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Antiviral Research 159 (2018) 63–67

Contents lists available at ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

The WHO R&D Blueprint: 2018 review of emerging infectious diseases requiring urgent research and development efforts

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ARTICLE INFO

Keywords:
Severe emerging infectious diseases
Prioritization
Multi-criteria decision analysis
Experts' opinions
Multidisciplinary method

ABSTRACT

The Research and Development (R&D) Blueprint is a World Health Organization initiative to reduce the time between the declaration of a public health emergency and the availability of effective diagnostic tests, vaccines, and treatments that can save lives and avert a public health crisis. The scope of the Blueprint extends to severe emerging diseases for which there are insufficient or no presently existing medical countermeasures or pipelines to produce them. In February 2018, WHO held an informal expert consultation to review and update the list of priority diseases, employing a prioritization methodology which uses the Delphi technique, questionnaires, multi-criteria decision analysis, and expert review to identify relevant diseases. The committee determined that, given their potential to cause a public health emergency and the absence of efficacious drugs and/or vaccines, there is an urgent need for accelerated R&D for (in no order of priority) Crimean-Congo haemorrhagic fever, Ebola virus and Marburg virus disease, Lassa fever, Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS), Nipah and henipaviral diseases, Rift Valley fever and Zika virus disease. The experts also included "Disease X," representing the awareness that a previously unknown pathogen could cause a major public health emergency. This report describes the methods and results of the 2018 prioritization review.

1. Introduction: the R & D Blueprint

In May 2015, at the request of its 194 Member States, the World Health Organization (WHO) convened a broad coalition of experts to develop a Research and Development (R&D) Blueprint for Action to Prevent Epidemics (WHO, 2016a). The R&D Blueprint aims to reduce the time lag between the identification of a nascent infectious disease outbreak and approval of the most advanced products that can be used to save lives and prevent larger crises. It focuses on severe emerging diseases for which no, or insufficient, diagnostic, preventive and curative solutions exist, and which have the potential to generate a public health emergency. Diseases such as influenza, tuberculosis and HIV/AIDS, which have established control initiatives, R&D programs or existing product pipelines or regulatory pathways, are outside the scope of the Blueprint.

As an interim measure, the WHO convened a consultation in December 2015, in which a panel of scientists and public health experts compiled an initial priority list of diseases (WHO, 2015). Because technical developments, increased understanding of disease and real world events, including public health emergencies, make it necessary to regularly review and update the list of priority diseases, the WHO has held additional consultations. The latest meeting, in February 2018, brought together experts in:

- the microbiology of severe diseases, including virology, bacteriology and mycology;
- clinical management of severe infections;
- epidemiology, in particular during health emergencies;
- public health policy, including emergency response;
- animal health, including veterinarians expert in zoonoses originating from both livestock and wildlife;
- anthropologists; and
- experts from defence or security sectors familiar with biological weapons.

Collectively, these experts formed the Prioritization Committee (Appendix A). They made use of a tailored prioritization methodology developed by WHO and validated by external experts, which uses the Delphi technique, questionnaires and multi-criteria decision analysis to identify relevant diseases and rank their relative importance, in terms

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https://doi.org/10.1016/j.antiviral.2018.09.009
Received 17 September 2018; Accepted 18 September 2018
Available online 24 September 2018
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of the need for research. This report describes the methods and results of the 2018 prioritization review.

2. The prioritization process

2.1. Developing the methodology

In order to ensure that the list of diseases prioritized under the R&D Blueprint is as accurate as possible, WHO developed a comprehensive methodology based upon established best practices and practical national experience in compiling similar lists. The resulting methodology also specifically addressed criticism of earlier attempts to prioritize diseases. The general approach and key criteria were identified at the December 2015 consultation (WHO, 2015). These were subsequently expanded by WHO, and an outline of the eventual methodology was presented to, and validated by, the R&D Blueprint Scientific Advisory Group (SAG) in May 2016. Following input from the SAG, the methodology was further developed to include specific disease scenarios, a series of sub-criteria to explore different factors that could affect the relevance of a disease to R&D Blueprint objectives. WHO also developed the tools for Multi-Criteria Decision Analysis (MCDA) through a custom implementation of an Analytic Hierarchy Process (AHP), developed in collaboration with leaders in the field.

The entire methodology, its supporting models and attendant tools were reviewed at a dedicated consultation in November 2016 (WHO, 2016b). The meeting validated a general approach, endorsing a system of annual reviews, biennial methodology reviews, supplemented as necessary with emergency reviews. The annual reviews use a combination of rounds of the Delphi technique, questionnaires and MCDA to review and update the R&D Blueprint's priority list of diseases (Fig. 1). Following their revision in light of feedback, insights and recommendations received at the meeting, the tools and models were subsequently validated via a silence procedure in January 2017. The resulting methodology was published on the WHO website (WHO, 2017a) and a peer-reviewed journal (Mehand et al., 2018).

After its first full implementation, WHO carried out an assessment of the prioritization methodology. This assessment demonstrated: (a) the ranking produced was robust across different sensitivity scenarios; (b) similar group ranking was generated using three different approaches; and (c) the criterion "availability of medical countermeasures" had very little impact on the final ranking despite a high weight (Mehand et al., 2018; WHO, 2017b). As a result, the prioritization criteria and sub-criteria were updated (Table 1). Furthermore, to address possible biases, WHO developed a more comprehensive procedure for input from regional offices and expanded the range of experts proposing diseases for inclusion and participating in the annual review. The updated methodology will undergo a comprehensive review later in 2018 or 2019.

Table 1
2018 prioritization criteria and weighting.

Criteria	Weights
Human-to-human transmission	23.87%
Severity or case fatality rate	16.25%
The human/animal interface	9.16%
The public health context of the affected area	13.78%
Potential societal impacts	12.85%
Evolutionary potential of the pathogen	12.58%
Other factors (including the pathogen's geographic range, shared epidemiological and/or genotypic characteristics with pathogens that pose an epidemic threat, the absence of robust protective immunity, a high risk of occupational exposure, or connections with biological weapons programmes)	11.51%

The prioritization criteria were first developed in 2015 by a group of experts (WHO, 2015), reviewed, validated and weighted by another group of experts in 2016 (WHO, 2016b). After the 2017 annual review and subsequent sensitivity analysis one of the criteria (availability of medical countermeasures) was moved to the disease screening phase of the process. Consequently, the remaining criteria were reweighted by a wider group of experts by using online survey. These criteria comply with the MDCA best practice: completeness, non-redundancy, nonoverlapping and preference independence (Marsh et al., 2016; Thokala et al., 2016).

2.2. The 2018 annual review

The 2018 annual review followed a five-step process (Fig. 2).

2.2.1. Generating a long list of diseases

According to the published methodology, diseases on the preceding list from January 2017, as well as any that had been forwarded via the Blueprint's tool for addressing new diseases were to be automatically included in the comprehensive review to be conducted at the annual meeting. As a result, the 10 diseases on the 2017 priority list were automatically included on the short list. No disease had been identified using the Blueprint's tool for unknown diseases.

Over 90 experts, including those nominated by each of the WHO regional offices, as well as all those who had been involved in the prioritization process since 2015, were asked to propose additional diseases to be considered in the 2018 review. Between August and December 2017, each expert was requested to propose two diseases relevant to the Blueprint. Expert proposals were compiled into a long list by 13 December 2017 (Table 2).

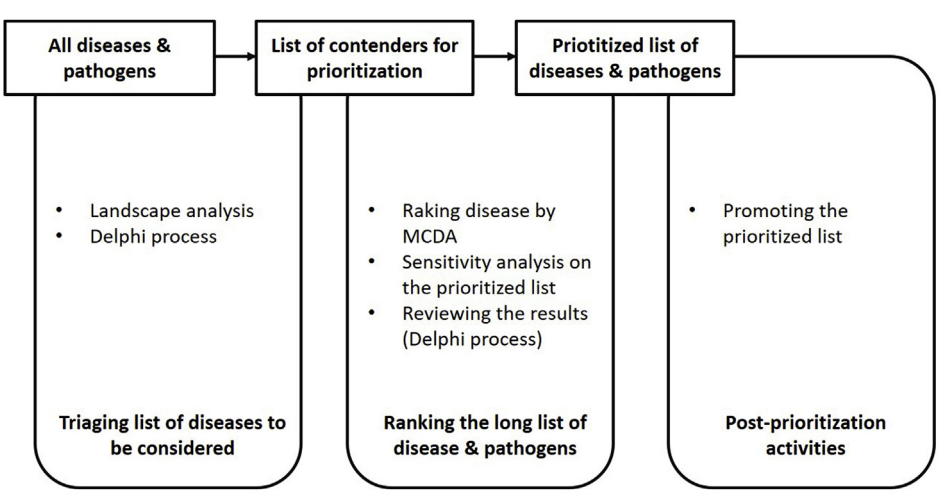

Fig. 1. Overview of the annual prioritization exercise. The process starts by gathering diseases candidates to consider for the annual prioritization. Through a Delphi process, several diseases are eliminated. For each remaining disease, a landscape analysis is commissioned before going into ranking through an MCDA method. The output of the MCDA is a ranked list of diseases. Several sensitivity analyses are performed on this list. These results are discussed through another Delphi process to produce the annual list of priority diseases. Finally, this list is promoted.

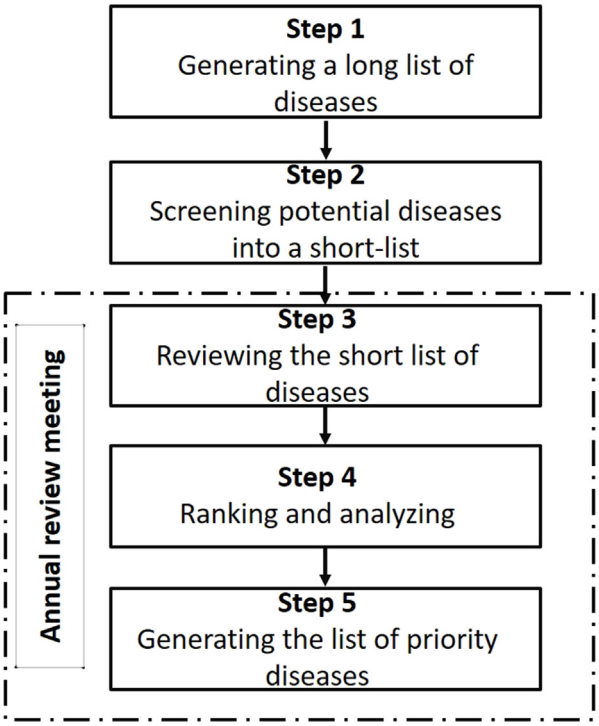

Fig. 2. The five-step annual process to review diseases prioritized under the WHO R&D Blueprint. This figure summarises the 2 steps (gathering the diseases candidates and narrowing their number) prior to the annual review meeting and the 3 steps (review of the remaining diseases, ranking them and the generation of the priority list of diseases) during the annual review meeting.

Table 2
Long list of additional diseases/pathogens proposed by global experts for inclusion in the priority list.

Disease/pathogen name	Reason for exclusion
Aflatoxicosis	Not in the top five suggestions from experts
Alphavirus diseases	Not in the top five suggestions from experts
Anthrax	Not in the top five suggestions from experts
Candida auris	Not in the top five suggestions from experts
Chandipura virus disease	Not in the top five suggestions from experts
Chikungunya	Low score- R&D recommended
Cholera	Outside the scope. Major control initiative exists, and a vaccine.
Endemic Kaposi syndrome	Not in the top five suggestions from experts
Kyasanur Forest disease	Not in the top five suggestions from experts
Leishmaniasis	Part of Neglected Tropical Diseases, funding is better channelled through there.
Mayaro virus disease	Not in the top five suggestions from experts
Necrotising cellulitis/fasciitis	Not in the top five suggestions from experts
Emerging non-polio enteroviruses	Low score- R&D recommended
Oropouche virus disease	Not in the top five suggestions from experts
Plague	Outside the scope, countermeasures exist.
Sindbis virus disease	Not in the top five suggestions from experts
South American haemorrhagic fevers	Not in the top five suggestions from experts
Usutu virus disease	Not in the top five suggestions from experts
West Nile virus disease	Outside the scope
Zoonotic brucellosis	Not in the top five suggestions from experts

2.2.2. Screening potential diseases into a short list

To identify which diseases from the long list should be considered alongside the 10 forwarded from the 2017 review, the same external experts (those nominated by the WHO regional offices and those who participated in past prioritization exercises) were asked to identify up to 5 diseases they felt were most relevant to the scope of the Blueprint. The top-scoring diseases were: chikungunya, plague, emerging non-polio enteroviruses, cholera, West Nile virus and leishmaniasis. Thus, the short list for the 2018 annual review consisted of:

- Arenaviral hemorrhagic fevers (including Lassa fever)
- Chikungunya
- Cholera
- Crimean-Congo haemorrhagic fever
- Filoviral diseases (including Ebola and Marburg)
- Leishmaniasis
- Middle East Respiratory Syndrome (MERS)
- Severe Acute Respiratory Syndrome (SARS) and other highly pathogenic coronaviral diseases
- Nipah and related henipaviral diseases
- Emerging non-polio enteroviruses
- Plague
- Rift Valley fever
- Severe Fever with Thrombocytopenia Syndrome
- West Nile virus disease
- Zika virus disease

In advance of the annual review meeting, a background document was compiled summarising the research landscape for each of these diseases. Contributions for this document were produced by disease-specific experts involved in the prioritization process and by a consultant commissioned by WHO. The information compiled for each disease covered its discovery, epidemiology, transmission, clinical course, as well as details of relevant surveillance and public health control measures.

2.2.3. Reviewing the short-listed diseases

Each of the diseases on the shortlist was discussed in turn after being introduced by an expert. There was an opportunity to share insights, seek clarifications, or explore relevant unpublished data. During the discussion on arenaviruses, a consensus was reached to separate Lassa Fever as a discrete entry for the 2018 review. It had previously listed by name and used as an example of relevant arenaviruses.

Following concerns raised during the short-listing process, the diseases were reviewed for their relevance to the scope of the Blueprint. It does not cover diseases if there are already major control initiatives, or extensive R&D pipelines, or existing funding streams, or established regulatory pathways. During the course of the meeting, it was determined that four of the short-listed diseases were outside the scope of the Blueprint:

- cholera has a major control initiative, through which any research and development efforts might be more appropriately channelled;
- leishmaniasis is officially considered a neglected tropical disease at WHO, and any R&D efforts might be more appropriately channelled through that forum;
- via a closed ballot a simple majority and over two-thirds majority of the Committee determined West Nile virus disease and plague respectively were outside of the scope of the Blueprint.

As a result, these diseases were removed from the short list. The remaining diseases were passed into the scoring process.

2.2.4. Disease ranking and analysis

Participants used the online survey tool developed by WHO to compare how the short-listed diseases corresponded with 29 factors of 7 different criteria contained in the prioritization methodology. The results were analysed using the AHP MCDA approach detailed in the prioritization methodology (more details in the peer-reviewed methodology and application (Mehand et al., 2018)). WHO Blueprint secretariat presented an overview of the results which was discussed and reviewed by the Committee. Results of a sensitivity analysis to measure the robustness of the ranking are presented in Appendix B.

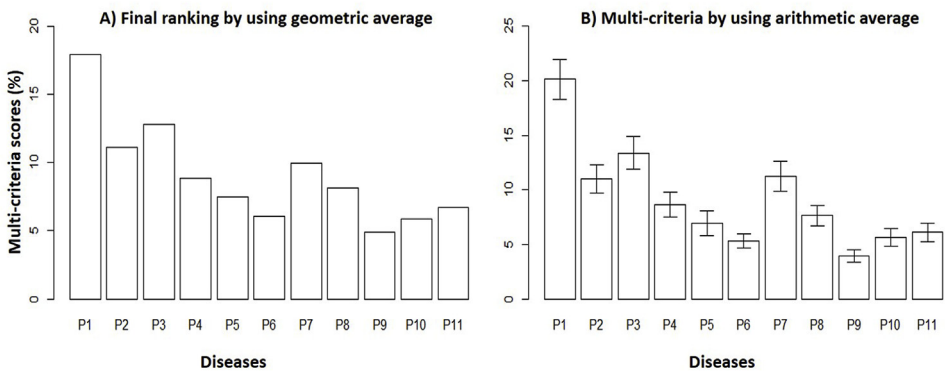

Fig. 3. Overall multi-criteria scores for diseases analysed using MCDA during the 2018 annual prioritization review. Panel A shows the results obtained using the geometric average the comparison matrices. Panel B shows the results obtained using the arithmetic average of the comparison values collected through the online questionnaire. The discordance internal are calculated through error propagation technique and presented in panel B (Mehand et al., 2018). (P1 = Ebola, P2 = Marburg, P3 = MERS, P4 = SARS, P5 = Lassa, P6 = Nipah, P7 = Rift Valley Fever, P8 = Zika, P9 = Crimean-Congo haemorrhagic fever, P10 = Severe Fever with Thrombocytopenia Syndrome, P11 = non-polio enteroviruses).

The Committee examined overall scores for each of the diseases (Fig. 3). These results could not be used directly to rank the short-listed diseases in a distinct order, as the discordance intervals (corresponding to the standard deviation calculated through error propagation) overlapped for many of them. However, the results demonstrated a sub-set of four low-scoring diseases (chikungunya, Rift Valley fever, non-polio enteroviruses, and Severe Fever with Thrombocytopenia Syndrome). Participants agreed that additional consideration was warranted as to whether the subset of low-scoring diseases should be prioritized under the Blueprint.

2.2.5. Generating the list of priority diseases

During a review of the four low-scoring diseases, participants made cases both for including them and for removing them from the priority list. A consensus quickly emerged that Rift Valley fever should remain on the list of priority diseases. Despite a thorough exchange of views amongst participants, there was no consensus as to what should be done with the other three diseases. There was broad recognition that they were relevant to the scope of the Blueprint and that additional R&D was necessary, but there was disagreement as to whether they should be prioritized to the same degree as the other diseases being considered.

As a result, an agreement was reached that the four low-scoring diseases should be captured in the report of the meeting, to highlight the importance of continued R&D, but they should not be included on the priority list. It was noted that one of them, Severe Fever with Thrombocytopenia Syndrome, was included in the 2017 list, and experts who had been present during that review recalled that it had been the lowest-scoring disease on the list. Equally, chikungunya was also considered during the last review but not included in the priority list. Several participants present at both 2017 and 2018 reviews suggested that had such a category been used last year (i.e. recommendations for further research but not a place on the priority list) both of these diseases would likely be in it. The third disease, emerging non-polio enteroviruses, was not on the longlist of diseases considered in 2017.

As a final step, participants discussed the most appropriate terminology to capture the diseases reviewed. Some minor changes were made to terms used previously. There was agreement that the list should contain diseases (as opposed to pathogens). There was also an effort to focus on specific diseases, rather than families of pathogens. For example, the entry 'filoviral diseases (including Ebola and Marburg)' was changed to read 'Ebola viral disease and Marburg disease'. MERS and SARS were combined into a single entry due to their relatedness and similar R&D approaches required.

3. Results of the 2018 prioritization review

The 2018 annual review determined that, given their potential to cause a public health emergency and the absence of efficacious drugs and/or vaccines, there is an urgent need for accelerated R&D for:

- Crimean-Congo haemorrhagic fever
- Ebola virus disease and Marburg virus disease
- Lassa fever
- MERS and SARS
- Nipah and henipaviral diseases
- Rift Valley fever
- Zika virus disease
- Disease X

The reader should note that the order of diseases on this list does not denote any ranking of priority, as there were no significant differences between the scores and no consensus on a ranked order. Arenaviral haemorrhagic fevers other than Lassa fever; chikungunya; highly pathogenic coronaviral diseases other than MERS and SARS; emergent non-polio enteroviruses (including EV71, D68); and Severe Fever with Thrombocytopenia Syndrome all pose major public health threats and require further R&D, including improved surveillance and diagnostic methods. They should be monitored carefully and considered again at the next annual review. Efforts in the interim to understand and mitigate them were encouraged.

The concept of "Disease X" was defined in the 2017 R&D Blueprint priority list of diseases as "any disease identified by the Blueprint's decision instrument for new diseases". It was formally added in the website in March 2017. Disease X represents the awareness that a serious international epidemic could be caused by a pathogen currently not recognized to cause human disease. Disease X may also be a known pathogen that has changed its epidemiological characteristics, for example by increasing its transmissibility or severity. The inclusion of Disease X on the priority list makes it clear that the Blueprint explicitly seeks to enable cross-cutting R&D preparedness that as far as possible is also relevant for currently unknown diseases.

This list of priority diseases does not aim to predict the next epidemic, and it is not exhaustive. Instead, it aims to focus WHO and global research efforts on diseases that need urgent R&D for the development of therapeutics, vaccines and diagnostics. Diseases on this list have been reported in 2018 in several countries, aptly demonstrating the importance and relevance of such a list: Lassa fever in Nigeria, Ebola virus disease in the Democratic Republic of the Congo, Nipah virus disease in India, as well as several cases of CCHF, MERS and Rift Valley fever. By focusing research attention on these emerging threats, health systems will be better prepared the next time they appear.

4. Diseases outside the scope of the prioritization review

During the course of the Blueprint's prioritization work, several diseases were determined to be outside of the current scope of the Blueprint: dengue, yellow fever, HIV/AIDs, tuberculosis, malaria, influenza causing severe human disease, smallpox, cholera, leishmaniasis, West Nile virus disease and plague. These diseases continue to pose

major public health problems, and further research and development is needed. In particular, the meeting heard of a need for improved diagnostics and vaccines for pneumonic plague and for additional support for more effective therapeutics against leishmaniasis. Although antimicrobial resistance is addressed through specific international initiatives, the possibility was not excluded that a resistant pathogen might emerge in the future and appropriately be prioritized.

Although not included on the list of diseases considered at the meeting (as they were not proposed by a sufficient number of experts), monkeypox and leptospirosis were also discussed, and experts stressed the risks they pose. There was agreement on the need for rapid evaluation of available potential countermeasures, the establishment of more comprehensive surveillance and diagnostics, and accelerated R&D and public health action.

5. Additional considerations

There was discussion of the impact of environmental issues on diseases with the potential to cause public health emergencies, and this may need to be considered in future reviews. Consideration of special populations such as refugees, internally displaced populations and victims of disasters was also noted as a core component of future discussions.

The value of a One Health approach was stressed, including a parallel prioritization process for animal health. Such an effort would support R&D to prevent and control animal diseases, minimising spillover to human populations and enhancing food security. The possible utility of animal vaccines for preventing human public health emergencies was also noted.

6. Next steps

The Prioritization Committee will provide feedback on the prioritization methodology, which will be reviewed by a separate expert group in late 2018 or 2019. The review will aim to ensure that the methodology is still fit for its purpose and as robust as possible. It will also be an opportunity to develop criteria for removing diseases from the list.

This prioritization is an integral step in the Blueprint process. Following the selection of diseases, R&D roadmaps will be developed by the WHO Blueprint secretariat and partners to articulate the R&D needs for each disease. These roadmaps will then feed into the broader Blueprint agenda of epidemic preparedness.

Acknowledgements

WHO is grateful to UK Department for International Development for financing this work and for members of the Prioritization Committee: Dr David Brett-Major, Dr Miles Carroll, Dr Gail Carson, Dr Inger Damon, Dr Peter Daszak, Dr Xavier De Lamballerie, Dr Christian Drosten, Dr Souha S Kanj, Dr Nadia Khellef, Dr Albert Icksang Ko, Dr Gary Kobinger, Dr Hilary Marston, Dr Stefano Messori, Dr Devendra Mourya, Dr Peninah Munyua, Dr Joshua Obasanya, Dr Janusz Paweska, Dr Chantal Reusken, Dr. Alfonso Rodriguez-Morales, Dr Pierre Rollin, Dr Cathy Roth, Dr Muhammad Salman, Dr Pedro Vasconcelos, Dr Supaporn Wacharapluesadee, Dr Jimmy Whitworth, Dr Annie Wilkinson, Dr Melissa Willis, Dr Yazdan Yazdanpanah, Dr Hervé Zeller for their time and input, and especially to Dr David Brett-Major, Dr Martine Denis, Dr Christian Drosten, Dr Peter Horby, Dr Xavier de Lamballerie, Dr Stefano Messori, Dr Alfonso Javier Rodriguez Morales, Dr Munyua Peninah, Dr Pedro Vasconcelo, Dr Herve Zeller, and Dr Jee Youngmee for compiling the background information on the candidate pathogens.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.antiviral.2018.09.009.

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