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Exploring the relationship between polio type 2 serum neutralizing antibodies and intestinal immunity using data from two randomized controlled trials of new bOPV-IPV immunization schedules

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ABSTRACT

Background: Inactivated polio vaccine (IPV) is now the only source of routine type 2 protection. The relationship, if any, between vaccine-induced type 2 humoral and intestinal immunity is poorly understood.
Methods: Two clinical trials in five Latin American countries of mixed or sequential bOPV-IPV schedules in 1640 infants provided data on serum neutralizing antibodies (NAb) and intestinal immunity, assessed as viral shedding following oral mOPV2 challenge. Analyses with generalized additive and quantile regression models examined the relationships between prechallenge NAb titers and proportion, duration and titers (magnitude) of viral shedding.
Results: We found a statistically significant ($p < .0001$) but weak relationship between NAb titer at the time of mOPV2 challenge and the Shedding Index Endpoint, the mean $\log_{10}$ stool viral titer over 4 post-challenge assessments. Day 28 post-challenge shedding was 13.4% (8.1%, 18.8%) lower and the Day 21 post-challenge median titer of shed virus was 3.10 $\log_{10}$ (2.21, 3.98) lower for subjects with NAb titers at the ULOQ as compared with LLOQ on day of challenge. Overall, there was a weak but significant negative relationship, with high NAb titers associated with lower rates of viral shedding, an effect supported by subset analysis to elucidate between-country differences.
Conclusions: Taken alone, the weak association between pre-challenge NAb titers following IPV or mixed/sequential bOPV/IPV immunization and differences in intestinal immunity is insufficient to predict polio type 2 intestinal immunity; even very high titers may not preclude viral shedding. Further research is needed to identify predictive markers of intestinal immunity in the context of global OPV cessation and IPV-only immunization.

1. Introduction

The Global Polio Eradication Initiative is on the verge of achieving its goal of interruption of wild polio virus (WPV) transmission [1]. To accelerate the progress made and to ensure transmission of all polioviruses is effectively interrupted, the Polio Eradication & Endgame Strategic Plan recommended the adoption of new polio vaccination schedules worldwide [2]. The first step was a switch in April 2016 from trivalent oral poliovirus vaccine (tOPV) to bivalent OPV (bOPV, types 1 and 3) in primary immunization series accompanied by introduction of at least one dose of inactivated poliovirus vaccine (IPV) in OPV-using countries.

Both humoral and mucosal immunity are important for polio eradication strategies [3]. Humoral immunity, measured as neutralizing antibody titers in serum post-vaccination, is an indicator of long-lasting individual protection against paralysis caused by

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poliovirus. Intestinal immunity, which develops after mucosal infection with wild or vaccine polioviruses and provides temporary protection against person-to-person transmission, is more difficult to assess [3–6]. Typically, pharyngeal or intestinal mucosal immunity are measured as the extent of viral excretion following an oral challenge with live attenuated vaccine. In settings of poor hygiene and sanitation, intestinal mucosal immunity is considered more relevant than pharyngeal immunity, and therefore most studies have focused on intestinal excretion of challenge viruses [3,7]. Alternative methods to assess intestinal mucosal immunity, such as directly measuring specific antibodies in excreta or circulating antigen-specific antigen-secreting cells (ASC) that express receptors for mucosal homing [5,6,8], are under evaluation with the promise of potentially replacing the accepted method of measuring shedding in the future.

IPV is now the only routinely available source of polio type 2 immunity. Although the per-dose effectiveness of IPV in producing humoral immunity as measured by seroconversion and neutralizing antibody (NAb) titers has been well established, its relationship to primary intestinal mucosal immunogenicity is limited and less clearly understood. Of interest, in relation to the global switch from tOPV to bOPV is the impact on type 2 intestinal immunogenicity from one or more dose(s) of IPV. Recent randomized controlled trials exploring bOPV–IPV schedules followed by mOPV2 challenge have concluded that although regimens including IPV reduce the duration and titer of viral shedding, they tend to be associated with limited overall impact on virus shedding, particularly during the time that virus excretion peaks, at around 7 days following oral challenge [9–11].

As there are often significant variations in levels of serum NAbs within vaccination regimens, we used data on polio type 2 circulating antibodies and virus excretion dynamics obtained from recent randomized controlled trials conducted in Latin America to directly explore a potential relationship between individual pre-challenge serum NAb levels and intestinal immunity that should add value to the evidence base on the new schedules of polio vaccination.

2. Materials and methods

Data were derived from two recently published randomized controlled trials performed in 2013–2014: study IPV001, performed in Colombia, the Dominican Republic, Guatemala and Panama, and registered on clinicatrials.gov as NCT01831050 [11], and study IPV002, performed in Chile and registered as NCT01841671 [9]. These were the only trials that met the three criteria we considered important to simulate an OPV2 cessation era for our analysis: (1) mixed or sequential primary series of IPV and bOPV; (2) mOPV2 used as a challenge vaccine to elicit type 2 excretion dynamics; (3) assessment of both duration and extent of viral shedding for 28 days following oral challenge as well as proportion of the challenged population shedding virus. Both trials were approved by all relevant national and institutional ethical bodies. For IPV001 the Centro de Estudios en Infectologia Pediatrica, Cali, Colombia; Hospital Maternidad Nuestra Señora de la Altagraci, Santo Domingo, Dominican Republic; Hospital Roosevelt Guatemala, Guatemala City, Guatemala; and Hospital del Niño, Panama City, Panama, and the Colorado Multiple Institutional Review Board and the Western Institutional Review Board, and for IPV002 the Faculty of Medicine at the University of Chile, the Servicio de Salud Metropolitano Norte, and the Servicio de Salud Metropolitano Sur, all located in Santiago, Chile. For our analysis, we combined data from all subjects who received bOPV and or IPV in the primary vaccination series from IPV001 and IPV002. In IPV001, data for IPV from three different manufacturers were combined within vaccination regimen, wherever relevant, and additional data for some subjects who received only three doses of tOPV were included as controls.

The primary endpoint used for this analysis was a shedding index endpoint (SIE) [9,11], computed for each subject as the average of the titers of shed virus in stool samples ($\log_{10}$ $CCID_{50}$/g) collected on days 7, 14, 21, and 28 post-mOPV2 challenge. Viral titers were assessed in stool samples that had detectable OPV using RT-PCR, with a viral titer of 0 recorded for samples negative for OPV. Defined in this way, the SIE captures both the magnitude and duration of viral shedding. Also measured were the titers of serum neutralizing antibody (NAbs) immediately prior to mOPV2 challenge. All subjects from both studies with sufficient data available to compute the SIE and pre-challenge NAbs were used for this analysis. Both the SIE and NAb titer values are subject to censoring at their respective lower and upper limits of quantitation (2.5 and 10.5 for NAbs [$\log_2$], 2.75 and 8.25 [$\log_{10}$] for SIE) as the assay workflows were set up for specific ranges of dilutions and values outside of these ranges were not captured, resulting in the described LLOQ and ULOQ. If a positive sample had a titer below the lower limit of quantitation (LLOQ), this limit was used for the data point. All other limits of quantitation were used as data points for values exceeding them.

2.1. Statistical methods

Regression models were fitted to endpoints using NAb titer and/or nominal stool collection day as predictors to describe the relationship between the likelihood and extent of viral shedding as a function of NAbs on day of challenge. Shedding positivity at each day post-challenge was modelled using an additive generalized linear model (GAM), implemented with the mgcv package [12] for R [13], using a binomial error structure and separate smooth functions of NAb titers for each post-challenge collection day, in addition to a model which also incorporates an interaction between NAb titers and (numeric, continuous) post-challenge collection day. The smoother basis dimension and model structure was selected via analysis of deviance for nested models, and Akaike's Information Criterion (AIC) elsewhere [14]. The quality of model fit is described with the area under the curve (AUC) of the receiver operating characteristic (ROC) curve.

The titer of shed virus at each post-challenge day was modelled using median regression, implemented in the quantreg package for R [15], and utilizing a cubic spline basis for the NAb predictor interacted with post-challenge collection day as a factor variable. The basis dimension and model structure was selected via Wald tests for nested models [16], and AIC elsewhere. The SIE was modelled in the same manner as titer of shed virus, with omission of the factor for day, and 4 degrees of freedom for the spline, selected via Wald tests for nested models, and AIC elsewhere. The quality of model fit is described by a goodness of fit measure for quantile regression [17], and expressed as percent reduction in unexplained variation by a more complex model relative to a simpler model.

To evaluate inter-country differences in the relationship between pre-challenge type 2 serum NAbs and viral shedding, due, perhaps, to different levels of passive type 2 exposure in the different study locations, a subset analysis of IPV001 data only was performed. IPV002 data were excluded to avoid confounding of country with regimen and timing; as randomization in IPV001 was balanced across country, the influence of regimen is not confounded with country in this subset. For all models, the NAb predictor was used in two different methods. The first considered the observed NAbs, using the limits of quantitation as observed data. The second method involved posing a pair of models for values above and below the limit of quantitation, respectively, as a sensitivity measure for the influence of this censoring. This second method involved repeatedly simulating the censored values from

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