WHO Research and Development Blueprint

2017 Annual review of diseases prioritized under the Research and Development Blueprint

Informal consultation

24-25 January 2017
Geneva, Switzerland

Meeting report

The meeting was organized under the WHO R&D Blueprint, which aims to reduce the time between declaration of a public health emergency and the availability of effective diagnostic tests, vaccines, antivirals and other treatments that can save lives and avert a public health crisis (http://www.who.int/csr/research-and-development/en/).

Executive summary

On 24-25 January 2017, the World Health Organization held an informal consultation in Geneva, Switzerland, to review the list of priority diseases for the WHO R&D Blueprint. The R&D Blueprint focuses on severe emerging diseases with potential to generate a public health emergency, and for which insufficient or no preventive and curative solutions exist. The original list of diseases that most readily meet these criteria and for which additional research and development is urgently required was agreed at an international consultation held in November 2015.

The January 2017 meeting brought together virologists, bacteriologists, vaccinologists, public and animal health professionals as well as infectious disease clinicians to review the list of priority diseases. These experts made use of a tailored prioritization methodology developed by WHO and validated at an informal consultation in November 2016. The methodology uses the Delphi technique, questionnaires, multi-criteria decision analysis, and expert review to identify relevant diseases.

The 2017 annual review determined there was an urgent need for research and development for:[1]

- Arenaviral hemorrhagic fevers (including Lassa Fever)
- Crimean Congo Haemorrhagic Fever (CCHF)
- Filoviral diseases (including Ebola and Marburg)
- Middle East Respiratory Syndrome Coronavirus (MERS-CoV)
- Other highly pathogenic coronaviral diseases (such as Severe Acute Respiratory Syndrome, (SARS))
- Nipah and related henipaviral diseases
- Rift Valley Fever (RVF)
- Severe Fever with Thrombocytopenia Syndrome (SFTS)
- Zika

In addition, any disease identified using the R&D Blueprints decision instrument for new diseases.

Chikungunya virus was discussed during the meeting and a number of experts stressed the risks it poses. Along with a number of other pathogens, there was agreement that Chickungunya Virus continues to warrant further research and development.

Other pathogens were considered during the review and a wide range of additional relevant research and development initiatives encouraged. In particular, participants noted the importance of cross-cutting research and development which would help to address a range of different pathogens or diseases at the same time.

The meeting also stressed the importance of continuing research and development on diseases other than those on the priority list. Further research and development is needed on a wide range of diseases. Where there are already substantive efforts to develop

[1] The order of diseases on this list does not denote any ranking of priority.

relevant medical measures any necessary further actions for such diseases could usefully be coordinated through the disease-specific initiatives (such as existing major disease control initiatives, extensive R&D pipelines, funding streams, or established regulatory pathways for improved interventions).

The value of a One Health approach was recognized, as well as the importance of working more closely with animal health to identify priority diseases and develop relevant countermeasures. The meeting also noted that whilst anti-microbial resistance is an issue being dealt with by thematic initiatives at the international level, specific diseases with resistance might be considered for prioritization in the future.

Feedback from the meeting on the methodology used and opportunities for further strengthening this process will be fed into its next review to be conducted within two years.

Introduction

At the request of its 194 Member States in May 2015, the World Health Organization (WHO) convened a broad coalition of experts to develop an R&D Blueprint for Action to Prevent Epidemics. The R&D Blueprint presents options to reduce the time lag between the identification of a nascent outbreak and approval of the most advanced products that can be used to save lives and stop larger crises. It focuses on severe emerging diseases with potential to generate a public health emergency, and for which no, or insufficient, preventive and curative solutions exist.

Activities under the R&D Blueprint are organized into three clusters of activities. The second cluster focuses on accelerating research and development processes. It includes work to assess epidemic threat and define a priority pathogens.

As an interim measure, an informal consultation was convened by WHO in December 2015 where a panel of scientists and public health experts compiled an initial list of diseases.[2] In light of technical developments, increased understanding of disease, or as a result of real world events, including subsequent public health emergencies, it is necessary to regularly review the list of priority diseases. This consultation was the first such review and the first use of a more robust methodology for compiling a list.

Disease prioritization methodology

In order to ensure the list of diseases prioritized under the R&D Blueprint is as accurate as possible, WHO has developed a comprehensive methodology. This is based upon established best practice and practical national experiences in compiling similar lists. The resulting methodology also specifically addressed criticism of earlier attempts to prioritize diseases.

The general approach and key prioritization criteria (Annex A) to be used in the prioritization process were identified at the December 2015 consultation[3]. These were subsequently expanded by WHO and an outline of the eventual methodology was presented to, and validated by, the R&D Blueprints Scientific Advisory Group (SAG) in May 2016.

Following input from the SAG, the methodology was further developed through: the inclusion of specific disease scenarios: a series of sub-criteria to explore different factors that could affect the relevance of a disease to R&D Blueprint objectives; and a semi-quantitative weighting of the prioritization criteria. WHO also developed the tools for Multi-Criteria Decision Analysis (MCDA) through a custom implementation of an Analytic Hierarchy Process (AHP), developed in collaboration with field leaders in these tools. This was then supplemented by online questionnaires to gather data from participants.

[2] http://www.who.int/medicines/ebola-treatment/WHO-list-of-top-emerging-diseases/en/
[3] http://www.who.int/csr/research-and-development/meeting-report-prioritization.pdf?ua=1

The entire methodology, its supporting models and attendant tools were reviewed at a dedicated consultation held in Geneva, Switzerland in November 2016.[4] The meeting validated a general approach, endorsing a system of annual reviews, biennial methodology reviews, supplemented as necessary with emergency reviews (Figure 1). The annual reviews are to utilize a combination of rounds of the Delphi technique, questionnaires and MCDA to review and update the R&D Blueprint's priority list of diseases. Following their revision in light of feedback, insights and recommendations received at the meeting, the tools and models were subsequently validated via a silence procedure in January 2017. The resulting methodology was published online.[5]

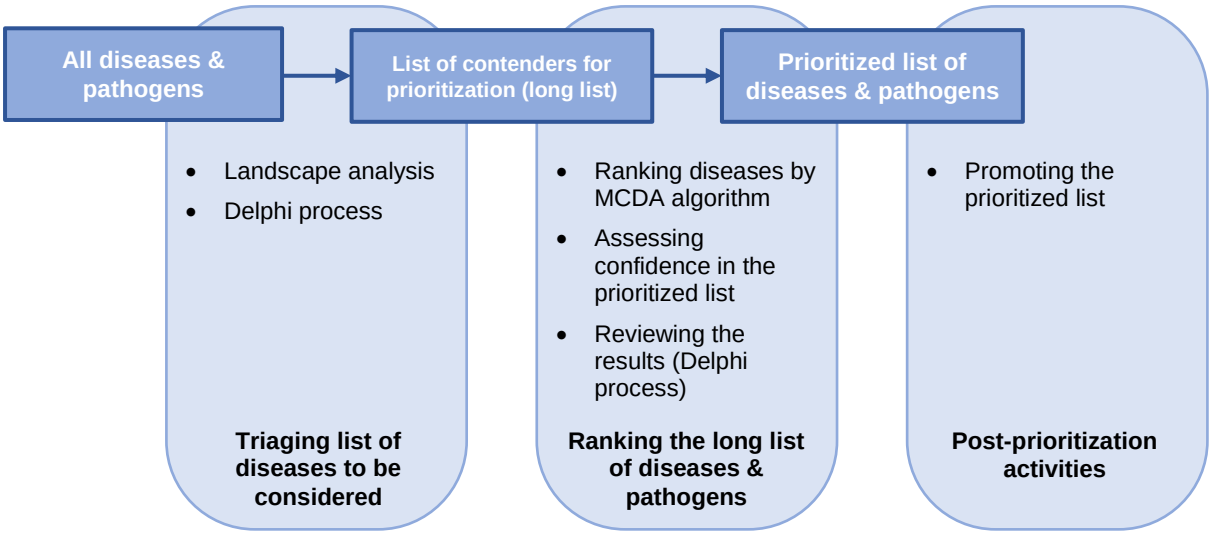

FIGURE 1: Overview of the annual prioritization exercise

Updating the list of priority diseases

In accordance with the published methodology, The January 2017 meeting brought together virologists, bacteriologists, vaccinologists, public and animal health professionals as well as infectious disease clinicians to review the list of priority diseases. These experts formed a Prioritization Committee (Annex B). Some, or all of them, might also be called on prior to the next annual review should an emergency prioritization exercise be warranted.

In future reviews, a landscape analysis will be conducted to provide participants with a snapshot of the current understanding of diseases currently on the priority list. As key tools under the methodology had only be finalised less than a fortnight before this annual review, it was not possible to commission such a work. Instead, prior to the meeting, participants were tasked with using the prioritization criteria to review the original priority list and consider in light of current knowledge whether all those diseases needed to remain on the list.

[4] http://www.who.int/csr/research-and-development/documents/prioritizing_diseases_progress/en/
[5] http://www.who.int/csr/research-and-development/RDBlueprint-PrioritizationTool-19Feb2017.pdf?ua=1

The Prioritization Committee were also asked whether there were additional diseases which should be considered. Each committee member was invited to propose up to 2 additional diseases that should be considered during the 2017 annual review.

In the lead up to the meeting, 1-2 experts were requested to provide short briefings on the diseases to be considered. For each disease on the original priority list two discussants were identified – one a disease specific expert with relevant peer-reviewed publications, and another whose primary interest lay with a similar but different disease. Those proposing additional diseases were requested to provide a short introduction to the disease. This was intended to provide other participants with an overview of current understanding of these diseases but with some degree of peer review to address selection and anchoring biases.

The meeting opened with WHO providing an overview of the R&D Blueprint, the methodology to be used to create a list of priority diseases, and a recap of the content of the original list of diseases.

The long list of diseases

The Prioritization Committee were then presented with a long list of diseases compiled from the content of the original 2015 priority list, diseases (such as dengue) which were not included in the original list but which were forwarded by the 2015 meeting for reconsideration following the creation of a more robust methodology, as well as those proposed by members of the committee in the lead up to the meeting.

The long list of diseases considered by the Prioritization Committee was:

- Crimean Congo Haemorrhagic Fever
- Chandipura Virus Disease
- Chikungunya
- Dengue
- Ebola Viral Disease
- Kyasanur Forest Disease
- Lassa Fever
- Marburg
- Mayaro
- Middle East Respiratory Syndrome Coronavirus
- Oropouche
- Nipah
- Plague
- Rift Valley Fever
- Severe Acute Respiratory Syndrome
- Severe Fever with Thrombocytopenia Syndrome
- South American Heamorrhagic Fevers
- Usutu
- Yellow fever
- Zika

The Prioritization Committee then undertook a two-step semi-quantitative Delphi technique to triage the long list of diseases into a shorter list to be considered by MCDA. The Prioritization Committee agreed by consensus that as this was the first use of the new methodology, meaning that it had not been used to assess those diseases already on the list, that they should be all revised using MCDA.

They proceeded to score each of the additional diseases on the long list from 0-1000 – where 1000 represented a perfect fit for the R&D Blueprint - a disease that has a notable

epidemic potential but for which there are no medical countermeasures, or a pipeline for developing them - and 0 represented diseases which had no epidemic potential and/or for which there are effective and commonly available medical countermeasures. Diseases were scored over such a large scale to assist with personal comparisons between different diseases and to enable participants to cluster diseases that are equally relevant to the R&D Blueprint. The results of this initial scoring process are recorded in Table 1.

Disease	Mean Score	% of experts scoring over 500
Chandipura	350	11%
Dengue	361	32%
Kyasanur Forest Disease	408	32%
Mayaro	443	37%
Oropouche	376	32%
Plague	361	26%
Severe Fever with Thrombocytopenia Syndrome	505	63%
South American Haemorrhagic Fevers	487	58%
Usutu	387	32%
Yellow fever	423	42%

TABLE 1: An initial scoring of diseases being considered for more detailed analysis

The Prioritization Committee then discussed the long list – considering both its content and each of the diseases. For each disease, a 2-3 minute overview was provided by those participants that been tasked with preparing remarks in advance of the meeting. Other members of the committee were then given the opportunity to add information, ask questions, or present opposing views. Participants were frequently reminded to focus the discussion on the prioritization criteria contained in the methodology. During these discussions four additional diseases were proposed for inclusion on the long list but were set aside prior to a second round of scoring: Bwamba Fever, Chikungunya, Hantaviral diseases, and O'nyong'nyong virus disease (see additional understandings).

Disease	Mean Score	% of experts scoring over 500
Bwamba Fever	-	-
Chandipura	350	33%
Chikungunya	-	-
Dengue	267	11%
Hantaviral diseases	-	-
Kyasanur Forest Disease	300	11%
Mayaro	461	22%
O'nyong'nyong virus disease	-	-
Oropouche	283	11%
Plague	489	44%
Severe Fever with Thrombocytopenia Syndrome	656	67%
South American Haemorrhagic Fevers	528	67%
Usutu	344	22%
Yellow fever	394	44%

TABLE 2: An second round of scoring of diseases being considered for more detailed analysis

Participants re-scored the additional diseases on the long list (Table 2). Discussion of the diseases had a notable impact on the scores. Whilst the scores for some diseases, such as yellow fever or Mayaro, remained largely the same, other diseases were now considered to be more relevant to the R&D Blueprint, including: Chandipura, where the percentage of those scoring this disease highly tripled even though the mean score remained the same; as well as plague, Severe Fever with Thrombocytopenia Syndrome and South American Haemorrhagic Fevers, where both the mean score and the percentage of those scoring it highly increased. Other diseases were considered to be less pertinent to the R&D Blueprint after discussion, including dengue, Kyasanur Forest Disease, Oropouche, and Usutu for which both the mean score and the percentage of participants scoring it highly both decreased.

The short list of diseases

The Prioritization Committee then used these scores to facilitate discussion of which diseases would be included in the MCDA. Two diseases, yellow fever and dengue, were set aside given the existence of large disease specific international public health programmes. This was consistent with the focus of the R&D Blueprint on those diseases that lack such support. There was broad recognition that additional research and development of countermeasures for these diseases was important but that such efforts should be supported through the disease-specific initiatives, rather than through the R&D Blueprint.

A second set of diseases were considered to pose a potential epidemic threat but the current state of understanding of these diseases was felt to be insufficient to warrant their inclusion in the 2017 annual review. These included: Bwamba Fever; Chandipura; Kyasanur Forest Disease; Mayaro; O'nyong'nyong virus disease, Oropouche; and Usutu. Further research on these diseases was felt to be important, in particular basic research which might help characterize the epidemic threat. These diseases might usefully be included in the next annual review of the priority list with the hope that their epidemic threat might be better understood.

As a result, the short list of diseases assessed using MCDA during the 2017 review of the list of priority diseases included:

- Crimean Congo Haemorrhagic Fever
- Ebola Viral Disease
- Hantaviral diseases
- Lassa Fever
- Marburg
- Middle East Respiratory Syndrome Coronavirus
- Nipah
- Plague
- Rift Valley Fever
- Severe Acute Respiratory Syndrome
- Severe Fever with Thrombocytopenia Syndrome
- South American Heamorrhagic Fevers
- Zika

Multi-Criteria Decision Analysis

The Prioritization Committee used the online surveys developed by WHO to compare how these diseases corresponded with 39 statements describing the sub-criteria contained in the prioritization methodology. Some participants experienced difficulties in using this system, which may have exceeded local IT capacity to support it. This provided a valuable test of these tools and led to the identification of a number of technical improvements, such as adding the ability to save results. In order to overcome these technical difficulties, several participants provided WHO with manual answers to the same questions and their results were added into the resulting database. The views of all members of the Prioritization Committee were fed into the MCDA analysis.

The results were analysed using the AHP MCDA approach detailed in the prioritization methodology and a forthcoming peer-reviewed article. WHO presented the Prioritization Committee with a summary overview of the results. This included, for each criterion, a representation of the score for each disease broken down by individual sub-criteria. A more detailed breakdown of results showing separate scores for each disease for all 39 sub-criteria were also available to the committee.

The Prioritization Committee reviewed the results. They identified ways in which they fit expectations (for example high scores in for human-to-human transition for those diseases known to spread rapidly). They also discussed unexpected results, where scores were higher or lower than expected. Several explanations were identified:

- In some cases, discussion of the results led to members of the committee explaining why they had scored the way they had.
- In other cases, it became clear that different interpretation of the statements used to capture the sub-criteria were leading participants to answer in very different ways. These challenges were noted and led to subsequent changes in the statements used in the methodology.
- It also became clear that there was also a more substantial methodological challenge. As the disease scores for each criterion are a function of the scores awarded to individual statements, in some areas using both binary and analogue statements was confusing results. For example, the section on human transmission had statements exploring whether there was any evidence of transmission as well as how much transmission occurs. As a result, diseases for which transmission is possible, but very low, were scoring higher than expected. This complicated differentiating these diseases from more transmissible diseases. This discovery also led to a discussion as to whether high levels of human-to-human transmission should be a separate criterion - with a heavy weighting to stress its importance. Some participants strongly supported this approach. Others strongly disputed it. It might usefully be explored in more detail during the next review of the methodology.

- Participants also felt that the results produced (for example with Ebola Virus Disease scoring highly across several criteria) were open to recall bias.

The Prioritization Committee then examined overall scores for each of the diseases (Figure 2).

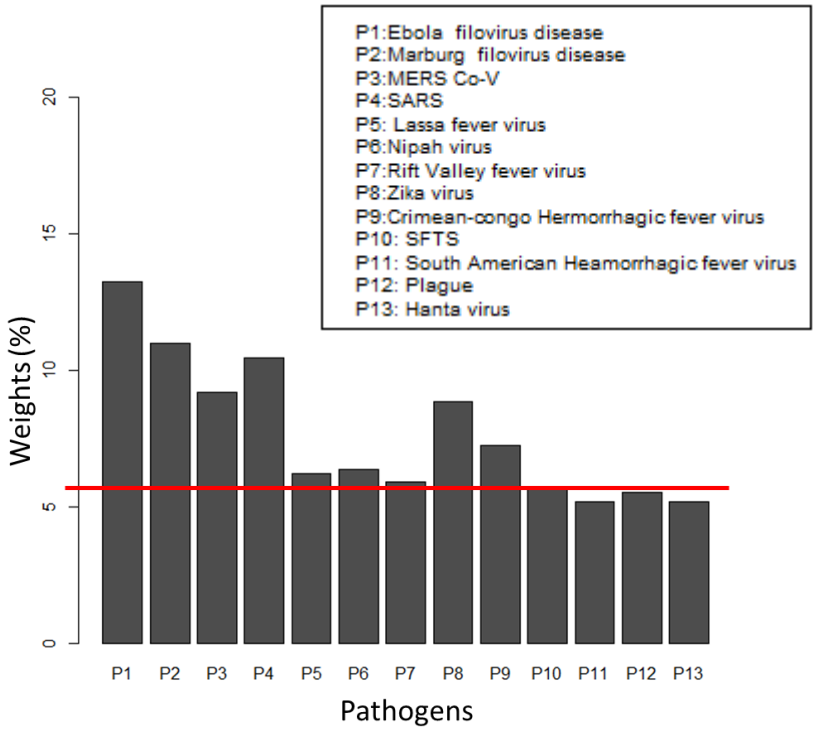

Figure 2: Overall scores for diseases analysed using MCDA during the 2017 annual prioritization review by using the geometric average

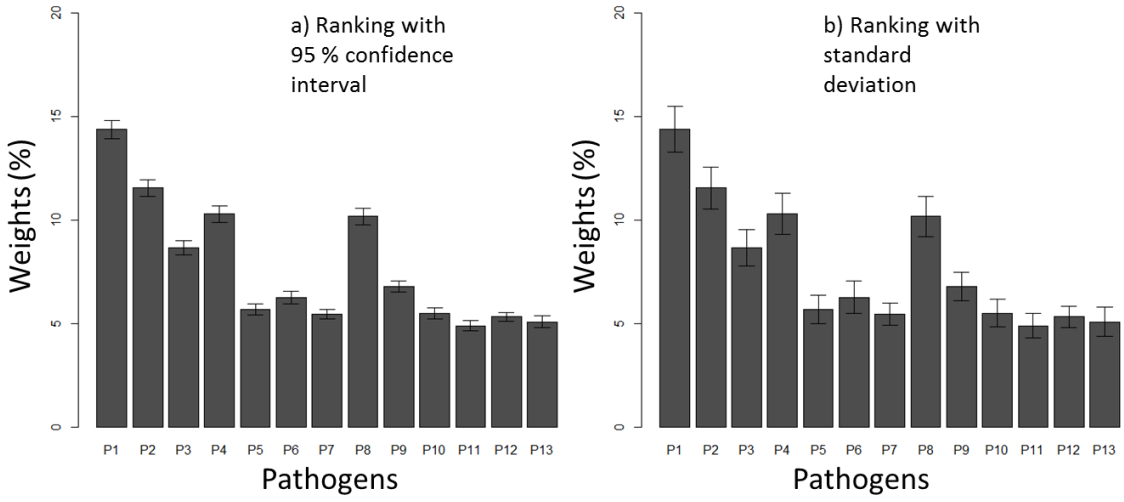

FIGURE 3: Overall scores for diseases analysed using MCDA during the 2017 annual prioritization review by using the arithmetic average

Participants were also provided with the arithmetic mean of the results (Figure 3). These results are indicative as the MCDA scores are relative, not absolute. Averaging these scores can also lead to a bias. In addition, these scores do not fully reflect covariance in the error propagation calculation, which can lead to an underestimation of the final error. Despite these shortcomings, this process can provide important insights into the discordance between the experts. Figure 3 shows both the 95% confidence interval and standard deviation of the MCDA scores – the former are lower, and the later higher. However, given the relatively small sample size and the likelihood of a non-normal distribution, considering the standard deviation of the results may better reflect discordance amongst expert opinions.

The Prioritization Committee noted that given overlapping results, as well as the methodological challenges identified during the review of results for different criteria, that it was not possible to use the output of the MCDA directly to rank the diseases considered. This finding was fully consistent with the anticipated outcome and in line with the prioritization methodology.

Further discussion of the overall rankings allowed the Prioritization Committee to divide the diseases into two categories: Subset A, with higher scores in both the geometric and arithmetic means - which were fed directly into the revised priority list (Ebola Virus Disease, Marburg, Middle East Respiratory Syndrome Coronavirus, Severe Acute Respiratory Syndrome, and zika); and Subset B that would require further discussion (Crimean-Congo Haemorrhagic Fever, Hantaviral diseases, Lassa Fever, Nipah, plague, Rift Valley Fever, Severe Fever with Thrombocytopenia Syndrome, and South American Haemorrhagic Fevers).

To assist this differentiation process, at the request of the Prioritization Committee, WHO reissued the results of the MCDA, focusing exclusively on subset B diseases.

Compiling the 2017 priority list

The Prioritization Committee reviewed each of the diseases in subset B once again, allowing participants to ask additional questions, provide more information or clarify why any of the diseases should, or should not, be included in a priority list.

These discussions led to two diseases being removed from consideration:

- After much debate, a decision was taken to set aside plague. Whilst there was broad recognition that the priority list could include diseases caused by pathogens other than viruses, many participants argued that despite is proven epidemic threat, and potential severity, that there were multiple countermeasures available and more in the later stages of development; and

- Discussion of Hantaviral diseases, determined that whilst it is a disease which could pose a public health emergency, that members of the Prioritization Committee did not feel it posed the same degree of risk as other diseases under consideration.

There was, therefore, an agreement to address this disease through an additional understanding (see below).

It was also decided that in 2017 a single list of priority diseases should be produced. The Prioritization Committee felt that using multiple tiered lists, as had been produced in 2015, complicated messaging around the importance of strengthening research and development for prioritized diseases.

There was also agreement that it was important to reflect new and emerging diseases that may result in a public health emergency prior to the next review. As a result, there was agreement to note this close to, but separately from the list of prioritized diseases. Participants also wanted to highlight the value of basic and cross cutting research and development that enable cross-pathogen or platform based approaches.

The Prioritization Committee then turned its attention to considering how diseases would be captured in the list: would each individual disease be a separate entry? Or would it make sense to group certain diseases (as had been done in some cases in 2015)? A number of iterations were discussed.

There was broad agreement that grouping diseases would be useful but only where diseases were both: caused by closely related pathogens against which it might be possible to develop a common countermeasure; and presented in similar manners, where the diseases themselves are similar. As a result:

- Ebola Virus Disease was grouped with Marburg.
- Middle East Respiratory Syndrome Coronavirus and Severe Acute Respiratory Syndrome were separated on the basis of an increased understanding of transmission routes, animal reservoirs and disease characterization since 2015.
- Furthermore, Severe Acute Respiratory Syndrome was changed into an example of an emerging highly pathogenic coronaviral diseases, partly in recognition that there other coronaviruses that might emerge but also that this disease is effectively eradicated.
- Lassa fever and South American Haemorrhagic Fevers were grouped together under a more generic heading of Arenaviral hemorrhagic fevers. The specific example of Lassa Fever was subsequently reintroduced to provide a concrete example and in deference to its established epidemic potential.
- In recognition of relatives of the Nipah Virus that could pose an epidemic threat and for which we are no more prepared, related henipaviral diseases were also included on the list.

The 2017 list of diseases to be prioritized under the R&D Blueprint

The 2017 annual review determined there is an urgent need for research and development for:[6]

- Arenaviral hemorrhagic fevers (including Lassa Fever)
- Crimean Congo Haemorrhagic Fever (CCHF)
- Filoviral diseases (including Ebola and Marburg)
- Middle East Respiratory Syndrome Coronavirus (MERS-CoV)
- Other highly pathogenic coronaviral diseases (such as Severe Acute Respiratory Syndrome, (SARS))
- Nipah and related henipaviral diseases
- Rift Valley Fever (RVF)
- Severe Fever with Thrombocytopenia Syndrome (SFTS)
- Zika

In addition to any disease identified by the Blueprint's decision instrument for new diseases.

Additional understandings

The meeting noted that several diseases discussed during the review, such as dengue, yellow fever, HIV/AIDs, tuberculosis, malaria, avian influenza causing severe human disease, antimicrobial resistance, and smallpox/monkey pox, continued to pose major public health problems and further research and development is needed. In this regard, participants recognized the existence of major disease control initiatives, extensive R&D pipelines, existing funding streams, or established regulatory pathways for improved interventions.

A number of additional pathogens were discussed and considered for inclusion in a priority list, such as: emerging flaviviruses with potential for haemorrhagic fever (such as Kyasanur Forest Disease) or those with potential for encephalitis (such as Usutu); emerging Bunyaviruses (such as Oropouche); emerging Alphaviruses (such as Chikungunya and Mayaro virus); rickettsia; plague; hantaviral diseases; and Chandipura virus disease. A potential threat need not be a virus and could be any type of pathogen. In many cases more research is needed before an assessment for prioritized countermeasure development for these diseases could be undertaken. Necessary research might include basic/fundamental and characterization research as well as epidemiological or entomological studies, or further elucidation of transmission routes. In some cases existing tools may need to be improved.

Certain types of cross-cutting research and development should be encouraged for the management of prioritized diseases and other potential public health threats, including a novel or deliberate threat. Participants highlighted the importance of validated diagnostic tests (including differential diagnosis), tools for identifying the cause of syndromes, as well as diverse countermeasures that work across different pathogens or diseases, including vector control.

[6] The order of diseases on this list does not denote any ranking of priority.

The value of a One Health approach was also stressed – both in terms of parallel prioritization processes to support research and development against animal diseases and joint efforts for pathogens in common. The possible utility of animal vaccines for preventing public health emergencies was also noted.

Although anti-microbial resistance is addressed through specific international initiatives the possibility was not excluded that in the future, a resistant pathogen might emerge and appropriately be prioritized.

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Annex A: Prioritization criteria

The 2015 WHO Consultation for Prioritization of Pathogens identified nine prioritization criteria. These were revised and reordered during the 2016 methodology review. The current prioritization criteria are:

1. Human transmission;

2. Medical countermeasures;

3. Severity or case fatality rate;

4.(a)(joint) The human/animal interface;

4.(b)(joint) Other factors (including the pathogens geographic range, shared epidemiological and/or genotypic characteristics with pathogens that pose an epidemic threat, the absence of robust protective immunity, a high risk of occupational exposure, or connections with biological weapons programmes);

6. The public health context of the affected area;

7. Potential societal impacts; and

8. Evolutionary potential.

Annex B: The 2017 Prioritization Committee

Dr. Celia ALPUCHE
Prof. Lucille BLUMBERG
Dr. David BRETT-MAJOR
Dr. Miles CAROLL
Dr. Inger DAMON
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