R&DBlueprint

Powering research
to prevent epidemics

WHO R&D Blueprint for Epidemics

Updating the WHO list of pathogens with epidemic and PHEIC potential

Concept Note

World Health Organization

Previous R&D Blueprint Prioritization

As per the World Health Assembly (WHA) resolution in 2016, the R&D Blueprint continues its work to accelerate research on a prioritized set of diseases that have epidemic or pandemic potential, and for which there are insufficient or no medical countermeasures available.

This effort is part of a larger scope of work in Emergency Preparedness and Response to:

- Accelerate research on disease threats before they emerge and integrate Disease X across research efforts,
- Shorten timelines in developing medical countermeasures (diagnostics, treatments and vaccines),
- Bridge gaps in research and infrastructure, and to expand both preclinical and clinical evaluation capacities in lower and middle-income countries (LMICs) according to GCP standards.

Since 2015, three prioritization exercises have taken place generating WHO recommended lists of priority diseases. The latest exercise dates to 2018 and identified the following pathogens of concern: *Crimean-Congo Haemorrhagic Fever (CCHF), Ebola, Marburg, Lassa Fever, MERS/SARS, Nipah, Henipaviruses, Rift Valley Fever, Zika, Chikungunya, Plague, and considerations for Pathogen X*. In early 2020, COVID-19 was added to the list.

Table 1 – R&D Blueprint achievements against the 2018 list of priority pathogens

DISEASE	Generic methodology	CCHF	Ebola & Marburg	Lassa fever	MERS-Cov & SARS	Nipah & henipavirviruses	Rift valley fever	Zika virus	Plague	Chikungunya	Pathogen X	COVID-19
R&D Roadmap	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓
Target Product Profile (TPP) vaccines	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	G	✓
Target Product Profile (TPP) therapeutics	✓		✓	✓								✓
Target Product Profile (TPP) diagnostics	✓	✓	✓	✓		✓		✓				✓
Regulatory pathways	✓	✓	✓	✓		✓		✓				✓
Vaccines trials design	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	G	LST
Therapeutics trials design	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
Decision tree for trials design	✓											
Trial simulator	✓											
Innovative analysis	Accumulating evidence during outbreaks and hybrid trial designs											
Good Participatory Practice for Clinical Trials of emerging pathogens (GPP-EP)	✓		✓									✓

✓ In progress ✓ Done G Generic LST Large Simple Trials

Over the past 5 years, the R&D Blueprint, together with the global scientific community, has made important progress in developing global R&D roadmaps for each priority pathogens; to develop Target Product Profiles (TPPs) that guide developers on the ideal attributes of the medical countermeasures; to tracks the clinical evaluation pipeline for vaccines, treatments and diagnostics for each priority pathogen; to landscapes clinical trials and compile the evidence and results; to develop appropriate clinical trial designs and standardized core protocols; and to implement clinical trials as needed including innovative analyses (see Table 1).

Updating the list of priority pathogens is long overdue and the R&D Blueprint is now launching a new prioritization exercises with the aim to have a revised list published sometime in the first half of 2023.

New Prioritization Approach

The prioritization exercise will draw on the lessons from COVID-19 and ensure that trust, equity and access for those at highest risk are central to future R&D efforts.

It will adopt a viral family approach to identify representative viruses (or prototypes) within a viral family as a pathfinder in generating science, evidence and filling knowledge gaps that may then be applicable to other viruses of threat in the same family. In recent years there has been growing support for this approach as it offers a framework to fast-track research and encourages research efforts on entire classes of viruses (e.g. flaviviruses), instead of just individual strains (e.g. zika virus), thus improving the capability to respond to unforeseen strains, zoonotic viruses (an animal virus that could jump to humans) and the potential threat of a Disease X. In addition, the prioritization will consider bacterial threats.

Table 2 – Recent prioritization exercises by viral family

No.	Viral Family	Virus	Australia (2022) [1]	NIH/NIAID (2022) [2]	UK Vaccine Network (2020) [3]	R&D Blueprint (2018) [4]	CEPI (2020) [5]
1	Arenavirus	Lassa	AUS	US	UK	RDB	CEPI
2	Coronavirus	MERS, SARS, COV	AUS		UK	RDB	CEPI
3	Filovirus	Ebola	AUS	US	UK	RDB	CEPI
4	Flavivirus	Zika	AUS	US		RDB	
5	Hantavirus	Hantavirus		US	UK	RDB	
6	Nairovirus	CCHF	AUS	US	UK	RDB	
7	Orthomyxovirus	Influenza	AUS				
8	Paramyxovirus	Nipah	AUS	US	UK	RDB	CEPI
9	Peribunyavirus	LaCrosse Virus		US			
10	Phenuivirus	Rift Valley Fever	AUS	US	UK	RDB	CEPI
11	Picornavirus	Enterovirus		US			
12	Togavirus	Chikungunya	AUS	US	UK	RDB	CEPI
13	Bacteria	Plague			UK	RDB	
14	Disease X	Pathogen X				RDB	CEPI
			9	10	9	11	7

[1] https://www.csiro.au/-/media/Services/Futures/Strengthening-Australias-pandemic-preparedness/22-00161_SER-FUT_REPORT_StrengtheningPandemicPreparedness_WEB_220527.pdf
[2] https://www.niaid.nih.gov/research/emerging-infectious-diseases-pathogens
[3] https://www.sciencedirect.com/science/article/pii/S0264410X19311971?via%3Dihub#f0010
[4] https://www.who.int/activities/prioritizing-diseases-for-research-and-development-in-emergency-contexts
[5] https://cepi.net/research_dev/priority-diseases/

The prioritization methodology will be implemented in two phases.

Phase 1: Scientific Review

The objective of phase one is to pare down a comprehensive list of virus and bacteria to a manageable number for deeper scientific review in order to end up with a shortlist of viral families, prototype viruses and bacteria, and Disease X recommendations.

The scientific review will be done by 20-25 viral family group of experts convened to shortlist viruses of concern. In addition, a separate bacterial group will be constituted to shortlist naturally occurring bacterial threats. These independent groups will represent a knowledge pool of over 300 international experts in microbiology of severe diseases (including virology or bacteriology), clinical management of severe infections; epidemiology, immunology and evolutionary biology, and expert in zoonoses and One Health. All groups will be led by an independent chair who will be responsible for its composition and ensuring gender balance and good representation of renowned experts from low and lower-middle income countries.

Each group will undertake the scientific review using a standardized tool developed by the R&D Blueprint. The chosen methodology for decision making will amplify the advantages of expert consultation while limiting its disadvantages (group think, dominating views…). It will ensure furthermore, that this consensus development approach is comparable, rigorous and transparent across all group.

The scientific review will involve the following 3 steps:

Step 1 – Pre-screening

Objective: To agree on a manageable list of relevant viruses and bacteria to start the expert review process, and by removing those widely agreed to be very unlikely to have epidemic and pandemic potential and can be dropped without further consideration.
Method: Group chairs (or a nominated member) propose a starting list to be reviewed and debated by the group. A pre-screening list is finalized during a group call with all members and forms the baseline list of viruses or bacteria.

Step 2 – Screening

Objective: To eliminate from the baseline list, those viruses or bacteria with low epidemic or pandemic potential.
Method: Delphi process using an online questionnaire containing 20+ screening questions focusing on: transmission in the absence of control measures, virulence (case fatality rates, sequelae rates), availability of medical countermeasures with a focus on vaccines and treatments.
Each group member completes a screening questionnaire for each virus or bacteria from the pre-screened list. The group results are compiled and fed back to each member individually. Each member is given a second opportunity to change any responses to the screening questionnaire considering the overall group results. Once done, the screening questionnaire is closed. The final group results are compiled and presented to the group. A group call is organized to agree on the final screened list of viruses or bacteria to carry forward to the next step of post-screening.

Step 3 – Post Screening

Objective: To shortlist viruses and bacteria with high epidemic or pandemic potential and no (or too few) diagnostics, treatments or vaccines.
Method: The screening and post-screening methodologies are the same. The difference resides in the post-screening questionnaire that contains 15+ additional questions on transmission, virulence and medical countermeasures. Once each group member has completed the post-screening questionnaire for each virus or bacteria carried forward from the screening phase, the results are compiled.
Each group organizes a call to debate the post-screening results and finalize their shortlist of that have the highest epidemic and pandemic potential and no or too few available medical countermeasures. Each group will further

recommend a prototype pathogen along with a pathogen that should be considered as a potential Disease X threat. In addition, review groups would provide suggestions for any data or evidence that can inform the prioritization phase.

Table 2 – Possible viral families for inclusion in the RDB prioritization exercise

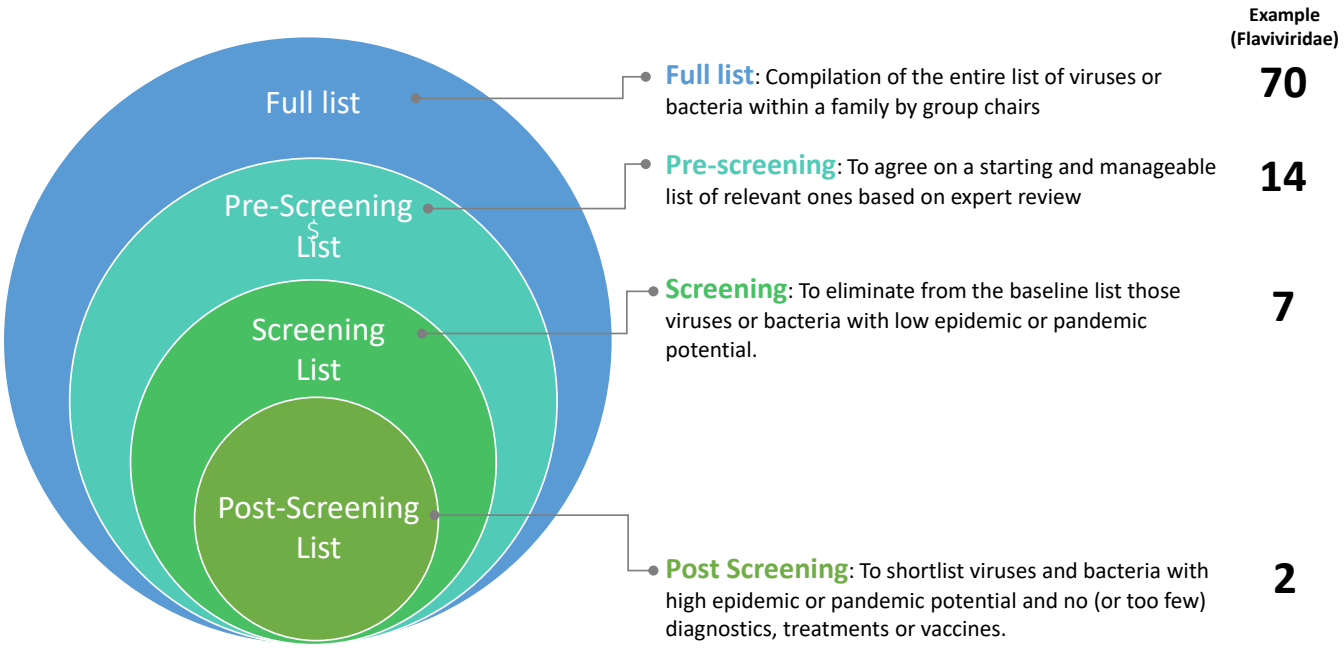
TABLE 201.3 Human Viral Infections Listed by Family[a]

Family Name	Representative Viruses[b]
Adenoviridae	Human adenovirus types 1 to 57 in seven species (human adenovirus species A to G)[28,29]
Anelloviridae[8]	Torque teno virus 1 (TTV1),[c] Torque teno mini virus 1, Torque teno midi virus 1[29] (type species for numerous viruses in 3 genera)
Arenaviridae	Lassa virus, lymphocytic choriomeningitis virus, Junin virus, Machupo virus, Guanarito virus, Sabiá virus, Whitewater Arroyo virus,[30] Chapare virus,[31] Lujo virus
Astroviridae	Human astroviruses (eight serotypes)
Bornaviridae	Mammalian 1 bornavirus (formerly Borna disease virus [BDV])[29]
Bunyaviridae	California encephalitis virus, Sin Nombre virus, La Crosse virus, Hantaan virus, Muerto Canyon virus, Crimean-Congo hemorrhagic fever virus, Sandfly fever viruses, Rift Valley fever virus, Heartland virus, and many others
Caliciviridae	Noroviruses, sapoviruses
Coronaviridae	SARS coronavirus; MERS coronavirus[29]; human coronaviruses OC43,[32] 229E, NL63,[33] and HKU1[34]; human torovirus and other human enteric coronaviruses
Filoviridae	Ebola viruses (e.g., Zaire ebolavirus, Bundibugyo ebolavirus, Reston ebolavirus, Sudan ebolavirus, Taï Forest ebolavirus),[29] Marburg virus
Flaviviridae	Genus *Alphavirus*: dengue virus, yellow fever virus, Japanese encephalitis virus, West Nile virus, Murray Valley encephalitis virus, Kyasanur encephalitis virus, tick-borne encephalitis virus, Zika virus, and others Genus *Hepacivirus*: hepatitis C virus (HCV) Genus *Pegivirus*[d]: GB virus-C[c] (GBV-C) (formerly hepatitis G virus [HGV])[35]
Hepadnaviridae	Hepatitis B virus (HBV)
Hepeviridae[9]	Hepatitis E virus (HEV)
Herpesviridae	Herpes simplex virus type 1, herpes simplex virus type 2, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, human herpesvirus 7, human herpesvirus 8 (i.e., Kaposi sarcoma-associated herpesvirus), herpes simian B virus
Orthomyxoviridae	Influenza A virus (e.g. subtype H1N1), influenza B virus, influenza C virus, Thogoto virus, Dhori virus,[36] Bourbon virus
Papillomaviridae	Human papilloma virus (>150 types with various degrees of oncogenicity)[37]
Paramyxoviridae	Measles (rubeola) virus, mumps virus, parainfluenza viruses, Hendra virus, Nipah virus, Menangle virus[38]
Parvoviridae	Human parvovirus B19, human bocavirus,[39] adeno-associated viruses[c,e]
Picobirnaviridae	Human picobirnavirus
Picornaviridae[40]	Genus *Enterovirus*: human rhinoviruses (>100 serotypes), enteroviruses (>100 serotypes, including poliovirus 1–3, coxsackievirus A and B, echoviruses, and other human enteroviruses) Genus *Hepatovirus*: hepatitis A virus (HAV) Genus *Parechovirus*: human parechoviruses Genus *Kobuvirus*: Aichi virus Genus *Cosavirus*: human cosaviruses[41] Genus *Cardiovirus*: Vilyuisk human encephalomyelitis virus, Saffold viruses[42] Genus *Salivirus*: human klassevirus,[43] salivirus A Genus *Senecavirus*: Seneca Valley virus[f] Unassigned: Syr-Darya Valley fever virus
Pneumoviridae	Respiratory syncytial virus, human metapneumoviruses
Polyomaviridae	JC virus, BK virus, KI virus, WU virus, Merkel cell polyomavirus, lymphotropic polyomavirus, human polyomavirus 6, human polyomavirus 7, trichodysplasia spinulosa-associated polyomavirus, human polyomavirus 9[44,45]
Poxviridae	Molluscum contagiosum virus, variola (smallpox) virus, monkeypox virus, vaccinia virus, orf virus, pseudocowpox virus, Tanapox virus, Yaba monkey tumor virus[46]
Reoviridae	Human rotavirus, Colorado tick fever virus, human reovirus,[c] Kemerovo virus
Retroviridae	Human immunodeficiency viruses types 1 and 2, human T-lymphocyte lymphotropic viruses,[47] xenotropic murine leukemia virus-related virus,[g] human endogenous retroviruses (HERVs), simian foamy virus
Rhabdoviridae	Rabies virus, vesicular stomatitis virus, Australian bat lyssavirus, Duvenhage virus, Mokola virus
Togaviridae	Rubella virus; Chikungunya virus; eastern equine, western equine, and Venezuelan equine encephalitis viruses; Ross River, Sindbis, and Semliki Forest viruses
Delta[h]	Hepatitis delta virus[e] (HDV)

[a]Examples listed correspond to common usage and do not necessarily comply with the official International Committee on Taxonomy of Viruses (ICTV) designations of virus species.
[b]Some zoonoses are included.
[c]Orphan virus for which a link to human disease has not been determined.
[d]Proposed genus name.
[e]Satellite virus requiring coinfection with heterologous virus for replication.
[f]Porcine virus being used clinically in humans as an oncolytic agent.[48]
[g]Possible laboratory contaminant.
[h]Floating genus, which is not currently assigned to a viral family. It bears some similarities to viroid pathogens of plants.

Source: Robert D Seigel. Classification of Human Viruses. Principles and Practice of Pediatric Infectious Diseases, Fifth Edition. Elsevier 2018. pp. 1044-1049 (Table 201.3 Human viral infections listed by family)

Fig 1: Proposed scientific review methodology



Phase 2: Scientific and Public Health Prioritization

An independent Prioritization Advisory Committee (PAC) will be convened to carry out the scientific and public health prioritization. The PAC will be composed of approximately 35 independent subject matter experts. An independent chair will be nominated to lead the work of the PAC and ensure the committee achieves the objective set out.

The committee will be composed of the chairs of each of the viral family and bacteria groups from phase one. In addition, membership will be expanded to ensure broader expertise is represented (in clinical management of severe infections, epidemiology during health emergencies, public health policy, health equity, social sciences, global health security…) and that a range of perspectives (key stakeholders including country and regional level perspectives) shape the final prioritization. The committee will make recommendations on any additional experts to be invited to join the PAC.

The final prioritization methodology will be transparent and replicable. It will involve agreeing a set of explicit criteria covering public health matters such as public health impact, health equity, economic and societal impact, to be added to the mainly scientific criteria used in Phase 1. Then each pathogen on a shortlist of candidates will be assessed against each criterion. The specifics of how to make the necessary trade-offs between ratings on different criteria will depend at least partly on the results of Phase 1, but it is likely to involve elements of Multiple Criteria Decision Analysis (MCDA) techniques such as pairwise comparison.

More specifically, methodology proposed will include the following four steps:

Step 1: Review of scientific screening results

The entire set of results from the scientific screening phase of work will be reviewed by the PAC. The chairs of the viral family and bacteria group will present their post-screening shortlist of priority and prototype pathogens along with their recommendation for Disease X. The full results will be discussed and debated during a scheduled call of the PAC.
It is estimated that approximately 20-25 viruses from 10-12 viral families will be carried forward into Phase 2 prioritization together with 1-3 bacteria.

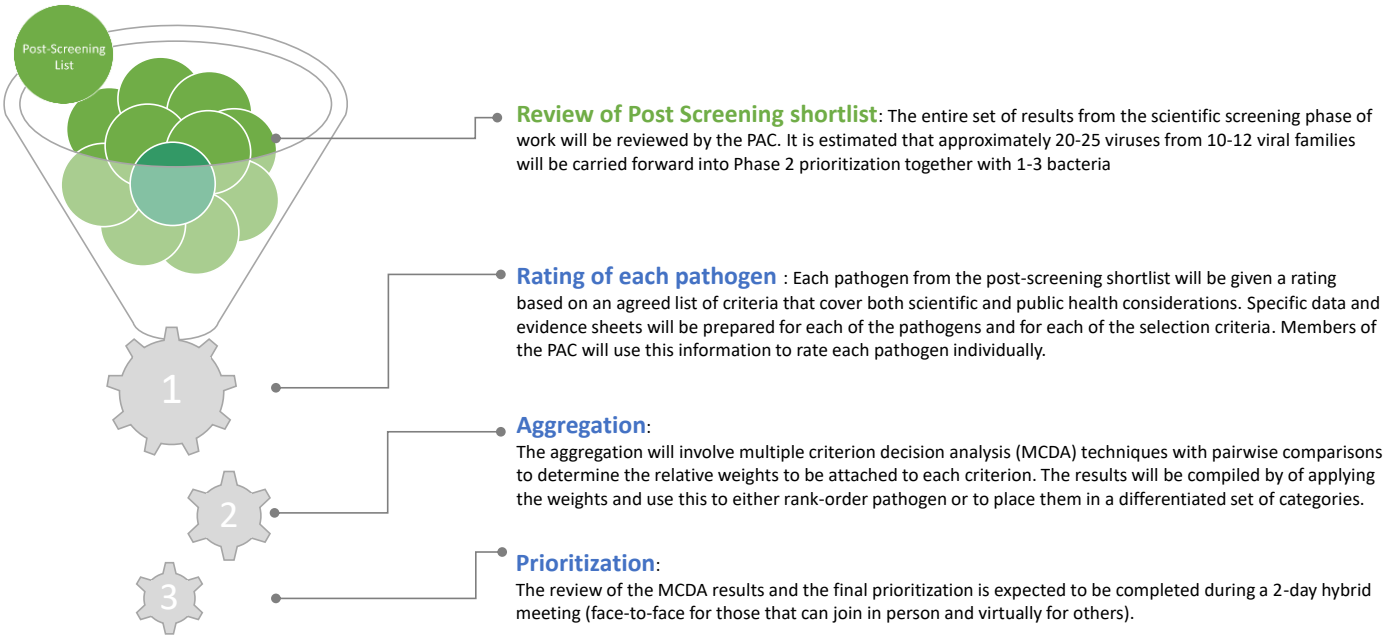
Step 2: Rating of each pathogen

Each member of the PAC will rate each pathogen from the post-screening shortlist using an agreed list of criteria and pathogen-specific data sheets.

The list of criteria to be used will be proposed by the WHO Secretariat for discussion with the PAC and will cover both scientific and public health considerations. The selection of criteria will draw on those used in other disease prioritization exercises (previous R&D Blueprint pathogen prioritization exercise, NIH/NIAID, UK Vaccine Network, HERA, France, Australia, CEPI). As much as possible, the criteria will be mutually exclusive, exhaustive and consistent with preference independence. Each criterion will include definitions of any categories used

The WHO Secretariat will prepare summary data sheets for each of the pathogens that will include information on transmission, virulence and medical countermeasures. Together with the list of criteria members of the PAC will use this information to rate each pathogen individually.

Fig 2: Proposed prioritization methodology



Step 3: Aggregation

Once the ratings of pathogens have been completed, the aggregation of results will involve multiple criterion decision analysis (MCDA) techniques such as pairwise comparisons to determine the relative weight to be attached to each criterion. The committee will need to decide whether the objective is to determine a rank-ordering of the pathogens, or to place them in a differentiated set of categories.

Step 4: Final Prioritization

The review of the MCDA results and the final prioritization is expected to be completed during a 2 day hybrid meeting (face-to-face for those that can join in person and virtually for others). Prior to the meeting the WHO Secretariat will brief the advisory committee during a virtual call and all materials will be shared in advance of the larger meeting.

Pandemic versus PHEIC

Given that the term pandemic is difficult to define, the R&D Blueprint prioritization exercise will adopt the WHO definition of a Public Health Emergency of International Concern (PHEIC) as: "*an extraordinary, serious, sudden global public health risk from international spread of a disease where a coordinated global response is required*". This definition is encoded by 2005 revision of the International Health Regulations (IHR) and its Emergency Committee announces PHEICs if any two of the four following questions are affirmed

- Is the public health impact of the event serious?
- Is the event unusual or unexpected?
- Is there a significant risk for international spread?
- Is there a significant risk for international travel or trade restrictions?

All nation states have a legal duty to respond to a PHEIC-