Overview of the Blueprint process and method of work

The key objective of the R&D Blueprint is to pre-empt the development of a public health emergency due to highly infectious pathogens by implementing a plan of action for research preparedness. The ultimate goal is to reduce delay between the declaration of an emergency and the availability of effective medical or other interventions in order to save lives and avoid social and economic disruption.

The development of the R&D Blueprint by the WHO secretariat will be steered through engagement with relevant stakeholders and technical experts through consultations and dedicated working groups with oversight from the Scientific Advisory Group (SAG).

The scope of the R&D Blueprint is vast, and the SAG recommended that WHO address more precisely where investment is most essential. At the same time, there was general agreement that the Blueprint should not focus solely on the development of medical interventions, but on all research aspects that will impact upon outbreak response.

The WHO secretariat proposed that within each of the five workstreams a WHO focal point lead the process and convene a working group composed of SAG members and further external experts in order to contribute to the development of the workstream’s objectives. The SAG recommended that the Blueprint should be a collaborative effort, with WHO working alongside international and local actors to share work, focus resources and identify both existing knowledge and knowledge-gaps. WHO was seen as a legitimate coordinator of the various actors, which should support the work of others and avoid duplication of efforts. Deliverables will need to be clear and concise. Lessons learned and a model showing the difference in R&D preparedness levels that can be achieved will help strengthen the case for the Blueprint.

The R&D Blueprint will be presented at the World Health Assembly 2016, with an introduction at the Executive Board early next year. For this to be possible, an advanced draft of the Blueprint should be ready by end March 2016 at the latest.

Workstream 1: Prioritization of pathogens and operational plan

WHO proposed that Workstream 1 address the following questions:
- Which severe emerging pathogens for which we lack the knowledge and tools for control or prevention are most likely to generate a public health emergency?
- How can the operational aspects of moving from research preparedness to action be streamlined and coordinated?

Priority actions:
- Prepare a prioritized list of severe emerging diseases with the potential to generate a public health emergency, which should be the focus of initial R&D efforts. This list would be based on a review of existing and new disease prioritization assessments, and would identify the matrix of disease risks and key R&D gaps.
Perform an annual review of the priorities. These would be reassessed in light of R&D achievements, other scientific and technological developments and occurrence of possible new outbreaks.

Develop an operational outline for the transition from preparedness to action, focussing on the commonalities, but including separate modules for the specific features of each prioritized pathogen.

The SAG agreed that the prioritization of pathogens most in need of research and development is an essential step to properly guide the allocation of resources and set the scope of research activities. While there is already broad consensus on the pathogens that are likely to top the list, the group stressed the importance of a matrix that shows a transparent and evidence-based method will be used to identify priority pathogens. The list would be reviewed and updated when needed to ensure that the priorities are current and that new pathogens can progress onto the priority list as research and development on “old” priority pathogens progresses.

There was agreement that the process of prioritisation would take some time, and that this should guide much of the scope of Blueprint workstream 2. The SAG therefore agreed that the priorities would need to be identified formally but also that, for progressing the work on the Blueprint and its presentation to the UN high-level panel, MERS CoV could already be identified as one of the priority pathogens.

A consultation will be organized in November 2015 (BARDA and WHO) to identify top priority diseases.

**Workstream 2: Identification of research priorities**

WHO proposed that Workstream 2 address the following questions:

- What is the current status of basic and applied research for the 5 to 10 priority epidemic-prone diseases identified through work on Workstream 1?
- Which technology platforms could be the most effective and versatile?
- How can R&D for effective diagnostics, vaccines, therapeutics and other medical and information technology be accelerated for priority epidemic-prone diseases?

**Priority actions:**

- Prepare and disseminate a summary of current status and gaps to be filled for the 5 to 10 priority epidemic-prone diseases identified through Workstream 1, in order to highlight which important research questions should be addressed urgently to ensure development and availability of appropriate diagnostic tools and to promote the development of a portfolio of promising treatments and vaccines to completion of Phase 1 clinical trials in humans. This will allow, in case of an emergency, the immediate initiation of advanced/large-scale/ efficacy clinical trials and timely deployment of effective health technologies.
- Develop such an R&D Roadmap focused on MERS CoV.
- Improve regulatory preparedness for emergency approval of new health technologies, with a focus on low-and middle-income countries
- Develop a plan for a network of development and production platforms for priority health technologies.

The SAG reflected on the fact that the scope of this workstream is very broad and would be dependent upon incorporation of activities performed by many different actors, facilitated through WHO coordination.
The SAG recommended that appropriately networked product development and production platforms be identified and/or established, and that an analysis should be carried out of limiting factors in the development chain. WHO proposed that the planned “request for suggestions” for product development and production platforms – to be advertised in October 2015 - be extended to include platform technologies.

The SAG agreed on the usefulness of an infographic showing how long it would take - in the event of an outbreak - to initiate efficacy or proof-of-principle clinical trials for the products currently under development for one of the priority pathogens. Workstream 2 was tasked to develop such an infographic for MERS CoV, together with a full roadmap identifying how to progress and accelerate R&D.

WHO stressed the importance of strengthening regulatory systems in low- and middle-income countries in order to allow for the development of emergency pathways in future affected countries. The Secretariat explained that mechanisms for taking forward what has been learned from Ebola will be consolidated in view of implementing best practices into future outbreak R&D responses.

**Workstream 3: Coordination of stakeholders and enhancement of capacity**

WHO proposed that Workstream 3 address the following questions:

- What “governance structure” would allow for national and International actors to work in concert in support of global R&D efforts before and during an outbreak?
- What existing capacities, platforms, tools and templates are available or should be developed to conduct an efficient R&D response during a public health emergency?
- What potential exists for collaborative research inclusive of scientists in countries at risk?

Priority actions:

- Seek consensus on a framework for global collaboration
- Develop a framework to guide review and oversight of R&D at country level during an outbreak
- Prepare a “toolbox” to empower and facilitate participation of affected countries in the design and implementation of R&D during an outbreak.

WHO clarified that the intention of workstream 3 was not to duplicate or replace arrangements already in place, but to bring them together in a “network of networks” and to develop a consensus on principles to govern this undertaking. There was general consensus that WHO should act as a convener and facilitator, and should take the lead in bringing together existing groups and initiatives towards a common goal.

Making better use of existing funding and ensuring alignment of research efforts towards identified priorities can be advanced through the implementation of different levels of research coordination:

- Passive coordination achieved through better sharing of information;
- Active coordination through networks of researchers and research funders agreeing on priorities and collaboration;
- Pooled funding.

As a good example for how active coordination and prioritization could work, WHO presented the **Malaria Vaccine Funders Group**. This group consists of technical focal points within the Wellcome Trust, NIH, BMGF, USAID, EC, EDCTP, EVI and WHO, and is facilitated by WHO. It was established more than 10 years ago in order to exchange information and opinions between internationally active funding bodies for malaria vaccine development with the hope that progress can be accelerated. The group aims to facilitate the coordination of vaccine research activities by defining and making use of synergies between ongoing and planned programmes/activities, structuring and
prioritizing vaccine research efforts, thereby reducing unnecessary overlaps, and identifying areas of research needs where support can be assembled in a complementary manner. The group’s activities are guided by the Malaria Vaccine Technology Roadmap, which enables a joint planning framework for R&D, within which agencies individually implement funds according to their own scope. The funders group meets face to face at least once a year or more often when needed. This process has proven to be sustainable and desirable for all agencies involved, particularly as it enables an ongoing global gap analysis.

Whether such active coordination might be organized around a pathogen, a group of pathogens, a platform technology or a single product depends on the complexity of the R&D challenge and the number of entities involved.

The SAG highlighted that this workstream should be cross-cutting – not stand alone - and strongly linked with the other workstreams. Engagement of the various groups (consortia, networks, etc.) already active in this area (such as BARDA, GlopPID-R and ISARIC) would be critical both to provide a reference on potential governance mechanisms and to ensure that the work conducted by WHO embraces the work undertaken by others and remains manageable. The SAG stressed that mapping the activities of these groups would be essential to ensuring efficient use of limited resources. Engagement would also be necessary with groups who are part of the “response” to better strive towards real-time data sharing, to strengthen the process of learning while doing, and to allow more research to be conducted without straining the response. Connecting research groups would also allow for capacities in LMICs to grow and for resources to be shared.

There was consensus that preparation of a generic “toolbox” and sharing of generic protocols and agreements would have value, and that these could be further customized as needed, rather than produced de novo during emergencies. Solutions to the question of which entities should bear liability for adverse reactions during deployment of new medical technologies – and vaccines in particular – would also be welcome.

Production of generic guidance documents for country level management of research would also facilitate the research response. Likewise, mapping of existing experts, networks and capacities would bring value and would facilitate identification and rectification of gaps – especially in countries where outbreaks are most likely to emerge. Such gaps include, for example, capacity to review research proposals, to provide ethical or regulatory oversight to clinical trials, and to collect and share information and samples of biological material.

**Workstream 4: Assessment of preparedness and impact of R&D intervention**

WHO proposed that Workstream 4 address the following questions:

- How can WHO ensure regular implementation of actions and reporting of progress to stakeholders?
- What would be the components of an “enabling environment” in support of efficient and timely R&D during an outbreak?
- What would be the elements of an evaluation plan to determine the impact of R&D emergency activities?

**Priority actions:**

- Establish a performance monitoring mechanism for the implementation of the R&D Blueprint, including indicators to monitor progress towards expected outcomes and targets
- In parallel, develop an evaluation plan to determine the effects of the R&D plans during the next emergency
- Develop a high level checklist to assess the enabling environment for R&D preparedness, using MERS as a pilot test.
The SAG reflected that lack of readily available funding might be a major challenge for the implementation of the R&D Blueprint, but that integrating the assessment tool fully into Workstreams 1 to 3 might enhance accountability and therefore better convince funders of the value of the investment.

WHO highlighted that the development of the monitoring and evaluation mechanism and checklist would be dependent on definition of measurable outcomes in each of the other workstreams. A consultation would be organized (early 2016) to discuss the proposed models and indicators. A pilot testing of the assessment check-list, concentrating on MERS CoV research preparedness, will be proposed for 2017.

The development of an evaluation plan and the definition of essential components of R&D preparedness (the environment necessary to make roll-out of research activities possible as soon as an emergency starts), was deemed highly important by the SAG. The evaluation and assessments will take into consideration quantitative and qualitative aspects and the information generated by the analysis of these aspects will be shared widely and in a timely way. An independent external evaluation (even if costly) should be considered to ensure objectivity and avoid any conflict of interest.

**Workstream 5: Development of innovative funding options**

WHO proposed that Workstream 5 address the following questions:
- How to ensure adequate and sustainable funding for the research identified as priority?
- How to align and make more efficient use of existing funding?
- How to make use of existing mechanisms and avoid overlap and duplication?
- How to ensure appropriate governance mechanisms for any selected funding model?

**Priority actions:**
- Map options for funding R&D preparedness and R&D during an outbreak
- Make recommendations for appropriate models
- Facilitate decision on funding R&D preparedness by major stakeholders

There was consensus that financing of the blueprint was essential to both its initial development and to making it a sustainable and effective plan. In order to fund the Blueprint, three main areas need addressing: funding for R&D preparedness during the inter-epidemic periods, funding for a research response during an outbreak and funding of the activities necessary to manage the Blueprint in a sustainable way.

WHO presented plans for a consultation of R&D experts, funders and policy-makers to be held in Oslo, on 29-30 October, by the Norwegian Institute of Public Health in collaboration with WHO. The consultation intends to identify existing funders, map potential new funders and funding mechanisms – including for other disease areas - from which sustainable funding options can be developed.

The discussion highlighted the fact that incentivizing funders, encouraging manufacturers to invest in this area of work and convincing governments to participate in a joint effort (and not to leave it up to one or two countries to support this alone) would be essential. Multiple methods to incentivize various stakeholders have already been well characterized, and the SAG stressed that new efforts should build upon and learn from established initiatives (and in particular from those used by BARDA and the European Commission). WHO was encouraged to seek complementarity with GloPID-R.

The SAG agreed that it would be important to emphasize to policy-makers that it is their responsibility to take risks, and to remind them of the economic impact of an outbreak. Global, long term considerations have to be at the forefront, and transparency of any proposed mechanism for funding will be paramount.
WHO proposed that documents clarifying the scope of workstream 5 be developed and shared prior to the Oslo consultation. A full analysis of the current landscape and presentation of options would need to be developed, from which proposals could be put forward and funders engaged.

**Next steps**

- **High-level Panel convened by the UN Secretary General to provide recommendations on the Global Response to Health Crises (HLP)**

WHO presented a draft document on the R&D Blueprint prepared for the HLP. The SAG provided comments on the document and suggestions on concrete outcomes to be expected from the implementation of the Blueprint. R. Robinson agreed to provide high-level costing for product R&D activities, based on BARDA’s experience.

WHO will revise the document according to suggestions from the SAG, with a view to sharing it with the HLP no later than the first week of October.

- **Further development of the R&D Blueprint**

Based on the recommendations of the SAG, each of the workstreams will develop their work plans, specific working groups and a list of consultations to be organized and studies to be commissioned. A list of priority outcomes and timelines will be produced for each workstream.

While SAG members are requested to advise on the scope and proposed outcomes of the R&D Blueprint as a whole, to provide feedback and to identify gaps, they are also kindly asked to contribute to and assist WHO in the implementation of the workstreams that are the closest to their specific interests and expertise.

A third meeting of the SAG will be held in Oslo on the 29 October, 2015, with those members who will be able to participate in the upcoming workstream 5 consultation.