



AN R&D BLUEPRINT FOR ACTION TO PREVENT EPIDEMICS

**PLAN OF ACTION
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**World Health
Organization**

AN R&D BLUEPRINT FOR ACTION TO PREVENT EPIDEMICS

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ACRONYMS

AVAREF	African Vaccine Regulatory Forum
CEPI	Coalition for Epidemic Product Innovation
CEWG	Consultative Expert Working Group on R&D Financing and Coordination
EUAL	Emergency Use Assessment and Listing
EVD	Ebola Virus Disease
GCP	Good Clinical Practices
GloPID-R	Global Research Collaboration for Infectious Disease Preparedness
GPP	Good Participatory Practices
ICMJE	International Committee of Medical Journal Editors
IP	Intellectual Property
LMICs	Low and Middle Income Countries
MOU	Memorandum of Understanding
MSF	Médecins Sans Frontières
MTA	Material Transfer Agreement
NGOs	Non Governmental Organizations
PHEIC	Public Health Emergency of International Concern
R&D	Research and Development
TDR	The UNICEF-UNDP-World Bank-WHO Special Programme for Research and Training in Tropical Diseases
VEBCON	Vesicular Stomatitis Virus Ebola Vaccine Consortium
WEF	World Economic Forum
WHO	World Health Organization
WWARN	Worldwide Antimalarial Resistance Network

1. AN R&D BLUEPRINT FOR ACTION TO PREVENT EPIDEMICS

In May 2015, the Sixty-Eighth World Health Assembly

"...welcomed the development of a blueprint, in consultation with Member States and relevant stakeholders, for accelerating research and development in epidemics or health emergency situations where there are no, or insufficient, preventive, and curative solutions, taking into account other relevant work streams within WHO".

At the request of its 194 Member States, WHO has convened a broad global coalition to develop the Blueprint as a platform for accelerating R&D.

This document, was prepared in advance of the 69th World Health Assembly based on a series of expert consultations and preparatory work to generate early deliverables. It presents the main directions for an effective R&D Preparedness strategy: the R&D Blueprint.²

¹ Decision WHA68(10).

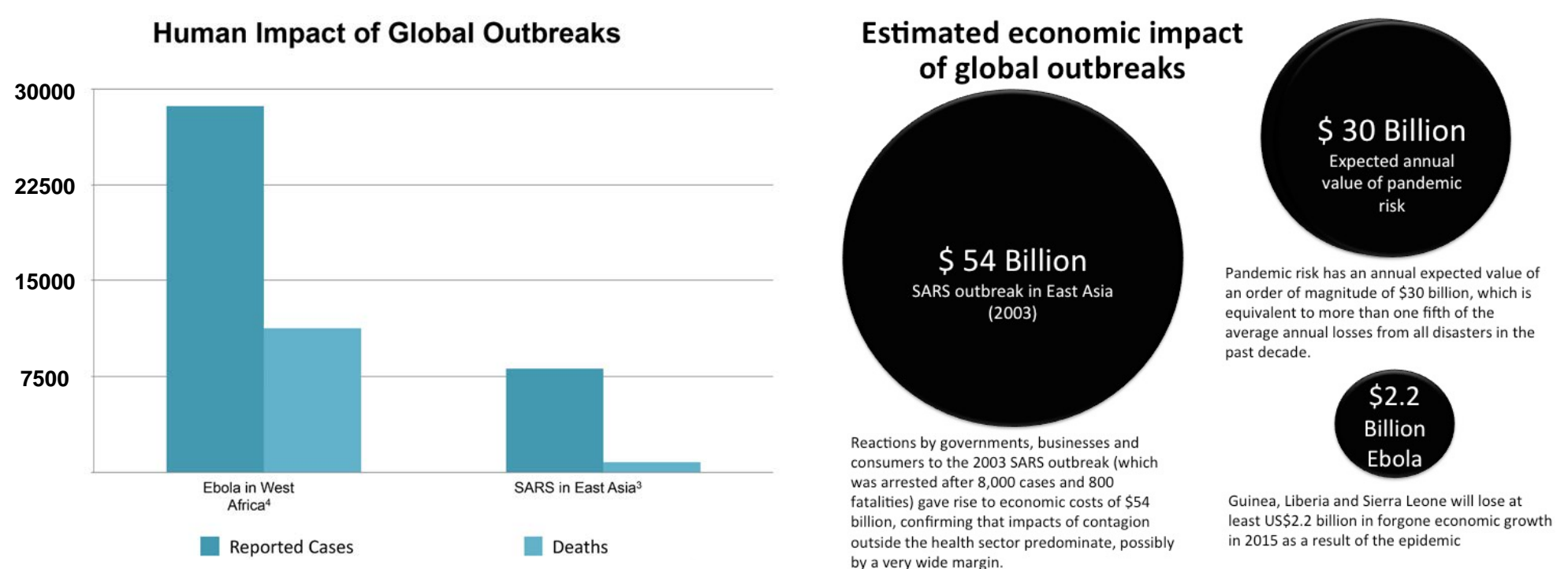
² <http://www.who.int/csr/research-and-development/en/>



2. INTRODUCTION

Infectious disease epidemics pose a clear and ongoing risk to global health, security, and economic prospects.

Figure 1. Human and Economic Impact of Global Outbreaks^{3,4,5}



Experience with past epidemics highlights the need, and the opportunity, to improve emergency preparedness. It also underlines the importance of research as an integral element of the response to any epidemic.

Moreover, the global health community increasingly recognizes the importance of proactive and coordinated research and product development efforts. These efforts - in advance of and during epidemics - must overcome existing market failures⁶ in addressing neglected tropical diseases, and in particular diseases with sporadic demand for countermeasures that are often concentrated in geographic areas with lower levels of health care spending.

³ World Bank Group Ebola Response Fact Sheet. The World Bank. (2016, April 6). Retrieved 26 April 2016, from <http://www.worldbank.org/en/topic/health/brief/world-bank-group-ebola-fact-sheet>

⁴ Jonas, Olga B., Pandemic Risk, World Development Report. The World Bank., 2013 (http://www.worldbank.org/content/dam/Worldbank/document/HDN/Health/WDR14_bp_Pandemic_Risk_Jonas.pdf)

⁵ Summary of Probable SARS Cases with onset of illness from 1 November 2002 to 31 July 2013. The World Health Organization. (http://www.who.int/csr/sars/country/table2004_04_21/en/)

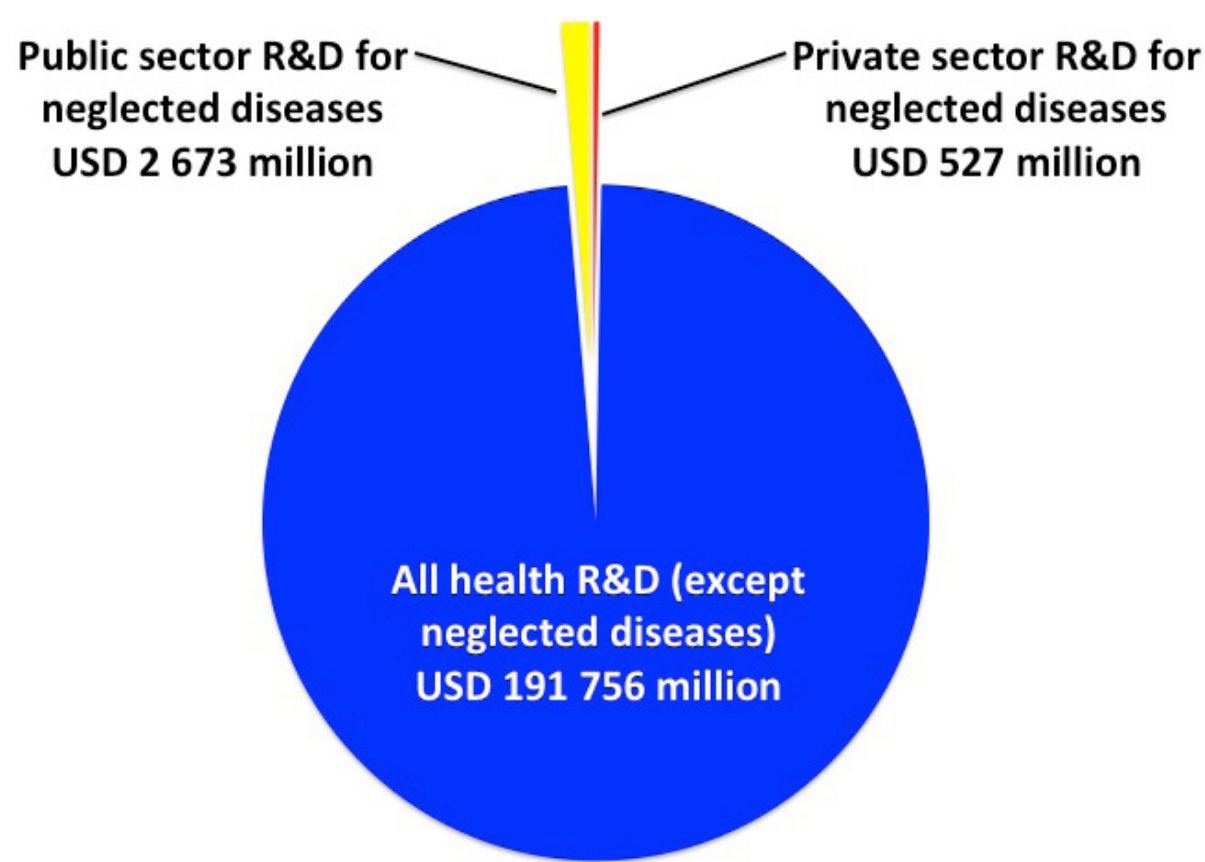
⁶ http://www.who.int/phi/CEWG_Report_5_April_2012.pdf

When the Ebola outbreak in West Africa erupted in the spring of 2014, the global health community was ill prepared to cope. There were no vaccines, no treatments, few diagnostics, and insufficient medical teams and trained responders.

In spite of this lack of R&D preparedness, the Ebola experience also demonstrates that it is possible to compress R&D timelines from a decade or longer to less than a single year.

WHO expert teams, an international scientific advisory board, and partners engaged through global forums are collaborating to articulate a novel R&D model for emerging pathogens likely to cause severe outbreaks in the near future, and for which few or no medical countermeasures exist. Already, several consultations have been held among national governments and public health agencies, researchers, social scientists and industry. They have identified major bottlenecks to international collaboration; agreed upon basic data sharing principles; and explored innovative approaches to conducting clinical trials.⁷

Figure 2. Health research and development spending



Source: Burrill Report & Policy Cures 2013

For priority infectious threats, the R&D Blueprint proposes to map the knowledge already accrued through efforts of research and development stakeholders, as well as remaining gaps. It will identify the main activities needed to promote strategic research in advance of, and during outbreaks.

⁷ <http://www.who.int/csr/research-and-development/en/>

3. WHO'S ROLE IN R&D DURING THE 2014-2015 EBOLA EPIDEMIC

The West African Ebola epidemic, the largest and longest Ebola outbreak in history, outlined several strengths and weaknesses in the R&D response and emphasized the need to be better prepared for the next epidemic. Research achievements by the international community throughout the outbreak were significant and progress was made in a record time, especially given the initial state of research.

At the beginning of the outbreak, despite the identification of the virus four decades ago, the previous occurrence of several deadly outbreaks, and despite many years of academic and biodefense research into Ebola and other filoviruses, there were no proven preventive or therapeutic products for Ebola virus disease (EVD) and research efforts had stalled at the preclinical level.

In a collaborative, inclusive and transparent effort, WHO coordinated a series of international consultations and activities contributing to unprecedented global efforts to develop and accelerate access to research interventions. The international scientific, ethics, regulatory, industry and funders' communities collaborated with West-African authorities and scientists, and participated in consortiums to set research priorities and facilitate the evaluation of the most advanced candidate medical products.⁸

For example, WHO collaborated with key stakeholders to facilitate the development and evaluation of several vaccine candidates from Phase 1 to Phase 3 clinical trials. The Vesicular Stomatitis Virus Ebola Consortium (VEBCON) was established to accelerate development of one of the priority Ebola vaccine candidates and worked with all relevant stakeholders to expedite Phase 1 clinical trials in Europe and Africa.⁹

A parallel effort leveraged the African Vaccine Regulatory Forum (AVAREF) to expedite ethical and regulatory reviews of Ebola vaccine Phase 1 and 2 clinical trials' applications, providing technical assistance to regulatory and ethical bodies of affected countries.¹⁰

⁸ <http://www.who.int/medicines/ebola-treatment/meetings/en/>

⁹ http://www.who.int/immunization/diseases/ebola/3-rVSV_Phase_1_Michael_29_Sep_14_v2.pdf

¹⁰ http://www.who.int/immunization_standards/vaccine_regulation/africa_network/en

In Guinea, WHO coordinated the implementation of an innovative vaccine Phase 3 clinical trial, and hired and trained National staff to conduct the study with full GCP compliance. Four months later, preliminary results on efficacy were announced and the trial was transformed into a public health intervention to control further spread of the disease.¹¹

Furthermore, to accelerate product evaluation and access, WHO designed a set of procedures to assess the performance, quality and safety of medical technologies during emergency situations. The Emergency Use Assessment and Listing procedure (EUAL) for Ebola diagnostics was successful in guiding international procurement for effective diagnostic tests.¹²

Unfortunately, emergency development of experimental products came too late to benefit the large majority of affected people.

There is broad consensus that global research efforts were hampered by insufficient collaboration and transparency that often led to a slow and uncoordinated research response in affected countries.

Moreover the research response suffered from insufficient local technical capacity and deficient understanding by international partners of the fundamental needs and culture of the affected communities.

In conclusion, the Ebola epidemic has demonstrated that it is possible to accelerate R&D during emergencies and that it is feasible to safely and effectively implement research interventions in affected countries. It also highlighted the imperative to advance R&D preparedness and effective collaboration frameworks ahead of any new epidemic.

It is a moral imperative for the global community to prevent a similar tragedy from occurring in the event of a future outbreaks of other severe infectious pathogens.

¹¹ <http://www.who.int/features/2015/guinea-ebola-vaccine/en/>

¹² <http://apps.who.int/medicinedocs/en/m/abstract/Js21987en/>



4. THE VISION AND PRINCIPLE

With more frequent travel, globalized trade and greater interconnectedness between countries, infectious disease outbreaks of international concern are becoming as inevitable as they remain unpredictable. The international community needs to invest to improve our ability to respond to new threats and prepare ourselves with a novel R&D paradigm to address future outbreaks and epidemics. The information that is generated through high quality research implemented in preparation for, in the middle of, and after an emergency is critical to our future capacity to better achieve the overarching goals of outbreak preparedness and response.

The vision the Blueprint is a world in which our R&D response to PHEIC caused by emerging pathogens is faster and more effective than ever before and in which we are able to ensure that a continuous effort aiming to accelerate the results of research but also adapt to the scientific, logistical and social challenges that are specific to epidemics.¹³

This strategy aims to avert and minimize life loss and economic disruption due to an outbreak.

¹³ http://www.who.int/csr/research-and-development/r_d_blueprint_brochure2015.pdf?ua=1

PRINCIPLES OF THE R&D BLUEPRINT

Figure 3. Four principles have guided the elaboration of the Blueprint plan.

1. An inclusive process with a clear mandate and defined milestones	2. Building on the efforts of others in the community	3. A collaborative effort with affected countries at its core	4. Driven by scientific knowledge
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The activities under this R&D Blueprint are also guided and informed by the principles and elements of the Global Strategy and Action Plan for Public Health, Innovation and Intellectual Property¹⁴ and of the Consultative Expert Working Group on R&D Coordination and Financing (CEWG).¹⁵

By promoting new thinking on innovation and access to medicines, a medium-term framework will be developed for securing an enhanced and sustainable base for needs-driven essential health research and development relevant to diseases that disproportionately affect developing countries, while proposing clear objectives and priorities for research and development, and estimating funding needs in this area.¹⁶

¹⁴ Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property. The World Health Organization. 2012 (http://www.who.int/phi/publications/Global_Strategy_Plan_Action.pdf?ua=1)

¹⁵ http://www.who.int/phi/CEWG_Report_5_April_2012.pdf

¹⁶ See note 19.

5. WHAT WOULD SUCCESS LOOK LIKE?

The R&D Blueprint is a global strategy and preparedness plan to ensure that targeted R&D will strengthen the emergency response by bringing medical technologies to populations and patients during epidemics.

The Blueprint aims to reduce the time between the declaration of a public health emergency of international concern and the availability of effective tests, vaccines and medicines that can be used to save lives and avert crisis.

The Blueprint is both a convening mechanism and an instrument to articulate technical guidance for R&D preparedness, especially in the area of coordination (e.g. avoiding unnecessary duplication, addressing priorities), which can be implemented effectively through appropriate incentives and other measures.

In parallel to the Emergency Response Reform, WHO aims to develop innovative ways of promoting R&D preparedness for priority pathogens with a focus on LMICs.

The Blueprint intends to facilitate the development of necessary mechanisms to improve coordination and increase funding for critical R&D activities for prioritized pathogens. These efforts will, in turn, affect market actors and key stakeholders in disease response.

Emergency preparedness and response should benefit from increased R&D funding and improved R&D collaboration. Ideally, these efforts should catalyze global changes, promote greater coordination and increase the range of medical technologies available to treat infectious disease. The net impact should be faster and more effective responses to public health emergencies across the globe.

The R&D Blueprint seeks to create an enabling environment through which the R&D community, through increased funding, data sharing and partnerships, can drive change in the public health landscape to provide an elevated level of global impact. This new environment will reduce the time for new medical technologies to reach developing countries in a public health crisis.



The global health community, national governments, the populations of developing countries, product development partnerships, pharmaceutical & biotechnical companies, must and can work together to increase investment in R&D for appropriate medical technologies, ensuring their availability to, and affordability for the populations in need by using innovative coordination and funding mechanisms and by taking into account the principles of the CEWG report, including delinking the price of products from the cost of research.

WHO is the United Nations specialized agency for public health providing technical cooperation, carrying out programmes to control and eradicate disease and striving to improve the quality of human life.

To fulfill its mandate, the Organization has a core responsibility in the area of “research and coordination of research.” WHO will use its convening power to make this vision a reality, but success will rely on the concerted efforts of all stakeholders.

The R&D Blueprint represents WHO's new start for a better R&D preparedness. The current lack of R&D preparedness is a problem that can be solved. Let's solve it together.



Box 1: Expert group's demands to WHO for R&D preparedness for pandemic diseases

In the wake of the 2014-15 Ebola outbreak, various reports on how to avert similar crises in the future were published, addressing among other things the question of how to improve R&D preparedness and response. Excerpts of some of the proposed actions are presented below.

The **Ebola Interim Assessment Panel** recommends that “WHO should play a central convening role in research and development efforts in future emergencies, including the acceleration of the development of appropriate diagnostics, vaccines, therapeutics and medical and information technology”.¹⁷

The **High-level Panel on the Global Response to Health Crises** recommends that “...WHO oversees the establishment and management of an international fund” to support R&D efforts for prioritized pathogens .¹⁸

The **Commission on a Global Health Risk Framework for the Future** sees WHO in a leading role in galvanizing R&D for pandemic preparedness through the creation of a Pandemic Product Development Committee.¹⁹

The **Independent Panel on the Global Response to Ebola**, a group of 19 experts convened by the London School of Hygiene & Tropical Medicine (LSHTM) and the Harvard Global Health Institute, published a set of ten recommendations, calling among other things for WHO to assist in establishing “a global fund to finance, accelerate and prioritize R&D”.²⁰

Declaration of the G7 Health Ministers (8 - 9 October 2015 in Berlin)

...”We underline the importance of direct collaboration between countries and health research funders, and we call for continued financing, collaboration and coordination on their collective response to emerging epidemics of global concern, including through initiatives such as the proposed WHO blueprint for research and development preparedness and rapid research response during future public health emergencies...”²¹



¹⁷ Report of the Ebola Interim Assessment Panel, July 2015, <http://www.who.int/csr/resources/publications/ebola/ebola-interim-assessment/en/>

¹⁸ Protecting humanity from future health crises. Report of the High-level Panel on the Global Response to Health Crises. January 2016. http://www.un.org/News/dh/infocus/HLP/2016-02-05_Final_Report_Global_Response_to_Health_Crises.pdf

¹⁹ The neglected dimension of global security. Report of the Commission on a Global Health Risk Framework for the Future, January 2016. <http://nam.edu/wp-content/uploads/2016/01/Neglected-Dimension-of-Global-Security.pdf>

²⁰ Will Ebola change the game? Ten essential reforms before the next pandemic. Report of the Harvard LSHTM Independent Panel on the Global Response to Ebola. Moon et al. The Lancet, 386 (10009),2204-21

²¹ http://www.bmg.bund.de/fileadmin/dateien/Downloads/G/G7-Ges.Minister_2015/G7_Health_Ministers_Declaration_AMR_and_EBOLA.pdf

6. A BLUEPRINT TO CATALYSE R&D ACTIVITIES FOR EMERGING PATHOGENS

In the last 12 months, WHO undertook initial preparatory work along the five workstreams reported in Figure 4.

Based on results obtained, three approaches are currently being used to improve preparedness under the Blueprint.

These approaches are aligned with the lessons learned during the 2014–2016 Ebola epidemic and with the recommendations from the various reviews on the Ebola epidemic conducted to date (see section 5 Box 1 for further details).

Figure 4: From five initial workstreams to three main approaches

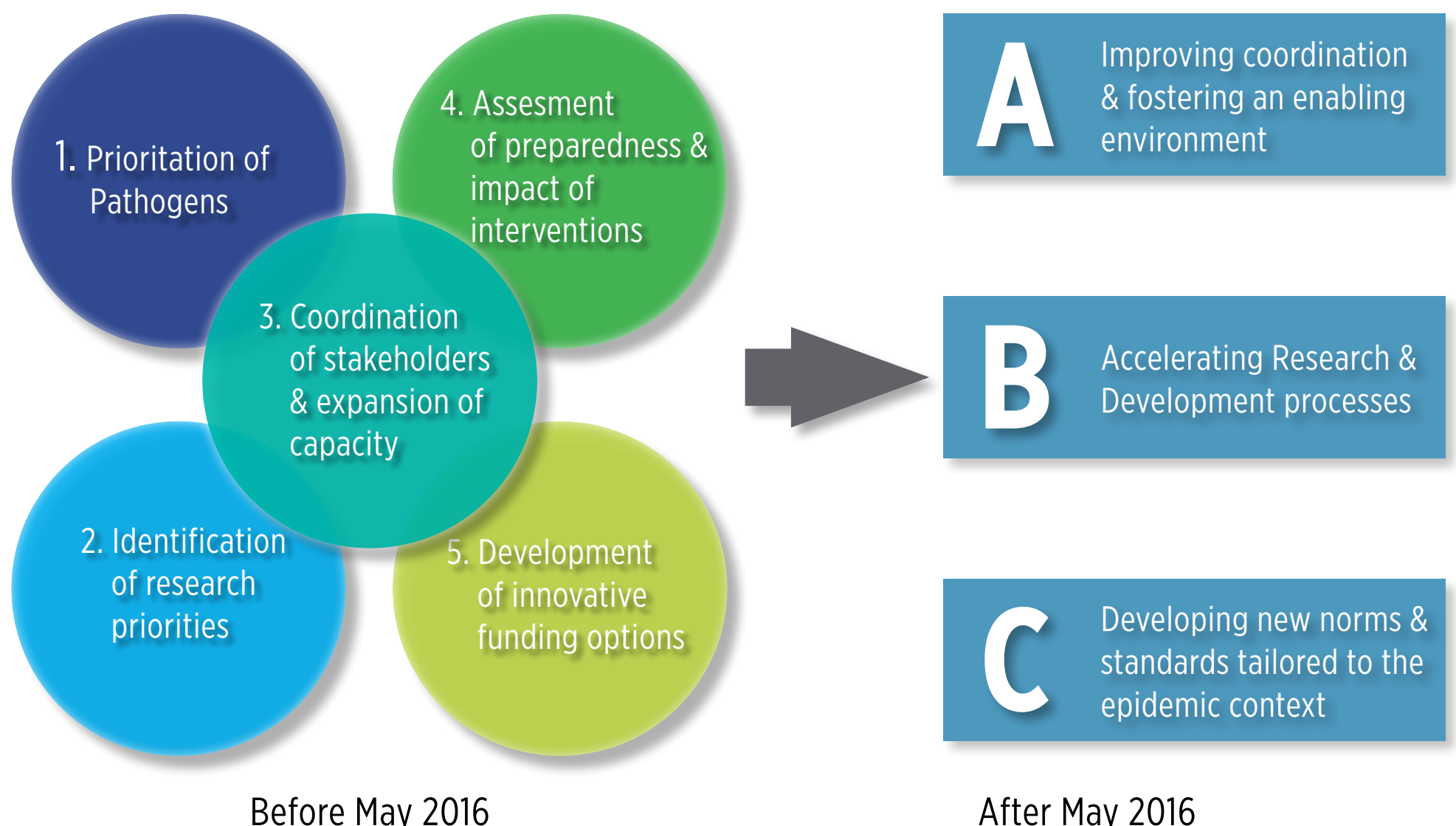


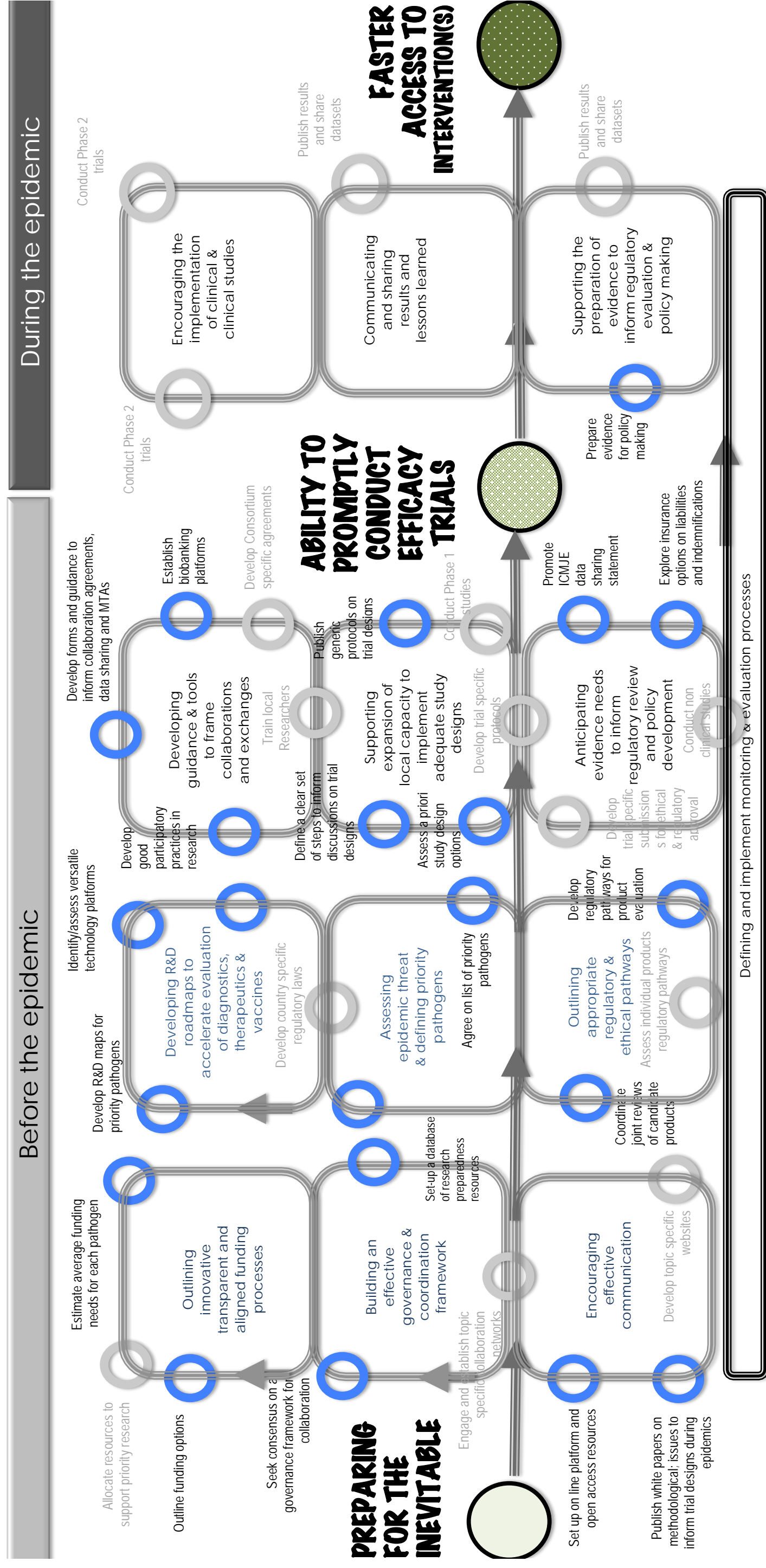
TABLE 1: DESCRIPTION OF THE THREE APPROACHES CURRENTLY USED TO IMPROVE PREPAREDNESS UNDER THE BLUEPRINT.

<div><div>A</div><div>Improving coordination & fostering an enabling environment</div></div> <p>This approach includes a set of interrelated actions – such as organizational, political, informational, and cultural – that impact on the global capacity to promptly conduct research in the context of epidemics.</p>	<div><div><div>1. Building an effective coordination framework.</div><div>2. Outlining innovative transparent and aligned funding processes.</div><div>3. Encouraging effective communication.</div></div></div>
<div><div>B</div><div>Accelerating Research & Development processes</div></div> <p>This approach includes all actions needed to implement critical research in a safe, effective and timely way. WHO’s facilitating role is to ensure that priority actions are designed and implemented in a consensual and coordinated fashion.</p>	<div><div><div>1. Assessing epidemic threat & defining priority pathogens</div><div>2. Developing R&D roadmaps to accelerate evaluation of diagnostics, therapeutics & vaccines</div><div>3. Outlining appropriate regulatory & ethical pathways</div></div></div>
<div><div>C</div><div>Developing new norms & standards tailored to the epidemic context</div></div> <p>Innovative international norms and standards are one way to overcome the scientific and coordination barriers faced by R&D during epidemics. WHO efforts will help to maximize consistency, robustness, and effectiveness of research efforts and interventions.</p>	<div><div><div>1. Supporting expansion of capacity to implement adequate study designs</div><div>2. Developing guidance & tools to frame collaborations and exchanges</div><div>3. Anticipating evidence needs to inform regulatory review and policy development</div></div></div>

FIGURE 5. SCHEMATIC DEPICTION OF MAIN ACTIVITIES FOR THE RESEARCH AND DEVELOPMENT BLUEPRINT: TURNING THE LESSONS LEARNED INTO ACTIONS TO BE BETTER PREPARED

ABOUT THIS ROUTE MAP

¹ In **Blue** color are depicted selected main actions where WHO is taking a leading/facilitating role. Only a selection of actions is depicted, because recent reviews of Ebola have noted that if not addressed they can constitute major bottlenecks. The aim is to illustrate both the complexity and the extent of the work needed in order to be better prepared. The order in which actions appeared does not denote a priority or temporal order.



IMPROVING COORDINATION & FOSTERING AN ENABLING ENVIRONMENT

A. 1. Building an effective coordination framework

A

Improving coordination & fostering an enabling environment

These efforts aim to build capacity and consensus amongst key global health actors charged with responding to outbreaks. This involves identifying stakeholders and activities and developing collaboration and coordination mechanisms.

What has been achieved?	What is planned?
<p>Mapping all key stakeholders by their areas or diseases of interest and current participation in collaborative networks was completed.</p> <p>A database of research preparedness resources - to be integrated into the WHO Global Health R&D Observatory- was set up.</p>	<p>A set of principles for a global collaboration framework will be developed.</p> <p>A template for a coordination framework to streamline global stakeholder collaboration will be drafted and consensus from key stakeholders will be sought. A functional global mechanism for coordination, initially including key global stakeholders as well as representatives from LMICs will be established.</p> <p>Completion and dissemination of the stakeholder map to promote further communication and collaboration among various stakeholders and networks. This will be reflected in an innovative electronic data visualization platform to present results of the stakeholder mapping in a way that is user friendly and accessible for all Member States and partners.</p>
What are the anticipated benefits?	
<p>Global response efforts are faster, more consistent, transparent and better coordinated, with less waste and redundancy.</p> <p>Ownership and buy-in from key stakeholders and communities are increased.</p> <p>The enabling environment allows effective, transparent and equitable collaboration between the contributing stakeholders to produce the desired result: an effective, faster response to public health emergencies.</p>	

A. 2. Increasing investment into R&D

The development of vaccines, therapeutics, and diagnostics is costly. Current funding is insufficient and unsustainable to enact the R&D required to address the Blueprint pathogens. New and innovative funding models are needed to more sustainably fund R&D for emergency preparedness and response.

In past years numerous innovative funding models have been discussed for R&D for neglected diseases and other poverty-related illnesses.²²

The Blueprint investigated options on how to ensure that the required research activities are financed and are taking place in the most efficient way, involving all necessary stakeholders (see table 2). The **Oslo Consultation**²³ highlighted the need to start quickly, with the focused objective of defining target product profiles (TPPs) for medical products for a specific set of emerging pathogens likely to cause severe outbreaks in the near future, and for which few or no medical countermeasures exist. The Oslo consultation also recommended a search for mechanisms to ensure sustainable financing, starting by engaging those stakeholders that are ready to move. This requires high-level political commitment to kick-start the process, the presence of which would be likely to motivate others to join.

Consultations with WHO Member states highlighted that any new funding mechanism should take into account the main principles for equitable R&D as proposed by the CEWG: open knowledge innovation and delinkage of R&D costs from product price in order to ensure equitable access.

While it is important to work towards more sustainable R&D funding, there is also a need for short-term action. The Blueprint is thus exploring and tests possible ways to make more efficient use of existing funding through better coordination using the experience from the pilot R&D Roadmap for MERS-Coronavirus and from R&D coordination for the development of malaria vaccines.

²² See the Report of the WHO Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG): http://www.who.int/phi/cewg_report/en/

²³ <http://www.who.int/medicines/ebola-treatment/Outcome.pdf>



Table 2: Identified Options for increased funding and coordination of R&D

Options for Preparedness	Options for Rapid Response
R&D Coordination at product/pathogen level Coordination through joint programming Pooled financing on global level Supranational R&D organization	Joint programming Joint calls for application by several funders Draw-down emergency accounts The WHO Contingency Fund World Bank Global Pandemic Emergency Facility

The proposed model includes two main elements:

- Convening regular meetings of key funders and researchers to increase funding and coordination.
- Facilitating communication and exchange of information and the identification of research gaps, as well as of unsuccessful approaches, through a central knowledge hub, the WHO Global Observatory on Health Research and Development

What has been achieved?	What is planned?
<p>In late 2015, WHO consulted with key stakeholders including government, industry, NGOs, academia and industry, to develop funding options for the R&D Blueprint.</p> <p>Options for funding, preparedness, and rapid response were identified.</p> <p>The average funding needs were estimated for each priority pathogen based on a report recently released by TDR.</p>	<p>A report on options for financing based on inputs from internal and external experts will be finalized.</p>
What are the anticipated benefits? Informed decisions by stakeholders on how to fund R&D. The options paper is used to inform R&D funding strategies.	

A. 3. Encouraging effective communication

Through the Blueprint, WHO will enable complex and effective communication by convening formal and informal interactions with partners and scientists worldwide to facilitate discussions on best practices for the timely and simultaneous testing of different vaccines, drugs and diagnostics as well as the rapid information sharing.

What has been achieved?	What is planned?
<p>Through the Blueprint, WHO has enabled complex and effective communication by convening formal and informal interactions with partners and scientists worldwide to facilitate discussions on best practices for the timely and simultaneous testing of different vaccines, drugs and diagnostics as well as the rapid information sharing.</p> <p>The WHO Bulletin initiated “ZIKA open”, a web platform to allow communication on emerging results from ongoing research during a PHEIC, while the manuscripts undergo peer-review (http://www.who.int/bulletin/online_first/zika_open/en/).</p> <p>A series of expert consultations were convened (http://www.who.int/csr/research-and-development/consultations/en/)</p> <p>Informed discussions were held on the Blueprint at the WHO Executive Board and bilateral and international meetings including but not limited to representatives of Member States.</p>	<p>Continue to communicate on ongoing research and to facilitate open access to research resources via face to face meetings and sharing of documentation in the web.</p> <p>Create a database of research preparedness resources to be integrated into the WHO Global Health R&D Observatory</p> <p>Building upon the global collaboration analysis, develop a template framework to streamline global stakeholder collaboration related to R&D activities for the prioritized list of pathogens</p> <p>Publication of white papers on methodological issues to inform trial designs during epidemics.</p>
What are the anticipated benefits?	
<p>Stronger, transparent and evidence based discussions on how to accelerate R&D efforts take place around all the priority pathogens, ahead of any future epidemic.</p>	



B. 1. Assessing epidemic threat & defining priority pathogens

B

Accelerating Research & Development processes

Resources for disease R&D are limited and the number of potential pathogens is very large; therefore, there is a pressing need to reduce fragmentation and make best use of the available resources.

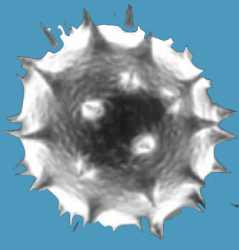

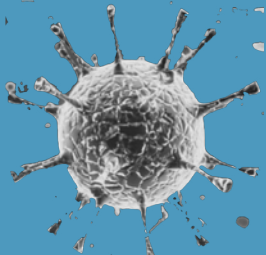
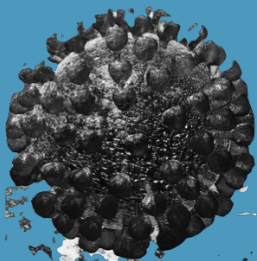
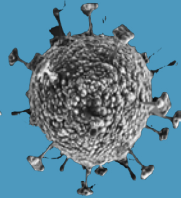
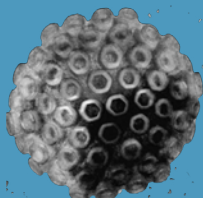
Coordinating resources around an agreed list of priority pathogens will enable the global community to better allocate finances in a cost-effective way.

What has been achieved?	What is planned?
<p>WHO convened an ad-hoc expert group to synthesize lessons learned from past global health experiences and to agree on a list of emerging pathogens likely to cause severe outbreaks and for which no or limited medical countermeasures exist (http://www.who.int/medicines/ebola-treatment/WHO-list-of-top-emerging-diseases/en/).</p> <p>The agreed priority list forms the backbone of the WHO Blueprint for R&D preparedness and focuses accelerated R&D on dangerous pathogens which are epidemic-prone.</p> <p>Generic disease scenarios using data from past epidemics and public health emergencies were developed for use in prioritization exercises and a draft decision tree for determining when a novel disease would trigger an interim prioritization assessment were outlined.</p>	<p>Future action in this area includes fine-tuning of the prioritization methodology (review and finalization of the draft prioritization methodology is expected by Q3, 2016) and the development of practical tools to assess any new diseases that may emerge.</p> <p>Efforts will be invested to monitor on a continual basis to reassess priorities (e.g. an annual performance review of the prioritized pathogens) and to plan for the transition from outbreak preparedness to outbreak response.</p>
What are the anticipated benefits?	
<p>Factors that are important to identify priority pathogens are known.</p> <p>A decision tree for determining when a novel disease would trigger an interim prioritization assessment is available.</p>	

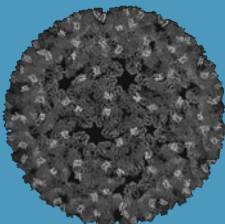
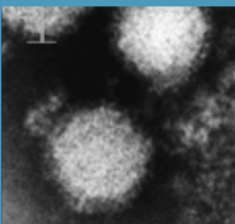
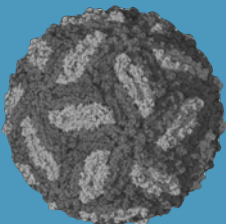
Box 2. An initial list of the top emerging pathogens likely to cause severe outbreaks in the near future

In December 2015, WHO convened a workshop to identify elements to be used to prioritize diseases and to agree on an initial list of diseases to be urgently addressed under the R&D Blueprint. The initial list of priority pathogens includes:

DISEASES TO BE URGENTLY ADDRESSED UNDER THE R&D BLUEPRINT, AS OF MAY 2016

			
Crimean-congo Hemorrhagic fever virus	Filovirus diseases (i.e. EVD & Marburg)	Highly pathogenic emerging coronaviruses relevant to humans (MERS Co-V & SARS)	Lassa fever virus
		Novel Agent a new severe infectious disease	
Nipah virus	Rift Valley fever virus		

SERIOUS DISEASES NECESSITATING FURTHER ACTION AS SOON AS POSSIBLE, AS OF MAY 2016

		
Chikungunya virus	Severe fever with thrombocytopenia syndrome	Congenital abnormalities and other neurological complications associated with Zika virus

At that time, experts noted recently reported unusual congenital abnormalities and other neurological complications associated with a Zika outbreak in Brazil, and recommended that this disease be treated as a priority if further evidence emerged supporting a connection - which is now the case.

B. 2. Developing R&D roadmaps to accelerate evaluation of Diagnostics, Therapeutics and Vaccines

Without a plan – or R&D Roadmap - of a comprehensive portfolio of interventions, actions could lead to incomplete pipelines, and the product development efforts risks being interrupted when financial resources run out.

The particular research capacity needs in LMICs span over proof of principle and preclinical studies, the conduct and regulation of clinical studies (before and during health crises), and the development of key enabling capacities. This involves establishing standard procedures to rapidly evaluate new health technologies in emergencies and strengthening regulatory capacity.

What has been achieved?	What is planned?
<p>A prototype of R&D roadmap for coronavirus-linked Middle East Respiratory Syndrome (MERS-CoV) has been developed (see Box 2) (http://www.who.int/csr/research-and-development/roadmap-consultation/en/).</p> <p>Another activity was the launch in October 2015 of a public consultation to identify and evaluate effective and versatile technology platforms that can address at least 3 of the priority pathogens (http://www.who.int/medicines/ebola-treatment/public_consult_platform-tech/en/).</p>	<p>Further activities in this area will aim at promoting critical R&D for prioritized MERS-CoV-related medical products and interventions (including behavioral interventions) as described in the roadmap.</p> <p>Using the MERS-CoV prototype, R&D Roadmaps for all priority diseases will be developed.</p> <p>In Q3, 2016, WHO will convene a meeting with R&D funders to facilitate further discussion on the identified R&D platform technologies by providing a forum that would address technical and cost feasibility.</p>
What are the anticipated benefits?	
<p>Clinical development, including Phase 1 to 2 clinical trials, is initiated for all priority pathogens. A forum is available to address the technical and cost feasibility of platform technologies.</p>	

Box 3: Public consultation on ideas for potential platforms to support development and production of health technologies for priority infectious diseases with epidemic potential.

In October 2015 WHO launched a public consultation on ideas for potential platforms to support development and production of health technologies for priority diseases with epidemic potential. The initiative was open to non-profit organizations, for-profit companies, international organizations, government agencies and academic institutions. The scope of health products considered included vaccines, therapeutics (drugs and blood products), diagnostics and enabling technologies. The platforms had to address three or more of the WHO priority pathogens.

Thirty-five proposals were received by the closing date on February 2016. After an initial screening to determine if the proposals were within scope, 33 ideas were selected addressing: vaccines (8); monoclonal antibodies (2); polyclonal immunoglobulin (3); antiviral (1); diagnostics (8); two or more product streams (5); and enabling technologies (6). Proposals that were out of scope were removed from further consideration and the applicant(s) informed.

Proponents of the 33 selected ideas were invited to present to an ad hoc Advisory Group (AG) during a 3-day technical workshop, held in Geneva, April 4-6 2016. The purpose of the workshop was to review and assess the ideas; to identify the promising ones for further development; and to foster discussions around potential future collaboration, as appropriate.

The AG experts assessed the strengths and weaknesses of each presented idea, specifically addressing the likelihood of meaningful participation by entities in LMICs; the strengths of the proposed organizational and management structures and the budget needed to operationalize the plans contained in the proposal(s); and the management of intellectual property (IP) rights.

The first round of revision was completed by April 28th 2016 and successful proponents were invited to submit an operational and costed plan, with agreed milestones for a second round of reviews by June 30th. The most promising ideas will then be presented to potential funders during a technical workshop.

Box 4: An R&D roadmap for MERS-CoV

The case of MERS-CoV provides a recent example of a deliberate R&D strategy for emergency preparedness.

MERS-CoV was first identified in 2012 and has since spread to more than 25 countries.²⁴ During that time, it has caused severe acute respiratory syndrome in more than 1,600 people and caused almost 600 deaths, carrying a case fatality rate near 40%.²⁵ The disease severity, broadening distribution and vaguely defined epidemiology have created an urgent need to develop effective countermeasures to mitigate the public health impact of this novel coronavirus.

In the absence of licensed therapeutics or vaccines, WHO launched a “Roadmap for Research and Product Development for MERS-CoV” (<http://www.who.int/csr/research-and-development/roadmap-consultation/en/>).

Following an expert consultation on 10-11 December 2015, WHO solicited public comments on the draft Roadmap (<http://www.who.int/csr/research-and-development/rd-mers-roadmap.pdf?ua=1>) in February 2016, with the objective of publishing the final document in May 2016. This work is coordinating across relevant stakeholders to prioritize R&D efforts and facilitate collaboration.

The MERS-CoV Roadmap is already serving as a useful tool for aligning research and product development efforts around specific public health needs. For example, the need for improved MERS-CoV diagnostics is widely acknowledged, but the Roadmap calls specifically for a “multivalent MERS-CoV point of care diagnostic as part of a panel, including RSV, influenza, and other respiratory infections.” Similarly, the Roadmap calls for development of therapeutic Target Product Profiles so that academic and commercial researchers can align their efforts accordingly. It also identifies MERS-CoV vaccines for camels as an orphan priority. Clinical trials for MERS-CoV products are expected to start in 2016.

²⁴ Kayvon Modjarrad, “MERS-CoV R&D: A Case Study for the WHO Blueprint”, Presentation to WHO, 7 September 2015.

²⁵ “Draft: A Roadmap for Research and Product Development against Middle East Respiratory Syndrome-Coronavirus (MERS-CoV)”, WHO, February 2016.

B. 3. Outlining appropriate regulatory & ethical pathways

In public health emergencies, regulators have responded promptly, vigorously and proactively. They have diverted human resources away from other projects to work, as a priority, on candidate products being developed to address the emergency.

Regulators and ethicists have worked collaboratively with each other, the stronger supporting the less-strong, to ensure that an appropriate level of independent scientific and ethical review is in place before candidate products are used in clinical trials.

The regulatory networking and support has extended beyond the emergency to obtain the necessary follow-up data needed to fully assess the quality, safety and efficacy of each candidate product.

What has been achieved?	What is planned?
<p>Regulatory pathways for product evaluation in public health emergencies were outlined.</p> <p>Joint clinical trial reviews of candidate products were conducted.</p> <p>Production of international reference preparations to support product evaluation was coordinated. Collaborations between expert regulatory laboratories were established.</p> <p>Guidelines on the quality, safety and efficacy of specific candidate products were developed. Guidelines on regulatory work-sharing in public health emergencies were drafted.²⁶</p> <p>Multi-country study designs to support safety evaluations were outlined.</p> <p>Initial steps to explore insurance options to address issues of liability in case of use of an experimental vaccine or product, which has not yet received authorization for use.</p>	<p>Further efforts to strengthen national, regulatory and ethics bodies to respond to public health emergencies will be implemented.</p> <p>A cadre of regulators working together on products being developed for priority pathogens will be established.</p> <p>Collaborations between expert regulatory laboratories will be continuously fostered.</p> <p>Discussions will be completed on insurance options to cover liability.</p>
What are the anticipated benefits?	
<p>A global regulatory resource is available to provide pro-active and convergent, but non-binding, advice concerning candidate products being developed against pathogens with the potential to cause public health emergencies of international concern.</p> <p>Global regulatory capacity to respond to public health emergencies of international concern is increased, and readiness improved.</p> <p>Issues of liability in case of mass vaccination with a product which has not yet been fully evaluated, do not slow down deployment of a needed vaccine.</p>	

²⁶ http://www.who.int/medicines/ebola-treatment/blueprint_phe_data-share-results/en/

Box 5: Managing liability associated with large scale vaccination in times of public health emergency

During the 2014-2015 epidemic of Ebola in West-Africa, concerns were raised about potential liability risks arising from the occurrence of adverse events following immunization of large numbers of individuals during an emergency, with an experimental Ebola vaccine that had not yet been fully tested as would normally be the case for other vaccines.

To address this issue and in the context of the R&D Blueprint, the WHO Secretariat is exploring a possible insurance solution with a two-prong approach as follows:

- A primary insurance contract would be negotiated which would provide liability protection associated with the use of an experimental vaccine and cover any claims made against public health officials and vaccine manufacturers for any severe adverse effects experienced by recipients in LMICs.

This primary insurance contract would also provide compensation in case of death or permanent complete disability of vaccinated persons.

The primary insurance contract and premium would be negotiated in advance.

- A secondary insurance contract would be negotiated with the provider of the main insurance contract to provision for a modest annual premium to be paid during periods between public health emergency in order to guarantee the availability of the terms of the main insurance contract during a public health emergency.

WHO is consulting with a number of insurance providers to assess the feasibility and cost of such a proposal.



Box 6: Leveraging regional networks

Various existing regulatory networks can play an important role in facilitating rapid concerted decisions, action and information exchange to make urgently needed products available.

To address the challenge of authorizing clinical trials of Ebola candidate vaccines for which limited data were available, the WHO African Vaccine Regulatory Forum (AVAREF) was used as a collaboration platform for regulators, ethics committees and sponsors to reach consensus on key ethical and regulatory questions.

WHO convened three joint reviews of clinical trial applications with AVAREF playing a convening and supportive role.

Regulators from Europe and North America provided their expertise and advice on key ethical and regulatory questions. The AVAREF platform accelerated regulatory approval and the experience can serve as model for further collaborative efforts.



C. DEVELOPING NORMS & STANDARDS TAILORED TO THE EPIDEMIC CONTEXT

C. 1. Supporting expansion of capacity to implement adequate study designs

C

Developing new norms & standards tailored to the epidemic context

As part of efforts to build capacity to conduct clinical trials for vaccines and therapeutics against emerging disease threats in LMICs, the promotion of scientific discussion on the design of R&D Roadmaps and clinical trials that include national and international actors and scientists in countries at risk as equal partners is critical.

An important element is also the need to agree a priori on standard procedures to rapidly evaluate new health technologies in emergencies while maintaining the highest scientific and ethical standards.

What has been achieved?	What is planned?
<p>A clear set of steps were outlined to inform discussions on trial designs for priority pathogens, as well as on an approach to assess each design in terms of methodological robustness and feasibility.</p> <p>A process leading to the development of generic annotated protocols for priority diseases has been mapped.</p>	<p>Completion of process to inform trial designs and open forum discussions on protocols for the Blueprint priority pathogens.</p> <p>Publication of white papers on methodological issues to inform trial designs during epidemics.</p> <p>Publication of protocols (with methodological annotations) for Blueprint priority diseases for scientific debate and review.</p> <p>Development of a trial simulator to inform trial design choices for Blueprint priority pathogens.</p>
What are the anticipated benefits?	
<p>Investigational therapeutics and vaccines are evaluated according to protocols which meet the highest scientific and ethical standards and which generate results to inform regulatory assessment and policy decisions, while ensuring that national and individual interests are respected.</p>	

Box 7: A clear set of steps to inform discussions on trial designs for priority diseases, an approach to assess each design in terms of methodological robustness and feasibility, and a process leading to the development of generic annotated protocols for priority diseases.

In March 2016, a group of experts met in Chamonix, France to discuss the rationale of designing a vaccine efficacy trial during public health emergencies.

The group included experts in public health, vaccine trial methodologists, biostatisticians, infectious disease modelers, regulators, ethicists and funders. The group agreed to conduct a collaborative research preparedness exercise around the Blueprint priority pathogens.

The objective of this preparedness work is to perform a prospective assessment of different vaccine efficacy design under different scenarios.

Experts agreed that it is important to provide researchers with a framework and a trial simulator to guide quantitative and qualitative assessments of the pertinence of trial designs in view of various epidemic scenarios for each priority pathogen.

In addition, experts proposed that White Papers be developed to discuss methodological issues relevant to the design of trials in the context of epidemics (e.g. optimal approaches for interim analyses). A trial simulator was identified as a desirable tool.

Lastly, examples of generic protocols – including annotated methodological discussions and trade-offs to be considered – will be drafted and made publicly available to promote further scientific, regulatory and ethics debate.

Overall, this preparedness work is expected to allow for a more consistent, collaborative and inclusive approach in designing a trial during emergencies and aims to put the scientific community as well as affected countries in an optimal position to test an experimental vaccine during an epidemic.

It is anticipated that a second meeting will take place late in Q3, 2016, when the draft of the agreed materials and tools will be reviewed.



C. 2. Developing guidance and tools to frame collaborations and exchanges

It is critical to identify agreements that foster data and sample sharing and which are inclusive of scientists from countries at risk in LMICs, that facilitate governance of multi-party collaborations, and that recognize both individual and shared priorities.

What has been achieved?	What is planned?
<p>The process for agreeing on principles for bio banking platforms was initiated.</p> <p>The concept was articulated for a Material Transfer Agreement (MTA) capacity building tool to inform negotiations at country level on sharing biological samples. This tool is informed by lessons learned from negotiations under the PIP Framework for equitable sharing of samples and of benefits.²⁷</p> <p>A revised guidance document on Good Participatory Practices in a research context as related to the prioritized list of pathogens is being produced.</p> <p>The review of generic agreement forms and guidelines that could support countries to negotiate and establish mechanisms for fair and transparent collaboration was initiated.</p>	<p>The MTA capacity building tool will be finalized through consultations with various stakeholders. It will then be converted into an electronic web-based tool that will provide support to partners engaging in MTA negotiations.</p> <p>The concept of biobanking "virtual" resource of (national) biobanks linked by an information-sharing platform will be further developed; together with the principles for a shared system of governance and decision-making.</p> <p>The guidance document on Good Participatory Practices in a research context as related to the prioritized list of pathogens will be finalized.</p> <p>The development of forms and guidelines that could support countries to negotiate and establish mechanisms for collaboration and data sharing will be completed.</p> <p>Guidance for national research committees in LMICs to review research protocols during an outbreak will be prepared.</p>
What are the anticipated benefits?	
<p>Research collaborations and exchanges during outbreaks will be facilitated through adoption of fair and transparent principles which will have been negotiated by all stakeholders ahead of an emergency.</p>	

²⁷ http://apps.who.int/iris/bitstream/10665/44796/1/9789241503082_eng.pdf

Box 8: Establishing biobanks to support equitable research

For epidemics of severe emerging diseases, biological samples represent a precious non-renewable resource that provides opportunities to advance knowledge of disease, improve and evaluate control tools and interventions, increase national capacity for research, and foster international collaborations.

They also present a moral imperative for prudent use to illuminate priority research questions—with an attendant emphasis on safety and biosecurity. The Ebola epidemic provided a real-world exemplar, having generated thousands of valuable samples in an international environment lacking plans and capacity for maintenance and handling. Most emerging diseases on the Blueprint priority list and new diseases like Zika present similar considerations.

WHO convened a global meeting to explore issues regarding bio banking, as well as a focused meeting in Sierra Leone to support the three most affected countries in their national plans for preservation of Ebola samples.

WHO has now developed options for a generic approach to sample sharing based on international collaboration; it is envisaged that this will generate distributed “virtual” resource of [national] bio-banks linked by an information-sharing platform; a shared system of governance and decision-making; and a systematic design adapted for each priority disease.

All such work would have to be conducted following an approach consistent with principles of existing relevant international frameworks, and principles of equity and benefit sharing.



C. 3. Anticipating evidence needs to inform research, regulatory review and policy development

Decisions on strategies to stop an outbreak and combat an epidemic must be based on the best available scientific evidence. It is therefore crucial that new information which might be relevant to the response to an infectious threat, be shared as quickly as possible with public health authorities for action, and with the global research community to generate new hypothesis for further investigation. While this imperative is broadly recognized, multiple barriers exist to efficient and effective information sharing during an outbreak.

WHO held a consultation in Geneva, Switzerland on 1-2 September 2015 to advance the development of data sharing norms, specifically in the context of public health emergencies.

What has been achieved?

A change in ICMJE guidelines such that pre-publication information sharing is acknowledged as the new norm in public health emergencies, following the recommendations of the above Blueprint consultation.

WHO Strategic Advisory Group of Experts on Immunization (SAGE) issued recommendations on evidence needs and potential scenarios for use of Ebola vaccines. (<http://www.who.int/wer/2015/wer9022.pdf?ua=1>)

What is planned?

Global norms for sharing data and results during public health emergencies will be further developed.

Additional recommendations will be articulated by SAGE on Ebola vaccines use.

What are the anticipated benefits?

The best evidence is available for decision-makers to optimize outbreak control strategies and minimize live loss and economic crises.

Clear WHO policy is available on how to use Ebola vaccines.

Box 9: Developing global norms for sharing data and results during public health emergencies

There are many reasons why researchers and others stakeholders are reluctant to share data and results. In order to help overcome these obstacles, WHO convened a diverse group of stakeholders, including scientists, ethicists, major journal editors, science funders, representatives of government health agencies, NGOs and industry, to begin development of global norms and standards for more rapid and transparent data-sharing during public health emergencies.

The International Committee of Medical Journal Editors has since revised its policy to explicitly encourage data-sharing, and to assuage concerns that subsequent scientific publication might be adversely affected. In addition, a large group of signatories from scientific foundations, government agencies, journals, and others have called for rapid and early data-sharing to rapidly acquire the knowledge we need to control Zika.

WHO has created ZikaOpen, a platform within the WHO bulletin, to facilitate such data-sharing. Other relevant initiatives are also underway through the WHO R&D Observatory, and through continuing engagement with stakeholders and partners.



7. CONNECTING THE BLUEPRINT WITH OTHER INTERNATIONAL EFFORTS

A number of new initiatives have been put in place or are under discussion by international stakeholders to increase R&D preparedness for severe and emerging infectious disease threats. These could complement the efforts of the Blueprint in ensuring coordination and alignment of efforts. Below are three examples of such initiatives.

The Coalition for Epidemic Product Innovation (CEPI)

The Coalition for Epidemic Preparedness Innovation (CEPI) is an initiative established following the Annual Meeting of the World Economic Forum in Davos in January 2016, where stakeholders from governments, foundations, industry and civil society discussed the urgent need for a fresh approach to the development of vaccines for infections of epidemic potential.

The meeting reached a consensus that new mechanisms are required to finance and otherwise support vaccine development in cases of market failure, and that a partnership linking different sectors would be the best approach to delivering this.

A process to create such a partnership is now underway, with a stakeholder group and a project management group established, and expert workstreams set up to consider issues such as prioritisation, clinical development, manufacturing capacity and regulation, potential models for partnership, and potential innovative financing arrangements.

The CEPI initiative is separate from but complementary to the WHO-led process to develop the R&D Blueprint, and both CEPI stakeholders and WHO are taking steps to ensure the two are properly aligned. CEPI is initially focused on vaccines, but if successful the model could be extended to cover drugs, diagnostics or other products.

The Global Research Collaboration for Infectious Disease Preparedness (GloPID-R)

The Global Research Collaboration for Infectious Disease Preparedness (GloPID-R) is a network of funders of emergency outbreak research. GLOPID-R has set the goal of initiating a coordinated international research response between its members, within 48 hours of a declared public health emergency. The network has 23 members from across the globe with WHO as an observer.

Following the lesson learnt from the Ebola virus outbreak, GloPID-R members have put to action the Interim Readiness Plan, as a response to the Zika Outbreak. The objective is to rapidly activate research funding in specific areas related to etiology, vaccines, diagnostics and data sharing.

The secretariat of GloPID-R initiative is funded through EU's Horizon 2020 programme and ran by Fondation Merieux and the University of Oxford. The European Commission's Directorate General for Research and Innovation is Chair with Vice Chairs coming from Brazil, Canada, France and South Africa.

The Chatham House project on data sharing in infectious disease surveillance

The Chatham House project aims to develop guidelines on how to create the right environment for public health data sharing and achieve good practice.

WHO is also engaging with a range of other partners involved in various aspects of advancing data-sharing. These include MSF and other NGOs, Institut Pasteur, WWARN, major academic institutions, journal editors, ethicists and leading scientific research foundations. All of whom are collaborating with WHO to define a set of principles, standards and practices applicable to many varieties of data and results.

Discussions are underway with the genomics community to promote alignment with their data publication and utilization practices.



8. MONITORING & EVALUATION FRAMEWORK

Strong monitoring and evaluation will allow WHO to measure the impact of the Blueprint on R&D preparedness and on availability of medical technologies for future outbreaks/epidemics, and to improve or sustain Blueprint activities accordingly.

Main Activities (June 2015 – June 2016)	Primary Benefits
<p>Outline how WHO will monitor and evaluate the Blueprint’s effectiveness, efficacy, and impact by developing an overarching M&E Framework that includes a performance monitoring mechanism defining when and how reporting will occur, and by/to whom.</p> <p>Develop an M&E framework specific to Zika and conduct a real-time evaluation.</p>	<p>The Blueprint is well designed from an M&E perspective, and there is buy-in from key stakeholder.</p> <p>Plans are available to determine the long-term impact of R&D plans on the next public health emergency identified.</p> <p>Progress is documented on Zika R&D.</p>



WHO has developed a monitoring and evaluation framework for the R&D Blueprint, which is focused on emerging pathogens likely to cause severe outbreaks in the near future, and for which few or no medical countermeasures exist.

This framework shows how activities and actions by WHO and others might be expected to contribute to the ultimate expected outcomes which is that public health emergencies can be pre-empted and when they do occur the R&D response is faster, more effective, more efficient and conducted with consideration to affected people.

The framework (see page 40) has four elements. The first is focused on planning for the Blueprint prior to the 2016 World Health Assembly (WHA). This element was initially organized around five workstreams. Each workstream was expected to produce particular milestones. Progress on these and other achievements will be reported to the World Health Assembly.

The second element is focused on implementing the Blueprint after May 2016. Implementation will be organized around three priorities – improved coordination & fostering an enabling research environment; accelerating research & development processes; and developing new norms & standards adapted to the epidemic context.

Progress will be tracked using a combination of specific milestones, indicators and qualitative questions. Leaders/facilitators of priority areas will report quarterly on progress in completing expected milestones and on performance against specific indicators. In addition, they will ensure that each priority is reviewed annually using identified qualitative questions.

The third element relates to when an outbreak or public health emergency occurs. In this situation a real-time evaluation will be conducted to assess the extent to which:

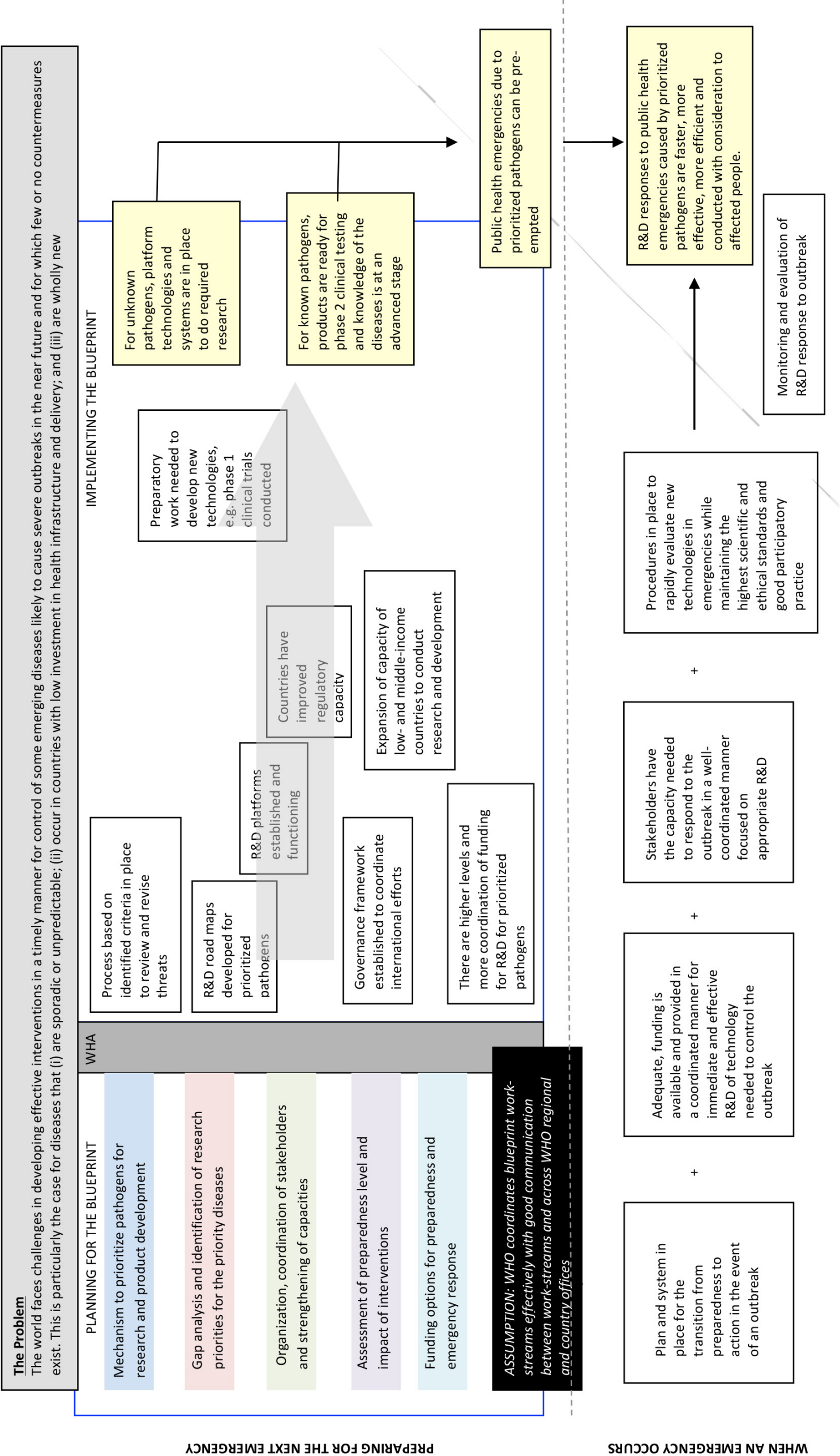
- The operational plan was put into practice as soon as the outbreak had been identified
- Sufficient, coordinated funding was available for appropriate R&D
- Stakeholders were able to respond in a coordinated manner in relation to R&D
- Procedures were in place to rapidly evaluate new technologies ensuring the highest scientific and ethical standards and good participatory practice.

This element is currently being tested in relation to Zika. The fourth element relates to assessing the expected Blueprint outcomes (see page 40). This will be assessed using qualitative questions. Details of the monitoring and evaluation framework, including detailed plans for the monitoring and evaluation activities can be found on the WHO R&D Blueprint website.²⁸

²⁸ <http://www.who.int/csr/research-and-development/workstream4-assessment/en/>



A DRAFT FRAMEWORK FOR MONITORING AND EVALUATING THE R&D BLUEPRINT



INDICATORS

Potential milestones and draft indicators

Element	Possible milestone(s)	Possible indicator(s)	Possible evaluation/ review question(s)
Effective framework for global coordination established	Database of research preparedness resources established and integrated into the WHO Global Health R&D Observatory Governance framework for collaboration agreed	Number of stakeholders agreeing to collaboration framework	To what extent are the agreed principles established to promote collaboration working effectively? What have been the main factors in facilitating effective collaboration? What have been the main barriers and obstacles to be overcome? To what extent does the global R&D stakeholder mapping for Blueprint priority diseases reflect the overall global R&D landscape?
Funding coordinated for R&D for prioritized pathogens	Funding options outlined Average funding needs estimated for each priority pathogen	Levels of R&D funding by prioritized pathogen	To what extent is the funding for R&D for prioritized pathogens well-coordinated?
There is more effective communication	Online platform set up for ongoing research and open access resources on Zika	Pipeline for Zika R&D updated every quarter	To what extent has communication relating to priority pathogens been more effective?
Process based on identified criteria in place to review and revise threats	Decision tree for prioritization of new diseases developed Working group convened to design more quantitative weighting method Disease scenarios developed for both decision trees and prioritization method Operational plan developed to move from planning to implementation if an emergency occurs	Annual meeting held to review and revise threats which: • Produces a revised/updated list of pathogens • Reviews methodology (every 2-3 years) • Makes data available from prioritization processes • Produces landscape analyses	To what extent has the review and revision process been implemented as planned? To what extent has the list of prioritized pathogens been used within the Blueprint's other work-streams? To what extent is the prioritization process based on clear elements, factors and criteria? To what extent are WHO and others using the prioritized list? To what extent is there harmonization between different approaches? What lessons have been learned through the review process and from other work-streams? To what extent have previous lessons learned been implemented?
R&D road maps developed for Blueprint priority pathogens	Road maps developed for (i) each and (ii) all prioritized pathogens	Number of road maps developed	What lessons have been learned from the first road maps that have been developed, e.g. for MERS? What worked well? What could have been done better? What criteria were used to determine which pathogen should be first to have a road map developed? To what extent do the road maps developed capture the main R&D needs by pathogen? Are there common themes or lessons learned across road maps? To what extent have the road maps served as practical tools for R&D related to prioritized pathogens? To what extent have road maps for prioritized pathogens been implemented and acted upon?

R&D technology platforms established	R&D technology platforms assessed and discussed with potential funders	Number of R&D technology platforms established among those prioritized by WHO	<p>To what extent are the R&D technology platforms prioritized by WHO have been established?</p> <p>What have their main successes been? What have been the main challenges?</p> <p>In what ways has WHO supported the establishment and functioning of these platforms? To what extent has WHO added value in its key areas of competency, such as convening power, creating a neutral space, ensuring all country perspectives are considered (e.g. in terms of creating fora; establishing advisory groups; facilitating new partnerships; providing advice; encouraging more open sharing of ideas)</p> <p>What lessons have been learned (including from experiences of such platforms established by others)?</p>
Countries have improved regulatory capacity	Regulatory pathways developed for product evaluation during Public Health Emergencies	<p>Number of countries with improved regulatory capacity including in particular:</p> <ul style="list-style-type: none"> National regulatory authorities with dedicated staff for public health emergencies caused by prioritized pathogens National laws allowing expedited procedures in cases of emergency 	<p>To what extent have countries increased their regulatory capacity?</p> <p>What have been the main factors in facilitating increases in regulatory capacity? What have been the main barriers and obstacles to be overcome?</p>
Expansion of capacity of low- and middle-income countries to conduct research and development according to international standards	<p>Steps defined to inform discussions on trial designs for priority diseases, an approach to assess each design in terms of methodological robustness and feasibility and, a process leading to the development of generic annotated protocols for priority diseases.</p> <p>A priori potential study design assessed</p> <p>Generic protocols for priority diseases published to encourage scientific debate and review</p> <p>Generic protocols and a R&D preparedness checklist developed</p>	<p>Proportion of trials considering a priori assessed protocols as appropriate designs</p>	<p>To what extent do stakeholders have greater capacity to conduct appropriate clinical trials for Blueprint priority pathogens?</p> <p>If there has been a change in the level of capacity, what have been the main factors behind that change? Were there any factors constraining that change?</p>
Guidance and tools developed to frame collaboration and exchanges	<p>Establishment of biobanking platforms facilitated</p> <p>Good participatory practices for research in an outbreak setting context published</p> <p>Generic agreement forms and guidelines available to support countries negotiating and establishing mechanism for collaboration, data sharing, samples sharing and management of intellectual property</p> <p>Guidance available for national research committees to review research protocols during an outbreak</p>	<p>Number of capacity building tools</p> <p>Number of times capacity building tools are downloaded</p>	<p>To what extent have capacity building tools been developed for use by country stakeholders to increase their capacity? How are partners using these tools?</p> <p>To what extent have analytical approaches been developed and adopted to ensure studies are effective and coordinated?</p> <p>To what extent are the perspectives of low- and middle- income countries shaping research and development activities?</p>
Evidence needs to inform regulatory review and policy development anticipated	Global norms for data sharing during public health emergencies	Number of funders making data sharing a compulsory element for awarding research grants	To what extent have data and information been shared expeditiously to inform regulatory review and policy development?

Approaches	Main activities	Expected completion Date								
		2015		2016			2017			
		Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2
A. Building an effective coordination framework & fostering an enabling environment										
1. Building an effective coordination framework	- Mapping all key stakeholders by their areas or diseases of interest and current participation in collaborative networks									
	- Set up a database of research preparedness resources - to be integrated into the WHO Global Health R&D Observatory									
	- Development of a set of principles for a global collaboration framework									
	- Develop a template for a coordination framework to streamline global stakeholders collaboration									
2. Increasing investment into R&D	- Completion of stakeholders mapping									
	- Outline Funding Options									
	- Estimate the average funding needs for each priority pathogen									
	- Set up an online platform for ongoing research and open access resources on Zika									
3. Encouraging effective communication	- Conduct a series of R&D consultations on Zika									
	- Conduct discussion at the WHO Executive Board and with key stakeholders in the community									
B. Accelerating R&D processes										
1. Assessing epidemic threat & defining priority pathogens	- Agree on list of priority pathogens									
	- Develop generic disease scenarios using data from past epidemic and past emergencies									
	- Fine-tuning and finalization of the prioritization methodology									
	- Develop roadmaps for all priority diseases- develop a prototype R&D roadmap for MERS-CoV and after for all priority diseases									
2. Developing R&D roadmaps to accelerate evaluation of diagnostics, therapeutics & vaccines	- Identify and evaluate effective and versatile technology platforms that can address at least 3 of the priority pathogens.									
	- Develop principles for joint reviews and regulatory pathways for product evaluation in Public Health Emergencies									
	- Coordinate joint clinical trial reviews of candidate products									
	- Coordinate production of international reference preparations to support product evaluation and establish collaboration between expert regulatory laboratories									
3. Outlining appropriate regulatory & ethical pathways	- Develop guidelines on safety, efficacy and quality of specific candidate products									
	- Draft guidelines on regulatory work sharing									
	- Outline multi-country study designs to support safety evaluations									
	- Initial steps to explore insurance options to address issues of liability in case of use of an experimental vaccine									
C. Developing new norms & standards tailored to the epidemic context	- Efforts to strengthen national, regulatory and ethics bodies to respond to public health emergencies									
	- Establish a cadre of regulators working together on products being developed for priority pathogens									
1. Supporting expansion of capacity to implement adequate study designs	- Define a clear set of steps to inform discussions on trial designs for priority diseases, an approach to assess each design in terms of methodological robustness and feasibility and, a process leading to the development of generic annotated protocols for priority diseases.									
	- A process leading to the development of generic annotated protocols for priority diseases has been mapped									
	- Publish protocols for priority diseases for scientific debate and review									
	- Completion of process to inform trial designs and open forum discussions on protocols for the Blueprint priority pathogens									
2. Developing guidance & tools to frame collaborations and exchanges	- Publication of white papers on methodological issues to inform trial designs during epidemics.									
	- Development of a trial simulator to inform trial design choices for Blueprint priority pathogens.									
	- Facilitate the establishment of a process for agreeing on principles for bio banking platforms									
	- Develop a concept for a Material Transfer Agreement (MTA) capacity building tool to inform negotiations on sharing biological samples									
3. Anticipating evidence needs to inform regulatory review and policy development	- Develop good participatory practices in a research context									
	- Develop generic agreement forms and guidelines that could support countries to negotiate and establish mechanism for collaboration, data sharing, samples sharing and intellectual property and guidance for national research committees to review research protocols during an outbreak									
	- Finalize the MTA capacity building tool through consultations with various stakeholders									
	- Complete development of the concept of biobanking "virtual" resource of [national] biobanks linked by an information-sharing platform									

9. THE DECLARATION OF A PHEIC FOR INCREASED NEUROLOGICAL DISORDERS AND NEONATAL MALFORMATIONS RELATED TO ZIKA VIRUS INFECTION: A FIRST TEST FOR THE R&D BLUEPRINT

The Zika virus outbreak in the Americas is serving as an important testing ground for the WHO Blueprint strategy. As the Blueprint work streams develop their activity plans, the virus is spreading; this concurrent timing enhances WHO's R&D coordination response while providing real-time feedback on how the Blueprint should be designed and executed.

WHO has activated internally and externally-facing coordination mechanisms to develop an appropriate R&D response to the Zika epidemic. These steps align with the Blueprint's preparedness approach, in order to accelerate Zika product development progress.

In the context of WHO's emergency response reforms, WHO began applying the emerging Blueprint strategy to the Zika Virus after the Public Health Emergency of International Concern (PHEIC) designation for microcephaly and other neurological disorders on February 1, 2016.

The first critical step of the Blueprint strategy was to map the current R&D technologies and regulatory preparedness. Based on a rapid landscaping effort in early 2016, WHO convened a consultation of academics, manufacturers, regulators and other interested parties to discuss the state of the art of Zika-related R&D and future priorities. WHO is now finalizing a set of Target Product Profiles (TPPs) for Diagnostics and Vaccines. The Emergency Use Assessment and Listing Procedure (EUAL) - established during the 2014 Ebola to expedite the availability of IVDs needed in public health emergency situations - was opened in February to candidate Zika in vitro diagnostics. Expedited regulatory pathways are being explored.

²⁹ <http://www.who.int/mediacentre/commentaries/zika-research-development/en/>

