-outs (Table 33). That said, against the situation a year earlier in 2012, a slight deterioration was noted.

Table 33: Summary statistics for countries reporting at least one national level stock-out event[1]

	2013	2012	2011	2010
Number of countries reporting stock-outs	39	34	35	43
Countries reporting stock-outs (%)	43%	37%	38%	47%
Number of stock-out events[2, 3]	69	56	63	74
BCG vaccine	*35*	*30*	*29*	*38*
DTP-containing vaccines	*10*	*8*	*11*	*18*
Measles-containing vaccines	*11*	*7*	*12*	*7*
OPV/IPV vaccines	*13*	*11*	*11*	*11*
Average number of stock-out events[3]	1.8	1.7	1.8	1.7
Average duration of a stock-out event (days)[3]	36.7	28.2	30.5	45.3

[1] For BCG and DTP, measles and polio-containing vaccines.
[2] Some countries reported multiple stock-outs in a given year, which is why this number is higher than the number of countries reporting stock-outs.
[3] For countries reporting stock-outs.

A single stock-out event is more the exception than the rule. For countries reporting national level stock-outs, multiple events occur within a reporting year (separate stock-out events in the same year for different vaccines). The number of stock-out events on average ranged from 1.65 to 1.80 per year for countries reporting stock-outs – almost 2 stock-out events per year on average. Given that stock-out events with a short duration (less than 30 days) were excluded from the analysis, it is not surprising that average duration of a stock-out event exceeded a month – anywhere between 28 to 45 days on average during the four-year period analysed. Table 34 shows the number of countries reporting national-level stock-outs.

Table 34: Number of countries reporting at least one national level stock-out event[a], by region, income group and population size

	No. of countries[1]	2013	2012	2011	2010
Grouping by region					
Americas Region	10	3 (4)	1 (3)	3 (6)	4 (7)
West Africa	16	10 (19)	4 (6)	5 (7)	8 (11)
Central Africa	8	5 (8)	4 (8)	4 (9)	6 (11)
East and southern Africa	14	7 (13)	9 (17)	9 (10)	9 (14)
Eastern Mediterranean Region	10	1 (3)	1 (1)	2 (5)	2 (2)
European Region	9	2 (3)	5 (7)	6 (17)	5 (11)
South-East Asia Region	9	3 (4)	3 (3)	1 (2)	3 (7)
Western Pacific Region	15	8 (15)	7 (11)	5 (7)	6 (11)
Grouping by income[2]					
Low income	34	16 (25)	15 (27)	17 (26)	16 (23)
Lower-middle income	47	20 (39)	18 (27)	14 (30)	22 (44)
Upper-middle income	10	3 (5)	1 (2)	4 (7)	5 (7)
Grouping by population size[3]					
<100 000	26	12 (19)	12 (18)	9 (16)	12 (20)
>100 000 but <500 000	32	11 (18)	9 (14)	9 (15)	12 (21)
>500 000	33	16 (32)	13 (24)	17 (32)	19 (33)

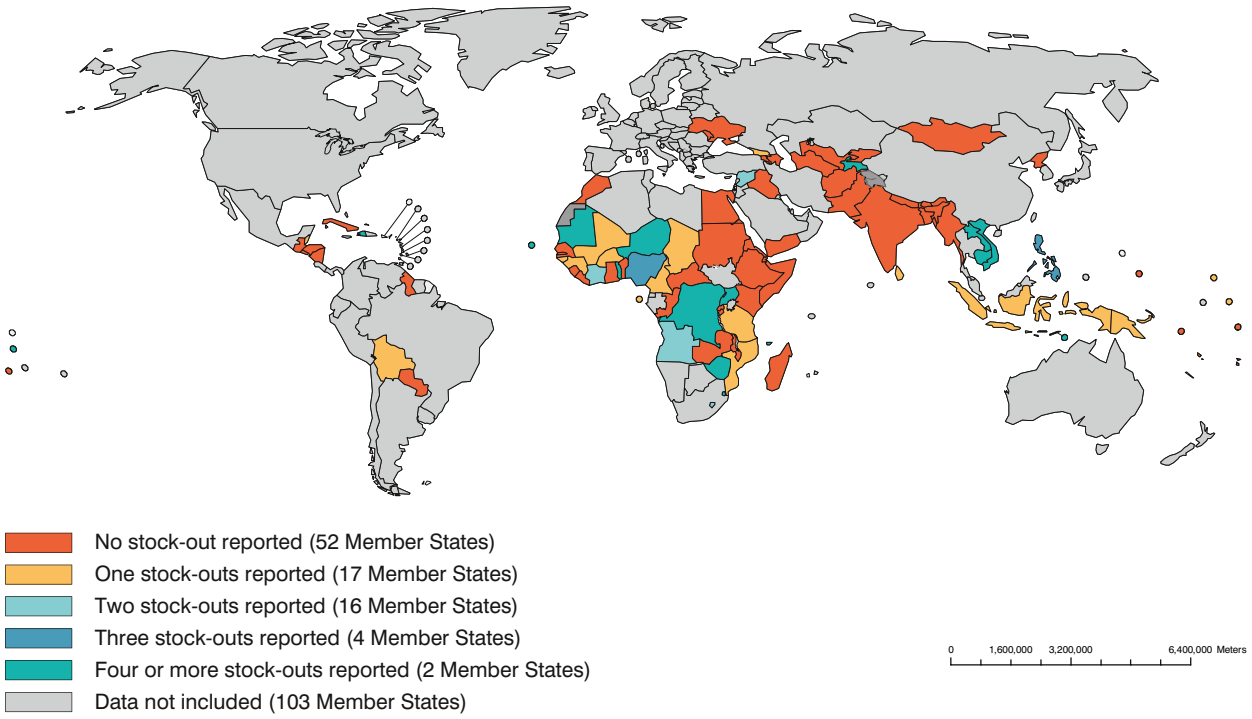
[a] Number of stock-out events in parentheses.
[1] This column represents the breakdown of the 91 focus countries by region, World Bank income group and population size.
[2] According to the World Bank classification of countries.
[3] As expressed by the number of births in the country.

A deeper analysis by vaccine indicates that BCG vaccine shortages represent half of the stock-out events reported (mainly related to supply issues due to the reduction of the number of manufacturers). The remaining stock-out events are fairly evenly spread between DTP/measles-containing vaccines and polio/IPV. Unfortunately, the information available for this analysis provides neither an understanding of the global supply situation of these vaccines nor whether global shortages in supply were the reasons behind the shortages reported in countries.

An in-depth review of the typology of countries suffering from national level stock-outs of vaccines reveals the following findings.

- The incidence of national stock-out of vaccines is concentrated in countries in sub-Saharan Africa and in the Western Pacific Region (see Figure 36). Of all countries reporting national-level stock-outs in 2013, a quarter of them (26%) are in west Africa.
- National level stock-outs of vaccine occur in countries of all income groups; 20 lower-middle income countries (or 51%) and 3 upper-middle income countries (or 8%) reported national level stock-outs in 2013.
- Close to 70% of countries reporting national level stock-outs have medium to large birth cohorts.

Figure 36: Vaccine availability in 91 Member States, 2013



Reference

1. Global vaccine action plan 2011-2020. Geneva: World Health Organization; 2013 (http://www.who.int/iris/bitstream/10665/78141/1/9789241504980_eng.pdf?ua=1, accessed 16 December 2014).

9. RESEARCH AND DEVELOPMENT INNOVATIONS MAXIMIZE THE BENEFITS OF IMMUNIZATION

NUMBER OF VACCINES THAT HAVE EITHER BEEN RE-LICENSED OR LICENSED FOR USE IN A CONTROLLED-TEMPERATURE CHAIN (CTC) AT TEMPERATURES ABOVE THE TRADITIONAL 2–8 °C RANGE (INDICATOR SO6.4)

Highlights

- A second vaccine has been licensed for use in a CTC.
- Eight manufacturers are considering CTC studies for at least 10 different vaccines.
- Regulatory guidelines to facilitate CTC re-licensing are under development.
- Three more countries are going to integrate a CTC approach into immunization campaigns.
- Country-level confidence in the CTC approach remains weak, emphasizing a need for improved advocacy and data collection.

TARGET	None specified
DEFINITION OF INDICATOR	This indicator measures the number of vaccines used in low- and middle-income countries that are licensed for use in a controlled temperature chain (CTC) for a limited period of time at ambient temperatures of up to 40°C CTC is defined as: • allowing vaccines to be kept and administered at ambient temperatures, up to 40°C, as per the conditions specified on their product label; • a single excursion for a limited period of time (length of time will vary by antigen and setting, though a minimum of three days is preferred by WHO) immediately preceding administration; • Up until this excursion, the vaccine should continue to be kept in the traditional 2–8°C cold chain
DATA SOURCES	To monitor outcomes (label change): Revised vaccine product inserts allowing for use of the vaccine at ambient temperatures up to 40°C, accessed from the WHO Vaccine Prequalification Database, manufacturers' websites and hard copies of product inserts To monitor progress: Public announcements made by vaccine companies of on-going studies to assess feasibility of using their vaccines in a CTC, including journal articles, media reports and conference presentations Private correspondence and information disclosed to WHO under non-disclosure agreements such as email correspondence and meeting minutes

Comments on quality of data

These data are highly reliable and generated primarily from the regular dialogue and progress tracking that WHO staff maintains with respective vaccine manufacturers who are undertaking thermostability studies with a view to an eventual label variation in support of a controlled temperature chain (CTC) approach. Once a vaccine's revised label is approved by the relevant NRA and subsequently approved for prequalification by WHO, the new licensure status is listed in the WHO vaccine prequalification database, which is available to the public online. In addition, hard copies of the vaccine product inserts serve as an additional source for verification of licensed label variations.

Country-level data on CTC uptake is confirmed first hand through the involvement of WHO staff in CTC implementation efforts. The current practice is for each CTC application to benefit from direct and dedicated technical support from WHO for both the planning and implementation phases. As countries begin to assume CTC planning and implementation independently, a more systematic approach to global-level reporting on the use of this approach will be introduced. While the WHO policy remains presently to only apply the CTC approach to campaigns and special strategies, the long-term expectation is that incorporation of CTC for certain vaccines in routine immunization may be feasible. At that point, specific monitoring mechanisms will be established in order to track progress and uptake of this approach. In the meantime each country experience with CTC is carefully documented, including specific data collection of population numbers vaccinated within a CTC strategy (versus the overall target for a given campaign) and recording best practices and lessons learned in a final report following each event/activity/campaign.

Results

Following the successful licensure and WHO prequalification and pilot implementation of MenAfriVac™ in a CTC, a second vaccine is following suit. Shantha Biotech is in the final stages of seeking approvals for a revision to the package insert of its oral cholera vaccine, Shanchol™, confirming compatibility with use in a CTC. As soon as both licensure and prequalification are confirmed for this product, guidance will be developed on when and how countries may take advantage of this new flexibility. A pilot effort to use Shanchol™ with the CTC approach is also expected.

The number of manufacturers interested in or already actively pursuing research and analysis associated with CTC has also doubled in the past year, with 8 vaccine companies currently engaged in dialogue with WHO on this subject and at least 10 vaccines under consideration, including tetanus toxoid vaccine (TT), pneumococcal conjugate vaccine (PCV), human papillomavirus (HPV) vaccine, typhoid Vi-TT conjugate vaccine, yellow fever vaccine, hepatitis B vaccine, hepatitis E vaccine, inactivated polio vaccine, measles vaccine and rotavirus vaccine.

A key outcome of the WHO regulatory consultations held on CTC in 2012 in Ottawa, Canada, and in 2013 in Langen, Germany, was the agreement to produce guidelines on the regulatory principles that apply to CTC licenses. WHO's Technologies, Standards, and Norms team is leading this effort and will produce a document entitled *Scientific Considerations for Regulatory Review of Vaccines Used in a Controlled Temperature Chain* finalized by the beginning of 2015. This work will facilitate the regulatory process by highlighting the key scientific and regulatory concerns that need to be addressed in the stability evaluation of vaccines under a controlled temperature chain. Further aiding the development and licensure of CTC-compatible vaccines is the current re-drafting of a generic preferred product profile for vaccines on heat stability by the Vaccine Presentation and Packaging Advisory Group.

Building on the success of the pilot implementation of MenAfriVac™ in a CTC in Benin in 2012, planning is under way for the integration of a CTC approach into additional national meningitis A campaigns scheduled for the end of 2014. With support from the GAVI Alliance, two to three countries (Côte D'Ivoire- *confirmed*, Togo-*confirmed* and Mauritania-*to be confirmed)* will be targeted for inclusion of CTC as part of a strategy to improve country-level uptake of CTC and to further document how this approach benefits immunization strategies by reducing constraints associated with the cold chain and logistics. Reducing these constraints will enable more people to be reached, costs to be reduced and health workers to be more efficient.

Analysis

While interest and momentum surrounding CTC have been on the rise among manufacturers and partner organizations involved in global immunization, country-level awareness and willingness to adopt this innovation have been considerably slower. To date, the application of CTC with a licensed vaccine has only occurred in one country. Despite the publication of that successful experience of delivering MenAfriVac™ in a CTC during a mass immunization campaign in Benin (appearing in the February 2014 issue of *Vaccine (1)*) and the availability of detailed guidance on how and when to use a CTC both in English and French, countries are not yet embracing this innovation. Even when country health experts have been informed about CTC innovation, they are reluctant to adopt it. Some of this reluctance can be attributed to concerns about undermining the training and messaging on the importance of cold chain adherence that have been a central feature of the EPI programme for 40 years. Decision-makers for immunization often hesitate to introduce any initiative that might cause confusion among health workers unless it is absolutely necessary. There has been insufficient orientation at the country-level on how this technical innovation could help increase campaign efficiency and coverage while also saving funds normally spent on maintaining the challenging cold chain at the 'last mile'. How the benefits outweigh the risks is not properly recognized, nor is it sufficiently documented and quantified. Yet there is little value in promoting CTC research among vaccine manufacturers if the targeted users are not adopting the innovation.

In order to maintain and justify the encouraging interest and headway associated with upstream developments related to CTC, the downstream demand for CTC must be stimulated as well. More effort and investment needs to be channelled towards informing countries of the existence and advantages of CTC innovation and the sharing of lessons learned. In parallel, additional data must be generated on the use, effectiveness and value addition of a CTC approach, including pharmacovigilance data, cost–benefit measurements, and health worker knowledge, attitude and practice surveys. Best practices need to be recorded and disseminated and general advocacy reinforced.

As countries begin to understand and seek out the advantages of CTC, it will become essential that adequate and uninterrupted supply of vaccines that are compatible with a CTC approach can be made available. In countries procuring vaccines through UN agencies, WHO prequalification is a key element bridging licensure and use. Understanding and documenting any key issues flagged during that process could help future submissions be stronger and allow the review process to be expedited.

Reference

1. Zipursky S, Harouna Djingarey M, Lodjo JC, Olodo L, Tiendrebeogo S, Ronveaux O. Benefits of using vaccines out of the cold chain: Delivering Meningitis A vaccine in a controlled temperature chain during the mass immunization campaign in Benin. Vaccine. 2014;32*(13)*:1431–1435.

NUMBER OF VACCINE DELIVERY TECHNOLOGIES (DEVICES AND EQUIPMENT) THAT HAVE RECEIVED WHO PREQUALIFICATION AGAINST THE 2010 BASELINE (INDICATOR SO6.5)

Highlights

- In total 238 products have been prequalified as of 31 December 2013 compared to 163 in 2010, corresponding to a 46% increase between 2010 and 2013.
- Newly introduced products include those that address the barriers or bottlenecks in Member States supply chains include the following:
  - Thirty-day electronic temperature monitoring device for refrigerators;
  - Twenty-day electronic shipping indicator, new generation;
  - Centralized temperature monitoring systems;
  - Auto-disable jet injector;
  - Solar direct drive refrigerators (without battery).
- Two new areas of work have been introduced this past year:
  - Long-term passive device to store small quantities of vaccines in immunization posts where electric-powered devices would not be justified;
  - Freeze-free cold box and vaccine carriers.

TARGET	None specified
DEFINITION OF INDICATOR	The number of products (cold chain equipment, injection devices and others) that have been prequalified by the WHO performance, quality and safety (PQS) system as of 31 December 2013, as compared to the number of prequalified products on 31 December 2010, which was 163 products It does not take into account the number of products that might have entered the list and been withdrawn in the interim period. Therefore, it is just the difference between two data points
DATA SOURCES	The WHO PQS programme database
COMMENTS ON DATA QUALITY	Data reflect the difference of the number of products that were listed in the PQS as prequalified on 31 December 2010 and those as of 31 December 2013. The record of the date after each change of a product's status ensures the quality of data

Background

The performance, quality and safety scheme for the prequalification of equipment selects immunization equipment to be purchased by UN agencies (details are available in the previous report). To summarize, it requires the industry to comply with criteria of performance, quality and safety based on an assessment by independent, WHO accredited laboratories. As more and more countries are now indicating the PQS prequalification in their tender for the procurement of immunization equipment, the PQS extends beyond UN purchase.

The intention is to build a system that will operate effectively over the long-term and to provide procurement agencies with a list of reliable immunization equipment and devices, each proven

to meet user needs. At the same time the system must encourage the continuous improvement of existing products while remaining open to innovation. To do so, a formal procedure has been established in 2013 in the context of the development of the GAVI Alliance immunization supply chain strategy. WHO has introduced the development of the target product profile (TPP), a key strategic document that lists the principal desired features of a product category intended for future PQS prequalification. In addition to having developed a written definition of TPP in the context of PQS, the Prequalification Team of the WHO Department of Essential Medicines and Health Products has drafted 2 TPPs about to be finalized – TPP01: Enhanced refrigerator or combined refrigerator and water-pack freezer: solar direct drive; and TPP02: Enhanced solar power system for vaccine refrigerator or combined refrigerator and water-pack freezer.. To ensure the suitability of new products to field conditions, the Prequalification Team does require that at least one field study be conducted to demonstrate the technical performance of the product in field conditions and to validate parameters such as usability, acceptability and reliability.

Results

Innovation: Efforts are now focusing on innovating products to meet the needs of the changing vaccine landscape. For example, responding to storage needs of a substantially increased volume of vaccines, as well as improved technologies to monitor the temperature at which vaccines are stored.

As vaccine costs and storage volumes increase, countries are much more demanding in terms of their storage and logistics needs and are looking for innovative solutions to address barriers or bottlenecks in their supply chains.

Newly introduced products that address these needs include the following:

1. 30-day electronic temperature monitoring device for refrigerators
2. 20-day electronic shipping indicator, new generation
3. Centralized temperature monitoring systems
4. Auto-disable jet injector
5. Solar direct drive refrigerators (without battery).

Two new areas of work have been introduced this past year: 1) a long-term passive device to store small quantities of vaccines in immunization posts where electric powered devices would not be justified; and 2) freeze-free cold box and vaccine carriers.

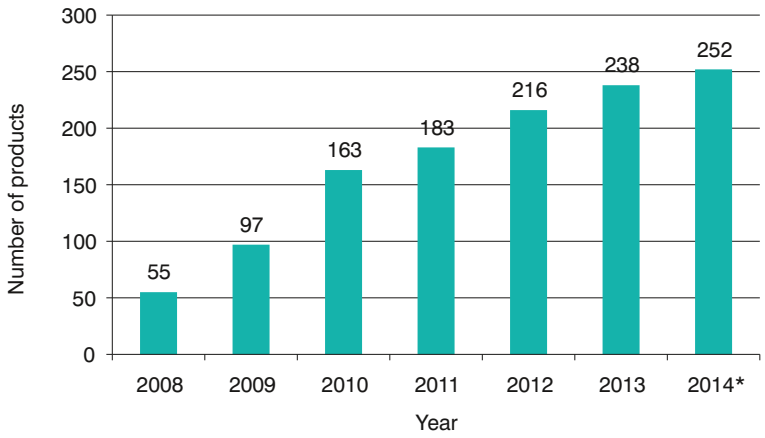
Products: Procurement agencies today can choose between 252 PQS prequalified products from 53 manufacturers (Table 35 and Figure 37); availability of products has been increasing steadily: for example, on 31 December 2010 there were only 163 prequalified products available, and a year later that increased to 238 products, corresponding to a 30% increase. If the number of withdrawn products is taken into account, the number then reflects a 43% increase in newly prequalified products.

Table 35: Number of prequalified products, 2008-2014

Description	Prequalified products 2008	Prequalified products 2009	Prequalified products 2010	Prequalified products 2011	Prequalified products 2012	Prequalified products 2013	Prequalified products 2014*
Cold rooms and related equipment	0	1	3	3	3	3	3
Refrigerators and freezers	0	8	14	23	33	36	40
Cold boxes and vaccine carriers	0	2	31	32	34	37	39
Water packs	0	1	15	16	18	17	17
Temperature monitoring devices	7	10	11	12	17	22	22
Auto-disable syringes for immunization	21	31	30	27	29	33	36
Waste management equipment	5	9	10	10	10	10	11
Therapeutic injection devices	22	35	49	60	72	80	84
Total	55	97	163	183	216	238	252

* As of 30 June 2014.

Figure 37: Number of prequalified products, 2008-2014



* As of 30 June 2014.

10. VACCINE PRICING

UPDATE ON VACCINE PRICING INDICATORS

Introduction

The Sixty-sixth World Health Assembly (2013) requested that the GVAP Secretariat prepare and transmit annual progress reports on the Decade of Vaccines to the World Health Assembly upon review by SAGE. Given the concern that middle-income countries are particularly challenged to introduce newer and costlier vaccines, the World Health Assembly requested that the GVAP report include an indicator on trends in vaccine prices, classified according to the procurement mechanisms used. SAGE was requested to advise on an appropriate indicator for monitoring such price trends.[33] At the Sixty-seventh World Health Assembly (2014), more than 20 Member States reinforced the need to monitor affordability of prices, particularly for middle-income countries.

The 2013 GVAP report made the first attempt to introduce a price indicator concluding that there are several interrelated market factors that affect vaccine price, including supply dynamics, which cannot be adequately captured through a price indicator alone.[34] Therefore, in the 2013 Annual GVAP Progress Report, vaccine prices were discussed in the form of a narrative report proposing possible themes for reporting in the future. The SAGE response to the first report indicated that the objective of reporting on vaccine prices in the 2013 GVAP report needed to be further clarified in order for appropriate and focused indicators to be developed.[35] Thus the objective of reporting on vaccine prices in the report has now been reformulated and new indicators proposed to assess progress against the objective.

It should be noted that the major challenges to reporting on vaccine prices are 1) the limited availability of price information particularly from middle-income countries and high-income countries; 2) the complexity of comparing price information due to multiple manufacturers, different procurement and delivery terms, vaccine presentations/formulations and other country-specific requirements, among others (see Annex 1). The only tool currently available for collection of price information that is designed to allow for comparisons of like information is the Vaccine Product, Price, and Procurement (V3P) Mechanism, which includes a database of vaccine prices. This database launched in June 2014 and consequently only very limited data are available at this stage to inform the current report. In order to be able to report to Member States and quantify trends and tendencies with a price indicator, it is key for Member States to share price information with WHO.

As noted in last year's report, vaccine prices depend largely on market dynamics, including level of maturity and competition, procurement mechanisms and contractual terms and conditions, to list a few variables. Furthermore, it should be stressed that willingness and ability to use newer vaccines is associated with various factors (e.g. disease burden, cost-effectiveness, local production) that go well beyond vaccine price alone.

Objective

The following chapters aim mainly at monitoring vaccine prices, acknowledging that they are only one of several factors that influence the introduction and uptake of newer vaccines. It will: 1) provide analyses and insights into vaccine price information (especially from middle-income countries), and 2) provide a high level summary of the specific vaccine markets from a global perspective, to better inform national and global strategies for the introduction of new vaccines in middle-income countries.

The following chapters will focus especially on middle-income countries that are not eligible to receive GAVI Alliance support for vaccine purchase and on DTwP-HepB-Hib, PCV, RV, HPV, IPV and measles-containing vaccines.[36] Given the scarcity of price data at present, to be able to achieve the report's main objective,

[33] WHA66. A66/19. Available at: http://apps.who.int/gb/ebwha/pdf_files/WHA66/A66_19-en.pdf.
[34] Page 86 of the Global Vaccine Action Plan monitoring, evaluation & accountability: Secretariat annual report 2013. Geneva: World Health Organization; 2013 (http://www.who.int/entity/immunization/global_vaccine_action_plan/GVAP_secretariat_report_2013.pdf?ua=1, accessed 25 November 2014).
[35] Page 17 of the Global Vaccine Action Plan Strategic Advisory Group of Experts on immunization: Assessment report 2013. Available at: http://www.who.int/immunization/global_vaccine_action_plan/sage_dov_gvap_progress_report_2013.pdf.
[36] These vaccines were selected by the GVAP price indicator working group in 2013 to reflect the GVAP's goals and both the current and proposed priorities throughout the GVAP time period.

the GVAP price report will also monitor country progress in data sharing over time. Annexes 1–3 provide background information on vaccine prices and the V3P Project as it relates to the GVAP Secretariat report.

Indicators

The indicators selected to measure progress against this objective are:

1. *Number of countries sharing price information through the Vaccine Product, Price, and Procurement (V3P)*[37] *Project by WHO region.*

This indicator aims at monitoring country progress in sharing pricing data over time.

2. *Annual average or unit vaccine prices as data permits*.[38] These will be analysed as:
   a. annual weighted average vaccine price (WAP), weighted by volume purchased, over time in relationship to procurement mechanism;
   b. unit prices of vaccines in relationship to country level of income and volume;
   c. minimum–maximum price range by country level of income.

This indicator aims to facilitate country planning for the introduction of new vaccines.

Conclusions

- *Indicator 1: Number of countries sharing price information publically through the Vaccine Product, Price, and Procurement (V3P) Mechanism:*
  - Only one country has currently submitted price information through V3P and eight additional countries have formally committed to do so. These countries are mostly from the European Region.

- *Indicator 2a. Annual weighted average vaccine price (WAP) over time in relationship to procurement mechanism.*
  - Initial data suggest that prices are declining over time for newer vaccines and that they are rising slightly for mature vaccines (e.g. measles). It does appear that prices of pentavalent vaccines to middle-income countries have decreased due to a maturing and increasingly competitive market. Analysis of price data from middle-income countries not eligible for GAVI Alliance assistance suggests that procurement method or volume purchases may impact price, with lower prices being obtained by UNICEF and the Pan American Health Organization (PAHO) Revolving Fund than through self-procurement[39] for the same antigen in the same presentation. However, the data are too scarce to support this conclusion, and several factors confound them.
  - The procurement experiences of GAVI Alliance/UNICEF and the PAHO Revolving Fund may provide some key lessons.
  - Availability of more data over time, particularly for non-GAVI-eligible middle-income countries, will allow for more conclusive and useful analysis of price trends.

- *Indicator 2b. Unit prices of vaccines in relationship to country level of income and volume.*
  - These analyses are confounded by grouping of prices across all years and by all manufacturers, but they nevertheless provide some indication that prices are differentiated by country income level.

- *Indicator 2c. Minimum–maximum price range by country level of income.*
  - The limited data suggest non-GAVI-eligible lower-middle income countries and upper-middle income countries experience higher min/max price ranges than GAVI-eligible low-income countries, and that there may be lessons to learn from the procurement experiences of the GAVI Alliance/UNICEF.

[37] http://www.who.int/immunization/programmes_systems/procurement/v3p/en/
[38] Data for 2014 is minimal and should be considered illustrative and not definitive. There are currently insufficient data for complete analyses using unit and min/max price ranges, but in subsequent years data may be sufficient to complete these analyses.
[39] From a total of 18 countries reporting total or partial self-procurement.

NUMBER OF COUNTRIES SHARING PRICE INFORMATION PUBLICALLY THROUGH THE VACCINE PRODUCT, PRICE, AND PROCUREMENT (V3P) DATABASE (INDICATOR VP1)

Until recently, there has been no mechanism to systematically collect vaccine price data from individual Member States. Outside of the pooled procurement of vaccines conducted by PAHO and UNICEF, a global source of information on prices paid for vaccines did not exist.

But over the past two years, two mechanisms, the Vaccine Product, Price, and Procurement (V3P) database and the WHO/UNICEF Joint Reporting Form (JRF), have been piloted for the purpose of collecting data related to vaccine price. Compared to the JRF, the V3P tool has the capacity to collect more detailed and accurate information and thus is chosen as the platform to facilitate country price data reporting. Table 36 shows the number of countries that have agreed to use the V3P database to date.

Table 36: Countries formally committed to reporting prices through the V3P in 2014, by WHO region

WHO region (total no. of countries)	Lower-income countries	Middle-income countries	High-income countries
European (53)	0/1	3/19	5/33
South-East Asia (11)	0/4	0/7	0/0
Western Pacific (27)	0/1	1/19	0/7
Americas (35)	0/1	0/25	0/9
African (47)	0/25	0/21	0/1
Eastern Mediterranean (21)	0/2	0/14	0/5

The V3P has currently collected price and procurement data from 17 non-GAVI-eligible middle-income countries already, but data were provided for platform development purposes. Only one of these 17 countries has currently provided validated data to share publicly. An additional six countries have formally agreed to provide data for public use through the V3P.

Over the past two years (2012-2013), WHO and UNICEF have used the JRF to request similar information to that collected in the V3P database in two pilot WHO regions, the European and Eastern Mediterranean Regions. As of 25 June 2014, 22 countries from the European and five from the Eastern Mediterranean Region have provided complete price information.

In addition, manufacturer-specific prices are available from UNICEF for vaccines procured under long-term agreements, and UNICEF is preparing to publish non-long-term agreement prices as well, which will cover more middle-income countries, particularly for newer vaccines. PAHO publishes weighted average prices (WAP) for every vaccine type and presentation procured on behalf of its Member States. Data from all of the above-mentioned countries have been used to perform the analyses in this report.

Generally, vaccine price data are difficult to compare because vaccines against the same disease may contain a different number of components and may be delivered in a differing number of doses or through a different presentation. Prices may vary according to volumes purchased and the income level of countries, and according to other terms and conditions of purchasing. In addition, the length of the contract may vary considerably between countries, and prices may be reported in different currencies and using different International Commercial Terms (Incoterms),

which include different transaction costs. The data reported through these various channels are not strictly comparable, further reducing ability to compare price trends. More and more comparable data provided through V3P would allow for improved analyses of price trends and the impacts of procurement method, volume purchasing and other factors, on price. In the future it is anticipated that the collection of price information from countries may be consolidated through a combined JRF/V3P process.

ANNUAL AVERAGE OR UNIT VACCINE PRICES (INDICATOR VP2)

Note: All data used for the analyses of prices in non-GAVI-eligible middle-income countries were sourced from the V3P database and the 2014 European and Eastern Mediterranean Regions JRFs. The V3P database contains pricing data collected for 17 middle-income countries for which the data have been validated for only one country and thus should be considered illustrative and not definitive as it may contain errors. The European and Eastern Mediterranean Regions JRFs provided data for 22 and five countries, respectively, but only from 2013 for the European Region and only from 2012 for Eastern Mediterranean Region. A total of 18 countries reported total or partial self-procurement and were classified under 'self-procurement'.

The data analysed are for pentavalent (DTP-HepB-Hib), inactivated polio vaccine (IPV), rotavirus vaccine (RV), pneumococcal conjugate vaccine (7-, 10- and 13-valent) (PCV), human papillomavirus (HPV) vaccine, and measles-containing vaccines in each presentation size from all manufacturers.

ANNUAL WEIGHTED AVERAGE VACCINE PRICE OVER TIME IN RELATIONSHIP TO PROCUREMENT MECHANISM[40] (INDICATOR VP2A)

This chapter analyses price over time in relation to procurement mechanisms (Tables 37–45). It should be noted that more than 27 middle-income countries that are not GAVI-eligible are currently self-procuring (or producing) vaccines.

Note for the tables in this chapter: Minimum/maximum prices for UNICEF/GAVI Alliance are shown for vaccines purchased in bulk at very high volumes (tens of millions). WAP prices are shown for specific middle-income countries procuring through UNICEF (generally at volumes <10 million) based on reported prices to the V3P database or through the JRF. Prices for most similar vaccines (in red), purchased by the US CDC's Vaccines for Children (VFC) Program, are shown for comparison purposes.

[40] Where prices are listed at 3 or more decimals, they are rounded up to the nearest cent.

Table 37: Prices of pentavalent vaccine (DTP-HepB-Hib), in US dollars

DTP-HepB-Hib												
Procurement mechanism	Presentation		Year									
	n = number of data points used for WAP		2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
UNICEF	1 dose liquid	Min/max	3.75	2.90/ 3.60	2.70/ 3.60	2.70/ 3.20	2.25/ 3.20	2.50/ 3.20	1.95/ 2.70	2.35/ 2.70	1.85/ 2.80	1.85/ 2.80
		WAP (n=20)	3.75	3.60		3.35	5.40	3.92	2.65			
	1 dose liq/lyo	WAP (n=1)					5.40					
	2 dose lyo	Min/max	3.50/ 3.60	3.50	3.50	2.25/ 2.95	2.25/ 2.95	2.95	1.97/ 2.95	1.96/ 2.95	1.95	1.94
		WAP (n=1)		5.40	5.40				2.99			
	10 dose liquid	Min/max					1.75/ 2.11	1.19*/ 2.11	1.19*/ 2.11	1.19*/ 2.11	1.34/ 2.11	1.34/ 2.11
		WAP (n=3)					2.50		1.85			
PAHO	1 dose liquid WAP		3.95	3.95	3.55	3.20	3.19	2.99	2.49			
	1 dose lyo WAP		3.92	3.92	3.60	3.30	2.95	2.88	2.52			
	10 dose liquid WAP								2.20**			
Self-procurement	1 dose liquid WAP (n=11)				9.07	5.92	6.60	4.08	3.80			
	1 dose liq / lyo WAP (n=5)			6.15	5.85		3.79	3.41				
	1 dose vial *DTaP-HepB-IPV US CDC VFC price*			48.75	48.75							
	1 dose prefilled syringe *DTaP-HepB-IPV US CDC VFC price*			48.75	48.75	49.75	51.15	52.10	52.58			

* Special terms apply.
** Price was offered but presentation was not procured.

Highlights

Pentavalent prices appear to be trending downwards for UNICEF and PAHO procurement, but the picture is less clear for middle-income countries that are self-procuring as these data show some year-to-year fluctuation. Prices in the United States for a different pentavalent combination vaccine against some of the same diseases (diphtheria, tetanus, pertussis and hepatitis B) have been increasing slightly over time.

Discussion

The data from self-procuring middle-income countries is insufficient to draw conclusions but the data suggest that prices are on the whole lower in 2012 and 2013 than they were in 2008 and 2009. Further data may confirm a similar trend to that observed for UNICEF and PAHO procurement.

Middle-income countries reported sourcing vaccines from three to five suppliers between 2010 and 2013 (inclusive) (data from earlier years are for single country in a given year). At the global level, the pentavalent market can now be classified as robust; seven manufacturers currently have WHO/UN prequalified vaccines in multiple presentations, with ample supply availability to meet demand (see Table 36).[41] The maturation of the market may account for the lowering cost of pentavalent vaccine in contrast to prices of newer vaccines.

Table 38: Prices of inactivated polio virus (IPV), in US dollars unless otherwise specified

Inactivated polio vaccine													
Procurement mechanism	Presentation		Year										
	n = number of data points used for WAP		2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
UNICEF	1 dose liquid	Min/max					3.30	3.30	2.80	2.80	2.80	2.80	
		WAP (n=1)				3.80							
	5 dose liquid	Min/max							1.90	1.90	1.90	1.90	1.50/ 1.90
	10 dose liquid	Min/max							€0.75/ 2.40*	€0.75/ 2.40*	€0.75/ 2.40*	€0.75/ 2.40*	€0.75/ 2.40*
PAHO	1 dose WAP		3.4	4.1	4.5	5.50	5.98	2.90–4.14	2.80				
Self-procurement	1 dose liquid WAP (n=3)		4.74	4.84			5.65						
	10 dose liquid WAP (n=1)			11.47									
	1 dose prefilled syringe *IPV US CDC VFC price*		11.48	11.51									
	10 dose vials *IPV US CDC VFC price*		11.48	11.51	11.74	11.97	12.24	12.42					

* Special terms apply.

Highlights

Prices of stand-alone IPV will be considerably lower in the coming years than they have historically been in the past. The price of IPV in combination vaccines is not considered here.

Discussion

The market for IPV has until recently been limited to a relatively few countries, and predominantly to high-income countries. However, with the recommendation for universal coverage with a least one dose of an IPV-containing vaccine (polio Endgame Plan), prices to low- and middle-income countries are set to be considerably lower than historical prices, particularly through UNICEF procurement where prices have been negotiated well into the future. There is currently historical pricing data for only three self-procuring middle-income countries, and these data do not cover a continuous time period.

Middle-income countries report sourcing vaccines from two suppliers between 2008 and 2012 (inclusive). At the global level, there are four manufacturers with WHO prequalified IPV. From the UNICEF perspective, supply is expected to be sufficient to meet demand

[41] UNICEF's Supply Division is finalizing a market update for pentavalent vaccine, which should be published on their website in August 2014. Available at: http://www.unicef.org/supply/index_vaccines.html.

for both GAVI-supported and non-GAVI-supported middle-income countries possibly procuring through UNICEF, although some flexibility may be required in terms of product presentation or timing of deliveries, during the rapid introductions expected as part of the Polio Endgame Plan over the next year.[42]

Table 39: Prices of rotavirus vaccine (RV), in US dollars unless otherwise specified

Rotavirus vaccine											
Procurement mechanism	Presentation		Year								
	n = number of data points used for WAP		2008	2009	2010	2011	2012	2013	2014	2015	2016
UNICEF	1 dose liquid (2 dose course)	Min/max					€1.88*	€1.88*	€1.88*	€1.88*	€1.88*
		WAP (n=5)					8.00	2.49			
	1 dose liquid (3 dose course)	Min/max					5.00	3.50/ 5.00	3.50/ 5.00	3.50/ 5.00	3.50
PAHO WAP	1 dose liquid (2 dose course)		7.50	7.90	7.50	7.50	6.88	6.50	6.50		
	1 dose liquid (3 dose course)			5.50	5.15	5.25	5.25	5.15			
Self-procurement	1 dose liquid (2 dose course)	WAP (n=5)			7.37	7.37	6.45	6.99			
		RV US CDC VFC price	82.25	83.25	83.75	89.25	91.02	92.15			
	1 dose liquid (3 dose course)	WAP (n=3)				9.5	9.5	9.95			
		RV US CDC VFC price	57.20	57.20	59.18	59.76	61.53	63.96			

* Special terms apply.

Highlights

For the coming years, prices of RV through UNICEF procurement are flat over time or decreasing, depending on the product. Through PAHO procurement they have been declining year-to-year. There are too few data from self-procuring middle-income countries to conclude a trend. Prices to the VFC have been increasing over time.

Discussion

GAVI Alliance commitments to support eligible countries in the purchase of RV vaccines appears to be having a positive impact on UNICEF prices observed, having been negotiated at a flat or declining price into the future. Greater demand forecasting and projection into the future might also benefit middle-income countries.

Middle-income countries report sourcing vaccines from two suppliers between 2010 and 2013 (inclusive). At the global level, there are two manufacturers with WHO/UN prequalified vaccines. The majority of demand from GAVI-supported countries procuring through UNICEF is for a specific RV product due to a 2-dose schedule and product characteristics (such as cold chain requirements and inclusion of vaccine vial

[42] UNICEF's Supply Division has published more information on the IPV market which is available at http://www.unicef.org/supply/index_66260.html.

monitors). Demand has been higher than supply for this product, although supply availability is improving. Supply availability of the other RV is sufficient to meet demand through UNICEF.[43]

Table 40: Prices of pneumococcal conjugate vaccine (PCV), in US dollars

Pneumococcal conjugate vaccine										
Procurement mechanism	Presentation		Year and price (US$)							
	n = number of data points used for WAP		2008	2009	2010	2011	2012	2013	2014	2015
UNICEF	1 dose liquid (13 val)	Min/max			7.00*	7.00*	7.00*	3.40/ 7.00*	3.30/ 7.00*	3.30/ 7.00*
		WAP (n=1)						3.40		
	1 dose liquid (10 val)	WAP (n=2)					8.00	16.00		
	2 dose liquid (10 val)	Min/max			7.00*	7.00*	7.00*	3.40/ 7.00*	3.40/ 7.00*	3.40/ 7.00*
PAHO	1 dose liquid (7 val)			21.75	20.00					
	1 dose liquid (13 val) WAP						16.34	15.84	15.68	
	1 dose liquid (10 val) WAP					14.85	14.24	14.12	14.12	
Self-procurement	1 dose liquid (13 val) WAP (n=24)		30.62	30.06	32.95	32.25	25.51	17.24		
	1 dose liquid (10 val) WAP (n=2)						13.35	15.33		
	1 dose liquid (7 val) prefilled syringe *PCV* *US CDC VFC price*		66.44	71.04						
	1 dose liquid (13 val) prefilled syringe *PCV* *US CDC VFC price*				91.75	97.21	102.03	107.12		

* Terms apply to advance market commitment.

Highlights

Prices reflected in Table 39 under the UNICEF procurement mechanism are mainly prices of PCV to the GAVI Alliance set by an advance market commitment. Manufacturers enter into 10-year supply agreements at a 'tail-price' capped at US$ 3.50 per dose and also receive an additional price per dose 'top-up' up to US$ 7.00 per dose for an initial proportion of the doses. The trend from 2012-2015 reflects some supply agreements transitioning from US$ 7.00 per dose (tail price and top-up) to the tail price alone, as well as the tail price declining slightly over time. In PAHO, prices are declining year-to-year but are higher than those negotiated by the GAVI Alliance. Based on the few data there are from self-procuring middle-income countries, prices in self-procuring countries have declined in 2013 to approximate prices in PAHO. In UNICEF-procured non-GAVI-eligible middle-income countries, prices range between those given to GAVI-eligible middle-income countries and self-procuring middle-income countries in 2012-2013. Prices to the VFC have been increasing over time.

[43] UNICEF's Supply Division has published more information on the RV market, which is available at http://www.unicef.org/supply/index_70173.html.

Discussion

GAVI Alliance commitments to support eligible countries in the purchase of PCV vaccines appears to be having a positive impact on price, having been negotiated at a flat or declining price into the future. For PAHO, prices dropped initially when competition between two manufacturers commenced. Greater demand forecasting and projection into the future might benefit middle-income countries.

Middle-income countries report sourcing vaccines from two suppliers between 2008 and 2013 (inclusive). At the global level there are two manufacturers with WHO/UN prequalified vaccines. Since the vaccine was first introduced in end 2010, demand from GAVI Alliance-supported countries procuring through UNICEF has been higher than supply availability, requiring some countries to postpone introductions. The supply situation continues to improve and more countries are able to introduce PCV sustainably, although careful monitoring and planning is still required, especially as manufacturers continue to scale-up capacity.[44]

Table 41: Prices of human papillomavirus vaccine, in US dollars

Human papillomavirus vaccine												
Procurement mechanism	Presentation		Year and price (US$)									
	n = number of data points used for WAP		2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
UNICEF	Liquid 1 dose (quadrivalent)	Min/max						4.50	4.50	4.50	4.50	4.50
	Liquid 2 dose (bivalent)	Min/max						4.60	4.60	4.60		
PAHO	Liquid 1 dose (bivalent) WAP				32.00	14.00	13.48	13.08				
	Liquid 1 dose (quadrivalent) WAP						14.25	13.79				
Self-procurement	Liquid 1 dose (quadrivalent)	WAP (n=1)						93.40				
		HPV US CDC VFC price	100.59	105.58	108.72	95.75	98.60	107.16				
	Liquid 1 dose (bivalent)	vials *HPV US CDC VFC price*			96.08							
		Prefilled syringe *HPV US CDC VFC price*			96.08	96.08	96.08	100.85				

[44] UNICEF's Supply Division has published more information on the PCV market, which is available at http://www.unicef.org/supply/index_67883.html.

Highlights

For the coming years prices of HPV (through UNICEF procurement) are flat over time. In PAHO prices are declining year-to-year, but are higher than for UNICEF. In the single self-procuring middle-income country, the price is approximately the same as that in high-income countries. Prices to the VFC have varied slightly over time.

Discussion

GAVI Alliance commitment to support eligible countries in the purchase of HPV vaccines appears to be having a positive impact on price through UNICEF procurement, having been negotiated at a flat or declining price into the future for GAVI-eligible countries. Greater demand forecasting and projection into the future might also benefit middle-income countries.

Only one of the V3P/JRF middle-income countries sourced HPV vaccine from a single supplier in 2013. At the global level, there are two manufacturers with WHO/UN prequalified vaccines. Supply is sufficient to meet demand, especially in the first years of demonstration programmes[45] and national introductions in GAVI Alliance-supported countries.[46]

Table 42: Prices of measles-containing vaccine, in US dollars

Measles-containing vaccine												
Procurement mechanism	Presentation		Year and price (US$)									
	n = number of data points used for WAP		2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
UNICEF	1 dose lyo	Min/max	0.18/ 0.26	0.18/ 0.27	0.19/ 0.28	0.19/ 0.30	0.19/ 0.32	0.19/ 0.34	0.22/ 0.43	0.22/ 0.45	0.23/ 0.48	0.23/ 0.50
		WAP (n=13)			0.27	0.34	0.306	0.28	0.51			
PAHO	Not used											
Self-procurement	1 dose lyo WAP (n=1)							3.39				
	10 dose lyo WAP (n=66)				3.75	3.98	3.92	4.72	6.17			
	United States CDC VFC not used											

[45] Demonstration programmes provide countries with the opportunity to test their ability to put in place the systems that would be needed to roll out a vaccine nationally and to inform their decisions.
[46] UNICEF's Supply Division market update on HPV will be published, http://www.unicef.org/supply/index_vaccines.html.

Table 43: Prices of MR vaccine, in US dollars

Measles, rubella vaccine (MR)												
Procurement mechanism	Presentation		Year and price (US$)									
	n = number of data points used for WAP		2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
UNICEF	10 dose lyo	Min/max	0.46/ 0.50	0.47/ 0.53	0.47/ 0.55	0.48/ 0.60	0.49/ 0.60	0.50/ 0.60	0.52	0.55	0.58	0.61
		WAP (n=1)						0.50				
PAHO	1 dose lyo WAP			1.35	1.35	1.35	1.45	1.65	1.70			
	10 dose lyo WAP			0.52	0.51	0.53	0.56	0.51	0.52			
Self-procurement	10 dose lyo WAP (n=2)						0.80	0.72				
	United States CDC VFC not used											

Table 44: Prices of measles, mumps, rubella vaccine (MMR), in US dollars

Measles, mumps, rubella vaccine (MMR)												
Procurement mechanism	Presentation		Year and price (US$)									
	n = number of data points used for WAP		2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
UNICEF	1 dose lyo	Min/max	1.50	1.50	1.50	1.75/ 2.90	1.85	1.95/ 3.10	2.05	2.15	2.25	2.37
		WAP (n=3)				5.20	5.20	5.20				
	2 dose lyo	Min/max							3.25	3.25	3.25	
		WAP (n=2)						3.25	5.20			
	5 dose lyo	Min/max				0.90	0.90	0.90	0.99	1.04	1.09	1.15
		WAP (n=2)				0.90	0.90					
	10 dose lyo	Min/max	0.86/ 1.42	0.86/ 1.49	0.86/ 1.57	0.93/ 1.60	0.93/ 1.63	0.93/ 1.65	0.98/ 1.80	1.03/ 1.89	1.08/ 1.99	1.13
		WAP (n=1)							0.97			

Measles, mumps, rubella vaccine (MMR)											
Procurement mechanism	Presentation		Year and price (US$)								
	n = number of data points used for WAP		2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
PAHO	1 dose lyo WAP	Zagreb		1.55		1.55	1.60	1.85	2.05			
		Urabe		2.65	2.65	2.65	2.70	3.50	3.60			
		Jeryl-Lynn			5.75				5.00			
		Leningrad			1.55							
	5 dose lyo WAP	Zagreb					0.85	0.85	0.99			
	10 dose WAP	Zagreb		0.90		0.92	0.92	0.92	0.98			
		Urabe		1.55	1.55		2.00					
		Leningrad			0.92							
Self-procurement	1 dose lyo	WAP (n=23)	1.89	2.66	6.16	4.68	4.74	5.03	4.53			
		Vials *CDC VFC price*		18.26	18.30	18.64	18.99	19.33	19.76			
	2 dose lyo	WAP (n=9)					20.49	2.80	3.82			
	10 dose	WAP (n=16)	1.72	1.82	2.00	1.81	2.56	2.25	1.03			

Highlights

Prices of measles-containing vaccine through UNICEF procurement are rising slightly year-on-year but remain low relative to prices of newer vaccines. PAHO and the United States CDC do not purchase measles vaccine outside of combinations with rubella and/or mumps. The data from self-procuring middle-income countries show variance from year-to-year with an unclear tendency.

Discussion

Prices for non-GAVI-eligible middle-income countries may be sensitive to volumes purchased in any given year. UNICEF may be capable of obtaining lower prices on behalf of middle-income countries based on larger purchase volumes. More data are needed from middle-income countries to determine trends.

Middle-income countries report sourcing measles vaccines from four vaccine suppliers, MR from a single supplier, and MMR from four suppliers between 2004 and 2013 (inclusive). At the global level, there are currently four manufacturers of WHO/UN prequalified vaccines, although one is not supplying (to UNICEF) and one is exiting the market, bringing the number of suppliers with available vaccine at the global level to two. Overall supply is sufficient to meet demand, but one manufacturer produces the majority of vaccine (approximately 80% through UNICEF) and also produces the only WHO prequalified measles and rubella (MR) vaccine. Therefore, detailed planning for future supply is required.[47] Table 42 shows the number of UN prequalified vaccine suppliers for various vaccines.

[47] UNICEF's Supply Division has published more information on the measles market, which is available at **http://www.unicef.org/supply/index_71360.html.**

Table 45: Number of WHO/UN prequalified vaccine suppliers reported by countries for various vaccines

Vaccine	No. of WHO/UN prequalified suppliers
Pentavalent (DTP-HepB-Hib)	7
IPV	4
RV	2
PCV	2
HPV	2
Measles	4
Measles-rubella (MR)	1
Measles, mumps, rubella (MMR)	4

Concluding remarks

While there is a suggestion that prices are declining over time for newer vaccines and that they are rising slightly for mature vaccines (e.g. measles), the data are too scarce to support this conclusion. It does appear that prices to middle-income countries reduced for pentavalent in a maturing and increasingly competitive market. The analysis of price data from non-GAVI-eligible middle-income countries suggests that procurement method or volume purchasing may impact price, with lower prices being obtained by UNICEF and the PAHO Revolving Fund than through self-procurement for the same antigen in the same presentation.

The data, however, are too scarce to support this conclusion, and several factors confound them. Price trends are not disaggregated by manufacturer and Incoterms used to report prices vary between buyers. Availability of more data over time, particularly for non GAVI-eligible middle-income countries, will allow for more conclusive and useful price trends analysis.

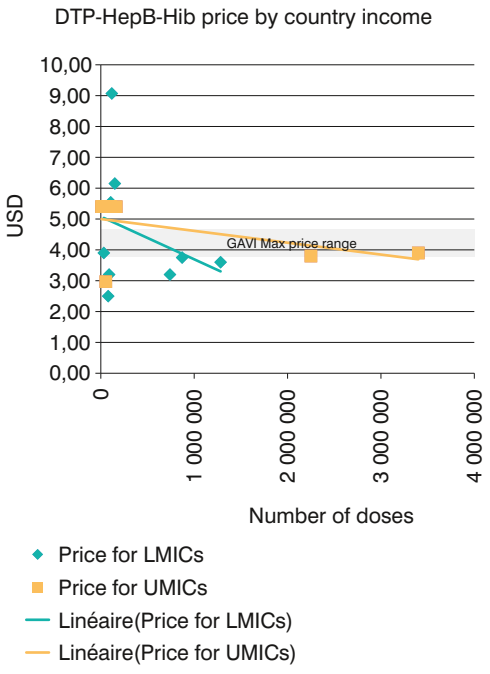
UNIT PRICES OF VACCINES IN MIDDLE-INCOME COUNTRIES IN RELATIONSHIP TO COUNTRY LEVEL OF INCOME AND VOLUME (2004-2013) INDEPENDENT OF PROCUREMENT METHOD (INDICATOR VP2B)

This chapter analyses prices in relation to income and volume (Figures 38–42). It should be noted that GAVI Alliance prices are shown here as 'proxy' for low-income countries, even though 39 GAVI-supported countries are also middle-income countries (mostly lower-middle income countries). Prices to GAVI-supported middle-income countries are not included in the analyses of prices to middle-income countries here.

DTP-HepB-Hib

There is a suggestion that price of DTP-HepB-Hib for lower-middle income countries tends to be lower than for upper-middle income countries when related to volumes purchased, but the data are too scarce to support this conclusion. At higher volumes, prices for upper-middle income countries approach those paid by the GAVI Alliance.

Figure 38: Unit prices of pentavalent (DTP-HepB-Hib) single dose



Discussion

There would appear to be some differentiation between prices to lower-middle income countries and upper-middle income countries for the pentavalent vaccine, although the difference is smaller than that observed for newer vaccines. However, there are insufficient data points from which to draw this conclusion with any certainty. Furthermore, trends may be confounded by the lack of disaggregation by manufacturer or by year (2007-2013), and pentavalent vaccine prices in this income level appear to be trending downward over time. By aggregating data, e.g. by all manufacturers, a downward trend in price from one manufacturer might be masked by an upward trend of another.

Inactivated polio vaccine, single dose

Insufficient data to discuss.

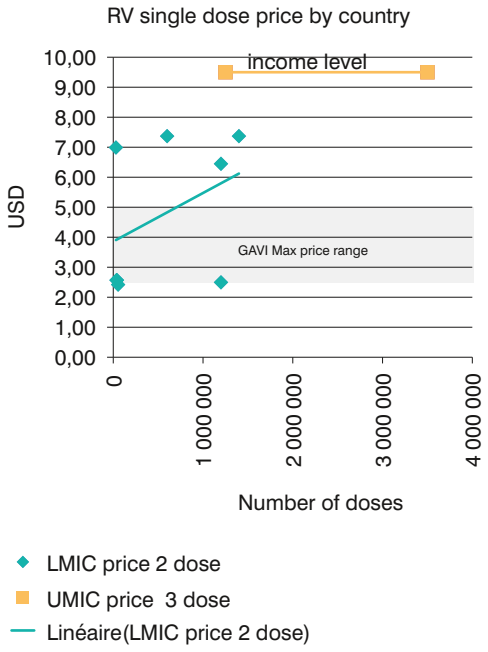
Rotavirus vaccine

There are too few data to draw conclusions. Prices from upper-middle income countries are insufficient to relate to volumes purchased. Overall, prices for RV are higher in both lower-middle income countries and upper-middle income countries than to prices paid by the GAVI Alliance.

Discussion

There would appear to be some price differentiation between prices to lower-middle income countries and upper-middle income countries for RV, but the lack of data alone may account for this discrepancy.

Figure 39: Unit prices of rotavirus vaccine single dose (2 and 3 dose courses combined)



Pneumococcal conjugate vaccine

Insufficient data to discuss.

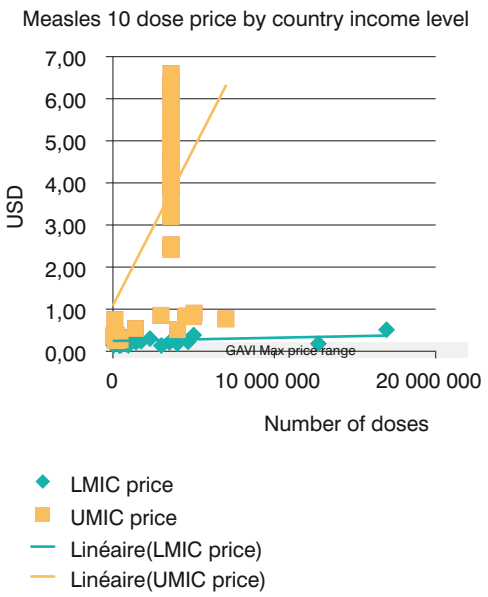
Human papillomavirus vaccine, single dose

Insufficient data to discuss.

Measles-containing vaccines

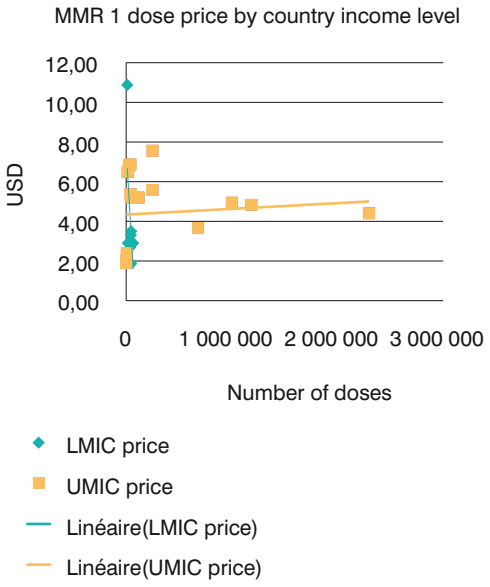
A single country accounts for the majority of data points for upper-middle income countries for measles 10-dose, and price in that country is increasing over time, which may account for the appearance of a positive relationship between increase in price with volume. Overall, prices for measles 10-dose in lower-middle income countries are in the same range as those paid by the GAVI Alliance.

Figure 40: Unit prices of measles 10-dose



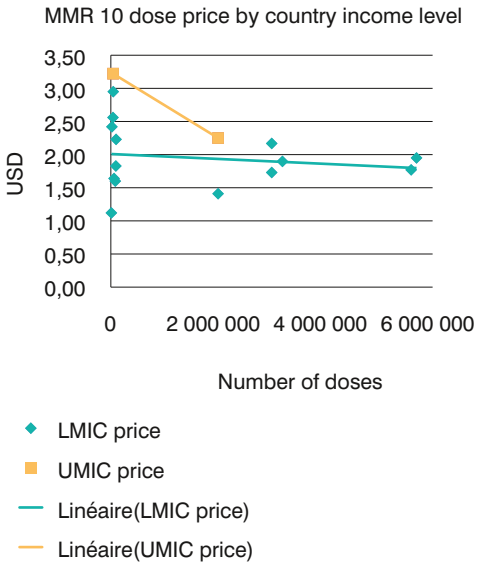
The linear trend for prices paid by lower-middle income countries for MMR single dose are skewed by a single value for lower-middle income countries, but the price paid is otherwise on the whole somewhat lower than that paid by upper-middle income countries.

Figure 41: Unit prices of MMR, single dose



The linear trend for the price paid by lower-middle income countries for MMR 10-dose is below the trend line for upper-middle income countries, but there are insufficient data from upper-middle income countries to make a comparison.

Figure 42: Unit prices of MMR 10-dose



Discussion

These data are confounded by an increase in price over time but appear to show modest price differentiation between lower-middle income countries and upper-middle income countries. Prices of stand-alone measles vaccines to upper-middle income countries are mostly higher than the GAVI Alliance maximum price range whereas prices to lower-middle income countries are generally within the GAVI Alliance maximum price range.

Measles-rubella (MR) vaccine

Insufficient data to discuss.

Concluding remarks

Analyses for IPV, PCV and HPV could not be made due to scarcity of data for non-GAVI-eligible middle-income countries. For pentavalent vaccines, RV and measles-containing vaccines, the analyses are confounded by grouping of prices across all years and by all manufacturers, but they nevertheless provide some indication as to whether prices may differ between lower-middle income countries and upper-middle income countries.

MINIMUM–MAXIMUM PRICE RANGE BY COUNTRY LEVEL OF INCOME (2004-2013, UNLESS OTHERWISE SPECIFIED) (INDICATOR VP2C)

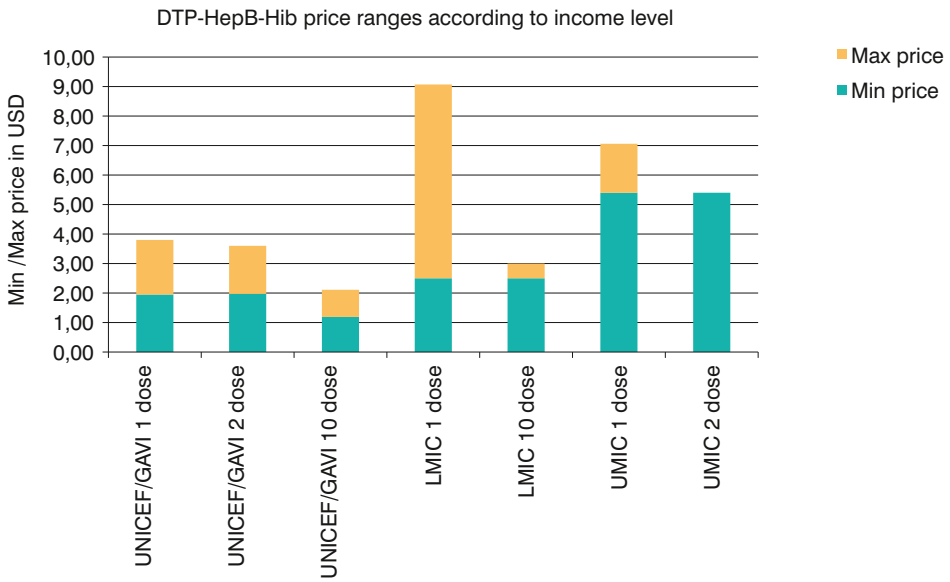
This chapter reviews the minimum and maximum price ranges of vaccines paid by countries (Figures 43–48).

DTP-HepB-Hib

Data suggest that the widest price range is in the lower-middle income country group for single dose DTP-HepB-Hib although it should be noted that these data represent a single country for the years 2007, 2008 and 2009.

While minimum prices are highest for upper-middle income countries, the minimum–maximum range tends to be smallest for this group of countries and widest for the lower-middle income countries based on available data.

Figure 43: Min–max price of DTP-HepB-Hib

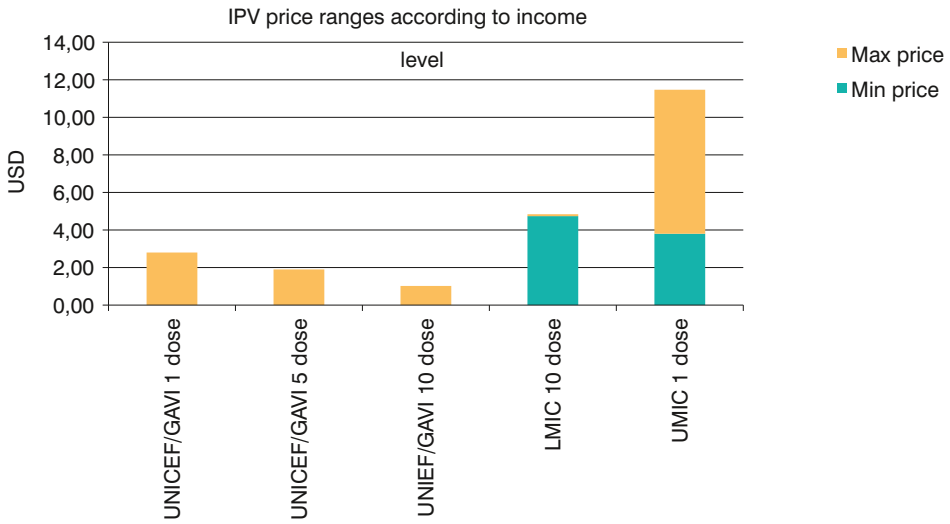


IPV

For IPV, price ranges are wider for middle-income countries than low-income countries, and is widest in the upper-middle income country group.

These data are highly influenced by price commitments for years going forward and only show historical data points in the upper-middle income country group.

Figure 44: Min–max price of inactivated polio vaccine*



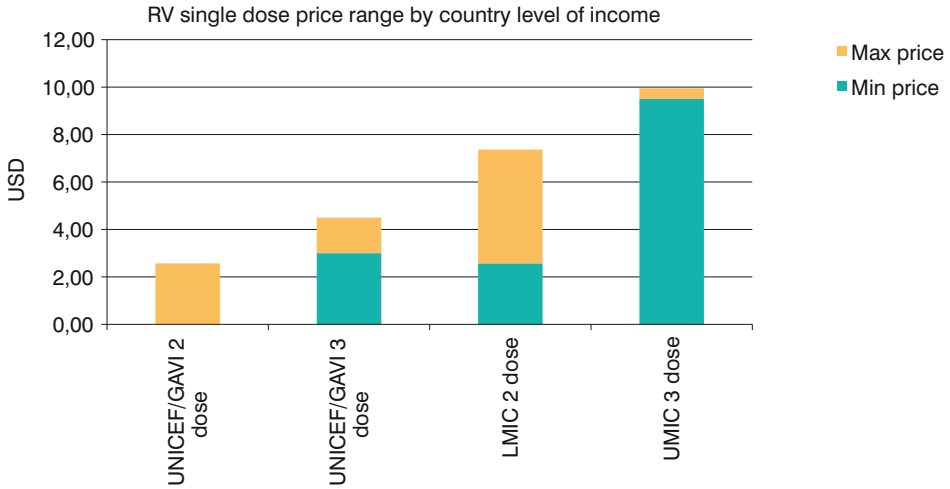
* 10-dose is for 2014, and prices committed for future years for specific lower-middle income countries and upper-middle income countries.

RV

These data show a much higher price range for lower-middle income countries than for GAVI, low-income countries and upper-middle income countries.

There is greater price heterogeneity in the lower-middle income country group and to a lesser extent in the GAVI Alliance group. However, as these data are not disaggregated by manufacturer or by year, they may not provide a true picture of price ranges in relation to country income level.

Figure 45: Min–max price of rotavirus vaccine

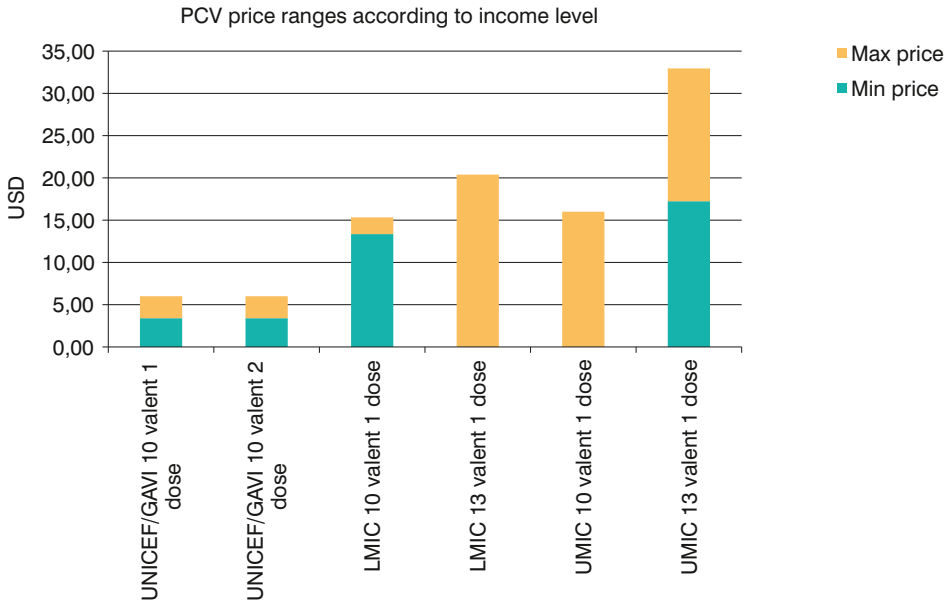


PCV

There were insufficient data (a single country in a single year) to show a price range for 13-valent 1 dose vaccines (paid by lower-middle income countries) and 10-valent 1 dose vaccines (paid by upper-middle income countries). Nevertheless, these data show that the price differential is greatest for the upper-middle income countries purchasing 13-valent 1 dose vaccines.

The lower pricing of PCV to GAVI-supported countries is a direct consequence of the advanced market commitment that secured a low price over the long-term for these countries.

Figure 46: Min–max price of pneumococcal conjugate vaccine



HPV

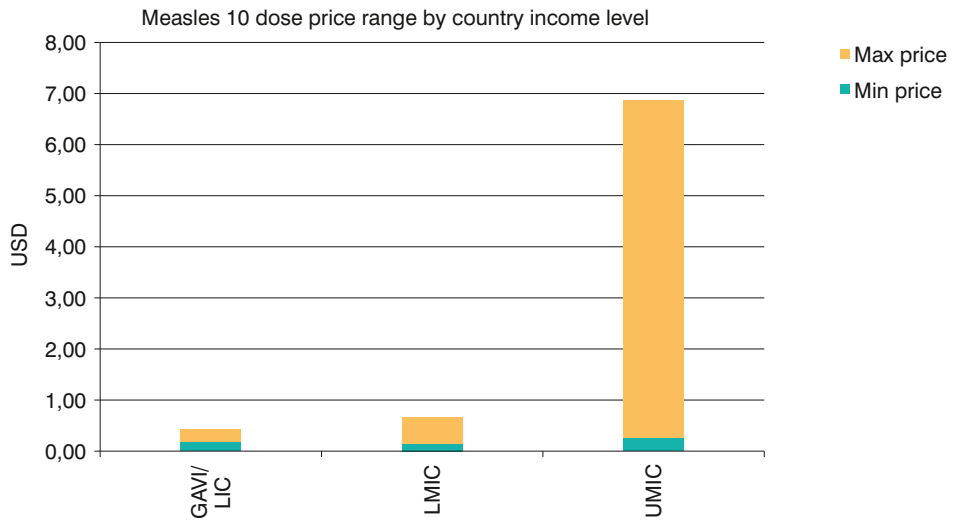
Insufficient data to discuss.

Measles 10-dose vaccine

For measles 10-dose vaccine, a considerable price differential is noted in the upper-middle income countries group.

The price range is smallest for the GAVI/low-income country group. The relatively high price range in upper-middle income countries may partly be explained by the relatively lower minimum price of measles-containing vaccines compared to prices of newer vaccines in this income group.

Figure 47: Min–max price of measles 10-dose vaccine

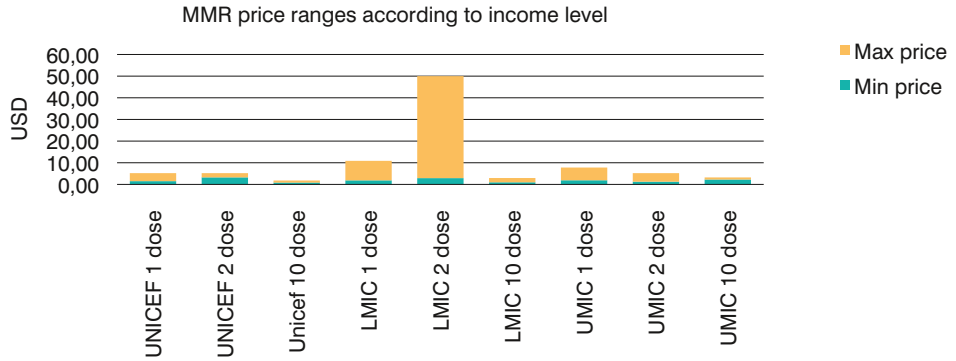


MMR vaccine

A considerable price differential is noted in the lower-middle income countries group for the measles, mumps, rubella vaccine.

The price range is on the whole smallest for the GAVI/ low-income country group.

Figure 48: Min–max price of measles, mumps, rubella vaccine



Concluding remarks

These limited data suggest that non-GAVI-eligible lower-middle income countries and upper-middle income countries experience higher minimum–maximum price ranges than GAVI/low-income countries and that there may be lessons to learn from GAVI/UNICEF's procurement experiences.

ANNEX 1: Background on vaccine prices

Historically, vaccine prices have varied significantly between countries. Price variations can be attributed to a number of factors including: market conditions (supply and demand dynamics); purchasing practices (procurement mechanisms and systems); donor support (funding mechanisms and demand forecasting); product characteristics and buyer preferences (numbers and types of antigens); and, value of local currencies and fluctuations in exchange rates.

Vaccine pricing today has become more complex than in the past. Traditional annual transactional procurement has shifted to more complex and longer-term procurement and financial arrangements for vaccines. Donors have created new markets by funding specific antigens such as the advance market commitment for pneumococcal vaccine. For mature vaccines, supply is often secured through multi-year contracts. All of these factors render the comparison of price components and contractual terms between purchasing countries less evident.

Prices to individual countries may vary because of international and domestic transport costs, insurance, storage, taxes, duties and other supply chain components and costs. Some countries may contract other goods and services, which can be reflected in the vaccine price. Direct price comparison between different procurement systems therefore requires the disaggregation of the inclusions of the reported prices and, where possible, the quantification or, at a minimum, the qualification of these inclusions.

As such, vaccine prices are particularly challenging to compare across countries, even when income level is very similar between countries, because purchases may differ greatly in volume, procurement systems, levees and taxes may be unique to a country. Also, the international commercial terms used by countries to report price (Incoterms) may vary greatly across countries, and the types and number of vaccine antigens, and their presentation, size and form vary considerably between countries. Given these differences, there may be very few data points that can be directly compared across countries.

ANNEX 2: Vaccine Product, Prices and Procurement (V3P) Project

Launched in September 2011, the V3P Project[48] is a three-year initiative led by WHO and funded by the Bill & Melinda Gates Foundation.

The lack of reliable, accurate and neutral vaccine product, price and procurement information and data has been identified as one of the obstacles to new vaccine introductions for both GAVI-graduating and other middle-income countries. Such information and data are essential to making informed decisions regarding the forecasting, budgeting and sustainable financing of new and priority vaccines.

The V3P has identified and developed a tool to collect accurate, reliable and useful data on vaccine product, price and procurement from countries. The V3P database can be accessed here: http://apps.who.int/immunization/vaccineprice.

The information is particularly targeted at decision-makers and managers of immunization programmes in countries as well as those providing advice, data and evidence for informed decisions on sustainable vaccine implementation in middle-income countries and GAVI-graduating countries.

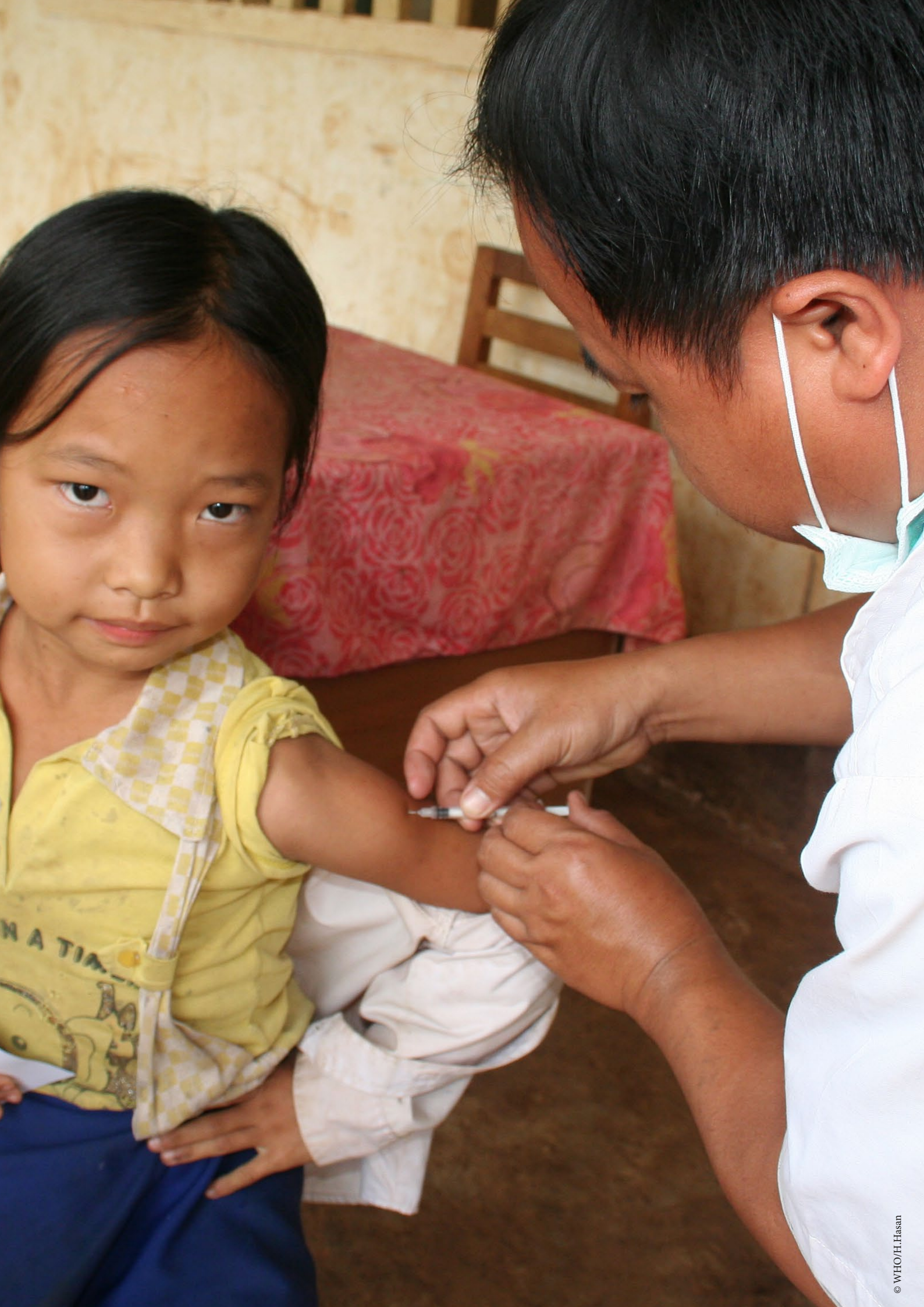
Many organizations have collaborated to the development of V3P and are engaged in its roll out including:
The Bill & Melinda Gates Foundation
Center for Global Development
GAVI Alliance Secretariat
The Global Fund to Fight AIDS, Tuberculosis and Malaria
PAHO Revolving Fund
Results for Development Institute
Supporting National Independent Immunization and Vaccine Advisory Committees (SIVAC) Initiative
Agence de Médecine Préventive
UNICEF, Supply Division
UNITAID
WHO, HQ and regional offices

[48] http://www.who.int/immunization/programmes_systems/procurement/v3p/en/.

ANNEX 3: The WHO/UNICEF Joint Reporting Form (JRF) and V3P

In an effort to strengthen collaboration and minimize the reporting burden, WHO and UNICEF jointly collect immunization information through a standard questionnaire (the Joint Reporting Form) sent to all Member States. The content of the Joint Reporting Form was developed through a consensus process among staff from UNICEF, WHO and selected ministries of health.

Over the past two years (2012-2013), for two pilot regions, the European and Eastern Mediterranean Regions, WHO/UNICEF used the JRF to gather information from countries similar to that collected in the V3P database, including vaccine types, number of doses per container, number of doses procured and the total amount paid or quoted.



II

Tracking resources invested in immunization: report on health account activities

Background

As per the M&E/A Framework presented to the Sixty-sixth World Health Assembly in May 2013, resources invested in immunization will be tracked and monitored on a yearly basis throughout the decade using the framework of the Organisation for Economic Co-operation and Development (OECD)/Eurostat/ WHO System of Health Accounts 2011 (SHA 2011). The SHA 2011[49] is an effort to create a single platform for collecting and analysing all of a country's health expenditures including those for priority programmes such as immunization.

The year 2013 marked the first time that the global standard for reporting health expenditures, the System of Health Accounts 2011, was introduced into countries (excluding OECD and European Union countries) using available grant monies from the Commission on Information and Accountability for Women's and Children's Health (COIA), BMGF, the Global Fund to Fight AIDS, Tuberculosis and Malaria, Family Planning 2020, and the GAVI Alliance plus resources from WHO.

Regional training workshops were held to kick off the work: for 11 countries each representing Anglophone and Francophone Africa in Hammamet, Tunisia in February 2014; for 13 Asian countries in Bangkok, Thailand in March 2014; for seven countries in Ouagadougo, Burkina Faso in October 2014, and; for 17 Eastern Mediterranean Region countries in Cairo, Egypt (abbreviated course) and for 12 countries in Johannesburg, South Africa in May 2015. A regional training workshop is planned for the Pacific Island countries and another one for countries in the Region of the Americas.

Results

A total of 27 countries have submitted their 1-2 year institutionalization work plans.

Eleven countries (excluding OECD and Eurostat countries) have completed their health accounts:

1. Benin
2. Burundi
3. Cameroon
4. Comoros
5. Democratic Republic of the Congo
6. Gabon
7. Ghana
8. Liberia
9. Niger
10. Sudan
11. United Republic of Tanzania

Only the Democratic Republic of the Congo and the Comoros have made their data official and publicly available. Data from all the other countries are still to be approved for official publication. Thus, the data cannot be circulated yet. The data, however, have been reviewed by the WHO Health Accounts team and some estimates have been flagged as needing to be re-evaluated. It is expected that the re-adjustment of the estimates will be done in the second year.

Another 34 countries or territories, in addition to the above, have indicated that they intend to start their health accounts this year. These are:

1. Armenia
2. Aruba, Curacao, Saint Martin (Netherlands)
3. Bhutan
4. Bosnia and Herzegovina
5. Cambodia[50]
6. Chad
7. China
8. Colombia
9. Côte d'Ivoire
10. Egypt
11. Gambia
12. Guyana
13. Honduras
14. Iraq
15. Kazakhstan
16. Kenya
17. Lao People's Democratic Republic
18. Malawi
19. Mauritania
20. Mozambique
21. Nigeria
22. Philippines
23. Sao Tome and Principe
24. Senegal
25. Seychelles
26. Sierra Leone
27. South Africa
28. Tajikistan
29. Thailand

[49] For more information about the GVAP and the System of Health Accounts 2011, please refer to p. 108 of the Global Vaccine Action Plan monitoring, evaluation & accountability: Secretariat annual report 2013. Geneva: World Health Organization; 2013 (http://www.who.int/entity/immunization/global_vaccine_action_plan/GVAP_secretariat_report_2013.pdf).

[50] The countries highlighted yellow are those expecting to complete their health accounts in the next month of 2014.

30. Togo
31. Tunisia
32. Uganda
33. Zambia
34. Zimbabwe

To provide technical assistance to the countries or territories, two certifying workshops have been held for consultants, one for Anglophones in December 2013 in Geneva, and another one for Francophones in Ouagadougou in April 2014. A total of 21 certified consultants are now available to provide technical assistance to countries.

In general, the process for institutionalizing health accounts in the countries is the following.

1. Country is invited to attend a regional training workshop where they are introduced to SHA 2011, the health accounts production and analysis tool, and are asked to draft a work plan for institutionalization.
2. The country then sends an official request for technical assistance to WHO, together with its work plan.
3. There will generally be three technical assistance visits: the first to map government expenditures, the second to map donor and NGO and household expenditures and the third to do analysis.
   The person(s) providing technical assistance can either be someone from WHO/HQ, its partner (USAID/Health finance and governance), or one of the above-mentioned consultants. Each country has a person from WHO HQ monitoring the work and the WHO country office takes an active role in facilitating the work.
4. The draft health accounts study is sent to WHO for review and feedback is provided.
5. The results are shared with stakeholders in the country for feedback and are then made official.
6. For the second year, all countries are expected to get T-1 expenditures. They will get one technical assistance visit each.

Lessons learned

1. Most countries would require about four visits in the first year; during an additional visit a workshop is conducted to raise awareness about the process among stakeholders and data providers.
2. Most countries would probably need two visits in the second year; one visit to get more technical assistance as they do their second year of health accounts and the second visit to learn to use the health accounts analysis tool.
3. Country ownership is key. Having a requirement on the part of the Global Fund to Fight AIDS, Tuberculosis and Malaria to provide evidence for counterpart financing is a good 'stick' to get countries to finish their health accounts in a timely manner.
4. It is not expected to get perfect results from the first year in a country. The first year usually serves to identify the weaknesses in the health account data and the second year is expected to redress this. This being said, better technical assistance can now be provided to countries, as more experience is now available with country work. The results from the countries doing their first health accounts in 2014 will be expected to produce better quality results than those from the first 10 countries.

III

Documenting and monitoring commitments for immunization: the PMNCH 2014 accountability report

In September 2010, the United Nations Secretary-General Ban Ki-moon launched the Global Strategy for Women's and Children's Health[51] to save 16 million lives in 49 countries by 2015.[52] With the target date of the Millennium Development Goals (MDGs) in sight, the Global Strategy represents the most significant global effort to accelerate progress towards the health-related MDGs: MDG 4 (child survival), MDG 5[53] (maternal and reproductive health), MDG 6 (HIV, TB and malaria), and MDG 1c (hunger). The Every Woman Every Child (EWEC) effort was established at the same time to advance the Global Strategy and to intensify global action to improve reproductive, maternal, newborn and child health.

A critical part of the Global Strategy was the creation of a global accountability framework for women's and children's health by COIA *(1)*. Following a recommendation of the COIA, the independent Expert Review Group (iERG) was established to report regularly to the United Nations Secretary-General on progress in women's and children's health. Two reports have been released by the iERG to date *(2, 3)*.

Since 2011, the Partnership for Maternal, Newborn and Child Health (PMNCH) has contributed to the accountability agenda for women's and children's health by analysing Global Strategy commitments and their implementation on an annual basis. These PMNCH reports on global strategy commitments have also supported the work of the iERG in its reporting to the United Nations Secretary-General about progress in the implementation of the Global Strategy.

The PMNCH 2014 accountability report *(4)* focuses exclusively on the commitments made to the Global Strategy that were specifically expressed in financial terms, i.e. financial commitments. It reviews progress made in implementing these financial commitments and how they have affected financing for reproductive, maternal, newborn and child health more broadly. While many significant non-financial commitments were also made to the Global Strategy (e.g. service delivery, policy and advocacy commitments), these are difficult to monetize and are not analysed in this report. Efforts by WHO and the Executive Office of the Secretary-General, in collaboration with PMNCH, are under way to develop a streamlined reporting platform that would bring the tracking and reporting of all commitments made to the Global Strategy and EWEC, both financial and non-financial, under one umbrella.

The PMNCH 2014 accountability report also assesses the degree to which financial commitments and overall funding of reproductive, maternal, newborn and child health are aligned with the priorities spelled out in the Global Investment Framework for Women's and Children's Health. The framework takes a forward-looking perspective and outlines the key reproductive, maternal, newborn and child health areas where additional investments are needed by the year 2035 in order to achieve substantial improvements not only in health but also considerable economic and social returns on that investment. The framework also was a key input to a broader, influential roadmap on investing in health, *Global Health 2035*, published by The Lancet Commission on Investing in Health in December 2013 *(5)*.[54] The roadmap of the Lancet Commission shows that investments in reproductive, maternal, newborn and child health, HIV, TB, malaria and neglected tropical diseases could lead to a "grand convergence" in global health within a generation—that is, a reduction in avertable infectious, maternal, newborn and child deaths to universally low levels.

As in previous PMNCH reports, the analysis in the 2014 report is focused on commitments that were listed on the EWEC website, and covers commitments for the time frame of the Global Strategy (2011-2015).[55] All commitments listed on the EWEC webpage as of 20 May 2014 are covered by this report. Some major initiatives that were brought under the umbrella of the Global Strategy and EWEC have a time frame beyond 2015. For example, most commitments made at the London Summit on Family Planning cover the period until 2020. For the purposes of the 2014 report, these commitments were prorated for the period until 2015. However, the report does not include assessments of initiatives that were not declared as explicit commitments to the Global Strategy or EWEC (for example, the Campaign for Accelerated Reduction of Maternal Mortality in Africa, led by the African Union; or commitments made at the Nutrition for Growth summit in London). This caveat should be kept in mind when reading the report.

However, despite these limitations, the analysis of financial commitments in the 2014 report shows a number of encouraging trends in the implementation of Global Strategy commitments and reproductive, maternal, newborn and child health financing more broadly, although it also points to important areas requiring more focus.

[51] http://www.everywomaneverychild.org/images/content/files/global_strategy/full/20100914_gswch_en.pdf.

[52] These were the 49 lowest-income countries according to the World Bank list of economies as of April 2008. These countries were in the focus of work of the Taskforce on Innovative International Financing for Health Systems and then became the focus countries of the Global Strategy. These are: Afghanistan, Bangladesh, Benin, Burkina Faso, Burundi, Cambodia, Central African Republic, Chad, Comoros, Côte d'Ivoire, Democratic Republic of the Congo, Democratic People's Republic of Korea, Eritrea, Ethiopia, Gambia, Ghana, Guinea, Guinea-Bissau, Haiti, Kenya, Kyrgyzstan, Lao People's democratic Republic, Liberia, Madagascar, Malawi, Mali, Mauritania, Mozambique, Myanmar, Nepal, Niger, Nigeria, Pakistan, Papua New Guinea, Rwanda, Sao Tome and Principe, Senegal, Sierra Leone, Solomon Islands, Somalia, Tajikistan, Togo, Uganda, United Republic of Tanzania, Uzbekistan, Viet Nam, Yemen, Zambia and Zimbabwe.

[53] MDG 5 has two targets: target 5A is to reduce by three quarters, between 1990 and 2015, the maternal mortality ratio; target 5B is to achieve, by 2015, universal access to reproductive health.

[54] See also: http://GlobalHealth2035.org.

[55] All commitments to the Global Strategy are listed on the Every Woman Every Child website: http://www.everywomaneverychild.org, accessed 01 March 2014.

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IV

Independent submissions from other stakeholders GAVI CSOs constituency independent stakeholders' report, July 2014

I. Introduction

Civil society's work at the community, district, national, regional and global levels to increase access to immunization is critical to saving children's lives and improving people's health. The role of Civil Society Organizations (CSOs) in immunization is broad and includes service delivery, demand creation, accountability, disease surveillance, advocacy for equitable access, affordability, funding and quality of services, as well as a wide array of "supporting roles" including assisting community health workers to deliver immunization. While these civil society roles are recognized by most immunization stakeholders, the sheer diversity of civil society presents challenges to adequately capturing the contributions of this broad group to the Global Vaccine Action Plan. Therefore, civil society presents this first independent report for inclusion in the 2014 Global Vaccine Action Plan (GVAP) Secretariat report. The purpose of this civil society report is to summarize CSO-reported *country-level* contributions to the achievement of the GVAP goals and Strategic Objectives (SOs); highlight challenges and missed opportunities in civil society's ability to fully contribute to GVAP implementation; and offer recommendations for consideration by the various GVAP working groups and the Strategic Advisory Group of Experts (SAGE) GVAP Working Group going forward.

This report was prepared by an independent consultant who was guided by the 20-member GAVI CSO Steering Committee and supported by the World Health Organization (WHO)/Immunization, Vaccines and Biologicals (IVB) team. The content for the report is based primarily on existing data and information collected by the GAVI CSO Constituency and available on the Constituency's website (http://www.gavi-cso.org/gavi-cso-hss-platforms). In addition, to elicit wider CSO input, the consultant developed two questionnaires that were distributed by email to the global GAVI CSO Constituency of approximately 300 organizations.

II. Civil society involvement in the development of the GVAP

Annex 5 of the GVAP lists more than 60 civil society groups that contributed to the elaboration of the Plan. Many of these are global organizations with presence in several countries or networks representing organizations at national, subnational, and/or community levels. For example, the GAVI CSO Constituency is listed as having provided input, but represents 300 or more CSOs around the world. Professional health associations and academia, often included in the definition of civil society, were listed separately and were mostly from developed countries.

Following the finalization of the GVAP at the global level, efforts are under way to develop or revise regional and country GVAPs. However, despite wide consultation at the global level, little is known among national, subnational and community-level CSOs about how regional and country plans are being developed/revised; specifically regarding the timeline, process, and the number and type of committees and working groups to be formed. At the country level, it is unclear if existing national immunization plans will be revised to align to the GVAP or if a separate GVAP-specific plan will be developed. CSOs, as committed partners, will be an important resource in GVAP development processes at both regional and country levels.

III. Civil society contributions in 2013 to GVAP goals and strategic objectives

In order for civil society to fully contribute to the achievement of the GVAP, local civil society organizations need to be aware of the contents of the Plan and whether a regional and/or country Plan is being/has been drafted. Two years after the World Health Assembly endorsed the GVAP, many CSOs, particularly those in GAVI-eligible countries, have "limited awareness" of the Plan, as cited in the preliminary report of the 2014 Civil Society Impact Survey[56] administered by Catholic Relief Services (CRS) on behalf of the GAVI CSO project. The GAVI CSO project was launched in 2011[57] to support country-level civil society actors in establishing functional national CSO platforms for effective engagement in immunization and health systems strengthening (HSS). It currently operates in 23 GAVI-eligible countries.[58] The Survey represents a first effort to assess civil society awareness of the GVAP and to capture civil society's contribution to the five GVAP goals and six GVAP strategic objectives (SOs). It should be emphasized that this was a *CSO-initiated effort* carried out with limited funding and *in the absence of a clear GVAP mechanism*

[56] The 2014 Civil Society Impact Survey was conducted from March through June 2014 in 9 of the 23 countries – Chad, Guinea, Haiti, India, Liberia, Malawi, Nigeria, Pakistan and Uganda.

[57] As a key activity to achieve Strategic Goal 2 of the 2011-2015 GAVI Strategy and Business Plan and more recently Strategic Objective 2.3./Programme Objective 2.3.1 of the updated 2013-2014 GAVI Business Plan.

[58] Bangladesh, Benin, Burkina Faso, Cameroon, Chad, Democratic Republic of the Congo, Ethiopia, Ghana, Guinea, Haiti, India, Kenya, Liberia, Madagascar, Malawi, Mali, Nigeria, Pakistan, Sierra Leone, South Sudan, Togo, Uganda, Zambia.

and process for CSOs to monitor and report their contributions. As a result, the number of CSO country platforms reporting contributions to the GVAP SOs was low and the information is more general.

Among nine country-level CSO platforms included in the Survey, seven[59] responded to questions related to their contributions to the GVAP SOs specifically. Despite the small sample of Survey countries and other limitations that were noted in the preliminary report, the full set of results presented in the report can be interpreted as basic indicators of: 1) how widely and effectively information about the GVAP is disseminated to stakeholders at the country level; 2) how CSOs interpret the definition of each GVAP SO; and 3) what processes and mechanisms are in place at the country level to enable CSOs to report their contributions to specific GVAP SOs. Overall, the results demonstrate clear shortcomings in these areas.

While work needs to be done to increase awareness of the GVAP among civil society in the Survey countries, as well as in other countries where national civil society platforms have been (or are in the process of being) established, the preliminary Survey report indicates that CSOs primarily contribute to SO 2 and to a lesser extent to SOs 1, 3 and 4. Of the 119 CSOs reported as implementing activities related to the GVAP SOs, 83% focused on SO 2 activities such as community sensitization and mobilization, and advocacy.

However, a review of questionnaire responses and GAVI CSO Project reports[60] indicate that country-level CSOs are contributing to most GVAP goals and SOs even though they do not realize they are. Although it appears that country-level CSOs are contributing more than they know and/or report, an analysis of CSO work plans and reports confirm that their efforts and outputs are more focused on SO 2 than on others – a finding consistent with results from the Survey.

Table 47 below captures CSO country contributions to each GVAP goal and SO based on the Survey results, questionnaire responses and GAVI CSO Project reports to GAVI. **Table 48** describes CSO-reported activities contributing to the GVAP SOs cited by Survey countries as well as other GAVI CSO Constituency member organizations responding to the questionnaire.

[59] CSOs in Chad and Malawi did not respond to Survey questions related to the GVAP.
[60] Catholic Relief Services 2013 quarterly reports and 2014 annual report to GAVI on the GAVI CSO Project

Table 46: Country-Level CSO Contributions to the GVAP Goals and Strategic Objectives

CSO COUNTRY PLATFORM ORGANIZED BY WHO REGION	GOAL 1 Achieve a world free of poliomyelitis	GOAL 2 Meet global and regional elimination targets	GOAL 3 Meet vaccination coverage targets in every region, country and community	GOAL 4 Develop and introduce new and improved vaccines and technologies	GOAL 5 Exceed Millennium Development Goal 4 target for reducing child mortality	SO 1 All countries commit to immunization as a priority	SO 2 Individuals and communities understand the values of vaccines and demand immunization as both their right and responsibility	SO 3 The benefits of immunization are equitably extended to all people	SO 4 Strong immunization systems are an integral part of a well-functioning health system	SO 5 Immunization programmes have sustainable access to predictable funding, quality supply and innovative technologies	SO 6 Country, regional and global research and development innovations maximize the benefits of immunization
WHO/Africa *(12)*											
Burkina Faso	X	X	X		X	X	X	X	X	X	
Cameroon	X	X	X				X	X		X	
Chad	X	X	X		X						
Democratic Republic of the Congo	X	X	X		X	X	X	X	X	X	
Ethiopia	X	X	X		X	X	X	X	X	X	
Ghana	X	X	X		X	X	X	X	X	X	
Guinea	X	X	X		X	X	X	X	X	X	
Kenya	X	X	X		X	X	X	X	X	X	
Liberia	X	X	X		X	X	X	X	X	X	
Malawi	X	X	X		X	X	X	X	X	X	
Nigeria	X	X	X		X	X	X	X	X	X	
Uganda	X	X	X		X	X	X	X	X	X	
WHO/Americas *(2)*											
Haiti	X	X	X		X	X	X	X	X	X	
Mexico							X				
WHO/Eastern Mediterranean *(1)*											
Pakistan	X	X	X		X	X	X	X	X	X	
WHO/South-East Asia *(2)*											
Bangladesh	X	X	X		X	X	X	X	X	X	
India	X	X	X		X	X	X	X	X	X	

Table 47: Summary of CSO-Reported Activities in Support of GVAP SOs

GVAP Strategic Objective (SO)	CSO-Reported Activities
SO 1: **All countries commit to immunization as a priority**	Support local CSOs and professional associations to contribute to national discussions on immunization and health
	Develop and disseminate the evidence base on the public health value of vaccines and immunization and the added value of achieving equity in access and use of immunization
	Include immunization in the agendas of governing body meetings at all levels and in other social, health and economic forums
	Create regional forums and peer-to-peer exchange of information, best practices and tools
	Create expanded and more transparent mechanisms for aggregating, sharing and using information to monitor commitments
SO 2: **Individuals and communities understand the value of vaccines and demand immunization as both their right and responsibility**	Engage in a dialogue that both transmits information and responds to people's concerns and fears
	Create incentives for households and health workers in favour of immunization
	Conduct social and/or programme research to improve the delivery of immunization services and the ability to meet the needs of diverse communities
	Train health workers in effective communication techniques and advocacy
	Engage, enable and support CSOs to advocate the value of vaccines to local communities, policymakers and local and global media
	Develop and implement targeted strategies to sensitize vulnerable communities on the need for vaccinations for their survival
	Utilize the internet, radio, and television to inform people and health professionals about vaccines featuring immunization champions such as film stars, famous athletes to communicate information
	Organize meetings with policymakers and health professionals to educate them about vaccines and correct any misinformation that creates doubt and controversies about their value
	Write and publish articles and educational books on vaccines for health workers
SO 3: **The benefits of immunization are equitably extended to all people**	Engage underserved and marginalized groups to develop locally tailored, targeted strategies for reducing inequities
	Prevent and respond to vaccine-preventable diseases during disease outbreaks and humanitarian crises, and in conflict zones
	Track each individual's immunization status
	Take advantage of community structures to enhance communication and deliver services
	Involve CSOs in community outreach and planning
	Develop new approaches to community engagement for urban and peri-urban areas
	Train health workers and CSOs in engaging communities
	Conduct research to identify strategies to reduce inequities and improve the quality and delivery of immunization services
	Advocate to health officials to ensure that vaccination campaigns cover mobile and rural populations, and minorities
SO 4: **Strong immunization systems are an integral part of a well-functioning health system**	Develop and promote the use of new technologies for collection, transmission and analysis of immunization data
	Increase levels of pre-service, in-service and post-service training for human resources, and develop new, relevant curricula that approach immunization as a component of comprehensive disease control
	Promote coordinated training and supervision of community-based health workers
	Establish information systems that help staff to track the available supply accurately

GVAP Strategic Objective (SO)	CSO-Reported Activities
SO 5: **Immunization programmes have sustainable access to predictable funding, quality supply and innovative technologies**	Engage in resource mobilization advocacy to increase domestic funding for health to 15% in line with the Abuja Declaration commitment
SO6: **Country, regional and global research and development (R&D) innovations maximize the benefits of immunization**	Advocate for new and/or more effective vaccines, affordable vaccine prices, funding for vaccine delivery equipment and their equitable distribution
	Conduct studies on the efficaciousness of specific vaccines in certain settings (e.g. Médecins Sans Frontières/Epicentre studies)

Overall, the GAVI CSO Constituency and the GAVI CSO country platforms have been documenting their contribution to ensuring access to immunization since 2011. CSOs working in immunization at all levels are contributing to the GVAP even if not currently reported as such due to lack of awareness, understanding, and monitoring and reporting processes. This includes global CSOs working across all goals and SOs in the areas of advocacy, resource mobilization, service delivery, and research and development (R&D) into new vaccines.

IV. Key challenges and missed opportunities to scaling up civil society contributions

Many of the challenges faced by CSOs that hinder their ability to contribute to achieving the GVAP goals and SOs and overall national (and subnational) immunization plans and programmes are not new. Results from the 2014 Civil Society Impact Survey, the 2013 CSO Survey,[61] questionnaire and other existing CSO documents cite many, often recurring difficulties in addressing the six main barriers outlined in GAVI's bottlenecks/barriers framework, a framework based on WHO's six health systems building blocks. These include challenges in:

1. Supply chain due to problems with distribution, infrastructure, and overall planning and management
2. Service delivery especially to poor, remote, mobile, female and/or rural populations due to weak road infrastructure and lack of adequately skilled, equipped, motivated, supervised, and socially- and culturally-appropriate staff
3. Demand generation due to social, cultural, and/or religious reasons as well as experiences with adverse events following immunization (AEFI)
4. Data collection, analysis, reporting, use, and quality due to lack of tools and training and skilled staff
5. Leadership, management, coordination, financing
6. Other areas such as political conflict and/or insecurity, frequent changes in government leadership and technical staff

These barriers cannot be resolved by civil society alone, but require a concerted, coordinated effort by multiple stakeholders.

Although there is an increasing number of positive examples of civil society partnerships and engagements with governments and development partners in the area of vaccines and immunization, including the support by WHO to develop this independent CSO report and GAVI's funding to CSOs to establish and strengthen national CSO platforms for immunization and HSS, overall, the role of civil society in expanding access to immunization lags well behind civil society's role in addressing other health issues and in other global health initiatives and partnerships such as those focusing on maternal, newborn and child health, HIV/AIDS, tuberculosis, malaria, cancer and other non-communicable diseases.

Collectively, CSOs working in immunization continue to voice frustration at not being regarded as a genuine and equal partner by governments and development partners. CSOs voice frustration at the lack of proactive, consistent and meaningful engagement and participation

[61] The 2013 survey was done on the first five countries supported by the GAVI CSO Project: Burkina Faso, DRC, Ghana, Kenya and Pakistan

in the development, implementation and monitoring of strategies, plans, programmes and funding decisions that affect them and ultimately the populations they serve. This includes: 1) limited deliberate and regular consultation with CSOs; 2) limited funding to expand reach, scale up of innovative approaches, and/or to sustain activities; and 3) lack of sufficient recognition and supportive treatment of CSOs as a critical partner by governments and development partners despite acknowledgement of the value of CSOs' on-the-ground experience working with vulnerable and hard-to-reach communities. In some instances, to participate, CSOs just need basic support in terms of internet and phone capability, funding to travel, and/or adequate advance notice of a meeting.

V. Recommendations

Reflecting on the current status of CSO awareness and contribution to the GVAP goals and SOs, the GAVI CSO Constituency offers the following recommendations. These recommendations focus specifically on how to better support country-level CSOs to contribute to the achievement of the GVAP. **The first four recommendations should be tracked and monitored annually as part of the GVAP monitoring process.**

For the 2014 GVAP Secretariat report, civil society recommends that:

1. National and regional immunization plans, programmes and strategies should clearly articulate in these documents civil society's role and expected contributions to their implementation and monitoring
2. Memorandum of understanding (MOU)s and signed agreements between governments or development partners and CSOs should be formalized and increased to enable CSOs to expand their reach and contribution to immunization plans and programmes
3. Immunization coordinating committees as well as technical and non-technical working groups at national and subnational levels (where they exist) should include CSOs working in immunization so that they can share their experiences (e.g. routine immunization, demand generation, etc.) and propose solutions to addressing barriers to increasing vaccine coverage
4. WHO and UNICEF country representatives and offices should organize roundtables with CSOs at national and subnational levels to increase overall awareness and understanding of the GVAP and civil society's role in its achievement
5. WHO should develop clear information on the timeline and processes to develop regional and country level GVAPs, and communicate this information widely across stakeholders, including CSOs; information should include the contact details for specific persons responsible for overseeing these efforts
6. WHO should include during its regional Expanded Programme on Immunization (EPI) meetings a forum for countries to exchange experiences and lessons on regional and country level GVAP development as well as on successes, challenges, and innovative approaches to addressing barriers to immunization scale up; CSO leadership from GAVI CSO country platforms should be invited to the annual regional and global EPI review meetings
7. GVAP Secretariat should convene a sub-working group within the GVAP Monitoring & Evaluation/Accountability working group to develop CSO or community-level indicators for each SO to be integrated in the GVAP M&E/ Accountability framework
8. GVAP Secretariat should task the GVAP M&E/ Accountability working group with developing CSO-friendly tools and processes to allow CSO contributions to the GVAP to be assessed and verified as part of a systematic and standardized process for reporting by all stakeholders to the GVAP
9. CSOs should be supported to carry out annual GVAP reporting at country, regional and global levels

ANNEX: CONTRIBUTORS

The GAVI Civil Society Stakeholders report was prepared with input from the GAVI CSO Constituency and country-level Civil Society platforms for immunization and health systems strengthening supported by the GAVI CSO Project. The report was reviewed and approved by the GAVI Civil Society Steering Committee, a body of approximately 20 CSOs that guide the work of the GAVI Civil Society Constituency.

These organizations include:

GAVI Civil Society Steering Committee members:

Civil Society in Malaria Control, Immunization and Nutrition (ACOMIN), Nigeria
ACTION, USA
15% Coalition Cameroon/Positive Generation, Cameroon
Alternative Santé, Cameroon
American Academy of Pediatrics, USA
American Cancer Society, USA
Asociación Mexicana de Vacunología/Mexican Vaccine Association, Mexico
BRAC, Bangladesh
CORE Group Polio Project (CGPP), India
Future Generations International (FUGI), Ghana
Global Health Advocates, France
Health Education Literacy Programme (HELP), Pakistan
Health NGOs Network (HENNET), Kenya
IMA World Health, USA
Indian Academy of Pediatrics (IAP), India
International Federation of Red Cross and Red Crescent Societies (IFRC), Switzerland
Kenya AIDS NGOs Consortium (KANCO), Kenya
Orphans Relief Services (ORES), United Republic of Tanzania
World AIDS Campaign International (WACI)/Africa Regional Civil Society Platform on Health, South Africa

GAVI civil society country-level platforms:

Bangladesh : Under development
Benin : Under development
Burkina Faso : Health Theme Group of the Secrétariat Permanent des ONG Burkina Faso
Cameroon : Under development
Chad : Plateforme des Organisations de la Société Civile pour le soutien à Vaccination et à l'Immunisation au Tchad
Democratic Republic of the Congo: Coalition of CSOs for Health and Immunization (COMAMA)
Ethiopia: Ethiopian Civil Society Health Forum, Consortium of Christian Relief and Development Associations
Ghana: Ghana Coalition of NGOs in Health
Guinea : Plateforme des Organisations de la société civile pour le Soutien à la Santé et la Vaccination
Haiti : Plateforme Haïtienne pour le Renforcement de la Vaccination
India: Alliance for Immunization in India
Kenya: Health NGOs Network
Liberia: Liberia Immunization Platform
Malawi: Malawi Health Equity Network
Madagascar : Under development
Mali: Plateforme des Organisations de la Société civile du Mali engagée pour renforcer la couverture vaccinale des enfants.
Nigeria: Nigerian CSO Platform in Health
Pakistan: Pakistan CSOs Coalition for Health and Immunization
Sierra Leone: Sierra Leone CSO Platform on Immunization
South Sudan: Community Organizing Program
Togo: Réseau des organisations de la société civile (OSC) Togolaise intervenant dans la santé de la mère, de l'enfant, la vaccination et le renforcement du système de santé
Uganda : Malaria and Child Illnesses Secretariat
Zambia: Under development

INTERNATIONAL FEDERATION OF PHARMACEUTICALMANUFACTURERS & ASSOCIATIONS (IFPMA) "SUSTAINABLE INNOVATION FOR A HEALTHIER FUTURE: HOW THE RESEARCH-BASED VACCINE MANUFACTURERS ARE CONTRIBUTING TO THE DECADE OF VACCINES GLOBAL VACCINE ACTION PLAN", REPORT JULY 2014

IFPMA Report

Sustainable Innovation for a Healthier Future: How the Research-based Vaccine Manufacturers are Contributing to the Decade of Vaccines Global Vaccine Action Plan

Vaccination is an incredible success story: the Expanded Programme on Immunization (EPI) initiated by the World Health Organization saves approximately 2.5 million lives annually and has just celebrated its 40th anniversary. Before EPI, only 5 percent of the world's children were protected from six diseases — polio, diphtheria, tuberculosis, pertussis, measles and tetanus. Today, that figure is 83 percent, with some developing countries reaching 99 percent immunization coverage. What started as an ambitious effort to tackle six vaccine-preventable diseases has become one of the world's most successful public health programs. Still, there is always progress to be made[i] and the Decade of Vaccines (DoV) Global Vaccine Action Plan (GVAP) aims to further prevent millions of deaths by 2020 through more equitable access to existing and new vaccines for people in all communities. A key element of this effort is a reinvigorated approach to innovation as well as reaching the under-vaccinated "fifth child."

As part of its coordinated approach, the GVAP outlines many roles for industry: to develop, produce and supply innovative and high-quality vaccines; to support research and education; to innovate manufacturing and pricing structures; and to work in collaboration with numerous partners to ensure sustainable access to vaccines for all. The research-based vaccine manufacturers are deeply committed to the GVAP as a crucial partner in this fight to save lives.[ii,iii,iv,v,vi] *Further information:* http://tinyurl.com/nkpwcbn

This year the progress and obstacles surrounding vaccine and immunization research are being tracked and discussed by DoV partners. From research to delivery, the research-based vaccine manufacturers are developing new approaches to ensure sustainable uptake and usage of existing and new vaccines and realize the full potential of vaccine innovation. These programs are designed to solve today's challenges in a way that can be maintained and strengthened for generations to come. *Hear more about the value of investing in vaccine innovation*[vii,viii]

Leading Innovation to Address Unmet Medical Needs

When the global health community works together, we are capable of changing the world. As companies, we work in partnership with international organizations, governments, non-governmental organizations, academics and many others to identify unmet medical needs as early as possible as well as the required features of new vaccines.

Today, biopharmaceutical research companies are testing and developing over 300 vaccines including both preventive and therapeutic candidates, to tackle some of the toughest diseases threatening at risk populations.[ix,x,xi]

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With a legacy of more than 230 years, Takeda is committed to being an important partner in the quest to improve global public health through access to safe, affordable, high-quality, effective vaccines. The company's vaccine development efforts are focused on norovirus and dengue, a WHO priority and a significant public health problem in emerging and developing countries where unmet needs exist. Takeda's norovirus vaccine is the most advanced candidate in clinical development worldwide and will soon enter Phase 3 trials. Currently in Phase 2 development, Takeda's tetravalent dengue vaccine candidate is a recombinant vaccine based on a live attenuated dengue type 2 virus, providing the genetic backbone for all four serotypes with the intent to provide broad protection.

GSK scientists, with others around the world, have been working for the past 30 years to develop a vaccine against malaria. Now, as a result of the involvement of over 200 experts, a vaccine candidate—RTS,S—is in development in partnership with PATH Malaria Vaccine Initiative (MVI) with grant monies from the Bill & Melinda Gates Foundation. GSK intends to submit a regulatory application for the vaccine to the European Medicines Agency (EMA) in 2014. If a positive opinion from the EMA is granted, the WHO has indicated a policy recommendation may be possible by end of 2015. Each year there are over 200 million cases of malaria globally and approximately 627,000 malaria deaths, most of which occur in Africa in children under the age of five. There is currently no licensed vaccine available for the disease. Learn more in the IFPMA case study at http://tinyurl.com/ovrcudy

The pharmaceutical industry remains a major funder of research and development for neglected conditions particularly prevalent in the developing world with over 20 of the current vaccines in development targeting diseases such as malaria, tuberculosis, dengue, diarrhoeal diseases, bacterial pneumonia, meningitis and Leishmaniasis. [xii,xiii]

Our efforts are also supported by partnerships with third parties to accelerate discovery and development of new vaccines and pharmaceutical industry R&D centers dedicated solely to diseases that disproportionately affect people in low-income countries (LICs) and lower-middle income countries (LMICs). Some companies integrate these R&D activities within their broader R&D organization while others provide financial and technical support to independent institutions.[xiii]

In addition to new vaccines, many companies are working to make current vaccines more accessible to children who currently cannot be vaccinated. These are important projects to ensure vaccination opportunities are not missed.

From Lab to Licensure

Once developed, vaccines receive regulatory approval from national and/or supranational regulatory authorities, including the WHO Prequalification process. Today, more than 100 prequalified vaccines, produced by IFPMA member companies, are available for purchase by UN agencies.[xiv] Completing the WHO Prequalification, which guarantees the manufacturing of high quality vaccines, facilitates the licensing process and can speed up the availability of vaccines globally. *Further information on the complex journey of a vaccine at http://tinyurl.com/ngyfrlb and infographic at http://tinyurl.com/obj2ppw*

IFPMA and its members have contributed to the foundations of a sustainable, science-based regulatory environment through collaboration with WHO Prequalification and international organizations supporting convergence of regulatory standards.

Daiichi is working with the Center for Research and Production of Vaccines and Biologicals (POLYVAC) in Hanoi, Viet Nam to transfer vaccine manufacturing technology. Begun in May 2013, after an agreement for Official Development Assistance was reached between the governments of Japan and Viet Nam, this program will enable POLYVAC to produce a measles-rubella vaccine locally in Viet Nam. Local production means both wider availability of, and lower costs for, the vaccine for Vietnamese children who are currently underserved. The technology transfer is expected to be completed in 2018.

As the world's population and demand for vaccines grow, so must high-quality manufacturing capacity. Significant investment in new, cutting-edge biotechnologies along with careful planning (e.g. stockpiling) and regulatory steps enable companies to make larger quantities of vaccine doses more efficiently and effectively to meet this growing demand.

Research-based vaccine manufacturers may also choose to begin making new vaccines at an existing facility, which means they will begin with a limited number of doses and scale up production, or they can build new, dedicated facilities that can immediately manufacture large quantities of a new vaccine as soon as it is licensed. By adopting this innovative approach, vaccines will be available for public immunization programs shortly after first regulatory approval provided proper recommendation for use and funding are in place.[xv]

Finally, several vaccine suppliers from both industrialized and developing countries are partnering in order to not only meet rapidly expanding demand for vaccines, but also to secure supply in other LICs and LMICs. In such cases technology transfer and regional production can be an effective and sustainable solution if the necessary economies of scale can be achieved.[xvi]

Developing a Path to Sustained Uptake and Usage

Ensuring everyone can enjoy the benefits of vaccine innovation means securing supplies and enhancing uptake and usage for all populations. These elements will vary according to the vaccine in question and the country or region concerned. This is why an approach tailored to each country or region is needed.

Once delivered to a country, vaccines must remain potent, be distributed in a timely manner to both clinics and outreach settings, and be safely administered. We create high quality vaccines that offer optimal protection against dangerous diseases. Quality cannot and should not be compromised while traveling "the last mile" to unimmunized populations in LICs and LMICs.

LICs and LMICs face a variety of delivery challenges. Warehouses, health-care facilities and delivery vehicles operate in a world of limited resources. In response, companies are developing formulations and presentations of their current vaccines that can: 1) withstand higher temperatures than experienced in many developed countries; 2) take up less space in delivery vehicles, refrigerators and cold rooms; 3)

Crucell, along with partners, has developed a compact, prefilled, auto-disable (cPAD) injection system for their pentavalent vaccine to further simplify/ facilitate EPI systems (Crucell's pentavalent vaccine in cPAD was co-developed with Novartis Vaccines). The new presentation within its innovative secondary packaging holds many advantages over current presentations, especially tailored to drive coverage in outreach and other difficult to reach areas. Key features that can facilitate coverage include: Its compact and lightweight design, the all-in-one injection system, ease of use through the reduction of manipulations required and, of course, the single dose and auto disable primary packaging.

enhance traceability and supply chain management; and 4) be packaged in either single- or multi-dose vials according to the needs of a community and health care system.

First, new technologies are addressing cold chain interruptions that can affect vaccine potency. Several research-based vaccine manufacturers are focusing their resources, especially for pneumococcal disease, human papillomavirus, hepatitis B, rotavirus, polio, and cholera, on testing the temperature robustness of current formulations for short periods of time and on developing in the longer term new technologies and formulations for vaccines in development or even existing ones.

Pfizer is leading a 2D bar coding pilot in Tanzania to support a safe and stable supply of vaccines. The company has implemented 2D bar codes on the Prevenar 13 labels, cartons and shipping packs. When the vaccine is received, and before it is administered, local dispensaries can scan the code and confirm that the vaccine came from the Prevenar 13 manufacturer. The company is working with other vaccine manufacturers and global institutions to implement the 2D bar code technology on all vaccines in Tanzania. After successful implementation, the company will work with GAVI, UNICEF, WHO and VPPAG to introduce the program in all GAVI-eligible countries.

Second, limited space in delivery vehicles, refrigerators and cold rooms along with suboptimal vaccine management practices can result in an insufficient number of vaccine doses reaching a remote location, leaving many children unprotected until the next shipment arrives. Since the Vaccine Presentation and Packaging Advisory Group (VPPAG)[xvii] was convened in 2008 by the World Health Organization (WHO), we have actively contributed expertise and strived to customize vaccines to address the needs of LICs, LMICs and partners involved in the delivery of vaccines to these countries. Several companies have decreased the size of their vaccine containers and packaging to reduce the cold chain space needed and introduced 2D barcodes on the packs to allow for better management of stock at delivery endpoints. Some companies have changed their containers from glass to plastic and replaced prefilled glass containers with compact, easy-to-use plastic squeeze tubes for oral vaccines. Others have built new filling lines specifically to package vaccines in compact, prefilled auto-disable injectable devices for LICs and LMICs.

Third, frontline health workers need flexibility in responding to varying numbers of children at vaccination sessions. Most companies are responding to this need by developing both single-dose and multi-dose containers. This means that frontline health workers can store enough vaccine via multi-dose vials to offer vaccination days or, with the single dose, can vaccinate one or two children without worrying about wasting unused content in a multi-dose vial. While they may consume more storage space, single-dose vials are an important tool in ensuring there are no missed opportunities to vaccinate people.

Eliminating diseases require strong, locally-run immunization programs. Shortly after the approval of its human papillomavirus (HPV) vaccine, MSD instituted a grant program to assist selected localities design, implement and evaluate HPV vaccination programs. Grantees had the assistance of leading experts to navigate barriers as they arose as well as access to free HPV vaccine donated by MSD. To date, MSD has donated over 1.3 million doses to 25 participants in 21 countries. Understanding the need for sustainable access, as the projects near completion, MSD is compiling lessons learned to disseminate for use in other HPV immunization programs and to hopefully avoid unnecessary delays in protecting girls and boys from this cancer-causing virus.

Beyond delivery challenges, vaccination partners including governments, non-profit organizations and industry must have an understanding of why

immunization rates remain stagnant or, in some cases, fall, and work together to overcome them. Research-based vaccine manufacturers are investing extensive time and resources to support these efforts. Practical frameworks should help vaccine program managers and other advocates to better understand and diagnose the coverage gap in a national or local vaccination program and better address those problems.

Control, Eliminate and Eradicate Disease

In an ideal world people would be vaccinated before a disease outbreak occurs. Unfortunately, this is not always possible. Emergency vaccination programs are still needed to protect individuals from disease outbreaks as diverse as cholera, meningococcal meningitis, yellow fever and measles. Enhancing the way disease outbreaks are monitored could help develop more effective vaccination campaigns to save lives. We are therefore applying our knowledge of how certain diseases develop and spread to help prepare for potential outbreaks. Early identification helps timely vaccination of vulnerable populations, particularly children, and saves lives.

Sanofi Pasteur has a longstanding commitment to the control of polio disease using both live attenuated polio vaccine (OPV) and inactivated polio vaccine (IPV), which they have manufactured since 1964 and 1983, respectively. A partner of the Global Polio Eradication Initiative (GPEI) for over 20 years, Sanofi Pasteur has made significant investments in modern technology to produce very large quantities of IPV. The company is working with WHO and national agencies to ensure IPV is approved for use in more than 110 countries. In order to support rapid and widespread adoption, Sanofi Pasteur will offer unparalleled volumes of high quality IPV across a broad range of countries and economic situations, at differential prices, in an unprecedented, global rollout.

Ultimately, our goal is to eliminate, and eventually eradicate, vaccine-preventable diseases. Eradication or elimination of any disease is a highly complex undertaking that requires the full commitment of not only the global health community but also governments and their citizens. Eradication of polio and elimination of measles and rubella are within our reach. Only through extensive innovative partnerships can the global health community finally declare victory for all people, regardless of where they are born, who they are, or where they live.

Ensuring a Viable Ecosystem for Vaccines

A successful ecosystem for vaccine innovation ensures patients have access to life-saving vaccines while maintaining an environment in which the research, development and delivery of vaccines can continue for many generations. This requires that all partners work together, including research-based biopharmaceutical companies, multi-national organizations, non-profit groups and governments. Only with policies in place that respect the contributions of each partner can we continue to develop life-saving vaccines for every child, adolescent and adult throughout the world.

In addition to researching and developing innovative vaccines, the research biopharmaceutical industry, through IFPMA, also contributes to enhanced vaccine access with its participation for over a decade as a partner in the GAVI Alliance – an innovative public-private partnership dedicated to making needed vaccines available in GAVI-eligible countries.

Our shared goal is to eliminate and eradicate vaccine-preventable diseases where and when possible, and control those diseases that cannot be eradicated. Everyone should benefit from the discoveries in our laboratories. Only through sustained investment in new vaccine technologies and

their effective introduction and rollout can the global vaccination community have the potential to save millions of more lives.

About IFPMA

IFPMA represents the research-based pharmaceutical companies and associations across the globe. The research-based pharmaceutical industry's 1.3 million employees research, develop and provide medicines and vaccines that improve the life of patients worldwide. Based in Geneva, IFPMA has official relations with the United Nations and contributes industry expertise to help the global health community find solutions that improve global health.

Additional Resources and Citations

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