ONLINE REPORT

World Health Organization Methodology to Prioritize Emerging Infectious Diseases in Need of Research and Development

Massinissa Si Mehand, Piers Millett, Farah Al-Shorbaji, Cathy Roth, Marie Paule Kieny, Bernadette Murgue

The World Health Organization R&D Blueprint aims to accelerate the availability of medical technologies during epidemics by focusing on a list of prioritized emerging diseases for which medical countermeasures are insufficient or nonexistent. The prioritization process has 3 components: a Delphi process to narrow down a list of potential priority diseases, a multicriteria decision analysis to rank the short list of diseases, and a final Delphi round to arrive at a final list of 10 diseases. A group of international experts applied this process in January 2017, resulting in a list of 10 priority diseases. The robustness of the list was tested by performing a sensitivity analysis. The new process corrected major shortcomings in the pre–R&D Blueprint approach to disease prioritization and increased confidence in the results.

Recent outbreaks of Ebola virus disease, Middle East respiratory syndrome, and Zika virus disease illustrate that emerging infectious diseases will continue to cause major public health emergencies. Further work is needed to strengthen defenses with medical countermeasures (MCMs) and other protective interventions. Building on recent experiences and at the request of the World Health Assembly in May 2015 (*1*), the World Health Organization (WHO) launched the R&D Blueprint for action to prevent epidemics. This global strategy and preparedness plan is designed to ensure that targeted research and development (R&D) will strengthen emergency response by accelerating availability of biomedical technologies to populations and patients during epidemics (*2*). The R&D Blueprint focuses on severe emerging diseases that pose a major risk for causing a public health emergency and for which MCMs or substantial R&D initiatives and pipelines are insufficient or nonexistent (*3*).

Experts compiled an initial list of relevant diseases at an informal consultation in December 2015 (*4*). A more robust methodology was needed, one that could be standardized and repeated regularly for reviewing and, if necessary, updating the list in the light of successful development of new interventions or the emergence of new disease threats.

WHO settled on a 3-pronged approach: 1) a methodology development and review process; 2) an annual review of a list of prioritized diseases; and 3) a decision instrument to guide decision-making on a novel disease (online Technical Appendix 1, https://wwwnc.cdc.gov/EID/article/24/9/17-1427-Techapp1.pdf). All 3 processes use a common set of weighted criteria and subcriteria, such as the human-to-human transmissibility of the disease or its potential societal impact (online Technical Appendix 2, https://wwwnc.cdc.gov/EID/article/24/9/17-1427-Techapp2.pdf). This process is inherently expert-driven because the R&D Blueprint addresses pathogens that are yet to be fully characterized and for which an understanding of how to diagnose, prevent, and treat the resulting diseases is incomplete. Further, these pathogens might behave differently on different occasions because of variation in the biologic, cultural, or environmental context. Decisions have to be made on the basis of partial information supplemented by expert opinion. Any methodology will be prone to biases (*3*).

This article assesses the application of this methodology for the 2017 annual review of the WHO R&D Blueprint priority list of diseases. We consider its effectiveness and assess the degree of confidence that can be placed in the list produced.

Developing a Prioritization Process

WHO developed a comprehensive methodology (*3*) to ensure the list of the R&D Blueprint prioritized diseases best reflects targeted global health needs and focuses on the most pressing threats. The approach taken drew heavily on established best practice (*5–7*) and is based on practical national and regional experiences in compiling similar lists (*8–14*). This approach also specifically addressed criticism of pre–R&D Blueprint attempts by WHO to prioritize diseases by developing tools for assessing confidence in the results generated and addressing potential biases (*5*).

Disease prioritization is not a straightforward task and requires a defined set of criteria on which to base prioritization (*7*). These criteria can be qualitative, intangible, or

Author affiliations: World Health Organization, Geneva, Switzerland (M. Si Mehand, P. Millett, F. Al-Shorbaji, M.P. Kieny, B. Murgue); Department for International Development, London, UK (C. Roth)

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subjective, changing for different stakeholders (*15*). The criteria can also be interdependent, complicating separate assessment (*16*). For instance, the case-fatality rate of a disease has a social effect, which in turn has an economic effect. Given the complexity and the challenges of disease prioritization, ensuring the process is transparent and reproducible is important (*5*,*7*,*17*).

Recent disease prioritization methods were summarized in a 2015 review by the European Centre for Disease Prevention and Control (ECDC) (*5*), which extrapolated a series of best practices. Several subsequent studies were also identified (online Technical Appendix 3, https://wwwnc.cdc.gov/EID/article/24/9/17-1427-Techapp3.pdf). Past disease prioritization studies have been conducted for different purposes, such as communicable diseases surveillance (*18*,*19*), biosecurity (*20*), and resource allocation (*21*,*22*), and have covered disease in humans, livestock, or wildlife. Many studies were conducted primarily at national (*8–10*,*19*,*21–36*) and regional (*11–14*,*16*,*20*,*37–43*) levels (e.g., Europe and North America) but rarely at a global level (*44*,*45*). None of the disease prioritization exercises matched the aims of the R&D Blueprint, its public health focus, and its global reach; thus, WHO needed to develop its own methodology.

Several different disease prioritization methods exist (*5*), including Delphi processes (*38*,*40*), multicriteria decision analysis (MCDA) (*14*,*26*,*28*,*36*,*46*), H-index (*42*,*43*), questionnaires (*11*,*13*,*22*), and qualitative algorithms (*47*,*48*). Each method has its own strengths, weaknesses, and context-dependent utility, but 3 methods most closely matched the requirements of the R&D Blueprint (*5*): 1) a semiquantitative Delphi process to narrow the list of diseases under consideration; 2) MCDA to rank the remaining diseases (online Technical Appendix 4, https://wwwnc.cdc.gov/EID/article/24/9/17-1427-Techapp4.pdf); and 3) questionnaires in the form of online survey tools to standardize information gathering from participating experts.

Methods and Tools

The resulting methodology was developed over a year-long process, involving informal consultations, internal and external expertise, and guidance from the R&D Blueprint Scientific Advisory Group (*4*). Methods and tools were subsequently reviewed and validated by an external group of experts (*49*) and used in the review of the list of priority diseases in January 2017 (*50*).

Prioritization Committee

Selecting the right group of experts is critical for ensuring an outcome as accurate as possible (*39*,*51*). Gathering a diverse field of expertise with a broad geographic distribution, including an in-depth knowledge of the diseases and pathogens being considered, is important. The multidisciplinary committee convened for the 2017 annual review included 24 experts drawn from Africa, Asia, Europe, North America, and South America (online Technical Appendix 2). The persons present at the meeting covered all 7 areas of expertise detailed in the methodology (online Technical Appendix 1) (*3*). To ensure the process was as transparent as possible, representatives from several additional organizations were present, including the World Organisation for Animal Health (OIE), which helped ensure a One Health approach was followed, as well as the Coalition for Epidemic and Preparedness Innovations and the Global Research Collaboration for Infectious Disease Preparedness, which facilitated cooperation, coordination, and the sharing of experiences outside of WHO. To minimize bias related to expert opinions, the prioritization committee is changed yearly (*7*).

Triage of the Diseases

To narrow the list of potential priority diseases, a 2-step semiquantitative Delphi technique was adapted from established environmental horizon scanning methods (*52*). Each proposed disease was scored from 0 to 1,000, where 1,000 represented a perfect fit for the R&D Blueprint and 0 represented diseases with no epidemic potential, diseases for which effective and commercially available MCMs exist, or both.

Disease Scoring

To rank the short list of diseases, an online survey tool was designed by using the slide-bar function of R Shiny (https://shiny.rstudio.com) (Figure 1). Because absolute scoring scales require broadly accepted standards (*53*) and these standards are not evident in the context of emerging infectious disease, for which many characteristic remain unclear or unknown, the WHO tool makes use of a relative scale that compares values between diseases rather than against absolute values (i.e., the impact of scoring diseases A and B at 3 and 5 is the same as scoring the same diseases at 7 and 9).

The data collected were processed by an in-house program implemented in R Studio. A custom analytic hierarchy process (AHP) implementation was used to calculate disease scores for each subcriterion (online Technical Appendix 5, https://wwwnc.cdc.gov/EID/article/24/9/17-1427-Techapp5.pdf). This process included normalization and weighting procedures. Comparison matrices were built from data provided by each expert and then averaged by using the geometric average (*54*). Disease scores for each subcriterion were computed, and an overall multicriteria score for each disease was ultimately computed by using the disease scores and criteria weights. Following best practices, the criteria definition and weighting steps were separated from the disease scoring (*5*,*7*,*14*,*36*,*38*).

The criteria were defined in 2015 by a group of experts (*4*) and were then reviewed, validated, and weighted by another group (*49*).

Sensitivity Analysis and Confidence Estimation

Past prioritization processes have used sensitivity analysis, commonly with lower and upper 95% CIs (*31*). Other processes included modifying the weight of criteria used (*9*,*55*) and removing them one at a time (*55*). We describe a series of sensitivity analyses, including setting all the criteria at the same weight, removing 1 criterion at a time, increasing the weight of each criterion by 20%, and doubling the weight of a criterion. This approach to sensitivity analysis enables assessment of the impact of different scenarios on the final disease ranking and provides important insights into the robustness of the ranking and the impact of potential biases (*9*,*55*).

As a confidence indicator, differences among expert opinions were considered. The arithmetic average scores and the corresponding SDs for each disease were calculated and tracked through the process by using an error propagation technique (online Technical Appendix 5).

Results

Compiling and Reviewing a Long List of Diseases

The long list of diseases was drawn from diseases identified as requiring urgent R&D support in the 2015 priority list, diseases recommended but not included by the 2015 consultation, and diseases suggested by participants in the 2017 review. As a result, 8 diseases on the original 2015 list were supplemented by another 10 diseases. In 2017, no additional disease was selected by the decision instrument.

Each of these 18 diseases was then considered in turn. Two experts introduced each of the diseases on the 2015 list and those selected at the 2015 consultation. A single expert introduced each of the diseases proposed by the 2017 committee. Consensus was rapidly reached that diseases on the 2015 list should be reassessed by using the MCDA tool. A triage of the remaining 10 diseases was then carried out. The results were discussed in detail, and a further 5 diseases were added to the short list (Figure 2). Additional considerations of those diseases not incorporated into the list were also discussed (online Technical Appendix 6, https://wwwnc.cdc.gov/EID/article/24/9/17-1427-Techapp6.pdf), such as the importance of continuing relevant R&D (*50*).

Ranking the Short List of Diseases

The MCDA tool was used to generate 1) scores for each disease against each subcriterion; 2) aggregated scores for each criterion for each disease; and 3) multicriteria scores for each disease. The aggregated scores for each criterion for each disease were considered in more depth (*50*). The multicriteria scores (Figure 3, panel A) were then used to rank diseases on the short list. Six diseases (P1, P2, P3, P4, P8, and P9) were highly ranked; a group of 3 diseases (P5, P6, and P7) were ranked next, and the final 4 diseases (P10, P11, P12, and P13) had the lowest ranking.

Figure 1. Example screenshot of tool developed in R Shiny (https://shiny.rstudio.com) using the slide bar function to compare candidate diseases for each criteria and subcriteria considered in the development of the World Health Organization R&D Blueprint to prioritize emerging infectious diseases in need of research and development. Experts were requested to compare candidate diseases to each other for each criteria, placing them in ranked order according to their knowledge. The World Health Organization Secretariat explained the meaning of the scale (0–10) to the experts before the survey. Asterisks indicate that an answer is required for each disease.

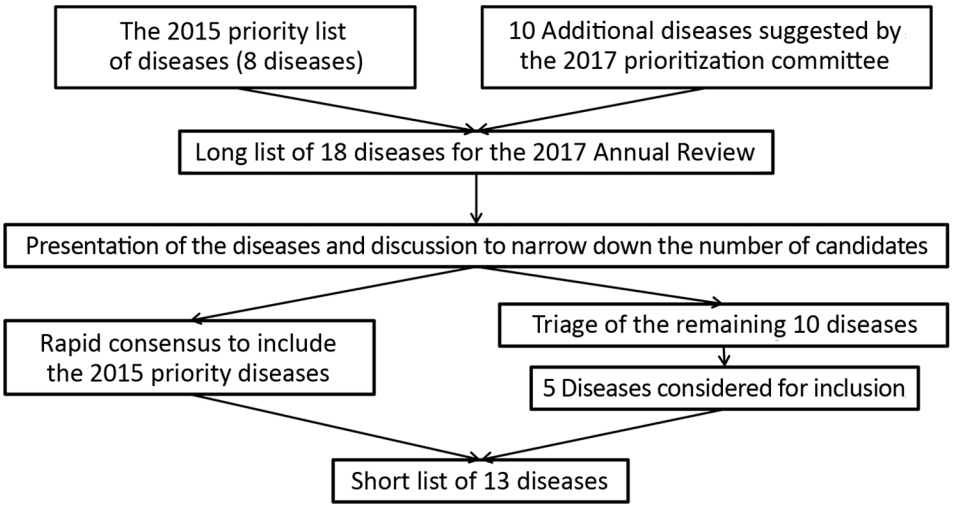

Figure 2. Process for compiling the short list of diseases for inclusion in the World Health Organization R&D Blueprint to prioritize emerging infectious diseases in need of research and development.

A consensus was quickly reached that the group of 6 top-ranking diseases (P1, P2, P3, P4, P8, and P9) should be on the 2017 priority list. An uncertainty analysis revealed overlapping results for the remaining pathogens, particularly noticeable for the lower 2 tiers (Figure 3, panel B). As a result, the multicriteria scores alone were insufficient to differentiate between the remaining 8 diseases. An additional round of the Delphi technique enabled the committee to compile a final list: arenaviral hemorrhagic fevers (including Lassa fever); Crimean-Congo hemorrhagic fever; filoviral diseases (including Ebola and Marburg virus infections); Middle East respiratory syndrome coronavirus infection; Nipah virus infection and related henipaviral diseases; other highly diseases coronaviral diseases (such as severe acute respiratory syndrome); Rift Valley fever; severe fever with thrombocytopenia syndrome; and Zika virus infection. A more detailed discussion as to how the list was compiled can be found in the WHO report on the 2017 prioritization exercise (*50*).

Assessing Confidence in the Results

The multiscenario sensitivity analysis detailed the influence of each criterion on the final ranking. When all the criteria were set at the same weight as those used in a similar exercise conducted in Kenya (*9*), the multicriteria scores were affected, but the overall ranking remained largely the same, with 2 diseases (P5 and P7) switching positions.

When highly weighted criteria, such as human-to-human transmissibility, were suppressed, major changes in the multicriteria scores were observed, but a much smaller impact was evident on the overall disease ranking. A notable exception was when the MCMs criterion was suppressed, after which no notable impact on the multicriteria scores or the final ranking was observed.

When the weight of each criterion was increased by 20%, no notable changes in ranking were observed. Doubling the weights of highly weighted criteria resulted in changes in the overall multi criteria scores but had a minimal impact on the overall ranking of diseases. Once again, doubling the weight of the MCMs criterion had minimal impact on the multicriteria scores and the overall disease ranking.

To further validate the 2017 priority list, the same data were analyzed by using the SMART Vaccines prioritization tool (*56*). Unlike the methodology discussed in this article, the SMART Vaccines tool makes use of absolute rather than relative values. This feature precludes a direct comparison of specific results but helps explore the reproducibility of the list as a whole. The results from the SMART Vaccines prioritization tool also grouped the same diseases together in the same 3 tiers (Figure 3, panel C).

Discussion

The 2017 annual review resulted in a list of diseases that pose a risk for a public health emergency and for which an urgent need for R&D exists (*50*). The earlier ECDC review highlighted numerous general weaknesses among published prioritization processes (*5*). It identified shortcomings in WHO approaches toward disease prioritization before the R&D Blueprint, including insufficient detail in reporting; a lack of transparency, in particular as to how the prioritization criteria were developed; a need for greater consideration on sources of bias; a better discussion of implementation challenges; methodologic anomalies, such as the use of only a single round of the Delphi technique; and a lack of external review of the methodology and subsequent publications.

The methodology developed by WHO for the R&D Blueprint explicitly addresses these shortcomings (e.g., mitigation of numerous sources of bias). Past methodologic anomalies have also been addressed (e.g., a 2-step semiquantitative Delphi technique is now being used). The reporting process has been strengthened; the methodology

has been published in full (*3*), as has a detailed report of its use during the 2017 annual review (*50*).

The new approach is also much more transparent, with all publications being more detailed and openly available. These publications explain the reasoning behind why certain diseases ultimately were (or were not) included on the list. The process by which the prioritization criteria were developed (online Technical Appendix 2) is also well documented in meeting reports (*4*,*49*).

Shortcomings in the review process have been addressed, in part, by separate committees to develop and implement the methodology because these committees effectively review each other's work. The methodology itself was validated through a dedicated expert consultation,

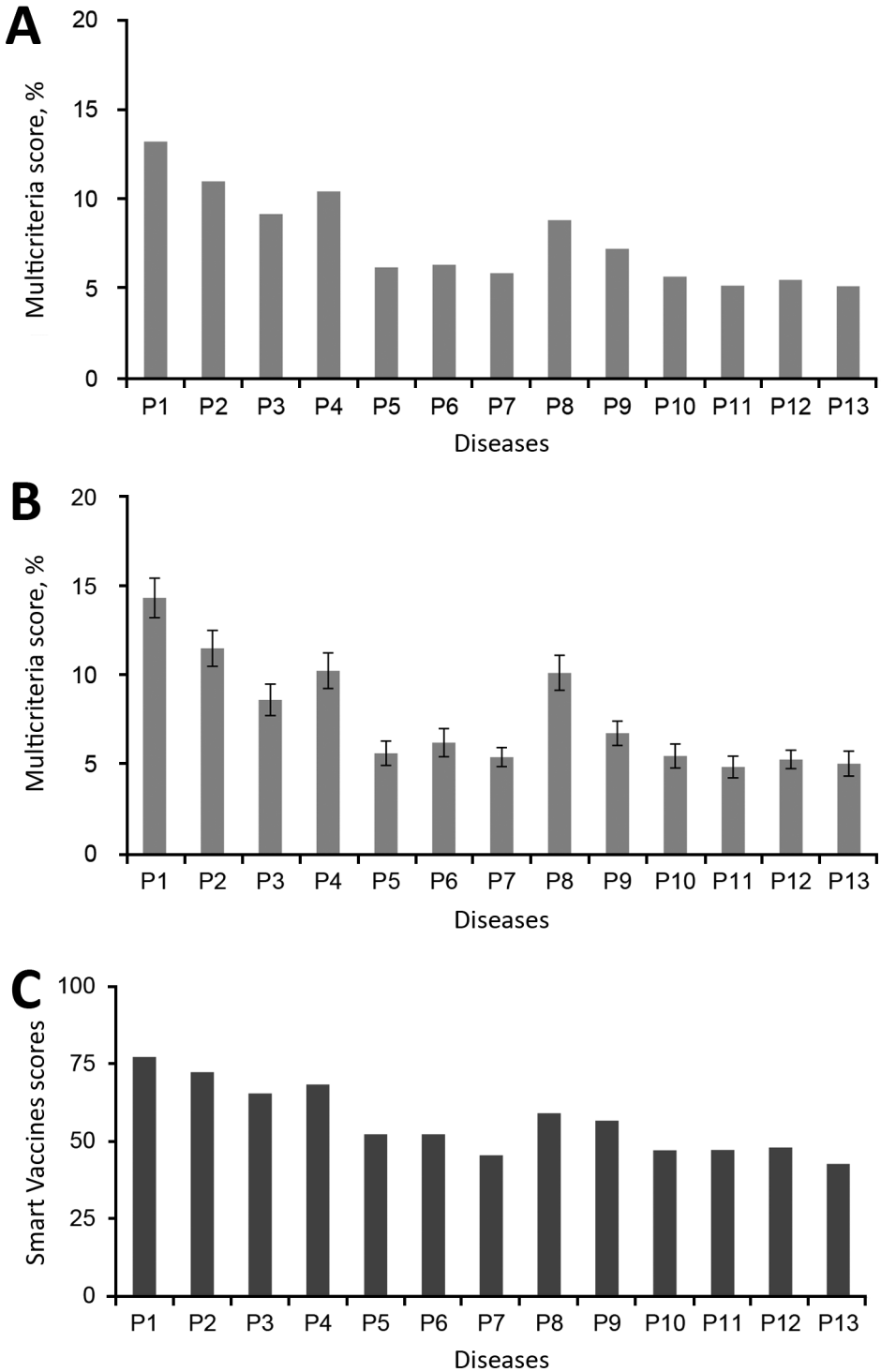

Figure 3. Multicriteria scores of diseases considered in the 2017 prioritization exercise for the development of the World Health Organization R&D Blueprint to prioritize emerging infectious diseases in need of research and development. A) Disease final ranking using the geometric average of the comparison matrices. B) Disease final ranking using the arithmetic average of the raw data. Error bars correspond to SD, indicating disagreement among experts. C) Disease final ranking using the SMART Vaccines prioritization tool (*56*). P1, Ebola virus infection; P2, Marburg virus infection; P3, Middle East Respiratory Syndrome coronavirus infection; P4, severe acute respiratory syndrome; P5, Lassa virus infection; P6, Nipah virus infection; P7, Rift Valley fever; P8, Zika virus infection; P9, Crimean-Congo hemorrhagic fever; P10, severe fever with thrombocytopenia syndrome; P11, South American hemorrhagic fever; P12, plague; P13, hantavirus infection.

improving the review procedures further. Finally, publication of this article further expands opportunities to review the approach and its implementation.

Several challenges to implementation exist. Other prioritization studies have invested extensive resources into identifying potentially relevant diseases. For example, Cox et al. conducted a bibliometric analysis of >3,000 infectious organisms in North America to identify the 651 pathogens relevant to their study (*43*). In Belgium, Cardoen et al. complimented a literature review with expert consultations (*36*). In the Netherlands, Havelaar et al. went a step further, supplementing their literature review with consultations with international, regional, and national experts to identify the relevant subset of pathogens (*26*).

At present, the community proposing additional diseases to be considered in an annual review of the R&D Blueprint is limited. To address this issue in future prioritization exercises and to better reflect regional factors in the long list of diseases, the WHO regional offices will be more actively involved in the inclusion of a wider range of experts.

The next methodology review should look at the reproducibility of these tools. In the interim, further improvement of the MCDA model might include reviewing the pertinence of the MCMs criterion given that it had little effect on the multicriteria scores of the diseases, reweighting the criteria, drawing on a wider community of relevant expertise and a larger sample size, and reviewing and simplifying the specific wording of the subcriteria.

The R&D Blueprint methodology was developed to mitigate numerous sources of bias, including flaws in study design, selection bias, interviewer bias, chronology bias, and recall bias (*3*). These efforts were largely successful; however, further work might be necessary to mitigate selection and recall bias.

The selection of experts to participate in the MCDA is important for mitigating selection biases. WHO's policies on geographic and gender representation go some way to address selection bias. Considerable resources were also expended to create a committee with the diverse range of expertise required, with experts from microbiology and virology, clinical management of severe infections, epidemiology and outbreak investigation and response, public health policy, animal health, mathematical modeling of disease, environmental and social science, nongovernmental organizations, and the security sector. This diversity is consistent with and exceeds the range of participants found in other studies, allowing for some variation based on their specific purposes (*8*,*9*,*11*,*13*,*26*,*30*). Ensuring that future reviews also have a sufficient range of expertise will be important.

The number of experts participating in the annual review meeting also deserves careful consideration. Larger groups increase the likelihood of reproducibility and decrease the risk for certain biases (*57*). Smaller groups can simplify the consensus-building process (*15*,*58*). Group size can also impact group dynamics. Too large a group can make face-to-face consultations impractical, complicating efforts to review and discuss the results, correct eventual inconsistencies, reach consensus, and avoid misunderstanding (*8*). Although exploring ways that a greater number of experts might be involved with developing an initial long list of diseases to be considered might be useful, a more limited group will probably need to continue to analyze the short list in the years to come.

Additional efforts are also needed to address recall bias. Discussions during the 2017 review highlighted that the diseases that enjoyed the greatest levels of support for inclusion in the revised priority list had all caused recent major outbreaks. An annual "landscape review" (in which each disease on the long list of proposed diseases is independently reviewed, considering factors such as the current knowledge regarding prioritization criteria, risk for emergence, and availability of countermeasures, regardless of recent events) should contribute to avoiding a disproportionate emphasis based on recent events. In the short term, participants in the next annual review should be briefed on, and discuss the impact of, recall bias before undertaking the MCDA scoring exercise. In the longer term, options for weighting against recent public health emergencies might be explored, perhaps through the development of a calibration curve, which has been used to mitigate recall bias in other types of processes (*59*).

This methodology is expert-driven, and despite all efforts to minimize biases related to their efforts, biases still occur. To address this problem, WHO should 1) change the composition of the prioritization committees yearly and expand the geographic range of the experts involved and 2) review the methodology separately with different experts.

The similarity between the WHO list of prioritized diseases and those found in other studies suggests a degree of consistency with previous findings (*8*–*11*,*13*,*14*,*35*,*41*). The results of the sensitivity analysis demonstrate that the R&D Blueprint ranking is robust, corresponding with earlier observations that the analytic hierarchy process is not sensitive to minor changes in criteria weights (*55*). Even when major changes on the weight of criteria were applied, the final ranking remained largely stable. Throughout all the scenarios used in this sensitivity analysis, the same 3 groupings of diseases remained consistent. In some scenarios, the ranking of diseases within the group changed, but this observation is consistent with the findings of other prioritization exercises (*9*). Being able to produce a similar 3-tiered group ranking using another model, the SMART Vaccines prioritization tool, also suggests that the approach employed for the R&D Blueprint is producing valid results.

However, the impact of the MCMs criterion needs further consideration. The sensitivity analysis showed that

the contribution of this criterion to the final ranking is limited despite its high weight. This observation is probably explained by the objectives of the R&D Blueprint itself, which focuses on diseases for which few or no MCMs exist, meaning that all the diseases considered score equally in this regard. Ensuring that sufficient attention is paid to this issue when selecting diseases for inclusion on the longlist will be useful as a screening process. Ensuring that distinct R&D gaps are a prerequisite for inclusion could result in this criterion being dropped from the MCDA.

In conclusion, the R&D Blueprint fills a considerable gap in public health preparedness by supporting R&D on highly infectious diseases for which few or no countermeasures exist. To translate this objective into effective action, WHO had to determine the diseases that most urgently required the commencement of work. For each of these priority diseases, WHO is developing roadmaps; target product profiles for vaccines, therapeutics, and diagnostics (*60*); and generic protocols for vaccine and therapeutic clinical trials. The R&D Blueprint is also enabling cross-cutting support activities, such as data and sample sharing norms, regulatory preparedness aspects, and overall research coordination (*61*). Aware of the shortcomings of past efforts to develop similar lists, WHO explored lessons learned and best practices for developing a new approach. The challenge was in balancing competing needs for a standardized, robust methodology that can be repeated on a regular basis, with a reliance on expert opinion. Because this methodology and its supporting tools will be subjected to a full review within 2 years, WHO hopes that the lessons learned through the R&D Blueprint's repeated use, including those we have identified, will be used to improve it further.

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About the Author

Dr. Si Mehand is a technical officer at the World Health Organization. His research interests are applied mathematics, outbreak preparedness and response, priority setting, decision aid, and risk analysis.

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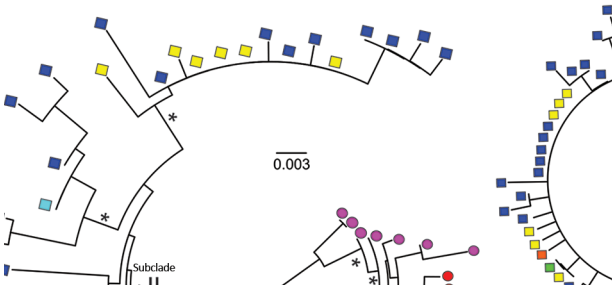
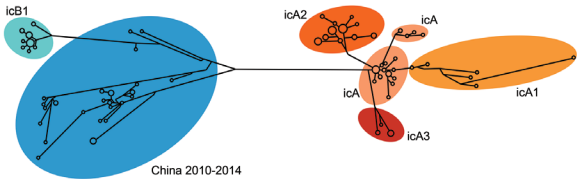
Address for correspondence: Massinissa Si Mehand, World Health Organization, Avenue Appia 20, 1211 GE 27, Geneva, Switzerland; email: simehandm@who.int

April 2017: **Emerging Viruses**

- Biologic Evidence Required for Zika Disease Enhancements by Dengue Antibodies
- Neurologic Complications of Influenza B Virus Infection in Adults, Romania
- Implementation and Initial Analysis of a Laboratory-Based Weekly Biosurveillance System, Provence-Alpes-Côte d'Azur, France



- Transmission of Hepatitis A Virus through Combined Liver–Small Intestine–Pancreas Transplantation
- Influence of Referral Pathway on Ebola Virus Disease Case-Fatality Rate and Effect of Survival Selection Bias
- *Plasmodium malariae* Prevalence and *csp* Gene Diversity, Kenya, 2014 and 2015
- Presence and Persistence of Zika Virus RNA in Semen, United Kingdom, 2016
- Three Divergent Subpopulations of the Malaria Parasite *Plasmodium knowlesi*
- Variation in *Aedes aegypti* Mosquito Competence for Zika Virus Transmission
- Outbreaks among Wild Birds and Domestic Poultry Caused by Reassorted Influenza A(H5N8) Clade 2.3.4.4 Viruses, Germany, 2016
- Highly Pathogenic Avian Influenza A(H5N8) Virus in Wild Migratory Birds, Qinghai Lake, China
- Design Strategies for Efficient Arbovirus Surveillance
- Detection and Molecular Characterization of Zoonotic Poxviruses Circulating in the Amazon Region of Colombia, 2014
- Reassortment of Influenza A Viruses in Wild Birds in Alaska before H5 Clade 2.3.4.4 Outbreaks
- Incidence and Characteristics of Scarlet Fever, South Korea, 2008–2015
- Markers of Disease Severity in Patients with Spanish Influenza in the Japanese Armed Forces, 1919–1920
- Molecular Identification of *Spirometra erinaceieuropaei* in Cases of Human Sparganosis, Hong Kong
- Zika Virus Seroprevalence, French Polynesia, 2014–2015
- Persistent Arthralgia Associated with Chikungunya Virus Outbreak, US Virgin Islands, December 2014–February 2016



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World Health Organization Methodology to Prioritize Emerging Infectious Diseases in Need of Research and Development

Technical Appendix 1

The three components of the Blueprint prioritization methodology

1. The annual review:

• Convening a suitable expert group (Prioritization Committee, Table) covering: 1) microbiology of severe pathogens, including virology, bacteriology and mycology, 2) clinical management of severe infections, 3) Epidemiology, in particular during health emergencies, 4) Public health policy, including emergency response, 5) Animal health, including veterinarians and experts in zoonoses from both livestock and wildlife, 6) experts from the defense or security sectors familiar with biological weapons and 7) other experts, including anthropologists, bioethicists, and other relevant social sciences.

• Identifying a long list of diseases to be fed into the annual review process.

• Triaging the long list into a shorter list for more detailed analysis.

• Conducting that analysis through the Analytic Hierarchy Process (AHP)/Multi-criteria Decision Analysis (MCDA) method and Delphi process.

• Communicating the outcome of the review.

Technical Appendix 1 Table. Prioritization Committee

Members	Sex	WHO region*
Prioritization Committee		
Dr. Celia ALPUCHE	Female	PAHO
Prof. Lucille BLUMBERG	Female	AFRO
Dr. David BRETT-MAJOR	Male	PAHO
Dr. Miles CAROLL	Male	EURO
Dr. Inger DAMON	Female	EURO
Dr. Peter DASZAK	Male	PAHO
Dr. Xavier DE LAMBALLERIE	Male	PAHO
Dr. Mourya DEVENDRA	Male	SAERO
Prof. Christian DROSTEN	Male	EURO
Dr. Delia ENRIA	Female	PAHO
Prof. Sahr GEVAO	Male	AFRO
Prof. Stephan GUENTHER	Male	EURO
Prof. Peter HORBY	Male	EURO
Prof. Roger HEWSON	Male	EURO
Dr. Nadia KHELEF	Female	EURO
Prof. Gary KOBINGER	Male	PAHO
Dr. Linda LAMBERT	Female	PAHO
Dr. Dieudonne NKOGHE	Male	AFRO
Dr. George WARIMWE	Male	AFRO
Dr. Mark WOOLHOUSE	Male	EURO
Dr. Youngmee Jee	Female	WIPRO
Dr. Stefano MESSORI	Male	EURO
Dr. Cathy ROTH	Female	EURO
Dr. Heinz FELDMANN	Male	PAHO
Observers		
Dr. Hinta MEIJERINK	Female	Coalition of Epidemic Preparedness Innovation, EURO
Ms. Stacey KNOBLER	Female	U.S. National Institutes of Health, PAHO
Dr. Ben MCCORMICK	Male	U.S. National Institutes of Health, PAHO

*EURO: European region, PAHO: American region, SAERO: south-east Asian region, AFRO: African region, WIPRO: West Pacific region. Detailed country members: http://www.who.int/about/regions/en.

2. The methodology review

In accordance with best practice, separate processes were used to develop the methodology and run the annual review (*1*–*5*). According to Brookes et al. 2015, separating these processes improves transparency "*by clearly separating decision-makers subjective opinions regarding the value of criteria from measurements for individual pathogens, as well as reducing opportunity for cognitive bias that can arise when directly valuing pathogens*" (*5*). In addition to the annual exercise to update the list, the methodology itself will be reviewed every 2 years. This methodology review involves: convening a group of suitable experts; examining and revising the prioritization criteria and sub-criteria; and updating the weightings applied to the criteria.

3. Decision tree

The broader prioritization process also includes a decision tree for consideration of an unknown disease or a known disease presenting with unusual characteristics. The decision instrument is intended to guide users through: considering available information, determining

whether an emergency prioritization review is warranted, and whether this disease should be considered for the next annual review.

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Technical Appendix 2

Prioritization Criteria

All three components of the prioritization process make use of a common set of criteria and sub-criteria. The criteria represent top level factors which might impact the relevance of a disease to the R&D Blueprint, such as the human transmissibility of the disease, or the societal impact. The sub-criteria then explore different facets of each of these areas, for example considering different types of countermeasures or their suitability for use in different resource settings.

In advance of the 2015 consultation, WHO reviewed criteria and sub-criteria used in earlier disease prioritization exercises. The results were included in background materials for the consultation (*1*). Nine prioritization criteria and numerous sub-criteria were identified through moderated discussions. Following feedback from the R&D Blueprint's Scientific Advisory Group in May 2016, and the subsequent work of the methodology review meeting in November 2016, the original nine criteria were compressed into the current eight criteria below to insure completeness, non-redundancy, nonoverlapping and preference independence (*2*).

1. Human Transmission

Subcriteria

a) There is evidence of human to human transmission

b) There is widespread human to human transmission

c) There is more than one route of human to human transmission

d) The disease frequently involves infectivity before the onset of symptoms

e) The pathogen is able to remain infectious for a prolonged period in an infected individual when convalescent or apparently recovered

f) There is evidence of superspreading events

g) The disease is likely to be amplified in a healthcare setting

2. Medical Countermeasures

Subcriteria

a) Diagnostics which are effective and suitable for use in the field are not available

b) Diagnostics which are effective and suitable for use in a clinic or local healthcare setting are not available

c) Effective Diagnostics are available but are only suitable for use in specialized facilities

d) Effective vaccines (human or animal, as appropriate) and prophylactics do not exist

e) Effective vaccines (human or animal, as appropriate) and prophylactics which are suitable for use in resource limited settings do not exist

f) Effective drugs or therapies do not exist

g) Effective drugs or therapies which are appropriate for use in resource limited settings do not exist

h) The outbreak cannot be controlled by the application of common public health measures (such as contact tracing, Isolation of infected patients, social distancing, closure of public events, schooling, changes to cultural practices, e.g., burial rights, vector control, strict management of livestock movement)

3. Severity or Case-Fatality Rate

Subcriteria

a) The disease causes high mortality

b) The disease frequently causes high morbidity, including severe complications or sequelae

4. The Human–Animal Interface

Subcriteria

a) The involvement of animals in transmitting (including arthropods) the disease to people is well characterized

b) There are transmission routes from animals (including arthropods) to humans likely to result in high levels of human infections

c) The pathogen is capable of infecting multiple animal species

d) The animal species transmitting the disease are widely distributed

e) The animal species transmitting the disease is abundant

f) Arthropod(s) are responsible for transmitting the disease

g) Arthropod(s) responsible for transmitting the disease are widely distributed

5. Other Factors

Subcriteria:

a) The geographic range of the pathogen has changed

b) The pathogen shares relevant epidemiologic and/or genotypic characteristics with agents which have caused important epidemics

c) The natural disease does not result in robust protective immunity

d) The disease carries a high risk of occupational exposure for those involved in a response (including for culling, vets, burial details, lab workers, first responders, healthcare workers)

e) The pathogen is an agent likely to be used to cause deliberate outbreaks

6. The Public Health Context of the Affected Area

Subcriteria

a) The disease requires targeted surveillance (i.e., not likely to be detected by routine surveillance but which might be detected by active or sentinel surveillance)

b) Disease control requires specialist interventions (such as highly skilled personnel; equipment, such as isolation units, respirators, PPE, etc.; and infection control measures)

7. Potential Societal Impacts

Subcriteria

a) The disease has a disproportionate impact on special populations (such as pregnant women, children, immunocompromised, etc.)

b) The disease can cause major social disruption

c) The disease can cause major fear

d) The disease can result in major economic impact

e) The disease can result in a major disruption to healthcare delivery

8. The Evolutionary Potential of the Pathogen

Subcriteria

a) There is evidence of rapid pathogen evolution

b) There is a trend toward increasing severity of the disease

c) There is a trend toward the increasing transmissibilty of the pathogen

From the outset, there was an understanding that these different criteria may not have an equal impact on relevance to the R&D Blueprint and therefore whether a disease needs to be prioritized. As an initial step, the 2015 consultation experts ranked the criteria they identified but recommended a semiquantitative approach be developed (*1*). During 2016 WHO developed the current process which uses the Analytic Hierarchy Process (AHP) to undertake a pair-wise review of criteria. Experts participating in the November 2016 Methodology Review committee were surveyed as to the relative importance of the prioritization criteria (*3*). The overall 2016 criteria weights are in Technical Appendix 2 Figure.

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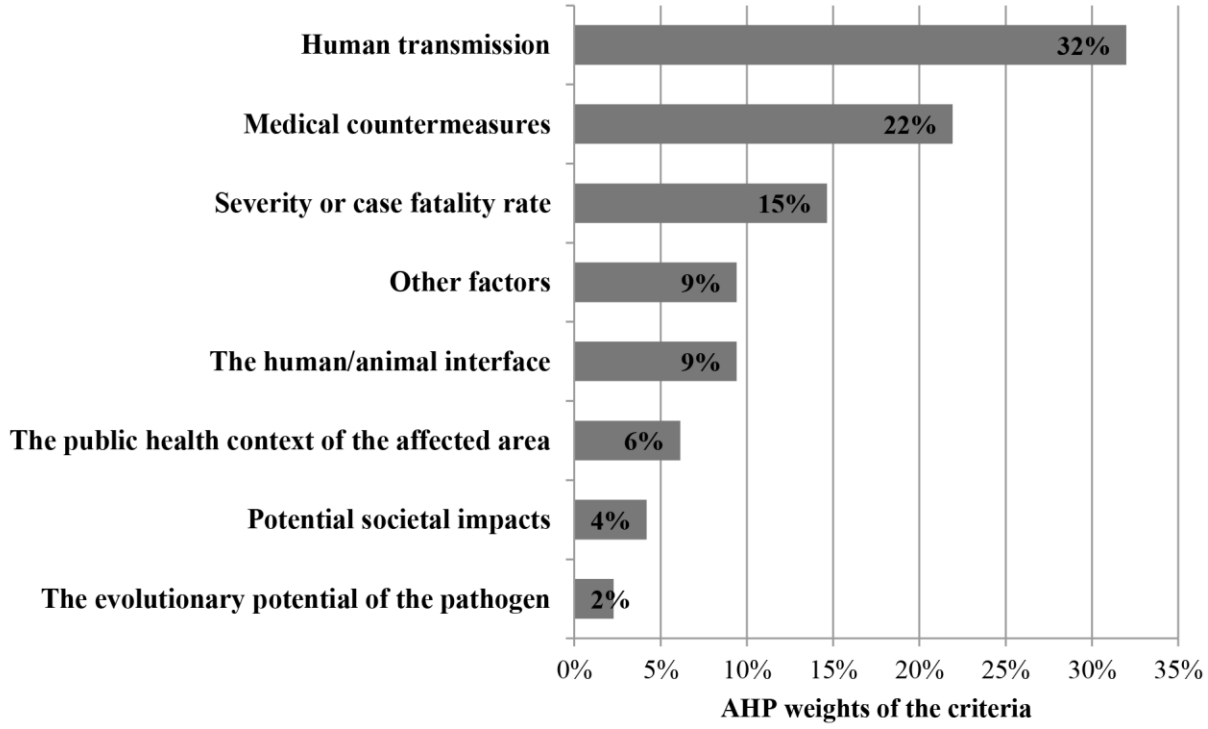

Technical Appendix 2 Figure. Relative importance of the criteria as indicated by their weights.

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Technical Appendix 3

Disease Prioritization Methodologies and Their Application Since 2015

Technical Appendix 3 Table. Recent disease prioritization methodologies and their application.

Study	Country	Purpose of the prioritization	Tools used in the methodology
Stebler et al. 2015 (*1*)	Switzerland	Zoonotic diseases prioritization in Switzerland for surveillance and control	Semiquantitative Delphi process
Garner et al. 2015 (*2*)	Canada	Methodological study for antimicrobial resistant disease risk prioritization and its application in Canada	Multi-Criteria Decision Analysis (MCDA)–PROMETHEE
Dahl et al. 2015 (*3*)	Sweden	Pathogens Prioritization according to their public health prevalence for resource allocation in Sweden	Delphi process with weighting
Ciliberti et al. 2015 (*4*)	EU	Prioritization of wildlife pathogens for surveillance programs in the EU	MCDA
Kadohira et al. 2015 (*5*)	Japan	Methodology for zoonosis prioritization and application for risk assessment in Japan	Risk profiling and AHP
M Bouwknegt et al. 2015 (*6*)	EU	"Risk ranking study to identify emerging diseases that could pose threats to the health and security of the EU"	MCDA
Siembieda et al. 2015 (*7*)	Vietnam	Zoonotic diseases prioritization in Vietnam for resource allocation	Questionnaire
Hongoh et al 2016 (*8*)	Canada (Quebec and Burkina Faso)	Infectious disease prioritization related to climate in Quebec and Burkina Faso for resource allocation	MCDA–PROMETHEE
Lapid et al. 2016 (*9*)	Israel	Prioritization of wildlife pathogens for surveillance in Israel	Rapid Risk Analysis
Stebler et al. 2016 (*10*)	Switzerland	Compare the zoonotic disease prioritization by students and public health professionals in Switzerland	Co-joint analysis questionnaires
McFadden et al. 2016 (*11*)	Mongolia	Zoonotic diseases prioritization for resource allocation	Multi-criteria ranking model
Brioudes al. 2016 (*12*)	Pacific Island countries and territories (PICTs)	Identification of animal pathogens for animal health resources allocation	Delphi process
Munyua et al. 2016 (*13*)	Kenya	Zoonotic diseases prioritization in Kenya for prevention and control strategies in Kenya	Analytic Hierarchy process (AHP)–Decision tree
Pieracci et al. 2016 (*14*)	Ethiopia	Zoonotic diseases prioritization in Ethiopia for prediction, prevention and response	AHP–Decision tree

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Technical Appendix 4

Multicriteria Decision Analysis

MCDA techniques can be compensatory or non-compensatory (*1*). Compensatory MCDA allow trade-offs between criteria whereas non-compensatory do not. According to Baltussen and Niessen 2006, MCDA compensatory methods are more suitable for use for public health purpose (*2*). Several MCDA compensatory techniques have been used for the prioritization of infectious diseases (*3–11*). One such technique is the Analytic Hierarchy Process (AHP) developed by Thomas Saaty (*12*).

AHP uses pair-wise comparisons based on expert judgement that directly incorporates expert knowledge (*13*). Saito et al. 2015 highlighted the ability of the AHP to enable an expert group "*to make trade-off and establish priorities among qualitative and quantitative inputs"*. This is particularly useful in animal and human health where many characteristics remain unclear or unknown (*13*).

Five past disease prioritization studies used AHP for criteria weighting but used different approaches for disease scoring (*8–11*,*14*). Zoonoses prioritization in Japan made use of a rating mode with absolute measures (*11*). A classical AHP scoring by pair-wise comparison was used for prioritization of animal infectious diseases in Chile (*9*). A decision tool to score diseases through a set of qualitative questions in the absence of expert opinion was developed by the CDC (*8*), and used recently in Kenya (*10*) and Ethiopia (*14*).

None of the past implementations of AHP were a good fit for the specific needs of the R&D Blueprint disease scoring. As a result, the WHO methodology includes a tailored

implementation of the AHP, using pair-wise comparisons for weighting criteria, but makes use of a different disease scoring process.

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Technical Appendix 5

Multicriteria Scores Calculation and Detailed Discordance Estimation Procedure

1. Multicriteria Scores Calculation

Subcriteria Weights

The criteria weights were calculated following the standard AHP procedure. The subcriteria were considered at equal importance, hence the weight of subcriteria *f* was equal to the weight of the corresponding criteria divided by its number of subcriteria. These weights were gathered in the weighting vector $\boldsymbol{W_{sub}}$.

Diseases Scores

The disease scores were calculated by using the normalization procedure of the AHP as explained below.

Let D_{ef} be the vector of expert *e*'s answers for sub-criterion *f*, $\boldsymbol{D_{ef}} = \begin{pmatrix} d_{ef1} \\ \vdots \\ d_{efp} \end{pmatrix}$ where *p* was the number of diseases.

Let $\boldsymbol{A_{ef}}$ be the comparison matrix of expert *e* for the sub-criterion *f* (*f = 1,2,…s,* where *s* is the total number of subcriteria). The matrix $\boldsymbol{A_{ef}}$ was built by using the answers in $\boldsymbol{D_{ef}}$ as explained in equation 1.

$$\boldsymbol{A_{ef}} = \begin{pmatrix} \boldsymbol{a_{ef\,11}} & \cdots & \boldsymbol{a_{ef1p}} \\ \vdots & \ddots & \vdots \\ \boldsymbol{a_{efp1}} & \cdots & \boldsymbol{a_{efpp}} \end{pmatrix} = \left(\boldsymbol{a_{efij}}\right) = \begin{cases} \boldsymbol{a_{efij} = 1 \; if \; i = j} \\ \boldsymbol{a_{efij} = d_{efi} - d_{efj} + 1 \; if \; d_{efi} - d_{efj} \geq 0} \\ \boldsymbol{a_{efij} = \frac{1}{1-(d_{efi}-d_{efj})} \; if \; d_{efi} - d_{efj} \leq 0} \\ \boldsymbol{a_{efij} = NA \; if \; d_{efi} = 0 \; or \; d_{efj} = 0} \end{cases} \quad \text{(Equation 1)}$$

Once these comparison matrices were built for each expert, they were averaged to the comparison matrices A_f. According to Saaty, the geometric mean should be used when aggregating people's opinions (*1*): "Two important issues in group decision making are: how to aggregate individual judgements in a group into a single representative judgement for the entire group and how to construct a group choice from individual choices. The reciprocal property plays an important role in combining the judgements of several individuals to obtain a single judgement for the group. Judgements must be combined so that the reciprocal of the synthesized judgements is equal to the syntheses of the reciprocals of these judgements. It has been proved that the geometric mean, not the frequently used arithmetic mean, is the only way to do that."

For this methodology, the arithmetic average was also used to compare the results and to estimate the confidence on the final ranking. For this purpose, the data were processed in a different way. First, when the expert answers "I do not know" to any of the subcriteria statements d_{efi} was set equal to *NA* then the data were arithmetically averaged to the vector d_f. If d_{fi} was equal to *NA*, it was set to *0*. The comparison matrices were then built by using equation 1.

After the averaging step, if some elements of matrix $\boldsymbol{A_f}$, a_{fij}, remained equal to *NA*, this meant that for the disease *i* or *j* the information was not known among the Prioritization Committee. Accordingly, we considered these diseases of equal importance for the sub-criterion *f* ($a_{fij} = 1$). In future prioritization exercises, the method of Bozóki et al. (2010) (*2*) will be used to solve this issue.

The weighting vectors $\boldsymbol{W_f}$ of the diseases for the sub-criterion *f* were calculated by following the steps described in equations 2 and 3. For the sake of clarity, the weighting vectors of the diseases were named scoring vectors.

The normalized comparison matrices of $\boldsymbol{A_f}$, $\boldsymbol{B_f}$, were computed by equation 2.

$$\boldsymbol{B_f} = (b_{fij}) = \left(\frac{a_{fij}}{\sum_i a_{fij}}\right) \text{ (Equation 2)}$$

The scoring vectors (an approximation of the principal eigenvector of matrix $\boldsymbol{A_f}$), $\boldsymbol{W_f} = \begin{pmatrix} w_{f1} \\ \vdots \\ w_{fn} \end{pmatrix}$,

of the diseases for the sub-criterion *f* were calculated by using equation 3.

$$\boldsymbol{w_{fi}} = \frac{\sum_j \boldsymbol{b_{fij}}}{\boldsymbol{n}} \text{ (Equation 3)}$$

Consistency Analysis

Once the scoring vectors computed, the consistency of this procedure was analyzed by calculating the consistency vectors, $\boldsymbol{C_v}$ as shown in equations 4 and 5.

$\boldsymbol{C} = \mathbf{A} \times \boldsymbol{W_f} = (\boldsymbol{c_f})$ (Equation 4)

$\mathbf{Cv} = (\boldsymbol{c_{v_f}}) = (\frac{\boldsymbol{c_f}}{\boldsymbol{w_f}})$ (Equation 5)

$\Lambda_{\mathbf{max}} = \frac{\sum_f^n \boldsymbol{c_{vf}}}{\boldsymbol{n}}$ (Equation 6)

Where Λ_{max} was the maximum averaged eigenvalue. As $\boldsymbol{W_f}$ was an approximation of the eigenvector of matrix $\boldsymbol{A_f}$, $\boldsymbol{A_f} \times \boldsymbol{W_f} = \lambda_{max} \times \boldsymbol{W_f}$ where λ_{max} was the eigenvalue of the matrix $\boldsymbol{A_f}$. If the comparison was completely consistent then $\Lambda_{max} = \lambda max = n$. Hence, the difference between Λ_{max} and λmax represented the lack of consistency. To measure inconsistency, the coherence index was computed by using equation 7.

$\boldsymbol{CI} = \frac{\Lambda_{\mathbf{max}} - \boldsymbol{n}}{\boldsymbol{n} - \mathbf{1}}$ (Equation 7)

The higher the *CI*, the more incoherent the comparison and the weighting were. Thomas L. Saaty introduced by experimentation a coherence ratio *CR*, equation 8, to give a reference for the coherence analysis. If *CR* was higher than 10% then the comparison and the weighting were not consistent.

$\boldsymbol{CR} = \frac{\boldsymbol{CI}}{\boldsymbol{RI}}$ (Equation 8)

Where *RI* is the random inconsistency index of a matrix of order n. This analysis can be explained as the level of random comparisons in matrix $\boldsymbol{A_f}$. If *CR* is low, then matrix $\boldsymbol{A_f}$ was filled logically through a scale and rational analysis. If *CR* was high, then matrix $\boldsymbol{A_f}$ was filled randomly.

Multicriteria Scores

The final step of this process was to compute the multicriteria scores to rank the diseases. These multicriteria scores were computed by gathering the scoring vectors $\boldsymbol{W_f}$ in a matrix, $\boldsymbol{T}$, and by multiplying it by the weighting vector of the subcriteria $\boldsymbol{W_{sub}}$ as explained in equations 9 and 10.

$$\boldsymbol{T} = \begin{pmatrix} \boldsymbol{t_{11}} & \cdots & \boldsymbol{t_{1n}} \\ \vdots & \ddots & \vdots \\ \boldsymbol{t_{p,1}} & \cdots & \boldsymbol{t_{pn}} \end{pmatrix} \boldsymbol{where\ W_f} = \begin{pmatrix} \boldsymbol{t_{1f}} \\ \vdots \\ \boldsymbol{t_{pf}} \end{pmatrix} \text{(Equation 9)}$$

$$\boldsymbol{M} = \boldsymbol{T} \times \boldsymbol{W_{sub}} \text{ (Equation 10)}$$

Where $\boldsymbol{M}$ was the multicriteria score vector. This vector ranked the diseases according to their level of priority given the eight prioritization criteria. The disease with the highest score was the one with the highest priority. The disease with the lowest score was the one with lowest priority.

2. Detailed Discordance Estimation Procedure

Let $\boldsymbol{\Sigma D_f}$ be the vector of standard deviation of the vector $\boldsymbol{D_f}$, $\boldsymbol{\Sigma D_f} = \begin{pmatrix} \sigma_{d_{f1}} \\ \vdots \\ \sigma_{d_{fp}} \end{pmatrix}$

Let $\boldsymbol{\Sigma A_f}$ be the matrix of standard deviation of the matrix $\boldsymbol{A_f}$.

$$\boldsymbol{\Sigma A_f} = \begin{pmatrix} \boldsymbol{\sigma_{a_{f11}}} & \cdots & \boldsymbol{\sigma_{a_{f1p}}} \\ \vdots & \ddots & \vdots \\ \boldsymbol{\sigma_{a_{fp1}}} & \cdots & \boldsymbol{\sigma_{a_{fpp}}} \end{pmatrix} = \left(\boldsymbol{\sigma_{a_{fij}}}\right) = \begin{cases} \boldsymbol{if\ i = j:\ \sigma_{a_{fij}} = 0} \\ \boldsymbol{if\ d_{fi} = 0\ or\ d_{fj} = 0:\ \sigma_{a_{fij}} = 0} \\ \boldsymbol{\text{Else}: \sigma_{a_{fij}} = \sqrt{\sigma^2_{d_{fi}} + \sigma^2_{d_{fi}}}} \end{cases} \text{(Equation 11)}$$

Thus the discordance on the normalized matrix $\boldsymbol{B_f}$, $\boldsymbol{\Sigma B_f}$, was given by equation 12.

$$\begin{cases} \boldsymbol{\Sigma B_f} = \begin{pmatrix} \boldsymbol{\sigma_{b_{f11}}} & \cdots & \boldsymbol{\sigma_{b_{f1p}}} \\ \vdots & \ddots & \vdots \\ \boldsymbol{\sigma_{b_{fp1}}} & \cdots & \boldsymbol{\sigma_{b_{fpp}}} \end{pmatrix} = \left(\boldsymbol{\sigma_{b_{fij}}}\right) \\ \boldsymbol{\sigma_{b_{fij}} = b_{fij}\sqrt{\frac{\sigma_{a^2_{fij}}}{a^2_{fij}} + \frac{\sum_i \sigma_{a^2_{fij}} + 2\times\sum_{l<k}\sigma_{(a_{flj})(a_{fkj})}}{\left(\sum_i a_{fij}\right)^2}}} \end{cases} \text{(Equation 12)}$$

Where $\sigma_{(a_{flj})(a_{fkj})}$ measured the dependence of the variables a_{flj}, a_{fkj}.

The discordance on the weighting vectors, $\boldsymbol{W_f}$, of the diseases for the criterion f was given by equation 13.

$$\begin{cases} \boldsymbol{\Sigma W_f} = \begin{pmatrix} \boldsymbol{\sigma_{t_{1f}}} \\ \vdots \\ \boldsymbol{\sigma_{t_{pf}}} \end{pmatrix} \\ \boldsymbol{\sigma_{t_i}} = \sqrt{\frac{\sum_i^p \sigma^2_{\mathbf{b}_{fij}} + 2\times\sum_{l<k}\sigma_{(\mathbf{b}_{fil})(\mathbf{b}_{fik})}}{p^2}} \end{cases} \text{(Equation 13)}$$

Where $\sigma_{(b_{fim})(b_{fik})}$ measured the dependence of the variables b_{fim}, b_{fik}.

The discordance on the final prioritization scores were computed by using the error propagation technique from matrix **T** to matrix **M** through equation 10. The discordance on the vector **M**, **ΣM**, was given by equations 14 and 15.

$$\mathbf{\Sigma M} = \begin{pmatrix} \boldsymbol{\sigma}_{\mathbf{m_1}} \\ \vdots \\ \boldsymbol{\sigma}_{\mathbf{m_p}} \end{pmatrix} \text{(Equation 14)}$$

Where

$$\boldsymbol{\sigma}_{\mathbf{m_i}} = \sqrt{\sum_{\mathbf{f}}^{\mathbf{n}} \mathbf{w}_{\mathbf{f}}^{\mathbf{2}} \times \boldsymbol{\sigma}_{\mathbf{t_{if}}}^{\mathbf{2}} + \mathbf{2} \times \sum_{\mathbf{l<k}} \mathbf{w_l w_k} \boldsymbol{\sigma}_{(\mathbf{t_{ih}})(\mathbf{t_{ik}})}} \text{ (Equation 15)}$$

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Technical Appendix 6

Additional Consideration of Diseases Not Incorporated into the Final List in the Development of the World Health Organization R&D Blueprint

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/monkeypox, continue 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 for these diseases, so they were ultimately excluded from the R&D Blueprint priority list.

Several additional pathogens were discussed and considered for inclusion in a priority list, such as: emerging flaviviruses with potential for hemorrhagic 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. It was noted that a potential threat need not be a virus and could be any type of pathogen. For several of these diseases more research is needed before even an assessment for prioritized countermeasure development can be undertaken. Necessary research might include basic/fundamental and characterization research, as well as epidemiologic 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.

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, as a specific threat.