Evidence Summary on Two-dose Inactivated Polio Vaccine (IPV) versus One-dose IPV for the prevention of **Poliomyelitis**

Service Line	Evidence Summary
Publication Date	13 July 2021
Summary Length	77 Pages
Prepared by	Health Technology Assessment Council Health Technology Assessment Unit
Contact details	hta@doh.gov.ph

Background

Burden of the disease

Poliomyelitis (Polio) is a highly infectious viral disease which affects children aged 5 years and below. It may spread from person to person via fecal-oral route or via a vehicle such as contaminated food or water. The virus multiplies in the intestines and affects the nervous system leading to paralysis of extremities. Poliomyelitis may be caused by any of the three polio serotypes: 1, 2 and 3. One in every 200 infections leads to irreversible paralysis. Of these, 5 to 10% lead to deaths due to respiratory paralysis (World Health Organization [WHO], 2019a).

There are three wild poliovirus types (WPV1, WPV2, WPV3) with the WPV1 type being the only wild type probably in circulation (WHO, 2017). WPV2 was certified to be eradicated in September 2015 and WPV3 was certified as eradicated in October 2019. Meanwhile, WPV1 was continuously detected in Afghanistan and Pakistan (GPEI, 2019a).

Aside from the wild poliovirus, circulating vaccine-derived poliovirus (cVDPV) is also noted with type 2 (cVDPV2) to be the most prevalent with 959 cases globally in 2020. This type is brought about by the spread of the virus through the stools excreted by children vaccinated with the oral polio vaccine (OPV). In communities with low immunization rates, the virus can mutate to cause paralysis similar to the wild poliovirus as the virus spreads between unvaccinated children, often over 12 to 18 months. Other than this, immunodeficiency-related vaccine-derived poliovirus (iVDPV) was noted in children with rare immune deficiency disorders. Due to their inability to clear the intestinal vaccine virus infection within the usual six to eight weeks, these children thus gain the iVDPV. Since 1962, only 111 cases have been reported globally. Finally, in a situation where VDPV is not circulating within a community and the infected individual is not immunocompromised, this type is called Ambiguous Vaccine-derived Poliovirus (aVDPV) (GPEI, n.d.c).

Current Management Options

Global perspective

There is no cure for polio and is thus prevented through vaccinations. In 2015 and 2019, the WHO declared that wild poliovirus type 2 and type 3 were eradicated, respectively. Southeast Asia was also declared poliovirus free in 2014. However, the final steps towards eradication have proven the most difficult. As such, prevention using a vaccine has been emphasized. The vaccine, given multiple times, can protect a person for life (WHO, 2019a). This is thus the heart of the current Global Polio Eradication Initiative (GPEI) with its Endgame Strategy 2022 to 2026 goals including permanent interruption of all poliovirus transmission in endemic countries, and stopping cVDPV transmission and preventing outbreaks in non-endemic countries.

Two types of polio vaccine are available – oral polio vaccine (OPV) and inactivated polio vaccine (IPV). Three types fall under OPV namely, monovalent, bivalent, and trivalent. Monovalent OPV (mOPV) contains any one individual type while bivalent OPV (bOPV) contains Types 1 and 3.

Trivalent OPV (tOPV) includes all three poliovirus types, however, the use of this type of the oral polio vaccine has been discontinued following the eradication of wild poliovirus type 2. OPV has been linked with cVDPV risk with 1,000 cases of cVDPV paralysis among 10 billion doses of OPV given to three billion children since the year 2000. Aside from this, vaccine-associated paralytic polio (VAPP) has been noted in three to four children among one million births. VAPP cannot spread between individuals and thus no outbreak response is required. On the other hand, IPV includes a mixture of inactivated, killed strains of all three poliovirus types. It is not linked to both cVDPV and VAPP (GPEI, n.d.d).

In November 2013, the WHO recommended the **rapid introduction of IPV** to protect infants against potential cVDPV type 2 outbreaks following OPV type 2 cessation. Specifically, they recommended that all OPV-only using countries should introduce at least one dose of IPV into their immunization schedules by the third quarter of 2015, and that IPV should be administered in addition to the 3-4 doses of OPV in the primary series.

Essentially, the rationale behind the recommendation to introduce IPV according to the WHO are as follows:

- ***To reduce risks.*** *Once OPV type 2 is withdrawn globally, if no IPV is used, there will be an unprecedented accumulation of children susceptible to type 2 poliovirus. IPV use will help maintain immunity to type 2. This will help prevent emergence of type 2 viruses should they be introduced after the type 2 component is removed from OPV. Thus, a region immunized with IPV would have a lower risk of re-emergence or reintroduction of wild or vaccine-derived type 2 poliovirus.*
- ***To interrupt transmission in the case of outbreaks.*** *Should monovalent OPV type 2 (mOPV type 2) be needed to control an outbreak, the immunity levels needed to stop transmission will be easier to reach with use of mOPV type 2 in an IPV-vaccinated population compared to use of mOPV type 2 in a completely unvaccinated population. Thus, introducing IPV now could facilitate future outbreak control.*

In 2014, this recommendation was reiterated in another WHO SAGE position paper and countries were given a deadline to set their targets to introduce IPV. In 2016, the WHO SAGE position paper focused on the global switch from tOPV to bOPV in light of the cVDPV and VAPP associated with type 2 poliovirus, but as regards IPV, the position paper has emphasized that the WHO still maintains the previous SAGE recommendation to include at least one dose of IPV in the vaccination schedule.

In 2020, the WHO SAGE recommended that a second IPV dose be introduced by all countries that currently administer one IPV dose and bOPV in their routine immunization schedule. SAGE noted that 2 doses of IPV provide higher immunogenicity against type 2 poliovirus than one dose of IPV. The preferred schedule is to administer the first IPV dose at 14 weeks of age, followed by a second dose at least 4 months later as this provides the highest immunogenicity, and may be carried out using full dose IPV or fractional intradermal IPV without loss of immunogenicity. SAGE, however, added that countries may consider alternative schedules based on local epidemiology, programmatic implications and feasibility of delivery. Lastly, regardless of the 2 dose IPV schedule used, introduction of the second IPV dose would not reduce the number of bOPV doses used in the routine immunization schedule.

In an Experts Consultation Meeting conducted with the WHO, it was found that as of June 2021, several countries have plans of introducing the second IPV dose in their national immunization programs, which are Lao PDR (introduction in 2022), Mongolia (September 2021), the Philippines (in a phased manner throughout 2021), Papua New Guinea (July 2021), and Vietnam (Quarter 3 of 2021). The WHO Experts Consultation Meeting noted the following countries implementing IPV as of June 2021:

Table 1. Countries implementing IPV in their NIP (Adapted from the WHO WPRO Meeting)

3 or more IPV doses *20 countries*	**bOPV + single IPV dose** *14 countries*	**Sequential iPV and bOPV** *1 country*
American Samoa Australia Brunei Darussalam French Polynesia Guam Hong Kong SAR (China) Japan Macao SAR (China) Malaysia Marshall Islands Micronesia New Caledonia New Zealand Niue Northern Mariana Islands Palau Republic of Korea Tokelau Tuvalu Wallis and Futuna	Cambodia Cook islands Fiji Kiribati Laos Mongolia (from 2018) Nauru Papua New Guinea Philippines Samoa Solomon Islands Tonga Vanuatu Vietnam (from 2018)	Singapore

In light of the COVID-19 pandemic, the WHO issued a draft catch-up vaccination program in October 2020 entitled, *Guiding principles for immunization activities during the COVID-19 pandemic* in an effort to help countries who have reported varying degrees of disruption to immunization services due to COVID-19 (WHO, 2020). The WHO SAGE expresses concerns regarding the impact of the pause in vaccination campaigns and surveillance on poliovirus eradication efforts. Hence, the WHO, in the same document, has provided guiding principles and considerations to support countries in their decision-making regarding provision of immunization services during the COVID-19 pandemic and was complemented by a range of WHO technical materials on response and mitigation measures for COVID-19. Nevertheless, the supply of IPV has significantly improved, making it possible to plan the introduction of a second dose of IPV into the routine immunization schedules of the 94 countries that are currently using one-dose IPV and bOPV (WHO, 2020).

Philippine perspective

The DOH Polio Vaccination Program through the years

Having no cure for polio, the Philippines has been involved in polio immunization programs since 1979 and has since been declared polio-free since October 2000. In 2002, the *Balik Patak Kontra Polio* door-to-door program was launched in response to the detection of the wild poliovirus in the last quarter of 2001. The program was able to immunize 102.7% of the targeted 12 million children aged five years and below nationwide (DOH, 2002). In the 24th Meeting of the Technical Advisory Group on Immunization and Vaccine-preventable Diseases of the WHO Western Pacific Region, all member countries using only OPV committed to introduce IPV into their national immunization program as well as shift from the tOPV to bOPV by April 2016 (WHO WPRO, 2015). Further, the DOH has issued Department Memorandum 2015-0164 and Department Memorandum 2015-0164-A which discuss the administration of IPV. The memorandum cited the introduction of IPV to the DOH National Immunization Program (DOH-NIP) in compliance with the World Health Assembly Global Polio Endgame (2019 to 2023) program. The rationale of which are those cited by the said program.

The Current Polio Vaccination Program of the DOH-NIP

Following the global recommendation to shift to IPV, the DOH-NIP currently implements the vaccination of bivalent OPV with the primary series consisting of three doses administered at 6 weeks, 10 weeks and 14 weeks of age. One dose of the standalone formulation of IPV is given alongside the third OPV dose. Currently, there are two types of IPV vaccine - Salk IPV and Sabin IPV (sIPV). Salk IPV contains wild virulent strains (Mahoney for polio type 1; MEF-1 for polio type 2; Saukett for polio type 3) which are inactivated using formalin, while Sabin IPV contains inactivated strains (Sabin strains) of poliovirus type 1, 2, and 3. The WHO has published a list of prequalified Sabin and Salk IPVs. In the Philippines, the DOH-NIP and the private sector have been using Salk IPV.

Currently in the Philippine National Formulary, both the OPV and IPV vaccines are listed with the following details:

Live Attenuated Bivalent Oral Polio Vaccine (Type 1 and 3), Oral: 2 mg vial (20 doses)
Indication: active immunization in all age groups against infection caused by poliomyelitis viruses of Type 1 and 3

Contraindications: those with known hypersensitivity to neomycin, polymyxin or any other component of the vaccine. in subjects having shown signs of hypersensitivity after previous administration of OPVs

Dose: Primary vaccination or booster dose should be given following official recommendations

Dose Adjustment: Renal and hepatic impairment: no information

Precautions: Hypersensitivity reactions, pregnancy, gastrointestinal infections

Adverse Drug Reactions: Fever, vomiting, diarrhea, Rare: Vaccine-associated paralysis

Drug Interactions: Can be administered at the same time as the *Haemophilus influenzae* type b vaccine, hepatitis B vaccine, diphtheria, pertussis and/or tetanus vaccine, measles, rubella, and/or mumps vaccine, yellow fever vaccine, or BCG vaccine if this fits into the vaccination schedule

Immunosuppressive treatment may reduce the immune response, may favor the multiplication of the vaccine viruses, and may increase the length of excretion of the vaccine viruses in the stools

Administration: For oral use only, do NOT inject. The vaccine is two drops (0.1 mL measured using a multi-dose container)

The vaccinating dose can be administered directly in the mouth or on a sugar lump. If a dropper is used, care must be taken not to contaminate the dropper with the saliva

Pregnancy Category: C

ATC Code: J07BF02

Inactivated Poliomyelitis Vaccine (Types 1, 2 and 3)
Inj: 0.5 mL per dose, suspension for injection single dose/ multidose vial (IM, SC)

Indication: active immunization against poliomyelitis caused by poliovirus type 1, 2 and 3.

Contraindication: Hypersensitivity to any component of the vaccine.

Dose: Immunization by IM or SC injection, ADULT (previously unvaccinated), three 0.5 mL doses, administer 2 doses at 1-2 month intervals and the third dose 6-12 months later; ADULT (incompletely vaccinated), for adults with <3 doses of OPV and/or IPV, administer at least one 0.5 mL dose; ADULT (completely vaccinated by at increased risk of exposure), one 0.5 mL dose.

Primary Immunization by IM or SC injection, CHILD and INFANT 6 weeks to 47 months, three 0.5 mL doses at 2, 4, and 6-18 months of age

Booster immunization, by IM or SC injection, CHILD 4 to 6 years, 0.5 mL as a single dose at least 6 months after last dose; administer final booster at less than or equal to 4 years of age, regardless of previous doses.

Precautions: Anaphylactoid or hypersensitivity reactions; syncope; acute illness; immunodeficiency; Elderly; Pregnancy

Adverse Drug Reaction: Common: irritability, tiredness, fever, anorexia, vomiting, injection site reactions, persistent crying; Less common: Agitation, anaphylactic shock, allergic reaction, anaphylaxis, hypersensitivity reactions, arthralgia, febrile seizures, somnolence, urticaria; Rare: Guillain-Barré syndrome

Drug interactions: Avoid concomitant use with Belimumab, Fingolimod, Immunosuppressants [Cytarabine, Liposomal]

TEST INTERACTION. May temporarily suppress tuberculin
skin test sensitivity (4–6 weeks).

Administration: For IM or SC administration into the mid lateral aspect of the thigh in infants and small children or in the deltoid area in adults or older children. Administer while the patient is seated or lying down to prevent syncope-related injuries.

Pregnancy Category: C

ATC Code: J07BF03

DTP+Inactivated Polio Vaccine
0.5 mL monodose vial (IM, SC)
0.5 mL pre-filled syringe (IM, SC)

Indications: Active immunization against diphtheria, tetanus, pertussis, and poliovirus

Contraindications: Hypersensitivity to any component of the vaccine; severe acute neurological illness within 7 days of pertussis vaccination; thrombocytopenia or any coagulation disorders

Dose: Immunization by IM injection, CHILD 4-6 years, 0.5 mL as a single dose

Administration: For IM administration only into the deltoid muscle. Do NOT administer by ID, IV, or SC.

Pregnancy Category: C

ATC Code: J07CA02

DTP + IPV + Hib
Inj: 0.5mL pre-filled syringe (IM, SC)

Indications: Acute immunization against diphtheria, tetanus, pertussis, poliovirus (types 1, 2, and 3) and invasive disease caused by *Haemophilus influenzae type b*

Contraindications: Hypersensitivity to any component of the vaccine; severe acute neurological illness within 7 days of pertussis vaccination; thrombocytopenia or any coagulation disorders

Dose: Immunization by IM injection, CHILD and INFANT 6 weeks to <5 years, four 0.5 mL doses at 2, 4, 6, and 15-18 months of age; first dose may be administered as early as 6 weeks of age

Administration: For IM administration only into the anterolateral aspect of the thigh in children <1 year of age or into the deltoid muscle of older children. Do NOT administer to the gluteal area or areas near a major nerve trunk. Do NOT administer by IV or SC

Pregnancy Category: C

ATC Code: J07CA06

In comparison to the practices of the National Immunization Program, the Pediatric Infectious Disease Society of the Philippines (PIDSP) identified that IPV is given along with OPV as a stand alone formulation or in combination with DPT-containing vaccines to children at least six weeks of age with a primary series of three doses given at least four weeks apart. A booster dose is given six months after the third dose. Unvaccinated infants aged 7 to 11 months are given the three doses of IPV with the first two doses given a month apart and the third dose given at least two months from the second dose but ideally at or after the first birthday of the child. (PIDS, 2021). We note that the private sector follows the PIDSP recommended regimen.

Table 1.1 presents the characteristics of IPV.

Table 1.1 Characteristics of *Inactivated Polio Vaccine*

Product Name	Inactivated Polio Vaccine (IPV)
Generic Name	Inactivated Polio Vaccine (Types 1, 2, 3), Salk
FDA approved indication	An inactivated viral vaccine that induces active immunity against poliovirus types 1, 2, and 3.
Indication/s	Active immunization against poliomyelitis caused by poliovirus 1, 2, and 3 infection.
Dosage Formulation/ Strength	Suspension for injection (IM/SC)
Storage Conditions	Store at temperatures 2-8 degrees Celsius. Do not freeze. Protect from light.
Packaging	5 mL Type I glass vial with vaccine vial monitor (Box of 10's). Multidose (10 doses)

Based on the data submitted by the DOH-NIP, the vaccination coverage of IPV in the country steadily increased since the start of its implementation in 2016 to 2019 (latest data available) which ranged from 51.20% to 93.92%**.** However, a reduction in vaccination coverage was observed from 93.92% in 2019 to 68.84% in 2020. This may be due to the limited service delivery as a result of the ongoing pandemic. In terms of budget, the DOH-NIP was able to utilize 100% of the budget allocated for procurement of IPV from 2016 to 2020. In 2019, the budget utilization exceeded the budget allocation by 12.94%. This excess was taken from the overall DOH-NIP budget. Table 1.2 presents both the ideal scenario (i.e., the target number of vaccines and allocated budget for IPV) and the actual scenario (i.e., actual total number of vaccines and the actual budget utilization) from 2016 to 2020.

From 2016 to 2020, IPV vaccine cost took up 4.81% to 12.50% of the budget of the overall DOH-NIP. Table 1.2 presents the overall budget allocation of the DOH-NIP versus the budget allocated for IPV.

In terms of the current monitoring of program implementation and prevalence of cVDPVs, these are done through quarterly desk review of vaccination coverage (both for bOPV and IPV) and the continuous epidemiologic surveillance using multiple indicators such as Acute Flaccid Paralysis (through the Epidemiology Bureau Philippine Integrated Disease Surveillance and Response) and the ongoing Environmental Surveillance (through the RITM).

Table 1.2. Vaccination coverage and budget for the implementation of 1-dose IPV from 2016 to 2020

Year	PSA: Number of live births	Planned number of doses to be procured[a]	Vaccination coverage for 1-dose IPV (submitted data)							IPV Vaccine Budget (Php) (submitted data)			% Budget Utilization for IPV vaccine procurement *(calculated by HTAU)*
			Target number of vaccinees[a]	**Actual Number of Procured doses** (Calculated as Utilized Budget/ Unit Cost)	**Actual number of vaccinees**[a]	**Wastage** (Actual number of procured doses*15%)[b]	**Computed Excess doses** [Number of procured doses - (number of actual vaccinees+ wastage)][b,c]	**% Doses utilized** [(Actual no. of vaccinees+ wastage)/ Number of Procured Doses)][b]	**% Vaccination coverage** (Actual no. of vaccinees/ number of live births)	**Unit cost of IPV (Php)**[a]	**Allocated Budget for IPV procurement**[a]	**Utilized Budget for IPV procurement**[a]	
2016	1,731,289	2,000,000	2,800,198	2,000,000	886,367	300,000	813,633	59.32%	51.20%	102	204,000,000	204,000,000	100.00%
2017	1,700,618	3,000,000	2,832,883	3,000,000	1,162,591	450,000	1,387,409	53.75%	68.36%	110	330,000,000	330,000,000	100.00%
2018	1,618,315	3,000,000	2,866,558	3,000,000	1,327,804	450,000	1,222,196	59.26%	82.05%	122	366,000,000	366,000,000	100.00%
2019	1,673,923	2,500,000	2,220,772	2,823,514	1,572,078	423,527	827,909	70.68%	93.92%	150	375,000,000	423,527,102	112.94%
2020	2,123,158 (projected)	5,000,000	2,123,158	5,000,000	1,461,632	750,000	2,788,368	44.23%	68.84%	181	905,000,000	905,000,000	100.00%

Notes:

a. Data provided by the program
b. Computations include a wastage factor of 15% according to NIP.
c. Computed excess doses may be overestimated since the calculations do not account for the underreporting in the actual number of vaccinees.

Current challenges and ways to move forward

In 2019, a polio outbreak due to newly emerged circulating vaccine-derived poliovirus type 1 (cVDPV1) and 2 (cVDPV2) was declared by the Department of Health (DOH). Samples collected from Manila and Davao confirmed the widespread circulation of the cVDPV1 and cVDPV2 in a very large zone stretching from Central Luzon through Mindanao. This prompted the DOH to conduct an outbreak response with OPV and strengthened routine immunization activities including IPV in the identified areas affected by the outbreak (e.g., National Capital Region, Central Luzon Region, CALABARZON Region and Mindanao Region). Environmental surveillance in these regions was also observed. Further, in a 2019 DOH press release, it was cited that the vaccination coverage in the past years fell below 95% of the target in the country. Moreover, poor surveillance was noted for acute flaccid paralysis, a severe sequela of the poliovirus.

Since then, the polio immunization program was strengthened, surveillance of children under 5 years old who developed sudden onset muscle weakness or paralysis was scaled up, and the implementation of the Zero Open Defecation program was instituted (DOH, 2019). In 2020, during the start of the COVID-19 pandemic, the DOH has issued DM 2020-0150 to ensure that while health system efforts are focused on addressing COVID-19, service delivery of other health programs such as the DOH-NIP will remain accessible.

GPEI polio endgame 2022 to 2026

In the recently published Global Polio Eradication Initiative Polio Endgame Strategy 2022-2026, two goals have been identified, first, the interruption of all poliovirus transmission in endemic countries and second, interruption of cVDPV transmission and prevention of outbreaks in non-endemic countries. Several challenges, strategic objectives and key activities have been cited per goal which are summarized in Table 1.3

Table 1.3 GPEI Polio Endgame Strategy Challenges, and strategic goals and key activities

Goal	Challenges	Strategic goals and key activities
Goal One: Permanently interrupt poliovirus transmission in the final WPV-endemic countries of Afghanistan and Pakistan	● In Afghanistan, ban on house-to-house immunization resulted in more than 1 million children persistently missed in southern areas by polio vaccination campaigns since May 2018 ● In Pakistan, several factors were noted: ○ complacency with declining cases from 2015 to mid-2018, including a few months without a single case; ○ transitions in national leadership and a	Political advocacy ● Gain and maintain access in Afghanistan through systematic advocacy with all. ● Intensify advocacy with provincial governments in Pakistan. Community engagement ● Conduct multidisciplinary research into vaccine hesitancy and community mistrust. ● Foster alliances with priority communities for co-design, ownership and delivery of gender-responsive programme innovations. Campaigns ● Recruit, train, and appropriately support a

	subsequent politicization of polio; ○ increase in vaccine hesitancy; ○ misalignment between nearly emerging challenges in priority areas and vaccination approaches that were better suited for a past era ○ misinformation about vaccines and vaccination programmes	motivated workforce that meets the needs of the community. ● Introduce monitoring innovations to enable faster data feedback loops and improve quality. ● Facilitate strengthening of essential immunization. Integration ● Deliver polio vaccines alongside basic public services to increase reach of both essential and supplementary immunization, with a focus on high-risk areas. ● Partner with governments, communities, and adjacent health programmes to support access and reduce missed communities and zero-dose children. Surveillance ● Improve timeliness for detection — from case onset to final results. ● Establish a pathway towards a sustainable integrated surveillance system.
Goal Two: Stop cVDPV transmission and prevent outbreaks in non-endemic countries	● declining mucosal immunity to type 2 virus among young children born after the switch to bOPV ● low essential immunization coverage with IPV ● regional migration patterns that allow the virus to jump from one population to another ● delays in detecting cVDPV2 outbreaks ● limited SIA scope driven by limited global vaccine stockpile availability ● delayed implementation of outbreak responses ● variable quality SIAs in outbreak response	Political ● Engage government and political stakeholders via integrated health advocacy to ensure emergency posture, resourcing and joint accountability for timely and effective outbreak response. Surveillance ● Implement technical innovations in surveillance and sample analysis to more rapidly detect, sequence and initiate response activities. Campaigns ● Deploy nOPV2 and improve campaign planning and execution through optimized response scope, mobile money payments, campaign digitization and other innovations Community engagement ● Engage nomadic and settled communities both before and during outbreak campaigns. Integration ● Ensure the success of the Gavi zero-dose strategy and leverage multi-antigen campaigns. ● Support global health emergencies with near-term focus on COVID-19.

		Enabling environment ● Pivot away from Sabin OPV2 to nOPV2 and ensure sucient vaccine supply. ● Move to a regional structure with global support that holds the GPEI and countries accountable for progress. ● Utilize a rapid gender analysis to shape the outbreak response.

Target year of the DOH-NIP for the discontinuation of OPV vaccines

As for the target year of the DOH-NIP for the discontinuation of OPV vaccines following the global recommendation, the initial global plan is to cease all use of OPV by 2020. The cessation of the OPV will depend on multiple factors such as status of poliovirus transmission, vaccine availability, and strength of routine immunization. However, the target to cease OPV use was not reached in 2020 due to the ongoing poliovirus transmission in many countries including the Philippines. Currently, the aim of the DOH-NIP is to improve population immunity against all types of poliovirus using bOPV and IPV. Thus, the timeframe for discontinuation of OPV in the country cannot be specifically determined.

Proposed introduction of 2-dose Inactivated Polio Vaccine (IPV)

With the persistence of the poliovirus and the reemergence of the virus in certain countries, a recommendation of shifting to two doses of IPV has been prompted. The Strategic Advisory Group of Experts (SAGE) on Immunization in October 2020 noted that two doses of IPV provide higher immunogenicity against type 2 poliovirus than a single dose (Faden et al 1990; Resik et al 2013). It further recommended the use of two-dose IPV to countries giving one-dose IPV and bOPV in their routine immunization schedule. The suggested schedule is to give the first dose of IPV at 14 weeks of age with a DTP-containing vaccine and the second dose at least four months after (WHO, 2020b). Thus, in 2021, the DOH-NIP has proposed to shift from 1-dose to 2-dose (IPV) for the same target of patients (i.e., infants less than 1 year of age) as shown in Table 1.4:

Table 1.4 Current and Proposed Polio Vaccination Schedule

Current Polio Vaccination	Proposed Polio Vaccination
3-dose bivalent oral polio vaccine (bOPV) + **1-dose IPV** **Current vaccination schedule** 6 weeks - bOPV 10 weeks- bOPV 14 weeks- bOPV + IPV *Eligible infants who missed their IPV at 14 weeks shall*	3-dose bivalent oral polio vaccine (bOPV) + **2-dose IPV** **Proposed vaccination schedule** 6 weeks - bOPV 10 weeks- bOPV 14 weeks- bOPV + **IPV** 9 months -Measles-containing vaccine (MCV) + **IPV**

receive IPV at first contact *Reference: Department Circular 2015-0164*	*Reference: SAGE Recommendation 2020*

The rationale provided by the DOH-DOH-NIP to introduce the shift to 2-dose vaccination are as follows:

- Based on the Polio Endgame Plan 2019-2023, elimination of VDPV is done through complete OPV cessation in routine immunization. The shift from tOPV to bOPV and the introduction of one-dose IPV can eliminate the threat of VDPVs since bOPV with IPV complement and improves the immune response against WPVs and VDPVs.
- Countries at risk of cVDPV emergence may benefit from additional measures such as pre-cessation of tOPV campaigns or the initiation of two-dose IPV. With the Philippines declaring a polio outbreak in September 2019 upon detection of cVDPV type 2 in both human and environmental samples, the country would benefit from the approach.
- The WHO SAGE Meeting reviewed the use of two-dose IPV with bOPV and noted higher immunogenicity against poliovirus type 2 compared to the one-dose regimen. Thus, SAGE recommends the administration of another IPV dose to those countries currently using a one-dose IPV in the routine immunization schedule.

In addition, the DOH-NIP proposed outcomes such as immunogenicity and reduction of cases as measures of benefit.

In a presentation made by the DOH-NIP, they presented their polio-specific strategic direction for the year 2022-2027 which includes the following:

- Creation of dedicated NIP personnel in all levels
- Establishment of National Immunization Technical Advisory Group (NITAG)
- Intensification of Acute Flaccid Paralysis (AFP) and environmental surveillance
- Redesigning of the procurement process
- Renewal of the commitment of all stakeholders
- Creation of accessible and accurate information gateway
- Nationwide implementation of Two-dose IPV (2022)
- Shift from bOPV to IPV only

The DOH-NIP also noted that following the 2019 outbreak of poliovirus, they have started a pilot introduction of two-dose IPV in high-risk poliovirus reinfection regions, namely NCR, Region III, Region IV-A, Region VII, and Mindanao. As mentioned prior, plans for a nationwide introduction of two-dose IPV have been pegged to be commenced by the year 2022.

Given these, this review was conducted to present evidence that will support the recommendation on whether the DOH-NIP should shift from 1-dose IPV to 2-dose IPV.

Policy Question

Among infants aged less than one year, should the DOH National Immunization Program shift from 1-dose IPV to 2-dose IPV?

Research Question

1. Clinical Effectiveness and Safety

- Among infants aged less than one year, what is the effectiveness of 2-dose IPV in combination with 3 doses of bOPV compared to 1-dose IPV in combination with 3 doses of bOPV in terms of reduction of polio cases and immunogenicity?
- Among infants aged less than one year, what is the safety of 2-dose IPV in combination with 3 doses of bOPV compared to 1-dose IPV in combination with 3 doses of bOPV in terms of adverse events?

2. Economic impact

- Does shifting from 1-dose to 2-dose IPV as part of the DOH-NIP represent good value for money in the Philippines?
- What is the likely 5-year budget impact/ vaccine procurement cost for the DOH-NIP to implement a 2-dose IPV vaccination versus the 1-dose IPV vaccination?

3. Ethical, legal, social, and health systems impact

- What are the ethical, legal, social, and health systems implications of shifting from 1-dose to 2-dose IPV as part of the DOH-NIP?

Responsiveness to Disease Magnitude, Severity, and Equity

Burden of the disease

Global perspective

Polio has been a disease faced by the global landscape. Since 1988, A 99% decline of wild poliovirus cases has been observed in such a way that by 2018, only 33 reported cases were noted compared to 125 endemic countries with about 350,000 cases noted. Of the three wild poliovirus types, wild poliovirus type 2 was eradicated in 1999 and there have been no further cases of wild poliovirus type 3 since 2012 in Nigeria (WHO, 2019a). The Global Polio Eradication Initiative (GPEI) contributed greatly to the vast improvement. The initiative was a joint effort of national governments, non-governmental agencies, and other organizations. Currently, the GPEI notes two endemic countries, namely, Pakistan and Afghanistan; five key at-risk countries (China, Indonesia, Mozambique, Myanmar, Papua New Guinea); and 26 outbreak countries among which the Western Pacific region outbreak countries are Malaysia and the Philippines (GPEI, n.d.a).

The WHO noted that one in 200 infections progresses to irreversible paralysis with 5 to 10% of which become morbidities when respiratory muscles become affected. Children under five years of age are thus noted to be most at risk for this disease (WHO, 2019a).

Polio in the Philippines

The last recorded wild poliovirus case in the Philippines was in 1993 and the country was certified as polio-free in 2000 (DOH, 2015). However, in the latter months of 2001, wild poliovirus was detected and was addressed with the *Balik Patak Kontra Polio* program (DOH, 2002). The circulating vaccine-derived poliovirus type (cVDPV1, cVDPV2) had been the disease type that was present in the country during the polio outbreak declared in September 2019 (GPEI, n.d.b). Four environmental samples from Tondo, Manila tested positive for the Vaccine derived Poliovirus Type 1 (VDPV1), two testing for VDPV2 in Davao and Tondo, and another from Lanao del Sur which presented with Acute Flaccid Paralysis (AFP) symptoms. Thus, the Philippine DOH initiated a comprehensive outbreak response in October 2019 which includes a mass polio immunization (WHO, 2019b).

As of the July 16, 2020 Situation Report of the WHO, the DOH noted a total of 14 circulating VDPV1 (cVDPV1) and 24 circulating VDPV2 (cVDPV2) environmental samples. Among human samples, one cVDPV1, 20 cVDPV2, one iVDPV2, and two VDPV1 were confirmed. The country's polio outbreak is now considered a public health emergency of international concern (WHO, 2020a).

In a letter dated 03 June 2021, the World Health Organization declared the official closure of the circulating vaccine-derived poliovirus (cVDPV) type 1 and type 2 in the Philippines. This is supported by a review of global polio eradication experts which confirmed that there is no evidence of continuous transmission of cVPDV in the country. However, in their presentation

to the DOH during the experts consultation, the WHO emphasized that the Philippines remains at high risk of polio virus type 2.

Equity in polio

Since Poliomyelitis affects children in geographically isolated and disadvantaged areas and that the majority of patients with VDPV are undergoing physiotherapy and are in need of financial assistance, the proposed intervention benefits the mentioned marginalized groups.

Safety and Efficacy

For efficacy, the evidence available was from a systematic review (Macklin, et al., 2019). Meanwhile for safety, the evidence available was from real world data.

Evidence from Literature

Efficacy

Evidence from systematic search

A systematic search of systematic reviews (SRs) with or without meta-analysis (MAs) was conducted last 19 March 2021 to detect currently existing reviews on the clinical benefit of our intervention of interest. Of the 637 searched articles, one study matched our clinical research question and was included in the review for evidence on efficacy (Macklin et al., 2019).

Study Characteristics

The SRMA (Macklin et al. 2019) included 17 RCTs among healthy infants (N=23,747) administered with either one-dose or two-dose IPV in combination with bOPV for immunogenicity against poliovirus. Immunogenicity outcomes were either (1) humoral immunity to poliovirus serotype 1, 2 and 3 measured four weeks after the most recent vaccine dose in terms of seroconversion, that is, a >1:4-fold increase in antibody titers; or as (2) intestinal immunity to poliovirus serotype 2 measured as the absence of shed virus seven days after challenge dose of OPV containing the Sabin type 2 strain. Direct and indirect data were synthesized through a random effect meta-analysis of single proportions and a random-effect network meta-analysis. The network meta-analysis utilized a Bayesian framework while the relative effects were presented as an effect ratio with 95% credible intervals (CrIs). Meanwhile, to ensure consistency within the trials, studies included were only those done outside western Europe or North America due to differences in immunogenicity and vaccine schedules.

Findings from the study

While the study (Macklin et al., 2019) assessed different vaccine schedules, we only presented here the efficacy data of one-dose versus two-dose IPV in combination with 3 bOPV which are the focus of this evidence summary.

ROB result (as described by study)

Using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials, the study found a low-to-moderate overall risk of bias for individual RCTs.

Efficacy Outcome 1: Humoral immunity to poliovirus serotypes

Macklin et al., 2019 reported its results as log risk ratios. We then converted these to risk ratios for easier interpretation.

Based on their findings, relative effects of pairwise comparison between one-dose IPV versus two-dose IPV showed different results across the serotypes.

- **Humoral immunity to poliovirus type 1:** There is inconclusive evidence to show that there is a difference between the seroconversion in 1-dose IPV + 3 bOPV versus 2-dose IPV + 3 bOPV [RR: 1.00 (95% CrI: 0.57-1.77) (rated as high certainty of evidence based on Macklin et al., 2019).
- **Humoral immunity to poliovirus type 2:** On the other hand, compared to 1-dose IPV + 3 bOPV, 2-dose IPV + 3 bOPV showed benefit [RR: 0.77 (95% CrI: 0.66-0.85)] (rated as high certainty of evidence based on Macklin et al., 2019).
- **Humoral immunity to poliovirus type 3:** Comparing 1-dose IPV + 3bOPV with 2-dose IPV + 3 bOPV regimen showed inconclusive results [RR: 1.09 (95% CrI: 0.83-1.60)] (rated as high certainty of evidence based on Macklin et al., 2019).

Table 3.1 presents the relative effects of pairwise comparison between one-dose IPV and two-dose IPV.

Table 3.1 Calculated relative effects of pairwise comparison between one-dose IPV and two-dose IPV against different poliovirus serotypes, reported as log risk ratio with 95% credible intervals

Poliovirus type	Number of studies	Log risk ratio (95% CrI)	Risk ratio (95% CrI) *HTAU calculated*
Type 1	2	0 (-0.57, 0.57)	1.00 (0.57,1.77)
Type 2	2	-0.26 (-0.42, -0.16)	0.77 (0.66, 0.85)
Type 3	2	0.09 (-0.19, 0.47)	1.09 (0.83, 1.60)

Efficacy Outcome 2: Intestinal immunity to poliovirus type 2

For intestinal immunity to poliovirus type 2, the study (Macklin et al., 2019) reported evidence on 1-dose IPV + 3 bOPV compared with 2-dose IPV + 3 bOPV. Pooled data from 4 study points showed that following a 1-dose IPV + 3 bOPV schedule, 25% (95% CI: 0.22 to 0.29) of individuals developed intestinal immunity (i.e. absence of viral shedding 7 days after an OPV challenge dose). Using a 2-dose IPV + 3 bOPV schedule did not result in significant difference in proportion of individuals who developed

intestinal immunity based on pooled data from 2 study points which showed that 28% (95% CI: 0.25 to 0.32) of individuals developed intestinal immunity.

Relevant recommendations of the study

- *"Our results provided evidence that individuals vaccinated with bOPV-only schedules have negligible immunity against poliovirus 2 (probably from passive type-2 exposure or antibody cross-neutralisation from types 1 and 3). This immunity deficit suggests that the estimated 43 million children across 33 countries who did not receive IPV because of supply shortages have no protection.*
- *"Notably, the addition of a single dose of IPV (at 14 weeks) improved humoral immunity against serotype 2, whereas a second dose (at 18 or 36 weeks) had a smaller impact and a single mIPV2 dose provided equivalent immunogenicity to two doses of trivalent IPV."*
- *"We show that a single dose of IPV improves humoral immunity against serotype 2 and suggest that in times of IPV supply constraints, equitable distribution of a single dose of IPV should be prioritized over cohorts receiving a second dose, taking into account country-specific risk. This IPV addition will be unlikely to prevent faecal–oral transmission of the virus, but would provide individual protection against paralytic disease."*

Critical appraisal of the study

We performed a critical appraisal on the study of Macklin et al. (2019) using A MeaSurement Tool to Assess Systematic Reviews (AMSTAR 2) with an overall rating of critically low. Noted critical flaws include failure to explicitly report the following: justification for excluding studies, investigation of causes of between-trial heterogeneity, discussion of the likely impact of included studies with moderate RoB, and assessment of presence and likely impact of publication bias. The critical appraisal of this study can be found in Appendix A.

Evidence from WHO on efficacy

The WHO presented the results of its systematic review and meta-analysis on the immunogenicity of IPV to support recommendations on the use of 2-dose IPV during its SAGE meeting last September 2020. Existing studies on the immunogenicity of IPV with no date limitation were screened and assessed. The review performed a meta-analysis of seroconversion rates of 1-dose vs 2-dose 2 IPV, among others (e.g., fractional IPV vs full-dose IPV). Note, however, that their analysis for 1-dose vs 2-dose 2 IPV included both conventional/Salk and Sabin (sIPV) preparations.

Based on this SRMA, the seroconversion for type 2 poliovirus was noted to be higher with the use of 2-dose IPV [seroconversion rate: 95.9% (95% CI: 95.9-98.2)] vs 1-dose IPV [seroconversion rate: 63.9% (95% CI: 55.7-71.3)], irrespective of age of immunization and interval between doses. This is consistent with the findings of Macklin et al. (2019) wherein the introduction of 2-dose IPV + 3 bOPV showed benefit [RR: 0.77 (95% CrI: 0.66-0.85)] compared to 1-dose IPV + 3 bOPV, based on high certainty of evidence as assessed by Macklin et al. (2019).

Safety

The study of Macklin et al. (2019) did not report adverse events in their analysis. We detected one recent RCT (He et al., 2020) in our search which measured safety outcomes of two-dose sabin IPV compared to one-dose sabin IPV as a secondary endpoint which included the rates of serious adverse events and important medical events. However, this was not considered due to mismatching intervention as the study analyzed Sabin IPV (i.e., 2-dose sIPV + 1 bOPV vs 2-dose IPV + 3 bOPV) and comparator (1-dose sIPV + 2 bOPV vs 1-dose IPV + 3 bOPV) while our research question was specific for Salk IPV.

In addition to the systematic search, we also performed targeted search of real world data on safety as well as relevant WHO statements or positions on IPV safety.

Evidence from countries implementing at least 2 doses of IPV

Regulatory agencies, ministries of health, and local studies implementing the two-dose IPV (i.e., China and Palau) and three-dose IPV (i.e., Marshall Islands, Malaysia, South Korea, and Tuvalu) as informed to us by the DOH-NIP were searched for reports on adverse events following immunization (AEFI) (Appendix C). Of these, only a trial from South Korea published a report on AEFI.

- **South Korea (2009-2011), 3-dose IPV**
    - The total adverse events observed after each dose of IPV were 133 (88.67%), 132 (88%), and 120 (80%) after dose 1, 2, and 3, respectively, with more adverse events occurring after doses 1 and 2. For the observed local adverse events (AEs), 65 (43.33%), 53 (35.33%), and 55 (36.67%) adverse events were observed after dose 1, 2, and 3, respectively, with more local adverse events occurring after dose 1. Meanwhile, for systemic AEs, 129 (86%), 126 (84%), and 110 (73.33%) were observed after dose 1, 2, and 3, respectively, with more systemic adverse events occurring after doses 1 and 2.
    - The most common solicited adverse events (AEs) among infants were injection site redness (*IPVAX™* = 45.00%; *Poliorix™* = 37.93%) and pain (*Imovax polio™* = 46.15%).
    - The most common solicited systemic AE was irritability, reported among 80.00%, 84.62%, and 81.03% of infants in the *IPVAX™*, *Imovax polio™*, and *Poliorix™* groups, respectively.
    - Unsolicited AEs were reported for 70.00%, 55.77%, and 63.79% of infants in the *IPVAX™*, *Imovax polio™*, and *Poliorix™* groups, respectively. Of them, upper respiratory infection was the most commonly reported unsolicited AE in all groups. Unsolicited AEs possibly related to vaccination were reported among 2.5%, 1.92%, and 1.72% of infants, respectively.
    - No adverse events above grade 2 were observed.
    - No severe AEs were reported

Evidence from WHO on Safety

The Global Advisory Committee on Vaccine Safety (GACVS) discussed the following during their session on IPV in 11-12 December 2013: (a) safety record of IPV; (b) adverse events following immunization (AEFI) reports related to IPV from the Vaccine Adverse Events Reporting System (VAERS) of the USA; and (c) issues related to the manufacturing process for IPV. The discussions during this meeting were focused on IPV in general and not necessarily on two-dose IPV.

Safety record of IPV

Though proven highly efficacious, the first polio vaccine developed by Salk resulted in one of the most serious vaccine safety events recorded due to the inadequate inactivation of the polio viruses during the manufacturing process, resulting in 61 cases of VAPP, 80 family contact cases, 17 community contact cases, and 11 deaths in the first year of its use in 1955 (GACVS, 2013). Following this incident, IPV manufacturing techniques were modified to ensure complete inactivation of the virus so as to reduce the potential risk of injecting live polio viruses. However, this also resulted in a reduction of the immunogenicity of IPV preparations.

Currently, IPV is offered as an individual vaccine or in vaccine combinations for primary immunization and for boosters. Current available data indicate that the known adverse events following the administration of IPV alone are limited to non-serious reactions, with local reactions being the most common. Meanwhile, adverse events due to IPV administered as a combination with other vaccines are difficult to differentiate from those induced by other vaccines. However, reviews have not documented any serious adverse events causally related to IPV.

Further, administration of a dose of IPV prior to a course of OPV actually reduces the risk of VAPP compared with an exclusively OPV series, as stated in the report on the meeting of the GACVS held on 11-12 December 2013. However, this regimen has been updated in the Polio vaccines position paper by the WHO (published on 25 March 2016) wherein they recommended the use of a primary series consisting of 3 bOPV doses plus one dose of IPV.

AEFI reports related to IPV from the VAERS of the USA

An assessment of AEFI in all ages indicated that most adverse events in VAERS reported from 1 January 1999 to 31 December 2012 were non-serious, with less than 1% of these reports being attributable to IPV given alone. Although sudden infant death syndrome is the most commonly coded term for deaths in infants for all IPV-containing vaccines, the causal relationship between SIDS and multiple vaccines was rejected. Based on the available data, the GACVS was reassured of the excellent safety profile of IPV and IPV-containing vaccines.

Issues related to the manufacturing process for IPV

During the meeting of the GACVS, the manufacturing process of IPV was presented by a licensed manufacturer. Complexities of the manufacturing process were noted, particularly the methods used to ensure virus inactivation and containment to prevent environmental contamination. Given this, it was noted that it is important to ensure appropriate technical support, training, and regulatory oversight to IPV vaccine manufacturers given the complexities of the IPV manufacturing process.

Evidence from Expert Consultation

In an expert consultation held last 29 June 2021, experts from the WHO, DOH-NIP and the professional societies (i.e., PIDSP, PSMID) were convened to further supplement evidence gathered for two-dose IPV.

Both statements of the WHO and DOH-NIP experts corroborate the inadequacy of the current polio vaccination policy (i.e., bOPV + one-dose IPV) considering that the Philippines is a high risk for poliovirus type 2. Cognizant of the inadequacy of protection of bOPV against type 2 as emphasized by the WHO during its early SAGE recommendation for IPV, one-dose IPV was initially introduced in 2016 in the Philippines. However, it was emphasized that one-dose IPV is not enough to confer protection, thus the push to implement the use of two-dose IPV especially now that closure of cVDPV type 1 and type 2 has just been achieved in the Philippines as of June 2021.

Household Financial Impact

Based on the consultation with PhilHealth and key professional societies on the relevant benefit packages for patients with poliomyelitis, nine benefit packages were identified in the management of poliomyelitis. Claims and hospital bills on these case rates were reviewed in order to estimate the cost-of-illness and the out-of-pocket costs. Overall, the cost of treating acute poliomyelitis ranges from **Php 21,000** to **Php 26,000.89.** According to consulted experts on pediatric infectious disease and pediatric neurology, additional cost of treatment is incurred if the patient develops osteopathy after poliomyelitis (Php 7,511.65). However, these treatment costs were deemed to underestimate the cost of illness of polio as case rates for other related treatment costs are not yet available such as rehabilitation therapy for polio patients, treatment and management of neurological complications and disability, as well as the use of orthotic or assistive devices. Further, as this cost only covers medical costs, it does not reflect direct non-medical costs (i.e. cost of transportation to health facilities), and indirect costs (i.e. long-term productivity loss for caregivers) which is relevant for this illness since patients are generally pediatric.

Meanwhile, in an economic evaluation of Inactivated Polio Vaccine (Kalkowska et al. 2021), the estimated treatment cost of one case of polio in a lower-middle income country is at 7,110 USD (Php 355,500, 1 USD = Php 50). The study noted that the costing included both treatment cost and cost of productivity loss.

Based on reported costs from PhilHealth claims, the support value for polio-specific case rates can be considered adequate. However, the actual costs may need to be validated. Details per case rate are summarized below:

For acute paralytic poliomyelitis, wild virus, imported:

- PhilHealth has issued a case rate of **Php 21,100** for patients with acute paralytic poliomyelitis, wild virus, imported (A80.1).
- There were a total of 7 claims for this case rate from 2017 to 2020. The median cost for *acute paralytic poliomyelitis, wild virus, imported* for the same period was **Php 21,100.**
- Reviewing the hospital bills collected by PhilHealth from 2017-2020, the median amount spent by patients with acute paralytic poliomyelitis, wild virus, imported is **Php 21,100.00.**
- From the same dataset, the calculated median out-of-pocket spending for patients with acute paralytic poliomyelitis, wild virus, imported is at **Php 0.00.**

For acute paralytic poliomyelitis, wild virus, indigenous:

- PhilHealth has issued a case rate of **Php 21,100** for patients with acute paralytic poliomyelitis, wild virus, indigenous (A80.2)
- There were a total of 5 claims for this case rate from 2017 to 2020. The median cost for *acute paralytic poliomyelitis, wild virus, indigenous* for the same period was **Php 21,100**.
- Reviewing the hospital bills collected by PhilHealth from 2017-2020, the median amount spent by patients with acute paralytic poliomyelitis, wild virus, indigenous is at **Php 21,457.00.**
- From the same dataset, the calculated median out-of-pocket spending for patients with acute paralytic poliomyelitis, wild virus, indigenous is at **Php 357.00.**

For acute poliomyelitis, unspecified:

- PhilHealth has issued a case rate of **Php 21,100** for patients with acute poliomyelitis, unspecified (A80.9)
- There were a total of 37 claims for this case rate from 2017 to 2020. The median cost for *acute poliomyelitis, unspecified* for the same period was **Php 21,100**
- Reviewing the hospital bills collected by PhilHealth from 2017-2020, the median amount spent by patients with acute poliomyelitis, unspecified, is at **Php 26,000.89.**
- From the same dataset, the calculated median out-of-pocket spending for patients with acute poliomyelitis, unspecified, is at **Php 1,860.89.**

For osteopathy after poliomyelitis:

- PhilHealth has issued a case rate of **Php 8,800** for patients with osteopathy after poliomyelitis (M89.6)
- There were a total of 4 claims for this case rate from 2017 to 2020. The median cost for *osteopathy after poliomyelitis, unspecified* for the same period was **Php 8,800**
- Reviewing the hospital bills collected by PhilHealth from 2017-2020, the median amount spent by patients with osteopathy after poliomyelitis is at **Php 7,511.65.**
- From the same dataset, the calculated median out-of-pocket spending for patients with osteopathy after poliomyelitis is at **Php 0.00.**

Cost-effectiveness

A systematic search of relevant economic evaluation studies was conducted on 19 March 2021. Of the 637 searched articles, one study (Kalkowska et al., 2021) matched our cost-effectiveness research question and was therefore included in the review for evidence on cost-effectiveness. We used the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (Husereau D, Drummond M, Petrou S, et al., 2013) to assess the adequacy or transparency of reporting of the study. Based on our review, the majority of the required items (79.17% or 19 of 24 items) in a CEA as recommended by the CHEERS checklist were reported in the study. Missing items include: measurement of effectiveness, characterising uncertainty, and conflicts of interest (Appendix D).

Description of the study

The study is an updated global model which used updated cost inputs to simulate possible poliovirus vaccine routine immunization (RI) policies of countries and characterize the expected vaccine costs for two reference cases (RCs), utilizing an updated dynamic poliovirus transmission, stochastic risk, and economic model. The model aims to estimate expected costs and cases over the time horizon of 2019-2029.

Population: Countries were stratified into blocks of approximately 107 million people assigned to varying 2019 World Bank income levels (WBIL), with 6 low-income (LI), 28 lower middle-income (LMI), 27 upper middle-income (UMI), and 11 high-income (HI) blocks to capture the heterogeneity that exists between countries, in terms of different conditions, costs, values, and preferences at the global level.

Intervention and comparators: *Various alternative prospective vaccine policy options* were compared with the following reference case scenarios:

- *RC2 scenario or the high control scenario* - represents our characterization of the GPEI path as of early 2020 (prior to the COVID-19 pandemic); includes ongoing use of bOPV and at least 1 dose of IPV in perpetuity in OPV-using countries since the updated global model does not anticipate eradication of serotype 1 WPV (WPV1) or subsequent globally-coordinated cessation of bivalent OPV (bOPV, containing OPV for serotypes 1 and 3)
- *RC2* scenario or the alternative eradication scenario* - assumes that eradication of WPV1 is achieved before 2023 and bOPV cessation on January 1, 2025 is implemented, at which time countries add a dose of IPV to their RI schedules

As for the *various alternative prospective vaccine policy options*, the study assumed the following given the different possible alternative prospective vaccine policy options and in consideration of the fact that countries can always do more than the minimum recommended policy:

- only LI and LMI countries that currently use OPV+IPV would opt for the minimum policies; and

- UMI and HI countries will use only IPV with a minimum of 3 doses after cessation of OPV, with many of these countries already using or likely to adopt a 4-dose schedule using an IPV-containing combination vaccine.

The various alternative prospective vaccine policy options (specific for LI and LMI) that were compared with the two reference case scenarios are described in Table 5.1 For HI and UMI blocks that use IPV-only or IPV/OPV RI schedules, the study assumed that countries in these income levels will not change their polio vaccine strategy (hence are not included in Table 5.1). To highlight, among the various policy options of the study, our specific interventions of interest in this evidence review are vaccination policies **2IPV2025** and **1IPV2025**, in the control and eradication scenarios, respectively. Meanwhile, RC2 and RC2* represent our current polio vaccination in the Philippines or the comparator in our research question, for the two scenarios.

Table 5.1 Polio vaccination policy scenarios included in the economic evaluation by Kalkowska et al. (2021)

Vaccination Policy name	Description
Control scenarios	
Reference case: **RC2** *2019-2029 OPV + IPV*	1 dose of IPV from 2019-2029
Alternative policy options compared against RC2	
tOPVRISIA *2019 to 2023 OPV+IPV 2024 to 2029 OPV-only*	1 dose of IPV from 2019 to 2023 followed by tOPV only from January 1, 2024, with planned, preventive supplemental immunization activities (pSIAs) - represent a return to control with tOPV only with planned SIAs, similar to the scenarios considered as the RC in some historical analyses
tOPVRI *2019 to 2023 OPV+IPV 2024 to 2029 OPV only*	1 dose of IPV in 2019 to 2023 followed by tOPV use only from January 1, 2024, without planned, preventive supplemental immunization activities (pSIAs) - represent a return to control with tOPV only without the planned SIAs, similar to the scenarios considered as the RC in some historical analyses
2IPV2025 *2019 to 2024 OPV+IPV 2025 to 2029 OPV + 2 IPV*	1 dose of IPV in 2019 to 2024 followed by 2 dose of IPV from January 1, 2025 - represents an addition of a second dose of IPV compared to their current RI schedule and reflects different timing for IPV introduction (1st dose in 2019; 2nd dose in 2025)
RC2noRestarts *2019 to 2029 OPV + IPV*	1 dose IPV 2019 to 2029 - in the previous scenarios, only OPV2 restart may occur since bOPV use remains in RI resulting in decreased population immunity to polio type 2 - for this scenario, OPV restart threshold was set to a level such that no OPV restarts trigger during the model time horizon

Eradication scenarios	
Reference case: **RC2*** *2019 to 2024 OPV+IPV* *2025-2029 IPV/IPV*	1 dose of IPV in 2019 to 2024 followed by 2 doses of IPV from January 1, 2025 - If successful eradication of WPV1 occurs and countries globally coordinate the cessation of all use of OPV-containing vaccines in RI, it is assumed that these countries introduce a second IPV dose starting in January 1, 2025 (i.e., at the time of bOPV cessation) and continue using 2 IPV doses throughout the time horizon. - includes restart of any OPV which may occur given bOPV cessation in 2025
Alternative policy option compared against RC2:*	
1IPV2025 *2019 to 2024 OPV+IPV 2025 to 2029 IPV*	1 dose of IPV in 2019 to 2029 - continued use of OPV and 1 IPV dose in RI through 2025 then shifting to 1 dose of IPV only from 2025 through 2029

Input parameters: Kalkowska et al. (2021) used updated costs and assumptions from the costing study by Thompson and Kalkowska (2020). All cost estimates were converted to 2019 US Dollars using the US Consumer Price Index (CPI). A 3% discount rate was used for both cost and health outcomes. Input parameters for each block are presented in Table 5.2. The framing of this analysis on vaccine costs excludes the consideration of global programmatic or other costs of polio eradication (e.g., surveillance, technical assistance, social mobilization, etc.) that could differ for the eradication scenarios compared to control scenarios.. To note, the study did not report the input data used for the assumed clinical efficacy of the vaccine.

Table 5.2 Input parameters used in the model based on the costing study of Thompson & Kalkowska (2020)

Input parameter	LI	LMI	UMI	HI
Number of countries	31	48	54	68
Number of people *(in millions)*	724	3,065	2,709	1,215
Number of children under five years old *(in millions)*	112	313	188	65
Number of surviving infants *(in millions)*	24	63	37	13
Vaccine price per dose				
OPV (any formulation)	$0.15	$0.15	$0.33	$8.75
nOPV (formulations containing any nOPV)	$0.30	$0.30	$0.66	$8.75
IPV, full dose, standalone	$2.50	$2.65	$4.75	$14.27
IPV, fractional dose, standalone	$0.50	$0.53	$0.95	NA
IPV component, combination, full dose	$3.50	$4.00	$6.58	$27.11

IPV, vaccine patch (dose-sparing)	$1.70	$1.73	$2.95	$27.11
Administration costs per dose				
OPV in RI or SIAs	$0.95	$0.95	$2.51	$3.18
IPV given with third OPV dose in RI (full)	$1.00	$1.00	$3.00	NA
IPV single antigen in RI or SIAs	$1.78	$1.78	$4.69	$17.06
IPV combination (hexavalent) in RI	$0.30	$0.30	$0.78	$2.84
IPV vaccine patch in RI or SIAs	$0.95	$0.95	$2.51	$3.18
IPV intradermal device (incremental)	$0.30	$0.30	$0.30	NA
Effective vaccine wastage				
OPV in RI	20%	20%	15%	10%
IPV in RI	15%	15%	10%	5%
IPV in IPV/OPV or OPV+IPV RI	20%	20%	15%	10%
IPV, fractional, in RI	30%	30%	20%	NA
IPV, fractional, in IPV/OPV or OPV+IPV RI	40%	40%	20%	NA
OPV or IPV in SIAs	15%	15%	10%	10%
IPV, vaccine patch	15%	15%	10%	10%
Treatment costs per case	$711	$7,110	$71,100	$711,000
Life expectancy at birth (years,population weighted)	64.1	68.8	75.9	81.0

* Note: LI = lower income; LMI = lower middle income; UMI = upper middle income; HI = high income; RI = routine immunization; SIA = supplemental immunization activity

Outcomes: Resulting cost-effectiveness values were expressed as incremental economic outcomes using the incremental cost-effectiveness ratios (ICERs) in US$2019 per polio case and US$2019 per disability-adjusted life-year (DALY) reported by WBIL; and, as incremental net benefits (INBs) in US$2019 reported by income level and as a global aggregate.

Assessment of Cost-effectiveness: The study set the following ICER comparator thresholds based on GNI per capita:

- Low income countries (LI): 866 USD per DALY
- Lower middle income countries (LMI): 2,310 USD per DALY
- Upper middle income countries (UMI): 9,140 USD per DALY
- High income countries (HI): not reported

ICERs of alternative vaccine policy scenarios compared to the reference cases were expressed as: cost saving, life saving; cost saving, life costing; dominated; or as the actual ICER value using the following interpretations:

- *cost saving, life saving (CSLS): negative incremental cost and positive prevented cases*
- *cost saving, life costing (CSLC): negative incremental cost and negative prevented cases*
- *dominated: positive incremental cost and negative prevented cases*
- *actual ICER value: positive incremental cost and positive prevented cases*

With the economic analysis framed according to WBIL, the study reported that the INB estimation used the same methods as other economic analyses and assumed a societal willingness to pay equal to the population-weighted GNI per capita (by WBIL) per DALY saved.

Uncertainty Analyses: The study ran the model with 100 stochastic iterations for each scenario for the time horizon of 2019–2029. We note, though, that the study did not perform deterministic sensitivity analysis.

Findings of the study

The study by Kalkowska et al. (2021) considered the implications of each prospective vaccination strategy with respect to the expected polio cases in order to characterize the health-related costs and total costs. Considering that the study is comprehensive and includes findings for other vaccination policies outside the scope of the assessment, this section shall focus on the findings that are relevant to our research question i.e., **RC2 versus 2IPV2025** (control scenarios); and, **RC2* versus 1IPV2025** (eradication scenarios).

Analysis of the control scenarios

Expected polio cases

Iterations of the model in the control scenarios showed that most cases occur in LMI countries. Further, modelling results show that 2IPV2025 strategy (OPV + one-dose IPV in 2019-2024, followed by OPV + two-dose IPV from January 1, 2025) resulted in a decrease in expected cases compared to RC2 strategy (OPV + 1-dose IPV from 2019-2029) due to the additional IPV dose thereby, delaying the timing of some OPV2 restarts beyond the end of the time horizon. However, low routine immunization coverage compromises the ability of OPV use to achieve eradication, which consequently reduces the benefits of IPV, which is more expensive, more difficult to deliver, and less effective at stopping transmission than OPV.

Incremental Economic Analysis Estimates

The study also presented the incremental economic analysis estimates according to WBIL over the 11-year time horizon. Overall, it was observed that increasing the minimum

of one IPV dose policy to 2 IPV doses by 2025 would decrease the expected incremental net benefit (INB) by 0.1 billion USD. Based on the resulting ICERs from the modelling, the use of 2 IPV doses is a cost-saving, life-saving option for UMI countries compared to RC2, based on their resulting ICERs and with an INB of 0.2 billion USD. Meanwhile, LI and LMI countries do not experience the same benefit with the implementation of a 2-dose IPV vaccination policy, with ICERs exceeding their corresponding thresholds *(LI ICER: 28,564 USD/DALY vs LI Threshold: 866 USD/DALY; LMI ICER: 55,870 USD/DALY vs LMI Threshold: 2,310 USD/DALY);* and, with negative INB values for LI and LMI. The details on the incremental economic analysis estimates for the 2IPV2025 versus RC2 are described in Table 5.3. Shifting to two-dose IPV also showed a decrease in the probability of triggering an OPV2 restart by 8% over the time horizon; however, the decreased probability of OPV2 restart does not offset the decline in INBs.

Table 5.3 Incremental economic analysis estimates for control scenarios comparing 1-dose and 2-dose IPV, by World Bank Income Level across the time horizon of 2019-2029 by Kalkowska et al.

Control Scenario: 2IPV2025 vs. RC2				
	LI	**LMI**	**UMI**	**Total**
Incremental financial costs (in 2019 USD billions)	0.1	0.4	-0.1	0.4
Paralytic polio cases prevented	4,018	6,295	465	10,778
ICER per polio case (in 2019 USD/case)	28,564	55,870	CSLS	NA
ICER per polio case (in 2019 USD/DALY)	28,564	55,870	CSLS	NA
Incremental net benefits (in 2019 USD)	-0.1	-0.2	0.2	-0.1

Note: CSLS- cost saving, life saving i.e. negative incremental cost and positive prevented cases

Analysis of the eradication scenarios

Expected polio cases

For the eradication scenarios, higher incidence was observed in LI and LMI countries in the 1IPV2025 strategy (1 dose of IPV in 2019-2029) compared to RC2* (1 dose of IPV in 2019 to 2024 followed by 2 doses of IPV from January 1, 2025) owing to the lower IPV use in these income levels, therefore leading to more cases and OPV restarts across the time horizon. No difference was observed in UMI and HI countries since they already utilize an IPV-only policy at the time of all OPV cessation on January 1, 2025 in both the RC2* and 1IPV2025 scenarios.

Incremental Economic Analysis Estimates

The incremental economic analysis estimates showed that, maintaining the minimum of 1 IPV dose after global OPV cessation (1IPV2025) instead of introducing a second IPV dose (RC2*) results in a total of 1.3 billion INBs. Based on the computed ICERs, the use of 1IPV2025 is a cost-saving, life-saving option for UMI countries but a cost saving, life costing option in LI and LMI countries compared to RC2*. 1IPV2025 has an INB of 0.4 billion USD and 0.8 billion USD compared to RC2* for LI and LMI, respectively. On the other hand, no incremental net benefit is expected in UMI countries. Maintaining a minimum of 1 IPV dose increases the probability of an OPV1 restart by 37% and OPV2 restart by 5% compared to RC2*. The study explained that these results reflect the already relatively high expected risks of OPV2 restart, and the insufficient population immunity to transmission for serotype 1 in RC2* prior to bOPV cessation to prevent the development of cVDPVs. These results also suggest the need to increase population immunity to transmission for serotype 1 prior to bOPV cessation in 2025 to reduce cVDPV1 risks and OPV1 restarts.

The details on the incremental economic analysis estimates for 1IPV2025 versus RC2* policy options are described in Table 5.4.

Table 5.4 Incremental economic analysis estimates for eradication scenarios comparing 1-dose and 2-dose IPV, by World Bank Income Level across the time horizon of 2019-2029 by Kalkowska et al.

Eradication scenario vaccine policies				
	LI	**LMI**	**UMI**	**Total**
1IPV2025 vs. RC2*				
Incremental financial costs (in 2019 USD billions)	-0.5	-1.0	-0.0	-1.4
Paralytic polio cases prevented	-634	-4,635	9	-5,260
ICER per polio case (in 2019 USD/case)	CSLC	CSLC	CSLS	NA
ICER per polio case (in 2019 USD/DALY)	CSLC	CSLC	CSLS	NA
Incremental net benefits (in 2019 USD)	0.4	0.8	0.0	1.3

Note: CSLS- cost saving, life saving i.e. negative incremental cost and positive prevented cases; CSLC- cost saving, life costing i.e. negative incremental costs and negative prevented cases

A general caveat regarding this model includes the censored analysis (i.e., ending the simulation in 2029) with respect to effects that would be observed beyond the time horizon, such as the possible artificial reduction of the modeled impacts of OPV restart. In the long term, scenarios that do not include eradication of live polioviruses may also lead to

continued transmission, cases, and associated treatment costs and productivity losses that may not be accounted for in the model.

Moreover, the study highlighted that the analysis is generally limited by the model structure and assumptions as well as the stochastic nature of the iterations. The impacts of the global COVID-19 pandemic on poliovirus transmission changes due to reduced population mobility and limited immunization activities, as well as the potential impact of new vaccine options, such as a new OPV strain, and/or new GPEI strategies, are not accounted for in this model.

Recommendations of the study

Although the GPEI and the WHO have recommended the inclusion of a minimum of two doses of IPV in routine immunization schedules and the Global Alliance for Vaccines and Immunizations (GAVI) will likely support this second dose IPV introduction, Kalkowska et al. (2021) highlighted that there is still considerable uncertainty about the prospective adoption of 2-dose IPV in routine immunizations due to the increase in costs of implementing two-dose IPV. Thus, further studies are still needed to model the impacts of this recommended change in dosing, which is expected to result in increased costs.

Affordability and Viability

As previously presented in Table 1.2, the total budget utilized by the Program in procuring 1-dose IPV from years 2016 to 2020 ranges from Php 204,000,000 to Php 905,000,000, with unit cost of the vaccine ranging from Php 102 to Php 181. The IPV vaccine coverage demonstrated an increasing trend from 2016 to 2019 ranging from 51.20% to 93.92%. However, the vaccine coverage decreased to 69.84% in 2020.

As for the comparative calculation of the total vaccine implementation cost of one-dose versus two-dose IPV, the main costing components are the actual vaccination roll-out and the resulting outbreak response cost. The immediately succeeding section shall present the comparative costing analysis for the vaccine roll out alone, without consideration of the outbreak response cost.

Costing analysis of the vaccination roll-out alone for 1-dose IPV vs 2-dose IPV

- For the cost of vaccines, the input unit cost per dose of IPV provided by the DOH-NIP is Php 181 (same unit cost as the 2020 procurement cost per dose). The target number of vaccines is 2.1 million infants.
- Costing inputs and assumptions for the projection of cost of consumables and programmatic costs were established based on the series of consultations with the DOH-NIP.

Based on the projected calculation presented in Table 6.1, the use of two-dose IPV, as expected, will incur additional cost of Php 450,600,721.72 compared to the cost of implementing one-dose IPV.

Table 6.1. Comparative cost of the vaccination roll-out of two-dose versus one-dose IPV (for one year)

Cost Component	1-dose	Remarks/ Assumptions for 1-dose scenario	2-dose	Remarks/ Assumptions for 2-dose scenario
Vaccine				
Unit cost of IPV	**Php 181.00**	Price offer of manufacturer to DOH as of 2021	**Php 181.00**	Price offer of manufacturer to DOH as of 2021
Number of doses per treatment cost	1		2	
Target vaccinees (2021 target vaccinees as computed by DOH EB)	2,128,056		2,128,056	
Wastage	15%	Wastage factor of 15% based on consultation with DOH-NIP	15%	Wastage factor of 15% based on consultation with DOH-NIP
Total number of doses needed	2,447,265.00		4,894,529.00	
Subtotal (Vaccines)	**Php 442,954,965.00**		**Php 885,909,749.00**	
Vaccine Consumables				
Auto-disable (AD) Syringe				
Quantity of AD syringe	2,447,265		4,894,529	
Unit cost of AD syringe	Php 2.39	Unit cost of AD syringe validated by DOH-NIP	Php 2.39	Unit cost of AD syringe validated by DOH-NIP
Total cost of syringe	Php 5,848,963.35		Php 11,697,924.31	
Safety boxes				
Quantity of safety boxes	26,920	Number of syringe / 100 (capacity per box) + 10% wastage	53,840	Number of syringe / 100 (capacity per box) + 10% wastage
Unit cost of safety boxes	Php 54.00	Unit cost of safety box validated by DOH-NIP	Php 54.00	Unit cost of safety box validated by DOH-NIP
Total cost of safety boxes	Php 1,453,680.00		Php 2,907,360.00	
Subtotal (Vaccine Consumables)	**Php 7,302,643.35**		**Php 14,605,284.31**	

Programmatic Costs				
Logistics Cost				
Hauling				
Quantity of biothermal packaging needed	136	1 box is expected to contain 1800 vials of the vaccine | 1 vial = 10 dose	272	1 box is expected to contain 1800 vials of the vaccine | 1 vial = 10 dose
Rental cost	Php 84,294.68	Hauling cost per box is assumed to be Php 600 and handling fee of Php 20.00	Php 168,589.33	Hauling cost per box is assumed to be Php 600 and handling fee of Php 20.00
Transport cost (land and sea) 60%	Php 65,260.40	1 box is 31.4 kg | 60% of the biothermal packaging will be transported by land and sea, unit cost per kg at Php 800	Php 130,520.77	1 box is 31.4 kg | 60% of the biothermal packaging will be transported by land and sea, unit cost per kg at Php 800
Transport (air) 40%	Php 190,342.83	1 box is 31.4 kg |40% of the biothermal packaging will be transported by air, with unit cost per kg at Php 3500	Php 380,685.59	1 box is 31.4 kg |40% of the biothermal packaging will be transported by air, with unit cost per kg at Php 3500
Valuation (insurance cost)	Php 3,398.98	Valuation (insurance cost) is set at 1% of the hauling cost	Php 6,797.96	Valuation (insurance cost) is set at 1% of the hauling cost
Subtotal hauling cost	**Php 343,296.90**		**Php 686,593.65**	
Storage				
Subtotal storage cost	**Php 0.00**	According to DOH-NIP, no storage cost will be incurred as the program will utilize the DOH warehouse in RITM.	**Php 0.00**	According to DOH-NIP, no storage cost will be incurred as the program will utilize the DOH warehouse in RITM.
Subtotal (Logistics)	**Php 343,296.90**		**Php 686,593.65**	
Service Delivery Cost				
Cost of administration (Mobilization Cost)				
Target vaccinees (2021 target vaccinees as computed by DOH EB)	2,128,056		2,128,056	

Target number of doses to be administered	2,128,056		4,256,112	
Number of vaccination teams	710	One vaccination team is composed of three members.	1419	One vaccination team is composed of three members.
Number of supervisors	237	One supervisor supervises three vaccination teams	473	One supervisor supervises three vaccination teams
Mobilization allowance per vaccination team member per day	Php 0.00	Routine immunization does not incur a separate mobilization cost	Php 0.00	Routine immunization does not incur a separate mobilization cost
Mobilization allowance per supervisor per day	Php 0.00	Routine immunization does not incur a separate mobilization cost	Php 0.00	Routine immunization does not incur a separate mobilization cost
Subtotal (Mobilization Cost)	Php 0.00		Php 0.00	
Surveillance Cost				
AFP Surveillance	Php 99,149,676.30		Php 99,149,676.30	
Polio Laboratory Support	Php 16,903,507.00		Php 16,903,507.00	
Subtotal (Surveillance Cost)	**Php 116,053,183.30**		**Php 116,053,183.30**	
Vaccination cost per infant	**₱266.28**		**₱478.02**	
TOTAL BUDGET IMPACT (VACCINATION ROLL-OUT COST)	**Php 566,654,088.55**		**Php 1,017,254,810.26**	
INCREMENTAL COST (likely additional cost incurred as a result of implementing 2-dose VS 1-dose IPV)	**Php 450,600,721.72**			

Costing analysis considering additional outbreak response cost for 1-dose IPV vs 2-dose IPV

A standard operating procedure on responding to a poliovirus event or outbreak by the GPEI (2019) detailed a four-step vaccination strategy to rapidly interrupt person-to-person transmission of poliovirus in the event of a polio outbreak which involves a rapid response vaccination campaign. The outbreak response initially targets the specific area where the polio case has been detected to stop further transmission quickly. This is followed by two high-quality large-scale supplemental immunization activities to vaccinate 90% of children and reach missed children in areas with poor vaccination coverage. Lastly, a mop-up round is conducted whenever monitoring suggests that there are children missed in certain areas. These vaccination activities ensure that interruption of transmission is achieved. Once a case of poliomyelitis is detected, all of these steps are activated and, thus, will incur additional costs to the DOH-NIP.

Outbreak response costs and corresponding assumptions were validated with the experts during a consultation meeting. Based on the presentation of the Pediatric Infectious Disease Society of the Philippines (PIDSP), future outbreaks with the continued use of only one-dose IPV are almost certain to occur. This is further supported by the statement of the WHO that the Philippines remains at risk of poliovirus type 2. Thus, the use of two-dose IPV is necessary and can potentially result in the prevention of future outbreaks in the country provided that several factors are in place (i.e., achievement of at least 95% coverage as the vaccine does not confer herd immunity but rather individual protection among children).

Based on these inputs from the experts, outbreaks are assumed to occur only with the continued use of one-dose IPV, while no potential outbreak is expected with two-dose IPV, provided that at least 95% coverage of this vaccine is maintained for a long time. To estimate the cost of outbreak response in this costing exercise, we used the cost of outbreak response experience of the country from 2019 to 2021 as provided by the DOH-NIP which amounted to Php 1.87B. This outbreak response cost was derived from:

- *Vaccine cost:* The amount of Php 90,308,700.00 was allocated for the procurement of 5.2M doses of bOPV. Note that the costs of the procurement of 11.2M doses of bOPV and 13.4M doses of mOPV2 were excluded in this analysis as these were donated by GPEI and WHO, respectively.
- *Operations cost:* Php 1,783,910,750.00 was used for the operations which reflected MR-bOPV supplemental immunization activity (SIA).

These values are consistent with the cost projections of the WHO citing 37.5M USD (breakdown: vaccination cost = 1.81M USD; operations cost = 35.68M USD). Further, we highlight that this outbreak response cost is underestimated since many vaccine doses have been donated by international partners.

Based on the calculations for the two scenarios which have considered both vaccine roll-out cost and the outbreak response cost, the use of one-dose IPV will incur a higher budget impact of Php 2.44B compared to the introduction of two-dose IPV (Php 1.02B). Hence, using two-dose IPV will demonstrate total savings to the government amounting to Php 1.42B compared to implementing one-dose IPV, mainly because of the averted outbreak response cost (assuming at least 95% coverage for 2-dose IPV). Full details on the comparative costing between one-dose IPV and two-dose IPV with outbreak are presented in Table 6.2.

Despite expected challenges such as projected cost of procuring doses for two-dose IPV implementation (i.e., Php 885,909,749.00) exceeding the 2021 budget allocation for IPV procurement (i.e., Php 724,000,000) and suboptimal coverage in the early years of implementation, the DOH-NIP is expected to attain high coverage later on to demonstrate savings to the healthcare system from averted cost of outbreak response. This is possible with the assumption that the DOH-NIP consistently achieves at least 95% vaccination coverage to reach the elimination target.

Table 6.2. Comparative cost of implementing two-dose versus one-dose IPV (for one year) with additional outbreak response cost

	1-dose	Remarks/ Assumptions for 1-dose scenario	2-dose	Remarks/ Assumptions for 2-dose scenario
Total cost of vaccination roll-out cost	Php 566,654,088.55	*Please refer to Table 6.1 for details*	Php 1,017,254,810.26	*Please refer to Table 6.1 for details*
Total cost of outbreak response	Php 1,874,219,450.00	The probability of an outbreak using 2-dose IPV is one.	Php 0	The probability of an outbreak using 2-dose IPV is zero.
TOTAL BUDGET IMPACT (with additional outbreak response cost)	**Php 2,440,873,538.55**		**Php 1,017,254,810.26**	
INCREMENTAL COST IF OUTBREAK CONSIDERED	**- Php 1,423,618,728.28**			

Ethical, Legal, Social, and Health Systems Impact

For social and ethical implications, a targeted search was conducted last 05 May 2021 to identify possible ethical and social concerns on the addition of a second dose IPV from the currently implemented immunization schedule. From this search, no studies were detected on the ethical and social impact of an additional dose of IPV to the currently implemented OPV + one dose IPV schedule. Hence, the discussion covered relevant social and ethical issues on IPV in general based on three emerging themes from the searched evidence namely equity, vaccine acceptability, and vaccine hesitancy. In addition to the search, we reviewed the regional vaccination coverage data reported by the DOH-NIP to determine any existing equity issues in terms of access to polio in the Philippines.

Meanwhile, for the health systems impact, a systematic search of relevant studies on country experiences in the implementation of IPV in PubMed was performed from inception to May 5, 2021 using MeSH terms for Inactivated polio vaccine and country experience as well as a focus on the pediatric population. No filters on study type, language and publication date were applied. A targeted search was conducted to supplement the systematic search.

Lastly, legal implications of IPV implementation were culled from regulatory documents and official DOH issuance relevant to immunization programs involving IPV.

Ethical and Social Impact

Equity

In 2016, the WHO published a report on the state of inequality in childhood immunization that presented data for 69 low-and middle- income countries (LMICs). Global monitoring of childhood immunization shows that inequalities have narrowed as national immunization coverage has increased in a substantial number of countries. However, inequalities within countries, particularly between the rich and the poor, and between children whose mothers have different levels of education remain. For polio, as many as 1 in 5 LMICs reported an absolute difference in coverage of at least 20 percentage points between the richest and the poorest household economic class and between the most- and the least- educated subgroup. In some countries, this difference went as high as greater than 40 percentage points. For absolute inequality in reference to place of residence, polio immunization demonstrated a low median difference between urban and rural areas at 1.4 percentage point (WHO, 2016).

As for local data, the only available data for analysis is the national polio vaccine coverage showing the coverage for three doses of OPV and the coverage for one-dose IPV from 2016 to 2020, then sub-grouped by region. For this discussion, we define OPV coverage as those who completed the three doses of OPV, while IPV coverage as those who received one dose of IPV. Polio vaccine coverage would be those who were able to complete all three doses of OPV and one dose of IPV. Based on our analysis:

- OPV coverage was higher compared to IPV coverage across all 17 regions from 2016 to 2020, indicating that not all who received three doses of OPV were able to receive one dose of IPV in order to complete their polio vaccine doses. According to the DOH-NIP, the global stock-out of IPV contributed to low coverage.
- There is a large disparity in the annual percent coverage across all regions, both for OPV or IPV. The difference in the coverage of regions with the lowest and the highest coverage ranged from 13.29 to 44.51 percentage points for OPV, and 33.65 to 65.52 percentage points for IPV.
- Specifically for OPV coverage analysis:
    - The level of vaccination coverage for OPV fluctuated over the years i.e., in 2016 (10/17), 2018 (15/17) and 2020 (9/17), the majority of the regions achieved a coverage of 70% or higher, while in 2017 (5/17) and 2019 (3/17), the majority fell below 70% coverage.
    - From 2017 to 2019, regions with the lowest OPV vaccination coverage were from Visayas (Region 8) and Mindanao (BARMM). Interestingly, Region 10 of Mindanao had the highest coverage in 2016, 2017 and 2020. *(Refer to EPI Coverage Report)*
- Specifically for IPV coverage analysis:
    - Vaccination coverage for one dose of IPV was consistently low across the 17 regions from 2016-2020, with the majority having coverage below 70%.
    - Notably, regions with lowest coverage for IPV from 2016 to 2019 were from Mindanao (BARMM) and Visayas (Region 8). Interestingly, the regions with the highest coverage from 2016 to 2020 except in 2019 were from the same island group (Region 11 in 2016 and 2017; Region 9 in 2018; Region 10 in 2020). *(Refer to EPI Coverage Report)*
- According to the DOH-NIP, for years 2016-2019, those who received IPV were those who also completed the OPV doses. Hence, polio vaccine coverage is equated to IPV coverage which ranged from 0% to 83.63%, across the regions during the same period. Meanwhile for 2020, the DOH-NIP revised its policy, which now requires that IPV shall be given to infants at 14 weeks of age regardless of OPV status. Hence, we cannot apply the same assumption with the data in 2016-2019 to estimate the polio vaccine coverage in 2020. DOH-NIP does not collect data on vaccination coverage on infants who received a complete polio vaccine regimen. Table 2.1 presents the final 2020 EPI coverage data.

Table 7.1 Summary of Polio vaccine coverage across the regions in the Philippines from 2016 to 2020

	2016	2017	2018	2019	2020
OPV coverage					
Region with the highest OPV coverage	Region 10 (80.99%)	Region 10 (78.63%)	NCR (72.34%)	NCR (98.47%)	Region 10 (90.57%)
Region with the lowest OPV coverage	Region 5 (43.85%)	BARMM (58.29%)	Region 8 (59.05%)	BARMM (53.95%)	Region 4B (56.153%)
Difference from the highest and lowest OPV coverage	37.14	20.34	13.29	44.51	34.42

Number of regions with OPV coverage below 70%	10/17	5/17	15/17	3/17	9/17
IPV coverage					
Region with the highest IPV coverage	Region 11 (65.52%)	Region 11 (70.43%)	Region 9 (61.45%)	Region 3 (83.63%)	Region 10 (85.99%)
Region with the lowest IPV coverage	Region 9 (0%)	BARMM (5.78%)	Region 12 (1.02%)	BARMM (31.28%)	Region 4B (52.34%)
Difference from the highest and lowest IPV coverage	65.52	64.65	60.42	52.35	33.65
Number of regions with IPV coverage below 70%	17/17	16/17	17/17	10/17	8/17

Vaccine acceptability

One study in the Philippines by Lopez, et al. (2018) looked at the possible effects of introducing IPV on health care providers' (HCPs) and infant caregivers' attitudes and practices. In general, the study found that there is general acceptance of multiple injections by HCPs and caregivers in the country. Among HCPs interviewed, the proportion of those who had already administered at least three injectable vaccines in a single visit increased to 92% post-introduction from 38% pre-introduction, with the majority of those that administered at least three vaccines post-introduction being at least comfortable giving that number. In addition, many of the HCPs showed willingness to administer at least three vaccines or any number recommended by the EPI program pre-introduction (65%) and post-introduction of IPV. Reasons cited for willingness to administer this number of vaccines include provision of maximum protection against disease and adherence to the vaccination schedule.

Lopez, et al. (2018) also noted that anecdotally, some HCPs in the primary health facilities try to avoid administering three vaccines (i.e., IPV + other vaccines under routine immunization) in a single visit by deliberately spreading out the scheduled vaccines over multiple visits. This is further supported by statements of the majority of parents whose children did not receive all three injections who said that they were not offered all three. The authors, however, noted that the parents would have likely accepted the three injections in a single visit had they been offered, as the overall acceptability of this vaccine was considered very high. Despite this, there is still an observed reluctance from some HCPs in administering three vaccines in a single visit.

The findings from the Philippine study are consistent with other international studies.

- Healy, et al. (2014), a study in the US among parents and providers concluded that providers more often underestimate the importance of some vaccines to parents and overestimate their concerns regarding routes of administration and number of injections.
- Meanwhile, Idako, et al. (2016), a study from Gambia among all health facilities offering immunization, noted 12.0% of infant caregivers expressed concern about a child receiving more than one injection in a single visit. On the human resources side, 9.9% of health care

providers shared an unwillingness to give more than two vaccines. Despite these hesitations, 98.8% and 90.9% of infants received all required vaccinations for the visit before and after IPV introduction.

- A study on parents with children for immunization from Southern Nigeria by Tagbo, et al. (2014) reported that 84.1% of parents had not heard of IPV before and 53% having had no knowledge of vaccine content, but with 40.2% willing to accept IPV for their children. During the post-intervention health education in the Tagbo, et al. study, a significant increase in acceptance of IPV was noted at 95.6% (p=0.0001). However, 35.3% expressed a fear of IPV with the majority citing a fear of pain. A rating scale of one to five was provided for the parents to rank healthcare workers in terms of reliability in informing the public about new vaccines. The study found that the parents rated doctors 4.7 while nurses and the staff of the Ministry of Health were both rated 4.0. Lastly, the Tagbo, et al. study found that the educational level of mothers (p = 0.048) was the only significant factor affecting IPV acceptability.

Vaccine hesitancy

The uptake of IPV was noted to be affected by the *Dengvaxia* controversy in 2017. Larson et al. (2018) found that the vaccine confidence in the Philippines plummeted after the incident where only 32% of the respondents strongly agree that vaccines are important in 2018, a dramatic drop from 95% in a survey conducted in 2015. Similarly, those who strongly agreed that vaccines are safe went down from 82% in 2015 to 22% in 2018.

Legal Impact

Inactivated Poliomyelitis Vaccine (Type 1, 2, and 3) is currently registered in the Philippine FDA and has a marketing authorization that is valid until 31 October 2023. The same vaccine is listed in the Philippine National Formulary (PNF) for active immunization against poliomyelitis caused by poliovirus serotypes 1, 2 and 3. Further, it is stated in the PNF that the primary immunization in children and infants aged 6 weeks to 47 months uses three 0.5 mL doses at 2, 4, and 6-18 months of age.

As previously mentioned, the implementation of polio vaccination is legally supported by the DOH Department Memorandum 2015-0164 (Administration of Inactivated Poliomyelitis virus vaccine) and Department Memorandum 2015-0164-A (Amendment to Department Memorandum 2015-0164 dated May 21, 2015 entitled Administration of Inactivated Poliomyelitis virus vaccine). There are no identified legal issues on introducing 2-dose IPV other than the need to seek a positive HTAC recommendation allowing its procurement and implementation.

Health Systems Impact

A systematic search was done yielding 66 records. Based on an independent screening by four reviewers, nine were included for full-text review after initial screening. Although none discussed shifting from one-dose to two-dose IPV, three studies (Idoko et al.., 2016; Falleiros-Arlent, Avila-

Aguero et al., 2014; Thacker et al., 2016) elaborated on country experiences and the preparations on the introduction of IPV in their respective national immunization programs. All three studies included in the systematic search were from low-middle income countries (LMIC). Table 7.2 describes the included studies.

Table 7.2 Characteristics of the included studies

Study (Year)	Country	Intervention	Study Objectives	Study Design
Idoko, et al. (2016)	Gambia	Introduction of IPV *(one-dose administered concomitantly with pentavalent vaccines and PCV)*	To assess Gambian healthcare providers' and infant caregivers' attitudes and practices related to the administration of multiple injectable vaccines to a child at a single immunization visit before and after the 2015 introduction of IPV.	Cross-sectional study
Falleiros-Arlent, Avila-Aguero, et al. (2014)	Latin American countries	Introduction of IPV *(four IPV doses (three doses in the primary schedule plus a booster dose)*	To analyze the best mechanisms to implement WHO's polio endgame strategy by switching from OPV to IPV and prepare an Action Plan with regards to polio vaccination in Latin America	Consensus document
Thacker, et al. (2016)	India	Introduction of IPV *(no explicit mention of doses)*	To discuss the role of GAVI in the introduction of IPV in India	Letter to the Editor

In addition to the results of the systematic search, a targeted search was done using databases and records of international health organizations and health regulatory agencies which yielded four documents from the WHO, one document from the Global Alliance of Vaccines and Immunization (GAVI), one document from the United Nations International Children's Emergency Fund (UNICEF), and one from the International Vaccine Access Center (IVAC). The key findings from both systematic and targeted search were clustered based on core themes and are presented as follows:

Pre-IPV introduction Recommendations

One study (Falleiros-Arlent, Avila-Aguero et al., 2014) tackled country experiences prior to the introduction of IPV. Falleiros-Arlent, Avila-Aguero et al. (2014) discussed the Action Plan of the Latin American Society of Pediatric Infectious Diseases (SLIPE) for 2014-2015 for polio vaccination. SLIPE took into account a lot of factors in their polio vaccination plan, such as current epidemiological data, adverse events of OPV, availability and efficacy of IPV, and the rationale of changing the vaccination schedule in Latin American countries. Because of this, they were able to have the following recommendations:

- The optimal proposed schedule consists of four IPV doses (three doses in the primary schedule plus a booster dose), whether IPV is combined or not with other indicated vaccines in the immunization program of the country. During the OPV to IPV transition phase, an alternative schedule is acceptable.

- Countries should set optimal strategies in order to maintain and improve vaccination coverage, and implement a nominal immunization registry.
- Countries should improve existing surveillance programs and set up strategies for introducing IPV in National Immunization Programs. Appropriate training should be given for vaccination teams.
- Scientific societies should be brought closer to decision makers.
- Countries should ensure optimal supply, prices, distribution, and storing logistics for IPV introduction.

Post IPV introduction: Lessons learned

Four documents (International Vaccine Access Center (IVAC), 2018; WHO case study in Nepal, 2014, WHO report from Yogyakarta, Indonesia, 2007; UNICEF report from Kenya, 2013) discussed the key findings from post-introduction results of IPV in their respective countries. The IVAC discussed case studies from Albania, Nigeria, and Tunisia on IPV introduction. Albania used a two-dose IPV, while Nigeria and Tunisia used a one-dose IPV. The WHO discussed case studies and reports from Nepal which introduced one-dose IPV and Yogyakarta, Indonesia which introduced four doses of IPV. Meanwhile, UNICEF findings from a focused group discussion in Kenya.

The following were the key issues and challenges identified from these countries' experiences:

Country	Challenges	Implemented or Recommended Strategies
Albania	Confusion on the eligibility criteria for the vaccine, which led to vaccination of children outside of the target age range and may have led to vaccine shortage. Condensed timeline on revising immunization cards	Using a date of birth cutoff was easier and more effective compared to using an "age at visit" eligibility policy. (i.e., all children older than 14 weeks of age). Improvisation of healthcare workers on the immunization cards and the use of an electronic Immunization information system helps with the tight timeline.
Nigeria	Condensed timeline Delays in planning	Rapid consensus among all stakeholders Use of training manuals rather than powerpoint presentations to maintain consistency at different levels of training
Tunisia		Availability of evidence and a standardized and centralized decision-making process were both important to prevent delays in planning

Nepal	Lack of understanding about the IPV Geographical challenges	Strategic messaging in forms of TV/radio announcements, printed materials, and advocacy meetings. Transportation of communication materials simultaneously with the vaccines for immediate roll-out and dissemination.
Yogyakarta, Indonesia	Vaccine wastage associated with the use of multi-dose vials.	Appropriate stock management and close monitoring of doses administered and vial utilization in health facilities to accurately predict vaccine demand and avoid stock-outs
Kenya	Lack of information on the introduction of IPV, dominant perception that injectable vaccines like IPV are better than oral vaccines, unanimous belief on the essentiality of appropriate trainings for health professional on IPV administration	Radio, audio (PA announcement), and face-to-face meetings ("barrassas") with influencers (with visual aids) are seen to be the most effective mode of communication, especially in small communities and refugee camps to address the lack of information on IPV. Comprehensive planning of vaccine storage should be in place to prevent loss of vaccine effectiveness. Appropriate training should be provided to vaccinators and supervisors. Additional efforts and strategies, including in communications, are needed to track and access nomadic and other vulnerable populations during all vaccination campaigns and reflect seasonality of nomadic movements.

Financing of IPV

Two studies (IVAC, 2018; Thacker et al., 2016) reported on funding in the introduction of IPV. IVAC (2018) reported that funding issues were one of the reasons behind Nigeria and Tunisia employing a one-dose instead of a two-dose IPV. Nigeria also noted that additional funding would have helped them address delays in the shipment of IPV into the country. On the other hand, Thacker et al. (2016) reviewed the role of the GAVI in supporting the introduction of IPV in the national immunization program financially and how the government of India utilized the funding. Being the most populous GAVI-eligible country, India received sufficient financial support such that the government of India allocated the funds to 12 states and 127 underperforming districts, strengthening the cold chain management of the vaccine.

Availability of IPV

Meanwhile, one study (GAVI, 2020) looked into the issue of the availability of IPV. The sheer pace and scale of IPV introductions coupled with technical difficulties of scaling up production capacity have led to severe supply constraints in the previous years, with SAGE advising countries to consider switching to fractional doses of IPV at the peak of the issue (GAVI, 2020). In 2016, SAGE advised countries to consider vaccinating children who missed IPV as a result of supply constraints as soon as sufficient IPV became available. Since then, foundations have been working with countries to ensure implementation of the SAGE recommendation and allocate available supplies of IPV, starting with the countries at highest risk of polio reintroduction (GAVI, 2020). 2018 was the first year in which sufficient supply of the vaccine was available and nearly all introductions which had been delayed or interrupted as a result of supply issues were resumed. Despite improvements, supply problems continue to cause an imbalance between supply and demand in the markets (GAVI, 2018). Introducing an extra dose into the polio vaccination program would add an additional strain to the supply side. Therefore, programs should ensure that adequate supply of 2 doses per person is available so as to not negatively impact individuals who may not be able to receive the desired dose in the event of a supply interruption.

Recommendation

The Health Technology Assessment Council **recommends the inclusion** of **Two-dose Inactivated Polio Vaccine (IPV)** in the Philippine National Formulary (PNF) for the **prevention of Poliomyelitis** due to the following reasons:

- This is in accordance with the global recommendation from the Global Polio Eradication Initiative (GPEI) and World Health Organization (WHO) to introduce two-dose IPV to all countries that are currently administering one-dose IPV and bivalent oral polio vaccine (bOPV) in their routine immunization schedule. This will pave the way for eventual OPV cessation which is a critical step to stop the occurrence of vaccine-associated paralytic poliomyelitis (VAPP) and to remove the primary risk of the emergence of all types of vaccine-derived poliovirus (VDPVs).
- The Philippines is a high-risk country for type 2 poliovirus, and bOPV does not confer protection against the said virus. Based on the most recent systematic review, two-dose IPV enhances humoral immunity against type 2 poliovirus conferred by one-dose IPV. Thus, this strengthens the need to include two-dose IPV in the program.
- Having just achieved the closure of cVDPV type 1 and 2 outbreaks in the country, the DOH-NIP should build on the success of this campaign and gain momentum by maintaining clearance of cVDPV with two-dose IPV.
- While Kalkowska et al, 2019 modelling results for LMIC have shown that introducing 2-dose IPV versus 1 dose IPV is not cost-effective, it is deemed that the study might have underestimated the value for money of 2-dose IPV for the following reasons:
    - The outbreak response costs for LMIC in Kalkowska et al (2019) is likely underestimated compared to the actual outbreak response cost in the Philippines, as the cost of vaccines per dose and operations cost per dose in the study are lower versus the actual costs in the Philippine setting.
    - Kalkowska et al. (2019) used a lower cost-effectiveness threshold for LMIC compared to the implicit threshold used in the Philippine setting.
- Despite the costly implementation of two-dose IPV due to expected suboptimal coverage in the early years of implementation, the DOH-NIP aims to achieve high coverage in later years. This will result in savings to the healthcare system because of the averted costs of outbreak response. However, the program should consistently achieve at least 95% vaccination coverage to reach the elimination or eradication target.

Moreover, in recognition of the impact of vaccine hesitancy on the overall success of this program, a localized information and education campaign could capacitate key stakeholders to decide for their children/infants to receive the vaccine.

References

1. Centers for Disease Control and Prevention. (2017). Morbidity and Mortality Weekly Report (MMWR): Introduction of Inactivated Poliovirus Vaccine and Impact on Vaccine-Associated Paralytic Poliomyelitis — Beijing, China, 2014–2016. https://www.cdc.gov/mmwr/volumes/66/wr/mm6649a4.htm
2. Child Health Division, Department of Health Services, UNICEF Nepal Country Office, & WHO Nepal Country Office. (2015). Introduction of inactivated polio vaccine (IPV) in Nepal: A public health milestone for polio free Nepal. Retrieved last 12 April 2021 from https://www.who.int/immunization/diseases/poliomyelitis/endgame_objective2/inactivated_polio_vaccine/Documentation_on_IPV_Introduction_in_Nepal_Final_lightversion.pdf?ua=1
3. Department of Health. (2002). Annual Report 2002. Retrieved on 14 April 2021 from https://doh.gov.ph/sites/default/files/publications/DOHAnnualReport2002.pdf
4. Department of Health (2015). Department Memorandum 2015-0164. Retrieved on 14 April 2021 from https://dohcalabarzonepi.weebly.com/uploads/4/8/4/2/48426749/dm2015-0164_administration_of_inactivated_poliomyelitis_virus_vaccine.pdf
5. Department of Health. (2019). DOH Intensifies efforts to prevent polio. Retrieved on 12 April 2021 from https://doh.gov.ph/press-release/DOH-INTENSIFIES-EFFORTS-TO-PREVENT-POLIO
6. Department of Health - National Immunization Program. (personal communication, 2021). EPI Coverage Report, Philippine 2015 to 2020.
7. Department of Health - National Immunization Program. (personal communication, 2021).Philippines Polio Outbreak Response Progress Report.
8. Department of Health - National Immunization Program (personal communication, 2021). Responses to the Feedback on the Polio Outbreak Response Progress Report.
9. Falleiros-Arlant, L. H., Avila-Agüero, M. L., Brea del Castillo, J., & Marino, C. (2014). El desafío del cambio de la vacuna inactivada contra poliomielitis en América Latina: Declaración de la Sociedad Latinoamericana de Infectología Pediátrica (SLIPE). *Revista Chilena De Infectología*, *31*(5), 590–596. https://doi.org/10.4067/s0716-10182014000500012
10. Global Alliance for Vaccines and Immunization. (2021). *Inactivated polio vaccine support.* Retrieved from https://www.gavi.org/types-support/vaccine-support/inactivated-polio-vaccine
11. Global Polio Eradication Initiative. (n.d.a). Where We Work. Retrieved on 12 April 2021 from https://polioeradication.org/where-we-work/
12. Global Polio Eradication Initiative. (n.d.b). Philippines. Retrieved on 12 April 2021 from https://polioeradication.org/where-we-work/philippines/
13. Global Polio Eradication Initiative. (n.d.c). Philippines. Retrieved on 12 April 2021 from https://polioeradication.org/polio-today/polio-prevention/the-virus/vaccine-derived-polio-viruses/
14. Global Polio Eradication Initiative. (n.d.d). Philippines. Retrieved on 12 April 2021 from https://polioeradication.org/wp-content/uploads/2018/07/GPEI-cVDPV-Fact-Sheet-20191115.pdf
15. Global Polio Eradication Initiative. (2019a). 2019 Annual Report. Retrieved on 12 April 2021 from https://polioeradication.org/wp-content/uploads/2020/11/GPEI-2019-Annual-report.pdf
16. Global Polio Eradication Initiative. (2019b). Polio Endgame Strategy 2019-2023. Retrieved on 12 April 2021 from https://polioeradication.org/wp-content/uploads/2019/06/english-polio-endgame-strategy.pdf
17. Global Polio Eradication Initiative. (2019c). Standard Operating Procedures: Responding to Poliovirus event or outbreak. Retrieved from: https://polioeradication.org/wp-content/uploads/2016/07/sop-polio-outbreak-response-version-20193101.pdf
18. Healy, M.C., Montesinos, D.O. & Middleman, A.B. (2014). Parent and provider perspectives on immunization: Are providers overestimating parental concerns? *Vaccine 32*(5) 579-584. https://doi.org/10.1016/j.vaccine.2013.11.076
19. Husereau D., Drummond M., Petrou S., et al. (2013) Consolidated health economic evaluation reporting standards (CHEERS)—explanation and elaboration: a report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force. Value Health. 16(2):231-250.
20. Idoko, O.T., Hampton, L.M., Mboizi, R.B., Agbla, S.C., Wallace, A.S., Harris, J.B., Sowe, D., Ehlman, D.C., Kampmann, B., Ota, M.O., & Hyde, T.B. (2016). Acceptance of multiple injectable vaccines in a single immunization visit in The Gambia pre and post introduction of inactivated polio vaccine. *Vaccine*, *34*(41), 5034–5039. https://doi.org/10.1016/j.vaccine.2016.07.021

21. International Vaccine Access Center (IVAC) Johns Hopkins Bloomberg School of Public Health. (2018). Case studies of IPV introduction: Albania, Nigeria, and Tunisia. Retrieved on 12 April 2021 from https://www.jhsph.edu/ivac/wp-content/uploads/2018/04/IPV-Case-Studies-in-Albania-Tunisia-and-Nigeria-FINAL.pdf
22. Jonville-Bera, A. P., Autret-Leca, E., & Radal, M. (1999). Adverse effects of the vaccines Tetracoq, IPAD/DTCP and DTCP. A French study of regional drug monitoring centers. Archives de Pediatrie. 6(5): 510-5. 10.1016/s0929-693x(99)80556-9
23. Kalkowska, D.A, & Thompson, K.M. (2021). Health and economic outcomes associated with polio vaccine policy options: 2019-2029. *Risk Analysis, 41*(2), 364-375. doi: 10.1111/risa.13664
24. Kwak, B. O., Ma, S. H., Park, S. E., Shin, S. H., Choi, K. M., Lee, T. J. ... Kim, D. H. (2020). Comparison of the Immunogenicity and Safety of Three Enhanced Inactivated Poliovirus Vaccines from Different Manufacturers in Healthy Korean Infants: A Prospective Multicenter Study. *Vaccines, 8*(2). https://doi.org/10.3390/vaccines8020200
25. Larson, H. J., Hartigan-Go, K., & de Figueiredo, A. (2019). Vaccine confidence plummets in the Philippines following dengue vaccine scare: why it matters to pandemic preparedness. Human vaccines & immunotherapeutics, 15(3), 625-627.
26. Lopez A. L., Haris, J.B,, Raguindin, P.F., Aldaba, J., Morales, M., Sylim, P., Wannemuehler, K., Wallace, A., Ehlman, D.C., Hyde, T.B., Fox, K, Nyambat, B., Ducisin, M.J., Hampton, L.M. (2019). Introduction of inactivated poliovirus vaccine in the Philippines: Effect on health care provider and infant caregiver attitudes and practices. *Vaccine 36*(48), 7399-7407. https://dx.doi.org/10.1016%2Fj.vaccine.2018.09.028
27. Macklin, G.R., Grassly, N.C., Sutter, R.W., Mach, O., Bandyopadhyay, A.S., Edmunds, W.J., & O'Reilly, K.M. (2019). Vaccine schedules and the effect on humoral and intestinal immunity against poliovirus: a systematic review and network meta-analysis. *The Lancet Infectious Diseases*, *19*(10), 1121–1128. https://doi.org/10.1016/s1473-3099(19)30301-9
28. Ministry of Health, Malaysia. (2001). *Health Technology Assessment Report on Childhood Immunisation. Health Technology Assessment Unit, Medical Development Division. MOH/P/PAK/47.02 (TR) 2001.* Retrieved April 14, 2021, from https://www.moh.gov.my/moh/resources/auto%20download%20images/587f137c11dcf.pdf
29. Pediatric Infectious Disease Society of the Philippines. (2021). Childhood Immunization Schedule 2021. Retrieved on 12 April 2021 from http://www.pidsphil.org/home/themencode- pdf-viewer/?file=http://www.pidsphil.org/home/wp-content/uploads/2021/02/CHILDHOOD-IMMUNIZATION-SCHEDULE-2021-edited.pdf
30. Platt, L. Gorham, K., & Privor-Dumm, L. (2015.) Case studies of IPV introductions: Albania, Nigeria, and Tunisia. Retrieved from https://www.jhsph.edu/ivac/wp-content/uploads/2018/04/IPV-Case-Studies-in-Albania-Tunisia-and-Nigeria-FINAL.pdf
31. Tagbo, B.N., Uhasoro, M.D., Esangbedo, D.O. (2014). Parental acceptance of inactivated polio vaccine in Southeast Nigeria: A qualitative cross-sectional interventional study. *Vaccine 32*(46) 6157-6162. https://doi.org/10.1016/j.vaccine.2014.08.053
32. Thacker, N., Thacker, D., & Pathak, A. (2016). Role of Global Alliance for Vaccines and Immunization (GAVI) in accelerating inactivated polio vaccine introduction. *Indian Pediatrics, 53*(1), 57-60. PMID: 27771641
33. Thompson, K.M., & Kalkowska, D.A. (2020). Potential future use, costs, and value of poliovirus vaccines. *Risk Analysis, 41*(2), 349-363. doi: 10.1111/risa.13557
34. UNICEF Kenya. (2013). Focus group discussion - key findings on the co-administration of IPV with OPV in polio outbreak response in the refugee camps and the host community of Dadaab district. Retrieved last 12 April 2021 from https://www.who.int/immunization/diseases/poliomyelitis/inactivated_polio_vaccine/case_study_kenya_en.pdf?ua=1
35. World Health Organization. (2007). Introducing IPC: The experience in Yogyakarta, Indonesia. Retrieved last 12 April 2021 from https://www.who.int/immunization/diseases/poliomyelitis/inactivated_polio_vaccine/case_study_indonesia_en.pdf?ua=1
36. World Health Organization. (2016). State of Inequality: Childhood Immunization. Retrieved 14 April 2021 from https://www.who.int/gho/health_equity/report_2016_immunization/en/
37. World Health Organization. (2019a). Poliomyelitis. Retrieved on 12 April 2021 from https://www.who.int/news-room/fact-sheets/detail/poliomyelitis

38. World Health Organization. (2019b). Polio Outbreak Situation Report 1. Retrieved on 12 April 2021 from https://www.who.int/docs/default-source/wpro—documents/countries/philippines/emergencies/polio/unicef-who-phl-sitrep1-polio-outbreak-19sep2019.pdf?sfvrsn=c8916d37_2
39. World Health Organization. (2020a). Polio Outbreak Situation Report 24. Retrieved on 12 April 2021 from https://reliefweb.int/sites/reliefweb.int/files/resources/PolioSitRep24_16July2020_final.pdf
40. World Health Organization. (2020b). Weekly Epidemiological Record: Meeting of the Strategic Advisory Group of Experts on Immunization, October 2020—conclusions and recommendations. Retrieved on 12 April 2021 from https://apps.who.int/iris/bitstream/handle/10665/337100/WER9548-eng-fre.pdf?ua=1
41. World Health Organization. (2020c). Introducing 2nd IPV dose in Routine Immunization: Systematic review and Meta-analysis of immunogenicity SAGE Working Group Meeting September 2020 [Powerpoint Slides].
42. World Health Organization Western Pacific Region. (2015). 24th Meeting of the Technical Advisory Group on Immunization and Vaccine-preventable Diseases. Retrieved on 14 April 2021 from https://apps.who.int/iris/bitstream/handle/10665/208792/RS_2015_GE_16_PHL_eng.pdf?sequence=1&isAllowed=y
43. Zimmerman, R. K., & Spann, S. J. (1999). Poliovirus vaccine options. *American Family Physician. 59*(1): 113-8, 125-6. PMID: 9917578.

Appendix A. AMSTAR Assessment for Macklin et. al, 2019

CRITICAL APPRAISAL

Vaccine schedules and the effect on humoral and intestinal immunity against poliovirus: a systematic review and network meta-analysis

Grace R Macklin, Nicholas C Grassly, Roland W Sutter, Ondrej Mach, Ananda S Bandyopadhyay, W John Edmunds, Kathleen M O'Reilly

Vaccine schedules and the effect on humoral and intestinal immunity against poliovirus: a systematic review and network meta-analysis (Macklin et al., 2019)
Link: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(19)30301-9/fulltext

General Information

Date form completed *(dd/mm/yyyy)*	04/06/2021
Name of person extracting data	Patrick Wincy Reyes Ma Angela Bermudez Yves Miel Zuniga
Reference citation	Macklin, G. R., Grassly, N. C., Sutter, R. W., Mach, O., Bandyopadhyay, A. S., Edmunds, W. J., & O'Reilly, K. M. (2019). Vaccine schedules and the effect on humoral and intestinal immunity against poliovirus: a systematic review and network meta-analysis. The Lancet Infectious Diseases, 19(10), 1121-1128.
Year of publication	2021
Language	☐ **English**. ☐ Non-English, specify____
Notes:	

Study Characteristics

Population	Healthy infants
Intervention	3 bOPV + 2 IPV (6, 10, 14, 14, 36 weeks)
Comparator	3 bOPV + 1 IPV (6, 10, 14, 14 weeks) and other immunization schedules
Outcomes	Seroconversion against serotype 1,2,3; intestinal immunity against S2
Study design of included studies	RCT
Does the study answer your research questions/s:	Yes on selected efficacy outcomes and comparators

Summary

Item	Result	
1	Y	
2*	PY	
3	Y	
4*	PY	
5	Y	
6	Y	
7*	N	**Overall rating:**
8	PY	**Critically Low**
9*	Y	*Four critical weaknesses and four non-critical weaknesses were found and may be attributable to the failure of the study to address the heterogeneity of the study, publication bias, and risk of bias.*
10	N	
11*	N	
12	N	
13*	N	
14	N	
15*	N	
16	Y	

**Critical domains*

AMSTAR 2 Checklist (2017)[1–3]

General instructions:

- Columns 3 and 4 are the spaces provided for your answers.
- For column 3: Statements or tables/figures from the study to support your judgment must be provided in this column using this format:
  Example for item 1:
  Population: "STATEMENT" (page X, paragraph X)
  Intervention: "STATEMENT" (page X, paragraph X)
  Comparator: "STATEMENT" (page X, paragraph X)
  Outcome: "STATEMENT" (page X, paragraph X)
  Timeframe: "STATEMENT" (page X, paragraph X)

- For column 4: Mark the box **Yes, Partial Yes** or **No** for your judgment on each item based on the compliance of the study to the checklist items/ criteria required. Highlight (with grey color) the specific sub-items in the checklist that is fulfilled by the study.
  Example for item 1:

  ☐Yes (ALL the following):
  - € Population
  - € Intervention
  - € Comparator group
  - € Outcome
  - € Timeframe for follow-up - Optional (Recommended)

  ☒No

- Items in the appraisal tool with colored cells are called **critical domains** and will be the basis for the scoring and overall rating

Box 1: AMSTAR 2 critical domains

- Protocol registered before commencement of the review (item 2)
- Adequacy of the literature search (item 4)
- Justification for excluding individual studies (item 7)
- Risk of bias from individual studies being included in the review (item 9)
- Appropriateness of meta-analytical methods (item 11)
- Consideration of risk of bias when interpreting the results of the review (item 13)
- Assessment of presence and likely impact of publication bias (item 15)

- OVERALL RATING: The overall rating is based on the following:

Box 2: Rating overall confidence in the results of the review

- **High**
- *No or one non-critical weakness*: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest
- **Moderate**
- *More than one non-critical weakness**: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review
- **Low**
- *One critical flaw with or without non-critical weaknesses*: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest
- **Critically low**
- *More than one critical flaw with or without non-critical weaknesses*: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence.

AMSTAR Item	Descriptor	Excerpt from paper/Page No.	Judgment as to compliance
1	**Did the research questions and inclusion criteria for the review include the components of PICO?**	*"We did a systematic review and network meta-analysis of randomised controlled trials comparing the immunogenicity of primary immunisation schedules for poliovirus vaccines in healthy infants and providing efficacy outcomes of the vaccination. Interventions of IPV-only, IPV-bOPV combination, and bOPV-only vaccine schedules were included, in comparison with each other or with a tOPV-only schedule. Interventions were included if the age of administration of the first vaccine dose (excluding a dose at birth) was between 4 and 8 weeks of age. A full study protocol outlining the population, intervention, comparison, and outcome criteria used is available in the appendix (p 3)." P.2*	☐**For Yes (ALL the following):** € **Population** € **Intervention** € **Comparator group** € **Outcome** € **Timeframe for follow-up - Optional (Recommended)** ☐No
2	**Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?**	*"We aim to estimate the relative immunogenicity of the different OPV and IPV routine immunisation schedules considered by WHO and member states in inducing humoral and intestinal immunity against poliovirus. This knowledge would be useful to inform global immunisation policy. " p.2* *"A full study protocol outlining the population, intervention, comparison, and outcome criteria used is available in the appendix (p 3)." P.2* *"We searched MEDLINE and Cochrane Library Central Register of Controlled Trials (CENTRAL) for randomised controlled trials published from Jan 1, 1980, to Nov 1, 2018, using the search terms: (polio OR poliovirus) AND vaccine AND (primary series OR routine OR infants) AND (seropositive OR seroconversion OR antibody OR mucosal immunity OR intestinal immunity). Trials were excluded if they were done in western Europe or North America, because of differences in vaccine immunogenicity and schedules used in these highincome settings, or if there was variation in age schedules (ie, age at administration of the vaccine) between study groups, to ensure consistency within the network of trials we analysed." P.2-3* *"We assessed the risk of bias in accordance with the Cochrane Collaboration's tool for assessing risk of bias in randomised trials, for individual elements from five domains (selection, performance, attrition, reporting, and other bias) and the overall quality of*	☐**For Partial Yes:** The authors state that they had a written protocol or guide that included ALL the following: € **review question(s)** € **a search strategy** € **inclusion/exclusion criteria** € **a risk of bias assessment** ☐For Yes: As for partial yes, plus the protocol should be registered and should also have specified: € **a meta-analysis/synthesis plan, if appropriate, *and*** € a plan for investigating causes of heterogeneity* € justification for any deviations from the protocol* ☐No

		evidence using the Grading of Recommendations Assessment, Development, and Evaluation framework" *We did a random-effect meta-analysis of single proportions, using an inverse variance pooling method and logit transformation, in the meta package in R (version 3.4.3). A random-effect network meta-analysis was developed for each outcome, with a binomial likelihood and log-link function and computed in a Bayesian framework using the GeMTC package in R (version 3.4.3). Markov chain Monte Carlo (MCMC) simulations estimated posterior* *distributions of relative treatment effects and SDs, with vague uniform priors. Four independent Markov chains were run with 10 000 burn-in iterations and 60 000 inference iterations per chain. Convergence of Markov chains was evaluated using the Gelman–Rubin– Brooke diagnostic and time-series plots. Autocorrelation* *plots were assessed to detect autocorrelation in the chains. Additional analysis included network metaregression to investigate the effect of study-level covariates, including the estimated mortality rate for children younger than 5 years due to diarrhoeal disease in the country of study location."* ***No specific plan for investigation of causes of heterogeneity and no indicated deviations (or lack thereof) from the protocol*** ***Not sure if protocol registered (appendix inaccessible)***	
3	**Did the review authors explain their selection of the study designs for inclusion in the review?**	*"Only trials done outside western Europe or North America and without variation in age schedules (ie, age at administration of the vaccine) between study groups were included in the analyses, because trials in high-income settings differ in vaccine immunogenicity and schedules from other settings and to ensure consistency within the network of trials."* p.1	☐ For **Yes,** the review should satisfy ONE of the following: € ***Explanation for* including only RCTs** € OR *Explanation for* including only NRSI € OR *Explanation for* including both RCTs and NRSI ☐No
4	**Did the review authors use a comprehensive**	*"We searched MEDLINE and Cochrane Library Central Register of Controlled Trials (CENTRAL) for randomized controlled trials published from Jan 1, 1980, to Nov 1, 2018, using the search terms:" p.2*	☐**For Partial Yes** (all the following): € **searched at least 2 databases (relevant to research question)**

	literature search strategy?		€ **provided key word and/or search strategy** € **justified publication restrictions** ☐For Yes, should also have (all the following): € searched the reference lists / bibliographies of included studies € searched trial/study registries € included/consulted content experts in the field € where relevant, searched for grey literature € conducted search within 24 months of completion of the review ☐No
5	**Did the review authors perform study selection in duplicate?**	*"The studies were reviewed and the data extracted independently by two of the investigators (GM and KMO'R).." P.3*	☐**For Yes**, either ONE of the following: € **at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include** € OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer. ☐No
6	**Did the review authors perform data extraction in duplicate?**	*"The studies were reviewed and the data extracted independently by two of the investigators (GM and KMO'R).." P.3*	☐**For Yes**, either ONE of the following: € **at least two reviewers achieved consensus on which data to extract from included studies** € OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at

			least 80 percent), with the remainder extracted by one reviewer. ☐No
7	**Did the review authors provide a list of excluded studies and justify the exclusions?**	*No list of excluded studies that are potentially relevant was provided both in the main paper and in the supplemental appendix.*	☐For Partial Yes: € provided a list of all potentially relevant studies that were read in full-text form but excluded from the review ☐For Yes, must also have: Justified the exclusion from the review of each potentially relevant study ☐**No**
8	**Did the review authors describe the included studies in adequate detail?**	*Full description found in Web Appendix 3 and 4*	☐For **Partial Yes** (ALL the following): € described populations € described interventions € described comparators € described outcomes € described research designs ☐For Yes, should also have ALL the following: € described population in detail € described intervention in detail (including doses where relevant) € described comparator in detail (including doses where relevant) € described study's setting € timeframe for follow-up ☐No
9	**Did the review authors use a satisfactory**	*"We assessed the risk of bias in accordance with the Cochrane Collaboration's tool for assessing risk of bias in randomised trials, for individual elements from five domains (selection, performance, attrition, reporting, and other bias) and the overall quality of*	RCTs ☐For Partial Yes, must have assessed RoB from

	technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	*evidence using the Grading of Recommendations Assessment, Development, and Evaluation framework" P. 3*	€ **unconcealed allocation, *and*** € **lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)** ☐**For Yes, must also have assessed RoB from:** € **allocation sequence that was not truly random, *and*** € **selection of the reported result from among multiple measurements or analyses of a specified outcome** ☐No ☐Includes only NRSI
			NRSI ☐For Partial Yes, must have assessed RoB: € from confounding, *and* € from selection bias ☐For Yes, must also have assessed RoB: € methods used to ascertain exposures and outcomes, *and* € selection of the reported result from among multiple measurements or analyses of a specified outcome ☐No ☐Includes only RCTs
10	**Did the review authors report on the sources of funding for the studies included in**	*No specified sources of funding for individual studies.*	☐For Yes Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this

	the review?		information but it was not reported by study authors also qualifies ☐**No**
11	**If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?**	*"We did a random-effect meta-analysis with single proportions and a network meta-analysis in a Bayesian framework to synthesise direct and indirect data." P.1* *No investigation of causes of between-trial heterogeneity*	RCTs ☐For Yes: € **The authors justified combining the data in a meta-analysis** € **AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.** € AND investigated the causes of any heterogeneity ☐**No** ☐No meta analysis done
			For NRSI ☐For Yes: € The authors justified combining the data in a meta-analysis € AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present € AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect

			estimates were not available € AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review ☐No ☐No meta analysis done
12	**If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?**	*"We found a low-to moderate risk of bias for individual studies and a moderate-to-high quality of evidence for each outcome (appendix p 14).." P.4* *No separate analyses were found for those with only low ROB RCTs*	☐For Yes: € included only low risk of bias RCTs € OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect. **☐No** ☐No meta analysis done
13	**Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?**	*No discussion was found for the potential impact of moderate ROB RCTs included*	☐ For Yes: ☐ included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results **☐No**
14	**Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the**	*"Our findings have several limitations. Consistency of the network is a fundamental assumption of network meta-analyses which was not met for serotypes 1 and 3 for which heterogeneity and inconsistency persisted through the subgroup and regression analyses (appendix p 18–20). The type, schedule, and immunogenicity of poliovirus vaccines varies by location.3 The studies in this analysis were done in eastern Mediterranean and Latin American countries that have primary vaccine schedules*	**☐For Yes:** € There was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and **discussed the impact of this on the results of the review**

	results of the review?	*in which the first (non-birth) dose is administered between 4 and 8 weeks. Therefore, our results are primarily useful for policy makers in these settings. The geographical and age-schedule variation in absolute immunogenicity is incorporated into our study as the network meta-analysis method models the relative effects between vaccines, thus eliminating differences in baseline immunogenicity of comparator schedules." P.7* *No investigation of sources of heterogeneity were found.*	☐**No**
15	**If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?**	*No analysis for impact of publication bias.*	☐For Yes: performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias ☐**No** ☐No meta analysis conducted
16	**Did the review authors report any potential sources of <u>conflict of interest,</u> including any <u>funding they received for conducting the review</u>?**	*"Role of the funding source* *The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication." P.4* *"We declare no competing interests." P. 7*	☐**For Yes:** € The authors reported no competing interests OR € **The authors described their funding sources and how they managed potential conflicts of interest** ☐No

1. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *Br Med J*. 2017;358:1-9. doi:10.1136/bmj.j4008
2. Shea BJ, Reeves BC, Wells G, et al. Supplementary appendix 1: AMSTAR 2 GUIDANCE DOCUMENT. *BMJ*. 2017;(358):1-8.
3. Shea BJ. Supplementary figure: AMSTAR 2 instrument. *BMJ*. 2017;(358).

Appendix B. Risk of Bias Assessment for He et al., 2020

Link	https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(19)30738-8/fulltext	
Study /Design	Open Label RCT	
Intervention	sIPV-sIPV-bOPV (2sIPV+1bOPV group), or sIPV-sIPV-sIPV (3sIPV group)	
Outcome assessed for risk of bias	Seroconversion; AEs, serious AEs (up to 30 days)	Seroconversion; AEs, serious AEs (up to 30 days)
Numerical result		
Assignment to intervention (Y/N?)	Y	Y
Adhering to intervention (Y/N?)	N	N
DOMAIN 1		
1.1	Y	Y
1.2	Y	Y
1.3	PN	N
ROB Judgment	Low	Low
Optional		
DOMAIN 2 (Assignment to intervention)		
2.1	Y	N
2.2	Y	N
2.3	N	NA
2.4	NA	NA
2.5	NA	NA
2.6	Y	Y
2.7	NA	NA
ROB Judgment	Low	Low
Optional		
DOMAIN 2 (Adhering to intervention)		
2.1	NA	NA
2.2	NA	NA
2.3	NA	NA
2.4	NA	NA
2.5	NA	NA
2.6	NA	NA

ROB Judgment	NA	NA
Optional		
DOMAIN 3		
3.1	Y	Y
3.2	NA	NA
3.3	NA	NA
3.4	NA	NA
ROB Judgment	Low	Low
Optional		
DOMAIN 4		
4.1	N	N
4.2	N	PN
4.3	Y	Y
4.4	PN	PN
4.5	NA	NA
ROB Judgement	Low	Low
Optional		
DOMAIN 5		
5.1	Y	Y
5.2	N	N
5.3	N	N
ROB Judgment	Low	Low
Optional		
OVERALL ROB JUDGMENT	**Low**	**Low**

Appendix C. AEFI from countries implementing at least 2-dose IPV

Country	Description
2 dose IPV	
China	**Reference:** World Health Organization (2021). Overview of current status of polio eradication [Powerpoint Slides]. According to the WHO, China has only started implementing 3-dose IPV in their national immunization program in January 2021.
Palau	No information available
3 dose IPV	
Marshall Islands	No information available
Korea	**Reference:** Kwak, B. O., Ma, S. H., Park, S. E., Shin, S. H., Choi, K. M., Lee, T. J., … Kim, D. H. (2020). Comparison of the Immunogenicity and Safety of Three Enhanced Inactivated Poliovirus Vaccines from Different Manufacturers in Healthy Korean Infants: A Prospective Multicenter Study. *Vaccines, 8*(2). https://doi.org/10.3390/vaccines8020200 The incidence of AEs was similar between three groups. There were no differences between three groups in the occurrence of solicited local AE. Although the high incidences of solicited systemic AEs to Polirix™ following the second and third doses were statistically significant, no AEs above grade 2 were observed. The most common solicited local AE was injection site redness, reported for 45.00% of infants in the IPVAX™ group and 37.93% of infants in the Poliorix™ group. In the Imovax polio™ group, pain was the most common solicited local AE, reported for 46.15% of infants. No significant difference was observed between the vaccine groups for local AE (p-value = 0.3238). The most common solicited systemic AE was irritability, reported for 80.00%, 84.62%, and 81.03% of infants in the IPVAX™, Imovax polio™, and Poliorix™ groups, respectively. Irritability was the most common systemic symptom considered by the investigator to be related to vaccination. Unsolicited AEs were reported for 70.00%, 55.77%, and 63.79% of infants in the IPVAX™ (Daewoong Pharmaceutical Co., Seoul, Korea), Imovax polio™ (Sanofi Pasteur Ltd., Lyon, France), and Poliorix™ groups (GlaxoSmithKline Biologicals, Brentford, United Kingdom), respectively. Of them, upper respiratory infection was the most common reported unsolicited AE in all groups. Unsolicited AEs possibly related to vaccination were reported for 2.5%, 1.92%, and 1.72% of infants, respectively. No SAEs were reported in this study.
Malaysia	No information available
Tuvalu	No information available

Appendix D. CHEERS Checklist for Kalkowska et al., 2021

Section	CHEERS Guide	[extracted from study] Reported on page no./line number	Points
Title and abstract			
Title	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	The title reflects that it is an assessment of health and economic outcomes associated with polio vaccine policy options being the intervention of the analysis. "Health and economic outcomes associated with polio vaccine policy options: 2019-2029" (p.1)	0.5
Abstract	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Methods, results, and conclusions are clearly stated in the abstract. No explicit mention of the objectives, perspective. Setting seems to be global, given the stratification of countries by their World Bank income levels. "The polio endgame remains complicated, with many questions about future polio vaccines and national immunization policies. We simulated possible future poliovirus vaccine routine immunization policies for countries stratified by World Bank Income Levels and estimated the expected costs and cases using an updated integrated dynamic poliovirus transmission, stochastic risk, and economic model. We consider two reference cases scenarios: one that achieves the eradication of all wild polioviruses (WPVs) by 2023 and one in which serotype 1 WPV (WPV1) transmission continues. The results show that the addition of inactivated poliovirus vaccine (IPV) to routine immunization in all countries substantially increased the expected costs of the polio endgame, without substantially increasing its expected health or economic benefits. Adding a second dose of IPV to the routine immunization schedules of countries that currently include a single IPV dose further increases costs and does not appear economically justified in the reference case that does not stop WPV transmission. For the reference case that includes all WPV eradication, adding a second IPV dose at the time of successful OPV cessation represents a cost- effective option. The risks and costs of needing to restart oral poliovirus vaccine (OPV) use change the economics of the polio endgame, although the time horizon used for modeling impacts the overall economic results. National health leaders will want to consider the expected health and economic net benefits of their national polio vaccine strategies recognizing that preferred strategies may differ.	0.5

Introduction			
Background and objectives	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions	The introduction gives a clear picture of the need for the updated health economic analysis due to the context of "delays in achieving eradication, challenges with OPV2 cessation, increases in IPV costs, and other changes that differ from prior analyses" (p. 2, paragraph 3). The specific study question was not explicitly stated but the introduction mentions that this economic analysis to be done is for "prospective polio vaccine policies" (p. 2, paragraph 3)	1
Methods			
Target population and subgroups	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Reference case scenarios were clearly described wherein Page 3: "To capture some of the heterogeneity that exists between countries, the model stratifies countries into blocks of approximately 107 million people each assigned to 2019 World Bank income levels (WBILs) (World Bank, 2019): 6 low-income (LI), 28 lower middle-income (LMI), 27 upper middle-income (UMI), and 11 high-income (HI) blocks (Kalkowska, Wassilak, et al., 2020). We assume that this stratification helps to represent the different conditions, costs, values, and preferences at the global level."	1
Setting and location	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	The study conducts the analysis in a global setting as it stratifies countries per World Bank Income Level to account the capacity of each country in implementing the recommended polio vaccination policies.	1
Study perspective	Describe the perspective of the study and relate this to the costs being evaluated.	The study utilizes a global perspective, being an analysis of health and economic outcomes associated with polio vaccine policy options that would affect immunization policies in countries globally. "We use updated cost inputs (Thompson & Kalkowska, 2020a) in an updated global model (Kalkowska, Wassilak, et al., 2020) to characterize the expected vaccine costs for RI for two reference cases (RCs)."	1
Comparators	Describe the interventions or strategies being compared and state why	The study conducts its analysis with the assumption that "LI and LMI countries that currently use OPV+IPV schedules would opt for the minimum policies, while UMI and HI will use only IPV with a minimum of 3 doses after cessation of the last OPV serotype, with many of these countries already using or likely to adopt a 4-dose schedule using an IPV-containing combination	1

	they were chosen.	vaccine" (p.3, paragraph 2) "Since the updated global model (Kalkowska, Wassilak, et al., 2020) does not anticipate eradication of serotype 1 WPV (WPV1) or subsequent globally-coordinated cessation of bivalent OPV (bOPV, containing OPV for serotypes 1 and 3), the RC2 scenario includes ongoing use of bOPV and at least 1 dose of IPV in perpetuity in OPV-using countries (Kalkowska, Pallansch, Cochi, et al., 2020).	
Time horizon	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 5: "We use a time horizon of 2019–2029 for this analysis of prospective polio immunization policies to facilitate consistency with prior modeling…	1
Discount rate	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 3 264-375: We use updated cost inputs (Thompson & Kalkowska, 2020a) in an updated global model (Kalkowska, Wassilak, et al., 2020) to characterize the expected vaccine costs for RI for two reference cases (RCs). Supplementary File: By using a constant $/DALY in US$2019, we implicitly assume that any inflation that would occur over time (e.g., a 3% increase in GNI per capita per year) cancels out with the discount rate used to account for the time value of money (e.g., a discount rate of 3%).	1
Choice of health outcomes	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 5 We calculate incremental economic outcomes using the incremental cost-effectiveness ratios (ICERs) in US$2019 per polio case and US$2019 per disability-adjusted life-year (DALY) reported by WBIL and the incremental net benefits (INBs) in US$2019 reported by income level and as a global aggregate.	1
Measurement of effectiveness	Single study-based estimates: Describe fully the design	Not reported	0

	features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.		
	Synthesis- based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Not reported	0
Measurement and valuation of preference based outcomes	If applicable, describe the population and methods used to elicit preferences for outcomes.	We calculate incremental economic outcomes using the incremental cost-effectiveness ratios (ICERs) in US$2019 per polio case and US$2019 per disability-adjusted life-year (DALY) reported by WBIL. With our economic analysis framed according to WBIL, for INB estimation we use the same methods as other economic analyses and assume a societal willingness to pay equal to the population-weighted GNI per capita (by WBIL) per DALY saved (Thompson & Kalkowska, 2020c).	1
Estimating resources and costs	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource	N/A	N/A

	item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.		
	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Page 3: 264-375: We use updated cost inputs (Thompson & Kalkowska, 2020a) in an updated global model (Kalkowska, Wassilak, et al., 2020) to characterize the expected vaccine costs for RI for two reference cases (RCs). Details on 349-363 (11th paper) Supplementary File: **Technical Appendix for Kalkowska and Thompson "Health and Economic Outcomes Associated with Polio Vaccine Policy Options: 2019-2029"** We use updated prospective (Table A1) income level-specific cost estimates reported elsewhere (Thompson & Kalkowska, 2020a). We estimate the disability-adjusted life-years (DALY) values over time by income level based on average life-expectancy using the entire global income groups (Table A2). To estimate the US$2019 per DALY values by income level, we use gross national income (GNI) per capita (Atlas method, 2018 current estimate adjusted to US$2019) using all countries in the WBIL (Table A1). We calculate societal willingness-to-pay (S) per case avoided by income level (il) by year (yr) in US$2019 as $S_{il}(yr) = DALY\ (yr) \times \$/DALY_{il}\ (US\$2019)$.	1
Currency, price date, and conversion	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated	page 3 264-375: We use updated cost inputs (Thompson & Kalkowska, 2020a) in an updated global model (Kalkowska, Wassilak, et al., 2020) to characterize the expected vaccine costs for RI for two reference cases (RCs).	1

	unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	The paper referenced is 349-363 (11th paper). 349-363 Page 5/page 353 For this analysis, to ensure consistent comparisons, we convert all financial estimates to 2019 US dollars (US$2019) by using the US Consumer Price Index (CPI) (Bureau of Labor Statistics, 2020).	
Choice of model	Describe and give reasons for the specific type of decision analytical model used. Providing a figure to show model structure is strongly recommended.	Page 3 (No illustration of the model provided) The updated integrated model (Kalkowska, Wassilak, et al., 2020) builds on a previously developed differential equation-based poliovirus transmission and OPV evolution model that included generic model inputs (Duintjer Tebbens et al., 2014; Duintjer Tebbens, Pallansch, Kalkowska, et al., 2013) developed following expert review (Duintjer Tebbens, Pallansch, et al., 2013a; Duintjer Tebbens, Pallansch, Kim, et al., 2013) and elicitation processes (Duintjer Tebbens, Pallansch, et al., 2013b), which **supported a prior integrated dynamic poliovirus transmission**, stochastic risk, and economic model (Duintjer Tebbens et al., 2015).	1

		$$ICER_{case}\ (AO\ vs.RC) = \frac{\sum_{yr=T_0}^{T_{end}}[(FC_{AO}(yr) - FC_{RC}(yr)) - T \times (PP_{RC}(yr) - PP_{AO}(yr))]}{\sum_{yr=T_0}^{T_{end}}(PP_{RC}(yr) - PP_{AO}(yr))}$$ $$ICER_{DALY}\ (AO\ vs.RC) = \frac{\sum_{yr=T_0}^{T_{end}}[(FC_{AO}(yr) - FC_{RC}(yr)) - T \times (PP_{RC}(yr) - PP_{AO}(yr))]}{\sum_{yr=T_0}^{T_{end}} DALY(yr)(PP_{RC}(yr) - PP_{AO}(yr))}$$ $$INB\ (AO\ vs.RC) = \sum_{yr=T_0}^{T_{end}} (T + S(yr)) \times (PP_{RC} - PP_{AO}) - (FC_{AO} - FC_{RC})$$ where FC_{RC} = financial costs associated with the reference case FC_{AO} = financial costs associated with the alternative policy PP_{RC} = number of polio cases with the reference case PP_{AO} = number of polio cases with the alternative policy T = treatment costs per polio case	
Assumptions	Describe all structural or other assumptions underpinning the decision-analytical model.	Page 3 ● Although we explore different vaccine policies,we recognize that countries can always do more than the minimum recommended policy (Thompson & Duintjer Tebbens, 2012). In this regard, we assume that **only LI and LMI countries that currently use OPV+IPV would opt for the minimum policies, while UMI and HI will use only IPV with a minimum of 3 doses after cessation of the last OPV serotype**, with many of these countries already using or likely to adopt a 4-dose schedule using an IPV-containing combination vaccine. Page 4 ● Given actual experience with IPV, we assume that 3 countries (i.e., Sri Lanka, India, and Bangladesh) will choose to continue to use 2 doses of fractional IPV in their immunization schedules, and we assume that all **other countries use 2 full IPV doses** for these scenarios. ● We use the updated global model (Kalkowska, Wassilak, et al., 2020) to integrate population and coverage estimates to support cost estimation for the immunization options. Thus, for the RC2, RC2*, and each alternative scenario, we estimate the total number of doses of each type of vaccine purchased, delivered, and wasted in each income level per year, then multiply these by the appropriate costs for those vaccines. The framing of this analysis on vaccine costs	1

		excludes the consideration of global programmatic or other costs of polio eradication (e.g., surveillance, technical assistance, social mobilization, etc.) that could differ some for the eradication scenarios compared to control scenarios (Thompson & Kalkowska, 2020c).	
Analytical methods	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty	Page 3 (Paragraph 2 line 10-15) To capture some of the heterogeneity that exists between countries, the model stratifies countries into blocks of approximately 107 million people each assigned to 2019 World Bank income levels (WBILs) (World Bank, 2019): 6 low-income (LI), 28 lower middle-income (LMI), 27 upper middle-income (UMI), and 11 high-income (HI) blocks (Kalkowska, Wassilak, et al., 2020). We use the health economic modeling inputs and methods based on updated cost and valuation assumptions, and report cost estimates as 2019 net present values, using 2019 US dollars (US$2019) by WBIL (Thompson & Kalkowska, 2020a).	0.5

Study parameters	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	**Table A1:** Updated prospective economic model inputs by World Bank Income Level (WBIL) for vaccine, treatment, and surveillance costs in US$2019	1

Input	LI	LMI	UMI	HI
Number of countries	31	48	54	68
Number of people (millions)	724	3,065	2,709	1,215
Number of children under 5 years old (millions)	112	313	188	65
Number of surviving infants (millions)	24	63	37	13
Vaccine price per dose				
- OPV (any formulation)	$ 0.15	$ 0.15	$ 0.33	$ 8.75
- nOPV (formulations containing any nOPV)	$ 0.30	$ 0.30	$ 0.66	$ 8.75
- IPV, full dose, standalone	$ 2.50	$ 2.65	$ 4.75	$ 14.27
- IPV, fractional dose, standalone	$ 0.50	$ 0.53	$ 0.95	NA
- IPV component, combination, full dose	$ 3.50	$ 4.00	$ 6.59	$ 27.11
- IPV, vaccine patch (dose-sparing)	$ 1.70	$ 1.73	$ 2.95	$ 27.11
Administration costs per dose				
- OPV in RI or SIAs	$ 0.95	$ 0.95	$ 2.51	$ 3.18
- IPV given with 3rd OPV dose in RI (full)	$ 1.00	$ 1.00	$ 3.00	NA
- IPV single antigen in RI or SIAs	$ 1.78	$ 1.78	$ 4.69	$ 17.06
- IPV intradermal device (incremental)	$ 0.30	$ 0.30	$ 0.30	NA
- IPV combination (hexavalent) in RI	$ 0.30	$ 0.30	$ 0.78	$ 2.84
- IPV vaccine patch in RI or SIAs	$ 0.95	$ 0.95	$ 2.51	$ 3.18
Effective vaccine wastage				
- OPV in RI	0.2	0.2	0.15	0.1
- IPV in RI	0.15	0.15	0.1	0.05
- IPV in IPV/OPV or OPV+IPV RI	0.2	0.2	0.15	0.1
- IPV, fractional, in RI	0.3	0.3	0.2	NA
- IPV, fractional, in IPV/OPV or OPV+IPV RI	0.4	0.4	0.2	NA
- OPV or IPV in SIAs	0.25	0.2	0.1	0.1
- IPV, vaccine patch	0.02	0.02	0.01	0.01
Number of doses in RI schedule				
- OPV-only (pre-2015)	3	3	3	NA
- OPV+IPV (started in 2015)	3+1	3+1	3+1	NA
- IPV/OPV sequential	2+2	2+2	2+2	3+1
- IPV-only standalone or patch	2	2	2	3
- IPV-only, combination	4	4	4	4
Treatment costs per case	$ 711	$ 7,107	$ 71,065	$ 710,652
$ per disability-adjusted life-year (DALY)	$ 866	$ 2,310	$ 9,140	$ 45,600

Abbreviations: DALY, disability-adjusted life year; GNI, gross national income; IPV, inactivated poliovirus vaccine; LI, low-income; LMI, lower middle-income; N/A, not applicable; OPV, oral poliovirus vaccine; oSIA, outbreak response SIA; pSIA, planned, preventive SIA; RI, routine immunization; SIA, supplemental immunization activity; UMI, upper middle-income; WBIL, World Bank Income Level

<table>
<tr>
<td></td>
<td></td>
<td>
Table A2: Disability-adjusted life-years (DALYs) per case for 2019-2029 (WBIL population (GPEI countries) weighted)
<table>
<tr><th>Year</th><th>LI</th><th>LMI</th><th>UMI</th><th>HI</th></tr>
<tr><td>2019</td><td>13.20</td><td>13.49</td><td>13.87</td><td>13.20</td></tr>
<tr><td>2020</td><td>13.22</td><td>13.50</td><td>13.88</td><td>13.22</td></tr>
<tr><td>2021</td><td>13.24</td><td>13.51</td><td>13.89</td><td>13.24</td></tr>
<tr><td>2022</td><td>13.26</td><td>13.52</td><td>13.90</td><td>13.26</td></tr>
<tr><td>2023</td><td>13.28</td><td>13.53</td><td>13.90</td><td>13.28</td></tr>
<tr><td>2024</td><td>13.30</td><td>13.54</td><td>13.91</td><td>13.30</td></tr>
<tr><td>2025</td><td>13.32</td><td>13.55</td><td>13.92</td><td>13.32</td></tr>
<tr><td>2026</td><td>13.33</td><td>13.56</td><td>13.93</td><td>13.33</td></tr>
<tr><td>2027</td><td>13.35</td><td>13.57</td><td>13.93</td><td>13.35</td></tr>
<tr><td>2028</td><td>13.37</td><td>13.58</td><td>13.94</td><td>13.37</td></tr>
<tr><td>2029</td><td>13.38</td><td>13.59</td><td>13.95</td><td>13.38</td></tr>
</table>
Abbreviations: HI, high-income; LI, low-income; LMI, lower middle-income; UMI, upper middle-income
</td>
<td></td>
</tr>
<tr>
<td>Incremental costs and outcomes</td>
<td>For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.</td>
<td>Page 7

Table 3(a) shows that shifting to tOPVRISIA or tOPVRI lead to expected INBs of 1.5 and 3.1 billion US$2019, respectively, increasing the minimum of one IPV dose policy to 2 IPV doses from 2025 on (i..e, 2IPV2025) decreases the expected INB by 0.1 billion US$2019, whereas continuing RC2 without restarting OPV2 use (i.e. RC2noRestarts) leads to expected INB of 0.2 billion US$2019. The ICER results suggest that returning to tOPV use represents a CSLS option for LI countries but does not represent a cost-effective option for UMI countries. For UMI countries, the use of 2 IPV doses represents a CSLS compared to RC2. For LMI, the ICER results shows the importance of pSIAs for the scenarios that switch to tOPV. As shown in Table 2, shifting to 2IPV2025 decreases the probability of triggering an OPV2 restart by 8% during the time horizon (compared to RC2, Table 2), but this does not offset the overall decline in INBs. Moreover, the RC2noRestarts option represents a CSLS option for UMI countries.

Page 18
See Table 3</td>
<td>1</td>
</tr>
</table>

Characterising uncertainty	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	N/A	
	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Not reported	0
Characterising heterogeneity	If applicable, report differences in costs, outcomes, or cost effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not	While not explicitly stated in the results section, Table 3 presents ICERs of the different scenarios stratified according to income level (LI, LMI, UMI).	0.5

	reducible by more information.		
Discussion			
Study findings, limitations, generalisability, and current knowledge	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Page 9: Even in the absence of strategies to address OPV2 restart risks, this analysis demonstrates that poliovirus vaccination for 2019–2029 will continue to cost billions of US$2019 per year, with lower costs in LI and LMI than in UMI and HI countries. The insights of this analysis remain limited by the model structure and assumptions (see details in (Kalkowska, Wassilak, et al., 2020) and its technical appendix), and the stochastic nature of the iterations. Future studies will need to consider the impacts of the global COVID-19 pandemic on poliovirus transmission changes due to reduced mixing and reduced immunization.	1
Other			
Source of funding	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 9: This publication was supported by Cooperative Agreement Number 5NU2RGH001913-03-00 funded by the Centers for Disease Control and Prevention.	1
Conflicts of interest	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we	Not reported	0

	recommend authors comply with International Committee of Medical Journal Editors recommendations.		
Total			**19**

Appendix E. Breakdown of the additional campaign cost (Php 437,878,351) incurred with 1-dose of IPV

Purpose	Amount (in PhP)
Mobilization Fund	30,000,000.00
Polio Laboratory Support	16,903,507.00
Orientation on Polio Outbreak Response for Brgy Officials, HRH, and Volunteers	628,080.00
AFP Surveillance	99,149,676.30
Mobilisation Fund	291,197,087.99
Total	**437,878,351**