Priority Needs for Conducting Pandemic-relevant Clinical Research With Children in Europe

A Consensus Study With Pediatric Clinician-researchers

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Background: Infectious disease (ID) pandemics pose a considerable global threat and can disproportionately affect vulnerable populations including children. Pediatric clinical research in pandemics is essential to improve children's healthcare and minimize risks of harm by interventions that lack an adequate evidence base for this population. The unique features of ID pandemics require consideration of special processes to facilitate clinical research. We aimed to obtain consensus on pediatric clinician-researchers' perceptions of the priorities to feasibly conduct clinical pediatric pandemic research in Europe.

Methods: Mixed method study in 2 stages, recruiting pediatric clinician-researchers with experience of conducting pediatric ID research in clinical settings in Europe. Stage 1 was an expert stakeholder workshop and interviews. Discussions focused on participant's experience of conducting pediatric ID research and processes to facilitate pandemic research. Information informed stage 2, an online consensus survey to identify pediatric inician-researchers priorities to enable ID pandemic research.

Results: Twenty-three pediatric clinician-researchers attended the workshop and 39 completed the survey. Priorities were primarily focused on structural and operational requirements of research design and regulation: (1) clarity within the European Clinical Trials Directive for pediatric pandemic research; (2) simplified regulatory processes for research involving clinical samples and data; and (3) improved relationships between regulatory bodies and researchers.

Conclusions: Results suggest that changes need to be made to the current regulatory environment to facilitate and improve pediatric research in the pandemic context. These findings can provide expert evidence to research policy decision-makers and regulators and to develop a strategy to lobby for change.

Key Words: children, infectious disease, outbreak, pandemic research, European Directive, Europe

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Infectious diseases (IDs) with pandemic potential pose a considerable global threat.[1] Clinical research is essential to ensure evidence-based public health responses and patient management in future ID pandemics (IDPs). The unique nature of IDPs presents challenges to the conduct of research, as implementation must be rapid and potentially include multiple countries. Strategies to facilitate IDP research include fast-track regulatory approval, pre-approved protocols, alternative consent models, novel trial designs and stakeholder engagement.[2–4]

In considering IDP research, the populations that may be affected should be considered. For example, pandemic influenza can disproportionately affect different populations in comparison to seasonal influenza. During the 2009 (H1N1) pandemic, children, adolescents and younger adults had the highest burden of disease, and there were severe and fatal cases in children with no preexisting risk factors.[5–10]

While children and young people (YP) are an obvious and relevant group to include in clinical research, they are frequently not recruited into trials.[11,12] There may be a number of reasons for this including the perceptions that including them is difficult, that approvals may be subject to greater delay and some clinicians are reluctant to approach parents of sick children about research participation. However, families are generally willing to be approached about research even in stressful situations.[13–15] Excluding children and YP from research has resulted in a lack of evidence for many medical interventions for this group and the practice to use off-label and unlicensed medicines guided only by clinicians' experience and extrapolation of adult data.[16,17]

There were few clinical research studies in the last influenza pandemics thus limiting the evidence base for improved care in the

future.[18] For example, following recommendations by organizations including the World Health Organization, Oseltamivir (Tamiflu) was widely stockpiled and prescribed during the 2009 H1N1 pandemic despite a lack of robust evidence on its efficacy and safety for this strain, and no clinical study was conducted during the outbreak to test this.[19] The aim of the EU-FP7 project "Platform for European Preparedness against (Re-) Emerging Epidemics (PREPARE)" (https://www.prepare-europe.eu) is to establish a research infrastructure to transform the research response to future IDPs and includes clinical observational and interventional studies recruiting YP and children.

We aimed to understand barriers and seek consensus on the priorities perceived by pediatric clinician-researchers to feasibly conduct pandemic-relevant pediatric clinical research in Europe. This is essential to inform pandemic study design and provide evidence for future European Commission policy and regulation.

METHODS

A mixed method study targeted at pediatric clinician-researchers with experience of conducting pediatric ID research in Europe. Stage 1, aimed to identify challenges and priorities through a workshop and face-to-face interviews. Stage 2, was an online survey to establish consensus on priorities.

Ethical Approval

Cardiff University School of Medicine Research Ethics Committee approved the study.

Recruitment

Stage 1: Workshop and Interviews

Thirty-four clinician-researchers conducting pediatric research in Europe and attending the European Society for Pediatric Infectious Diseases (ESPID) conference, Leipzig (May 2015) were identified through the PREPARE consortium (https://www.prepare-europe.eu), invited by e-mail to participate in a 2-hour workshop and to suggest additional people to invite. Those unable to attend were invited to an interview during ESPID.

Stage 2: Consensus

Potential participants were identified by members of the Pediatric European Network for the Treatment of AIDS and Infectious Diseases network (http://penta-id.org) and the PREPARE consortium. Eighty-five pediatric clinician-researchers from 17 EU and EU-associated countries were invited by personal e-mail to participate (2016). Up to 3 reminders were sent.

Data Collection

Stage 1: Workshop and Interviews

A task and hypothetical scenario based topic guide was developed to guide discussions around experience and perceptions of conducting pediatric ID research and processes to facilitate IDP research. The scenarios focused on (1) an adaptive pediatric ID trial of licensed pharmacologic interventions in an intensive care unit using deferred consent and (2) an observational ID study using broad/waived consent to access clinical data and surplus/additional clinical samples. Discussions were audio-recorded and anonymized.

Stage 2: Consensus Survey

Key priorities from stage 1 informed the survey. A data collection website in the English language was developed using Survey Monkey. Data were collected from April 14, 2016, to August 25, 2016. The survey comprised of 2 sections: (1) demographic information (country of work, experience of research and ID outbreaks) and (2) 17 "research priority statements" (with a short explanation). Participants were asked to assign a rating score (1–5, with 5 being the highest and 1 the lowest) to how important they thought each statement was to making pediatric pandemic research more feasible (national and European level). An "I don't know" option was available. Free text comments and additional priorities were invited.

Data Analysis

Stage 1: Workshop and Interviews

Key thematic areas were identified as patterns in participant narratives that reflected areas to facilitate IDP research. Audio-recordings were analyzed by 2 researchers in parallel. Findings were reviewed by participants for validation.

Stage 2: Consensus Survey

Responses from all countries were combined. Data were analyzed in 2 groups: (1) priority at European level and (2) national level. As an a priori cut off, ratings of 4 and 5 were considered affirmative. Statements receiving affirmative ratings from ≥70% of participants would be considered to have achieved group consensus. Median and interquartile range and frequency distribution were calculated. Comments and additional priorities were not included in the analysis but were considered for the discussion.

RESULTS

Stage 1: Workshop and Interviews

Participants

Pediatric researcher-clinicians from 10 countries (Estonia, Finland, Greece, Germany, Italy, Lithuania, the Netherlands, Spain, Switzerland, United Kingdom) attended the workshop (n = 23) or participated in an interview (n = 4) at ESPID. These included 24 participants who had received an initial e-mail invitation (70.6%). All participants had conducted pediatric ID research in hospital settings. Thirteen had worked during an ID pandemic or outbreak.

Key Findings

Participants discussed their experiences of conducting pediatric clinical research within and across European countries. Some significant country differences were reported; however, many common challenges were highlighted. There was general agreement that alternative approaches to conducting research are needed to conduct pediatric IDP research. Key thematic discussion areas are provided in (Table, Supplemental Digital Content 1, http://links.lww.com/INF/D302).

Stage 2: Consensus Survey

Participants

Pediatric clinician-researchers [n = 39 (46% of those invited)] working in 15 countries completed the survey (Table, Supplemental Digital Content 2, http://links.lww.com/INF/D303). Three had also participated in the workshop. Respondents completed all questions. Thirty-eight (95%) had experience of research in the last 5 years and 32 (80%) had experience of working in an ID outbreak including influenza-like illness [n = 28 (70%)], Ebola [n = 4 (10%)], Dengue (n = 1), severe acute respiratory syndrome (n = 1), Hantavirus (n = 1), cholera (n = 1), West Nile virus (n = 1) and other ID gastrointestinal outbreaks (n = 3). Other experience included laboratory research (n = 17), research regulation (n = 8) and social science research (n = 2).

Consensus

A single consensus round was conducted as all priorities exceeded the a priori consensus criteria. Results are given in Table 1.

TABLE 1. Priority to Make Pediatric Epi/Pandemic Research More Feasible at a National and European Level (Median and IQR for Each Rated Statement)

Area	n	Area Required to Make Pediatric Epi/Pandemic Research More Feasible at a National and European Level	Priority at National Level Rated Scores, Median (IQR), (1-Low Priority) to 5-High Priority)	Priority at European Level Rated Scores, Median (IQR), (1-Low Priority) to 5-High Priority)
EU Directive	1	Clarity within the new clinical trials Directive for epi/pandemic observational research including children	5.00 (5.00–4.00)*	
	2	Clarity within the new clinical trials Directive for epi/pandemic clinical trials including children	5.00 (5.00–4.00)*	
Regulatory processes	3	Recognition of a common purpose and improved relationship between regulatory bodies, ethics committees and researchers	5.00 (5.00–4.00)	5.00 (5.00–4.00)
	4	Simplified regulatory processes for observational research involving collection, use and sharing of anonymized clinical data (relevant to ID epidemics/IDP)	5.00 (5.00–4.00)	5.00 (5.00–4.00)
	5	Simplified regulatory processes for research involving the collecting, using and sharing of anonymized surplus clinical samples (relevant to ID epidemics/IDP)	5.00 (5.00–4.00)	5.00 (5.00–3.25)
Preapproved protocols	6	Acceptance of preapproved protocols for epi/pandemic research	4.00 (5.00–4.00)	4.00 (5.00–4.00)
Alternative consent models	7	Regulatory approval of alternative models of obtaining patient informed consent for research involving the use of clinical data in an epi/pandemic	4.00 (5.00–4.00)	4.00 (5.00–3.25)
	8	Coordinated processes for the early identification of potential new outbreak cases and pathogens	4.00 (5.00–4.00)	4.00 (5.00–3.00)
	9	Regulatory approval of alternative models of obtaining patient informed consent for research involving the use of clinical samples (excluding genetic testing) in an epi/pandemic (eg, deferred consent, opt-out consent and alternatives to written consent)	4.00 (5.00–4.00)	4.00 (5.00–3.00)
	10	Regulatory approval of alternative models of obtaining patient informed consent for "low-risk" research trials (eg, comparative effectiveness) in an epi/pandemic (eg, deferred consent, opt-out consent and alternatives to written consent)	4.00 (4.75–4.00)	4.00 (5.00–3.00)
	11	Regulatory approval of alternative models of obtaining patient informed consent for "high-risk" research trials (eg, novel agent) in an epi/pandemic (eg, deferred consent, opt-out consent and alternatives to written consent)	4.00 (5.00–3.00)	4.00 (5.00–3.00)
Adaptive trial design	13	Recognition of the benefits of novel trial designs, for example, adaptive platform trials by regulatory and ethics committees	4.00 (5.00–3.25)	4.00 (5–3.25)
Communication and trust	14	Good 2-way communicating between researchers and senior government regarding research requirements for emerging ID outbreaks	4.00 (5.00–4.00)	4.00 (5.00–4.00)
	12	Establishing trust between researchers and senior government regarding research requirements for emerging IDs outbreaks	4.00 (5.00–4.00)	4.00 (5.00–4.00)
	15	A strategy for engagement and good communications with the media to aid positive reporting of research for IDPs including children	4.00 (5.00–4.00)*	
	16	Parent and young person engagement and education about epi/pandemic research	4.00 (5.00–3.00)*	
Training	17	Training of front-line clinical staff in the procedures of preapproved protocols for epi/pandemic research	4.00 (5.00–3.00)	4.00 (5.00–3.00) (at local level)

*Not asked to discriminate between National and European level.
IQR indicates interquartile range.

Participants Additional Priorities

Additional priorities included open access publication, ensuring rapid pan-European availability of research data, laboratory standardization and the establishment of research networks.

DISCUSSION

IDP research that includes children and YP is essential to enable evidence-based healthcare for these populations. We identified pediatric clinician-researchers' key priorities for facilitating this IDP research to provide evidence to research regulators and policy makers. Priority areas identified include clarity for IDP research within the European Clinical Trials Directive (Regulation), improving relationships between ethics committees and researchers, simplified regulatory processes for sharing data and clinical samples, coordinated networks for early identification of pathogens, consideration of alternative consent processes, preapproved research protocols, improved stakeholder engagement and novel research design. These priorities are discussed below.

Provision of greater clarity within the European Clinical Trial Directive for both clinical trials applying low-risk procedures and observational (noninterventional) IDP pediatric studies, was a key priority for pediatric clinician-researchers. (The Clinical Trials Regulation superseded the Directive following this study's data collection). The Regulation includes a definition for observational studies; however, it includes neither a legal framework for

obtaining regulatory approvals for this type of research in different EU member states nor provides guidance specifically for pediatric research in the pandemic context. This omission, in addition to a potential lack of knowledge of the new framework and pediatric ethical issues among ethics committees, will pose a considerable barrier to the implementation of multicountry IDP research.[20,21] Lobbying European Commissioners for provision of greater clarity for observational and low-risk interventional studies and including special consideration of pandemic pediatric research in the Regulation is essential to enable successful IDP studies that cannot be restricted by geographic boundaries.

A breakdown in the relationship between clinician-researchers and ethics committees was highlighted in the workshop and consensus. This can result in delays of approvals and some countries being excluded from pediatric ID research. Recognition of a common purpose between regulatory bodies and researchers is essential for IDP research due to the need for rapid approvals and study set-up. Solutions would include education of regulators around the unique nature of ID outbreak research, setting up designated ethical committees for IDP research and preparation of preapproved IDP "sleeping" protocols, which would be "ready to implement" as soon as a pandemic is officially declared. Sleeping protocols have been developed in the NIHR HTA pandemic portfolio and within the International Severe Acute Respiratory and Emerging Infection Consortium (https://isaric.tghn.org).[22,23]

While the collection, storage and access to clinical data and samples are essential for observational IDP research, there are currently no regulatory provisions or shared collection resources in Europe to enable this. Even within countries, access and sharing of samples and data are often disparate and difficult. If routinely collected anonymized clinical data and excess samples could be made available for research, it would reduce the need for additional studies to collect these. Coordinating IDP research with Public Health Authorities (PHAs) (responsible for surveillance, collection of samples and associated research) could be key to enabling this, with reference to countries settings where these processes have been implemented. Engagement with PHAs and other stakeholders (eg, public health policy makers) to develop a coordinated approach and strategy may need to be driven by an International research consortium like PREPARE. Wider consultation may need to include regulators, clinicians, patients and members of the public to ensure understanding and acceptability. Furthermore, embedding of research into routine clinical practice, availability of Biobanks and compliance with the 2018 General Data Protection Regulations must be considered in developing any strategy and plan to address this priority.

Linked to the above is the need for establishing national and pan-European networks and shared systems to rapidly identify new pathogens and outbreak cases. Delayed information sharing can lead to delays in outbreak identification. While specialist laboratories and surveillance systems exist, a European wide coordinated approach would be hard to achieve when even national implementation of shared systems was viewed as challenging in countries that have numerous healthcare systems. Alongside the set-up of shared systems, implementation of nationally agreed laboratory protocols is needed. Local laboratories may also not have the required technologies or expertise to identify new pathogens. In Australia, a pediatric enhanced disease surveillance system has been established, and this model may prove useful.[24]

Research recruitment is a further area for discussion. It could be argued that consent requirements for IDP research may not be equivalent to those operating in nonpandemic situations and models of consent require some consideration. Deferred and opt-out consent may provide ethically valid and useful models for some observational IDP research in the emergency setting for example where collection of clinical samples for research takes place at the same time as routine sample collection or if excess sample is used.[15,21,25] Deferred consent is now included in the Clinical Trials Regulation, which is useful for some pandemic-relevant studies; however, there is some conflict in emergency situations.[21] Opt-out consent where study information is publicized at waiting room, hospital and ward level, is implemented in some countries for observational studies, but in others regulatory and data protection agencies do not permit this. Differences in parental consent requirements for IDP research may also complicate IDP research; currently, in some countries, only one parent must sign, whereas in others both parents must give written consent.[26] This may be difficult if a parent is also incapacitated or unavailable in the case of a pandemic. While variable practice in consent requirements poses a challenge in emergency research situations, cultural factors in different European countries must also be carefully considered when aiming for more universally acceptable models. Acceptance and understanding of IDP research and consent scenarios is likely to require wide public education and engagement.

Stakeholder engagement, education and gaining trust are crucial for pediatric IDP research, and again large ID research networks like PREPARE may be ideally placed to negotiate this. Stakeholders may include members of the public, politicians, the media and PHAs. While research to gain patient and public opinions about research has been conducted [27,28], there is a clear need to extend this to pediatric relevant IDP research. A further need is to improve relationships and work more closely with government, as politicians were perceived as disinclined to trust scientific experts. Good media communication also becomes important as the media can influence public opinion of research potentially affecting decisions to participate in research. Closer working with public health agencies, which are among the first responders in a public health emergency such as an ID outbreak, may be critical for pandemic research.

Trial design will be crucial for the pandemic or IDP or outbreak scenario. Trials with outcome-adaptive randomization may be ideally suited to the time-sensitive pandemic setting especially if these are set-up and ready to rapidly respond in the case of an outbreak or pandemic being declared. However, these designs will also need to address some ethical concerns.[29,30] Demonstrating parent and YP acceptability of this study design and providing information to ethics committees is a key to avoid delays in approvals processes.

In the workshop discussions, participants briefly indicated how they had overcome some of the challenges in their ID pediatric studies. It would be useful next step to gather these scenarios in more detail to provide other researchers with knowledge of potential solutions and as evidence to facilitate regulatory approvals.

STRENGTHS AND LIMITATIONS

This study calls attention to a neglected area in pandemic-preparedness, pediatric clinical research. It reflects the viewpoint of pediatric clinician-researchers with experience of pediatric ID research in Europe and an understanding of IDP challenges. Most priorities were common to all participants, and this commonality is a likely indication of generalizability of results to a wider group of pediatric clinician-researchers. Applicability of our initial findings to a broader group was confirmed by the survey results where the majority of respondents agreed on the priorities and proposed only a small number of additions.

Sources of potential bias are the identification of participants, the required response within a limited time frame and responder bias. Only participants attending ESPID were eligible for the workshops and interviews, and it could be argued that our

participants were not representative of all clinician-researchers. Our participants volunteered to participate and may have had particular experiences of problematic issues in conducting pediatric research. Therefore their views may be over-represented and not generalizable to a wider group.

There were some country-specific differences that may be useful to explore in a subsequent study. Describing clear examples of innovative research practice applicable to IDP research would be valuable.

This study identified priority areas for change but did not develop a work plan or specific strategy for addressing each priority need.

CONCLUSIONS

Pediatric clinician-researchers perceived the need for key changes to facilitate pediatric IDP research. The study findings can be used to inform a strategy and action plan addressing the priority needs, to provide expert evidence to International research policy decision-makers, regulators and ethics committees and to lobby for changes.

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