Summary of PRELIMINARY results ahead of print:
Immunogenicity of mOPV2 administered as 1-drop or 2-drops

Background

Africa has experienced several outbreaks of circulating vaccine-derived poliovirus type 2 (cVDPV2) since the switch from trivalent oral poliovirus vaccine (tOPV) to bivalent (bOPV) without the type 2 component [1]. The scope and number of these outbreaks have been higher than what had been predicted. Therefore, a stockpile of monovalent OPV type 2 (mOPV2) that was created to respond to these outbreaks is now running low. GPEI is at risk of exhausting all available mOPV2 stock in early 2020. While new mOPV2 manufacturing capacities are being explored; and while development of new genetically stable OPV2 vaccine (nOPV2) is accelerated, alternative strategies to stretch existing supplies of mOPV2 are being explored. One such strategy is use of one drop of the vaccine instead of two drops as an immunizing dose. Here we present preliminary results from a trial conducted in Mozambique between March and July 2019 on comparison of immunogenicity of mOPV2 administered as 1-drop or 2-drops.

Scientific Justification

The recommended titer of Sabin type 2 virus in one dose (2 drops) of tOPV or mOPV2 is 10^5 +/- 0.5 log TCID 50 (50% Tissue culture Infective Dose). But the testing results show that the antigenic content is exceeded in most batches by 2-4 times of this minimum cut off.

This “overdose” of virus content is built in intentionally in the final formulated mOPV2 batches to compensate for any loss of titre with heat exposure and as well as for variation in testing results. We believe that at least double the quantity of Sabin virus above the standard recommended content remains up to the point of administration.

We therefore hypothesized that half of the conventional dose of 2 drops of the vaccine (i.e. 1-drop) will provide sufficient immunogenicity while providing opportunity to successfully vaccinate double the amount of children with the same amount of vaccine.

Methods

We enrolled children between the ages of 9 and 22 months. These children were naive to live type 2 poliovirus. Some of them received one dose of IPV prior to this study.

The study design was a parallel, open label, two-arm, randomized controlled trial where one arm received one drop of mOPV2 and the other arm received 2 drops. This was a non-inferiority trial to demonstrate non-inferiority with delta=10%.

Blood samples were collected at visits 1 (prior to mOPV2 administration) and at visit 2 (one month post mOPV2 administration). The samples were transported in cold chain to CDC Atlanta, USA, tested using standard micro-neutralization assay to measure titers of antibodies against poliovirus types 1, 2 and 3.

The primary outcome was seroconversion which was defined as change from non-detectable to detectable antibodies in children with no detectable antibodies at visit 1 (baseline). If children had detectable antibodies at baseline, boosting was calculated which was a 4-fold rise in antibody titer from visit 1 to visit 2. Immune response was defined as either seroconversion or boosting [2].

The study coincided with the mOPV2 campaign in Mozambique in response to cVDPV2 outbreak in that country. This was done to satisfy containment requirements regarding use of mOPV2. This provided a limitation on the number of children we were able to enroll; which in the end limited the power of the study.

Results

Baseline characteristics of the study population are in Table 1.

Table 1: Baseline characteristics

Baseline characteristics	1-drop		2-drops	
Median Age in months, median, (IQR)	14, (11-18), n=184		14, (11-17), n=191	
Sex, (Male) (n/N %)	n/N 92/184	% 50.0	n/N 104/191	% 54.2
bOPV dose history (based on cards) 0 doses 1-3 doses >3 doses	 11/163 76/163 76/163	 6.8 46.6 46.6	 4/159 75/159 80/159	 2.5 47.2 50.3
IPV history (based on cards) Yes	 106/138	 76.8	 114/133	 85.7
Diarrhea in the 24 hours before visit 1	1/182	0.5	3/190	1.6
Median baseline titers Type 1* Type 2* Type 3*	 ≥10.5 (10.2-≥10.5) 3.3 (<3-3.5) 9.8 (9.2-10.2)		 10.2 (10.2-≥10.5) 3.2 (<3-3.5) 9.8 (9.5-10.2)	

*Note: Bootstrap confidence intervals

Table 2 provides the primary outcome findings. The seroconversion rates in 1-drop was (35/54) 65% (95% CI: 51 to 77) while 2-drops was (50/74) 68% (95% CI: 56 to 78). The difference between 1-drop and 2-drops seroconversion was -3% (-19 to 14). Boosting was 45% (33 to 57) in 1-drop; 52% (39-65) in 2-drops (Difference = -7% (-24 to 11)); Immune response: 54% (45 to 63) in 1-drop vs 60% (56 to 73) in 2-drops (difference = -7% (-19 to 5)).

There were no differences observed in the distribution of pre and post titers of type 2 antibodies between the one- and two-drop groups.

Table 2: Primary outcome

Results	1-drop			2-drops			Difference (95% CI)
	%	95%CI	n/N	%	95%CI	n/N	
Seroconversion	**64.8**	50.6 – 77.3	35/54	**67.6**	55.7 – 78.0	50/74	-2.8 (-19.4, 13.8)
Boosting	**45.1**	33.2 – 57.3	32/71	**51.6**	38.6 – 64.5	32/62	-6.5 (-23.5, 10.5)
Immune response	**53.6**	44.5 – 62.6	67/125	**60.3**	56.1 – 73.4	82/136	-6.7 (-18.7, 5.3)

Note: Only those samples that could further enhance protection (boost further) were considered for the above analyses (titers above 362 (or 8.5log2) were excluded for the above analyses).

mOPV2 is usually administered in 3 rounds of outbreak response vaccination campaigns. Table 3 shows what difference in immunogenicity could be assumed assuming the same rates of immune response and 100% coverage (Table 3). It was found that the projected immunogenicity loss after three rounds of mOPV2 vaccination was low (between 1% to 4%).

Table 3: Projected immune response after three rounds of vaccination

	Immune Response			Seroconversion only		
mOPV2 rounds	1-drop immune response	2-drops immune response	Diff (%)	1-drop immune response	2-drops immune response	Diff (%)
	%	%		%	%	
Round 1	53.6	60.3	-6.7	64.8	67.6	-2.8
Round 2	78.5	84.2	-5.7	87.6	89.5	-1.9
Round 3	90.0	93.7	-3.7	95.6	96.6	-1.0

There were no severe adverse events related to the study procedures observed.

Interpretation and program impact

Immune response was 53.6% (CI95%: 44.5 – 62.6) vs 60.3% (CI95%: 56.1 – 73.4) for 1 drop and 2 drops respectively. The 10% non-inferiority hypothesis could not be rejected. However, after 3 mOPV2 rounds the projected population immunity will be very similar regardless of 1 and 2 drops (difference in population immunity <2%).

As previously demonstrated, development of mucosal immunity is closely correlated with seroconversion after OPV therefore we assume same mucosal response after 1 or 2 drops of mOPV2.

This study suggested that by administering one instead of two drops of mOPV2, we may lose little in terms of immune response while preserving precious vaccine supplies.

References:

1. GPEI-Global synchronisation and the switch [Internet]. [cited 2019 Aug 29]. Available from: http://polioeradication.org/news-post/global-synchronisation-and-the-switch/

2. Cáceres VM, Sutter RW. Sabin monovalent oral polio vaccines: review of past experiences and their potential use after polio eradication. Clin Infect Dis Off Publ Infect Dis Soc Am. 2001 Aug 15;33(4):531–41.