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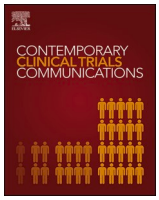

Recruitment and retention of pediatric participants for pandemic preparedness research: Experience from the PREMISE EV-D68 Pilot Study

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ABSTRACT

Recruitment and retention are challenges for prospective pediatric cohort studies, particularly those involving serial venipunctures. We investigated factors underlying enrollment and retention in the Pandemic Response Repository through Microbial and Immune Surveillance and Epidemiology (PREMISE) Enterovirus D68 (EV-D68) Pilot Study, a multicenter prospective longitudinal cohort study assessing the utility of immunologic surveillance for pandemic preparedness. This study enrolls children ≤10 years for two blood draws, pre- and post-EV-D68 season, separated by 6–18 months. Overall, 174 children were enrolled in Cohort 1 of the study and 120 (69 %) of children completed the study, with follow-up blood samples obtained from 101 (58 %) of participants. Families were primarily motivated to participate by a desire to help other children, advance science, and better prepare for the next pandemic. Adding research blood draws to clinically indicated blood draws improved enrollment, and multiple study touch points facilitated retention. These findings can be applied to improve recruitment and retention in future pandemic preparedness efforts and longitudinal pediatric cohort studies.

1. Introduction

Efforts to prepare for and combat the next pandemic are crucial in preventing a potentially devastating global catastrophe. Pandemic preparedness efforts encompass a wide range of activities that include the development of on-the-shelf vaccines/therapeutics and understanding the seroepidemiology of critical pathogens. One such effort, as described in the National Institute of Allergy and Infectious Diseases (NIAID) Pandemic Preparedness Plan [1], is the Pandemic Response Repository: Microbial and Immune Surveillance and Epidemiology (PREMISE) program at the NIAID Vaccine Research Center (VRC) [2].

The PREMISE Enterovirus D68 (EV-D68) Pilot Study was conceived as a test case study within the PREMISE program [3]. The objective of this multicenter prospective longitudinal pediatric cohort observational study is to assess the utility of immunologic surveillance for pandemic preparedness using EV-D68. However, recruitment and retention represent major challenges for pediatric studies, particularly those involving serial blood samples [4,5]. Inadequate recruitment and low retention can impact critical study components such as statistical power, study validity, study duration, and overall costs [6]. Multiple factors contribute to inadequate recruitment and retention; these include time constraints, social determinants of health, no direct benefit, perceived burden/discomfort of procedures, and mistrust of scientific research [6–9]. Therefore, determining strategies for successful recruitment and retention are critical for the success of the PREMISE program and similar studies in difficult-to-enroll populations such as young children.

The purpose of this paper is to highlight our experiences and lessons learned in the recruitment and retention of pediatric participants for the

Abbreviations: EV-D68, Enterovirus D68; NIAID, National Institute of Allergy and Infectious Diseases; PREMISE, Pandemic Response Repository through Microbial and Immune Surveillance and Epidemiology; VRC, Vaccine Research Center.

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first cohort of the PREMISE EV-D68 Pilot Study. We aimed to characterize factors associated with enrollment and retention to inform future study cohorts and future pediatric studies.

2. Methods

2.1. Study design

This paper focuses on recruitment and retention data collected as part of the PREMISE EV-D68 Pilot Study, a multicenter, prospective longitudinal cohort observational study with a target enrollment of 500 children over three cohorts [3]. Enrollment occurred at the University of Colorado Anschutz Medical Campus, University of North Carolina at Chapel Hill, and Weill Cornell Medicine. Inclusion criteria included age ≤10 years and weight ≥8 kg. Exclusion criteria included conditions putting a participant at risk for study procedure completion (e.g. anemia) and having a household contact already enrolled in the study. Consent was obtained from parents/guardians and assent from children ≥7 years. This study was approved by the Colorado Multiple Institutional Review Board which served as the single IRB for the study.

2.2. Recruitment

Eligible children admitted inpatient and those with scheduled outpatient general/subspeciality clinic visits were approached. Parents/guardians were asked verbally an open-ended interview question about reasons for choosing to or not to participate. These reasons, recruitment location, age group, and blood draw access were documented using the secure HIPAA-compliant Research Electronic Data Capture application hosted at the University of Colorado [10,11].

2.3. Study procedures

The study consisted of three visits: two required in-person pre- (Visit 1, January–June 2022) and post- (Visit 3, January–June 2023) EV-D68 season and one optional during EV-D68 season (defined as July–December 2022, Visit 2). At required Visits 1 and 3 participant information (e.g., demographics, medical history) and a blood sample were collected. Between the two required visits, families could elect to participate in "Visit 2" consisting of optional every two-week symptom surveys sent July–December focused on capturing interim respiratory illnesses through multiple scheduled touchpoints with research team members. Parents completed these surveys via phone, text, or email based on preference. A positive symptom survey prompted research team members to ask parents to collect a nasal swab from their child within 14 days of symptom onset using a pre-packaged kit shipped to their residence and mailed back to the team. Total study duration for participants was six-to-18-months depending on when participants enrolled/followed-up. Biospecimens were banked at the VRC. Participants were reimbursed $50 per required study visit and an additional $50 for participating in optional Visit 2. Descriptive statistics (percentage, median, interquartile range (IQR)) for demographic variables and procedure completion were conducted using SAS Analytics Software (Version 9.2). Reasons for/not enrolling were grouped into common themes by two study team members and adjudicated as needed by a third member.

3. Results

3.1. Recruitment

Target enrollment for Cohort 1 was 166 participants. Among 488 eligible children approached, 174 (36 %) consented and enrolled in Cohort 1. Among consented participants, 156 (90 %) provided a Visit 1 blood sample. Demographics of enrolled participants reflected the diversity of populations in the catchment areas. The median age of enrolled participants was 3 years (IQR: 1.92, 6.37) and slightly more males enrolled than females (55 % vs 45 %). Among 173 enrolled participants providing data on reasons for participating, key motivating factors included wanting to help other children, contribute to science, and help prevent the next pandemic (Fig. 1a). Amongst those approached who did not consent, reasons for declining most often included concerns about a blood draw, not interested in research, and being too stressful of a time. Notably, families did not express major concerns about specimen banking, genetic testing, or confidentiality (Fig. 1b).

Regarding the influence of blood draw method on enrollment, we found that having an in-dwelling intravenous line (among inpatients) or needing a new venipuncture to participate in the study led to practically equal enrollment proportions (Fig. 2). Adding the research blood draw to an existing clinically indicated blood draw led to more participants enrolling (Fig. 2).

3.2. Retention

Visit 3 was completed by 120 (69 %) participants with follow-up blood sample obtained from 101 (58 %) participants; three participants withdrew from the study during follow-up. With regards to race, 100 % of American Indian/Alaskan Native participants returned for Visit 3 with a blood sample collected compared to 66.7 % of Black/African American, 63.2 % identifying as more than one race, 62.5 % of Asian, and 53.8 % of White participants. In terms of ethnicity, 60.5 % of Non-Hispanic/Non-Latino participants returned for Visit 3 with a blood sample collected versus 50.9 % of Hispanic/Latino participants.

For optional procedures, 136 (78 %) participants in Cohort 1 consented into optional Visit 2. Among the participants who did not withdraw from the study, 127 of 134 (94 %) responded to at least one survey. Participants who opted into optional Visit 2 were more likely to return for Visit 3 with a blood draw than those who did not (81 % vs. 74 %, Table 1).

4. DISCUSSION/CONCLUSIONS

Despite the challenges of recruitment and retention for pediatric studies, we exceeded target enrollment for Cohort 1 of the PREMISE EV-D68 Pilot Study. Additionally, we attained a high retention rate (69 %) for a longitudinal follow-up visit and successfully obtained a second blood sample from 101 (58 %) participants. Though participation did not directly benefit the child, families were motivated to enroll primarily due to a desire to help others and contribute to science. This demonstrates that strategies focused on these societal benefits can lead to successful pandemic preparedness research recruitment.

The most common reason for reluctance to participate involved concerns over venipuncture, reflecting similar participation barriers noted in other studies [5]. Adding research blood draws to clinically-indicated blood draws to minimize venipunctures was a useful strategy to overcome this barrier. Additionally, given busy schedules and for convenience, it was advantageous to coordinate study visits with clinical visits to facilitate recruitment and retention. For subsequent cohorts we expanded recruitment to more outpatient settings to increase efforts to provide convenient options for research visits coordinated with already scheduled clinical visits and clinically-indicated venipunctures.

Loss to follow-up remains a major challenge for pediatric longitudinal studies [6,7]; however, we demonstrated a nearly 70 % retention rate (58 % with a second blood sample obtained) during the follow-up period. We found that continued, frequent contact with participants via multiple touch points was associated with improved study retention. Given this, we adapted our study to incorporate the optional surveys to be required for future cohorts to improve retention. Future studies requiring longitudinal follow-up should consider timing/frequency of touch points with the research team over the study period to help

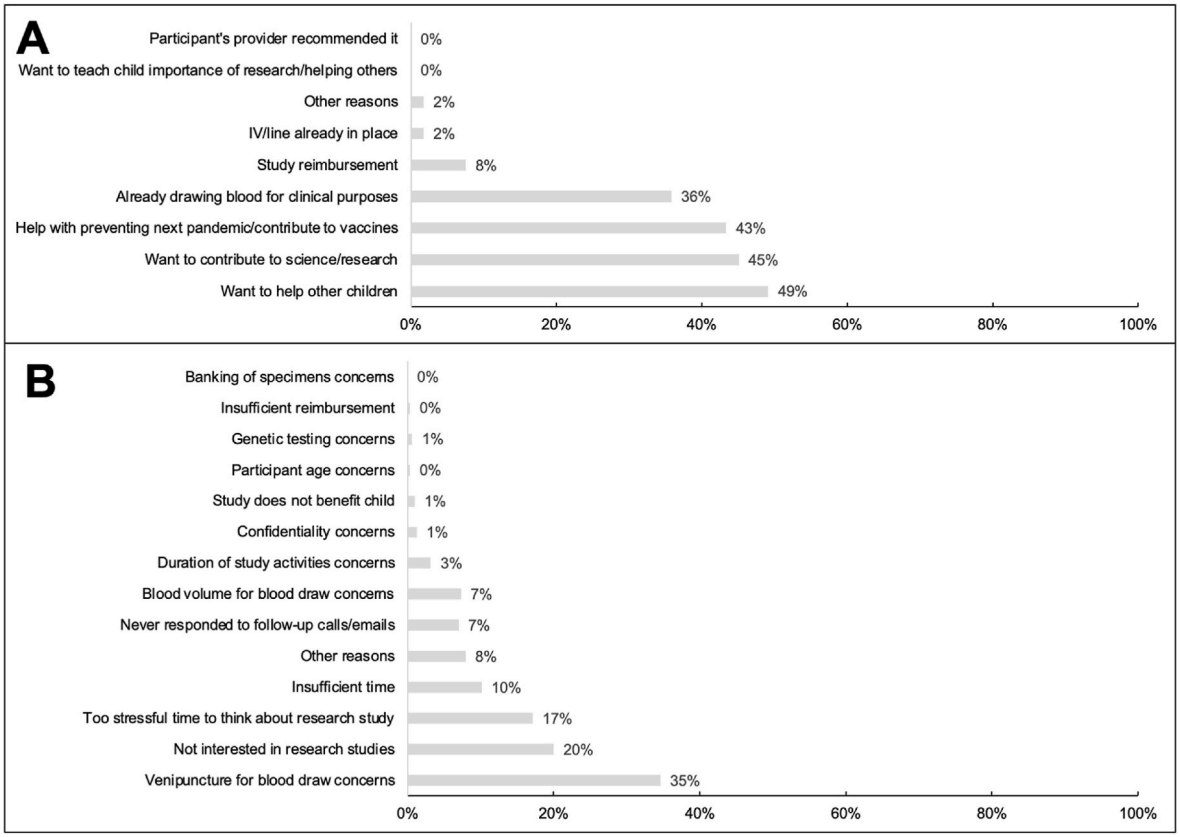

Fig. 1. Reasons for consenting to enroll (A) or declining to enroll (B) in the PREMISE EV-D68 Pilot Study. A) Percentage among N = 173 enrollees with data captured (could cite more than one reason). B) Percentage among N = 315 declines (could cite more than one reason).

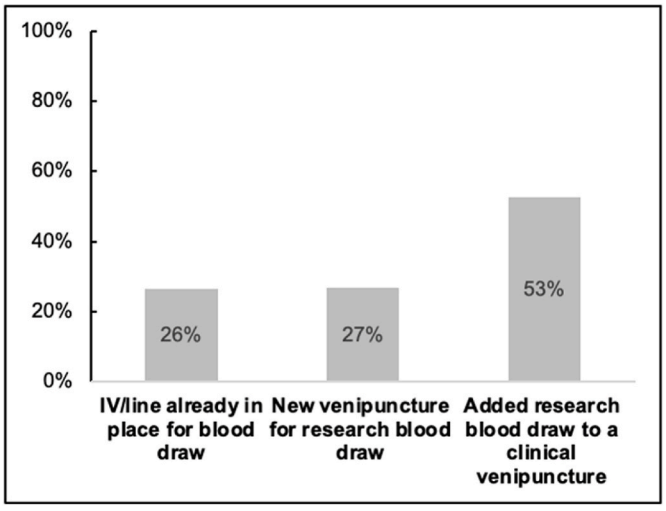

Fig. 2. Blood draw type influence on enrollment. Percentage of patients approached that were enrolled by each blood draw type. Excludes 1 blood draw type not reported.

mitigate loss to follow-up over prolonged time periods without research team contact.

We recognize this study has limitations. We did not inquire about reasons participants did/did not return for Visit 3; therefore, there may be factors not related to our study design that contributed to retention. Our study involved two venipunctures separated six-to-18-months apart, so this may not be fully generalizable to studies requiring more frequent study procedures. However, our ability to recruit and retain a diverse cohort of participants including young children over an extended time provides important insights into how similar challenges can be overcome with pediatric longitudinal studies, especially those requiring enrollment and venipuncture of very young children.

Though prospective longitudinal pediatric cohort studies face significant challenges with recruitment and retention, the success of the PREMISE EV-D68 Pilot Study demonstrates the feasibility of this study design for pandemic preparedness research in children. Working with families to facilitate study participation by providing convenient research visits/procedures coordinated with clinical visits and clinically-indicated blood draws, and maintaining frequent contact with research participants were all helpful for recruitment and retention. These lessons will be applied to future PREMISE EV-D68 Pilot Study cohorts and can be applied to future pandemic preparedness efforts and longitudinal pediatric cohort studies.

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CRediT authorship contribution statement

Hai Nguyen-Tran: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Alicen B.**

Table 1
Comparing Cohort 1 participants who returned for Visit 3 with a blood draw versus those who did not return for Visit 3 or returned for Visit 3 but without a blood draw.

	Returned for Visit 3 with blood draw obtained (N = 101)	Did not return for Visit 3 or returned for Visit 3 with no blood draw obtained (N = 70)[a]
Demographics		
Age Group, n (%)		
0 to <2 years	26 (26 %)	17 (24 %)
2 to <4 years	30 (30 %)	24 (34 %)
4 to <6 years	13 (13 %)	12 (17 %)
6 to <8 years	14 (14 %)	9 (13 %)
8 to ≤10 years	18 (18 %)	8 (11 %)
Sex, n (%)		
Male	55 (54 %)	40 (57 %)
Female	46 (46 %)	30 (43 %)
Race, n (%)[b]		
American Indian or Alaska Native	5 (5 %)	2 (3 %)
Asian	9 (9 %)	4 (6 %)
Black or African American	31 (31 %)	17 (24 %)
Native Hawaiian or Other Pacific Islander	0 (0 %)	0 (0 %)
White	59 (58 %)	48 (69 %)
Unknown or not reported	8 (8 %)	9 (13 %)
Ethnicity, n (%)		
Hispanic or Latino	27 (27 %)	24 (34 %)
Not Hispanic or Latino	72 (71 %)	46 (66 %)
Unknown or Not Reported	2 (2 %)	0 (0)
Contact		
Preferred language for contact, n (%)		
English	96 (95 %)	64 (91 %)
Spanish	3 (3 %)	6 (9 %)
Unknown or Not Reported	2 (2 %)	0 (0)
Preferred method of contact, n (%)		
Phone-Text	64 (63 %)	43 (61 %)
Phone-Call	0 (0 %)	0 (0)
Email	37 (37 %)	27 (39 %)
Optional Procedures		
Optional visit 2 participation, n (%)		
Yes	82 (81 %)	52 (74 %)
No	19 (19 %)	18 (26 %)
Optional Visit 2 participation and completed at least one survey, n (%)		
Yes	79 (96 %)	48 (92 %)
No	3 (4 %)	4 (8 %)
Procedures		
Pre-EV season blood draw obtained, n (%)		
Yes	90 (89 %)	64 (91 %)
No	11 (11 %)	6 (9 %)
Completed post-EV Season survey, n (%)		
Yes	101 (100 %)	19 (27 %)
No	0 (0 %)	51 (73 %)

[a] Excludes 3 withdrawals, 1 from each site.
[b] More than one race could be selected.

Spaulding: Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Kevin Messacar:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization. **Matthew R. Vogt:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Perdita Permaul:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Daniel C. Douek:** Writing – review & editing, Funding acquisition, Conceptualization. **Abe Mittelman:** Writing – review & editing, Funding acquisition, Conceptualization. **Careese Thompson:** Writing – review & editing, Data curation. **Sandy Grubbs:** Writing – review & editing, Data curation. **Christine Magana:** Writing – review & editing, Data curation. **Michelle L. Hernandez:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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