

Cessation Risk Assessment Meeting, June 13-14, 2017: Summary

Attendees:

BMGF: Jay Wenger, Ananda Bandyopadhyay, Apoorva Mallya, John Modlin (via phone), Arie Voorman (secretariat)

CDC: Mark Pallansch, Steve Wassilak, John Vertefeuille, Steve Cochi

UNICEF: Phil Smith, Ian Lewis

WHO: Rolland Sutter, Graham Tallis, Arshad Quddus, Hiro Okayasu, Ondrej Mach (via phone)

Imperial College: Nick Grassly, Natalie Molodecky, Isobel Blake

IDM: Hil Lyons, Mike Famulare, Steve Kroiss, Kevin McCarthy

Kid Risk: Rad Tebbens, Kim Thompson

Independent: Brent Burkholder

Key Outcomes:

1. OPV2-Cessation progress, based on data available to date

Summary:

- Isolation of Sabin 2 strains rapidly declined following the switch in most countries, based on available environmental and AFP surveillance data, and in the past six months most countries have not isolated any Sabin 2 or VDPV2.
- However, there have been 5 cVDPV2 outbreaks that likely originated from vaccine used before OPV2 cessation, compared to 3 or fewer cVDPV2 outbreaks which were forecast by IDM and used by the GPEI for budget and vaccine planning. These occurred largely in areas which had a high rate of VDPV emergencies in the pre-cessation era, and likely had insufficient tOPV immunization prior to the switch.
 - Stopping these and possible future cVDPV2 outbreaks with an aggressive mOPV2 response should be a priority for the GPEI. Failure of the initial outbreak response will result in the need for more prolonged and possibly larger responses made more difficult by limited availability of mOPV2 and declining mucosal immunity to Type 2 poliovirus (See key point #2).
 - In addition to the 5 cVDPV2 outbreaks that likely originated from vaccine used before OPV2 cessation, 1 cVDPV2 outbreak may have originated from unauthorized tOPV use after OPV2 cessation, which highlights the need for further efforts to remove tOPV from all vaccine supply chains.
- The CRTT anticipates fewer new VDPV2 emergencies in the coming year due to vaccine used in the pre-switch era. However, the number of new emergencies from any source will likely be higher than originally forecast due to the need to use mOPV2 to stop serotype 2 transmission in some areas and the possibility of unauthorized tOPV use leading to cVDPV2s, and the GPEI should be prepared for at least 1 large scale mOPV2 response in a new area in addition to ongoing responses to current outbreaks.
- Maintaining a current mOPV2 stockpile of 150mds of finished mOPV2 and 500mds of bulk mOPV2 appears adequate for outbreak response over the next 2-3 years, unless the GPEI fails to use the available mOPV2 stockpile to stop outbreaks. Long-term vaccine forecasts will be developed depending on further evaluation of scenarios the program will need to be prepared for (region or country-wide responses, regional or global OPV2 re-introduction, etc).

- Based on the above review of the data, it is too early to conclude whether the program is on track to succeed in stopping all Type 2 transmission following the switch. The outcome of the current round of outbreak responses is unclear, and additional epidemiologic evaluation will be critical over the next 6-12 month period.

Discussion

Isolation of Type-2 poliovirus declined dramatically after tOPV was withdrawn from global use in April 2016. As of Jun 13, in 2017 only 13 countries have isolated a Type-2 poliovirus (Figure 1).



Figure 1: Countries isolating Type 2 Poliovirus in 2017: Afghanistan (aVDPV2, SL2), Azerbaijan (SL2), Cameroon (SL2), Chad (SL2, aVDPV2), DRC (cVDPV2), Egypt (iVDPV2), India (aVDPV2), Mozambique (aVDPV2), The Netherlands (WPV2), Niger (SL2), Nigeria (i, aVDPV2, SL2), Pakistan (VDPV2, SL2), Syria (cVDPV2).

However, it was anticipated that VDPV2 events would be detected after cessation due to OPV2 used in the pre-cessation era. The GPEI planned for 0-3 cVDPVs outbreaks in the first year after cessation, assuming that high-quality tOPV SIAs would reduce the chances of outbreaks (Table 1). However, in this period we observed 6 cVDPV outbreaks in 4 countries: Nigeria (2), Pakistan, DRC (2), and Syria (Figure 2). These have occurred in areas with chronically poor immunity and a history of cVDPV emergences, often attributed to inaccessible/partially inaccessible populations. In Pakistan and Nigeria, co-circulation of WPV1 has complicated the outbreak response. At least 3 of these outbreaks (DRC (2), Syria) will continue into the second year after cessation, requiring mOPV2 response. It is unclear whether the outbreaks in Nigeria and Pakistan have been controlled by campaigns already conducted.

In addition, there have been 13 ambiguous or unclassified VDPV2 emergences in 8 countries and 6 iVDPVs in 5 countries attributable to pre-cessation tOPV use. The GPEI had anticipated 4 – 25 separate aVDPV emergences, most of which wouldn't require an mOPV2 response. While each isolation is concerning, the occurrence of ambiguous or unclassified VDPV2s appears roughly in line with expectations.

mOPV2 outbreak responses have either been conducted or planned in 8 countries, requiring release of 79mds of mOPV2. The target population of the responses varied from 200,000 (Mozambique) to 48 million (Nigeria and Lake Chad). These SIAs have resulted in additional SL2 isolates inside and outside the response region, as would be expected in vaccine recipients and their contacts. Isolation of SL2 has declined after the mOPV2 response mostly as expected. This fits with the projection at the last CRTT

meeting that mOPV2 would continue to be safe to use and would not persist outside the response region, at least in the first 18-24 months following cessation.

Multiple aVDPVs have been found in areas of mOPV2 response in Nigeria and Pakistan, some of which are linked but do not meet the technical criteria for cVDPV classification. These are extremely concerning and should be carefully investigated. If circulation is established, it would indicate a low-quality response which not only may have not have interrupted transmission of the original cVDPV2 virus, but possibly seeded new cVDPV. These may require further mOPV2 use in those areas, and underscore the urgent need for high quality mOPV2 responses that achieve high type 2 immunity across the entire response region. However, also note that most of these aVDPV have been found in environmental surveillance (ES); it is possible that some VDPV isolates may be expected in ES in the response region during the course of a successful outbreak response.

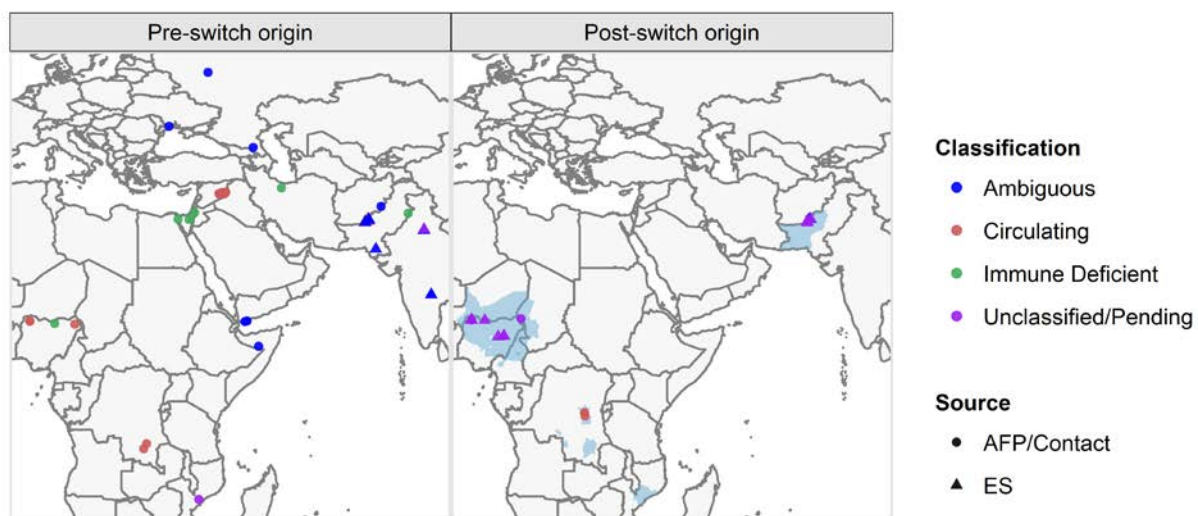


Figure 2: VDPV2 events detected post-cessation. Those with likely post-switch source are overlaid with mOPV2 response areas (blue shading).

The number of cVDPV outbreaks has been higher than anticipated in the first year following cessation, while the number of aVDPV events attributable to pre-switch tOPV use has been largely as expected. The number of VDPV2 events following mOPV2 responses was also higher than anticipated. The possibility that one cVDPV2 outbreak (Maniema, DRC) was due to illicit tOPV use post-cessation also highlights the risk of emergence elsewhere. Thus, the CRTT anticipates that both ongoing cVDPV2 outbreaks and new emergences of cVDPV will require mOPV2 vaccination responses in the second year after tOPV cessation. While a conservative estimate of the number of new outbreaks is likely above the two that were forecast, there was no consensus on a conservative upper bound. Experience from the first year after cessation is suggestive that these may be in areas of chronically poor immunization.

Vaccine and resource planning should include ongoing responses in 6 cVDPV2 outbreak zones, at least 1 large scale cVDPV2 outbreak in a new area, and additional smaller scale outbreaks. A stockpile of 150 million finished doses and corresponding financial and human resources should be sufficient for this in the short-term (for the next 2 years), but more bulk and/or semi-finished mOPV2 may be needed for longer-term contingency planning.

Table 1: Predicted vs Observed VDPV events in first year after cessation

	cVDPV outbreaks		Ambiguous or unclassified VDPV emergences		iVDPV
Virus Source	Pre-switch	Post-switch	Pre-switch	Post-switch	Pre-switch
Forecast	0 - 3	- NA	4 – 25	- NA	- NA
Observed	5 (4 countries)	1*	13 (8 countries)	14 (3 countries)	6

*While the genetic characteristics of the cVDPV outbreak in Maniema, DRC may suggest OPV2 used post-switch, they are also compatible with a pre-switch origin.

2. Outbreak Response: experience and recommendations based on changing climate of risk

Summary:

- Of the 35 events reviewed by the mOPV2 Advisory Group (AG), 6/6 cVDPVs and 4/29 VDPV2 events (Jigawa, Mozambique, Russia, Sokoto) elicited a recommendation for mOPV2 response. While it is still unclear whether responses were successful in controlling the outbreak virus, the CRTT had general comments:
 - None of the VDPV2 events have showed evidence of on-going circulation, irrespective of the response.
 - Speed, quality, and scope of the response varied widely. Some responses (Quetta, DRC) had concerning delays between AG recommendation of a response and implementation and issues related to quality.
 - Sabin 2 detection outside of the response regions was limited in most contexts, demonstrating the relative safety of mOPV2 use as an outbreak response tool.
 - Linked aVDPV2s within the response region are extremely concerning, particularly in Quetta. These highlight the risk of development of new cVDPV2s, as well as indicating a low-quality response which may have been insufficient to stop the original outbreak virus.
- For future responses, the CRTT had general comments:
 - **Circumstances for a vaccination response:** The CRTT supports the qualitative situational assessment approach used by the mOPV2 AG. cVDPV2s will continue to require an mOPV2 vaccination response. In areas where ambiguous or otherwise unclassified VDPV2s are considered a risk, resources and preparation for a high-quality response should be made for the event that circulation is established.
 - **Vaccine choice:** cVDPV2 events will continue to require an aggressive mOPV2 response. mOPV2 remains the only vaccine available that can prevent person-to-person transmission of type-2 poliovirus among un-immunized children. *Stopping the outbreak virus should outweigh concerns over the risk of using mOPV2.*
 - **Role of IPV:** The CRTT again reviewed the utility of IPV use in outbreak control in addition to mOPV2. While there was not unanimity on a position on its use, all agreed that use (if any) should be limited to special circumstances. IPV may have a role in 1) boosting intestinal immunity for OPV-exposed children and in 2) preventing paralysis. However, with mOPV2 already in use, only the very small fraction of IPV recipients who do not take to any of the mOPV2 doses but who do take to the IPV dose get protected from paralysis by IPV. Therefore, the benefit of adding IPV to VDPV2 response strategies in the current context appears to be limited the on-going supply constraints. The on-going supply constraints and risk of complicating the operational logistics of SIAs also limit its use.

- **Quality:** Good SIA quality was considered critical to control outbreaks and minimize the risk of creating new cVDPV2s (i.e. over the course of the OBR, the entire target population should be reached with high coverage). Speed remains critically important, but there was no explicit recommendation on the tradeoff between speed and quality of the first response SIA. Kid Risk stated that prior work showed that speed trumps coverage for the first round, as long as the subsequent rounds reach high quality.
- **Scope:** The scope of outbreak SIAs should be guided by the situation. However, as Type-2 immunity continues to decline, outbreak responses will generally need to be larger to prevent spread or stop possible transmission in linked populations.

Discussion

The mOPV2 Advisory Group (AG) met approximately 59 times in the first year after cessation. cVDPV2 outbreaks required an mOPV2 response as suggested in the protocol. The majority of ambiguous or unclassified events (22/29) were considered low-risk and no vaccination response was recommended. This differs from the original protocol which had originally suggested a default mOPV2 vaccination response of 500,000 doses. However, this was not pursued in most areas since events were either relatively close to the switch (< 6 months), in areas of historically high immunity, or secondary to mOPV2 SIAs. Of those ambiguous or unclassified VDPV2 events where a response was recommended, 3 used IPV (Pakistan (Hyderabad), India (Hyderabad), and Yemen), while 4 used mOPV2 (Nigeria (Jigawa), Mozambique, Russia, and Nigeria (Sokoto)).

Those low-risk scenarios where vaccination wasn't carried out have not resulted in any further VDPV2 isolates to date. However, as new birth cohorts have no type-2 mucosal immunity and mucosal immunity in previously immunized individuals wanes, the immunity gap will be increasingly relevant. Risk assessments should consider this deteriorating immunity status when evaluating the potential for spread.

While there were fewer initial responses than planned, the scales of response in both the first and subsequent SIAs were larger than anticipated (Table 2). This was due to the Nigeria / Lake Chad response, where SIAs were conducted far outside the area of detection owing to estimated low immunity.

	Planned	Actual: Average (range)
SIA1 (n=8)	500k	1.3m (3k- 2.6m)
SIA2-3 (n=7)	2.3m	9.7m (612k-48.3m)

The diversity of outbreak responses to VDPV2s provides a considerable challenge for vaccine supply, management, and budgeting. However, modeling did not provide general rules for the appropriate scale of response. It was suggested by Imperial College that larger responses will be needed in areas of lower Type-2 mucosal immunity (Figure 3), implying that over time larger mOPV2 responses should be considered. Kid Risk results agree with this finding and also suggested the need for larger response to control outbreaks in areas with higher poliovirus transmissibility (R_0). A failure to respond aggressively initially will ultimately create greater demand from the stockpile because it allows the outbreak to spread geographically.

Optimal vaccination response to cVDPV2 outbreak in Pakistan and Afghanistan

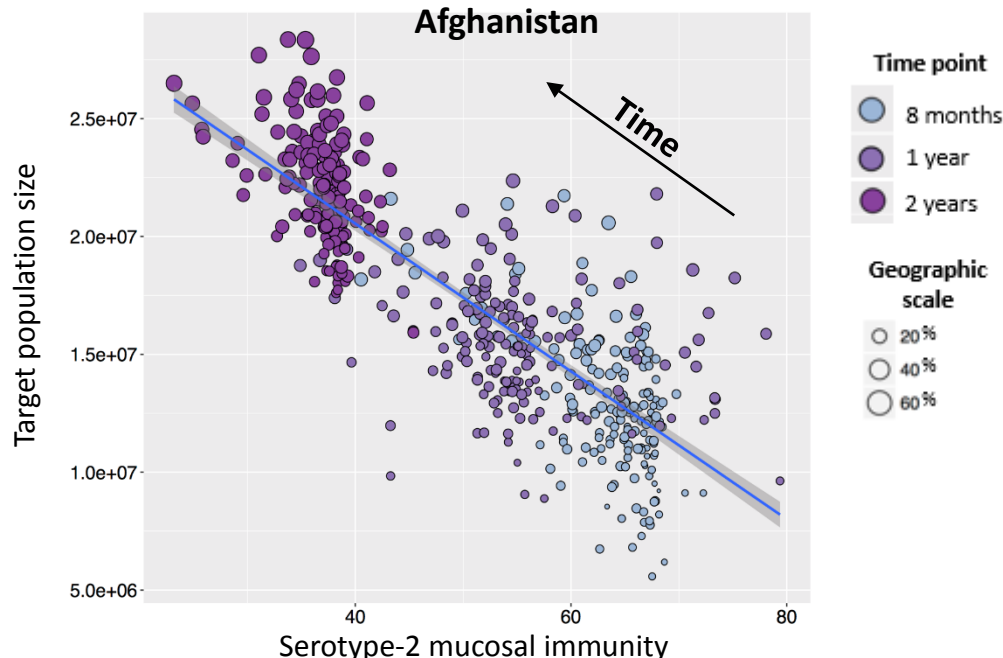


Figure 3: Optimal vaccination response size, as a function of Type-2 immunity in Pakistan. Points represent an outbreak originating in each of the 163 districts was simulated at 8, 12, and 24 months after cessation. (Imperial College London)

All groups agreed that mOPV2 is essential in controlling a cVDPV2 outbreak. While there is concern among the CRTT that mOPV2 used in outbreak response may spread and persist outside of the response area, the need to stop a cVDPV2 with mOPV2 continues to outweigh these concerns. It is the only vaccine available which can induce Type 2 mucosal immunity in naïve children, who are typically the majority of individuals who contribute to cVDPV2 transmission and are a growing demographic in the post-cessation era. IPV can boost mucosal immunity of individuals who have already been immunized with OPV2. However, groups were divided on whether IPV use would be beneficial in an outbreak response. Kid Risk and IDM have argued that the impact of IPV in outbreak response is minimal compared to mOPV2 and mOPV2 is easier to deliver. Imperial College has conducted an observational, retrospective analysis of data from Nigeria and Pakistan which suggested that the addition of IPV to tOPV may have reduced infection and disease in Nigeria, possibly by accessing populations that aren't reached in OPV-only campaigns, but not in Pakistan. However, the reported reduction in cases for Nigeria depended on the findings from a single district that only experienced cases before and not after a series of one tOPV+IPV SIA followed by multiple tOPV-only SIAs. In addition, simulations from Imperial College showed that IPV used outside the response region may help contain OPV2 used in the response. Kid Risk modeling suggests that it is better to expand the mOPV2 outbreak response areas than to use IPV around the response region.

The CRTT was unanimous that high quality of outbreak response campaigns is essential, though measurement and verification of sufficient outbreak response is difficult. The AG and WHO suggested that, while quantitative campaign quality measurements are often high, they are not always well-measured and in general don't include populations that are inaccessible or partially accessible by

vaccination programs. Some surveillance/virologic data do reflect on campaign quality. Disappearance of the outbreak virus is required to verify a sufficient response. In addition, the persistence of Sabin 2 viruses and cVDPV2 emergence following an mOPV2 use indicates a lower-quality or insufficient response. The emergence of linked aVDPV2s in Nigeria and Pakistan are thus concerning.

Kid Risk and IDM stressed that both the quality and number of SIAs should be emphasized, and expressed concern that the 2-SIA recommendation in the current outbreak response protocol does not sufficiently communicate the importance of the quality response.

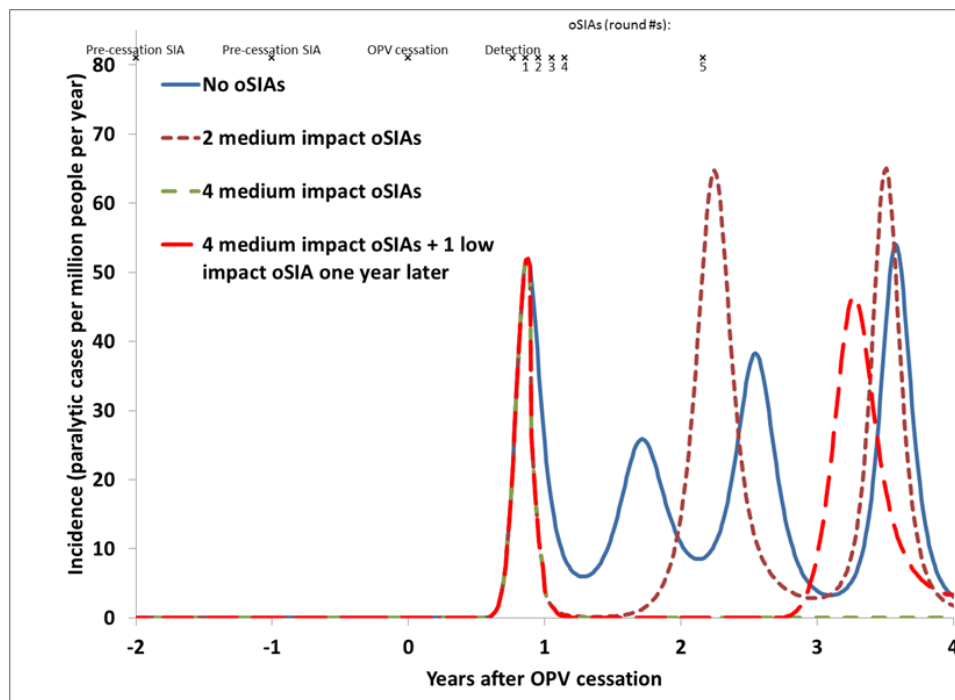


Figure 4: Importance of quality and the number of rounds in response to a cVDPV2 outbreak (Kid Risk. DOI: 10.1093/infdis/jit838.)

3. Conclusions on risk-mitigating and enabling activities

- **Collection and use of sequencing data:** It was agreed that genetic data should be shared among the key partner groups. An expanded data sharing agreement established by the WHO-DG should be investigated as a mechanism for greater sharing of these genetic sequences within the partnership. In addition to current sequencing data, whole-genome and/or next-generation sequencing could be useful in risk assessment.
- **Epidemiological context:** Those involved in the mOPV2 AG and outbreak response consistently recommended that existing epidemiological data could be optimized to better guide risk assessment. For instance, when dose histories are presented from NP-AFP cases, they should account for the likely type of vaccine received based on the child's age to provide serotype-specific estimates of population immunity.
- **Ad-hoc serosurveys:** It was recommended that a protocol for ad-hoc serosurveys be developed for rapid deployment. Possible uses include risk assessment for VDPV spread, measurement of immunological impact of an outbreak response campaign, or risk assessment of mOPV2 spread to surrounding areas.
- **Environmental surveillance outbreak guidelines:** A protocol for ad-hoc environmental surveillance was presented which is aimed at streamlining the process of enhancing ES following VDPV2 detection, or a subsequent response with mOPV2. The objective of such an approach is to assess evidence of continued circulation of the VDPV2, or to monitor the outbreak and/or vaccine virus circulation and new emergence following a vaccination response. Ensuring the quality of ad-hoc surveillance sites and managing increased lab and cost burden need to be explicitly addressed in the final plan. The CRTT supported continued work on this front to finalize and implement the protocol for enhanced ES for VDPV2 detection and response.
- **nOPV:** The CRTT noted the progress made in getting the new OPV2 into clinical trials, and expressed support for further clinical development to have a potentially safer alternative to mOPV2 for the long term.

4. Areas for future work

The CRTT discussed the following areas for further work. Another CRTT meeting will be held in 6 months (18-months post- OPV2 cessation). The primary purpose of the 18-month meeting will be to analyze SL2 and a/i/cVDPV2 evolution and persistence as mucosal immunity to Type-2 virus continues to decline and make appropriate recommendations for control/elimination of VDPV2 risks.

Several additional outstanding issues will be addressed through teleconferences prior to the 18 month meeting. These include:

- **Planning for OPV1,3 cessation.** The CRTT opened discussion on pre-bOPV cessation SIAs, vaccine management, stockpile needs, and their common characteristics with tOPV cessation. Maintenance of bOPV SIAs and intensification prior to cessation will decrease risk of cVDPV1,3 emergence and WPV1 importation outbreaks, and mOPV1,3 will need to be stockpiled in order to respond to outbreaks after cessation. However, additional work is needed for development of the strategy for bOPV cessation. Vaccine supply planning should be conservative enough to allow the possibility of both sustained bOPV SIAs and

mOPV1,3 stockpiles of a similar or larger order than mOPV2 for response activities after bOPV cessation.

- **Long-term stockpile planning** OPV needs to be available for outbreaks long after cessation, which have the potential to be large and even require OPV2 re-introduction. Several scenarios were discussed of varying size (<1 billion doses – 10 billion doses) and likelihood of each occurring. Quantifying which are most likely and what an appropriate response may be will require continued discussion at the CRTT. High-level input on long-term risk tolerance and budget will also be needed.
- **How to monitor SIA quality with virologic data.** CDC and IDM presented on the virologic characteristics of SL2 and VDPV2 emergences. Research from IDM suggested that genetic characteristics (synonymous vs non-synonymous mutation rates) could be used to inform risk assessments. Imperial College also suggested that deep-sequencing would be useful to characterize diversity of infections and number of infected individuals. How these laboratory and data analyses could be carried out and shared will be addressed in a future teleconference.
- **Indicators for countries to provide for the mOPV2 Advisory Group.** It was suggested that better use could be made of epidemiological data for the mOPV2 advisory group, and the CRTT will evaluate the currently available data and suggest a useful approach.
- **Further clarification on tradeoffs on SIA number/quality/speed.** While all modeling groups emphasized the need for sufficient quality, number, and speed of outbreak response, there was insufficient discussion around the tradeoffs between quality and speed of the first mOPV2 response, and how this relates to the immunity achieved by iteratively improving quality over multiple rounds. Prior work by Kid Risk suggested that speed trumps coverage for the first round, as long as the subsequent rounds reach high quality (Thompson et al., Risk Analysis 2006;26(6):1541-1556). Additional work will be done to make a useful recommendation on this issue.
- **Consolidated view on IPV utility in outbreaks.** While all agreed that mOPV2 would be needed to stop circulation of a VDPV2, the use of IPV was still debated. It was proposed that the CRTT come up with a consensus recommendation on IPV-use in outbreak response. The CRTT will review the model results and assess its impact on its previous recommendation to not prioritize IPV use in outbreak control.
- **Experience with mOPV2 SIA effectiveness.** The heterogeneity of speed, quality, and scope of mOPV2 SIAs should make it possible to evaluate effectiveness of different outbreak response strategies. However, it is too early to tell which have been effective in controlling the outbreak and preventing Sabin-2 persistence. The CRTT will continue to monitor outbreaks and recommend modifications in risk assessment and response strategies based on experience.