Celebrating Research Participation and Collaboration: Unexplained Hepatitis in Children

Stakeholder Roundtable: Report

1. Overview

The world's first discovery that a severe paediatric hepatitis outbreak in 2022 may have arisen due to co-infection with two viruses, adenovirus and AAV2 in children that possess a certain genetic background was published in Nature in March 2023 (Ho *et al.*). **This publication was a culmination of an outstanding rapid, multi-partner led research response to viral outbreaks and will contribute to future national and global preparedness.** Importantly, it demonstrated the strength of the collaborative links and infrastructure between Scottish academic institutions, the NHS and public health bodies in responding to emerging viral outbreaks. The investigation was led by a team of researchers at the MRC-University of Glasgow Centre for Virus Research (CVR) in collaboration with several academic, clinical and public health organisations across the Scotland and the UK, following the activation of the Clinical Characterisation Protocol authored by the ISARIC4C consortium.

In early 2024, the research team at the CVR organised a thank you event, where key contributors to the investigation and outcomes were invited to hear about the journey 'From Illness to Insight', i.e. from initial clinical observation to the scientific findings and publication. Contributors included clinicians, clinical research teams, public health leads and, importantly, families that took part in the study that led to these findings. One key part of this event was to host a Stakeholder roundtable. This meeting brought together clinical, research and public health leads to discuss reflections and recommendations that may influence clinical practice guidelines in the diagnosis and treatment of paediatric hepatitis. Shortly after the event, a new diagnostic test for AAV2 was made available by NHS England, though more work is needed to improve accessibility and consistency of use in the Four Nations.

Stakeholder Roundtable Attendees

- *Clinicians/clinical research teams:* Rachel Tayler, Louisa Pollock, Paul Henderson, Louise Gannon
- *CVR Research Leads*: Toni Ho, Emma Thomson, Ana Filipe, Massimo Palmarini
- *Public Health Scotland*: Kirsty Roy, Kimberly Marsh
- *Scottish National Blood Transfusion Service*: David Turner
- *ISARIC4C joint chief investigator*: Calum Semple

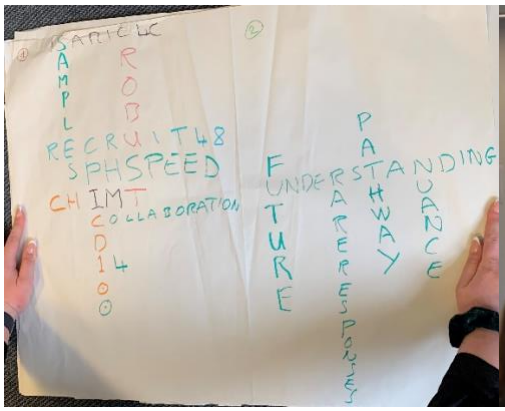
Methods

Stakeholders were split into three groups, each with representation from clinical, research and public health leads. Each group discussed a set of questions relating to at least one of three themes: Highlights and Lessons Learnt, Recommendations and Next Steps.

Questions for discussion:

1. What are you most proud of with this research? OR What went well?
2. What are the key outcomes that could be implemented in clinical practice?

3. What are the key lessons learnt?
4. What are the approaches we could take to assess uptake of this research into clinical practice?
5. Who are the key audiences to target?
6. What questions should we be asking in a survey to clinical teams/policymakers about the future impact of this research?



2. Highlights and Lessons Learnt

This stakeholder roundtable was a fantastic opportunity to bring together leads from the various organisations involved in this outbreak response, not only to consider next steps towards impact but to celebrate the achievements of the study and consortium. It was evident that the teams were extremely proud of the efforts to rapidly respond to this worrying outbreak. Moreover, these efforts highlighted the considerable linked infrastructure, collaborative working and team-driven ethos developed and strengthened by these organisations and is a real asset to the Scottish health and innovation landscape.

Rapid response: The response from initial observation was very quick, due to the existing strong collaborations between academic, NHS and public health organisations as well as clear pathways for action in the ISARIC4C protocol. The coordination across Scotland was excellent and demonstrated a good model for effective cross-organisational working. Notable achievements include: 48-hour turnaround from first call to recruitment of the first patient, clear and rapid case definition, establishing the Public Health diagnostic group, rapid biochemistry response, publication of epidemiology within two weeks and publication of virology within 100 days.

Clinical sample testing and surveillance: Clinical sample testing and background linkage were critical in this outbreak response. There was good communication regarding potential cases as well as coordination of hepatitis screening results from the various health boards (for routine causes of hepatitis, e.g. autoantibodies and viruses associated with paediatric hepatitis). Additionally, there was an extremely strong genetic association identified via HLA typing, which had never been seen before and provided a key breakthrough in understanding susceptibility to hepatitis caused by adenovirus-AAV2 co-infection. Moreover, ensuring linkage of data to epidemiology helped to quickly inform clinical outcomes.

Research outcomes: The outstanding research conducted by the teams at the CVR in collaboration with organisations across the UK led to significant advances in understanding molecular mechanisms

of disease, resulting in this high impact publication in Nature and the development of cross-disciplinary research infrastructure links that can tackle complex clinical research questions quickly and effectively.

Team-led approach: One of the most significant benefits of the consortium was that it comprised a community of team-led, open-minded partners who are willing to work collaboratively across organisations without assumptions of remit or limitation; for example, clinicians who treated the children were directly involved in recruitment, and coordinated with research teams to arrange for research blood tests at the same time as clinical blood tests in order to reduce burden on the children. This ethos was critical to the success of the research investigation and the experiences of children and families during this stressful and difficult situation.

Lessons learnt: The groups also addressed issues faced with this study and effective responses to the outbreak. Limitations identified during this investigation included lack of specific diagnostic testing, poor access to toxicology expertise, the need for stronger direct links between PHS and each speciality involved in the clinical pathway and increased knowledge of existing expertise and accessibility to sharing advice, experiences and best practice. There were also concerns of inconsistencies between nations and clinical organisations in testing and processing of samples to gain key information quickly.

3. Recommendations

A major goal for this consortium is to influence changes to clinical practice in the diagnosis and management of paediatric hepatitis. Further research endeavours are required to better understand the mechanism of infection and illness and develop optimal diagnostic and management pathways for children with possible AAV2-associated hepatitis. Therefore, it is difficult to identify specific recommendations at this stage that would lead to policy changes. Nevertheless, this investigation should be documented as a case study and accessible to organisations UK-wide as an exemplar of an effective silo-free response to outbreaks of unknown origin. Practical recommendations based on learnings from this investigation are summarised below:

Clinical:

- Highlight the outbreak and results of research investigations to wider clinical communities, such Grand Rounds, putting up posters in outpatient clinics/A&E departments, and present at conferences attended by paediatricians.
- Develop guidance on the use of steroids in treatment of AAV2-associated hepatitis.
- Develop a clear pathway to investigation of rarer cases of hepatitis in children: diagnosis of unexplained hepatitis cases involves time consuming exclusion of other more common causes and can be detrimental to patient outcomes.
- Ensure access to virology leads at all major hospitals to advise on critical diagnostic requirements for effective early intervention.

Laboratory:

- Standardise diagnostic testing for AAV2 in paediatric hepatitis including genomics and whole blood testing.

- Introduce robust sample management across clinical laboratories nationally, including defined standardised protocols for early acquisition and storage and for speed of transfer to research laboratories.
- Implement metagenomic testing as standard of care – this is an incredibly powerful approach informing clinical decision-making in infectious disease management.

Public Health/Academic:

- Develop a Four-Nations approach to collaborative working between research, NHS and public health to ensure nationally standardised approaches to care pathways, avoiding traditional silos in clinical remit.
- Improve access to toxicology capabilities within public health organisations.
- Create a directory of experts easily available online that would support the need to understand where expertise and knowledge can be accessed.

4. Next steps

Firstly, it will be important to disseminate information about this investigation and then evaluate the current understanding of these findings in the wider healthcare communities, as well as thoughts on the recommendations identified in this report. This will be done via a survey targeted at key stakeholders and audiences including (but not limited to):

- Collaborators
- Liver units
- Royal College of Paediatrics and Child Health (RCPCH)
- General and Adolescent Paediatric Research Collaborative UK and Ireland (GAPR-UKI)
- British Association of General Paediatrics
- British Society of Paediatric Gastroenterology, Hepatology and Nutrition
- British Paediatric Allergy, Immunity and Infection Group
- Scottish Paediatric Society

A follow up discussion will be needed to shape the survey, but it will be driven by questions around understanding the importance of the findings and subsequent diagnostics tests available and feasibility of implementing the recommendations listed above.

Additionally, it will be important to develop a strong public involvement initiative to ensure affected families can inform clinical practice and co-create effective pathways that support positive outcomes and patient experience. The research team will seek funding opportunities to develop these initiatives to support a pathway to impact.