Rapid Research Needs Appraisal Protocol
v.1.0

6 December 2017
Rapid research needs appraisal for outbreaks protocol

Background information

The UK Public Health Rapid Support Team (PHRST)

The UK PHRST is a UK Government funded initiative jointly run by Public Health England (PHE) and an academic partnership consisting the London School of Hygiene and Tropical Medicine, the University of Oxford and King’s College London. The UK PHRST monitors infectious diseases globally, this team of trained experts are ready to respond to urgent requests from countries receiving Official development assistance (ODA) from the UK Government, from the WHO and the Global Outbreak and Response Network (GOARN). The team will work together with local health providers to prevent local disease outbreaks from becoming global epidemics. In addition to responding to outbreaks, the UK PHRST will conduct research to improve the response to epidemics in the future and to build the local capacity within low and middle income countries (LMICs) and for public health reservists in the UK through training modules.

The need for a Rapid research needs appraisal

The evidence for making decisions in the midst of an epidemic is often extremely limited, with decisions often based on expert opinion. The barriers for conducting research during epidemics includes the unpredictability, short timeframes and challenging logistics of running field research in resource limited countries. Research is often the lowest priority during an epidemic, and if there is an opportunity to perform research, the priorities and research gaps need to be identified as quickly as possible. The aim of this work is to perform a rapid scoping exercise to identify the key knowledge and research gaps, in order to help identify and prioritise research questions that need addressing. The premise, if possible is to take advantage of time differences across the globe to enable the rapid appraisal of existing evidence to be conducted over five days.
**Project aims and objective:**

The aim is to develop a rigorous, transparent and replicable methodology for researchers and clinicians to conduct an accelerated evidence review at the early stages of an epidemic to identify key knowledge gaps to prioritise patient-centred clinical research.

**Key objectives:**

- A written protocol for completing a rigorous evidence review within 5 days of recognition of the need for a rapid research needs appraisal in response to an outbreak.
- Development of a model where global partnerships, and efficient use of teams in different global time-zones, are optimised for rapid implementation of the research needs appraisal.
- Evaluation of the methodology using an outbreak scenario.
- Publication of final protocol on the conduct of a rapid research needs appraisal.
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This protocol was produced in a collaborative effort by the Epidemic Disease Research Group and UK Rapid Support Team at the Centre for Tropical Medicine and Global Health at University of Oxford, Evidence Aid and Cochrane Response.

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1. Background

Systematic reviews might require time and resources that are not available in a rapidly emerging area such as a (re-) emerging infectious disease outbreak. Even rapid evidence reviews often take weeks to months to complete. At the initial stages of an outbreak, researchers, policy makers, and funders are in need to rapidly identify gaps in evidence and knowledge to inform and prioritise rapid clinical and public health research responses. This document presents a methodology for carrying out a rapid research needs appraisal (RRNA) within a limited time-frame. The aim is to review existing evidence covering a range of areas to identify gaps in knowledge and evidence. The results will be used to rapidly inform research priorities with a focus on clinical research to advance diagnostics, clinical management, integrated with public health responses.

The protocol contains standardised pre-defined tables that are designed to be generic and to capture clinical data relevant for rapid, clinical research responses. These can be rapidly reviewed and modified if needed, depending on the nature of each outbreak. If an evidence management system is used, the protocol can be pre-programmed into the system, then modified slightly if required in response to an outbreak.

The methodology is designed to be used for emerging outbreaks, where the clinical evidence base is expected to be limited. The aim of the methodology is to identify gaps in knowledge and evidence to inform clinical research priorities in response to emerging outbreaks.
2. Management and responsibilities

The decision to carry out a rapid research needs appraisal (RRNA) will be taken by a steering group comprising of infectious diseases specialists, clinical researchers and content experts as relevant to the outbreak scenario. Once the steering has taken the decision to undertake a rapid research needs appraisal, the steering group will convene a coordinating team that will coordinate the process as outlines in Figure 1. It is recommended that the systematic evidence search is carried out by an experienced health information specialist, and that the screening of papers for inclusion and data extraction is carried out by a minimum of three people with experience in systematic reviews to ensure rigour and quality. The number of systematic reviewers can be scaled up depending on the nature of the outbreak and the volume of evidence identified. Use of a systematic review software will enable scaling up of resources as required depending on volume of evidence retrieved, and allow processes such as screening and data extraction to be done in parallel by several reviewers. Resources can also be scaled up by use of global teams of systematic reviewers and efficient use of time-zones.

The method is designed to be used to rapidly synthesis existing evidence to identify knowledge gaps in response to a (re-) emerging infectious disease outbreak. It is expected that the volume of existing clinical relevant evidence will be limited. The outcome of the rapid research needs appraisal will be a summary of existing clinical evidence, which will highlight where gaps in knowledge and evidence exists and inform clinical research priorities.
2.1 Trigger for conducting a rapid research needs appraisal

The trigger to carry out a rapid, research needs appraisal will be in response to an emerging outbreak. It will be based on information from global outbreak reports or risk assessments produced by the UK Rapid Support Team, CDC, ECDC, WHO or in response to a request from local stakeholders, e.g. clinicians working in an affected region. This information will be reviewed by a steering group including infectious disease and clinical research experts who will decide whether there is a need for an RRNA (section 2.2).
2.2 Rapid research needs appraisal steering group

If a trigger is identified or a request for a rapid research needs appraisal received by the steering group (RRNA SG), it is the steering group’s responsibility to review the information in a timely manner (Table 1). The RRNA SG will review the information available and consult with content experts as appropriate depending on the nature of the outbreak. The decision to undertake a RRNA will be informed by risk assessments produced by organisations as described in section 2.1 and consultations with content experts 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 prioritise in response to the outbreak.

To enable an informed decision about carrying out a rapid, research needs appraisal it is recommended that the steering group consists of at least one:

- Infectious disease specialist
- Clinical researcher
- Additional specialists as appropriate depending on the nature of the outbreak

Depending on the assessment, the decision taken will be either that:

1. There is need for an RRNA
2. There is no need for an RRNA
3. The information is insufficient at this moment in time. The need for a RRNA will be re-assessed within a set time frame.

When the decision is taken to start a RRNA this is Day 1 of the RRNA process. The RRNA SG will then convene a coordinating team. Depending on the structure of the organisation and resources the steering group and coordinating group can be the same.

<table>
<thead>
<tr>
<th>Steering group responsibilities</th>
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<tbody>
<tr>
<td>To risk assess the emerging outbreak and the need for a RRNA</td>
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<tr>
<td>To consult with additional content experts as appropriate to assess the situation and inform the decision to undertake a RRNA</td>
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<tr>
<td>If a decision is taken to carry out a RRNA to convene the coordinating team the same day to start the process (= Day 1).</td>
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Table 1. Responsibilities of the steering group
2.3 Rapid research needs appraisal coordinating team

The rapid research needs appraisal coordinating team (RRN CT) is responsible for coordinating the rapid needs appraisal process from notification of the need for a RRNA from the steering group, through to completion (Table 2).

Composition of the coordinating team:

- An infectious disease specialist
- Additional content experts as required depending on the nature of the outbreak
- Researcher with experience in systematic evidence reviews
- Administrative support

The RRN CT will meet on Day 1 to:

- Alert the information specialist and systematic review team/s of the need for a RRNA.
- Review the protocol and identify if any adaptions are needed depending on the nature of the outbreak.
- Finalise and send the protocol together with a brief overview of the situation and clinical background information to the information specialist and systematic review team/s by end of Day 1.
- Provide a verbal briefing to the information specialist and systematic review team/s.
- Advise on if specific language expertise might be required in regards to the location of the outbreak.
- Register the protocol on the Open Science Framework.

During the process the coordinating team will be at hand to answer clinical or content specific queries from the systematic review teams.

<table>
<thead>
<tr>
<th>Responsibilities of the coordinating team</th>
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<tr>
<td><strong>Day 1</strong></td>
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<tr>
<td><strong>Day 2 - 4</strong></td>
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<tr>
<td><strong>Day 5</strong></td>
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</table>

Table 2. Responsibilities of the coordinating team
### 2.4 Information specialist

An experienced information specialist should be identified and engaged in the process in advance so they are prepared to respond when the need for an RNNA arises.

The information specialist will be responsible for carrying out a systematic evidence search across all domain question as soon as the CT has reviewed and made any necessary amendments to the protocol. They will then forward the search results, after de-duplication of records, together with full text articles to the systematic review team/s. Responsibilities of the information specialist (Table 3).

<table>
<thead>
<tr>
<th>Information specialist responsibilities</th>
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<tr>
<td><strong>Day 1 - 2</strong></td>
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<tr>
<td><strong>Day 2-3</strong></td>
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</table>

Table 3. Responsibilities of the information specialist

### 2.5 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. Use of systematic review software is recommended to enable systematic reviewers in different locations globally to work on the screening and data extraction process in parallel and for audit. However it is not a requirement.

A minimum of two systematic reviewers are essential for quality. Depending on the volume of evidence retrieved the number of systematic reviewers can be scaled up. Responsibilities of the systematic review team/s (Table 4).
The systematic review team/s will be notified about the need for carrying out a RRNA in response to a (re-) emerging outbreak by the RRNA coordinating team on Day 1. The review teams will be sent the protocol after review by the coordinating team by the end of Day 1. The coordinating team will also provide a brief with information about the outbreak and pathogen involved in writing and by phone or Skype. The coordinating team will be available to answer questions during the screening and data extraction process.

The systematic review teams will receive the search results from the information specialist by day 2. The team/s will then screen the titles and abstracts, full text papers, and extract the data into the data extraction template (Table 10). The systematic review team/s will send the completed data outcome templates to the coordinating team by mid-day on day 5.

<table>
<thead>
<tr>
<th>Responsibilities of the systematic review team</th>
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<tbody>
<tr>
<td><strong>Day 1</strong></td>
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<td><strong>Day 1-2</strong></td>
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<td><strong>Day 3 - 4</strong></td>
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<td><strong>Day 5</strong></td>
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Table 4. Responsibilities of the systematic review team
Level of expertise needed

<table>
<thead>
<tr>
<th>Minimum of two experienced systematic reviewer</th>
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<tbody>
<tr>
<td>Depending on the outbreak relevant language expertise might be required</td>
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</table>

Table 5. Systematic review expertise

Systematic review software

It is important to identify and engage organisations with systematic review expertise in advance, so they are prepared to respond rapidly to an emerging outbreak. Global teams of systematic reviewers can be identified and engaged in advance, to ensure capacity, contingency and to enable effective use of time-zones if required depending on the type of the outbreak. To optimise resources, allow processes to run in parallel without the need for handovers, and for rapid scaling up of resources if needed, it is advised to use a Systematic review software accessible by all teams. Using a systematic review software also allows continuous monitoring of progress, rapid identification of issues and audit.

Reporting responsibilities

The systematic review team/s are responsible for submitting the completed data outcome tables with any associated brief comments or notes as appropriate, by mid-day on day 5 to the coordinating team via e-mail. The review team will also complete and submit the PRISMA diagram, including number of papers screened and numbers excluded at each step of the screening process.
3. Protocol

The figure below outlines the overall methodology and process over the five days, from the decision is taken to start the rapid research needs appraisal process (Day 1) through to the final report submission on Day 5 (Figure 2). The protocol is described in detail in the following section. On day 1 the coordinating team will review this protocol and make any amendments as required depending on each outbreak. It is recommended to use a systematic review software to enable steps in the protocol to be carried out in parallel. It will also allow pre-programming of the protocol in advance.

**Figure 2. Rapid research needs appraisal process**
**Outbreak scenario**

Description of the outbreak to be added for each outbreak, using risk assessments published by the Centre for Disease Control and Prevention (CDC), the European Centre for Disease Prevention and Control (ECDC) or the World Health Organisation (WHO).
3.1 Scoping questions

It is important to make sure the scoping questions are well defined and specific to the emerging threat. The RRNA coordinating team will review the pre-defined questions for each domain and modify if needed, depending on each outbreak on Day 1. The domain template has been developed as a standard template to cover key clinical infectious disease research questions (Table 6). This template will be reviewed by the coordinating team for each outbreak scenario and modified if appropriate on Day 1 then submitted to the information specialist and systematic review teams.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Question(s)</th>
<th>Population</th>
</tr>
</thead>
</table>
| Clinical phenotype and natural history of disease | What are the signs and symptoms of the disease?  
What are the laboratory (haematology, biochemistry, coagulation etc) features of disease?  
Which constellations of clinical features distinguish disease from differential diagnoses?  
Are there distinct clinical syndromes amenable to staging/grading?  
Does asymptomatic infection occur?  
What is the mortality rate? | Neonates  
Infants  
Children  
Adults  
Elderly  
Pregnant |
| Transmission                            | What is the incubation period of the disease?  
What are the routes of transmission?  
What are the infective body fluids? When and how long are they infectious for? | Children  
Adults  
Elderly  
Pregnant |
| Prevention                              | How effective is vaccination (if it exists) at preventing disease?  
What are the side effects of vaccination?  
How effective is drug prophylaxis (if it exists) at preventing disease?  
How effective is post-exposure drug prophylaxis (if it exists) at preventing disease?  
What are the side effects of drug prophylaxis? | Adults  
Elderly  
Pregnant |
| Diagnostics                             | What is the sensitivity and specificity of different diagnostic tests? In different bodily fluids (e.g., blood, CSF, urine)? | Pregnant   |
| Immune response                         | What is the serological response to infection? | Pregnant   |
| Drug therapy effect                     | What is the effect of drug therapy on:  
- length of hospital stay?  
- complications  
- mortality rate?  
What is the effect of different doses, routes and frequencies of drug therapy on the response? | Pregnant   |
Table 6. The domain questions to be covered
The scoping question criteria should be defined using (PI (E) COs): Population, Interventions, Exposure, Comparator, Outcomes.

The RRNA coordinating team will review the template and modify as appropriate depending on each outbreak on day 1.

3.2 Evidence search

Since the RRNA will be used for emerging infectious disease outbreaks where there might be very limited evidence published prior to the outbreak, the search needs to be inclusive. Therefore, all types of studies published in peer reviewed publications, grey literature and unpublished data might be considered to be included, depending on each specific outbreak. The table below will be used as a template and reviewed by the coordinating team for each RRNA request and modified/restricted as appropriate on Day 1.

The evidence search should be carried out centrally across all domains by an experienced information specialist. The information specialist will carry out the search once the final protocol with the specified search strategy has been received from the coordinating team, by Day 1 - 2. It is recommended that the information specialist is assigned to a University library to enable automatic uploading of full text papers into Endnote.

The information specialist will send the search results as an Endnote file with full text articles to the systematic review team/s by Day 2.
Sources of evidence
The main databases to be covered by the search are listed in table 7. These will be reviewed and modified as appropriate depending on the nature of the outbreak by the coordinating team on day 1.

<table>
<thead>
<tr>
<th>Databases</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PubMed, Embase, Cochrane Library, DARE, Epistomonikos, Prospero</td>
<td></td>
</tr>
<tr>
<td>Clinical trial registries (clinicaltrials.gov, ISRCTN registry)</td>
<td></td>
</tr>
<tr>
<td>Grey literature e.g.: WHO, CDC, ECDC</td>
<td></td>
</tr>
</tbody>
</table>

Table 7. Databases to be covered

Search restrictions
To be defined for each outbreak.

Study designs to include

<table>
<thead>
<tr>
<th>Hierarchy</th>
<th>Study designs to always include</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Systematic reviews and meta-analyses</td>
</tr>
<tr>
<td>2</td>
<td>Randomised controlled trials (RCT)</td>
</tr>
<tr>
<td>3</td>
<td>Other controlled studies (e.g. non-RCT, randomized cross-over studies)</td>
</tr>
<tr>
<td>4</td>
<td>Cohort studies incl. before and after studies (prospective/retrospective)</td>
</tr>
<tr>
<td>5</td>
<td>Case-control studies</td>
</tr>
<tr>
<td>6</td>
<td>Cross-sectional studies (including audits)</td>
</tr>
<tr>
<td>7</td>
<td>Case series</td>
</tr>
<tr>
<td>8</td>
<td>Case reports</td>
</tr>
<tr>
<td>9</td>
<td>Conference abstracts</td>
</tr>
</tbody>
</table>

Table 8
The table shows the study types to be included and the hierarchy of evidence.

Retrieving full text articles
The information specialist will retrieve the full text articles through Endnote and University library access. The information specialist will send the Endnote library will upload the search results to Dropbox and send an alert to all teams. The information specialist will then retrieve the full text papers using the Endnote automatic retrieval function, and once completed, upload the library to Dropbox and send out another alert. Once the screeners have included papers, they will send a list of included papers where the full text article is not available to the information specialist, who will then carry out a manual search for these. Papers retrieved from this search will also be uploaded to Dropbox and an alert sent to all
teams when completed. Papers that are not identified after the manual search will be noted in the final report.

After screening of titles and abstracts are completed, the systematic reviewers will send a list with included papers not yet retrieved to the information specialist. The information specialist will manually search for these. If at this stage full text papers are still not accessible, a note including the details of the paper, should be made in the report.

3.3 Screening

Once the information specialist has completed the evidence search, it will be sent to the systematic review team/s as an Endnote library (see section above). Once received the systematic review team will upload the file to Distiller and send an alert to all teams that it has been completed to start screening. The review team uploading the library to Distiller depends on the time of the day the search is completed. The review teams will organise this internally.

The systematic review team will then start the screening of abstract and titles. To ensure rigour and quality there needs to be a minimum of two systematic reviewers. As it is expected that there will be limited evidence published it is key to ensure that the screening strategy is rigorous as well as inclusive. If they have access to a systematic review software, this means that once the Endnote file is uploaded work can be ongoing in parallel, and it is easy to keep track of tasks that has been done or need doing.

Once the Endnote library with full text papers are uploaded to Dropbox by the information specialist, the review teams will upload it to Distiller. As above, the review team responsible for this depends on the time of the day and will be organised by the review teams internally.

- Title and abstracts will be screened for inclusion by one experienced systematic reviewer. A second experienced systematic reviewer will screen the articles excluded by the first reviewer for inclusion. Any disagreements will be included.

- Papers include where there is no full text paper retrieved by Endnote, will be listed. This list will be sent to the information specialist via e-mail for a manual search of the papers. Once the manual search is complete the information specialist will upload additional papers retrieved manually to Dropbox and alert the review teams. If it is not possible to obtain and assess a full text article within the time and resources available, a note will be made in the report, and these papers will be listed with full bibliography in the final report.

- Full text articles will be screened by two reviewers and disagreements checked by a third reviewer with experience in infectious diseases for consensus.

- Depending on the nature of the outbreak, if it is expected that key evidence has been published in a language other than English, then a reviewer or a review team
from that region or with the specific language skills will be ideal to engage at the start of the process whenever possible.

- In general, for papers in languages other than English, if possible a reviewer with the required language expertise should review and extract the data, especially if it is a high quality paper. If it is not possible to identify a reviewer with required language skills a note should be made in the report, and any papers not extracted listed with full bibliography.

**Inclusions and exclusions**

As the volume of evidence is expected to be limited, and it is therefore important to ensure all relevant evidence is included, there will not be many restrictions on the inclusions. The focus is on clinical studies in humans. Animal studies will be excluded. The inclusion and exclusion criteria will be reviewed and adapted as appropriate depending on each outbreak.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical research</td>
<td>Animal studies</td>
</tr>
<tr>
<td>No language restrictions</td>
<td>Cell culture studies</td>
</tr>
<tr>
<td></td>
<td>Non-clinical studies</td>
</tr>
</tbody>
</table>

**Table 9. Inclusion and exclusion criteria**

**3.4 Data extraction**

The aim of the rapid evidence appraisal is to identify gaps in knowledge to inform prioritisations of rapid research responses. With limited time the data extraction needs to be limited to essential data. Data will be extracted into a pre-defined outcomes table (Table 10).

- Data will be extracted into the pre-defined data outcomes template by one experienced systematic reviewer.
- A second reviewer will check 10% of all data and 100% of the numeric data.
- Additional brief notes in bullet style format (linked to relevant papers) to be added as appropriate under the data outcome table.
- Data from case series, case reports and conference abstracts will only be extracted if no higher level of evidence for that domain questions identified.
Table 10. Data outcome table for the data extraction

The table shows the data to be extracted into the data outcome table. If a paper is covering more than one outcome, enter data as appropriate in separate rows. If several papers are covering the same study, or same cohort, enter all data in separate rows and make a note.

The result section should report primary and secondary outcome statistical data.

Data covering study design, setting, n numbers and PI (E) COs: Population, Interventions, Exposure, Comparator, Outcomes.

*Data reporting should include description of the populations covered, including:

- Male/Females and age range
- Neonates/infants/children/young people and age range
- Pregnant women/Post-partum/breastfeeding women
- People who are immunosuppressed by illness or medication
- Malnutrition
- Comorbidities

3.5. Reporting the results

The aim of the rapid evidence appraisal is to review and rapidly synthesis minimum data sets from existing evidence to identify where there are gaps in knowledge. This information will be used to inform research prioritise for rapid, clinical research responses.
The systematic review teams are responsible for submitting the completed data outcome tables generated to the coordinating team by mid-day on Day 5. The coordinating team are responsible for collating the results from all domains and systematic review team/s into the final report. The coordinating team is also responsible for submitting the final report to the steering group by the end of Day 5. Once the steering group has reviewed the report and any queries has been followed and the report approved by the steering group, it will be circulated to the systematic review teams and can at this stage be shared with external stakeholders. The steering group will use the report to inform research prioritisation decisions, through discussions with external stakeholders and content experts as appropriate.

Final report template:

- **Title**

- **Background:**
  - Brief overview of the outbreak and data available
  - Aims and objective of the RRNA

- **Results**
  - PRISMA flow diagram
  - The data outcome tables submitted by the review team/s for all domains and associated notes
  - Associated notes and comments, including papers included, but were data were not extracted due to e.g. language other than English, or the full text paper not accessible.

- **Methodology:**
  - Teams and experts involved
  - Abbreviated methods section to include a checklist of items
  - Search protocol and search terms

3.6 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 outbreak by experts in infectious diseases, clinical research and by consultation with content experts as required, and modified as appropriate. The information specialist and systematic review teams will be engaged and trained in the protocol in advance and notified as soon as the decision for undertaking an RRNA is made. Ensuring that the teams have experience of systematic reviews will also ensure rigour, consistency and quality. The final report will be reviewed by infectious disease specialist and content experts, with experience relevant to the specific outbreak and clinical domain questions.