Methodology for Prioritizing Severe Emerging Diseases for Research and Development

Background

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:

1. Assessing epidemic threat and defining priority pathogens;

2. Developing R&D roadmaps to accelerate evaluation of diagnostics, therapeutics and vaccines; and

3. Outlining appropriate regulatory and ethical pathways.

This methodology is intended to help identify the top global disease threats as part of an ongoing process to reassess priorities in light of changing circumstances.

Evolution of the methodology

This methodology was originally outlined by participants at the WHO Consultation for Prioritization of Pathogens held in Geneva, Switzerland from 8-9 December 2015.[1] Experts at that meeting reviewed best practice in conducting disease prioritization processes, amending it to fit the needs of the R&D Blueprint (Annex 1). They also reviewed practical examples of national disease prioritization processes and benefit from the input of experts involved in such assessments. There was broad agreement that any methodology for prioritizing diseases and pathogens would need to be transparent and be responsive to changes in understanding and current events.

It was recommended that two separate prioritization processes were necessary:

1. An annual prioritization exercise to review and revise a list of prioritized diseases and pathogens (Part 1); and

2. A separate process for dealing with a new disease or pathogen, or one that is presenting in a new manner and likely to cause a public health emergency (Part 2).

There was agreement that the methodology would need regular review, at least every three years, to ensure that it continues to offer the optimum approach for prioritizing diseases. Such a review of the methodology might be held adjacent to, but separate from, the annual prioritization exercise.

Based upon this guidance, the methodology was further developed by WHO through the development of a number of disease scenarios (Annex 2) and a decision tree for new diseases. The R&D Blueprint's Scientific Advisory Group reviewed drafts of both parts of the methodology.

The entire methodology was reviewed by a cross-discipline expert group at an informal consultation convened in Geneva, Switzerland from 17-18 November 2016. The meeting brought together experts in human and animal health, epidemiology, applied mathematics and safety as well as relevant researchers and clinicians. It validated a general approach, endorsing a system of annual reviews, biennial methodology reviews, supplemented as necessary with emergency reviews. The annual reviews will utilize a combination of rounds of the Delphi technique, questionnaires and multi-criteria decision analysis to review and update the R&D Blueprint's priority list of diseases. The meeting also

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[1] http://www.who.int/csr/research-and-development/meeting-report-prioritization.pdf?ua=1

examined a set of draft tools to be used in this process, refining some and detailing a roadmap for the completion of others.

This methodology was the result of the comments, feedback, and improvements received during and after the November 2016 methodology review. It was validated through a silence procedure in January 2017. It is anticipated that it will be reviewed again before the end of 2019.

<u>The need for a different prioritization approach</u>

There have been numerous past efforts to identify a subset of infectious diseases that needs to be prioritized for research, development, preparedness or other pre-emptive action. A recent systematic review of many such processes noted different methodological approaches including bibliometric indexes, Delphi techniques, Multi-Criteria Decision Analysis (MCDA), qualitative algorithms, and questionnaires. Some were more suitable than others for the prioritization under the R&D Blueprint (Table 1).

Scenarios	Methodology	Comments
Rapid or large-scale risk ranking for large number of pathogens	H-index or qualitative algorithm	Both methods are suitable for ranking a large volume of pathogens within a short time period or with limited resources.
Scoping exercise to generate an initial ranking for further study	H-index or qualitative algorithm	As both methods can quickly rank a large volume of pathogens, they can be used to provide a short list for risk ranking using a more comprehensive technique.
Comprehensive risk ranking including novel, emerging and established infections	MCDA or Delphi	Both methods provide a comprehensive method for risk ranking. Where resource is restricted, consider limiting the number of criteria or the number of diseases for ranking.
Emerging infections with little published data about them	H-index	In lieu of standard data, such as burden of disease, h-index can indicate a level of professional interest/concern which may be used as an informal proxy measure of disease impact.
	Qualitative algorithm	This method combines expert opinion and evidence (where available). The qualitative nature allows for greater flexibility in decision-making and for the detailed recording of that rationale. This is particularly useful in emerging infections where decisions may be more based on expert opinion than epidemiological data.
	Qualitative algorithm or questionnaires	In qualitative methodologies, including a mechanism for respondents to identify gaps in knowledge or areas for further work could lead to improved evidence upon which to base future decisions.
	MCDA	This method can incorporate information from a variety of sources, which is useful in emerging infections where information is sparse. Ranking the risk of alternative scenarios is suitable for situations where there is less certainty about the potential course of the disease. Additionally, new information can be incorporated as it emerges, without needing to rerun the entire ranking exercise

TABLE 1: Scenarios and suggested methodologies for risk-ranking exercises[2]

The current WHO prioritization process is most closely aligned to a "Comprehensive risk ranking including novel, emerging and established infections". As a result, a combination of Delphi techniques and MCDA was recommended. The methodology also makes use of the questionnaires, which were highlighted as useful in cases where there may be little published data available on the diseases involved. As a result, this methodology uses a Delphi approach to a short list of diseases to review in more detail, and MCDA to assess those diseases, questionnaires to illicit data from participants and a final round of the Delphi technique to review the provisional results.

The review of best practice in disease prioritization also highlighted a number of ways in which past WHO processes might usefully be improved:

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[2] Table from: O'Brien, E. C., et al. "Best practices in ranking communicable disease threats: a literature review, 2015." Euro surveillance: bulletin Européen sur les maladies transmissibles= European communicable disease bulletin 21.17 (2016). http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=22459

Reporting lacked detail, as it was a report of a meeting to give participants experience of such an exercise. Unclear how criteria were developed. Potential sources of bias and mitigations are not reported. The publication was not peer-reviewed and it is unclear if any other review took place. Implementation issues were not discussed but Delphi scoring was limited to one round. Did not meet all of the key communicable disease facets. 95% confidence intervals used to aid discussion of discrepancies in scoring.[3]

As a result, a single round of the Delphi technique has been doubled for the initial triaging of diseases and supplemented with a more rigorous MCDA assessment.

Rather than making use of a single meeting the process by which the prioritization methodology is developed has been strengthened. First, a general framework was agreed by a group of eminent experts during the 2015 prioritization meeting. Details criteria for assessment were then added. The resulting draft methodology was presented to the Scientific Advisory Board of the R&D Blueprint and amended in light of their recommendations. The implementation of the modelling used in this methodology was reviewed by leading international experts and revised following their feedback. The revised methodology was presented to, reviewed, and further developed by, an additional group of external experts, including experts in public health, infectious disease, modelling of disease and relevant methodologies. Finally, the methodology itself is being made public.

Two particular recommendations by the WHO R&D Blueprint Scientific Advisory Board have particularly shaped this document: (1) the methodology should be better documented and made publicly available; and (2) to develop estimates of confidence in the results achieved:

- *On documentation* - the reports of the initial prioritization exercise in 2015, the methodological review in 2016 and the annual review of the priority list in 2017 all document the evolution of this methodology and its implementation. These reports are publicly available and published on WHO's website. This document records how WHO creates its priority list and is to be made publicly available. It will be supplemented by a peer-reviewed article following its use to revise the list of priority diseases. The entire methodology will be reviewed through a dedicated, transparent process every few years.

- *On estimates of confidence* - to better structure the organization and analysis of the decisions being taken an Analytic Hierarchy Process (AHP) was employed. This technique, based upon developments in mathematics and psychology, is a framework for structuring decision making - representing and quantifying relevant elements, connecting them to overall goals, and for evaluating alternative solutions. It also enables the consistency of different views amongst participant to be analysed. The consistency indicates the level of randomness in the comparison. The application of the AHP approach in this context and for the specific aims of the prioritization process was reviewed by a number of prominent academics in the field. Furthermore, the methodology makes use of error propagation techniques to produce uncertainty estimation – effectively using the differences between opinions to assess discordance on the ranking.

Particular attention was placed on identifying and mitigating sources of bias. In 2010, Pannucci and Wilkins identified a number of different biases present in clinical trials.[4] A number of similar biases could be present in this prioritization exercise. Tailored measures have been taken to minimize their possible impact:

- *Flaws in study design* – there is a need to: (a) clearly define risk and outcome, preferably with objective or validated methods; and (b) standardize and blind data collection. This methodology is effectively a protocol validated by the relevant expert community. It makes

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

[4] C.J. Pannucci, & E.G. Wilkins. Identifying and Avoiding Bias in Research, Plastic Reconstructive Surgery, August 2010; 126(2): 619–625. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2917255/pdf/nihms-198809.pdf

use blinded surveys and questionnaires for much of its data collection, specifically to ensure a standardized, blinded approach;

- *Selection bias* – Subjects of the study should be selected through a rigorous criteria designed to avoid confounding results. The standardized approach to identifying a long list of diseases to be considered, a transparent triaging process and the use of surveys is al intended to provide a rigorous approach to selecting the disease and pathogens selected for inclusion and prioritization. Furthermore, the identification of key knowledge sets, expertise and a broad geographic representation of experts all contribute to minimizing the impact of selection bias on participants;

- *Interviewer bias* – Standardizing interviewer's (or participant's) interaction with the process is important. This methodology uses surveys during the MCDA process to ensure a standardized experience;

- *Chronology bias* – given the comparative infrequency of public health emergencies, this methodology will, by necessity, make use of historical data. Adopting approaches allowing assessment of confidence in the results produces help to mitigate such a bias.

- *Recall bias* – another major challenge for prioritization processes is that those participating will be privy to, and drawing upon, knowledge and data that might not be in the public domain. This makes it difficult to ensure arguments being made are supported with objective data sources. The use of Delphi techniques to share knowledge amongst participants and enable a limited peer review during discussion of the diseases and pathogens covered, helps explore the technical basis of data not in the public domain. Efforts to approximate confidence levels in the results achieved, may also help to alleviate this bias.

PART 1

Annual Prioritization Exercise

A. Overview of the annual prioritization exercise

This annual prioritization exercise is the final step in a larger process. It has been preceded by efforts to identify criteria against which to assess diseases and pathogens, the weighting of the criteria according to their relative importance (Annex 1), and a thorough review of the methodology.

In general, the annual exercise is intended to move through a number of sequential steps to get from all known diseases and pathogens to a short-list of around 10 pathogens to be prioritized under the R&D Blueprint (Figure 1).
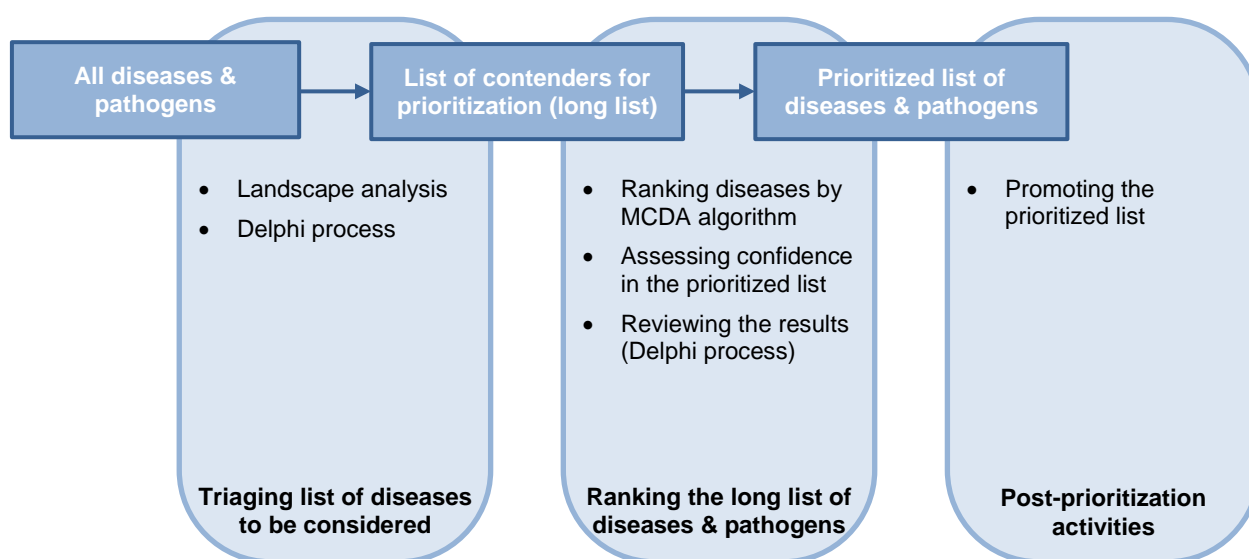

Figure 1: Overview of the annual prioritization exercise

As a first phase, it is necessary to have prepared a sub-set of diseases and pathogens that will be considered for potential prioritization. Early in the annual review process it will be important to understand whether there have been any technical developments relevant to diseases currently prioritized (Section B). This will be fed into subsequent discussions. In any given annual review, it will not be possible to score and rank every known disease or pathogen. A triaging process is needed (Sections D and E), drawing upon a range of potentially relevant disease scenarios (Annex 2).

A second phase is then to bring together a wide range of expertise (Section C). These experts will review candidate diseases and pathogens. They will score them according to the predetermined criteria (Section F), in line with the identified weightings (Section G), using established procedures (Sections H-K).

Successful completion of this exercise will result in a revised list of priority diseases and pathogens. An assessment as to the degree of confidence in the results produced may then be necessary (Section L). A subsequent round of discussion to reflect on the process might also be necessary (Section M).

A final phase will then promote the results of the annual prioritization exercise (Section N). This might include WHO press releases, the development of a publication, or other tools as required.

Setting aside the initial planning activities to be undertaken by WHO and their commissioning of a landscape analysis, an annual review exercise will take 3-4 months to conduct (Figure 2). There are steps that will need to be taken in advance of the annual review meeting, such as setting up the

Prioritization Committee (Sections C) and triaging the diseases to be reviewed (Sections D). Other activities will form part of the meeting itself, such as reviewing the long list of disease and pathogens (Section E), assessing them against the weighted criteria (Section H), compiling a priority list (Section K), assessing confidence in it (Section L) and reflecting on the process (Section M). A few, such as promoting the results (Section N) occur after the meeting.
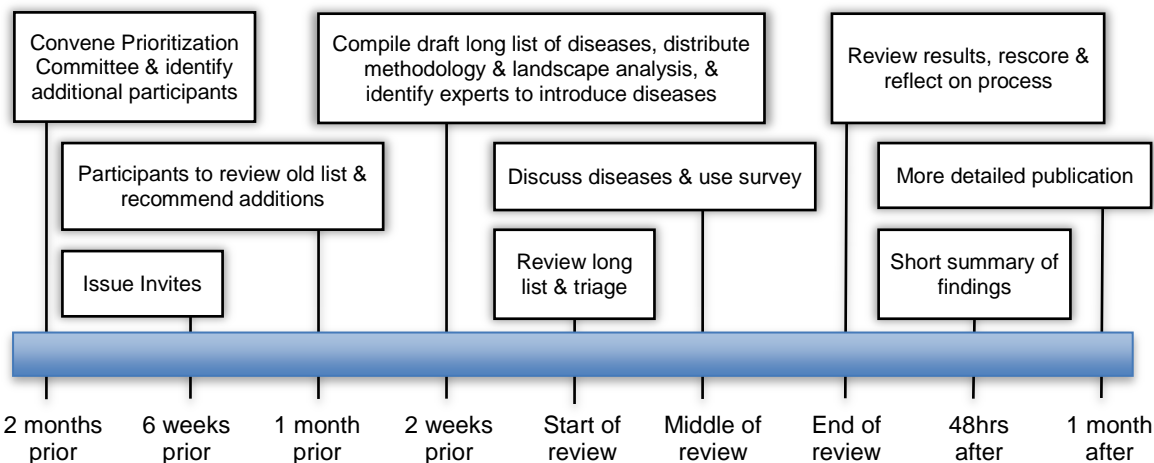
Convene Prioritization Committee & identify additional participants		Compile draft long list of diseases, distribute methodology & landscape analysis, & identify experts to introduce diseases			Review results, rescore & reflect on process		
Participants to review old list & recommend additions		Discuss diseases & use survey		More detailed publication	
Issue Invites		Review long list & triage		Short summary of findings	

| 2 months prior | 6 weeks prior | 1 month prior | 2 weeks prior | Start of review | Middle of review | End of review | 48hrs after | 1 month after |

Figure 2: Timings of key steps within an annual prioritization exercise

B. Landscape analysis

Prior to the annual prioritization exercise, WHO should commission a review of technical developments associated with the diseases and pathogens on the most recent priority list. This could usefully cover both developments in understanding, such as those generated by basic research, as well as those in more applied fields such as progress in developing the necessary medical countermeasures. The aim of the landscape analysis is to identify developments which might lead participants to think very differently about the relative risks posed by the disease or pathogen in the context of the R&D Blueprint. It is envisaged that such major developments are comparatively rare.

The results of this landscape analysis will be fed into the annual exercise, preferable through a presentation near the start of the meeting (Annex 3). It will provide important background information for participant and help to ensure common ground for subsequent discussions.

This landscape analysis will need to be carried out sufficiently early in the annual cycle so as to allow it to be as comprehensive as possible but close enough to the annual exercise so that its results will not be out of date.

C. Prioritization Committee

Key stages of this exercise are expert-driven. It is important to have sufficient and diverse expertise on which to draw. The 2016 methodology review recommended that participants be as geographically diverse as possible and, depending upon the diseases and pathogens to be considered, could include experts in:

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 expert in zoonoses from both livestock and wildlife
6. Other experts, including anthropologists, bioethicists, and other relevant social sciences, as well as experts from the defence or security sectors familiar with biological weapons

To the extent possible, it is also desirable to include both disease specific experts (where it is known in advance a pathogen or disease will be included in the long list to be reviewed) as well as the

authors of important review articles on emerging infectious disease. This will help ensure the presence of both narrow and broad expertise.

A core group of representative experts should be convened as a Prioritization Committee. This group will provide expert guidance when running the annual prioritization exercise, provide many of the participants for the annual prioritization meeting, and be expected to make themselves available to undertake an emergency prioritization exercise, should it become necessary as a results of a novel disease or pathogens (Part 2). It may be necessary to supplement the Prioritization Committee with additional expertise in some circumstances, for example disease specific knowledge when conducting an emergency prioritization exercise.

D. Triaging possible diseases and pathogens

As a first step, it is necessary to identify a sub-set of all possible diseases that might be assessed more systematically for potential prioritization.

In other settings, similar processes have developed exhaustive, resource intensive processes to accomplish this goal. In the case of a prioritization process under the R&D Blueprint, and taking into account the regular nature of the review and the limited resources available, a streamlined process has been developed:

1.   As an initial input diseases or pathogens on the previous prioritized list should be fed into the annual review.

2.   Any additional diseases forwarded for re-consideration by the previous prioritization exercise, or any emergency prioritization exercise (conducted in accordance with Part 2 of this document) should also be fed into the annual review.

3.   Furthermore, approximately three weeks prior to the convening of the meeting for the annual prioritization exercise, the Prioritization Committee will be requested each to provide and additional 2-3 diseases or pathogens that might be included in the exercise.

To help guide the experts in preparing these submissions, a number of identified disease scenarios were identified (Annex 2). Participants should be reminded that the R&D Blueprint focuses on diseases "where there are no, or insufficient, preventive, and curative solutions". As a result, participants should 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/or established regulatory pathways for improved interventions. Examples of such diseases identified during previous R&D Blueprint prioritization exercises include HIV/AIDS, tuberculosis, malaria, avian influenza causing severe human disease, antimicrobial resistance (as a generic category), smallpox/monkeypox, and dengue.

Diseases and Pathogens identified during steps 1-3 should then be compiled into a long-list of diseases and pathogens to be considered during the annual review. This long list should only include around 10-15 diseases or pathogens. If more diseases have been fed into the process, two rounds of blinded Delphi technique can be used to reduce the size of list to be considered.

The long-list fed into the annual review should be compiled in such a manner as to anonymise submissions. Suitable experts from within WHO might also be requested to input diseases or pathogens on to this list as it will be later reviewed by external experts.

A draft long-list should be compiled a week to 10 days prior to the meeting. WHO should then identify one to two members of Prioritization Committee to introduce the disease during the annual prioritization exercise. One expert should ideally be a subject matter expert, able to make a short introduction (2-3 min) as to why the disease or pathogen might be relevant to this process. If logistically feasible and based upon the composition of the Prioritization Committee, second expert might also review available data and comment (2-3 mins) on its potential relevance to this exercise. This second expert might not be an expert in that particular disease or pathogen but be suitably informed as to be able to review its potential relevance in short order. The two experts should not work together on their comments and should ideally represent a range of views and opinions. Both should be encouraged to use the 8 prioritization criteria discussed in Section F when preparing their comments.

E. Reviewing the Long-list of potential diseases and pathogens

Early in the meeting for the annual prioritization exercise (Annex 3), participants should be given the opportunity to review and discuss the content of the long-list of disease and pathogens. This should be a general discussion as to the composition of the list and not an in-depth assessment of each of the diseases on it. The landscape analysis commissioned by WHO (Section B) should be introduced, ensuring all participants are familiar with technical developments pertinent to diseases and pathogens previously prioritized. Experts asked to prepared comments on specific diseases or pathogens should not make those comments at this point (unless needed as part of a Deliphi technique to reduce the size of the long list of diseases to be considered during the meeting).

The discussions at this step should enable additional diseases or pathogens to be added to the list. Alternatively, it may also be desirable to remove diseases or pathogens from the long list. If necessary a Delphi technique may be used to reduce the size of the long list to ensure adequate time during the meeting can be dedicated to considering each of the diseases. Any such decisions to amend the long list, and the rationale behind them, will need to be carefully recorded.

By the end of this step, it is desirable to have developed a consensus on the contents of the long list so that participants begin the exercise from a common position.

F. 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;
6. The public health context of the affected area;
7. Potential societal impacts; and
8. Evolutionary potential.

There was recognition that not all of these prioritization criteria were equally important that some weighting of individual components was necessary (Section G).

To further elaborate the prioritization criteria, a series of associated statements to explore different facets of the criteria were developed during the 2016 methodology review and updated in light of the use of the methodology during the 2017 annual review.

1. Human transmission
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: commercialised products or advanced candidates (such as those undergoing clinical trials)
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 specialised 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
a) The disease causes high mortality
b) The disease frequently causes high morbidity, including severe complications or sequelae

4.(a) Human/Animal Interface
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

4.(b) Other factors
a) The geographic range of the pathogen has changed
b) The pathogen shares relevant epidemiological 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. Public health context of the affected area
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
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. Evolutionary potential
a) There is evidence of rapid pathogen evolution
b) There is a trend towards increasing severity of the disease
c) There is a trend towards the increasing transmissibilty of the pathogen

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It is not intended that participants in annual prioritization exercises review or amend the identified prioritization criteria or associated statements. This is a task reserved for a separate methodology review process. In accordance with established best practice, these two processes need to be clearly separated.

G. Weighting prioritization criteria

Each prioritization criteria may not have an equal impact on whether a disease needs to be prioritized. For example, its economic impact may be less important than its transmissibility. As a result, it is necessary to weigh the individual criteria.

As an initial step, at the 2015 WHO Consultation for Prioritization of Pathogens the experts undertook an exercise to weigh the various identified criteria – ranking their relative impact on a public health emergency. However, a more quantitative approach was recommended.

During the development of a more robust methodology in 2016, a second group of external group of experts was surveyed as to the relative importance of the prioritization criteria. Unlike the 2015 assessment, a quantitative methodology was used. The overall 2016 assessment was:

Human transmissibility:	32%
Medical countermeasures:	21.90%
Severity:	14.65%
Human/animal interface:	9.42%
Other contributing factors:	9.42%
Public health context of the affected area:	6.13%
Potential social impacts:	4.18%
Evolutionary potential:	2.28%

The results were similar to those obtained in 2015 but benefitted from the consequent conceptual development of the R&D Blueprint. This helped tailor the criteria to the specific needs of the Blueprint. For example, in this context the availability of medical countermeasures was felt to be of greater importance than when considering factors that affect a response to a public health emergence more broadly. As a result, this criterion was moved from being 4th in relative importance to 2nd.

It is not intended that participants in annual prioritization exercises review or amend the weightings of prioritization criteria. This is a task reserved for a separate methodology review process. In accordance with established best practice, these two processes need to be clearly separated.

H. Assessing diseases and pathogens against the weighted prioritization criteria

This task, and subsequent steps to review and discuss survey results will form the basis of most of the meeting convened for the annual exercise.

In accordance with best practice, it is necessary to have separate weighting and assessment exercises. It is also important to use the components developed in earlier stages of the process (Sections F,G, I, and J) and to involve experts from different regions and disciplines (Section C). It is also necessary to provide all available evidence in support of the decisions being made.

In general, it may be useful to schedule a series of working sessions to discuss the diseases and pathogens under review. This enables participants to share data not widely available, and to debate the diseases in the specific context of the R&D Blueprint. Strict time keeping will be important during this part of the annual prioritization exercise. A suitable chair will need to be identified in advance and they should be empowered to keep strictly to the allocated timings.

If following the model agenda outline in Annex 3, No more than 15 minutes should be spent on each pathogen or disease. The two experts invited to make prepared comments should each be provided up to 3 minutes to make their remarks. The remaining time should be allocated for a discussion as to the relevance of the pathogen or disease to the prioritization exercise. Participants should be asked to focus on the prioritization criteria in Section F and to make all interventions exceedingly short. They should also be reminded that the R&D Blueprint focuses on diseases "where there are no, or insufficient, preventive, and curative solutions". As a result, participants should 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/or established regulatory pathways for improved interventions.

Following these discussions, participants should then be asked to complete the online survey. To simplify the scoring process, for each disease or pathogen participants are requested to agree or disagree with each of the statements detailed in Section F. Participants can select a relevant position on a sliding indicator which ranges from 'Strongly Agree' to 'Strongly disagree'. Using the sliders facilitates the quantification of results, allowing answers to be coded into a specific score that can be adjusted by the identified weightings, and fed into an algorithm (section J) to determine an overall score for each disease or pathogen being assessed.

Plenty of time should be set aside for this exercise and facilities provided for participants to work in a shared space. They should have the opportunity of interacting with each other individually or collectively to seek clarifications, discuss relevant data and take full advantage of the expertise present in the room. In general, it may be useful to involve all the participants in these discussions, sharing the insights generated as widely as possible. In some cases, participants might wish to be able to interact on a one-to-one basis.

It might also be useful to use a rapporteur during these discussions (not one of the expert participants) as a summary of this discussion will provide important supporting evidence of how decisions where reached, in line with established best practice.

It is not intended that participants in annual prioritization exercises review or amend the methodology being used to assess diseases and pathogens against the weighted prioritization criteria. This is a task reserved for a separate methodology review process. In accordance with established best practice, these two processes need to be clearly separated.

I. Data processing

Answers provided by participants are collected through an online survey. The survey makes use of the prioritozation criteria and associated statements (Section F) and the associated weightings (Section G).

To rank the short list of diseases, the participants complete an online survey tool. To simplify data collection, a visualization tool was built using the slide-bar function of *R-Shiny.* The tool makes use of a relative scale – comparing values between diseases rather than 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).
According to Saaty 1990:

"*Absolute measurement needs standard to make it possible to judge whether the alternative is acceptable or not. Absolute measurement is useful in areas where there is fairly good agreement on standards which are then used to rate alternatives on at a time*".[5]

This is not the case in the context of emerging and re-emerging infectious diseases where many characteristic remain unclear or unknown.
Allowing participants, at a glance, to compare scoring between diseases helps to capture their views for each sub-criteria (statement) (Figure 3). The visualization tool also allows experts to record where a sub-criteria might be equally important for two diseases - setting the slider to the same value. It also intuitively allows the expert to represent the comparative ratio of importance of a criteria between diseases – by increasing or decreasing the gaps between their relative positions. The tool also allowed experts to opt out of scoring a particular disease or criteria - by setting the slider to zero.

[5] Saaty, T. L. How to make a decision: the analytic hierarchy process. *European journal of operational research* **48**, 9-26 (1990)
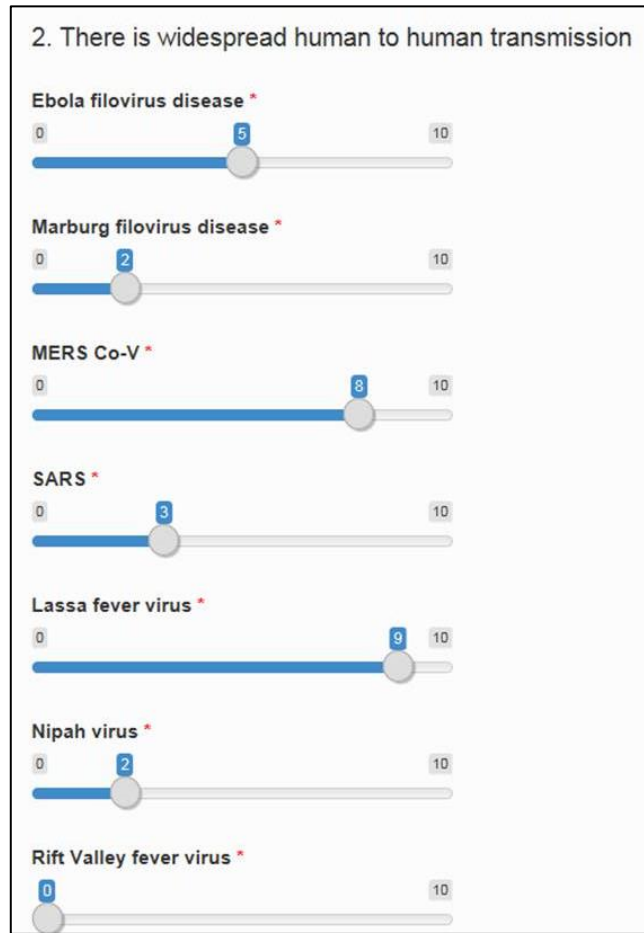
FIGURE 3: Example of the scoring process.

J. Prioritization algorithm

To prioritize diseases a custom Analytic Hierarchy Process (AHP) is used. It is traditionally used to help policy makers in decision-making processes when confronted to complex decisions.[6] The AHP method gives a complete and rational structure for the decision making process by representing the problem in hierarchic structure, evaluating and quantifying each criteria that influences the decision, linking them to the objectives, evaluating the alternatives and ranking them.

AHP is useful for the prioritization of diseases because it can rank them according to prioritization criteria. To being with the problem is stratified. The algorithm used in this methodology has four levels: the first presents the aim of the process (prioritization of diseases); the second level covers the prioritization criteria; the third level presents the statements associated with the criteria; and the fourth level is the diseases being reviewed.

The first step in the algorithm requires mapping the hierarchic structure of the prioritization problem. As an example, Figure 4 presents the first step of the prioritization algorithm for one of the criteria (human transmissibility). When fully implemented, similar hierarchical structures are mapped for each criterion.

The second step of this algorithm weights the criteria, in accordance with Section G. Using the results of the 2016 methodology review, the criteria are classified according to their importance as follow:

C_1: human transmissibility;
C_2: the availability of countermeasures;
C_3: severity (or case fatality rate); the potential scope of outbreak (risk of international spread);
C_{4-1}: the human animal interface

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[6] Saaty, T.L. (2008). Decision making with the analytic hierarchy process. *Int. J. Services Sciences, Vol. 1, No. 1, 2008.*

C_{4-2}: Other contribution factors;
C_6: the public health context of the affected area;
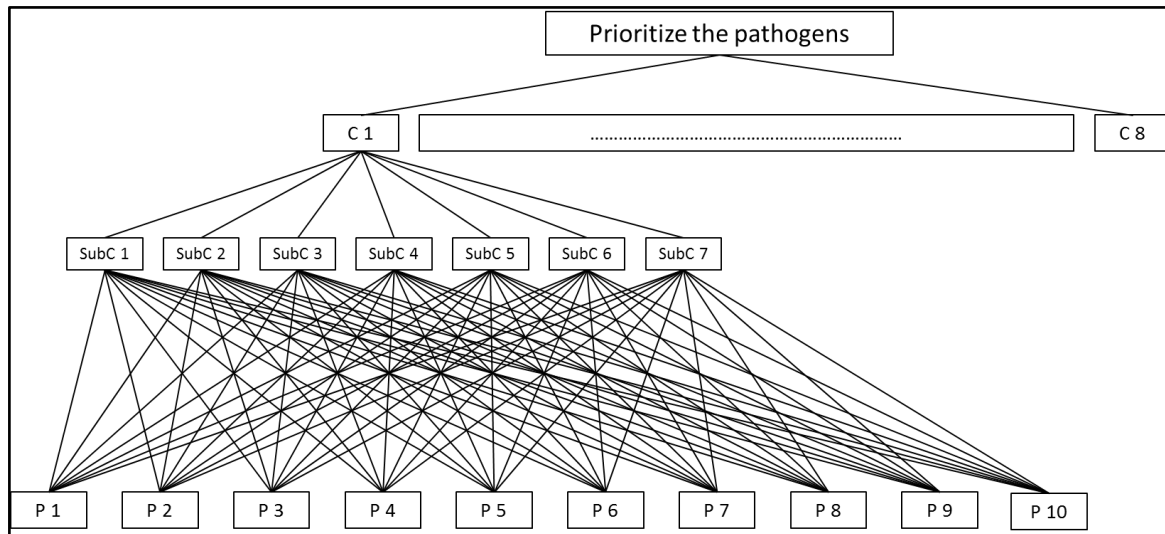C_7: potential societal impacts;
C_8: the evolutionary potential.

Figure 4: Hierarchic prioritization problem.
Where $C_1, C_2...C_8$, $SubC_1...SubC_7$ and $P_1, P_2...P_{10}$ represent the prioritization criteria, the sub-criteria for criterion C_1 and the ten pathogens, respectively.

The third step in the algorithm is to make a pairwise comparison between the pathogens for each sub-criterion (statement) by using the model developed for this methodology and being published in a forthcoming peer-reviewed article. The answers provided by the participating experts are used to make this comparison. The scores provided by the individual experts are averaged and the weighted scores computed. If there is inconsistency amongst the views held (and scores provided) by different experts when considered a specific statement, perhaps due to judgement differences, the discordance will be recorded and the group tasked with considering this facet of the criteria further.

The final step of this algorithm is to compute the multi-criteria scores to rank the pathogens by using the results of steps 2 and 3.

K. Compiling the list of priority diseases and pathogens

WHO will present participants with a breakdown of the results of the survey and the output of the prioritization algorithm. The information provided should include details of the mean scores for each statement for each criterion as well as the deviation between participants' answers. These results should be presented in an accessible format during a session specifically to review the results.

In accordance with Section J, time will be needed to revisit discordant results, where there was particular disagreement in the views of participants. A working session might usefully be set aside to accomplish this (Annex 3). During this time, participants will have an opportunity to discuss the findings under each relevant prioritization criteria in more detail. This is effectively a second round of discussion, similar to that envisaged in Section H but focused specifically at those areas where there is greatest disagreement.

Having considered each of the prioritization criteria (and associated statements) across all of the diseases being reviewed and revisited any particularly discordant results, a draft prioritized list should be made available to participants. This should include the comparative overall scores for each pathogen, if possible broken down with an indication of the comparative importance of each criterion in determining the overall score.

As a final step, the draft prioritized list will need to be subjected to expert discussion to ensure the results are internally consistent and fit within the broader technical environment. Depending upon the views of participants, it may be necessary to adjust the output of the process. In general any alteration

to the ranking produced by this mechanism should be agreed by consensus and justifications recorded. Time for a substantive discussion will be required and a dedicated working session might be necessary (Annex 3). A final round of Delphi technique or anonymized voting may be required to ensure that the views of all participants are sufficiently reflected.

Some consideration will also be required as to how best to present the results. For example, is there sufficient difference between the pathogens or diseases reviewed and adequate confidence in the results generated, to be able to produce a ranked listing? If not, would the clarity of a single list without any internal ranking be a sensible output, as was the case in the 2017 annual review. Alternatively, are the results better suited to produce a striated listing, where a number of pathogens or diseases are grouped together? For example, during the 2015 prioritization exercise diseases and pathogens were placed into two categories: those requiring urgent action; and serious, necessitating further action as soon as possible. Initially such a striation will likely need to be a qualitative process. As subsequent annual prioritization exercises are carried it, it may be able to identify quantifiable thresholds for such categories.

L. Assessing confidence in the list

It is important to assess the degree of confidence that might be placed in the prioritized list. The confidence is estimated by using the error propagation method. This method considers the variance in the original sample (the differences in the answers of the experts for the same criterions leads to different scores for that same criterion) and its propagation when manipulating the data for the prioritization. The variance in the original sample is systematically tracked through all the equations used for ranking in the AHP process which lead to a ranked list with discordance intervals. The detailed procedure developed specifically for use in this methodology in contained in the forthcoming peer-reviewed article.

M. Closing the annual prioritization exercise

At the end of the annual review, participants might also be asked to reflect on how the methodology might be further improved. Suggestions should be carefully recorded and fed into the next methodology review.

Before closing the exercise, it is important to ensure that time is set aside for participants to reflect on the process and raise any issues they might have. Any identified issues should be openly discussed, potentially resulting in gathering more supporting evidence, caveats or other useful notes that may need to accompany the results of this exercise.

N. Promoting the results of the exercise

It is critical that both the prioritization process and the annual exercise are seen as transparent and robust. As much information should be made publicly available as possible. A comprehensive report of the annual prioritization exercise is a minimal requirement.

It may also be desirable to promote the revised priority list of diseases or pathogens. This might usefully include press releases from WHO. It may also be desirable to explore opportunities to actively promote the list at appropriate public health events and venues. Peer reviewed publications might also be considered.

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PART 2

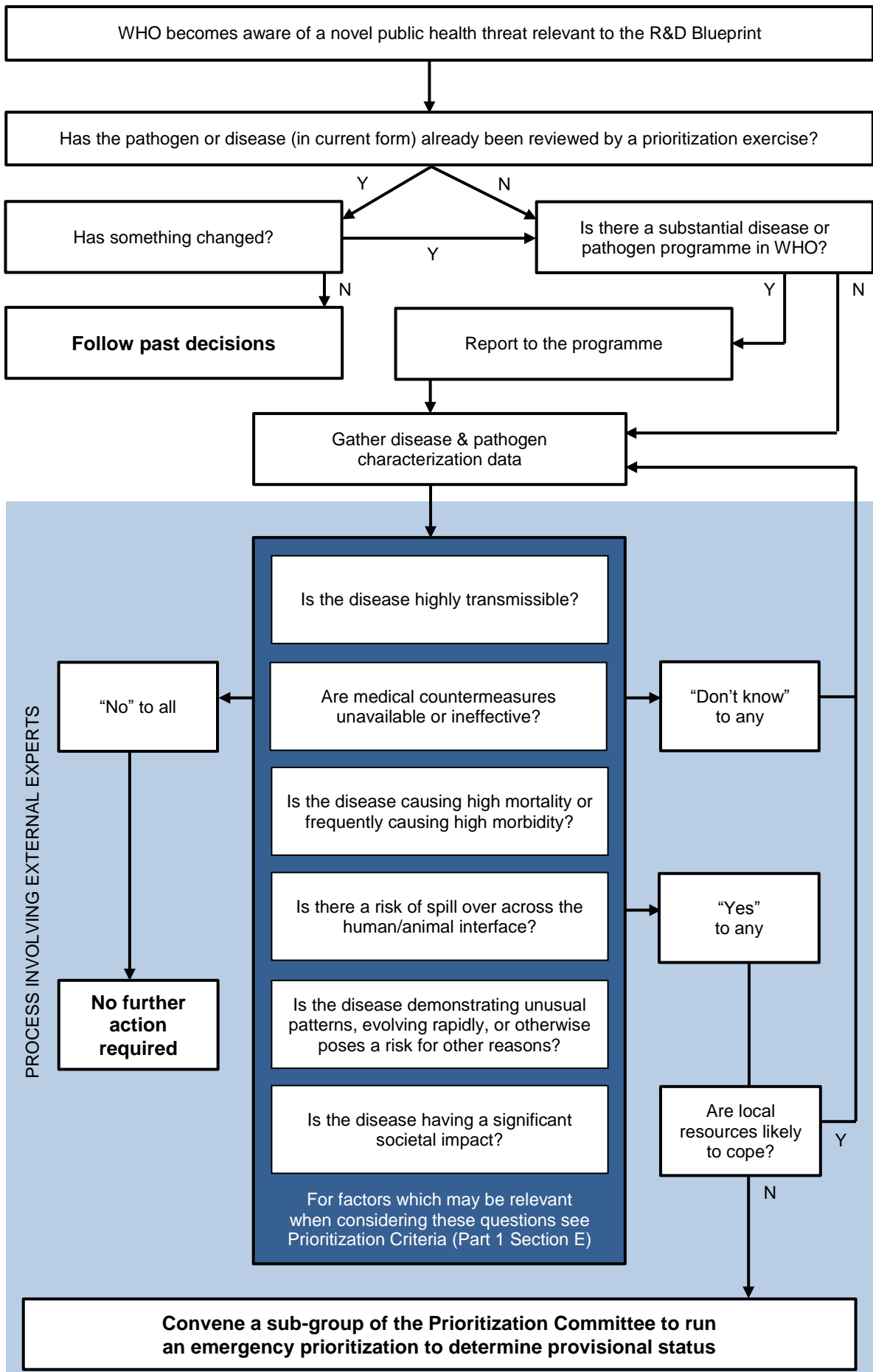## Decision instrument for new diseases or pathogens, or one that is presenting in a new manner

It is possible that an unusual outbreak involving a pathogen or disease might need to be prioritized between annual exercises. Such an event might involve a brand new pathogen, or a pathogen which has not been considered in past annual prioritization exercises (e.g. presenting in a modified or altered manner). This decision instrument is intended to guide users through considering available information and determining what action to take. It is not intended as formal guidance or binding in any manner but is intended as a tool to facilitate planning and response.

The decision instrument helps the user navigate via a series of logical steps. The outcome of each step determines the next. Numerous different paths through the instrument are possible. It begins with WHO becoming aware of a novel public health risk relevant to the R&D Blueprint, progresses through internal and external interactions, and results in a range of different outcomes. In some cases, an outbreak might warrant convening an emergency review to grant the disease or pathogen preliminary priority status, thereby triggering a more comprehensive R&D response component. In other cases, the disease or pathogen, whilst having the potential to cause a public health emergency might not warrant immediate action (beyond monitoring ongoing events) and can be safely fed into the next annual prioritization exercise. There may times where there is insufficient information on which to base an assessment and contact with experts or additional consultations might be required. Alternatively, after careful reflection, no further action may be needed.
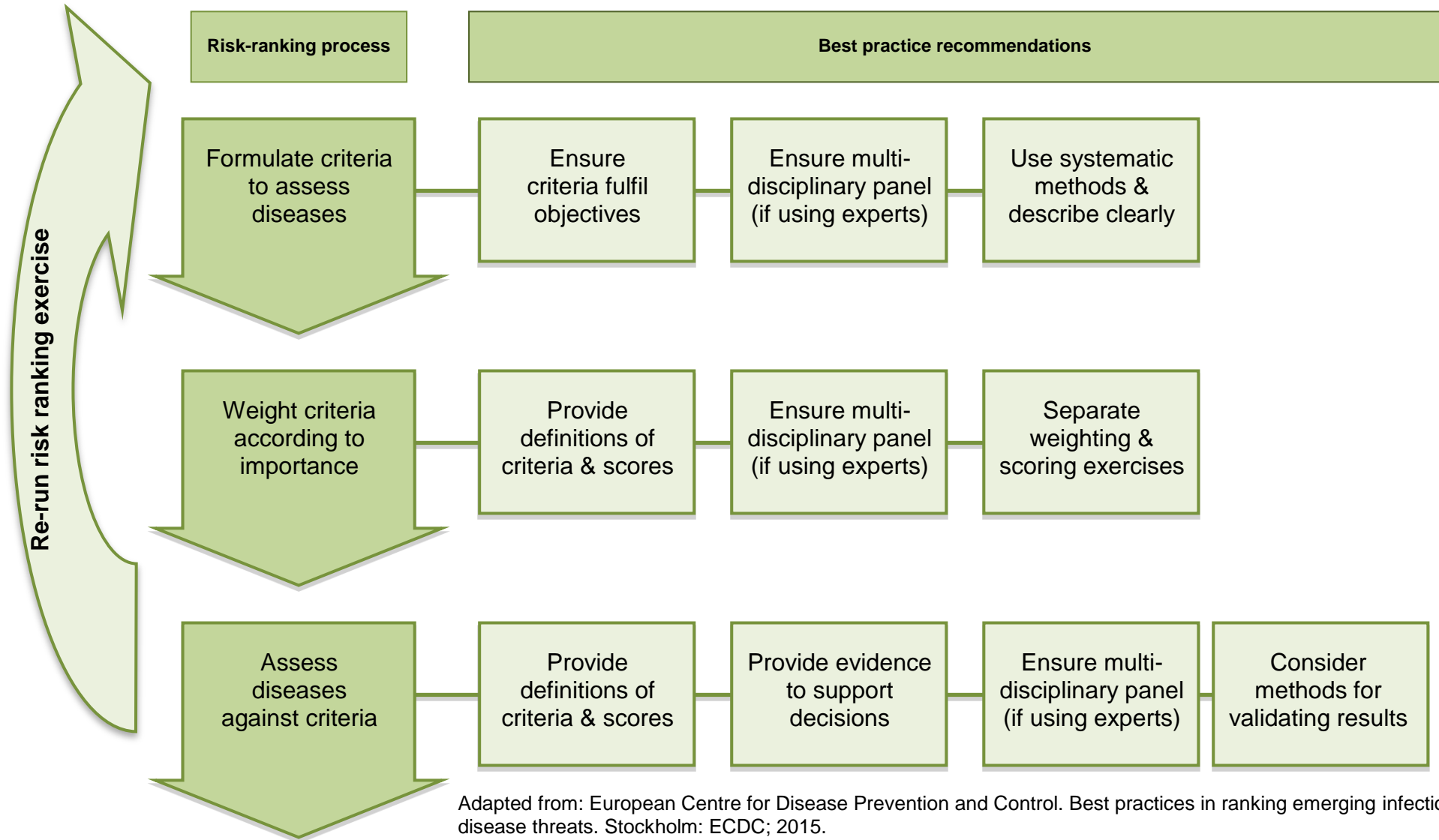
The decision instrument is divided into two phases. The first is an internal assessment for WHO. It connects this process with the organization's other efforts, including the annual prioritization process, disease or pathogen-specific programmes and consideration of the public health impact of an event. In general, should this there be evidence of a public health emergency, a more detailed assessment involving external expertise may be needed. If there is insufficient evidence, the user is guided to monitor the situation and gather more information until satisfied that no further action is necessary. This phase should start immediately on WHO becoming aware of a disease event and could last hours or days until external expertise is sought or a decision taken that no further action is necessary.

The second phase takes the user through gathering relevant information from outside the WHO. It looks at properties of the pathogen involved, such as pathogenicity or transmissibility. The impacts of the disease are also considered, such as whether there is evidence of unusual patterns or significant disruption. The user is also guided to consider broader public health contexts, such as the availability of medical or public health countermeasures and, embracing the One Health approach, information on animal disease impact. These steps correspond to criteria used in the annual prioritization exercise. If a user identifies areas of concern in the pathogen's properties, the disease's impact or in the broader public health context, they are guided to initiate an emergency prioritization process. Such a process should take advantage of the Prioritization Committee convened under the Annual Prioritization Exercise (Part 1, Section C) and should take place within a week of the process being triggered. If an emergency prioritization exercise is not warranted, the user is guided to monitor the situation and gather more information until satisfied that no further action is necessary. This phase may last for days or weeks depending upon the nature of the disease event.

If it is necessary to convene an emergency review, additional actions are envisaged. If a decision is taken that the disease or pathogen should be prioritized, a temporary working group on the R&D components of the disease should be convened. Such a group would be an important resource for WHO to map current capabilities. In particular, the temporary working group would assist in conducting a pipeline analysis – determining what possible countermeasures are in which stages of development. The pipeline analysis can then be fed into a research meeting which would bring together key stakeholders from different fields to consider identify sensible next steps. Ultimately, these resources can be combined to produce a series of relevant product profiles. If the review determines the disease is not an immediate priority, it is expected that it will be fed into the long list of diseases to be considered at the next annual review (Part 1, Section D). These additional activities phase might be pursued in the weeks or months following the emergency prioritization review.

WHO becomes aware of a novel public health threat relevant to the R&D Blueprint

Has the pathogen or disease (in current form) already been reviewed by a prioritization exercise?

Y   N

Has something changed?

Y

Is there a substantial disease or pathogen programme in WHO?

N

Follow past decisions

Report to the programme

Y

N

Gather disease & pathogen characterization data

PROCESS INVOLVING EXTERNAL EXPERTS

Is the disease highly transmissible?

"No" to all

Are medical countermeasures unavailable or ineffective?

"Don't know" to any

Is the disease causing high mortality or frequently causing high morbidity?

Is there a risk of spill over across the human/animal interface?

"Yes" to any

No further action required

Is the disease demonstrating unusual patterns, evolving rapidly, or otherwise poses a risk for other reasons?

Is the disease having a significant societal impact?

Are local resources likely to cope?

Y

N

For factors which may be relevant when considering these questions see Prioritization Criteria (Part 1 Section E)

Convene a sub-group of the Prioritization Committee to run an emergency prioritization to determine provisional status

ANNEX 1
Outline of the prioritization process

Re-run risk ranking exercise

Risk-ranking process	Best practice recommendations

Formulate criteria to assess diseases

Ensure criteria fulfil objectives	Ensure multi-disciplinary panel (if using experts)	Use systematic methods & describe clearly

Weight criteria according to importance

Provide definitions of criteria & scores	Ensure multi-disciplinary panel (if using experts)	Separate weighting & scoring exercises

Assess diseases against criteria

Provide definitions of criteria & scores	Provide evidence to support decisions	Ensure multi-disciplinary panel (if using experts)	Consider methods for validating results

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 2
Disease scenarios

Disease scenarios involving pathogenicity

- Diseases causing severe mortality
- Diseases causing severe morbidity
- Diseases with associated severe complications
- Diseases with severe sequela

Disease scenarios involving transmissibility

- Diseases with effective human-to-human airborne transmission
- Diseases with effective human-to-human sexual transmission
- Diseases with effective foodborne transmission
- Diseases with a common intermediate host
- Diseases with a common vector
- Diseases with a common reservoir

Disease scenarios with unusual patterns

- Localised diseases beginning to spread
- Diseases rapidly spreading
- Diseases spreading to new areas
- Diseases demonstrating novel resistance to common countermeasures

Disease scenarios causing disruption

- Diseases perceived by the general public to pose a particular risk
- Diseases causing civil disruption
- Diseases causing economic disruption

Counter-measures

- There are no, or insufficient effective counter measures
- Counter-measures are too expensive, complicated or unavailable for widescale use
- There is increasing resistance to relevant countermeasures

Other disease scenarios

- Diseases causing severe animal morbidity or mortality
- Diseases resistant (or becoming resistant) to common countermeasures (including lack of vaccine or therapeutics)

ANNEX 3
Model Programme for Annual Prioritization Exercise Meeting

DAY 1

9.00-9.30   **Opening session**

Welcome remarks
Overview of meeting aims and prioritization methodology

9.30-10.30   **Session 1: Discussion of the long list of diseases and pathogens**

Introduction of landscape analysis

(Participants will have the opportunity to discuss the content of the long list of diseases, explaining why they think items should be (or should not be) included. If necessary, the long list of diseases will be triaged to contain around 12 diseases.)

10.30-11.00   Coffee Break

11.00-12.30   **Session 2: Discussion of diseases and pathogens to be prioritized**

(Invited experts will provide short introductions to the diseases and pathogens to be prioritized. Participants will have the opportunity to discuss each disease in turn. Both the introductions and participant discussion will make use of the prioritization criteria.)

12.30-13.30   Lunch

13.30-15.00   **Session 3: Discussion of diseases and pathogens to be prioritized (Cont.)**

(Invited experts will provide short introductions to the diseases and pathogens to be prioritized. Participants will have the opportunity to discuss each disease in turn. Both the introductions and participant discussion will make use of the prioritization criteria.)

15.00-15.30   Coffee break

15.30-17.00   **Session 4: Completion of the prioritization survey**

Overview of the survey

Completion of the survey

(Participants will be tasked with completing the survey – for each disease agreeing or disagreeing with statements derived from the prioritization criteria. Participants will have the opportunity to interact with each other to facilitate the completion of the surveys.)

DAY 2

09.00-10.30   **Session 5: Presentation of survey results**

(WHO will present the results of the survey, highlighting where there is agreement and disagreement between participants on each element of the prioritization criteria. Participants will have the opportunity to compare results across the diseases and pathogens being prioritized.)

10.30-11.00   Coffee break

11.00-12.30   **Session 6: Discussion of discordant results**

(Participants will revisit those statements where there was particular variation in the views expressed, discuss associated data and have the opportunity to re-score them.)

12.30-13.30   Lunch

13.30-15.00   **Session 7: Finalize ranking for the 2017 list of priority diseases**

(WHO will present the draft ranking of diseases and pathogens and in accordance with the validated methodology, participants will undertake a final round of the Deplhi approach to finalise the ranking.)

15.00- 15.30   Coffee Break

15.30-17.00   **Closing Session**

Review of exercise
Opportunities to improve the process
Plenary discussion (all participants)
Closing remarks and next steps (WHO)

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