UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES
AND THE FOOD AND DRUG ADMINISTRATION

PETITION FOR ADMINISTRATIVE ACTION TO REQUIRE CLINICAL TRIAL OF IPOL TO ASSESS THE SAFETY OF THIS PRODUCT	**:**	**Docket No.**

CITIZEN PETITION

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CITIZEN PETITION

This petition is being submitted pursuant to 21 C.F.R. § 10.30 and related relevant provisions of the Federal Food, Drug, and Cosmetic Act and Public Health Service Act, the Public Health and Welfare at, *inter alia*, 42 U.S.C. § 262(a)(2)(A)-(C), 42 U.S.C. § 262(j), and 42 U.S.C. § 300aa-10 *et seq.*, to request that the Commissioner of Food and Drugs (the "**Commissioner**") withdraw or suspend the approval granted by the Food and Drug Administration ("**FDA**") for IPOL for infants and toddlers until a properly controlled and properly powered double-blind trial of sufficient duration is conducted to assess the safety of this product as required pursuant to applicable federal statutes and regulations for licensing this product. *See, e.g.*, 21 U.S.C. § 393 (The FDA "shall promote the public health by … reviewing clinical research and taking appropriate action … [to] protect the public health by ensuring that …. drugs are safe and effective.")

The clinical trials relied upon to license this product did not include a control group and only assessed safety for up to three days after injection. These trials therefore did not comply with the applicable federal statutory and regulatory requirements necessary to prove the product was "safe" prior to licensure. The FDA therefore must either withdraw or suspend the approval of this product until an appropriate clinical trial, as required by law, is conducted to determine its safety.

Furthermore, the product label for IPOL should be amended to note that this product does not prevent infection and transmission.

A. ACTION REQUESTED

1. Petitioner requests that the FDA withdraw or suspend the approval for IPOL for infants, toddlers, and children until a properly controlled and properly powered double-blind trial of sufficient duration is conducted to assess the safety of this product.

2. Petitioner further requests that the FDA amend the product label for IPOL to note that: "IPOL does not prevent intestinal infection and therefore does not prevent poliovirus transmission."

B. STATEMENT OF GROUNDS

3. IPOL is a vaccine for poliomyelitis. The Centers for Disease Control and Prevention ("**CDC**") Recommended Child and Adolescent Immunization Schedule recommends universal vaccination of all infants and children with inactivated polio vaccine ("**IPV**") with a 4-dose series administered at 2-months, 4-months, 6-months, and 4-years of age.[1] The only stand-alone vaccine for poliomyelitis used in the United States is Poliovirus Vaccine Inactivated

[1] *See* https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html#note-polio (last visited August 23, 2022).

(Monkey Kidney Cell), trade named IPOL, licensed in 1995 ("**IPOL**").[2]

4. IPOL is unlike the inactivated polio vaccine invented by Jonas Salk or the oral polio vaccine ("**OPV**"), made from a live attenuated virus, invented by Albert Sabin. As described in the package insert for IPOL, the "culture technique and improvements in purification, concentration, and standardization of poliovirus antigen produce a more potent and consistent immunogenic vaccine than the inactivated poliovirus vaccine (IPV) available in the US prior to 1988."[3] Indeed, while Salk's IPV contained 20, 2 and 4 D antigen units of PV types 1, 2, and 3, by introducing a new culture technique using cells on microcarrier beads in suspensions cultured in large stainless steel tanks, IPOL contains 40, 8 and 32 D antigen units of types 1, 2, and 3. Meaning, vaccine production methods for IPOL allow for higher concentrations of vaccine antigens in IPOL than were attainable in previous inactivated polio vaccines.[4]

5. Moreover, unlike Salk's vaccine, the virus used in IPOL is "grown in vero cells, a continuous line of monkey kidney cells cultivated on microcarriers."[5] Vero cells have modified chromosomes which cause them to multiple forever, like cancer cells.[6] These cells are susceptible to infection by dozens of viruses, including HPV, measles, rubella, reovirus, SV40 virus, and SV-5.[7]

6. The Informed Consent Action Network ("**ICAN**") is a non-profit organization that advocates for informed consent and disseminates information necessary for same with regard to all medical interventions. In 2017, a supporter of ICAN advised the organization that the clinical trial relied upon by the FDA to license IPOL reviewed safety for only three days after injection. ICAN found this claim incredible. It sounded nothing short of a conspiracy theory.

7. Indeed, the FDA states that the clinical trial relied upon for licensure is typically "1 to 4 years"[8] and that the duration of a clinical trial should "reflect the product and target condition."[9] The time frame for the safety review should be longer for minors, and in particular for babies and toddlers, since autoimmune, neurological, and developmental disorders will often not be diagnosed until after babies are at least a few years old.[10] Indeed, a 2019 review of 306

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[2] https://www.fda.gov/vaccines-blood-biologics/vaccines/ipol-poliovirus-vaccine-inactivated-monkey-kidney-cell (last visited August 23, 2022).

[3] https://www.fda.gov/media/75695/download (last visited August 23, 2022).

[4] *See McBean, A.M., A Comparison of the Serologic Response to Oral and Injectable Trivalent Polio Vaccine*, Rev Infect Dis., (May 1, 1984) available at https://www.icandecide.org/wp-content/uploads/2022/08/Combined-IPOL-production-Vol-1F-Vol.-4A-Vol.-4B.pdf.

[5] https://www.fda.gov/media/75695/download (last visited August 23, 2022)

[6] https://admin.phe-culturecollections.org.uk/media/122249/vero-cell-line-profile.pdf

[7] https://www.atcc.org/products/all/ccl-81.aspx#characteristics

[8] https://www.fda.gov/patients/drug-development-process/step-3-clinical-research (last visited August 23, 2022).

[9] https://www.fda.gov/media/102332/download (last visited August 23, 2022).

[10] For example, according to the CDC, even for a common neurological disorder such as ADHD, "5 years of age was the average age of diagnosis for children reported as having severe ADHD." https://www.cdc.gov/ncbddd/adhd/features/key-findings-adhd72013.html (last visited August 23, 2022). As another example, learning disabilities, a group of common developmental issues, are often "identified once a child is in school."

pediatric studies, authored by researchers at the FDA and Duke University, explained that, compared to licensing a drug for adults, "data on drug efficacy and safety in children may require an additional 6 years."[11]

8. Moreover, Congress mandated that the FDA only license drugs that their sponsors have proven to be "safe and effective." The FDA relies upon clinical trial reports provided by the sponsor of the drug to make this determination. The clinical trial information submitted must be sufficient to demonstrate the product is "safe." While there are many ways to demonstrate a product is safe, three days of safety data would be patently insufficient to demonstrate safety. Moreover, a trial lacking a proper control group renders any "safety" data of limited value.

9. Hence, the claim that IPOL was licensed by the FDA based on only a few days of safety data after each injection sounded like science fiction. ICAN simply found the claim not credible. That was until ICAN reviewed the package insert for IPOL which described its pre-licensure clinical trials. To ICAN's amazement, it indicates that safety in these clinical trials was reviewed for only three days after the injection of each dose into babies.

10. Hence, ICAN submitted a FOIA request to the FDA for, "A copy of the report for each clinical trial relied upon by the FDA when approving IPOL in 1990." The FDA subsequently provided four documents containing data from three pre-licensure clinical trials: (1) "A Comparison of the Serologic Response to Oral and Injectable Trivalent Polio Vaccine," by Dr. A. Marshall McBean and co-investigators (1984); (2) "Merieux Inactivated Poliovirus Vaccine Final Report of Clinical Studies at Suny/Children's Hospital, Buffalo, New York and Johns Hopkins University, Baltimore, Maryland," the final report on the study of P. Ogra and H. Faden (1989); (3) a progress report on the study of P. Ogra and H. Faden (1987); and (4) "Serologic Response to Oral Polio Vaccine and Enhanced-Potency Inactivated Polio Vaccines" (1988).

11. None of the studies relied upon by the FDA to license IPOL, either individually or collectively, prove the product was "safe" prior to licensure and, therefore, neither the product nor the FDA approval comply with the applicable federal statutory and regulatory requirements.

a. The first study by McBean did not address safety (it only addressed serologic response). This study cannot be used to support any finding of safety of IPOL.
b. The second document is a final study with two protocols in which IPOL was compared to a group received OPV or a combination of OPV and IPV. Many of the children also received the DTP vaccine concomitantly with the polio vaccine. In one protocol, the Buffalo protocol, the safety of IPOL was not reviewed after the actual immunization appointment. In the second protocol, the Johns Hopkins protocol, safety was reviewed via telephone call for only three days after each injection.
c. The third document is only an incomplete progress report of the above study.

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https://www.nichd.nih.gov/health/topics/learning/conditioninfo/diagnosed (last visited August 23, 2022). Even for asthma, a very common autoimmune condition, whose symptoms are obvious, diagnosis can be difficult for children under 5 years of age because lung function tests aren't accurate before 5 years of age and "[s]ometimes a diagnosis can't be made until later, after months or even years of observing symptoms." https://www.mayoclinic.org/diseases-conditions/childhood-asthma/diagnosis-treatment/drc-20351513 (last visited August 23, 2022).

[11] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6526087/.

d. The fourth document is a journal article reporting results of a trial wherein the serologic response to three doses of two enhanced potency IPVs was compared with the response to three doses of OPV. In that trial, children received either one of two IPV or OPV doses, in addition to the DTP vaccine. Parents were contacted three days after the vaccination of their children to report adverse reactions which occurred within 48 hours of administration

12. Clinical trials that only review safety for up to three days after administration, even assuming a proper control group, cannot support the safety of this product. As such, the FDA could not have fulfilled its statutory duty to assure the safety of IPOL prior to licensing it for injection into infants, toddlers, and children.

13. Furthermore, there is confusion in the marketplace as to the effectiveness of IPOL. It is widely, and wrongly, believed that this product can prevent infection and transmission. For example: *Polio in New York State - August 2022*, NY Department of Health, https://www.health.ny.gov/diseases/communicable/polio/ ("In communities with lower vaccination rates, polio can spread even more easily. … The best way to keep New York polio-free is to maintain high immunity across the population through vaccination.") (last visited Aug. 22, 2022); Mani, Neritan, MD, *Polio in New York in 2022: Are You at Risk?*, Health Matters (Aug. 19, 2022), https://healthmatters.wphospital.org/blog/august/2022/polio-in-new-york-in-2022-are-you-at-risk/ (According to the Associate Medical Director at White Plains Hospital, "Vaccination is strongly recommended to protect children and adults from the polio virus and to prevent it from spreading."); *Polio*, Cleveland Clinic, https://my.clevelandclinic.org/health/diseases/15655-polio (stating, "Vaccine-derived polioviruses can only spread where not many people are vaccinated.") (last visited Aug. 22, 2022).

14. But as the CDC recently explained, "IPV does not prevent intestinal infection and therefore does not prevent poliovirus transmission"[12] The FDA should therefore also amend the product label for IPOL to note that "IPOL does not prevent intestinal infection and therefore does not prevent poliovirus transmission."

15. The undersigned therefore respectfully urges that the action requested above be adopted forthwith.

C. ENVIRONMENTAL IMPACT

16. The undersigned hereby states that the relief requested in this petition will have no environmental impact and therefore an environmental assessment is not required under 21 C.F.R. Sections 25.30 and 25.31.

D. ECONOMIC IMPACT

17. Economic impact information will be submitted upon request of the commissioner.

[12] https://www.cdc.gov/mmwr/volumes/71/wr/pdfs/mm7133e2-H.pdf

E. CERTIFICATION

18. The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

19. The Petitioner, therefore, respectfully urges that this request be granted forthwith.

Respectfully submitted,

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Footnote 1

Recommended Child and Adolescent Immunization Schedule
for ages 18 years or younger

UNITED STATES
2022

Vaccines in the Child and Adolescent Immunization Schedule*

Vaccine	Abbreviation(s)	Trade name(s)
Dengue vaccine	**DEN4CYD**	Dengvaxia®
Diphtheria, tetanus, and acellular pertussis vaccine	**DTaP**	Daptacel® Infanrix®
Diphtheria, tetanus vaccine	**DT**	No trade name
Haemophilus influenzae type b vaccine	**Hib (PRP-T)** **Hib (PRP-OMP)**	ActHIB® Hiberix® PedvaxHIB®
Hepatitis A vaccine	**HepA**	Havrix® Vaqta®
Hepatitis B vaccine	**HepB**	Engerix-B® Recombivax HB®
Human papillomavirus vaccine	**HPV**	Gardasil 9®
Influenza vaccine (inactivated)	**IIV4**	Multiple
Influenza vaccine (live, attenuated)	**LAIV4**	FluMist® Quadrivalent
Measles, mumps, and rubella vaccine	**MMR**	M-M-R II®
Meningococcal serogroups A, C, W, Y vaccine	**MenACWY-D**	Menactra®
	MenACWY-CRM	Menveo®
	MenACWY-TT	MenQuadfi®
Meningococcal serogroup B vaccine	**MenB-4C**	Bexsero®
	MenB-FHbp	Trumenba®
Pneumococcal 13-valent conjugate vaccine	**PCV13**	Prevnar 13®
Pneumococcal 23-valent polysaccharide vaccine	**PPSV23**	Pneumovax 23®
Poliovirus vaccine (inactivated)	**IPV**	IPOL®
Rotavirus vaccine	**RV1** **RV5**	Rotarix® RotaTeq®
Tetanus, diphtheria, and acellular pertussis vaccine	**Tdap**	Adacel® Boostrix®
Tetanus and diphtheria vaccine	**Td**	Tenivac® Tdvax™
Varicella vaccine	**VAR**	Varivax®
Combination vaccines *(use combination vaccines instead of separate injections when appropriate)*		
DTaP, hepatitis B, and inactivated poliovirus vaccine	**DTaP-HepB-IPV**	Pediarix®
DTaP, inactivated poliovirus, and *Haemophilus influenzae* type b vaccine	**DTaP-IPV/Hib**	Pentacel®
DTaP and inactivated poliovirus vaccine	**DTaP-IPV**	Kinrix® Quadracel®
DTaP, inactivated poliovirus, *Haemophilus influenzae* type b, and hepatitis B vaccine	**DTaP-IPV-Hib-HepB**	Vaxelis®
Measles, mumps, rubella, and varicella vaccine	**MMRV**	ProQuad®

*Administer recommended vaccines if immunization history is incomplete or unknown. Do not restart or add doses to vaccine series for extended intervals between doses. When a vaccine is not administered at the recommended age, administer at a subsequent visit. The use of trade names is for identification purposes only and does not imply endorsement by the ACIP or CDC.

How to use the child and adolescent immunization schedule

1 Determine recommended vaccine by age **(Table 1)**

2 Determine recommended interval for catch-up vaccination **(Table 2)**

3 Assess need for additional recommended vaccines by medical condition or other indication **(Table 3)**

4 Review vaccine types, frequencies, intervals, and considerations for special situations **(Notes)**

5 Review contraindications and precautions for vaccine types **(Appendix)**

Recommended by the Advisory Committee on Immunization Practices (www.cdc.gov/vaccines/acip) and approved by the Centers for Disease Control and Prevention (www.cdc.gov), American Academy of Pediatrics (www.aap.org), American Academy of Family Physicians (www.aafp.org), American College of Obstetricians and Gynecologists (www.acog.org), American College of Nurse-Midwives (www.midwife.org), American Academy of Physician Associates (www.aapa.org), and National Association of Pediatric Nurse Practitioners (www.napnap.org).

Report

- Suspected cases of reportable vaccine-preventable diseases or outbreaks to your state or local health department
- Clinically significant adverse events to the Vaccine Adverse Event Reporting System (VAERS) at www.vaers.hhs.gov or 800-822-7967

Questions or comments

Contact www.cdc.gov/cdc-info or 800-CDC-INFO (800-232-4636), in English or Spanish, 8 a.m.–8 p.m. ET, Monday through Friday, excluding holidays

Download the CDC Vaccine Schedules app for providers at www.cdc.gov/vaccines/schedules/hcp/schedule-app.html

Helpful information

- Complete Advisory Committee on Immunization Practices (ACIP) recommendations: www.cdc.gov/vaccines/hcp/acip-recs/index.html
- *General Best Practice Guidelines for Immunization* (including contraindications and precautions): www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html
- Vaccine information statements: www.cdc.gov/vaccines/hcp/vis/index.html
- Manual for the Surveillance of Vaccine-Preventable Diseases (including case identification and outbreak response): www.cdc.gov/vaccines/pubs/surv-manual
- ACIP Shared Clinical Decision-Making Recommendations www.cdc.gov/vaccines/acip/acip-scdm-faqs.html

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Scan QR code for access to online schedule

CS310020-A

Table 1 Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2022

These recommendations must be read with the notes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars.
To determine minimum intervals between doses, see the catch-up schedule (Table 2).

Vaccine	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos	18 mos	19–23 mos	2–3 yrs	4–6 yrs	7–10 yrs	11–12 yrs	13–15 yrs	16 yrs	17–18 yrs
Hepatitis B (HepB)	1st dose	◄---- 2nd dose ----►			◄---------- 3rd dose ----------►												
Rotavirus (RV): RV1 (2-dose series), RV5 (3-dose series)			1st dose	2nd dose	See Notes												
Diphtheria, tetanus, acellular pertussis (DTaP <7 yrs)			1st dose	2nd dose	3rd dose			◄---- 4th dose ----►				5th dose					
Haemophilus influenzae type b (Hib)			1st dose	2nd dose	See Notes		◄-- 3rd or 4th dose, See Notes --►										
Pneumococcal conjugate (PCV13)			1st dose	2nd dose	3rd dose		◄---- 4th dose ----►										
Inactivated poliovirus (IPV <18 yrs)			1st dose	2nd dose	◄---------- 3rd dose ----------►							4th dose					
Influenza (IIV4)					Annual vaccination 1 or 2 doses								or	Annual vaccination 1 dose only			
or																	
Influenza (LAIV4)											Annual vaccination 1 or 2 doses			Annual vaccination 1 dose only			
Measles, mumps, rubella (MMR)					See Notes		◄---- 1st dose ----►					2nd dose					
Varicella (VAR)							◄---- 1st dose ----►					2nd dose					
Hepatitis A (HepA)					See Notes		2-dose series, See Notes										
Tetanus, diphtheria, acellular pertussis (Tdap ≥7 yrs)														1 dose			
Human papillomavirus (HPV)														See Notes			
Meningococcal (MenACWY-D ≥9 mos, MenACWY-CRM ≥2 mos, MenACWY-TT ≥2years)			See Notes											1st dose		2nd dose	
Meningococcal B (MenB-4C, MenB-FHbp)														See Notes			
Pneumococcal polysaccharide (PPSV23)											See Notes						
Dengue (DEN4CYD; 9-16 yrs)														Seropositive in endemic areas only (See Notes)			

Range of recommended ages for all children

Range of recommended ages for catch-up vaccination

Range of recommended ages for certain high-risk groups

Recommended vaccination can begin in this age group

Recommended vaccination based on shared clinical decision-making

No recommendation/ not applicable

Table 2 Recommended Catch-up Immunization Schedule for Children and Adolescents Who Start Late or Who Are More than 1 Month Behind, United States, 2022

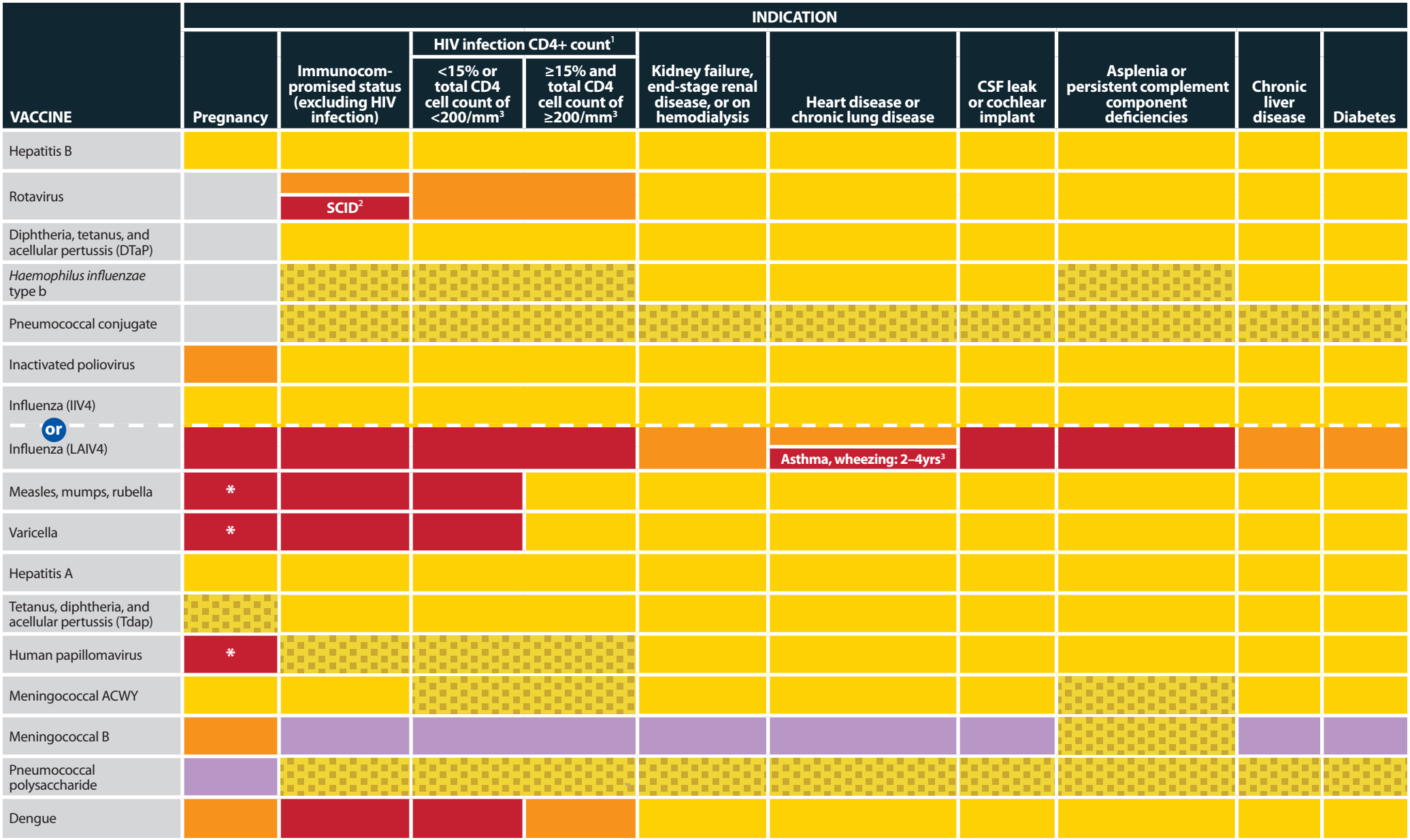
The table below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age. **Always use this table in conjunction with Table 1 and the Notes that follow.**

Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
Children age 4 months through 6 years					
Hepatitis B	Birth	**4 weeks**	**8 weeks *and* at least 16 weeks after first dose** minimum age for the final dose is 24 weeks		
Rotavirus	6 weeks Maximum age for first dose is 14 weeks, 6 days.	**4 weeks**	**4 weeks** maximum age for final dose is 8 months, 0 days		
Diphtheria, tetanus, and acellular pertussis	6 weeks	**4 weeks**	**4 weeks**	**6 months**	**6 months**
Haemophilus influenzae type b	6 weeks	**No further doses needed** if first dose was administered at age 15 months or older. **4 weeks** if first dose was administered before the 1st birthday. **8 weeks (as final dose)** if first dose was administered at age 12 through 14 months.	**No further doses needed** if previous dose was administered at age 15 months or older **4 weeks** if current age is younger than 12 months ***and*** first dose was administered at younger than age 7 months ***and*** at least 1 previous dose was PRP-T (ActHib®, Pentacel®, Hiberix®), Vaxelis® or unknown **8 weeks *and* age 12 through 59 months (as final dose)** if current age is younger than 12 months ***and*** first dose was administered at age 7 through 11 months; OR if current age is 12 through 59 months ***and*** first dose was administered before the 1st birthday ***and*** second dose was administered at younger than 15 months; OR if both doses were PedvaxHIB® and were administered before the 1st birthday	**8 weeks (as final dose)** This dose only necessary for children age 12 through 59 months who received 3 doses before the 1st birthday.	
Pneumococcal conjugate	6 weeks	**No further doses needed** for healthy children if first dose was administered at age 24 months or older **4 weeks** if first dose was administered before the 1st birthday **8 weeks (as final dose for healthy children)** if first dose was administered at the 1st birthday or after	**No further doses needed** for healthy children if previous dose was administered at age 24 months or older **4 weeks** if current age is younger than 12 months and previous dose was administered at <7 months old **8 weeks (as final dose for healthy children)** if previous dose was administered between 7–11 months (wait until at least 12 months old); OR if current age is 12 months or older and at least 1 dose was administered before age 12 months	**8 weeks (as final dose)** This dose only necessary for children age 12 through 59 months who received 3 doses before age 12 months or for children at high risk who received 3 doses at any age.	
Inactivated poliovirus	6 weeks	**4 weeks**	**4 weeks** if current age is <4 years **6 months (as final dose)** if current age is 4 years or older	**6 months (minimum age 4 years for final dose)**	
Measles, mumps, rubella	12 months	**4 weeks**			
Varicella	12 months	**3 months**			
Hepatitis A	12 months	**6 months**			
Meningococcal ACWY	2 months MenACWY-CRM 9 months MenACWY-D 2 years MenACWY-TT	**8 weeks**	See Notes	See Notes	
Children and adolescents age 7 through 18 years					
Meningococcal ACWY	Not applicable (N/A)	**8 weeks**			
Tetanus, diphtheria; tetanus, diphtheria, and acellular pertussis	7 years	**4 weeks**	**4 weeks** if first dose of DTaP/DT was administered before the 1st birthday **6 months (as final dose)** if first dose of DTaP/DT or Tdap/Td was administered at or after the 1st birthday	**6 months** if first dose of DTaP/DT was administered before the 1st birthday	
Human papillomavirus	9 years	**Routine dosing intervals are recommended.**			
Hepatitis A	N/A	**6 months**			
Hepatitis B	N/A	**4 weeks**	**8 weeks *and* at least 16 weeks after first dose**		
Inactivated poliovirus	N/A	**4 weeks**	**6 months** A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months after the previous dose.	A fourth dose of IPV is indicated if all previous doses were administered at <4 years or if the third dose was administered <6 months after the second dose.	
Measles, mumps, rubella	N/A	**4 weeks**			
Varicella	N/A	**3 months** if younger than age 13 years. **4 weeks** if age 13 years or older			
Dengue	9 years	**6 months**	6 months		

Table 3

Recommended Child and Adolescent Immunization Schedule by Medical Indication, United States, 2022

Always use this table in conjunction with Table 1 and the Notes that follow.



1 For additional information regarding HIV laboratory parameters and use of live vaccines, see the *General Best Practice Guidelines for Immunization*, "Altered Immunocompetence," at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html and Table 4-1 (footnote J) at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html.
2 Severe Combined Immunodeficiency
3 LAIV4 contraindicated for children 2–4 years of age with asthma or wheezing during the preceding 12 months

Notes

Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2022

For vaccination recommendations for persons ages 19 years or older, see the Recommended Adult Immunization Schedule, 2022.

Additional information

COVID-19 Vaccination

COVID-19 vaccines are recommended for use within the scope of the Emergency Use Authorization or Biologics License Application for the particular vaccine. ACIP recommendations for the use of COVID-19 vaccines can be found at www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19.html**.**

CDC's interim clinical considerations for use of COVID-19 vaccines can be found at www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html**.**

- Consult relevant ACIP statements for detailed recommendations at www.cdc.gov/vaccines/hcp/acip-recs/index.html.
- For calculating intervals between doses, 4 weeks = 28 days. Intervals of ≥4 months are determined by calendar months.
- Within a number range (e.g., 12–18), a dash (–) should be read as "through."
- Vaccine doses administered ≤4 days before the minimum age or interval are considered valid. Doses of any vaccine administered ≥5 days earlier than the minimum age or minimum interval should not be counted as valid and should be repeated as age appropriate. **The repeat dose should be spaced after the invalid dose by the recommended minimum interval.** For further details, see Table 3-1, Recommended and minimum ages and intervals between vaccine doses, in *General Best Practice Guidelines for Immunization* at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/timing.html.
- Information on travel vaccination requirements and recommendations is available at www.cdc.gov/travel/.
- For vaccination of persons with immunodeficiencies, see Table 8-1, Vaccination of persons with primary and secondary immunodeficiencies, in *General Best Practice Guidelines for Immunization* at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html, and Immunization in Special Clinical Circumstances (In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:67–111).
- For information about vaccination in the setting of a vaccine-preventable disease outbreak, contact your state or local health department.
- The National Vaccine Injury Compensation Program (VICP) is a no-fault alternative to the traditional legal system for resolving vaccine injury claims. All routine child and adolescent vaccines are covered by VICP except for pneumococcal polysaccharide vaccine (PPSV23). For more information, see www.hrsa.gov/vaccinecompensation/index.html.

Dengue vaccination (minimum age: 9 years)

Routine vaccination

- Age 9–16 years living in dengue endemic areas **AND** have laboratory confirmation of previous dengue infection
  - 3-dose series administered at 0, 6, and 12 months
- Endemic areas include Puerto Rico, American Samoa, US Virgin Islands, Federated States of Micronesia, Republic of Marshall Islands, and the Republic of Palau. For updated guidance on dengue endemic areas and pre-vaccination laboratory testing see www.cdc.gov/mmwr/volumes/70/rr/rr7006a1.htm?s_cid=rr7006a1_w and www.cdc.gov/dengue/vaccine/hcp/index.html

Diphtheria, tetanus, and pertussis (DTaP) vaccination (minimum age: 6 weeks [4 years for Kinrix® or Quadracel®])

Routine vaccination

- 5-dose series at age 2, 4, 6, 15–18 months, 4–6 years
  - **Prospectively:** Dose 4 may be administered as early as age 12 months if at least 6 months have elapsed since dose 3.
  - **Retrospectively:** A 4th dose that was inadvertently administered as early as age 12 months may be counted if at least 4 months have elapsed since dose 3.

Catch-up vaccination

- Dose 5 is not necessary if dose 4 was administered at age 4 years or older and at least 6 months after dose 3.
- For other catch-up guidance, see Table 2.

Special situations

- Wound management in children less than age 7 years with history of 3 or more doses of tetanus-toxoid-containing vaccine: For all wounds except clean and minor wounds, administer DTaP if more than 5 years since last dose of tetanus-toxoid-containing vaccine. For detailed information, see www.cdc.gov/mmwr/volumes/67/rr/rr6702a1.htm.

Haemophilus influenzae type b vaccination (minimum age: 6 weeks)

Routine vaccination

- **ActHIB®, Hiberix®, Pentacel®, or Vaxelis®:** 4-dose series (3 dose primary series at age 2, 4, and 6 months, followed by a booster dose* at age 12–15 months)
  - *Vaxelis® is not recommended for use as a booster dose. A different Hib-containing vaccine should be used for the booster dose.
- **PedvaxHIB®:** 3-dose series (2-dose primary series at age 2 and 4 months, followed by a booster dose at age 12–15 months)

Catch-up vaccination

- **Dose 1 at age 7–11 months:** Administer dose 2 at least 4 weeks later and dose 3 (final dose) at age 12–15 months or 8 weeks after dose 2 (whichever is later).
- **Dose 1 at age 12–14 months:** Administer dose 2 (final dose) at least 8 weeks after dose 1.
- **Dose 1 before age 12 months and dose 2 before age 15 months:** Administer dose 3 (final dose) at least 8 weeks after dose 2.
- **2 doses of PedvaxHIB® before age 12 months:** Administer dose 3 (final dose) at 12–59 months and at least 8 weeks after dose 2.
- **1 dose administered at age 15 months or older:** No further doses needed
- **Unvaccinated at age 15–59 months:** Administer 1 dose.
- **Previously unvaccinated children age 60 months or older who are not considered high risk:** Do not require catch-up vaccination

For other catch-up guidance, see Table 2. Vaxelis® can be used for catch-up vaccination in children less than age 5 years. Follow the catch-up schedule even if Vaxelis® is used for one or more doses. For detailed information on use of Vaxelis® see www.cdc.gov/mmwr/volumes/69/wr/mm6905a5.htm.

Special situations

- **Chemotherapy or radiation treatment:**
  Age 12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

  Doses administered within 14 days of starting therapy or during therapy should be repeated at least 3 months after therapy completion.
- **Hematopoietic stem cell transplant (HSCT):**
  - 3-dose series 4 weeks apart starting 6 to 12 months after successful transplant, regardless of Hib vaccination history
- **Anatomic or functional asplenia (including sickle cell disease):**
  Age 12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

  Unvaccinated persons age 5 years or older*
  - 1 dose
- **Elective splenectomy:**
  Unvaccinated persons age 15 months or older*
  - 1 dose (preferably at least 14 days before procedure)
- **HIV infection:**
  Age 12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

  Unvaccinated persons age 5–18 years*
  - 1 dose
- **Immunoglobulin deficiency, early component complement deficiency:**
  Age 12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

**Unvaccinated* = Less than routine series (through age 14 months) OR no doses (age 15 months or older)*

Notes

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Hepatitis A vaccination
(minimum age: 12 months for routine vaccination)

Routine vaccination
- 2-dose series (minimum interval: 6 months) at age 12–23 months

Catch-up vaccination
- Unvaccinated persons through age 18 years should complete a 2-dose series (minimum interval: 6 months).
- Persons who previously received 1 dose at age 12 months or older should receive dose 2 at least 6 months after dose 1.
- Adolescents age 18 years or older may receive the combined HepA and HepB vaccine, **Twinrix®**, as a 3-dose series (0, 1, and 6 months) or 4-dose series (3 doses at 0, 7, and 21–30 days, followed by a booster dose at 12 months).

International travel
- Persons traveling to or working in countries with high or intermediate endemic hepatitis A (www.cdc.gov/travel/):
  - **Infants age 6–11 months**: 1 dose before departure; revaccinate with 2 doses, separated by at least 6 months, between age 12–23 months.
  - **Unvaccinated age 12 months or older**: Administer dose 1 as soon as travel is considered.

Hepatitis B vaccination
(minimum age: birth)

Birth dose (monovalent HepB vaccine only)
- **Mother is HBsAg-negative:**
  - **All** medically stable infants ≥2,000 grams: 1 dose within 24 hours of birth
  - Infants <2,000 grams: Administer 1 dose at chronological age 1 month or hospital discharge (whichever is earlier and even if weight is still <2,000 grams).
- **Mother is HBsAg-positive:**
  - Administer **HepB vaccine** and **hepatitis B immune globulin (HBIG)** (in separate limbs) within 12 hours of birth, regardless of birth weight. For infants <2,000 grams, administer 3 additional doses of vaccine (total of 4 doses) beginning at age 1 month.
  - Test for HBsAg and anti-HBs at age 9–12 months. If HepB series is delayed, test 1–2 months after final dose.
- **Mother's HBsAg status is unknown:**
  - Administer **HepB vaccine** within 12 hours of birth, regardless of birth weight.
  - For infants <2,000 grams, administer **HBIG** in addition to HepB vaccine (in separate limbs) within 12 hours of birth. Administer 3 additional doses of vaccine (total of 4 doses) beginning at age 1 month.
  - Determine mother's HBsAg status as soon as possible. If mother is HBsAg-positive, administer **HBIG** to infants ≥2,000 grams as soon as possible, but no later than 7 days of age.

Routine series
- 3-dose series at age 0, 1–2, 6–18 months (use monovalent HepB vaccine for doses administered before age 6 weeks)
- Infants who did not receive a birth dose should begin the series as soon as feasible (see Table 2).
- Administration of **4 doses** is permitted when a combination vaccine containing HepB is used after the birth dose.
- **Minimum age** for the final (3rd or 4th) dose: 24 weeks
- **Minimum intervals:** dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 8 weeks / dose 1 to dose 3: 16 weeks (when 4 doses are administered, substitute "dose 4" for "dose 3" in these calculations)

Catch-up vaccination
- Unvaccinated persons should complete a 3-dose series at 0, 1–2, 6 months.
- Adolescents age 11–15 years may use an alternative 2-dose schedule with at least 4 months between doses (adult formulation **Recombivax HB®** only).
- Adolescents age 18 years or older may receive a 2-dose series of HepB **(Heplisav-B®)** at least 4 weeks apart.
- Adolescents age 18 years or older may receive the combined HepA and HepB vaccine, **Twinrix®**, as a 3-dose series (0, 1, and 6 months) or 4-dose series (3 doses at 0, 7, and 21–30 days, followed by a booster dose at 12 months).
- For other catch-up guidance, see Table 2.

Special situations
- Revaccination is not generally recommended for persons with a normal immune status who were vaccinated as infants, children, adolescents, or adults.
- **Post-vaccination serology testing and revaccination** (if anti-HBs < 10mIU/mL) is recommended for certain populations, including:
  - **Infants born to HBsAg-positive mothers**
  - **Hemodialysis patients**
  - **Other immunocompromised persons**

For detailed revaccination recommendations, see www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hepb.html.

Human papillomavirus vaccination
(minimum age: 9 years)

Routine and catch-up vaccination
- HPV vaccination routinely recommended at **age 11–12 years (can start at age 9 years)** and catch-up HPV vaccination recommended for all persons through age 18 years if not adequately vaccinated
- 2- or 3-dose series depending on age at initial vaccination:
  - **Age 9–14 years at initial vaccination**: 2-dose series at 0, 6–12 months (minimum interval: 5 months; repeat dose if administered too soon)
  - **Age 15 years or older at initial vaccination**: 3-dose series at 0, 1–2 months, 6 months (minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 12 weeks / dose 1 to dose 3: 5 months; repeat dose if administered too soon)
- **Interrupted schedules:** If vaccination schedule is interrupted, the series does not need to be restarted.
- No additional dose recommended when any HPV vaccine series has been completed using the recommended dosing intervals.

Special situations
- **Immunocompromising conditions, including HIV infection:** 3-dose series, even for those who initiate vaccination at age 9 through 14 years.
- **History of sexual abuse or assault:** Start at age 9 years.
- **Pregnancy:** Pregnancy testing not needed before vaccination; HPV vaccination not recommended until after pregnancy; no intervention needed if vaccinated while pregnant

Influenza vaccination
(minimum age: 6 months [IIV], 2 years [LAIV4], 18 years [recombinant influenza vaccine, RIV4])

Routine vaccination
- Use any influenza vaccine appropriate for age and health status annually:
  - 2 doses, separated by at least 4 weeks, for **children age 6 months–8 years** who have received fewer than 2 influenza vaccine doses before July 1, 2021, or whose influenza vaccination history is unknown (administer dose 2 even if the child turns 9 between receipt of dose 1 and dose 2)
  - 1 dose for **children age 6 months–8 years** who have received at least 2 influenza vaccine doses before July 1, 2021
  - 1 dose for **all persons age 9 years or older**
- For the 2021-2022 season, see www.cdc.gov/mmwr/volumes/70/rr/rr7005a1.htm.
- For the 2022–23 season, see the 2022–23 ACIP influenza vaccine recommendations.

Special situations
- **Egg allergy, hives only**: Any influenza vaccine appropriate for age and health status annually
- **Egg allergy with symptoms other than hives** (e.g., angioedema, respiratory distress) or required epinephrine or another emergency medical intervention: see Appendix listing contraindications and precautions
- **Severe allergic reaction (e.g., anaphylaxis) to a vaccine component or a previous dose of any influenza vaccine:** see Appendix listing contraindications and precautions

Measles, mumps, and rubella vaccination
(minimum age: 12 months for routine vaccination)

Routine vaccination
- 2-dose series at age 12–15 months, age 4–6 years
- MMR or MMRV may be administered

Note: For dose 1 in children age 12–47 months, it is recommended to administer MMR and varicella vaccines separately. MMRV may be used if parents or caregivers express a preference.

Catch-up vaccination
- Unvaccinated children and adolescents: 2-dose series at least 4 weeks apart
- The maximum age for use of MMRV is 12 years.
- Minimum interval between MMRV doses: 3 months

Special situations
International travel
- **Infants age 6–11 months:** 1 dose before departure; revaccinate with 2-dose series at age 12–15 months (12 months for children in high-risk areas) and dose 2 as early as 4 weeks later.
- **Unvaccinated children age 12 months or older:** 2-dose series at least 4 weeks apart before departure

Notes

Meningococcal serogroup A,C,W,Y vaccination (minimum age: 2 months [MenACWY-CRM, Menveo], 9 months [MenACWY-D, Menactra], 2 years [MenACWY-TT, MenQuadfi])

Routine vaccination

- 2-dose series at age 11–12 years; 16 years

Catch-up vaccination

- Age 13–15 years: 1 dose now and booster at age 16–18 years (minimum interval: 8 weeks)
- Age 16–18 years: 1 dose

Special situations

Anatomic or functional asplenia (including sickle cell disease), HIV infection, persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use:

- **Menveo**
  - Dose 1 at age 2 months: 4-dose series (additional 3 doses at age 4, 6 and 12 months)
  - Dose 1 at age 3–6 months: 3- or 4- dose series (dose 2 [and dose 3 if applicable] at least 8 weeks after previous dose until a dose is received at age 7 months or older, followed by an additional dose at least 12 weeks later and after age 12 months)
  - Dose 1 at age 7–23 months: 2-dose series (dose 2 at least 12 weeks after dose 1 and after age 12 months)
  - Dose 1 at age 24 months or older: 2-dose series at least 8 weeks apart
- **Menactra**
  - **Persistent complement component deficiency or complement inhibitor use:**
    - Age 9–23 months: 2-dose series at least 12 weeks apart
    - Age 24 months or older: 2-dose series at least 8 weeks apart
  - **Anatomic or functional asplenia, sickle cell disease, or HIV infection:**
    - Age 9–23 months: Not recommended
    - Age 24 months or older: 2-dose series at least 8 weeks apart
    - **Menactra®** must be administered at least 4 weeks after completion of PCV13 series.
- **MenQuadfi®**
  - Dose 1 at age 24 months or older: 2-dose series at least 8 weeks apart

Travel in countries with hyperendemic or epidemic meningococcal disease, including countries in the African meningitis belt or during the Hajj (www.cdc.gov/travel/)**:**

- Children less than age 24 months:
  - **Menveo® (age 2–23 months)**
    - Dose 1 at age 2 months: 4-dose series (additional 3 doses at age 4, 6 and 12 months)
    - Dose 1 at age 3–6 months: 3- or 4- dose series (dose 2 [and dose 3 if applicable] at least 8 weeks after previous dose until a dose is received at age 7 months or older, followed by an additional dose at least 12 weeks later and after age 12 months)
    - Dose 1 at age 7–23 months: 2-dose series (dose 2 at least 12 weeks after dose 1 and after age 12 months)
  - **Menactra® (age 9–23 months)**
    - 2-dose series (dose 2 at least 12 weeks after dose 1; dose 2 may be administered as early as 8 weeks after dose 1 in travelers)
- Children age 2 years or older: 1 dose Menveo®, Menactra®, or MenQuadfi®

First-year college students who live in residential housing (if not previously vaccinated at age 16 years or older) or military recruits:

- 1 dose **Menveo®, Menactra®,** or **MenQuadfi®**

Adolescent vaccination of children who received MenACWY prior to age 10 years:

- **Children for whom boosters are recommended** because of an ongoing increased risk of meningococcal disease (e.g., those with complement deficiency, HIV, or asplenia): Follow the booster schedule for persons at increased risk.
- **Children for whom boosters are not recommended** (e.g., a healthy child who received a single dose for travel to a country where meningococcal disease is endemic): Administer MenACWY according to the recommended adolescent schedule with dose 1 at age 11–12 years and dose 2 at age 16 years.

Note: Menactra® should be administered either before or at the same time as DTaP. MenACWY vaccines may be administered simultaneously with MenB vaccines if indicated, but at a different anatomic site, if feasible.

For MenACWY **booster dose recommendations** for groups listed under "Special situations" and in an outbreak setting and additional meningococcal vaccination information, see www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm.

Meningococcal serogroup B vaccination (minimum age: 10 years [MenB-4C, Bexsero®; MenB-FHbp, Trumenba®])

Shared clinical decision-making

- **Adolescents not at increased risk** age 16–23 years (preferred age 16–18 years) based on shared clinical decision-making:
  - **Bexsero®:** 2-dose series at least 1 month apart
  - **Trumenba®:** 2-dose series at least 6 months apart; if dose 2 is administered earlier than 6 months, administer a 3rd dose at least 4 months after dose 2.

Special situations

Anatomic or functional asplenia (including sickle cell disease), persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use:

- **Bexsero®:** 2-dose series at least 1 month apart
- **Trumenba®:** 3-dose series at 0, 1–2, 6 months

Note: Bexsero® and **Trumenba®** are not interchangeable; the same product should be used for all doses in a series.

For MenB **booster dose recommendations** for groups listed under "Special situations" and in an outbreak setting and additional meningococcal vaccination information, see www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm.

Pneumococcal vaccination (minimum age: 6 weeks [PCV13], 2 years [PPSV23])

Routine vaccination with PCV13

- 4-dose series at age 2, 4, 6, 12–15 months

Catch-up vaccination with PCV13

- 1 dose for healthy children age 24–59 months with any incomplete* PCV13 series
- For other catch-up guidance, see Table 2.

Special situations

Underlying conditions below: When both PCV13 and PPSV23 are indicated, administer PCV13 first. PCV13 and PPSV23 should not be administered during same visit.

Chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure); chronic lung disease (including asthma treated with high-dose, oral corticosteroids); diabetes mellitus:

Age 2–5 years

- Any incomplete* series with:
  - 3 PCV13 doses: 1 dose PCV13 (at least 8 weeks after any prior PCV13 dose)
  - Less than 3 PCV13 doses: 2 doses PCV13 (8 weeks after the most recent dose and administered 8 weeks apart)
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after completing all recommended PCV13 doses)

Age 6–18 years

- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after completing all recommended PCV13 doses)

Cerebrospinal fluid leak, cochlear implant:

Age 2–5 years

- Any incomplete* series with:
  - 3 PCV13 doses: 1 dose PCV13 (at least 8 weeks after any prior PCV13 dose)
  - Less than 3 PCV13 doses: 2 doses PCV13 (8 weeks after the most recent dose and administered 8 weeks apart)
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose)

Age 6–18 years

- No history of either PCV13 or PPSV23: 1 dose PCV13, 1 dose PPSV23 at least 8 weeks later
- Any PCV13 but no PPSV23: 1 dose PPSV23 at least 8 weeks after the most recent dose of PCV13
- PPSV23 but no PCV13: 1 dose PCV13 at least 8 weeks after the most recent dose of PPSV23

Sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiency; HIV infection; chronic renal failure; nephrotic syndrome; malignant neoplasms, leukemias, lymphomas, Hodgkin disease, and other diseases associated with treatment with immunosuppressive drugs or radiation therapy; solid organ transplantation; multiple myeloma:

Age 2–5 years

- Any incomplete* series with:
  - 3 PCV13 doses: 1 dose PCV13 (at least 8 weeks after any prior PCV13 dose)
  - Less than 3 PCV13 doses: 2 doses PCV13 (8 weeks after the most recent dose and administered 8 weeks apart)
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose) and a dose 2 of PPSV23 5 years later

Age 6–18 years

- No history of either PCV13 or PPSV23: 1 dose PCV13, 2 doses PPSV23 (dose 1 of PPSV23 administered 8 weeks after PCV13 and dose 2 of PPSV23 administered at least 5 years after dose 1 of PPSV23)
- Any PCV13 but no PPSV23: 2 doses PPSV23 (dose 1 of PPSV23 administered 8 weeks after the most recent dose of PCV13 and dose 2 of PPSV23 administered at least 5 years after dose 1 of PPSV23)
- PPSV23 but no PCV13: 1 dose PCV13 at least 8 weeks after the most recent PPSV23 dose and a dose 2 of PPSV23 administered 5 years after dose 1 of PPSV23 and at least 8 weeks after a dose of PCV13

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Chronic liver disease, alcoholism:
Age 6–18 years
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose)

**Incomplete series* = Not having received all doses in either the recommended series or an age-appropriate catch-up series See Tables 8, 9, and 11 in the ACIP pneumococcal vaccine recommendations (www.cdc.gov/mmwr/pdf/rr/rr5911.pdf) for complete schedule details.

Poliovirus vaccination (minimum age: 6 weeks)

Routine vaccination
- 4-dose series at ages 2, 4, 6–18 months, 4–6 years; administer the final dose on or after age 4 years and at least 6 months after the previous dose.
- 4 or more doses of IPV can be administered before age 4 years when a combination vaccine containing IPV is used. However, a dose is still recommended on or after age 4 years and at least 6 months after the previous dose.

Catch-up vaccination
- In the first 6 months of life, use minimum ages and intervals only for travel to a polio-endemic region or during an outbreak.
- IPV is not routinely recommended for U.S. residents age 18 years or older.

Series containing oral polio vaccine (OPV), either mixed OPV-IPV or OPV-only series:
- Total number of doses needed to complete the series is the same as that recommended for the U.S. IPV schedule. See www.cdc.gov/mmwr/volumes/66/wr/mm6601a6.htm?s_%20cid=mm6601a6_w.
- Only trivalent OPV (tOPV) counts toward the U.S. vaccination requirements.
  - Doses of OPV administered before April 1, 2016, should be counted (unless specifically noted as administered during a campaign).
  - Doses of OPV administered on or after April 1, 2016, should not be counted.
  - For guidance to assess doses documented as "OPV," see www.cdc.gov/mmwr/volumes/66/wr/mm6606a7.htm?s_cid=mm6606a7_w.
- For other catch-up guidance, see Table 2.

Rotavirus vaccination (minimum age: 6 weeks)

Routine vaccination
- **Rotarix®:** 2-dose series at age 2 and 4 months
- **RotaTeq®:** 3-dose series at age 2, 4, and 6 months
- If any dose in the series is either **RotaTeq®** or unknown, default to 3-dose series.

Catch-up vaccination
- Do not start the series on or after age 15 weeks, 0 days.
- The maximum age for the final dose is 8 months, 0 days.
- For other catch-up guidance, see Table 2.

Tetanus, diphtheria, and pertussis (Tdap) vaccination (minimum age: 11 years for routine vaccination, 7 years for catch-up vaccination)

Routine vaccination
- **Adolescents age 11–12 years:** 1 dose Tdap
- **Pregnancy:** 1 dose Tdap during each pregnancy, preferably in early part of gestational weeks 27–36.
- Tdap may be administered regardless of the interval since the last tetanus- and diphtheria-toxoid-containing vaccine.

Catch-up vaccination
- **Adolescents age 13–18 years who have not received Tdap:** 1 dose Tdap, then Td or Tdap booster every 10 years
- **Persons age 7–18 years not fully vaccinated* with DTaP:** 1 dose Tdap as part of the catch-up series (preferably the first dose); if additional doses are needed, use Td or Tdap.
- **Tdap administered at age 7–10 years:**
  - **Children age 7–9 years** who receive Tdap should receive the routine Tdap dose at age 11–12 years.
  - **Children age 10 years** who receive Tdap do not need the routine Tdap dose at age 11–12 years.
- **DTaP inadvertently administered on or after age 7 years**:
  - **Children age 7–9 years**: DTaP may count as part of catch-up series. Administer routine Tdap dose at age 11–12 years.
  - **Children age 10–18 years**: Count dose of DTaP as the adolescent Tdap booster.
- For other catch-up guidance, see Table 2.

Special situations
- **Wound management** in persons age 7 years or older with history of 3 or more doses of tetanus-toxoid-containing vaccine: For clean and minor wounds, administer Tdap or Td if more than 10 years since last dose of tetanus-toxoid-containing vaccine; for all other wounds, administer Tdap or Td if more than 5 years since last dose of tetanus-toxoid-containing vaccine. Tdap is preferred for persons age 11 years or older who have not previously received Tdap or whose Tdap history is unknown. If a tetanus-toxoid-containing vaccine is indicated for a pregnant adolescent, use Tdap.
- For detailed information, see www.cdc.gov/mmwr/volumes/69/wr/mm6903a5.htm.

**Fully vaccinated* = 5 valid doses of DTaP OR 4 valid doses of DTaP if dose 4 was administered at age 4 years or older

Varicella vaccination (minimum age: 12 months)

Routine vaccination
- 2-dose series at age 12–15 months, 4–6 years
- VAR or MMRV may be administered*
- Dose 2 may be administered as early as 3 months after dose 1 (a dose inadvertently administered after at least 4weeks may be counted as valid)

*****Note****: For dose 1 in children age 12–47 months, it is recommended to administer MMR and varicella vaccines separately. MMRV may be used if parents or caregivers express a preference.

Catch-up vaccination
- Ensure persons age 7–18 years without evidence of immunity (see *MMWR* at www.cdc.gov/mmwr/pdf/rr/rr5604.pdf) have a 2-dose series:
  - **Age 7–12 years**: routine interval: 3 months (a dose inadvertently administered after at least 4 weeks may be counted as valid)
  - **Age 13 years and older**: routine interval: 4–8 weeks (minimum interval: 4 weeks)
  - The maximum age for use of MMRV is 12 years.

Appendix Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2022

Guide to Contraindications and Precautions to Commonly Used Vaccines

Adapted from Table 4-1 in Advisory Committee on Immunization Practices (ACIP) General Best Practice Guidelines for Immunization: Contraindication and Precautions available at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html *and ACIP's Recommendations for the Prevention and Control of 2021-22 seasonal influenza with Vaccines available at* www.cdc.gov/mmwr/volumes/70/rr/rr7005a1.htm.

Interim clinical considerations for use of COVID-19 vaccines including contraindications and precautions can be found at
www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html

Vaccine	Contraindications[1]	Precautions[2]
Influenza, egg-based, inactivated injectable (IIV4)	• Severe allergic reaction (e.g., anaphylaxis) after previous dose of any influenza vaccine (i.e., any egg-based IIV, ccIIV, RIV, or LAIV of any valency) • Severe allergic reaction (e.g., anaphylaxis) to any vaccine component[3] (excluding egg)	• Guillain-Barré syndrome (GBS) within 6 weeks after a previous dose of any type of influenza vaccine • Persons with egg allergy with symptoms other than hives (e.g., angioedema, respiratory distress) or required epinephrine or another emergency medical intervention: Any influenza vaccine appropriate for age and health status may be administered. If using egg-based IIV4, administer in medical setting under supervision of health care provider who can recognize and manage severe allergic reactions. May consult an allergist. • Moderate or severe acute illness with or without fever
Influenza, cell culture-based inactivated injectable [(ccIIV4), Flucelvax® Quadrivalent]	• Severe allergic reaction (e.g., anaphylaxis) to any ccIIV of any valency, or to any component[3] of ccIIV4	• Guillain-Barré syndrome (GBS) within 6 weeks after a previous dose of any type of influenza vaccine • Persons with a history of severe allergic reaction (e.g., anaphylaxis) after a previous dose of any egg-based IIV, RIV, or LAIV of any valency. If using ccIV4, administer in medical setting under supervision of health care provider who can recognize and manage severe allergic reactions. May consult an allergist. • Moderate or severe acute illness with or without fever
Influenza, recombinant injectable [(RIV4), Flublok® Quadrivalent]	• Severe allergic reaction (e.g., anaphylaxis) to any RIV of any valency, or to any component[3] of RIV4	• Guillain-Barré syndrome (GBS) within 6 weeks after a previous dose of any type of influenza vaccine • Persons with a history of severe allergic reaction (e.g., anaphylaxis) after a previous dose of any egg- based IIV, ccIIV, or LAIV of any valency. If using RIV4, administer in medical setting under supervision of health care provider who can recognize and manage severe allergic reactions. May consult an allergist. • Moderate or severe acute illness with or without fever
Influenza, live attenuated [LAIV4, Flumist® Quadrivalent]	• Severe allergic reaction (e.g., anaphylaxis) after previous dose of any influenza vaccine (i.e., any egg-based IIV, ccIIV, RIV, or LAIV of any valency) • Severe allergic reaction (e.g., anaphylaxis) to any vaccine component[3] (excluding egg) • Children age 2 – 4 years with a history of asthma or wheezing • Anatomic or functional asplenia • Immunocompromised due to any cause including, but not limited to, medications and HIV infection • Close contacts or caregivers of severely immunosuppressed persons who require a protected environment • Pregnancy • Cochlear implant • Active communication between the cerebrospinal fluid (CSF) and the oropharynx, nasopharynx, nose, ear or any other cranial CSF leak • Children and adolescents receiving aspirin or salicylate-containing medications • Received influenza antiviral medications oseltamivir or zanamivir within the previous 48 hours, peramivir within the previous 5 days, or baloxavir within the previous 17 days	• Guillain-Barré syndrome (GBS) within 6 weeks after a previous dose of any type of influenza vaccine • Asthma in persons aged 5 years old or older • Persons with egg allergy with symptoms other than hives (e.g., angioedema, respiratory distress) or required epinephrine or another emergency medical intervention: Any influenza vaccine appropriate for age and health status may be administered. If using LAIV4 (which is egg based), administer in medical setting under supervision of health care provider who can recognize and manage severe allergic reactions. May consult an allergist. • Persons with underlying medical conditions (other than those listed under contraindications) that might predispose to complications after wild-type influenza virus infection [e.g., chronic pulmonary, cardiovascular (except isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus)] • Moderate or severe acute illness with or without fever

1. When a contraindication is present, a vaccine should NOT be administered. Kroger A, Bahta L, Hunter P. ACIP General Best Practice Guidelines for Immunization. www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html
2. When a precaution is present, vaccination should generally be deferred but might be indicated if the benefit of protection from the vaccine outweighs the risk for an adverse reaction. Kroger A, Bahta L, Hunter P. ACIP General Best Practice Guidelines for Immunization. www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html
3. Vaccination providers should check FDA-approved prescribing information for the most complete and updated information, including contraindications, warnings, and precautions. Package inserts for U.S.-licensed vaccines are available at www.fda.gov/vaccines-blood-biologics/approved-products/vaccines-licensed-use-united-states

Appendix

Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2022

Vaccine	Contraindications[1]	Precautions[2]
Dengue (DEN4CYD)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • Severe immunodeficiency (e.g., hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, long- term immunosuppressive therapy or patients with HIV infection who are severely immunocompromised)	• Pregnancy • HIV infection without evidence of severe immunosuppression • Moderate or severe acute illness with or without fever
Diphtheria, tetanus, pertussis (DTaP) Tetanus, diphtheria (DT)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • For DTaP only: Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) not attributable to another identifiable cause within 7 days of administration of previous dose of DTP or DTaP	• Guillain-Barré syndrome (GBS) within 6 weeks after previous dose of tetanus-toxoid–containing vaccine • History of Arthus-type hypersensitivity reactions after a previous dose of diphtheria-toxoid— containing or tetanus-toxoid– containing vaccine; defer vaccination until at least 10 years have elapsed since the last tetanus-toxoid- containing vaccine • For DTaP only: Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, progressive encephalopathy; defer DTaP until neurologic status clarified and stabilized • Moderate or severe acute illness with or without fever
Haemophilus influenzae type b (Hib)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • For Hiberix, ActHib, and PedvaxHIB only: History of severe allergic reaction to dry natural latex • Less than age 6 weeks	• Moderate or severe acute illness with or without fever
Hepatitis A (HepA)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] including neomycin	• Moderate or severe acute illness with or without fever
Hepatitis B (HepB)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] including yeast • For Heplisav-B only: Pregnancy	• Moderate or severe acute illness with or without fever
Hepatitis A- Hepatitis B vaccine [HepA-HepB, (Twinrix®)]	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] including neomycin and yeast	• Moderate or severe acute illness with or without fever
Human papillomavirus (HPV)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3]	• Moderate or severe acute illness with or without fever
Measles, mumps, rubella (MMR)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • Severe immunodeficiency (e.g., hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, long-term immunosuppressive therapy or patients with HIV infection who are severely immunocompromised) • Pregnancy • Family history of altered immunocompetence, unless verified clinically or by laboratory testing as immunocompetent	• Recent (≤11 months) receipt of antibody-containing blood product (specific interval depends on product) • History of thrombocytopenia or thrombocytopenic purpura • Need for tuberculin skin testing or interferon-gamma release assay (IGRA) testing • Moderate or severe acute illness with or without fever
Meningococcal ACWY (MenACWY) [MenACWY-CRM (Menveo®); MenACWY-D (Menactra®); MenACWY-TT (MenQuadfi®)]	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • For MenACWY-D and Men ACWY-CRM only: severe allergic reaction to any diphtheria toxoid– or CRM197–containing vaccine • For MenACWY-TT only: severe allergic reaction to a tetanus toxoid-containing vaccine	• For MenACWY-CRM only: Preterm birth if less than age 9 months • Moderate or severe acute illness with or without fever
Meningococcal B (MenB) [MenB-4C (Bexsero®); MenB-FHbp (Trumenba®)]	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3]	• Pregnancy • For MenB-4C only: Latex sensitivity • Moderate or severe acute illness with or without fever
Pneumococcal conjugate (PCV13)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • Severe allergic reaction (e.g., anaphylaxis) to any diphtheria-toxoid– containing vaccine or its component[3]	• Moderate or severe acute illness with or without fever
Pneumococcal polysaccharide (PPSV23)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3]	• Moderate or severe acute illness with or without fever
Poliovirus vaccine, inactivated (IPV)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3]	• Pregnancy • Moderate or severe acute illness with or without fever
Rotavirus (RV) [RV1 (Rotarix®), RV5 (RotaTeq®)]	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • Severe combined immunodeficiency (SCID) • History of intussusception	• Altered immunocompetence other than SCID • Chronic gastrointestinal disease • RV1 only: Spina bifida or bladder exstrophy • Moderate or severe acute illness with or without fever
Tetanus, diphtheria, and acellular pertussis (Tdap) Tetanus, diphtheria (Td)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • For Tdap only: Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) not attributable to another identifiable cause within 7 days of administration of previous dose of DTP, DTaP, or Tdap	• Guillain-Barré syndrome (GBS) within 6 weeks after a previous dose of tetanus-toxoid–containing vaccine • History of Arthus-type hypersensitivity reactions after a previous dose of diphtheria-toxoid— containing or tetanus-toxoid– containing vaccine; defer vaccination until at least 10 years have elapsed since the last tetanus-toxoid– containing vaccine • For Tdap only: Progressive or unstable neurological disorder, uncontrolled seizures, or progressive encephalopathy until a treatment regimen has been established and the condition has stabilized • Moderate or severe acute illness with or without fever
Varicella (VAR)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • Severe immunodeficiency (e.g., hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, long- term immunosuppressive therapy or patients with HIV infection who are severely immunocompromised) • Pregnancy • Family history of altered immunocompetence, unless verified clinically or by laboratory testing as immunocompetent	• Recent (≤11 months) receipt of antibody-containing blood product (specific interval depends on product) • Receipt of specific antiviral drugs (acyclovir, famciclovir, or valacyclovir) 24 hours before vaccination (avoid use of these antiviral drugs for 14 days after vaccination) • Use of aspirin or aspirin-containing products • Moderate or severe acute illness with or without fever

1. When a contraindication is present, a vaccine should NOT be administered. Kroger A, Bahta L, Hunter P. ACIP General Best Practice Guidelines for Immunization. www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html
2. When a precaution is present, vaccination should generally be deferred but might be indicated if the benefit of protection from the vaccine outweighs the risk for an adverse reaction. Kroger A, Bahta L, Hunter P. ACIP General Best Practice Guidelines for Immunization. www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html
3. Vaccination providers should check FDA-approved prescribing information for the most complete and updated information, including contraindications, warnings, and precautions. Package inserts for U.S.-licensed vaccines are available at www.fda.gov/vaccines-blood-biologics/approved-products/vaccines-licensed-use-united-states.

Footnote 2

IPOL - Poliovirus Vaccine Inactivated (Monkey Kidney Cell)

STN:103930
Proper Name: Poliovirus Vaccine Inactivated
Tradename: IPOL
Manufacturer: Sanofi Pasteur, SA
Indications:

- IPOL vaccine is indicated for active immunization of infants (as young as 6 weeks of age), children, and adults for the prevention of poliomyelitis caused by poliovirus Types 1, 2, and 3.

Product Information

- Package Insert - IPOL (/media/75695/download)

Supporting Documents

- June 2, 2022 Approval Letter - IPOL (/media/158923/download)
- Supporting Documents older than three years - IPOL (http://wayback.archive-it.org/7993/20170723031336/https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm180053.htm) (http://www.fda.gov/about-fda/website-policies/website-disclaimer)

Footnote 3

Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

AHFS Category: 80:12 **IPV**

Poliovirus Vaccine Inactivated

IPOL®

Rx only

DESCRIPTION

IPOL®, Poliovirus Vaccine Inactivated, produced by Sanofi Pasteur SA, is a sterile suspension of three types of poliovirus: Type 1 (Mahoney), Type 2 (MEF-1), and Type 3 (Saukett). IPOL vaccine is a highly purified, inactivated poliovirus vaccine with enhanced potency. Each of the three strains of poliovirus is individually grown in vero cells, a continuous line of monkey kidney cells cultivated on microcarriers. (1) (2) The cells are grown in Eagle MEM modified medium, supplemented with newborn calf bovine serum tested for adventitious agents prior to use, originated from countries free of bovine spongiform encephalopathy. For viral growth, the culture medium is replaced by M-199, without calf bovine serum. This culture technique and improvements in purification, concentration, and standardization of poliovirus antigen produce a more potent and consistent immunogenic vaccine than the inactivated poliovirus vaccine (IPV) available in the US prior to 1988. (3) (4)

After clarification and filtration, viral suspensions are concentrated by ultrafiltration, and purified by three liquid chromatography steps; one column of anion exchanger, one column of gel filtration, and again one column of anion exchanger. After re-equilibration of the purified viral suspension with Medium M-199 and adjustment of the antigen titer, the monovalent viral suspensions are inactivated at +37°C for at least 12 days with 1:4000 formalin.

Each dose (0.5 mL) of trivalent vaccine is formulated to contain 40 D antigen units of Type 1, 8 D antigen units of Type 2, and 32 D antigen units of Type 3 poliovirus. For each lot of IPOL vaccine, D-antigen content is determined *in vitro* using the D-antigen ELISA assay. IPOL vaccine is produced from vaccine concentrates diluted with M-199 medium. Also present are 0.5% of 2-phenoxyethanol and a maximum of 0.02% of formaldehyde per dose as preservatives. Neomycin, streptomycin, and polymyxin B are used in vaccine production; and, although purification procedures eliminate measurable amounts, less than 5 ng neomycin, 200 ng streptomycin, and 25 ng polymyxin B per dose may still be present. The residual calf bovine serum albumin is less than 50 ng/dose in the final vaccine.

The vaccine is clear and colorless and should be administered intramuscularly or subcutaneously.

The vial stopper is not made with natural rubber latex.

CLINICAL PHARMACOLOGY

Poliomyelitis is caused by poliovirus Types 1, 2, or 3. It is primarily spread by the fecal-oral route of transmission but may also be spread by the pharyngeal route.

Approximately 90% to 95% of poliovirus infections are asymptomatic. Nonspecific illness with low-grade fever and sore throat (minor illness) occurs in 4% to 8% of infections. Aseptic meningitis occurs in 1% to 5% of patients a few days after the minor illness has resolved. Rapid onset of asymmetric acute flaccid paralysis occurs in 0.1% to 2% of infections, and residual

paralytic disease involving motor neurons (paralytic poliomyelitis) occurs in approximately 1 per 1,000 infections. (5)

Prior to the introduction of inactivated poliovirus vaccines in 1955, large outbreaks of poliomyelitis occurred each year in the United States (US). The annual incidence of paralytic disease of 11.4 cases/100,000 population declined to 0.5 cases by the time oral poliovirus vaccine (OPV) was introduced in 1961. Incidence continued to decline thereafter to a rate of 0.002 to 0.005 cases per 100,000 population. Of the 127 cases of paralytic poliomyelitis reported in the US between 1980 and 1994, six were imported cases (caused by wild polioviruses), two were "indeterminate" cases, and 119 were vaccine associated paralytic poliomyelitis (VAPP) cases associated with the use of live, attenuated oral poliovirus vaccine (OPV). (6) An all IPV schedule was adopted in 1999 to eliminate VAPP cases. (7)

Poliovirus Vaccine Inactivated induces the production of neutralizing antibodies against each type of virus which are related to protective efficacy. Antibody response in most children was induced after receiving fewer doses (8) of IPV vaccine than the vaccine available in the United States prior to 1988.

Studies in developed (8) and developing (9), (10) countries with a similar enhanced IPV manufactured by the same process as IPOL vaccine in primary monkey kidney cells have shown a direct relationship exists between the antigenic content of the vaccine, the frequency of seroconversion, and resulting antibody titer. Approval in the US was based upon demonstration of immunogenicity and safety in US children. (11)

In the US, 219 infants received three doses of a similar enhanced IPV at two, four, and eighteen months of age manufactured by the same process as IPOL vaccine except the cell substrate for IPV was using primary monkey kidney cells. Seroconversion to all three types of poliovirus was demonstrated in 99% of these infants after two doses of vaccine given at 2 and 4 months of age. Following the third dose of vaccine at 18 months of age, neutralizing antibodies were present at a level of ≥1:10 in 99.1% of children to Type 1 and 100% of children to Types 2 and 3 polioviruses. (3)

IPOL vaccine was administered to more than 700 infants between 2 to 18 months of age during three clinical studies conducted in the US using IPV only schedules and sequential IPV-OPV schedules. (12) (13) Seroprevalence rates for detectable serum neutralizing antibody (DA) at a ≥1:4 dilution were 95% to 100% (Type 1); 97% to 100% (Type 2) and 96% to 100% (Type 3) after two doses of IPOL vaccine depending on studies.

Table 1: US Studies with IPOL Vaccine Administered Using IPV Only or Sequential IPV-OPV Schedules

Age (months) for				Post Dose 2				Post Dose 3				Pre Booster				Post Booster			
2	4	6	12 to 18		Type 1	Type 2	Type 3		Type 1	Type 2	Type 3		Type 1	Type 2	Type 3		Type 1	Type 2	Type 3
Dose 1	Dose 2	Dose 3	Booster	N*	%DA†	%DA	%DA	N*	%DA	%DA	%DA	N*	%DA	%DA	%DA	N*	%DA	%DA	%DA
STUDY 1 [11] ‡																			
I(s)	I(s)	NA§	I(s)	56	97	100	97		–	–	–	53	91	97	93	53	97	100	100
O	O	NA	O	22	100	100	100		–	–	–	22	78	91	78	20	100	100	100
I(s)	O	NA	O	17	95	100	95		–	–	–	17	95	100	95	17	100	100	100
I(s)	I(s)	NA	O	17	100	100	100		–	–	–	16	100	100	94	16	100	100	100
STUDY 2 [10] ¶																			
I(c)	I(c)	NA	I(s)	94	98	97	96		–	–	–	100	92	95	88	97	100	100	100
I(s)	I(s)	NA	I(s)	68	99	100	99		–	–	–	72	100	100	94	75	100	100	100
I(c)	I(c)	NA	O	75	95	99	96		–	–	–	77	86	97	82	78	100	100	97
I(s)	I(s)	NA	O	101	99	99	95		–	–	–	103	99	97	89	107	100	100	100
STUDY 3 [10] ¶																			
I(c)	I(c)	I(c)	O	91	98	99	100	91	100	100	100	41	100	100	100	40	100	100	100
I(c)	I(c)	O	O	96	100	98	99	94	100	100	99	47	100	100	100	45	100	100	100
I(c)	I(c)	I(c) + O	O	91	96	97	100	85	100	100	100	47	100	100	100	46	100	100	100

* N = Number of children from whom serum was available

† Detectable antibody (neutralizing titer ≥1:4)

‡ IPOL vaccine given subcutaneously

§ NA – No poliovirus vaccine administered

¶ IPOL vaccine given intramuscularly

I IPOL vaccine given either separately in association with DTP in two sites (s) or combined (c) with DTP in a dual chambered syringe

O OPV

In one study, (13) the persistence of DA in infants receiving two doses of IPOL vaccine at 2 and 4 months of age was 91% to 100% (Type 1), 97% to 100% (Type 2), and 93% to 94% (Type 3) at twelve months of age. In another study, (12) 86% to 100% (Type 1), 95% to 100% (Type 2), and 82% to 94% (Type 3) of infants still had DA at 18 months of age.

In trials and field studies conducted outside the US, IPOL vaccine, or a combination vaccine containing IPOL vaccine and DTP, was administered to more than 3,000 infants between 2 to 18 months of age using IPV only schedules and immunogenicity data are available from 1,485 infants. After two doses of vaccine given during the first year of life, seroprevalence rates for detectable serum neutralizing antibody (neutralizing titer ≥1:4) were 88% to 100% (Type 1); 84% to 100% (Type 2) and 94% to 100% (Type 3) of infants, depending on studies. When three doses were given during the first year of life, post-dose 3 DA ranged between 93% to 100% (Type 1); 89% to 100% (Type 2) and 97% to 100% (Type 3) and reached 100% for Types 1, 2, and 3 after the fourth dose given during the second year of life (12 to 18 months of age). (14)

In infants immunized with three doses of an unlicensed combination vaccine containing IPOL vaccine and DTP given during the first year of life, and a fourth dose given during the second year of life, the persistence of detectable neutralizing antibodies was 96%, 96%, and 97% against poliovirus Types 1, 2, and 3, respectively, at six years of age. DA reached 100% for all types after a booster dose of IPOL vaccine combined with DTP vaccine. (11) A survey of Swedish children and young adults given a Swedish IPV only schedule demonstrated persistence of detectable serum neutralizing antibody for at least 10 years to all three types of poliovirus. (15)

IPV is able to induce secretory antibody (IgA) produced in the pharynx and gut and reduces pharyngeal excretion of poliovirus Type 1 from 75% in children with neutralizing antibodies at levels less than 1:8 to 25% in children with neutralizing antibodies at levels more than 1:64. (4) (14) (16) (17) (18) (19) (20) (21) (22) There is also evidence of induction of herd immunity with IPV, (15) (23) (24) (25) (26) and that this herd immunity is sufficiently maintained in a population vaccinated only with IPV. (26)

VAPP has not been reported in association with administration of IPOL vaccine. (27) It is expected that an IPV only schedule will eliminate the risk of VAPP in both recipients and contacts compared to a schedule that included OPV. (7)

INDICATIONS AND USAGE

IPOL vaccine is indicated for active immunization of infants (as young as 6 weeks of age), children, and adults for the prevention of poliomyelitis caused by poliovirus Types 1, 2, and 3. (28)

INFANTS, CHILDREN AND ADOLESCENTS

General Recommendations

It is recommended that all infants (as young as 6 weeks of age), unimmunized children, and adolescents not previously immunized be vaccinated routinely against paralytic poliomyelitis. (29) Following the eradication of poliomyelitis caused by wild poliovirus from the Western

Hemisphere (including North and South America) (30), an IPV-only schedule was recommended to eliminate VAPP. (7)

All children should receive four doses of IPV at ages 2, 4, 6 to 18 months, and 4 to 6 years. OPV is no longer available in the US and is not recommended for routine immunization. (7)

Previous clinical poliomyelitis (usually due to only a single poliovirus type) or incomplete immunization with OPV are not contraindications to completing the primary series of immunization with IPOL vaccine.

Children Incompletely Immunized

Children of all ages should have their immunization status reviewed and be considered for supplemental immunization as follows for adults. Time intervals between doses longer than those recommended for routine primary immunization do not necessitate additional doses as long as a final total of four doses is reached (see **DOSAGE AND ADMINISTRATION** section).

ADULTS

General Recommendations

Routine primary poliovirus vaccination of adults (generally those 18 years of age or older) residing in the US is not recommended. Unimmunized adults who are potentially exposed to wild poliovirus and have not been adequately immunized should receive polio vaccination in accordance with the schedule given in the **DOSAGE AND ADMINISTRATION** section. (28)

Persons with previous wild poliovirus disease who are incompletely immunized or unimmunized should be given additional doses of IPOL vaccine if they fall into one or more categories listed.

The following categories of adults are at an increased risk of exposure to wild polioviruses: (28) (31)

• Travelers to regions or countries where poliomyelitis is endemic or epidemic.

• Healthcare workers in close contact with patients who may be excreting polioviruses.

• Laboratory workers handling specimens that may contain polioviruses.

• Members of communities or specific population groups with disease caused by wild polioviruses.

IMMUNODEFICIENCY AND ALTERED IMMUNE STATUS

IPOL vaccine should be used in all patients with immunodeficiency diseases and members of such patients' households when vaccination of such persons is indicated. This includes patients with asymptomatic HIV infection, AIDS or AIDS-Related Complex, severe combined immunodeficiency, hypogammaglobulinemia, or agammaglobulinemia; altered immune states due to diseases such as leukemia, lymphoma, or generalized malignancy; or an immune system compromised by treatment with corticosteroids, alkylating drugs, antimetabolites or radiation. Immunogenicity of IPOL vaccine in individuals receiving immunoglobulin could be impaired, and patients with an altered immune state may or may not develop a protective response against paralytic poliomyelitis after administration of IPV. (32)

As with any vaccine, vaccination with IPOL vaccine may not protect 100% of individuals.

Use with other vaccines: refer to **DOSAGE AND ADMINISTRATION** section for this information.

CONTRAINDICATIONS

IPOL vaccine is contraindicated in persons with a history of hypersensitivity to any component of the vaccine, including 2-phenoxyethanol, formaldehyde, neomycin, streptomycin, and polymyxin B.

No further doses should be given if anaphylaxis or anaphylactic shock occurs within 24 hours of administration of one dose of vaccine.

Vaccination of persons with an acute, febrile illness should be deferred until after recovery; however, minor illness, such as mild upper respiratory infection, with or without low grade fever, are not reasons for postponing vaccine administration.

WARNINGS

Neomycin, streptomycin, polymyxin B, 2-phenoxyethanol, and formaldehyde are used in the production of this vaccine. Although purification procedures eliminate measurable amounts of these substances, traces may be present (see **DESCRIPTION** section), and allergic reactions may occur in persons sensitive to these substances (see **CONTRAINDICATIONS** section).

Systemic adverse reactions reported in infants receiving IPV concomitantly at separate sites or combined with DTP have been similar to those associated with administration of DTP alone. (11) Local reactions are usually mild and transient in nature.

Although no causal relationship between IPOL vaccine and Guillain-Barré Syndrome (GBS) has been established, (28) GBS has been temporally related to administration of another inactivated poliovirus vaccine. Deaths have been reported in temporal association with the administration of IPV (see **ADVERSE REACTIONS** section).

PRECAUTIONS

GENERAL

Prior to an injection of any vaccine, all known precautions should be taken to prevent adverse reactions. This includes a review of the patient's history with respect to possible sensitivity to the vaccine or similar vaccines.

Healthcare providers should question the patient, parent or guardian about reactions to a previous dose of this product, or similar product.

Epinephrine injection (1:1000) and other appropriate agents should be available to control immediate allergic reactions.

Healthcare providers should obtain the previous immunization history of the vaccinee, and inquire about the current health status of the vaccinee.

Immunodeficient patients or patients under immunosuppressive therapy may not develop a protective immune response against paralytic poliomyelitis after administration of IPV.

Administration of IPOL vaccine is not contraindicated in individuals infected with HIV. (33) (34) (35)

Special care should be taken to ensure that the injection does not enter a blood vessel.

Syncope (fainting) has been reported following vaccination with IPOL. Procedures should be in place to avoid injury from fainting.

INFORMATION FOR PATIENTS

Patients, parents, or guardians should be instructed to report any serious adverse reactions to their healthcare provider.

The healthcare provider should inform the patient, parent, or guardian of the benefits and risks of the vaccine.

The healthcare provider should inform the patient, parent, or guardian of the importance of completing the immunization series.

The healthcare provider should provide the Vaccine Information Statements (VISs) which are required to be given with each immunization.

DRUG INTERACTIONS

There are no known interactions of IPOL vaccine with drugs or foods. Concomitant administration of other parenteral vaccines, with separate syringes at separate sites, is not contraindicated. The first two doses of IPOL vaccine may be administered at separate sites using separate syringes concomitantly with DTaP, acellular pertussis, *Haemophilus influenzae* type b (Hib), and hepatitis B vaccines. From historical data on the antibody responses to diphtheria, tetanus, acellular pertussis, Hib, or hepatitis B vaccines used concomitantly or in combination with IPOL vaccine, no interferences have been observed on the immunological end points accepted for clinical protection. (11) (16) (36) (See **DOSAGE AND ADMINISTRATION** section.)

If IPOL vaccine has been administered to persons receiving immunosuppressive therapy, an adequate immunologic response may not be obtained. (See **PRECAUTIONS – GENERAL** section.)

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Long-term studies in animals to evaluate carcinogenic potential or impairment of fertility have not been conducted.

PREGNANCY

Animal reproduction studies have not been conducted with IPOL vaccine. It is also not known whether IPOL vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. IPOL vaccine should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

It is not known whether IPOL vaccine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when IPOL vaccine is administered to a nursing woman.

PEDIATRIC USE

SAFETY AND EFFECTIVENESS OF IPOL VACCINE IN INFANTS BELOW SIX WEEKS OF AGE HAVE NOT BEEN ESTABLISHED. (12) (20) (See **DOSAGE AND ADMINISTRATION** section.)

In the US, infants receiving two doses of IPV at 2 and 4 months of age, the seroprevalence to all three types of poliovirus was demonstrated in 95% to 100% of these infants after two doses of vaccine. (12) (13)

ADVERSE REACTIONS

Body System As A Whole

In earlier studies with the vaccine grown in primary monkey kidney cells, transient local reactions at the site of injection were observed. (3) Erythema, induration and pain occurred in 3.2%, 1% and 13%, respectively, of vaccinees within 48 hours post-vaccination. Temperatures of ≥39°C (≥102°F) were reported in 38% of vaccinees. Other symptoms included irritability, sleepiness,

fussiness, and crying. Because IPV was given in a different site but concurrently with Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (DTP), these systemic reactions could not be attributed to a specific vaccine. However, these systemic reactions were comparable in frequency and severity to that reported for DTP given alone without IPV. (12) Although no causal relationship has been established, deaths have occurred in temporal association after vaccination of infants with IPV. (37)

Four additional US studies using IPOL vaccine in more than 1,300 infants, (12) between 2 to 18 months of age administered with DTP at the same time at separate sites or combined have demonstrated that local and systemic reactions were similar when DTP was given alone.

Table 2 (12): Percentage of Infants Presenting with Local or Systemic Reactions at 6, 24, and 48 Hours of Immunization with IPOL Vaccine Administered Intramuscularly Concomitantly at Separate Sites with Sanofi* Whole-Cell DTP Vaccine at 2 and 4 Months of Age and with Sanofi Acellular Pertussis Vaccine (Tripedia®) at 18 Months of Age

	AGE AT IMMUNIZATION								
REACTION	**2 Months (n=211)**			**4 Months (n=206)**			**18 Months† (n=74)**		
	6 Hrs.	**24 Hrs.**	**48 Hrs.**	**6 Hrs.**	**24 Hrs.**	**48 Hrs.**	**6 Hrs.**	**24 Hrs.**	**48 Hrs.**
Local, IPOL vaccine alone‡									
Erythema >1"	0.5%	0.5%	0.5%	1.0%	0.0%	0.0%	1.4%	0.0%	0.0%
Swelling	11.4%	5.7%	0.9%	11.2%	4.9%	1.9%	2.7%	0.0%	0.0%
Tenderness	29.4%	8.5%	2.8%	22.8%	4.4%	1.0%	13.5%	4.1%	0.0%
Systemic§									
Fever >102.2°F	1.0%	0.5%	0.5%	2.0%	0.5%	0.0%	0.0%	0.0%	4.2%
Irritability	64.5%	24.6%	17.5%	49.5%	25.7%	11.7%	14.7%	6.7%	8.0%
Tiredness	60.7%	31.8%	7.1%	38.8%	18.4%	6.3%	9.3%	5.3%	4.0%
Anorexia	16.6%	8.1%	4.3%	6.3%	4.4%	2.4%	2.7%	1.3%	2.7%
Vomiting	1.9%	2.8%	2.8%	1.9%	1.5%	1.0%	1.3%	1.3%	0.0%
Persistent Crying	Percentage of infants within 72 hours after immunization was 0.0% after dose one, 1.4% after dose two, and 0.0% after dose three.								

* Sanofi Pasteur Inc. formerly known as Aventis Pasteur Inc.

† Children who have been vaccinated with Tripedia vaccine.

‡ Data are from the IPOL vaccine administration site, given intramuscularly.

§ The adverse reaction profile includes the concomitant use of Sanofi whole-cell DTP vaccine or Tripedia vaccine with IPOL vaccine. Rates are comparable in frequency and severity to that reported for whole-cell DTP given alone.

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Digestive System

Anorexia and vomiting occurred with frequencies not significantly different as reported when DTP was given alone without IPV or OPV. (12)

Nervous System

Although no causal relationship between IPOL vaccine and GBS has been established, (28) GBS has been temporally related to administration of another inactivated poliovirus vaccine.

Post-marketing Experience

The following adverse events have been identified during postapproval use of IPOL vaccine. Because these events are reported voluntarily from a population of uncertain size, it may not be possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Adverse events were included based on one or more of the following factors: severity, frequency of reporting or strength of evidence for a causal relationship.

- ***Blood and lymphatic system disorders:*** lymphadenopathy
- ***General disorders and administration site conditions:*** agitation, injection site reaction including injection site rash and mass
- ***Immune system disorders:*** type I hypersensitivity including allergic reaction, anaphylactic reaction, and anaphylactic shock
- ***Musculoskeletal and connective tissue disorders:*** arthralgia, myalgia
- ***Nervous system disorders:*** convulsion, febrile convulsion, headache, paresthesia, somnolence, syncope

- ***Skin and subcutaneous tissue disorders:*** rash, urticaria

Reporting of Adverse Events

The National Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act of 1986, requires physicians and other healthcare providers who administer vaccines to maintain permanent vaccination records and to report occurrences of certain adverse events to the US Department of Health and Human Services. Reportable events include those listed in the Act for each vaccine and events specified in the package insert as contraindications to further doses of that vaccine. (38) (39) (40)

Reporting by parents or guardians of all adverse events after vaccine administration should be encouraged. Adverse events following immunization with vaccine should be reported by healthcare providers to the US Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS). Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 1-800-822-7967. (38) (39) (40)

Healthcare providers also should report these events to the Pharmacovigilance Department, Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call 1-800-822-2463.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The vial and its packaging should be inspected prior to use for evidence of leakage or a faulty seal. If evidence of such defects are observed, the vaccine should not be used. Do not remove the vial stopper or the metal seal holding it in place.

After preparation of the injection site, using a suitable sterile needle and aseptic technique, immediately administer IPOL vaccine intramuscularly or subcutaneously. In infants and small children, the mid-lateral aspect of the thigh is the preferred site. In older children and adults, IPOL vaccine should be administered intramuscularly or subcutaneously in the deltoid area. IPOL should not be combined through reconstitution or mixed with any other vaccine.

To help avoid HIV (AIDS), HBV (Hepatitis), and other infectious diseases due to accidental needlesticks, contaminated needles should not be recapped or removed, unless there is no alternative or that such action is required by a specific medical procedure.

Care should be taken to avoid administering the injection into or near blood vessels and nerves. If blood or any suspicious discoloration appears in the syringe, do not inject but discard contents and repeat procedures using a new dose of vaccine administered at a different site.

DO NOT ADMINISTER VACCINE INTRAVENOUSLY.

Children

The primary series of IPOL vaccine consists of three 0.5 mL doses administered intramuscularly or subcutaneously, preferably eight or more weeks apart and usually at ages 2, 4, and 6 to 18 months. Under no circumstances should the vaccine be given more frequently than four weeks apart. The first immunization may be administered as early as six weeks of age. For this series, a booster dose of IPOL vaccine is administered at 4 to 6 years of age. (41)

Use with Other Vaccines

From historical data on the antibody responses to diphtheria, tetanus, whole-cell or acellular pertussis, Hib, or hepatitis B vaccines used concomitantly with IPOL vaccine, no interferences have been observed on the immunological end points accepted for clinical protection. (11) (16) (36) (See **DRUG INTERACTIONS** section.)

If the third dose of IPOL vaccine is given between 12 to 18 months of age, it may be desirable to administer this dose with Measles, Mumps, and Rubella (MMR) vaccine and/or other vaccines using separate syringes at separate sites, (28) but no data on the immunological interference between IPOL vaccine and these vaccines exist.

Use in Previously Vaccinated Children

Children and adolescents with a previously incomplete series of polio vaccine should receive sufficient additional doses of IPOL vaccine to complete the series.

Interruption of the recommended schedule with a delay between doses does not interfere with the final immunity. There is no need to start the series over again, regardless of the time elapsed between doses.

The need to routinely administer additional doses is unknown at this time. (28)

Adults

Unvaccinated Adults

A primary series of IPOL vaccine is recommended for unvaccinated adults at increased risk of exposure to poliovirus. While the responses of adults to primary series have not been studied, the recommended schedule for adults is two 0.5 mL doses given at a 1 to 2 month interval and a third 0.5 mL dose given 6 to 12 months later. If less than 3 months but more than 2 months are available before protection is needed, three doses of IPOL vaccine should be given at least 1 month apart. Likewise, if only 1 or 2 months are available, two 0.5 mL doses of IPOL vaccine should be given at least 1 month apart. If less than 1 month is available, a single 0.5 mL dose of IPOL vaccine is recommended. (28)

Incompletely Vaccinated Adults

Adults who are at an increased risk of exposure to poliovirus and who have had at least one dose of OPV, fewer than three doses of conventional IPV or a combination of conventional IPV or OPV totaling fewer than three doses should receive at least one 0.5 mL dose of IPOL vaccine. Additional doses needed to complete a primary series should be given if time permits. (28)

Completely Vaccinated Adults

Adults who are at an increased risk of exposure to poliovirus and who have previously completed a primary series with one or a combination of polio vaccines can be given a 0.5 mL dose of IPOL vaccine.

The preferred injection site of IPOL vaccine for adults is in the deltoid area.

HOW SUPPLIED

Multi-dose vial , 5mL: NDC 49281-860-78. Supplied as package: NDC 49281-860-10.

STORAGE

The vaccine is stable if stored in the refrigerator at 2°C to 8°C (35°F to 46°F). The vaccine must not be frozen.

Protect from light.

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Product Information as of May 2022

Manufactured by:

Sanofi Pasteur SA

Marcy L'Etoile France

US Govt License #1724

Distributed by:

Sanofi Pasteur Inc.

Swiftwater PA 18370 USA

1-800-VACCINE (1-800-822-2463)

Footnote 4

MERIEUX INSTITUTE, INC.

April 28, 1983

John C. Petricciani, M.D.
Director
Office of Biologics HFN-800
National Center for Drugs & Biologics
8800 Rockville Pike
Bethesda, Maryland 20205

REFERENCE: 83-087

Dear Dr. Petricciani:

Enclosed is a report from Dr. A. Marshall McBean and co-investigators on a comparison of oral and Merieux killed polio vaccine.

The Merieux vaccine was produced from primary monkey kidney cells, however, it was made by the same basic methods used to produce the current polio vaccine from VERO cells.

This data was recently presented at the International Polio Symposium held at PAHO, Washington, D.C., March 14-17, 1983.

Because of the similarity of the final products, which differ only in cell substrate, this data on potency and efficacy is submitted in support of this application under Item 26.d.

Sincerely,

Pinya Cohen

Pinya Cohen, Ph.D.
Vice President
Quality Control
and Regulatory Affairs
FOR C. CHARBONNIER
PC/(b) (6)
83282

Attachments

1200 N.W. 78th Avenue, Suite 109 / Miami, Florida 33126 / Telephone (305) 593-9577 / Telex: 807387

A Comparison of the Serologic Response to Oral and Injectable Trivalent Polio Vaccine

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Institutions: Johns Hopkins University School of Hygiene and Public Health, Baltimore, MD; Prince George's County Health Department, Prince George's County, MD; Bureau of Biologics, F.D.A., Bethesda, MD; Centers for Disease Control, Atlanta, GA.

Running Head: Serologic Response to IPV and OPV

1. The authors gratefully acknowledge the assistance of the nursing and medical staff of the pediatric clinics of the cooperating agencies. In particular we thank Dr. Helen McAllister of the Prince George's County Health Department; Dr. Lindsey Grossman and Dr. John Neff of the Baltimore City Hospitals; Dr. John Krager of the Baltimore County Health Department, Dr. Venita Thweat of the Baltimore City Health Department; and Dr. Ruth Steerman of the Prince George's County General Hospital.

2. This research is supported by contract #200-80-0512(P) of the Centers for Disease Control, United States Department of Health and Human Services.

3. Informed consent was obtained from the parents of children in the study and guidelines for human experimentation of the United States Department of Health and Human Services and the Johns Hopkins University School of Hygiene and Public Health were followed in the conduct of the clinical research.

4. Please address requests for reprints to Dr. A. Marshall McBean, Johns Hopkins University School of Hygiene and Public Health, 615 North Wolfe Street, Baltimore, Maryland 21205

ABSTRACT

American children two months of age were randomly assigned to two groups which received either the commercially available oral trivelant polio vaccine (OPV) or an injectable trivalent polio vaccine (IPV) with a confirmed minimum D-antigen content of 27, 3.5 and 29 units for polio virus type I, II and III respectively. Vaccine was given at 2, 4, and 18 months of age. Sera was obtained at 2, 4, 6 months of age on 439 children and on 85 children at 18 and 20 months of age and examined for neutralizing antibodies.

The percent of children with detectable antibodies and the reciprocal geometric mean titers (GMTs) were similar for both groups at two months of age for all three polio types. At twenty months of age, all children but one had detectable antibodies to all three polio types. Significantly higher GMTs against types I and III were noted at twenty months for the IPV group.

I. Introduction

Protection of the United States population against poliomyelitis has been greatly facilitated by the availability of two very effective and safe types of vaccine: inactivated poliovirus vaccine (IPV) and live attenuated oral poliovirus vaccine (OPV). During the period from 1955 to 1961, immunization efforts using IPV were successful in reducing the number of reported paralytic polio cases from 13,850 (7.9/100,000 population) in 1955 to 820 (0.7/100,000) in 1961 [1]. In spite of this tremendous achievement, "The Cutter Incident" [2] in which the virus in the IPV was not inactivated, and the contamination of monkey kidney cells in which the IPV virus was grown by SV-40 virus which is oncogenic in hamsters, helped create an environment in which the use of IPV was rapidly discontinued after OPV became available in 1962. The decision to use OPV was also based on its ease of administration and acceptance; expected long lasting (perhaps life-long) immunity; rapid production of bowel immunity which could interrupt wild virus transmission, even in epidemic situations; and the spread of OPV virus to unvaccinated persons which could induce immunity in these people [3,4]. The continued reduction in the number of cases of paralytic disease in the era of OPV use has been reported annually by the Center for Disease Control (CDC), Atlanta, Georgia, U.S.A. By 1972, the number of cases has been reduced to 29 per year (0.01/100,000). During the years 1973-79, 82 cases of paralytic polio have been reported to CDC, an average of 12 cases per year.

Thus, the efficacy of both the IPV and OPV in inducing immunity and protecting recipients is well documented. However, there are reports of areas where children were given IPV and antibody levels were detectable in only 65 to 74% of the children who had received multiple doses of IPV [5]. For IPV, the seroconversion rates, post-immunization titers and the duration of immunity have been proportional to the potency of the vaccine; i.e., are dose-dependent

[6]. Vaccine production methods reported by (b) (6) of the Rijks Instituut Voor de Volksgezondheid, Bilthoven, The Netherlands, allow for higher concentrations of vaccine antigens than were attainable in previous IPV.

This study will compare the immunologic response in American infants given three doses of IPV made by the new production techniques with three doses of commercially available OPV. Data available through February, 1983 will be presented.

II. Materials and Methods

Participants: Children attending Well-child Clinics in Maryland were enrolled in the study and randomly assigned to receive either the OPV or the IPV. Children entered the study when they were between 6 and 13 weeks ("2 months") of age, and either OPV or IPV was administered at that time. Sixty days later, when the child was "4 months" of age, a second dose of the same vaccine was given. A third dose of the same polio vaccine was given at "18 months" of age. Diphtheria, Tetanus, Pertussis vaccine (DTP) and either an oral or injectable polio placebo were administered at the same time as the polio vaccines. As shown in Table 1, blood specimens were taken at 2, 4, 6, 18 and 20 months of age.

Vaccines: The OPV used was the commercially licensed available vaccine manufactured by Lederle Laboratories (Wayne, New Jersey, U.S.A.). It contained 800,000 $TCID_{50}$ of type I, 100,000 $TCID_{50}$ of type II, and 500,000 $TCID_{50}$ of type III per 0.5cc dose. The IPV was manufactured by the Merieux Institute (Lyon, France). It had a minimum potency of 27 D-antigen units of type I, 3.5 D-antigen units of type II, and 29 D-antigen units of type III per 0.5cc dose. The DTP contained (b) (4) Lf of diphtheria toxoid, 5 Lf of tetanus toxoid and 4 Units of pertussis per 0.5cc dose. The potency of the IPV, as measured by D-antigen content, was confirmed every three months at the Rijks Instituut.

Blood Specimen Handling: After collection, blood specimens were allowed

to clot, and the serum was drawn off. Specimens were then refrigerated and frozen within 4 to 8 hours. They were stored at -20°C until examined in the laboratory. Specimens were coded prior to being sent to the laboratory to insure unbiased laboratory analysis.

Laboratory Testing: Serum polio neutralizing antibodies were measured at the Bureau of Biologics, FDA, DHHS, Bethesda, Maryland (U.S.A.) by a virus cytopathic effect (CPE) neutralization test in microtiter trays (96 well, flat-bottomed, Microtest II, Falcon, Oxnard, CA). Each day a known serum prepared by the Rijks Instituut for each polio type was tested with the experimental sera. A conversion factor was then calculated to convert the observed reciprocal of the serum dilution which neutralized CPR in 50% of the wells to International Units (IU).

III. Results

Of the 558 children enrolled in the study to date, serum specimens from 484 have been analyzed for neutralizing antibodies. Of the 119 children not included in the analysis, 103 have been lost to follow-up, and sixteen were deleted because of lost specimens, broken collection tubes, or insufficient data. Therefore, 439 children comprise the study population, of which 196 received OPV, and 243 received IPV. All of these children have completed their 6-month visit, and 85 have completed their twenty-month visit.

As a confirmation of the randomization process, the sex distribution, the number of siblings living with the participants, and the number of siblings who received oral polio vaccine during the time of the study were similar for the two study groups. In addition, the percentage of children with detectable antibodies and the reciprocal geometric mean titers (GMTs) to the three polio virus types were the same for the children in each vaccine group at two months of age (Tables 2 and 3).

Comparing the two vaccine groups at each age for each virus type, there is

no difference in the percent of children in each group with detectable antibodies. Approximately 25% of all children do not have antibodies against type III at 2 months of age, but this decreases to 17% at 4 months of age and 5% or less, from 6 months on. At 6 months of age (2 months after the second dose of vaccine), a minimum of 93% of the children have antibodies against two polio types, I and II. The percent is unchanged between 6 and 18 months. At 20 months (2 months after the third dose of vaccine), all but one child has demonstrable antibodies.

At four months of age, the GMTs in the OPV group are significantly higher for type II and type III virus, compared with themselves at 2 months of age and with the IPV group at 4 months of age. The GMT against type I is similar for both vaccine groups and shows no change from 2 months of age. At six months of age, the GMT against type I poliovirus is significantly higher in the IPV group, and the GMT against type II is significantly higher in the OPV group. The GMTs against type III are similar in both groups.

The results from the analysis of the eighty-five children who have completed the 18 and 20-month visits reveal that, at eighteen months, the GMT in the OPV group remains significantly higher than the IPV group for type II polio virus. At twenty months, the GMTs against type II have become similar for both vaccine groups, while the GMTs against types I and III are now significantly greater for the IPV group.

IV. Discussion

An ideal study of the serologic response to polio vaccines would involve the administration of vaccine to children without antibodies to any of the polio virus types (triple negative children). Enrolling children into this study when they are 2 months of age precludes that possibility. In fact, only 12 of the 439 children were triple negative upon entry into this study, and three others were triple negative at 4 months of age. Thus, discussion of our results will

focus on the ability of the two vaccines to stimulate antibody production and protect the entire group of children given each vaccine.

If we take the presence of detectable serum neutralizing antibodies to indicate protection against polio, then both vaccines as well as residual maternal antibodies protect a similar percent of children during their first six months of life even though at 4 months of age the antibody level, as measured by the GMT, is lower in the IPV group to types I and II. The equivalency of the two vaccines in stimulating demonstrable antibodies is verified by the results at 18 and 20 months of age.

Although the percent of children with detectable antibodies at 4 months is not significantly greater than at 2 months in either group, the immunizing effect on the children receiving the first dose of OPV can be seen for types II and III by the increases in the GMTs. For the IPV and the type I oral vaccine, the GMTs decrease or remain the same after 1 dose of vaccine. The lower response to the IPV at 4 months of age is probably due to the presence of maternal antibodies in the children who received IPV at 2 months of age. On the other hand, the first dose of OPV, particularly types II and III, is able to multiply in the intestine, and stimulate the production of measurable serum antibodies at 4 months of age.

The ability of antibodies to type III to reach the same level for both OPV and IPV and a higher level for IPV to type I after the administration of the second dose of IPV may reflect either a significant primary response due to the high potency of the vaccine in the presence of declining maternal antibodies at the time of this dose, or the presence of an unmeasurable response to the first dose of IPV which is then boosted by the dose given at 4 months of age. The booster effect of the third dose of IPV is clearly seen by the great increase in GMTs to all three types between 18 and 20 months. The duration of protection cannot be estimated. However, it is likely that the higher the level of antibodies the more long lasting they will be.

Currently the Advisory Committee on Immunization Practice recommends three doses of the previously available IPV in the first year of life with a booster at 18 months. The preliminary data from this study indicates that 2 doses in the first year of life will probably be sufficient. This schedule is effective even when begun at 2 months of age when maternal antibodies are high.

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TABLE I

Schedule of immunizations and blood collection

Immunizations	2 Months	4 Months	6 Months	18 Months	20 Months
Dose of either OPV or IPV	1	2	-	3	-
Dose of DTP	1	2	3	4	-
Blood Collection	yes	yes	yes	yes	yes

Table 2

A Comparison of the Serologic Response to Oral and Injectable Trivalent Polio Vaccine

Number and Percent of Children 2, 4, 6, 18 and 20 Months of Age with Detectable Antibodies to the Three Types of Wild Polio Virus

	Polio Virus Type I			Polio Virus Type II			Polio Virus Type III		
	Number of children with antibodies	Number of children receiving vaccine	Percent of children with antibodies	Number of children with antibodies	Number of children receiving vaccine	Percent of children with antibodies	Number of children with antibodies	Number of children receiving vaccine	Percent of children with antibodies
2 MONTHS OF AGE									
Oral Vaccine	162	183	88.5	173	186	93.0	133	174	76.4
Injectable Vaccine	203	224	90.6	224	233	96.1	161	214	75.2
4 MONTHS OF AGE									
Oral Vaccine	159	187	85.0	189	194	97.4	158	190	83.2
Injectable Vaccine	210	228	92.1	218	228	95.6	186	225	82.7
6 MONTHS OF AGE									
Oral Vaccine	175	189	92.6	191	192	99.5	181	191	94.8
Injectable Vaccine	234	237	98.7	235	238	98.7	232	235	98.7
18 MONTHS OF AGE									
Oral Vaccine	41	45	91.1	46	46	100.0	45	46	97.8
Injectable Vaccine	39	40	97.5	41	42	97.6	41	42	97.6
20 MONTHS OF AGE									
Oral Vaccine	43	44	97.7	45	45	100.0	45	45	100.0
Injectable Vaccine	41	41	100.0	41	41	100.0	41	41	100.0

None of the differences between the oral and injectable vaccine groups is significant

Table 3

A Comparison of the Serologic Response to Oral and Injectable Trivalent Polio Vaccine

Reciprocal Geometric Mean Titers (in International Units) to Three Types of Wild Polio Virus In Children 2, 4, 6, 18&20 Months of Age

	Polio Virus Type I	Polio Virus Type II	Polio Virus Type III
		2 MONTHS OF AGE	
Oral Vaccine	0.42	1.03	0.31
Injectable Vaccine	0.43	1.13	0.27
		4 MONTHS OF AGE	
Oral Vaccine	0.43	7.90 *	1.87 *
Injectable Vaccine	0.30	0.66	0.34
		6 MONTHS OF AGE	
Oral Vaccine	1.10 *	16.93 *	4.22
Injectable Vaccine	1.90	3.54	4.71
		18 MONTHS OF AGE	
Oral Vaccine	2.31	16.30 *	2.91
Injectable Vaccine	1.53	6.04	2.65
		20 MONTHS OF AGE	
Oral Vaccine	4.74 *	20.35	4.38 *
Injectable Vaccine	11.36	20.40	18.75

* Difference in Reciprocal Geometric meanTiter between Oral and injectable Vaccine Groups significant at $p < 0.01$

MERIEUX INSTITUTE, INC.

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October 9, 1987

Elaine C. Esber, M.D., Director
Office of Biologics Research & Review
ATT: Division of Product Certification,
HFN-825
Room 9B-05, Parklawn Building
5600 Fishers Lane
Rockville, MD 20857

REFERENCE NO. 83-087

Dear Dr. Esber:

Enclosed is a progress report on the study of P. Ogra and H. Faden, SUNY, Buffalo.

This report covers data currently available on the results of two primary doses of Merieux IPV. Data from Johns Hopkins are not as advanced and are not included in this report.

Sincerely yours,

Pinya Cohen

Pinya Cohen, Ph.D.
Vice President
Quality Control and
Regulatory Affairs

PC (b) (6)
87507

Attachments

CLINICAL STUDIES OF MERIEUX IPV AT SUNY/CHILDRENS HOSPITAL, BUFFALO

PROGRESS REPORT

SUMMARY

Two doses of Merieux IPV at 2 and 4 months of age gave excellent neutralizing antibody responses at 5 months to three types of poliovirus. IPV and OPV alone produced similar levels of neutralizing antibody and IgA in the nasopharyngeal secretions. A combined schedule of IPV and OPV resulted in a strong priming effect by IPV on mucosal immune response of OPV for neutralizing antibody and IgA in the nasopharyngeal secretions and for IgA in the stool. Merieux IPV induced comparable responses in premature and full term infants. Single and two dose boosters in adults showed high anamestic responses in all recipients and that a second dose of IPV did not increase the GMT compared to only one dose.

Introduction

The Merieux Inactivated Polio Vaccine (M-IPV) produced from continuous cell lines of Vero cells using micro-carrier culture has been extensively tested in Finland, Israel, India, Brazil, Indonesia, Mali, France, and the United States. This highly purified more potent vaccine has been shown to be safe, highly immunogenic and efficacious when used in a two-dose schedule for primary immunization followed by a booster dose.

A clinical trial at Johns Hopkins comparing M-IPV to the oral polio vaccine

currently used in the United States showed that approximately 99% of children had neutralizing antibodies to all three types of polio virus after receiving M-IPV at 2 and 4 months of age and that a significant boost in titers occurred after the third dose at 18 months of age. The titers to M-IPV for Types I and III poliovirus were superior to OPV, but equivalent for Type II when given in the same 3 dose schedule. This vaccine was made exactly as the Vero cell vaccine intended for license except the cell substrate for the Johns Hopkins trial was primary monkey kidney cells.

The Office of Biologics requested, December 1985, that 75-100 children and 25-30 adults be immunized according to the United States schedule. In response to this request clinical studies on children and adults were carried out at Childrens Hospital/State University of New York, Buffalo by Drs. H. Faden and P. Ogra. Supplemental studies on groups of children using only IPV or a combined schedule were also initiated at Johns Hopkins by Drs. McBean and Modlin at a later date.

To meet the FDA request for M-IPV licensure, data are now presented on sufficient children and adults only from Buffalo. The studies are still in progress at Buffalo and Baltimore and will be completed in late 1988.

METHODS

Details of the methods used are outlined in the protocols already submitted under IND. Merieux IPV Lots Z1102, Z1103 and A0304 were used. The general approach was to compare immunogenicity of two primary doses of M-IPV. OPV or a combined schedule in children 2 months old. Originally, a minimum of 15-20 children were to be recruited in Groups A, C, and D and 50-60 were to be recruited in Group B.

At this time, 114 children are available for analysis. The groups and vaccines are shown below:

IMMUNIZATION PLAN FOR CHILDREN

GROUP	2 MONTHS	4 MONTHS	12 MONTHS
A	OPV	OPV	OPV
B	IPV	IPV	IPV
C	IPV	OPV	OPV
D	IPV	IPV	OPV

Blood samples for antibody determinations were collected at 2 and 4 months of age just prior to administration of vaccine and one month after the second and third doses of vaccine. There are insufficient data on the booster dose given at 12 months for presentation at this time. A detectable antibody titer was considered $\geq$ 1:10. GMT's were computed and also expressed in international units based on the FDA reference serum results.

Groups B and D are identical for the first two doses of vaccine, therefore, their data have been combined for this report.

The numbers of subjects in the OPV control (Group A) was small at the time of this report.

For the adult studies, 30 individuals were immunized and available for the analysis. Half received one dose (Group F1) and half received a second dose 4 weeks later (Group F2). Serum antibody titers were done prior to immunization

and 4 weeks after each dose of vaccine.

RESULTS IN CHILDREN

M-IPV induced detectable neutralizing antibodies after two doses of vaccine in 97.6% (Type I), 100% (Type II) and 97.6% (Type III) of the children (Table 1). Two doses of OPV gave 100% response for all types of poliovirus and a mixed schedule of IPV + OPV induced nearly 95% response for Types I and III and 100% response for Type II.

The GMT (Table I) was the same in all groups for Type I. For Type II two doses of IPV gave lower GMT's than OPV or a mixed schedule. The GMT obtained for Type III with a mixed schedule was significantly lower than in the other two groups.

Table 2 shows that two doses of M-IPV produced neutralizing antibodies in the nasopharyngeal secretions (NPS) to Type I polovirus in 34%, to Type II in 53% and to Type III in 42% of the children. OPV produced neutralizing antibodies to Type I in 50%, to Type II in 70%, and to Type III in 50% of the children. The mixed schedule resulted in NPS neutralizing antibody in 47, 90 and 42% of the children, respectively. The GMT for Type II antibody in the mixed schedule was significantly higher than schedules of only IPV or only OPV indicating a priming effect by IPV on Type II OPV induced antibody.

The percentage of children with IgA antibodies in the NPS (Table 3) were generally at similar levels for M-IPV and OPV for all types of poliovirus, but were highest in children receiving the mixed schedule. The GMT of IgA was

highest in the mixed schedule suggesting IPV exerts a priming effect on a subsequent dose of OPV. The GMT for all OPV or all IPV recipients was similar for types I and II but OPV was higher for type III.

The percentage of children with detectable neutralizing antibody in the stool (Table 4) was generally 5 to 33% regardless of schedule except for Type II poliovirus with OPV (56%) and the mixed schedule (42%). The percentage of children with detectable stool neutralizing antibody for Types I & II poliovirus was low in those receiving OPV, however the number of children analyzed was small. The GMT's for OPV, IPV and mixed schedules
were similar.

The percent detectable IgA levels in the stool ranged from 5 to 20% for IPV, 11 to 33% for OPV and 15 to 36% for the mixed schedule (Table 5). The mixed schedule resulted in the highest GMT's for Types II and III antibodies. IPV induced a moderate priming effect for OPV for Type II antibody.

Tables 6 and 7 summarize results of serum neutralizing antibodies in children 6 to 13 weeks of age at the time of entry into the study compared to those over 13 weeks. The percentage with detectable neutralizing antibody was the same for the two groups, however, those over 13 weeks of age had higher GMT values.

The NPS neutralizing antibody data for the two age groups (Tables 8 and 9) showed that OPV, IPV or a mixed schedule induced detectable antibody to any type of poliovirus in approximately 60% to 93% of recipients. In 6-13 week old children, combined use of IPV and OPV produced detectable Type I and II antibody in nearly

twice the number of vaccinees compared to IPV only and in nearly 50% more recipients of OPV only. The GMT for Type II was 6 times higher in children immunized with a mixed schedule than in children receiving only IPV and twice the level of children receiving only OPV. Similar NPS data was obtained for children over 13 weeks who received a combined schedule. The data from both age groups suggest a strong priming effect exerted by IPV on a subsequent dose of OPV.

Tables 10 and 11 show that neutralizing antibody in the stool specimens was highest with OPV only, intermediate with a mixed schedule and lowest with IPV only.

Detectable IgA in the NPS ranging from 50 to 100% was observed in children 6-13 weeks old and those over 13 weeks regardless of the vaccines used and virus types (Tables 12 & 13). The combined schedule of IPV and OPV gave GMT's for IgA two to nearly 10 times greater than schedules of OPV or IPV alone.

Overall 50% or less of recipients for either age group or for any vaccine schedule had detectable stool IgA antibody. The combined schedule gave percentages of detectable stool IgA twice those observed for IPV alone and GMT's approximately 50% higher (Tables 14 & 15).

Premature and full term infants developed detectable serum neutralizing antibody levels with equal frequency to two doses of M-IPV and had comparable GMT's (Table 16).

Children who had potential contact with an OPV recipient had significantly higher

GMT's for serum neutralizing antibody (Tables 17 & 18), NPS neutralizing antibody (Tables 19 & 20) and NPS IgA (Tables 21 & 22). This difference was not seen in stool neutralizing antibody levels of children who had contact with OPV compared to those whom were not exposed to OPV (Tables 23 & 24) or in stool IgA levels of the same children (Tables 25 & 26), however, this analysis is based on small numbers of children with
OPV contacts.

RESULTS IN ADULTS

Nearly all adults had detectable neutralizing antibodies at the time of entry into the study so that a single dose of M-IPV ensured a 100% response (Table 27).

A single dose of M-IPV induced increases in GMT of nearly 30 fold for Type I, 50 fold for Type II and 125 fold for Type III. A second dose of IPV did not significantly increase the GMT compared to only a single dose (Table 27).

The results of neutralizing antibodies in the NPS (Table 28) show that the percent of subjects with detectable antibody was the same with one or two doses and suggests that a greater increase over base titer and higher GMT is obtained in individuals who had a lower antibody titer upon entry.

In contrast, both the percent of individuals with stool neutralizing antibody and the GMT were higher in adults receiving two doses of M-IPV compared to only one dose (Table 29).

The IgA antibody levels in the NPS and stool were similar for one or two doses although there was a higher percentage of detectable antibody in NPS of recipients of two doses compared to one dose of M-IPV (Tables 30 & 31).

There were no major differences in antibody responses whether this was exposure or nonexposure to OPV (Tables 32 & 33).

DISCUSSION

The interim results of this study have demonstrated that two doses of M-IPV given at 2 and 4 months of age produce excellent neutralizing antibody responses to all three types of poliovirus one month after the second dose. The percentage of children at 5 months of age with detectable antibody to the Vero cell vaccine is similar to and the GMT's higher than results obtained with children 6 months old in the earlier Johns Hopkins/CDC/FDA study with M-IPV produced in primary monkey kidney cells.

Two children (b)(6) immunized at the same private clinic with two doses of M-IPV formed good neutralizing antibody titers to Type II but not the Types I and III poliovirus. The Type II preimmunization titer and titer one month post 12 month booster was 320 for both children. The Types I and III titers at baseline and post booster were for (b)(6) 10 and 10 and 40 and 20, respectively, and for (b)(6) 10 and 10 and 10 and 20 respectively. Both children had normal IgG at 5 months of age and measurable tetanus antibody levels at 13 months of age. The children are apparently immunocompetent but the reasons for poor Types I and III response are unclear.

This study has shown that children given two doses of only OPV or only IPV produce similar levels of neutralizing antibodies and IgA in the NPS, however, of particular interest was the finding that a dose of IPV followed by a dose of OPV produced significantly higher levels of neutralizing antibody and IgA in the NPS than two doses of OPV or two doses of IPV. This clearly shows that the M-IPV has a strong priming effect on the mucosal antibody induced by OPV and that it is greater than the priming effect of OPV alone. This finding confirms the observation of Ogra etal with less potent, killed poliovirus vaccine. However, in the earlier studies of Ogra, priming was seen using three doses of IPV followed by an OPV booster whereas in his current study priming was seen with only a single dose of the new M-IPV. These data clearly show that IPV stimulates local immunity when used alone or in combination with OPV.

Based on stool antibody data "gut immunity" appears to be a concept applicable to both M-IPV and OPV. Both vaccines used alone or in combination gave detectable neutralizing antibody in the stool with similar GMT's. Furthermore both IPV and OPV, alone or in combination, induced stool IgA. The GMT Type II IgA was the same for IPV or OPV alone and lower for Types I and III when IPV was used alone. Of particular interest is that the highest GMT for Types II and III IgA antibodies was obtained with a combined schedule, again demonstrating that a single dose of IPV can prime a subsequent dose of OPV producing a GMT of IgA higher than either vaccine alone.

The relatively low percentage of children (approximately 50%) with detectable

stool neutralizing antibodies and detectable IgA antibodies (30%) is surprising in view of the "gut immunity" usually attributed to OPV. In fact, the GMT's for IPV and OPV were similar for Types I & III neutralizing antibody and for Type II IgA antibody.

Because nearly 30% of the infants receiving two doses of IPV were premature births it was possible to compare responses to full term infants. Although full term infants had higher maternal antibody levels, as expected, both premature and full term infants had similar percentages of responders and comparable GMT's after two doses of IPV.

The studies in adults showed that a single dose of M-IPV produced booster responses of very high titers of neutralizing antibodies and that a second dose is unnecessary. However, stool neutralizing antibody levels were higher in adults receiving a second dose of IPV.

TABLE 1

Polio Protocol 01

SERUM NEUTRALIZING ANTIBODIES

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		2 Months		4 Months		5 Months	
I	PLAN A	9/10	(90.0)	7/10	(70.0)	10/10	(100.0)
	PLAN BD	66/85	(77.6)	53/84	(63.1)	81/83	(97.6)
	PLAN C	15/19	(78.9)	16/19	(84.2)	18/19	(94.7)
II	PLAN A	10/10	(100.0)	10/10	(100.0)	10/10	(100.0)
	PLAN BD	72/85	(84.7)	80/84	(95.2)	83/83	(100.0)
	PLAN C	18/19	(94.7)	19/19	(100.0)	19/19	(100.0)
III	PLAN A	9/10	(90.0)	10/10	(100.0)	10/10	(100.0)
	PLAN BD	62/85	(72.9)	68/84	(81.0)	81/83	(97.6)
	PLAN C	14/19	(73.7)	15/19	(78.9)	18/19	(94.7)
ANY	PLAN A	10/10	(100.0)	10/10	(100.0)	10/10	(100.0)
	PLAN BD	83/85	(97.6)	84/85	(98.8)	83/85	(97.6)
	PLAN C	18/19	(94.7)	19/19	(100.0)	19/19	(100.0)

GEOMETRIC MEAN TITERS

		2 Months		4 Months		5 Months	
TYPE		N	GMT	N	GMT	N	GMT
I	PLAN A	10	25.81	10	28.35	10	259.92
	PLAN BD	85	17.11	84	7.94	83	251.92
	PLAN C	19	19.08	19	12.46	19	263.53
II	PLAN A	10	60.63	10	519.84	10	3151.73
	PLAN BD	85	33.11	84	33.01	83	857.28
	PLAN C	19	79.07	19	38.57	19	2212.41
III	PLAN A	10	27.66	10	52.78	10	735.17
	PLAN BD	85	13.37	84	17.65	83	889.04
	PLAN C	19	10.14	19	17.74	19	131.77

GEOMETRIC MEAN TITERS IN INTERNATIONAL UNITS

		2 Months		4 Months		5 Months	
TYPE		N	GMT	N	GMT	N	GMT
I	PLAN A	10	0.30	10	0.33	10	3.03
	PLAN BD	85	0.20	84	0.09	83	2.94
	PLAN C	19	0.22	19	0.15	19	3.08
II	PLAN A	10	0.34	10	2.94	10	17.81
	PLAN BD	85	0.19	84	0.19	83	4.84
	PLAN C	19	0.45	19	0.22	19	12.50
III	PLAN A	10	0.28	10	0.53	10	7.35
	PLAN BD	85	0.13	84	0.18	83	8.89
	PLAN C	19	0.10	19	0.18	19	1.32

TABLE 2

Polio Protocol 01

NASOPHARYNGEAL SECRETIONS NEUTRALIZING ANTIBODIES

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		2 Months	4 Months	5 Months
I	PLAN A	0/ . (0.0)	3/ 9 (33.3)	5/10 (50.0)
	PLAN BD	0/ . (0.0)	1/82 (1.2)	27/79 (34.2)
	PLAN C	0/ . (0.0)	0/18 (0.0)	9/19 (47.4)
II	PLAN A	0/ . (0.0)	7/ 9 (77.8)	7/10 (70.0)
	PLAN BD	0/ . (0.0)	1/82 (1.2)	42/79 (53.2)
	PLAN C	0/ . (0.0)	2/18 (11.1)	17/19 (89.5)
III	PLAN A	0/ . (0.0)	2/ 9 (22.2)	5/10 (50.0)
	PLAN BD	0/ . (0.0)	2/82 (2.4)	33/79 (41.8)
	PLAN C	0/ . (0.0)	1/18 (5.6)	8/19 (42.1)
ANY	PLAN A	0/ . (0.0)	7/10 (70.0)	7/10 (70.0)
	PLAN BD	0/ . (0.0)	3/85 (3.5)	49/85 (57.6)
	PLAN C	0/ . (0.0)	3/19 (15.8)	17/19 (89.5)

GEOMETRIC MEAN TITERS

		2 Months		4 Months		5 Months	
TYPE		N	GMT	N	GMT	N	GMT
I	PLAN A	0	.	9	1.71	10	3.03
	PLAN BD	6	1.00	82	1.02	79	1.90
	PLAN C	0	.	18	0.00	19	3.10
II	PLAN A	0	.	9	8.00	10	9.19
	PLAN BD	6	1.00	82	1.03	79	3.30
	PLAN C	0	.	18	1.17	19	19.20
III	PLAN A	0	.	9	2.00	10	5.28
	PLAN BD	6	1.00	82	1.03	79	2.82
	PLAN C	0	.	18	1.08	19	2.40

GEOMETRIC MEAN TITERS IN INTERNATIONAL UNITS

		2 Months		4 Months		5 Months	
TYPE		N	GMT	N	GMT	N	GMT
I	PLAN A	0	.	9	0.02	10	0.04
	PLAN BD	6	0.01	82	0.01	79	0.02
	PLAN C	0	.	18	0.00	19	0.04
II	PLAN A	0	.	9	0.05	10	0.05
	PLAN BD	6	0.01	82	0.01	79	0.02
	PLAN C	0	.	18	0.01	19	0.11
III	PLAN A	0	.	9	0.02	10	0.05
	PLAN BD	6	0.01	82	0.01	79	0.03
	PLAN C	0	.	18	0.01	19	0.02

Polio Protocol 01

TABLE 3

NASOPHARYNGEAL SECRETIONS (b) (4) IgA ANTIBODIES

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		2 Months	4 Months	5 Months
I	PLAN A	0/ . (0.0)	7/ 9 (77.8)	6/10 (60.0)
	PLAN BD	0/ . (0.0)	33/82 (40.2)	45/80 (56.3)
	PLAN C	0/ . (0.0)	9/18 (50.0)	15/19 (78.9)
II	PLAN A	0/ . (0.0)	7/ 9 (77.8)	6/10 (60.0)
	PLAN BD	0/ . (0.0)	33/82 (40.2)	49/80 (61.3)
	PLAN C	0/ . (0.0)	9/18 (50.0)	16/19 (84.2)
III	PLAN A	0/ . (0.0)	7/ 9 (77.8)	8/10 (80.0)
	PLAN BD	0/ . (0.0)	34/82 (41.5)	49/80 (61.3)
	PLAN C	0/ . (0.0)	10/18 (55.6)	17/19 (89.5)
ANY	PLAN A	0/ . (0.0)	7/10 (70.0)	8/10 (80.0)
	PLAN BD	0/ . (0.0)	39/85 (45.9)	53/85 (62.4)
	PLAN C	0/ . (0.0)	10/19 (52.6)	17/19 (89.5)

GEOMETRIC MEAN TITERS

		2 Months		4 Months		5 Months	
TYPE		N	GMT	N	GMT	N	GMT
I	PLAN A	0	.	9	8.63	10	7.46
	PLAN BD	6	0.00	82	3.13	80	5.81
	PLAN C	0	.	18	4.50	19	14.87
II	PLAN A	0	.	9	8.00	10	7.46
	PLAN BD	6	0.00	82	3.29	80	6.01
	PLAN C	0	.	18	4.16	19	16.59
III	PLAN A	0	.	9	9.33	10	13.93
	PLAN BD	6	0.00	82	3.32	80	6.39
	PLAN C	0	.	18	5.66	19	21.42

TABLE 4

Polio Protocol 01

STOOL SPECIMENS NEUTRALIZING ANTIBODIES

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		2 Months	4 Months	5 Months
I	PLAN A	0/ . (0.0)	1/10 (10.0)	1/ 9 (11.1)
	PLAN BD	0/ . (0.0)	0/75 (0.0)	4/78 (5.1)
	PLAN C	0/ . (0.0)	0/18 (0.0)	3/19 (15.8)
II	PLAN A	0/ . (0.0)	4/10 (40.0)	5/ 9 (55.6)
	PLAN BD	0/ . (0.0)	3/75 (4.0)	9/78 (11.5)
	PLAN C	0/ . (0.0)	0/18 (0.0)	8/19 (42.1)
III	PLAN A	0/ . (0.0)	1/10 (10.0)	3/ 9 (33.3)
	PLAN BD	0/ . (0.0)	2/75 (2.7)	6/78 (7.7)
	PLAN C	0/ . (0.0)	0/18 (0.0)	2/19 (10.5)
ANY	PLAN A	0/ . (0.0)	4/10 (40.0)	5/10 (50.0)
	PLAN BD	0/ . (0.0)	4/85 (4.7)	16/85 (18.8)
	PLAN C	0/ . (0.0)	0/18 (0.0)	8/19 (42.1)

GEOMETRIC MEAN TITERS

		2 Months		4 Months		5 Months	
TYPE		N	GMT	N	GMT	N	GMT
I	PLAN A	0	.	10	1.15	9	1.17
	PLAN BD	5	0.00	75	0.00	78	1.10
	PLAN C	0	.	18	0.00	19	1.44
II	PLAN A	0	.	10	3.73	9	5.04
	PLAN BD	5	0.00	75	1.08	78	1.22
	PLAN C	0	.	18	0.00	19	2.49
III	PLAN A	0	.	10	1.15	9	1.59
	PLAN BD	5	0.00	75	1.06	78	1.16
	PLAN C	0	.	18	0.00	19	1.29

GEOMETRIC MEAN TITERS IN INTERNATIONAL UNITS

		2 Months		4 Months		5 Months	
TYPE		N	GMT	N	GMT	N	GMT
I	PLAN A	0	.	10	0.01	9	0.01
	PLAN BD	5	0.00	75	0.00	78	0.01
	PLAN C	0	.	18	0.00	19	0.02
II	PLAN A	0	.	10	0.02	9	0.03
	PLAN BD	5	0.00	75	0.01	78	0.01
	PLAN C	0	.	18	0.00	19	0.01
III	PLAN A	0	.	10	0.01	9	0.02
	PLAN BD	5	0.00	75	0.01	78	0.01
	PLAN C	0	.	18	0.00	19	0.01

Polio Protocol 01

TABLE 5

STOOL SPECIMENS (b) (4) IgA ANTIBODIES

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		2 Months	4 Months	5 Months
I	PLAN A	0/ . (0.0)	2/10 (20.0)	3/ 9 (33.3)
	PLAN BD	0/ . (0.0)	5/74 (6.8)	4/77 (5.2)
	PLAN C	0/ . (0.0)	1/18 (5.6)	3/19 (15.8)
II	PLAN A	0/ . (0.0)	1/10 (10.0)	1/ 9 (11.1)
	PLAN BD	0/ . (0.0)	9/74 (12.2)	8/77 (10.4)
	PLAN C	0/ . (0.0)	3/18 (16.7)	7/19 (36.8)
III	PLAN A	0/ . (0.0)	3/10 (30.0)	3/ 9 (33.3)
	PLAN BD	0/ . (0.0)	8/74 (10.8)	15/77 (19.5)
	PLAN C	0/ . (0.0)	3/18 (16.7)	7/19 (36.8)
ANY	PLAN A	0/ . (0.0)	3/10 (30.0)	3/10 (30.0)
	PLAN BD	0/ . (0.0)	13/85 (15.3)	16/85 (18.8)
	PLAN C	0/ . (0.0)	4/19 (21.1)	7/19 (36.8)

GEOMETRIC MEAN TITERS

TYPE		2 Months N	2 Months GMT	4 Months N	4 Months GMT	5 Months N	5 Months GMT
I	PLAN A	0	.	10	1.52	9	2.00
	PLAN BD	6	0.00	74	1.17	77	1.12
	PLAN C	0	.	18	1.13	19	1.39
II	PLAN A	0	.	10	1.23	9	1.36
	PLAN BD	6	0.00	74	1.35	77	1.29
	PLAN C	0	.	18	1.47	19	2.23
III	PLAN A	0	.	10	1.87	9	2.33
	PLAN BD	6	0.00	74	1.30	77	1.55
	PLAN C	0	.	18	1.53	19	2.49

TABLE 6

Polio Protocol 01

SERUM NEUTRALIZING ANTIBODIES
AGE 6 - 13 WEEKS

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		2 Months		4 Months		5 Months	
I	Plan A	9/10	(90.0)	7/10	(70.0)	10/10	(100.0)
	Plan BD	58/70	(82.9)	43/69	(62.3)	66/68	(97.1)
	Plan C	13/15	(86.7)	12/15	(80.0)	14/15	(93.3)
II	Plan A	10/10	(100.0)	10/10	(100.0)	10/10	(100.0)
	Plan BD	64/70	(91.4)	66/69	(95.7)	68/68	(100.0)
	Plan C	14/15	(93.3)	15/15	(100.0)	15/15	(100.0)
III	Plan A	9/10	(90.0)	10/10	(100.0)	10/10	(100.0)
	Plan BD	53/70	(75.7)	55/69	(79.7)	66/68	(97.1)
	Plan C	11/15	(73.3)	12/15	(80.0)	14/15	(93.3)
ANY	Plan A	10/10	(100.0)	10/10	(100.0)	10/10	(100.0)
	Plan BD	70/70	(100.0)	69/70	(98.6)	68/70	(97.1)
	Plan C	14/15	(93.3)	15/15	(100.0)	15/15	(100.0)

GEOMETRIC MEAN TITERS

		2 Months		4 Months		5 Months	
TYPE		N	GMT	N	GMT	N	GMT
I	Plan A	10	25.81	10	28.35	10	259.92
	Plan BD	70	22.55	69	7.75	68	213.62
	Plan C	15	22.30	15	9.56	15	228.14
II	Plan A	10	60.63	10	519.84	10	3151.73
	Plan BD	70	48.79	69	31.44	68	666.63
	Plan C	15	94.82	15	40.00	15	2228.61
III	Plan A	10	27.66	10	52.78	10	735.17
	Plan BD	70	14.94	69	16.77	68	748.45
	Plan C	15	9.87	15	15.90	15	78.82

GEOMETRIC MEAN TITERS IN INTERNATIONAL UNITS

		2 Months		4 Months		5 Months	
TYPE		N	GMT	N	GMT	N	GMT
I	Plan A	10	0.30	10	0.33	10	3.03
	Plan BD	70	0.26	69	0.09	68	2.49
	Plan C	15	0.26	15	0.11	15	2.66
II	Plan A	10	0.34	10	2.94	10	17.81
	Plan BD	70	0.28	69	0.18	68	3.77
	Plan C	15	0.54	15	0.23	15	12.59
III	Plan A	10	0.28	10	0.53	10	7.35
	Plan BD	70	0.15	69	0.17	68	7.48
	Plan C	15	0.10	15	0.16	15	0.79

TABLE 7

Polio Protocol 01

SERUM NEUTRALIZING ANTIBODIES
AGE > 13 WEEKS

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		2 Months		4 Months		5 Months	
I	Plan BD	8/15	(53.3)	10/15	(66.7)	15/15	(100.0)
	Plan C	2/ 4	(50.0)	4/ 4	(100.0)	4/ 4	(100.0)
II	Plan BD	8/15	(53.3)	14/15	(93.3)	15/15	(100.0)
	Plan C	4/ 4	(100.0)	4/ 4	(100.0)	4/ 4	(100.0)
III	Plan BD	9/15	(60.0)	13/15	(86.7)	15/15	(100.0)
	Plan C	3/ 4	(75.0)	3/ 4	(75.0)	4/ 4	(100.0)
ANY	Plan BD	13/15	(86.7)	15/15	(100.0)	15/15	(100.0)
	Plan C	4/ 4	(100.0)	4/ 4	(100.0)	4/ 4	(100.0)

GEOMETRIC MEAN TITERS

		2 Months		4 Months		5 Months	
TYPE		N	GMT	N	GMT	N	GMT
I	Plan BD	15	4.72	15	8.86	15	531.99
	Plan C	4	10.64	4	33.64	4	452.55
II	Plan BD	15	5.42	15	41.27	15	2681.07
	Plan C	4	40.00	4	33.64	4	2152.69
III	Plan BD	15	7.96	15	22.30	15	1940.12
	Plan C	4	11.25	4	26.75	4	905.10

GEOMETRIC MEAN TITERS IN INTERNATIONAL UNITS

		2 Months		4 Months		5 Months	
TYPE		N	GMT	N	GMT	N	GMT
I	Plan BD	15	0.06	15	0.10	15	6.21
	Plan C	4	0.12	4	0.39	4	5.28
II	Plan BD	15	0.03	15	0.23	15	15.15
	Plan C	4	0.23	4	0.19	4	12.16
III	Plan BD	15	0.08	15	0.22	15	19.40
	Plan C	4	0.11	4	0.27	4	9.05

TABLE 8

Polio Protocol 01

NASOPHARYNGEAL SECRETIONS NEUTRALIZING ANTIBODIES
AGE 6 - 13 WEEKS

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		2 Months	4 Months	5 Months
I	Plan A	0/ . (0.0)	3/ 9 (33.3)	5/10 (50.0)
	Plan BD	0/ . (0.0)	1/67 (1.5)	23/65 (35.4)
	Plan C	0/ . (0.0)	0/67 (0.0)	8/15 (53.3)
II	Plan A	0/ . (0.0)	7/ 9 (77.8)	7/10 (70.0)
	Plan BD	0/ . (0.0)	1/67 (1.5)	34/65 (52.3)
	Plan C	0/ . (0.0)	2/14 (14.3)	14/15 (93.3)
III	Plan A	0/ . (0.0)	2/ 9 (22.2)	5/10 (50.0)
	Plan BD	0/ . (0.0)	2/67 (3.0)	29/65 (44.6)
	Plan C	0/ . (0.0)	1/14 (7.1)	6/15 (40.0)
ANY	Plan A	0/ . (0.0)	7/10 (70.0)	7/10 (70.0)
	Plan BD	0/ . (0.0)	3/70 (4.3)	41/70 (58.6)
	Plan C	0/ . (0.0)	3/15 (20.0)	14/15 (93.3)

GEOMETRIC MEAN TITERS

		2 Months		4 Months		5 Months	
TYPE		N	GMT	N	GMT	N	GMT
I	Plan A	0	.	9	1.71	10	3.03
	Plan BD	1	1.00	67	1.02	65	1.96
	Plan C	0	1.00	14	1.00	15	3.82
II	Plan A	0	.	9	8.00	10	9.19
	Plan BD	1	1.00	67	1.03	65	3.23
	Plan C	0	1.00	14	1.22	15	18.38
III	Plan A	0	.	9	2.00	10	5.28
	Plan BD	1	1.00	67	1.04	65	3.13
	Plan C	0	1.00	14	1.10	15	2.19

GEOMETRIC MEAN TITERS IN INTERNATIONAL UNITS

		2 Months		4 Months		5 Months	
TYPE		N	GMT	N	GMT	N	GMT
I	Plan A	0	.	9	0.02	10	0.04
	Plan BD	1	0.01	67	0.01	65	0.02
	Plan C	0	0.01	14	0.01	15	0.04
II	Plan A	0	.	9	0.05	10	0.05
	Plan BD	1	0.01	67	0.01	65	0.02
	Plan C	0	0.01	14	0.01	15	0.10
III	Plan A	0	.	9	0.02	10	0.05
	Plan BD	1	0.01	67	0.01	65	0.03
	Plan C	0	0.01	14	0.01	15	0.02

TABLE 9

Polio Protocol 01

NASOPHARYNGEAL SECRETIONS NEUTRALIZING ANTIBODIES
AGE > 13 WEEKS

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		2 Months	4 Months	5 Months
I	Plan BD	0/ . (0.0)	0/ . (0.0)	4/14 (28.6)
	Plan C	0/ . (0.0)	0/ . (0.0)	1/ 4 (25.0)
II	Plan BD	0/ . (0.0)	0/ . (0.0)	8/14 (57.1)
	Plan C	0/ . (0.0)	0/ . (0.0)	3/ 4 (75.0)
III	Plan BD	0/ . (0.0)	0/ . (0.0)	4/14 (28.6)
	Plan C	0/ . (0.0)	0/ . (0.0)	2/ 4 (50.0)
ANY	Plan BD	0/ . (0.0)	0/ . (0.0)	8/15 (53.3)
	Plan C	0/ . (0.0)	0/ . (0.0)	3/ 4 (75.0)

GEOMETRIC MEAN TITERS

TYPE		2 Months N	2 Months GMT	4 Months N	4 Months GMT	5 Months N	5 Months GMT
I	Plan BD	5	1.00	15	1.00	14	1.64
	Plan C	0	1.00	4	1.00	4	1.41
II	Plan BD	5	1.00	15	1.00	14	3.62
	Plan C	0	1.00	4	1.00	4	22.63
III	Plan BD	5	1.00	15	1.00	14	1.72
	Plan C	0	1.00	4	1.00	4	3.36

GEOMETRIC MEAN TITERS IN INTERNATIONAL UNITS

TYPE		2 Months N	2 Months GMT	4 Months N	4 Months GMT	5 Months N	5 Months GMT
I	Plan BD	5	0.01	15	0.01	14	0.02
	Plan C	0	0.01	4	0.01	4	0.02
II	Plan BD	5	0.01	15	0.01	14	0.02
	Plan C	0	0.01	4	0.01	4	0.13
III	Plan BD	5	0.01	15	0.01	14	0.02
	Plan C	0	0.01	4	0.01	4	0.03

TABLE 10

Polio Protocol 01

STOOL SPECIMENS NEUTRALIZING ANTIBODIES
AGE 6 - 13 WEEKS

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		2 Months	4 Months	5 Months
I	Plan A	0/ . (0.0)	1/10 (10.0)	1/ 9 (11.1)
	Plan BD	0/ . (0.0)	0/10 (0.0)	4/63 (6.3)
	Plan C	0/ . (0.0)	0/ . (0.0)	2/15 (13.3)
II	Plan A	0/ . (0.0)	4/10 (40.0)	5/ 9 (55.6)
	Plan BD	0/ . (0.0)	3/61 (4.9)	8/63 (12.7)
	Plan C	0/ . (0.0)	0/61 (0.0)	5/15 (33.3)
III	Plan A	0/ . (0.0)	1/10 (10.0)	3/ 9 (33.3)
	Plan BD	0/ . (0.0)	2/61 (3.3)	5/63 (7.9)
	Plan C	0/ . (0.0)	0/61 (0.0)	1/15 (6.7)
ANY	Plan A	0/ . (0.0)	4/10 (40.0)	5/10 (50.0)
	Plan BD	0/ . (0.0)	4/70 (5.7)	14/70 (20.0)
	Plan C	0/ . (0.0)	0/70 (0.0)	5/15 (33.3)

GEOMETRIC MEAN TITERS

		2 Months		4 Months		5 Months	
TYPE		N	GMT	N	GMT	N	GMT
I	Plan A	0	.	10	1.15	9	1.17
	Plan BD	1	1.00	61	1.00	63	1.13
	Plan C	0	1.00	14	1.00	15	1.45
II	Plan A	0	.	10	3.73	9	5.04
	Plan BD	1	1.00	61	1.10	63	1.25
	Plan C	0	1.00	14	1.00	15	2.41
III	Plan A	0	.	10	1.15	9	1.59
	Plan BD	1	1.00	61	1.07	63	1.17
	Plan C	0	1.00	14	1.00	15	1.26

GEOMETRIC MEAN TITERS IN INTERNATIONAL UNITS

		2 Months		4 Months		5 Months	
TYPE		N	GMT	N	GMT	N	GMT
I	Plan A	0	.	10	0.01	9	0.01
	Plan BD	1	0.01	61	0.01	63	0.01
	Plan C	0	0.01	14	0.01	15	0.02
II	Plan A	0	.	10	0.02	9	0.03
	Plan BD	1	0.01	61	0.01	63	0.01
	Plan C	0	0.01	14	0.01	15	0.01
III	Plan A	0	.	10	0.01	9	0.02
	Plan BD	1	0.01	61	0.01	63	0.01
	Plan C	0	0.01	14	0.01	15	0.01

TABLE 11

Polio Protocol 01

STOOL SPECIMENS NEUTRALIZING ANTIBODIES
AGE) 13 WEEKS

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		2 Months	4 Months	5 Months
I	Plan BD	0/ . (0.0)	0/ . (0.0)	0/ . (0.0)
	Plan C	0/ . (0.0)	0/ . (0.0)	1/ 4 (25.0)
II	Plan BD	0/ . (0.0)	0/ . (0.0)	1/15 (6.7)
	Plan C	0/ . (0.0)	0/ . (0.0)	3/ 4 (75.0)
III	Plan BD	0/ . (0.0)	0/ . (0.0)	1/15 (6.7)
	Plan C	0/ . (0.0)	0/ . (0.0)	1/ 4 (25.0)
ANY	Plan BD	0/ . (0.0)	0/ . (0.0)	2/15 (13.3)
	Plan C	0/ . (0.0)	0/ . (0.0)	3/ 4 (75.0)

GEOMETRIC MEAN TITERS

TYPE		2 Months N	2 Months GMT	4 Months N	4 Months GMT	5 Months N	5 Months GMT
I	Plan BD	4	1.00	14	1.00	15	1.00
	Plan C	0	1.00	4	1.00	4	1.41
II	Plan BD	4	1.00	14	1.00	15	1.10
	Plan C	0	1.00	4	1.00	4	2.83
III	Plan BD	4	1.00	14	1.00	15	1.15
	Plan C	0	1.00	4	1.00	4	1.41

GEOMETRIC MEAN TITERS IN INTERNATIONAL UNITS

TYPE		2 Months N	2 Months GMT	4 Months N	4 Months GMT	5 Months N	5 Months GMT
I	Plan BD	4	0.01	14	0.01	15	0.01
	Plan C	0	0.01	4	0.01	4	0.02
II	Plan BD	4	0.01	14	0.01	15	0.01
	Plan C	0	0.01	4	0.01	4	0.02
III	Plan BD	4	0.01	14	0.01	15	0.01
	Plan C	0	0.01	4	0.01	4	0.01

TABLE 12

Polio Protocol v1

NASOPHARYNGEAL SECRETIONS (b)(4) IgA ANTIBODIES
AGE 6 - 13 WEEKS

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		2 Months	4 Months	5 Months
I	Plan A	0/ . (0.0)	7/ 9 (77.8)	6/10 (60.0)
	Plan BD	0/ . (0.0)	30/67 (44.8)	38/66 (57.6)
	Plan C	0/ . (0.0)	8/14 (57.1)	12/15 (80.0)
II	Plan A	0/ . (0.0)	7/ 9 (77.8)	6/10 (60.0)
	Plan BD	0/ . (0.0)	31/67 (46.3)	41/66 (62.1)
	Plan C	0/ . (0.0)	8/14 (57.1)	12/15 (80.0)
III	Plan A	0/ . (0.0)	7/ 9 (77.8)	8/10 (80.0)
	Plan BD	0/ . (0.0)	31/67 (46.3)	40/66 (60.6)
	Plan C	0/ . (0.0)	9/14 (64.3)	13/15 (86.7)
ANY	Plan A	0/ . (0.0)	7/10 (70.0)	8/10 (80.0)
	Plan BD	0/ . (0.0)	36/70 (51.4)	44/70 (62.9)
	Plan C	0/ . (0.0)	9/15 (60.0)	13/15 (86.7)

GEOMETRIC MEAN TITERS

TYPE		2 Months N	2 Months GMT	4 Months N	4 Months GMT	5 Months N	5 Months GMT
I	Plan A	0	.	9	0.00	10	7.46
	Plan BD	1	1.00	67	3.46	66	6.09
	Plan C	0	1.00	14	0.00	15	14.59
II	Plan A	0	.	9	8.00	10	7.46
	Plan BD	1	1.00	67	3.96	66	6.48
	Plan C	0	1.00	14	5.38	15	13.30
III	Plan A	0	.	9	9.33	10	13.93
	Plan BD	1	1.00	67	3.88	66	6.69
	Plan C	0	1.00	14	7.61	15	19.25

TABLE 13

Polio Protocol 01

NASOPHARYNGEAL SECRETIONS (b)(4) IgA ANTIBODIES
AGE > 13 WEEKS

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		2 Months	4 Months	5 Months
I	Plan BD	0/ . (0.0)	3/15 (20.0)	7/14 (50.0)
	Plan C	0/ . (0.0)	1/ 4 (25.0)	3/ 4 (75.0)
II	Plan BD	0/ . (0.0)	2/15 (13.3)	8/14 (57.1)
	Plan C	0/ . (0.0)	1/ 4 (25.0)	4/ 4 (100.0)
III	Plan BD	0/ . (0.0)	3/15 (20.0)	9/14 (64.3)
	Plan C	0/ . (0.0)	1/ 4 (25.0)	4/ 4 (100.0)
ANY	Plan BD	0/ . (0.0)	3/15 (20.0)	9/15 (60.0)
	Plan C	0/ . (0.0)	1/ 4 (25.0)	4/ 4 (100.0)

GEOMETRIC MEAN TITERS

		2 Months		4 Months		5 Months	
TYPE		N	GMT	N	GMT	N	GMT
I	Plan BD	5	1.00	15	2.00	14	4.64
	Plan C	0	1.00	4	0.00	4	16.00
II	Plan BD	5	1.00	15	1.45	14	4.20
	Plan C	0	1.00	4	1.68	4	38.05
III	Plan BD	5	1.00	15	1.66	14	5.12
	Plan C	0	1.00	4	2.00	4	32.00

TABLE 14

Polio Protocol 01

STOOL SPECIMENS (b) (4) IgA ANTIBODIES
AGE 6 - 13 WEEKS

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		2 Months	4 Months	5 Months
I	Plan A	0/ . (0.0)	2/10 (20.0)	3/ 9 (33.3)
	Plan BD	0/ . (0.0)	4/60 (6.7)	4/63 (6.3)
	Plan C	0/ . (0.0)	1/14 (7.1)	2/15 (13.3)
II	Plan A	0/ . (0.0)	1/10 (10.0)	1/ 9 (11.1)
	Plan BD	0/ . (0.0)	6/60 (10.0)	7/63 (11.1)
	Plan C	0/ . (0.0)	3/14 (21.4)	5/15 (33.3)
III	Plan A	0/ . (0.0)	3/10 (30.0)	3/ 9 (33.3)
	Plan BD	0/ . (0.0)	5/60 (8.3)	11/63 (17.5)
	Plan C	0/ . (0.0)	3/14 (21.4)	5/15 (33.3)
ANY	Plan A	0/ . (0.0)	3/10 (30.0)	3/10 (30.0)
	Plan BD	0/ . (0.0)	9/70 (12.9)	12/70 (17.1)
	Plan C	0/ . (0.0)	4/15 (26.7)	5/15 (33.3)

GEOMETRIC MEAN TITERS

TYPE		2 Months		4 Months		5 Months	
		N	GMT	N	GMT	N	GMT
I	Plan A	0	.	10	0.00	9	2.00
	Plan BD	2	1.00	60	1.18	63	1.15
	Plan C	0	1.00	14	0.00	15	1.32
II	Plan A	0	.	10	1.23	9	1.36
	Plan BD	2	1.00	60	1.27	63	1.30
	Plan C	0	1.00	14	1.64	15	2.09
III	Plan A	0	.	10	1.87	9	2.33
	Plan BD	2	1.00	60	1.22	63	1.50
	Plan C	0	1.00	14	1.72	15	2.30

TABLE 15

Polio Protocol 01

STOOL SPECIMENS (b) (4) IgA ANTIBODIES
AGE > 13 WEEKS

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		2 Months	4 Months	5 Months
I	Plan BD	0/ . (0.0)	1/14 (7.1)	0/ . (0.0)
	Plan C	0/ . (0.0)	0/14 (0.0)	1/ 4 (25.0)
II	Plan BD	0/ . (0.0)	3/14 (21.4)	1/14 (7.1)
	Plan C	0/ . (0.0)	0/14 (0.0)	2/ 4 (50.0)
III	Plan BD	0/ . (0.0)	3/14 (21.4)	4/14 (28.6)
	Plan C	0/ . (0.0)	0/14 (0.0)	2/ 4 (50.0)
ANY	Plan BD	0/ . (0.0)	4/15 (26.7)	4/15 (26.7)
	Plan C	0/ . (0.0)	0/15 (0.0)	2/ 4 (50.0)

GEOMETRIC MEAN TITERS

		2 Months		4 Months		5 Months	
TYPE		N	GMT	N	GMT	N	GMT
I	Plan BD	4	1.00	14	1.16	14	1.00
	Plan C	0	1.00	4	0.00	4	1.68
II	Plan BD	4	1.00	14	1.72	14	1.22
	Plan C	0	1.00	4	1.00	4	2.83
III	Plan BD	4	1.00	14	1.72	14	1.81
	Plan C	0	1.00	4	1.00	4	3.36

TABLE 16

Polio Protocol 01

SERUM NEUTRALIZING ANTIBODIES
PLAN BD

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		2 Months		4 Months		5 Months	
I	PREME	12/19	(63.2)	8/19	(42.1)	19/19	(100.0)
	TERM	54/66	(81.8)	45/65	(69.2)	62/64	(96.9)
II	PREME	16/19	(84.2)	16/19	(84.2)	19/19	(100.0)
	TERM	56/66	(84.8)	64/65	(98.5)	64/64	(100.0)
III	PREME	15/19	(78.9)	14/19	(73.7)	19/19	(100.0)
	TERM	47/66	(71.2)	54/65	(83.1)	62/64	(96.9)
ANY	PREME	18/19	(94.7)	19/19	(100.0)	19/19	(100.0)
	TERM	65/66	(98.5)	65/66	(98.5)	64/66	(97.0)

GEOMETRIC MEAN TITERS

TYPE		2 Months N	2 Months GMT	4 Months N	4 Months GMT	5 Months N	5 Months GMT
I	PREME	19	6.88	19	4.39	19	308.54
	TERM	66	22.25	65	9.44	64	237.21
II	PREME	19	20.02	19	24.92	19	1147.31
	TERM	66	38.27	65	35.83	64	786.23
III	PREME	19	14.78	19	15.15	19	888.74
	TERM	66	12.99	65	18.45	64	889.13

GEOMETRIC MEAN TITERS IN INTERNATIONAL UNITS

TYPE		2 Months N	2 Months GMT	4 Months N	4 Months GMT	5 Months N	5 Months GMT
I	PREME	19	0.08	19	0.05	19	3.60
	TERM	66	0.26	65	0.11	64	2.77
II	PREME	19	0.11	19	0.14	19	6.48
	TERM	66	0.22	65	0.20	64	4.44
III	PREME	19	0.15	19	0.15	19	8.89
	TERM	66	0.13	65	0.18	64	8.89

TABLE 17

Polio Protocol 01

SERUM NEUTRALIZING ANTIBODIES
PATIENTS HAD CONTACT WITH OPV

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		2 Months		4 Months		5 Months	
I	Plan A	2/ 2	(100.0)	2/ 2	(100.0)	2/ 2	(100.0)
	Plan BD	14/19	(73.7)	10/18	(55.6)	18/18	(100.0)
	Plan C	2/ 3	(66.7)	3/ 3	(100.0)	3/ 3	(100.0)
II	Plan A	2/ 2	(100.0)	2/ 2	(100.0)	2/ 2	(100.0)
	Plan BD	16/19	(84.2)	17/18	(94.4)	18/18	(100.0)
	Plan C	3/ 3	(100.0)	3/ 3	(100.0)	3/ 3	(100.0)
III	Plan A	1/ 2	(50.0)	2/ 2	(100.0)	2/ 2	(100.0)
	Plan BD	12/19	(63.2)	13/18	(72.2)	18/18	(100.0)
	Plan C	2/ 3	(66.7)	2/ 3	(66.7)	3/ 3	(100.0)
ANY	Plan A	2/ 2	(100.0)	2/ 2	(100.0)	2/ 2	(100.0)
	Plan BD	19/19	(100.0)	18/19	(94.7)	18/19	(94.7)
	Plan C	3/ 3	(100.0)	3/ 3	(100.0)	3/ 3	(100.0)

GEOMETRIC MEAN TITERS

TYPE		2 Months N	2 Months GMT	4 Months N	4 Months GMT	5 Months N	5 Months GMT
I	Plan A	2	28.28	2	80.00	2	640.00
	Plan BD	19	13.09	18	4.89	18	570.18
	Plan C	3	11.70	3	20.00	3	806.35
II	Plan A	2	40.00	2	452.55	2	14481.55
	Plan BD	19	22.34	18	32.59	18	1810.19
	Plan C	3	50.40	3	25.20	3	1612.70
III	Plan A	2	6.32	2	160.00	2	2560.00
	Plan BD	19	8.56	18	13.29	18	1185.12
	Plan C	3	5.85	3	7.37	3	507.97

GEOMETRIC MEAN TITERS IN INTERNATIONAL UNITS

TYPE		2 Months N	2 Months GMT	4 Months N	4 Months GMT	5 Months N	5 Months GMT
I	Plan A	2	0.33	2	0.93	2	7.47
	Plan BD	19	0.15	18	0.06	18	6.65
	Plan C	3	0.14	3	0.23	3	9.41
II	Plan A	2	0.23	2	2.56	2	81.82
	Plan BD	19	0.13	18	0.18	18	10.23
	Plan C	3	0.28	3	0.14	3	9.11
III	Plan A	2	0.06	2	1.60	2	25.60
	Plan BD	19	0.09	18	0.13	18	11.85
	Plan C	3	0.06	3	0.07	3	5.08

TABLE 18

SERUM NEUTRALIZING ANTIBODIES
PATIENTS DID NOT HAVE CONTACT WITH OPV

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		2 Months	4 Months	5 Months
I	Plan A	7/ 8 (87.5)	5/ 8 (62.5)	8/ 8 (100.0)
	Plan BD	52/66 (78.8)	43/66 (65.2)	63/65 (96.9)
	Plan C	13/16 (81.3)	13/16 (81.3)	15/16 (93.8)
II	Plan A	8/ 8 (100.0)	8/ 8 (100.0)	8/ 8 (100.0)
	Plan BD	56/66 (84.8)	63/66 (95.5)	65/65 (100.0)
	Plan C	15/16 (93.8)	16/16 (100.0)	16/16 (100.0)
III	Plan A	8/ 8 (100.0)	8/ 8 (100.0)	8/ 8 (100.0)
	Plan BD	50/66 (75.8)	55/66 (83.3)	63/65 (96.9)
	Plan C	12/16 (75.0)	13/16 (81.3)	15/16 (93.8)
ANY	Plan A	8/ 8 (100.0)	8/ 8 (100.0)	8/ 8 (100.0)
	Plan BD	64/66 (97.0)	66/66 (100.0)	65/66 (98.5)
	Plan C	15/16 (93.8)	16/16 (100.0)	16/16 (100.0)

GEOMETRIC MEAN TITERS

TYPE		2 Months N	2 Months GMT	4 Months N	4 Months GMT	5 Months N	5 Months GMT
I	Plan A	8	25.22	8	21.87	8	207.49
	Plan BD	66	18.48	66	9.06	65	200.92
	Plan C	16	20.92	16	11.40	16	213.68
II	Plan A	8	67.27	8	538.17	8	2152.69
	Plan BD	66	37.08	66	33.12	65	697.00
	Plan C	16	86.03	16	41.77	16	2347.33
III	Plan A	8	40.00	8	40.00	8	538.17
	Plan BD	66	15.20	66	19.07	65	821.01
	Plan C	16	11.25	16	20.92	16	102.31

GEOMETRIC MEAN TITERS IN INTERNATIONAL UNITS

TYPE		2 Months N	2 Months GMT	4 Months N	4 Months GMT	5 Months N	5 Months GMT
I	Plan A	8	0.29	8	0.26	8	2.42
	Plan BD	66	0.22	66	0.11	65	2.34
	Plan C	16	0.24	16	0.13	16	2.49
II	Plan A	8	0.38	8	3.04	8	12.16
	Plan BD	66	0.21	66	0.19	65	3.94
	Plan C	16	0.49	16	0.24	16	13.26
III	Plan A	8	0.40	8	0.40	8	5.38
	Plan BD	66	0.15	66	0.19	65	8.21
	Plan C	16	0.11	16	0.21	16	1.02

TABLE 19

Polio Protocol 01

NASOPHARYNGEAL SECRETIONS NEUTRALIZING ANTIBODIES
PATIENTS HAD CONTACT WITH OPV

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		2 Months	4 Months	5 Months
I	Plan A	0/ . (0.0)	1/ 2 (50.0)	1/ 2 (50.0)
	Plan BD	0/ . (0.0)	0/ 2 (0.0)	9/18 (50.0)
	Plan C	0/ . (0.0)	0/ . (0.0)	2/ 3 (66.7)
II	Plan A	0/ . (0.0)	2/ 2 (100.0)	1/ 2 (50.0)
	Plan BD	0/ . (0.0)	0/ 2 (0.0)	14/18 (77.8)
	Plan C	0/ . (0.0)	0/ . (0.0)	3/ 3 (100.0)
III	Plan A	0/ . (0.0)	1/ 2 (50.0)	1/ 2 (50.0)
	Plan BD	0/ . (0.0)	1/19 (5.3)	11/18 (61.1)
	Plan C	0/ . (0.0)	0/19 (0.0)	2/ 3 (66.7)
ANY	Plan A	0/ . (0.0)	2/ 2 (100.0)	1/ 2 (50.0)
	Plan BD	0/ . (0.0)	1/19 (5.3)	16/19 (84.2)
	Plan C	0/ . (0.0)	0/19 (0.0)	3/ 3 (100.0)

GEOMETRIC MEAN TITERS

TYPE		2 Months N	2 Months GMT	4 Months N	4 Months GMT	5 Months N	5 Months GMT
I	Plan A	0	.	2	2.00	2	8.00
	Plan BD	0	.	19	1.00	18	3.05
	Plan C	0	.	3	1.00	3	4.00
II	Plan A	0	.	2	11.31	2	11.31
	Plan BD	0	.	19	1.00	18	6.86
	Plan C	0	.	3	1.00	3	20.16
III	Plan A	0	.	2	11.31	2	11.31
	Plan BD	0	.	19	1.08	18	5.88
	Plan C	0	.	3	1.00	3	6.35

GEOMETRIC MEAN TITERS IN INTERNATIONAL UNITS

TYPE		2 Months N	2 Months GMT	4 Months N	4 Months GMT	5 Months N	5 Months GMT
I	Plan A	0	.	2	0.02	2	0.09
	Plan BD	0	.	19	0.01	18	0.04
	Plan C	0	.	3	0.01	3	0.05
II	Plan A	0	.	2	0.06	2	0.06
	Plan BD	0	.	19	0.01	18	0.04
	Plan C	0	.	3	0.01	3	0.11
III	Plan A	0	.	2	0.11	2	0.11
	Plan BD	0	.	19	0.01	18	0.06
	Plan C	0	.	3	0.01	3	0.06

TABLE 20

Polio Protocol 01

NASOPHARYNGEAL SECRETIONS NEUTRALIZING ANTIBODIES
PATIENTS DID NOT HAVE CONTACT WITH OPV

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		2 Months	4 Months	5 Months
I	Plan A	0/ . (0.0)	2/ 7 (28.6)	4/ 8 (50.0)
	Plan BD	0/ . (0.0)	1/63 (1.6)	18/61 (29.5)
	Plan C	0/ . (0.0)	0/63 (0.0)	7/16 (43.8)
II	Plan A	0/ . (0.0)	5/ 7 (71.4)	6/ 8 (75.0)
	Plan BD	0/ . (0.0)	1/63 (1.6)	28/61 (45.9)
	Plan C	0/ . (0.0)	2/15 (13.3)	14/16 (87.5)
III	Plan A	0/ . (0.0)	1/ 7 (14.3)	4/ 8 (50.0)
	Plan BD	0/ . (0.0)	1/63 (1.6)	22/61 (36.1)
	Plan C	0/ . (0.0)	1/15 (6.7)	6/16 (37.5)
ANY	Plan A	0/ . (0.0)	5/ 8 (62.5)	6/ 8 (75.0)
	Plan BD	0/ . (0.0)	2/66 (3.0)	33/66 (50.0)
	Plan C	0/ . (0.0)	3/16 (18.8)	14/16 (87.5)

GEOMETRIC MEAN TITERS

TYPE		2 Months		4 Months		5 Months	
		N	GMT	N	GMT	N	GMT
I	Plan A	0	.	7	1.64	8	2.38
	Plan BD	6	1.00	63	1.02	61	1.65
	Plan C	0	1.00	15	1.00	16	2.95
II	Plan A	0	.	7	7.25	8	8.72
	Plan BD	6	1.00	63	1.03	61	2.66
	Plan C	0	1.00	15	1.20	16	19.03
III	Plan A	0	.	7	1.22	8	4.36
	Plan BD	6	1.00	63	1.02	61	2.27
	Plan C	0	1.00	15	1.10	16	2.00

GEOMETRIC MEAN TITERS IN INTERNATIONAL UNITS

TYPE		2 Months		4 Months		5 Months	
		N	GMT	N	GMT	N	GMT
I	Plan A	0	.	7	0.02	8	0.03
	Plan BD	6	0.01	63	0.01	61	0.02
	Plan C	0	0.01	15	0.01	16	0.03
II	Plan A	0	.	7	0.04	8	0.05
	Plan BD	6	0.01	63	0.01	61	0.02
	Plan C	0	0.01	15	0.01	16	0.11
III	Plan A	0	.	7	0.01	8	0.04
	Plan BD	6	0.01	63	0.01	61	0.02
	Plan C	0	0.01	15	0.01	16	0.02

TABLE 21

Polio Protocol 01

NASOPHARYNGEAL SECRETIONS (b)(4) IgA ANTIBODIES
PATIENTS HAD CONTACT WITH OPV

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		2 Months	4 Months	5 Months
I	Plan A	0/ . (0.0)	1/ 2 (50.0)	1/ 2 (50.0)
	Plan BD	0/ . (0.0)	9/19 (47.4)	14/18 (77.8)
	Plan C	0/ . (0.0)	1/ 3 (33.3)	2/ 3 (66.7)
II	Plan A	0/ . (0.0)	1/ 2 (50.0)	1/ 2 (50.0)
	Plan BD	0/ . (0.0)	9/19 (47.4)	15/18 (83.3)
	Plan C	0/ . (0.0)	1/ 3 (33.3)	3/ 3 (100.0)
III	Plan A	0/ . (0.0)	1/ 2 (50.0)	2/ 2 (100.0)
	Plan BD	0/ . (0.0)	9/19 (47.4)	15/18 (83.3)
	Plan C	0/ . (0.0)	1/ 3 (33.3)	3/ 3 (100.0)
ANY	Plan A	0/ . (0.0)	1/ 2 (50.0)	2/ 2 (100.0)
	Plan BD	0/ . (0.0)	9/19 (47.4)	15/19 (78.9)
	Plan C	0/ . (0.0)	1/ 3 (33.3)	3/ 3 (100.0)

GEOMETRIC MEAN TITERS

TYPE		2 Months N	2 Months GMT	4 Months N	4 Months GMT	5 Months N	5 Months GMT
I	Plan A	0	.	2	0.00	2	4.00
	Plan BD	0	.	19	0.00	18	13.72
	Plan C	0	.	3	0.00	3	20.16
II	Plan A	0	.	2	5.66	2	4.00
	Plan BD	0	.	19	4.80	18	14.81
	Plan C	0	.	3	2.52	3	25.40
III	Plan A	0	.	2	4.00	2	16.00
	Plan BD	0	.	19	4.63	18	16.00
	Plan C	0	.	3	2.52	3	40.32

Polio Protocol 01

TABLE 22

NASOPHARYNGEAL SECRETIONS (b)(4) IgA ANTIBODIES
PATIENTS DID NOT HAVE CONTACT WITH OPV

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		2 Months	4 Months	5 Months
I	Plan A	0/ . (0.0)	6/ 7 (85.7)	5/ 8 (62.5)
	Plan BD	0/ . (0.0)	24/63 (38.1)	31/62 (50.0)
	Plan C	0/ . (0.0)	8/15 (53.3)	13/16 (81.3)
II	Plan A	0/ . (0.0)	6/ 7 (85.7)	5/ 8 (62.5)
	Plan BD	0/ . (0.0)	24/63 (38.1)	34/62 (54.8)
	Plan C	0/ . (0.0)	8/15 (53.3)	13/16 (81.3)
III	Plan A	0/ . (0.0)	6/ 7 (85.7)	6/ 8 (75.0)
	Plan BD	0/ . (0.0)	25/63 (39.7)	34/62 (54.8)
	Plan C	0/ . (0.0)	9/15 (60.0)	14/16 (87.5)
ANY	Plan A	0/ . (0.0)	6/ 8 (75.0)	6/ 8 (75.0)
	Plan BD	0/ . (0.0)	30/66 (45.5)	38/66 (57.6)
	Plan C	0/ . (0.0)	9/16 (56.3)	14/16 (87.5)

GEOMETRIC MEAN TITERS

TYPE		2 Months N	2 Months GMT	4 Months N	4 Months GMT	5 Months N	5 Months GMT
I	Plan A	0	.	7	0.00	8	8.72
	Plan BD	6	1.00	63	2.75	62	4.52
	Plan C	0	1.00	15	0.00	16	14.05
II	Plan A	0	.	7	8.83	8	8.72
	Plan BD	6	1.00	63	2.94	62	4.63
	Plan C	0	1.00	15	4.59	16	15.32
III	Plan A	0	.	7	11.89	8	13.45
	Plan BD	6	1.00	63	3.00	62	4.89
	Plan C	0	1.00	15	6.65	16	19.03

TABLE 23

Polio Protocol 01

STOOL SPECIMENS NEUTRALIZING ANTIBODIES
PATIENTS HAD CONTACT WITH OPV

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		2 Months	4 Months	5 Months
I	Plan A	0/ . (0.0)	1/ 2 (50.0)	0/ . (0.0)
	Plan BD	0/ . (0.0)	0/ 2 (0.0)	2/17 (11.8)
	Plan C	0/ . (0.0)	0/ . (0.0)	1/ 3 (33.3)
II	Plan A	0/ . (0.0)	1/ 2 (50.0)	1/ 2 (50.0)
	Plan BD	0/ . (0.0)	0/ 2 (0.0)	2/17 (11.8)
	Plan C	0/ . (0.0)	0/ . (0.0)	2/ 3 (66.7)
III	Plan A	0/ . (0.0)	1/ 2 (50.0)	0/ . (0.0)
	Plan BD	0/ . (0.0)	1/18 (5.6)	2/17 (11.8)
	Plan C	0/ . (0.0)	0/18 (0.0)	1/ 3 (33.3)
ANY	Plan A	0/ . (0.0)	1/ 2 (50.0)	1/ 2 (50.0)
	Plan BD	0/ . (0.0)	1/19 (5.3)	5/19 (26.3)
	Plan C	0/ . (0.0)	0/19 (0.0)	2/ 3 (66.7)

GEOMETRIC MEAN TITERS

		2 Months		4 Months		5 Months	
TYPE		N	GMT	N	GMT	N	GMT
I	Plan A	0	.	2	2.00	2	1.00
	Plan BD	0	.	18	1.00	17	1.33
	Plan C	0	.	3	1.00	3	1.59
II	Plan A	0	.	2	5.66	2	2.83
	Plan BD	0	.	18	1.00	17	1.18
	Plan C	0	.	3	1.00	3	2.52
III	Plan A	0	.	2	2.00	2	1.00
	Plan BD	0	.	18	1.08	17	1.18
	Plan C	0	.	3	1.00	3	1.59

GEOMETRIC MEAN TITERS IN INTERNATIONAL UNITS

		2 Months		4 Months		5 Months	
TYPE		N	GMT	N	GMT	N	GMT
I	Plan A	0	.	2	0.02	2	0.01
	Plan BD	0	.	18	0.01	17	0.02
	Plan C	0	.	3	0.01	3	0.02
II	Plan A	0	.	2	0.03	2	0.02
	Plan BD	0	.	18	0.01	17	0.01
	Plan C	0	.	3	0.01	3	0.01
III	Plan A	0	.	2	0.02	2	0.01
	Plan BD	0	.	18	0.01	17	0.01
	Plan C	0	.	3	0.01	3	0.02

TABLE 24

Polio Protocol 01

STOOL SPECIMENS NEUTRALIZING ANTIBODIES
PATIENTS DID NOT HAVE CONTACT WITH OPV

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		2 Months	4 Months	5 Months
I	Plan A	0/ . (0.0)	0/ . (0.0)	1/ 7 (14.3)
	Plan BD	0/ . (0.0)	0/ . (0.0)	2/61 (3.3)
	Plan C	0/ . (0.0)	0/ . (0.0)	2/16 (12.5)
II	Plan A	0/ . (0.0)	3/ 8 (37.5)	4/ 7 (57.1)
	Plan BD	0/ . (0.0)	3/57 (5.3)	7/61 (11.5)
	Plan C	0/ . (0.0)	0/57 (0.0)	6/16 (37.5)
III	Plan A	0/ . (0.0)	0/ . (0.0)	3/ 7 (42.9)
	Plan BD	0/ . (0.0)	1/57 (1.8)	4/61 (6.6)
	Plan C	0/ . (0.0)	0/57 (0.0)	1/16 (6.3)
ANY	Plan A	0/ . (0.0)	3/ 8 (37.5)	4/ 8 (50.0)
	Plan BD	0/ . (0.0)	3/66 (4.5)	11/66 (16.7)
	Plan C	0/ . (0.0)	0/66 (0.0)	6/16 (37.5)

GEOMETRIC MEAN TITERS

TYPE		2 Months N	2 Months GMT	4 Months N	4 Months GMT	5 Months N	5 Months GMT
I	Plan A	0	.	8	1.00	7	1.22
	Plan BD	5	1.00	57	1.00	61	1.05
	Plan C	0	1.00	15	1.00	16	1.41
II	Plan A	0	.	8	3.36	7	5.94
	Plan BD	5	1.00	57	1.11	61	1.23
	Plan C	0	1.00	15	1.00	16	2.48
III	Plan A	0	.	8	1.00	7	1.81
	Plan BD	5	1.00	57	1.05	61	1.16
	Plan C	0	1.00	15	1.00	16	1.24

GEOMETRIC MEAN TITERS IN INTERNATIONAL UNITS

TYPE		2 Months N	2 Months GMT	4 Months N	4 Months GMT	5 Months N	5 Months GMT
I	Plan A	0	.	8	0.01	7	0.01
	Plan BD	5	0.01	57	0.01	61	0.01
	Plan C	0	0.01	15	0.01	16	0.02
II	Plan A	0	.	8	0.02	7	0.03
	Plan BD	5	0.01	57	0.01	61	0.01
	Plan C	0	0.01	15	0.01	16	0.01
III	Plan A	0	.	8	0.01	7	0.02
	Plan BD	5	0.01	57	0.01	61	0.01
	Plan C	0	0.01	15	0.01	16	0.01

TABLE 25

Polio Protocol 01

STOOL SPECIMENS (b) (4) IgA ANTIBODIES
PATIENTS HAD CONTACT WITH OPV

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		2 Months	4 Months	5 Months
I	Plan A	0/ . (0.0)	1/ 2 (50.0)	0/ . (0.0)
	Plan BD	0/ . (0.0)	1/18 (5.6)	0/ . (0.0)
	Plan C	0/ . (0.0)	0/18 (0.0)	1/ 3 (33.3)
II	Plan A	0/ . (0.0)	0/ . (0.0)	0/ . (0.0)
	Plan BD	0/ . (0.0)	2/18 (11.1)	1/17 (5.9)
	Plan C	0/ . (0.0)	0/18 (0.0)	1/ 3 (33.3)
III	Plan A	0/ . (0.0)	1/ 2 (50.0)	0/ . (0.0)
	Plan BD	0/ . (0.0)	0/ 2 (0.0)	1/17 (5.9)
	Plan C	0/ . (0.0)	0/ . (0.0)	1/ 3 (33.3)
ANY	Plan A	0/ . (0.0)	1/ 2 (50.0)	0/ . (0.0)
	Plan BD	0/ . (0.0)	3/19 (15.8)	1/19 (5.3)
	Plan C	0/ . (0.0)	0/19 (0.0)	1/ 3 (33.3)

GEOMETRIC MEAN TITERS

TYPE		2 Months		4 Months		5 Months	
		N	GMT	N	GMT	N	GMT
I	Plan A	0	.	2	0.00	2	1.00
	Plan BD	0	.	18	0.00	17	1.00
	Plan C	0	.	3	0.00	3	2.00
II	Plan A	0	.	2	1.00	2	1.00
	Plan BD	0	.	18	1.31	17	1.13
	Plan C	0	.	3	1.00	3	2.00
III	Plan A	0	.	2	2.83	2	1.00
	Plan BD	0	.	18	1.00	17	1.13
	Plan C	0	.	3	1.00	3	2.52

TABLE 26

Polio Protocol 01

STOOL SPECIMENS (b)(4) IgA ANTIBODIES
PATIENTS DID NOT HAVE CONTACT WITH OPV

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		2 Months	4 Months	5 Months
I	Plan A	0/ . (0.0)	1/ 8 (12.5)	3/ 7 (42.9)
	Plan BD	0/ . (0.0)	4/56 (7.1)	4/60 (6.7)
	Plan C	0/ . (0.0)	1/15 (6.7)	2/16 (12.5)
II	Plan A	0/ . (0.0)	1/ 8 (12.5)	1/ 7 (14.3)
	Plan BD	0/ . (0.0)	7/56 (12.5)	7/60 (11.7)
	Plan C	0/ . (0.0)	3/15 (20.0)	6/16 (37.5)
III	Plan A	0/ . (0.0)	2/ 8 (25.0)	3/ 7 (42.9)
	Plan BD	0/ . (0.0)	8/56 (14.3)	14/60 (23.3)
	Plan C	0/ . (0.0)	3/15 (20.0)	6/16 (37.5)
ANY	Plan A	0/ . (0.0)	2/ 8 (25.0)	3/ 8 (37.5)
	Plan BD	0/ . (0.0)	10/66 (15.2)	15/66 (22.7)
	Plan C	0/ . (0.0)	4/16 (25.0)	6/16 (37.5)

GEOMETRIC MEAN TITERS

		2 Months		4 Months		5 Months	
TYPE		N	GMT	N	GMT	N	GMT
I	Plan A	0	.	8	0.00	7	2.44
	Plan BD	6	1.00	56	1.19	60	1.16
	Plan C	0	1.00	15	0.00	16	1.30
II	Plan A	0	.	8	1.30	7	1.49
	Plan BD	6	1.00	56	1.36	60	1.33
	Plan C	0	1.00	15	1.59	16	2.28
III	Plan A	0	.	8	1.68	7	2.97
	Plan BD	6	1.00	56	1.41	60	1.70
	Plan C	0	1.00	15	1.66	16	2.48

TABLE 27

Polio Protocol 01

SERUM NEUTRALIZING ANTIBODIES

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		Visit 1		Visit 2		Visit 3	
I	PLAN F1	14/15	(93.3)	14/15	(93.3)	15/15	(100.0)
	PLAN F2	15/15	(100.0)	15/15	(100.0)	15/15	(100.0)
II	PLAN F1	14/15	(93.3)	15/15	(100.0)	15/15	(100.0)
	PLAN F2	15/15	(100.0)	15/15	(100.0)	15/15	(100.0)
III	PLAN F1	14/15	(93.3)	15/15	(100.0)	15/15	(100.0)
	PLAN F2	14/15	(93.3)	15/15	(100.0)	15/15	(100.0)
ANY	PLAN F1	14/15	(93.3)	15/15	(100.0)	15/15	(100.0)
	PLAN F2	15/15	(100.0)	15/15	(100.0)	15/15	(100.0)

GEOMETRIC MEAN TITERS

		Visit 1		Visit 2		Visit 3	
TYPE		N	GMT	N	GMT	N	GMT
I	PLAN F1	15	172.90	15	4816.60	15	4888.79
	PLAN F2	15	335.13	15	4003.74	15	5615.74
II	PLAN F1	15	250.23	15	7760.48	15	12319.00
	PLAN F2	15	531.99	15	17828.90	15	17828.88
III	PLAN F1	15	143.72	15	13511.81	15	17828.90
	PLAN F2	15	345.80	15	14150.80	15	19555.19

GEOMETRIC MEAN TITERS IN INTERNATIONAL UNITS

		Visit 1		Visit 2		Visit 3	
TYPE		N	GMT	N	GMT	N	GMT
I	PLAN F1	15	2.02	15	56.21	15	57.05
	PLAN F2	15	3.91	15	46.72	15	65.54
II	PLAN F1	15	1.41	15	43.85	15	69.60
	PLAN F2	15	3.01	15	100.73	15	100.73
III	PLAN F1	15	1.44	15	135.12	15	178.29
	PLAN F2	15	3.46	15	141.51	15	195.55

TABLE 28

Polio Protocol 01

NASOPHARYNGEAL SECRETIONS NEUTRALIZING ANTIBODIES

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		Visit 1	Visit 2	Visit 3
I	PLAN F1	0/15 (0.0)	11/15 (73.3)	8/15 (53.3)
	PLAN F2	4/15 (26.7)	9/15 (60.0)	10/15 (66.7)
II	PLAN F1	2/15 (13.3)	12/15 (80.0)	10/15 (66.7)
	PLAN F2	1/15 (6.7)	12/15 (80.0)	10/15 (66.7)
III	PLAN F1	4/15 (26.7)	13/15 (86.7)	14/15 (93.3)
	PLAN F2	6/15 (40.0)	12/15 (80.0)	11/15 (73.3)
ANY	PLAN F1	5/15 (33.3)	14/15 (93.3)	14/15 (93.3)
	PLAN F2	8/15 (53.3)	14/15 (93.3)	14/15 (93.3)

GEOMETRIC MEAN TITERS

		Visit 1		Visit 2		Visit 3	
TYPE		N	GMT	N	GMT	N	GMT
I	PLAN F1	15	0.00	15	6.35	15	6.65
	PLAN F2	15	1.45	15	3.17	15	5.79
II	PLAN F1	15	1.45	15	7.29	15	9.62
	PLAN F2	15	1.15	15	9.19	15	7.64
III	PLAN F1	15	1.74	15	12.70	15	20.16
	PLAN F2	15	2.19	15	10.56	15	11.58

GEOMETRIC MEAN TITERS IN INTERNATIONAL UNITS

		Visit 1		Visit 2		Visit 3	
TYPE		N	GMT	N	GMT	N	GMT
I	PLAN F1	15	0.00	15	0.07	15	0.08
	PLAN F2	15	0.02	15	0.04	15	0.07
II	PLAN F1	15	0.01	15	0.04	15	0.05
	PLAN F2	15	0.01	15	0.05	15	0.04
III	PLAN F1	15	0.02	15	0.13	15	0.20
	PLAN F2	15	0.02	15	0.11	15	0.12

Polio Protocol 01

TABLE 29

STOOL SPECIMENS NEUTRALIZING ANTIBODIES

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		Visit 1	Visit 2	Visit 3
I	PLAN F1	0/15 (0.0)	3/15 (20.0)	1/15 (6.7)
	PLAN F2	2/15 (13.3)	2/14 (14.3)	2/15 (13.3)
II	PLAN F1	0/15 (0.0)	2/15 (13.3)	1/15 (6.7)
	PLAN F2	2/15 (13.3)	2/14 (14.3)	7/15 (46.7)
III	PLAN F1	0/15 (0.0)	3/15 (20.0)	5/15 (33.3)
	PLAN F2	1/15 (6.7)	7/14 (50.0)	7/15 (46.7)
ANY	PLAN F1	0/15 (0.0)	6/15 (40.0)	5/15 (33.3)
	PLAN F2	3/15 (20.0)	8/15 (53.3)	8/15 (53.3)

GEOMETRIC MEAN TITERS

		Visit 1		Visit 2		Visit 3	
TYPE		N	GMT	N	GMT	N	GMT
I	PLAN F1	15	0.00	15	1.32	15	1.20
	PLAN F2	15	1.26	14	1.28	15	1.45
II	PLAN F1	15	0.00	15	1.32	15	1.32
	PLAN F2	15	1.32	14	1.49	15	3.48
III	PLAN F1	15	0.00	15	1.59	15	2.19
	PLAN F2	15	1.15	14	2.97	15	3.48

GEOMETRIC MEAN TITERS IN INTERNATIONAL UNITS

		Visit 1		Visit 2		Visit 3	
TYPE		N	GMT	N	GMT	N	GMT
I	PLAN F1	15	0.00	15	0.02	15	0.01
	PLAN F2	15	0.01	14	0.01	15	0.02
II	PLAN F1	15	0.00	15	0.01	15	0.01
	PLAN F2	15	0.01	14	0.01	15	0.02
III	PLAN F1	15	0.00	15	0.02	15	0.02
	PLAN F2	15	0.01	14	0.03	15	0.03

TABLE 30

Polio Protocol 01

NASOPHARYNGEAL SECRETIONS (b)(4) IgA ANTIBODIES

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		Visit 1	Visit 2	Visit 3
I	PLAN F1	8/14 (57.1)	11/15 (73.3)	10/15 (66.7)
	PLAN F2	10/15 (66.7)	10/15 (66.7)	12/15 (80.0)
II	PLAN F1	10/14 (71.4)	10/15 (66.7)	10/15 (66.7)
	PLAN F2	10/15 (66.7)	10/15 (66.7)	13/15 (86.7)
III	PLAN F1	10/14 (71.4)	12/15 (80.0)	11/15 (73.3)
	PLAN F2	11/15 (73.3)	10/15 (66.7)	14/15 (93.3)
ANY	PLAN F1	10/15 (66.7)	12/15 (80.0)	11/15 (73.3)
	PLAN F2	11/15 (73.3)	10/15 (66.7)	14/15 (93.3)

GEOMETRIC MEAN TITERS

		Visit 1		Visit 2		Visit 3	
TYPE		N	GMT	N	GMT	N	GMT
I	PLAN F1	14	8.41	15	8.77	15	13.93
	PLAN F2	15	12.13	15	6.96	15	10.56
II	PLAN F1	14	9.28	15	8.77	15	12.70
	PLAN F2	15	8.00	15	7.29	15	14.59
III	PLAN F1	14	13.79	15	13.30	15	19.25
	PLAN F2	15	10.56	15	10.08	15	20.16

TABLE 31

Polio Protocol 01

STOOL SPECIMENS (b)(4) IgA ANTIBODIES

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		Visit 1	Visit 2	Visit 3
I	PLAN F1	3/15 (20.0)	2/15 (13.3)	5/15 (33.3)
	PLAN F2	3/15 (20.0)	1/15 (6.7)	3/15 (20.0)
II	PLAN F1	3/15 (20.0)	4/15 (26.7)	6/15 (40.0)
	PLAN F2	4/15 (26.7)	6/15 (40.0)	5/15 (33.3)
III	PLAN F1	3/15 (20.0)	5/15 (33.3)	6/15 (40.0)
	PLAN F2	3/15 (20.0)	5/15 (33.3)	4/15 (26.7)
ANY	PLAN F1	3/15 (20.0)	5/15 (33.3)	7/15 (46.7)
	PLAN F2	4/15 (26.7)	8/15 (53.3)	6/15 (40.0)

GEOMETRIC MEAN TITERS

		Visit 1		Visit 2		Visit 3	
TYPE		N	GMT	N	GMT	N	GMT
I	PLAN F1	15	1.82	15	1.32	15	2.19
	PLAN F2	15	1.82	15	1.15	15	1.59
II	PLAN F1	15	1.66	15	1.82	15	2.52
	PLAN F2	15	1.91	15	2.30	15	2.19
III	PLAN F1	15	1.82	15	2.19	15	2.52
	PLAN F2	15	1.59	15	2.19	15	2.00

TABLE 32

Polio Protocol 01

SERUM NEUTRALIZING ANTIBODIES
PATIENTS HAD CONTACT WITH OPV

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		Visit 1	Visit 2	Visit 3
I	Plan F1	7/ 7 (100.0)	7/ 7 (100.0)	7/ 7 (100.0)
	Plan F2	5/ 5 (100.0)	5/ 5 (100.0)	5/ 5 (100.0)
II	Plan F1	7/ 7 (100.0)	7/ 7 (100.0)	7/ 7 (100.0)
	Plan F2	5/ 5 (100.0)	5/ 5 (100.0)	5/ 5 (100.0)
III	Plan F1	7/ 7 (100.0)	7/ 7 (100.0)	7/ 7 (100.0)
	Plan F2	5/ 5 (100.0)	5/ 5 (100.0)	5/ 5 (100.0)
ANY	Plan F1	7/ 7 (100.0)	7/ 7 (100.0)	7/ 7 (100.0)
	Plan F2	5/ 5 (100.0)	5/ 5 (100.0)	5/ 5 (100.0)

GEOMETRIC MEAN TITERS

		Visit 1		Visit 2		Visit 3	
TYPE		N	GMT	N	GMT	N	GMT
I	Plan F1	7	215.34	7	8400.23	7	7608.30
	Plan F2	5	422.24	5	2940.67	5	5881.34
II	Plan F1	7	430.69	7	6891.02	7	12482.72
	Plan F2	5	211.12	5	8914.46	5	8914.44
III	Plan F1	7	118.88	7	10240.02	7	16800.50
	Plan F2	5	557.15	5	17828.92	5	23525.40

GEOMETRIC MEAN TITERS IN INTERNATIONAL UNITS

		Visit 1		Visit 2		Visit 3	
TYPE		N	GMT	N	GMT	N	GMT
I	Plan F1	7	2.51	7	98.03	7	88.79
	Plan F2	5	4.93	5	34.32	5	68.64
II	Plan F1	7	2.43	7	38.93	7	70.53
	Plan F2	5	1.19	5	50.37	5	50.37
III	Plan F1	7	1.19	7	102.40	7	168.00
	Plan F2	5	5.57	5	178.29	5	235.25

TABLE 33

Polio Protocol 01

SERUM NEUTRALIZING ANTIBODIES
PATIENTS DID NOT HAVE CONTACT WITH OPV

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		Visit 1		Visit 2		Visit 3	
I	Plan F1	7/ 8	(87.5)	7/ 8	(87.5)	8/ 8	(100.0)
	Plan F2	10/10	(100.0)	10/10	(100.0)	10/10	(100.0)
II	Plan F1	7/ 8	(87.5)	8/ 8	(100.0)	8/ 8	(100.0)
	Plan F2	10/10	(100.0)	10/10	(100.0)	10/10	(100.0)
III	Plan F1	7/ 8	(87.5)	8/ 8	(100.0)	8/ 8	(100.0)
	Plan F2	9/10	(90.0)	10/10	(100.0)	10/10	(100.0)
ANY	Plan F1	7/ 8	(87.5)	8/ 8	(100.0)	8/ 8	(100.0)
	Plan F2	10/10	(100.0)	10/10	(100.0)	10/10	(100.0)

GEOMETRIC MEAN TITERS

TYPE		Visit 1		Visit 2		Visit 3	
		N	GMT	N	GMT	N	GMT
I	Plan F1	8	142.68	8	2960.63	8	3319.91
	Plan F2	10	298.57	10	4671.71	10	5487.48
II	Plan F1	8	155.60	8	8610.79	8	12177.50
	Plan F2	10	844.49	10	25213.87	10	25213.84
III	Plan F1	8	169.68	8	17221.64	8	18780.27
	Plan F2	10	272.43	10	12606.92	10	17828.90

GEOMETRIC MEAN TITERS IN INTERNATIONAL UNITS

TYPE		Visit 1		Visit 2		Visit 3	
		N	GMT	N	GMT	N	GMT
I	Plan F1	8	1.67	8	34.55	8	38.74
	Plan F2	10	3.48	10	54.52	10	64.04
II	Plan F1	8	0.88	8	48.65	8	68.80
	Plan F2	10	4.77	10	142.46	10	142.46
III	Plan F1	8	1.70	8	172.22	8	187.80
	Plan F2	10	2.72	10	126.07	10	178.29

MERIEUX INSTITUTE, INC.

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April 21, 1989

Dr. Paul Parkman
Director
Center for Biologics Evaluation
and Research
ATTN: Division of Product
Certification, ATTN: HFN-825
Parklawn Building, Room 9B-05
5600 Fishers Lane
Rockville, MD 20857

REFERENCE NO. 83-087

Dear Dr. Parkman:

Enclosed in triplicate is a final summary report of the results of clinical trials on our enhanced Poliovirus Vaccine, inactivated. The data represents the immunogenicity studies of Drs. Pearay Ogra and Howard Faden, State University of New York/Children's Hospital, Buffalo and Drs. Marshall McBean and John Modlin, Johns Hopkins University, Baltimore.

The results of these trials show that the Merieux vaccine has excellent immunogenicity and safety.

Sincerely yours,

Pinya Cohen

Pinya Cohen, Ph.D.
Vice President
Quality Control and
Regulatory Affairs

PC/(b)
89286

4-21-89

MERIEUX INACTIVATED POLIOVIRUS VACCINE

FINAL REPORT OF CLINICAL STUDIES AT

SUNY/CHILDREN'S HOSPITAL, BUFFALO, NEW YORK
JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND

SUMMARY

Two doses of Merieux Inactivated Poliovirus Vaccine (M-IPV) at 2 and 4 months of age, followed by a booster dose at 12 months of age, gave excellent neutralizing antibody responses to three types of poliovirus. IPV and OPV alone produced similar levels of neutralizing antibody and IgA in the nasopharyngeal secretions. A combined schedule of IPV and OPV resulted in a slight priming effect after primary immunization for Type II poliovirus by IPV on mucosal immune response of OPV for neutralizing antibody and IgA in the naso-nasopharyngeal secretions and for IgA in the stool. This priming effect was not seen after immunization with a booster dose.

Merieux IPV induced comparable responses in premature and full term infants.

Single and two dose boosters in adults showed high anamnestic responses in all recipients and that a second dose is unnecessary.

There were no significant adverse reactions.

INTRODUCTION

The Merieux Inactivated Polio Vaccine (M-IPV) produced from continuous cell lines of Vero cells using microcarrier culture has been extensively tested in Finland, Israel, India, Brazil, Indonesia, Mali, France and the United States. This highly purified more potent vaccine has been shown to be safe, highly immunogenic and efficacious when used in a two dose schedule for primary immunization followed by a booster dose.

A clinical trial at Johns Hopkins comparing M-IPV to the oral polio vaccine currently used in the United States, showed that approximately 99% of children had neutralizing antibodies to all three types of polio virus after receiving M-IPV at 2 and 4 months of age, and that a significant boost in titers occurred after the third dose at 18 months of age (Amer. J. Epid. 128: 615-618, 1988). The titers to M-IPV were superior to OPV given in the same 3 dose schedule. This vaccine was made exactly as the Vero cell vaccine intended for license, except the cell substrate for the Johns Hopkins trial was primary monkey kidney cells.

In December 1985, the Office of Biologics requested that 75-100 children and 25-30 adults be immunized according to the United States schedule. In response to this request, clinical studies on children and adults were carried out at

State University of New York/Children's Hospital, Buffalo by Drs. H. Faden and P. Ogra. Supplemental studies on groups of children using three of the four groups tested in Buffalo (only IPV or combined schedules) were initiated at Johns Hopkins by Drs. M. McBean and J. Modlin at a later date.

To meet the FDA request for M-IPV licensure, data are now presented on children and adults from Buffalo and on children only from Baltimore.

METHODS

Details of the methods used are outlined in the protocols already submitted under IND. Merieux IPV Lots Z1102, Z1103, A1243, A0301 and A0304 were used. The general approach was to compare immunogenicity of two primary doses of M-IPV, OPV, or a combined schedule in 2 month old children. Originally the recruitment targets were a minimum of 15-20 children each in Groups A, C and D, and 50-60 children were to be recruited in Group B. These numbers were exceeded for all groups. The groups and vaccine schedules are shown below:

IMMUNIZATION PLAN FOR CHILDREN

GROUP	2 MONTHS	4 MONTHS	12 MONTHS
A	OPV	OPV	OPV
B	IPV	IPV	IPB
C	IPV	OPV	OPV
D	IPV	IPV	OPV

Buffalo enrolled children in all groups; Johns Hopkins enrolled children in all groups except Group A.

Blood samples for antibody determinations were collected at 2 and 4 months of age just prior to administration of vaccine and one month after the second and third doses of vaccine. A detectable serum neutralizing antibody titer was considered >1:10; for neutralizing antibody in the nasopharyngeal secretions and stool >1:4 and for (b) (4) IgA in the NPS and stool >1:8. GMT's were computed and also expressed in international units based on the FDA reference serum results.

For the adult studies, 30 individuals were immunized and available for the analysis. Half received one dose (Group F1) and half received a second dose 4 weeks later (Group F2). Serum antibody titers were done prior to immunization and 4 weeks after each dose of vaccine.

RESULTS IN CHILDREN

M-IPV induced detectable neutralizing antibodies after two doses of vaccine in 97.8% to 100% (Type I), 100% (Type II), and 96.7% to 100% (Type III) of the children (Table 1). Two doses of OPV gave 100% response for all types of poliovirus and a mixed schedule of IPV and OPV induced 96.6% response for Types I and III and 100% response for Type II. The booster dose did not appreciably change the response rates.

The GMT (Table 2) rose approximately 10-fold after two doses and nearly 100-fold post-booster in all groups for Type I. For Type II, two doses of IPV gave lower GMT's than OPV or a mixed schedule, but produced overall even greater titers and fold increases pre- and post-booster than Types I or III. The GMT obtained for Type III with mixed schedules was significantly lower with a mixed regimen of IPV-OPV-OPV than IPV-IPV-OPV or the other two regimens using all IPV or all OPV.

Table 3 presents similar neutralizing antibody data expressed in international units.

Table 4 shows that two primary doses and a booster dose of M-IPV produced neutralizing antibodies in the nasopharyngeal secretions (NPS) in 64% of the children compared to 90% in all OPV recipients and 58% to 68% in recipients of mixed schedules.

After primary immunization, the GMT for Type II was slightly higher in recipients of the IPV-OPV schedule than with OPV alone indicating a priming effect by IPV on OPV-induced antibody (Table 5). The priming effect was not seen post-booster. The NPS neutralizing antibody levels for all types were highest post-booster in children who received only OPV. The data expressed as international units are shown in Table 6.

The percentage of children with IgA antibodies in the NPS (Table 7) were generally at similar levels for M-IPV,

mixed schedule, and OPV for all types of poliovirus after only two doses but were highest in children receiving the mixed schedule of IPV-OPV-OPV. This advantage disappeared post-booster in favor of the all OPV schedule. This pattern was also reflected in the GMT (Table 8).

The percentage of children receiving only IPV with detectable neutralizing antibody in the stool was less than 15% and did not show any appreciable change even after a booster (Table 9). Recipients of either of the mixed schedules or only OPV developed substantial increases in stool antibody, ranging from 23% to 57% for the three types post-booster. Both the percentage with antibody and the GMT were highest for Type II (Tables 10 and 11).

As was the case with neutralizing antibody in the stool, the percentage of children with detectable IgA levels in the stool was essentially unchanged following primary and booster doses of only IPV (Table 12). The mixed schedules resulted in approximately 35% detectable IgA for all three polio types and OPV only ranged from 35% to 55% detectable IgA. The GMT followed a similar pattern (Table 13).

Premature and full-term infants responded equally to primary and booster doses of M-IPV. The percent with detectable antibody titers was essentially 100% to all three types of poliovirus (Tables 14, 15, 16).

RESULTS IN ADULTS

Nearly all adults had detectable neutralizing antibodies at the time of entry into the study, so that a single dose of M-IPV ensured a 100% response (Table 17).

A single dose of M-IPV induced increases in GMT of nearly 30-fold for Type I, 50-fold for Type II and 125-fold for Type III. A second dose of IPV did not significantly increase the GMT compared to only a single dose.

The results of neutralizing antibodies in the NPS (Table 18) show that the percent of subjects with detectable antibody was the same with one or two doses, suggesting that a greater increase over base titer and higher GMT is obtained in individuals who had a lower antibody titer upon entry.

In contrast, both the percent of individuals with stool neutralizing antibody and the GMT were higher in adults receiving two doses of M-IPV compared to only one dose (Table 19).

The IgA antibody levels in the NPS and stool were similar for one or two doses, although there was a higher percentage of detectable antibody in NPS of recipients of two doses compared to one dose of M-IPV (Tables 20 and 21).

There were no major differences in antibody responses whether there was exposure or nonexposure to OPV (Tables 22 and 23).

ADVERSE REACTIONS

There were no serious adverse reactions reported at either Buffalo or Johns Hopkins.

The Johns Hopkins protocol was set up to include telephone follow up with the patients at 24 hours, 2 and 3 days after each polio immunization to inquire about adverse reactions. Surveillance at Buffalo was limited to an interview during each immunization visit and no adverse experiences were reported other than one adult complaining of redness at the injection site.

Johns Hopkins enrollment is shown below:

Group	No. Enrolled	No. Completing Study
B	54	44
C	16	14
D	16	16

The reactions were summarized as follows:

Immunization #	No. of Reaction Forms	No. Children with >100.6	% with Temps. >100.6
1	86	9	10
2	79	14	18
3	75	5	7

There were no serious local or systemic reactions in any of the children in this study.

Most of the children received DTP at the same time they received the IPV or OPV at 2 and 4 months of age.

One child had a temperature of 103, four children experienced temperatures of 102.

Of the 9 children who had temperatures 100.6 or greater at the time of the first polio immunization, 7 also had local reactions to DTP.

Of the 14 children who had temperatures 100.6 or greater at the time they received the second polio immunization, 9 also had local reactions to DTP. Four of these chil-dren received OPv at this time.

Of the 5 children with temperatures 100.6 or greater at the time of the third polio immunization, 2 had colds.

DISCUSSION

This study has demonstrated that two primary doses of M-IPV given at 2 and 4 months of age followed by a booster dose at 12 months of age produce excellent neutralizing antibody responses to all three types of poliovirus. The percentage of children with detectable antibody to the Vero cell vaccine was comparable to and the GMT's higher than results obtained in the earlier Johns Hopkins/CDC/FDA study with M-IPV produc-ed in primary monkey kidney cells.

Two children (b)(6), immunized at the same pri-vate clinic with two doses of M-IPV, formed good neutralizing antibody titers to Type II but not to the Types I and III poliovirus. The Type II baseline titer and titer one month post 12-month booster, was 320 for both children. The Types

I and III titers at baseline and post-booster were for (b) (6) 10 and <10 and 40 and 20, respectively; for (b) (6) 10 and <10 and <10 and 20, respectively. Both children had normal IgG at 5 months of age and measurable tetanus antibody levels at 13 months of age. It appears the children were immunocompetent, but the reason for poor Types I and III response are unclear.

This study has shown that children given two doses of only OPV or only M-IPV produce similar levels of neutralizing antibodies and IgA in the NPS. Following the booster dose, the number of children with neutralizing antibody and the neutralizing antibody level increases further but is approximately one-half that for OPV in IPV recipients. Nevertheless this level of neutralizing antibody produced by enhanced IPV in the nasopharyngeal secretions is noteworthy.

The strong priming effect of one dose of M-IPV on the mucosal antibody induced by a dose of OPV seen earlier in the primary immunization phase of the study is not maintained in the GMT following booster doses. One month after the booster dose, either of the mixed schedules induced lower GMT's than a schedule of only OPV. Nevertheless, these data clearly show that enhanced M-IPV stimulates local immunity when used alone or in a combination schedule with OPV.

Based on stool antibody data, "gut immunity" appears to be a concept applicable to both M-IPV and OPV. Both vaccines

used alone or in combination gave detectable neutralizing antibody in the stool with similar GMT's.

Because approximately 25% of the infants receiving two doses of IPV were premature births, it was possible to compare responses to full-term infants. Although full-term infants had higher maternal antibody levels, as expected, both premature and full-term infants had similar percentages of responders and comparable GMT's after two doses of IPV.

The studies in adults showed that a single dose of M-IPV produced booster responses with very high titers of neutralizing antibodies and that a second dose is unnecessary. However, stool neutralizing antibody levels were higher in adults receiving a second dose of IPV.

Serum Neutralizing Antibodies
Percent with Detectable Antibody Titer
Efficacy Patients

Type I

Mos	A	B	C	D
2	17/ 23 (73.9)	92/116 (79.3)	28/ 32 (87.5)	29/ 34 (85.3)
4	17/ 22 (77.3)	68/ 93 (73.1)	23/ 29 (79.3)	27/ 29 (93.1)
5	22/ 22 (100.0)	89/ 91 (97.8)	28/ 29 (96.6)	29/ 29 (100.0)
12	17/ 22 (77.3)	78/ 85 (91.8)	27/ 29 (93.1)	26/ 27 (96.3)
13	20/ 20 (100.0)	81/ 83 (97.6)	28/ 28 (100.0)	26/ 26 (100.0)

Type II

Mos	A	B	C	D
2	22/ 23 (95.7)	100/116 (86.2)	30/ 32 (93.8)	32/ 34 (94.1)
4	21/ 22 (95.5)	89/ 93 (95.7)	29/ 29 (100.0)	29/ 29 (100.0)
5	22/ 22 (100.0)	91/ 91 (100.0)	29/ 29 (100.0)	29/ 29 (100.0)
12	20/ 22 (90.9)	79/ 85 (92.9)	26/ 29 (89.7)	25/ 27 (92.6)
13	20/ 20 (100.0)	83/ 83 (100.0)	28/ 28 (100.0)	26/ 26 (100.0)

Type III

Mos	A	B	C	D
2	19/ 23 (82.6)	87/116 (75.0)	23/ 32 (71.9)	26/ 34 (76.5)
4	17/ 22 (77.3)	78/ 93 (83.9)	24/ 29 (82.8)	23/ 29 (79.3)
5	22/ 22 (100.0)	88/ 91 (96.7)	28/ 29 (96.6)	29/ 29 (100.0)
12	17/ 22 (77.3)	77/ 85 (90.6)	25/ 29 (86.2)	24/ 27 (88.9)
13	20/ 20 (100.0)	83/ 83 (100.0)	26/ 28 (92.9)	26/ 26 (100.0)

Type Any

Mos	A	B	C	D
2	22/ 23 (95.7)	115/116 (99.1)	31/ 32 (96.9)	33/ 34 (97.1)
4	22/ 22 (100.0)	93/ 93 (100.0)	29/ 29 (100.0)	29/ 29 (100.0)
5	22/ 22 (100.0)	91/ 91 (100.0)	29/ 29 (100.0)	29/ 29 (100.0)
12	22/ 22 (100.0)	82/ 85 (96.5)	28/ 29 (96.6)	26/ 27 (96.3)
13	20/ 20 (100.0)	83/ 83 (100.0)	28/ 28 (100.0)	26/ 26 (100.0)

Serum Neutralizing Antibodies
Reciprocal Geometric Mean Titers
Efficacy Patients

Type I

	A		B		C		D	
Mos	N	GMT	N	GMT	N	GMT	N	GMT
2	23	21.29	116	20.97	32	25.78	34	30.07
4	22	35.70	93	12.16	29	10.26	29	22.90
5	22	273.36	91	208.84	29	250.04	29	354.70
12	22	67.04	85	74.19	29	157.56	27	110.77
13	20	1470.33	83	2101.29	28	1599.45	26	2629.17

Type II

	A		B		C		D	
Mos	N	GMT	N	GMT	N	GMT	N	GMT
2	23	50.41	116	36.24	32	66.34	34	56.54
4	22	492.39	93	41.52	29	41.96	29	51.17
5	22	2726.51	91	552.15	29	1442.49	29	709.40
12	22	403.46	85	128.45	29	504.35	27	203.44
13	20	3377.94	83	5120.00	28	4305.39	26	6337.16

Type III

	A		B		C		D	
Mos	N	GMT	N	GMT	N	GMT	N	GMT
2	23	17.05	116	15.40	32	11.66	34	15.05
4	22	17.85	93	21.15	29	17.08	29	15.89
5	22	351.72	91	605.15	29	72.15	29	1200.22
12	22	78.48	85	84.99	29	46.96	27	95.83
13	20	1522.19	83	4332.44	28	570.50	26	1960.92

TABLE 3

Serum Neutralizing Antibodies
Reciprocal Geometric Mean Titers in International Units
Efficacy Patients

Type I

	A		B		C		D	
Mos	N	GMT	N	GMT	N	GMT	N	GMT
2	23	0.25	116	0.24	32	0.30	34	0.35
4	22	0.42	93	0.14	29	0.12	29	0.27
5	22	3.19	91	2.44	29	2.92	29	4.14
12	22	0.78	85	0.87	29	1.84	27	1.29
13	20	17.16	83	24.52	28	18.67	26	30.68

Type II

	A		B		C		D	
Mos	N	GMT	N	GMT	N	GMT	N	GMT
2	23	0.28	116	0.20	32	0.37	34	0.32
4	22	2.78	93	0.23	29	0.24	29	0.29
5	22	15.40	91	3.12	29	8.15	29	4.01
12	22	2.28	85	0.73	29	2.85	27	1.15
13	20	19.09	83	28.93	28	24.33	26	35.80

Type III

	A		B		C		D	
Mos	N	GMT	N	GMT	N	GMT	N	GMT
2	23	0.17	116	0.15	32	0.12	34	0.15
4	22	0.18	93	0.21	29	0.17	29	0.16
5	22	3.52	91	6.05	29	0.72	29	12.00
12	22	0.78	85	0.85	29	0.47	27	0.96
13	20	15.22	83	43.32	28	5.70	26	19.61

Nasopharyngeal Neutralizing Antibodies
Percent with Detectable Antibody Titer
Efficacy Patients

Type I

Mos	A	B	C	D
4	6/ 22 (27.3)	5/ 93 (5.4)	1/ 29 (3.4)	0/ 29 (0.0)
5	6/ 22 (27.3)	23/ 91 (25.3)	11/ 29 (37.9)	6/ 29 (20.7)
12	7/ 22 (31.8)	6/ 85 (7.1)	3/ 29 (10.3)	2/ 27 (7.4)
13	14/ 20 (70.0)	27/ 83 (32.5)	12/ 28 (42.9)	9/ 26 (34.6)

Type II

Mos	A	B	C	D
4	15/ 22 (68.2)	4/ 93 (4.3)	3/ 29 (10.3)	0/ 29 (0.0)
5	15/ 22 (68.2)	32/ 91 (35.2)	20/ 29 (69.0)	10/ 29 (34.5)
12	15/ 22 (68.2)	10/ 85 (11.8)	9/ 29 (31.0)	4/ 27 (14.8)
13	17/ 20 (85.0)	39/ 83 (47.0)	18/ 28 (64.3)	15/ 26 (57.7)

Type III

Mos	A	B	C	D
4	4/ 22 (18.2)	5/ 93 (5.4)	2/ 29 (6.9)	0/ 29 (0.0)
5	9/ 22 (40.9)	34/ 91 (37.4)	6/ 29 (20.7)	10/ 29 (34.5)
12	8/ 22 (36.4)	10/ 85 (11.8)	2/ 29 (6.9)	2/ 27 (7.4)
13	15/ 20 (75.0)	40/ 83 (48.2)	8/ 28 (28.6)	7/ 26 (26.9)

Type Any

Mos	A	B	C	D
4	16/ 22 (72.7)	6/ 93 (6.5)	4/ 29 (13.8)	0/ 29 (0.0)
5	16/ 22 (72.7)	43/ 91 (47.3)	21/ 29 (72.4)	13/ 29 (44.8)
12	16/ 22 (72.7)	14/ 85 (16.5)	12/ 29 (41.4)	6/ 27 (22.2)
13	18/ 20 (90.0)	53/ 83 (63.9)	19/ 28 (67.9)	15/ 26 (57.7)

Nasopharyngeal Neutralizing Antibodies
Reciprocal Geometric Mean Titers
Efficacy Patients

Type I

	A		B		C		D	
Mos	N	GMT	N	GMT	N	GMT	N	GMT
4	22	1.86	93	1.25	29	1.17	29	0.00
5	22	1.82	91	1.88	29	2.54	29	1.43
12	22	2.31	85	1.25	29	1.24	27	1.14
13	20	5.66	83	2.17	28	2.63	26	2.05

Type II

	A		B		C		D	
Mos	N	GMT	N	GMT	N	GMT	N	GMT
4	22	7.19	93	1.22	29	1.29	29	0.00
5	22	6.83	91	2.33	29	7.81	29	2.31
12	22	7.91	85	1.38	29	2.31	27	1.40
13	20	17.15	83	3.29	28	7.25	26	6.29

Type III

	A		B		C		D	
Mos	N	GMT	N	GMT	N	GMT	N	GMT
4	22	1.74	93	1.24	29	1.23	29	0.00
5	22	2.92	91	2.63	29	1.50	29	2.31
12	22	3.17	85	1.41	29	1.27	27	1.11
13	20	6.50	83	3.35	28	1.95	26	2.41

Nasopharyngeal Neutralizing Antibodies
Reciprocal Geometric Mean Titers in International Units
Efficacy Patients

Type I

	A		B		C		D	
Mos	N	GMT	N	GMT	N	GMT	N	GMT
4	22	0.02	93	0.01	29	0.01	29	0.01
5	22	0.02	91	0.02	29	0.03	29	0.02
12	22	0.03	85	0.01	29	0.01	27	0.01
13	20	0.07	83	0.03	28	0.03	26	0.02

Type II

	A		B		C		D	
Mos	N	GMT	N	GMT	N	GMT	N	GMT
4	22	0.04	93	0.01	29	0.01	29	0.01
5	22	0.04	91	0.01	29	0.04	29	0.01
12	22	0.04	85	0.01	29	0.01	27	0.01
13	20	0.10	83	0.02	28	0.04	26	0.04

Type III

	A		B		C		D	
Mos	N	GMT	N	GMT	N	GMT	N	GMT
4	22	0.02	93	0.01	29	0.01	29	0.01
5	22	0.03	91	0.03	29	0.02	29	0.02
12	22	0.03	85	0.01	29	0.01	27	0.01
13	20	0.06	83	0.03	28	0.02	26	0.02

TABLE 7

Nasopharyngeal (b) (4) IgA Antibodies
Percent with Detectable Antibody Titer
Efficacy Patients

Type I

Mos	A	B	C	D
4	17/ 22 (77.3)	53/ 93 (57.0)	21/ 29 (72.4)	18/ 29 (62.1)
5	16/ 22 (72.7)	59/ 91 (64.8)	22/ 29 (75.9)	16/ 29 (55.2)
12	22/ 22 (100.0)	68/ 85 (80.0)	26/ 29 (89.7)	22/ 27 (81.5)
13	20/ 20 (100.0)	65/ 83 (78.3)	24/ 28 (85.7)	19/ 26 (73.1)

Type II

Mos	A	B	C	D
4	17/ 22 (77.3)	55/ 93 (59.1)	20/ 29 (69.0)	19/ 29 (65.5)
5	16/ 22 (72.7)	60/ 91 (65.9)	24/ 29 (82.8)	20/ 29 (69.0)
12	22/ 22 (100.0)	69/ 85 (81.2)	26/ 29 (89.7)	22/ 27 (81.5)
13	20/ 20 (100.0)	67/ 83 (80.7)	26/ 28 (92.9)	20/ 26 (76.9)

Type III

Mos	A	B	C	D
4	17/ 22 (77.3)	50/ 93 (53.8)	23/ 29 (79.3)	20/ 29 (69.0)
5	17/ 22 (77.3)	59/ 91 (64.8)	23/ 29 (79.3)	21/ 29 (72.4)
12	22/ 22 (100.0)	72/ 85 (84.7)	26/ 29 (89.7)	22/ 27 (81.5)
13	20/ 20 (100.0)	69/ 83 (83.1)	26/ 28 (92.9)	20/ 26 (76.9)

Type Any

Mos	A	B	C	D
4	17/ 22 (77.3)	59/ 93 (63.4)	23/ 29 (79.3)	22/ 29 (75.9)
5	18/ 22 (81.8)	65/ 91 (71.4)	25/ 29 (86.2)	22/ 29 (75.9)
12	22/ 22 (100.0)	72/ 85 (84.7)	27/ 29 (93.1)	22/ 27 (81.5)
13	20/ 20 (100.0)	71/ 83 (85.5)	26/ 28 (92.9)	20/ 26 (76.9)

Nasopharyngeal (b) (4) IgA Antibodies
Reciprocal Geometric Mean Titers
Efficacy Patients

Type I

	A		B		C		D	
Mos	N	GMT	N	GMT	N	GMT	N	GMT
4	22	13.09	93	5.62	29	11.35	29	6.15
5	22	15.02	91	7.31	29	13.86	29	5.08
12	22	61.30	85	15.47	29	17.61	27	15.20
13	20	68.59	83	14.80	28	22.63	26	12.59

Type II

	A		B		C		D	
Mos	N	GMT	N	GMT	N	GMT	N	GMT
4	22	12.29	93	6.47	29	10.56	29	7.81
5	22	13.24	91	7.71	29	14.20	29	7.10
12	22	61.30	85	16.25	29	18.91	27	16.42
13	20	97.01	83	15.95	28	33.62	26	13.63

Type III

	A		B		C		D	
Mos	N	GMT	N	GMT	N	GMT	N	GMT
4	22	13.09	93	5.37	29	13.42	29	9.02
5	22	17.04	91	7.77	29	15.62	29	7.63
12	22	92.32	85	19.28	29	25.20	27	19.15
13	20	128.00	83	19.98	28	40.99	26	15.17

Stool Neutralizing Antibodies
Percent with Detectable Antibody Titer
Efficacy Patients

Type I

Mos	A	B	C	D
4	1/ 22 (4.5)	6/ 93 (6.5)	1/ 29 (3.4)	3/ 29 (10.3)
5	6/ 22 (27.3)	6/ 91 (6.6)	4/ 29 (13.8)	2/ 29 (6.9)
12	1/ 22 (4.5)	4/ 85 (4.7)	6/ 29 (20.7)	0/ 27 (0.0)
13	7/ 20 (35.0)	7/ 83 (8.4)	10/ 28 (35.7)	6/ 26 (23.1)

Type II

Mos	A	B	C	D
4	4/ 22 (18.2)	9/ 93 (9.7)	1/ 29 (3.4)	3/ 29 (10.3)
5	10/ 22 (45.5)	10/ 91 (11.0)	8/ 29 (27.6)	5/ 29 (17.2)
12	6/ 22 (27.3)	9/ 85 (10.6)	11/ 29 (37.9)	1/ 27 (3.7)
13	11/ 20 (55.0)	10/ 83 (12.0)	16/ 28 (57.1)	11/ 26 (42.3)

Type III

Mos	A	B	C	D
4	1/ 22 (4.5)	7/ 93 (7.5)	1/ 29 (3.4)	3/ 29 (10.3)
5	6/ 22 (27.3)	9/ 91 (9.9)	3/ 29 (10.3)	2/ 29 (6.9)
12	4/ 22 (18.2)	6/ 85 (7.1)	5/ 29 (17.2)	0/ 27 (0.0)
13	8/ 20 (40.0)	9/ 83 (10.8)	7/ 28 (25.0)	6/ 26 (23.1)

Type Any

Mos	A	B	C	D
4	4/ 22 (18.2)	12/ 93 (12.9)	1/ 29 (3.4)	3/ 29 (10.3)
5	13/ 22 (59.1)	17/ 91 (18.7)	8/ 29 (27.6)	6/ 29 (20.7)
12	7/ 22 (31.8)	9/ 85 (10.6)	13/ 29 (44.8)	1/ 27 (3.7)
13	12/ 20 (60.0)	12/ 83 (14.5)	16/ 28 (57.1)	11/ 26 (42.3)

Stool Neutralizing Antibodies
Reciprocal Geometric Mean Titers
Efficacy Patients

Type I

	A		B		C		D	
Mos	N	GMT	N	GMT	N	GMT	N	GMT
4	22	1.07	93	1.26	29	1.17	29	1.61
5	22	1.74	91	1.25	29	1.49	29	1.26
12	22	1.10	85	1.17	29	1.56	27	0.00
13	20	2.92	83	1.36	28	2.24	26	1.93

Type II

	A		B		C		D	
Mos	N	GMT	N	GMT	N	GMT	N	GMT
4	22	1.82	93	1.34	29	1.17	29	1.61
5	22	3.83	91	1.31	29	2.13	29	1.52
12	22	2.00	85	1.31	29	2.58	27	1.05
13	20	6.94	83	1.47	28	5.33	26	4.18

Type III

	A		B		C		D	
Mos	N	GMT	N	GMT	N	GMT	N	GMT
4	22	1.07	93	1.30	29	1.17	29	1.61
5	22	1.74	91	1.31	29	1.42	29	1.23
12	22	1.71	85	1.20	29	1.52	27	0.00
13	20	3.47	83	1.41	28	1.89	26	2.09

TABLE 11

Stool Neutralizing Antibodies
Reciprocal Geometric Mean Titers in International Units
Efficacy Patients

Type I

	A		B		C		D	
Mos	N	GMT	N	GMT	N	GMT	N	GMT
4	22	0.01	93	0.01	29	0.01	29	0.02
5	22	0.02	91	0.01	29	0.02	29	0.01
12	22	0.01	85	0.01	29	0.02	27	0.01
13	20	0.03	83	0.02	28	0.03	26	0.02

Type II

	A		B		C		D	
Mos	N	GMT	N	GMT	N	GMT	N	GMT
4	22	0.01	93	0.01	29	0.01	29	0.01
5	22	0.02	91	0.01	29	0.01	29	0.01
12	22	0.01	85	0.01	29	0.01	27	0.01
13	20	0.04	83	0.01	28	0.03	26	0.02

Type III

	A		B		C		D	
Mos	N	GMT	N	GMT	N	GMT	N	GMT
4	22	0.01	93	0.01	29	0.01	29	0.02
5	22	0.02	91	0.01	29	0.01	29	0.01
12	22	0.02	85	0.01	29	0.02	27	0.01
13	20	0.03	83	0.01	28	0.02	26	0.02

TABLE 12

Polio Protocol

Stool (b)(4) IgA Antibodies
Percent with Detectable Antibody Titer
Efficacy Patients

Type I

Mos	A	B	C	D
4	4/ 22 (18.2)	19/ 93 (20.4)	4/ 29 (13.8)	4/ 29 (13.8)
5	4/ 22 (18.2)	16/ 91 (17.6)	4/ 29 (13.8)	3/ 29 (10.3)
12	6/ 22 (27.3)	18/ 85 (21.2)	6/ 29 (20.7)	5/ 27 (18.5)
13	7/ 20 (35.0)	15/ 83 (18.1)	6/ 28 (21.4)	10/ 26 (38.5)

Type II

Mos	A	B	C	D
4	2/ 22 (9.1)	17/ 93 (18.3)	6/ 29 (20.7)	5/ 29 (17.2)
5	3/ 22 (13.6)	16/ 91 (17.6)	8/ 29 (27.6)	3/ 29 (10.3)
12	9/ 22 (40.9)	18/ 85 (21.2)	6/ 29 (20.7)	2/ 27 (7.4)
13	11/ 20 (55.0)	17/ 83 (20.5)	10/ 28 (35.7)	9/ 26 (34.6)

Type III

Mos	A	B	C	D
4	4/ 22 (18.2)	20/ 93 (21.5)	5/ 29 (17.2)	4/ 29 (13.8)
5	4/ 22 (18.2)	20/ 91 (22.0)	8/ 29 (27.6)	6/ 29 (20.7)
12	8/ 22 (36.4)	19/ 85 (22.4)	5/ 29 (17.2)	4/ 27 (14.8)
13	10/ 20 (50.0)	17/ 83 (20.5)	10/ 28 (35.7)	10/ 26 (38.5)

Type Any

Mos	A	B	C	D
4	6/ 22 (27.3)	26/ 93 (28.0)	7/ 29 (24.1)	7/ 29 (24.1)
5	4/ 22 (18.2)	23/ 91 (25.3)	8/ 29 (27.6)	7/ 29 (24.1)
12	9/ 22 (40.9)	23/ 85 (27.1)	6/ 29 (20.7)	5/ 27 (18.5)
13	11/ 20 (55.0)	22/ 83 (26.5)	11/ 28 (39.3)	10/ 26 (38.5)

Stool (b) (4) IgA Antibodies
Reciprocal Geometric Mean Titers
Efficacy Patients

Type I

	A		B		C		D	
Mos	N	GMT	N	GMT	N	GMT	N	GMT
4	22	1.51	93	1.92	29	1.56	29	1.73
5	22	1.69	91	1.68	29	1.45	29	1.35
12	22	2.42	85	1.77	29	1.94	27	1.51
13	20	3.13	83	1.70	28	1.89	26	3.12

Type II

	A		B		C		D	
Mos	N	GMT	N	GMT	N	GMT	N	GMT
4	22	1.21	93	1.69	29	1.76	29	1.86
5	22	1.54	91	1.66	29	2.03	29	1.39
12	22	3.01	85	1.80	29	1.89	27	1.20
13	20	5.44	83	1.79	28	2.73	26	2.59

Type III

	A		B		C		D	
Mos	N	GMT	N	GMT	N	GMT	N	GMT
4	22	1.51	93	1.88	29	1.64	29	1.73
5	22	1.74	91	1.85	29	2.13	29	1.72
12	22	3.21	85	1.82	29	1.80	27	1.43
13	20	5.63	83	1.83	28	3.09	26	3.12

TABLE 14

Polio Protocol

Serum Neutralizing Antibodies
Percent with Detectable Antibody Titer
Plan B

Type I

Mos	PREMATURE	FULL TERM
2	9/ 13 (69.2)	44/ 53 (83.0)
4	3/ 11 (27.3)	32/ 46 (69.6)
5	11/ 11 (100.0)	43/ 45 (95.6)
12	9/ 9 (100.0)	39/ 44 (88.6)
13	9/ 9 (100.0)	42/ 44 (95.5)

Type II

Mos	PREMATURE	FULL TERM
2	12/ 13 (92.3)	47/ 53 (88.7)
4	9/ 11 (81.8)	44/ 46 (95.7)
5	11/ 11 (100.0)	45/ 45 (100.0)
12	9/ 9 (100.0)	42/ 44 (95.5)
13	9/ 9 (100.0)	44/ 44 (100.0)

Type III

Mos	PREMATURE	FULL TERM
2	10/ 13 (76.9)	41/ 53 (77.4)
4	7/ 11 (63.6)	38/ 46 (82.6)
5	11/ 11 (100.0)	43/ 45 (95.6)
12	9/ 9 (100.0)	40/ 44 (90.9)
13	9/ 9 (100.0)	44/ 44 (100.0)

Type Any

Mos	PREMATURE	FULL TERM
2	13/ 13 (100.0)	53/ 53 (100.0)
4	11/ 11 (100.0)	46/ 46 (100.0)
5	11/ 11 (100.0)	45/ 45 (100.0)
12	9/ 9 (100.0)	42/ 44 (95.5)
13	9/ 9 (100.0)	44/ 44 (100.0)

TABLE 15

Polio Protocol

Serum Neutralizing Antibodies
Reciprocal Geometric Mean Titers
Plan B

Type I

Mos	PREMATURE N	PREMATURE GMT	FULL TERM N	FULL TERM GMT
2	13	9.34	53	26.81
4	11	2.57	46	3.97
5	11	150.23	45	191.49
12	9	54.43	44	63.55
13	9	2031.87	44	1938.78

Type II

Mos	PREMATURE N	PREMATURE GMT	FULL TERM N	FULL TERM GMT
2	13	37.28	53	45.81
4	11	19.20	46	38.62
5	11	438.51	45	663.16
12	9	160.00	44	131.10
13	9	6450.80	44	5716.91

Type III

Mos	PREMATURE N	PREMATURE GMT	FULL TERM N	FULL TERM GMT
2	13	18.01	53	17.19
4	11	9.22	46	19.62
5	11	320.00	45	720.19
12	9	50.40	44	118.08
13	9	4063.75	44	5453.01

Serum Neutralizing Antibodies
Reciprocal Geometric Mean Titers in International Units
Plan B

Type I

	PREMATURE		FULL TERM	
Mos	N	GMT	N	GMT
2	13	0.11	53	0.31
4	11	0.03	46	0.12
5	11	1.75	45	2.23
12	9	0.64	44	0.74
13	9	23.71	44	22.63

Type II

	PREMATURE		FULL TERM	
Mos	N	GMT	N	GMT
2	13	0.21	53	0.26
4	11	0.11	46	0.22
5	11	2.48	45	3.75
12	9	0.90	44	0.74
13	9	36.45	44	32.30

Type III

	PREMATURE		FULL TERM	
Mos	N	GMT	N	GMT
2	13	0.18	53	0.17
4	11	0.09	46	0.20
5	11	3.20	45	7.20
12	9	0.50	44	1.18
13	9	40.64	44	54.53

Polio Protocol 01

SERUM NEUTRALIZING ANTIBODIES

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		Visit 1		Visit 2		Visit 3	
I	PLAN F1	14/15	(93.3)	14/15	(93.3)	15/15	(100.0)
	PLAN F2	15/15	(100.0)	15/15	(100.0)	15/15	(100.0)
II	PLAN F1	14/15	(93.3)	15/15	(100.0)	15/15	(100.0)
	PLAN F2	15/15	(100.0)	15/15	(100.0)	15/15	(100.0)
III	PLAN F1	14/15	(93.3)	15/15	(100.0)	15/15	(100.0)
	PLAN F2	14/15	(93.3)	15/15	(100.0)	15/15	(100.0)
ANY	PLAN F1	14/15	(93.3)	15/15	(100.0)	15/15	(100.0)
	PLAN F2	15/15	(100.0)	15/15	(100.0)	15/15	(100.0)

GEOMETRIC MEAN TITERS

		Visit 1		Visit 2		Visit 3	
TYPE		N	GMT	N	GMT	N	GMT
I	PLAN F1	15	172.90	15	4816.60	15	4888.79
	PLAN F2	15	335.13	15	4003.74	15	5615.74
II	PLAN F1	15	250.23	15	7760.48	15	12319.00
	PLAN F2	15	531.99	15	17828.90	15	17828.88
III	PLAN F1	15	143.72	15	13511.81	15	17828.90
	PLAN F2	15	345.80	15	14150.80	15	19555.19

GEOMETRIC MEAN TITERS IN INTERNATIONAL UNITS

		Visit 1		Visit 2		Visit 3	
TYPE		N	GMT	N	GMT	N	GMT
I	PLAN F1	15	2.02	15	56.21	15	57.05
	PLAN F2	15	3.91	15	46.72	15	65.54
II	PLAN F1	15	1.41	15	43.85	15	69.60
	PLAN F2	15	3.01	15	100.73	15	100.73
III	PLAN F1	15	1.44	15	135.12	15	178.29
	PLAN F2	15	3.46	15	141.51	15	195.55

Polio Protocol 01

NASOPHARYNGEAL SECRETIONS NEUTRALIZING ANTIBODIES

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		Visit 1	Visit 2	Visit 3
I	PLAN F1	0/15 (0.0)	11/15 (73.3)	8/15 (53.3)
	PLAN F2	4/15 (26.7)	9/15 (60.0)	10/15 (66.7)
II	PLAN F1	2/15 (13.3)	12/15 (80.0)	10/15 (66.7)
	PLAN F2	1/15 (6.7)	12/15 (80.0)	10/15 (66.7)
III	PLAN F1	4/15 (26.7)	13/15 (86.7)	14/15 (93.3)
	PLAN F2	6/15 (40.0)	12/15 (80.0)	11/15 (73.3)
ANY	PLAN F1	5/15 (33.3)	14/15 (93.3)	14/15 (93.3)
	PLAN F2	8/15 (53.3)	14/15 (93.3)	14/15 (93.3)

GEOMETRIC MEAN TITERS

		Visit 1		Visit 2		Visit 3	
TYPE		N	GMT	N	GMT	N	GMT
I	PLAN F1	15	0.00	15	6.35	15	6.65
	PLAN F2	15	1.45	15	3.17	15	5.79
II	PLAN F1	15	1.45	15	7.29	15	9.62
	PLAN F2	15	1.15	15	9.19	15	7.64
III	PLAN F1	15	1.74	15	12.70	15	20.16
	PLAN F2	15	2.19	15	10.56	15	11.58

GEOMETRIC MEAN TITERS IN INTERNATIONAL UNITS

		Visit 1		Visit 2		Visit 3	
TYPE		N	GMT	N	GMT	N	GMT
I	PLAN F1	15	0.00	15	0.07	15	0.08
	PLAN F2	15	0.02	15	0.04	15	0.07
II	PLAN F1	15	0.01	15	0.04	15	0.05
	PLAN F2	15	0.01	15	0.05	15	0.04
III	PLAN F1	15	0.02	15	0.13	15	0.20
	PLAN F2	15	0.02	15	0.11	15	0.12

TABLE 19

Polio Protocol 01

STOOL SPECIMENS NEUTRALIZING ANTIBODIES

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		Visit 1	Visit 2	Visit 3
I	PLAN F1	0/15 (0.0)	3/15 (20.0)	1/15 (6.7)
	PLAN F2	2/15 (13.3)	2/14 (14.3)	2/15 (13.3)
II	PLAN F1	0/15 (0.0)	2/15 (13.3)	1/15 (6.7)
	PLAN F2	2/15 (13.3)	2/14 (14.3)	7/15 (46.7)
III	PLAN F1	0/15 (0.0)	3/15 (20.0)	5/15 (33.3)
	PLAN F2	1/15 (6.7)	7/14 (50.0)	7/15 (46.7)
ANY	PLAN F1	0/15 (0.0)	6/15 (40.0)	5/15 (33.3)
	PLAN F2	3/15 (20.0)	8/15 (53.3)	8/15 (53.3)

GEOMETRIC MEAN TITERS

		Visit 1		Visit 2		Visit 3	
TYPE		N	GMT	N	GMT	N	GMT
I	PLAN F1	15	0.00	15	1.32	15	1.20
	PLAN F2	15	1.26	14	1.28	15	1.45
II	PLAN F1	15	0.00	15	1.32	15	1.32
	PLAN F2	15	1.32	14	1.49	15	3.48
III	PLAN F1	15	0.00	15	1.59	15	2.19
	PLAN F2	15	1.15	14	2.97	15	3.48

GEOMETRIC MEAN TITERS IN INTERNATIONAL UNITS

		Visit 1		Visit 2		Visit 3	
TYPE		N	GMT	N	GMT	N	GMT
I	PLAN F1	15	0.00	15	0.02	15	0.01
	PLAN F2	15	0.01	14	0.01	15	0.02
II	PLAN F1	15	0.00	15	0.01	15	0.01
	PLAN F2	15	0.01	14	0.01	15	0.02
III	PLAN F1	15	0.00	15	0.02	15	0.02
	PLAN F2	15	0.01	14	0.03	15	0.03

Polio Protocol 01

NASOPHARYNGEAL SECRETIONS (b)(4) IgA ANTIBODIES

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		Visit 1		Visit 2		Visit 3	
	PLAN F1	8/14	(57.1)	11/15	(73.3)	10/15	(66.7)
I	PLAN F2	10/15	(66.7)	10/15	(66.7)	12/15	(80.0)
	PLAN F1	10/14	(71.4)	10/15	(66.7)	10/15	(66.7)
II	PLAN F2	10/15	(66.7)	10/15	(66.7)	13/15	(86.7)
	PLAN F1	10/14	(71.4)	12/15	(80.0)	11/15	(73.3)
III	PLAN F2	11/15	(73.3)	10/15	(66.7)	14/15	(93.3)
	PLAN F1	10/15	(66.7)	12/15	(80.0)	11/15	(73.3)
ANY	PLAN F2	11/15	(73.3)	10/15	(66.7)	14/15	(93.3)

GEOMETRIC MEAN TITERS

TYPE		Visit 1		Visit 2		Visit 3	
		N	GMT	N	GMT	N	GMT
	PLAN F1	14	8.41	15	8.77	15	13.93
I	PLAN F2	15	12.13	15	6.96	15	10.56
	PLAN F1	14	9.28	15	8.77	15	12.70
II	PLAN F2	15	8.00	15	7.29	15	14.59
	PLAN F1	14	13.79	15	13.30	15	19.25
III	PLAN F2	15	10.56	15	10.08	15	20.16

Polio Protocol 01

STOOL SPECIMENS (b) (4) IgA ANTIBODIES

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		Visit 1	Visit 2	Visit 3
	PLAN F1	3/15 (20.0)	2/15 (13.3)	5/15 (33.3)
I	PLAN F2	3/15 (20.0)	1/15 (6.7)	3/15 (20.0)
	PLAN F1	3/15 (20.0)	4/15 (26.7)	6/15 (40.0)
II	PLAN F2	4/15 (26.7)	6/15 (40.0)	5/15 (33.3)
	PLAN F1	3/15 (20.0)	5/15 (33.3)	6/15 (40.0)
III	PLAN F2	3/15 (20.0)	5/15 (33.3)	4/15 (26.7)
	PLAN F1	3/15 (20.0)	5/15 (33.3)	7/15 (46.7)
ANY	PLAN F2	4/15 (26.7)	8/15 (53.3)	6/15 (40.0)

GEOMETRIC MEAN TITERS

		Visit 1		Visit 2		Visit 3	
TYPE		N	GMT	N	GMT	N	GMT
	PLAN F1	15	1.82	15	1.32	15	2.19
I	PLAN F2	15	1.82	15	1.15	15	1.59
	PLAN F1	15	1.66	15	1.82	15	2.52
II	PLAN F2	15	1.91	15	2.30	15	2.19
	PLAN F1	15	1.82	15	2.19	15	2.52
III	PLAN F2	15	1.59	15	2.19	15	2.00

Polio Protocol 01

SERUM NEUTRALIZING ANTIBODIES
PATIENTS HAD CONTACT WITH OPV

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		Visit 1	Visit 2	Visit 3
I	Plan F1	7/ 7 (100.0)	7/ 7 (100.0)	7/ 7 (100.0)
	Plan F2	5/ 5 (100.0)	5/ 5 (100.0)	5/ 5 (100.0)
II	Plan F1	7/ 7 (100.0)	7/ 7 (100.0)	7/ 7 (100.0)
	Plan F2	5/ 5 (100.0)	5/ 5 (100.0)	5/ 5 (100.0)
III	Plan F1	7/ 7 (100.0)	7/ 7 (100.0)	7/ 7 (100.0)
	Plan F2	5/ 5 (100.0)	5/ 5 (100.0)	5/ 5 (100.0)
ANY	Plan F1	7/ 7 (100.0)	7/ 7 (100.0)	7/ 7 (100.0)
	Plan F2	5/ 5 (100.0)	5/ 5 (100.0)	5/ 5 (100.0)

GEOMETRIC MEAN TITERS

		Visit 1		Visit 2		Visit 3	
TYPE		N	GMT	N	GMT	N	GMT
I	Plan F1	7	215.34	7	8400.23	7	7608.30
	Plan F2	5	422.24	5	2940.67	5	5881.34
II	Plan F1	7	430.69	7	6891.02	7	12482.72
	Plan F2	5	211.12	5	8914.46	5	8914.44
III	Plan F1	7	118.88	7	10240.02	7	16800.50
	Plan F2	5	557.15	5	17828.92	5	23525.40

GEOMETRIC MEAN TITERS IN INTERNATIONAL UNITS

		Visit 1		Visit 2		Visit 3	
TYPE		N	GMT	N	GMT	N	GMT
I	Plan F1	7	2.51	7	98.03	7	88.79
	Plan F2	5	4.93	5	34.32	5	68.64
II	Plan F1	7	2.43	7	38.93	7	70.53
	Plan F2	5	1.19	5	50.37	5	50.37
III	Plan F1	7	1.19	7	102.40	7	168.00
	Plan F2	5	5.57	5	178.29	5	235.25

TABLE 23

SERUM NEUTRALIZING ANTIBODIES
PATIENTS DID NOT HAVE CONTACT WITH OPV

PERCENT WITH DETECTABLE ANTIBODY TITER

TYPE		Visit 1		Visit 2		Visit 3	
I	Plan F1	7/ 8	(87.5)	7/ 8	(87.5)	8/ 8	(100.0)
	Plan F2	10/10	(100.0)	10/10	(100.0)	10/10	(100.0)
II	Plan F1	7/ 8	(87.5)	8/ 8	(100.0)	8/ 8	(100.0)
	Plan F2	10/10	(100.0)	10/10	(100.0)	10/10	(100.0)
III	Plan F1	7/ 8	(87.5)	8/ 8	(100.0)	8/ 8	(100.0)
	Plan F2	9/10	(90.0)	10/10	(100.0)	10/10	(100.0)
ANY	Plan F1	7/ 8	(87.5)	8/ 8	(100.0)	8/ 8	(100.0)
	Plan F2	10/10	(100.0)	10/10	(100.0)	10/10	(100.0)

GEOMETRIC MEAN TITERS

		Visit 1		Visit 2		Visit 3	
TYPE		N	GMT	N	GMT	N	GMT
I	Plan F1	8	142.68	8	2960.63	8	3319.91
	Plan F2	10	298.57	10	4671.71	10	5487.48
II	Plan F1	8	155.60	8	8610.79	8	12177.50
	Plan F2	10	844.49	10	25213.87	10	25213.84
III	Plan F1	8	169.68	8	17221.64	8	18780.27
	Plan F2	10	272.43	10	12606.92	10	17828.30

GEOMETRIC MEAN TITERS IN INTERNATIONAL UNITS

		Visit 1		Visit 2		Visit 3	
TYPE		N	GMT	N	GMT	N	GMT
I	Plan F1	8	1.67	8	34.55	8	38.74
	Plan F2	10	3.48	10	54.52	10	64.04
II	Plan F1	8	0.88	8	48.65	8	68.80
	Plan F2	10	4.77	10	142.46	10	142.46
III	Plan F1	8	1.70	8	172.22	8	187.80
	Plan F2	10	2.72	10	126.07	10	178.29

Attachment 2

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SEROLOGIC RESPONSE TO ORAL POLIO VACCINE AND ENHANCED-POTENCY INACTIVATED POLIO VACCINES

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THE FIELD STAFF AND COORDINATING COMMITTEE[4]

McBean, A. M. (The Johns Hopkins U. School of Hygiene and Public Health, Baltimore, MD 21205), M. L. Thoms, P. Albrecht, J. C. Cuthie, R. Bernier, and the Field Staff and Coordinating Committee. The serologic response to oral polio vaccine and enhanced-potency inactivated polio vaccines. *Am J Epidemiol* 1988;128:615–28.

In a randomized, controlled trial carried out from November 1980 to July 1983 involving 1,114 infants in Baltimore City and in Baltimore and Prince George's counties, Maryland, the serologic response to three doses of two enhanced-potency inactivated polio vaccines was compared with the response to three doses of oral polio vaccine. The mean ages at vaccination were 2.2, 4.7, and 19.9 months, respectively, for the three doses. Seroconversion after the first dose varied from 35% to 84%, and it was higher after oral polio vaccine than after either of the enhanced-potency inactivated polio vaccines for polioviruses types 2 and 3. Approximately two and one-half and 16 months after the second dose, almost all inactivated polio vaccine recipients had antibodies against all three virus types (98–100%). Fewer oral polio vaccine recipients had detectable antibodies to type 1 (89–92%) and to type 3 (96%). After three doses of vaccine, all children had antibodies against types 2 and 3. Approximately 1% of the inactivated polio vaccine recipients and 3% of the oral polio vaccine recipients lacked antibody to type 1. One or two doses of oral polio vaccine stimulated higher reciprocal geometric mean antibody titers against type 2 poliovirus than did the inactivated polio vaccine. For the other two types, the results were mixed. The third dose of inactivated polio vaccine produced significant increases in the reciprocal geometric mean titers against each of the three poliovirus types and resulted in significantly higher reciprocal geometric mean titers after three doses of vaccine for recipients of inactivated polio vaccine than for recipients of oral polio vaccine.

poliomyelitis; poliovirus; poliovirus vaccine; serology

Since 1962, the Immunization Practices Advisory Committee (1), the Committee on Infectious Diseases of the American Academy of Pediatrics (2), and other groups (3)

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have recommended oral trivalent polio vaccine as the principal polio vaccine for use in the United States. During this time, the annual number of reported paralytic polio cases decreased from 820 cases in 1961 (0.7/100,000) to seven in 1984 (<0.01/100,000) (4), confirming the remarkable effectiveness of this vaccine.

From 1973 through 1984, a total of 138 cases of paralytic polio were reported to the Centers for Disease Control (an average of 11.5 cases per year). One hundred and five of these (76 per cent) were associated with the administration of oral polio vaccine. During the most recent three years for which reporting is complete (1982–1984), 29 cases were reported, and all but one were vaccine-associated. Estimates of the overall risk of paralysis in oral polio vaccine recipients, based on the number of cases of paralytic polio reported in the United States and the number of doses of vaccine administered from 1973 through 1984, are one case per 2.6 million doses distributed, or approximately one case per 500,000 for the first dose given and one case per 13,000,000 for subsequent doses (5).

While the United States has relied almost exclusively on oral polio vaccine for the past 24 years, other countries (Sweden, Finland, and the Netherlands) have achieved control of polio with the use of trivalent inactivated polio vaccine. Prior to the outbreak of nine cases of paralytic polio and one case of aseptic meningitis in Finland in 1984–1985 (6), the circulation of wild poliovirus had not been documented in Sweden and Finland since the early 1960s, and the few cases reported from Sweden and the Netherlands were in immigrants or in people or groups who had refused to be vaccinated (7–9).

The 1984–1985 outbreak in Finland, while raising alarm about the effectiveness of inactivated polio vaccine, was felt to be due to a combination of 1) a decrease in vaccination coverage (the vaccination coverage rate in three-year-old children dropped from 99 per cent to 78 per cent from the 1970s to 1983), 2) antigenic differences between the Finland wild virus strain and the type 3 component of the Finnish inactivated polio vaccine, and 3) low immunogenicity of the type 3 component of the inactivated polio vaccine used in Finland. Finnish authorities continue to express confidence in inactivated polio vaccine, and in 1986 Finland began administering an enhanced-potency inactivated polio vaccine similar to that described below (6).

In the past eight years, new methods have been developed by van Wezel et al. (10) at the Rijks Instituut voor de Volksgezondheid, The Netherlands, for the production of a higher-potency inactivated polio vaccine by means of the microcarrier technique and tertiary monkey kidney cells. Similar vaccines are also made by the Institut Merieux, France, and Connaught Laboratories Ltd., Canada. Salk and colleagues (11–13) have reported excellent antibody responses following one and two doses of this type of vaccine. This paper reports the results of a study that compares the serologic response in healthy American infants given three doses of enhanced-potency inactivated polio vaccine made by the new production methods with the response of children given three doses of commercially available oral polio vaccine.

Materials and Methods

Participants and study design

Children aged six through 13 weeks ("two months") attending well-child clinics in Baltimore City and Baltimore County (hereafter called Baltimore) and Prince

ment, and Dr. Ruth L. Steerman of the Prince George's County Hospital.

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George's County, Maryland, were enrolled in the study between November 1980 and July 1983. In all cases, parents or guardians were given complete information about the study, and their written informed consent was obtained. In each geographic area (Baltimore or Prince George's County), the children were randomly assigned to receive either oral polio vaccine or one of two enhanced-potency inactivated polio vaccines described below. The children were scheduled to receive additional doses of the same polio vaccine at four and 18 months of age. Diphtheria-tetanus-pertussis vaccine was administered at the same time as the polio vaccine, as was either an oral or injectable placebo corresponding to the kind of polio vaccine that the child did not receive. Blood specimens were obtained at each vaccination and two months after the dose given at four months and at 18 months, that is, at ages two, four, six, 18, and 20 months.

Vaccines

Commercially licensed oral polio vaccine manufactured by Lederle Laboratories, Inc. (Wayne, NJ) was used. It contained 800,000 $TCID_{50}$ (tissue culture infectious dose, 50 per cent infectivity) of type 1, 100,000 $TCID_{50}$ of type 2, and 500,000 $TCID_{50}$ of type 3 per 0.5 cm^3 dose. The enhanced-potency inactivated polio vaccines were manufactured by the Institut Merieux, Lyon, France (designated as inactivated polio vaccine A) and by Connaught Laboratories Ltd., Willowdale, Ontario, Canada (designated as inactivated polio vaccine B). Upon receipt of the vaccine in Baltimore and approximately every four months, samples of the enhanced-potency inactivated polio vaccines were sent to the Rijks Instituut, Bilthoven, The Netherlands, where vaccine potency, measured by D-antigen content, was determined by Dr. van Wezel. The range of potency for the Institut Merieux vaccine was 24 to 38, 3.6 to 6.5, and 28 to 36 for types 1, 2, and 3, respectively. The range of potency was 20 to 25, 7.0 to 9.2, and 26 to 30, respectively, for the Connaught vaccine. The Connaught vaccine became available 20 months after the start of the study. As a result, the initial 593 children described in this study were randomized to receive either inactivated polio vaccine A or oral polio vaccine. The last 521 children enrolled were randomized among all three vaccines, with 72 per cent of them allocated to receive inactivated polio vaccine B.

The diphtheria-tetanus-pertussis vaccine contained 12.5 Lf of diphtheria toxoid, 5 Lf of tetanus toxoid, and 4 mouse protective units of pertussis per 0.5 cm^3 dose.

Blood specimens

With Microtainer (Becton-Dickinson, Rutherford, NJ) capillary tubes, approximately 2 cm^3 of blood was obtained by a finger- or heel-stick. After collection, the blood was allowed to clot and was centrifuged. The serum was drawn off, and the serum specimens were refrigerated. They were placed in a freezer and stored at −20 C until examined in the laboratory. Unbiased laboratory analysis was ensured by coding specimens before sending them to the laboratory.

Adverse reactions

At administration of each dose of vaccine, parents were told they would be contacted for the next three days for information on possible adverse local or systemic reactions in their children. They were given a copy of the data form on which the site coordinators would record reaction information on erythema, pain, and induration at the sites of injection, as well as the systemic signs of fever, fussiness, sleepiness, spitting up, decreased eating, increased crying, or seizures. Erythema at the injection site was recorded as present or absent. Pain was rated as "none," "some" (child moved limb or responded negatively when the site was touched), or "much" (child cried when the site was touched). Parents were also instructed in how to take their children's temperatures and were

given a thermometer. When the children returned for a follow-up visit, parents were asked if any severe reactions had occurred since the previous visit.

Laboratory testing

Serum poliovirus-neutralizing antibodies were measured at the Office of Biologics Research and Review, Food and Drug Administration, Department of Health and Human Services (Bethesda, MD), by a sensitive virus cytopathic effect neutralization test in microtiter trays (14). Each day, a serum reference provided by the Rijks Instituut was tested with the experimental sera. This reference was standardized against the World Health Organization International Standard for Antipoliovirus Sera and was assigned values of 11 International Units (IU) of antibody against poliovirus type 1, 50 IU against poliovirus type 2, and 12 IU against poliovirus type 3. A conversion factor was calculated with each test for converting the observed reciprocals of the serum dilution titers to International Units. One International Unit of antibody corresponds to a serum titer of 1:110 for type 1, 1:70 for type 2, and 1:110 for type 3 poliovirus antibody.

RESULTS

Specimens were lost or collection tubes were broken for 20 of 1,134 children enrolled in the study. Of the remaining 1,114 children, 371 received enhanced-potency inactivated polio vaccine A, 366 received oral polio vaccine, and 377 received enhanced-potency inactivated polio vaccine B. In 88 instances, there was not enough serum to perform antibody determinations to all three poliovirus types starting at a dilution of 1:4. Seventy-two of these cases were in infants two months of age. When serum dilutions began at 1:8 or higher for a poliovirus type and no neutralizing activity was found, the data were omitted for that determination, but other serologic data on that child were included in the analysis.

Prevaccination

At enrollment, the percentage of children with antibodies to each of the three poliovirus types was similar for the inactivated polio vaccine A and oral polio vaccine groups (table 1 and figure 1). Approximately 90 per cent had antibodies to type 1, 95 per cent to type 2, and 78 per cent to type 3. More children in the inactivated polio vaccine B group had antibodies to type 2 poliovirus than did children in the oral polio vaccine group and to type 3 poliovirus than did children in either the inactivated polio vaccine A group or the oral polio vaccine group. However, the reciprocal geometric mean titers were similar for all three virus types for each vaccine group (table 2 and figure 2). The differences in the percentage of children with detectable antibodies were probably artifactual and were probably caused by the fact that the inactivated polio vaccine B group children were enrolled later (because enhanced-potency inactivated polio vaccine B was not available at the start of the study). After testing approximately one third of the two-, four-, and six-month blood samples from enhanced-potency inactivated polio vaccine A and oral polio vaccine recipients, we introduced a change in the virus neutralization test that increased its sensitivity approximately threefold (the serum-virus mixtures were incubated overnight at 36 C rather than at 4 C (14)). This explains the higher seropositivity rates in the inactivated polio vaccine B recipients before and after the first dose of vaccine. The change in the antibody technique had no effect, or a minimal effect, on the seropositivity rate at age six months and no effect at 18 or 20 months of age. Modifications in the performance of the neutralization test had no effect on the value of the geometric mean titers, expressed in International Units.

Post first dose

Two and one-half months after the first dose of inactivated polio vaccine, a signifi-

TABLE 1

Percentage of children with detectable antibodies to the three types of wild poliovirus at ages 2, 4, 6, 18, and 20 months, Maryland, 1980–1983

Age (months) at visit and vaccine group*	Mean age (months)	Type 1		Type 2		Type 3	
		No. of children	% with detectable antibodies	No. of children	% with detectable antibodies	No. of children	% with detectable antibodies
Two (prevaccination)							
IPV-A	2.2	331	90.9	338	96.5	318	78.3
OPV	2.2	337	89.6	343	94.2	323	78.0
IPV-B	2.2	332	93.4	351	98.9	317	89.6
Four							
IPV-A	4.6	309	93.5†	311	96.1	306	85.3
OPV	4.7	289	86.5	303	97.7	295	85.4
IPV-B	4.7	312	93.9	324	100.0	311	93.6
Six							
IPV-A	7.0	297	99.0	298	99.0	296	99.0
OPV	7.0	269	92.2	273	99.6	273	96.0
IPV-B	7.1	313	99.0	319	100.0	319	99.7
18							
IPV-A	20.2	225	98.7	229	99.6	228	97.8
OPV	19.8	187	88.8	189	100.0	189	97.4
IPV-B	20.2	245	97.6	247	99.6	247	98.4
20							
IPV-A	22.9	219	99.1	219	100.0	219	100.0
OPV	22.5	192	96.9	193	100.0	193	100.0
IPV-B	22.9	224	100.0	224	100.0	223	100.0

* IPV-A, trivalent enhanced-potency inactivated polio vaccine produced by the Institut Merieux, France; OPV, trivalent oral polio vaccine; IPV-B, trivalent enhanced-potency inactivated polio vaccine produced by Connaught Laboratories Ltd., Canada.

† Brackets indicate a difference between the two numbers that is significant at $p < 0.01$.

cant increase in the percentage of children with detectable antibodies was seen only in the inactivated polio vaccine A group and only against type 3 poliovirus, where it increased from 78 per cent to 85 per cent (table 1). Correspondingly, all of the geometric mean titers in the inactivated polio vaccine groups decreased or remained the same compared with the levels seen before vaccination was begun except the titers against type 3 poliovirus for the inactivated polio vaccine A recipients (table 2). After one dose of oral polio vaccine, there was a significant increase from 78 per cent to 85 per cent in the number of children who had detectable antibodies against type 3 poliovirus (table 1). No change was seen for types 1 and 2. Significant increases were seen in the geometric mean titers against types 2 and 3. These geometric mean titers were also statistically greater than the titers obtained after one dose of either of the enhanced-potency inactivated polio vaccines (table 2). For type 1, the geometric mean titer in the oral polio vaccine recipients did not change.

Figure 3 shows the percentage of children who demonstrated seroconversion to each of the vaccines after one dose of vaccine. (Seroconversion is defined as the presence of antibodies four or more times greater than the expected value at the second blood specimen, based on the level of maternal antibodies detected at the first vaccination and their estimated subsequent reduction.) A half-life of 28 days for the maternal antibodies was used in the calculation (15, 16). In general, this meant that children who had an antibody level at the four-month visit that equaled or exceeded the

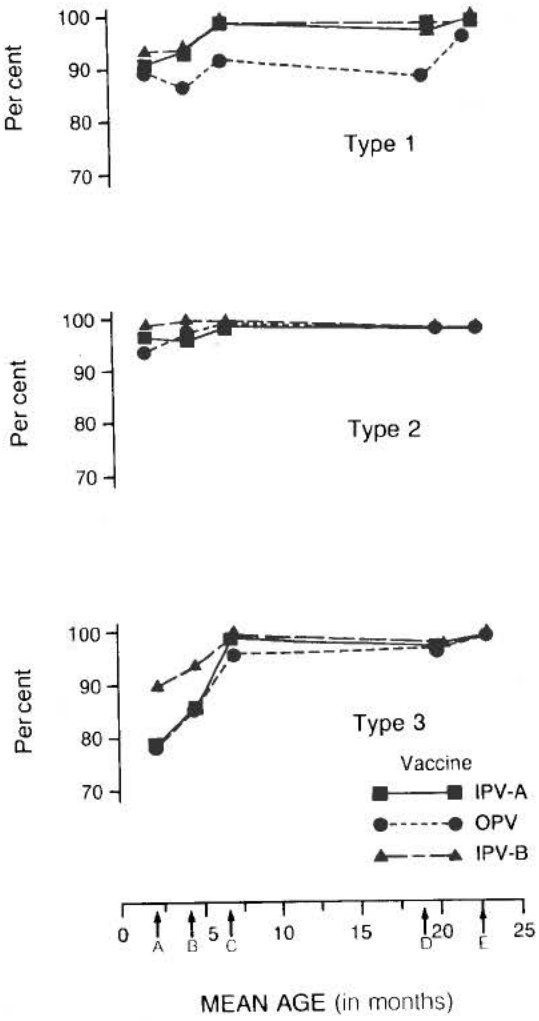

FIGURE 1. Percentage of children with detectable poliovirus-neutralizing antibodies at or after each dose of vaccine for each study group and poliovirus type: Baltimore City and Baltimore and Prince George's counties, Maryland, 1980–1983. *A*, preimmunization titer at age two months; *B*, titer two months post first dose; *C*, titer two months post second dose; *D*, titer at time of third dose; *E*, titer two months post third dose. IPV-A, trivalent enhanced-potency inactivated polio vaccine produced by the Institut Merieux, France; OPV, trivalent oral polio vaccine; IPV-B, trivalent enhanced-potency inactivated polio vaccine produced by Connaught Laboratories Ltd., Canada.

titer measured at two months of age were considered to have seroconverted. All three vaccines caused roughly the same amount of seroconversion to type 1 poliovirus (35 per cent to 42 per cent). Oral polio vaccine induced seroconversion to a greater degree than did either of the enhanced-potency inactivated polio vaccines against both type 2 and type 3 (84 per cent and 71 per cent, respectively). However, the enhanced-potency inactivated polio vaccines were able to stimulate seroconversion in a significant number of children in the presence of readily detectable maternal antibodies. For type 2, the range was between 35 per cent and 43 per cent; for type 3, it was between 54 per cent and 61 per cent.

Post second dose

Two and one-half months after receiving the second dose of vaccine, 99 per cent of the enhanced-potency inactivated polio vaccine recipients had detectable antibodies to type 1 poliovirus, while significantly fewer children (92.2 per cent) in the oral polio vaccine group had antibodies to this type. The geometric mean titers for all groups after the second dose of vaccine were significantly greater than they were after one dose. The enhanced-potency inactivated polio vaccine A stimulated the highest titers to type 1 poliovirus.

All three groups had 99 per cent or more children with detectable antibodies to type 2 poliovirus after the second dose of vaccine. The geometric mean titer for the oral polio vaccine group was significantly higher than that for either of the inactivated polio vaccine groups, and the geometric mean titer for the inactivated polio vaccine B group was significantly higher than that for the inactivated polio vaccine A group. The geometric mean titers for all groups were significantly higher than they were after one dose of vaccine.

After the second dose of vaccine, 99 per cent or more of the children in the enhanced-potency inactivated polio vaccine groups had detectable antibodies to type 3 poliovirus compared with 96 per cent for the oral polio vaccine group. The difference was significant between the inactivated polio vaccine B group and the oral polio vaccine group. The geometric mean titers for all groups were significantly greater than they were after one dose of

TABLE 2

Reciprocal geometric mean titers (GMT), in International Units, of antibody to the three types of wild poliovirus in children at ages 2, 4, 6, 18, and 20 months, Maryland, 1980–1983

Age (months) at visit and vaccine group*	Mean age (months)	Type 1		Type 2		Type 3	
		No. of children	GMT	No. of children	GMT	No. of children	GMT
Two							
IPV-A	2.2	331	0.39	338	1.07	318	0.25
OPV	2.2	337	0.38	343	0.92	323	0.25
IPV-B	2.2	332	0.36	351	0.84	317	0.20
Four							
IPV-A	4.6	309	0.28 †	311	0.64	306	0.32
OPV	4.7	289	0.39	303	7.73	295	1.94
IPV-B	4.7	312	0.17	324	0.60	311	0.20
Six							
IPV-A	7.0	297	2.10	298	3.64	296	4.98
OPV	7.0	269	1.04	273	17.01	273	4.37
IPV-B	7.1	313	1.29	319	6.77	319	3.33
18							
IPV-A	20.2	225	1.37	229	4.43	228	1.78
OPV	19.8	187	0.96	189	9.45	192	2.67
IPV-B	20.2	245	0.51	247	4.21	247	1.35
20							
IPV-A	22.9	219	12.96	219	25.44	219	16.42
OPV	22.5	192	2.69	193	19.20	193	4.41
IPV-B	22.9	224	7.98	224	28.14	223	17.75

* IPV-A, trivalent enhanced-potency inactivated polio vaccine produced by the Institut Merieux, France; OPV, trivalent oral polio vaccine; IPV-B, trivalent enhanced-potency inactivated polio vaccine produced by Connaught Laboratories Ltd., Canada.

† Brackets indicate a difference between the two numbers that is significant at $p < 0.01$.

vaccine and were not significantly different from each other.

The percentage of children with antibodies to all the poliovirus types for which their serum was tested was 97 for inactivated polio vaccine A, 90 for oral polio vaccine, and 99 for inactivated polio vaccine B. No child who received inactivated polio vaccine B was seronegative to more than one poliovirus type. One inactivated polio vaccine A recipient lacked antibodies to types 2 and 3. Five oral polio vaccine recipients lacked antibodies to types 1 and 3, and one lacked antibodies to types 2 and 3.

Pre third dose

In the 12- to 13-month interval between the third and fourth blood specimens, there was no statistically significant change in the percentage of children with detectable antibodies, and the geometric mean titers did not drop more than two dilutions.

We examined separately the results from children for whom paired serum specimens were available after the second dose and at the time the third dose of vaccine was given (table 3). The results for these children are essentially the same as those shown in table 2. During this interval, which averaged 13 months, there was less than a one-dilution decrease in the titers in the children who received oral polio vaccine. In the enhanced-potency inactivated polio vaccine groups, the decreases seen in titers were generally greater than for the oral polio vaccine group, but in no case were they more than two serial dilutions.

Post third dose

Two and one-half months after receiving the third dose of vaccine, all children had measurable antibodies against poliovirus types 2 and 3. All children who received enhanced-potency inactivated polio vac-

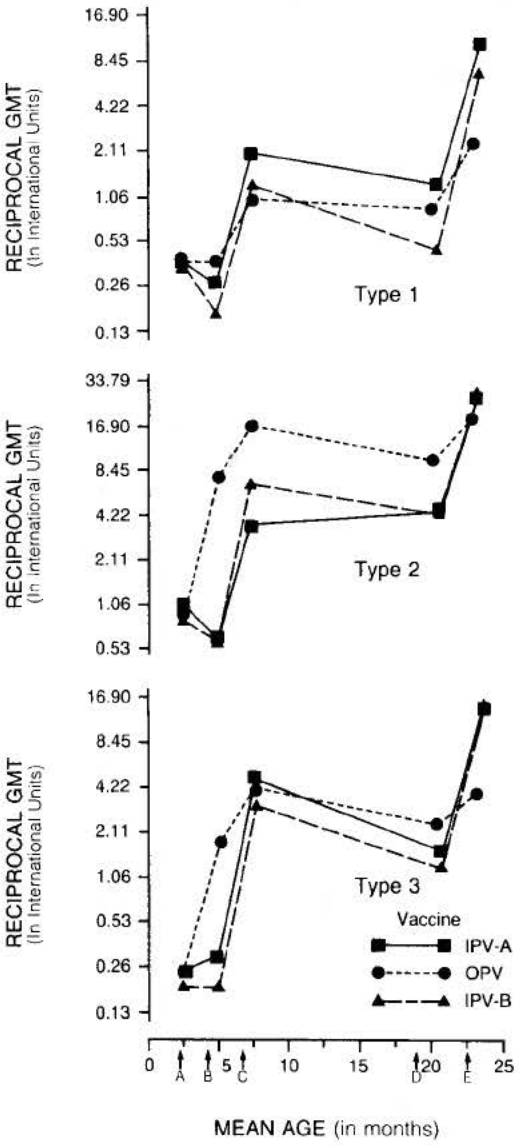

FIGURE 2. Reciprocal geometric mean titers (International Units) of poliovirus-neutralizing antibodies in children at or after each dose of vaccine for each study group and poliovirus type: Baltimore City and Baltimore and Prince George's counties, Maryland, 1980–1983. *A*, preimmunization titer at age two months; *B*, titer two months post first dose; *C*, titer two months post second dose; *D*, titer at time of third dose; *E*, titer two months post third dose. IPV-A, trivalent enhanced-potency inactivated polio vaccine produced by the Institut Merieux, France; OPV, trivalent oral polio vaccine; IPV-B, trivalent enhanced-potency inactivated polio vaccine produced by Connaught Laboratories Ltd., Canada.

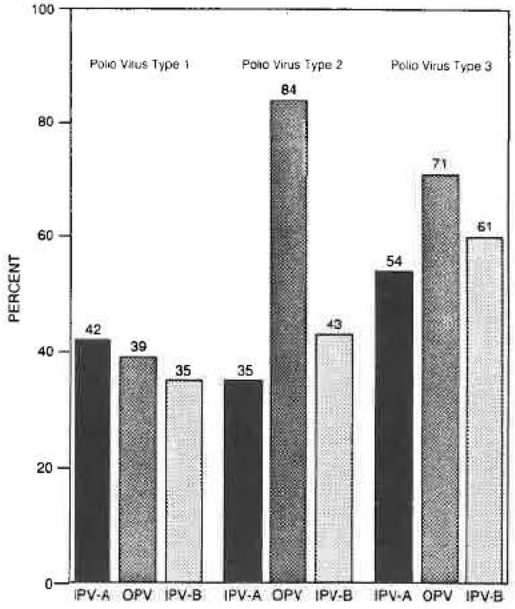

FIGURE 3. Percentage of children with seroconversion to one dose of either inactivated polio vaccine or oral polio vaccine given at two months of age: Baltimore City and Baltimore and Prince George's counties, Maryland, 1980–1983. See text for definition of seroconversion. IPV-A, trivalent enhanced-potency inactivated polio vaccine produced by the Institut Merieux, France; OPV, trivalent oral polio vaccine; IPV-B, trivalent enhanced-potency inactivated polio vaccine produced by Connaught Laboratories Ltd., Canada.

cine B were also protected against type 1. Only 1 per cent of the 219 children given three doses of enhanced-potency inactivated polio vaccine A did not produce antibodies to type 1, and only 3 per cent of the oral polio vaccine group did not have measurable antibodies to this type. At a group mean age of 22 or 23 months, the children who received the new enhanced-potency inactivated polio vaccines had significantly higher geometric mean titers to all three poliovirus types than did the children who received oral polio vaccine. The inactivated polio vaccine A group had significantly higher titers for type 1 than did the inactivated polio vaccine B group.

Adverse reactions

Table 4 presents information obtained about adverse reactions that occurred dur-

TABLE 3

Reciprocal geometric mean titers, in International Units, of poliovirus-neutralizing antibodies in children at ages 6 and 18 months for whom both specimens were taken, Maryland, 1980–1983

Poliovirus type and vaccine group*	No. of children	Geometric mean titer		p value
		Age six months	Age 18 months	
Type 1				
IPV-A	215	2.186	1.338	0.0001
OPV	175	1.068	1.027	0.7701
IPV-B	236	1.365	0.527	0.0001
Type 2				
IPV-A	215	3.724	4.416	0.1746
OPV	175	17.744	9.713	0.0001
IPV-B	236	6.855	4.133	0.0001
Type 3				
IPV-A	215	5.021	1.786	0.0001
OPV	175	4.612	2.556	0.0001
IPV-B	236	3.407	1.328	0.0001

* IPV-A, trivalent enhanced-potency inactivated polio vaccine produced by the Institut Merieux, France; OPV, trivalent oral polio vaccine; IPV-B, trivalent enhanced-potency inactivated polio vaccine produced by Connaught Laboratories Ltd., Canada.

ng the 48 hours after administration of the accines. Parents had the opportunity to provide information for the time periods of less than six, 6–23, and 24–48 hours after vaccination. Almost all parents (95.9 per cent) provided information for all three time periods. The data in table 5 represent reports following the administration of 991 first doses of polio vaccine, 893 second doses, and 544 third doses.

As mentioned above, the study groups were stratified according to geographic area, and the children were then randomized according to the polio vaccine they received. The marked difference in the adverse reaction rates according to the geographic area in which the child lived indicates the importance of the stratification. The reported adverse reaction rates recorded in children from Baltimore are higher for all but one reaction than they are for participants from the Prince George's County Health Department clinics. Interestingly, the only systemic reaction for which there is not a significant difference between the two geographic areas is a temperature ≥39 C, which is the most objective of all the observations ($p > 0.05$).

Comparison of the local reactions (erythema, pain, and induration) to inactivated polio vaccine A and to the injectable placebo given to the oral polio vaccine group for each geographic area shows no statistically significant differences. Likewise, there were no significant differences in any of the systemic reactions. Comparison of these two groups is mentioned first because it is only for these two groups that the infants were truly randomized. As was explained above, inactivated polio vaccine B was not made available for the study until 593 children (53 per cent) had been enrolled in either the inactivated polio vaccine A group or the oral polio vaccine group. Thus, rigorously speaking, the inactivated polio vaccine A and oral polio vaccine groups are historical controls for the inactivated polio vaccine B group. This fact notwithstanding, there were no significant differences between the inactivated polio vaccine B group and the two other groups in the reported rates of local reactions and for four of the six systemic reactions. A greater proportion of the children who received inactivated polio vaccine B were reported to be sleepier than usual, and in Prince George's County, a slightly greater percentage were reported to have a temperature ≥39 C.

Temperatures of >40 C were reported in 12 children. All these episodes occurred during the first 24 hours following vaccination, and they were similarly distributed in the three vaccine groups. One child who received the third dose of oral polio vaccine with the fourth dose of diphtheria-tetanus-pertussis vaccine was reported as having two convulsions within eight hours of receiving the vaccines. This child was seen by a private physician, and no neurologic sequelae were reported after 12 months of follow-up. Thus, we observed one convulsion per 834 fourth doses of diphtheria-tetanus-pertussis vaccine given, or one convulsion per 2,428 doses. No fainting or

TABLE 4

Frequency of reported local adverse reactions in vaccinated children at the site of inactivated polio vaccine or placebo injection and mild systemic reactions reported during the first 48 hours after vaccination, by geographic area and vaccine group per 100 children, Maryland, 1980–1983

	Baltimore				Prince George's County			
	IPV-A*	OPV (IPV placebo)	IPV-B	Total	IPV-A	OPV (IPV placebo)	IPV-B	Total
Number of doses	371	388	352	1,111	459	376	482	1,317
Local reaction								
Erythema	3.2	4.6	5.1	4.3	0.2	0.5	0.4	0.4
Pain								
Some	10.2	13.6	16.2	13.3	1.3	0.5	1.0	1.0
Much	2.7	1.8	1.1	1.9	0.2	0.0	0.0	0.1
Total	12.9	15.4	17.3	15.2	1.5	0.5	1.0	1.1
Induration								
<2 inches	1.1	1.3	2.8	1.7	0.2	0.0	0.0	0.1
2–4 inches	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.1
Systemic reaction								
Temperature ≥39 C	38.5	34.5	31.5	34.9	25.7	29.2	33.8 †	31.8
Sleepier than usual	40.9	36.8	59.9	54.0	5.7	6.6	12.8	8.6
Fussier than usual	63.6	64.0	69.3	63.7	18.9	21.0	26.8	23.4
Spitting up more than usual	8.9	9.2	11.1	11.7	1.3	1.5	<0.1	1.0
Eating less than usual	15.4	14.7	23.8	17.8	2.1	2.1	2.9	2.4
Crying more than usual	28.0	29.4	33.8	27.1	7.2	8.2	5.8	5.8

* IPV-A, trivalent enhanced-potency inactivated polio vaccine produced by the Institut Merieux, France, OPV, trivalent oral polio vaccine; IPV-B, trivalent enhanced-potency inactivated polio vaccine produced by Connaught Laboratories Ltd., Canada.

† Brackets indicate a difference between the vaccine groups for each geographic area that is significant at $p < 0.01$.

other neurologic events were reported for any of the children in the three days following vaccination or in the rest of the period between vaccinations.

The rates of local reactions at the site of diphtheria-tetanus-pertussis vaccinations are shown in table 5. Again, there is a marked difference in the rates for each of the two geographic areas. In no case is the rate for children who received enhanced-potency inactivated polio vaccine plus diphtheria-tetanus-pertussis vaccine significantly higher than for the children who received oral polio vaccine plus diphtheria-tetanus-pertussis vaccine.

Potentially confounding factors

Because this study was carried out in the United States, where oral polio vaccine is routinely administered, it is possible that study participants could have been exposed to vaccine virus given to a sibling or other close contact which would have stimulated the production of polio antibodies. This concern was, in part, addressed by the finding that in the 12- to 13-month interval between the third and fourth blood specimens, there was a drop in antibody titers in all three groups against all three virus serotypes except in the inactivated polio vaccine A group, which had a higher, although not statistically greater, type 2 antibody titer at the 18-month visit compared with the six-month visit (tables 2 and 3).

In addition, at each visit, parents were asked about the administration of oral polio vaccine to a sibling or other child living in the same household. Table 6 compares the

TABLE 5

Frequency of local adverse reactions in vaccinated children at the site of diphtheria-tetanus-pertussis (DTP) injection during the first 48 hours after vaccination, by geographic area and vaccine group per 100 children, Maryland, 1980–1983

	Baltimore				Prince George's County			
	IPV-A*	OPV	IPV-B	Total	IPV-A	OPV	IPV-B	Total
Number of doses	371	388	352	1,111	459	376	482	1,317
Local reaction at site of DTP injection								
Erythema	19.2	26.8	23.9	23.4	3.1	3.5	4.3	3.6
Pain								
Some	23.4	38.4	44.9 †	35.5	4.1	5.6	7.9	5.9
Much	10.8	10.3	10.5	10.5	0.2	0.0	0.2	0.2
Total	34.2	48.7	55.4	46.0	4.3	5.6	8.1	6.0
Induration								
<2 inches	22.6	22.9	28.1	24.5	1.5	2.9	4.8	3.1
2–4 inches	1.1	0.5	0.2	0.6	0.2	0.0	0.0	0.1

* IPV-A, trivalent enhanced-potency inactivated polio vaccine produced by the Institut Merieux, France; OPV, trivalent oral polio vaccine; IPV-B, trivalent enhanced-potency inactivated polio vaccine produced by Connaught Laboratories Ltd., Canada.

† Brackets indicate a difference between the vaccine groups for each geographic area that is significant at $p < 0.01$.

TABLE 6

Reciprocal geometric mean titers (GMT), in International Units, of poliovirus-neutralizing antibodies in children two months after the third dose of polio vaccine, by whether or not a sibling received oral polio vaccine during the study, Maryland, 1980–1983

Vaccine group* and poliovirus type	GMT if sibling received OPV	GMT if sibling did not receive OPV	*p* value
IPV-A	($n = 54$)†	($n = 165$)	
1	10.732	13.778	0.2508
2	24.296	25.827	0.6826
3	14.559	17.083	0.4224
OPV	($n = 37$)	($n = 156$)	
1	1.527	3.081	0.0673
2	13.136	21.015	0.0201
3	3.027	4.826	0.0394
IPV-B	($n = 60$)	($n = 164$)	
1	9.234	7.564	0.2073
2	31.146	27.120	0.1295
3	20.033	16.975	0.2351

* IPV-A, trivalent enhanced-potency inactivated polio vaccine produced by the Institut Merieux, France; OPV, trivalent oral polio vaccine; IPV-B, trivalent enhanced-potency inactivated polio vaccine produced by Connaught Laboratories Ltd., Canada.

† Number of children.

reciprocal geometric mean titers two months after the third dose of vaccine in study participants who had siblings who received oral polio vaccine during the course of the study with those who did not. If the oral polio vaccine had had a contaminating effect, one would expect to see higher titers in the children whose siblings received it. For the children who received inactivated polio vaccine A or oral polio vaccine, the data show the opposite trend. For the inactivated polio vaccine B recipients, the titers are slightly higher for children whose siblings received oral polio vaccine, but the differences are not statistically significant.

DISCUSSION

The results of this study confirm and extend the data presented by Salk (12) and Salk et al. (11) concerning the ability of the new enhanced-potency inactivated polio vaccines to stimulate antibody production in almost all children after two doses of vaccine. The initial report by Salk et al. (11) primarily involved Finnish children in

whom vaccination was begun at five months of age when the level of maternal antibodies would have waned to one eighth the level at two months of age, the age at which children were enrolled in this study. The data presented here demonstrate the ability of one dose of the new enhanced-potency inactivated polio vaccines to stimulate seroconversion in 35 per cent to 61 per cent of these younger children in spite of the higher maternal antibody levels. Although Salk (12) has argued that one dose of the enhanced-potency inactivated polio vaccine is sufficient to provide protection, the data in this study show the impact of the second and third doses of enhanced-potency inactivated polio vaccine. The second dose results in seroconversion in essentially all the enhanced-potency inactivated polio vaccine recipients and provides them with measurable protection against paralytic disease (17). As shown in table 2 and figure 2, the third dose of enhanced-potency inactivated polio vaccine causes a major rise (5.7- to 15.8-fold) in reciprocal geometric mean titers against each of the three poliovirus types. Thus, while the first two doses are important for stimulating detectable antibodies and assuring protection for all children, the third dose stimulates significantly higher antibody titers which are greater than those seen after three doses of oral polio vaccine.

This study has shown the superior ability of oral polio vaccine to induce seroconversion after one dose of vaccine in a population with high levels of maternal antibody. However, it is also clear that the second dose of oral polio vaccine is needed to bring about seroconversion in those who do not respond to the first dose and to enhance the level of antibody among all the recipients. The third dose of oral polio vaccine is important to increase the percentage of children with demonstrable antibodies against type 1 to 97 per cent and to increase the reciprocal geometric mean titer (2.5-fold) against this type. For types 2 and 3, the third dose of oral polio vaccine adds little to the reciprocal geometric mean titer. There is approximately a twofold increase bringing recipients to about the same level of antibodies they had two and one-half months after the second dose of oral polio vaccine, but it assures measurable protection in all the children (100 per cent have antibodies). Thus, we have reconfirmed the capability of oral polio vaccine to induce excellent levels of protection in almost all children who receive three doses of vaccine (18).

A US immunization program which relies on either oral polio vaccine or enhanced-potency inactivated polio vaccines should require a three-dose schedule during the first 15 to 18 months of life. Although it might be possible to give fewer doses if the first dose were withheld until children were six to seven months of age, we believe that the greatest number of children can be continuously protected by beginning polio immunization in the United States at two months of age, with a second dose at four months of age, as in this trial. Figure 1 shows the excellent situation that exists in the United States. Of those children who receive their first dose of vaccine by age two months, no more than 13.5 per cent are susceptible to type 1 poliovirus, no more than 6 per cent to type 2, and no more than 22 per cent to type 3. Because of the risk of infection with wild virus which still remains, however, susceptibility of the childhood population should not be allowed to drop below these levels by delaying the time at which polio immunization is begun.

The three-dose schedule of enhanced-potency inactivated polio vaccine is important for other elements of immunity conferred by that vaccine. It is well recognized that the lower-potency inactivated polio vaccines were not as efficient as was oral polio vaccine in protecting exposed people from incubating and shedding wild virus (19). In an epidemic in Rhode Island (19), pharyngeal shedding of virus was decreased from 75 per cent to 33 per cent in children with detectable antibody following inactivated polio vaccine administration, but shedding in the stool was decreased only ir

those children with high antibody titers (>1:128). Similar data were reported by Glezen et al. (17). They showed that in children vaccinated with inactivated polio vaccine who were given a challenge dose of type 1 oral poliovirus vaccine, the frequency of pharyngeal and fecal shedding was inversely proportional to the level of antibody present at the time of challenge. Thus, three doses of enhanced-potency inactivated polio vaccine would reduce the degree of shedding of virus and of community spread of either wild or vaccine virus to a greater extent than would two doses of enhanced-potency inactivated polio vaccine. Horstmann (20) postulates that the new enhanced-potency inactivated polio vaccines may increase the amount of secretory immune globulin A produced and thus reduce the amount of virus shed more than did the previously used inactivated polio vaccines.

The similarity in the local and systemic reaction rates presented in tables 4 and 5 ıdicates that the simultaneous adminis- ration of inactivated polio vaccine with diphtheria-tetanus-pertussis vaccine does not increase the rate of either local or systemic reactions over the simultaneous administration of oral polio vaccine with diphtheria-tetanus-pertussis vaccine. In addition, fever (temperature ≥39 C) and the mild systemic reactions reported in the oral polio vaccine group are generally similar to or lower than those reported in the literature following the administration of diphtheria-tetanus-pertussis vaccine (21, 22). Two exceptions are "crying more than usual" and "eating less than usual," which are more frequently reported in the Baltimore children in this study. However, the site coordinators asked mothers if their children were "crying more" or "eating less" than usual, not whether they were anorexic or exhibiting high-pitched, inconsolable crying, which are the signs reported in the literature. Thus, the higher rate could be expected.

The potentially confounding role of the spread of oral polio vaccine from a vaccinated sibling was addressed by the data presented in table 6. In addition, Ogra (23) and Dhar and Ogra (24), studying children in groups of six to 12, have shown that a dose of oral polio vaccine given seven months after three doses of the less potent inactivated polio vaccine given at two, three, and four months of age will result in a significantly greater booster effect than that seen with an additional dose of inactivated polio vaccine. Thus, because we did not see higher titers in the enhanced-potency inactivated polio vaccine recipients whose siblings received oral polio vaccine, it is unlikely that the very good response we have ascribed to the new enhanced-potency inactivated polio vaccines is due to contamination and unintentional immunization with oral polio vaccine shed by other children.

The presence of such high titers of antibodies following the three-dose enhanced-potency inactivated polio vaccine schedule used in this study indicates that a change could be made in the current Immunization Practices Advisory Committee recommendation to give three doses of inactivated polio vaccine at two, four, and six months of age, followed by a fourth dose one year later. For vaccines of D-antigen content comparable to those used in this study, two doses of vaccine given in the first year of life, beginning as early as two months of age, followed by a third dose at 15 to 18 months, would be appropriate.

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Exhibit 5

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AHFS Category: 80:12 **IPV**

Poliovirus Vaccine Inactivated

IPOL®

Rx only

DESCRIPTION

IPOL®, Poliovirus Vaccine Inactivated, produced by Sanofi Pasteur SA, is a sterile suspension of three types of poliovirus: Type 1 (Mahoney), Type 2 (MEF-1), and Type 3 (Saukett). IPOL vaccine is a highly purified, inactivated poliovirus vaccine with enhanced potency. Each of the three strains of poliovirus is individually grown in vero cells, a continuous line of monkey kidney cells cultivated on microcarriers. (1) (2) The cells are grown in Eagle MEM modified medium, supplemented with newborn calf bovine serum tested for adventitious agents prior to use, originated from countries free of bovine spongiform encephalopathy. For viral growth, the culture medium is replaced by M-199, without calf bovine serum. This culture technique and improvements in purification, concentration, and standardization of poliovirus antigen produce a more potent and consistent immunogenic vaccine than the inactivated poliovirus vaccine (IPV) available in the US prior to 1988. (3) (4)

After clarification and filtration, viral suspensions are concentrated by ultrafiltration, and purified by three liquid chromatography steps; one column of anion exchanger, one column of gel filtration, and again one column of anion exchanger. After re-equilibration of the purified viral suspension with Medium M-199 and adjustment of the antigen titer, the monovalent viral suspensions are inactivated at +37°C for at least 12 days with 1:4000 formalin.

Each dose (0.5 mL) of trivalent vaccine is formulated to contain 40 D antigen units of Type 1, 8 D antigen units of Type 2, and 32 D antigen units of Type 3 poliovirus. For each lot of IPOL vaccine, D-antigen content is determined *in vitro* using the D-antigen ELISA assay. IPOL vaccine is produced from vaccine concentrates diluted with M-199 medium. Also present are 0.5% of 2-phenoxyethanol and a maximum of 0.02% of formaldehyde per dose as preservatives. Neomycin, streptomycin, and polymyxin B are used in vaccine production; and, although purification procedures eliminate measurable amounts, less than 5 ng neomycin, 200 ng streptomycin, and 25 ng polymyxin B per dose may still be present. The residual calf bovine serum albumin is less than 50 ng/dose in the final vaccine.

The vaccine is clear and colorless and should be administered intramuscularly or subcutaneously.

The vial stopper is not made with natural rubber latex.

CLINICAL PHARMACOLOGY

Poliomyelitis is caused by poliovirus Types 1, 2, or 3. It is primarily spread by the fecal-oral route of transmission but may also be spread by the pharyngeal route.

Approximately 90% to 95% of poliovirus infections are asymptomatic. Nonspecific illness with low-grade fever and sore throat (minor illness) occurs in 4% to 8% of infections. Aseptic meningitis occurs in 1% to 5% of patients a few days after the minor illness has resolved. Rapid onset of asymmetric acute flaccid paralysis occurs in 0.1% to 2% of infections, and residual

paralytic disease involving motor neurons (paralytic poliomyelitis) occurs in approximately 1 per 1,000 infections. (5)

Prior to the introduction of inactivated poliovirus vaccines in 1955, large outbreaks of poliomyelitis occurred each year in the United States (US). The annual incidence of paralytic disease of 11.4 cases/100,000 population declined to 0.5 cases by the time oral poliovirus vaccine (OPV) was introduced in 1961. Incidence continued to decline thereafter to a rate of 0.002 to 0.005 cases per 100,000 population. Of the 127 cases of paralytic poliomyelitis reported in the US between 1980 and 1994, six were imported cases (caused by wild polioviruses), two were "indeterminate" cases, and 119 were vaccine associated paralytic poliomyelitis (VAPP) cases associated with the use of live, attenuated oral poliovirus vaccine (OPV). (6) An all IPV schedule was adopted in 1999 to eliminate VAPP cases. (7)

Poliovirus Vaccine Inactivated induces the production of neutralizing antibodies against each type of virus which are related to protective efficacy. Antibody response in most children was induced after receiving fewer doses (8) of IPV vaccine than the vaccine available in the United States prior to 1988.

Studies in developed (8) and developing (9), (10) countries with a similar enhanced IPV manufactured by the same process as IPOL vaccine in primary monkey kidney cells have shown a direct relationship exists between the antigenic content of the vaccine, the frequency of seroconversion, and resulting antibody titer. Approval in the US was based upon demonstration of immunogenicity and safety in US children. (11)

In the US, 219 infants received three doses of a similar enhanced IPV at two, four, and eighteen months of age manufactured by the same process as IPOL vaccine except the cell substrate for IPV was using primary monkey kidney cells. Seroconversion to all three types of poliovirus was demonstrated in 99% of these infants after two doses of vaccine given at 2 and 4 months of age. Following the third dose of vaccine at 18 months of age, neutralizing antibodies were present at a level of ≥1:10 in 99.1% of children to Type 1 and 100% of children to Types 2 and 3 polioviruses. (3)

IPOL vaccine was administered to more than 700 infants between 2 to 18 months of age during three clinical studies conducted in the US using IPV only schedules and sequential IPV-OPV schedules. (12) (13) Seroprevalence rates for detectable serum neutralizing antibody (DA) at a ≥1:4 dilution were 95% to 100% (Type 1); 97% to 100% (Type 2) and 96% to 100% (Type 3) after two doses of IPOL vaccine depending on studies.

Table 1: US Studies with IPOL Vaccine Administered Using IPV Only or Sequential IPV-OPV Schedules

Age (months) for				Post Dose 2				Post Dose 3				Pre Booster				Post Booster			
2	4	6	12 to 18		Type 1	Type 2	Type 3		Type 1	Type 2	Type 3		Type 1	Type 2	Type 3		Type 1	Type 2	Type 3
Dose 1	Dose 2	Dose 3	Booster	N*	%DA†	%DA	%DA	N*	%DA	%DA	%DA	N*	%DA	%DA	%DA	N*	%DA	%DA	%DA
STUDY 1 [11] ‡																			
I(s)	I(s)	NA§	I(s)	56	97	100	97		–	–	–	53	91	97	93	53	97	100	100
O	O	NA	O	22	100	100	100		–	–	–	22	78	91	78	20	100	100	100
I(s)	O	NA	O	17	95	100	95		–	–	–	17	95	100	95	17	100	100	100
I(s)	I(s)	NA	O	17	100	100	100		–	–	–	16	100	100	94	16	100	100	100
STUDY 2 [10] ¶																			
I(c)	I(c)	NA	I(s)	94	98	97	96		–	–	–	100	92	95	88	97	100	100	100
I(s)	I(s)	NA	I(s)	68	99	100	99		–	–	–	72	100	100	94	75	100	100	100
I(c)	I(c)	NA	O	75	95	99	96		–	–	–	77	86	97	82	78	100	100	97
I(s)	I(s)	NA	O	101	99	99	95		–	–	–	103	99	97	89	107	100	100	100
STUDY 3 [10] ¶																			
I(c)	I(c)	I(c)	O	91	98	99	100	91	100	100	100	41	100	100	100	40	100	100	100
I(c)	I(c)	O	O	96	100	98	99	94	100	100	99	47	100	100	100	45	100	100	100
I(c)	I(c)	I(c) + O	O	91	96	97	100	85	100	100	100	47	100	100	100	46	100	100	100

* N = Number of children from whom serum was available

† Detectable antibody (neutralizing titer ≥1:4)

‡ IPOL vaccine given subcutaneously

§ NA – No poliovirus vaccine administered

¶ IPOL vaccine given intramuscularly

I IPOL vaccine given either separately in association with DTP in two sites (s) or combined (c) with DTP in a dual chambered syringe

O OPV

In one study, (13) the persistence of DA in infants receiving two doses of IPOL vaccine at 2 and 4 months of age was 91% to 100% (Type 1), 97% to 100% (Type 2), and 93% to 94% (Type 3) at twelve months of age. In another study, (12) 86% to 100% (Type 1), 95% to 100% (Type 2), and 82% to 94% (Type 3) of infants still had DA at 18 months of age.

In trials and field studies conducted outside the US, IPOL vaccine, or a combination vaccine containing IPOL vaccine and DTP, was administered to more than 3,000 infants between 2 to 18 months of age using IPV only schedules and immunogenicity data are available from 1,485 infants. After two doses of vaccine given during the first year of life, seroprevalence rates for detectable serum neutralizing antibody (neutralizing titer ≥1:4) were 88% to 100% (Type 1); 84% to 100% (Type 2) and 94% to 100% (Type 3) of infants, depending on studies. When three doses were given during the first year of life, post-dose 3 DA ranged between 93% to 100% (Type 1); 89% to 100% (Type 2) and 97% to 100% (Type 3) and reached 100% for Types 1, 2, and 3 after the fourth dose given during the second year of life (12 to 18 months of age). (14)

In infants immunized with three doses of an unlicensed combination vaccine containing IPOL vaccine and DTP given during the first year of life, and a fourth dose given during the second year of life, the persistence of detectable neutralizing antibodies was 96%, 96%, and 97% against poliovirus Types 1, 2, and 3, respectively, at six years of age. DA reached 100% for all types after a booster dose of IPOL vaccine combined with DTP vaccine. (11) A survey of Swedish children and young adults given a Swedish IPV only schedule demonstrated persistence of detectable serum neutralizing antibody for at least 10 years to all three types of poliovirus. (15)

IPV is able to induce secretory antibody (IgA) produced in the pharynx and gut and reduces pharyngeal excretion of poliovirus Type 1 from 75% in children with neutralizing antibodies at levels less than 1:8 to 25% in children with neutralizing antibodies at levels more than 1:64. (4) (14) (16) (17) (18) (19) (20) (21) (22) There is also evidence of induction of herd immunity with IPV, (15) (23) (24) (25) (26) and that this herd immunity is sufficiently maintained in a population vaccinated only with IPV. (26)

VAPP has not been reported in association with administration of IPOL vaccine. (27) It is expected that an IPV only schedule will eliminate the risk of VAPP in both recipients and contacts compared to a schedule that included OPV. (7)

INDICATIONS AND USAGE

IPOL vaccine is indicated for active immunization of infants (as young as 6 weeks of age), children, and adults for the prevention of poliomyelitis caused by poliovirus Types 1, 2, and 3. (28)

INFANTS, CHILDREN AND ADOLESCENTS

General Recommendations

It is recommended that all infants (as young as 6 weeks of age), unimmunized children, and adolescents not previously immunized be vaccinated routinely against paralytic poliomyelitis. (29) Following the eradication of poliomyelitis caused by wild poliovirus from the Western

Hemisphere (including North and South America) (30), an IPV-only schedule was recommended to eliminate VAPP. (7)

All children should receive four doses of IPV at ages 2, 4, 6 to 18 months, and 4 to 6 years. OPV is no longer available in the US and is not recommended for routine immunization. (7)

Previous clinical poliomyelitis (usually due to only a single poliovirus type) or incomplete immunization with OPV are not contraindications to completing the primary series of immunization with IPOL vaccine.

Children Incompletely Immunized

Children of all ages should have their immunization status reviewed and be considered for supplemental immunization as follows for adults. Time intervals between doses longer than those recommended for routine primary immunization do not necessitate additional doses as long as a final total of four doses is reached (see **DOSAGE AND ADMINISTRATION** section).

ADULTS

General Recommendations

Routine primary poliovirus vaccination of adults (generally those 18 years of age or older) residing in the US is not recommended. Unimmunized adults who are potentially exposed to wild poliovirus and have not been adequately immunized should receive polio vaccination in accordance with the schedule given in the **DOSAGE AND ADMINISTRATION** section. (28)

Persons with previous wild poliovirus disease who are incompletely immunized or unimmunized should be given additional doses of IPOL vaccine if they fall into one or more categories listed.

The following categories of adults are at an increased risk of exposure to wild polioviruses: (28) (31)

• Travelers to regions or countries where poliomyelitis is endemic or epidemic.

• Healthcare workers in close contact with patients who may be excreting polioviruses.

• Laboratory workers handling specimens that may contain polioviruses.

• Members of communities or specific population groups with disease caused by wild polioviruses.

IMMUNODEFICIENCY AND ALTERED IMMUNE STATUS

IPOL vaccine should be used in all patients with immunodeficiency diseases and members of such patients' households when vaccination of such persons is indicated. This includes patients with asymptomatic HIV infection, AIDS or AIDS-Related Complex, severe combined immunodeficiency, hypogammaglobulinemia, or agammaglobulinemia; altered immune states due to diseases such as leukemia, lymphoma, or generalized malignancy; or an immune system compromised by treatment with corticosteroids, alkylating drugs, antimetabolites or radiation. Immunogenicity of IPOL vaccine in individuals receiving immunoglobulin could be impaired, and patients with an altered immune state may or may not develop a protective response against paralytic poliomyelitis after administration of IPV. (32)

As with any vaccine, vaccination with IPOL vaccine may not protect 100% of individuals.

Use with other vaccines: refer to **DOSAGE AND ADMINISTRATION** section for this information.

CONTRAINDICATIONS

IPOL vaccine is contraindicated in persons with a history of hypersensitivity to any component of the vaccine, including 2-phenoxyethanol, formaldehyde, neomycin, streptomycin, and polymyxin B.

No further doses should be given if anaphylaxis or anaphylactic shock occurs within 24 hours of administration of one dose of vaccine.

Vaccination of persons with an acute, febrile illness should be deferred until after recovery; however, minor illness, such as mild upper respiratory infection, with or without low grade fever, are not reasons for postponing vaccine administration.

WARNINGS

Neomycin, streptomycin, polymyxin B, 2-phenoxyethanol, and formaldehyde are used in the production of this vaccine. Although purification procedures eliminate measurable amounts of these substances, traces may be present (see **DESCRIPTION** section), and allergic reactions may occur in persons sensitive to these substances (see **CONTRAINDICATIONS** section).

Systemic adverse reactions reported in infants receiving IPV concomitantly at separate sites or combined with DTP have been similar to those associated with administration of DTP alone. (11) Local reactions are usually mild and transient in nature.

Although no causal relationship between IPOL vaccine and Guillain-Barré Syndrome (GBS) has been established, (28) GBS has been temporally related to administration of another inactivated poliovirus vaccine. Deaths have been reported in temporal association with the administration of IPV (see **ADVERSE REACTIONS** section).

PRECAUTIONS

GENERAL

Prior to an injection of any vaccine, all known precautions should be taken to prevent adverse reactions. This includes a review of the patient's history with respect to possible sensitivity to the vaccine or similar vaccines.

Healthcare providers should question the patient, parent or guardian about reactions to a previous dose of this product, or similar product.

Epinephrine injection (1:1000) and other appropriate agents should be available to control immediate allergic reactions.

Healthcare providers should obtain the previous immunization history of the vaccinee, and inquire about the current health status of the vaccinee.

Immunodeficient patients or patients under immunosuppressive therapy may not develop a protective immune response against paralytic poliomyelitis after administration of IPV.

Administration of IPOL vaccine is not contraindicated in individuals infected with HIV. (33) (34) (35)

Special care should be taken to ensure that the injection does not enter a blood vessel.

Syncope (fainting) has been reported following vaccination with IPOL. Procedures should be in place to avoid injury from fainting.

INFORMATION FOR PATIENTS

Patients, parents, or guardians should be instructed to report any serious adverse reactions to their healthcare provider.

The healthcare provider should inform the patient, parent, or guardian of the benefits and risks of the vaccine.

The healthcare provider should inform the patient, parent, or guardian of the importance of completing the immunization series.

The healthcare provider should provide the Vaccine Information Statements (VISs) which are required to be given with each immunization.

DRUG INTERACTIONS

There are no known interactions of IPOL vaccine with drugs or foods. Concomitant administration of other parenteral vaccines, with separate syringes at separate sites, is not contraindicated. The first two doses of IPOL vaccine may be administered at separate sites using separate syringes concomitantly with DTaP, acellular pertussis, *Haemophilus influenzae* type b (Hib), and hepatitis B vaccines. From historical data on the antibody responses to diphtheria, tetanus, acellular pertussis, Hib, or hepatitis B vaccines used concomitantly or in combination with IPOL vaccine, no interferences have been observed on the immunological end points accepted for clinical protection. (11) (16) (36) (See **DOSAGE AND ADMINISTRATION** section.)

If IPOL vaccine has been administered to persons receiving immunosuppressive therapy, an adequate immunologic response may not be obtained. (See **PRECAUTIONS – GENERAL** section.)

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Long-term studies in animals to evaluate carcinogenic potential or impairment of fertility have not been conducted.

PREGNANCY

Animal reproduction studies have not been conducted with IPOL vaccine. It is also not known whether IPOL vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. IPOL vaccine should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

It is not known whether IPOL vaccine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when IPOL vaccine is administered to a nursing woman.

PEDIATRIC USE

SAFETY AND EFFECTIVENESS OF IPOL VACCINE IN INFANTS BELOW SIX WEEKS OF AGE HAVE NOT BEEN ESTABLISHED. (12) (20) (See **DOSAGE AND ADMINISTRATION** section.)

In the US, infants receiving two doses of IPV at 2 and 4 months of age, the seroprevalence to all three types of poliovirus was demonstrated in 95% to 100% of these infants after two doses of vaccine. (12) (13)

ADVERSE REACTIONS

Body System As A Whole

In earlier studies with the vaccine grown in primary monkey kidney cells, transient local reactions at the site of injection were observed. (3) Erythema, induration and pain occurred in 3.2%, 1% and 13%, respectively, of vaccinees within 48 hours post-vaccination. Temperatures of ≥39°C (≥102°F) were reported in 38% of vaccinees. Other symptoms included irritability, sleepiness,

fussiness, and crying. Because IPV was given in a different site but concurrently with Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (DTP), these systemic reactions could not be attributed to a specific vaccine. However, these systemic reactions were comparable in frequency and severity to that reported for DTP given alone without IPV. (12) Although no causal relationship has been established, deaths have occurred in temporal association after vaccination of infants with IPV. (37)

Four additional US studies using IPOL vaccine in more than 1,300 infants, (12) between 2 to 18 months of age administered with DTP at the same time at separate sites or combined have demonstrated that local and systemic reactions were similar when DTP was given alone.

Table 2 (12): Percentage of Infants Presenting with Local or Systemic Reactions at 6, 24, and 48 Hours of Immunization with IPOL Vaccine Administered Intramuscularly Concomitantly at Separate Sites with Sanofi* Whole-Cell DTP Vaccine at 2 and 4 Months of Age and with Sanofi Acellular Pertussis Vaccine (Tripedia®) at 18 Months of Age

	AGE AT IMMUNIZATION								
REACTION	**2 Months (n=211)**			**4 Months (n=206)**			**18 Months† (n=74)**		
	6 Hrs.	**24 Hrs.**	**48 Hrs.**	**6 Hrs.**	**24 Hrs.**	**48 Hrs.**	**6 Hrs.**	**24 Hrs.**	**48 Hrs.**
Local, IPOL vaccine alone‡									
Erythema >1"	0.5%	0.5%	0.5%	1.0%	0.0%	0.0%	1.4%	0.0%	0.0%
Swelling	11.4%	5.7%	0.9%	11.2%	4.9%	1.9%	2.7%	0.0%	0.0%
Tenderness	29.4%	8.5%	2.8%	22.8%	4.4%	1.0%	13.5%	4.1%	0.0%
Systemic§									
Fever >102.2°F	1.0%	0.5%	0.5%	2.0%	0.5%	0.0%	0.0%	0.0%	4.2%
Irritability	64.5%	24.6%	17.5%	49.5%	25.7%	11.7%	14.7%	6.7%	8.0%
Tiredness	60.7%	31.8%	7.1%	38.8%	18.4%	6.3%	9.3%	5.3%	4.0%
Anorexia	16.6%	8.1%	4.3%	6.3%	4.4%	2.4%	2.7%	1.3%	2.7%
Vomiting	1.9%	2.8%	2.8%	1.9%	1.5%	1.0%	1.3%	1.3%	0.0%
Persistent Crying	Percentage of infants within 72 hours after immunization was 0.0% after dose one, 1.4% after dose two, and 0.0% after dose three.								

* Sanofi Pasteur Inc. formerly known as Aventis Pasteur Inc.

† Children who have been vaccinated with Tripedia vaccine.

‡ Data are from the IPOL vaccine administration site, given intramuscularly.

§ The adverse reaction profile includes the concomitant use of Sanofi whole-cell DTP vaccine or Tripedia vaccine with IPOL vaccine. Rates are comparable in frequency and severity to that reported for whole-cell DTP given alone.

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Digestive System

Anorexia and vomiting occurred with frequencies not significantly different as reported when DTP was given alone without IPV or OPV. (12)

Nervous System

Although no causal relationship between IPOL vaccine and GBS has been established, (28) GBS has been temporally related to administration of another inactivated poliovirus vaccine.

Post-marketing Experience

The following adverse events have been identified during postapproval use of IPOL vaccine. Because these events are reported voluntarily from a population of uncertain size, it may not be possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Adverse events were included based on one or more of the following factors: severity, frequency of reporting or strength of evidence for a causal relationship.

- ***Blood and lymphatic system disorders:*** lymphadenopathy
- ***General disorders and administration site conditions:*** agitation, injection site reaction including injection site rash and mass
- ***Immune system disorders:*** type I hypersensitivity including allergic reaction, anaphylactic reaction, and anaphylactic shock
- ***Musculoskeletal and connective tissue disorders:*** arthralgia, myalgia
- ***Nervous system disorders:*** convulsion, febrile convulsion, headache, paresthesia, somnolence, syncope

- ***Skin and subcutaneous tissue disorders:*** rash, urticaria

Reporting of Adverse Events

The National Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act of 1986, requires physicians and other healthcare providers who administer vaccines to maintain permanent vaccination records and to report occurrences of certain adverse events to the US Department of Health and Human Services. Reportable events include those listed in the Act for each vaccine and events specified in the package insert as contraindications to further doses of that vaccine. (38) (39) (40)

Reporting by parents or guardians of all adverse events after vaccine administration should be encouraged. Adverse events following immunization with vaccine should be reported by healthcare providers to the US Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS). Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 1-800-822-7967. (38) (39) (40)

Healthcare providers also should report these events to the Pharmacovigilance Department, Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call 1-800-822-2463.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The vial and its packaging should be inspected prior to use for evidence of leakage or a faulty seal. If evidence of such defects are observed, the vaccine should not be used. Do not remove the vial stopper or the metal seal holding it in place.

After preparation of the injection site, using a suitable sterile needle and aseptic technique, immediately administer IPOL vaccine intramuscularly or subcutaneously. In infants and small children, the mid-lateral aspect of the thigh is the preferred site. In older children and adults, IPOL vaccine should be administered intramuscularly or subcutaneously in the deltoid area. IPOL should not be combined through reconstitution or mixed with any other vaccine.

To help avoid HIV (AIDS), HBV (Hepatitis), and other infectious diseases due to accidental needlesticks, contaminated needles should not be recapped or removed, unless there is no alternative or that such action is required by a specific medical procedure.

Care should be taken to avoid administering the injection into or near blood vessels and nerves. If blood or any suspicious discoloration appears in the syringe, do not inject but discard contents and repeat procedures using a new dose of vaccine administered at a different site.

DO NOT ADMINISTER VACCINE INTRAVENOUSLY.

Children

The primary series of IPOL vaccine consists of three 0.5 mL doses administered intramuscularly or subcutaneously, preferably eight or more weeks apart and usually at ages 2, 4, and 6 to 18 months. Under no circumstances should the vaccine be given more frequently than four weeks apart. The first immunization may be administered as early as six weeks of age. For this series, a booster dose of IPOL vaccine is administered at 4 to 6 years of age. (41)

Use with Other Vaccines

From historical data on the antibody responses to diphtheria, tetanus, whole-cell or acellular pertussis, Hib, or hepatitis B vaccines used concomitantly with IPOL vaccine, no interferences have been observed on the immunological end points accepted for clinical protection. (11) (16) (36) (See **DRUG INTERACTIONS** section.)

If the third dose of IPOL vaccine is given between 12 to 18 months of age, it may be desirable to administer this dose with Measles, Mumps, and Rubella (MMR) vaccine and/or other vaccines using separate syringes at separate sites, (28) but no data on the immunological interference between IPOL vaccine and these vaccines exist.

Use in Previously Vaccinated Children

Children and adolescents with a previously incomplete series of polio vaccine should receive sufficient additional doses of IPOL vaccine to complete the series.

Interruption of the recommended schedule with a delay between doses does not interfere with the final immunity. There is no need to start the series over again, regardless of the time elapsed between doses.

The need to routinely administer additional doses is unknown at this time. (28)

Adults

Unvaccinated Adults

A primary series of IPOL vaccine is recommended for unvaccinated adults at increased risk of exposure to poliovirus. While the responses of adults to primary series have not been studied, the recommended schedule for adults is two 0.5 mL doses given at a 1 to 2 month interval and a third 0.5 mL dose given 6 to 12 months later. If less than 3 months but more than 2 months are available before protection is needed, three doses of IPOL vaccine should be given at least 1 month apart. Likewise, if only 1 or 2 months are available, two 0.5 mL doses of IPOL vaccine should be given at least 1 month apart. If less than 1 month is available, a single 0.5 mL dose of IPOL vaccine is recommended. (28)

Incompletely Vaccinated Adults

Adults who are at an increased risk of exposure to poliovirus and who have had at least one dose of OPV, fewer than three doses of conventional IPV or a combination of conventional IPV or OPV totaling fewer than three doses should receive at least one 0.5 mL dose of IPOL vaccine. Additional doses needed to complete a primary series should be given if time permits. (28)

Completely Vaccinated Adults

Adults who are at an increased risk of exposure to poliovirus and who have previously completed a primary series with one or a combination of polio vaccines can be given a 0.5 mL dose of IPOL vaccine.

The preferred injection site of IPOL vaccine for adults is in the deltoid area.

HOW SUPPLIED

Multi-dose vial , 5mL: NDC 49281-860-78. Supplied as package: NDC 49281-860-10.

STORAGE

The vaccine is stable if stored in the refrigerator at 2°C to 8°C (35°F to 46°F). The vaccine must not be frozen.

Protect from light.

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Product Information as of May 2022

Manufactured by:

Sanofi Pasteur SA

Marcy L'Etoile France

US Govt License #1724

Distributed by:

Sanofi Pasteur Inc.

Swiftwater PA 18370 USA

1-800-VACCINE (1-800-822-2463)

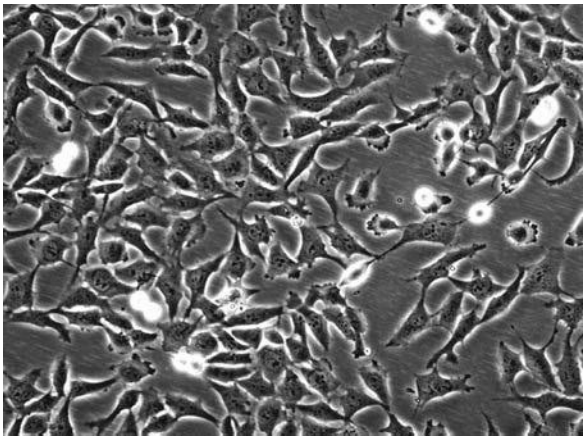
Footnote 6

Cell line profile

Vero (ECACC catalogue no. 84113001)

Cell line history

The original Vero cell line was established from the kidney of an African green monkey in 1962 by Y. Yasumura and Y. Kawakita at the Chiba University in Japan[1]. It is currently one of the most used continuous cell lines in the world and has been cited in over 10,000 research publications. The cell line was originally described as derived from African green monkey of the genus Cercopithecus, confusingly used synonymously with the terms Grivet and Vervet monkey. This has been replaced with the genus *Chlorocebus*. The species designation of Vero is commonly cited as *Chlorocebus aethiops*. However, recent whole genome sequencing has re-designated the species as the closely related *Chlorocebus sabaeus*[2].



Key characteristics

The Vero cell line is continuous and aneuploid. Continuous cell lines of mammalian origin have been an extremely valuable resource for the production of biological pharmaceuticals. Vero is susceptible to infection from a number of viruses such as SV-40, measles virus, arboviruses, rubella virus, polioviruses, influenza viruses and simian syncytial viruses[3]. It is also susceptible to bacterial toxins including diphtheria toxin and Shiga-like toxins. Interestingly, when the whole genome of Vero was sequenced it was found there was a 9-Mb deletion on chromosome 12, which resulted in the loss of the type 1 interferon gene cluster, in addition to the cyclin-dependent kinase inhibitor genes. The authors suggested this could be the reason for the continuous nature of the cell line and its susceptibility to a variety of pathogens[2].

Applications

Due to the continuous nature of the cell lines and its sensitivity to a number of different viruses, Vero has been used extensively in the fields of vaccine production and to study various types of emerging pathogens such as H5N1 influenza virus, middle-eastern

respiratory syndrome (MERS) coronavirus, Zika virus and a number of haemorrhagic fever viruses.

A number of cell lines have been clonally derived from the parent cell line, which display different phenotypes. Vero 76 exhibits a lower saturation density and the cells are susceptible to human haemorrhagic fever viruses. Vero C1008 is a sub-clone of Vero 76. They show some degree of contact inhibition and are suitable for supporting the growth of slowly replicating viruses. Vero/hSLAM was derived by transfection of Vero cells with an expression plasmid (pCAG-hSLAM) encoding the human signalling lymphocytic activation molecule (SLAM), also known as CDw150, which is a receptor for measles virus. Vero/hSLAM cells can be used to isolate measles virus from human clinical samples and are a substitute for the B95a cell line for this purpose. Mumps susceptibility has also been demonstrated at the depositor's laboratory.

Vero (AC-free) and Vero-Hektor are both variants adapted to grow in serum free media. They are often used as seed cultures in biopharmaceutical processes.

Culture tips

Care should be taken when working with Vero and the different Vero derivatives available. Most have been clonally selected and adapted to grow on different media to the parental cell line.

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   Sheets, Ph.D., USPHS CBER/OVRR/DVRPA/VVB for the Vaccines and Related Biological Products Advisory Committee Meeting to be held on May 12, 2000 OPEN SESSION

Related cell lines	Catalogue number	Description
Vero 76	85020205	Derived from Vero. Support the growth of haemorrhagic viruses
Vero C1008	85020206	Derived from Vero 76. Supports the growth of slow growing viruses
Vero/hSLAM	04091501	Transfected Vero cell lines used to isolate measles virus from human clinical isolates
Vero (AC-free)	08011101	African Green monkey kidney cells, serum-free adapted to grow in animal component free medium
Vero-Hektor	03092503	African Green Monkey kidney cells, serum-free. This cell line is substrate dependent i.e. adherent and may be suitable for the replication of viral particles.

MA104	**85102918**	Another African green monkey derived cell lines used to propagate simian rotavirus SA11
B95a	**01092505**	Much more sensitive to the measles virus than the original Vero cell line. Has a similar use to Vero/hSLAM

Footnote 7

Vero

CCL-81™

The Vero cell line was initiated in 1962 from the kidney tissue derived from a normal, adult African green monkey. The cell line can be used in a variety of applications, including the detection of verotoxins, detection of virus in ground beef, efficacy testing, the study of malaria, media testing, vaccine development, protein expression, and mycoplasma testing. The Vero cell line is also a suitable transfection host.

99/100
Bioz Stars
5,328 Product Citations

Product category

Animal cells

Organism

Cercopithecus aethiops

Morphology

epithelial

Tissue

kidney

Disease

Normal

Applications

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3D cell culture

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Media testing
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Bioproduction

Product format

Frozen

Storage conditions

Vapor phase of liquid nitrogen

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Documentation

Product sheet

Certificate of analysis

Safety data sheet

Biosafety Level 1

ATCC determines the biosafety level of a material based on our risk assessment as guided by the current edition of *Biosafety in Microbiological and Biomedical Laboratories (BMBL)*, U.S. Department of Health and Human Services. It is your responsibility to understand the hazards associated with the material per your organization's policies and procedures as well as any other applicable regulations as enforced by your local or national agencies.

ATCC highly recommends that appropriate personal protective equipment is always used when handling vials. For cultures that require storage in liquid nitrogen, it is important to note that some vials may leak when submersed in liquid nitrogen and will slowly fill with liquid nitrogen. Upon thawing, the conversion of the liquid nitrogen back to its gas phase may result in the vial exploding or blowing off its cap with dangerous force creating flying debris. Unless necessary, ATCC recommends that these cultures be stored in the vapor phase of liquid nitrogen rather than submersed in liquid nitrogen.

Required Products

These products are vital for the proper use of this item and have been confirmed as effective in supporting functionality. If you use alternative products, the quality and effectiveness of the item may be affected.

Eagle's Minimum Essential Medium (EMEM)
30-2003

Quantity

ADD TO CART

Fetal Bovine Serum (FBS)
30-2020

Quantity

AD

DETAILED PRODUCT INFORMATION

ADD TO LIST

ADD T

Related Products

VERO 76

CRL-1587

Price: **$664.00** ea

Quantity

ADD TO CART

ADD TO LIST

Vero-SF-ACF

CCL-81.5

Price: **$645.00** ea

Quantity

ADD T

ADD T

Detailed product information

+ EXPAND ALL − COLLAPSE ALL

General +

Characteristics −

Growth properties

Adherent

Passage history

The cell line was brought to the Laboratory of Tropical Virology, National Institute of Allergy and Infectious Diseases, National Institutes of Health in the 93rd passage from Chiba University by B. Simizu on June 15, 1964.

Derivation

The Vero cell line was initiated from the kidney of a normal adult African green monkey on March 27, 1962, by Y. Yasumura and Y. Kawakita at the Chiba University in

Chiba, Japan.

Age

adult

Karyotype

This is a cell line with the hypodiploid chromosome count. The modal chromosome number was 58 occurring in 66% of cells. In most cells, over 50% of the chromosomes in each cell complement belonged to structurally altered marker chromosomes. Normal A3, A4, B4, and B5 were absent; B2, B3 and B7 were occasionally paired; and B9, C1 and C5 were mostly paired. The rate of cells with higher ploidies was 1.7%. Other chromosomes were mostly present in single copy.

Virus susceptibility

Human poliovirus 1
Human poliovirus 2
Human poliovirus 3
Getah virus
Pixuna virus
Ross River virus
Semliki Forest virus
Kokobera virus
Modoc virus
Tacaribe virus
SV-5 (parainfluenza type 2)
SV40 virus
Measles virus
Rubella virus
Reovirus type 2
Reovirus 3
Simian adenovirus 3
Simian adenovirus 17
Simian adenovirus 11
Simian adenovirus 1
Simian adenovirus 20
Simian adenovirus 20
Simian adenovirus 18
Simian adenovirus 16

Simian adenovirus 8
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Simian adenovirus 34
Simian adenovirus 31

Handling information +

Quality control specifications +

History +

Legal disclaimers +

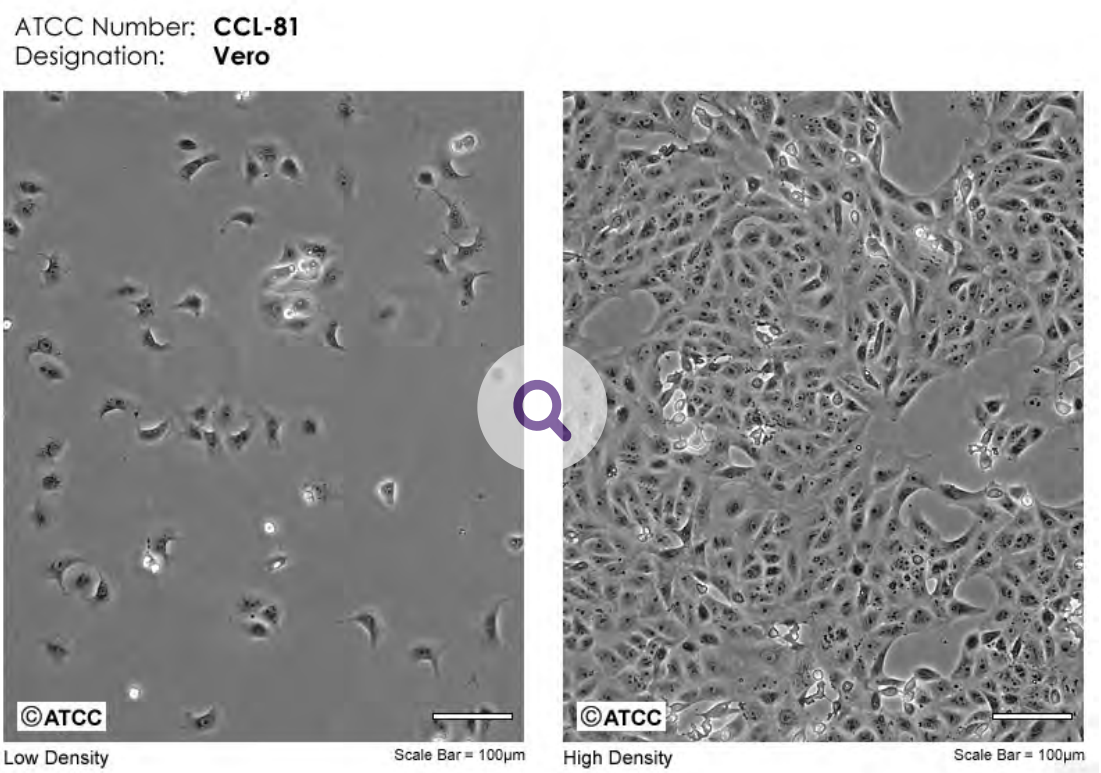
Permits & Restrictions

Import Permit for the State of Hawaii

If shipping to the U.S. state of Hawaii, you must provide either an import permit or documentation stating that an import permit is not required. We cannot ship this item until we receive this documentation. Contact the Hawaii Department of Agriculture (HDOA), Plant Industry Division, Plant Quarantine Branch to determine if an import permit is required.

MORE INFORMATION ABOUT PERMITS AND RESTRICTIONS >

Images



References

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- [ ] Generated (GENER)
- [ ] Mouse Assay (MICE)
- [ ] Transfection (TNSF)
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- [ ] Neutralization (NEUT)
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- [ ] Sequencing (SEQ)
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(IF)
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(CYTO-TOX)
- Luciferase
(LUCIF)
- Plaque Reduction Neutralization Test
(PRNT)
- Quantitative RT-PCR
(qRT-PCR)
- Enzyme-linked Immunosorbent Assay
(ELISA)
- Selection
(SELECT)
- Western Blot
(WB)

Curated Citations

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Footnote 8

Step 3: Clinical Research

While preclinical research answers basic questions about a drug's safety, it is not a substitute for studies of ways the drug will interact with the human body. "Clinical research" refers to studies, or trials, that are done in people. As the developers design the clinical study, they will consider what they want to accomplish for each of the different Clinical Research Phases and begin the Investigational New Drug Process (IND), a process they must go through before clinical research begins.

On this page you will find information on:

- Designing Clinical Trials
- Clinical Research Phase Studies
- The Investigational New Drug Process
- Asking for FDA Assistance
- FDA IND Review Team
- Approval

Designing Clinical Trials

Researchers design clinical trials to answer specific research questions related to a medical product. These trials follow a specific study plan, called a protocol, that is developed by the researcher or manufacturer. Before a clinical trial begins, researchers review prior information about the drug to develop research questions and objectives. Then, they decide:

- Who qualifies to participate (selection criteria)
- How many people will be part of the study
- How long the study will last
- Whether there will be a control group and other ways to limit research bias

- How the drug will be given to patients and at what dosage
- What assessments will be conducted, when, and what data will be collected
- How the data will be reviewed and analyzed

Clinical trials follow a typical series from early, small-scale, Phase 1 studies to late-stage, large scale, Phase 3 studies.

What are the Clinical Trial Phases?

Watch this video to learn about the three phases of clinical trials.

Clinical Research Phase Studies

Phase 1

Study Participants: 20 to 100 healthy volunteers or people with the disease/condition.

Length of Study: Several months

Purpose: Safety and dosage

During Phase 1 studies, researchers test a new drug in normal volunteers (healthy people). In most cases, 20 to 80 healthy volunteers or people with the disease/condition participate in Phase 1. However, if a new drug is intended for use in cancer patients, researchers conduct Phase 1 studies in patients with that type of cancer.

Phase 1 studies are closely monitored and gather information about how a drug interacts with the human body. Researchers adjust dosing schemes based on animal data to find out how much of a drug the body can tolerate and what its acute side effects are.

As a Phase 1 trial continues, researchers answer research questions related to how it works in the body, the side effects associated with increased dosage, and early information about how effective it is to determine how best to administer the drug to limit risks and maximize possible benefits. This is important to the design of Phase 2

studies.

Approximately 70% of drugs move to the next phase

Phase 2

Study Participants: Up to several hundred people with the disease/condition.

Length of Study: Several months to 2 years

Purpose: Efficacy and side effects

In Phase 2 studies, researchers administer the drug to a group of patients with the disease or condition for which the drug is being developed. Typically involving a few hundred patients, these studies aren't large enough to show whether the drug will be beneficial.

Instead, Phase 2 studies provide researchers with additional safety data. Researchers use these data to refine research questions, develop research methods, and design new

Phase 3 research protocols.

Approximately 33% of drugs move to the next phase

Phase 3

Study Participants: 300 to 3,000 volunteers who have the disease or condition

Length of Study: 1 to 4 years

Purpose: Efficacy and monitoring of adverse reactions

Researchers design Phase 3 studies to demonstrate whether or not a product offers a treatment benefit to a specific population. Sometimes known as pivotal studies, these studies involve 300 to 3,000 participants.

Phase 3 studies provide most of the safety data. In previous studies, it is possible that less common side effects might have gone undetected. Because these studies are larger and longer in duration, the results are more likely to show long-term or rare side

effects

Approximately 25-30% of drugs move to the next phase

Phase 4

Study Participants: Several thousand volunteers who have the disease/condition

Purpose: Safety and efficacy

Phase 4 trials are carried out once the drug or device has been approved by FDA during the Post-Market Safety Monitoring

Learn more about Clinical Trials (/clinical-trials-what-patients-need-know).

The Investigational New Drug Process

Drug developers, or sponsors, must submit an Investigational New Drug (IND) application to FDA before beginning clinical research.

In the IND application, developers must include:

- Animal study data and toxicity (side effects that cause great harm) data
- Manufacturing information
- Clinical protocols (study plans) for studies to be conducted
- Data from any prior human research
- Information about the investigator

Asking for FDA Assistance

Drug developers are free to ask for help from FDA at any point in the drug development process, including:

- Pre-IND application, to review FDA guidance documents and get answers to questions that may help enhance their research
- After Phase 2, to obtain guidance on the design of large Phase 3 studies
- Any time during the process, to obtain an assessment of the IND application

Even though FDA offers extensive technical assistance, drug developers are not required to take FDA's suggestions. As long as clinical trials are thoughtfully designed, reflect what developers know about a product, safeguard participants, and otherwise meet Federal standards, FDA allows wide latitude in clinical trial design.

FDA IND Review Team

The review team consists of a group of specialists in different scientific fields. Each member has different responsibilities.

- Project Manager: Coordinates the team's activities throughout the review process, and is the primary contact for the

sponsor.

- Medical Officer: Reviews all clinical study information and data before, during, and after the trial is complete.
- Statistician: Interprets clinical trial designs and data, and works closely with the medical officer to evaluate protocols and safety and efficacy data.
- Pharmacologist: Reviews preclinical studies.
- Pharmakineticist: Focuses on the drug's absorption, distribution, metabolism, and excretion processes.Interprets blood-level data at different time intervals from clinical trials, as a way to assess drug dosages and administration schedules.
- Chemist: Evaluates a drug's chemical compounds. Analyzes how a drug was made and its stability, quality control, continuity, the presence of impurities, etc.
- Microbiologist: Reviews the data submitted, if the product is an antimicrobial product, to assess response across different classes of microbes.

Approval

The FDA review team has 30 days to review the original IND submission. The process protects volunteers who participate in clinical trials from unreasonable and significant risk in clinical trials. FDA responds to IND applications in one of two ways:

- Approval to begin clinical trials.
- Clinical hold to delay or stop the investigation. FDA can place a clinical hold for specific reasons, including:
    - Participants are exposed to unreasonable or significant risk.
    - Investigators are not qualified.
    - Materials for the volunteer participants are misleading.
    - The IND application does not include enough information about the trial's risks.

A clinical hold is rare; instead, FDA often provides comments intended to improve the quality of a clinical trial. In most cases, if FDA is satisfied that the trial meets Federal standards, the applicant is allowed to proceed with the proposed study.

The developer is responsible for informing the review team about new protocols, as well as serious side effects seen during the trial. This information ensures that the team can monitor the trials carefully for signs of any problems. After the trial ends, researchers must submit study reports.

This process continues until the developer decides to end clinical trials or files a marketing application. Before filing a marketing application, a developer must have adequate data from two large, controlled clinical trials.

Footnote 9

U.S. FOOD & DRUG ADMINISTRATION

22 CASE STUDIES WHERE PHASE 2 AND PHASE 3 TRIALS HAD DIVERGENT RESULTS

January 2017

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22 Case Studies Where Phase 2 and Phase 3 Trials Had Divergent Results

I. Overview

Pre-market clinical testing usually progresses in phases, with increasingly rigorous methods at each phase. Product candidates that appear insufficiently safe or effective at one phase may not proceed to the next phase. Roughly 9 in 10 drugs/biologics that are tested in humans are never submitted to FDA for approval.[1] Typically, a candidate drug is submitted to the FDA for marketing approval after phase 3 testing. In recent years, there has been growing interest in exploring alternatives to requiring phase 3 testing before product approval, such as relying on different types of data and unvalidated surrogate endpoints.

To better understand the nature of the evidence obtained from many phase 2 trials and the contributions of phase 3 trials, we identified, based on publicly available information, 22 case studies of drugs, vaccines and medical devices since 1999 in which promising phase 2 clinical trial results were not confirmed in phase 3 clinical testing.[*] Phase 3 studies did not confirm phase 2 findings of effectiveness in 14 cases, safety in 1 case, and both safety and effectiveness in 7 cases. These unexpected results could occur even when the phase 2 study was relatively large and even when the phase 2 trials assessed clinical outcomes. In two cases, the phase 3 studies showed that the experimental product increased the frequency of the problem it was intended to prevent.

This paper is not intended to assess why each of these unexpected results occurred or why further product development was not pursued. Rather, these cases, chosen from a large pool of similar examples, illustrate the ways in which controlled trials of appropriate size and duration contribute to the scientific understanding of medical products.

II. Clinical Trials: Understanding Medical Product Testing

In the classical drug development paradigm, pre-market clinical trials for drugs are conducted in three phases. The trials at each phase have a different purpose and help scientists answer different questions.

- *Phase 1 Trials.* In phase 1, researchers test the potential product in humans for the first time, to identify rudimentary product characteristics, such as how the body metabolizes a drug and how long it stays in the body, and to provide evidence that the product is not too toxic for further human testing. The treatment group is small (typically 20 – 80 healthy volunteers), but allows researchers to begin to evaluate the treatment's safety, adjust dosing schemes, and start to identify side effects. This information guides the design of phase 2 studies.

- *Phase 2 Trials.* Phase 2 studies are intended to explore the effectiveness of the product for a particular indication over a range of doses, and to assess short-term side effects. These studies typically involve a few hundred patients who have the target condition, but do not generally have other diseases that might obscure the effect of the drug on the target condition. Phase 2 trials may be randomized and/or controlled, but often measure laboratory values or other biomarkers rather than clinical outcomes (i.e., effects on how a patient feels, functions, or survives). When a phase

[*] For the purposes of this analysis, the terms "trial" and "study" are used interchangeably.

2 study does assess clinical outcomes, it is usually for relatively short periods of time and in a relatively small number of people. Sponsors assess phase 2 results to determine if the preliminary results are sufficiently promising to justify a phase 3 study.

- *Phase 3 Trials*. Compared to phase 2 trials, the goal of phase 3 trials is to test the experimental product in larger groups of people (typically 300 – 3000), in people who are more similar to those likely to use the product once marketed, and for longer periods of time. Phase 3 studies generally assess clinical outcomes, and are designed to determine whether the demonstrated benefits of the product outweigh its risks.

As discussed in Section III, below, the appropriate size and duration of clinical trials varies significantly from condition to condition, and product to product.[†]

For most approved drug products, clinical evaluation may be continued even after a product is on the market. These studies are termed phase 4 trials, and can be helpful to uncover information on new uses that can be shared with health care providers to refine prescribing advice or can indicate that new warnings should be added to the product's label.

III. Flexibility in Clinical Trial Design

In practice, clinical testing progression and design has become increasingly flexible as the science of clinical trials has evolved. Phase 1 might be combined with phase 2 if the drug is expected to have toxicity unacceptable for healthy volunteers. If the product's mechanism of action and safety profile are well characterized, phase 2 testing may be shortened or skipped altogether. When there is sufficient evidence that a change in a biomarker reliably predicts a clinical benefit, the biomarker can serve as a surrogate measure for that clinical benefit in a trial, and the effect of the product on the surrogate measure can be a basis for product approval. Surrogate measures are often biomarkers that help diagnose or monitor a disease, such as blood pressure to predict stroke risk or the amount of human immunodeficiency virus in the blood to predict the development of acquired immunodeficiency syndrome.

The nature of definitive trials also varies. Larger and longer trials may be needed if, for example, the condition to be treated is chronic or if the event the drug is intended to prevent occurs infrequently. Smaller or shorter trials may be needed where, for example, the drug produces a dramatic improvement in patients, or is intended for short-term conditions like many infections. Other factors, such as whether the condition is widespread or rare, whether it is life-threatening, and whether there are other effective treatments for the condition are also important in determining what kind of clinical testing is appropriate.

Where a drug or biologic is intended to treat a serious condition for which there are limited available alternative therapies, FDA has implemented four separate expedited development and review programs.[2] For example, when there is evidence that a biomarker is "reasonably likely to predict"

[†] Medical device testing often does not follow this "phase 1 - 3" paradigm or use the same "phase 1 – 3" vocabulary. In some cases, practical limitations related to the device or disease condition may limit the feasibility of a large randomized, controlled trial design. But the need, in certain circumstances, for one or more large well controlled studies to determine whether a device actually improves clinical outcomes can be equally applicable. Such trials serve a purpose similar to phase 3 drug and biologic trials. For editorial convenience, we use the phrase "phase 3" throughout the document to refer to both phase 3 drug and biologics trials, as well as "pivotal" and similar trials for devices.

clinical benefit, that biomarker can be a basis for approval under FDA's accelerated approval authority. In these situations, sponsors have been required to conduct post-market confirmatory studies to further define the clinical benefit of the drug.

While clinical testing progression and design has become increasingly flexible, and advances in biomedical science and statistics have enabled introduction of non-traditional study designs and data sources into phase 3 testing, a randomized, controlled, clinical trial (RCT) of a size and duration that reflect the product and target condition remains the gold standard for determining whether there is an acceptable benefit/risk profile for drugs and biologics. For more discussion on clinical trial design, including the unique features of RCTs that make such trials more likely to be definitive, see Appendix A.

IV. Case Studies

The methods underlying case selection, as well as a discussion of the limitations of this study, are described in Appendix B.

A. Phase 3 Trials Demonstrating Lack of Efficacy in a Promising Experimental Therapy

1. Bitopertin

Product	Bitopertin
Sponsor	Roche
Purpose	Add-on treatment of schizophrenia
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite statistically significant results in reducing the symptoms of schizophrenia in phase 2, in phase 3 trials Bitopertin failed to improve the negative symptoms of schizophrenia.

Schizophrenia is a chronic brain disorder in which people abnormally interpret reality and features three symptom categories: positive, negative and cognitive. Positive symptoms include hallucinations and delusions, while negative symptoms may include social withdrawal, lack of motivation, and reduced emotional reactivity. Cognitive symptoms include problems with memory and concentration.

Schizophrenia typically requires lifelong treatment with antipsychotic medications, which come in two types: typical and atypical. Both types block the brain's dopamine pathway, but atypical antipsychotics are less likely to cause certain undesired side effects (e.g., movement problems), making them useful for long-term management of patients with schizophrenia. However, atypical antipsychotics are still associated with undesirable side effects such as weight gain, increased cholesterol, and movement disruption.

Like dopamine, glycine is a neurotransmitter that has been implicated in the schizophrenia disease process. Over the past years, researchers have noted that people with schizophrenia have a decreased level of glycine in their blood and cerebrospinal fluid.[3] Bitopertin increases the availability of glycine in the synapse (the connection between nerve cells), suggesting a novel approach in the treatment of schizophrenia. A placebo-controlled, double-blind, eight week study randomized over 320 patients across 66 sites worldwide. The study found a statistically significant 25% reduction in negative symptoms among those patients who received the drug compared to those who received placebo.[4]

Three subsequent double-blind, placebo-controlled phase 3 studies evaluated the efficacy and safety of bitopertin when added to conventional drugs in patients with negative symptoms of schizophrenia. These studies together followed over 1800 patients for one year or more, and measured improvement in a patient's negative symptoms compared to symptoms before treatment began. However, results from two of these phase 3 studies found no evidence of a statistically significant improvement in negative symptoms over baseline in patients who received bitopertin add-on therapy compared to those who received placebo.[5, 6]

2. Brivanib

Product	Brivanib
Sponsor	Bristol-Myers Squibb
Purpose	Treatment of hepatocellular cancer
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite promising anti-tumor activity in phase 2 trials, in phase 3 trials Brivanib failed to improve overall survival of patients compared to approved treatment, and demonstrated identified unexpected toxicities.

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, occurring in four out of five cancers that start in the liver.[7] Treatment options for liver cancer, depending on the stage and severity of cirrhosis, include surgery to remove the tumor, embolization to block blood supply to the tumor, radiation, and transplantation.[8, 9]

The only FDA-approved drug is sorafenib, which delays tumor growth and improves survival by inhibiting certain signals used in cell growth or function.[10, 11] Generally, sorafenib is administered to patients who are not candidates for local-directed therapies. To treat those patients who do not respond to sorafenib or who have severe side effects related to the drug, brivanib was developed. Brivanib inhibits a novel growth factor, in addition to those growth factors targeted by sorafenib.

A phase 2 trial was conducted in which 55 patients with advanced HCC received a daily dose of brivanib in the first-line setting.[12] According to the published report, using computed tomography (CT)/magnetic resonance imaging (MRI) measurements of tumor volume, one patient had a complete response, three had a partial response, and 24 had stable disease following exposure to brivanib. A second cohort of 46 patients received brivanib after failing sorafenib therapy or discontinuing sorafenib due to intolerable side effects.[13] Using the same CT/MRI tumor measurement criteria, according to the published report, two patients had a partial response and 19 had stable disease following treatment. Together the studies showed that brivanib showed antitumor activity, with almost half of participants being classified as having stable disease following treatment. The investigators also reported a manageable safety profile for patients with advanced HCC.

Several phase 3 RCTs designed to isolate the effects of brivanib, confirmed statistically significant antitumor activity, but found no evidence that treatment with brivanib improves the overall survival of patients with HCC. One phase 3 study, designed to compare brivanib to sorafenib, randomized over 1,100 patients with advanced HCC who had no prior drug treatment to receive either brivanib or sorafenib.[14] The median overall survival was 9.5 months in the brivanib group and 9.9 months in the sorafenib group, and the primary objective (i.e., non-inferiority of survival) of the study was not met. The authors concluded that brivanib was "less well-tolerated" than sorafenib, as patients receiving brivanib had significantly higher rates of decreased appetite, fatigue, hypertension, nausea, and low blood sodium levels. The authors also stated that patients who received brivanib had a more pronounced decline in physical function and in role function.

Another phase 3 study randomized 395 patients with advanced HCC in patients who previously received sorafenib to receive either brivanib or placebo.[15] This study did not demonstrate a statistically significant improvement in overall survival in patients who received brivanib as compared to placebo.

A third phase 3 study investigated whether brivanib could increase survival compared to placebo in Asian patients with advanced hepatocellular carcinoma who failed prior treatment with sorafenib; however, this study was discontinued by its sponsors and no results are available.[16]

A fourth phase 3 study compared brivanib as an additional treatment to chemoembolization with those receiving only chemoembolization in patients with HCC.[17] However, this trial was terminated early after the two other phase 3 studies mentioned above failed to show improvement in overall survival of patients with HCC. At termination, this study showed that brivanib had not improved overall survival (26.4 vs. 26.1 months).

3. Capsaicin Topical Patch (Qutenza) ‡

Product	Capsaicin topical patch (Qutenza)
Sponsor	NeurogesX
Purpose	Treatment of HIV-associated nerve pain
FDA-approved for any indication at time of initiation of phase 3 trial	Yes, treatment of shingles-associated nerve pain.
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite demonstrated efficacy in a related condition and positive clinical results in a proof of concept study, in an RCT pain control was similar in the Qutenza and control groups.

Many HIV patients experience a burning-type of pain, often in the feet or hands, as a result of nerve damage. Called HIV-associated distal symmetric polyneuropathy (HIV-DSP), it is the most common nerve complication of HIV infection, affecting over 50% of patients.[18-20]

Qutenza is made from capsaicin, the pungent component that makes chili peppers hot. Capsaicin acts on certain pain receptors in the skin by desensitizing nerve endings, resulting in analgesia and pain relief. In 2009, FDA approved Qutenza (8% patch) as a medicated skin patch for pain relief in patients with post-herpetic neuralgia, a painful complication following shingles.[21]

Researchers also studied the efficacy of capsaicin in a related intended use, painful HIV-DSP. An open-label pilot study assessed the efficacy and safety of NGX-4010 (capsaicin 8% patch) in twelve patients with HSV-DSP.[22] Following a single 60-minute NGX-4010 application, these patients were followed up for 12 weeks. The majority of these patients reported a significant reduction in pain, prompting the researchers to proceed to a large, controlled clinical trial.

In two similarly designed RCTs, 800 patients with HIV-DSP were randomized to receive NGX-4010 or a 0.04% concentration control patch. This low concentration control patch was considered too weak to actually treat HIV-DSP, but strong enough to cause the localized skin reactions that are common with capsaicin so that patients would not know to which group they had been assigned. While the initial study found significant pain relief with NGX-4010 over 12 weeks of treatment compared to controls, these findings were not replicated in the second study.[22, 23]

In 2012, a FDA Advisory Committee analyzed the two controlled trials and agreed that there was no substantial evidence of effectiveness for Qutenza in treating HIV-DSP.[24] The Advisory Committee did not recommend the approval of Qutenza, and FDA did not approve the drug.[25]

‡ Product names in parentheses are brand names.

4. Darapladib

Product	Darapladib
Sponsor	GlaxoSmithKline
Purpose	Add-on to a statin for prevention of cardiovascular disease complications in patients with prior heart attack
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite exciting biomarker evidence in phase 2, in phase 3 trials darapladib failed to reduce the risk of heart attack or cardiac death compared with placebo in patients with chronic cardio vascular disease.

Cholesterol builds up in blood vessels of patients with cardiovascular disease, hardening the arteries in an inflammatory process called atherosclerosis.[26] Atherosclerosis restricts blood flow to the heart muscle, causing heart attacks.

Atherosclerosis is thought to be driven by inflammation. Lp-PLA2 is a protein produced by inflammatory cells, and blood levels of Lp-PLA2 are thought to predict heart attack risk.[27] A phase 2 study found both impressively reduced blood levels of Lp-PLA2 and stabilized atherosclerotic plaques in patients administered darapladib in addition to a statin (a cholesterol-reducing medication), compared to placebo plus a statin.[28] Another phase 2 study indicated that darapladib significantly reduced interleukin-6, another cardiovascular inflammatory marker.[29] Mechanistically, then, darapladib seemed promising. Human Genome Science CEO Tom Watkins predicted that darapladib was a "blockbuster in the making."[30]

The phase 3 STABILITY trial randomized over 15,000 patients with chronic, stable heart disease to take darapladib and a statin or a placebo and a statin, and monitored their cardiovascular outcomes over a median of 3.7 years.[31] The STABILITY trial's primary outcome measures were cardiovascular death, heart attack, and hospitalization for acute cardiac events. An additional phase 3 trial, the SOLID-TIMI 52 trial, randomized over 13,000 patients to receive either darapladib or a placebo within 30 days of a heart attack and followed their cardiovascular outcomes over a median of 2.5 years.[32] The study's primary outcome measures were cardiovascular death, nonfatal heart attack, and nonfatal stroke.

Neither study demonstrated benefit. Primary outcome event rates were 10.4% on placebo and 9.7% on darapladib in STABILITY, a difference that was not statistically significant. Primary outcome event rates in SOLID-TIMI 52 were 15.6% on placebo and 16.3% on darapladib, a lean in the opposite direction that was also not statistically significant.[33]

5. Dexmecamylamine

Product	Dexmecamylamine
Sponsor	Targacept/AstraZeneca
Purpose	Add-on treatment of depression
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite statistically significant results on measures of depression in phase 2, in the phase 3 trial dexmecamylamine proved no more effective than a placebo as add-on treatment for depression.

First-line therapies for depression include selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). These drugs increase the amount of serotonin and norepinephrine in the brain − neurotransmitters known to have a role in mood.[34]

Researchers have also hypothesized that drugs that activate certain other receptors called nicotinic neural receptors, such as the drug dexmecamylamine, could normalize the activity in these receptors and potentially be a treatment for depression.[35] In 2009, a phase 2 trial randomized 270 participants on SSRIs to receive either dexmecamylamine or placebo over a course of eight weeks. The study found that those who took dexmecamylamine improved more on a standard depression scale compared to placebo.[36]

With these promising phase 2 results, dexmecamylamine underwent four phase 3 studies in which a total of 614 study participants whose depression did not improve with standard SSRI or SNRI therapies were randomized to receive dexmecamylamine or placebo while continuing their SSRI or SNRI therapy. After eight weeks of add-on treatment, these studies found no difference between the treatment effects of dexmecamylamine and placebo in treating depression on standard depression scales in any of the phase 3 studies.[37-39]

6. Exhale Drug-Eluting Stent

Product	Exhale Drug-Eluting Stent
Sponsor	Broncus Technologies
Purpose	Reduction of shortness of breath in patients with emphysema
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent result in phase 3 trial	Despite statistically significant results on measures of lung function and symptoms in phase 2, in the phase 3 trial the Exhale Stent failed to improve lung function or symptoms in patients with emphysema.

Emphysema is a disease in which air sacs in the lungs called alveoli are gradually destroyed. Alveoli inflate and deflate with breathing, allowing inhaled oxygen to enter the blood and carbon dioxide to be exhaled. In emphysema, the alveoli hyperinflate and eventually rupture, trapping air in the lungs. As a result, fresh, oxygen-rich air cannot enter the lungs properly, causing progressive shortness of breath. It is frequently caused by many years of smoking and has no cure. Treatment for emphysema is intended to relieve symptoms, prevent complications, and slow disease progression. Therapies may involve smoking cessation, oxygen supplementation, medications such as bronchodilators (drugs that widen airway passages), surgery to reduce lung volume, and lung transplantation.[40]

A new bronchoscopic procedure was designed to reduce hyperinflation and improve airflow in emphysema. Called airway bypass, the procedure involves insertion of a flexible tube called a bronchoscope through the mouth so that the airways can be visualized. Once a diseased site is identified, a needle pierces the airway wall to create a new passage so that trapped air can escape.[41] A device smaller than a pencil eraser called the Exhale Drug-Eluting Stent is then placed in the newly created passageway to keep it open. A drug is included in the stent to prevent tissue growth in the new passage. A phase 2 study assessed the effects of the Exhale stents in 35 patients with severe emphysema by measuring how well their lungs took in and released air and whether their symptoms improved.[42] At the 6-month follow-up, there were statistically significant improvements in symptoms and various indices of lung function, as compared to baseline, leading researchers to conclude that the stents reduce hyperinflation and provide clinical improvement.

A phase 3 study further investigated whether these Exhale airway stents could improve lung function and reduce breathlessness in severely affected emphysema patients.[43] More than 300 patients were randomized to undergo either the airway bypass with Exhale stent placement or a sham procedure (a fake procedure in which bronchoscopes were used, but no airway walls were pierced and no stents were placed).[44] At 6 months, there were no differences in lung volume or shortness of breath between the two groups. The study thus concluded that Exhale airway stents provide no sustained benefit in patients with emphysema.

7. Experimental HSV-2 Vaccine

Product	Experimental HSV-2 Vaccine
Sponsor	Chiron (now Novartis Vaccines & Diagnostics)
Purpose	Prevention of genital herpes
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite positive biomarker results in phase 2, in the phase 3 trials the vaccine did not prevent genital herpes.

Genital herpes is a common sexually transmitted disease caused by herpes simplex virus type 1 (HSV-1) or the generally more serious type 2 (HSV-2). Most people with herpes have no symptoms, but others may have painful genital sores that tend to recur. People with weakened immune systems, including individuals with HIV/AIDS, organ transplants, and cancer, are at increased risk for severe herpes infections. Pregnant women can also pass the infection to newborns, causing neonatal herpes, a rare but potentially life-threatening disease.[45] There is no cure for herpes, but there are medicines to prevent recurrences or shorten the duration of those recurrences.

An HSV-2 vaccine was developed by Chiron. Two phase 2 studies randomized over a hundred persons with no antibodies to HSV-2 in their blood to receive one of three different doses of the vaccine. The studies showed that the vaccine induced an antibody response similar to persons who had a naturally-acquired HSV-2 infection.[46]

Two phase 3 RCTs followed, involving almost 2,400 persons with no detectable antibodies for HSV-2 who were followed for one year after their final immunization.[47] These studies, however, showed that despite producing an antibody response similar to natural HSV-2 infection, vaccine recipients acquired HSV-2 infection at a rate similar to placebo (4.6% of placebo group versus 4.2% of vaccine group). Researchers concluded that the vaccine produced only a partial and transient protection against HSV-2 infection.[48]

8. Glutamic Acid Decarboxylase Vaccine

Product	Glutamic Acid Decarboxylase (GAD) Vaccine
Sponsor	Diamyd Medical
Purpose	Preservation of insulin secretion for patients with recent-onset type 1 diabetes
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite promising biomarker results in phase 2, in the phase 3 study treatment with GAD vaccine did not improve pancreatic function or clinical outcomes.

Type 1 diabetes is an autoimmune disease in which a person's pancreas stops producing insulin. It affects adults and children and occurs when the body's immune system attacks and destroys the insulin-producing cells in the pancreas, called beta-cells. While intensive insulin therapy can delay the onset and slow progression of kidney failure, blindness, and nerve damage, these complications continue to cause high rates of morbidity and mortality.[49]

Vaccination with Glutamic Acid Decarboxylase (GAD) to control the abnormal immune response was proposed as a strategy to prevent or delay loss of beta-cell function. Although intensive insulin therapy improves glycemic control and is the therapeutic gold standard, insulin itself does not treat the underlying disease process. Treatment with therapies that down-regulate other parts of the immune system, including specific antibodies targeting important mediators of the immune response, have been tried but to date have not proved effective and have caused serious adverse reactions.[50]

In a phase 2 study, 70 patients recruited within 18 months of their type 1 diabetes diagnosis were randomly assigned to receive injections of GAD or placebo.[51] The primary endpoint was the change from baseline to month 15 in C-peptide levels, a measure of beta-cell function that drops as beta cell function declines. The C-peptide levels gradually decreased in both study groups, but patients receiving GAD injections showed significantly less decline in C-peptide levels than the patients receiving a placebo injection. This suggested that vaccination with GAD could potentially preserve the insulin-producing function of beta cells. The researchers claimed that the results provided a preliminary proof of concept.

In the phase 3 trial, 334 patients were randomly assigned to one of three study treatments and followed for 15 months: four doses of GAD, two doses of GAD followed by two doses of placebo, or four doses of placebo. The same time points from the phase 2 trial were used to measure C-peptide levels and other clinical outcomes such as insulin requirement, plasma glucose, glycosylated hemoglobin levels and rate of hypoglycemia.[52] The primary outcome was the change in C-peptide levels between the baseline visit and the 15-month visit. The phase 3 trial did not confirm the preliminary results and concluded that treatment with GAD did not significantly reduce the loss of C-peptide or improve any important clinical outcomes over a 15-month period.

9. Imiquimod (Aldara 5% Cream)

Product	Imiquimod (Aldara 5% Cream)
Sponsor	3M
Purpose	Treatment of molluscum contagiosum (MC) lesions in children
FDA-approved for any indication at time of initiation of phase 3 trial	Yes, treatment of external anogenital warts.
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite demonstrated efficacy in another viral skin infection and promising phase 2 results on clearance of MC lesions, in the phase 3 trial treatment with imiquimod cream was no more likely to clear MC lesions than treatment with placebo.

Molluscum contagiosum (MC) is a relatively common viral skin infection that primarily affects children. It is characterized by clusters of pearly, flesh-colored, dome-shaped bumps on the skin surface. These lesions are usually painless, but may be itchy and inflamed. If scratched, the lesions can spread to other areas of the body or to other persons, and can become infected with bacteria. MC disappears spontaneously, typically after 6 to 12 months, but some bumps can last up to four years.[53]

Common treatments for MC include cryotherapy (freezing with liquid nitrogen), curettage (scraping), topical agents, and lasers.[54] These treatment modalities can be effective but uncomfortable, especially for children. There are no FDA-approved drug treatments for MC.[55]

Imiquimod is a topical drug that is FDA-approved to treat external genital and perianal warts, which are caused by a different skin virus.[56] The drug works by stimulating the immune system's reaction to the virus, thereby strengthening the body's ability to fight off the infection. Researchers hypothesized that because imiquimod was effective for one viral skin infection, it might also be effective for others, leading researchers to investigate imiquimod's efficacy in MC.

A randomized, single blinded phase 2 clinical trial compared weekly cryotherapy to daily topical imiquimod in 74 children over 16 weeks. This study suggested impressive drug efficacy, with over 90% of those receiving imiquimod experiencing complete clearance of MC lesions at 12 weeks.[57] In the cryotherapy group, all lesions were cleared.[57] However, pain, blistering, and scarring were significantly more common in the cryotherapy group, making imiquimod look promising as a better tolerated, effective treatment for MC.[57]

Imiquimod cream was then evaluated in two double-blind phase 3 RCTs involving a total of 702 pediatric MC patients aged 2-12.[58] These children received imiquimod cream or placebo cream three times per week for up to 16 weeks and were assessed at week 18 for complete clearance of MC lesions. In the first study, the complete clearance rate was 24% in the imiquimod group compared with 26% in the vehicle group. In the second study, the clearance rate was 24% in the imiquimod group compared with 28% in the vehicle group. These studies thus failed to demonstrate any efficacy against MC. In addition, children who received imiquimod were more likely to experience application site reactions, conjunctivitis, low white blood cell counts, and inflamed lymph nodes.[58]

10. Iniparib

Product	Iniparib
Sponsor	Sanofi
Purpose	Add-on treatment of "triple negative" breast cancers
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite promising phase 2 results on both tumor response and survival, in the phase 3 trial adding iniparib to an established chemotherapy regimen did not improve survival.

Breast cancer is the most common cancer in women.[59] Triple-negative breast cancer is a subtype of breast cancer that is aggressive and difficult to treat. It is called triple-negative because the cancer cells do not over-express three different receptors; the cancer could otherwise be treated by chemotherapies and/or agents targeted to the receptors.

Iniparib showed strong activity in preclinical testing, enhancing the effects of standard chemotherapy on triple-negative metastatic breast cancer cells.[60, 61] In phase 2 testing, 123 patients with metastatic triple-negative breast cancer were randomized to receive either standard chemotherapy or standard chemotherapy plus iniparib. Adding iniparib to a standard chemotherapy regimen significantly improved tumor response and overall survival, without increasing toxicity.[62]

Despite promising phase 2 results, iniparib was not shown to be effective in phase 3 testing. Five hundred nineteen patients with metastatic triple-negative breast cancer were randomly assigned to receive either standard chemotherapy regimen or the standard regimen plus iniparib. The phase 3 trial did not identify any significant safety concerns, but the addition of iniparib to the standard regimen did not demonstrate any improvement in overall or progression-free survival.[63] Overall survival of the patients receiving standard chemotherapy was 11.1 months, versus 11.8 months for those also receiving iniparib.[63]

11. Lithium

Product	Lithium
Sponsor	King's College London (UK)
Purpose	Add-on treatment to delay disease progression of amyotrophic lateral sclerosis
FDA-approved for any indication at time of initiation of phase 3 trial	Yes, treatment of bipolar disorder.
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite positive effects on disease progression and survival in a phase 2 trial, in the phase 3 trial treatment with lithium did not improve survival, health status or quality of life.

Amyotrophic lateral sclerosis (ALS), sometimes called Lou Gehrig's disease (after the famous baseball player who was diagnosed with it), is a nervous system disease that causes muscle weakness. In ALS, the nerve cells that control the movement of muscles gradually die, leading to progressive weakness. Affected patients gradually lose ability to move their arms and legs, speak, eat, and breathe. Most ALS patients die within 2 to 5 years of diagnosis.[64]

Most cases of ALS have an unknown cause, but scientists believe that there is a genetic mutation in up to 10% of cases.[64-66] There is no cure for ALS, and riluzole is the only FDA-approved drug for the treatment of ALS.[67, 68] This drug extends patient survival by two to three months.[67, 69],

A proof of concept study randomized 44 ALS patients to receive daily doses of either riluzole or riluzole plus lithium.[70] Over a 15-month period, the study compared the survival rate and disease progression between the two groups. For disease progression, the study measured muscle strength and lung function (volume of air expired after a full inspiration) every three months. At the end of the study, all patients treated with lithium and riluzole were alive while 30% of patients who received riluzole alone had died. The study also showed that patients who received lithium had a slower disease progression compared to those who did not. The researchers thus concluded that lithium delays ALS progression.

A phase 3 placebo-controlled study followed and randomized over 200 ALS patients.[71] This study evaluated the safety and efficacy of lithium combined with riluzole, compared to placebo combined with riluzole. Over an 18-month period, the study compared (1) the overall survival of patients, and (2) health outcomes such as mobility, self-care, usual activities, pain or discomfort, anxiety, and depression. At the end of the study, the number of patients alive was similar between the treatment groups (50% in the lithium group versus 59% in the placebo group).[72] As for health outcomes, there was a marked deterioration in functional health status and quality of life in patients assigned to both groups with no difference between groups in their rates of decline. The study thus concluded that, while there was no safety concern, lithium has no evidence of benefit in patients with ALS.

12. MAGE-A3 vaccine

Product	MAGE-A3 vaccine
Sponsor	GlaxoSmithKline
Purpose	Treatment of patients with non-small cell lung cancer (NSCLC) following surgery
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite a promising proof of concept trial of this targeted immune therapy, in the phase 3 trial the MAGE-A3 vaccine conferred no clinical benefit when compared to a placebo.

Broadly, lung cancer comes in two forms: small cell and NSCLC. Current therapies for treatment of NSCLC include surgical removal of the cancer, chemotherapy, and radiation therapy, yet long-term survival rates remain low.[73]

Recent advances in cancer research indicate the potential for treating NSCLC by harnessing the body's immune system. Certain tumor cells exhibit surface molecules (antigens) that can be targeted by therapeutic cancer vaccines, potentially preserving healthy cells.[74] One example of these cell surface antigens is MAGE-A3, a tumor-specific antigen present on the surface of certain tumor cells. Approximately 33% of NSCLCs express MAGE-A3, which is not seen in normal lung cells, thus making it a potential target for NSCLC therapies.

A phase 2 study evaluated a MAGE-A3 vaccine as a treatment for patients with MAGE-A3-positive NSCLC. Following surgery to remove as much of the tumor as possible, 182 patients were randomized to receive either the MAGE-A3 vaccine or placebo 13 times over 27 months. The results showed a non-statistically significant improvement in disease-free survival and overall survival among patients receiving this cancer vaccine.[75] The study was only large enough only to provide proof of concept. The sponsor determined that the results were promising enough to propel the vaccine to the largest phase 3 trial of a NSCLC therapy ever undertaken.[76]

In the phase 3 MAGRIT trial, investigators randomized 2,272 patients with completely resected MAGE-A3-positive NSCLC to receive 13 intramuscular injections of either the vaccine or placebo using the same schedule as the phase 2 trial.[77] The study, however, did not demonstrate that treatment with MAGE-A3 cancer vaccine increased patients' disease-free survival (60.5 months vs. 57.9 months, a statistically non-significant difference).[77] The results of the study led the researchers to conclude that this cancer vaccine offers no clinical benefit in patients with NSCLC.[77]

13. NicVAX Vaccine

Product	NicVAX vaccine
Sponsor	Nabi Biopharmaceuticals
Purpose	Smoking cessation
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results of phase 3 trial	Despite phase 2 evidence suggesting positive biomarker and clinical results, in the phase 3 trials the abstinence rate in the NicVAX group was similar to that in the placebo group.

Nicotine is the primary addictive agent in tobacco. Nicotine vaccines aim to stimulate the immune system to produce nicotine-specific antibodies, which would bind with the nicotine in the bloodstream and prevent or slow the rate at which the nicotine reaches the brain.[78] This, in turn, might reduce the urge to smoke, leading to cessation.

One phase 1/2 and four phase 2 trials of one such vaccine, NicVAX, were conducted by Nabi Biopharmaceuticals.[79] All of these trials, which enrolled between 11 and 301 patients, focused on the safety and immunogenicity of NicVAX, and identifying the best dosing regimen. The phase 2b placebo-controlled trial with 301 patients also assessed efficacy of NicVAX for smoking cessation in smokers who wanted to quit.[80] In this study, those smokers who developed the highest concentrations of anti-nicotine antibodies in response to the vaccine were significantly more likely to maintain abstinence for 8 weeks than smokers receiving placebo. Collectively, these trials identified a 6-injection, high-dose regimen as the most likely to be effective, based on the anti-nicotine antibodies measured.[81]

Two phase 3 RCTs were conducted in which about 2,000 patients were given 6 vaccinations of NicVAX or placebo.[81] The last vaccination was at week 26, and the primary endpoint was the number of patients who remained abstinent for 16 weeks. This timeframe corresponded to the peak anti-nicotine antibody levels observed in the phase 2 trials. Despite the suggestions of efficacy in the phase 2b trial, one of phase 3 trials reported similar abstinence rates of approximately 11% in the NicVAX and placebo groups, failing to demonstrate efficacy.[81] The other phase 3 trial also failed to demonstrate efficacy.[§][81]

[§] Data for the second phase 3 trial were not reported in the paper.

14. Velimogene Aliplasmid (Allovectin-7)

Product	Velimogene Aliplasmid (Allovectin-7)
Sponsor	Vical
Purpose	Treatment of metastatic melanoma
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite evidence of tumor shrinkage in phase 2, in the phase 3 trial Allovectin-7 reduced tumor size in significantly fewer patients than two marketed therapies in late-stage melanoma patients.

A largely curable disease if detected early and surgically removed, melanoma is relatively resistant to treatment and generally deadly in its advanced stages. Melanoma has been shown to respond to therapies that stimulate the immune system to recognize and target melanoma cells.

In early phase 1 studies in advanced melanoma patients, one such therapy−Allovectin-7, a gene transfer therapy directly injected into melanoma tumors–was able to shrink tumors, including those distant from injected tumors.[82] Additional apparent evidence of effectiveness was generated in subsequent studies, most notably in an uncontrolled phase 2 study revealing complete or partial tumor shrinkage in 11.8% of late-stage melanoma patients who had previously failed on or could not tolerate conventional chemotherapy who were injected with Allovectin-7. Tissue examinations from two patients revealed no evidence of melanoma.[83] Based on the results of this study, the drug advanced to a phase 3 multinational clinical trial.

That trial featured 390 patients with stage III and IV melanoma who were randomly assigned to receive Allovectin-7 or one of two marketed therapies used to treat advanced melanoma.[84] Allovectin-7 failed to meet its endpoints. Allovectin-7 proved significantly less effective than these therapies, registering a favorable tumor response rate in 4.6% of patients receiving it for at least 24 months compared to 12.3% of patients on the other treatments.

B. Phase 3 Trials Demonstrating Lack of Safety in a Promising Experimental Therapy

15. Olanzapine Pamoate (Zyprexa Relprevv)

Product	Olanzapine Pamoate (Zyprexa Relprevv)
Sponsor	Eli Lilly
Purpose	Long-acting injection treatment for schizophrenia
FDA-approved for any indication at time of initiation of phase 3 trial	Yes, in oral short-acting formulation for treatment of schizophrenia
Problem identified in phase 3 trial	Lack of safety
Divergent result in phase 3 trials	Although a different formulation of this drug was already approved, the phase 3 studies identified a serious safety risk of the long-acting formulation, requiring safety monitoring.

Schizophrenia is a chronic brain disorder characterized by an altered perception of reality. Symptoms may include hallucinations, delusions, and disordered thinking and behavior.[85, 86] Medication compliance in schizophrenia is a challenge, as roughly half of the patients with the disease have difficulty adhering to medical treatment.[87] A useful option is to inject patients with a long-acting formulation of the desired drug to ensure sustained treatment without the need for daily oral doses or daily injections.

Eli Lilly thus developed a long-acting, injectable formulation of its atypical antipsychotic olanzapine for use in patients with schizophrenia. Early phase studies showed evidence of non-inferiority to oral olanzapine, and did not identify new safety concerns.[88]

A subsequent phase 3 trial evaluated the efficacy of long-acting olanzapine injectable compared to placebo, and another phase 3 trial compared its efficacy with oral olanzapine. Both studies confirmed that the new long-acting formulation was effective in reducing the severity and frequency of schizophrenia symptoms.[88] However, early in these trials, two episodes of profound sedation occurred in the first hour after injection. These episodes triggered a review of all adverse events reported in trials of the injection formulation, as well as ongoing surveillance. Other incidents of sedation, dizziness, confusion and/or loss of consciousness in the immediate post-injection period were reported,** some occurring as late as three hours after injection.[88] This phenomenon became known as post-injection delirium sedation syndrome (PDSS).

In 2008, an FDA Advisory Committee reviewed the compiled evidence, which showed clear efficacy along with sometimes profound PDSS in 0.07% of injections and about 1.2% of patients.[89] The Advisory Committee determined that it would be worth trying to manage the risks of the injectable formulation in order to make the product available for patients with a history of non-adherence. It recommended approval, but with the imposition of a mandatory post-injection period of observation.[90] The FDA went on to approve the long-acting drug with a Risk Evaluation and Mitigation Strategy, which requires that all patients be observed by healthcare professionals for three hours after injection to ensure medical care is available if needed.[91]

** PDSS mimics olanzapine overdose, leading investigators to hypothesize that the injected olanzapine may have entered a blood vessel, leading to rapidly rising blood levels instead of the planned gradual release of the drug. Citrome L. Olanzapine pamoate: A stick in time. International Journal of Clinical Practice. 2009;63:140–50.

C. Phase 3 Trials Demonstrating Lack of Efficacy and Lack of Safety in a Promising Experimental Therapy

16. Aliskiren (Rasilez, Tekturna)

Product	Aliskiren (Rasilez, Tekturna)
Sponsor	Novartis
Purpose	Add-on treatment for prevention of congestive heart failure (CHF) complications
FDA-approved for any indication at time of initiation of phase 3 trial	Yes, treatment of hypertension.
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite approval of the drug for a related indication and positive biomarker effects in a proof of concept study, in the phase 3 trial adding aliskiren to standard therapy did not reduce cardiovascular-related death or CHF re-hospitalization after discharge, and increased the incidence of kidney failure and low blood pressure.

Congestive heart failure (CHF) occurs when the heart fails to pump enough blood to meet the needs of the body. When the heart fails to pump effectively, the amount of a hormone called renin rises in the bloodstream, causing fluid to build up in the body. Fluid overload can be quantified using a lab test called brain natriuretic peptide (BNP); an elevated BNP is associated with greater fluid overload and is indicative of a CHF exacerbation.[92]

It is well established that drugs that block the effects of renin can improve heart failure, but they also raise renin levels, thereby limiting the effectiveness of the medication. Pharmaceutical companies have developed drugs called direct renin inhibitors in hopes of improving treatment for CHF and high blood pressure. One such drug is aliskiren, which significantly reduced plasma BNP and renin activity compared to placebo in a proof of concept trial.[93]

Investigators evaluated aliskiren's clinical efficacy in the 2013 ASTRONAUT trial by randomizing over 1,600 patients hospitalized for CHF to take aliskiren or placebo for a year, in additional to standard therapy. The primary outcome measure was a composite including cardiovascular-related death or CHF-related rehospitalization. While BNP levels decreased, adding aliskiren to standard therapy did not reduce cardiovascular-related death or CHF rehospitalization after discharge compared to placebo: 10% of the patients receiving aliskiren and 11% of the patients receiving placebo died, indicating no significant mortality benefit to taking the drug. Moreover, patients receiving aliskiren had significantly higher rates of kidney failure and low blood pressure, as well as elevated potassium levels (not statistically significant), compared with patients who received placebo.[94]

17. CoStar Drug-Eluting Stent

Product	CoStar Drug-Eluting Stent
Sponsor	Conor Medsystems
Purpose	Reduction of heart attack risk in patients with coronary artery disease
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy, lack of safety
Divergent results in phase 3 trial	Despite approval in the European Union and positive results in a small trial, in an RCT patients who received a CoStar stent had worse outcomes than those who received a different stent.

The heart's main blood supply comes from the coronary arteries. Coronary artery disease (CAD) results in a narrowing of these arteries, which restricts blood flow to the heart. Poor blood flow to the heart can lead to heart attacks and poor cardiac function. Coronary stents are wire-mesh tubes implanted in narrowed heart arteries to prop open the vessels, thereby preventing serious cardiac events. Drug-eluting stents are coated with a drug intended to augment the device's mechanical effects to help keep the artery open, and have gained popularity in recent years.

One such stent was the CoStar, which was coated with paclitaxel, an anti-cancer drug that inhibits scar formation around a stent, thus preventing re-narrowing of the artery. A small clinical study of the CoStar stent conducted outside the U.S. suggested that this stent performed as well as other marketed stents.[95] On this basis, the stent received European Union approval and was widely used in Europe.[96] Before approval in the U.S., however, the FDA insisted upon a large, double-blind, controlled study to demonstrate the CoStar stent's safety and comparability to available products.

Investigators conducted a clinical trial of 1,700 patients in the U.S. to support an application for FDA approval. The CoSTAR II trial was a RCT comparing the CoStar stent with the Boston Scientific Taxus Express2™ paclitaxel-eluting stent in the treatment of CAD. The primary outcome measure was major adverse cardiac events (MACE) at eight months, defined as a composite of target vessel re-narrowing, heart attack, and cardiac-related death. In the study, the CoStar stent showed a significantly higher MACE rate (11%) than the Taxus stent (6.9%).[97] Vessels in which the CoStar stent had been placed were significantly more likely to re-narrow (32%) than those in the comparison group (24%) and patients treated with the CoStar stent had a nearly 2-fold higher rate of needing a repeat coronary artery procedure to treat a recurrent blockage. The heart attack and stent thrombosis rates were numerically higher in patients treated with the CoStar stent, though the difference was not statistically significant.

18. Figitumumab

Product	Figitumumab
Sponsor	Pfizer
Purpose	Add-on treatment of advanced non-small cell lung cancer (NSCLC)
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy, lack of safety
Divergent results in phase 3 trial	Despite positive clinical results in phase 2 for this targeted therapy, adding figitumumab to established chemotherapy regimens in phase 3 failed to improve survival, and in combination with one regimen increased serious adverse events and deaths.

Broadly, lung cancer comes in two forms: small cell and NSCLC. Current therapies for treatment of NSCLC include surgical removal of the cancer, chemotherapy, and radiation therapy, yet long-term survival rates remain low.[73]

Figitumumab was developed to inhibit a specific growth factor (IGF-1R) thought to contribute to the development and progression of NSCLC, among other cancers.[98, 99] In animal testing, it enhanced the anti-tumor effects of standard chemotherapies, and in phase 1 testing figitumumab appeared to inhibit the target pathway and showed signs of antitumor activity against several types of cancers, including NSCLC.[98] In a phase 2 study, NSCLC patients receiving figitumumab in combination with a standard chemotherapy regimen (carboplatin and paclitaxel) appeared to show a higher response rate than patients receiving carboplatin and paclitaxel alone.[98, 100]

Based on these results, two phase 3 trials were conducted comparing figitumumab plus various standard therapies to the standard therapies alone, in a total of 1264 patients with NSCLC.[101, 102] Both studies were halted early because figitumumab failed to improve overall survival. Further, combining figitumumab with one of these standard regimens showed a trend toward decreased overall survival and increased the incidence of treatment-related serious adverse events (SAEs) and deaths, with 21% of patients receiving figitumumab experiencing SAEs, compared with 12% of patients receiving the standard chemotherapy regimen alone.[102] The rate of treatment-related-death in patients receiving figitumumab was 5%, versus 1% in the standard regimen patients.[102]

After the phase 3 trials were terminated early for lack of efficacy and safety concerns, Pfizer retracted the article describing the phase 2 data.[103] The company discovered that tumor shrinkage had not been confirmed in all responding patients, deviating from Pfizer's standard operating procedures. The corrected data showed a lower response rate.

19. Recombinant Factor VIIa (NovoSeven)

Product	Recombinant Factor VIIa (NovoSeven)
Sponsor	Novo Nordisk
Purpose	Reduction of intracerebral bleeding and hematoma size in patients with stroke
FDA-approved for any indication at time of initiation of phase 3 trial	Yes, treatment of hemophilia.
Problem identified in phase 3 trial	Lack of efficacy, lack of safety
Divergent results in Phase 3 Trial	Despite positive clinical results in phase 2, in the phase 3 trials patients with intracerebral bleeding who received recombinant factor VIIa experienced no clinical benefits and an increased incidence of serious adverse events compared to patients who received placebo.

A stroke is a disruption of the brain's blood supply, leading to brain cell death. There are two kinds of stroke: ischemic and hemorrhagic. Ischemic stroke accounts for over 85% of all strokes, and occurs when blood flow to the brain is blocked by a blood clot. Hemorrhagic stroke is less common than ischemic stroke, and occurs when blood flow to the brain is disrupted by a bleed in the brain. Hemorrhagic stroke is often devastating because there is no effective treatment to stop the bleeding.

Factor VIIa is an essential protein in the body's clot-forming pathway. Recombinant factor VIIa (rFVIIa) is a product that has been used for a number of years to treat individuals with hemophilia who do not respond to conventional treatment. Researchers hypothesized that giving rFVIIa to patients experiencing an acute hemorrhagic stroke could reduce bleeding, and thus reduce the severity of bleeding and disability. In a placebo-controlled, double-blinded trial with 399 patients, researchers were heartened to find that treatment with rFVIIa within four hours after the onset of a hemorrhagic stroke reduced the amount of bleeding in the brain, reduced mortality, and improved patients' functional outcomes at 90 days.[104]

Subsequently, in order to further evaluate the efficacy of rFVIIa in improving survival and functional outcomes among patients, investigators randomized nearly 850 patients with acute hemorrhagic stroke to either placebo, 20 micrograms per kilogram rFVIIa, or 80 micrograms per kilogram of rFVIIa in the phase 3 FAST trial. The primary outcome measure was severe disability or death 90 days after the stroke. Although patients who received either dose of the study drug did have smaller bleeding volumes than those in the placebo group, they experienced no clinical benefit; approximately 20% of patients died no matter what they received, and rates of significant disability were comparable between the three groups.[105] Patients who received rFVIIa also experienced a statistically significant increase in thromboembolic events compared to those who received placebo.

20. Semagacestat

Product	Semagacestat
Sponsor	Eli Lilly
Purpose	Improvement of cognitive and functional status in persons with Alzheimer's Disease
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy, lack of safety
Divergent results in Phase 3 Trial	Despite promising biomarker results in phase 2, the phase 3 trial was terminated early because patients who received semagacestat had worsened cognitive and functional status and an increased risk of skin cancer compared to patients who received placebo.

Alzheimer's Disease (AD) is chronic and progressive; survival after diagnosis can range from four to 20 years, depending on the individual and other coexisting health conditions.[106] Currently, there are several FDA-approved medications for the condition – three cholinesterase inhibitors (Aricept/donepezil, Exelon/rivastigmine, Razadyne/galantamine) and one N-methyl-D-aspartate receptor antagonist (Namenda/memantine) – but their efficacy is limited and they do not slow disease progression.

AD is associated with a buildup of amyloid-beta protein in the brain, and that protein is thought by many to play an important role in the disease process. Brain amyloid has been considered a biomarker with potential clinical meaning, and researchers have hypothesized that reducing amyloid-beta may improve disease symptoms. Semagacestat blocks gamma-secretase, an enzyme involved in the creation of amyloid-beta, and thus is intended to prevent the buildup of amyloid-beta in the brain; semagacestat was also expected to reduce blood concentrations of amyloid-beta protein.[107] A phase 2 trial that examined the effect of semagacestat in AD did show a reduction in blood levels of amyloid-beta among patients receiving the drug daily for 14 weeks.[108] Investigators were hopeful that semagacestat's effect on the levels of this [peptide] in blood would translate into clinically meaningful improvements in the disease.

A phase 3 trial randomized over 1,500 patients to receive placebo or semagacestat for 18 months.[109] The primary outcomes were the change in cognition from baseline to month 18 in the ADAS-cog and ADCS-ADL, which are measures of cognition and function, respectively. The trial was terminated before completion because patients taking semagacestat experienced worse cognitive and overall functioning over the course of the trial compared to those taking a placebo.[109] Treatment with semagacestat was associated with decreases in blood concentrations of amyloid-beta, but was also associated with a statistically significant dose-related decline in primary outcomes including activities of daily living, global functioning, cognitive functioning, and quality of life, compared to placebo. Patients taking semagacestat had more adverse events – including infections, skin cancers, and total cancers – compared to placebo. In fact, patients receiving semagacestat had at least double the risk of developing skin cancer compared to patients receiving placebo.

21. Torcetrapib

Product	Torcetrapib
Sponsor	Pfizer
Purpose	Prevention of cardiovascular events in patients with a history of cardiovascular disease or type 2 diabetes
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy, lack of safety
Divergent results of phase 3 trial	Even though torcetrapib improved biomarker (cholesterol) levels in phase 2 testing, in the phase 3 trial it increased mortality and cardiac events compared with placebo in patients at high cardiovascular risk.

Having high cholesterol puts patients at risk of developing heart disease, the leading cause of death among Americans. Cholesterol is carried in the blood stream in different ways. HDL-cholesterol (HDL-C) is sometimes referred to as "good" cholesterol because higher levels of HDL-C are associated with a lower risk of cardiovascular disease; conversely, LDL-cholesterol (LDL-C) is sometimes referred to as "bad" cholesterol because higher levels of LDL-C are associated with an increased risk of adverse cardiovascular events.[110] Consequently, clinicians often aim to raise HDL-C and to reduce LDL-C in an attempt to reduce a patient's cardiovascular risk.

Cholesteryl ester transfer protein (CETP) is an enzyme that transfers cholesterol molecules from HDL to LDL. Torcetrapib blocks CETP, thereby simultaneously raising HDL-C and lowering LDL-C. The drug performed well on measures of LDL-C and HDL-C in phase 2 trials, although small increases in blood pressure were sometimes observed with torcetrapib treatment.[111, 112] Pfizer executive Jeff Kindler said that torcetrapib might be "one of the most important developments in our generation."[113] Pfizer reportedly spent over $800 million to develop and test torcetrapib.[114]

A phase 3 study randomized over 15,000 participants with coronary artery disease, history of stroke, diabetes, or peripheral artery disease to receive either torcetrapib or placebo in addition to a statin. The primary outcome measure was the time to first occurrence of a major cardiovascular disease event (e.g., heart attack, stroke); other outcomes measures included cholesterol levels and blood pressure. Although HDL-C increased and LDL-C decreased significantly among those receiving torcetrapib compared with those receiving placebo, the drug was not shown to be effective and proved to be dangerous. Patients who received torcetrapib were 25% more likely to suffer a major adverse cardiac event, and were 58% more likely to die from any cause, than those taking the placebo (both results were statistically significant).[115] The torcetrapib group also showed a significant increase in blood pressure.[115] The trial was halted three years earlier than expected because of these compelling and unexpected safety concerns.[113]

22. V710 vaccine

Product	V710 vaccine
Sponsor	Intercell (nowValneva) / Merck
Purpose	Vaccine to prevent Staphylococcus aureus infection
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy, lack of safety
Divergent results in Phase 3 trial	Despite promising biomarker results in phase 2, a phase 3 study of V710 vaccine was terminated due to lack of efficacy and with potential risk for serious adverse events and death.

Staphylococcus aureus, called "staph" for short, is one of the most common bacteria found on the skin and nose of even healthy persons. It does not usually cause any harm other than skin infections like infected pimples and boils. However, staph can cause serious and life-threatening infections if it enters the bloodstream. Between 10% and 30% of patients with staph in their blood will die from this infection.[116] Staph infection can be prevented by good hygiene especially hand-washing, sterile wound dressings, and antibiotics prior to certain medical procedures. An effective staph vaccine has not been made.[117]

V710 is an investigational staph vaccine that elicited a good immune response in early studies.[118] A phase 2 study randomized 206 chronic hemodialysis patients (who are at high risk for staph) to receive either V710 or placebo on days 1, 28, and 180. The study results indicated that V710 produced an antibody response evident by day 28 and which was sustained for up to one year after initial vaccination.[119] There were no serious adverse effects attributed to the vaccine.

A phase 3 study followed, involving almost 8000 patients from 26 countries.[120] These patients, scheduled to have cardiothoracic surgery, were randomized to receive a single injection of either V710 or placebo. This study was designed to determine whether the vaccine could prevent staph infection in the blood and/or chest wound infection for up to 90 days following the surgery. However, this study was terminated early because of safety concerns and low efficacy. The study showed that V710 did not prevent staph infection any better than placebo (2.6 v. 3.2 infections per 100 person-years). There were also more cases of multi-organ failure and death among those who acquired staph infection in the V710 group compared to placebo. The researchers concluded that, in addition to the identified safety concerns, V710 was unlikely to yield a significant clinical benefit.[121]

V. Discussion

The following summarizes the wide range of circumstances in which phase 2 findings did not accurately predict safety and/or efficacy and provides some additional observations stemming from these case studies.

A. Large RCTs Can Produce Unexpected Results Across all Types of Products, Patients, and Conditions

These case studies demonstrate that large phase 3 RCTs can generate critical evidence across all types of products, patients, and diseases. Both safety and efficacy failures occurred even when the phase 2 studies were relatively large (e.g., recombinant VIIa), and even when the product was already approved for another condition (e.g., aliskiren). In some cases, the phase 3 study revealed that short-term results found in the phase 2 study were not associated with a long-term benefit (e.g., bitopertin) or that the product had toxicity that was not uncovered in the phase 2 study (e.g., semagacestat). Unexpected evidence from a phase 3 trial does not always result in non-approval -- in one case, the evidence led to the addition of a safety monitoring requirement (long-acting formulation of olanzapine pamoate). The Summary Table in Appendix C provides an overview of the type of unexpected results in the phase 3 studies presented here.

We identified unexpected results in phase 3 trials whether the underlying disease was acute (e.g., V710 vaccine) or chronic (e.g., Qutenza); common (e.g., CoStar drug-eluting stent) or rare (e.g., lithium); and preventative (e.g., HSV-2 vaccine) or intended to treat symptoms (e.g., dexmecamylamine). Similarly, unexpected results occurred whether the experimental product targeted early disease (e.g., GAD vaccine) or later stages (e.g., figitumumab), and whether the product targeted adults (e.g., darapladib) or children (imiquimod). There were unexpected failures in phase 3 trials whether the promise in phase 2 was a positive response on a potential surrogate endpoint (e.g., torcetrapib) or on clinical outcomes (e.g., iniparib). Unexpected failures in phase 3 occurred with all types of medical products – drugs, vaccines and other biologics, and devices.

In several cases where more limited data from phase 2 studies seemed to show a benefit, the more conclusive phase 3 evidence revealed that the experimental product actually increased the frequency of the problem it was intended to prevent. For example, torcetrapib, which was intended to reduce heart attacks by increasing “good” cholesterol (HDL) and lowering “bad” cholesterol (LDL), showed in phase 2 trials that the drug did in fact increase HDL and lower LDL. Yet, the phase 3 trial, which examined whether the drug actually reduced heart attacks, showed that patients taking the drug were actually 25% more likely to suffer a major cardiac event than those in the control group.

B. An Experimental Product’s Presumed Mechanism of Action Does Not Automatically Predict Clinical Effects

As these case studies show, a medical product’s apparent mechanism of action does not automatically predict clinical outcomes.[122] There was a plausible mechanism of action associated with most products in these case studies, but that often did not translate into clinical benefit. Down-regulating specific immune functions associated with diabetes did not delay progression of the disease (GAD vaccine). A vaccine targeting proteins present on certain tumor cells but not on normal lung cells was not effective against lung cancer (MAGE-A3 vaccine). A compound that inhibited growth factors associated with lung and other cancers (figitumumab) was not proven effective.

These cases also show that phase 2 data do not necessarily predict the product's safety and efficacy, even where the product is already approved for a related condition and phase 2 data seem promising for the second condition. In several of the cases reviewed here, the experimental product was already approved for one condition and seemed promising for a different but related condition, but full testing failed to show that the drug was effective and/or demonstrated that the drug was dangerous for the related condition. Imiquimod turned out to be effective against some skin viruses but not others. Qutenza proved effective against nerve pain associated with shingles, but not nerve pain associated with HIV. Recombinant Factor VIIa was shown to stimulate blood clotting in a way that helps those with hemophilia but not patients with hemorrhagic stroke. Safety failures occurred even where the phase 3 trial tested a new formulation of an already-approved product (olanzapine pamoate in a long-acting formulation to treat schizophrenia).

Many medical conditions are complex; targeting a single component of a condition cannot be presumed to have a positive effect on the patient unless there is objective clinical evidence. This array of unexpected results from phase 3 studies demonstrates the complexity of the interaction between a medical product and the patient, and how logical presumptions without corroborating clinical evidence can be unreliable.

C. Many Biomarkers Do Not Reliably Predict Clinical Outcomes[††]

While biomarkers have many important uses in clinical practice and product testing, most have not been shown to reliably predict clinical outcomes. As several of these case studies illustrate, promising biomarker data in phase 2 do not necessarily translate into effective product performance. Biomarker data were promising in phase 2 testing in products targeting conditions ranging from heart disease (aliskiren, darapladib, torcetrapib) to Staph infection (V710 vaccine), and from AD (semagacestat) to herpes infection (HSV-2 vaccine). These experimental products were not proven effective when tested in phase 3 trials.

VI. Conclusions

Rapid advances in biomedical sciences are now helping researchers improve the predictive capacity of phase 1 and phase 2 trials in certain circumstances. Improved molecular understanding of cancer, for instance, is already helping us design phase 1 and phase 2 trials that can demonstrate clinical benefits persuasively, by matching the patient to a specific experimental drug based on molecular mutations rather than tumor type.

At the same time, the 22 cases explored in this paper demonstrate that phase 2 results can inaccurately predict safety and/or effectiveness for medical products in a wide range of diseases and patient populations. These cases also help illustrate the potential public health implications of undue reliance on phase 2 studies and the benefits of conducting Phase III studies. As a result of the Phase III studies discussed in this paper, patients outside of clinical trials were not subjected to drugs that would not benefit them or to the risk of unnecessary serious toxicities, and did not suffer unnecessary financial expenditures. Where effective alternative therapies existed, they were not diverted from proven

[††] For a review of the array of uses of biomarkers, from use in disease monitoring to use as surrogates for clinical outcomes, see U.S. Food and Drug Administration-National Institutes of Health Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet]. Silver Spring (MD): Food and Drug Administration (US); 2016-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK326791/ Co-published by National Institutes of Health (US), Bethesda (MD).

treatments; where an implanted medical device was at issue, patients were spared unnecessary surgical procedures.

Phase 3 trials help care providers understand when a medical product provides clinical benefit to patients that outweigh the risks. They also help researchers understand when a purported mechanism of action is credible and merits further development, allowing researchers to avoid investing substantial time and resources going in the wrong direction, resources that could be deployed to identify a truly effective product. As we continue to explore alternatives to requiring phase 3 testing, it is important to keep in mind the benefits they provide to both patients and to the medical research enterprise.

Appendix A: RCTs and Clinical Trial Design Considerations

In many cases, demonstration of an acceptable benefit/risk profile requires a randomized, controlled, clinical trial, of a size and duration that reflect the product and target condition. Since the 1940s, when the first RCTs were done, the practice of medicine has greatly benefited from the availability of the unbiased, evidence-based information they produce.[123] Three crucial elements of the RCT that make it more likely to be definitive are: comparing the product to a control; randomizing patients between the control and treatment groups; and, where possible and appropriate, blinding the patients and clinicians as to whether patients are receiving the product being studied or the control.

Control: The control group is a group of patients that is as close to the treated group as possible in all relevant characteristics, other than whether they receive the medical product being tested. The purpose of the control group is to ensure that any improvement in the treated group is above and beyond that resulting from the natural course of the disease, supportive medical care received as part of the trial, or a placebo effect. The control need not be a placebo; the experimental product may be tested against one or more known effective therapies.

Randomization: Randomizing patients between the control and treatment groups helps ensure that any difference observed between the treated and controlled groups is likely caused by the product being studied. It does so by ensuring that factors that might affect the outcome, such as age, gender, and other medical conditions, are approximately equally distributed between the treated and control groups.

Blinding: Blinding means not allowing various parties to the trial to know who has been assigned to the treated or control groups. Blinding is intended to reduce the possibility that unconscious bias, rather than the medical product, caused any difference between the treatment and control groups.

Together, these features of RCTs make it possible to separate the effects of the product being tested from other influences. Advances in biomedical science and statistics, however, can also enable a more flexible approach to determining which trial designs can be considered "adequate and well controlled." The agency has issued an array of draft and final guidances describing circumstances under which trial designs that do not follow the typical paradigms may provide reliable evidence, including:

Use of adaptive designs, potentially allowing changes in trial protocol based on interim trial results. This can allow enrollment of fewer patients and potentially shorter trial duration, but requires significant safeguards to avoid introduction of bias.[124]

Use of enrichment designs, potentially allowing highly targeted selection of trial patients. This can allow enrollment of fewer patients and those who are more likely to respond to the test product, but may present challenges with regard to the interpretability and generalizability of the trial results.[125]

Use of historical controls instead of a classically controlled trial, potentially allowing patients outside the trial to serve as the control. This may allow enrollment of fewer patients and allow all patients in the trial to receive the test product, but sacrifices randomization and blinding.[126] Historical control designs are usually reserved for circumstances where the natural history of the disease is very well characterized and relatively uniform.[127]

Appendix B: Methods

We present a set of 22 phase 3 RCTs published or otherwise publicly reported in sufficient detail since 1999, in which the study produced unexpected evidence despite phase 2 results suggesting that the product could be safe and effective. The intent of these case studies is to shed light on the kinds of medical insights Phase 3 trials can generate, and illustrate the ways that the results of phase 2 trials, alone, can be misleading. We selected examples from among numerous additional candidates, to represent as wide an array of conditions, types of patients, and types and formulations of prescription medical products as possible.

A. Sources

We identified candidate case studies through expert elicitation, and review of published scientific articles and the trade press.

- Expert elicitation. We engaged FDA medical product reviewers and scientists in the following Offices. These experts identified examples of phase 3 RCTs that had produced unexpected results, and provided insights into ways that the information from phase 3 trials is used, beyond the approval decision (see discussion in section VI).

    - Office of the Commissioner: Deputy Commissioner for Medical Products and Tobacco; Office of Pediatric Therapeutics; the Office of Orphan Products Development.
    - Center for Drug Evaluation and Research (CDER): the Deputy Center Director for Clinical Science
    - CDER, Office of New Drugs, Office of Drug Evaluation: the Division of Cardiovascular and Renal Products; the Office of Antimicrobial Products; the Office of Hematology and Oncology Products; the Division of Neurology Products; the Division of Psychiatry Products; the Division of Pediatric and Maternal Health; the Division of Metabolism and Endocrinology Products; and the Division of Anesthesia, Analgesia, and Addiction Products.
    - Center for Biologics Evaluation and Research: the Center Director, Deputy Director, and the Office of Cellular, Tissue, and Gene Therapy.
    - Center for Devices and Radiologic Health: the Deputy Center Director for Science.

- Review of published, peer-reviewed, literature. The scientific information on the phase 2 and 3 trials examined in these case studies was obtained from PubMed and ClinicalTrials.gov. The Centers for Disease Control and Prevention and National Institute of Health websites provided additional epidemiologic information.

- Trade press and other public/online sources. We reviewed trade press and annual compilations of pipeline failures published by FierceBioTech and Genengnews.com to identify candidates for review and possible analysis. While we relied primarily on peer-reviewed literature for the actual analyses, in a few cases, where the failed phase 3 trial was not published, we used company press releases where these were sufficiently detailed. For some case studies, an Advisory Committee transcript provided additional information on the phase 3 trial results.

B. Limitations

This is not an analysis of "success rates" or the predictive accuracy of phase 2 data broadly. A rigorous study involving all or a random sample of all medical products that enter phase 3 is not possible. Many phase 3 trials are never published and are otherwise not in the public domain; cases that could not be

presented using only public sources could not be included. Even FDA may be unaware of certain phase 3 trials, if they are conducted abroad and not under an Investigational New Drug Application.[‡‡] Reporting of results to Clinicaltrials.gov was not required by statute until 2008; further, during the time of this study, summary results were only required for approved, licensed, or cleared products. The bias toward publishing only successful trials has been well documented.[128] When product development is halted, the sponsor often releases only a press announcement, or makes no announcement at all, and the scientific issues behind the termination of product development are not available.[129]

Rather, we attempted to identify cases that could be illustrative across different types of products, conditions, and patients. Further, we focused on the medical information produced in phase 3 trials, not business or other non-scientific reasons for halting product development.

[‡‡] When a drug sponsor wants to test its potential drug in humans for the first time, the sponsor must submit an Investigational New Drug Application to the FDA providing, among other things, the preclinical data that shows that the drug is reasonably safe for initial testing in humans, and the sponsor's protocols for proposed clinical studies. The sponsor may proceed after 30 days, unless FDA objects.

Appendix C: Summary Table

Summary Table: An overview of the types of divergent results observed in the phase 3 studies

Product	Purpose	Lack of			Approved for Any Indication at Time of Phase 3 Trial	Page
		Efficacy	**Safety**	**Efficacy and Safety**		
Aliskiren (Rasilez, Tekturna)	Add-on treatment of prevention of congestive heart failure (CHF) complications	✓			✓	21
Bitopertin	Add-on treatment of schizophrenia	✓				5
Brivanib	Treatment of hepatocellular cancer	✓				6
Capsaicin Topical Patch (Qutenza)	Treatment of HIV-associated nerve pain	✓			✓	8
CoSTAR Drug-Eluting Stent	Reduction of heart attack risk in patients with coronary artery disease			✓		22
Darapladib	Prevention of cardiovascular disease complications in patients with prior heart attack	✓				9
Dexmecamylamine	Add-on treatment of depression	✓				10
Exhale Drug-Eluting Stent	Reduction of shortness of breath in patients with emphysema	✓				11
Experimental HSV-2 Vaccine	Prevention of genital herpes	✓				12
Figitumumab	Treatment of advanced non-small cell lung cancer			✓		23
Glutamic Acid Decarboxylase Vaccine	Preservation of insulin secretion in patients with recent-onset type 1 diabetes	✓				13
Imiquimod (Aldara)	Treatment of molluscum contagiosum lesions	✓			✓	14
Iniparib	Add-on treatment of “triple negative” breast cancers	✓				15
Lithium	Treatment to delay disease progression of amyotrophic lateral sclerosis	✓			✓	16
MAGE-A3 Vaccine	Treatment of patients with non-small cell lung cancer following surgery	✓				17
NicVAX Vaccine	Smoking cessation	✓				18
Olanzapine Pamoate (Zyprexa Relprevv)	Long-acting treatment for schizophrenia		✓		✓	20
Recombinant Factor VIIa (NovoSeven)	Reduction of intracerebral bleeding and hematoma size in patients with stroke			✓	✓	24

Semagacestat	Improvement of cognitive and functional status in Alzheimer's disease		✓	25
Torcetrapib	Prevention of cardiovascular disease events in patients with a history of cardiovascular disease or type 2 diabetes		✓	26
V710 Vaccine	Vaccine to prevent *Staphylococcus aureus* infection		✓	27
Velimogene Aliplasmid (Allovectin-7)	Treatment of metastatic melanoma	✓		19

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Footnote 10

Trends in the Parent-Report of Health Care Provider-Diagnosis and Medication Treatment for ADHD: United States, 2003—2011

Researchers from the Centers for Disease Control and Prevention (CDC) and the Health Resources and Services Administration have published a study: "Trends in the Parent-Report of Health Care Provider-Diagnosed and Medicated ADHD: United States, 2003—2011." Read the abstract [1]. See below for a summary of the findings from this article.

Health care providers who care for children with attention-deficit/hyperactivity disorder (ADHD) and public health practitioners should be aware that an estimated two million more US children were reported by their parents to be diagnosed by a health care provider with ADHD and a million more were reported to be taking medication for ADHD in 2011, compared to 2003. These health professionals should also be aware of the changing patterns of ADHD in the United States.

About attention-deficit/hyperactivity disorder and this study:

ADHD is a neurobehavioral disorder of childhood that often persists into adulthood. CDC uses national surveys that ask parents about their child's health to monitor the number of children with ADHD and the treatment patterns for these children. The largest of these surveys is the National Survey of Children's Health, which has been collected every four years since 2003. Previous results from the 2003 and 2007 surveys found that 7.8% and 9.5% of US children aged 4-17 years were reported by their parents to have ever been diagnosed with ADHD by a health care provider in 2003 and 2007, respectively. The current study looked at data from the third National Survey of Children's Health, conducted in 2011-2012. The findings tell us more about ADHD diagnosis and treatment patterns, and reflect the substantial impact that ADHD has on families.

Learn more about the data source: National Survey of Children's Health

Important findings from this study include:

More than 1 in 10 (11%) US school-aged children had received an ADHD diagnosis by a health care provider by 2011, as reported by parents.

- 6.4 million children reported by parents to have ever received a health care provider diagnosis of ADHD , including:
  - 1 in 5 high school boys
  - 1 in 11 high school girls

The percentage of US children 4-17 years of age with an ADHD diagnosis by a health care provider, as

The percentage of children 4-17 years of age taking medication for ADHD, as reported by parents, increased by 28% between 2007 and 2011.

- Percentage of children taking medication for ADHD was:
  - 4.8% in 2007
  - 6.1% in 2011
- Average annual increase was approximately 7% per year

The average age of ADHD diagnosis was 7 years of age, but children reported by their parents as having more severe ADHD were diagnosed earlier.

- 8 years of age was the average age of diagnosis for children reported as having ***mild*** ADHD
- 7 years of age was the average age of diagnosis for children reported as having ***moderate*** ADHD
- 5 years of age was the average age of diagnosis for children reported as having ***severe*** ADHD

More US children were reported by their parents to be receiving ADHD treatment in 2011 compared to 2007, however treatment gaps may exist.

- In 2011, as many as 17.5% of children with current ADHD were reported by their parents as **not** receiving either medication for ADHD or mental health counseling
- More than one-third of children reported by their parents as **not** receiving treatment were also reported to have moderate or severe ADHD

The patterns in ADHD diagnosis and medication treatment showed increases in the percentages overall, however some new patterns emerged between 2007 and 2011.

- The percentage of children reported by their parents to have a history of health care provider diagnosed ADHD increased for most demographic groups (for example, across racial groups, boys and girls) from 2003 to 2011; however,
- Between 2007 and 2011, the percentage of children reported by their parents to have a history of a health care provider diagnosed ADHD:
  - Was similar among older teens
  - Decreased among multiracial children and children of other races when compared to black or white children

The number of US families impacted by ADHD continues to increase.

- An estimated 2 million more children were reported by their parents to be diagnosed by a health care professional with ADHD in 2011, compared to 2003
  - By 2011, 6.4 million children were reported by their parents to be diagnosed by a health professional with ADHD compared to 4.4 million in 2003
- An estimated 1 million more children were reported by their parents to be taking medication for ADHD in 2011, compared to 2003.
  - By 2011, 3.5 million children were reported by their parents to be taking medication for ADHD compared to 2.5 million in 2003

ADHD: CDC's Activities

CDC monitors the number of children who have been diagnosed with ADHD through the use of national survey data. Including questions about ADHD on national or regional surveys helps us learn more about the number of children with ADHD, their use of ADHD treatments, and the impact of ADHD on children and their families. CDC has previously used national survey data to document increasing estimates of the number of children with ADHD from 2003-2007.[2] CDC has also used these data to estimate the percentage of children taking medication for ADHD, nationally and by state.[3]

families. The National Resource Center operates a call center with trained, bilingual staff to answer questions about ADHD. Their phone number is 1-800-233-4050.

More Information

To learn more about ADHD, please visit https://www.cdc.gov/adhd.

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How are learning disabilities diagnosed?

Learning disabilities are often identified once a child is in school. The school may use a process called “response to intervention” to help identify children with learning disabilities. Special tests are required to make a diagnosis.

Response to Intervention

Response to intervention usually involves the following[1]:

- Monitoring all students’ progress closely to identify possible learning problems
- Providing children who are having

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problems with help on different levels, or tiers
- Moving children to tiers that provide increasing support if they do not show sufficient progress

Students who are struggling in school can also have individual evaluations. An evaluation can[2]:

- Identify whether a child has a learning disability
- Determine a child's eligibility under federal law for special education services
- Help develop an individualized education plan (IEP) that outlines help for a child who qualifies for special education services
- Establish benchmarks to measure the child's progress

A full evaluation for a learning disability includes the following[3]:

- A medical exam, including a neurological exam, to rule out other possible causes of the child's difficulties. These might include emotional disorders, intellectual and developmental disabilities, and brain diseases.

Science Update: Infants' brains may respond to faces, other visual stimuli earlier than previously thought, NIH-funded study suggests (/newsroom/news/112321-infant-response-faces)

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All related news (/newsroom/news?topic=learning)

- Reviewing the child's developmental, social, and school performance
- A discussion of family history
- Academic and psychological testing

Usually, several specialists work as a team to do the evaluation. The team may include a psychologist, a special education expert, and a speech-language pathologist. Many schools also have reading specialists who can help diagnose a reading disability.[4]

Role of School Psychologists

School psychologists are trained in both education and psychology. They can help diagnose students with learning disabilities and help the student and his or her parents and teachers come up with plans to improve learning.[5]

Role of Speech-Language Pathologists

All speech-language pathologists are trained to diagnose and treat speech and language disorders. A speech-language pathologist can do a language evaluation and assess the child's ability to organize his or her thoughts and possessions. The speech-language pathologist may evaluate the child's learning skills, such as

understanding directions, manipulating sounds, and reading and writing.[6]

Citations

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MAYO CLINIC

Childhood asthma

Diagnosis

Asthma can be hard to diagnose. Your child's doctor will consider the symptoms and their frequency and your child's medical history. Your child might need tests to rule out other conditions and to identify the most likely cause of the symptoms.

A number of childhood conditions can have symptoms similar to those caused by asthma. To complicate the issue further, these conditions also commonly occur with asthma. So your child's doctor will have to determine whether your child's symptoms are caused by asthma, a condition other than asthma, or both asthma and another condition.

Conditions that can cause asthma-like symptoms include:

- Rhinitis
- Sinusitis
- Acid reflux or gastroesophageal reflux disease (GERD)
- Airway abnormalities
- Dysfunctional breathing
- Respiratory tract infections such as bronchiolitis and respiratory syncytial virus (RSV)

The following are tests your child might need.

- **Lung function tests (spirometry).** Doctors diagnose asthma with the same tests used to identify the disease in adults. Spirometry measures how much air your child can exhale and how quickly. Your child might have lung function tests at rest, after exercising and after taking asthma medication.

Another lung function test is brochoprovocation. Using spirometry, this test measures how your lungs react to certain provocations, such as exercise or exposure to cold air.

- **Exhaled nitric oxide test.** If the diagnosis of asthma is uncertain after lung function tests, your doctor might recommend measuring the level of nitric oxide in an exhaled sample of your child's breath. Nitric oxide testing can also help determine whether steroid medications might be helpful for your child's asthma.

The asthma tests used, however, aren't accurate before 5 years of age. For younger children, your doctor will rely on information you and your child provide about symptoms. Sometimes a diagnosis can't be made until later, after months or even years of observing symptoms.

Allergy tests for allergic asthma

If your child seems to have asthma that's triggered by allergies, the doctor might recommend allergy skin testing. During a skin test, the skin is pricked with extracts of common allergy-causing substances, such as animal dander, mold or dust mites, and observed for signs of an allergic reaction.

Treatment

Initial treatment depends on the severity of your child's asthma. The goal of asthma treatment is to keep symptoms under control, meaning that your child has:

- Minimal or no symptoms
- Few or no asthma flare-ups
- No limitations on physical activities or exercise
- Minimal use of quick-relief (rescue) inhalers, such as albuterol (ProAir HFA, Ventolin HFA, others)
- Few or no side effects from medications

Treating asthma involves both preventing symptoms and treating an asthma attack in progress. The right medication for your child depends on a number of things, including age, symptoms, asthma triggers and what seems to work best to keep his or her asthma under control.

For children younger than age 3 who have mild symptoms of asthma, the doctor might use a wait-and-see approach. This is because the long-term effects of asthma medication on infants and young children aren't clear.

However, if an infant or toddler has frequent or severe wheezing episodes, a medication might be prescribed to see if it improves symptoms.

Long-term control medications

Preventive, long-term control medications reduce the inflammation in your child's airways that leads to symptoms. In most cases, these medications need to be taken daily.

Types of long-term control medications include:

- **Inhaled corticosteroids.** These medications include fluticasone (Flovent Diskus, Flovent HFA), budesonide (Pulmicort Flexhaler), mometasone (Asmanex HFA), ciclesonide (Alvesco), beclomethasone (Qvar Redihaler) and others. Your child might need to use these medications for several days to weeks before getting the full benefit.

  Long-term use of these medications has been associated with slightly slowed growth in children, but the effect is minor. In most cases, the benefits of good asthma control outweigh the risks of possible side effects.

- **Leukotriene modifiers.** These oral medications include montelukast (Singulair), zafirlukast (Accolate) and zileuton (Zyflo). They help prevent asthma symptoms for up to 24 hours.
- **Combination inhalers.** These medications contain an inhaled corticosteroid plus a long-acting beta agonist (LABA). They include fluticasone and salmeterol (Advair Diskus, Advair HFA), budesonide and formoterol (Symbicort), fluticasone and vilanterol (Breo Ellipta), and mometasone and formoterol (Dulera).

  In some situations, long-acting beta agonists have been linked to severe asthma attacks. For this reason, LABA medications should always be given to a child with an inhaler that also contains a corticosteroid. These combination inhalers should be used only for asthma that's not well-controlled by other medications.

- **Theophylline.** This is a daily pill that helps keep the airways open. Theophylline (Theo-24) relaxes the muscles around the airways to make breathing easier. It's mostly used with inhaled steroids. If you take this drug, you'll need to have your blood checked regularly.
- **Immunomodulatory agents.** Mepolizumab (Nucala), dupilumab (Dupixent) and benralizumab (Fasenra) might be appropriate for children over the age of 12 who have severe eosinophilic asthma. Omalizumab (Xolair) can be considered for children age 6 or older who have moderate to severe allergic asthma.

Quick-relief medications

Quick-relief medications quickly open swollen airways. Also called rescue medications, quick-relief medications are used as needed for rapid, short-term symptom relief during an asthma attack — or before exercise if your child's doctor recommends it.

Types of quick-relief medications include:

- **Short-acting beta agonists.** These inhaled bronchodilator medications can rapidly ease symptoms during an asthma attack. They include albuterol (ProAir HFA, Ventolin HFA, others) and levalbuterol (Xopenex HFA). These medications act within minutes, and effects last several hours.
- **Oral and intravenous corticosteroids.** These medications relieve airway inflammation caused by severe asthma. Examples include prednisone and methylprednisolone. They can cause serious side effects when used long term, so they're only used to treat severe asthma symptoms on a short-term basis.

Treatment for allergy-induced asthma

If your child's asthma is triggered or worsened by allergies, your child might benefit from allergy treatment, such as the following, as well:

- **Omalizumab (Xolair).** This medication is for people who have allergies and severe asthma. It reduces the immune system's reaction to allergy-causing substances, such as pollen, dust mites and pet dander. Xolair is delivered by injection every two to four weeks.
- **Allergy medications.** These include oral and nasal spray antihistamines and decongestants as well as corticosteroid, cromolyn and ipratropium nasal sprays.
- **Allergy shots (immunotherapy).** Immunotherapy injections are generally given once a week for a few months, then once a month for a period of three to five years. Over time, they gradually reduce your child's immune system reaction to specific allergens.

Don't rely only on quick-relief medications

Long-term asthma control medications such as inhaled corticosteroids are the cornerstone of asthma treatment. These medications keep asthma under control and make it less likely that your child will have an asthma attack.

If your child does have an asthma flare-up, a quick-relief (rescue) inhaler can ease symptoms right away. But if long-term control medications are working properly, your child shouldn't need to use a quick-relief inhaler very often.

Keep a record of how many puffs your child uses each week. If he or she frequently needs to use a quick-relief inhaler, take your

child to see the doctor. You probably need to adjust the long-term control medication.

Inhaled medication devices

Inhaled short- and long-term control medications are used by inhaling a measured dose of medication.

- **Older children and teens** might use a small, hand-held device called a pressurized metered dose inhaler or an inhaler that releases a fine powder.
- **Infants and toddlers** need to use a face mask attached to a metered dose inhaler or a nebulizer to get the correct amount of medication.
- **Babies** need to a use a device that turns liquid medication into fine droplets (nebulizer). Your baby wears a face mask and breathes normally while the nebulizer delivers the correct dose of medication.

Asthma action plan

Work with your child's doctor to create a written asthma action plan. This can be an important part of treatment, especially if your child has severe asthma. An asthma action plan can help you and your child:

- Recognize when you need to adjust long-term control medications
- Determine how well treatment is working
- Identify the signs of an asthma attack and know what to do when one occurs
- Know when to call a doctor or seek emergency help

Children who have enough coordination and understanding might use a hand-held device to measure how well they can breathe (peak flow meter). A written asthma action plan can help you and your child remember what to do when peak flow measurements reach a certain level.

The action plan might use peak flow measurements and symptoms to categorize your child's asthma into zones, such as the green zone, yellow zone and red zone. These zones correspond to well-controlled symptoms, somewhat-controlled symptoms and poorly controlled symptoms. This makes tracking your child's asthma easier.

Your child's symptoms and triggers are likely to change over time. You'll need to observe symptoms and work with the doctor to adjust medications as needed.

If your child's symptoms are completely controlled for a time, your child's doctor might recommend lowering doses or stopping

asthma medications (step-down treatment). If your child's asthma isn't as well-controlled, the doctor might want to increase, change or add medications (step-up treatment).

Lifestyle and home remedies

Taking steps to reduce your child's exposure to asthma triggers will lessen the possibility of asthma attacks. Steps to help avoid triggers vary depending on what triggers your child's asthma. Here are some things that may help:

- **Maintain low humidity at home.** If you live in a damp climate, talk to your child's doctor about using a device to keep the air drier (dehumidifier).
- **Keep indoor air clean.** Have a heating and air conditioning professional check your air conditioning system every year. Change the filters in your furnace and air conditioner according to the manufacturer's instructions. Also consider installing a small-particle filter in your ventilation system.
- **Reduce pet dander.** If your child is allergic to dander, it's best to avoid pets with fur or feathers. If you have pets, regularly bathing or grooming your pets also might reduce the amount of dander. Keep pets out of your child's room.
- **Use your air conditioner.** Air conditioning helps reduce the amount of airborne pollen from trees, grasses and weeds that finds its way indoors. Air conditioning also lowers indoor humidity and can reduce your child's exposure to dust mites. If you don't have air conditioning, try to keep your windows closed during pollen season.
- **Keep dust to a minimum.** Reduce dust that can aggravate nighttime symptoms by replacing certain items in your bedroom. For example, encase pillows, mattresses and box springs in dustproof covers. Consider removing carpeting and installing hard flooring, particularly in your child's bedroom. Use washable curtains and blinds.
- **Clean regularly.** Clean your home at least once a week to remove dust and allergens.
- **Reduce your child's exposure to cold air.** If your child's asthma is worsened by cold, dry air, wearing a face mask outside can help.

Alternative medicine

While some alternative remedies are used for asthma, in most cases more research is needed to see how well they work and to determine possible side effects. Alternative treatments to consider include:

- **Breathing techniques.** These include structured breathing programs, such as the Buteyko breathing technique, the Papworth method and yoga breathing exercises (pranayama).

- **Relaxation techniques.** Techniques such as meditation, biofeedback, hypnosis and progressive muscle relaxation might help with asthma by reducing tension and stress.
- **Herbal remedies and supplements.** A few herbal remedies have been tried for asthma, including black seed, fish oil and magnesium. However, further studies are needed to assess their benefit and safety.

  Herbs and supplements can have side effects and can interact with other medications your child is taking. Talk to your child's doctor before trying any herbs or supplements.

Coping and support

It can be stressful to help your child manage asthma. Keep these tips in mind to make life as normal as possible:

- **Make treatment a regular part of life.** If your child has to take daily medication, don't make a big deal out of it — it should be as routine as eating breakfast or brushing teeth.
- **Use a written asthma action plan.** Work with your child's doctor to develop your child's action plan, and give a copy to all of your child's caregivers, such as child care providers, teachers, coaches and the parents of your child's friends.

  Following a written plan can help you and your child identify symptoms early, providing important information on how to treat your child's asthma from day to day and how to deal with an asthma attack.
- **Be encouraging.** Focus attention on what your child can do, not on limitations. Involve teachers, school nurses, coaches, relatives and friends in helping your child manage asthma.

  Encourage normal play and activity. Don't limit your child's activities out of fear of an asthma attack — work with your child's doctor to control exercise-induced symptoms.
- **Be calm and in control.** Don't get rattled if asthma symptoms worsen. Focus on your child's asthma action plan, and involve your child in each step so that he or she understands what's happening.
- **Talk to other parents of children with asthma.** Chat rooms and message boards on the internet or a local support group can connect you with parents facing similar challenges.
- **Help your child connect with others who have asthma.** Send your child to "asthma camp" or find other organized activities for children with asthma. This can help your child feel less isolated and gain a better understanding of asthma and its treatment.

Preparing for your appointment

You're likely to start by taking your child to your family doctor or your child's pediatrician. However, when you call to set up an appointment, you may be referred to an allergist, lung doctor (pulmonologist) or other specialist. Here's some information to help you get ready for your child's appointment.

What you can do

Make a list of:

- **Your child's symptoms,** how severe they are and when they occur. Note when symptoms bother your child most — for example, if symptoms tend to get worse at certain times of the day; during certain seasons; when your child is exposed to cold air, pollen or other triggers; or when he or she is playing hard or participating in sports.
- **Key personal information,** including any major stresses or recent life changes your child has had.
- **All medications,** vitamins and supplements your child takes, including doses.
- **Write down questions to ask** the doctor.

For asthma or asthma-like symptoms, questions to ask your doctor include:

- Is asthma the most likely cause of my child's breathing problems?
- What else could be causing my child's symptoms?
- What tests does my child need?
- Is my child's condition likely temporary or chronic?
- What treatment do you suggest?
- My child has these other health conditions. How can we best manage them together?
- Are there restrictions my child needs to follow?
- Should my child see a specialist?
- Are there brochures or other printed materials I can have? What websites do you recommend?

Don't hesitate to ask other questions.

What to expect from your child's doctor

The doctor is likely to ask questions, including:

- When did you notice your child's symptoms?
- Does your child have difficulty breathing most of the time or only at certain times or in certain situations?
- Does your child have allergies such as hay fever?
- What, if anything, appears to worsen your child's symptoms?
- What, if anything, seems to improve your child's symptoms?
- Do allergies or asthma run in your child's family?

By Mayo Clinic Staff

Footnote 11

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Duration of Pediatric Clinical Trials Submitted to the US Food and Drug Administration

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Abstract

IMPORTANCE—The increasing prevalence of pediatric chronic disease has resulted in increased exposure to long-term drug therapy in children. The duration of recently completed drug trials that support approval for drug therapy in children with chronic diseases has not been systematically evaluated. Such information is a vital first step in forming safety pharmacovigilance strategies for drugs used for long-term therapy in children.

OBJECTIVE—To characterize the duration of clinical trials submitted to the US Food and Drug Administration (FDA) for pediatric drug approvals, with a focus on drugs used for long-term therapy.

DESIGN AND SETTING—A review was performed of all safety and efficacy clinical trials conducted under the Best Pharmaceuticals for Children Act or the Pediatric Review Equity Act and submitted to the FDA from September 1, 2007, to December 31, 2014, to support the approval of drugs frequently used for long-term therapy in children. Statistical analysis was performed from July 1, 2015, to December 31, 2017.

MAIN OUTCOMES AND MEASURES—Maximum duration of trials submitted to support FDA approval of drugs for children.

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Author Contributions:

Dr Zimmerman had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition, analysis, or interpretation of data: Zimmerman, Smith, Temeck, Avant, McCune. *Drafting of the manuscript:* Zimmerman, McMahon, Murphy.

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Disclaimer:

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RESULTS—A total of 306 trials supporting 86 drugs intended for long-term use in children were eligible for the primary analysis. The drugs most commonly evaluated were for treatment of neurologic (25 [29%]), pulmonary (16 [19%]), and anti-infective (14 [16%]) indications. The median maximum trial duration by drug was 44 weeks (minimum, 1.1 week; maximum, 364 weeks). For nearly two-thirds of the drugs (52 [61%]), the maximum trial duration was less than 52 weeks. For 10 of the drugs (12%), the maximum trial duration was 3 years or more. Maximum duration of trials did not vary by therapeutic category, minimum age of enrollment, calendar year, or legislative mandate.

CONCLUSIONS AND RELEVANCE—Pediatric clinical trials designed to sufficiently investigate drug safety and efficacy to support FDA approval are of relatively limited duration. Given the potential long-term exposure of patients to these drugs, the clinical community should consider whether new approaches are needed to better understand the safety associated with long-term use of these drugs.

During the past 20 years, research has established marked differences between children and adults in drug pharmacokinetics and pharmacodynamics. If pharmacokinetics and pharmacodynamics are not adequately considered in pediatric dosing, ontogenesis of drug receptors and pathways of biotransformation can lead to therapeutic failure or drug toxic effects.[1–5]

Through mechanisms and incentives provided in the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), the US government recognizes the importance of studying drug safety and efficacy within pediatric populations.[1] These legislative acts have had notable success, resulting thus far in more than 700 changes in US Food and Drug Administration (FDA) product labels to include pediatric information.[6] However, the study of drugs within pediatric populations is complex. Chronic disease is becoming more prevalent among children and often requires lifelong drug therapy.[7–9] Furthermore, the administration of some drugs during vulnerable periods of growth and development may have implications for the attainment of adequate growth and development among children.[10–12] Given the potential for long-term administration of drugs to pediatric patients, drug safety may need to be assessed for prolonged durations and during vulnerable periods of growth and development.

We have limited understanding of the current state of long-term drug safety evaluations in children. To improve our understanding, we evaluated the duration of clinical trials submitted to the FDA under BPCA and PREA, with a focus on drugs potentially administered to children with chronic health conditions. We then reviewed the literature for other studies conducted for children or adults that could provide guidance for feasibility and alternative methods for gathering data on long-term drug administration in children. Such efforts are necessary first steps toward understanding the availability of data on long-term drug safety in children.

Methods

Data Sources and Inclusion Criteria

We used the FDA's Document Archiving, Reporting, and Regulatory Tracking System electronic database as our data source for clinical trial submissions to the agency. Within this database, we identified all drugs submitted to and reviewed by the FDA, under BPCA and PREA, for pediatric drug approval from September 1, 2007, to December 31, 2014. Drugs that did not receive FDA approval for the intended pediatric indication were excluded. We also excluded drugs administered topically (including administration to the skin, eye, or ear) unless previous evidence suggested substantial systemic absorption. We extracted deidentified data from prospective drug trials in humans as well as FDA medical, statistical, and pharmacokinetic reviews of the primary data. This research study did not require Research Involving Human Subjects Committee review and approval because it is exempt from the requirements of 45 CFR §46.101b(4).

A committee of 4 pediatricians (K.O.Z., A.W.M., J.T., and S.M.), each with clinical and regulatory experience, characterized the potential uses of the drugs as short-term, intermediate, or long-term, based on the typical or expected clinical use in pediatric populations. The safety and efficacy data sufficient for FDA approval of a drug for its intended length of use may not include data on longer-term use. The analysis described herein focused on the trial length for drugs potentially used for the long-term medical management of children, excluding trials whose primary objective was to evaluate bioequivalence, pharmacokinetics, or a device.

Our literature review included articles referenced in Medline and PubMed as of February 12, 2018. Search terms were limited to "safety" AND the generic or brand name for the specific drug of interest OR "long-term" AND "safety" AND the generic or brand name for the specific drug of interest.

Definitions and Outcomes

The committee defined *short-term therapy* as drugs typically administered for less than 3 months, *intermediate therapy* as drugs typically administered for 3 to 6 months, and *long-term therapy* as drugs typically administered for longer than 6 months. Drugs classified as long-term therapy were further classified as continuous or intermittent. Continuous drugs were those administered on a scheduled basis dependent on drug pharmacokinetics (ie, daily, weekly, or monthly), while intermittent drugs were those administered seasonally.

We classified drugs into the following therapeutic categories according to the primary indication or affected organ system: anti-infectives, biologics, cardiology, dermatology, endocrinology and metabolism, gastroenterology, hematology, neurology, pulmonology, and miscellaneous. The miscellaneous category included drugs for urologic indications (eg, overactive bladder) and those for ophthalmologic disease without anti-infective activity. We designated the following age groups according to the minimum age required for enrollment in each trial: infants (<1 year), children (1 to <9 years), preadolescents (9 to <12 years), and adolescents (12 to ≤17 years).

For our analysis, we identified all trials submitted as primary evidence for pediatric drug efficacy and safety. We defined trial duration as the sum of controlled and uncontrolled periods during which children received drug therapy. The entire duration of crossover trials and trials with cyclical drug administration, including interval periods of drug washout or time off therapy, was included. For each drug (unit of analysis), we identified the median maximum trial duration. We then compared the maximum trial duration with the study durations identified in our literature review and identified specific drugs and drug classes that might warrant further safety assessments based on available data.

Data Collection

We collected the following information regarding each drug trial: therapeutic area, indication, clinical trial design (eg, open-label uncontrolled, randomized controlled, or long-term extension), ages studied, duration of drug receipt (weeks), year of FDA evaluation, and legislation under which the study took place (ie, BPCA or PREA). In our literature review, we extracted information regarding patient population, type and duration of evaluation, and any noted safety concerns or calls for additional long-term data in children.

Statistical Analysis

Statistical analysis was performed from July 1, 2015, to December 31, 2017. We used standard summary statistics, including counts (with percentages) and medians (25th and 75th percentiles) to describe the study variables. We evaluated outcomes by therapeutic classification and age category, and made comparisons using a Wilcoxon rank sum test. Changes in trial duration by study year were evaluated using Kruskal-Wallis equality-of-populations rank test. We used STATA, version 14.1 (StataCorp) to perform all statistical analyses. All P values were from 2-sided tests and results were deemed statistically significant at $P < .05$.

Results

We identified 201 drugs submitted for pediatric labeling during the study period. Of these, we excluded 33 drugs that were not approved, 19 vaccines, 3 drugs used for imaging studies, and 19 topical drugs. Of the remaining 127 drugs, we identified 33 that would be used for short-term indications, 5 for intermediate-length indications, and 86 drugs potentially used for long-term therapy. Pharmacokinetic trials were submitted for only 3 drugs. A total of 306 trials supporting the 86 long-term therapy drugs were eligible for our analysis (eTable in the Supplement). Of the 86 drugs, 19 (22%) were characterized as long-term intermittent and 67 (78%) as long-term continuous (Figure 1).

A total of 25 (29%) of the 86 included drugs were for neurologic indications, 16 (19%) were for pulmonary indications, and 14 (16%) were for anti-infective indications (Table 1). Trials for nearly half of the drugs (40 [47%]) were conducted in response to BPCA alone or BPCA and PREA, and the remainder were in response to PREA alone. For 24 of the drugs (28%), the minimum age of enrollment in the trials was younger than 1 year. A total of 42 drugs (49%) had trials that initiated enrollment at ages 1 to 8 years, 7 (8%) initiated enrollment at ages 9 to 11 years, and 10 (12%) initiated enrollment at ages 12 to 17 years.

The median (25th and 75th percentiles) maximum trial duration by drug was 44 weeks (12 weeks and 53 weeks). For nearly two-thirds of the drugs (52 [61%]), the duration was less than 52 weeks (<1 year) (Table 2). The longest trial duration by drug (364 weeks/7 years) investigated the safety and efficacy of a phenyalanine hydroxylase activator for children with phenylketonuria, while the shortest duration (1.1 week) investigated the efficacy and safety of montelukast for the indication of exercise-induced asthma (longer studies were done for the other pediatric indications for montelukast).

Although trial duration appeared different between therapeutic categories, the overall distributions of trial durations were statistically similar because of the wide variability in the trial lengths. For example, the median (25th and 75th percentiles) maximum duration for biologic drug trials was 132 weeks (52 weeks and 260 weeks); for cardiovascular drugs, median maximum duration was 54 weeks (53 weeks and 57 weeks; $P = .44$) (Figure 2). Similarly, trial duration did not vary according to classification as a long-term intermittent or long-term continuous drug, with median (25th and 75th percentiles) maximum durations of 12 weeks (8 weeks and 52 weeks) for long-term intermittent drugs and 48 weeks (15 weeks and 58 weeks) for long-term continuous drugs ($P = .08$).

Overall distribution of trial duration varied inconsistently by indication within a therapeutic category. For example, within the neurology category, drugs with a primary indication for seizures had a median (25th and 75th percentiles) maximum trial duration (139.5 weeks [242 weeks and 291 weeks]) that was statistically significantly different from those with a nonseizure indication (29 weeks [8 weeks and 48 weeks]; $P = .04$). However, within the pulmonary category, drugs with a primary asthma indication had a similar median (25th and 75th percentiles) maximum trial duration (34 weeks [8 weeks and 52 weeks]) compared with those without such an indication (25 weeks [14 weeks and 52 weeks]; $P = .91$). The FDA labels for drugs denoted as long-term continuous were each labeled for “maintenance therapy” or “for treatment of” a specified chronic condition. Labels for long-term intermittent drugs most often had specified durations of short-term use consistent with durations of clinical trials submitted to support labeling for the specified drug.

Trials enrolling participants of minimum ages of 0 (infant), 1 (child), or 12 (adolescent) years all had similar median (25th and 75th percentiles) maximum durations (infant, 42 weeks [10 weeks and 59 weeks]; child, 50 weeks [16 weeks and 54 weeks]; and adolescent, 52 weeks [12 weeks and 53 weeks) (Figure 3). Median (25th and 75th percentiles) maximum trial duration did not vary according to whether the trial was mandated by BPCA and PREA (48 weeks [15 weeks and 100 weeks]) or PREA alone (29 weeks [10.7 weeks and 52 weeks]) ($P = .17$). Furthermore, trial duration did not change significantly over time: in 2007, the median (25th and 75th percentiles) maximum duration was 52 weeks (12 weeks and 54 weeks); in 2014, this duration was 39 weeks (25 weeks and 86 weeks) ($P = .70$). Approximately 35% of included drugs (30) had extension trials, most commonly occurring for neurologic drugs (14 of 25 [56%]). Only 3 of the 30 drugs (10%) with extension trials used a controlled study design.

According to our review of the literature, long-term evaluations exceeded the duration of trials submitted as primary evidence to the FDA for 69 (80%) of the 86 drugs. For 67 drugs

(78%),long-term evaluations included prospective studies, most often characterized as nonrandomized, open-label, observational studies with standardized follow-up evaluation. Children were included in evaluations for 37 (43%) of the drugs.

Several safety findings with potential long-term implications emerged from our literature review. First, although most studies did not identify substantial effects of inhaled cortico steroids on linear growth or the hypothalamic-pituitary-axis, investigators and clinicians remain concerned about this potential phenomenon and highlight a need for more prolonged evaluations, particularly at critical times of pediatric growth and development.[13–18] Second, proton pump inhibitors have been associated with gastric hyperplasia among those with long-term use, and existing evaluations in children are considered inadequate to rule out this adverse event.[19–21] Third, short-term and longer-term evaluations of stimulants have been associated with insomnia, concern for abnormal cognitive development, and impaired growth; quantification of risks are not fully elucidated.[22–24] Mood stabilizers and anti-psychotics have shown associations with weight gain and metabolic derangements, the long-term effects of which are unclear.[25–27]Omalixumab carries an FDA warning because heart and brain issues have not been ruled out with existing studies.[28] Finally, tenofovir may have implications for long-term renal function.[29–32] We did not identify substantial long-term safety concerns for other evaluated drugs or drug classes.

Discussion

In our analysis of data submitted to the FDA from 2007 to 2014 to support pediatric indications for drugs that are commonly used for chronic conditions, we found that the median maximum trial duration by drug infrequently exceeded 1 year. Furthermore, trial duration did not notably vary with therapeutic category, minimum age of enrollment, calendar year, or legislative mandate. Review of the literature suggests that longer-term data in nonrandomized, observational studies are available for many drugs and may provide potentially important information regarding safety signals.

Admittedly, our study is limited given its purely descriptive nature. We have categorized our data to facilitate analysis, but recognize that the available data are heterogeneous with respect to the drugs evaluated, indications for therapy, study populations, and disease processes. Such categorization does not allow for evaluation of more subtle differences between trials. Finally, we have characterized drugs as long-term intermittent or long-term continuous based on clinical experience and prior documentation of long-term use of drugs even in cases for which the labeled indication may not support such use (eg, proton pump inhibitors).[33] We therefore acknowledge that this classification introduces some bias in our analysis. Nonetheless, our study provides important baseline information that can inform discussion regarding long-term drug safety data in children.

Our findings suggest that these pediatric studies may not provide complete safety data across all critical periods of growth and development. This observation may be important because multiple periods of critical pediatric growth and development exist, including marked deceleration in linear growth and weight gain during the first 2 years of life, and initiation of puberty around ages 11 to 13 years, accompanied by acceleration in linear growth that may

last for 3 to 4 years.[34,35] Although the first 3 years of life are often considered more critical than older ages for brain development, biochemical studies of brain metabolism suggest that high brain metabolic rates characteristic of early childhood may not decline to adult levels until ages 16 to 18 years, suggesting that the school-age and adolescent periods are equally critical periods of brain development.[36] Given this information, even the longest trial duration identified in our study (364 weeks/7 years) does not completely evaluate potential critical stages of all pediatric growth and development periods, nor does it begin to characterize the exposure associated with lifelong therapy.[1]

Administration of dexamethasone to premature infants provides a pertinent example in which long-term follow-up after limited administration in the neonatal period revealed important information regarding drug safety associated with exposure during critical periods of cognitive development. Extensive investigation dating to 1990 identified dexamethasone as an effective therapy for facilitation of extubation and prevention of bronchopulmonary dysplasia in premature infants.[37] However, in long-term follow-up studies,[38] investigators identified a statistically significantly increased risk of cerebral palsy among infants who received dexamethasone, compared with those who did not, with a number needed to harm of 4. Examples such as this one underscore potential issues with limited long-term data on drug safety in children.

On average, more than 1 decade elapses between initial laboratory formulation of a drug to readiness for public use in adults.[39] Public availability of data on drug efficacy and safety in children may require an additional 6 years.[40] Requiring that studies be designed to cover all the potential periods of critical development would make pediatric drug development infeasible. Furthermore, although investigators have traditionally touted the controlled clinical trial as the most rigorous source of data, multiple barriers to the conduct of clinical trials exist and may be exacerbated when clinical trials are of prolonged duration.[41,42] A recent investigation of more than 500 clinical trials conducted for children found that nearly 20% were discontinued early, largely owing to poor patient accrural.[43] Previous investigators have long documented attrition rates as high as 15% in longitudinal pediatric studies and up to 44% in some interventional studies in specific pediatric populations.[44–46] Furthermore, the relatively small sample sizes of pediatric trials compared with adult trials, combined with the lack of a control group in many extension trials, may raise concern about the level of evidence for safety such trials can provide.[47,48] Innovative approaches to acquire information on long-term drug safety in children are needed that continue to make important therapeutics available to children in a timely manner.

Multiple approaches are likely needed to obtain high-quality, long-term safety data for drugs used to treat chronic pediatric conditions. Currently, the FDA evaluates need for long-term safety assessment based on any safety concerns related to the specific effects of the drugs, the intended duration of treatment, and potential exposure during critical periods of growth and development, despite lack of conclusive evidence that all drugs used long-term in children will have specific effects on growth and development. In addition, the Food and Drug Administration Amendments Act of 2007 required increased activities for active post marketing risk identification and analysis. More importantly, it may be possible to leverage safety information from other populations, including adults and other pediatric age groups.

Our review of the literature suggests that long-term data can take many forms, ranging from open-label extension trials[49–51] after randomized studies, to registries[52] that capture data for specific disease processes, or prospective longitudinal studies[53] designed to answer specific scientific questions. Furthermore, with increasing administration of drugs for chronic conditions such as attention-deficit/hyperactivity disorder and asthma, we have a ready source of real-world data from which to potentially evaluate longer-term safety.[54]

Although we were able to identify potentially important safety signals from different data sources in the literature, each source has benefits and limitations, and our search may have introduced bias due to the nature of our study question. In general, ability to use the data in a meaningful way hinges on collecting quality data from an adequate pediatric population. To this end, the following approaches may enhance data quality: 1) use of existing literature to highlight areas for more urgent evaluation and lessons learned about specific data sources for specific drugs/drug classes; 2) collaboration between stake-holders and formation of networks for large sample sizes and acquisition of protocol-directed data collection in prospective observational studies for specific safety signals; 3) investigation of methods to decrease attrition and improve data collection in extension phases of clinical trials or other prospective evaluations; and 4) application of rigorous pharmacoepidemiologic analysis methods to existing data sources (‘real-world data’) and naturally occurring cohorts (eg, clinical cohorts, members of disease registries). Concerted efforts among all stakeholders will enable us to continue to advance pediatric drug development with regard to long-term pediatric drug safety while maintaining efficient and timely access to approved therapies for all children.

Limitations

This study has some limitations. As mentioned above, our study is limited by its purely descriptive nature; the available data are heterogeneous with respect to the drugs evaluated, indications for therapy, study populations, and disease processes, which did not allow us to evaluate more subtle differences between trials. Also, our classification (long-term intermittent vs continuous) is based on experience, which may have introduced bias into our analyses.

Conclusions

Pediatric clinical trials that are designed to sufficiently investigate drug safety and efficacy to support FDA approval are of relatively limited duration. Given the potential long-term exposure of patients to these drugs, the clinical community should consider whether new approaches are needed to better understand the safety of long-term use of these drugs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

Question

What are the durations of pediatric clinical trials recently submitted to the US Food and Drug Administration, and how can this knowledge inform discussions of safety pharmacovigilance follow-up for drugs that might be used for long-term therapy in the pediatric population?

Findings

This study found that nearly two-thirds of pediatric clinical trials submitted to support the approval of drugs with potential long-term use in the pediatric population are shorter than 52 weeks.

Meaning

Pediatric clinical trials that are sufficient to support US Food and Drug Administration drug approval may require additional strategies to ensure data availability for understanding long-term drug safety in children.

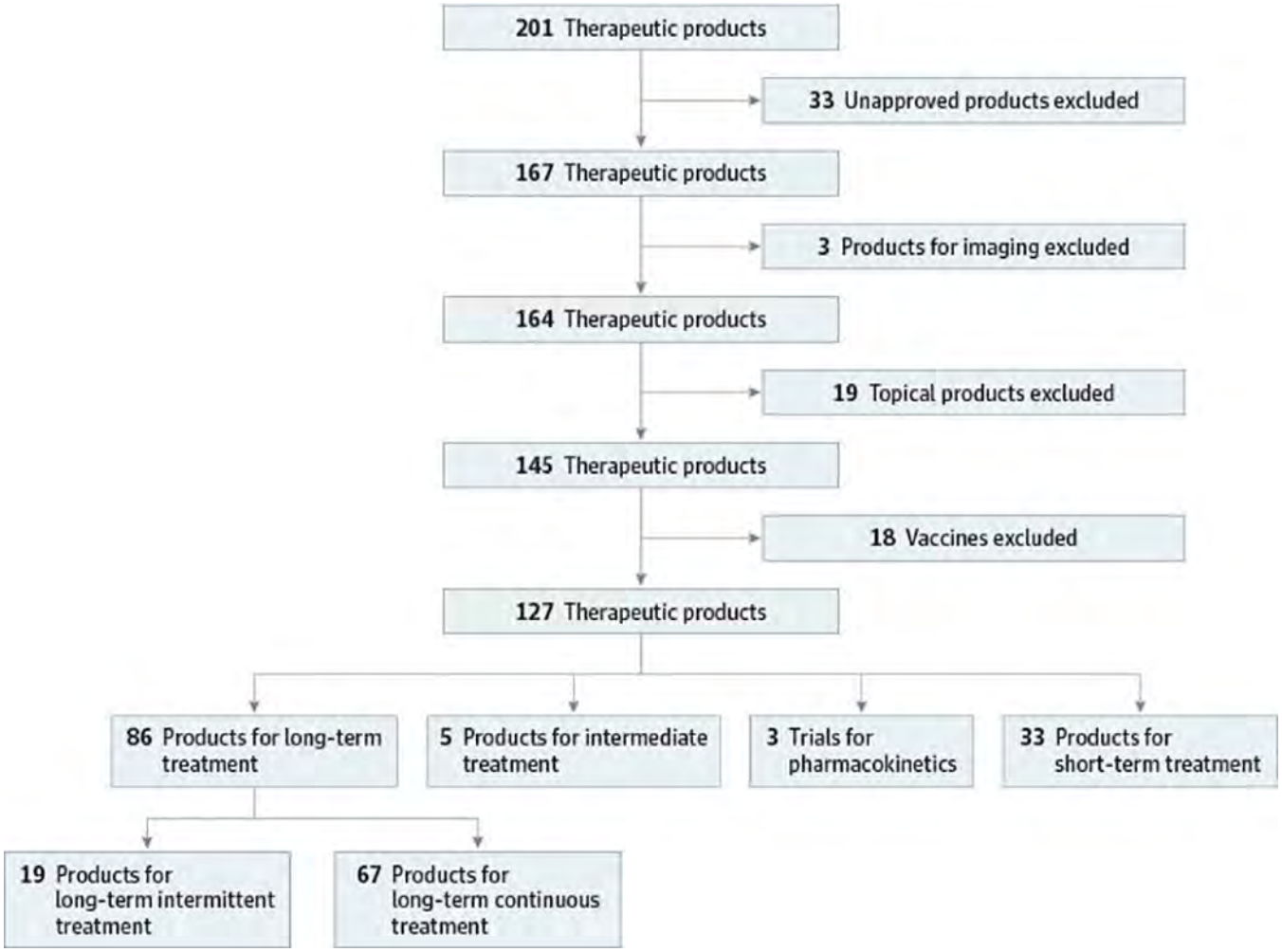

Figure 1.
CONSORT Diagram

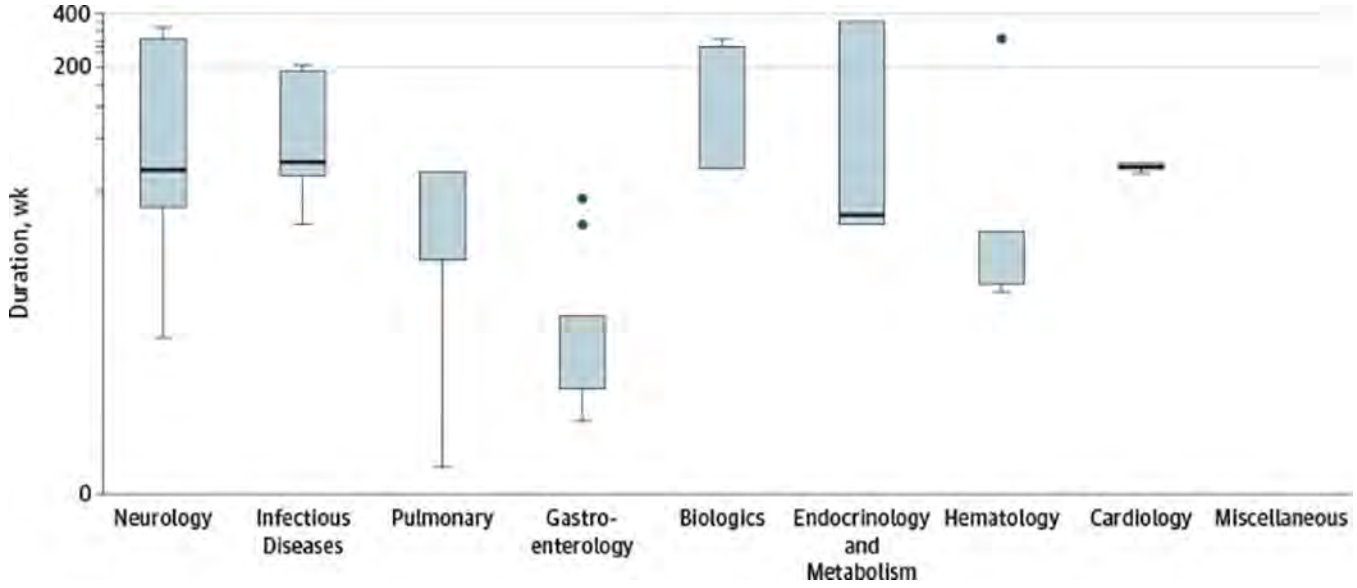

Figure 2. Maximum Trial Duration by Therapeutic Category

The black lines represent the median duration per therapeutic category. Upper and lower bounds of the box represent the 75th (quartile 3 [Q3]) and 25th (quartile 1 [Q1]) percentiles, respectively. The whiskers represent the following values:Q3 + 1.5(Q3 − Q1) andQ1 − 1.5(Q3 − Q1). Outliers within each therapeutic category are denoted by circles.

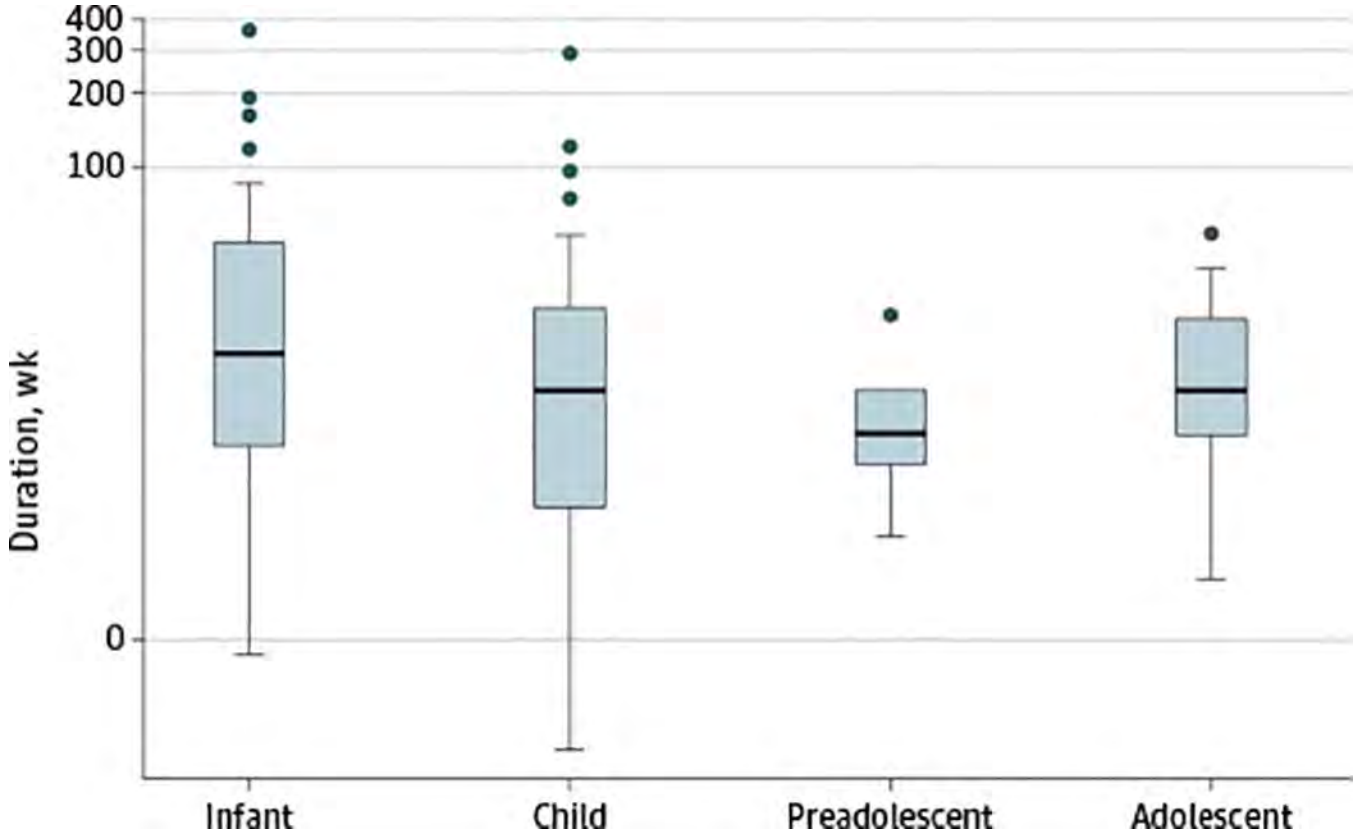

Figure 3. Maximum Trial Duration by Age Category

The black lines represent the median duration per age group. Upper and lower bounds of the box represent the 75th (quartile 3 [Q3]) and 25th (quartile 1 [Q1]) percentiles, respectively. The whiskers represent the following values:Q3 + 1.5(Q3 − Q1) and Q1 − 1.5(Q3 − Q1). Outliers within age group category are denoted by circles.

Table 1.

Drugs Used for Long-term Therapy and Supporting Trials by Therapeutic Category

	Drugs, No. (%)		
Category	**Overall (N = 86)**	**With Extension Trials (n = 30)**	**Trials, No. (%) (N = 306)**
Neurology	25 (29)	14 (47)	109 (35.6)
Pulmonary	16 (19)	3 (10)	91 (29.7)
Infectious diseases	14 (16)	3 (10)	35 (11.4)
Gastrointestinal	10 (12)	0	26 (8.5)
Biologic	6(7)	4(13)	20 (6.5)
Cardiology	5 (6)	5(17)	8 (2.6)
Hematology	5 (6)	0	6 (2.0)
Endocrine	4(5)	1(3)	6 (2.0)
Miscellaneous	1 (1)	0	5 (1.6)
Dermatology	0	0	0

Table 2.

Percentage of Drugs by Maximum Trial Duration for Long-term Therapeutics

	Drugs, No. (%)		
Maximum Trial Duration, Median, wk	**Total (N = 86)**	**Long-term Intermittent (n = 19)**	**Long-term Continuous (n = 67)**
<52	**52 (61)**	**13 (68)**	**39 (58)**
≥52 to <104	**21 (24)**	**5(26)**	**16 (24)**
≥104 to<156	**3(4)**	**0**	**3(5)**
≥156 to <208	**2(2)**	**0**	**2 (3)**
≥208 to <260	**2 (2)**	**0**	**2 (3)**
≥260	**6 (7)**	**1(5)**	**5 (8)**

Footnote 12

Public Health Response to a Case of Paralytic Poliomyelitis in an Unvaccinated Person and Detection of Poliovirus in Wastewater — New York, June–August 2022

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On August 16, 2022, this report was posted as an MMWR *Early Release on the* MMWR *website (https://www.cdc.gov/mmwr).*

On July 18, 2022, the New York State Department of Health (NYSDOH) notified CDC of detection of poliovirus type 2 in stool specimens from an unvaccinated immunocompetent young adult from Rockland County, New York, who was experiencing acute flaccid weakness. The patient initially experienced fever, neck stiffness, gastrointestinal symptoms, and limb weakness. The patient was hospitalized with possible acute flaccid myelitis (AFM). Vaccine-derived poliovirus type 2 (VDPV2) was detected in stool specimens obtained on days 11 and 12 after initial symptom onset. To date, related Sabin-like type 2 polioviruses have been detected in wastewater* in the patient's county of residence and in neighboring Orange County up to 25 days before (from samples originally collected for SARS-CoV-2 wastewater monitoring) and 41 days after the patient's symptom onset. The last U.S. case of polio caused by wild poliovirus occurred in 1979, and the World Health Organization Region of the Americas was declared polio-free in 1994. This report describes the second identification of community transmission of poliovirus in the United States since 1979; the previous instance, in 2005, was a type 1 VDPV (*1*). The occurrence of this case, combined with the identification of poliovirus in wastewater in neighboring Orange County, underscores the importance of maintaining high vaccination coverage to prevent paralytic polio in persons of all ages.

Case Findings

In June 2022, a young adult with a 5-day history of low-grade fever, neck stiffness, back and abdominal pain, constipation, and 2 days of bilateral lower extremity weakness visited an emergency department and was subsequently hospitalized with suspected AFM; the patient was unvaccinated against polio (Figure). As part of national AFM surveillance,† the suspected case was reported to NYSDOH and then to CDC. The patient was discharged to a rehabilitation facility 16 days after symptom onset with ongoing lower extremity flaccid weakness. A combined nasopharyngeal/oropharyngeal swab and cerebrospinal fluid sample were negative by reverse transcription–polymerase chain reaction (RT-PCR) testing for enteroviruses and human parechovirus, as well as for a panel of common respiratory pathogens and encephalitic viruses by molecular methods (*2*). RT-PCR and sequencing of a stool specimen by the NYSDOH laboratory identified poliovirus type 2. Specimens were tested at CDC using RT-PCR (*3*) and sequencing, confirming the presence of poliovirus type 2 in both stool specimens. Additional sequencing identified the virus as VDPV2 (*4*), differing from the Sabin 2 vaccine strain by 10 nucleotide changes in the region encoding the viral capsid protein, VP1, suggesting transmission for up to 1 year although the location of that transmission is unknown.

Based on the typical incubation period for paralytic polio, the presumed period of exposure occurred 7 to 21 days before the onset of paralysis.§ Epidemiologic investigation revealed that the patient attended a large gathering 8 days before symptom onset and had not traveled internationally during the presumed exposure period. No other notable or known potential exposures were identified.

Public Health Response

Upon notification of the poliovirus-positive specimen, CDC, NYSDOH, and local health authorities launched an investigation and response on July 18, 2022. Activities included issuing a NYSDOH advisory on July 22 to increase health care provider awareness,¶ enhancing surveillance for potentially infected persons, testing wastewater from Rockland and surrounding New York counties, assessing vaccination coverage in the patient's community, supplying inactivated polio vaccine (IPV) to county immunization providers, and launching vaccination clinics throughout Rockland County.

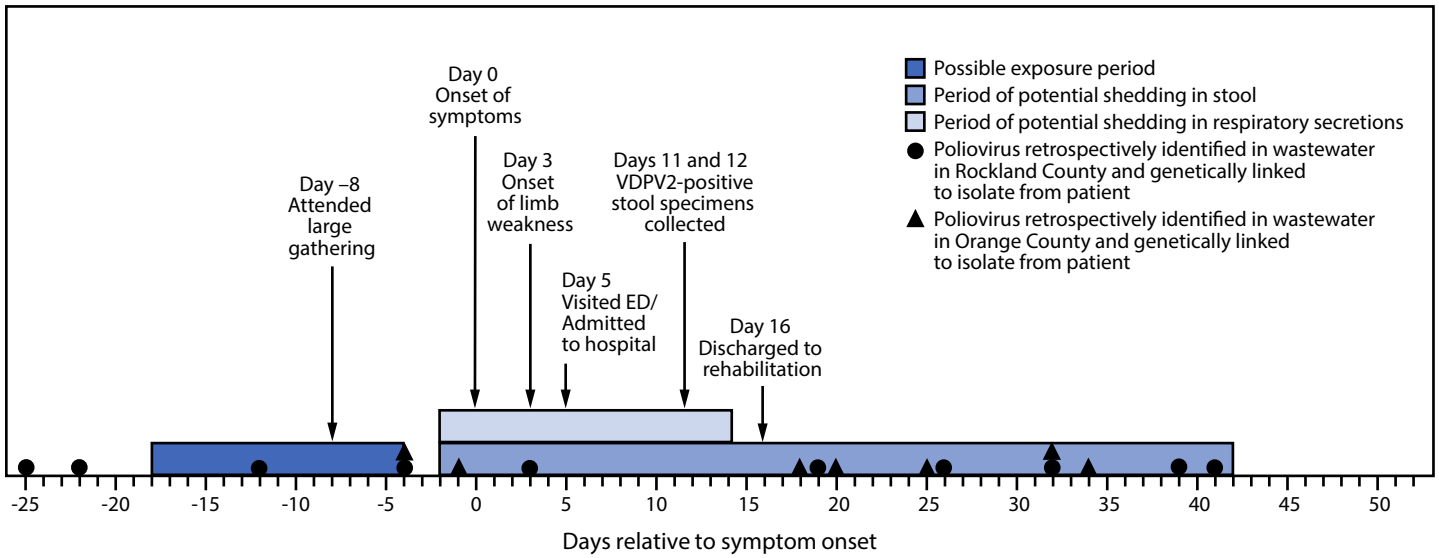
* Wastewater, also referred to as sewage, includes water from household or building use (e.g., toilets, showers, and sinks) that can contain human fecal waste and water from non-household sources (e.g., rain and industrial use). https://www.cdc.gov/healthywater/surveillance/wastewater-surveillance/wastewater-surveillance.html#how-wastewater-surveillance-works

† https://www.cdc.gov/acute-flaccid-myelitis/hcp/case-definitions.html

§ https://www.cdc.gov/vaccines/pubs/pinkbook/polio.html

¶ https://health.ny.gov/diseases/communicable/polio/docs/2022-07-29_han.pdf

FIGURE. Timeline of patient activities, potential poliovirus exposures, shedding, and poliovirus-positive wastewater* samples† genetically linked to a patient with a case of type 2 vaccine-derived poliovirus — New York, May–August 2022



Abbreviations: ED = emergency department; VDPV2 = type 2 vaccine-derived poliovirus.

* Wastewater, also referred to as sewage, includes water from household or building use (e.g., toilets, showers, and sinks) that can contain human fecal waste and water from non-household sources (e.g., rain and industrial use).

† More than one positive wastewater sample might have been collected on the same day in Rockland County or Orange County.

Enhanced surveillance defined persons under investigation (PUIs) as those who met clinical criteria and who lived in or traveled to specific counties or neighborhoods in New York or had international travel since May 1, 2022.** As of August 10, three additional persons have been classified as PUIs; available specimens from the PUIs (i.e., stool, cerebrospinal fluid, serum, nasopharyngeal, or oropharyngeal swabs) yielded negative poliovirus test results.

As of August 10, a total of 260 wastewater samples from treatment plants in Rockland and Orange Counties, including samples originally collected for SARS-CoV-2 surveillance, were tested for poliovirus. Among these samples, 21 (8%) yielded positive poliovirus test results using RT-PCR and partial genome sequencing, including 13 from Rockland County and eight from Orange County. Twenty specimens from wastewater samples collected during May, June, and July were genetically linked to virus from the patient's stool samples; one additional sample, from April in Orange County, was sequenced as poliovirus type 2, but the sequence was incomplete, precluding assessment of genetic linkage to the case. After these results, in August 2022, additional clinical and public health surveillance activities, including additional outreach to local providers and syndromic surveillance, were launched to identify the presence of symptomatic nonparalytic infection (characterized by mild symptoms [e.g., low-grade fever and sore throat] or more severe symptoms [e.g., aseptic meningitis])†† and asymptomatic infection in the counties with poliovirus-positive wastewater findings.

According to the New York State Immunization Information System, 3-dose polio vaccination coverage among infants and children aged <24 months living in Rockland County was 67.0% in July 2020 and declined to 60.3% by August 2022, with zip code–specific coverage as low as 37.3%.§§ National coverage for IPV by age 24 months was 92.7% among infants born during 2017–2018 (*5*). The Rockland County Department of Health launched a countywide catch-up

** The full case definition included epidemiologic, clinical, and laboratory criteria. Epidemiologic criteria included being a person who lived in or traveled to specific counties or neighborhoods in the state of New York or traveled internationally since May 1, 2022. Clinical criteria included 1) acute onset of flaccid paralysis of one or more limbs with decreased or absent tendon reflexes in the affected limbs, without other apparent cause, and without sensory or cognitive loss, or 2) meningitis, with either a positive enterovirus test result in any specimen or, if adequate testing for enteroviruses was not available, the absence of another apparent cause. Laboratory criteria included detection of wild or vaccine-derived poliovirus in a clinical specimen. PUIs were persons who met both epidemiologic and clinical criteria; confirmed cases of paralytic polio were defined as meeting both laboratory criteria and clinical criterion 1. Confirmed nonparalytic polio cases were defined as meeting laboratory criteria and clinical criterion 2, or meeting laboratory but not clinical criteria.

†† https://www.cdc.gov/vaccines/pubs/pinkbook/polio.html

§§ https://www.cdc.gov/vaccines/imz-managers/coverage/schoolvaxview/data-reports/index.html

vaccination effort on July 22, 2022. Although there was a brief increase in administration of polio-containing vaccines (IPV alone and combination vaccines including IPV), the number of doses administered at temporary and established clinics was not sufficient to meaningfully increase population IPV coverage levels.

Discussion

The findings in this report represent only the second community transmission of poliovirus identified in the United States since 1979 (*1*). At present, the origin of the VDPV2 detected in the patient's stool and in sewage samples remains unknown. Because the patient had not traveled internationally during the potential exposure period, detection of VDPV2 in the patient's stool samples indicates a chain of transmission within the United States originating with a person who received a type 2-containing oral polio vaccine (OPV) abroad; OPV was removed from the routine immunization schedule in the United States in 2000. Genome sequence comparisons have identified a link to vaccine-related type 2 polioviruses recently detected in wastewater in Israel and the United Kingdom.[¶¶] In general, approximately one in 1,900 poliovirus type 2 infections among unvaccinated persons is expected to result in paralysis (*6*). As of August 10, 2022, no additional poliomyelitis cases have been identified, although the detection of VDPV2 genetically linked to virus from the patient in wastewater specimens from two counties in New York State over the course of ≥2 months indicates community transmission and ongoing risk for paralysis to unvaccinated persons.

VDPVs can emerge when live, attenuated OPV is administered in a community with low vaccination coverage. Replication of OPV in a person who was recently vaccinated can result in viral reversion to neurovirulence, which can cause paralytic poliomyelitis in unvaccinated persons who are exposed to the vaccine-derived virus. Since removal of OPV from the routine U.S. immunization schedule in 2000, IPV has been the only polio vaccine used in the United States. An inactivated vaccine, IPV does not replicate, revert to VDPV, or cause vaccine-associated paralytic polio. Vaccination with 3 doses of IPV is >99% effective in preventing paralysis[***]; however, IPV does not prevent intestinal infection and therefore does not prevent poliovirus transmission.

Before this case, the last detection of poliovirus in a person in the United States was in 2013, in an immunocompromised infant who received OPV in India and then immigrated to the United States (*1*). VDPVs were identified in the United States in 2005 and 2008 in unvaccinated or immunodeficient persons who were in contact with a person who had recently received OPV; the 2008 case did not result in community transmission. Globally, type 2-containing vaccine (OPV2) has not been used in routine immunization since 2016, although monovalent OPV2 is used for specific vaccination campaigns to control circulating VDPV2 outbreaks (*7*).

Low vaccination coverage in the patient's county of residence indicates that the community is at risk for additional cases of paralytic polio. Even a single case of paralytic polio represents a public health emergency in the United States. Vaccination plays a critical role in protecting persons from paralysis if they are exposed to poliovirus. During the COVID-19 pandemic, routine vaccination services were disrupted, leading to a decline in vaccine administration and coverage (*8,9*), including with IPV, and leaving many communities at risk for outbreaks of vaccine-preventable diseases. Until poliovirus eradication is achieved worldwide, importations of both wild polioviruses and VDPVs into the United States are possible. This case highlights the risk for paralytic disease among unvaccinated persons; all persons in the United States should stay up to date on recommended IPV vaccination to prevent paralytic disease.[†††]

Summary

What is already known about this topic?

Sustained poliovirus transmission has been eliminated from the United States for approximately 40 years; vaccines are highly effective in preventing paralysis after exposure.

What is added by this report?

In June 2022, poliovirus was confirmed in an unvaccinated immunocompetent adult resident of New York hospitalized with flaccid lower limb weakness. Vaccine-derived poliovirus type 2 was isolated from the patient and identified from wastewater samples in two neighboring New York counties.

What are the implications for public health practice?

Unvaccinated persons in the United States remain at risk for paralytic poliomyelitis if they are exposed to either wild or vaccine-derived poliovirus; all persons in the United States should stay up to date on recommended poliovirus vaccination.

[¶¶] https://polioeradication.org/news-post/vaccine-derived-poliovirus-type-2-vdpv2-detected-in-environmental-samples-in-london-uk/

[***] https://www.cdc.gov/vaccines/pubs/pinkbook/polio.html

[†††] https://www.cdc.gov/vaccines/vpd/polio/public/index.html

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