World Health Organization

From Vaccine Development to Policy: A Brief Review of WHO Vaccine-Related Activities and Advisory Processes (2017)

1. Introduction

To help achieve the implementation of the Global Vaccine Action Plan (GVAP), WHO's strategic goals for vaccines for the period of 2015-2030 are as follows[1]:

- Promote the development of new vaccines and vaccine delivery technologies to meet public health priorities
- Establish norms and standards for vaccines and delivery technologies
- Ensure vaccines and delivery technologies are of assured quality

WHO conducts a number of activities under these core areas that support vaccines and delivery technologies from the early development stages through to WHO global policy. The precise nature of these activities inherently depends on the specific approach against the pathogen and product technologies that are to be developed, as well as the needs of WHO, Member States, and the broader community. To this end, WHO seeks to adapt its processes as appropriate, in order to make efficient use of time and resources needed to achieve the overall public health objective for each pathogen. This document describes general processes established at WHO to support attainment of WHO's mission *to support all countries to deliver quality immunization services as part of an integrated, people-centred platform of disease prevention that spans the human life-course,* through product development and evidence-based policy.

2. Vaccine Development to Policy

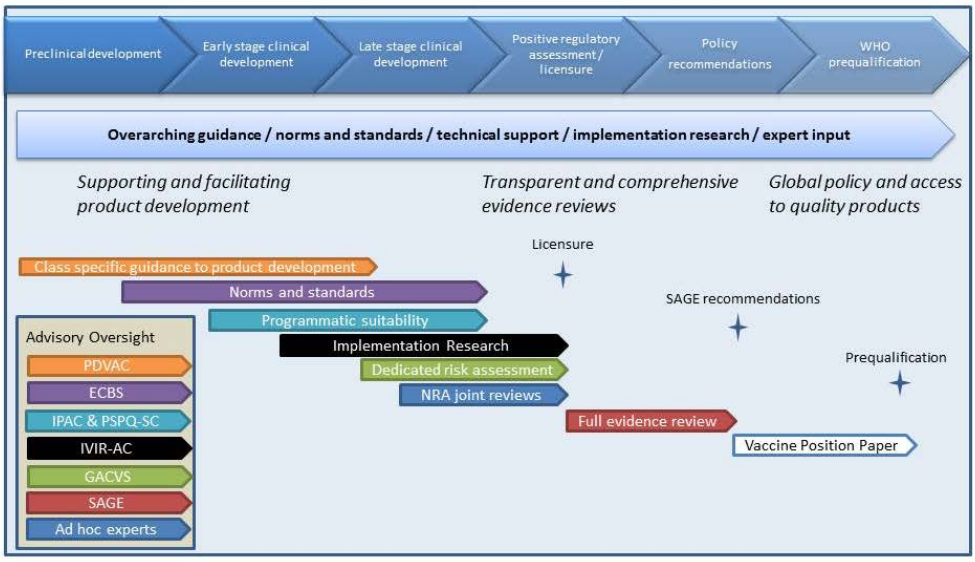

Figure 1. Overview of key areas of work and advisory input from vaccine development through to WHO policy.[2] *Note: All of these domains/areas of work extend across the lifespan of products; this*

[1] WHO's vision and mission in immunization and vaccines 2015-2030: http://www.who.int/immunization/documents/general/WHO_Mission_VIsion_Immunization_Vaccines_2015_2030.pdf

diagram is for illustrative purposes only, focusing on specific tasks/strategic areas in support of processes leading to policy development. It does not reflect the work done on a continual basis after WHO issues a policy recommendation to review evidence and sustain/update existing guidance and policy. It also does not reflect the important areas of work post-policy in access and implementation.

2.1 Supporting and facilitating product development

WHO's engagement in vaccine development begins with an assessment of unmet public health need. Landscape analyses and candidate pipeline reviews are undertaken to identify pathogens for which vaccine development is a public health priority and for which WHO can play a strategic role in facilitating and accelerating vaccine development. Examples of WHO activities that are undertaken for priority pathogens include the development of Strategic Goals for Vaccine Development and R&D Technology Roadmaps. WHO has also developed Preferred Product Characteristics (PPCs) to help guide vaccine development towards WHO's preferences focusing on public health need where disease burden is greatest. Rarely, WHO has developed Target Product Profiles (TPPs) in the context of public health emergencies for which minimally acceptable criteria are provided in addition to preferences; these are in contrast to company TPPs that are product specific and guide their internal development processes. WHO PPCs and WHO TPPs are class and not product specific. Such work supporting vaccine product development is done under the guidance of PDVAC.

In some instances, WHO has constituted independent technical expert groups to provide advice to WHO on issues concerning the evaluation of vaccines in pivotal trials, including advice on aspects of trial design (including case definition, endpoint, duration of follow-up, analysis methods and geographical extent), the interpretation of trial results, and data needs to support a future policy decision by SAGE; constitution of such groups is based on public health importance and utility of such an interaction, guided by PDVAC's recommendation (see section 3.2). Examples include the Joint Technical Expert Group on malaria vaccines and the dengue vaccine Technical Advisory Group. Assessment of disease burden and a business case for new product development may also be undertaken, under the guidance of IVIR-AC.

A core function of WHO is to develop, establish and promote norms and standards in the form of 1) global written standards to assist in the appropriate regulation of quality, safety, and efficacy; and 2) global measurement standards as tools for product development, licensing and lot release. By adopting or taking into account WHO guidelines in their regulatory decision making, pharmacopoeias or equivalent legislation, national regulatory authorities can ensure that the products manufactured and used in their country conform to current international standards. WHO norms and standards are also the standards used for prequalification of vaccines. WHO has produced key documents that are generalizable across products (e.g. the recently revised Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations) as well as pathogen-specific norms and

[2] Abbreviations: PDVAC: Product Development for Vaccines Advisory Committee; ECBS: Expert Committee on Biological Standardization; IPAC: Immunization Practices Advisory Committee; PSPQ-SC: Programmatic Suitability of Vaccine Candidates for WHO Prequalification Standing Committee; IVIR-AC: Immunization and vaccine related implementation research advisory committee; GACVS: Global Advisory Committee on Vaccine Safety; SAGE: Strategic Advisory Group of Experts on Immunization.

standards (e.g. Guidelines on the quality, safety and efficacy by pathogen and vaccine class). All such documents are reviewed by ECBS prior to publication in the WHO Technical Report Series.

2.2 Transparent and comprehensive evidence reviews

Since 1998, to fulfil its mission for vaccines, the WHO has published vaccine position papers with global recommendations for vaccine use (Section 2.3). Guidance outlining the development of evidence-based vaccine-related recommendations is available (Appendix 1). Topics that are explicitly considered in evidence reviews to generate global recommendations include: epidemiologic features of the disease, clinical characteristics of the targeted vaccine, other options for disease control and prevention, vaccine and immunization characteristics, economic considerations, health system considerations, social impacts, legal considerations, and ethical considerations.

The overall comprehensive evidence review takes into account all of these areas and includes a process of systematic reviews of the evidence, GRADing of the quality of the evidence, and a reflection of benefits and harms, values, resource use, equity, acceptability and feasibility considerations of the intervention within evidence-to-recommendation tables. The process of reviewing the evidence and drafting evidence-based recommendations is overseen through the SAGE committee and associated Working Groups. Independent evidence-based recommendations are provided to WHO by SAGE.

Within the scope of these larger topics, key issues such as effectiveness and population impact, safety, indirect effects, cost-effectiveness, affordability, cold chain and logistical concerns, vaccine schedules, social and programmatic acceptability, ability to reach target populations, ability to monitor programme impact, and impact of vaccine introduction on the wider health system are addressed. More focused advisory committees such as GACVS, IVIR-AC, and IPAC provide inputs that feed into these areas as part evidence review process.

2.3 Global policy recommendation

WHO provides global policy recommendations to Member States on the basis of a transparent and systematic evidence review process. During a time of increasing availability of vaccines, competing priorities, challenges with affordability, and special-interest groups, it is important that WHO provides support for country decision-making around introduction and use of new vaccines. In developing and formulating policy recommendations, WHO considers factors in addition to the benefit-risk assessment performed by regulators, e.g. important contextual elements such as the feasibility of implementation, epidemiological factors that influence performance of the vaccine, the value of the vaccine in the context of other control measures, and the likely cost-effectiveness of the intervention in different settings. WHO will issue a policy recommendation only after a vaccine has been licensed by a functional national regulatory authority (NRA) or given a positive regulatory assessment by the European Medicines Agency Article 58 procedure.

Based on SAGE recommendations, WHO issues global policy through vaccine position papers, published with open access in the *Weekly Epidemiological Record*. These represent WHO's official position on vaccines and combinations of vaccines against diseases or vaccine-related issues that have an international public health impact. These papers are generally concerned with the use of vaccines in large-scale immunization programmes. The position papers are intended for use mainly

by national public health officials and managers of immunization programmes, as well as to provide information for national disease control programmes. The vaccine position papers may also be of interest to international funding agencies, vaccine advisory groups, vaccine manufacturers, the medical community, scientific media and the general public. All materials and evidence reviews done in service to a global policy recommendation are made available on the WHO website. Notably, regulatory decision-making and immunization policy decision-making are distinct with different data requirements and considerations.

Because the recommendations in position papers are not normally product specific, they apply across products with the same general characteristics and performance profile and do not need updating each time a new vaccine becomes available. However, position papers are updated as new data or novel products become available that impact the recommendations.

2.4 Access to quality products that are programmatically suitable for global use

A SAGE recommendation for use of vaccines against the specific pathogen is required prior to official issuance of WHO prequalification. Prequalification is required for procurement of the product by UN agencies and for financing by other agencies, including Gavi. The WHO prequalification process acts as an international assurance of quality, safety, efficacy and suitability for low and middle-income country immunization programs. WHO encourages vaccine developers and manufacturers to be aware of the WHO prequalification process, even at the early stages of development and to discuss the product and the regulatory requirements with the WHO prequalification staff early in the process. Registration by a NRA, or European Medicines Agency in the case of the centralized procedure for marketing authorization in Europe, will be required prior to any consideration of prequalification. Furthermore the prequalification process requires regulatory oversight by the NRA of Record, which is usually the NRA of the country where the vaccine is manufactured or the NRA of the country of finishing and distribution, and such an NRA should have been assessed as functional by WHO. Vaccine developers should check that the planned NRA of Record for the prequalification procedure is considered functional by WHO.

The WHO prequalification process involves a set of review criteria to assess the Programmatic Suitability for Prequalification (PSPQ). In addition to meeting quality, safety and efficacy requirements established by the ECBS, it is also important that developers and manufacturers understand WHO's preferences for parameters that have a direct operational impact on immunization programs. Low programmatic suitability of new vaccines could result in delaying introduction and deployment, given that introduction of new vaccines that have higher volume, cold chain capacity or disposal demands could have a negative impact on existing operations of immunization programs. Therefore early stage consideration of presentation and packaging parameters is encouraged. Deferring these considerations may lead to additional costs and delays associated with reformulation later in the development pathway. To facilitate early attention on these issues, WHO has published several documents that describe WHO preferences for vaccine presentations and packaging and programmatic suitability. The PSPQ criteria of vaccine characteristics that determine programmatic suitability and affect the acceptance for prequalification are divided into three categories: Mandatory, Critical and Unique or Innovative characteristics.

In order for a vaccine to be prequalified by WHO, product summary files (PSFs) are prepared by the manufacturer, post-licensure, and assessed by the WHO Secretariat to determine the suitability of the vaccine for the immunization services where it is intended to be used. Vaccine candidates that are non-compliant with a critical criterion, as described in the PSPQ guidance document, or that have unique or innovative characteristics, are referred to the PSPQ Standing Committee (PSPQ-SC) for deliberation and recommendation as to whether prequalification evaluation should proceed. Manufacturers can also seek PSPQ-SC review through the WHO Secretariat at any stage of product development, including very early on in product design and planning.

Any proposed changes to the PSPQ process and criteria require IPAC endorsement. IPAC provides guidance in identifying and implementing innovative technologies, tools and systems to strengthen immunization programmes, and in improving vaccine packaging and presentation in relation to the programmatic suitability of vaccines for use in the public sector.

2.5 Timelines

WHO recognizes the need to accelerate the timelines for access to safe and effective products that can have a public health impact. Therefore, strategic planning in consultation with external partners and stakeholders occurs throughout product development, and activities overlap where possible, to minimize any time delay associated on the pathway to licensure and subsequent WHO policy recommendation. As an example, a comprehensive evidence review by SAGE may begin prior to licensure of the product by a functional NRA, but no SAGE session for decision will occur until after licensure.

Box 1. Key steps from product development to WHO policy

- Consensus building to define priority public health goals for a vaccine candidate
- Facilitation and acceleration of product development to achieve WHO public health goals in accordance with WHO recommended norms and standards
- Registration of product by a functional National Regulatory Authority
- Review of key evidence inputs by SAGE to inform optimal use of vaccine from public health perspective, including safety, operational issues and implementation research, and programmatic suitability, as well as the quality of the evidence, values and preferences, equity, feasibility, etc.*
- SAGE recommendations to WHO are adapted into global policy published as Vaccine Position Paper†
- After a SAGE recommendation for widespread use, companies can submit their dossier for WHO prequalification

*For complete list see http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf
† For complete process see http://www.who.int/immunization/position_papers/position_paper_process.pdf

3. Vaccine-related advisory structures at WHO

Evidence-based guidance on immunization and vaccine-related policy and programming is provided by a network of advisory committees at the global level. Through open calls for nomination they are constituted with the world's leading experts and independence is assured through careful screening, management and posting of declarations of interest, including financial and intellectual. Advisory committees are in service to WHO and discuss issues that are of relevance to WHO. For vaccines,

multiple advisory committees support WHO and are anchored in the WHO Immunization, Vaccines and Biologicals (IVB) department (IPAC, IVIR-AC, PDVAC, and SAGE) or the Essential Medicines and Health Products (EMP) department (ECBS, GACVS, and PSPQ-SC). These two departments thus work closely together to ensure the full pathway from product development to policy is coordinated across the different respective domains.

3.1 SAGE

The principal advisory group to WHO for vaccines and immunization is SAGE, which reports directly to the WHO Director-General. SAGE is charged with advising WHO on overall global policies and strategies, ranging from vaccines and technology, research and development, to delivery of immunization and its linkages with other health interventions. SAGE typically considers antigen-specific issues, but rarely handles product-specific matters unless only one product is available. SAGE Working Groups are established to review the evidence relating to issues addressed in the vaccine position papers and propose recommendations for SAGE consideration. After discussion and deliberation, SAGE makes recommendations on the use of vaccines which are then incorporated by WHO into the vaccine position papers (Figure 2). WHO's IVB department scans the horizon of emerging products and available guidance on a semi-annual basis to determine the topics that require consideration by SAGE. As new products proceed to late stage clinical development, SAGE often is briefed in readiness for licensure. Timelines are carefully optimized to ensure that policy recommendations are promptly available so that countries are informed to make decisions. For example, SAGE was briefed in April 2013 on dengue vaccines, followed by the first registration in December 2015 and the first SAGE recommendation at the following meeting in April 2016. Similarly, SAGE discussed respiratory syncytial virus (RSV) vaccines in April 2016 as the leading vaccine candidate began Phase III clinical testing in the elderly and pregnant women.

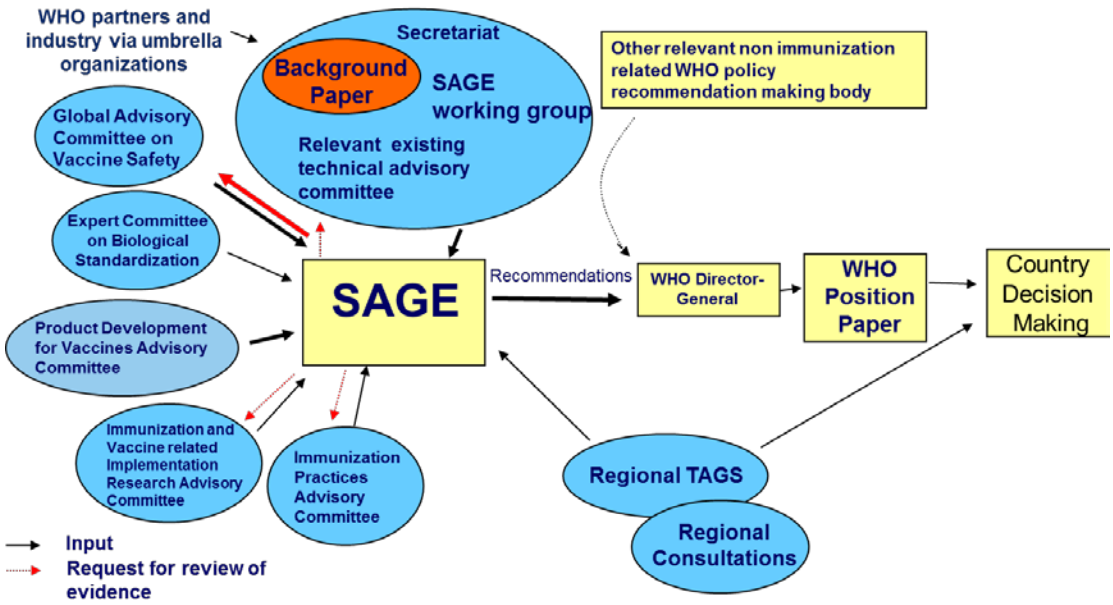

Figure 2. Pathways for WHO policy recommendations on vaccine use.

SAGE and IVB are supported and/or work in concert with a number of other WHO technical advisory committees.

3.2 Additional WHO advisory committees related to vaccines and immunizations

The WHO **Expert Committee on Biological Standardization (ECBS)** was established in 1947 to provide detailed recommendations and guidelines for the manufacturing, licensing and control of blood products and related in vitro diagnostic tests, biotechnology products and vaccines along with the establishment of WHO Biological Reference Materials. This committee sets norms and standards for the manufacturing, licensing and quality control to ensure the quality of vaccines and other biological products. The ECBS meets on an annual basis and reports directly to the Executive Board, the executive arm of the World Health Assembly.

The **Global Advisory Committee on Vaccine Safety (GACVS)** was established in 1999 and provides scientific advice on issues of vaccine safety that are of potential global or regional concern and may have an impact on national immunization programmes. GACVS conducts an independent risk assessment that is taken into consideration by SAGE together with all of the inputs that go into a policy recommendation. These include pre-licensure and post-licensure safety assessments. It provides independent, authoritative, scientific advice to WHO on vaccine safety issues of global or regional concern with the potential to affect in the short- or long-term national immunization programmes.

The **Immunization Practices Advisory Committee (IPAC)** was established in 2010 and advises WHO on the formulation of immunization strategies and operational standards, the tools and technologies necessary to reach and sustain high levels of immunization coverage and to promote immunization services of high quality. This committee has a number of topic-specific working groups comprising of external experts that review and provide evidence-based information and options to IPAC for further consideration.

The **Immunization and Vaccine Related Implementation Research Advisory Committee (IVIR-AC)** was established in 2007 (under the name QUIVER) and provides advice and recommendations on immunization and vaccine-related implementation research, including reviews of the relevance and applicability of quantitative methods, agenda setting and prioritization of research, and reviews of implementation progress and best practices. IVIR-AC contributes to early stage clinical development through advice on methods for assessing burden of disease and analytical decision making tools for disease and economic impact of immunization programs. The IVIR-AC's agenda is organized around three overarching themes. (1) Research to minimize barriers and improve coverage of vaccines currently in use. (2) Research to conduct impact evaluation of vaccines in use, and (3) Research to improve methods for monitoring of immunization programs.

The **Product Development for Vaccines Advisory Committee (PDVAC)** was established in 2014 and provides strategic advice and recommendations to WHO related to vaccines at the Phase 2 stage of clinical evaluation or earlier. The committee's remit is for disease areas where there is substantial disease burden in low and middle income countries, no licensed vaccines or products currently exist, and there is some ongoing product development activity which may benefit from guidance from WHO. This committee may also have a role where first generation vaccines are licensed but development of improved second generation products is a priority for WHO. PDVAC does not provide product-specific scientific advice but rather guidance on WHO's preferences for a class of products as a whole, e.g. RSV vaccines.

The **Programmatic Suitability of Prequalified Vaccines Standing Committee (PSPQ-SC)** was established in 2010 and is tasked by WHO/EMP to review WHO-referred exceptions to the programmatic suitability of prequalified vaccines process and provide recommendations to WHO (see also 2.4).

3.3 Advisory committee processes and integration

The scope and Terms of Reference of each technical advisory committee is outlined on the WHO website. WHO Secretariat focal points for each committee help to shape the work streams and meeting agendas and ensure coordination across the organization and with other committees. The agenda for each SAGE meeting is developed by SAGE and WHO in consultation with partners; input from industry is also solicited. Similarly, the consultation agendas of the additional advisory committees are developed with consideration of the following: 1) Needs of WHO and relevant departments; 2) Requests from SAGE or reviews in service to the SAGE evidence review and/or follow up of policy; 3) Topics of interest to the committee and key stakeholders.

WHO's advisory structures are well co-ordinated and integrated. There are a number of mechanisms that ensure continuity and synergy across advisory committees. The Chairs of all non-SAGE Advisory Committees attend and provide a report of activities to SAGE at SAGE meetings. Either the SAGE Chair or SAGE Secretariat attends each consultation of the other committees. To support the comprehensive evidence reviews, SAGE frequently requests input from the other IVB/EMP Advisory Committees on specific topics relevant to the topic – for example, a review of programmatic considerations across vaccine candidates (e.g. IPAC briefing paper on Considering the potential programmatic impact of new vaccines, with reference to Japanese Encephalitis vaccines) or a review of modelling efforts that inform SAGE recommendations (e.g. IVIR-AC review of the Dengue vaccine modelling comparison exercise). In some cases there are dedicated representatives of each committee on a SAGE Working Group (e.g. as Secretariat for the Ebola Working Group). In other cases, advisory committees are explicitly linked. For example, IPAC has a formal relationship with the PSPQ-SC. The PSPQ-SC consists of five members, of which at least two are also IPAC members. For pathogen-specific issues, the relevant advisory committees in the disease program areas at WHO are involved (e.g. SAGE and the Malaria Policy Advisory Committee, MPAC, jointly issued recommendations in 2015 for the first malaria vaccine). The precise method of interaction across advisory committees is specific to each topic area and the associated needs for IVB and other relevant WHO departments.

3.4 External interactions

All interactions relevant to policy processes for a specific pathogen or product, including engagement with WHO advisory committees, should be channelled through the organizational focal point for that disease (individual focal points available on request from vaccines@who.int). In addition, any communications from external partners relevant to any WHO advisory committee should be channelled through the appropriate WHO Secretariat focal point (Table 2), not individual committee members. Solicited input or participation from industry related to WHO's work in vaccines is typically organized through industry organizations such as IFPMA and DCVMN.

Table 2. WHO vaccine-related Advisory Committee reporting and contacts.

Committee	Reports to	Typical Meeting Schedule	Contact	More information
SAGE	DG	Twice yearly	sageexecsec@who.int	http://www.who.int/immunization/policy/sage/en/
ECBS	Health Assembly	Once yearly	empinfo@who.int	http://www.who.int/biologicals/WHO_ECBS/en/
PSPQ-SC	Director EMP	As required	empinfo@who.int	http://www.who.int/immunization_standards/vaccine_quality/ps_pq/en/
GACVS	Director EMP	Twice yearly	gvsi@who.int	http://www.who.int/vaccine_safety/committee/en/
IPAC	Director IVB	Every 12-18 months and continuous virtual discussion forums.	vaccines@who.int	http://www.who.int/immunization/programmes_systems/policies_strategies/ipac/en/
IVIR-AC	Director IVB	Twice yearly	VaccineResearch@who.int	http://www.who.int/immunization/research/committees/ivir_ac/en/
PDVAC	Director IVB	Once yearly	VaccineResearch@who.int	http://www.who.int/immunization/research/committees/pdvac/en/

4. Beyond Policy

This document has focused on key steps for WHO processes from the early stages of vaccine development to an initial WHO policy. However, the work of WHO does not end with this policy recommendation. Many of the steps outlined in this document are relevant for 2nd generation vaccines, and continuous efforts to improve use of existing vaccines through increasing coverage, optimizing vaccination schedules, identifying missed opportunities, addressing areas of vaccine demand and vaccine hesitancy, and integrating vaccination with other health services and improving the overall health system. As vaccines are evaluated in the post-licensure phase, safety, effectiveness, and impact data are regularly assessed, and SAGE revisits and updates existing policy as appropriate to optimize the public health benefit. These are just a few examples of the work undertaken by WHO throughout the product development lifecycle that support WHO's vision of the highest attainable standard of health for all individuals and communities through preventing disease.

For questions or clarifications, please contact vaccines@who.int with "WHO Vaccine Development to Policy" in the subject line.

Appendix 1. Examples of key areas of work, outputs, and advisory structures to support vaccine development and evidence-based global policy.

Areas of Work	Examples of Outputs	Advisory Structures	Illustrative Examples
Class specific guidance to product development	Pathogen Prioritization R&D Technology Roadmaps PPCs/TPPs Independent Expert Advice on Pivotal Trials	PDVAC	Modjarrad K, et al. WHO consultation on Respiratory Syncytial Virus Vaccine Development Report from a World Health Organization Meeting held on 23-24 March 2015. Vaccine. 2016 Jan 4;34(2):190-7. A Roadmap for Research and Product Development against MERS-Coronavirus: http://www.who.int/csr/research-and-development/roadmap-consultation/en/ WHO Preferred Product Characteristics (PPC) for Malaria Vaccines: http://apps.who.int/iris/bitstream/10665/149822/1/WHO_IVB_14.09_eng.pdf Zika virus vaccine TPP for use in an emergency: http://www.who.int/immunization/research/development/zika/en/index2.html Technical advisory group on dengue vaccines in late stage development (May 2012-March 2015): http://www.who.int/immunization/research/committees/dengue_tag/en/
Development of Norms / Standards	Guidance on clinical evaluation Assay standardization	ECBS	Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations [link pending] Guidelines on the quality, safety and efficacy of dengue tetravalent vaccines (live, attenuated): http://www.who.int/biologicals/areas/vaccines/TRS_979_Annex_2.pdf WHO collaborative study to assess the suitability of a WHO International Reference Panel for Ebola virus VP40 antigen: http://www.who.int/biologicals/expert_committee/BS2302_Ebola_Virus_antibodies.pdf
Programmatic Suitability	Assessing the programmatic suitability of vaccine candidates for WHO prequalification	IPAC PSPQ-SC	Assessing the Programmatic Suitability of Vaccine Candidates for WHO Prequalification: http://www.who.int/immunization/documents/policies/WHO_IVB_14.10/en/ Considering the potential programmatic impact of new vaccines, with reference to Japanese Encephalitis vaccines:

			http://www.who.int/immunization/sage/meetings/2014/october/Considering_potential_programmatic_impact_new_vaccines_JE_vaccines.pdf
Implementation Research	Advice on public health and economic impact of a vaccine program, protocols and methods	IVIR-AC	IVIR-AC Meeting reports: http://www.who.int/immunization/research/committees/ivir_ac/en/index4.html
Independent Safety Reviews	Dedicated product reviews Statements on emerging safety concerns	GACVS	Reports for all topics covered in past meetings: http://www.who.int/vaccine_safety/committee/topics/en/ Statement on Safety of HPV vaccines: http://www.who.int/vaccine_safety/committee/GACVS_HPV_statement_17Dec2015.pdf
Full evidence review including efficacy/effectiveness, safety, duration of protection, etc.	Background papers for SAGE decision	SAGE	Guidance for the development of evidence-based vaccine-related recommendations: http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf Example Comprehensive Background Papers: Dengue vaccines: http://www.who.int/immunization/sage/meetings/2016/april/1_Background_Paper_Dengue_Vaccines_2016_03_17.pdf Yellow fever vaccines: http://www.who.int/immunization/sage/meetings/2013/april/1_Background_Paper_Yellow_Fever_Vaccines.pdf
Global guidance on vaccine use	Vaccine Position Papers Table of Vaccine Schedules	SAGE and broader community	WHO Vaccine Position Papers: http://www.who.int/immunization/documents/positionpapers/en/ http://www.who.int/immunization/position_papers/position_paper_process.pdf WHO recommendations for routine immunization - summary tables: http://www.who.int/immunization/policy/immunization_tables/en/