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STUDY PROTOCOL

REVISED Living Rapid Research Needs Appraisal (RRNA) for Priority Diseases Protocol

[version 2; peer review: 2 approved, 1 approved with reservations]

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Abstract

Systematic reviews require time and resources to conduct that might not be available in a rapidly developing context such as during new and (re-) emerging infectious disease outbreaks. As part of the Pandemic-PACT program at the Pandemic Sciences Institute at the University of Oxford we have, in collaboration with Cochrane Response and Cochrane South Africa, developed a "living" Rapid Research Needs Appraisal (RRNA) methodology. The aim is to develop a protocol for rapidly and robustly identify key evidence gaps across pre-defined research domains to inform research prioritisation and coordination in preparedness time and during outbreaks. The RRNA utilises modified systematic review methods, a global relay of reviewers, and systematic review software. The objective is to strengthen capability for carrying out RRNAs, and establish a baseline evidence platform for priority infectious diseases that can be readily updated as new evidence emerges, utilising an adaptable "living" RRNA protocol. This data will be of relevance to funders, researchers, clinical and public health stakeholders involved in management of infectious diseases of epidemic and pandemic potential.

Plain language summary

This document presents a methodology for carrying out a rapid research needs appraisal (RRNA) to be able to rapidly and robustly

Open Peer Review

Approval Status ? ✓ ✓

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identify existing published evidence on infectious diseases of epidemic and pandemic potential in preparedness time and in response to new infectious disease outbreaks. These findings will be important for identifying where there are gaps in our evidence base, e.g. on effective treatment and vaccines for different population groups such as children, adults, older people, pregnant women, or people with pre-existing illnesses. This data will be important for informing prioritisation of research to address these gaps, to generate the evidence to inform clinical and public health management to prevent infections, reduce risk of transmission, and improve patient and outbreak outcomes.

Keywords
Priority Diseases: Emerging Infections: Rapid Research Needs Appraisal: Evidence Gaps: Research Prioritisation

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REVISED **Amendments from Version 1**

The protocol has been updated following peer-review to improve clarity of the methodology and process. Updates includes details of the multidisciplinary expertise involved in developing the research domain categories, including experts in emerging infectious disease research and response, and specialists in One Health, review methodologies, data managers, epidemiology, public health, entomologists, veterinarians, social and behavioural sciences. Further specifics to clarify methodological processes, including data extraction quality checks and core analyses, and additional information e.g. on open-access free tools to emphasis and facilitate implementation in any resourced settings.

Any further responses from the reviewers can be found at the end of the article

Introduction

Systematic reviews require time and resources that might not be available in a rapidly developing context such as during a (re-)emerging infectious disease outbreak. Even rapid evidence reviews often take months to complete.[1,2] At the initial stages of an outbreak, researchers, policy makers and funders need to rapidly identify gaps in evidence and knowledge to inform and prioritise clinical and public health research responses. During outbreaks, the complexity associated with research prioritisation is compounded by the need for a rapid response. Experiences from outbreaks show that this takes time, and for protracted outbreaks priorities may change as the outbreak progresses and new evidence and needs are identified.[3]

This document presents a methodology for establishing a platform of 'living' rapid research needs appraisal (RRNA). The aim is to rapidly and robustly identify gaps in evidence across pre-defined research domains for new and re-emerging diseases of epidemic and pandemic potential, where existing evidence and knowledge is limited, to inform research prioritisation and coordination in preparedness time and during outbreaks. The RRNA can be pivoted to provide additional evidence from the identified records to inform clinical and public health strategies if and when required. The focus is on identifying gaps in the evidence base across domain topics and for different at risk populations and settings. The benefit of the RRNA is that it covers key domains relevant for prevention and early outbreak control to protect communities and healthcare workers. This breadth of evidence would not be feasible to cover in a traditional systematic review, however, if the RRNA identifies sufficient evidence for a specific domain it can readily be pivoted to a full systematic review if needed and resources allows. The RRNA methodology is specifically developed for new and (re-)emerging infectious diseases where existing evidence is limited. Diseases that have been well researched over the years, such as Dengue and COVID-19 are out of scope for a full RRNA, but could be considered for a targeted RRNA focused on specific domain/s and sub-domain questions. The protocol is designed in a modular approach, with flexibility to target RRNAs depending on the disease, context, and recognised need. We aim to establish a platform of RRNAs for infectious diseases prioritised for research and development by the World Health Organisation and international experts.[4] The objectives are to provide a baseline of evidence highlighting key gaps across a set of pre-defined, key research domain categories, which can be readily updated as new evidence emerges during outbreaks. A secondary objective is to provide a repository of published evidence that can readily be pivoted to present existing published evidence to inform research and public health strategies. This data will be of relevance to researchers, funders and policy makers to inform research prioritisation, coordination and pre-positioning of research ready to be implemented at outbreak outset to strengthen our global preparedness for a coordinated, effective and equitable research response to outbreaks, to generate evidence to inform strategies to protect populations, and improve outcomes.

Protocol

This protocol has been developed in collaboration with methodologists, information specialists, infectious disease researchers with experience in outbreak response, public health specialists and social scientists at the University of Oxford, in collaboration with experts from Cochrane Response and Cochrane South Africa, and in consultation with multidisciplinary external experts. It builds on a prototype protocol developed earlier,[5] which has been expanded in scope and flexibility to create a living modular platform that can readily and flexibly be implemented in a targeted approach. The research domain categories have been informed by consultations with experts in emerging infectious disease research and response, and specialists in One Health, review methodologies, epidemiology, public health, entomologists, veterinarians, social and behavioural sciences. They are focused on evidence relevant to prevention and early outbreak response to protect communities and health workers to protect populations and improve outbreak outcomes. By designing it in a modular approach researchers can adopt the concept and process and modify domains as requires for other purposes, e.g. add or remove new domains or domain questions and modify the search strategy and eligibility criteria accordingly. The methodology is derived from systematic evidence review methodologies and modified to allow the rapid and robust identification of evidence-gaps on emerging infectious diseases during outbreaks. The protocol is developed following PRISMA-P guidelines. The systematic evidence search will be carried out by a health information specialist, and the

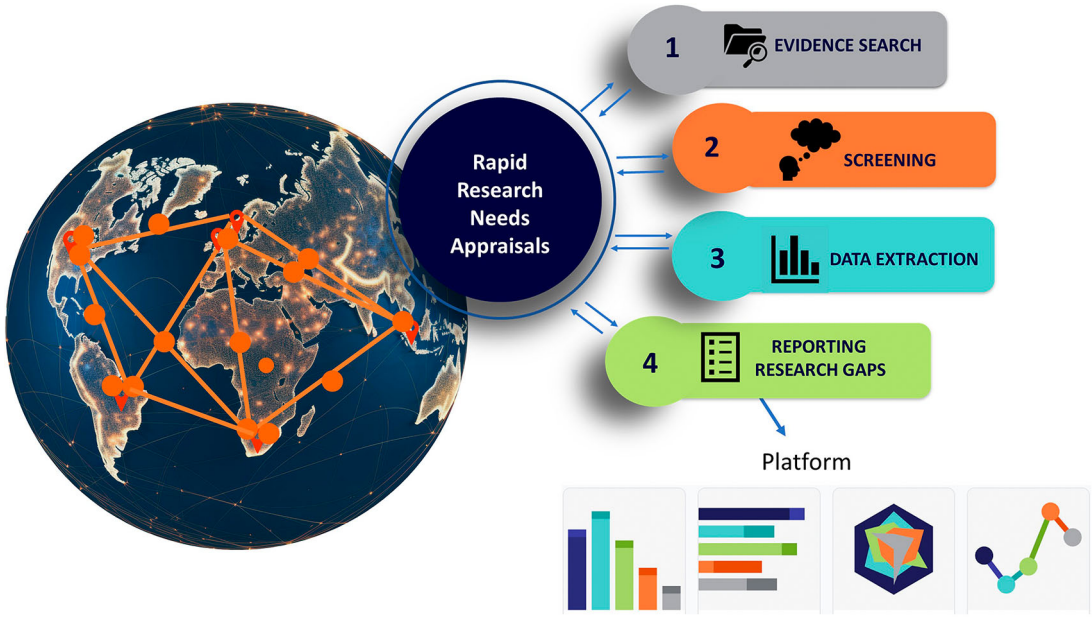


Figure 1. Rapid Research Needs Appraisal (RRNA) Process. Image credit: Cochrane South Africa.

screening of records and data extraction by reviewers based in different time-zones, who are trained in the methodology to ensure rigour and quality. The minimum number of systematic reviewers at each stage is laid out in detail in later sections and can be scaled up depending on the volume of evidence identified at the search stage. The use of a web-based systematic review software will enable scaling up of resources as required and will allow processes such as screening and data extraction to be carried out in parallel by multiple reviewers. Using a pre-programmed systematic review software facilitates standardisation of data extraction and quality assurance, as well as rapid initiation of an RRNA and update of an existing RRNA in response to outbreaks. This is an open-access protocol describing a method for rapidly and systematically identifying gaps in the evidence base to inform research prioritisation for implementation in any resourced settings.

It is developed to facilitate implementation in any resourced setting, and global collaboration across regional time zones for effectiveness, quality and applicability. In the interest of global preparedness and response, it is advised to share generated data via open-access data sharing platforms. The RRNA utilises modified systematic review methodologies and a global relay model for efficiency, regional expertise and quality (Figure 1). The protocol methodology and management process is described in detail below.

RRNA team roles and responsibilities

The decision to undertake an RRNA will be informed by available risk assessments, consultations with content experts and recognised need as appropriate depending on each outbreak. An RRNA will only be undertaken if after consultations it is deemed that there is insufficient evidence available to base an informed decision on clinical research priorities (Figure 2). An RRNA steering group (SG) is responsible for informing the need and scope for an RRNA, and the capability and feasibility of implementing an RRNA in preparedness time and during outbreaks. The SG will review outbreak alerts and stakeholder requests and will decide when and if there is a need for an update. The SG will also take a decision on the need to target of the RRNA depending on each disease, disease family, outbreak and context, in consultation with the coordinating team and stakeholders as appropriate. The SG is responsible for resource management and for overseeing the project, scope, targeting, quality, analysis and dissemination of the findings. Moreover, deciding on need for and overseeing engagement and consultations with external stakeholders and experts if appropriate.

Coordinating Team (CT)

It is recommended to sustain a standing CT trained in the methodology to ensure readiness and rapid mobilization when needed. The CT will be responsible for coordinating the process from notification of the need for a RRNA from the SG, through to completion (Table 1). The CT will also be responsible for training reviewers in advance and for scaling up implementation during outbreaks. This protocol and associated training video available via the Pandemic PACT website (https://www.pandemicpact.org/) can aid in scale up. The SG and CT may be the same team depending on need and resources.



Figure 2. RRNA methodology overview. Abbreviations: CT: coordinating team; RRNA: Rapid Research Needs Appraisal; SG: Steering Group; SR: systematic reviews.

Table 1. Coordinating team responsibilities.

Coordination	To coordinate the overall process including tools and teams from the start through to dissemination of the findings. Registers the core protocol (e.g., in OSF). Ensure the review software is pre-programmed and reviewers and other stakeholders involved are trained in the methodology and process.
Day 1–2: Preparation & alert phase	To review the need for refinement of the protocol depending on the disease and context. Consult with experts and carry out an initial search for available systematic reviews already addressing any of the domains, and target the protocol accordingly, Pilot and finalise the search strategy. Liaise with information specialist, reviewers and internal and external experts as appropriate to inform the need for any amendments to the protocol for each disease and outbreak context.
	To finalise amendments and targeting of the protocol.
	To submit the final protocol with any amendments clearly highlighted in track changes to the search specialist and systematic review team/s.
	To provide a brief overview of the disease with relevant background information.
Day 2–10	To retrieve full text articles not identified by the reference manager systems (e.g. EndNote) automatic retrieval function and be on stand-by to provide clinical or content specific advice as required.
Day 4–14	To support screening of articles and data extraction.
	To monitor the progress and help find solutions to any unexpected issues.
Day 6–10	Full text screening and data extraction
Day 10–14	To collate, tidy and present the data outcome tables and notes from the systematic review team/s with gaps analysis in the final report and submit the report to the steering group and collaborators for review and approval.

Abbreviation: OSF: Open Science Framework.

Recommended composition of the CT:

- Clinical researcher with experience in infectious disease research;
- Researcher with experience in systematic evidence review methodologies;
- Additional content experts, such as infectious disease epidemiologists, public health professional, social scientist, diseases specific experts as required depending on the nature of the outbreak;
- Administrative support.

Responsibilities of the CT:

- Signs-off the final protocol and any amendments. Ensures the protocol is registered in an open-accessible database such as the Open Science Framework and that the review software is pre-programmed, and all stakeholders involved are trained and familiar with the process and review software used.
- Alert the information specialist and systematic review team/s of the need for a RRNA.
- Review the protocol and identify if any adaptions or targeting are needed depending on the nature of the outbreak.
- Review the initial pilot search and systematic reviews identified to inform targeting of the final search (terms, restrictions in terms of sub-domain terms, and inclusion years), and protocol (targeting by disease, domains, sub-domains, level of study design to include, years to include, data charting and extraction scope).
- Share the protocol with collaborators and external partners to review as appropriate before starting the RRNA relay.
- Finalise and send the protocol together with a brief overview of the situation and clinical background information, to the search specialist and systematic review team/s by the end of Day 1.
- Provide a verbal briefing to the search specialist and systematic review team/s.
- Advise if specific language expertise might be required e.g. depending on disease endemic regions where evidence is likely to be generated.
- Register the protocol on the Open Science Framework (OSF) or similar platform.
- During the process the coordinating team will be at hand to answer clinical and content specific queries from the systematic review teams.

Information specialist

The information specialist will be responsible for carrying out a systematic evidence search across all domain questions after the CT has reviewed and made any necessary amendments to the protocol depending on each disease. The information specialist will liaise with the CT and will carry out a pilot search for SRs and primary research to inform the final search. They will forward the search results, after automatic de-duplication of records in the reference manager system, as a library data file to the CT (Table 2). The CT will run an automatic full text article retrieval and upload the library with full texts retrieved to the systematic review program.

Systematic review team

To ensure rigour and quality, it is essential that the systematic review team/s involved are trained in the methodology and in screening and data extraction in advance. A minimum of three systematic reviewers is essential for quality. Depending on the volume of records retrieved, the number of systematic reviewers can be scaled up if required. The responsibilities of the systematic review team/s are outlined in Table 3, and ideal multidisciplinary expertise of the review team in Table 5.

The review teams will be sent the protocol, with any edits made visible in track changes on Day 1. The team will refine the systematic review software programming (or if using Excel, the Excel data extraction template) as/if required. They will

Table 2. Information specialist responsibilities.

Day 1	Provide specialist advice to refine the search terms and pilot the search to inform the final search strategy.
	Carry out an initial search for systematic reviews and a pilot search for primary research studies to inform targeting of the search strategy, protocol and resource planning.
Day 1–2	Carry out the systematic search of three databases using the final agreed search strategy, across the relevant domains when they receive the final protocol from the coordinating team.
	De-duplicate search records.
	Share the search results as a reference manager data library file, methods statement and search strategies with the SG and CT. The coordinating team sends out an alert when the results are uploaded to the systematic review software and ready to screen.
Day 3–14	On stand-by to support queries, evaluation of the search strategy as and if required. Provide information on the search strategy to inform the final report and publications.

Table 3. Responsibilities of the systematic review team.

Preparation	Programs and pilots the systematic review software data extraction template/program. Familiarizes themselves with the protocol, the aims, objectives, eligibility criteria, and the domain questions and the disease specific background brief.
Day 1–2	Review the RRNA protocol, set up the extraction templates and tools.
	Inform refinement of the protocol. Program the systematic review software; screening and data extraction templates. Identify additional reviewers with specific language skills if needed and feasible.
	Review the background briefings (e.g. from WHO/CDC websites) to familiar themselves with the disease.
	Establish an instant messenger chat platform (e.g. Slack) for all involved in the RRNA.
	Once the deduplicated search results are received, upload it to the systematic review software*, run a second deduplication using the review software or manually, then run an automatic full text article retrieval, send an alert to all reviewers via the chat and e-mail to start screening.
Day 2–6	Screen titles and abstracts, followed by full text screening with data mapping.
	If full texts are not retrieved automatically, search for them in PubMed, Google, or the University online library. If still not accessible, exclude as inaccessible, document exclusion reason, and provide bibliography to these in the appendix of the final report.
	At full text screening stage, map key data including study design, domain, sub-domain and key population groups included (young children (<5 yrs), children & young people (CYP 5–17 yrs, adults (18+), pregnant women to provide a rapid overview of the available studies and inform data extraction prioritisation.
Day 3–6	When full text screening and data mapping is complete, review the interim data and liaise with the CT to discuss need for data extraction prioritisation by domain/sub-domain and study design (Table 4). E.g. if sufficient high level of data is available to address a sub-domain, then lower level of evidence does not need to be extracted as the focus is to identify gaps in the evidence base.
	Start full data extraction of those domains and records pivoted to full extraction.
Day 4–10	Complete data extraction, clean the data – check for missing and inconsistent data for key data on: study setting study design, key focus and population groups, follow up as/if required to correct.
	Submit the data extraction tables for all domains to the coordinating team for a final review and data analysis. Analysis can be facilitated in advance by programming codes for descriptive analysis/tabulation and creation of graphs (see examples in our extended data available at: 10.17605/OSF.IO/TWFNR), this will facilitate data dissemination and updates if required as new evidence emerges.

*Depending on resources and access to review software, Microsoft Excel is an alternative if no access to a review software.

refine the systematic review program if updates have been made to the protocol, e.g. updates to the screening eligibility, and/or the extraction program, e.g. activate or deactivate individual sub-domain categories/questions or whole domains to be included in the mapping/data extraction.

The lead systematic reviewer will upload the reference manager library file to the systematic review software. The reviewers will then start the screening (titles and abstracts, followed by full text screening), extract the data into a

Table 4. **Study designs and the hierarchy of evidence.**

Hierarchy	Study designs
1a	Systematic reviews with meta-analyses
1b	Systematic reviews (without meta-analysis)
Interventional studies	
2a	Randomised controlled trials (RCT) (e.g., randomised treatment, supportive care, vaccine trials with control arm, Phase 2 and 3 vaccine* trials, adaptive RCTs)
2b	Randomised controlled studies (e.g., randomised qualitative intervention with control arm)
	Non-randomised interventional studies (e.g. non randomised trials, before-and-after study/ pre-post study/single arm, quasi-experiment, Phase 1 and non-randomised Phase 2 vaccine studies)
Observational studies	
4	Cohort studies* (prospective/retrospective) *a group of individuals exposed to a putative risk factor with or without an unexposed control group followed over time to determine the occurrence of disease. Participants selected based on the exposure status.
5	Case-control studies* e.g., cases of people and matched controls, human samples and control samples, diagnostic development studies with control *compares two groups of people or human samples: those with the disease or condition under study (cases) and a group of people who do not have the disease or condition (controls). Participants selected based on the outcome.
6	Cross-sectional studies (e.g. survey/focus groups, healthcare data analysis, diagnostic studies without control, outbreak reports) * measures the prevalence of health outcomes or determinants of health, or both, in a population at a point in time or over a short period. Participants selected based on the study inclusion and exclusion criteria.)
7	Case series/Case reports
8	Opinion pieces (e.g. comments, letters, viewpoints) if they present primary data (for new and emerging viruses, early data may be presented in rapid comments)

Table 5. **Systematic review expertise.**

Minimum of three experienced systematic reviewers trained in the methodology, familiar with infectious disease research, prevention and response, the systematic review software and tools used for the RRNA.
Ideally based in different time zones to allow scalability and to bring in diverse language skills and expertise, e.g. knowledge of diseases endemic in different regions.

pre-defined data extraction template using the review software. Alternatively, if no access to review software, then the screening decisions and the data extraction can be made using Microsoft Excel. Using a shared Microsoft Excel platform will facilitate collaboration and coordination of the review process. The systematic review team/s will export and send the completed data outcome templates to the coordinating team by mid-day by day 10. The systematic review software enables screening and data extraction processes to run in parallel and reduce the need for lengthy handovers, while minimizing knowledge transfer loss.

Systematic review software

If access to a systematic review management software (e.g. DistillerSR, RedCAP, Rayyan, Covidence)s this will allow processes to run in parallel without the need for handovers, and facilitate standardisation of data mapping/extractions and future updates as new evidence emerges. A systematic review software also enables continuous monitoring of progress, rapid identification of issues and facilitate audits and quality checks. A program such as Microsoft Excel can be used as an alternative, but requires more manual administrative management, allocating records for screening and data extraction to reviewers and progress monitoring and manual extraction, versus tick-box options.

Reporting responsibilities

The systematic review team/s are responsible for submitting the completed data extraction tables to the coordinating team via e-mail or other sharing platform as soon as completed for timely data sharing. The CT will review and clean the data as appropriate. The final clean data extraction tables can also be shared using an appropriate, secure systems (e.g. Figshare, GitHub) for open-access data sharing. The reviewers will complete and submit the PRISMA-ScR diagram (Scoping — PRISMA statement template), presenting the number of records identified from different sources, reasons for exclusions and final numbers included. This will be presented in the final report.

RRNA process

The process is derived from modified systematic and rapid evidence review methodologies (Figure 3).

Research domain categories

We will leverage our protocol to create an in-depth, 'living' RRNA platform presenting evidence across key health protection domains for different population groups. We will focus on specific priority pathogens/diseases or pathogen families. This framework will support continuous, needs-driven identification of evidence available across at-risk population groups for topics listed below:

1. Clinical characteristics, epidemiology
2. Immune response, seroprevalence
3. Transmission (human-to-human)*
4. Risk factors for infection, severe disease, death, long term-complications
5. Vaccine and therapeutic prophylaxis research
6. Diagnostic methods
7. Therapeutic research
8. Supportive care
9. Social and behavioural factors

*A research domain focused on animal-to-human transmission is available as an add-on option.

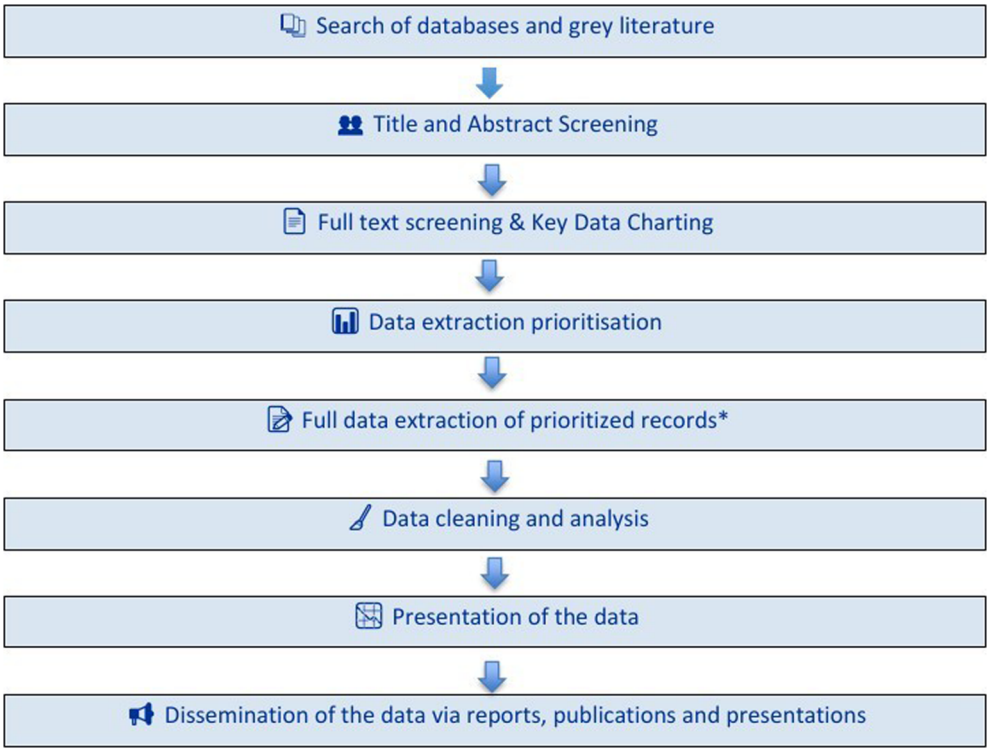


Figure 3. RRNA process flowchart.

The protocol is developed in an adaptable, modular approach, to facilitate adaptation depending on the disease, disease family, recognised gaps or request for specific data. The domains have been informed by multidisciplinary experts via consensus, focused on key essential data for protection of populations and healthcare workers from new and (re-)emerging priority pathogens. If the first rapid search for systematic reviews (SR) identifies a robust SR that fully addresses a domain or domain question for all population groups (e.g., by age, sex-at-birth, immunosuppression and by setting if relevant), then the adaptable approach allows deactivation of that domain from the full RRNA, i.e., no need to extract lower level of evidence already included in the SR, since the focus is on identifying gaps in the evidence base.

Evidence will be identified through a peer-reviewed search, complemented by a grey literature search (e.g. of international, regional/national public health, WHO, CDC databases) when required. We will search for studies including humans or human samples. No language restriction. By utilising a global relay of trained reviewers and a systematic review software ensure effectiveness, quality and minimise knowledge transfer loss.

We will perform a descriptive analysis and present interim analysis to stakeholders as appropriate and incorporate feedback received before finalising the report. We will disseminate the data directly to policy makers and via our Pandemic PACT website, reports and publications as appropriate to facilitate wide dissemination of the findings.

Eligibility criteria

Studies focused on new and (re-)emerging priority infectious diseases of epidemic and pandemic potential with a limited evidence base, focused on at least one of the domain topics in the protocol and includes humans or human samples (Table 6).

Inclusions:

Studies focused on the disease;

AND

• Includes human or human samples e.g. (blood, semen, urine, faeces)

AND

• Focused on studying at least one of the RRNA research sub-domain categories in Table 7

• No language restriction

Table 6. Eligibility criteria.

Inclusion criteria	Exclusion criteria*
Studies focused on the specified disease/s that involves humans or human samples.	Pure animal, vector (insect, parasite), virus/pathogen studies, Data modelling studies.
Studies presenting primary data and focused on at least one of the research sub-domains in our protocol (Table 7). Preprints should mainly be considered for very rare diseases or during outbreaks only.	Pure cell culture and *in vitro* studies.
Any language.	Conference abstracts, Book chapters, Narrative reviews, Scoping reviews, Mapping reviews, Opinion pieces not presenting primary data, Pre-prints*

*These will be reviewed and modified depending on each outbreak and context. E.g. for new, emerging diseases with emerging evidence expected, pre-prints may be included.

Table 7. Data extraction table. Grey text indicates data fields that can be added for extracting additional information, depending on need and resources.

Step 1: Key Data Charting	
Demographics	**For all studies extract:**
Bibliography	Authors, Year, Title, Journal, Doi/weblink (if grey lit. website include date accessed)
Disease/s	Multiple choice if including more than one disease (e.g. viral family RRNA)
Domains and Sub-domains	Multiple choice x =1 – 9, If x, populate and select sub-domains for x – tick all
Participants	Number
Key population groups	Neonates/Infants (0–<1 yrs), Young Children (1 – <5 yrs), Children & Young People (CYP) (5–17yrs), Adults (18+), Pregnant women, NR
Cases	Number
Cases: key population groups	Neonates/Infants (0-<1 yrs), Young Children (1–<5), CYP (5–17), Adults (18+), Pregnant women, NR
Study type	Interventional, Observational
Control group included (Yes/No)	Yes, No
Study design	SR (systematic review), RCT, Randomised study, Non-randomised study, Cohort study, Case-control study, Cross-sectional study, Case series/ report >10 cases, Case series/report ≤10 cases, Opinion piece with primary data, Other (specify):
Study Year/s	YYYY – YYYY or NR
Study Setting (Country)	Multiple choice
Study Abstract	Copy in (if not abstract is available, copy in the main summary of the study)
Step 2: Records prioritised for full data extraction	
Participant characteristics:	
Age (mean/median/ range):	- Minimum age (youngest person included in study) - Maximum age (oldest person included in the study) - Median/Mean (IQR/SD/range) as presented or NR
Sex	Females include – Y/N/NR, If yes: (% , n/N) females included, NR
Ethnicity	Arab, Asian, Black, Indigenous (specify), Mixed, White, Other ethnicity (specify): , NR
Occupational risk populations:	Emergency Responders, Farmers/Herders, Funeral staff, Healthcare workers, Military workers, Other animal workers, Slaughter staff, Veterinarians, Waste workers/ Cleaners, Wildlife/Forestry workers/Hunters, Other (specify), NR
Specific population groups:	Breastfeeding women, Care home residents, Drug users, General Population Healthcare workers, Hospital patients, Malnourished, Men who have sex with men, Other sexual/gender minority groups, Obese, People living with disabilities, People living with HIV, People living with other comorbidities (specify:), Prisoners, Pregnant women, Refugees /Internally displaced persons/Migrants, Sex workers, Students, Other specified vulnerable population groups (specify:), NR
Healthy participants/ samples	Number
Case contacts (n)	Number
Domain	**Sub-domain questions**
1.Clinical characteristics, epidemiology	• Cases (confirmed and probable) (n) • Case fatality rate (%, n/N) • Signs and symptoms (dropdown list – see Excel file)

Table 7. *Continued*

Domain	Sub-domain questions
Sub-domains: Signs & Symptoms Case Fatality Rate (CFR) Biomarkers (symptoms, lab, genomic/proteomic) Complications: acute Complications: pregnancy Complications: long term	• Key clinical features that may distinguish the disease from other diagnoses studied? Yes No, If yes, extract the data: • Acute complications reported (e.g. liver, kidney, respiratory failure, secondary bacterial infection, sepsis, psychological etc.) – if yes, specify data: • Pregnancy complications reported Yes, No, NR • Long-term sequelae or complications (post-acute) studied, if yes, specify: • Biomarkers for diagnosing/identifying the disease studied? Yes No, if yes – tick box: a laboratory marker (e.g. CRP), clinical sign (e.g. hypertension), OR genomics, OR proteomics, OR a model (e.g. a clinical score system) OR a clinical validation system or other biomarker (specify): • Biomarkers/indicators for a risk of severe disease studied? Yes No, if yes – tick box: a laboratory marker (e.g. CRP), clinical sign (e.g. hypertension), OR genomics, OR proteomics, OR a model (e.g. a clinical score system) OR a clinical validation system (several established clinical markers, e.g. CRP, procalcitonin, blood pressure, and fever, etc.), or other biomarker (specify): • Data on risk of re-infection after natural infection? Yes No
2. Immune response/ Seroprevalence **Sub-domains:** Acute immune response Seroprevalence Re-infection after infection	• Data on: dropdown: T cells, CD4+/CD8+ cytokines, other? • Seroprevalence data? Yes No • Data on risk of re-infection after natural infection? Yes No

3a. Transmission (human-to-human)
 	
Sub-domains:
Pathogen in human samples
Transmission routes (human-to-human)
Transmission risk/infectivity from human samples
Effectiveness of healthcare IPC
Effectiveness of PPE
	• Incubation period? Yes No NR
	• Asymptomatic, prodromal, post-acute transmission reported? Yes No NR
	• Routes of human-to-human transmission studied (e.g.. airborne, direct contact, droplet, indirect contact, saliva, sexual)?
	• If yes, extract the data:
	• Virus detected in human samples? If yes, indicate sample type:
	• Risk of infection from human body fluids studied?
	  ○ (if yes, indicate: blood, conjunctival fluids, breast milk, saliva, semen, stool, transplant tissue, urine)?
	  ○ If yes, period/length of infection/persistence of virulence/virus in body fluids – extract the data.
	• Effectiveness of infection prevention control methods to reduce risk of transmission in healthcare settings? Yes No
	• Effectiveness of personal protective equipment (e.g., facemasks, eye shields) studied? Yes No

4. Risk factors for infection and severe disease **Sub-domains:** Risk factors for disease Risk factors for severe disease	• Host risk factors for infection identified (e.g. sex, age), comorbidities)? if yes, specify: • Host risk factors for severe disease or acute complications studied? if yes specify: • Host risk factors for long-term complications/sequela identified? If yes, specify:
5. Vaccine & therapeutic prophylaxis **Sub-domains:** Vaccine studies Vaccine antibody response Post-exposure prophylaxis	A. **Human vaccine tested?** If yes extract data on: • Name of vaccine: • What stage is it tested at? (dropdown list: Phase 1, Phase 2, Phase 3, Phase 4, Unknown) • Which populations is it tested in? tick all Neonates/Infants (<1 yrs), Young children (1-5yrs), CYP (5-17 years), adults (18+ years), pregnant women, any other specific population (specify), NR • Specify the number of doses: (drop-down options: 1, 2, > 2, unknown) – If > 1 dose, specify the dose interval: (specify months; years, NR) • Route of vaccine: oral, intranasal, injected (subcutaneous, intramuscular), other • Data on the effectiveness of the vaccine in preventing? (select): Disease, Severe disease, Transmission, Re-infection? • Data on vaccine effectiveness against different virus strains? Yes, No • Data on vaccine effectiveness against different pathogens? Yes, No, If yes, which ones? • Data on waning antibody response after vaccination over time? Yes No • Data on risk of re-infection after vaccination? Yes No:

Table 7. *Continued*

Domain	Sub-domain questions
	B. **Therapeutic prophylaxis studied pre- or post- exposure prophylaxis)**? Yes No, If yes, extract data on: • Pre-exposure, Post-exposure, NR (tick all) • Name of Therapeutic: • Populations tested on: Neonates/Infants (<1 yrs), Young children (1-5 yrs), CYP (5-17 years), adults (18+ years), pregnant women, any other specific population (specify), NR • Data on effectiveness: Yes No NR

6. Diagnostics
 	
Sub-domains:
Rapid Diagnostic Tests (RDT)
Other diagnostic tests
	• Diagnostic tests trialled/tested/evaluated? Yes No
	  • If yes, specify type of test: (Dropdown menu: ELISA, immunofluorescence, nucleic acid test, Rapid Diagnostic test (RDT), RT PCR, Sequencing Serology, Viral culture, other: specify or NR)?
	  • Which samples were used/tested? (Dropdown menu: Blood, Cerebrospinal fluid, Dried Blood Spots, Faeces, Nasopharyngeal swab, Sputum, Tissues (biopsies/post-mortem), Urine, Other (specify): or NR)
	  • Is it a multiplex assay? Yes No
	  • If yes which viruses can the test detect? Free text or NR

7. Therapeutics
Therapeutic studies
	• Therapeutic treatment studied? Yes No, If yes,
	  • Name of therapeutic/s studied:
	  • Specify administration route/s for each tested (e.g. oral, I.V.) or NR:
	  • Populations included in the study, tick all: Young children (5yrs), CYP (5-17 years), adults (18+ years), pregnant women, any other specific population (specify), NR
	  • Data on effect of therapeutics on (tick box answers): (risk of transmission; Reduction in isolation period; recovery time; length of hospital stay; risk of severe disease; fatality rate, other: specify) studied?
	  • Any severe* side effects identified? Yes No

8. Supportive care
Supportive care studies
	• Effectiveness of supportive care (e.g. oxygen, fluids, pain relief, psychological) studied? Yes No
	  • If yes, what supportive care was studied?
	  • Data on effectiveness? Yes, No, NR
	  • Any severe* side effects identified? Yes No

9. Social and behavioural factors **Sub-domains:** Knowledge Attitude Access Uptake Healthcare implementation	This includes studies focused on evaluating the below and those focused on exploring factors that impact on the below (e.g., stigma, trust, engagement, information, socioeconomic etc.) • **Knowledge of** (dropdown list: Diagnostics, Disease, PPE, Prevention or control methods, Prophylaxis, Risk factors for transmission/infection, Severe disease, Treatment, Vaccines, Other (specify:)). • **Attitude to** (dropdown list: Disease, Medical countermeasures (diagnostics, treatments, vaccines), Risk factors for transmission/infection/severe disease, Prevention or Control methods, Other (specify:)). • **Access to** (dropdown list: Diagnostics, Information/guidance, post-exposure prophylaxis, PPE, Prevention and control tools, Therapeutics, Supportive care, Vaccines, Other (specify:)) • **Uptake of (**dropdown list: Diagnostics/guided or self-testing, Post-exposure prophylaxis, PPE, Prevention and control methods, Therapeutics, Vaccines, Other (specify:)) • **Are there studies exploring healthcare staff** (dropdown list: Training in identifying or managing the disease, Capacity/capability in managing the disease, Facilitators/challenges to implementing care/IPC, Other (specify:)

Abbreviations: CYP: Children & Young People, IPC: Infection Prevention Control, NA: Not applicable, NR: Not reported, PPE: Personal Protective Equipment.

Exclusions:

- Studies not focused on the disease/pathogen
- Studies focused only on animals, vectors (insects, ticks), virus, data modelling
- Conference abstracts, book chapters, non-systematic reviews (scoping reviews, narrative reviews, mapping reviews)
- Opinion pieces unless they present primary data (during outbreaks rapid early data may be published in a rapid letter/commentary)

Depending on each disease, systematic reviews and pre-prints may be included or excluded.

E.g. for diseases that were detected decades ago, it may be of relevance to include systematic reviews. For new diseases and ongoing outbreaks, it may be important to include pre-prints, as they are a means to rapidly disseminate data during ongoing outbreaks. However, for well known viruses older pre-prints are likely to be duplicated in an updated peer-reviewed publication, and therefore pre-prints may be excluded. This decision will be made for each RRNA, and will be communicated in the protocol, programmed in the review software to guide the reviewers, and communicated to the reviewers.

Optional Module 3b: Transmission (animal-to-human transmission)

If there is a need to include a module focused on the animal to human interface, please find a module that can be implemented below.

- **Search strategy:** Do not include an animal exclusion filter when searching for records.
- **Eligibility criteria:** Include studies focused on humans or human samples, including those focused on the animal to human interface.
- **Data extraction:**

  Part 1: Key data charting: include an option to select Domain 3b

  Part 2: Full data extraction: program in the research domain questions in Domain 3b.

Optional module 3: Animal-to-human transmission. Grey text indicates data fields that can be added to extract additional supporting information, depending on need and resources.

3b. Transmission (animal to humans) Risk activities Effectiveness of prevention & control measures Prevention and control implementation challenges/facilitators	• Host risk factors for transmission from animal to humans studied? Yes No, If yes, tick all: age, gender, ethnicity, demographics; occupational risk factors, other (specify) • If available, extract key results, (%, n/N vs. %, n/N, OR, p-values) • Data on risk activities for animal to human transmission studied? Yes No, if yes, extract key findings (%, n/N vs. %, n/N, OR, p-values) • Virus detected in animals/animal samples? Yes No, If yes, which animals and samples was the virus detected in? Extract data: • Study on risk of infectivity from animal samples? Yes No, if yes extract the results. • Study on risk pathways for animal to human spillover risk? Yes No if yes, extract data. • Study on effectiveness of measures to prevent animal-to-human transmission? Yes/No, If yes extract the results with significance values: • Study on effectiveness of animal-to-human transmission control measures? Yes/No, If yes, extract the results with significance values: • Study on behaviours impacting on spill over risk/risk behaviour? Yes No • Study on social, cultural, environmental, societal factors impacting on spillover risk? Yes No • Study on factors impacting on implementation of prevention and control methods? Yes No

Evidence search strategy

The databases to be searched will be reviewed and modified depending on the nature of the outbreak by the coordinating team. An information specialist will be responsible for searching three databases. They will pilot the search strategy for each RRNA, and after presenting the pilot search and consultation with the CT, finalise the search strategy and conduct the final search. As the focus is on identifying gaps in the evidence base and rapidly during the outbreak, it is important to ensure the search terms are inclusive but also specific when needed to reduce noise.

Table 8. Databases to be searched for primary research.

MEDLINE (PubMed), Ovid Embase, Scopus.
Grey literature^: Google, WHO, Regional CDCs, Regional/National Public Health, Ministry of Health websites in endemic countries and or countries of ongoing outbreak/s.

^To be adapted for each disease and context as relevant.

There are two main search strategies that will be considered:

- Search of all databases using the name/s for the disease and pathogen may be sufficient, to cast a wide net when the evidence base is limited. If a disease is set in a non-English speaking region, we will do an initial search for names of the disease in the languages spoken in this region, and if needed will add these to the search.

- Search all bibliographic databases of peer-reviewed literature using combinations of search terms presented below. For targeted RRNAs focused only on a selection of domains, these will be edited as appropriate.

- These searches will be complemented by a manual search of grey literature by the CT and review team using search terms based on the disease and pathogen name, to include primary data presented in grey literature, e.g. in outbreak reports (Table 8).

Search timeframe: To be defined depending on each disease and need, e.g. from database inception or from date of disease detection in humans, or from first large outbreak when evidence may be expected to be generated. For rare diseases we will search from inception, for diseases where the pilot search identifies a large amount of records it may be modified to a relevant more recent year to include up to date evidence and recent systematic reviews that will likely cover the earlier studies, for relevance and feasibility.

For updates: The protocol and programmes are developed to facilitate regular updates as and if required as new evidence emerges. For emerging and re-emerging infectious diseases new evidence is most likely to be generated during or after outbreaks, therefore there is no fixed time-frame stipulated for updates. Updates searches are recommended to be done from the final inclusion date of the previous RRNA.

Search terms: The search strategies use keywords and thesaurus headings, where available, to search in text words and controlled vocabulary, in conjunction with terms relating to the disease AND the research domains and sub-domains AND humans (human*, patient*, participant*, infant*, child*, female, male, pregna*, case*, woman, women, man, men, child, neonat*). The terms for the different questions (domains and sub-domains) are: incubation, symptom*, severity, “natural history”, “clinical features”, transmission, infectiousness, vaccin*, prophyla*, chemoprophyla*, prevention, protection, diagnosis, diagnostic, RDT*, screening, detection, immunity, immune*, antibod*, serology, waning, treatment, management, therapy, drug*, intervention*,“supportive care”, fluid*, electrolyte*, supplement*, mortality, death, “adverse events”, “side effect*”, complications, sequela*, immunocompromise*, “personal protective equipment”, “infection prevention control”, knowledge attitude*, behavio*, practice*, social, acceptance, uptake, adherence, trust, stigma, “engagement”, communication, ethical, implementation, access, guidance, protocol, staff, training, management, capacity, capability, effectiveness.

Exclude: In the search, where possible, book chapters, conference abstracts and references with “scoping review”, “narrative review”, “mapping review”, or “systematic review” (if excluded) in the title field, with an animal and vector exclusion filter if relevant and if the team agree to use one. References retrieved will be exported to the reference manager and will be deduplicated automatically using the reference managers deduplication features, followed by the review software systems deduplication and a manual deduplication to ensure all duplicative records are removed prior to screening.

Grey literature search strategy

The peer-review search may be complemented by a grey literature searching Google, WHO, Regional CDCs, National Public Health and Minister of Health websites. This is especially important for new and rare diseases where the evidence base is expected to be limited, or for diseases set in non-English speaking countries where data may not always be published in English journals. The grey literature search will be carried out manually by the CT and reviewers by defining search terms to use for each website, based on: ‘disease name’ AND ‘human*’. Note: if the disease is mainly known by a non-English name in the endemic countries, searches for both the English and the local disease name, will be carried out

searches for grey literature in endemic countries' native languages when appropriate and feasible. For the search using Google, the date of the search will be recorded, and the records identified copied into an offline source e.g. Word, to facilitate the screening of the first 50 hits by title and abstract by two reviewers. The records included for full text screening will be manually uploaded into the systematic review software for full text screening, data charting and extraction.

Retrieving full text articles

Full text articles will be retrieved through the reference managers automatic functionality, supplemented by manually searching for articles using Oxford University library access, PubMed and Google since the automatic functionality does not identify everything. If the full text article is not identified after searching these databases, then it will be excluded due to being non-accessible. Articles retrieved manually will be uploaded into the systematic review software. Articles can either be uploaded directly or saved on a computer for later bulk upload. For bulk upload, the articles may need to be renamed and saved with the systematic review software ID system before bulk upload. The articles that are eligible for inclusion but de-prioritised for data extraction can be listed in the appendix of the final report.

Screening

For newly emerging diseases where the evidence base is expected to be limited, it is key to ensure that the screening strategy is rigorous as well as inclusive. Therefore, title and abstracts and full text records will be screened by two reviewers independently. Any disagreements will be resolved through consensus or by a third reviewer. We may use an accelerated screening approach whereby one reviewer is needed for inclusion and two for exclusion. By using a systematic review software, this means that once the records (search results) are uploaded, work can be ongoing in parallel, as it facilitates keeping track of tasks that has been done and those left to complete without need for lengthy handovers.

For records in languages other than English, abstracts and articles will be translated either using a translation software such as Google translate and/or by a reviewers with good knowledge of the language, before screening. Both the original article and the translated version will be uploaded into the systematic review software. If required, a reviewer with specific language skills will be consulted to support the review. For each RRNA, if key evidence is expected to be published in non-English languages, engaging reviewers or review teams from that region is recommended. If it is not possible to translate an article, it will be excluded from the data extraction and instead listed with full bibliography in the supplemental file, with the reason documented.

Data extraction

The aim of the RRNA is to identify gaps in knowledge and the evidence base. This means that minimal data such as: Disease, Research Domains and Sub-domains, Study design, Key Population Groups (Young children (<5 yrs), Children & Young People (5–17 yrs), Adults (18+ yrs) and Pregnant women and Study Setting will be collected to identify evidence gaps across these key parameters. If data is available, ethnicity will be recorded (Table 7). This data will be used to inform the need for full data extraction for all or specific domains and sub-domain research categories. For those diseases and domains where full data extraction is needed, these records will continue to full extraction, extracting more detailed Population parameters, Intervention (Exposure), Comparator, Outcome (PI(E)COs)) to identify gaps and provide an overview of existing evidence to inform research prioritisation and coordination. Data will be extracted into a pre-defined outcomes table.

Step 1: Key data charting

Key data will be extracted (chartered) into the pre-defined data template by one experienced systematic reviewer.

- A second reviewer will check a minimum of 30% and up to 70% of the data, depending on volume of records, resources and need for rapid data sharing. Key data to check includes: study design, setting, number of participants, demographics of study participants and cases included (age, specific risk groups, sex, ethnicity) and the research domains and sub-domains covered in the results.

- The final data will be exported into Excel for data cleaning and interim analysis.

- The data will be reviewed by the CT and reviewers to identify need for pivoting to further Dextraction across all or specific domains.

- If high level of evidence exists that addresses sub-domains, then data extraction can be prioritised so that lower level of evidence is not extracted. The bibliography of the non-extracted records may instead be listed in the appendix.

- The data prioritisation step will be informed by the initial key data charting analysis. Extraction may be prioritised so that if there are a high number of studies addressing a domain, extraction will be prioritised by study design, so that studies of higher evidence level (Table 4) will be extracted.

Step 2: Full data extraction

- For those domains and sub-domains identified as requiring full data extraction, a decision regarding which level of study design to be extracted will be documented.

- Data will be extracted by one reviewer, with a second reviewer checking up to 70% of the data.

- Data reporting should include description of the populations covered with the numbers and proportions (% (n/N)) for each specific population group presented.

- Missing data should be recorded as: NR (not reported). Data that are not applicable to a study as Non applicable (NA).

- The result section should report a key summary of primary and secondary outcome data, and data covering study design, setting, n numbers and PI(E)COs: Population, Interventions (Exposure), Comparator, Outcomes.

- To facilitate data checking, cleaning and analysis, the main objectives and study abstract will be extracted. Further, data extracted concisely with sufficient context for another reviewer to interpret it. This includes ensuring that abbreviations are spelt out and checking that symbols, such as μ are presented correctly in the extraction sheet.

Definitions

- **Cases:** Clinically or laboratory probable and confirmed cases as reported by the study authors

- **Previous cases:** Seropositive cases/samples e.g. in follow-up studies, seroprevalence studies

- **Contacts:** Contact of acute confirmed/probable case in case-contact studies

- **Healthy participants:** e.g. in case-control studies, participants in social and behavioural studies

- **Total participants:** All participants included in a study (e.g. cases + contacts)

- **Age ranges^:** Neonates (<3 months), Infants (<12 months), Young Children (1 - < 5years); Children & Young People (CYP, 5–17 years), Adults (18+ years), Older adults (>65 years)

- **Ethnicity:** Arab, Asian, Black, White, Mixed, Indigenous (specify:), Other ethnicity (specify):

^Age-groups: to identify important evidence-gaps it is of relevance to collect specific age group data, since risk factors for disease and severe disease and response to medical countermeasure varies by age and immune status. If the data is not available to delineate between these groups, they can be aggregated at the analysis stage.

Vaccine study phases

- **Phase 1 Interventional, no control**. The vaccine is administered to a small number of healthy volunteers for the initial assessment of safety and immune response generation.

- **Phase 2: Interventional, usually with controls**. The vaccine is administered to a large number of volunteers from the target population groups, to further assess its safety and ability to generate an immune response. Usually includes a control group.

- **Phase 3: Interventional, controlled study**. Administered to thousands of volunteers and compared with a matched control group, receiving a comparator to assess vaccine effectiveness.

- **Phase 4: Post-approval study, observational or interventional:** To collect additional information about how well it works, and monitor safety among a larger number of participants and long term outcomes, safety surveillance, and to assess efficacy and in response to regulatory requirements.

Data analysis and dissemination

The systematic review team/s are responsible for exporting the completed data outcomes tables from the review software and for collating, tidying, analysing and submitting the results in a Microsoft Excel file to the CT by day 10–12 of the RRNA process. During cleaning, key data to check for consistency include study design, study setting, population groups included, number of total participants and cases, and to check mapping to the correct domains and sub-domains. It is recommended to scan through each extraction row to check that these key data points are consistently extracted and add or update any errors or missing data spotted. The CT will do a second review of the data export for completeness and accuracy with a focus on these key parameters, and will coordinate or analyse the data descriptively (find examples of key parameters to present in the extended data files). Creating analysis codes to facilitate analysis for future updates and new RRNAs, can facilitate rapid data analysis and data dissemination for action.

The results will be reviewed and signed off by the CT and SG, then disseminated as open access to inform research and public health prioritisation and coordination strategies. Developing a generic final report template can facilitate future RRNA reports and timely dissemination of the findings as new evidence emerges. The RRNA does not include a risk of bias analysis, nor explorations of consistency, or meta-analysis since the focus is on identifying key gaps in the evidence-base across domains and population groups, and develop a rapid but systematic method for doing so both in preparedness time and during outbreaks as new evidence emerges. The strength of the studies will be assessed by study design, number of participants and cases included, for the purpose of identifying if there is gaps in the evidence base. The data may be disseminated as a report or a dashboard via a dedicated website, directly to stakeholders, presentations and publications. We will disseminate the data with the bibliographies of the included study as open-access to facilitate dissemination, access and facilitate the ability for others to readily pivot to a full systematic reviews if needed.

If need arises, e.g. during an outbreak, the key data charted (mapped) in step 1 will be analysed rapidly to facilitate rapid identification of key gaps evidence across sub-domains by level of evidence and inclusion of different population groups (e.g. young children, CYP, adults, pregnant women), settings and study domains and if available data on ethnicity. This data can be disseminated rapidly to stakeholders, supplemented with links to the records, bibliographies and study abstracts to inform incident teams, research prioritisation and coordination during outbreaks.

Quality control

Quality will be maintained by ensuring that the organisations and teams involved have previous necessary experience as described above and the resources needed. The protocol will be reviewed for each disease by experts in the infectious disease, domains included and by consultation with content experts as required and modified as appropriate. The search specialist and systematic reviewers will be engaged and trained in the protocol in advance. Ensuring that the teams have experience of systematic reviews will ensure rigour, consistency and quality. Using systematic review software will facilitate quality checks, audit and evaluation. By including a grey literature search and by engaging external experts with expertise in specific diseases, we will cross-check that key studies have been included in the peer-review search, and that the interpretation captures key needs. The final data identified will be reviewed by infectious disease specialist and by content experts with experience relevant to the specific outbreak and clinical domain questions before dissemination.

RRNA updates

The RRNAs can be updated when new key evidence emerges, e.g. during and after outbreaks, or implementation of new therapeutic or vaccine trials. For updates, update the search timeframe (from the end of the previous RRNA till the current date), repeat the deduplication against the new search results and deduplicate against the existing RRNA records, screen and map and extract data and update the descriptive analysis and report. Note, if pre-prints were included in the earlier RRNA, these should be replaced with the peer-reviewed publication, if identified in the new search. The decision to update the RRNA will be taken by the SG in collaboration with the CT and other stakeholders. Requests for an RRNA or update from external stakeholders will be reviewed by the SG to inform a decision for if the request is reasonable, relevant and fit for an RRNA (full or targeted) and if there is sufficient resources to run the RRNA.

Discussion

The outcome of the RRNA will be a summary of existing evidence across pre-defined research domains, by population groups and settings, to identify where there are gaps in evidence. This will provide baseline data to inform research prioritisation and coordination strategies in preparedness time and during outbreaks. As a secondary objective, the methodology facilitates pivoting to an in-depth evidence review, to inform clinical and public health strategies if required.

This protocol is developed to facilitate rapid, systematic, robust appraisal of published evidence to identify gaps in the evidence base, to inform research prioritisation and coordination of research responses in preparedness time and during outbreaks. It is developed to facilitate implementation in any resourced setting and collaborative partnership working to optimise resources. We welcome others to adopt and adapt the protocol. We will establish and disseminate a baseline of RRNAs for high priority diseases, to provide a baseline to inform preparedness activities and for rapid update as new evidence emerges, with the aim to strengthen preparedness to new and (re-)emerging epidemic and pandemics to protect populations and improve outcomes.

Data availability statement

All data generated through the Living Rapid Research Needs Appraisal (RRNA) platform as part of the Pandemic PACT evidence tracker project are curated and managed within the University of Oxford's secure REDCap environment, hosted by the Nuffield Department of Medicine. The resulting datasets are made openly available via the **RRNA Project Figshare**, hosted under the **Pandemic PACT Figshare group repository** within the University of Oxford Figshare instance: https://portal.sds.ox.ac.uk/pandemicpact[6]

Select visualisations of RRNA outputs will be available on the **Pandemic PACT public website** (https://www.pandemicpact.org/rapid-research-needs-appraisals)[7] under the dedicated RRNA section. All underlying data and figures displayed on this platform can be downloaded directly or accessed through the linked Figshare repository. All code developed for data processing and visualisation is available under an MIT open-source license on GitHub: https://github.com/enovatedesign/pandemic-pact.[8]

Extended data

Extended materials supporting the study – including the data extraction tables, evidence maps, bibliographies of eligible studies, and study characteristic tables; will be available via the RRNA Project Figshare, hosted under the Pandemic PACT Figshare group repository: (DOI 10.25446/oxford.30480455)[9] and the **Open Science Framework (OSF)** repository: DOI 10.17605/OSF.IO/TWFNR.[10]

This project contains the following extended data in OSF:

A. Evidence map example

B. Data dissemination examples

C. Study characteristics table examples

D. Table example for documenting eligible studies deprioritized from data extraction

All extended data are open access under the Creative Commons Attribution 4.0 International License (CC BY 4.0). You may use, distribute, and reproduce this material in any medium, provided the original source and authors are credited.

Protocol registration: https://osf.io/twfnr/ DOI 10.17605/OSF.IO/TWFNR

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Open Peer Review

Current Peer Review Status: ? ✓ ✓

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✓ **Bruno Pozzetto**
CHU de Saint-Etienne, Saint-Etienne, France

As specified at the beginning of the manuscript, “this document presents a methodology for establishing a platform of ‘living’ rapid research needs appraisal (RRNA). The aim is to rapidly and robustly identify gaps in evidence across pre-defined research domains for new and re-emerging diseases of epidemic and pandemic potential, where existing evidence and knowledge is limited, to inform research prioritisation and coordination in preparedness time and during outbreaks.” I agree with the two other reviewers about the ambition of this project. I read attentively the protocol proposed by the authors and I globally agree with the methodologies that are proposed and that are in accordance with those usually recommended for conducting a review on an emerging subject.
However I am a bit puzzled by the amount of expert work that will be required to conduct this kind of prospective evaluation for a single subject and to actualize regularly the document according to the proposed deadlines, given the high number of “new and re-emerging diseases of epidemic and pandemic potential” listed in different reviews on this subject. I would be interested to know the numbers of persons necessary to conduct such an ambitious task and which Institution (the University of Oxford?) would be prospectively in charge of the governance of this project. Who will decide about the prioritization of the topics and of size of the projects? For instance, if the topic of viral hemorrhagic fevers is chosen, will it be limited to a single agent (or one species of a viral genus) or will it treat simultaneously for instance all the viruses involved in a same geographic area or sharing the same zoonotic reservoir? I think that different methodologies and different timescales will be necessary according to the size of the treated subjects. In this perspective, I wonder whether a single methodology is adapted. Do the authors tested their protocol on a few instances of recent (re-)emergencies (i.e; arboviral disease as Oropouche, zoonotic disease as *Orthohantavirus andesense*, or *Orthoebolavirus bundibugyoense*). Such experiments of the protocol would be useful to test its practical feasibility.
Another question addresses the place of IA-tools in the generation of this kind of bibliographic inquiries. I saw that the other reviewers addressed the same question. If the project is hosted by the University of Oxford, I think it seems feasible to incorporate an IA-driven assistance to the projects so that it could be possible to restart automatically the protocol without needing to activate again all the circuits described in the flowchart of the project.

I am sorry not to be more helpful for improving this ambitious task. Globally I adhere to the idea of conducting prospectively a bibliographic surveillance of infectious (re-)emergencies, even if I stay a bit puzzled by the means needed to conduct this surveillance at a large scale with human means based on traditional reviewing processes. Regarding the protocol, I endorse the general organization, even if the times scheduled for the first days in Figure 2 seem a bit under-estimated for all the tasks that are listed.
All my best wishes with this helpful project for the community.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Partly

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Medical virology - Public Health

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 05 February 2026

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James Scott Parrott
Rutgers University, Newark, New Jersey, USA

This is a very ambitious effort to create living rapid research needs appraisal (RRNA) pipeline and platform. If feasible, it should provide useful information for evidence synthesis professionals, clinicians and policy makers regarding infectious disease outbreaks.
The process, as described, maps to standards for gap analysis or rapid reviews.
As this is a protocol, I interpret the goals (specifically the timeframe) as aspirational rather than (at

least currently) realistic. Whether they are able to (or how often or under what conditions they are able to) meet their targets as specified in Figure 2, I take to be an empirical question. As this is a data charting effort (rather than a systematic review where ROB and results extraction are expected), it may be realistic—though I have my doubts but would be thrilled to be proved wrong.
I did have some questions about specific details:
It wasn't entirely clear to me what would count as a trigger or how this monitoring would be systematically carried out.
There is very little information regarding the software/platform that will be used. Given that, on p.7, they make the statement, "will extract the data into a pre-defined data extraction template using the review software or alternatively directly in Microsoft Excel" leads me to believe that they have not yet worked out the basic specifications of the system that would be needed. The following statement is completely unrealistic regarding software/platform updates, "The review teams will be sent the protocol, with any edits made visible in track changes on Day 1. The team will refine the systematic review software if required." I am wondering if they are considering (there does not seem to be a concrete plan) to adapt some of the open source evidence synthesis platform code like Eppi Reviewer or SRDR+ (now decommissioned but available on github). At any rate, all of this is left to the reader's imagination. Without a highly integrated platform tailored for this specific use, I see the feasibility of the timeline as unrealistic.
I was surprised to see nothing about AI-scaffolded title/abstract screening as this has now become the standard within the evidence synthesis field.
Regarding data charting and extraction (pp.13-14), the authors say, "A second reviewer will check up to 70% of the data." This is very vague and could mean anywhere from a negligible amount to the majority. And, there are no rules specified for determining how many studies should be evaluated by a second reviewer.
In summary, this protocol, in general provides an overview of an ambitious but useful project. There are some crucial details left out, but it may be that those details need to be worked out in situ rather than in the abstract.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

No

Are the datasets clearly presented in a useable and accessible format?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Evidence synthesis methodology with a specific focus on data extraction and warehousing platforms.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 15 Apr 2026

Louise Sigfrid

Thank you for your review of our protocol, please find a point-by-point response below.
This is a very ambitious effort to create living rapid research needs appraisal (RRNA) pipeline and platform. If feasible, it should provide useful information for evidence synthesis professionals, clinicians and policy makers regarding infectious disease outbreaks.
The process, as described, maps to standards for gap analysis or rapid reviews.
As this is a protocol, I interpret the goals (specifically the timeframe) as aspirational rather than (at least currently) realistic. Whether they are able to (or how often or under what conditions they are able to) meet their targets as specified in Figure 2, I take to be an empirical question. As this is a data charting effort (rather than a systematic review where ROB and results extraction are expected), it may be realistic—though I have my doubts but would be thrilled to be proved wrong.
Response: We agree that the timeline presented in the protocol is particularly relevant to outbreaks, when evidence gaps need to be identified rapidly to inform research response prioritisation for effective use of limited resources. Our pilots have shown that it is feasible, particularly if a relay of reviewers collaboration across time-zones is available, supported by review software. The feasibility will depend on the volume of records available, which is why it is developed in a modular approach whereby it can be targeted as relevant and if needed, e.g. restricted to key domains and by search time-frame. By establishing the methodology we have strengthened preparedness for timely implementation, and also developed an online training program to facilitate scale-up. Once an RRNA has been implemented, future updates can be implemented very rapidly, e.g. during prolonged outbreak where there is a need to revisit prioritisation as new evidence emerges.

I did have some questions about specific details:
It wasn't entirely clear to me what would count as a trigger or how this monitoring would be systematically carried out.

- **Response:** We have clarified further in the protocol that a trigger is an event such an outbreak or a public health emergency, and for updates, as new evidence is available which for most domains will be as new outbreak emerges.

There is very little information regarding the software/platform that will be used. Given that, on p.7, they make the statement, "will extract the data into a pre-defined data extraction template using the review software or alternatively directly in Microsoft Excel" leads me to believe that they have not yet worked out the basic specifications of the system that would be needed. The following statement is completely unrealistic regarding software/platform updates, "The review teams will be sent the protocol, with any edits made visible in track changes on Day 1. The team will refine the systematic review software if required." I am wondering if they are considering (there does not seem to be a concrete plan) to adapt some of the open source evidence synthesis platform code like Eppi Reviewer or SRDR+ (now decommissioned but available on github). At any rate, all of this is left to the reader's imagination. Without a highly integrated platform tailored for this specific use, I see the feasibility of the timeline as unrealistic.

- **Response:** Thank you for your comment. We have clarified in the protocol that the coordinating team is responsible for ensuring that the review software is pre-programmed to enable rapid implementation and rapid refinements as appropriate

for each disease, need and context.
- Further, that using a review software guides and facilitates standardisation of the extractions by limiting need for open ended extractions, which facilitates completion and quality assurance. The programme can be rapidly targeted, e.g. hiding domains or sub-domains or adding specific questions to a domain, since the protocol is designed in an adaptable, modular approach.

I was surprised to see nothing about AI-scaffolded title/abstract screening as this has now become the standard within the evidence synthesis field.
- **Response:** We agree that AI-assisted title and abstract screening has a potential to improve efficiency, and this may be used if available in the review software. However, we have designed the protocol to facilitate implementation in any resourced settings, recognising that access to review software may be limited. Hence, we have not included this, and in our experiences when implementing the protocol, existing technology has limited benefit for the purpose of the RRNA, which covers a wide range of domain topics. Further for emerging infections existing evidence is generally limited to lower study designs, and often contain inconsistent or incomplete reporting. This creates challenges for reliable AI-based identification without prior calibration and validation. This is definitely an area to explore further for the future as AI methodologies may become more reliable to apply and open accessible.

Regarding data charting and extraction (pp.13-14), the authors say, “A second reviewer will check up to 70% of the data.” This is very vague and could mean anywhere from a negligible amount to the majority. And, there are no rules specified for determining how many studies should be evaluated by a second reviewer.
- **Response:** Thank you for highlighting this. We have further refined this on page 18: “A second reviewer will check a minimum of 30% and up to 70% of the data, depending of volume of records, need and resources.”

Competing Interests: Senior Author

Reviewer Report 05 January 2026

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Christian Morgenstern
MRC Centre for Global Infectious Disease Analysis & WHO Collaborating Centre for Infectious Disease Modelling, Jameel Institute, School of Public Health, Imperial College London, London, England, UK

Thank you for inviting me to review this paper, which addresses a critically important subject. Access to high-quality data on infectious diseases at the outset of an outbreak is crucial to enable timely interventions, whether pharmaceutical or non-pharmaceutical (NPIs). The authors make a substantial contribution by setting out a protocol for the rapid review of research needs to support early outbreak response.

One overarching observation is that the study protocol implicitly assumes that, for each outbreak, this work would start from scratch with no prior systematic review which could be utilised. This assumption may have been correct before the COVID-19 pandemic. However, initiatives such as the WHO Global Repository for Epidemiological Parameters (grEPI, https://github.com/WHO-Collaboratory/collaboratory-epiparameter-community?tab=readme-ov-file) by the WHO Hub for Pandemic and Epidemic Intelligence, supported by Imperial College London (ICL), the London School of Hygiene and Tropical Medicine (LSHTM) and the Public Health Authority of Canada (PHAC), in collaboration with a wide range of other institutions, provide a basis for the WHO Priority Pathogens already. Systematic reviews on four priority pathogens have already been published[1–3], alongside a publicly available database and an R package (epireview: https://github.com/mrc-ide/epireview).

For re-emerging diseases, grEPI, alongside other complementary databases, could serve as a starting point for informing the research community about the latest available data and estimates. Focusing on how that rapid update looks in an outbreak situation is challenging, and it would be excellent to see the authors expand significantly on the RRNA update section on page 15 (version 1 of the paper). For new pathogens, the study protocol provided is excellent, though I have several more specific comments.

All page numbers refer to version 1 of the paper:

- *Page 5, composition of the CT:* Besides clinical researchers, the core team should also include infectious disease epidemiologists, who are a key consumer of this data.
- *Page 5, systematic review team:* The authors state that to ensure rigour and quality, the systematic review team needs to be trained in advance. I agree with this, but it implies that the team must be established before any outbreak or rapid response. It would be helpful to state this more explicitly in the study protocol.
- *Tables 1 and 3:* Why is EndNote, as a specific system, mentioned in the protocol, but for all other tasks, the authors talk generically about the review software? Would it be better to say reference manager?
- *Table 4:* It might be helpful to say meta-analysis and data synthesis, as some data might not lend themselves to meta-analysis but could be synthesised using other statistical techniques (e.g. Bayesian Synthetic Likelihood methods).
- *Page 7, first paragraph:* What do the authors mean by ‘the team will refine the systematic review software if required’? Given the very tight timelines, is that feasible? What type of changes do the authors have in mind, and what do they mean by software in this context?
- *Page 7, second paragraph:* Is extracting into Microsoft Excel a realistic option if a global team does this across time zones? Should this not be captured in a robust database?
- *Page 7, Systematic review software:* Why is the systematic review software included in the study protocol? It would be better to abstract any software components from the study protocol and include a general section outlining what this software should be able to do. Furthermore, this paragraph reads as if the authors intend to use this study protocol solely for themselves rather than provide a generic tool such as PRIMSA, which is a shame, as the

main benefit for the wider community is in that.

- *Page 7, reporting responsibilities*: Is e-mail an appropriate system to coordinate data? Should this not be done via a database that keeps records of amendments/changes, or via a tool such as GitHub, which also provides change tracking via commits and allows for reviews?
- *Page 7, research domain categories*: Point 3 should be expanded to include a broader range of data, including the full range of epidemiological parameters and models. Restricting to just human-to-human seems extreme, particularly for vector-borne diseases such as Zika.
- *Page 8, research domain categories*: Point 4, the risk factor outcomes seem narrow. Why not include other risk factor outcomes, such as death, as well?
- *Page 8, research domain categories*: One category which is missing and would be beneficial to add is Genetics. Understanding evolutionary mutation rates, phylodynamics, and phylogeography is essential. The other missing category is non-pharmaceutical interventions.
- *Page 8*: The authors say that results will be disseminated through the Pandemic PACT website. Why is that included in the study protocol?
- *Page 9, Table 6*: The inclusion criteria are limited to human-to-human transmission, which seems too restrictive, especially for vector-borne diseases (e.g., Zika, Dengue). Why are data modelling studies excluded, as they are critical to domain 3? Do the authors intend to exclude theoretical modelling studies that are not fitted to data? Having an asterisk on preprints is ambiguous, and it might be better to state that during non-outbreak periods, preprints are explicitly excluded, but during outbreaks, they are included. Also, why are systematic reviews not excluded? If data are extracted and a meta-analysis is performed, the analysis would consist of study results and summary estimates, potentially double-counting some studies but not others, leading to biased estimates. I understand that the aim is to use systematic reviews to map the existing evidence base. Still, the protocol needs to treat systematic reviews more carefully so that they are not included in any meta-analysis or data synthesis.
- *Page 9, Table 7*: Step 1: Cases should account for the possibility that some papers may report on multiple outbreaks. Study years would be better captured as study dates, allowing the extraction to capture actual dates if available. Step 1 is suitable for capturing the overall information for the paper; however, it is critical to capture the context for each estimate in each sub-domain, as these may vary (by age group, risk population, location, number of observations/cases, etc.) and could introduce errors in subsequent analysis, particularly if other groups use the extracted data for follow-on work, if not captured accurately.
- *Page 10, domain 1*: CFR is the case fatality ratio. This is not a rate because it lacks an associated time unit. If the authors prefer to call it a risk, that would be okay, but it is not a rate. Also, it should be captured if this CFR estimate is a naïve or adjusted estimate (or unspecified).
- *Page 10, domain 2*: Do the authors intend to extract the seroprevalence data? This would be of enormous benefit, but it requires much more information in the study protocol, as this is a complex task. Also, this would require the extraction team to be trained and to have sufficient knowledge of serology. This is another example in the manuscript where it is unclear whether the aim is only to highlight gaps or to actually extract data, which is a much more difficult task.
- *Page 10, domain 3*: Why is only the incubation period being extracted/recorded? This should extend to all delays, including the serial interval, the onset-to-hospitalisation interval, etc. Also, it would be great to capture whether only sample summary statistics (mean, median, min, max, etc.) are reported or whether distributions are fitted.

- *Page 10, domain 3:* It would be good to capture reproduction number estimates. More generally, several transmission parameters, such as overdispersion, should be included in this domain to enable infectious disease epidemiologists to build models.
- *Page 12, search terms*: Thank you for including the search terms. In an outbreak situation, this is only possible since the last RRNA update, as otherwise one would get too many titles and abstracts to screen (e.g., for Ebola or SARS-CoV-2, this would exceed 10,000 papers if the databases are searched since inception).
- *Page 13, Screening*: Has the use of Google Translate been tested and validated for inclusion in the study protocol? Is there a risk that the translation introduces errors?
- *Page 13*: A second reviewer will check up to 70% of the data – this is huge. Why can't there be some double extraction at the beginning until the extractors converge to a consistent extraction? Otherwise, this may not be feasible given the time frame.
- *Page 14, full data extraction*: This would be nice, but how feasible is that unless the team is already in place, fully trained, has all the tools at their disposal and only needs to update since the last entry into the database? Even in the most minimal form, this would be a considerable effort, especially if up to 70% of extracted data is double-checked.
- *Page 14, Definitions*: Please be more specific about the case definition.
- *Page 14, Definitions*: The age ranges should be more flexible, as each paper will use its own definition.
- *Page 14, data analysis and dissemination*: The authors state that they will provide the analysis code. Why is this included in a study protocol? Would it not be better to set out the requirements and standards for the analysis? Also, several tools already exist for this (epiverse, epireview) and are in use.
- *Page 14, data analysis and dissemination*: In the second paragraph, the authors provide a helpful discussion of what should be done during preparedness time versus during an outbreak. It may be helpful to consider existing work in this area (https://mrc-ide.github.io/epireview/) as well as broader WHO initiatives, such as grEPI.
- *Page 15, RRNA updates*: It would be helpful if the authors could expand this section substantially. This is non-trivial, and setting this out in the protocol would be helpful. A good example is how database entries should be updated between preprints and the final published paper.

In the discussion, the authors raise the essential point of collaborative partnerships, which will be critical to this type of work. However, the key question is who convenes and funds this (not to be answered by this paper).

During non-emergency periods, systematic reviews with meta-analysis and data synthesis should be strongly preferred as the gold standard. These reviews should be designed to be updated, and the underlying extracted data should be publicly available. This paper fills a critical gap in the literature on how these datasets can be rapidly updated to support outbreak response. Overall, this is an excellent contribution to the literature, but it would benefit from a more precise separation of the study protocol from tools such as the systematic review software, reference manager, or dissemination tools. For the study protocol itself, it would be helpful to separate the use case of mapping existing data from that of extracting it, which is a more complex task.

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3. Doohan P, Jorgensen D, Naidoo T, McCain K, et al.: Lassa fever outbreaks, mathematical models, and disease parameters: a systematic review and meta-analysis. *The Lancet Global Health*. 2024; **12** (12): e1962-e1972 Publisher Full Text

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Partly

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious disease epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 15 Apr 2026

Louise Sigfrid

Thank you for your thorough review of our protocol, please find a point-by-point response below:

- We have now clarified the recommendation to search for existing systematic reviews to inform targeting of the protocol and expanded on the updates.
- See: Table on page 8: "To review the need for refinement of the protocol depending on the disease and context. Consult with experts and carry out an initial search for available systematic reviews already addressing any of the domains, and target the protocol accordingly."
- AND On page 16: "The protocol and programmes are developed to facilitate regular updates as and if required as new evidence emerges. For emerging and re-emerging infectious diseases new evidence is most likely to be generated during or after outbreaks, therefore there is no fixed time-frame stipulated for updates. Updates searches are recommended to be done from the final inclusion date of the previous RRNA."
- AND on Page 16, Table 6. We have deleted the Systematic review databases, which were incorrectly entered in this table.

- We have also clarified the aims and remits of the RRNA further in the background on page 4, which addresses a number of the questions below:

- " The focus is on identifying gaps in the evidence base across domain topics and for different at risk populations and settings. As a secondary utility, if sufficient evidence is identified for a domain, it can readily be pivoted to a full systematic review if required and resources allows. The benefit of the RRNA is that it covers key domains relevant for prevention and early outbreak control to protect communities including healthcare workers This breadth of evidence would not be feasible to cover in a systematic review, however, if the RRNA identifies sufficient evidence for a specific domain it can readily be pivoted to a full systematic review if needed and resources allows. The RRNA methodology is specifically developed for new and (re-) emerging infectious diseases where existing evidence is limited. Diseases that have been well researched over the years, such as Dengue and COVID-19 are out of scope for a full RRNA, but could be considered for a very targeted RRNA focused on one domain or a few sub-domain questions."

All page numbers refer to version 1 of the paper:

- *Page 5, composition of the CT:* Besides clinical researchers, the core team should also include infectious disease epidemiologists, who are a key consumer of this data.
- Thank you this has been updated – see page "Additional content experts, such as infectious disease epidemiologists, public health professional, social scientist, diseases specific experts as required depending on the nature of the outbreak;"
- *Page 5, systematic review team:* The authors state that to ensure rigour and quality, the systematic review team needs to be trained in advance. I agree with this, but it implies that the team must be established before any outbreak or rapid response. It would be helpful to state this more explicitly in the study protocol.

- We have clarified the need to ensure there are staff pre-trained in the methodology on page 7 & 8: "It is recommended to sustain a standing CT trained in the methodology to ensure readiness and rapid mobilization when needed. The CT will be responsible for coordinating the process from notification of the need for a RRNA from the SG, through to completion (Table 1). The CT will also be responsible for training reviewers in advance and for scaling up implementation during outbreaks. This protocol and associated training video can aid in scale up."

- **CT responsibilities**: Signs-off the final protocol and any amendments. Ensures the protocol is registered in an open-accessible database such as the Open Science Framework and that the review software is pre-programmed, and all stakeholders involved are trained and familiar with the process and review software used.
- *Tables 1 and 3:* Why is EndNote, as a specific system, mentioned in the protocol, but for all other tasks, the authors talk generically about the review software? Would it be better to say reference manager?
- We have updated the text throughout to state "reference manager" rather than specifically EndNote.

- *Table 4:* It might be helpful to say meta-analysis and data synthesis, as some data

might not lend themselves to meta-analysis but could be synthesised using other statistical techniques (e.g. Bayesian Synthetic Likelihood methods).

- Our screening is specifically set up to identify systematic reviews with meta-analysis, as these are clearly identifiable at the title and abstract screening stage. It would require additional resources to assess if other systematic reviews are using other analysis methods. The RRNA is developed to balance rigour with effectiveness to enable rapid response during outbreaks. Other systematic reviews will be captured amongst systematic reviews and can be pivoted to further assessments if required.

- *Page 7, first paragraph:* What do the authors mean by 'the team will refine the systematic review software if required'? Given the very tight timelines, is that feasible? What type of changes do the authors have in mind, and what do they mean by software in this context?

- We have clarified that the program needs to be pre-programmed, which will enable rapid refinements as/if required on page 8: "To coordinate the overall process and teams involved from the start through to dissemination of the findings. Registers the core protocol (e.g. in OSF). Ensure the review software is pre-programmed and reviewers and other stakeholders involved are trained in the methodology and process."

- **"CT responsibilities:** Signs-off the final protocol and any amendments. Ensures the protocol is registered in an open-accessible database such as the Open Science Framework and that the review software is pre-programmed, and all stakeholders involved are trained and familiar with the process and review software used."

- On Page 11: "They will refine the systematic review program if updates have been made to the protocol, e.g. updates to the screening eligibility, and/or the extraction program, e.g. activate or deactivate individual sub-domain categories/questions or whole domains to be included in the mapping/data extraction."

- *Page 7, second paragraph:* Is extracting into Microsoft Excel a realistic option if a global team does this across time zones? Should this not be captured in a robust database?

- We have clarified this on page 11: "The reviewers will then start the screening (titles and abstracts, followed by full text screening). Followed by data extraction using the pre-defined data extraction template programmed earlier. Alternatively, if the researchers do not have access to a review software then the screening decisions and the data extraction can be made using Microsoft Excel. Using a shared Microsoft Excel platform will facilitate collaboration and coordination of the review process.

- *Page 7, Systematic review software:* Why is the systematic review software included in the study protocol? It would be better to abstract any software components from the study protocol and include a general section outlining what this software should be able to do. Furthermore, this paragraph reads as if the authors intend to use this study protocol solely for themselves rather than provide a generic tool such as PRIMSA, which is a shame, as the main benefit for the wider community is in that.

- We have rephrased the paragraph to specify the key features of a systematic review software, see page 12. “If access to a systematic review management software (e.g. DistillerSR, RedCAP, Rayyan, Covidence) s this this will allow processes to run in parallel without the need for handovers, and facilitate standardisation of extractions through pre-programmed data extraction forms, and future updates as new evidence emerges. A systematic review software also enables continuous monitoring of progress, rapid identification of issues and facilitate audits and quality checks. A program such as Microsoft Excel can be used as an alternative, but requires more manual administrative management, allocating records for screening and data extraction to reviewers and progress monitoring and manual open-ended extractions.”

- *Page 7, reporting responsibilities*: Is e-mail an appropriate system to coordinate data? Should this not be done via a database that keeps records of amendments/changes, or via a tool such as GitHub, which also provides change tracking via commits and allows for reviews?

- Thank you for this suggestion, we have clarified this on page 12: “The systematic review team/s are responsible for submitting the completed data extraction tables to the coordinating team via secure e-mail or other sharing platform as soon as completed for rapid data sharing. The completed data extraction tables can also be shared using an appropriate, secure systems (e.g. Figshare, GitHub) for open-access data sharing”

- *Page 7, research domain categories*: Point 3 should be expanded to include a broader range of data, including the full range of epidemiological parameters and models. Restricting to just human-to-human seems extreme, particularly for vector-borne diseases such as Zika.
- Thank you for this valid comment. Our approach emphases the importance of adopting a modular approach by activating domains that are of essential for the topic studied, including the option to include additional modules. We provide an optional module focused on animal-to-human transmission (see appendix). However, piloting shows that it is not feasible to include more domains to the core set of domains. We have reviewed the potential for including vector-borne transmission, however it is not feasible to expand the RRNA further, and since we include domains focused on effectiveness of prevention and control methods, and implementation factors associated with these, this would require a very different search for vector borne diseases.
- A key eligibility criteria for our RRNA is the inclusion of humans or human samples in the study, as health protection is our focus and to make it manageable. For vector borne disease prevention and control we would risk missing field studies that did not include humans, and thereby risk misinterpreting the evidence landscape. If we changed the search and screening to include vectors only it would create too much noise and make the process infeasible. The existing focus has been informed by expert consultations and piloting and defined to the existing domain categories for relevance for community protection and the early response to outbreaks, and to

ensure feasibility and quality. However, the RRNA concept can be applied to other research questions.

- We have clarified how the domain categories were identified on page 5: "The research domain categories has been informed by consultations with experts in emerging infectious diseases research and response, and specialists in One Health, review methodologies, epidemiology, public health, entomologists, veterinarians, social and behavioural sciences. They are focused on evidence relevant to prevention and early outbreak response to protect communities and health workers to improve outcomes."

Page 8, research domain categories: Point 4, the risk factor outcomes seem narrow. Why not include other risk factor outcomes, such as death, as well?

- We have made it explicit that this category includes death, and also long-term sequela, which are all a sign of more severe disease. See page 13 & 23 (table): Risk factors for infection, severe disease, death, long term-complications

- *Page 8, research domain categories*: One category which is missing and would be beneficial to add is Genetics. Understanding evolutionary mutation rates, phylodynamics, and phylogeography is essential. The other missing category is non-pharmaceutical interventions.

- We agree that non-pharmaceutical interventions (NPIs) are important, especially for priority disease outbreaks where there is limited or no other medical countermeasures. These are captured in the Supportive care domain which includes any support to manage symptoms, including e.g. salt fluids, nutrition, psychological support (domain 8). NPIs are also captured in effectiveness of prevention and control methods for infection (domain 3) and factors impacting on implementation of these (domain 9). Further, as part of the domain capturing knowledge, attitude, practice and access (domain 9).

- For genetics, this is partly covered in domain 1 and can be expanded upon in this domain. We have piloted inclusion of phylogenetic studies however, it was not feasible to include, nor deemed immediately essential by the expert. Since the protocol has been designed in a modular approach it can be integrated if deemed relevant, as long as the search terms and eligibility and program is updated accordingly.

- We have clarified how the domain categories were identified on page 5: "The research domain categories has been informed by consultations with experts in emerging infectious diseases research and response, and specialists in One Health, review methodologies, epidemiology, public health, entomologists, veterinarians, social and behavioural sciences. They are focused on evidence relevant to prevention and early outbreak response to protect communities and health workers to improve outcomes."

- *Page 8*: The authors say that results will be disseminated through the Pandemic PACT website. Why is that included in the study protocol?

- Thank you for pointing this out. We have deleted references to how we will disseminate our data from the protocol.

- *Page 9, Table 6*: The inclusion criteria are limited to human-to-human transmission, which seems too restrictive, especially for vector-borne diseases (e.g., Zika, Dengue). Why are data modelling studies excluded, as they are critical to domain 3? Do the authors intend to exclude theoretical modelling studies that are not fitted to data? Having an asterisk on preprints is ambiguous, and it might **be better to state that during non-outbreak periods, preprints are explicitly excluded, but during outbreaks, they are included.** Also, why are systematic reviews not excluded? If data are extracted and a meta-analysis is performed, the analysis would consist of study results and summary estimates, potentially double-counting some studies but not others, leading to biased estimates. I understand that the aim is to use systematic reviews to map the existing evidence base. Still, the protocol needs to treat systematic reviews more carefully so that they are not included in any meta-analysis or data synthesis.

- We acknowledge that modelling studies are relevant in infectious disease preparedness and response. We have reflected on whether to include these, however, due to feasibility and our piloting showing that due to our eligibility criteria being focused on humans or human samples, we would not systematically be able to capture all modelling studies. Researchers can adapt the RRNA concept to include such studies, any modifications will require refining search strategies and eligibility criteria and clearly communicate this to all stakeholders involved. We have clarified this on page 5: By designing it in a modular approach researchers can adapt the concept and modify domains as requires for other purposes, e.g. modify the search strategy and eligibility criteria and target domains focus, add new domains or domain questions.

- We have clarified that systematic reviews are used for informing need and potential for targeting the protocol and that pre-prints will only be considered for rare or new disease with very limited data available and during outbreaks, where pre-prints can provide early evidence relevant to inform strategies during the outbreak.

- Page 14 (table): Preprints should mainly be considered for very rare diseases or during outbreaks only.

- *Page 9, Table 7*: Step 1: Cases should account for the possibility that some papers may report on multiple outbreaks. Study years would be better captured as study dates, allowing the extraction to capture actual dates if available. Step 1 is suitable for capturing the overall information for the paper; however, it is critical to capture the context for each estimate in each sub-domain, as these may vary (by age group, risk population, location, number of observations/cases, etc.) and could introduce errors in subsequent analysis, particularly if other groups use the extracted data for follow-on work, if not captured accurately.
- We agree that this level of information would be of importance for a systematic reviews and meta-analysis. For the RRNA methodology the aim is to balance rigour

with speed, to be able to respond during outbreaks. Further, our piloting shows that this level of information is not consistently presented, and often not available. Hence for the purpose of evidence gaps identification and feasibility we only record study years, and accept that there may be overlap in cases between records, which is acceptable when identifying gaps. Our analysis is descriptive.

Page 10, domain 1: CFR is the case fatality ratio. This is not a rate because it lacks an associated time unit. If the authors prefer to call it a risk, that would be okay, but it is not a rate. Also, it should be captured if this CFR estimate is a naïve or adjusted estimate (or unspecified).

- Thanks for spotting this, it has been corrected to case fatality ratio. All data is extracted as reported by the study authors.

- *Page 10, domain 2*: Do the authors intend to extract the seroprevalence data? This would be of enormous benefit, but it requires much more information in the study protocol, as this is a complex task. Also, this would require the extraction team to be trained and to have sufficient knowledge of serology. This is another example in the manuscript where it is unclear whether the aim is only to highlight gaps or to actually extract data, which is a much more difficult task.
- We agree that extracting seroprevalence data is beneficial, but we also acknowledge that it is complex and out of scope for the purpose of the RRNA. We are extracting /mapping key data such as study design, study year, setting, populations groups to show where there are gaps in data and provide a repository of existing studies. Hence, if there are a sufficient number of studies identified on any of the domain topics, these can readily be pivoted to a full systematic review if needed and resources are available.

Page 10, domain 3: Why is only the incubation period being extracted/recorded? This should extend to all delays, including the serial interval, the onset-to-hospitalisation interval, etc. Also, it would be great to capture whether only sample summary statistics (mean, median, min, max, etc.) are reported or whether distributions are fitted.

- Based on our piloting of the protocol we have found that it is not systematically reported for us to meaningfully report on it. The RRNA is developed for emerging infectious diseases where the evidence base and knowledge is limited. For these diseases the published evidence is generally also limited by study design, numbers included, and quality of reporting. Many studies are cross-sectional reporting sparse data from healthcare centres in resource limited settings, often lacking in reporting even of basic demographics. We collect and extract available data in the format available, whether this is mean or median or just an age range. Due to the nature of the publication landscape for these disease, the RRNA is focused on essential data mapping. If there were a large number of records identified, these can be pivoted to more in-depth extraction due to the benefit of the adaptive protocol.

- *Page 10, domain 3:* It would be good to capture reproduction number estimates. More generally, several transmission parameters, such as overdispersion, should be included in this domain to enable infectious disease epidemiologists to build models. Can be targeted depending on the disease—resource and quality
- Based on our piloting of the protocol we have found that it is not systematically reported for us to meaningfully report on it. See previous comment.

- *Page 12, search terms*: Thank you for including the search terms. In an outbreak situation, this is only possible since the last RRNA update, as otherwise one would get too many titles and abstracts to screen (e.g., for Ebola or SARS-CoV-2, this would exceed 10,000 papers if the databases are searched since inception).
- We agree with this observation, hence we have specified that the search strategy and inclusion dates should be defined for each disease and context. Further that the protocol is developed for disease where the evidence base is limited. Ebola and SARS-CoV-2 is not fit for a full RRNA. For other re-emerging diseases which has been researched over time, it may be relevant to limit the search strategy to ensure inclusion of up-to-date data only, whereas for rare diseases with sporadic outbreaks only we recommend to include data from first detection of the disease.
- *Page 13, Screening*: Has the use of Google Translate been tested and validated for inclusion in the study protocol? Is there a risk that the translation introduces errors?
- Based on our piloting where we have compared Google translate and checked the translations with reviewers fluent in the language, which has shown that for many common languages it is reliable enough for the purpose of the RRNA. However, it does not work for all languages, in which case a reviewers with the language skills needs to be identified, or the record excluded from the data extraction and instead listed with a full bibliography in the appendix. This has been updated on page 18.

Page 13: A second reviewer will check up to 70% of the data – this is huge. Why can't there be some double extraction at the beginning until the extractors converge to a consistent extraction? Otherwise, this may not be feasible given the time frame.

- In our experience we find that this is feasible, since the data extraction is focused on mapping key variables, rather than open ended extractions. Depending on the volume of articles identified and the need for rapid results, the proportion can be reduced, that is where we state up to 70%, we have further refined this to 30 to 70% of the data depending on volume of records, needs and resources. For rare diseases this is feasible, for high volume RRNAs it can be reduced as required. The data can be checked in the review software or in the exported Excel data file during the data cleaning and analysis process. This has been clarified on page 18: "A second reviewer will check a minimum of 30% and up to 70% of the data, depending of volume of records, need and resources."

- *Page 14, full data extraction*: This would be nice, but how feasible is that unless the team is already in place, fully trained, has all the tools at their disposal and only needs to update since the last entry into the database? Even in the most minimal form, this would be a considerable effort, especially if up to 70% of extracted data is double-checked.
- *Page 14, Definitions*: Please be more specific about the case definition.
- We have specified these further, see page 14.
- *Page 14, Definitions*: The age ranges should be more flexible, as each paper will use its own definition.
- We have included wide age groups definitions to allow for that flexibility, and again this can be adapted as required/needed for each RRNA. For emerging infectious diseases we are aware that certain population groups have not been included in

studies in the past for different reasons, even though they are often of higher risk of severe disease. Therefore, it is important to include specific age groups especially for children, where the risk factors are different depending on age, e.g. neonates/infants, young children versus older children. If aiming to collect these but the data is not there, they can be aggregated at the analysis stage. We have clarified this on page 14: For age-groups, it is of relevance for identifying evidence-gaps to collect data on different risk populations. If the data is not available, age groups (e.g. neonates/infants can be aggregated at the analysis stage.

Page 14, data analysis and dissemination: The authors state that they will provide the analysis code. Why is this included in a study protocol? Would it not be better to set out the requirements and standards for the analysis? Also, several tools already exist for this (epiverse, epireview) and are in use.

- Thank you, we have deleted this statement from the protocol.
- *Page 14, data analysis and dissemination*: In the second paragraph, the authors provide a helpful discussion of what should be done during preparedness time versus during an outbreak. It may be helpful to consider existing work in this area (https://mrc-ide.github.io/epireview/) as well as broader WHO initiatives, such as grEPI.
- Thank you for this suggestion. We have kept the text general, as we acknowledge that different groups might adapt the protocol for different purposes. For the purpose of the RRNA we are identifying and including published evidence in manuscripts and reports as defined in the eligibility criteria. Data repositories are out of scope for the RRNA. The data collected can be deposited in repositories in adherence with good data sharing practices.
- *Page 15, RRNA updates*: It would be helpful if the authors could expand this section substantially. This is non-trivial, and setting this out in the protocol would be helpful. A good example is how database entries should be updated between preprints and the final published paper.
- We have expanded on the updating of the RRNA as described in earlier comment, to clarify that this can be done as new evidence is generated e.g. during or after outbreaks. Since the RRNA is focused on identifying gaps in the evidence-base and providing a method that can be implemented systematically and rapidly in response to outbreaks/when need arises, we can allow some duplication of data, since we are identifying gaps in the evidence base, not performing a systematic review.
- We have also clarified that we will only include pre-prints if deemed relevant, e.g. during outbreaks when key data may be published first in a rapid pre-print, and waiting for the peer-reviewed publication would not make the data available in a timely manner to inform response strategies
- If the RRNA is updated subsequently the pre-print may be removed if the subsequent publication is available – updated on page 28: “The RRNAs can be updated when new key evidence emerges, e.g. during and after outbreaks, or implementation of new therapeutic or vaccine trials. Such update could include updating the reference library to include newly identified studies and revising aggregate counts accordingly. If pre-prints were included in the earlier RRNA, these can be updated with the subsequent publication if available.”

- In the discussion, the authors raise the essential point of collaborative partnerships,

which will be critical to this type of work. However, the key question is who convenes and funds this (not to be answered by this paper). Rapid and robust protocol that could be done quickly. Rapidly and can pivot to proper systematic reviews. During non-emergency periods, systematic reviews with meta-analysis and data synthesis should be strongly preferred as the gold standard. These reviews should be designed to be updated, and the underlying extracted data should be publicly available. This paper fills a critical gap in the literature on how these datasets can be rapidly updated to support outbreak response. Overall, this is an excellent contribution to the literature, but it would benefit from a more precise separation of the study protocol from tools such as the systematic review software, reference manager, or dissemination tools. For the study protocol itself, it would be helpful to separate the use case of mapping existing data from that of extracting it, which is a more complex task.

Competing Interests: Senior Author