

Polio vaccines: WHO position paper, March 2016

References with abstracts cited in the position paper in the order of appearance.

Polio Eradication and Endgame Strategic Plan 2013–2018. Available at <http://www.polioeradication.org/resourcelibrary/strategyandwork.aspx>, accessed March 2016. (No abstract available).

Bernier R. Some observations on poliomyelitis lameness surveys. *Rev Infect Dis.* 1984;May-Jun:6 Suppl 2:S371-375.

Since 1974, greater than 100 different surveys have been carried out throughout the developing world to estimate the prevalence of lameness due to poliomyelitis. Reported prevalence rates have ranged from less than 1 to a high of 25 per 1,000 children surveyed and have prompted many countries to undertake polio vaccination programs. A review of surveys conducted to date reveals considerable variation in both the choice and use of survey methods and in the assumptions made in the analysis and interpretation of findings. More precise and comparable data about the risk of poliomyelitis could be obtained in future surveys by incorporating a standard case definition, by using house-to-house case-finding methods in representative community-based samples, by analyzing and presenting rates in more clearly defined ways, and by selecting stable populations for study.

Sutter RW, et al. Poliovirus vaccine-live. In: Plotkin SA, Orenstein WA, Offit PA, *Vaccines*, 6th edition 2013. Philadelphia: Elsevier-Saunders, 598-645. (No abstract available).

WHO-IVB, Polio Laboratory Manual 2004.(<http://www.who.int/vaccines/en/poliolab/WHO-Polio-Manual-9.pdf>, accessed February 2016). (No abstract available).

Sutter RW et al. Defining surrogate serologic tests with respect to predicting protective vaccine efficacy: Poliovirus vaccination. Williams JC, Goldenthal KL, Burns D, Lewis BP (eds), in *Combined Vaccines and Simultaneous Administration: Current Issues and Perspectives*. New York Academy Sciences, New York, 1995;289-299.

Inactivated and trivalent oral poliovirus vaccines contain either formalin-inactivated or live, attenuated poliovirus, respectively, of the three serotypes. Interference among the three attenuated poliovirus serotypes was minimized with a "balanced-formulation" vaccine, and serologic responses after IPV were optimized by adjusting the antigenic content of each inactivated poliovirus serotype. Seroconversion is dependent on both the relative content as well as the absolute quantity of virus in the vaccine. The "gold standard" method to assess humoral antibody responses following vaccination is the neutralization assay. Any detectable titer of neutralizing antibody against poliovirus is considered protective against clinical paralytic diseases. Recently, standard procedures were adopted for conducting neutralization assays. Efforts are being undertaken now to develop a combined diphtheria and tetanus toxoids and pertussis vaccine and IPV vaccine in the United States using a dual-chambered syringe that mixes the content of both vaccines at the time of injection; this approach is necessary to overcome the potential detrimental effect of thimerosal on IPV (the preservative in DTP). Other vaccines that combine DTP and/or *Haemophilus influenzae* type b and/or hepatitis B with IPV appear feasible but require further investigation. New combination vaccines should induce similar or superior levels of neutralizing antibody in serum for individual protection against paralytic disease and mucosal immunity that effectively decreases viral replication in the intestine and pharynx for population protection against transmission of poliovirus.

Sabin AB, Boulger LR. History of Sabin attenuated poliovirus oral live vaccine strains. J Biol Standardization. 1973;1:115-118.

The full data concerning the history of attenuated poliovirus strains developed by one of us (Sabin, 1965) for vaccine production do not appear in a single journal. Over the past few years we have had frequent requests for the details such as isolation and attenuation and accordingly we felt that bringing the data together in the report below would be both helpful and informative to those involved in the production and control of poliovirus vaccine (oral) prepared from these strains.

Recommendations to assure the quality, safety and efficacy of live attenuated poliomyelitis vaccine (oral). [Replacement of: WHO Technical Report Series (TSR) 904, Annex 1 and Addendum TRS 910, Annex 1]. Geneva, World Health Organization, 2012. Available at http://www.who.int/biologicals/vaccines/BS2185_OPV_Post_ECBS_DB_TZ_DBFinal12Feb2013.pdf, accessed February 2016. (No abstract available).

Platt LR et al. Vaccine-associated paralytic poliomyelitis: a review of the epidemiology and estimation of the global burden. J Infect Dis. 2014;210 suppl 1:S380–9.

Background. Vaccine-associated paralytic poliomyelitis (VAPP) is a rare adverse event associated with oral poliovirus vaccine (OPV). This review summarizes the epidemiology and provides a global burden estimate.

Methods. A literature review was conducted to abstract the epidemiology and calculate the risk of VAPP. A bootstrap method was applied to calculate global VAPP burden estimates.

Results. Trends in VAPP epidemiology varied by country income level. In the low-income country, the majority of cases occurred in individuals who had received >3 doses of OPV (63%), whereas in middle and high-income countries, most cases occurred in recipients after their first OPV dose or unvaccinated contacts (81%). Using all risk estimates, VAPP risk was 4.7 cases per million births (range, 2.4–9.7), leading to a global annual burden estimate of 498 cases (range, 255–1018). If the analysis is limited to estimates from countries that currently use OPV, the VAPP risk is 3.8 cases per million births (range, 2.9–4.7) and a burden of 399 cases (range, 306–490).

Conclusions. Because many high-income countries have replaced OPV with inactivated poliovirus vaccine, the VAPP burden is concentrated in lower-income countries. The planned universal introduction of inactivated poliovirus vaccine is likely to substantially decrease the global VAPP burden by 80%–90%.

Sutter RW et al. A new epidemiologic and laboratory classification system for paralytic poliomyelitis cases. Am Public Health. 1989;79:495-498.

An epidemiologic classification of paralytic poliomyelitis cases (ECPPC) has been in use in the United States since 1976. In 1985, this classification system was reviewed because of recent changes in the epidemiology of paralytic poliomyelitis and improved laboratory capability to definitively characterize poliovirus strains. An alternative classification system was devised, the epidemiologic and laboratory classification of paralytic polio cases (ELCPPC), that incorporated virus isolation and strain characterization with epidemiologic information. Reported paralytic poliomyelitis cases for 1980-86 were classified by both the ECPPC and the ELCPPC classification systems. The new ELCPPC system classified 91 per cent of the reported cases as vaccine-associated, while the ECPPC system classified only 71 per cent of the reported cases as vaccine-associated. The proposed classification system provides more specific and useful information particularly concerning vaccine-associated paralytic poliomyelitis.

Kohler KA et al. Vaccine-associated paralytic poliomyelitis in India during 1999: decreased risk despite massive use of oral polio vaccine. Bull World Health Organ. 2002;80(3):210-216.

OBJECTIVE: Vaccine-associated paralytic poliomyelitis (VAPP) is a rare but serious consequence of the administration of oral polio vaccine (OPV). Intensified OPV administration has reduced wild poliovirus transmission in India but VAPP is becoming a matter of concern.

METHODS: We analysed acute flaccid paralysis (AFP) surveillance data in order to estimate the VAPP risk in this country. VAPP was defined as occurring in AFP cases with onset of paralysis in 1999, residual weakness 60 days after onset, and isolation of vaccine-related poliovirus. Recipient VAPP cases were a subset with onset of paralysis between 4 and 40 days after receipt of OPV.

FINDINGS: A total of 181 AFP cases met the case definition. The following estimates of VAPP risk were made: overall risk, 1 case per 4.1 to 4.6 million OPV doses administered; recipient risk, 1 case per 12.2 million; first-dose recipient risk, 1 case per 2.8 million; and subsequent-dose recipient risk, 1 case per 13.9 million.

CONCLUSION: On the basis of data from a highly sensitive surveillance system the estimated VAPP risk in India is evidently lower than that in other countries, notwithstanding the administration of multiple OPV doses to children in mass immunization campaigns.

Considerations for the timing of a single dose of IPV in the routine immunization schedule

http://www.who.int/immunization/sage/meetings/2013/november/1_Sutter_IPV_age_tech_background_14_October_2013_final.pdf, accessed February 2016). (No abstract available).

Dömök I. Experiences associated with the use of live poliovirus vaccine in Hungary, 1959-1982. Rev Infect Dis. 1984 May-Jun;6 Suppl 2:S413-8.

Live Sabin poliomyelitis vaccine has been given in Hungary since December 1959. Generally, monovalent vaccines--administered in the sequence type 1, 3, and 2--have been used in annually repeated nationwide campaigns. Each type was administered within a week all over the country, with an interval of five to eight weeks between administrations. In the initial campaigns, children younger than 14 years of age were vaccinated. Since 1962, children between two and 38 months of age have been vaccinated annually. As a result of the vaccination program, the mean annual incidence of poliomyelitis declined to 0.03 per 100,000 population between 1961 and 1982 from a level of 12 per 100,000 observed over the previous five years. Epidemiologic and virologic evidence indicated that 47 (82%) of 57 cases registered since 1961 were vaccine-associated. Circumstances connected with the special vaccination practice in Hungary gave an opportunity to estimate the risk of vaccine-associated poliomyelitis. For recipients receiving the vaccine for the first time, the estimated risks for each type of vaccine were type 1, 0.99; type 2, 0.65; and type 3, 8.91 per million and for susceptible contacts, type 1, 0; type 2, 3.62; and type 3, 4.97 per million. The author's opinion is that these rates of risk are acceptable in view of the benefits provided by the live vaccine, especially under circumstances when importation of wild polioviruses that circulate widely in extended regions of the world may commonly occur.

Estívariz CF et al. (2008). A large vaccine-derived poliovirus outbreak on Madura Island—Indonesia. J Inf Dis. 2005;197:347–354.^

Between June and October 2005, 45 laboratory-confirmed type 1 vaccine-derived poliovirus (VDPV) cases were identified on Madura Island in Indonesia. Genetic sequencing data on VDPV isolates were consistent with replication and circulation for up to approximately 2 years. Concurrent circulation with type 1 wild poliovirus (WPV) enabled comparisons of VDPV and WPV cases and found that clinical and epidemiological features of both were similar. Attack rates for VDPV were as high as those for WPV. Of 41 VDPV case patients with known vaccination status, 25 (61%) had received zero oral polio vaccine (OPV) doses. Low population immunity due to low routine OPV coverage in rural areas and the absence of WPV circulation for more than a decade were major predisposing factors for the emergence of VDPV. Suboptimal surveillance and a limited initial immunization response may have contributed to widespread circulation. Sensitive surveillance and prompt high-quality immunization responses are recommended to prevent the spread of VDPVs.

Jenkins HE et al. Implications of a circulating vaccine-derived poliovirus in Nigeria for polio eradication. N Eng J Med. 2010;362:2360-2369.

BACKGROUND: The largest recorded outbreak of a circulating vaccine-derived poliovirus (cVDPV), detected in Nigeria, provides a unique opportunity to analyze the pathogenicity of the virus, the clinical severity of the disease, and the effectiveness of control measures for cVDPVs as compared with wild-type poliovirus (WPV).

METHODS: We identified cases of acute flaccid paralysis associated with fecal excretion of type 2 cVDPV, type 1 WPV, or type 3 WPV reported in Nigeria through routine surveillance from January 1, 2005, through June 30, 2009. The clinical characteristics of these cases, the clinical attack rates for each virus, and the effectiveness of oral polio vaccines in preventing paralysis from each virus were compared.

RESULTS: No significant differences were found in the clinical severity of paralysis among the 278 cases of type 2 cVDPV, the 2323 cases of type 1 WPV, and the 1059 cases of type 3 WPV. The estimated average annual clinical attack rates of type 1 WPV, type 2 cVDPV, and type 3 WPV per 100,000 susceptible children under 5 years of age were 6.8 (95% confidence interval [CI], 5.9 to 7.7), 2.7 (95% CI, 1.9 to 3.6), and 4.0 (95% CI, 3.4 to 4.7), respectively. The estimated effectiveness of trivalent oral polio vaccine against paralysis from type 2 cVDPV was 38% (95% CI, 15 to 54%) per dose, which was substantially higher than that against paralysis from type 1 WPV (13%; 95% CI, 8 to 18%), or type 3 WPV (20%; 95% CI, 12 to 26%). The more frequent use of serotype 1 and serotype 3 monovalent oral polio vaccines has resulted in improvements in vaccine-induced population immunity against these serotypes and in declines in immunity to type 2 cVDPV.

CONCLUSIONS: The attack rate and severity of disease associated with the recent cVDPV identified in Nigeria are similar to those associated with WPV. International planning for the management of the risk of WPV, both before and after eradication, must include scenarios in which equally virulent and pathogenic cVDPVs could emerge.

Duintjer Tebbens RJ et al. Oral poliovirus vaccine evolution and insights relevant to modelling the risks of circulating vaccine-derived polioviruses. Risk Analysis. 2013;33(4):680-702.

The live, attenuated oral poliovirus vaccine (OPV) provides a powerful tool for controlling and stopping the transmission of wild polioviruses (WPVs), although the risks of vaccine-associated paralytic polio (VAPP) and circulating vaccine-derived poliovirus (cVDPV) outbreaks exist as long as OPV remains in use. Understanding the dynamics of cVDPV emergence and outbreaks as a function of population immunity and other risk factors may help to improve risk management and the development of strategies to respond to possible outbreaks. We performed a comprehensive review of the literature related to the process of OPV evolution and information available from actual experiences with cVDPV outbreaks. Only a relatively small fraction of poliovirus infections cause

symptoms, which makes direct observation of the trajectory of OPV evolution within a population impractical and leads to significant uncertainty. Despite a large global surveillance system, the existing genetic sequence data largely provide information about transmitted virulent polioviruses that caused acute flaccid paralysis, and essentially no data track the changes that occur in OPV sequences as the viruses transmit largely asymptotically through real populations with suboptimal immunity. We updated estimates of cVDPV risks based on actual experiences and identified the many limitations in the existing data on poliovirus transmission and immunity and OPV virus evolution that complicate modeling. Modelers should explore the space of potential model formulations and inputs consistent with the available evidence and future studies should seek to improve our understanding of the OPV virus evolution process to provide better information for policymakers working to manage cVDPV risks.

Duintjer Tebbens RJ et al. Modeling the prevalence of immunodeficiency-associated long-term vaccine-derived poliovirus excretors and the potential benefits of antiviral drugs. BMC Infect Dis 2015;15(379)

Background

A small number of individuals with B-cell-related primary immunodeficiency diseases (PIDs) may exhibit long-term (prolonged or chronic) excretion of immunodeficiency-associated vaccine-derived polioviruses (iVDPVs) following infection with oral poliovirus vaccine (OPV). These individuals pose a risk of live poliovirus reintroduction into the population after global wild poliovirus eradication and subsequent OPV cessation. Treatment with polio antiviral drugs may potentially stop excretion in some of these individuals and thus may reduce the future population risk.

Methods

We developed a discrete event simulation model to characterize the global prevalence of long-term iVDPV excretors based on the best available evidence. We explored the impact of different assumptions about the effectiveness of polio antiviral drugs and the fraction of long-term excretors identified and treated.

Results

Due to the rarity of long-term iVDPV excretion and limited data on the survival of PID patients in developing countries, uncertainty remains about the current and future prevalence of long-term iVDPV excretors. While the model suggests only approximately 30 current excretors globally and a rapid decrease after OPV cessation, most of these excrete asymptotically and remain undetected. The possibility that one or more PID patients may continue to excrete iVDPVs for several years after OPV cessation represents a risk for reintroduction of live polioviruses after OPV cessation, particularly for middle-income countries. With the effectiveness of a single polio antiviral drug possibly as low as 40 % and no system in place to identify and treat asymptomatic excretors, the impact of passive use of a single polio antiviral drug to treat identified excretors appears limited. Higher drug effectiveness and active efforts to identify long-term excretors will dramatically increase the benefits of polio antiviral drugs.

Conclusions

Efforts to develop a second polio antiviral compound to increase polio antiviral effectiveness and/or to maximize the identification and treatment of affected individuals represent important risk management opportunities for the polio endgame. Better data on the survival of PID patients in developing countries and more longitudinal data on their exposure to and recovery from OPV infections would improve our understanding of the risks associated with iVDPV excretors and the benefits of further investments in polio antiviral drugs.

Global Polio Eradication Initiative (2015). Reporting and classification of vaccine-derived polioviruses. Available at http://www.polioeradication.org/Portals/0/Document/Resources/VDPV_ReportingClassification.pdf , accessed February 2016. (No abstract available).

Kew OM et al. Outbreak of poliomyelitis in Hispaniola associated with circulating type 1 vaccine-derived poliovirus. *Science*. 2002;296:356–359.

An outbreak of paralytic poliomyelitis occurred in the Dominican Republic (13 confirmed cases) and Haiti (8 confirmed cases, including 2 fatal cases) during 2000-2001. All but one of the patients were either unvaccinated or incompletely vaccinated children, and cases occurred in communities with very low (7 to 40%) rates of coverage with oral poliovirus vaccine (OPV). The outbreak was associated with the circulation of a derivative of the type 1 OPV strain, probably originating from a single OPV dose given in 1998-1999. The vaccine-derived poliovirus associated with the outbreak had biological properties indistinguishable from those of wild poliovirus.

Alexander JP et al. Transmission of imported vaccine-derived poliovirus in an under-vaccinated community: Minnesota, USA. *J Inf Dis*. 2009;391–397.

BACKGROUND: Oral poliovirus vaccine (OPV) has not been used in the United States since 2000.

Type 1 vaccine-derived poliovirus (VDPV) was identified in September 2005, from an unvaccinated Amish infant hospitalized in Minnesota with severe combined immunodeficiency. An investigation was conducted to determine the source of the virus and its means of transmission.

METHODS: The infant was tested serially for poliovirus excretion. Investigations were conducted to detect poliovirus infections or paralytic poliomyelitis in Amish communities in Minnesota, neighboring states, and Ontario, Canada. Genomic sequences of poliovirus isolates were determined for phylogenetic analysis.

RESULTS: No source for the VDPV could be identified. In the index community, 8 (35%) of 23 children tested, including the infant, had evidence of type 1 poliovirus or VDPV infection. Phylogenetic analysis suggested that the VDPV circulated in the community for approximately 2 months before the infant's infection was detected and that the initiating OPV dose had been given before her birth. No paralytic disease was found in the community, and no poliovirus infections were found in other Amish communities investigated.

CONCLUSIONS: This is the first demonstrated transmission of VDPV in an undervaccinated community in a developed country. Continued vigilance is needed in all countries to identify poliovirus infections in communities at high risk of poliovirus transmission.

Hird TR et al. Systematic review of mucosal immunity induced by oral and inactivated poliovirus vaccines against virus shedding following oral poliovirus vaccine challenge. *PLoS Pathogens*. 2012;8(4)e1002599.

Inactivated poliovirus vaccine (IPV) may be used in mass vaccination campaigns during the final stages of polio eradication. It is also likely to be adopted by many countries following the coordinated global cessation of vaccination with oral poliovirus vaccine (OPV) after eradication. The success of IPV in the control of poliomyelitis outbreaks will depend on the degree of nasopharyngeal and intestinal mucosal immunity induced against poliovirus infection. We performed a systematic review of studies published through May 2011 that recorded the prevalence of poliovirus shedding in stool samples or nasopharyngeal secretions collected 5-30 days after a "challenge" dose of OPV. Studies were combined in a meta-analysis of the odds of shedding among children vaccinated according to IPV, OPV, and combination schedules. We identified 31 studies of shedding in stool and four in nasopharyngeal samples that met the inclusion criteria. Individuals vaccinated with OPV were protected against infection and shedding of poliovirus in stool samples collected after challenge compared with unvaccinated individuals (summary odds ratio [OR] for shedding 0.13 (95% confidence interval [CI] 0.08-0.24)). In contrast, IPV provided no protection against shedding compared with unvaccinated individuals (summary OR 0.81 [95% CI 0.59-1.11]) or when given in

addition to OPV, compared with individuals given OPV alone (summary OR 1.14 [95% CI 0.82-1.58]). There were insufficient studies of nasopharyngeal shedding to draw a conclusion. IPV does not induce sufficient intestinal mucosal immunity to reduce the prevalence of fecal poliovirus shedding after challenge, although there was some evidence that it can reduce the quantity of virus shed. The impact of IPV on poliovirus transmission in countries where fecal-oral spread is common is unknown but is likely to be limited compared with OPV.

Bar-On ES et al. Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae b (HIB).Cochrane Database Systematic Review. 2012

BACKGROUND: Advantages to combining childhood vaccines include reducing the number of visits, injections and patient discomfort, increasing compliance and optimising prevention. The World Health Organization (WHO) recommends that routine infant immunisation programmes include a vaccination against Haemophilus influenzae (H. influenzae) type B (HIB) in the combined diphtheria-tetanus-pertussis (DTP)-hepatitis B virus (HBV) vaccination. The effectiveness and safety of the combined vaccine should be carefully and systematically assessed to ensure its acceptability by the community.

OBJECTIVES: To compare the effectiveness of combined DTP-HBV-HIB vaccines versus combined DTP-HBV and separate HIB vaccinations.

SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2011, Issue 4), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (January 1966 to week 1, November 2011), EMBASE (January 1990 to November 2011) and www.clinicaltrials.gov (up to April 2011).

SELECTION CRITERIA: Randomised controlled trials (RCTs) or quasi-RCTs comparing vaccination with any combined DTP-HBV-HIB vaccine, with or without three types of inactivated polio virus (IPV) or concomitant oral polio vaccine (OPV) in any dose, preparation or time schedule, compared with separate vaccines or placebo, administered to infants up to two years old.

DATA COLLECTION AND ANALYSIS: Two review authors independently inspected references identified by the searches and evaluated them against the inclusion criteria, extracted data and assessed the methodological quality of included trials.

MAIN RESULTS: Data for the primary outcome (prevention of disease) were lacking. We performed a meta-analysis to pool the results of 20 studies with 5874 participants in an immunogenicity analysis and 5232 participants in the reactogenicity analysis. There were no data on clinical outcomes for the primary outcome (prevention of disease) and all studies used immunogenicity and reactogenicity (adverse events). The number of vaccine doses differed significantly between the studies.

Heterogeneous interventions, study location, healthcare environment and combining research across disparate geographical locations, may have lead to bias. The risk of bias was unclear across most of the included studies. Comparisons found little heterogeneity. In two immunological responses the combined vaccine achieved lower responses than the separate vaccines for HIB and tetanus. No significant differences in immunogenicity were found for pertussis, diphtheria, polio and hepatitis B. Serious adverse events were comparable with mainly hospitalisation and acute bronchiolitis cases. Minor adverse events such as pain and redness were more common in children given the combined vaccine. Overall, the direction shown by the results is in favour of the DTPw (diphtheria-tetanus-whole cell pertussis)-HBV-HIB vaccine rather than the DTPa (diphtheria-tetanus-acellular pertussis)-HBV-HIB vaccine when compared to the separate vaccines (size of effect: risk ratio (RR) 1.43; 95% confidence interval (CI) 0.98 to 2.10, for 5269 participants).

AUTHORS' CONCLUSIONS: We could not conclude that the immune responses elicited by the combined vaccine were different from or equivalent to the separate vaccines. There was significantly less immunological response for HIB and tetanus and more local reactions in the combined injections. However, these differences rely mostly on one study each. Studies did not use an intention-to-treat (ITT) analysis and we were uncertain about the risk of bias in many of the studies. These results are

therefore inconclusive. Studies addressing clinical end points whenever possible, using correct methodology and a large enough sample size should be conducted.

McBean AM et al. Serologic response to oral polio vaccine and enhanced potency inactivated polio vaccines. *Am J Epidemiol.* 1988;128:615-628.

In a randomized, controlled trial carried out from November 1980 to July 1983 involving 1,114 infants in Baltimore City and in Baltimore and Prince George's counties, Maryland, the serologic response to three doses of two enhanced-potency inactivated polio vaccines was compared with the response to three doses of oral polio vaccine. The mean ages at vaccination were 2.2, 4.7, and 19.9 months, respectively, for the three doses. Seroconversion after the first dose varied from 35% to 84%, and it was higher after oral polio vaccine than after either of the enhanced-potency inactivated polio vaccines for polioviruses types 2 and 3.

Approximately two and one-half and 16 months after the second dose, almost all inactivated polio vaccine recipients had antibodies against all three virus types (98-100%). Fewer oral polio vaccine recipients had detectable antibodies to type 1 (89-92%) and to type 3 (96%). After three doses of vaccine, all children had antibodies against types 2 and 3. Approximately 1% of the inactivated polio vaccine recipients and 3% of the oral polio vaccine recipients lacked antibody to type 1. One or two doses of oral polio vaccine stimulated higher reciprocal geometric mean antibody titers against type 2 poliovirus than did the inactivated polio vaccine. For the other two types, the results were mixed. The third dose of inactivated polio vaccine produced significant increases in the reciprocal geometric mean titers against each of the three poliovirus types and resulted in significantly higher reciprocal geometric mean titers after three doses of vaccine for recipients of inactivated polio vaccine than for recipients of oral polio vaccine.

Kim-Farley RJ et al Outbreak of paralytic poliomyelitis, Taiwan. *Lancet.* 1984;2:1322-1324.

Taiwan had been free of major poliomyelitis outbreaks since 1975, but from May 29 to Oct 26, 1982, 1031 cases of type 1 paralytic poliomyelitis were reported to the Taiwan health authorities. Before the outbreak approximately 80% of infants had received at least 2 doses of trivalent oral poliovaccine (OPV) by their first birthday. Of the 86% of poliomyelitis patients whose vaccination status was known 65% had not had poliovaccine, 19% had received one dose, 8% had received two doses, and 8% had received three or more doses. Vaccine efficacy was calculated to be 82% after one dose, 96% after two doses, and 98% after three or more doses. Failure to vaccinate rather than vaccine failure was the most important risk factor in this outbreak. A child who had not had any vaccine was 80 times more likely to become a case than one who had received three or more doses of poliovaccine, independent of sanitation facilities at home. A child was 5 times more likely to become a case if he received water from non-municipal rather than municipal sources. Furthermore, for children who received municipal water, the risk was doubled if the family shared a toilet with at least one other family. This outbreak shows that major epidemics can occur in areas that have high overall community vaccination levels. Identification and vaccination of subpopulations with low coverage is essential for the control of poliomyelitis.

Sutter RW et al. Outbreak of paralytic poliomyelitis in Oman: evidence for widespread transmission among fully vaccinated children. *Lancet.* 1991;338:715-720.

From January, 1988, to March, 1989, a widespread outbreak (118 cases) of poliomyelitis type

1 occurred in Oman. Incidence of paralytic disease was highest in children younger than 2 years (87/100,000) despite an immunisation programme that recently had raised coverage with 3 doses of oral poliovirus vaccine (OPV) among 12-month-old children from 67% to 87%. We did a case-control study (70 case-patients, 692 age-matched controls) to estimate the clinical efficacy of OPV, assessed the immunogenicity of OPV and extent of poliovirus spread by serology, retrospectively evaluated the cold chain and vaccine potency, and sought the origin of the outbreak strain by genomic sequencing. 3 doses of OPV reduced the risk of paralysis by 91%; vaccine failures could not be explained by failures in the cold chain nor on suboptimum vaccine potency. Cases and controls had virtually identical type 1 neutralising antibody profiles, suggesting that poliovirus type 1 circulation was widespread. Genomic sequencing indicated that the outbreak strain had been recently imported from South Asia and was distinguishable from isolates indigenous to the Middle East. Accumulation of enough children to sustain the outbreak seems to have been due to previous success of the immunisation programme in reducing spread of endemic strains, suboptimum efficacy of OPV, and delay in completing the primary immunisation series until 7 months of age. Additionally, the estimated attack rate of infection among children aged 9-23 months exceeded 25% in some regions, suggesting that a substantial proportion of fully vaccinated children had been involved in the chain of transmission.

Patriarca PA. Factors affecting the immunogenicity of OPV in developing countries: a review. Rev Inf Dis. 1991;Sep-Oct;13(5):926-939.

Although rates of seroconversion following administration of trivalent oral poliovirus vaccine (TOPV) approach 100% in industrialized countries, only 73% (range, 36%-99%) and 70% (range, 40%-99%) of children in developing countries have detectable antibody to poliovirus types 1 and 3, respectively, after three doses. While factors accounting for these differences have not been fully elucidated, available data suggest that type 2 vaccine virus and enteric pathogens often interfere with responses to types 1 and 3 vaccine viruses but that this interference may be overcome by modifying the absolute and relative dosage of the three Sabin types. Increasing the interval between doses beyond 30 days may also be important, in view of the prolonged excretion of vaccine virus and the potential for interference with responses to subsequent doses. Although advances in molecular biology may ultimately lead to the development of more-immunogenic vaccine candidates, approaches such as increasing the number of doses of TOPV, mass vaccination campaigns, and combined use of oral and inactivated vaccines should also be considered.

Estívariz CF et al. Immunogenicity of poliovirus vaccines administered at age 6-9 months in Moradabad District, India: A randomized controlled phase 3 trial. Lancet Inf Dis. 2012;12:128-35.

BACKGROUND: The continued presence of polio in northern India poses challenges to the interruption of wild poliovirus transmission and the management of poliovirus risks in the post-eradication era. We aimed to assess the current immunity profile after routine doses of trivalent oral poliovirus vaccine (OPV) and numerous supplemental doses of type-1 monovalent OPV (mOPV1), and compared the effect of five vaccine formulations and dosages on residual immunity gaps. **METHODS:** We did a community-based, randomised controlled trial of healthy infants aged 6-9 months at ten sites in Moradabad, India. Serum neutralising antibody was measured before infants were randomly assigned to a study group and given standard-potency or higher-potency mOPV1,

intradermal fractional-dose inactivated poliovirus vaccine (IPV, GlaxoSmithKline), or intramuscular full-dose IPV from two different manufacturers (GlaxoSmithKline or Panacea). Follow-up sera were taken at days 7 and 28. Our primary endpoint was an increase of more than four times in antibody titres. We did analyses by per-protocol in children with a blood sample available before, and 28 days after, receiving study vaccine (or who completed study procedures). This trial is registered with Current Controlled Trials, number ISRCTN90744784.

FINDINGS: Of 1002 children enrolled, 869 (87%) completed study procedures (ie, blood sample available at day 0 and day 28). At baseline, 862 (99%), 625 (72%), and 418 (48%) had detectable antibodies to poliovirus types 1, 2, and 3, respectively. In children who were type-1 seropositive, an increase of more than four times in antibody titre was detected 28 days after they were given standard-potency mOPV1 (5/13 [38%]), higher-potency mOPV1 (6/21 [29%]), intradermal IPV (9/16 [56%]), GlaxoSmithKline intramuscular IPV (19/22 [86%]), and Panacea intramuscular IPV (11/13 [85%]). In those who were type-2 seronegative, 42 (100%) of 42 seroconverted after GlaxoSmithKline intramuscular IPV, and 24 (59%) of 41 after intradermal IPV ($p<0.0001$). 87 (90%) of 97 infants who were type-3 seronegative seroconverted after intramuscular IPV, and 21 (36%) of 49 after intradermal IPV ($p<0.0001$).

INTERPRETATION: Supplemental mOPV1 resulted in almost total seroprevalence against poliovirus type 1, which is consistent with recent absence of poliomyelitis cases; whereas seroprevalence against types 2 and 3 was expected for routine vaccination histories. The immunogenicity of IPV produced in India (Panacea) was similar to that of an internationally manufactured IPV (GSK). Intradermal IPV was less immunogenic.

Grassly NC et al. Protective efficacy of a monovalent oral type 1 poliovirus vaccine. Lancet. 2007;369:1356-1362.

BACKGROUND: A high-potency monovalent oral type 1 poliovirus vaccine (mOPV1) was developed in 2005 to tackle persistent poliovirus transmission in the last remaining infected countries. Our aim was to assess the efficacy of this vaccine in India.

METHODS: We estimated the efficacy of mOPV1 used in supplementary immunisation activities from 2076 matched case-control pairs of confirmed cases of poliomyelitis caused by type 1 wild poliovirus and cases of non-polio acute flaccid paralysis in India. The effect of the introduction of mOPV1 on population immunity was calculated on the basis of estimates of vaccination coverage from data for non-polio acute flaccid paralysis.

FINDINGS: In areas of persistent poliovirus transmission in Uttar Pradesh, the protective efficacy of mOPV1 was estimated to be 30% (95% CI 19-41) per dose against type 1 paralytic disease, compared with 11% (7-14) for the trivalent oral vaccine. 76-82% of children aged 0-23 months were estimated to be protected by vaccination against type 1 poliovirus at the end of 2006, compared with 59% at the end of 2004, before the introduction of mOPV1.

INTERPRETATION: Under conditions where the efficacy of live-attenuated oral poliovirus vaccines is compromised by a high prevalence of diarrhoea and other infections, a dose of high-potency mOPV1 is almost three times more effective against type 1 poliomyelitis disease than is trivalent vaccine. Achieving high coverage with this new vaccine in areas of persistent poliovirus transmission should substantially improve the probability of rapidly eliminating transmission of the disease.

WHO Collaborative Study Group on Oral and Inactivated Poliovirus Vaccines.

Combined immunization of infants with oral and inactivated poliovirus vaccines: results of a randomized trial in the Gambia, Oman, and Thailand. Bulletin of the World Health Organization, 1996, 74 (3): 253-268.

To assess an immunization schedule combining oral (OPV) and inactivated poliovirus vaccines (IPV), we conducted a clinical trial in the Gambia, Oman, and Thailand. Children were randomized to receive one of the following schedules: OPV at birth, 6, 10, and 14 weeks of age; OPV at birth followed by both OPV and IPV at 6, 10, and 14 weeks of age; or placebo at birth followed by IPV at 6, 10, and 14 weeks of age. A total of 1685 infants were enrolled; 24-week serum specimens were available for 1291 infants (77%). Across the study sites at 24 weeks of age, the proportion of seropositive children in the combined schedule group was 95-99% for type 1, 99-100% for type 2, and 97-100% for type 3. In the Gambia and Oman, the combined schedule performed significantly better than OPV for type 1 (95-97% versus 88-90%) and type 3 (97-99% versus 72-73%). In the Gambia and Oman, seroprevalences in the IPV group were lower for type 1 (significantly lower in the Gambia); significantly lower for type 2; and significantly higher for type 3, compared with the OPV group. In Thailand, the IPV group had significantly lower proportions of children who were seropositive for each of the three types, compared with the OPV group. The responses to OPV in the Gambia, Oman, and Thailand were consistent with previous studies from these countries. IPV given at 6, 10, and 14 weeks of age provided inadequate serological protection against poliovirus, especially type 1. The combined schedule provided the highest levels of serum antibody response, with mucosal immunity equivalent to that produced by OPV alone.

Sutter RW et al. Immunogenicity of bivalent types 1 and 3 oral poliovirus vaccine: a randomised, double-blind, controlled trial. Lancet. 2010;376 (9753):1682-1688.

BACKGROUND: Poliovirus types 1 and 3 co-circulate in poliomyelitis-endemic countries. We aimed to assess the immunogenicity of a novel bivalent types 1 and 3 oral poliovirus vaccine (bOPV).

METHODS: We did a randomised, double-blind, controlled trial to assess the superiority of monovalent type 2 OPV (mOPV2), mOPV3, or bOPV over trivalent OPV (tOPV), and the non-inferiority of bivalent vaccine compared with mOPV1 and mOPV3. The study was done at three centres in India between Aug 6, 2008, and Dec 26, 2008. Random allocation was done by permuted blocks of ten. The primary outcome was seroconversion after one monovalent or bivalent vaccine dose compared with a dose of trivalent vaccine at birth. The secondary endpoints were seroconversion after two vaccine doses compared with after two trivalent vaccine doses and cumulative two-dose seroconversion. Parents or guardians and study investigators were masked to treatment allocation. Because of multiple comparisons, we defined $p \leq 0.01$ as statistically significant. This trial is registered with Current Controlled Trials, ISRCTN 64725429.

RESULTS: 900 newborn babies were randomly assigned to one of five vaccine groups (about 180 patients per group); of these 70 (8%) discontinued, leaving 830 (92%) for analysis. After the first dose, seroconversion to poliovirus type 1 was 20% for both mOPV1 (33 of 168) and bOPV (32 of 159) compared with 15% for tOPV (25 of 168; $p > 0.01$), to poliovirus type 2 was 21% (35 of 170) for mOPV2 compared with 25% (42 of 168) for tOPV ($p > 0.01$), and to poliovirus type 3 was 12% (20 of 165) for mOPV3 and 7% (11 of 159) for bOPV compared with 4% (7 of 168) for tOPV (mOPV3 vs tOPV $p = 0.01$; bOPV vs tOPV; $p > 0.01$). Cumulative two-dose seroconversion to poliovirus type 1 was 90% (151 of 168) for mOPV1 and 86% (136 of 159) for bOPV compared with 63% (106 of 168) for tOPV

($p < 0.0001$), to poliovirus type 2 was 90% (153 of 170) for mOPV2 compared with 91% (153 of 168) for tOPV ($p > 0.01$), and to poliovirus type 3 was 84% (138 of 165) for mOPV3 and 74% (117 of 159) for bOPV compared with 52% (87 of 168) for tOPV ($p < 0.0001$). The vaccines were well tolerated. 19 serious adverse events occurred, including one death; however, these events were not attributed to the trial interventions.

INTERPRETATION: The findings show the superiority of bOPV compared with tOPV, and the non-inferiority of bOPV compared with mOPV1 and mOPV3.

John TJ. Immunisation against polioviruses in developing countries. *Rev Med Virol* 1993; 3: 149-160.

Interrupting the transmission of wild polioviruses in developing countries remains the most difficult step towards global eradication of poliomyelitis. The global strategy ought to be to achieve this using either or both vaccines, without waiting for socio-economic development to result in a reduced power of wild virus transmission. In developed countries with low transmission potential, the protective efficacy and the herd effect of either OPV or IPV/APV-E are sufficient to eradicate wild viruses. Developing countries are not uniform in their poliovirus epidemiology: broadly they can be divided into those in which protective efficacy of OPV is high but herd effect is poor and others in which both are poor. Large countries such as India may have regions representing both epidemiological patterns. The same strategy applies everywhere, but the tactical use of the vaccines should be intelligently designed in order to achieve eradication in all areas with differing epidemiological patterns in the shortest possible time. Where the epidemiology is varied, the tactic of immunisation should also be modified to meet this challenge. Exaggerated claims of the properties of either vaccine have not only led to controversies but also to inadequate immunisation schedules and have resulted in delays in the design and application of appropriate immunisation tactics in many developing countries. Consequently hundreds of thousands of children in developing countries have suffered from paralytic poliomyelitis which could have been prevented if scientists and policymakers had been more objective and dispassionate.

Bhaskaram P et al. Systemic and mucosal immune response to polio vaccination with additional dose in newborn period. *J Trop Paediatrics*. 1997;43(4): 232-234

Administration of supplementary dose of oral polio vaccine (OPV) during neonatal period is recommended by WHO in countries like India, where host response to the regular three-dose schedule is not satisfactory and poliomyelitis continues to be a problem. The efficacy of this dose +3, and +5 doses of OPV in terms of seropositivity, seroconversion, systemic, and mucosal antibody responses were measured in 51 infants in a follow-up study from birth to 30 weeks. Administration of the additional dose in the newborn period significantly improved seropositivity and seroconversion rates compared to the conventional 3 or 5 dose schedules. Systemic antibody titres improved with each dose of the vaccine and 40-60 per cent of infants had $> 1:128$ titres to the three types of polioviruses that could prevent re-infection of the gut and 50 per cent of them had mucosal antibodies as evidenced by specific IgA in nasopharyngeal secretions. Therefore, administration of OPV in the neonatal period should be made compulsory in countries where poliomyelitis still continues to be a problem.

De-Xiang D et al. Immunization of neonates with trivalent oral poliomyelitis vaccine (Sabin). Bull World Health Organ. 1986; 64(6):853–860.

A study was carried out between November 1981 and April 1982 on the immunological effect of administering trivalent live, oral polio vaccine to 200 mature healthy neonates from Henan Province, China. The initial dose of vaccine was given at 3 days of age, and 2 months thereafter antibodies to poliovirus types 1, 2, and 3, respectively, were detected in 46.7%, 60.7% and 48.6% of the neonates; after the second dose, the levels were 86.9%, 95.3%, and 97.2%, with geometric mean titres of 1:106.2, 1:349.8, and 1:232.5. Almost 100% of neonates exhibited antibodies after the fourth dose of vaccine. Eighty-two percent of the neonates excreted poliovirus for at least a week after the initial dose of vaccine, and this increased to 99% after the second dose. Seroconversion at 4 months of age was similar to that of a group of controls who received their initial dose of vaccine at 2 months of age; however, immunization of neonates induced immunity to poliovirus at the earliest possible age.

John TJ et al. Monovalent type 1 oral poliovirus vaccine among infants in India: report of two randomized double-blind controlled clinical trials. Vaccine. 2011 Aug 5;29(34):5793–5801

BACKGROUND: To provide the polio eradication initiative with more immunogenic oral poliovirus vaccines (OPVs), we evaluated newly developed monovalent type 1 OPV (mOPV1) among infants in India.

METHODS: Two double-blind randomized controlled clinical trials compared two mOPV1s (mOPV1 A and mOPV1 B) versus trivalent OPV (tOPV X) given at birth (trial I), or assessed two products of higher-potency mOPV1 (mOPV1 C and mOPV1 D) versus regular-potency mOPV1 (mOPV1 B) or tOPV Y given at birth and at 30 days (trial II).

RESULTS: In trial I, 597 newborns were enrolled, 66 withdrawn or excluded, leaving 531 (88.9%) subjects for analysis. Seroconversion to poliovirus type 1 was 10.4% for mOPV1 A, 15.6% for mOPV1 B and 10.2% for tOPV X. In trial II, 718 newborns were enrolled, 135 withdrawn or excluded, leaving 583 (81.2%) subjects for analysis. Seroconversion to poliovirus type 1 following a birth dose was 15.1%, 19.7%, 18.0% and 10.6%, following the 30-day dose 87.1%, 89.2%, 84.4%, or 55.9%, and cumulative for both doses 90.4%, 90.3%, 89.5% and 61.9% for mOPV1s B, C, and D and tOPV Y, respectively.

CONCLUSIONS: In both studies, seroconversion rates were unexpectedly low to poliovirus type 1 after mOPV1 or tOPV given at birth but high for all formulations of mOPV1 given at age 30 days. The cause for low immunogenicity of OPV at birth in India is not known.

Mateen FJ et al. Oral and inactivated poliovirus vaccines in the newborn: a review. Vaccine. 2013;31(21):2517-2524.

BACKGROUND: Oral poliovirus vaccine (OPV) remains the vaccine-of-choice for routine immunization and supplemental immunization activities (SIAs) to eradicate poliomyelitis globally. Recent data from India suggested lower than expected immunogenicity of an OPV birth dose, prompting a review of the immunogenicity of OPV or inactivated poliovirus vaccine (IPV) when administered at birth.

METHODS: We evaluated the seroconversion and reported adverse events among infants given a single birth dose (given ≤ 7 days of life) of OPV or IPV through a systematic review of published articles and conference abstracts from 1959 to 2011 in any language found on PubMed, Google Scholar, or reference lists of selected articles.

RESULTS: 25 articles from 13 countries published between 1959 and 2011 documented seroconversion rates in newborns following an OPV dose given within the first seven days of life.

There were 10 studies that measured seroconversion rates between 4 and 8 weeks of a single birth dose of TOPV, using an umbilical cord blood draw at the time of birth to establish baseline antibody levels. The percentage of newborns who seroconverted at 8 weeks range from 6-42% for poliovirus type 1, 2-63% for type 2, and 1-35% for type 3. For mOPV type 1, seroconversion ranged from 10 to 76%; mOPV type 3, the range was 12-58%; and for the one study reporting bOPV, it was 20% for type 1 and 7% for type 3. There were four studies of IPV in newborns with a seroconversion rate of 8-100% for serotype 1, 15-100% for serotype 2, and 15-94% for serotype 3, measured at 4-6 weeks of life. No serious adverse events related to newborn OPV or IPV dosing were reported, including no cases of acute flaccid paralysis.

CONCLUSIONS: There is great variability of the immunogenicity of a birth dose of OPV for reasons largely unknown. Our review confirms the utility of a birth dose of OPV, particularly in countries where early induction of polio immunity is imperative. IPV has higher seroconversion rates in newborns and may be a superior choice in countries which can afford IPV, but there have been few studies of an IPV dose for newborns.

Gamage D et al. Achieving high seroprevalence against polioviruses in Sri Lanka-Results from a serological survey, 2014. J Epidemiol Glob Health. 2015 Dec;5(4 Suppl 1):S67–71

The immunization program in Sri Lanka consistently reaches >90% coverage with oral poliovirus vaccines (OPV), and no polio supplementary vaccination campaigns have been conducted since 2003. We evaluated serological protection against polioviruses in children. A cross-sectional community-based survey was performed in three districts of Sri Lanka (Colombo, Badulla, and Killinochi). Randomly selected children in four age groups (9-11 months, 3-4 years, 7-9 years, and 15 years) were tested for poliovirus neutralizing antibodies. All 400 enrolled children completed the study. The proportion of seropositive children for poliovirus Type 1 and Type 2 was >95% for all age groups; for poliovirus Type 3 it was 95%, 90%, 77%, and 75% in the respective age groups. The vaccination coverage in our sample based on vaccination cards or parental recall was >90% in all age groups. Most Sri Lankan children are serologically protected against polioviruses through routine immunization only. This seroprevalence survey provided baseline data prior to the anticipated addition of inactivated poliovirus vaccine (IPV) into the Sri Lankan immunization program and the switch from trivalent OPV (tOPV) to bivalent OPV (bOPV).

Nishio O et al. The trend of acquired immunity with live poliovirus vaccine and the effect of revaccination: follow up of vaccinees for ten years. J Biol Standardization. 1984;12(1):1–10.

The persistence of neutralizing antibody (NA) against three types of poliovirus acquired after two doses of trivalent live attenuated poliovirus vaccine (LPV) has been followed up for ten years in individual vaccinees. Sixty-seven children were bled once a year over a five year period following the primary vaccination. More than 80% of them retained NA against all three types of poliovirus. Thirty-two individuals whose NA titres were 1:16 or over for types 1 and 2 and 1:4 or over for type 3 at the fifth year were further followed up for a further five years and it was shown that during this period some of them had a naturally-acquired antibody rise, mostly against type 3 virus. At the sixth to eighth year after the primary vaccination, one further dose of the trivalent vaccine was administered to the children whose NA titres were down to 1:8 or less and the effect of booster vaccination on NA was followed. Other subjects were revaccinated with LPV and their fecal excretion of the vaccine virus was investigated. The results showed that a decrease in serum antibody level could be a good indicator of the

local resistance of the alimentary tract and that reinfection could occur if serum NA had decreased to 1:8 or less, which allowed a virus excretion in the stools.

WHO prequalified vaccines [online database]; available at http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/index.html, accessed February 2016). (No abstract available).

Patel M et al. Influence of oral polio vaccines on performance of the monovalent and pentavalent rotavirus vaccines. *Vaccine*. 2012;30, Supplement 1, A30–A35.

In recent years, two live, oral rotavirus vaccines have been successfully tested in developing and industrialized countries, and both vaccines are now recommended by the World Health Organization for all children worldwide. Both immunogenicity and efficacy of these rotavirus vaccines has been lower in developing compared to industrialized settings. We reviewed the data on the effect of trivalent OPV on the immunogenicity and efficacy of two rotavirus vaccines currently recommended by the WHO. While rotavirus vaccines have not affected immune responses to OPV, in general, the immune responses (i.e., antibody levels) to rotavirus vaccination were lower when rotavirus vaccines were co-administered with OPV. Limited data suggests that the interference is greater after the first dose of OPV, presumably because the first dose is associated with greatest intestinal replication of vaccine polio virus strains, and this interference is largely overcome with subsequent rotavirus vaccine doses. Despite the lower immunogenicity, one large efficacy study in middle income Latin American countries showed no decrease in protective efficacy of rotavirus vaccine in infants receiving concurrent OPV. While these data are encouraging and support simultaneous administration of rotavirus vaccines and OPV, additional evidence should be gathered as rotavirus vaccines are used more widely in developing country settings, where OPV is routinely used, rather than inactivated polio vaccine.

Kollaritsch H et al. Safety and Immunogenicity of Live Oral Cholera and Typhoid Vaccines Administered Alone or in Combination with Antimalarial Drugs, Oral Polio Vaccine, or Yellow Fever Vaccine. *The Journal of Infectious Diseases* 1997;175:871–875.

The effects of concomitant administration of antimalarial drugs, oral polio vaccine, or yellow fever vaccine on the immune response elicited by the *Vibrio cholerae* CVD103-HgR and *Salmonella typhi* Ty21a live oral vaccines were investigated. Healthy adults were immunized with CVD103-HgR alone or combined with Ty21a. Subjects were randomized to simultaneously receive mefloquine, chloroquine or proguanil, or oral polio or yellow fever vaccine. The vibriocidal antibody seroconversion rate was significantly reduced ($P = .008$) only in the group that received chloroquine with the CVD103-HgR. The geometric mean vibriocidal antibody titer was significantly decreased in the groups that received chloroquine ($P = .001$) or mefloquine ($P = .02$) compared with titers in groups that received CVD103-HgR alone. However, similar immunosuppressive effects were not observed in the groups immunized with Ty21a and CVD103-HgR. Only the concomitant administration of proguanil effected a significant ($P = .013$) decline in the anti-S. typhi lipopolysaccharide antibody response. These results indicate that chloroquine and proguanil should not be simultaneously administered with the CVD103-HgR and Ty21a vaccine strains, respectively.

Yang C. et al. Intratypic recombination among lineages of type 1 vaccine-derived poliovirus emerging during chronic infection of an immunodeficient patient, *J Virol*. 2005;79(20): 12623-12634.

We determined the complete genomic sequences of nine type 1 immunodeficient vaccine-derived poliovirus (iVDPV) isolates obtained over a 337-day period from a poliomyelitis patient from Taiwan with common variable immunodeficiency. The iVDPV isolates differed from the Sabin type 1 oral poliovirus vaccine (OPV) strain at 1.84% to 3.15% of total open reading frame positions and had diverged into at least five distinct lineages. Phylogenetic analysis suggested that the chronic infection was initiated by the fifth and last OPV dose, given 567 days before onset of paralysis, and that divergence of major lineages began very early in the chronic infection. Key determinants of attenuation in Sabin 1 had reverted in the iVDPV isolates, and representative isolates of each lineage showed increased neurovirulence for PVR-Tg21 transgenic mice. None of the isolates had retained the temperature-sensitive phenotype of Sabin 1. All isolates were antigenic variants of Sabin 1, having multiple amino acid substitutions within or near neutralizing antigenic sites 1, 2, and 3a. Antigenic divergence of the iVDPV variants from Sabin 1 followed two major independent evolutionary pathways. The emergence of distinct coreplicating lineages suggests that iVDPVs can replicate for many months at separate sites in the gastrointestinal tract. Some isolates had mosaic genome structures indicative of recombination across and within lineages. iVDPV excretion apparently ceased after 30 to 35 months of chronic infection. The appearance of a chronic VDPV excretor in a tropical, developing country has important implications for the strategy to stop OPV immunization after eradication of wild polioviruses.

Duintjer Tebbens RJ et al. Risks of paralytic disease due to wild or vaccine-derived poliovirus after eradication. Risk Analysis. 2006;26(6):1471-1505.

After the global eradication of wild polioviruses, the risk of paralytic poliomyelitis from polioviruses will still exist and require active management. Possible reintroductions of poliovirus that can spread rapidly in unprotected populations present challenges to policymakers. For example, at least one outbreak will likely occur due to circulation of a neurovirulent vaccine-derived poliovirus after discontinuation of oral poliovirus vaccine and also could possibly result from the escape of poliovirus from a laboratory or vaccine production facility or from an intentional act. In addition, continued vaccination with oral poliovirus vaccines would result in the continued occurrence of vaccine-associated paralytic poliomyelitis. The likelihood and impacts of reintroductions in the form of poliomyelitis outbreaks depend on the policy decisions and on the size and characteristics of the vulnerable population, which change over time. A plan for managing these risks must begin with an attempt to characterize and quantify them as a function of time. This article attempts to comprehensively characterize the risks, synthesize the existing data available for modeling them, and present quantitative risk estimates that can provide a starting point for informing policy decisions.

Hennessey KA et al. Poliovirus vaccine shedding among persons with HIV in Abidjan, Côte d'Ivoire. J Inf Dis. 2005; 192:2124– 2128.

BACKGROUND: As polio eradication nears, the development of immunization policies for an era without the disease has become increasingly important. Outbreaks due to circulating vaccine-derived poliovirus (VDPV) and rare cases of immunodeficient persons with prolonged VDPV shedding lend to the growing consensus that oral poliovirus vaccine (OPV) use should be discontinued as soon after polio eradication as possible. The present study was conducted to assess whether persons

infected with human immunodeficiency virus (HIV) experience prolonged VDPV shedding and serve as a source of reintroduction of virus into the population.

METHODS: Adults infected with HIV had specimens tested (1) 8 months after a mass OPV campaign, to determine whether poliovirus related to OPV administered during the campaign was present (i.e., prolonged excretion), and (2) starting 7 weeks after a subsequent campaign, to determine whether poliovirus could be detected after the height of OPV exposure.

RESULTS: A total of 419 participants were enrolled--315 during the 8-12 months after an OPV campaign held in 2001 and 104 during the 7-13 weeks after a 2002 campaign. No poliovirus was isolated from any participants.

CONCLUSIONS: It appears unlikely that adults infected with HIV experience prolonged vaccine virus shedding, and, therefore, they probably represent a minimal risk of reintroducing vaccine virus into the population after poliovirus has been eradicated.

Vernon A et al. Paralytic poliomyelitis and HIV infection in Kinshasa, Zaire . In: Proceedings of the Sixth International Conference on AIDS . San Francisco, CA; June 20–24 1990.

OBJECTIVE: To determine whether the presence of HIV infection and the associated immunodepression increases the risk of paralytic poliomyelitis in children under the age of 15 years in Kinshasa, Zaire, an area endemic for both infections. **METHODS:** To ascertain cases of paralytic poliomyelitis, biweekly visits were made from October 1988 thru September 1989 to a network of 27 clinical sites, including the principal pediatric and rehabilitation services in Kinshasa. To identify risk factors associated with possible concurrent HIV and paralytic polio infection, a case-control study was performed. Cases of paralytic polio were children under the age of 15 years with acute onset of asymmetric flaccid paralysis, without sensory changes, and which persisted for at least 60 days if the child survived, and with no other apparent cause. Controls were age (+/- 4 months) and neighborhood-matched children. HIV infection was determined by ELISA and immunoblot. For logistic reasons, the case-control study was limited to a systematic one-third sample of cases.

RESULTS: A total of 131 cases of paralytic poliomyelitis were identified. Two 2(4.5%) of 44 case children and 4(9.5%) of 42 case mothers were HIV(+). Case-control groups have thus far been constituted for 35 cases. The odds ratio comparing the HIV infection rate in case children with that in control children was not significantly different from 1.0 (p greater than 0.05). The same was true for case and control mothers. **CONCLUSION:** In our Kinshasa study population, paralytic poliomyelitis was not associated with a statistically significantly increased risk of HIV infection. These data provide support for continued use of live oral polio vaccine in immunization programs in HIV-endemic areas of Africa.

Clements CJ et al. How about HIV infection and routine childhood immunization: a review. Bull World Health Organ. 1987; 65(6):905–911

This review summarizes current experience with immunization of children infected with human immunodeficiency virus (HIV), relevant data on immunization of HIV-infected adults, and in vitro studies with vaccine antigens and HIV-infected cells. Theoretical concerns about the possible effects of repeated antigenic stimulation on the course of HIV infection are also summarized. Finally, available information on the course of vaccine preventable diseases in HIV-infected children is reviewed. Together these studies provide a current data base for decisions about immunization of HIV-infected children.

McKinlay MA et al. Progress in the development of poliovirus antiviral agents and their essential role in reducing risks that threaten eradication. J Infect Dis. (2014) 210 (suppl 1): S447–S453.

Chronic prolonged excretion of vaccine-derived polioviruses by immunodeficient persons (iVDPV) presents a personal risk of poliomyelitis to the patient as well as a programmatic risk of delayed global eradication. Poliovirus antiviral drugs offer the only mitigation of these risks. Antiviral agents may also have a potential role in the management of accidental exposures and in certain outbreak scenarios. Efforts to discover and develop poliovirus antiviral agents have been ongoing in earnest since the formation in 2007 of the Poliovirus Antivirals Initiative. The most advanced antiviral, pocapavir (V-073), is a capsid inhibitor that has recently demonstrated activity in an oral poliovirus vaccine human challenge model. Additional antiviral candidates with differing mechanisms of action continue to be profiled and evaluated preclinically with the goal of having 2 antivirals available for use in combination to treat iVDPV excretors.

Bakker WAM, et al. Inactivated polio vaccine development for technology transfer using attenuated Sabin poliovirus strains to shift from Salk-IPV to Sabin-IPV. Vaccine. 2011;29(41):7188–7196.

Industrial-scale inactivated polio vaccine (IPV) production dates back to the 1960s when at the Rijks Instituut voor de Volksgezondheid (RIV) in Bilthoven a process was developed based on micro-carrier technology and primary monkey kidney cells. This technology was freely shared with several pharmaceutical companies and institutes worldwide. In this contribution, the history of one of the first cell-culture based large-scale biological production processes is summarized. Also, recent developments and the anticipated upcoming shift from regular IPV to Sabin-IPV are presented. Responding to a call by the World Health Organization (WHO) for new polio vaccines, the development of Sabin-IPV was continued, after demonstrating proof of principle in the 1990s, at the Netherlands Vaccine Institute (NVI). Development of Sabin-IPV plays an important role in the WHO polio eradication strategy as biocontainment will be critical in the post-OPV cessation period. The use of attenuated Sabin strains instead of wild-type Salk polio strains will provide additional safety during vaccine production. Initially, the Sabin-IPV production process will be based on the scale-down model of the current, and well-established, Salk-IPV process. In parallel to clinical trial material production, process development, optimization and formulation research is being carried out to further optimize the process and reduce cost per dose. Also, results will be shown from large-scale (to prepare for future technology transfer) generation of Master- and Working virus seedlots, and clinical trial material (for phase I studies) production. Finally, the planned technology transfer to vaccine manufacturers in low and middle-income countries is discussed.

Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (inactivated). WHO Technical Report Series 993, 2014. Geneva, World Health Organization. Available at http://who.int/biologicals/vaccines/Annex3_IPV_Recommendations_eng.pdf?ua=1, accessed February 2016). (No abstract available).

Application of WHO Multi-Dose Vial Policy for Inactivated Polio Vaccine. Available at http://www.who.int/immunization/diseases/poliomyelitis/inactivated_polio_vaccine/MDVP_Nov2014.pdf, accessed February 2016. (No abstract available).

Vidor E., et al. Poliovirus vaccine-inactivated. In O. W. Plotkin SA, Vaccines, 2013, 6th edition 2013. Philadelphia: Elsevier-Saunders, pp 573-597. (No abstract available)

Iqbal S et al. Preparation for global introduction of inactivated poliovirus vaccine: safety evidence from the US Vaccine Adverse Event Reporting System, 2000–12. Lancet Infect Dis 2015. Volume 15, No. 10, p1175–1182, October 2015.

BACKGROUND: Safety data from countries with experience in the use of inactivated poliovirus vaccine (IPV) are important for the global polio eradication strategy to introduce IPV into the immunisation schedules of all countries. In the USA, IPV has been included in the routine immunisation schedule since 1997. We aimed to analyse adverse events after IPV administration reported to the US Vaccine Adverse Event Reporting System (VAERS).

METHODS: We analysed all VAERS data associated with IPV submitted between Jan 1, 2000, and Dec 31, 2012, either as individual or as combination vaccines, for all age and sex groups. We analysed the number and event type (non-serious, non-fatal serious, and death reports) of individual reports, and explored the most commonly coded event terms to describe the adverse event. We classified death reports according to previously published body-system categories (respiratory, cardiovascular, neurological, gastrointestinal, other infectious, and other non-infectious) and reviewed death reports to identify the cause of death. We classified sudden infant death syndrome as a separate cause of death considering previous concerns about sudden infant syndrome after vaccines. We used empirical Bayesian data mining methods to identify disproportionate reporting of adverse events for IPV compared with other vaccines. Additional VAERS data from 1991 to 2000 were analysed to compare the safety profiles of IPV and oral poliovirus vaccine (OPV).

FINDINGS: Of the 41,792 adverse event reports submitted, 39,568 (95%) were for children younger than 7 years. 38,381 of the reports for children in this age group (97%) were for simultaneous vaccination with IPV and other vaccines (most commonly pneumococcal and acellular pertussis vaccines), whereas standalone IPV vaccines accounted for 0.5% of all reports. 34,880 reports were for non-serious events (88%), 3905 reports were for non-fatal serious events (10%), and 783 reports were death reports (2%). Injection-site erythema was the most commonly coded term for non-serious events (29%), and pyrexia for non-fatal serious events (38%). Most deaths (96%) were in children aged 12 months or younger; most (52%) had sudden infant death syndrome as the reported cause of death. The safety profiles of combined IPV and whole-cell pertussis vaccines, OPV and whole-cell pertussis vaccines, and OPV and acellular pertussis vaccines were similar. We noted no indication of disproportionate reporting of adverse events after immunisation with IPV-containing vaccines compared with other vaccines between 1990 and 2013.

INTERPRETATION: Fairly few adverse events were reported for the more than 250 million IPV doses distributed between 2000 and 2012. Sudden infant death syndrome reports after IPV were consistent with reporting patterns for other vaccines. No new or unexpected vaccine safety problems were identified for fatal, non-fatal serious, and non-serious reports in this assessment of adverse events after IPV.

Vidor E et al. The place of DTP/eIPV vaccine in routine paediatric vaccination. Rev Med Virol. 1994;4:261-277. (No abstract available).

Böttiger M. Polio immunity to killed vaccine: an 18-year follow-up. Vaccine. 1990 Oct;8(5):443-5.

Two hundred and fifty children born in 1967 and vaccinated with killed polio vaccine in Sweden were followed for 18 years and tested for neutralizing antibodies against polio. All of them had demonstrable antibodies at the age of 18. Sixty-four children were tested in samples collected throughout the years. After a more marked fall of antibody titres during the first few

years after vaccination, the decline levelled off to a mean decrease in titre of 0.05-0.10 log₁₀ per year. In half of them, the routine vaccination comprising a fourth dose at 6 years of age was changed and this booster was postponed to the age of ten. The children given the booster dose at ten had significantly higher antibody levels at 18 years of age than those given it at six.

Böttiger M. The elimination of polio in the Scandinavian countries. Public Health Rev. 1993-1994;21(1-2):27-33.

The Nordic countries, i.e., Denmark, Finland, Iceland, Norway, and Sweden, together with Holland, have all continued to use the killed poliovaccine introduced in the middle of the 1950s and they still use it today. In Denmark, combined vaccination has been practised since 1966, starting with three doses of the killed vaccine and continuing with the oral vaccine. Norway used oral vaccine alone during the 14-year period from 1965 to 1979. In all these countries, the immunizations with the killed vaccine were immediately successful. Poliomyelitis was practically eliminated already by the beginning of the 1960s. After this initial successful period, the different countries experienced different events, from which valuable conclusions can be drawn: 1. Nationwide vaccination with killed vaccine was highly effective. 2. It is of the utmost importance that the potency of the killed vaccine is high. 3. Oral vaccine may cause higher rates of vaccine-associated secondary cases than have been reported in general. 4. In the Nordic countries, the general circulation of wild virus appeared to cease simultaneously with the disease. 5. When virus is reintroduced into the country, unvaccinated groups are vulnerable. Outbreaks in unvaccinated "pockets" have occurred. This phenomenon, however, has also been experienced in countries using oral vaccine. 6. In Stockholm, both wild poliovirus and vaccine-like polio strains were isolated from the sewage water, indicating a constant import of both types of viruses. Virus isolation from thousands of patients with meningitis or diarrhoea have been negative throughout the years.

Faden H et al. Comparative evaluation of immunization with live attenuated and enhanced-potency inactivated trivalent poliovirus vaccines in childhood: systemic and local immune responses. J Inf Dis. 1990;162:1291-1297.

Serum neutralizing, nasopharyngeal neutralizing, and IgA antibodies were determined in 123 infants immunized with one of four schedules containing live oral vaccine (OPV), inactivated vaccine (IPV), or combinations of the two trivalent poliovirus vaccines: OPV-OPV-OPV, IPV-IPV-IPV, IPV-OPV-OPV, or IPV-IPV-OPV. Nearly 100% of individuals formed serum neutralizing antibodies. The highest geometric mean titer (GMT) of antibody to polioviruses 1, 2, and 3 occurred in groups IPV-IPV-OPV, IPV-OPV-OPV, and IPV-IPV-IPV, respectively. Local neutralizing and IgA antibody responses were detected in 41%-88% and 75%-100%, respectively. Peak GMT of nasopharyngeal antibodies differed minimally between immunization groups. The data suggest that incorporation of at least one dose of IPV at the start of the immunization schedule tends to increase systemic as well as local antibody production.

Cuba IPV Study Collaborative Group. Randomized, placebo-controlled trial of inactivated poliovirus vaccine in Cuba. N Engl J Med. 2007 Apr 12;356(15):1536-44.

BACKGROUND: After poliomyelitis has been eradicated, access to live polioviruses will be highly restricted and the use of oral poliovirus vaccine (OPV) will probably be discontinued.

Countries using OPV must decide whether to switch to inactivated poliovirus vaccine (IPV) or stop polio vaccination. Because data on the immunogenicity of IPV in tropical developing countries are limited, we conducted a randomized, controlled trial of IPV in Cuba.

METHODS: The study population consisted of healthy infants born in Havana. A total of 166 infants were randomly assigned to two groups. Group A received a combination of the diphtheria-pertussis-tetanus (DPT) vaccine, the Haemophilus influenzae type b (Hib) vaccine, and IPV (DPT-Hib-IPV) at 6, 10, and 14 weeks of age. Group B, the control group, received a combination of the DPT vaccine and the Hib vaccine at 6, 10, and 14 weeks of age. Another group (group C, 100 infants), which did not undergo randomization at the same time as groups A and B, received the DPT-Hib-IPV combination at 8 and 16 weeks of age. Serum samples were collected before vaccination and at least 4 weeks after the last dose. Stool samples were obtained before and 7 days after challenge with OPV. **RESULTS:** The seroconversion rates in group A were 94%, 83%, and 100% for types 1, 2, and 3 poliovirus, respectively. There were no seroconversions in group B. The seroconversion rates in group C were 90%, 89%, and 90% for poliovirus types 1, 2, and 3, respectively. For groups A, B, and C, the virus isolation rates after challenge with OPV were 94%, 91%, and 97%, respectively, and the mean log₁₀ viral titers of any serotype were 3.46, 3.89, and 3.37, respectively. There was one major adverse event, an episode of hypotonia. **CONCLUSIONS:** Vaccination with two or three doses of IPV resulted in a rate of seroconversion of at least 90%, except for seroconversion against type 2. The viral titer of OPV shed in the stool after OPV challenge was reduced in both groups receiving IPV.

Resik S et al. Priming after a fractional dose of inactivated poliovirus vaccine. New Eng J Med. 2013;368:416-24.

BACKGROUND: To reduce the costs of maintaining a poliovirus immunization base in low-income areas, we assessed the extent of priming immune responses after the administration of inactivated poliovirus vaccine (IPV).

METHODS: We compared the immunogenicity and reactogenicity of a fractional dose of IPV (one fifth of a full dose) administered intradermally with a full dose administered intramuscularly in Cuban infants at the ages of 4 and 8 months. Blood was collected from infants at the ages of 4 months, 8 months, 8 months 7 days, and 8 months 30 days to assess single-dose seroconversion, single-dose priming of immune responses, and two-dose seroconversion. Specimens were tested with a neutralization assay.

RESULTS: A total of 320 infants underwent randomization, and 310 infants (96.9%) fulfilled the study requirements. In the group receiving the first fractional dose of IPV, seroconversion to poliovirus types 1, 2, and 3 occurred in 16.6%, 47.1%, and 14.7% of participants, respectively, as compared with 46.6%, 62.8%, and 32.0% in the group receiving the first full dose of IPV ($P < 0.008$ for all comparisons). A priming immune response to poliovirus types 1, 2, and 3 occurred in 90.8%, 94.0%, and 89.6% of participants, respectively, in the group receiving the fractional dose as compared with 97.6%, 98.3%, and 98.1% in the group receiving the full dose ($P = 0.01$ for the comparison with type 3). After the administration of the second dose of IPV in the group receiving fractional doses, cumulative two-dose seroconversion to poliovirus types 1, 2, and 3 occurred in 93.6%, 98.1%, and 93.0% of participants, respectively, as compared with 100.0%, 100.0%, and 99.4% in the group receiving the full dose ($P < 0.006$ for the comparisons of types 1 and 3). The group receiving intradermal injections had the greatest number of adverse events, most of which were minor in intensity and none of which had serious consequences.

CONCLUSIONS: This evaluation shows that vaccinating infants with a single fractional dose of IPV can induce priming and seroconversion in more than 90% of immunized infants.

Dayan GH et al. Serologic response to inactivated polio vaccine: a randomized clinical trial comparing 2 vaccination schedules in Puerto Rico. J Inf Dis. 2007;195:12-20.

BACKGROUND: The World Health Organization (WHO) recommends the discontinuation of oral poliovirus vaccine after eradication of wild poliovirus. Studies assessing inactivated poliovirus vaccine (IPV) immunogenicity in tropical countries, using the WHO Expanded Programme on Immunization (EPI) schedule, have been limited. METHODS: We conducted a randomized clinical trial in Ponce, Puerto Rico. Infants were assigned to 1 of 2 study arms: those in the EPI arm received IPV at 6, 10, and 14 weeks of age, and those in the US arm received IPV at 2, 4, and 6 months of age. Neutralizing antibody titers against poliovirus types 1, 2, and 3 were tested on serum specimens obtained before administration of the first dose of IPV and 28-45 days after administration of the last dose of IPV. RESULTS: Seroconversion rates for the EPI (n=225) and US (n=230) arms, respectively, were 85.8% and 99.6% for poliovirus type 1 ($P<.001$), 86.2% and 100% for poliovirus type 2 ($P<.001$), and 96.9% and 99.1% for poliovirus type 3 ($P=.08$). Seroconversion rates were lower among infants in the EPI arm who had high maternal antibody levels for all 3 poliovirus types ($P<.001$). CONCLUSIONS: The EPI schedule resulted in lower seroconversion rates for poliovirus types 1 and 2. These results are relevant for tropical countries planning to use IPV in a posteradication environment.

Marine, WM et al. Limitation of fecal and pharyngeal poliovirus excretion in Salk-vaccinated children. A family study during a type 1 poliomyelitis epidemic. Am J Hyg. 1962;76:173-195. (No abstract available)

Jafari H et al. Efficacy of inactivated poliovirus vaccine in India. Science 2014;345:922–925

Inactivated poliovirus vaccine (IPV) is efficacious against paralytic disease, but its effect on mucosal immunity is debated. We assessed the efficacy of IPV in boosting mucosal immunity. Participants received IPV, bivalent 1 and 3 oral poliovirus vaccine (bOPV), or no vaccine. A bOPV challenge was administered 4 weeks later, and excretion was assessed 3, 7, and 14 days later. Nine hundred and fifty-four participants completed the study. Any fecal shedding of poliovirus type 1 was 8.8, 9.1, and 13.5% in the IPV group and 14.4, 24.1, and 52.4% in the control group by 6- to 11-month, 5-year, and 10-year groups, respectively (IPV versus control: Fisher's exact test $P < 0.001$). IPV reduced excretion for poliovirus types 1 and 3 between 38.9 and 74.2% and 52.8 and 75.7%, respectively. Thus, IPV in OPV-vaccinated individuals boosts intestinal mucosal immunity.

John J et al. Effect of a single inactivated poliovirus vaccine dose on intestinal immunity against poliovirus. Lancet. 2014; Oct 25 384(9953):1505–1512.

BACKGROUND: Intestinal immunity induced by oral poliovirus vaccine (OPV) is imperfect and wanes with time, permitting transmission of infection by immunised children. Inactivated poliovirus vaccine (IPV) does not induce an intestinal mucosal immune response, but could boost protection in children who are mucosally primed through previous exposure to OPV. We aimed to assess the effect of IPV on intestinal immunity in children previously vaccinated with OPV.

METHODS: We did an open-label, randomised controlled trial in children aged 1-4 years from Chinnallapuram, Vellore, India, who were healthy, had not received IPV before, and had had their last dose of OPV at least 6 months before enrolment. Children were randomly assigned (1:1) to receive 0.5 mL IPV intramuscularly (containing 40, 8, and 32 D antigen units for serotypes 1, 2, and 3) or no vaccine. The randomisation sequence was computer generated with a blocked randomisation procedure with block sizes of ten by an independent statistician. The laboratory staff did blinded

assessments. The primary outcome was the proportion of children shedding poliovirus 7 days after a challenge dose of serotype 1 and 3 bivalent OPV (bOPV). A second dose of bOPV was given to children in the no vaccine group to assess intestinal immunity resulting from the first dose. A per-protocol analysis was planned for all children who provided a stool sample at 7 days after bOPV challenge. This trial is registered with Clinical Trials Registry of India, number CTRI/2012/09/003005. FINDINGS: Between Aug 19, 2013, and Sept 13, 2013, 450 children were enrolled and randomly assigned into study groups. 225 children received IPV and 225 no vaccine. 222 children in the no vaccine group and 224 children in the IPV group had stool samples available for primary analysis 7 days after bOPV challenge. In the IPV group, 27 (12%) children shed serotype 1 poliovirus and 17 (8%) shed serotype 3 poliovirus compared with 43 (19%) and 57 (26%) in the no vaccine group (risk ratio 0.62, 95% CI 0.40-0.97, $p=0.0375$; 0.30, 0.18-0.49, $p<0.0001$). No adverse events were related to the study interventions.

INTERPRETATION: The substantial boost in intestinal immunity conferred by a supplementary dose of IPV given to children younger than 5 years who had previously received OPV shows a potential role for this vaccine in immunisation activities to accelerate eradication and prevent outbreaks of poliomyelitis

Anis E. Insidious reintroduction of wild poliovirus into Israel, 2013. Euro Surv. 2013;Sep 19;18(38).

Israel was certified as polio-free country in June 2002, along with the rest of the World Health Organization European Region. Some 11 years later, wild-type polio virus₁ (WPV₁) was isolated initially from routine sewage samples collected between 7 and 13 April 2013 in two cities in the Southern district. WPV₁-specific analysis of samples indicated WPV₁ introduction into that area in early February 2013. National supplementary immunisation with oral polio vaccine has been ongoing since August 2013.

Kalkowska DA et al. Modeling options to manage type 1 wild poliovirus imported into Israel in 2013. J Infect Dis 2015;211(11):1800–1812.

Robertson SE et al. Clinical efficacy of a new, enhanced-potency, inactivated poliovirus vaccine. Lancet. 1988; Apr 23;1(8591):897-99.

The 1986-87 outbreak of paralytic poliomyelitis in Senegal, with 676 reported cases, provided an opportunity to evaluate the efficacy of an enhanced-potency inactivated poliovirus vaccine (N-IPV) in the Kolda region, where this vaccine has been used since 1980. 89 cases, confirmed to have poliomyelitis with residual paralysis, were enrolled in a case-control study, up to 5 matched controls being obtained for each case. The clinical efficacy for one dose of N-IPV was 36% (95% confidence interval 0%, 67%) and for two doses was 89% (95% CI 62%, 97%).

Simasathien S et al. Comparison of enhanced potency inactivated poliovirus vaccine (EIPV) versus standard oral poliovirus vaccine (OPV) in Thai infants. Scand J Inf Dis. 1994;26:731-738.

Enhanced potency inactivated poliovirus vaccine (EIPV), combined with diphtheria-tetanus-pertussis (DTP) vaccine, was compared with oral poliovirus vaccine (OPV) regarding immunogenicity in Thai infants, vaccinated at 2, 4 and 6 months of age. EIPV induced significantly higher seroconversion rates than OPV to all 3 poliovirus types after the second and third immunization. After 3 doses of each vaccine, at 7 months of age, all infants receiving EIPV proved seropositive for poliovirus type 1, type 2 and type 3 neutralizing antibodies, whereas of those receiving OPV, 9% remained seronegative (titre < 1:4) for type 1 ($p = 0.0042$) and 11% for type 3 ($p = 0.0013$). All participating

children were given an additional dose of OPV at the age of 9 months and tested again at 12 months of age. At that point, virtually all infants had poliovirus neutralizing antibodies, but the geometric mean titres to each poliovirus type were significantly higher in the vaccinees who had received EIPV. It is concluded that the greater immunogenicity of EIPV vis-à-vis 3 doses of OPV may be biologically significant for protection against poliovirus types 1 and 3 in countries where cases of poliomyelitis occur in young children. These findings warrant considering EIPV, alone or in combination with OPV, for an immunization programme in Thailand and similar countries in the future.

Anand A et al Early priming with inactivated poliovirus vaccine (IPV) and intradermal fractional dose IPV administered by a microneedle device: A randomized controlled trial. Vaccine, 2015 Nov 27;33(48):6816–6822.

INTRODUCTION: Inactivated poliovirus vaccine (IPV) introduction and phased oral poliovirus vaccine (OPV) cessation are essential for eradication of polio.

METHODS: Healthy 6-week old infants in Bangladesh were randomized to one of five study arms: receipt of trivalent OPV (tOPV) or bivalent OPV (bOPV) at ages 6, 10 and 14 weeks, intramuscular IPV or intradermal one-fifth fractional dose IPV (f-IPV) at ages 6 and 14 weeks, or f-IPV at ages 6 and 14 weeks with bOPV at age 10 weeks (f-IPV/bOPV). All participants received tOPV at age 18 weeks.

RESULTS: Of 975 infants randomized, 95% (922) completed follow-up. Type 1 seroconversion after 3 doses at 6, 10 and 14 weeks was higher with bOPV compared with tOPV (99% vs 94%, $p=0.019$). Seroconversions to types 1 and 3 after 2 IPV doses at ages 6 and 14 weeks were no different than after 3 doses of tOPV or bOPV at ages 6, 10 and 14 weeks. A priming response, seroconversion 1 week after IPV at 14 weeks among those who did not seroconvert after IPV at 6 weeks, was observed against poliovirus types 1, 2 and 3 in 91%, 84% and 97%, respectively. Compared with IPV, f-IPV failed non-inferiority tests for seroconversion with 1 or 2 doses and priming after 1 dose.

DISCUSSION: The findings demonstrate considerable priming with IPV at age 6 weeks, comparable immunogenicity of tOPV and bOPV, and inferior immunogenicity of one-fifth f-IPV compared with IPV. If IPV induced priming at age 6 weeks is similar to that at age 14 weeks, IPV could be administered at a younger age and possibly with a higher coverage

Carlsson RM et al. Antibody persistence in five-year-old children who received a pentavalent combination vaccine in infancy. Ped Inf Dis J. 2002;21(6):535-41.

BACKGROUND: Antibody persistence was studied in 5.5-year-old Swedish children who in infancy completed a vaccine trial of a combined diphtheria toxoid, tetanus toxoid, acellular pertussis, inactivated polio and Haemophilus influenzae type b conjugate vaccine. Three priming doses at ages 2-4-6 months induced higher geometric mean concentrations of antibodies for all antigens than did two doses at 3-5 months, but there were no differences in proportions with protective antibody concentrations. After the booster dose administered at 13 or 12 months of age, respectively, there were no differences in concentrations or proportions between the groups. **METHODS:** In the present follow-up serum samples from 180 of the 228 vaccinees, 88 from the 4-dose and 92 from the 3-dose group, were 4.5 years later again tested for antibodies. **RESULTS:** The two groups did not differ significantly in antibody concentrations or proportions with antibodies above protective or other defined levels, with the exception of poliovirus type 3 ($P < \text{or} = 0.01$).

Langue J et al. Persistence of antibodies at 5-6 years of age for children who had received a primary series vaccination with a pentavalent whole-cell pertussis vaccine and a first booster with a pentavalent acellular pertussis vaccine. Vaccine, 2004;22(11-12):1406-14.

The main objective of this study was to assess in 5-6-year-old French children (n=162) the persistence of antibodies induced by a primary series vaccination (at 2-4 months of age) with a pentavalent whole-cell pertussis combined vaccine (DTwcp-IPV-Hib; Pentacoq) and a first booster (at 12-16 months of age) with a pentavalent two-component acellular pertussis combined vaccine (DTacP-IPV-Hib; Pentavac). The second objective was to evaluate in these 5-6-year-old French children the safety and the immunogenicity of a tetravalent pertussis combined vaccine (DTacP-IPV, Tetravac) given as a second booster. RESULTS: before the 2nd booster, more than 90% of children had antibody titers above the defined threshold for polyribosyl ribitol phosphate (PRP), tetanus, diphtheria and poliomyelitis; antibody titers were very low for pertussis. One month after the second booster, all children had seroprotective post-booster titers for tetanus, diphtheria and poliomyelitis types 1-3; over 90% of children had a four-fold rise in titers against DTacP-IPV antigens. Adverse events were mostly solicited reactions, with no serious adverse event. A strong anamnestic response was also observed after the second booster injection with Tetravac, with a satisfactory safety profile. CONCLUSION: Pentavac and Tetravac (acellular pertussis containing vaccines) may thus be administered as first and second boosters respectively, in children primed with Pentacoq (whole-cell pertussis containing vaccine).

von Magnus H, Petersen I. Vaccination with inactivated poliovirus vaccine and oral poliovirus vaccine in Denmark. Rev Infect Dis. 1984 May-Jun;6 Suppl 2:S471-4.

In Denmark a polio vaccination program including both inactivated poliovirus vaccine (IPV) and oral poliovirus vaccine (OPV) has been in use since 1968. Three injections of IPV are given when the children are five, six, and 15 months of age. Subsequently, three vaccinations with trivalent OPV are administered at the age of three, four, and five years. The acceptance rate is high-93%-98%-and greater than 95% of the population has antibodies to poliovirus. The geometric mean titer of serum antibodies is much greater than 10 IU for all three types. The epidemiology of poliomyelitis and the background for the development of the present vaccination schedule are reviewed. The epidemiology of poliomyelitis and the background for the development of the present vaccination schedule are reviewed.

Klein NP et al. An open-label, randomized, multi-center study of the immunogenicity and safety of DTaP-IPV (Kinrix™) co-administered with MMR vaccine with or without varicella vaccine in healthy pre-school age children. Vaccine. 2012 Jan 11;30(3):668-674.

BACKGROUND: In the US, it is recommended that 4-6 year old children receive diphtheria-tetanus-acellular pertussis (DTaP), inactivated poliovirus (IPV), measles-mumps-rubella (MMR), varicella (V), and influenza vaccines. Data relating to the concomitant administration of combination DTaP-IPV vaccine (Kinrix™; GlaxoSmithKline Biologicals) and influenza or V vaccines are currently limited. This study was undertaken to evaluate the immunogenicity and reactogenicity of Kinrix™ when co-administered with MMR (M-M-RII®), Merck & Co.) and Varivax™ (Merck & Co.) in 4-6 year old children.

METHODS: Phase IIIb, open-label, non-inferiority study (NCT00871117). We randomized (1:1) healthy 4-6 year olds to receive Kinrix™+MMR+V on day 0 (Group 1), or Kinrix™+MMR on day 0, followed by V at month 1 (Group 2). We measured DTaP-IPV immunogenicity before and 1 month post-vaccination (prior to V vaccination in Group 2). We collected local and general solicited symptoms within 4 days after vaccination and serious adverse events (SAEs) through 6 months post-vaccination.

RESULTS: We enrolled 478 subjects. One month post-vaccination, >95% of subjects in both groups had booster responses to diphtheria, tetanus and pertussis antigens and all subjects had seroprotective anti-poliovirus antibody titers. Immune responses in Group 1 were non-inferior to Group 2 for responses to DTaP-IPV antigens according to pre-specified criteria. Reporting of solicited local events at the DTaP-IPV site appeared to be similar between the two vaccine groups, as was reporting of solicited general adverse events within 4 days of vaccination; no vaccine related SAEs were reported.

CONCLUSION: Concomitant administration of varicella vaccine with Kinrix™ and MMR did not impact the immunogenicity of diphtheria, tetanus, pertussis or poliovirus antigens. Both vaccine regimens were well tolerated. These results support the co-administration of DTaP-IPV, MMR, and V vaccines in 4-6-year-old children, providing protection against multiple diseases in a timely and efficient manner.

Barbi M et al. Antibody response to inactivated polio vaccine (E-IPV) in children born to HIV positive mothers. Euro J Epidemiol. 1992;8:211-6.

In order to evaluate the response to immunization of HIV-infected children we studied the humoral response to an enhanced potency inactivated poliovaccine (E-IPV) of 43 children born of HIV seropositive mothers. All these subjects have been followed for 32 (15-48) months in order to ascertain their infection status. After a course of 2 doses of E-IPV, 88% of children had neutralizing antibody (n.a.) titers greater than 1:4 to the 3 poliovirus serotypes and 100% to at least 2 polio strains. No statistically significant differences both as rates of n.a. positive subjects and as antibody levels were found between HIV infected children and those who lost HIV antibodies. The poorest response was observed in subjects with full-blown immunodeficiency (CD4 less than 1000/mm³, reduced response to PWM). Sixteen children also received a booster dose of vaccine one year after the completion of the primary cycle. Infected and non-infected subjects responded to the same extent with high levels of n.a. to this immunization. Interestingly, the recall dose was also able to induce high n.a. titers in those HIV infected children who showed significant decreases of n.a. titers in the months following the end of the primary cycle.

Varon D et al. Response of hemophilic patients to poliovirus vaccination: correlation with HIV serology and with immunological parameters. J Med Virol. 1993;40:91-5.

Hemophilic patients may present immunological dysfunctions resulting from either human immunodeficiency virus (HIV) infection, or other factors like impure factor VIII concentrate and other viral infections. We evaluated prospectively the serologic response to polio vaccination of Israeli hemophilic patients who were vaccinated during an outbreak of poliomyelitis. Eighty-two hemophilic patients, 43 seronegative and 39 seropositive for human immunodeficiency virus (HIV), were vaccinated with enhanced inactivated poliovirus (eIPV). Titers of antibodies for poliovirus types 1-3 were determined before and 4 weeks after immunization. T helper and suppressor lymphocytes (T4 and T8), B and T lymphocyte mitogenic response, and natural killer cells were tested and correlated

with the response to vaccination. Both groups responded to vaccination with increased titers of antibodies to the three viral types, 4 weeks after immunization. HIV-seronegative patients, however, exhibited higher titers than the HIV-seropositive group. The same pattern was found when 21 patients were tested 1 year after the exposure to eIPV. HIV seropositive patients were grouped according to their T4 count (between 16/microliter and 500/microliter). There was no statistically significant difference in the response of these different groups to vaccination. No correlation was found between the response to vaccination and other immune parameters. These results suggest that asymptomatic HIV-seropositive hemophilic patients respond well to eIPV, irrespective of their T4 count.

Sipila R et al. Good seroresponse to enhanced-potency inactivated poliovirus vaccine in patients on chronic dialysis. *Nephrol Dialysis Transplant.* 1990;5:352–5.

The outbreak of paralytic poliomyelitis in Finland in 1984 was halted by nationwide oral poliovirus vaccination campaign. Immunocompromised patients, including those with chronic uraemia and on continuous dialysis, were excluded from the oral vaccination group and instead were given a dose of the new enhanced-potency inactivated poliovirus vaccine before the campaign. We studied the antibody response to this vaccine in 49 patients on chronic dialysis, using conventional antigen of all three serotypes and two additional type 3 strains. It was observed that 86% (42 of 49) of patients either had a satisfactory concentration of neutralising poliovirus antibodies against all three serotypes prior to vaccination, or responded with at least a four-fold increase of antibodies. Fourteen of 21 patients originally seronegative to at least one of the five virus strains used showed a striking seroconversion. One patient remained seronegative to type 1 poliovirus while two and four other patients were left with low (less than 8) titres of type 1 and 3 antibodies respectively. The latter seven patients showed moderate or good responses to the other two serotypes. We conclude that the enhanced-potency inactivated poliovirus vaccine produces a good antibody response in uraemic patients.

Engelhard D et al. Immune response to polio vaccination in bone marrow transplant recipients. *Bone Marrow Transplant.* 1991;8:295 – 300.

Following a small outbreak of poliomyelitis which occurred in the summer of 1988 in Israel, two sequential doses of inactivated polio vaccine (IPV) were administered to 42 bone marrow transplant (BMT) recipients (aged 2-50 years) who were 6-96 months (median 16 months) after transplantation. Prior to vaccination, only 68-80% patients (n = 42) had protective (greater than or equal to 4) antibody levels against the three serotypes of poliovirus, compared with 92-96% (n = 25) before BMT (p = 0.02 for types 1 and 3). After the second dose of IPV, 89-98% (n = 27) of the recipients had protective antibody levels. The pre-vaccination antibody titers were lower than before BMT (p = 0.006, 0.0007 and 0.0008 for types 1, 2 and 3, respectively). After the first dose of IPV, antibody titers rose in the 42 patients (p = 0.002, 0.043 and 0.002 for types 1, 2 and 3, respectively) and following the second dose, a further increase in antibody levels was noted. Regression analysis revealed that graft-versus-host disease, pre-BMT polio antibody titers, age and type of transplantation (allogeneic versus autologous) were significant explanatory variables for the specific antibody levels, while the time lapse between BMT and vaccination, and primary disease proved of no significance. Vaccination against poliovirus after BMT is advocated, as it reinstates and raises the lost specific humoral immunity.

du Chatelet IP et al. Serological response and poliovirus excretion following different combined oral and inactivated poliovirus vaccines immunization schedules. *Vaccine*. 2003;21:1710–1718.

A controlled study was conducted in Karachi, Pakistan to compare humoral and mucosal immune responses against polioviruses in infants who received oral poliovirus vaccine (OPV) at birth and at 6, 10, and 14 weeks according to the Expanded Program on Immunization (EPI) with infants who received either three doses of inactivated poliovirus vaccine (IPV) at 6, 10, and 14 weeks together with OPV or one additional dose of IPV at 14 weeks together, with the last dose of OPV. A total of 1429 infants were enrolled; 24-week serum specimens were available for 898 infants (63%). They all received a challenge dose of OPV type 3 at 24 weeks of age. The addition of three doses of IPV to three doses of OPV induced a significantly higher percentage of seropositive children at 24 weeks of age for polio 1 (97% versus 89%, $P < 0.001$) and polio 3 (98% versus 92%) compared to the EPI schedule. However, the one supplemental dose of IPV at 14 weeks did not increase the serological response at 24 weeks. Intestinal immunity against the challenge dose was similar in the three groups. Combined schedules of OPV and IPV in the form of diphtheria-pertussis-tetanus-IPV vaccine (DPT-IPV) may be useful to accelerate eradication of polio in developing countries.

Goldblum N et al. Poliomyelitis control in Israel, the West Bank and Gaza Strip: changing strategies with the goal of eradication in an endemic area. *Bull World Health Organ*. 1994; 72(5):783–796.

Israel has faced the challenge presented by epidemic poliomyelitis by using different immunization strategies. In the 1950s, inactivated poliovirus vaccine (IPV) helped to reduce the total burden of the disease, but cases continued to occur. Introduction of oral poliovirus vaccine (OPV) in mid-1961 had a dramatic effect in controlling an extensive epidemic of poliomyelitis; however, poliovirus activity and cases continued during the 1970s, and at a low level in the 1980s. A localized outbreak of 15 cases of poliomyelitis in 1988 occurred in an area using enhanced potency IPV (eIPV) only. This led to a revision of poliomyelitis immunization policy. The successful poliomyelitis control in the West Bank and the Gaza Strip using both OPV and IPV since 1978 shows the advantages of a combined approach. This programme was therefore adopted in modified form in the whole of Israel, the West Bank and Gaza. Since late 1988, no cases of poliomyelitis have occurred in any of these three areas, indicating the success of the combined poliomyelitis immunization programme. These experiences may be helpful to other countries, especially those where there is a danger of importation of wild poliovirus, and to prevent vaccine-associated disease. The combined approach provides an additional immunization model in the international effort to eradicate poliomyelitis.

Alexander LN et al. Vaccine policy changes and epidemiology of poliomyelitis in the United States. *JAMA*. 2004;292(14):1696-701.

CONTEXT: The last case of poliomyelitis in the United States due to indigenously acquired wild poliovirus occurred in 1979; however, as a consequence of oral poliovirus vaccine (OPV) use that began in 1961, an average of 9 cases of vaccine-associated paralytic poliomyelitis (VAPP) were confirmed each year from 1961 through 1989. To reduce the VAPP burden, national vaccination policy changed in 1997 from reliance on OPV to options for a sequential schedule of inactivated poliovirus vaccine (IPV) followed by OPV. In 2000, an exclusive IPV schedule was adopted. **OBJECTIVE:** To review the epidemiology of paralytic poliomyelitis and document the association between the vaccine schedule changes and VAPP in the United States. **DESIGN AND SETTING:** Review of national surveillance data from 1990 through 2003 for cases of confirmed paralytic poliomyelitis. **MAIN**

OUTCOME MEASURES: Number of confirmed paralytic poliomyelitis cases, including VAPP, and ratio of VAPP cases to number of doses of OPV distributed that occurred before, during, and after implementation of policy changes. RESULTS: From 1990 through 1999, 61 cases of paralytic poliomyelitis were reported; 59 (97%) of these were VAPP (1 case per 2.9 million OPV doses distributed), 1 case was imported, and 1 case was indeterminate. Thirteen cases occurred during the 1997-1999 transitional policy period and were associated with the all-OPV schedule; none occurred with the IPV-OPV schedule. No cases occurred after the United States implemented the all-IPV policy in 2000. The last imported poliomyelitis case occurred in 1993 and the last case of VAPP occurred in 1999. CONCLUSION: The change in polio vaccination policy from OPV to exclusive use of IPV was successfully implemented; this change led to the elimination of VAPP in the United States.

Hanlon P, et al. Serological comparisons of approaches to polio vaccination in the Gambia. Lancet.1987;1(8536):800-1. (No abstract available).

Moriniere BJ et al. Immunogenicity of a supplemental dose of oral versus inactivated poliovirus vaccine. Lancet. 1993;Jun 19;341(8860):1545-50.

In many developing countries, the immunogenicity of three doses of live, attenuated, oral poliovirus vaccine (OPV) is lower than that in industrialised countries. We evaluated serum neutralising antibody responses in 368 children aged 6 months and 346 children aged 9 months in Côte d'Ivoire who had previously received three doses of OPV at 2, 3, and 4 months of age, and who were then randomised to receive a supplemental dose of OPV or enhanced-potency inactivated poliovirus vaccine (IPV) at the time of measles vaccination. Although both vaccines increased seroconversion to all three poliovirus types, antibody responses were greater in the IPV group. Among children with no detectable antibody at baseline, IPV was 2 to 14 times more likely than OPV to induce seroconversion (type 1, 80% vs 40% at 6 months [$p < 0.001$] and 81% vs 14% at 9 months [$p < 0.001$]; type 3, 76% vs 22% at 6 months [$p < 0.001$], and 67% vs 5% at 9 months [$p < 0.001$]). Among children with detectable antibody at baseline, IPV was 1.4 to 7 times more likely than OPV to elicit 4-fold or more rises in antibody titre ($p < 0.01$). Geometric mean titres (GMTs) to all three poliovirus types were also consistently higher among IPV recipients than in OPV recipients when measured 4-6 weeks and 13-17 months after vaccination. Administration of a supplemental dose of IPV or OPV, which requires no additional visits or changes in the existing immunisation schedule, might improve protection against paralytic poliomyelitis in communities with suboptimum seroconversion rates after three doses of OPV.

Scientific evidence in support of: Note for the Record: 5th Meeting of the SAGE Working Group, World Health Organization, Geneva, September 3-4, 2012
(http://www.who.int/immunization/sage/meetings/2012/november/3_SAGE_WG_Scientific_Evidence22Oct2012.pdf, accessed February 2016). (No abstract available).

Sutter RW et al. Immunogenicity of a new routine vaccination schedule for global poliomyelitis prevention: an open-label, randomised controlled trial. Lancet 2015. 18 September 2015
([http://dx.doi.org/10.1016/S0140-6736\(15\)00237-8](http://dx.doi.org/10.1016/S0140-6736(15)00237-8)).

BACKGROUND: Polio eradication needs a new routine immunisation schedule--three or four doses of bivalent type 1 and type 3 oral poliovirus vaccine (bOPV) and one dose of inactivated poliovirus

vaccine (IPV), but no immunogenicity data are available for this schedule. We aimed to assess immunogenicity of this vaccine schedule.

METHODS: We did an open-label, randomised controlled trial in four centres in India. After informed consent was obtained from a parent or legally acceptable representative, healthy newborn babies were randomly allocated to one of five groups: trivalent OPV (tOPV); tOPV plus IPV; bOPV; bOPV plus IPV; or bOPV plus two doses of IPV (2IPV). The key eligibility criteria were: full-term birth (≥ 37 weeks of gestation); birthweight ≥ 2.5 kg; and Apgar score of 9 or more. OPV was administered at birth, 6 weeks, 10 weeks, and 14 weeks; IPV was administered intramuscularly at 14 weeks. The primary study objective was to investigate immunogenicity of the new vaccine schedule, assessed by seroconversion against poliovirus types 1, 2, and 3 between birth and 18 weeks in the per-protocol population (all participants with valid serology results on cord blood and at 18 weeks). Neutralisation assays tested cord blood and sera collected at 14 weeks, 18 weeks, 19 weeks, and 22 weeks by investigators masked to group allocation. This trial was registered with the India Clinical Trials Registry, number CTRI/2013/06/003722.

FINDINGS: Of 900 newborn babies enrolled between June 13 and Aug 29, 2013, 782 (87%) completed the per-protocol requirements. Between birth and age 18 weeks, seroconversion against poliovirus type 1 in the tOPV group occurred in 162 of 163 (99.4%, 95% CI 96.6-100), in 150 (98.0%, 94.4-99.6) of 153 in the tOPV plus IPV group, in 153 (98.7%, 95.4-99.8) of 155 in the bOPV group, in 155 (99.4%, 96.5-100) of 156 in the bOPV plus IPV group, and in 154 (99.4%, 96.5-100) of 155 in the bOPV plus 2IPV group. Seroconversion against poliovirus type 2 occurred in 157 (96.3%, 92.2-98.6) of 163 in the tOPV group, 153 (100%, 97.6-100.0) of 153 in the tOPV plus IPV group, 29 (18.7%, 12.9-25.7) of 155 in the bOPV group, 107 (68.6%, 60.7-75.8) of 156 in the bOPV plus IPV group, and in 121 (78.1%, 70.7-84.3) of 155 in the bOPV plus 2IPV group. Seroconversion against poliovirus type 3 was achieved in 147 (90.2%, 84.5-94.3) of 163 in the tOPV group, 152 (99.3%, 96.4-100) of 153 in the tOPV plus IPV group, 151 (97.4%, 93.5-99.3) of 155 in the bOPV group, 155 (99.4%, 96.5-100) of 156 in the bOPV plus IPV group, and 153 (98.7%, 95.4-99.8) of 155 in the bOPV plus 2IPV group. Superiority was achieved for vaccine regimens including IPV against poliovirus type 3 compared with those not including IPV (tOPV plus IPV vs tOPV alone, $p=0.0008$; and bOPV plus IPV vs bOPV alone, $p=0.0153$). 12 serious adverse events occurred (six in the tOPV group, one in the tOPV plus IPV group, three in the bOPV group, zero in the bOPV plus IPV group, and two in the bOPV plus 2IPV group), none of which was attributed to the trial intervention.

INTERPRETATION: The new vaccination schedule improves immunogenicity against polioviruses, especially against poliovirus type 3.

O’Ryan M et al. Inactivated poliovirus vaccine given alone or in a sequential schedule with bivalent oral poliovirus vaccine in Chilean infants: a randomized, controlled, open-label, phase 4, non-inferiority study. *Lancet Infect Dis* 2015;15:1273–1282.

BACKGROUND: Bivalent oral poliovirus vaccine (bOPV; types 1 and 3) is expected to replace trivalent OPV (tOPV) globally by April, 2016, preceded by the introduction of at least one dose of inactivated poliovirus vaccine (IPV) in routine immunisation programmes to eliminate vaccine-associated or vaccine-derived poliomyelitis from serotype 2 poliovirus. Because data are needed on sequential IPV-bOPV schedules, we assessed the immunogenicity of two different IPV-bOPV schedules compared with an all-IPV schedule in infants.

METHODS: We did a randomised, controlled, open-label, non-inferiority trial with healthy, full-term (>2.5 kg birthweight) infants aged 8 weeks (± 7 days) at six well-child clinics in Santiago, Chile. We

used supplied lists to randomly assign infants (1:1:1) to receive three polio vaccinations (IPV by injection or bOPV as oral drops) at age 8, 16, and 24 weeks in one of three sequential schedules: IPV-bOPV-bOPV, IPV-IPV-bOPV, or IPV-IPV-IPV. We did the randomisation with blocks of 12 stratified by study site. All analyses were done in a masked manner. Co-primary outcomes were non-inferiority of the bOPV-containing schedules compared with the all-IPV schedule for seroconversion (within a 10% margin) and antibody titres (within two-thirds log₂ titres) to poliovirus serotypes 1 and 3 at age 28 weeks, analysed in the per-protocol population. Secondary outcomes were seroconversion and titres to serotype 2 and faecal shedding for 4 weeks after a monovalent OPV type 2 challenge at age 28 weeks. Safety analyses were done in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, number NCT01841671, and is closed to new participants.

FINDINGS: Between April 25 and August 1, 2013, we assigned 570 infants to treatment: 190 to IPV-bOPV-bOPV, 192 to IPV-IPV-bOPV, and 188 to IPV-IPV-IPV. 564 (99%) were vaccinated and included in the intention-to-treat cohort, and 537 (94%) in the per-protocol analyses. In the IPV-bOPV-bOPV, IPV-IPV-bOPV, and IPV-IPV-IPV groups, respectively, the proportions of children with seroconversion to type 1 poliovirus were 166 (98·8%) of 168, 95% CI 95·8-99·7; 178 (100%), 97·9-100·0; and 175 (100%), 97·9-100·0. Proportions with seroconversion to type 3 poliovirus were 163 (98·2%) of 166, 94·8-99·4; 177 (100%), 97·9-100·0, and 172 (98·9%) of 174, 95·9-99·7. Non-inferiority was thus shown for the bOPV-containing schedules compared with the all-IPV schedule, with no significant differences between groups. In the IPV-bOPV-bOPV, IPV-IPV-bOPV, and IPV-IPV-IPV groups, respectively, the proportions of children with seroprotective antibody titres to type 1 poliovirus were 168 (98·8%) of 170, 95% CI 95·8-99·7; 181 (100%), 97·9-100·0; and 177 (100%), 97·9-100·0. Proportions to type 3 poliovirus were 166 (98·2%) of 169, 94·9-99·4; 180 (100%), 97·9-100·0; and 174 (98·9%) of 176, 96·0-99·7. Non-inferiority comparisons could not be done for this outcome because median titres for the groups receiving OPV were greater than the assay's upper limit of detection (log₂ titres >10·5). The proportions of children seroconverting to type 2 poliovirus in the IPV-bOPV-bOPV, IPV-IPV-bOPV, and IPV-IPV-IPV groups, respectively, were 130 (77·4%) of 168, 95% CI 70·5-83·0; 169 (96·0%) of 176, 92·0-98·0; and 175 (100%), 97·8-100. IPV-bOPV schedules resulted in almost a 0·3 log reduction of type 2 faecal shedding compared with the IPV-only schedule. No participants died during the trial; 81 serious adverse events were reported, of which one was thought to be possibly vaccine-related (intestinal intussusception).

INTERPRETATION: Seroconversion rates against polioviruses types 1 and 3 were non-inferior in sequential schedules containing IPV and bOPV, compared with an all-IPV schedule, and proportions of infants with protective antibodies were high after all three schedules. One or two doses of bOPV after IPV boosted intestinal immunity for poliovirus type 2, suggesting possible cross protection. Additionally, there was evidence of humoral priming for type 2 from one dose of IPV. Our findings could give policy makers flexibility when choosing a vaccination schedule, especially when trying to eliminate vaccine-associated and vaccine-derived poliomyelitis.

Duintjer Tebbens RJ et al, Economic analysis of the global polio eradication initiative. Vaccine. 2010;29(2), 334–343.

The global polio eradication initiative (GPEI), which started in 1988, represents the single largest, internationally coordinated public health project to date. Completion remains within reach, with type 2 wild polioviruses apparently eradicated since 1999 and fewer than 2000 annual paralytic poliomyelitis cases of wild types 1 and 3 reported since then. This economic analysis of the GPEI reflects the status of the program as of February 2010, including full consideration of post-

eradication policies. For the GPEI intervention, we consider the actual pre-eradication experience to date followed by two distinct potential future post-eradication vaccination policies. We estimate GPEI costs based on actual and projected expenditures and poliomyelitis incidence using reported numbers corrected for underreporting and model projections. For the comparator, which assumes only routine vaccination for polio historically and into the future (i.e., no GPEI), we estimate poliomyelitis incidence using a dynamic infection transmission model and costs based on numbers of vaccinated children. Cost-effectiveness ratios for the GPEI vs. only routine vaccination qualify as highly cost-effective based on standard criteria. We estimate incremental net benefits of the GPEI between 1988 and 2035 of approximately 40-50 billion dollars (2008 US dollars; 1988 net present values). Despite the high costs of achieving eradication in low-income countries, low-income countries account for approximately 85% of the total net benefits generated by the GPEI in the base case analysis. The total economic costs saved per prevented paralytic poliomyelitis case drive the incremental net benefits, which become positive even if we estimate the loss in productivity as a result of disability as below the recommended value of one year in average per-capita gross national income per disability-adjusted life year saved. Sensitivity analysis suggests that the finding of positive net benefits of the GPEI remains robust over a wide range of assumptions, and that consideration of the additional net benefits of externalities that occurred during polio campaigns to date, such as the mortality reduction associated with delivery of Vitamin A supplements, significantly increases the net benefits. This study finds a strong economic justification for the GPEI despite the rising costs of the initiative.

Griffiths UK et al. The cost-effectiveness of alternate polio immunization policies in South Africa. *Vaccine*. 2006;24:5670-5678.

AIMS: To assess the cost-effectiveness of switching from oral polio vaccine (OPV) to inactivated poliovirus vaccine (IPV), or to cease polio vaccination in routine immunization services in South Africa at the time of OPV cessation globally following polio eradication.

METHODS: The cost-effectiveness of nine different polio immunization alternatives were evaluated. The costs of introducing IPV in a separate vial as well as in different combination vaccines were estimated, and IPV schedules with 2, 3 and 4 doses were compared with the current 6-dose OPV schedule. Assumptions about IPV prices were based on indications from vaccine manufacturers. The health impact of OPV cessation was measured in terms of vaccine associated paralytic paralysis (VAPP) cases and disability adjusted life years (DALYs) averted.

CONCLUSIONS: The use of OPV in routine immunization services is predicted to result in 2.96 VAPP cases in the 2005 cohort. The cost-effectiveness of the different IPV alternatives varies between US\$ 740,000 and US\$ 7.2 million per VAPP case averted. The costs per discounted DALY averted amount to between US\$ 61,000 and US\$ 594,000. Among the IPV strategies evaluated, the 2-dose schedule in a 10-dose vial is the most costeffective option. At the assumed vaccine prices, all IPV options do not appear to be costeffective in the South African situation. OPV cessation without IPV replacement would result in cost savings of US\$ 1.6 million per year compared to the current situation. This is approximately a 9% decrease in the budget for vaccine delivery in South Africa. However, with this option there is a risk (albeit small) of vaccine-derived poliovirus circulating in a progressively susceptible population. For IPV in a single dose vial, the break-even price, at which the costs of IPV delivery equal the current OPV delivery costs, is US\$ 0.39.

Tucker AW et al. Cost-effectiveness analysis of changing from live oral poliovirus vaccine to inactivated poliovirus vaccine in Australia. Aust N Z J Public Health. 2001;25(5):411-6.

OBJECTIVE: Estimate the economic impact of introducing inactivated poliovirus vaccine (IPV) into the Australian childhood immunisation schedule to eliminate vaccine-associated paralytic poliomyelitis (VAPP). **METHODS:** Cost-effectiveness of two different four-dose IPV schedules (monovalent vaccine and IPV-containing combination vaccine) compared with the current four-dose oral poliovirus vaccine (OPV) schedule for Australian children through age six years. Model used estimates of VAPP incidence, costs, and vaccine utilisation and price obtained from published and unpublished sources. Main outcome measures were total costs, outcomes prevented, and incremental cost-effectiveness, expressed as net cost per case of VAPP prevented. **RESULTS:** Changing to an IPV-based schedule would prevent 0.395 VAPP cases annually. At \$20 per dose for monovalent vaccine and \$14 per dose for the IPV component in a combination vaccine, the change would incur incremental, annual costs of \$19.5 million (\$49.3 million per VAPP case prevented) and \$6.7 million (\$17.0 million per VAPP case prevented), respectively. Threshold analysis identified break-even prices per dose of \$1 for monovalent and \$7 for combination vaccines. **CONCLUSIONS:** Introducing IPV into the Australian childhood immunisation schedule is not likely to be cost-effective unless it comes in a combined vaccine with the IPV-component price below \$10. **IMPLICATIONS:** More precise estimates of VAPP incidence in Australia and IPV price are needed. However, poor cost-effectiveness will make the decision about switching from OPV to IPV in the childhood schedule difficult.

68th World Health Assembly, 2015, agenda item 15.2. Poliomyelitis. Available at http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_R3-en.pdf, accessed February 2016. (No abstract available).