



GLOPID-R

Global Research Collaboration for Infectious
Disease Preparedness (GloPID-R)

Final Report - Work Package 2

Connecting and Mapping: Exploring the capacities, capabilities,
and barriers to a rapid response to outbreaks among funders and
research networks

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Prepared by the GloPID-R Secretariat

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EXECUTIVE SUMMARY

This *Connecting and Mapping* study aims to explore the capacities and capabilities of research networks and funders to respond rapidly to epidemics and pandemics. It also seeks to explore any political, ethical, administrative, regulatory, logistical, economic, and social (PEARLES) barriers and bottlenecks to rapid outbreak responses. This study is one of two work packages co-ordinated by ISARIC investigators in conjunction with their role in GloPID-R's Secretariat.

Utilising mixed methods, this project was divided into two parts, where the first (Part I) was a quantitative study based on the dissemination of surveys, and the second (Part II) utilised qualitative methods to explore issues raised in part I in greater detail by analysing three case studies on research projects undertaken during the West African Ebola outbreak.

A total of 33 research networks, with activities in over 110 different countries worldwide, responded to the *Capacities and Capabilities Survey*, while the *PEARLES Barriers Survey* received 39 responses. Twenty-one different funding organisations from 15 countries responded to the *Funders Survey*, half of whom were GloPID-R members. The main findings indicate that there is significant capacity and capability within the participating research networks for the rapid conduct of research in an outbreak situation, including for international multi-site clinical trials. More than half of all networks have expertise in infectious diseases research, epidemiology, and clinical trials, and networks reported recruiting patients across a broad range of age groups and socioeconomic backgrounds. A majority of respondents have access to research infrastructure and support, and were experienced or trained to conduct a clinical research response to an outbreak. The vast majority were also interested in further developing their capacity, or collaborating to develop another network's capacity, for clinical outbreak preparedness. The main concern for networks in the event of an outbreak was reported to be the access to funding.

Main findings

- While research capacity and capability exists in networks, early funding is required to mobilise in an epidemic.
- Research responses should be integrated into routine clinical care.
- Partnerships with local researchers should be facilitated prior to outbreaks
- Capacity building in LMICs should be integrated into response efforts
- Pre-established collaboration between academic and non-academic partners would limit delays to the response.
- 'Triggers' for accelerated responses identified and agreed in advance.
- Emergency procedure protocols for funding initiatives should be trialled.

While a majority of research networks would be able to conduct studies, many would only be able to do so if allocated funding to cover costs related to trials and the necessary staffing.

Though most networks reported that they hold significant experience, and that rapid approval initiatives exist, there are still barriers and bottlenecks in rapidly conducting research. The timelines for expedited schemes are, although adequate for conventional studies, still too slow for pandemic research. Timelines vary regionally and issues such as the lack of centralised approval for multiple centres, staff costs, and time necessary for the preparation of study documents often cause delays. Overall, the time required for getting observational studies ethically approved was between 1 and 2 months, while more time was required for the approval of randomized studies of investigational medicinal products. The same pattern was observed with regards to regulatory approval, though the process could take longer. Pre-approval of protocols for the quick implementation of studies in the event of an epidemic or pandemic was available in more than half of the countries included in this study, though only 40% of the same respondents had ever used pre-approval schemes. Another major hurdle to a rapid response was related to contracting between the sponsor of a study and the relevant study sites, which, respondents reported, could take between 1- 6 months or longer.

Finally, the findings from the *Funders' Survey*, suggested that there was considerable funding allocated towards pandemic research during the recent West African EVD outbreak, but that funders mainly budget for annual pre-planned funding calls. Results indicate that funders recognized the importance of funding pandemic research, both before and during the Ebola outbreak, but that there is little coordination between funders in terms of joint funding calls or otherwise coordinated calls. Additionally, timelines to allocate funding were significant and whilst some respondents had faster processes in place in the event of an epidemic or pandemic, this could still vary between 1 and 8 months or longer.

The qualitative part of the study sought to explore the research response to the West African EVD outbreak in greater detail. The study, which built on the survey responses and a literature review, was conducted through a series of seven semi-structured interviews, which were held with the Principal Investigators (PIs), including one local Principal Investigator, and relevant funding representatives of three chosen EVD research projects.

The main findings show that capacity building should be integrated into the implementation of studies in low-resource settings, that local researchers should be involved in the development of

protocols and research tools, and community engagement is important for the successful implementation of research. Further, collaborative research poses a challenge to the traditional instruments of academic credit, which may pose a barrier to research in studies that include more than one PI. There is a need for multi-disciplinary collaboration between researchers in different fields, and prominent humanitarian organisations, to take place ahead of outbreaks in order to expedite the drafting of protocols and signing of contracts between partners, and to facilitate rapid ethical and regulatory approvals. Finally, though some funders have accelerated processes in place for rapid funding initiatives, they had not been utilised before the Ebola outbreak. Funders would welcome a broader discussion to identify the ‘triggers’ for an accelerated response ahead of future outbreaks, and there is a need to test emergency procedures before they are utilised for a response effort. The in-kind contributions paid by both academic institutions and funders were very significant, and funders interviewed considered a 48 hour roll out of funding initiatives to be very unlikely. They did, however, welcome more coordination and communication between funders in an outbreak.

This study is the first to explore this research topic from both a funders’ and researchers’ perspective, and it offers clear insights into how rapid research response efforts can be improved. Further work to increase the geographical spread of respondents to the Part I survey, would increase the robustness of our findings, as some countries and regions were not adequately represented. As would interviewing more local investigators for the Ebola research projects to help inform future ‘North-South’ collaborative efforts. However our results suggest that establishing and maintaining a global database of capacity and capabilities, facilitating collaborations between research networks, improving global research capacity building, understanding PEARLES barriers in these regions, pre-designing potential research trials, facilitating pre-approved studies, and ensuring practical systems and agreements in are in place to facilitate rapid access to funding, would speed up the research response significantly. For each of these processes, coordination among research networks and funders through initiatives such as ISARIC and GloPID-R, and engaging with other key stakeholders, such as public health, regulatory agencies, ethical review boards, industry, and non-governmental organisations (NGOs) is crucial in order to ensure a more rapid and efficient response. The on-going changes to the WHO structure and governance to facilitate rapid coordination of research activities during outbreaks will also play a significant role in how any response unfolds in the future. Therefore, the WHO requires adequate, flexible resources from its member states to function effectively.

PART I: CONNECTING AND MAPPING

INTRODUCTION

In 2011, the Heads of International Research Organisations (HIROs) called for the creation of the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) in an aim to develop and coordinate ways to speed up the research response to outbreaks.¹ Similarly, the Global Research Collaboration for Infectious Disease Preparedness (GloPID-R) was initiated in 2014 by the European Commission, following discussions with the HIROs and in collaboration with other funding bodies globally (Appendix I), as a network of major funders with the goal of funding and facilitating a research response within 48 hours of an infectious disease outbreak.²

The first cases of Ebola Virus Disease (EVD) in West Africa occurred at the end of 2013 in a remote part of Guinea. However, the outbreak was not officially reported to the Guinean Ministry of Health or the World Health Organization (WHO) until March 2014. EVD infection was confirmed shortly after at the Jean Mérieux-INSERM biosafety level 4 laboratory in Lyon, France (1). With the porous borders between Guinea, Liberia and Sierra Leone crossing through highly mobile communities (2), the outbreak had spilled over into Liberia by March 2014 and into Sierra Leone by May 2014 (3). Already, five months had elapsed since the first case. It would be a further three months until the Director-General of the WHO declared a Public Health Emergency of International Concern (PHEIC) on 8 August 2014 and five months before the first clinical research trial began in October 2014 (4, 5).

The world had never seen an outbreak like this; Ebola historically occurred in isolated, rural villages that were relatively easy to quarantine, but in 2014, it had reached populations in densely populated urban centres (2). With access to millions of potentially susceptible individuals, very weak health systems and few other significant national structures in place to control the outbreak, it spread rapidly, reaching a peak in October 2014 (2, 3). Despite a significant international effort to control the outbreak and stop transmission, it continued to smoulder for another year (6). The longevity of the outbreak allowed for the completion of a handful of research studies during the second year. However, this is not usually the case in outbreaks of emerging diseases of epidemic

¹ isaric.tghn.org

² glopid-r.org

or pandemic potential. During the influenza A(H1N1) pandemic of 2009, for instance, the global pandemic was declared over within 16 months (7) and no large scale clinical trials were able to be completed due to the time lag between detection of the outbreak, acknowledgement of a public health emergency, and the instigation of a research response (8).

By the end of January 2016, with Guinea, Liberia, and Sierra Leone having interrupted all chains of transmission from the original outbreak that began more than two years earlier, the questions remain: What does it take to rapidly implement a clinical research trial during an outbreak, and what are the political, economic, administrative, regulatory, logistic, ethical and social (PEARLES) barriers and bottlenecks limiting this? More importantly, which research networks and researchers throughout the world currently have the capability and capacity in place to participate in such clinical studies during the next pandemic? This is the focus of the current study, *Connecting and Mapping*, which is being conducted by members of ISARIC and its Coordinating Centre within the GloPID-R Secretariat. This report aims to explore the capacities and capabilities among research networks and funders alike in responding to outbreaks of pandemic potential. It also aims to explore the PEARLES barriers to rapid pandemic research in greater detail.

METHODS

This project is composed of two complementary quantitative and qualitative methodologies. The report has been divided into two parts for pragmatic reasons, to reflect the sequential nature of these methodologies and to facilitate rapid dissemination of the results to inform GloPID-R's activities. Part I, which was presented in December as an Interim Report, aims to map the capacities and capabilities of research networks and funders to respond to outbreaks, and the PEARLES barriers related to rapid outbreak responses, by quantitative means through the dissemination of three surveys. The study has since been updated and complemented by Connecting and Mapping (Part II), which aims to expand on themes identified by Part I, through a qualitative study focused on a series of semi-structured interviews with funding representatives and principal investigators involved with the implementation of therapeutic trials during the West African Ebola outbreak. This final report includes both Part I and Part II, and culminates with a conclusion that reflects on the findings of the collected body of work constituted by the combination of both parts of the study. This part of the report is particularly dedicated to Part I of the study.

The Capacities and Capabilities Survey was developed from an earlier Capacities and Capabilities Survey commissioned by ISARIC (the Capacities and Capabilities Survey that was sent out to ISARIC members in 2012 and 2013). All of the names of the investigators that contributed to the previously developed surveys are included in the Acknowledgements on page 59 of this report. The PEARLES Study was informed by an EARL's (Ethical, Administrative, Regulatory, and Logistical) Barriers survey prepared as part of PREPARE's (Platform for European Preparedness Against (Re-)emerging Epidemics, FP7 Programme under grant number 602525) work package 1 in 2014. Investigators that were involved in the development and analysis of the previous ISARIC and PREPARE surveys contributed to the development of the GloPID-R surveys. The Funders' Survey was developed on the basis of the themes identified in the research network surveys but tailored to reflect the particular activities of the funding organisations. Each of the surveys were trialled and validated by a carefully selected group of researchers and funders during the iterative drafting process, and approved by the GloPID-R Chair ahead of distribution.

The two surveys, when modified to suit GloPID-R, were distributed to ISARIC's membership and Fondation Merieux' network contacts, which added up to a total number of 108 research networks.

Another survey, the Funders' Survey, was sent to 43 funding organisations, including both GloPID-R members and non-members. Following the interim report, a second round of the quantitative study was initiated to address identified gaps (i.e. a number of incomplete survey responses, and a low number of responses from networks and funders in South and Central America and Africa). Both the responses of the first and second round have been included in this final report and the numbers presented here represent the total number of recipients and participants per survey.

The respondents were considered expert representatives of their networks or institutions and asked to provide their professional/official opinions and views. While the research networks were identified due to their previous involvement with outbreak research and pandemic preparedness, the funders were identified on the basis of established track-record of funding research that is or could be related to infectious disease outbreaks and/or research preparedness. While half of the funders were included in the study due to their GloPID-R membership, which in itself is an indicator of their interest in outbreak and/or preparedness related research, the other half were included due to their funding activities related to outbreak research in that they have funded research during current or past outbreaks of pandemic potential (e.g. SARS, H1N1, H7N9, H5N1, MERS-CoV, seasonal influenza, or EVD), nationally, regionally, or globally. The research networks and funders included in the second round were selected to particularly target gaps that were identified in the first round

The surveys were designed on and distributed through the open source survey web application *LimeSurvey*, and the links to the surveys were made available to participants online. The surveys can be accessed through the links included in Appendix III. The application was installed on the University College Dublin's secured servers and the survey data was stored on these systems. Only the research team had access to the systems and the data collected. Each identified respondent received an email inviting them to participate in the surveys (see Appendix II), alongside a link to the relevant surveys. For the first round of dissemination a total of four reminders were sent to the potential respondents over a period of six weeks until the surveys were closed, while two reminders were sent for the second round. Virtual tokens (passwords) were created for a number of respondents who missed the deadline for the first round, enabling them to respond to the relevant survey after it was closed, but before the data was extracted for analysis. The second round was conducted in an expedited manner, and did not allow for tokens. However, as some of the respondents who provided incomplete responses to the first round

quoted technological difficulties and difficulties connecting to the web interface as a reason for the incomplete responses, a Word version of the surveys was sent out on request. The data collected through the Word version of the survey were manually inserted into LimeSurvey by the research team.

Once the surveys were completed the data was exported to Excel, SPSS and R for analysis. All data that was provided as free text, as opposed to multiple-choice answers, was imported into NVivo for coding of themes and analysis. Participants were anonymised using participant keys. Only the research team had access to these keys and to the exported data.

This project (Part I and Part II) has been reviewed by, and received ethics approval by the University of Oxford Central University Research Ethics Committee (references: MS-IDREC-C1-2015-122 and MS-IDREC-C1-2015-217).

RESULTS

Capabilities and Capacities Survey

A total number of 108 clinical research networks were contacted, and a total of 33 networks completed the survey. Additionally, 17 respondents partially completed the survey and a further 12 respondents declined the invitation to complete the survey for a number of reasons ranging from the lack of time and resources to their not representing research networks. The partially completed survey responses have not been included in the results presented here.

Descriptive characteristics

Based in 18 different countries, approximately 70% of responding networks (n=23) were established within the past 10 years (since 2005), and 39% (n=13) consider themselves multinational networks. Multinational networks operated in an average of 17.5 countries (range 2-45). With each respondent naming up to 8 countries where their networks carry out research, it was determined that responding networks operate in at least 110 countries of all resource settings (Figure 1).

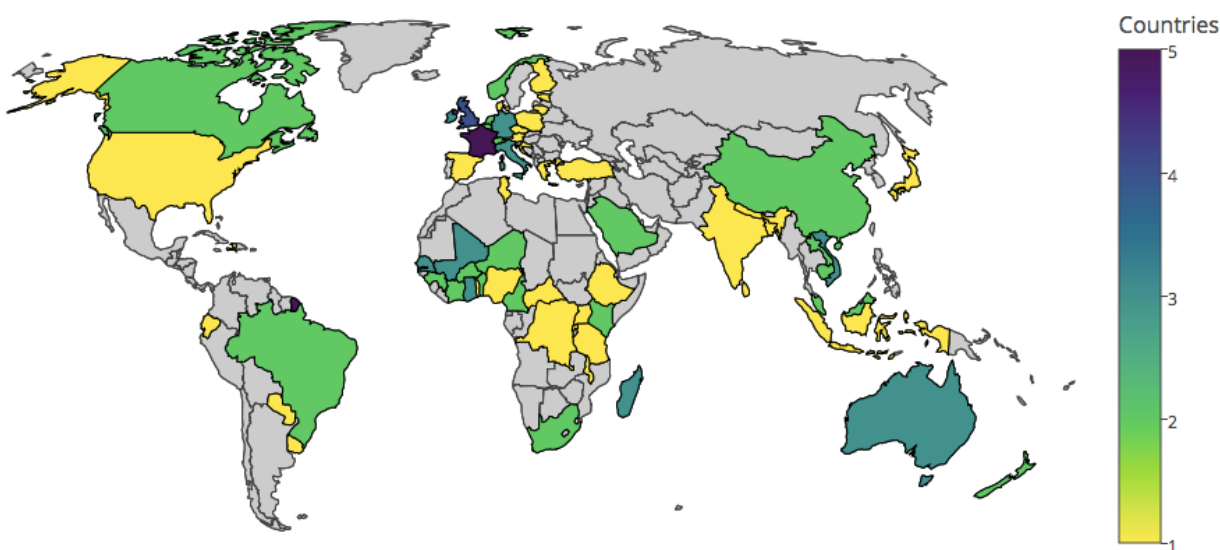


Figure 1. Countries where responding research networks operate

One third of the respondents declared that their network included between 20 and 50 hospitals and/or clinics (n=11), and more than 100 hospitals and/or clinics (n=6) reported. Responding

networks had a similar number of intensive care units (ICUs), with 27% of respondents (n=9) reported having 20 to 50 ICUs operated by the hospitals in their networks (see Figure 2).

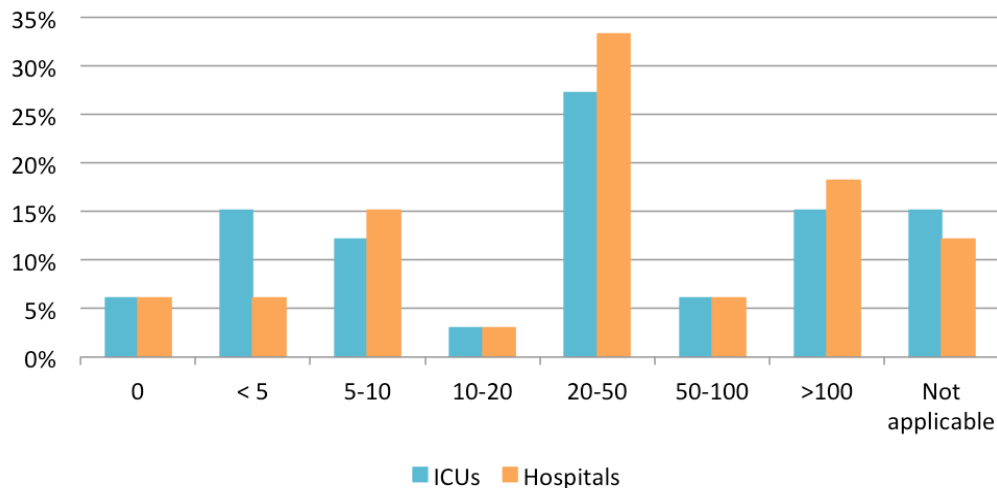


Figure 2. Number of hospitals and Intensive Care Units (ICUs) per network

In describing their area of expertise (Figure 3), nearly 80% of networks reported that their membership conducts infectious diseases research, while approximately 75% also study epidemiology, which was closely followed by Clinical Trials at 67%. Pandemic research was conducted by 55% of networks and animal research by 6% (n=2). None of the networks noted the Humanities or Mental Health as being an area of expertise, while 15% of respondents said that their networks consider Social Science to be a main area of expertise.

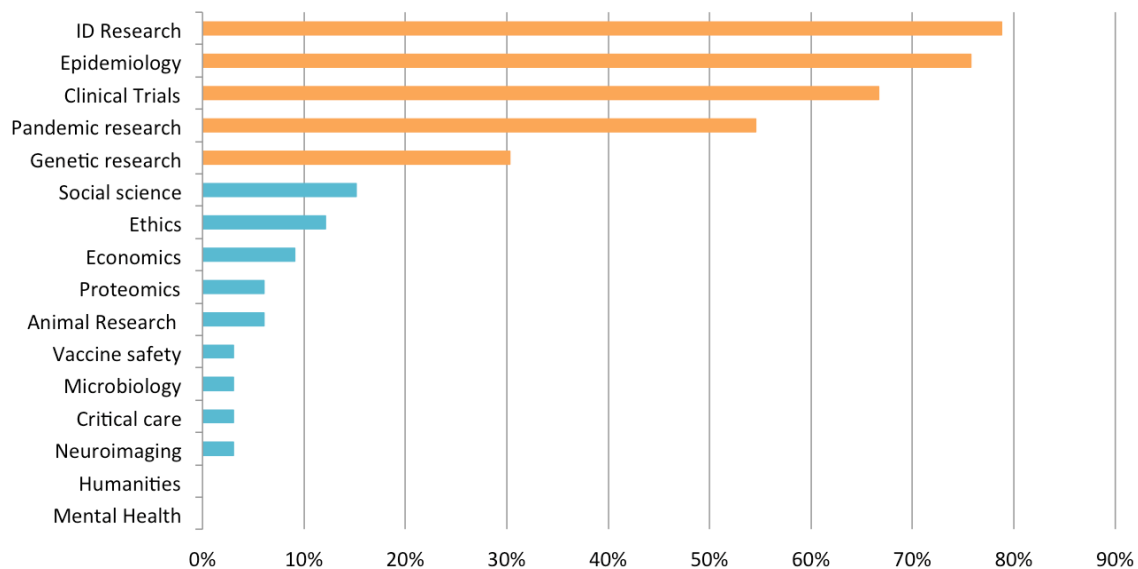


Figure 3. Areas of research expertise among responding networks

Study populations

While 55% of respondents (n=18) claimed that their study populations did not have any unique features that potentially affect spread of an infectious disease, such as cultural practices, environmental issues, or geographical features that may potentially affect the spread of disease, 15% (n=5) declined to answer the question, and 30% (n=10) did report the presence of these factors in their study populations. The most commonly reported features were geographical remoteness and the mobility of populations. Other features mentioned were access to water, cultural beliefs about the origin of disease, diversity of populations, high population density, the cost of healthcare, the high frequency of animal contact, natural disasters, and of antimicrobial resistance.

Networks reported recruiting patients across a broad range of age groups, with 94% of networks (n=31) recruiting adult patients, 67% (n=22) recruiting paediatric patients, and 73% (n=24) recruiting adults over 65 years.

In terms of the socio-economic backgrounds of patient populations, 21% of responding networks (n=7) mainly recruit patients in mid- and high-income countries, 18% (n=6) recruit within the poorest populations in low-income countries, 15% recruit from within all populations in low- and middle-income countries, and 15% recruit from all populations in all resource settings. One respondent claimed their studies specifically recruit within migrant populations (Figure 4).

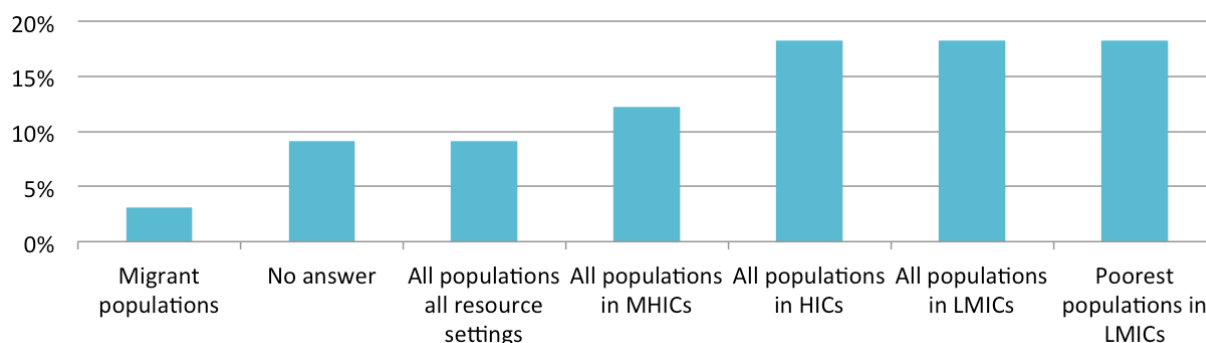


Figure 4. Socioeconomic background of responding networks' study populations. HICs = high-income countries, MHICs = middle- to high-income countries, LMICs = low- to middle-income countries

In terms of engagement with local communities or their representatives, 52% of networks (n=17) responded that they do engage with local communities in some way, while 42% (n=14) do not. Four networks said they engage through Community Advisory Groups and two said they engage through Patient or Relative Groups. Other activities within the community included outreach,

recruiting, surveying and participatory data collection. Networks also engage various local groups such as clinicians, healthcare settings, regulatory agencies, Ministries of Health, NGOs, and universities.

Research experience

While 82% of respondents (n=27) reported that they have previous experience running clinical observational studies, a majority of whom had included between 100-10,000 patients in these studies (n=27), 73% had run interventional clinical trials, including a slightly smaller number of randomised patients (n=24) (Figure 5). Forty-two per cent of responding networks (n=14) have experience conducting animal research, though only 5 of these networks have access to non-human primates for research purposes.

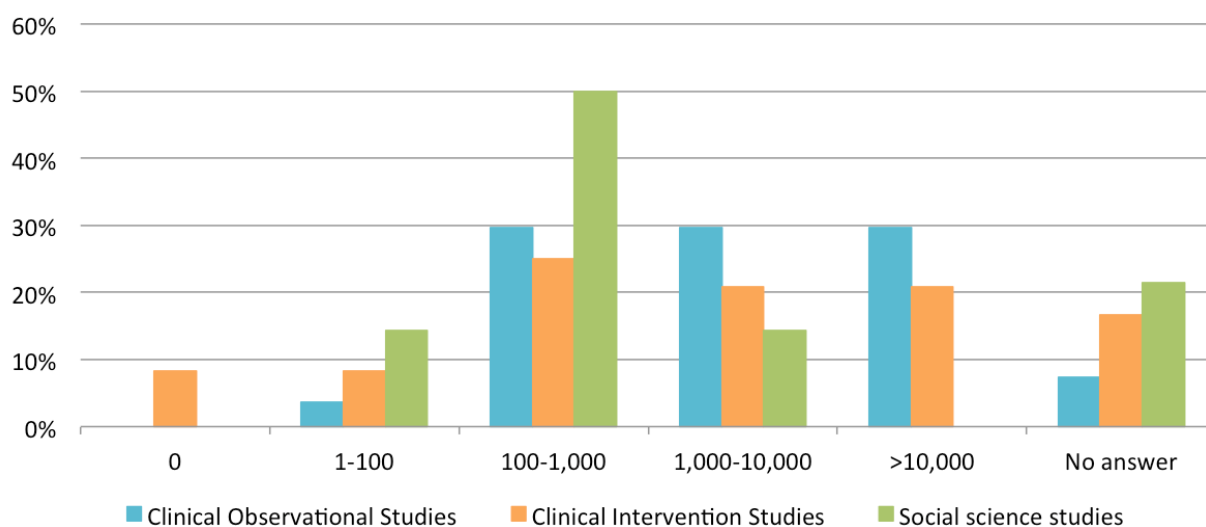


Figure 5. Number of patients enrolled by networks, by study type.

In terms of research collaboration with other networks, and extending in-house expertise beyond their own network, respondents said that they were interested in collaborating over multisite trials and recruitment into trials, biological and laboratory studies, and on topics concerning specific diseases (e.g. arbovirus, influenza, undifferentiated febrile illness, AMR, TV, lung infections, sepsis, and ARDS) (Figure 6).

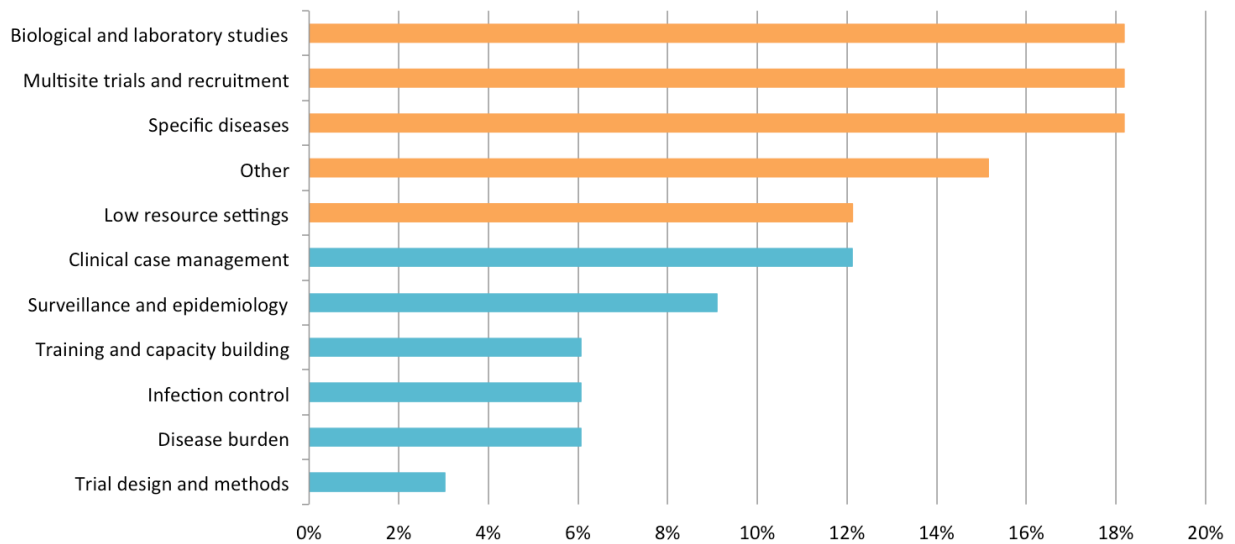


Figure 6. Areas where responding networks are keen to collaborate

Research infrastructure

A clear majority of all networks (79%) declared that they have access to centralised project and data management facilities, while 88% of respondents have access to statistical support within their clinical research infrastructure.

Seventy percent of networks conduct clinical trials, and more than half have access to research nurses at their research sites. The three networks that reported a lack of clinical research nurses claimed that recruitment into their trials is done by the individual sites, infectious disease physicians, or medical doctors. Of researchers involved with studies run within and by the networks, nearly 70% were reported to have been GCP (Good Clinical Practice) trained.

The availability of research staff and funding came out on top of the wish lists presented by respondents, to improve recruitment processes for their clinical trials. Other items included integration of research into clinical care, training, incentives for potential investigators, and patient registry access. With regards to the latter suggestion, less than half of the networks (45%) reported that they have access to registry data, such as diagnosis and outcome measures for all patients admitted to ICUs and hospitals. When access was specified by country, an even distribution between resource settings was observed - though with a slight bias for higher and middle income resource countries. Nearly half of the registries accounted for were reported to maintain data related to outcome at discharge and the demographics of patients. A third included

physiological data such as blood pressure, four registries included post-discharge outcome data, while only one of the registries included mortality data through records linkage.

When choosing which types of biological samples networks had experience collecting, transporting, storing and/or analysing, 85% of networks (n=28) had experience with whole blood, plasma or serum. This was followed by sputum, bronchoalveolar lavages (58%) and urine samples (39%). Nearly a third of networks had collected, transported, stored, and/or analysed cerebrospinal fluid (Figure 7).

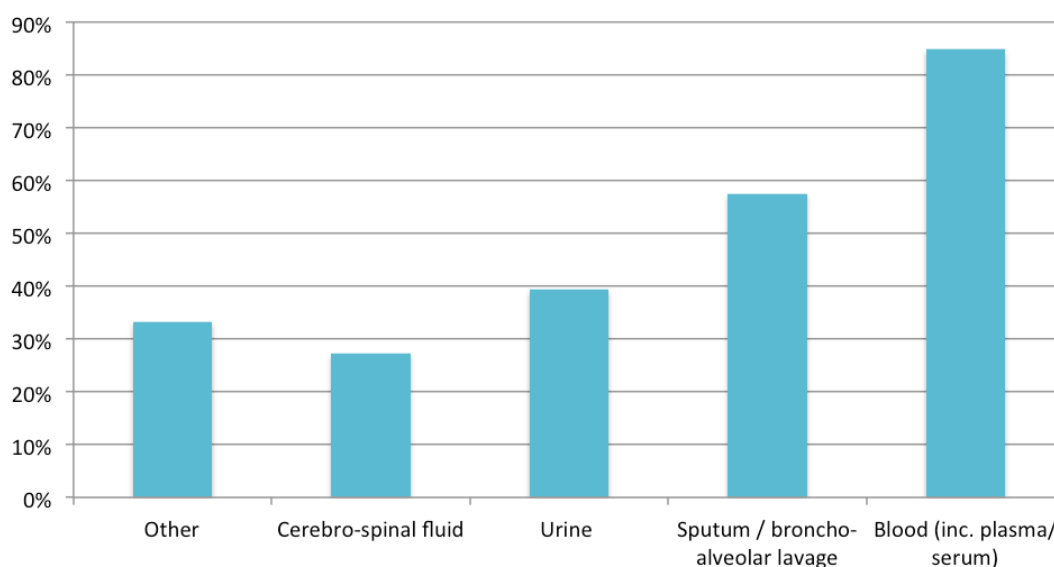


Figure 7. Biological samples collected, transported, stored, and/or analysed by networks.

Less than one third of the networks (n=9) reported conducting pre-clinical non-animal research, while a majority (64%) were not involved.

Clinical network

Of the responding networks, 64% (n=21) had experience providing a non-research, clinical response to outbreaks in the past, 88% (n=29) were confident that most of their members were properly trained to conduct a clinical response to an outbreak and 91% (n=30) have established links with local and/or national public health bodies. Despite the majority of networks being experienced or trained to conduct a clinical response to an outbreak, 82% (n=27) were interested in further developing their capacity for clinical outbreak preparedness.

Laboratory capacity

The majority of networks had the ability to store infectious or contagious biological materials at -80°C (73%, n=24), with 49% (n=16) able to store samples between -20°C and -80°C, and 27% (n=9) only capable of storing at below -80°C. Six percent (n=2) of respondents were unsure of their networks' storage capability. Only 12% of networks did not have the capability to transport infectious or contagious biological materials (n=3), or were unsure of this capability (n=1).

In terms of biosafety, 24% of respondents (n=8) claimed to have access to BSL4 laboratories within their network. A further 42% of networks (n=14) reported that they had access to BSL3 lab facilities, while 58% (n=19) and 45% (n=15) have access to BSL2 and BSL1 facilities, respectively (Figure 8).

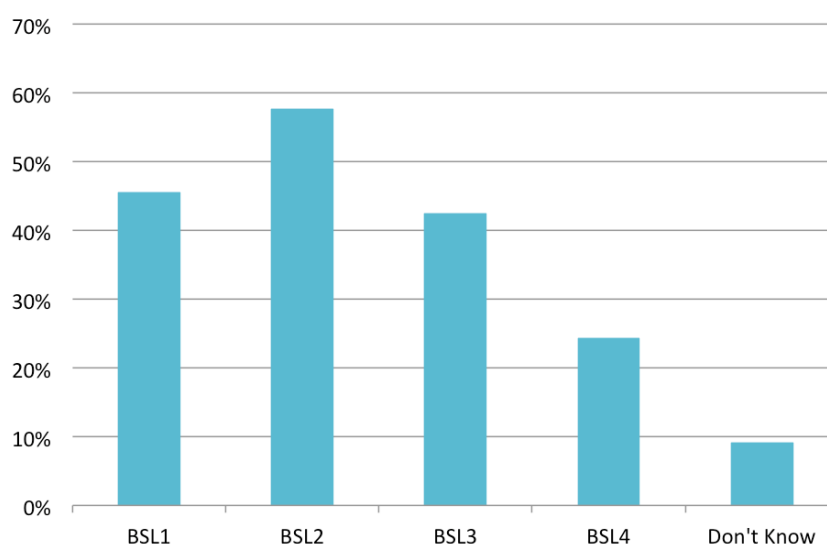


Figure 8. Proportion of networks with access to laboratories of various biosecurity levels

A majority of networks reported that they had access to between 1 and more than 10 virological and microbiological laboratories in their networks, with 33% of respondents (n=11) reporting access to more than 10 laboratories. Two of the respondents (6%) did not know how many and four (12%) did not respond to the question.

The majority of networks were well equipped in terms of diagnostic and PCR capacity for virology, microbiology and parasitology, with most capacity either site-based or centralised. Only 6% (n=2) of respondents lacked the capacity to perform parasitology diagnostics, virology diagnostics or virology PCR, while 15% (n=5) lacked PCR methods for parasitology (Figure 9).

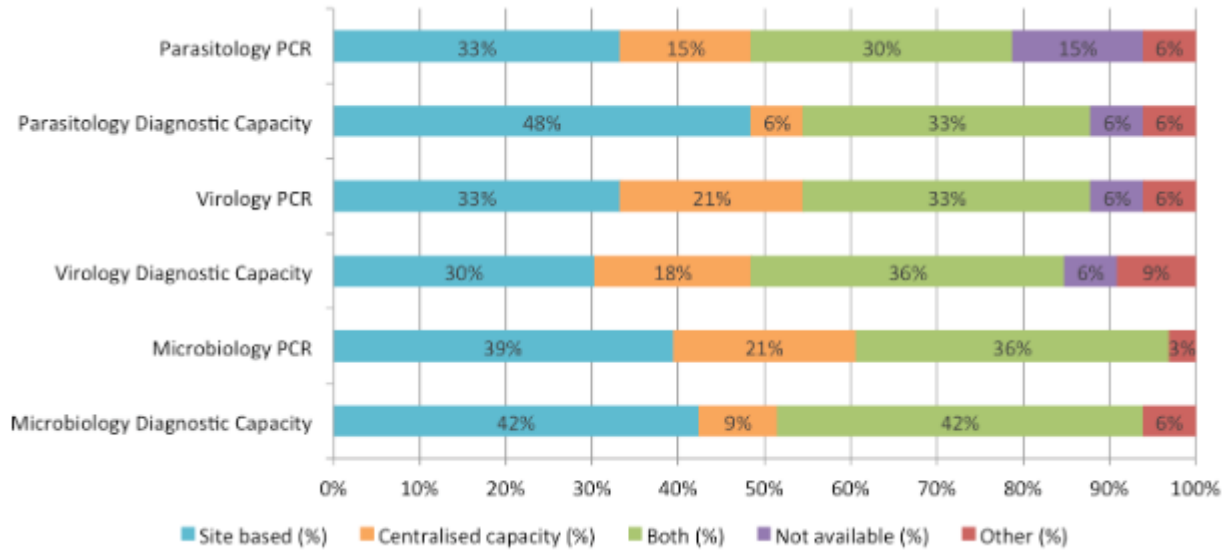


Figure 9. Proportion of networks with the capability to run diagnostic tests and studies using microbiology, PCR or parasitology methods

Networks had a lower capacity to conduct laboratory studies in parasitology, with only 55% of respondents (n=18) capable of undertaking such a study. However, respondents were generally well equipped to conduct studies in virology, bacteriology, host responses, pathogen genetics, host genetics, and parasitology, with eleven networks (33%) reporting the capacity to undertake studies in all six research areas. Overall, networks were most equipped to conduct studies in virology (82%), bacteriology (79%) and host response (76%) (Figure 10).

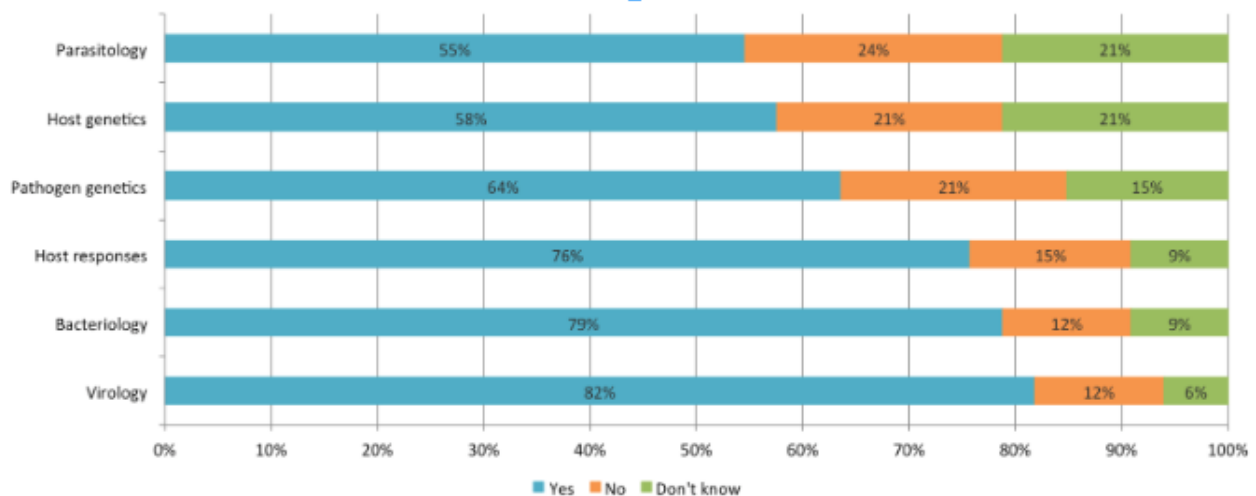


Figure 10. Capability of responding networks to undertake studies in areas relevant to emerging infectious disease

Outbreak Capacity

When faced with an outbreak, about half of all responding networks would be able to initiate an observational study, but 49% would need additional funding, while 67% would need additional funding to run a randomised controlled trial (RCT). Almost three-quarters of the networks would also be able to carry out mechanistic/sample collection studies, or social science guided research, but would rely on additional funding (Figure 11). The main reason given for not being able to roll out studies was related to the lack of expertise (particularly for RCTs and qualitative studies) and lack of funding (applicable to all study types).

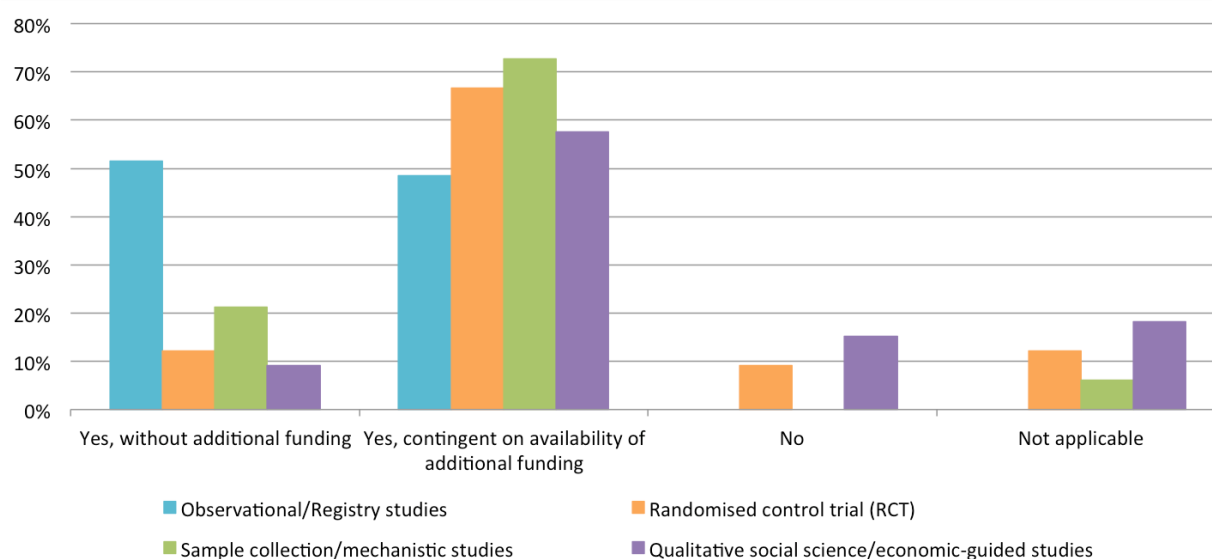


Figure 11. The capacity to respond to an outbreak with the following research activities among responding networks: observational or registry studies, randomised control trials, sample collection or mechanistic studies, qualitative social science or economic-guided studies

Access to funding for research activities was the main concern for the networks in the event of an outbreak compared to additional expertise. The top five elements that would be required by networks to increase their capacity to do research in the event of an epidemic were funding for staff (33%), materials (15%), setting up laboratories or laboratory related expenses (12%), funding for all components of the study (25%) and other (25%). Funding for central infrastructure and pre-approved protocols was needed by very few of the responding networks, as was additional expertise (Figure 12).

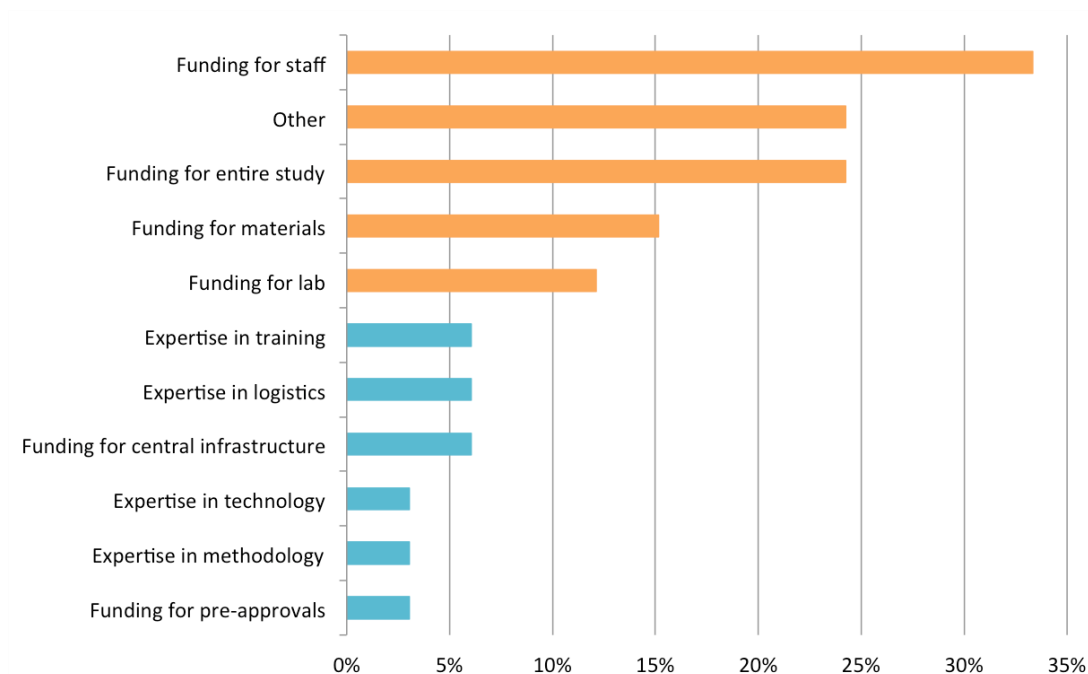


Figure 12. Areas of funding and expertise that would be needed by responding networks to conduct research during an outbreak.

Funding

The primary funders of clinical research in the countries where networks were located were thought to be governmental funding organisations, with 33% and 30% identifying their country's national institutes of health (NIH) and national medical research councils (MRC), respectively. The least likely funders were identified as being professional societies and industry (both 3%). This was not entirely reflected in the responses given by the networks when asked about their current sources of funding. While NIHs remained the most likely source with 24% of networks reporting this source, it was closely followed by private foundations (21%). However, national MRCs funded the activities of 18% of the networks. Overall, a majority of the research networks reported a total amount of funding received for the network to be more than \$100,000 USD, while 24% of the networks had received more than \$10M in funding altogether.

In the case of a pandemic outbreak occurring in the region where responding networks are active, the funding organisations that were assumed to be the most likely to support any related research activities were NIHs (21%), followed by Ministries of Health (15%) and MRCs (15%). Private foundations were also thought likely to fund such research (15%). None of the respondents thought that funding would come from industry or professional societies and 24% of respondents did not know which funder would be likely to support pandemic research activities. In terms of

existing rapid funding initiatives designated for outbreak or epidemic research in their region, a majority of networks (52%) said that they did not know of any such initiatives, and 18% chose not to answer the question. Of the 30% who did know of rapid funding initiatives, six respondents said these were governmental initiatives run by organisations such as INSERM, the European Commission, US NIH, public health agencies, and Ministries of Health. Two of the respondents knew of initiatives launched by the Wellcome Trust, a philanthropic organisation.

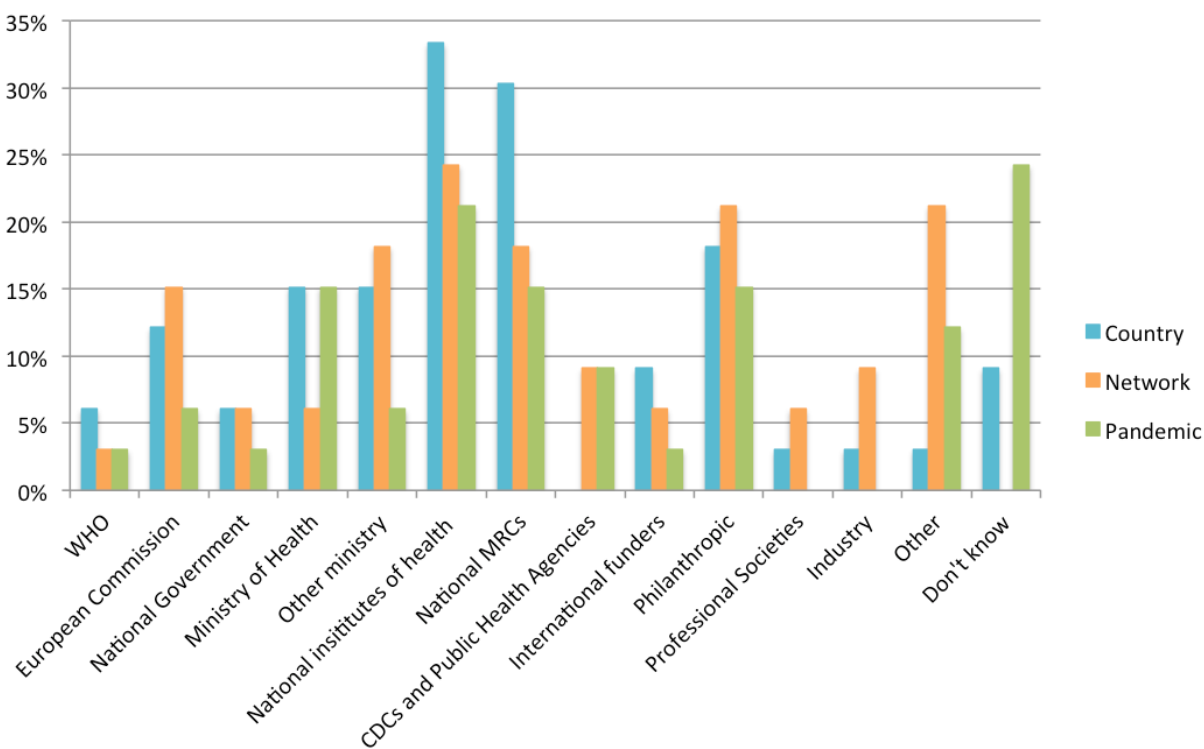


Figure 13. Sources of funding known by responding network, including primary funders of research in the network's country according to respondents, the current sources of funding for network activities, and where the networks thought funding would come from in the case of a pandemic.

Nine responding networks (27%) claimed to have industrial partnerships in place for research or the implementation of trials. The relevant research topics on which they collaborated with industry included drug development, compound screening, technology evaluation, vaccine evaluation, providing products for clinical trials, and running clinical trials. Of the nine networks that collaborated with industry, four chose not to specify what proportion of their budget consisted of industrial funding, while two networks reported that industry funding accounted for less than 5% of their budget, and three networks reported funding for 5-20% of their budget.

PEARLES Barriers Survey

This survey aimed to understand research networks' perception of the political, economic, administrative, regulatory, logistical, ethical and social (PEARLES) barriers and bottlenecks to conducting clinical research. This survey was sent to 108 research networks and completed by 39 network representatives, based in 21 countries. Their distribution is given in Figure 14.

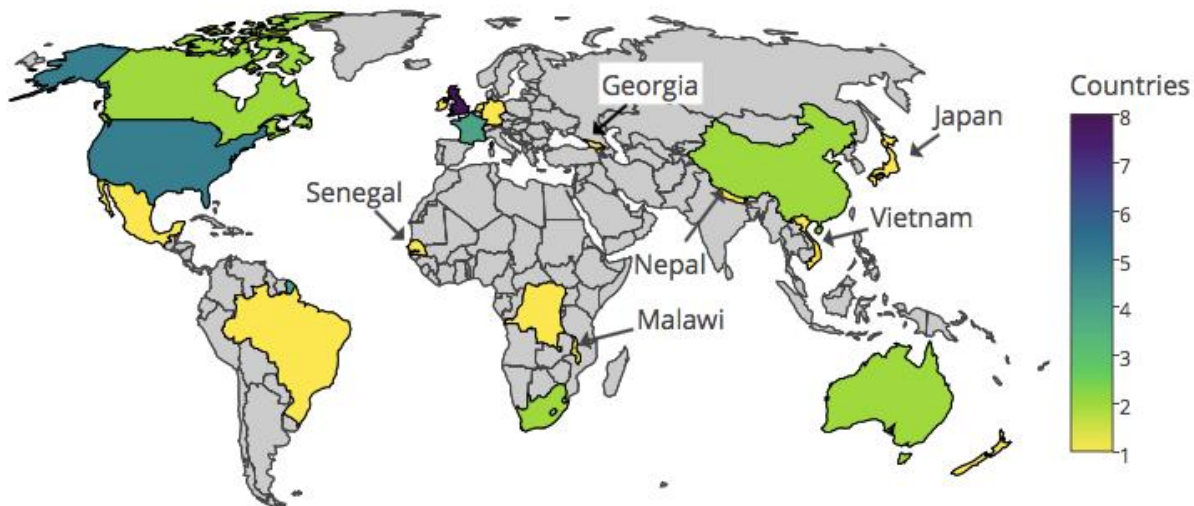


Figure 14. Country wise distribution of networks responded

Pandemic preparedness

Most of the respondents (67%, n=26) reported that a pandemic preparedness plan exists in their country. However, only about a quarter (n=9) of them said that it specifically addresses clinical trials, and 29% (n=11) reported that it addresses observational studies. Approximately 36% (n=14) of respondents reported that there are many political and cultural sensitivities that should be considered when conducting clinical research in their country. These included access to certain populations, especially indigenous and remote populations. Research involving children and pregnant women was cited as a politically and culturally sensitive issue. Some suggested that there are particular sensitivities associated with the storage of biological samples.

Ethical approval

Questioned on the type of ethical approvals required for conducting clinical research involving hospitalised patients, 67% (n=26) of respondents reported that they needed approval from local ethics committees to conduct research. About 23% (n=9) needed approval from regional ethics

committees and almost a half (n=19) said that they needed approval from national ethics committees to conduct clinical trials on humans in their country.

A detailed analysis of the responses shows 28% (n=11) of the respondents would need approval only from local ethical boards to conduct clinical trials involving hospitalized patients. Five per cent (n=2) said they would need approval only from regional ethics committee, and 18% (n=7) said they needed only national approval. About 28% (n=11) reported they needed approval from committees from any two levels and 10% (n=4) said they needed approval from committees of all three levels, that is; local, regional and national ethics boards. About 31% of respondents (n=12) reported that they are required to pay a fee for applying for ethical approval.

The process of obtaining ethical approval was similar in most of the countries represented in this survey. Local approval is mandatory in a majority of the countries, i.e. each site needs approval from their local hospital or Institutional Research Ethics Board. In some countries, like Brazil for instance, national level approval is mandatory for studies using international protocols, genetic studies, and studies in vulnerable populations. In other countries, such as in the Netherlands, ethical approval from one ethics committee will lead to expedited approval from other sites for multi-centre studies.

A majority (56%, n=22) of respondents reported that there are different approval process for studies involving vulnerable populations in the countries where they are based and 23% (n=9) reported that there are additional or different approval processes for studies involving biological samples. Some of the respondents reported that studies involving biological samples need to undergo higher scrutiny in the countries where they are based. This, they said, included a detailed description of risk and benefits as well as a demonstration of the investigators' training and knowledge of the safe handling of samples. Almost a third (n=12) of respondents reported that there is a separate ethical approval process in their countries for studies involving the use of medicinal products in humans.

The collected data shows that there are wide variations with regards to getting ethical approval for different study types. Getting ethical approval for observational studies without the collection of biological samples takes less than a month according to 24% of respondents, between 1 and 2 months for 55%, between 2 and 3 months for 18% and 4 or more months for just 3% of the respondents. For observational studies involving biological sample collection, only 6% reported

they could get ethical approval in less than one month, while 46% of the respondents estimated that getting ethical approval could take between 1 and 2 months, 39% of respondents said that it could take 2 to 3 months and 9% reported it would take 4 or more months for them to get the study approved. For studies involving the randomisation of investigational medicinal products, 36% said that it would take more than 4 months to get ethical approval, while 33% of respondents maintained that it would take between 1 and 2 months, 27% said it would take them between 2 and 3 months, and just 3% could get the study approved in under one month. As shown in Figure 15, the complexity of the study has an impact on the time it takes to get ethical approval.

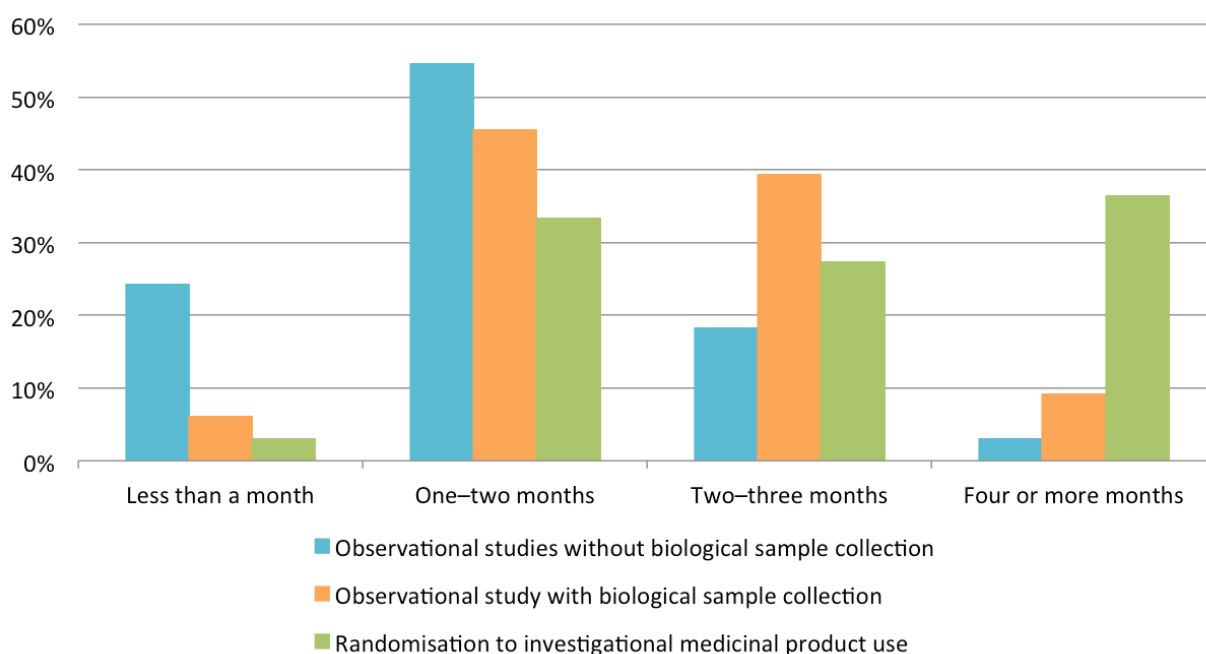


Figure 15. Time it has taken respondents to get ethical approval for different types of clinical trials

With regards to fast-track approvals/expedited review, almost half (n=19) of respondents said that it is possible to obtain fast-track ethical approval in their country - e.g. in Brazil, China, France, Georgia, Mexico, Singapore, UK, and Vietnam. Approximately 72% of respondents who claimed that expedited reviews were possible specified that the process is available for observational studies both with and without biological samples. However only a quarter of respondents (n=10) said that the expedited process was available for randomized studies of investigational medicinal products.

With regards to the pre-approval of protocols³, 56% (n=20) of respondents reported that a pre-approval process is available in their countries for the quick implementation of studies in the event of an epidemic or pandemic. However only 35% (n=7) of those respondents who reported that pre-approval was available in their country ever had study protocols pre-approved successfully. Almost 72% (n=28) of the respondents said that they had access to templates for the study documents required for ethical approval applications in their countries.

Asked to reflect on main issues or obstacles in obtaining ethical approval in the country where their networks are based, respondents particularly identified regional variations in approval processes, the lack of centralisation and coordination, delays in obtaining approvals from multiple centres, the staff costs and time necessary for the preparation of study documents, and understaffed and disorganised ethics committees as major issues that caused delay.

Consent process

When asked about the process of seeking consent in different types of studies that involve vulnerable participants, 23% of respondents reported that consent can be waived for observational studies without biological sample collection. Forty-four percent of the network representatives said that next of kin consent is normally used, and 21% reported that participant consent is used, while 18% said deferred consent is normally used in observational studies without biological sample collection. For observational studies with biological sample collection, 53% reported that next of kin consent is normally utilised. 32% reported that participant consent is normally used, 18% said that deferred consent is used, while only about 8% of respondents said that consent is waived for observational studies with biological sample collection.

For studies involving investigational medicinal products, half of respondents said that next of kin consent is normally used, while 32% reported participant consent would be required, and 16% said deferred consent is normally used in projects they have been involved with. Only 5% reported that consent could be waived for vulnerable participants in studies of randomised investigational medicinal products.

³ Pre-approval here refers to the advance approval of studies which may be observational or interventional. Though it would be reasonable that final approval should occur to ensure applicability and for the safety review of potential interventions, and fine-tuning in the event of an epidemic, it is feasible that a significant amount of the ethical review of issues such as recruitment, consent-collection, and storage of data could occur in a broad sense in advance.

Regulatory approval

For regulatory approvals, 69% of respondents said that there is a specific body or organisation in the country where they are based that is responsible for regulating clinical trials of investigational medicinal products (CTIMPs). Twenty-eight per cent of respondents (n=11) reported that they would have to pay a fee when applying for regulatory approval, whereas 22% of respondents said that no fees are required. However, 50% of the networks said that they do not know whether there is a fee applicable to applications for regulatory approval or not. This illustrates a potential lack of knowledge about the regulatory systems among researchers in some of the countries included in this study.

Regarding the average time that it takes to get regulatory approval, only one respondent said that it would take less than 1 month to get approval from the medicinal regulatory agency in their country. Thirteen per cent (n=5) of respondents said that it would take 1-2 months, and 23% (n=9) said it would take 2-3 months to get the regulatory approval. Slightly more than 15% (n=6) reported that it may take more than 3 months to get regulatory approval in the country where their network is based. A total of 38% (n=15) reported they do not know how long it may take to get the regulatory approval.

Less than a quarter of the respondents (n=9) reported that it is possible to obtain regulatory pre-approval for study protocols in their country, while approximately 15% said that it is not possible to obtain regulatory pre-approval. A majority of the respondents (54%, n=21) say that they do not know whether regulatory pre-approval is available in their countries or not. About a quarter (n=10) reported that they usually need the approval from an agency other than the clinical trial/medicinal regulatory authority to conduct clinical research in their country.

Contracting

More than 80% of the respondents said that they need some kind of sponsorship (including insurance) from a legal entity for conducting clinical research in the countries where they are based. Approximately 14% of respondents reported that it would take between 1 and 2 months to draft and sign contracts between a sponsor and a trial site in their country. A quarter (n=10) of networks said that this would take 2-3 months, while 20% said it would take between 3 and 4 months, and about a quarter estimated that contracts could be signed in 4-6 months. One respondent said that it could take more than 6 months to get the contracts signed in their country.

Challenges to rapidly setting up studies

The respondents were asked to rank the factors that they thought were the most challenging when rapidly setting up clinical research studies. The majority (57%) of the respondents said that obtaining regulatory approvals in a timely manner was the main challenge to setting up a study rapidly. About 55% reported that obtaining ethical approval is the main bottleneck, closely followed by getting access to funding (51%). These were followed by contracting (31%), obtaining other regulatory approvals (26%), and the availability of clinical staff for research purposes (26%), as illustrated in Figure 16.

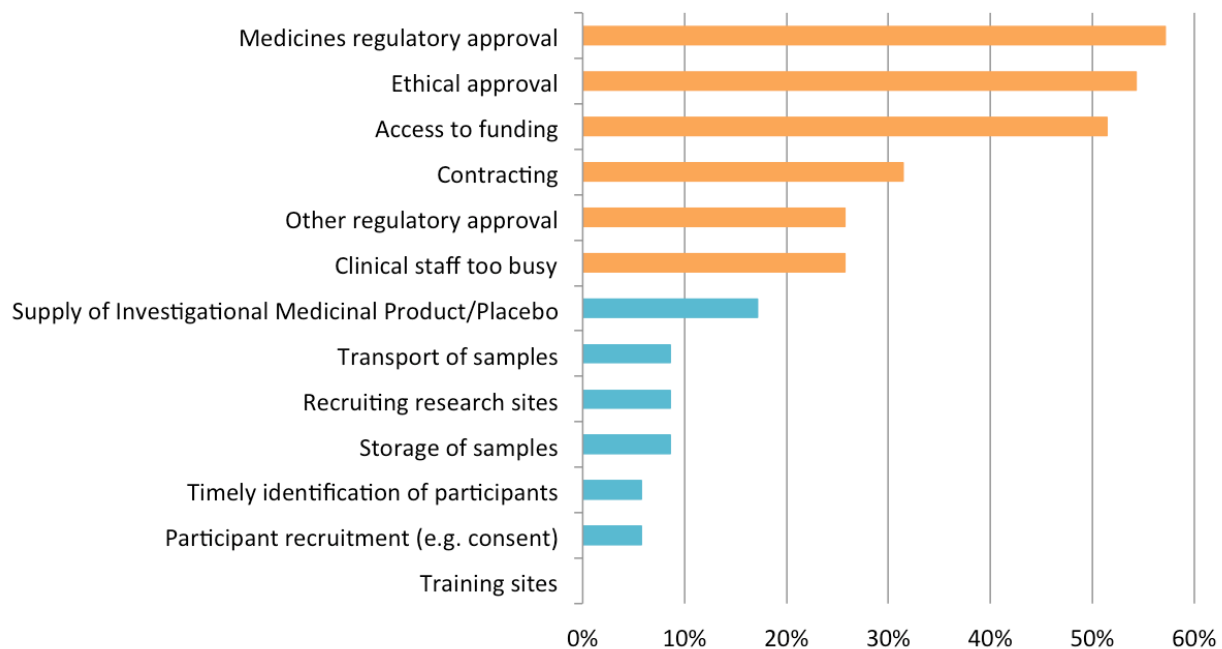


Figure 16. The main challenges to rapidly setting up a study, according to respondents.

Approximately 65% of respondents reported that there are logistical barriers that pose a challenge to the setting up and conduct of a rapidly initiated study in their countries. The reported logistical barriers include biosafety requirements, maintaining specimen quality, the sharing of data among sites, and the handling and movement of samples.

Asked whether they think that there is a need for key changes that would improve the application process for rapid research approval, about 35% of the respondents said that changes are necessary. Their suggested improvements include streamlined and centralised application processes, faster communications between regulatory agencies and researchers, simplifying the application process, and having pre-approved protocols.

Funders' Survey

Respondents to the Funders' Survey included 21 funding organisations from 15 countries. Approximately 76% (n=16) of the participating organisations are government agencies, one agency is a charitable organisation, one is a private organisation and three agencies reported they belong to the "others" category. All organisations that participated in this survey reported that they have funded or are funding research related to epidemic or pandemic outbreaks.

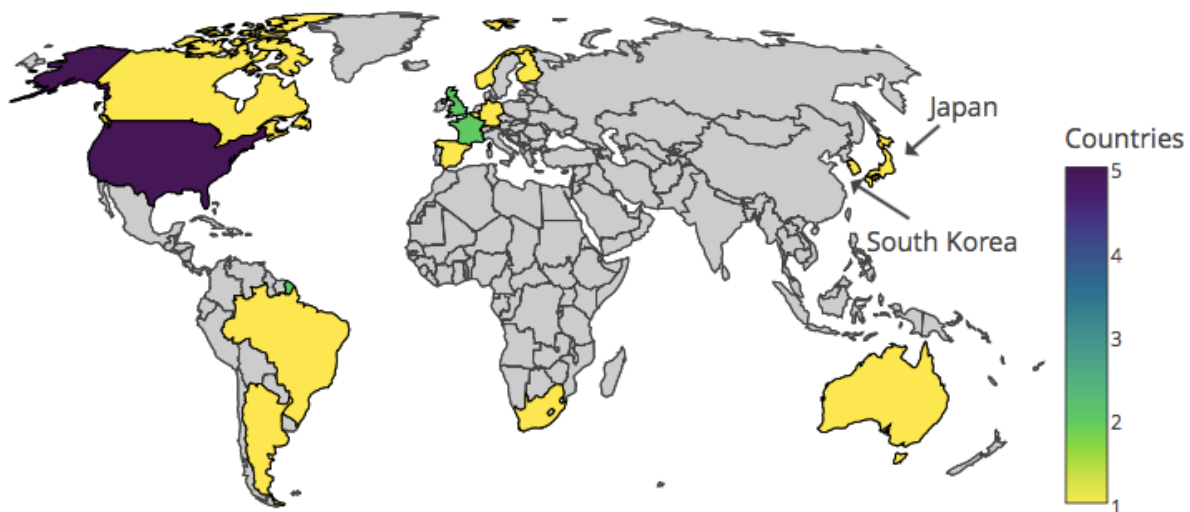


Figure 17. Country-wise distribution of funding organisations that participated in the survey

Remit of current funding

Nine of the respondents reported that their remit of funding lies within the countries where their institutions are headquartered, while one organisation reported they fund research conducted regionally, and eleven respondents said that they fund research conducted globally.

A majority of the funders (52%, n=11) reported that there are geographic requirements in place for principal investigators whose projects are funded by their institutions, and for most of them (n=9), this requirement is applicable to pandemic research as well. A majority of the funders 85% (n=18) said that their institutions take part in collaborative and co-funded initiatives with other funding organisations.

Figure 18 shows their main areas of funding as reported by the respondents. Clinical research (90.5%), biomedical research (90.5%), public health (85.7%), medical sciences (81%), virology

(76.2%) epidemiology (76.2%), microbiology (71.4%) global health (71.4%) and pharmacology (71.4%) are listed as the major areas of funding for most of the organisations represented among the respondents.



Figure 18. The main academic research areas that funding organisations fund.

With regards to the different types of funding calls provided by the funders (Figure 19), the types of funding calls most commonly provided by the represented funders were competitive project funding through planned funding calls (81%), innovation and application-oriented research funding (76%), collaborative inter-disciplinary research (71%), academic and research fellowships (71%), infrastructure funding (66%), academic-industrial partnership funding (66%), and rapid emergency funding (57%).



Figure 19. Types of funding provided by the funding organisations responding to the survey.

When asked how planned calls are developed within their respective funding organisations, respondents said that it depended on governmental healthcare policies, the input from scientific panels or advisory boards, the input from experts and stakeholders, and any predetermined themes guided by the strategic policies in place within the organisation.

Funding for pandemic research

More than one third of the respondents (n=8) operate a yearly funding budget of over \$500m (USD), and a further 20% (n= 4) disburse \$100-\$500m annually (Figure 20a). In terms of annual funding for pandemic research, about half of the respondents (n=10) indicated that they do have designated funds for epidemic and pandemic research, while half also reported that their institution has a system in place to provide rapid funding for research in the event of an outbreak of a novel or emerging pathogen of pandemic potential. About 42% (n=9) respondents reported that their institution provides funding for pre-approved projects or platforms that can be rapidly initiated in the event of an outbreak. However, only 4 funders (19%) said that their institutions would consider committing a small amount of funding (e.g. €1/\$1/£1 or equivalent) to a collective trust that could be used to trial a coordinated research funding response to an epidemic.

With regards to the timelines in place for funding calls during the interpandemic period, 35% (n=7) of the funder representatives indicated that it would take more than 8 months from launching of a call to committing the allocated funds, and the same percentage of respondents said that it would take 6-8 months. Two of the respondents said the process would take between 4 and 6 months to allocate funding. However, one of the funding representatives said that it would take their institution between 1 and 2 months to commit funding following the launching of a call in the interpandemic period.

This said, the respondents reported that the timeline would decrease substantially during an epidemic or pandemic, with seven funders (35%) saying that it would take their institutions between 1 and 2 months from launching a call to allocating funding, and five organisations (24%) saying that the process would take them between 2 and 4 months. Three organisations said that it would take them 4-6 months to allocate funding, and two other organisations said that it would take them more than 8 months to complete the funding call process during an epidemic or pandemic.

About 28% (n=6) of the funders reported that they allocate between \$1m and \$10m annually for pandemic research. Approximately 38% (n=8) said that they disburse more than \$10m annually for pandemic research, while 23% (n=5) disburse up to \$1m towards pandemic research annually (Figure 20b).

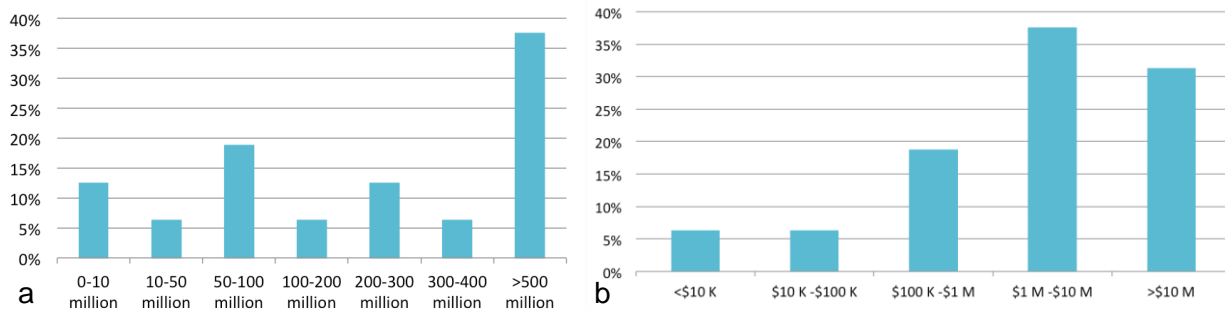


Figure 20. a) Estimate of the annual funding budget of responding funding organisations and b) the approximate annual funding budget for pandemic research. Estimates in USD

Eight respondents (40%) claimed that their organisation had received spontaneous applications for funding during past outbreaks (e.g. EVD, SARS, H1N1, H5N1, H7N9, etc.), with one of these organisations providing full funding and the other four partial funding for spontaneous applications. The remaining three were uncertain whether funding had been provided. An additional 25% (n=4) of respondents were uncertain about whether their organisations had received spontaneous applications, while 40% (n=8) had not received any such applications.

Only 10 funding representatives (47%) responded to the question about their institutions' past outbreak related rapid funding initiatives. Half of them reported that they spent between \$1m and \$4m towards these initiatives, whereas two institutions provided between \$50m and \$100m. One respondent reported that they spent more than \$100m for this initiative, while one was uncertain of the amount provided by their institution. Eleven of the responding funding organisations initiated rapid funding calls specifically in response to the West African Ebola outbreak in West Africa, with 81% of these (n=9) providing more than \$1m towards Ebola-related research. Four institutions reported that they had provided funding towards between 1 and 3 EVD-related projects during the outbreak, and six institutions said they had funded more than 10 projects. One of the represented funding institutions reported that they had funded between 5 and 7 Ebola-related projects.

DISCUSSION

The quantitative part of this study has described the circumstances that shape the actions and capabilities of clinical research networks and research funders when mounting a response to infectious disease outbreaks. It has offered valuable insights into the potential for coordinated high-quality research during pandemics and points to possible solutions for an improved clinical research response in the future.

As the *Capacities and Capabilities Survey* suggests, there is already a significant amount of capacity among the surveyed research networks who responded in this study. Many of them have clinical trial experience during outbreak situations and in the interpandemic period. They have access to research tools, patients, ICUs, and laboratories - though less than 25% of networks have access to the BSL4 laboratories that would be required for research on highly pathogenic biological agents, such as EVD. Whilst most networks have the capability and capacity to run different diagnostic and PCR-based tests, a much smaller proportion would have the capacity to use these capabilities to conduct research studies. Importantly the majority of research groups are interested in expanding their knowledge and capacity to conduct trials in pandemics in the future.

Establishing and maintaining a global database of research network capacity and capabilities could facilitate collaborations between research networks and improve global research capacity building. It could allow pre design of potential clinical interventional or observational research studies, involvement and capacity building amongst local communities and give greater transparency to the public and funders as to the actions and goals of clinical researchers.

Though having the competence and often the adequate capacity to roll out clinical trials, a majority of the networks would require further funding to do so rapidly in an outbreak situation. This includes either complete funding for the specific projects (such as clinical trials) or partial funding for components of the project such as materials and facilities and running costs of the network sites implementing the studies (e.g. staff costs). It is important that this need for timely resources is communicated to potential funders.

With regards to the *PEARLES Barriers Survey*, the results revealed that although there is significant experience within each of the responding networks and the general process of approval

is similar, the timeline for research approval, while adequate for conventional studies, is too slow for pandemic research. Whilst some of the countries within which respondents were based have initiated expedited review processes, the timelines indicated still seem too slow for an outbreak situation, especially as the complexities of trials increase. However almost 60% of those surveyed have access to a pre-approval process, although there also seems to be rather limited experience and success among the respondents with these processes. An opportunity therefore exists to develop knowledge and capacity in pre-planning and pre-approval of studies to avoid or reduce these specific delays. This approach seems the only plausible approach to overcome some of the complexities and negotiations required to successfully set-up and commence a multi-centre clinical trial.

Another major hurdle to a rapid response was reported as being related to contracting between the sponsor of a study and the relevant study sites, which, respondents reported, could take between 1- 6 months or longer (25% of the respondents said that contracting could take between 4-6 months, or longer in the countries where they are based).

Finally, the findings from the *Funders' Survey*, suggested that there was considerable funding allocated towards pandemic research during the recent West African EVD outbreak, but that research funders mainly budgeted for pre-planned funding calls. Results indicate that funders recognized the importance of funding pandemic research, both before and during the Ebola outbreak, but that there is little coordination between funders in terms of joint funding calls or otherwise coordinated calls. In addition, timelines to allocate funding were significant (more than 8 months in some cases) and whilst there were faster processes generally in place in the event of an epidemic or pandemic this could still vary between 1-8 months or longer.

In order to get a more complete picture of the funding landscape, it would be necessary to include more non-governmental funders, such as philanthropic funders, other private funding bodies into the study. It would be interesting to explore any existing or the potential for public-private partnership initiatives that underpin pandemic research. It is also important to extend the study to national and regional research funders in currently under represented regions and countries in the world. None of the funding bodies that participated in this study are headquartered in Asia or Africa (with the exception of South Africa).

Limitations

One of the limitations for this part of the study is the lack of representation from networks and funders in low- and middle-income countries, and specifically in much of Africa, Central Asia, and South and Latin America. A relatively small proportion of research networks responded to the survey, which was partially due to some of the invited respondents not identifying themselves as being eligible to respond on behalf of networks.

Additionally, there was bias towards respondents from high to middle income settings, which could have an effect on the results presented here. ICUs are, for instance, less commonly available in hospitals in low resource settings than in high to middle income countries, as are laboratories with high levels of biosecurity. The initial selection of networks from the ISARIC membership and the contacts and partners of Fondation Merieux may have limited the selection of respondents to Anglophone and Francophone networks that have well-functioning connections with international partners. This may have led to an exclusion of national or regional networks that function outside of international collaborations but whose responses would have been equally valid and important to this survey. The list of funders was also limited to GloPID-R members and funders known by the members of research team as being likely to provide funding for a research response to outbreaks. Although the second round of dissemination sought to rectify this problem, it is likely that a longer third round, with increased and personalised follow-up, could increase the number of responses from underrepresented countries and regions.

Finally, with regards to the *Funders' Survey*, the question that concerns the average amount budgeted for pandemic research may have been skewed due to the question being asked during the Ebola response, which may have increased the average annual funding budget for epidemic and pandemic research. The question concerning funding provided during the last outbreak (non-Ebola specific) also did not provide the same response options as a subsequent question concerning funding for Ebola-related funding, which does little to illustrate whether or not the Ebola outbreak changed anything in terms of the funding made available for outbreak responses.

PART II: EBOLA RESPONSE CASE STUDY

INTRODUCTION

Objectives and research question

As an addition to the quantitative part of Connecting and Mapping (Part I) as presented in the first part of this report, this qualitative study, which makes up Part II of Connecting and Mapping, is specifically focusing on the recent Ebola Virus Disease (EVD) outbreak research response in West Africa. The qualitative study offers an opportunity to gather, if not real-time, fresh qualitative data that has not been influenced by significant retrospective reflection or discussion over a significant period of time. The aim is for this data to be fed back into GloPID-R's processes and infrastructure to optimise future rapid outbreak responses.

Secondly, the study will provide a methodological platform that may be utilised or modified for use in future studies of outbreak responses of the same or other pathogens. It could also form a basis for further exploration of this particular EVD outbreak, and may therefore provide valuable insights for the evaluation of the international Ebola response effort overall.

In line with the objectives outlined above and those presented with regards to the quantitative study, the research question that the qualitative study seeks to answer is: *Which bottlenecks and barriers do funders and principal investigators identify as applicable to the implementation of a rapid research response to the current Ebola Virus Disease outbreak in West Africa?*

Literature review

A literature review was initiated, partially in order to shape the interview guide for the study, and partially in order to explore the potential contribution of this study to pre-existing literature specifically focusing on the EVD outbreak. The bibliometric search, which utilised the Web of Science database, found that a search using the keyword 'Ebola' resulted in 5928 articles published in 2014 or 2015⁴, more than a 6-fold increase since January 2015 when 961 articles were found. As the search included many publications that were considered irrelevant to the research question for this study, it was narrowed down in five parts by adding words stemming

⁴ The search was conducted 19/08/15.

from 'rapid' (259 articles), 'response' (977 articles), 'emergency' (246 articles), 'trial' (313 articles), and 'research' (343 articles)⁵. Not considering technical or scientific articles related to matters such as the mathematical modelling and simulation as part of the *response* effort, or articles discussing *emergency* medicine and healthcare guidelines, the total number of articles included in the review was, when omitting overlapping articles that were captured in one or more of the searches, 1725⁶.

The majority of the sources found in the current review were journal articles relating to lessons learned from past and present outbreaks (9-19), recommendations for priorities in future research (19-35), preparedness and outbreak control (12, 13, 36), ethical and practical considerations in clinical trial study design (19, 37-42), international policy and coordination (15, 28, 43, 44), and more recently, preliminary results of clinical trials (42, 45-51). The search also returned many shorter news stories, commentaries or editorials in scientific publications that were related to the overall public health response to Ebola but without a specific reference to research (52-54). Since autumn 2014, however, quite a few news articles relating to planned, ongoing or completed vaccine or therapeutic trials and financial situations of funders were published, which in some cases helped to elucidate challenges and barriers researchers are facing, and innovative ways they are managing to overcome them (55-58)⁷.

The declaration of Ebola as a Public Health Emergency of International Concern (PHEIC) by the World Health Organization (WHO) in August 2014, allowed for expedition and flexibility of processes such as compassionate use and accelerated regulatory approvals of investigative interventions (27, 55, 59). Since 2001, the US government has spent half a billion dollars on Ebola research and made great progress in understanding the basic science (60, 61), but products developed were rarely moved out of the laboratory and into clinical trials sufficient for licensure. Studies on these products relied on irregular, short-term support with lengthy contracting processes needed for each phase of research, which made it difficult to conduct the large-scale human clinical trials needed for regulatory approval and stockpiling (62-64). As a result, all of the candidates' interventions remained in the early stages of clinical trials and unprepared to scale-

⁵ 'Articles' as defined here included commentaries, news articles published in scientific journals, and reports in so far as they appeared in the Web of Science search.

⁶ Search terms: (TS=Ebola[#1] AND TS=rapid) OR (#1 AND TS=response*) OR (#1 AND TS=trial*) OR (#1 AND TS=research) OR (#1 AND TS=emergency NOT TS=medicine) NOT TS=model*

⁷ Articles cited in this paragraph represent examples of the types of sources being described.

up production of potential agents for large clinical trials and subsequent widespread availability. Thus, the call for urgent prioritization and funding of interpandemic research and stockpiling of treatments, vaccines and diagnostics, especially for NIAID Category A Priority Pathogens, was a recurrent theme in search results (26, 62, 65, 66).

Current regulatory processes also contribute to delayed availability of interventions, as the majority of countries have individual regulatory bodies with differing requirements for approval. In many cases, this involves multiple clinical trials in the manufacturing country and the target country. Over the past year, US and UK regulatory bodies have co-operated with researchers to streamline approvals and minimize liability of manufacturers, and WHO has worked with African regulators to facilitate more rapid reviews (62, 67). It is unclear whether this acceleration process will continue, or if it will be utilised in future emergency situations. Roca, Afolabi (30) advocated for the creation of a centralized, international regulatory body to approve trials, from which data could be shared widely to local stakeholders, while Hacker (68) called for flexibility and expedition of interventions for unmet needs and emergencies to be written into international and national regulatory laws and guidelines (68). This would greatly reduce the costs and time consumption of regulatory approval and ultimately ensure widespread availability as soon as possible (30).

Many articles engaged in the ongoing debate on the ethical and practical implications of clinical trial study design. In October 2014, the WHO Ethics Working Group determined that adaptive, flexible, and potentially un-placebo-controlled study designs for Ebola interventions were ethically acceptable, and gave approval to undertake phase II and III vaccine trials simultaneously in the interest of time (33). While this expedited Phase III treatment and vaccine trials in West Africa, it created new debates as to which study designs would ensure robust efficacy results while equitably distributing potentially life-saving therapies to maintain community trust.

While the randomized control trial (RCT) design using placebo or standard-of-care (SOC) controls remains the “gold standard” in clinical research, Adebamowo and Bah-Sow (38), Caplan and Plunkett (69) and the WHO Ethics Working Group (2014) argued that in this unprecedented outbreak with case fatality rates (CFR) of 30-70%, the most important objective is to find an efficacious treatment rapidly, so that scale-up and deployment of successful candidates can occur as soon as possible (38, 41, 69). The authors stressed the dangers of eroding community trust when using a placebo or SOC control arm that is seen to be ineffective. Not only could these put healthcare workers in danger of attacks by angry community members who may not fully

understand the reasoning behind the study, but it could also dissuade patients from seeking treatment at study sites (38, 41, 69). As clinical trials are already a race against the epidemic, with constant shifting of infection rates between different geographic regions and dropping rates in many areas, the aversion of potential participants would further decrease sample size and endanger the validity and power of studies (24, 39, 70, 71). Options that were evaluated by the WHO Ethics Working Group include stepped-wedge clinical trials (SWCT), individual and cluster randomized studies, single-arm comparison studies, and ring vaccination techniques, with all studies constantly undergoing evaluation and having the freedom to adapt their protocols as needed (17, 31, 37-41, 70).

As of July 2015, researchers have initiated trials in West Africa on five investigative therapeutic options: brincidofovir (BCV), TKM-Ebola (TKM), ZMapp, favipiravir, and convalescent whole blood or plasma transfusions (72). Investigators in the RAPIDE Consortium used a single-arm drug triaging trial design to evaluate BCV and TKM, which allowed for rapid efficacy evaluation and quick transition between drugs (55, 60). ZMapp trials, led by the NIH, are ongoing in Sierra Leone using a multisite RCT (clinicaltrials.gov identifier: NCT02363322), and convalescent plasma studies are being completed in Guinea and Sierra Leone (clinicaltrials.gov identifiers: NCT02333578, NCT02342171) (73). The vaccines, chAd3-ZEBOV (GlaxoSmithKline and PHAC) and rVSV-EBOV (NewLink Genetics and Merck Vaccines USA), are being investigated in a Phase II/III randomized control trial in Liberia. Interim results from a Phase III rVSV-EBOV ring vaccination trial in Guinea were recently published reporting very high efficacy (42, 74), and a clustered, non-blinded, individually randomized trial with this vaccine continues in Sierra Leone (75).

Funding for these studies came from many sources. The European Commission Directorate-General for Research and Innovation (DG RTD), for instance, initiated an emergency funding procedure through the Horizon 2020 programme in September 2014 to provide €24.4 million to five Ebola research projects. Although the official start date was 1 November, grant agreements weren't signed until the end of that month, and most clinical trials were initiated in November and December 2014 (76). The Horizon 2020 programme also mobilized €114 million to establish the Ebola+ programme within the Innovative Medicines Initiative 2, with an additional €101 million contributed by private pharmaceutical companies involved. Ebola+ call for proposals were launched on 6 November 2014, and the first project began on 1 January 2015 (76). On 21 August 2015 The Wellcome Trust announced their contribution of more than £10 million towards an Ebola

funding initiative and awarded at least £5 million of this by 19 September (60). These are just a few of the many examples of funding organizations and governments committing large sums of money to be allocated on an expedited timeline. However, they were all much too slow in regards to the typical timeline of an outbreak. For example, the recent outbreak of MERS-Coronavirus in South Korea affected 186 individuals, and lasted less than three months, and no research was conducted (77).

Moving away from experimental treatment of individuals, a point of particular and poignant concern to Dawson (25), was the WHO's focus on individualistic, traditional medical ethics in clinical medicine, despite there being no treatment option close to being proven safe and effective, and the unprecedented scale of this true *public health* emergency, which requires old, simple public health responses (78) rather than individualistic clinical treatment (25). On the latter point, he argues that not only were the WHO ethical guidelines unclear (41), but that they were wrong to focus on clinical rather than public health interventions.

There is widespread agreement that public health surveillance and response systems in resource-poor countries need to be improved, both before and during epidemics (10, 12, 65, 79). A passive surveillance and reporting system is crucial for early response and control, but may not be sufficient to control an ongoing outbreak. Therefore, Wiwanitkit and Tambo (13) call for more research on effective active surveillance systems, such as mass screenings and the use of comprehensive software platforms, which could identify asymptomatic individuals and increase understanding of transmission dynamics (13). Large scale serosurveys have been performed during previous Ebola outbreaks (80); however, such activities require handling of biological samples, which inherently poses a safety threat when using currently available blood collection instruments, containers and diagnostic systems (81). Additionally, testing costs and complexity are extremely prohibitive in resource-limited settings (30). In this regard, the development of less expensive and safer blood collection and diagnostic technologies should be prioritized for use in future epidemics, not limited to Ebola.

Focusing in more specifically on the lack of national or regional African capacity for surveillance systems and bottlenecks in outbreak response that affected the unprecedented geographical migration of Ebola across West Africa, Tambo and Ugwu (12) underlined the need for capacity building in health systems, research and networking to take place on the African continent, and that funding to support such efforts was needed urgently (12). Tomori (9) criticises the history of

mismanagement of international aid by African governments in general and calls for greater ownership and leadership in research and capacity building, while international researchers must devote a greater effort to training and collaboration. At the first meeting of a Commission for a Global Health Risk Framework, a panel of experts including David Navarro, Barbara Stocking and Ilona Kickbusch called for a strategy to build resilient health systems with strong national ownership and community involvement (82). The panel emphasized that qualitative research data and community involvement should be standardized and used to shape quantitative research studies, and that private sector response efforts, especially local industries, should be more integrated with public sector responses. Both of these aspects need to be prepared and strategized before an outbreak emerges in order to be successful (82).

Already while the outbreak was still ongoing, Bill Gates (2015) and others have sought to explain why the response was delayed: the lack of infrastructure and funding for local and regional health systems, disease surveillance structures, and data sharing systems in West Africa, the failure to invest into interpandemic preparedness, the initial lack of international concern, the lack of a trained local and international emergency response force or a way to quickly transport them into the countries, the lack of a strong, central coordinating body and the failure of many countries to meet the criteria agreed upon in the International Health Regulations (14, 15, 26). However, in searching for perspectives on the research response to the Ebola outbreak, this literature review has yielded limited explanations as to the challenges that investigators faced in launching their clinical studies, and especially in the areas of observational, public health, and implementation research, or contracting and regulatory approval processes in clinical trials.

It would, therefore, be of interest to go into greater depth with regards to the bottlenecks and barriers to the research response as identified and expressed by both funders and researchers and see where they overlap or differ and, if so, try to discern why they would differ, as neither topic has been discussed by other authors. The literature review helped to extract many research themes, but it was combined with the outcomes of the quantitative study to elucidate the most prominent common barriers and further investigate processes behind them.

METHODS

Semi-structured interviews

The qualitative method chosen for this study employs a series of semi-structured interviews that have been analysed through the use of discourse analysis. The interviews, 7 in total, took between 45 minutes and 1½ hours, and were conducted in person by two different interviewers who followed the same interview guide that included the same standard set of questions. The standard set of questions (see Appendix IV) was made available to interviewees ahead of the interviews. Though a standard set of interview questions was developed ahead of the interviews, the semi-structured makeup of the interviews allowed scope for additional questions to be included in the interviews should they be necessary or wanted by either the interviewee or the interviewer. All interviews were audio recorded and transcribed ahead of data analysis.

Discourse analysis through NVivo

Once transcribed, all interviews were uploaded into NVivo (Version 10) where they were analysed utilising theme-oriented discourse analysis (see for instance, Phillips and Hardy (83)) through which the research themes were translated into ‘nodes’ and entered into ‘relationships’ across cases as they appeared in the transcribed text. The data analysis was conducted by two different teams, who later compared their individual coding frameworks. A merged coding framework has been included in Appendix V. This study also includes an ‘ethnographic’ feature by including ‘communicative ecology’ as an ‘add-on’ to the textual analysis. Recorded through written notes during or directly following the interviews, ‘communicative ecology’ aims to capture the way in which themes are discussed, mentioned, explored, or reflected upon, which – when put into context, may offer further interpretation and understanding or explanation in the analysis process (84). Examples of themes that make up the communicative ecology of a conversation or interview are frames, contextualisation cues, facework, social identity, and rhetorical devices, for instance. The parallel excavation of textual and ‘external’ elements such as culture and context creates a two-layered distinction in the construction of discourse, where both layers provide an equal contribution to any given social reality (85).

Research themes and interview questions

The contextual themes described above may not fully define the research themes that lay the foundation for the research question and interview questions for this study. Therefore, the research themes have been identified on the basis of both the quantitative survey results and the literature review, as described in Figure 21 below.

Researcher themes	Funder themes
<p>Researchers' and funders' respective involvement in the initiation of Ebola research partnerships or consortiums</p>	
<p>Timelines and hurdles in partnership contracting, including decisions concerning study design, the disbursement of funds, staff and patient recruitment, and study site selection</p>	<p>Timelines and hurdles in funding, including getting access to emergency funds, developing selection criteria, reviewing applications, the selection process, and disbursement</p>
<p>Approval processes by ethical and regulatory boards</p>	<p>Previous involvement in emergency funding calls, including whether a rapid funding mechanism existed pre-Ebola and/or currently</p>
<p>Involvement in and/or understanding of the political process of guideline and standards creation, particularly with regards to clinical trial study design</p>	<p>Barriers to providing rapid access to funds from the funder's perspectives, and suggestions for improvement</p>
<p>The capacity and capability to run trials, including capacity building exercises before and during the studies</p>	<p>How capacity building and local involvement factored into the selection process</p>
<p>Perspectives on collaboration with internal and external parties (e.g. public health, local/national government, humanitarian organisations, drug companies, other study groups, the local community etc.)</p>	
<p>Lessons learnt from ongoing or recent outbreak response</p>	

Figure 21. Research themes for Connecting and Mapping Part II

By targeting these research themes, we aim to identify key processes that lead to delays in study start dates and elements, events and practices that prohibit robust study results. We also aim to identify successes in terms of rapid disbursement of funds and approval processes, and in establishing necessary international and local partnerships in order to determine best practices for undertaking research in response to outbreaks. See Appendix IV for the complete set of pre-decided semi-structured interview questions.

Study participants

The interviewees were chosen on the basis of their involvement in the Ebola outbreak as funder representatives, Principal Investigators (PIs), and in one case - as local co-PIs, for the three chosen projects. The aim was to include local co-PIs for all three projects, but it proved difficult to achieve within the timeframe allowed for the report. The three projects, which are referred to as Study A, Study B, and Study C were selected on the basis of the responses collected through the quantitative study. The three studies were successfully awarded funding from UN-based, foundation, governmental or private funding organizations. The interviewees also referred to studies that were not among the three chosen studies in their interviews.

A total of 9 participants were interviewed over the course of 7 separate interviews, and at least one funder and one researcher were interviewed for each of the three projects. All interviewees were contacted by email and sent participant information sheets and the interview guide ahead of the interviews, and written consent was taken. All interviewees agreed to be recorded, and a majority wanted to approve any direct quotes ahead of publication. The interviewees gave their consent to participating in the interviews on the basis that their data would be anonymised and their projects would not be recognised. The reason for the want of anonymity was that the interviews raised issues that were politically or otherwise sensitive to interviewees or the organisations they represented, and some of the topics discussed were confidential or likely to be perceived to affect the reputation, organisational or personal integrity, or emotional comfort of the study participants.

Each interviewee has been given an alias by which they are known to the research team. However, to further protect their anonymity, the interviewees are known as members of research teams or funding organisation representatives as related to one of the three studies, in this report. A key to de-identify the interviewees is kept in a single file on a local server at Oxford University,

and in a locked drawer alongside the written consent form. The key is kept separately from any data collected.

The audio data and transcriptions have been labelled with the participant identifier/alias and uploaded to an encrypted folder on a secure local server at the University of Oxford's Centre for Tropical Medicine and Global Health. All data collected from anonymised interviewees is stored for five years (until December 2020) in a digital folder, as per policies specified by University of Oxford. Only the core study group will have access to the research data collected for this study.

All data is kept and handled in accordance to the Data Protection Act 1998 <http://www.admin.ox.ac.uk/councilsec/compliance/dataprotection/> and University of Oxford's Policy on Data Protection www.admin.ox.ac.uk/councilsec/compliance/dataprotection/policy/.

Three rapid responses to the EVD outbreak

With all three studies forming part of a rapid research response to the EVD outbreak in West Africa that was initiated under similar circumstances, e.g. through the means of rapid or accelerated funding initiatives, and following the WHO Ethics Working Group decision to allow adaptive, flexible, and potentially non-randomised study designs without control arms for Ebola interventions as being ethically acceptable (41), there are common denominators between them. However, as each of the projects were exploring the use of a different vaccine or therapeutic, in different locations in West Africa, and were run by different research groups and on funding provided by different funders, each included study has encountered slightly or very different barriers, bottlenecks, and issues during their planning and implementation.

All of the research teams seem to have had close interactions with one another during the implementation of the studies in West Africa, though they were not all operating in the same country, or funded by the same funder.

All interviewees have been asked to comment on the parts of the below descriptions as particularly related to their roles in either being part of the research teams or funding bodies involved with Studies A, B, and C.

RESULTS

Study A

Overview

Study A was conducted by a research group that had previous contacts in the country where it was being set up, which, according to both the funding representative and the PI, was of great benefit in terms of setting it up rapidly. The implementation of Study A took place in Ebola Treatment Units (ETUs) that were run by international humanitarian organisations, and both national and international staff was employed to implement research activities. Study A submitted applications to two different funders before the study was funded, and received major funding from one of these organisations. Though the research group received a significantly larger amount of funding from the organisation mentioned above, an additional organisation contributed substantial in-kind support.

Researcher perspectives

With the support and encouragement nationally, the research group had approached funders and developed a proposal in August and September 2014. The rejection from the first funder approached was a setback in terms of a rapid response and was considered politically motivated by the research group. The second funder approached accepted the proposal in October, and the study was ready to begin in December. According to the research team, the study could have been rolled out approximately one month earlier had it not been for the setback that came with the rejection from the initial funding organisation. As the research team already had established connections in the affected country, the study was initiated more rapidly than would have otherwise been the case. The research team highlighted their ability to gain the trust and necessary credibility among local stakeholders, NGOs and the public as a key to the rapid roll-out of the study and suggested that this should be a factor that funding organisations should consider as eligibility criteria for evaluating studies to fund during future outbreaks.

Reflecting on the discussion concerning study design for clinical studies during the outbreak, the Study A research team said that the issue is complex as randomised studies were unlikely to work within the local context due to the lack of trust among the population or the relevant government infrastructure to support the roll-out of randomised designs early on and at the peak of the outbreak. Running a randomised design was more likely to succeed after accepted Standard of Care (SOC) had been agreed on and when there was more trust within the local population.

The Study A research team reported that they shared interim data semi-confidentially with the local government, and also with partners in the study. However, in terms of data-sharing before publication, the research team feels that sharing data is a significant issue. Early sharing of data has delayed their publications by months as journals may not see the article as valuable anymore, since data has been released already. This makes it impractical for junior researchers to share data early, as their careers and salaries depend on the value of their publications.

In working with humanitarian organisations, the research team underlined the importance of collaborating due to their understanding of the local population and any pre-existing infrastructure in place. However, they noted that working with smaller local branches of humanitarian organisations was more easily facilitated than working with the headquarters of such NGOs, as these can be restricted by larger bureaucratic structures and regulations that could create barriers to the rapid implementation of trials. Further, contracts, ethical approvals, and agreeing on eligibility criteria were issues that came up as challenges in particular, when partnering with large humanitarian organisations.

Reflecting on the three (or more) lessons learnt from their contribution to the outbreak response, the Study A research team listed:

1. That clinical research is possible in hostile and challenging circumstances, such as during an epidemic involving highly pathogenic agents.
2. Non-randomised clinical trials are attractive to patients and governments as they offer potential treatment, and that regardless of drug efficiency, the trial may stimulate the early referral of patients to sites that provide good standard of care (SOC). This is important, as many patients only sought treatment or were referred to ETUs when it was already too late for the standard of care to make a difference.
3. Clinical research must be done alongside and within clinical care. Being a professional caregiver (e.g. clinician) makes a difference to the smooth running of a clinical study as being able to offer a good SOC and understanding the need for offering care to patients (as much as and together with statistical concepts and research tools) became part of the success Study A.
4. The outbreak response has developed networks and partnerships, and increased the awareness of the capacities that each stakeholder holds.

5. It is very important to work in partnership with NGOs as they are well organised, have access to patients, and they are interested in research.
6. It is important to factor in the in-kind contributions paid by research institutions and agencies in supporting research studies such as these. When research teams and other employees supporting research teams give up a lot of their time and effort, and redistribute funds, their usual day-to-day activities need to be covered, and the in-kind contribution needs to be acknowledged and compensated somehow.

Funder perspectives

The funding organisation that provided a majority of the funding required to run Study A initiated an accelerated funding procedure in September 2014. The funding initiative was not announced via a call for proposals as foreseen in the legislation in exceptional and duly substantiated emergencies, but rather research groups had previously contacted the funding organisation through spontaneous applications or enquiries, and these research groups were contacted by the funding organisation and told about the initiative. Less than 10 proposals were submitted and Study A was one of 5 proposals that were funded. The funded initiatives were evaluated according to all the normal procedures as during normal non-accelerated circumstances, though the cycle was running quicker than usual. From initiation of the emergency procedure to the awarding of grants, the process took about two months, and certain projects started retroactively before the grant agreements were signed.

Although the organisation had a framework for an accelerated emergency procedure already approved in the organisation's legislation at the time for the outbreak, it had never been utilised before the EVD outbreak in West Africa. Initiating the accelerated procedure posed a number of challenges to the funding organisation concerned. The electronic submission infrastructure that was meant to support funding applications was, for instance, half-way through a major upgrade and the necessary protocols and procedures had not been developed or were untested. Additionally, the process posed a challenge to internal resource management in relation to redistributing staff and duties to accommodate the process, while maintaining day-to-day activities and keeping other tasks running as usual.

Another challenge was political, and related to stakeholders who felt that they had not been sufficiently informed about the emergency procedure. The derogation foreseen in the legislation, however, allowed for awarding grants without publishing a call for proposals in exceptional and

duly substantiated emergencies. There was much support internally for the rapid funding initiative, and one of the funding representatives said that it had asked experts from different stakeholder groups to advise, but many could not. Thus, it was impossible to include all stakeholders' opinions due to the need to act quickly.

Reflecting on the three (or more) lessons learnt from their contribution to the outbreak response, the Study A funder listed:

1. Well-defined and internationally agreed triggers for the initiation of a rapid funding response framework are needed ahead of the next outbreak.
2. Coordination between funders is necessary. There is a need to communicate as to who does what, and how priorities are to be set and who is going to decide on what the priorities are. Duplication should be avoided where possible.
3. Communication between funders need to be improved. Communication took up a lot of time unnecessarily due to the lack of established channels of communication.

Study B

Overview

Study B was initiated by a research group that had previously visited the country for site evaluations, though they had not previously worked with the clinical site where the study took place. The Study was funded by two funding organisations, and had close links to two other related ongoing studies in West Africa. Study B employed few international team members and relied primarily on domestic staff in their implementation of the research activities. Study B perceived that the presence and activities of another study were detrimental to the conduct of their study due to, firstly, the alteration in the usual referral pathway for patients to be sent to the nearest ETU and, secondly, a perturbation in the local economy where research staff who were trained up and working on Study B without notice absented themselves to work for another study.

Researcher perspectives

Study B investigators were invited to support a local team of investigators who intended to conduct a trial of convalescent plasma produced using apheresis machines donated by a diaspora organization. However local political problems meant these apheresis machines were not available when the study was ready to start. A rapid collaboration was established with another research group that had access to equipment, without which Study B could not have been conducted. This collaboration provided many beneficial resources but also brought challenges by blurring the lines of communication and leadership roles. Another important challenge was that this mutual partnership collaboration risked voiding the traditional academic instruments of credit imposed by academic research institutions. Academic institutions do, for instance, offer different appreciation or credit for main PIs than they do for co-PIs or other positions within project teams. Funders also do not always recognize the difficulties this particular example poses to collaborating PIs. Collaboration was also a challenge due to the occasional lack of communication between collaborating partners, especially where other PIs did not share information or include their collaborating PIs in meetings and discussions that directly affected their studies. In one case this resulted in a new partner coming onboard for Study B, who ended up leaving the partnership before the study came to an end - leading to insufficient funds. Overall, due to the complexity of the research response, trust had to be built very quickly, and often in situations where collaborative efforts had previously not existed. This was highlighted as a challenge by the Study B research team.

As for contacts with in-country partners, the research team said that though they had established good relationships with local investigators and the local staff, local and national political tensions did cause the implementation of the study to slow down. The study team also highlighted the need to engage with the local community and how building trust within the community is crucial for the successful running of projects. The research team engaged much in capacity building at the research site, which has left a positive impact on the local research team. Most capacity building, training and infrastructure development occurred after the study had been completed, as it was neither possible, nor appropriate during the peak of the outbreak. Including the local research team in the development of the research tools, GCP training modules and laboratory technique helped the research team in overcoming challenges to efficient collaboration and the implementation of Study B in the selected study site. The Study B research team attempted to continue with its capacity building efforts by helping two local researchers enrol in specific training programmes in overseas, but it has been difficult to arrange for visas for local researchers to

attend training opportunities. Visas have recently been issued on a case by case basis, which has enabled some overseas capacity building. Local researches have been successfully supported to access training programs in Africa.

In working with the funders, the Study B research team highlighted that one funder was more directly engaged with Study B than the other as that funder had a more hands-on approach in its relationship with the research team. An example of this was that this particular funder joined the Study B team during the site selection visit. The same funder also engaged regularly with the study team, approximately once every two weeks.

Reflecting on the three (or more) lessons learnt from their contribution to the outbreak response, the Study B research team listed:

1. The need to have local support for the study, through local investigators who are likely to engage and champion the study, and that the local investigator be accepted by the government and relevant agencies.
2. Particularly in countries broken or recovering from conflict, logistics can be a real challenge as moving money and equipment is influenced by the local economy, the health of the banking system, and (sometimes) corrupt practices. Partnering with already existing and functional logistical infrastructures is a key to success.
3. Communication was surprisingly very easy as mobile phone telephony is well established in West Africa.
4. Collaboration and cooperation between research studies was vital, if challenging at times.

Funder perspectives

Though previously providing funding during an outbreak situation, one of Study B's funders had never initiated a similar rapid response initiative before. They will, however, be able to utilise the infrastructure developed during the Ebola response 'next time'. Their funding call was published publicly in August, and they received hundreds of expressions of interest. More than 30 applications were channeled through an accelerated review. Applications were considered on a rolling basis, and proposals were accepted while the protocols and research tools they meant to utilise were being developed. This accelerated the process significantly, but it was a caveat that was put in place due to the severity of the situation and the need for a rapid response. Despite the accelerated process, proposals were reviewed according to the same procedures as they are for calls published under normal circumstances - but more rapidly.

The main challenges identified by the funding representatives relate to internal resource management as staff needed to be reassigned to support the Ebola response, and additional staff members were brought on board, if temporarily. Another challenge related to the lack of communication with other funders, though the interviewees were not directly engaged with such relationships and therefore unable to provide any details with regards to the communication and coordination between funders.

Reflecting on the three (or more) lessons learnt from their contribution to the outbreak response, the Study B funder listed:

- 1) Resource management needs to be planned by a core team, should a similar event happen again. That core team would need to include staff from different parts of the organisations, such as the finance, legal, science, innovation, and communications departments.
- 2) Conducting interviews with PIs rather than going through the normal evaluation process probably would have enabled them to answer questions from the review committee directly, which would significantly accelerate the process between application and award.
- 3) Better communication methods with other funders need to be explored. Would it result in sharing applications and speed up the process? Or would it result in an information overload and slow it down instead?
- 4) Coordination would be helpful to get an understanding for how many different sites were going to be utilised and the capacity that would be necessary to run the many different studies that were funded. Problems arise when more than one study team approach a clinical site, for instance, which is going to impact on research.

Study C

Overview

The research group that initiated Study C approached and received funding from one funding organisation. As the funding organisation that funded Study C is the same as the funder that funded Study B, their account will not be repeated here. The research group that ran Study C had not previously collaborated with the identified local investigators or the international humanitarian organisations within whose clinical facilities the study was taking place. Study C employed both international and national staff for the implementation of the study.

Researcher perspectives

The Study C research team particularly highlighted contracts and the signing of agreements between partners to be an issue that slowed down the implementation of the study. The contracts contained clauses that had to occupy the space between protecting intellectual property and open data-sharing to be considered acceptable to both the industrial partner and the humanitarian organisation involved. As the PI put it, there was a clash between organisational cultures and goals that had to be navigated, and the Study C research team found that they were often on middle ground, between industrial partners and humanitarian organisations.

Issues concerning liability and insurance also slowed down the process to the point that the PIs academic institution eventually had to arrange for insurance, which the research team highlighted as being unfair as it constituted a very significant risk to the academic institution. Ensuring that the research tools and the specifications about eligibility criteria was acceptable to the humanitarian organisation slowed down the process further.

With regards to the relationship between the PI and the local PI for Study C, there were conflicting views and misunderstandings about the financial management of the study.

The accounts of the interviewees also differ in that the PI maintained that the responsibility for recruiting and training local staff rested with the local PI and the humanitarian organisation. However, the local PI stated that it was under the control of the humanitarian organisation and that the chain of command was ultimately with the international PI and their academic institution. One way to streamline Study C, the local PI suggested, would be to include the local investigator earlier on in the process, and include them into the development of the proposal and protocol design. The local PI was left feeling as if they were mainly included in Study C to ensure that national ethical and regulatory approvals were in place, and would have wanted to be considered a partner rather than being demoted to facilitator.

With regards to capacity building, the training arranged for the local staff was directly related to the implementation of the study. However, the local PI would have liked to have received assistance and contributions to the country's ability to conduct sample analysis in BSL 3 laboratories, and to strengthen Infection Control and Prevention, including the capacity to use incubators and incinerators in-country. The international PI said that as international staff were required to receive training in the country where the international PI was based before arriving in West Africa, it proved impossible to secure visas for potential African team members to attend

this training. Further, following the end of Study C, the research team did not pursue additional projects in-country as local staff and government was overwhelmed and flooded by bilateral offers.

In terms of data-sharing platforms, setting up an electronic in-country data-sharing platform would have been beneficial according to the local-PI, as it could have been used after the end of the Ebola outbreak. Discussing the idea of data-sharing, the international PI said that data was shared with WHO. However, though many other stakeholders kept asking for data to be shared more widely, the Study C research team felt that sharing data before the end of a study could lead to prejudicing conclusions and decision-making based on incomplete data, which could potentially do more harm than good.

Despite the critical feedback given by the local PI for Study C, this individual would welcome further collaboration with research teams from the PIs academic institution in the future, and with other international partners. And the local PI was positive about the network that had been built through Study C.

Reflecting on the three (or more) lessons learnt from their contribution to the outbreak response, the Study C research team listed:

1. You can conduct rapid research under very challenging circumstances.
2. Working with NGOs is very important when dealing with vulnerable populations such as refugee populations or during infectious diseases outbreaks, and the research community should do more to engage with them.
3. Drawing up and agreeing on contracts, such as clinical trial agreements, is the most challenging bottleneck, and more ought to be done to facilitate that process and agree on the core components of contracts as early on as possible.
4. It is important to engage in a dialogue between academics, NGOs, industry, and regulators ahead of other outbreaks in order to get cultures more aligned.
5. Academic institutions should not be asked to indemnify research. Rather, it would be worth exploring what governments or international institutions could step up, or whether pooled funding could be used for this purpose.
6. There was a lack of coordination and engagement with local stakeholders in-country, which contributed to an apparent lack of transparency. Local investigators should have

been involved from the conception of the study to the development of the research tools, submission of the proposal, and implementation of the study.

7. More international effort should have been put towards strengthening the in-country research capacity by developing, for instance, BSL 3 laboratories and the capability to run them, rather than shipping samples abroad. This would have given the local research community more ownership of the situation.

DISCUSSION

A number of themes became particularly prominent as the interviews progressed and following the data analysis. The first eight themes as listed below were particularly highlighted through the interviews held with research teams, and the last theme particularly relates to matters that GloPID-R should consider, from a funder's perspective.

Role of the World Health Organization

Overall, the WHO was key in creating partnerships and collaborations by holding meetings regarding the prioritisation of therapeutic products and vaccines. They either directly suggested that investigators work together, or provided the platform for investigators to initiate partnerships independently. All three studies maintained close links with WHO before, during, and after their life-cycles, and funders also attended related WHO meetings ahead of preparing funding calls.

Contracts and Agreements

Contracts and agreements between partners were a major factor that delayed the initiation and implementation of studies. The main challenges in setting up agreements were two-fold. One issue concerned the alignment of the written study protocol and Standard Operating Procedures (SOPs) with large NGOs and other partners. While collaborators were relatively flexible and were able to standardise protocols between themselves without much difficulty, large, independent NGOs were not as flexible. Their main concerns were about managing the risk of the investigational product, for example, not including pregnant women in the eligibility criteria. The other challenge concerned indemnity and liability for the trial within a large consortium with many partners. In all three of the studies, the liable sponsor for the trial was an academic institution. One investigator interviewed stated that academic institutions should not be asked to take such a large risk, and suggested that what is needed is a new way of indemnifying research during outbreaks in the future, whether it is by governments, banks or pooled funding.

Contracts with industry did not pose a large challenge. Study A had good industrial connections and was able to sign a contract with them within two months. There were no specific negative comments about contracting with industrial entities from the other studies.

Only one study had a consortium-wide agreement put in place, most likely because the funder required it. The other trial did not enact a consortium-wide agreement, as they did not feel it was necessary. From the local PI and co-investigators perspective, however, a consortium-wide agreement may have made the collaboration more transparent and less risky from financial and data sharing perspectives.

In Study B, partnerships were often agreed upon informally, and in some cases, in the absence of the PI. As these partnerships were overall beneficial to the PI, they were deemed acceptable. However, it did present challenges in that the new partners were not legally required to remain in the partnership until the end of the study. As a result, they backed out, leaving the study with insufficient equipment and funds.

Ethical and regulatory approvals

All of the studies seem to have been fast-tracked through an accelerated approval system as far as gaining ethical and regulatory approval was concerned. There were no major concerns about the amount of time taken to obtain approvals, and all partners were relatively content with the speed of the processes. However, the Study C research team suggested that what actually took more time was the review process rather than finally gaining approvals. Both the Study A and Study C research teams noted that it took slightly longer to get their studies ethically approved through the ethical review boards of their humanitarian organisation partners than it took to get it approved in-country.

Data-sharing

Data-sharing was flagged as a complex issue as sharing data before the end of a trial could lead others to draw hasty and prejudiced conclusions upon which misinformed decisions could be made. Also, data-sharing ahead of publication was flagged as an issue as high-ranking journals continue to place high value on publications containing unpublished data, resulting in the delay of published reports. As the impact and value of publications is critical in determining the career advancement and salaries of researchers, careers of early researchers could be jeopardised by

having to share data too early. However, all three studies did share their data with WHO and/or local government entities during the implementation of the trials.

Community and local engagement

A majority of the research teams considered community and local engagement a very important stepping stone towards the successful implementation of the studies. However, many interviewees saw it as a challenge, and often required facilitation through their local partners. Though challenging, interviewees generally reported a very positive experience gained through working with communities, and claimed that it improved and eased the running of their research trials.

Research staff: local and International

Studies A, B, and C had varying levels of local and international involvement. Study B was run by mostly local clinicians and nurses who were already working at the ETU, which was a hospital, and therefore more permanently established. Study A was conducted by half local, half international staff, and Study C, was conducted mostly by international staff. Local staff were recruited, but only by the international NGO hosting the clinical trial.

One trial stated that they wanted to bring in a key list of researchers from other African countries, but as pre-deployment training took place in the UK, they were not able to secure visas for these researchers, and thus, were not able to employ them.

Collaboration across resource settings

Of the three studies explored for this study, it seemed that previous relationships and familiarity with the context in which the study was taking place had a positive effect on the implementation of the study, and the rapidity by which studies were set up. As the Study A research team had been working in the area and with the local investigators for up to six months, they seemed to have a head start. Study B benefited from being initiated by the local research team, including their involvement in the development of SOPs and training modules, though there were political barriers in place that influenced the launching of the study. Study C, on the other hand, has been criticised by the local PI for not being inclusive enough early on in the initiation of the study and having a lack of engagement with local stakeholders. Interviewing the local investigators involved with Study A and Study B would have been of interest to explore these issues further, to clarify

the attitudes and experiences of their respective local PIs, and aid in the comparison between the three studies in relation to foreign versus local perspectives.

Conducting research with the private sector

One theme that came up during the interviews was that while industry conduct research purely with the aim of evaluating the efficacy of a drug or vaccine in order to get it licensed for market, academic researchers and their humanitarian partners also conduct research with the hope of understanding the best ways to conduct research in an emergency outbreak situation, as well as to evaluate the community response and acceptance to different types of research in these situations. As a result, industry partners ended their participation early in two studies. This posed major problems for the teams involved in the concerned studies, as one study, for instance, had to re-allocate their funding to pay for equipment previously provided by the industry partner. The other study had to stop altogether, and thus had unnecessarily put research staff and patients in danger for a study that would ultimately produce no results.

Funder perspectives for GloPID-R to consider

There seem to have been accelerated processes in place, at least for the funding organisations included in this study, though they were either informal or untested before the West African Ebola outbreak. Now having tested them, funders are drawing lessons from their experiences and finding ways in which to put in place a better system should similar outbreaks happen again. This may provide a good opportunity to exchange lessons learnt with regards to the processes utilised to accelerate funding initiatives.

Judging from the responses gathered through this study, there is general agreement that funders would like to know more about the priorities, activities and projects funded by other funders in order to avoid duplication. However, funders are unsure as to whether increased communication between them would help or hinder their rapid response efforts.

One of the funding representatives whose organisation had funded Study B and Study C said, for instance, that GloPID-R should consider how it functions collectively, and expressed concerns regarding the ability to mobilise funding within 48 hours without processes being pre-determined, and having funding already pooled and waiting for an outbreak to occur.

The funding representative whose organisation funded Study A said that it is crucial for funders to discuss what triggers would lead to a rapid funding response. This representative also recommended that GloPID-R should consider how it aims play a role in coordinating communications between funders. From responses received, it is recommended that this process be streamlined, easy and informative, to incentivize funders to contribute information about their role in funding emerging epidemics research during outbreaks, and in 'peace-time'.

CONCLUSIONS

When the two parts of this study are put together, a number of themes emerge that are worthy of note for future pandemic response efforts.

1. Capacity Strengthening and Engagement

There is sufficient research capacity and capability available within upper-middle and high-income settings that can be mobilized quickly as long as the necessary funding can be secured for projects. However, there is significantly less capacity and capability in low to middle income countries – and the West African Ebola outbreak response efforts explored here have underlined the need for capacity building activities to be built into future response activities, though it may not be appropriate or possible during the acute response to outbreaks. Capacity building during or after the acute response increases the ownership felt by local investigators in providing local responses and being included in the design of study tools and documents, which also ensures that they are appropriately designed for the context in which they are to be implemented and used. Capacity building in the form of infrastructure strengthening and formal training of local personnel will help the affected country be better able to prevent and respond to future outbreaks, and will strengthen the health care system in general. Further, it is important to engage directly with the communities where research is to take place as this will help build the trust necessary for the smooth running of clinical studies within local populations.

2. Partnerships, Collaborations and Contracts

Multidisciplinary collaboration is crucial for an appropriate outbreak response. There is a need for research groups to work more closely with government agencies, regulatory and ethical committees, humanitarian organisations, and industry – ahead of outbreaks. Pre-existing collaborations, an understanding of different sectors' values and negotiated template contracts, for instance, could reduce the time spent on negotiations, agreements, and approvals during the outbreak. Additionally, Investigators who have past or current experience in the affected country, and those with strong existing contacts with local investigators should be prioritized in funding calls, as they will be most likely to have the capability of rapidly initiating a research study.

Other issues, such as those related to indemnity insurance and study sponsorship, also need to be addressed. The international community might consider discussing an alternative system for the indemnity of trials involving highly investigative therapeutic and vaccine products during outbreaks, for example, through government or financial institutions. The role of WHO in

coordination, expertise, and forming partnerships during a research response effort was also highlighted by all interviewees as crucial to the Ebola outbreak response. This is further justified by the survey responses in Part I, as most research networks said that they have links with both national and international public health agencies.

3. Flexibility

As research teams and networks are asked to collaborate during outbreaks and between outbreaks, and studies often have more than one PI, there is a need for both academic institutions and funders to recognize that increased collaboration challenges the traditional funding mechanisms and address this within their organisations' processes. It may, for instance, be necessary to issue individual sub-award letters to co-investigators from certain regions of the world in order for PIs to be able to accept a funding award and begin their study rapidly.

4. Preparedness and Response Plans

A fourth reflection concerns the increased need for in-kind contributions from within research institutions and funding bodies alike during outbreaks need to be addressed. Operational planning for pandemics needs to be an integrated part of pandemic preparedness, thus, both research institutions, funding institutions and other stakeholders should develop and test operational plans for outbreaks, including designation of human resources, templates and protocols, electronic systems for application submission and data collection and communication channels.

5. Feasibility of Rapid Funding

The final conclusion drawn is related to the availability of accelerated funding call processes within funding organisations. In survey responses from Part I, eleven funding organisations indicated that they had provided funding towards the Ebola research response, and nine funders had protocols in place for pre-approval of projects that could be initiated in the case of an outbreak. However, it is possible to assume – on the basis of the two interviews with funders conducted for the Ebola Response Case Study in Part II – that few accelerated initiatives had been utilised or trialed before the West African Ebola outbreak. Though significantly accelerated, both initiatives took months and weeks rather than 48 hours to plan and implement, and representatives expressed doubt that this goal was achievable. Some funding organisations have put in place an emergency funding procedure in response to the Ebola outbreak; thus, it is necessary that they develop and test the proper tools needed during the launch of this procedure in the interpandemic period to ensure that it works smoothly. Though most respondents to the *Funders Survey*

indicated that they were not interested in contributing any amount of funds to an independent, collective trust, four funding organisations would consider allocating a portion of funds to their “emergency reserve” for rapid deployment during public health emergencies, rather than re-allocating earmarked funds when emergency funding is needed. This is a strategy that should be tested for feasibility.

Demarcation

Many of the limitations of the quantitative survey study have been listed following the discussion of the results presented in Part I. For Part II it would have been desirable to interview more than one local PI, as this would have produced more in-depth data concerning the bottlenecks and barriers faced by local research teams in international studies such as the ones chosen for this study. It would also have facilitated a more robust comparison between the studies, and decreased the amount of foreign bias in Studies B and C, where the local PIs could not be reached for interviews. These accounts would be important to improve upon future collaborative efforts in outbreak situations that occur in LMIC settings similar to those of the West African Ebola outbreak, and ensure an adequate amount of local engagement and participation. It should also be taken into account that interviews were conducted by two researchers, whose different interview styles may have contributed to the collection of differing amounts or types of data.

Another limitation lies in the requirement to anonymise the researchers, funders, and trials, included in this study, which has inevitably led to the loss of some of the rich and detailed data gathered for the qualitative part of this study. Anonymisation was necessary in order to ensure that participants would be comfortable sharing specific details about processes, partnerships, collaborations, and in some cases, the political and bureaucratic context of their studies. Though this study could not disclose all of these specificities, the researchers have aimed to transform important points and anecdotes into more general overviews.

This study has highlighted the significant potential that exists for coordination among research networks and funders through initiatives such as ISARIC and GloPID-R, and we believe that inviting other key players such as those involved in legislation, data collection and protection, drug and research development, local community members and public health officials to engage with these existing platforms in the interpandemic period will ensure a faster, more efficient and comprehensive response to the next to pandemic.

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APPENDIX I: GLOPID-R MEMBERS (AS OF 9 MARCH, 2016)

Africa: African Academy of Sciences

Argentina: Ministry of Science, Technology and Productive Innovation

Australia: National Health and Medical Research Council

Brazil: Instituto Butantan

Brazil: Instituto Fiocruz

Brazil: Sao Paulo Research Foundation

Canada: Canadian Institutes of Health Research

Canada: International Development Research Centre

Europe: European Commission

France: Institut de Microbiologie et des Maladies Infectieuses

Germany: Federal Ministry of Education and Research

India: Indian Council of Medical Research

Italy: Ministry of Health

Japan: Japan Agency for Medical Research and Development

Korea: National Research Foundation of Korea

Mexico: Consejo Nacional de Ciencia y Tecnología

Norway: Research Council of Norway

South Africa: South African Medical Research Council

Spain: Instituto de Salud Carlos III

Thailand: Thai National Institute of Health, Department of Medical Sciences

USA: Bill & Melinda Gates Foundation

USA: U.S. Department of Health and Human Services

UK: Wellcome Trust

**APPENDIX II: EXPRESSION OF INTEREST (EOI)
EOI FOR THE CAPACITIES AND CAPABILITIES SURVEY
AND THE PEARLES BARRIERS SURVEY
(FIRST SENT 4 AUGUST, 2015)**

Dear Colleague,

You are invited to participate in important research we are conducting to explore the capacities and capabilities and barriers to an efficient and rapid outbreak response among research networks globally. This is a joint initiative between GloPID-R (the Global Research Collaboration for Infectious Disease Preparedness) and ISARIC (the International Severe Acute Respiratory and Emerging Infection Consortium), and your responses will feed into GloPID-R's pandemic preparedness efforts and future funding initiatives.

GloPID-R is a network that aims to bring together research funding organisations on a global scale. It aims to facilitate a coordinated and effective research response within 48 hours of any severe infectious disease outbreak. ISARIC is, through the University of Oxford, leading the Work Package for this project. We are also, together with Fondation Mérieux, the Secretariat for GloPID-R, which is funded by the European Commission (Horizon 2020, grant 643434).

You are invited as you represent a research network or conduct research that is central to an efficient outbreak response, and your input would be very valuable to this project. If you feel that one of your colleagues would be better placed to answer one or both surveys, please feel free to forward this email to them.

The surveys should take about 20 minutes each to complete. All of your answers will be kept strictly confidential and will be used only for legitimate research purposes.

The surveys close on 3 September 2015 – your early submission is welcomed.

If you have any questions about the survey, please email:
kajsa-stina.longuere@ndm.ox.ac.uk

For more information, and to learn more about the organisations involved and to begin the surveys, please click the survey links below:

Capability and Capacity Survey
PEARLES Barriers Survey

Thank you for your participation.

Dr Gail Carson
Principal Investigator

EOI FOR THE FUNDERS' SURVEY

(FIRST SENT 25 AUGUST, 2015)

Dear [title, name],

You are invited to participate in important research we are conducting to explore the capacities and capabilities and barriers to an efficient and rapid outbreak response among funding organisations globally. This is a GloPID-R initiative and you are being contacted as a representative for a GloPID-R member organisation. Your responses will feed into GloPID-R's pandemic preparedness efforts and future funding initiatives.

If you feel that one of your colleagues would be better placed to answer this survey, please feel free to forward this email to them.

The survey should take about 15 minutes to complete. All of your answers will be kept strictly confidential and will be used only for legitimate research purposes.

The survey closes on 18 September 2015 – your early submission is welcomed.

If you have any questions about the survey, please email:
kajsa-stina.longuere@ndm.ox.ac.uk

For more information, to learn more about the organisations involved, and to begin the surveys, please click the survey link below:

GloPID-R Funders' Survey

Thank you for your participation.

Dr Gail Carson
Principal Investigator

APPENDIX III: SURVEY LINKS

Each of the three surveys can be accessed following these links:

Capacities and Capabilities Survey: <http://prepare.ucd.ie/surveys/index.php/784844>

PEARLES Barriers Survey: <http://prepare.ucd.ie/surveys/index.php/995319>

Funders' Survey: <http://prepare.ucd.ie/surveys/index.php/177411>

Please note that these links are 'dummy' links, and that any answers to the survey questions will not be saved.

APPENDIX IV: SEMI-STRUCTURED INTERVIEW GUIDE

QUESTIONS FOR RESEARCHERS

Researchers' involvement in the initiation of Ebola research partnerships or consortiums

1. How was this project originally conceived?

Potential follow-on questions:

a. Can you clarify the dates of contact in regards to this project?

2. Can you describe the process of finding partners and forming your consortium/project team, including funders, private industry, local investigators, and local stakeholders?

Potential follow-on questions:

a. Did you or any of the members of your study have collaborations with each other prior to this study?

b. Did any members have prior or on-going experience working in West Africa?

3. Did any of your team members have prior experience with Ebola research?

Potential follow-on questions:

a. What was the context of this previous research?

b. Did this research feed into or influence the current project?

4. How did your team decide on the product that was tested? (only for therapeutic or vaccine trials)

Potential follow-on questions:

a. Had you previously worked with this product or the manufacturer of the product?

b. Which groups did you consult on this decision?

Timelines and hurdles in partnership contracting, including decisions concerning study design, and disbursement of funds.

5. Can you describe the process of writing contracts or memorandums of understanding?

Potential follow-on questions:

a. Which organizations within your consortium/project team had contracts?

b. Were there multiple contracts, or one common contract for the entire study?

- c. How were data and sample sharing addressed in your contracts?
 - d. What were the main issues that caused a delay in signing contracts?
 - e. How were these issues resolved?
 - f. Can you think of a more efficient way that they could have been resolved?
 - g. Would you be willing and able to share a copy of your contracts?
6. Your team applied for funding with _____ and _____. How did you find out about the funding opportunities that you received?

Potential follow-on questions:

- a. Had anyone on your team received funding from these organizations in the past?
 - b. Was the funding process streamlined?
 - c. Did the funding body implement its own streamlining process, or did any member of your team negotiate with funding bodies to increase the speed of decisions or disbursements?
 - d. Can you describe the process and details of this negotiation?
 - e. Can you confirm the dates of call announcement, application submission, award announcement, and fund disbursement?
7. During protocol development, how did your team decide on the design of the trial? (If needed, examples include: literature review, participation at WHO Ethics Board meetings, instructions in call for proposals, etc.)

Potential follow-on questions:

- a. Which factors were considered when deciding? (ethical, sample size, cultural aspects, etc.)
- b. Which team members were involved in protocol development?
- c. Were there any internal disagreements about study design?
- d. Were any of your team members involved in the political processes of guidelines and standards creation at the WHO, particularly with regards to clinical trial study design?
- e. How was adaptability written into the original study protocol?
- f. Did you have to implement these adaptations during the study?
- g. Did you adapt the study in anyway that was not written into the original protocol, and what was the reasoning?

Approval processes by ethical and regulatory boards

8. You applied to _____ and _____ for ethical approval. Did any of these ethics boards grant you fast-track approval, and if so, can you please describe the process?

Potential follow-on questions:

- a. Who was involved in negotiating and/or managing the ethics approvals at each of the sites involved?
- b. What could have helped to improve the fast-tracking process?
- c. Confirm dates of submission, feedback, re-submission, approval, etc.

9. You applied to _____ and _____ for regulatory approval. Did any of these regulatory bodies grant you fast-track approval, and if so, can you please describe the process?

Potential follow-on questions:

- a. Who was involved in negotiating and/or managing the regulatory approvals at each of the sites involved?
- b. What could have helped to improve the fast-tracking process?
- c. Confirm dates of submission, feedback, re-submission, approval, etc.

Timelines and hurdles in staff recruitment, study site selection and patient recruitment

10. Can you describe the process of selecting your study site(s)?

Potential follow-on questions:

- a. Which factors did you consider in choosing the study site?
- b. Who was involved in the selection process?
- c. Who was consulted in the selection process?
- d. What could have helped identify a better study site, or streamline the process of site selection?

11. Can you describe the local staff recruitment process?

Potential follow-on questions:

- a. Who was in charge of local staff recruiting?
- b. Did you employ local staff who were already employed by your study site? / local staff who were not already employed by your study site?
- c. Was local staff previously involved in clinical care?
- d. What duties did local staff fill in your study?
- e. Was local staff offered benefits? Were benefits included in funding proposal?

12. Can you describe the international staff recruitment process?

Potential follow-on questions:

- a. Who was in charge of international staff recruiting?
- b. How were opportunities advertised?
- c. From where did staff come from?
- d. What duties did international staff fill in your study?
- e. Were there issues with obtaining visas? What was the timeline with visas?
- f. Was international staff offered benefits?
- g. Did you have an emergency repatriation plan for all staff? If no, why not?
- h. How long were staff members deployed?
- i. What were the biggest challenges in international staff recruitment?

13. Can you describe the international staff training process?

Potential follow-on questions:

- a. Who was in charge of international staff training?
- b. Were teams of staff members trained before deployment?
- c. Do you have suggestions for improvement in the international staff training process?
- d. Do you have an itinerary for staff training that you could share?

14. Can you describe the local staff training process?

Potential follow-on questions:

- a. Who was in charge of local staff training?
- b. Do you have an itinerary for local staff training that you could share?
- c. Where were training sessions held?

15. Can you describe the patient recruitment process?

Potential follow-on questions:

- a. What were the major challenges in patient recruitment?
- b. Do you have suggestions as to how patient recruitment could have been improved?

Capacity and capability to run trials, including capacity building exercises before and during the studies

16. Can you describe the infrastructure and equipment that was available at the study location?

Potential follow-on questions:

- a. How did this figure into your selection of study site?
- b. Which equipment was permanent and which was brought by international staff?
- c. Were there logistical challenges in transporting equipment or supplies, or in maintenance of equipment or supplies?

17. How was your team involved in capacity building before starting the trial?

Potential follow-on questions:

- a. Was capacity building written into your funding proposal?
- b. Did your team engage in capacity building throughout the trial and in what way?

Perspectives on collaboration with internal and external parties (e.g. public health, local/national government, humanitarian organisations, drug companies, other study groups, the local community etc.)

18. Was your team involved in data sharing within or outside the members of the team?

Potential follow-on questions:

- a. Can you describe the platform used for sharing data?
- b. What were the concerns, if any in sharing data within or outside the members of the team?
- c. What could be improved for next time in order to accelerate or ease the difficulty of sharing data?

19. Was your team involved in sample sharing within or outside the members of the team?

Potential follow-on questions:

- a. Were samples shipped outside of West Africa, and which type of samples?
- b. If yes, which company was used and did you face logistical or other boundaries in shipping these samples?
- c. Who was involved in primary analysis of samples?
- d. Were samples shared with any additional partners?
- e. Were all partners listed above included in the contracts previously discussed?
- f. What could be improved for next time to accelerate or ease the difficulty of sharing samples?

20. Can you describe your team's relationship with the Ministry of Health or other government officials in the country of your project(s), and their involvement (if any) in your recent study?

Lessons learnt from on-going or recent outbreak response

21. From your involvement with the Ebola response, what are the three key lessons you learnt?

Potential follow-on questions:

- a. What could have been done differently?
- b. Reflecting on your partners and any local partnerships, how easy did you find collaboration?
- c. What could be improved for next time?

22. Would you say that your project leaves a 'legacy' in West Africa?

Potential follow-on questions:

- a. Will you continue working with the partners and contacts you have identified and collaborated with after the end of the project?
- b. Apart from meeting the objectives of your project, did your project result in any long term outcomes that went beyond the planned outcomes for the project?

QUESTIONS FOR FUNDERS

Funders' involvement in the initiation of funding calls for Ebola research

1. How did your institution decide to invest in Ebola research during the West African outbreak?

Potential follow-on questions:

- a. Can you clarify the dates of significant internal decisions in regards to this project? (if not fully clarified in the summary sheet)
2. Can you describe the process of drafting and publishing the Ebola-related funding call? Including finding partners and forming your consortium/project team, including funders, private industry, local investigators, and local stakeholders?

Potential follow-on questions:

- a. Did your institution consult or interact with stakeholders (e.g. research networks, industry, public health, humanitarian organisations etc.) ahead of publishing the call?
- b. If so, what did the consultation look like, and would you say that it was beneficial to the final drafting of the call?
- c. Can you confirm the dates and location of this consultation?
- d. Was the call a joint effort with other funding institutions?
- e. If so, how did the collaboration shape the call?
3. Has your institution previously funded Ebola-related projects?

Potential follow-on questions:

- a. Did prior investment in Ebola research influence your decisions during the West African outbreak?
- b. If not, has your institution previously funded research during infectious disease outbreaks?
- c. What was the context of any previous related calls?
- d. Did the outcomes of the research funded through previous calls influence the latest Ebola-related call?

4. How much money was set aside for the call, and how many projects were funded?

Potential follow-on questions:

- a. How did your organization get or change access to those funds? (e.g. were they originally allocated for another purpose, or were they always emergency funds, etc.)
- b. Can you clarify the timeline for getting access to these funds, including dates of approvals and disbursements?
- c. Did you fund projects in full or partially?
- d. If partial funding was provided, what was the reasoning?

Barriers to providing a rapid funding call

5. a. *If funder indicated they have a process for 'rapid' funding disbursement:*
Did you call for proposals and disbursements follow the timeframes defined in your pre-established rapid' funding mechanism?

Potential follow-on questions:

- a. Has your institution previously provided 'rapid' or 'accelerated' funding in an outbreak situation, according to the mechanisms in place?
- b. During the West African outbreak, what further measures were put in place within your organisation in order to accelerate the call?
- c. What caused any delays in the proposed timeline?
- d. What measures would you say that your institution should put into place in order to increase the success of accelerated calls?

- b. *If funder did not indicate they have a process for 'rapid' funding disbursement:*
Was the call a 'rapid' funding call, or did it follow the processes and timeframes usually applicable to your institution?

Potential follow-on questions:

- e. If yes, has your institution previously provided 'rapid' or 'accelerated' funding in an outbreak situation?
 - f. During the West African outbreak, what measures were put in place within your organisation in order to accelerate the call?
 - g. If no, would you institution consider providing rapid/accelerated funding in an outbreak situation?
 - h. What measures would you say that your institution would have to put into place in order to have accelerated calls?
6. What would you say are the main challenges in providing rapid funding that go outside of your ordinary funding cycles/processes? (unless already answered in Question 5)

Timelines and hurdles in the selection process

7. By what criteria did your institution choose the funded projects?

Potential follow-on questions:

- a. Which factors did you consider in choosing the successful applicants?
 - b. Who was involved in the selection process?
 - c. Who was consulted in the selection process?
 - d. Was the selection process itself accelerated, and if so, did it result in any specific challenges or issues?
 - e. Looking back, what additional criteria should have been included, or alternatively, should not have been included in the selection process?
8. Did the call include 'capacity building' or 'outreach work' as part of successful proposals?

Lessons learnt from on-going or recent outbreak response

9. From your institution's involvement with the Ebola response, what are the three key lessons you learnt?

Potential follow-on questions:

- a. What could have been done differently?
 - b. If the call required external collaboration, how easy did you find collaboration?
 - c. What could be improved for next time?
10. Would you say that your funded project leaves a 'legacy' in West Africa or elsewhere?

APPENDIX V: CODING FRAMEWORKS

Coding framework: Researchers interviews

Collaboration

Project Conception and Initiation

- Adapted previous protocol
- Desperately seeking intervention
- Morally and ethically demanding
- Open access motivated
- Role of ISARIC
- Timely funding call
- Role of WHO
- Motivation

Finding partners

- Some good partners
- Prior Ebola experience
- Rigid partners
- Prior experience in country

Investigational product selection

- Availability
- Stage of development
- Criteria for selection
- Prioritising candidate drugs

Contracts

- Delay in contracting
- Multiple contracts needed
- Strict regulations
- Contract templates
- Data sharing
- Sponsor
- Industry
- NGO
- University

Trial design

- Adaptability
- Randomisation
- Eligibility Criteria
- Complex process during difficult circumstances

Local investigators not involved
Protocol sharing to collect common outcome
Partners involved

Working with partners

Transparency
Coordination

Funding call and application process

Launch of call and submissions

Call for funds
Open call
Letter of intention
Complicated funding call
Applying to multiple funders
Funding priorities
Confusion about timing and requirements
Fast-track – formal process in place
Fast-track – informal process
Application peer reviewed
Independent award letters
Independent funding not provided
Lost time to find funding
Management of Funds
Transparency

Regulatory and ethical approval

Fast-track – formal process in place
Fast-track – informal process
Amendments
Conditional approval
Ethical Review Boards giving approval
Lack of experience with clinical trials
Informed Consent
Strict requirements
Local Investigator

Study implementation

Study site selection

Visits
Criteria
Areas to improve

- Logistics
- Availability of equipment
- Shipping
- Laboratory
- Finances

Staff

- International staff recruitment
- Visas
- Local partners
- Local staff recruitment
- Training
- Patient recruitment

Capacity building

- Infrastructure
- Formal training

Data and sample sharing

- Data sharing and intellectual property
- Informal and easy data sharing
- Concerns with interim data sharing
- Data stealing
- No external data sharing happened
- No samples shipped internationally
- Role of partners shared with

Lessons learnt

- Legacy
- Lessons learned
- Areas to improve

Sentiment

- Challenges
- Positive
- Negative
- Power struggle

Coding framework: Funders interviews

Funders Interviews

Conception and Initiation

- Availability of emergency funds
- Meetings attended
- Spontaneous inquiries
- Funding priorities
- Stakeholders involved
- NGO Participation
- Public engagement
- Funders collaboration
- Getting support
- Launch of call
- Grant without call in emergency

Funding call process

- Fast-track – formal process in place
- Fast-track – informal process
- Other mechanisms
- Eligibility
- Deadline
- Evaluation
- External Review
- Flexibility
- Submission
- Human resources

Lessons learnt

- Legacy
- Lessons learned
- Areas to improve