Blueprint for R&D preparedness and response to public health emergencies due to highly infectious pathogens

WORKSHOP ON PRIORITIZATION OF PATHOGENS

8-9 December 2015

Executive summary

On 8-9 December, a group of experts met in Geneva to prepare a process for prioritization of pathogens under the Blueprint for accelerated R&D for severe emerging diseases with potential to generate a public health emergency, and for which no, or insufficient, preventive and curative solutions exist. The group included experts in virology, microbiology, immunology, public health, clinical medicine, mathematical and computational modelling, product development, and respiratory and severe emerging infections.

An initial list of seven diseases requiring urgent R&D was agreed. This comprised: (1) Crimean-Congo haemorrhagic fever; (2) Filovirus diseases (i.e. EVD & Marburg); (3) Highly pathogenic emerging Coronaviruses relevant to humans (MERS Co-V & SARS); (4) Lassa Fever; (5) Nipah; (6) Rift Valley Fever, and (7) R&D preparedness for a new disease. Also listed were three further diseases determined to be serious, necessitating further action as soon as possible: chikungunya, severe fever with thrombocytopenia syndrome, and zika.

Many other diseases were considered. Given the focus on improving current capacity, some disease (such as HIV or influenza) were set aside where there are major disease control initiatives, an extensive R&D pipeline, existing funding streams, and established regulatory pathways. Others (such as dengue) were deemed important for inclusion in future reviews. The importance of reviewing diseases in light of new findings was also highlighted (such as for information emerging into the public domain for zika and congenital abnormalities at the time of the meeting).

The group also undertook the first phase of the development of a set of practical tools to evaluate proposed diseases for focussed and accelerated R&D. The facilitation of R&D is expected to improve interventions and products such as diagnostics, vaccines, and therapeutics, behavioural interventions, and fill critical gaps in scientific knowledge to allow the design of better disease control measures.

Background

Current, market-driven models of medical R&D do not cater for the application of new or improved technologies for diseases that are sporadic or unpredictable, especially when they occur in countries with low investment in health infrastructure and delivery. The challenge becomes even greater when faced with a wholly new disease. The international community has recognised the need to invest to improve our ability to respond to new threats and prepare itself with a novel R&D paradigm to address future epidemics. Beyond preparedness, R&D should be recognized as an integral part of the response to an epidemic. The Executive Board of the World Health Assembly in its special session on the Ebola emergency, in January 2015, adopted resolution EBSS3.R1 in which the Director-General was requested to provide options for strengthening information sharing and for enhancing WHO's capacity to facilitate access to diagnostic, preventive and therapeutic products. Subsequently, WHO convened an R&D Summit on 11- 12 May 2015 to discuss future R&D preparedness, based on an analysis of the lessons learned from the West African Ebola crisis. It aimed to provide a clearer understanding of the interests and constraints for countries, partners, and funders in building collaborations to accelerate access to novel interventions during public-health emergencies.

Subsequent to the Summit, the World Health Assembly "welcomed the development of a Blueprint for accelerating research and development in epidemics or other health emergency situations where there are no, or insufficient, preventive, and curative solutions, taking into account other relevant work-streams within WHO".

The R&D Blueprint

The R&D Blueprint being developed aims to map existing knowledge and good practices, identify gaps and establish a roadmap for R&D preparedness, through an enabling environment in affected countries. It is a collaborative effort with Member States and other relevant stakeholders that includes interconnected work streams for:

- Prioritization of highly dangerous pathogens for urgent R&D preparedness activities
- Identification of R&D priorities including those for the designated priority diseases under a range of headings including, e.g. selection of candidate products, diagnostics, drug and vaccine development, production platforms, behavioural interventions, and relevant key knowledge gaps.
- Development of governance options, promotion of collaborative research inclusive of scientists from the countries at risk, identification of networks and capacity gaps, and preparation of needed tools and frameworks
- Exploration of innovative funding models for R&D preparedness and response
- Monitoring and evaluation of R&D preparedness and impact, for continuing improvement.

As an initial step in the Workstream for prioritization of pathogens for urgent R&D preparedness activities, the WHO convened an expert workshop from 8-9 December 2015 in Geneva, Switzerland.

Prioritization workshop

The workshop brought together experts in virology, microbiology, immunology, public health, clinical medicine, mathematical and computational modelling, product development, and respiratory and severe emerging infections. Workshop participants were tasked with identifying a short-list of pathogens to be prioritized immediately under the R&D Blueprint, and to commence the development of a robust methodology and practical tools for use in future prioritization exercises.

During the course of the workshop, participants identified nine *prioritization elements* and used them to develop a consensus list of six known diseases urgently requiring accelerated R&D. The needs for research preparedness for a new disease were also deemed to fit into the 'urgent' category. A further list of three other serious diseases was identified to be addressed as soon as possible.

In order to provide for a more thorough and comprehensive assessment during future prioritization exercises under the Blueprint, workshop participants also laid out a framework for developing a more rigorous, semi-quantitative, methodology. The workshop also considered the structure of such reviews, factors or criteria to be considered when assessing relevant *prioritization elements*, and associated weightings.

Prioritization elements

In order to be able to determine those pathogens and diseases to be prioritized under the R&D Blueprint, the following nine elements were identified:

1. Human transmissibility (including population immunity, behavioural factors, etc.)
2. Severity or case fatality rate
3. Spillover potential
4. Evolutionary potential
5. Available countermeasures
6. Difficulty of detection or control
7. Public health context of the affected area(s)
8. Potential scope of outbreak (risk of international spread)
9. Potential societal impacts

Priority diseases

To ensure that efforts under the R&D Blueprint were focussed, productive, careful with limited resources, and that work commences with minimal delay, an initial priority list of diseases was needed. This list was identified through a rapid prioritization exercise, taking account of many earlier prioritization exercises performed by governments agencies in several countries and by other groups. The WHO Blueprint prioritization process learned from these earlier efforts, all of which had their own purpose, target context, and desired outcomes, different in some or many respects to the needs of WHO, which had to be focussed on the specific mandate and address the needs of all Member States, while remaining especially alert to the needs of LMICS.

In line with the aims of the R&D Blueprint and with the decision of the WHA to focus on diseases "where there are no, or insufficient, preventive, and curative solutions", participants were asked to set aside diseases, even those with epidemic potential, for which there already are major disease control initiatives, an extensive R&D pipeline, existing funding streams, and established regulatory pathways for improved interventions. These include HIV/AIDS, tuberculosis, malaria, avian influenza causing severe human disease, antimicrobial resistance (as a generic category), smallpox/monkeypox, and dengue. In order to reduce the potential for dilution of scarce resources and duplication of effort, any necessary further actions for such diseases might be coordinated through the disease-specific initiatives.

Using the prioritization elements as a guide, 7 diseases were identified for urgent action: (1) Crimean-Congo haemorrhagic fever; (2) filovirus diseases (i.e. EVD & Marburg); (3) Highly pathogenic emerging coronaviruses relevant to humans (MERS Co-V & SARS); (4) Lassa Fever; (5) Nipah; (6) Rift Valley Fever, and (7) a new disease. A further three diseases were also listed as serious, necessitating further action as soon as possible: chikungunya; severe fever with thrombocytopenia syndrome; and zika.

A number of other diseases were discussed by experts. For example:

- Information about a possible aetiological connection between zika virus and congenital abnormalities, particularly microcephaly, was beginning to receive public attention at the time of the workshop. Although few details were then available, the experts noted that if strong evidence for a link were to be presented, the very serious public health implications mean that the group should consider moving zika to the top 'urgent' category, for accelerated countermeasure development
- Dengue fever was felt by several participants to be a strong candidate for prioritization due to its major and growing public health impact, whereas others felt that there would be little value added to the substantial existing R&D efforts through the attention of this program, and that it might distract scarce resources from the underserved diseases the Blueprint was designed to address. Some experts felt that that dengue fever should be included in the first annual review of the prioritized list, making use of the more quantitative assessment methodology to be developed
- Plague was also discussed but the existence of sufficient medical countermeasures and other proven public health interventions was noted
- Carbapenem-resistant enterobacteriaceae were discussed, but it was considered that they are being addressed under existing AMR initiatives. However, the possibility was not excluded that in the future, a resistant pathogen might emerge and appropriately be prioritized

Many other diseases with actual or potential impact on human health, including animal diseases with the potential for transboundary spread, and diseases affecting the food supply, were also considered.

The prioritization process

Process outline

The prioritization process under the R&D Blueprint should have three stages: (1) formulation or revision of elements against which to prioritize; (2) weighting of those elements according to importance; and (3) assessing the diseases against the weighted *prioritization elements*. A number of previously identified best practices associated with each of the three stages were highlighted (Annex I).

The prioritization process will need to be repeated at regular intervals to take into account relevant developments and advancements in knowledge and understanding.

Factors to consider when prioritizing diseases

A wide range of factors or criteria to be considered when prioritizing diseases were identified (Annex II), including those connected to:

- Agent-based factors;
- Host-based factors, such as those associated with the immunopathology of the disease;
- Clinical factors, including those related to the provision of clinical care
- Public health factors, including those related to public health capacity
- Epidemiological factors
- Contextual factors (socio-economic, environmental, etc.)

Weighting prioritization elements

Each of the *prioritization elements* may not have an equal impact on whether a disease needs to be prioritized. For example, challenges in detecting a pathogen may be less important than its transmissibility. As a result, it is necessary to weight individual elements on the basis of the constituent criteria.

As an initial step, the experts undertook an exercise to weight the various identified elements as a generic approach. In summary, participants felt that the most highly weighted *prioritization element* was: transmissibility; followed by the severity (or case fatality rate) and the potential scope of outbreak (risk of international spread); the availability of countermeasures; the public health context of the affected area; the difficulty of detection or control; potential societal impacts; the spillover potential; and the evolutionary potential.

Following this initial exercise, the experts highlighted the need for a more rigorous and quantitative weighting methodology. This would entail considering more detailed criteria under each element and the potential scenarios for different diseases

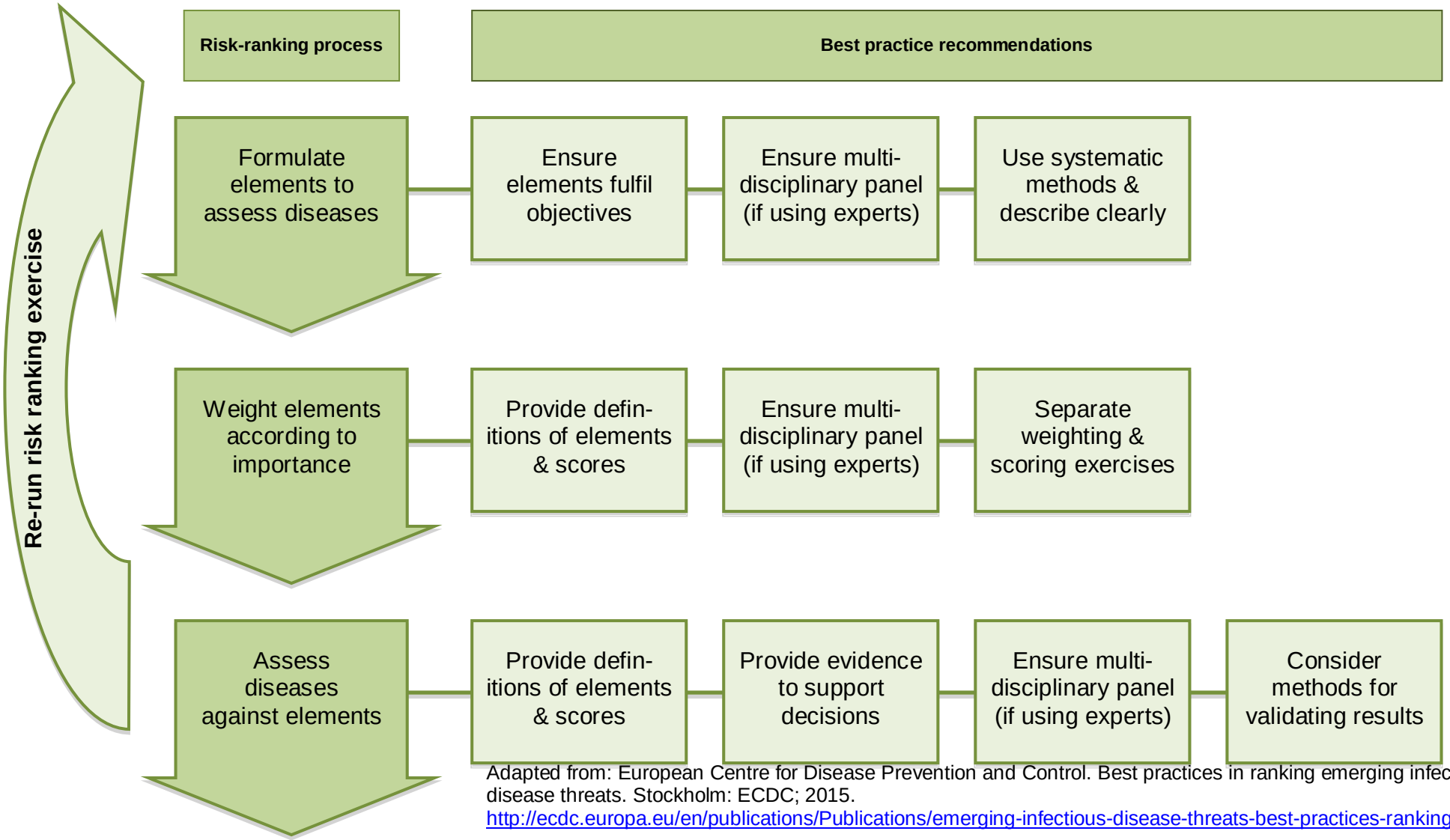
Future action and next steps

The list of priority pathogens will need to be revisited on a regular basis. Within a year, the processes should be rerun using the tools and methodology to be developed following the workshop. To this end, the next steps include:

- Developing a decision tree for prioritization of new diseases based upon the *prioritization elements* and identified factors/criteria;
- Constructing a prioritization tool by structuring the factors/criteria to be considered and integrating under the respective *prioritization elements*;
- Convening a working group to design and demonstrate a more quantitative weightings methodology to be applied to the prioritized diseases.
- Drawing, upon invited and present participants for emergency urgent prioritization advice, as necessary, pending the development of the above tools.

ANNEX I

Outline of the prioritization process



Adapted from: European Centre for Disease Prevention and Control. Best practices in ranking emerging infectious disease threats. Stockholm: ECDC; 2015.
http://ecdc.europa.eu/en/publications/Publications/emerging-infectious-disease-threats-best-practices-ranking.pdf

ANNEX II
Factors to consider when prioritizing diseases

Agent-based factors

Agent-based factors are connected to properties of the pathogen causing the disease. Those agents posing the greatest risk of epidemic or pandemic potential might include agents:

1. Which are particularly pathogenic;
2. Where the mechanism of transmission are likely to result in high levels of human to human transmission;
3. Which can infect humans;
4. Which exhibited any human to human transmission;
5. Which exhibited efficient human to human transmission or efficient vector-mediated transmission to humans;
6. With a natural reservoir that can spill over into humans;
7. With a close relative with a medical countermeasures;
8. Resistant to the use of medical countermeasures;
9. Without medical countermeasures;
10. With robust environmental survival capabilities;
11. With similar phenotypic characteristics to those responsible for historical epidemics and pandemics;
12. Which can rapidly evolve;
13. Which can easily take up relevant characteristics from other pathogens (such as horizontal gene transfer); and
14. Agents which elude detection and diagnosis

Host-based factors

Host-based factors are connected to properties of the host, often associated with the immunopathology of the disease. Those diseases posing the greatest risk of epidemic or pandemic potential might include those which:

1. Can evade the host's immune system;
2. Can disrupt the host's immune system;
3. There is a deleterious and severe host response;
4. Involve immunologically privileged locations within the host;
5. There is little or no cross-immunity;
6. There was no population immunity; and
7. Natural protective immunity after infection is not robust.

Health factors

Health factors include those related to the clinical presentation of the disease, public health capacity, and epidemiological factors.

Clinical presentation

Clinical presentation factors are connected to how medical personnel and public health infrastructure will experience the disease. Diseases posing the greatest risk of epidemic or pandemic potential might include those:

1. Which are difficult to recognise - including those with non-specific early features or easily confused with more common diseases (e.g. pneumonias);
2. Which result in large number of deaths;
3. Which have a prolonged infectious prodrome;
4. With prolonged infectivity;
5. With a long duration;
6. With evidence of increasing severity;
7. With evidence of increasing transmissibility; and
8. Which cause complications or sequelae.

Public health capacity

Public health capacity factors are connected to the existence of the necessary resources to respond to the disease. Diseases posing the greatest risk of epidemic or pandemic potential might include those requiring:

1. Specialised detection or diagnostics;
2. Specialised surveillance;
3. Specialised interventions - including things not used on a regular basis, or are not available to most countries, or which are not regularly used in other species (including highly skilled personnel, equipment, availability of isolation units, respirators, PPE, etc) and infection control measures;
4. The investment of significant public health resources; and
5. Capability to employ and emergency response.

Epidemiological factors

Epidemiological factors are connected to how the disease spreads. Diseases posing the greatest risk of epidemic or pandemic potential might include those:

1. Which typically infect health personnel;
2. Which carry a high risk of occupational exposure (including for culling, vets, burial details, lab workers, first responders)
3. Which cause clusters of cases;
4. Which disproportionately affect special populations;
5. Where epidemiological links might hidden or difficult to discern;
6. With certain modes of transmission, such as airborne transmission; and
7. With evidence of increasing geographic range.

4. Context-based factors

Impacts, other than those felt directly in a health setting, can influence whether a disease should be prioritized. Diseases which might need to be prioritized could include those which:

1. Cause major disruptions to food and water supply (including Production, distribution, alternative sources, ability to readily decontaminate);
2. Cause major economic impacts;
3. Cause major social disruptions (Including Stigma, DALY);
4. Cause major environmental impacts;
5. Are traditionally associated with deliberate outbreaks;
6. Cause health care system disruption;
7. Are present in high density and or highly inter-connected human populations;
8. Affect people whose behaviour is likely to increase transmission; and
9. Occur in places with poor public health infrastructure.

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