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## Monovalent Type 1 Oral Poliovirus Vaccine in Newborns

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### ABSTRACT

#### BACKGROUND

In 1988, the World Health Assembly resolved to eradicate poliomyelitis. Although substantial progress toward this goal has been made, eradication remains elusive. In 2004, the World Health Organization called for the development of a potentially more immunogenic monovalent type 1 oral poliovirus vaccine.

#### METHODS

We conducted a trial in Egypt to compare the immunogenicity of a newly licensed monovalent type 1 oral poliovirus vaccine with that of a trivalent oral poliovirus vaccine. Subjects were randomly assigned to receive one dose of monovalent type 1 oral poliovirus vaccine or trivalent oral poliovirus vaccine at birth. Thirty days after birth, a single challenge dose of monovalent type 1 oral poliovirus vaccine was administered in all subjects. Shedding of serotype 1 poliovirus was assessed through day 60.

#### RESULTS

A total of 530 subjects were enrolled, and 421 fulfilled the study requirements. Thirty days after the study vaccines were administered, the rate of seroconversion to type 1 poliovirus was 55.4% in the monovalent-vaccine group, as compared with 32.1% in the trivalent-vaccine group ( $P < 0.001$ ). Among those with a high reciprocal titer of maternally derived antibodies against type 1 poliovirus ( $>64$ ), 46.0% of the subjects in the monovalent-vaccine group underwent seroconversion, as compared with 21.3% in the trivalent-vaccine group ( $P < 0.001$ ). Seven days after administration of the challenge dose of monovalent type 1 vaccine, a significantly lower proportion of subjects in the monovalent-vaccine group than in the trivalent-vaccine group excreted type 1 poliovirus (25.9% vs. 41.5%,  $P = 0.001$ ). None of the serious adverse events reported were attributed to the trial interventions.

#### CONCLUSIONS

When given at birth, monovalent type 1 oral poliovirus vaccine is superior to trivalent oral poliovirus vaccine in inducing humoral antibodies against type 1 poliovirus, overcoming high preexisting levels of maternally derived antibodies, and increasing the resistance to excretion of type 1 poliovirus after administration of a challenge dose. (Current Controlled Trials number, ISRCTN76316509.)

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**I**N 1988, THE WORLD HEALTH ASSEMBLY resolved to eradicate poliomyelitis by the year 2000.<sup>1</sup> Substantial progress toward eradication has been made with the use of the trivalent oral poliovirus vaccine — with the number of countries in which the circulation of poliovirus was never interrupted decreasing from more than 125 in 1988 to 5 in 2005 and the number of cases of poliomyelitis decreasing by more than 99% in the same period. Nevertheless, eradication remains elusive.<sup>2</sup> The last documented case of transmission of indigenous wild-type poliovirus type 2 was reported from Aligarh, India, in October 1999.<sup>3</sup> The last isolation of type 1 poliovirus in Egypt was reported in January 2005. During the second half of 2007, type 1 poliovirus continued to circulate after it was imported into five countries in Africa (Angola, Chad, Democratic Republic of Congo, Niger, and Sudan). In mid-2008, types 1 and 3 poliovirus were endemic in Afghanistan, India, Nigeria, and Pakistan.

Through 2004, progress toward the goal of eradicating poliomyelitis had been particularly difficult in the densely populated tropical and subtropical areas of Asia and Africa. To provide the eradication initiative with a more immunogenic vaccine, the Global Polio Eradication Initiative was advised in October 2004 to develop, as quickly as possible, a monovalent type 1 oral poliovirus vaccine,<sup>4</sup> partly to correct for the low immunogenicity of the trivalent oral poliovirus vaccine in developing countries.<sup>5-17</sup> The manufacturers responded rapidly, and the first monovalent type 1 oral poliovirus vaccine was developed and licensed by a large vaccine producer in less than 6 months.

Although a monovalent type 1 oral poliovirus vaccine (as well as monovalent type 2 and type 3 oral poliovirus vaccines) had been used extensively in 1959 and the early 1960s in many industrialized and developing countries, the licensure of a trivalent oral poliovirus vaccine in 1963 in the United States relegated the monovalent vaccines to history. A monovalent type 1 oral poliovirus vaccine has been used in the past 30 years only in Hong Kong, the Gaza Strip, Kuwait, and South Africa,<sup>18,19</sup> and for control of the 1978 outbreak in the Netherlands.<sup>20</sup> A review of available trials of the monovalent type 1 oral poliovirus vaccine<sup>21</sup> suggests that it is two to three times as immunogenic as the trivalent oral poliovirus vaccine, even at potency levels that are substantially lower than the corresponding potency of the trivalent vaccine. A case-control study examining the use of mono-

valent type 1 oral poliovirus vaccine in Northern India in 2005 showed that the efficacy of the monovalent vaccine was approximately three times as high as the efficacy of the trivalent vaccine.<sup>22</sup>

To permit an unbiased evaluation of monovalent type 1 oral poliovirus vaccine, we selected a clinical study design in which newborns were enrolled and vaccinated with either monovalent type 1 or trivalent oral poliovirus vaccine before they had an opportunity to be exposed to poliovirus through routine vaccination with trivalent oral poliovirus vaccine (since 2003, Egypt has recommended a dose of trivalent oral poliovirus vaccine at birth),<sup>23</sup> secondary exposure to vaccine virus from recently vaccinated children, or infection with wild-type poliovirus. The study was designed to provide a head-to-head comparison of the immunogenicity of monovalent type 1 and trivalent oral poliovirus vaccines.

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## METHODS

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### STUDY OBJECTIVES AND PROTOCOL

The study had three specific objectives: to compare humoral antibody responses (seroconversion and antibody titer) after a single dose of either monovalent type 1 or trivalent oral poliovirus vaccine; to quantify mucosal immunity after administration of a challenge dose of monovalent type 1 oral poliovirus vaccine in study participants; and to determine adverse events after oral poliovirus vaccination.

Written or oral informed consent for the participation of the newborns was obtained from parents or guardians in accordance with ethical principles, including the Declaration of Helsinki. The study was carried out in compliance with Good Clinical Practice guidelines and was approved by the Ministry of Health and Population in Egypt; the institutional review boards of Ain Shams University, Cairo, and the Centers for Disease Control and Prevention (CDC), Atlanta; and the ethical review committee of the World Health Organization (WHO), Geneva. The data and safety monitoring board was established for this trial and assumed the responsibility for monitoring adverse events and data quality. All the authors vouch for the completeness and accuracy of the data and analysis presented.

The field work of the study was conducted from August 2005 through October 2005 at three clinical sites (Ain Shams University, Cairo; Kasr El Aini Hospital, University of Cairo, Cairo; and Alexan-

dria University, Alexandria); outreach activities, including the collection of stool samples, were conducted by the Ministry of Health and Population in Egypt. A minimum sample size of 138 participants in each of the two study groups was needed to detect a difference in response with the monovalent type 1 oral poliovirus vaccine as compared with the trivalent vaccine of 20% or more, at an alpha level of 0.05 and a beta level of 0.10 (two-tailed test).

#### STUDY DESIGN

Expectant mothers and fathers were contacted either during prenatal visits or at the time of admission for delivery. They were provided information about the study and asked whether they were willing to participate. Newborns were eligible for participation if they were healthy at birth (and the delivery was not high-risk), if they had a birth weight of 2.75 kg or more, if they had an Apgar score of 9 or higher 5 minutes after delivery, if their family resided in the same governorate as the study site and not further than 30 km away, if the family did not plan to move during the study period, and if written or oral informed consent was given by at least one parent or guardian.

Subjects were randomly assigned to receive at birth either a dose of monovalent type 1 oral poliovirus vaccine (Z5181, Sanofi Pasteur), formulated to contain at least  $10^6$  median cell-culture infective doses ( $CCID_{50}$ ) of Sabin type 1 poliovirus strain, or a dose of trivalent oral poliovirus vaccine (Z5285, Sanofi Pasteur), formulated to contain at least  $10^6$ ,  $10^5$ , and  $10^{5.6}$   $CCID_{50}$  of Sabin types 1, 2, and 3 poliovirus, respectively. At 30 days of age, all subjects received a dose of monovalent type 1 oral poliovirus vaccine. The vaccines were shipped on dry ice from the manufacturer to Cairo.<sup>24</sup>

For the trivalent oral poliovirus vaccine, the mean potency values were provided by the manufacturer as part of lot-release testing. The potency titer for the monovalent vaccine was  $10^{6.8}$  for type 1 poliovirus. The titers for the trivalent vaccine were  $10^{6.9}$  for type 1,  $10^{5.5}$  for type 2, and  $10^{6.5}$  for type 3. Tests performed by the French Health Products Safety Agency (Agence Française de Sécurité Sanitaire des Produits de Santé) showed a titer of  $10^{6.7}$  for the monovalent type 1 oral poliovirus vaccine and titers of  $10^{6.6}$  for type 1,  $10^{5.4}$  for type 2, and  $10^{6.1}$  for type 3 for the trivalent vaccine.

Blood specimens were collected at birth (cord

blood) and 30 and 60 days after birth. After coagulation, the serum was separated, frozen, and stored at  $-20^{\circ}\text{C}$  at the study site until shipment to the CDC. The specimens were tested in triplicate with the use of modified neutralization assays for antibodies to types 1, 2, and 3 poliovirus.<sup>25</sup> The initial dilution was a reciprocal titer of 8. Seropositivity was defined as a reciprocal titer of 8 or higher.<sup>25</sup> Seroconversion was defined as an increase by a factor of 4 in the antibody titer over the expected decline in the titer of maternally derived antibodies in a successive specimen. The half-life of antibody decay was assumed to be 28 days. For subjects who were seronegative at enrollment, a change to seropositivity (i.e., a reciprocal titer  $\geq 8$ ) was considered to indicate seroconversion; for those with titers just below the highest dilution tested, a change to the highest dilution was considered to represent seroconversion. For subjects with positive results at the highest dilution tested (reciprocal titer,  $\geq 1448$ ) for all three serum samples tested (those obtained at birth, 30 days, and 60 days), the samples were retested with a higher initial dilution (1:256) to determine whether they had undergone seroconversion.

Stool specimens were collected 30 days after birth and on days 7, 14, 21, and 28 thereafter; specimens were transported on the day of collection to a central storage location in Alexandria or Cairo and placed immediately in a freezer until shipment to the National Institute for Public Health and the Environment, Bilthoven, the Netherlands, for assessment for the presence of poliovirus. Isolation and identification of poliovirus in the stool specimens were made by the observation of growth on L20B cells, typing by polymerase-chain-reaction (PCR) and serum neutralization assays, and differentiation between wild-type and vaccine-related strains by PCR and by enzyme-linked immunosorbent assay with cross-absorbed antiserum, according to standard procedures established by the World Health Organization (WHO).<sup>26</sup>

#### STATISTICAL ANALYSIS

Statistical analyses were performed with the use of R<sup>27</sup> and SAS<sup>28</sup> statistical packages. Comparisons of the proportion of subjects with seroconversion in the two groups were made with the use of the chi-square test with Yates' correction. The differences in the distribution of antibody titers were tested with the use of the Kolmogorov-Smirnov nonparametric method.<sup>29</sup> The 95% confidence intervals were calculated for the median values.<sup>30</sup>

## RESULTS

**STUDY POPULATION**

The parents or guardians of 583 newborns were contacted; the parent of 1 newborn refused to participate, and 52 newborns did not meet the enrollment criteria. Of the 530 newborns enrolled, 43 (8.1%) were withdrawn during the 60-day follow-up period, and 3 died; 484 subjects completed the study. Sixty-three subjects were excluded from the analyses because they received extra doses of trivalent oral poliovirus vaccine through routine immunization services. Thus, a total of 421 subjects (79.4% of those enrolled in the study) completed the study requirements and were included in the analyses (Fig. 1).

**IMMUNOGENICITY OF THE BIRTH DOSE**

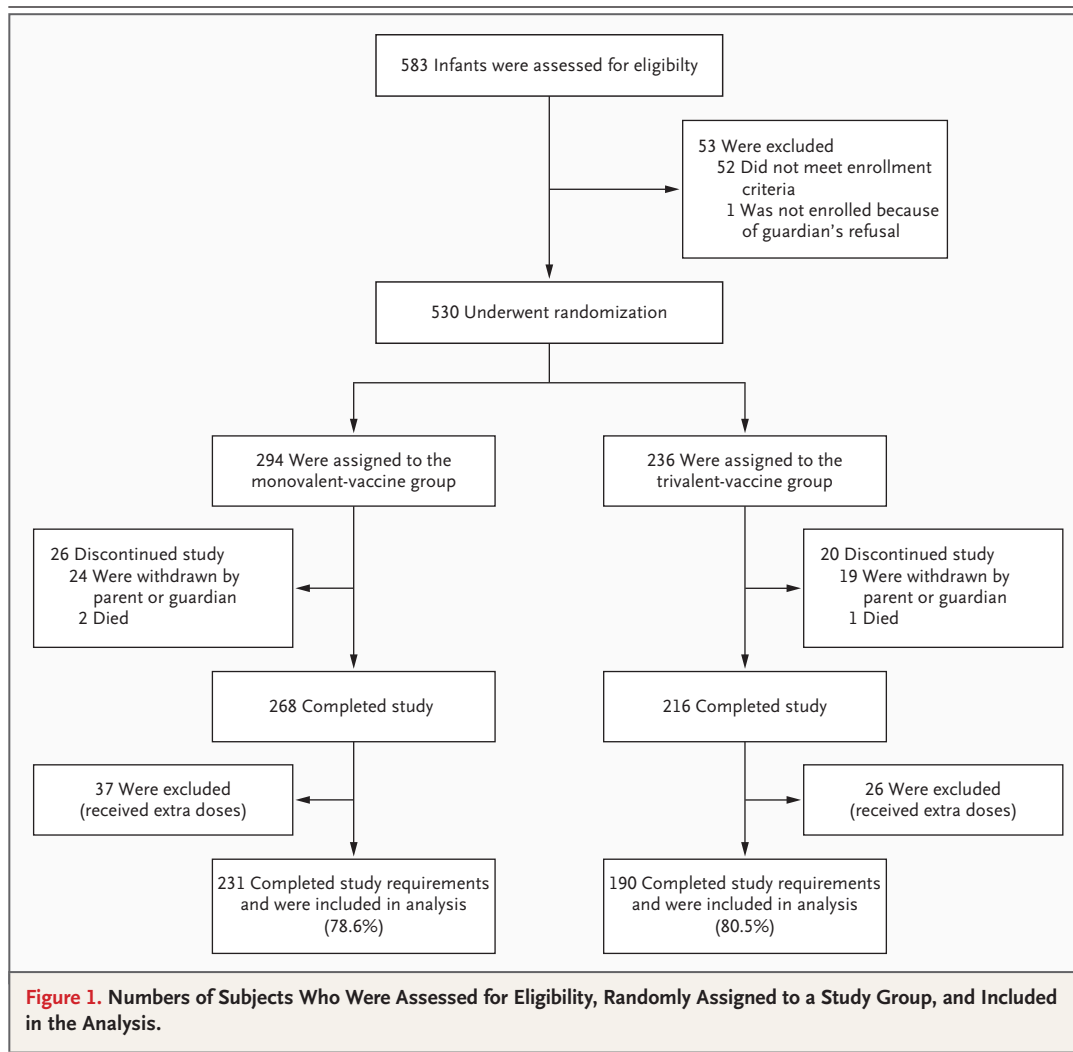
There were no significant differences among the study subjects in baseline characteristics (sex, birth weight, interval from birth to vaccine administration, and levels of seroprevalence) according to study site. After random assignment to either the monovalent-vaccine group or the trivalent-vaccine group, the subjects in the two groups did not differ significantly with respect to baseline characteristics, seroprevalence, or titers of poliovirus antibodies. Seroprevalence was 97.0% in the monovalent-vaccine group and 95.8% in the trivalent-vaccine group for type 1 poliovirus, 92.6% and 96.8%, respectively, for type 2 poliovirus, and 82.3% and 86.8%, respectively, for type 3 poliovirus (Table 1).

The rate of seroconversion to type 1 poliovirus at the 30-day visit after administration of the study vaccine at birth was 55.4% in the monovalent-vaccine group, as compared with 32.1% in the trivalent-vaccine group ( $P<0.001$ ); the rates of seroconversion to type 2 were 7.8% and 62.1%, respectively; and the rates of seroconversion to type 3 were 0.8% and 16.8%, respectively (Table 2). Among subjects who underwent seroconversion, there were no significant differences in median titers according to serotype or study group (Table 2). In the monovalent-vaccine group, the median reciprocal titer in the overall sample increased from 181 to 1448 or higher for type 1, decreased from 114 to 14 for type 2, and decreased from 36 to 7 for type 3. In the trivalent-vaccine group, the overall median reciprocal titer increased from 144 to 1152 for type 1, increased from 114 to

1152 for type 2, and decreased from 57 to 14 for type 3. The overall median titers differed significantly within the study groups according to the visit ( $P<0.01$  for all comparisons). Similarly, the overall median titers at the 30-day and 60-day visits differed significantly between the study groups for each serotype ( $P<0.01$ ) (Fig. 2).

The presence of maternally derived antibodies was a risk factor for failure to undergo seroconversion to type 1 poliovirus in the monovalent-vaccine group and to types 1 and 2 in the trivalent-vaccine group. In the monovalent-vaccine group, 53 of 68 subjects (77.9%) with low levels of maternally derived antibodies (defined as a reciprocal titer of  $\leq 64$ ) underwent seroconversion, as compared with 75 of 163 subjects (46.0%) with high levels (defined as a reciprocal titer of  $>64$ ) ( $P<0.001$ ). In the trivalent-vaccine group, 32 of 54 subjects (59.3%) with low levels of maternally derived antibodies underwent seroconversion, as compared with 29 of 136 (21.3%) with high levels ( $P<0.001$ ). Among subjects with high levels of maternally derived antibodies, the between-group differences in seroconversion were significant (46.0% in the monovalent-vaccine group vs. 21.3% in the trivalent-vaccine group,  $P<0.001$ ). In the trivalent-vaccine group, 56 of 67 subjects (83.6%) with low levels of type 2 maternally derived antibodies underwent seroconversion, as compared with 62 of 123 (50.4%) with high levels ( $P<0.001$ ), and 21 of 105 subjects (20.0%) with low levels of type 3 maternally derived antibodies underwent seroconversion as compared with 11 of 85 (12.9%) with high levels ( $P=0.27$ ).

In the monovalent-vaccine group, seroconversion was significantly affected by socioeconomic status, with the rate of seroconversion to type 1 poliovirus increasing from 38.6% (22 of 57 subjects) among subjects whose mothers had received less than 5 years of formal education to 50.7% (36 of 71 subjects) among those whose mothers had received between 5 and 9 years of formal education and to 68.0% (70 of 103 subjects) among those whose mothers had received 10 years or more of formal education. In the trivalent-vaccine group, the mother's formal education did not affect the rate of seroconversion to type 1 poliovirus: less than 5 years of formal education, 31.6% (18 of 57 subjects); 5 to 9 years, 33.3% (16 of 48); and 10 years or more, 31.8% (27 of 85). Seroconversion was not affected by birth weight, the num-



ber of children younger than 5 years of age in the household, or the interval between birth and administration of the study vaccine.

#### IMMUNOGENICITY OF THE CHALLENGE DOSE

At the 30-day visit, all subjects received a challenge dose of monovalent type 1 oral poliovirus vaccine. Among those who had not undergone seroconversion to the birth dose, the rate of seroconversion to type 1 in the monovalent-vaccine group was 58.3% (60 of 103 subjects), and the rate of seroconversion to type 1 in the trivalent-vaccine group was 66.7% (86 of 129 subjects,  $P=0.24$ ) (Table 2). At the end of the study (at the 60-day visit), 81.4% of the subjects (188 of 231) in the monovalent-vaccine group (who had received two doses of monovalent type 1 oral poliovirus vaccine) had

undergone seroconversion, as compared with 77.4% of the subjects (147 of 190) in the trivalent-vaccine group (who had received a dose of trivalent oral poliovirus vaccine at birth and a dose of monovalent type 1 oral poliovirus vaccine at the 30-day visit) ( $P=0.37$ ).

#### VIRUS EXCRETION AFTER THE CHALLENGE DOSE

Mucosal immunity was assessed by measuring viral excretion after the challenge dose of monovalent type 1 oral poliovirus vaccine, administered at the 30-day visit. Stool specimens were collected immediately before the challenge (day 0 of the challenge) and on days 7, 14, 21, and 28 thereafter. On day 0 of the challenge, 9.5% of the subjects (40 of 421) excreted type 1 poliovirus, 12.1% (51 of 421) excreted type 2 poliovirus, 6.7% (28 of 421)

**Table 1. Baseline Characteristics of the Infants According to Study Group.\***

Characteristic	Monovalent-Vaccine Group (N=231) <sup>†</sup>	Trivalent-Vaccine Group (N=190) <sup>‡</sup>
Male sex — no./total no. (%)	122/231 (52.8)	95/190 (50.0)
Birth weight — kg		
Median	3.3	3.3
95% CI	3.2–3.3	3.25–3.4
Interval from birth to administration of study vaccine — min		
Median	60	60
95% CI	55–60	55–64
Type 1 poliovirus		
Seroprevalence at birth — % <sup>§</sup>	97.0	95.8
Reciprocal titer — median (95% CI)	181 (144–181)	144 (114–228)
Type 2 poliovirus		
Seroprevalence at birth — % <sup>§</sup>	92.6	96.8
Reciprocal titer — median (95% CI)	114 (91–144)	114 (91–144)
Type 3 poliovirus		
Seroprevalence at birth — % <sup>§</sup>	82.3	86.8
Reciprocal titer — median (95% CI)	36 (23–45)	57 (36–72)

\* None of the differences between groups were significant at the 0.05 level.

<sup>†</sup> Subjects in the monovalent-vaccine group received one dose of monovalent type 1 oral poliovirus vaccine at birth and one dose at the 30-day visit.

<sup>‡</sup> Subjects in the trivalent-vaccine group received a dose of trivalent oral poliovirus vaccine at birth and a dose of monovalent type 1 oral poliovirus vaccine at the 30-day visit.

<sup>§</sup> Seroprevalence refers to a reciprocal antibody titer of 8 or higher.

excreted type 3 poliovirus, and 0.5% (2 of 421, both of whom were in the monovalent-vaccine group) excreted a mixture of type 2 and type 3. No wild-type poliovirus was detected in any of the stool samples. Overall, 42.3% of the study infants (161 of 381) excreted type 1 poliovirus at any visit after the challenge — 32.7% (66 of 202) of the subjects in the monovalent-vaccine group as compared with 53.1% (95 of 179) in the trivalent-vaccine group ( $P<0.001$ ). The subjects in the monovalent-vaccine group had lower excretion rates than those in the trivalent-vaccine group at each assessment point (7, 14, 21, and 28 days) after the challenge (Table 3). The difference in excretion of type 1 poliovirus between the two groups was significant before the challenge (day 0) ( $P=0.03$ ) and on day 7 after the challenge ( $P=0.001$ ) but not at the other post-challenge visits.

#### ADVERSE EVENTS AFTER VACCINATION

No immediate serious adverse events and only five minor adverse events (all involving vomiting) were

noted during a 30-minute observation period after administration of the vaccine. Five subjects were admitted to the hospital within 2 days after birth to receive phototherapy for jaundice. One subject was hospitalized because of heart failure due to a congenital heart defect. Three other subjects were reported to have severe adverse events (pneumonia, sepsis, and congenital heart disease); all three subjects (who were from the same study site) died; two of the infants (one with pneumonia and one with sepsis) were in the monovalent-vaccine group, and one infant (with congenital heart disease) was in the trivalent-vaccine group. None of the adverse events or deaths were attributed to the trial intervention.

#### DISCUSSION

These data have implications for the use of monovalent type 1 oral poliovirus vaccine in the global initiative to eradicate poliomyelitis. First, this vaccine is significantly more immunogenic than

**Table 2. Rates of Seroconversion and Median Reciprocal Titers of Antibodies to Types 1, 2, and 3 Poliovirus after Vaccination at Birth and at 30 Days and Cumulative Rates and Reciprocal Titers at 60 Days, According to Study Group.\***

Vaccination Response	Monovalent-Vaccine Group (N = 231)†	Trivalent-Vaccine Group (N = 190)‡	P Value
<b>Type 1</b>			
Response to birth dose			
Seroconversion — %	55.4	32.1	<0.001
Reciprocal titer — median (95% CI)	≥1448 (≥1448 to ≥1448)	1176 (910 to ≥1448)	NS
Response to challenge dose at 30 days			
Seroconversion — %§	58.3	66.7	NS
Reciprocal titer — median (95% CI)	≥1448 (≥1448 to ≥1448)	≥1448 (≥1448 to ≥1448)	NS
Cumulative response at 60 days			
Seroconversion — %	81.4	77.4	NS
Reciprocal titer — median (95% CI)	≥1448 (≥1448 to ≥1448)	≥1448 (910 to ≥1448)	NS
<b>Type 2</b>			
Response to birth dose			
Seroconversion — %	7.8	62.1	<0.001
Reciprocal titer — median (95% CI)	1176 (1176 to ≥1448)	1261 (1176 to ≥1448)	NS
Response to challenge dose at 30 days			
Seroconversion — %§	2.4	9.7	0.002
Reciprocal titer — median (95% CI)	724 (576 to ≥1448)	910 (455 to ≥1448)	NS
Cumulative response at 60 days			
Seroconversion — %	10.0	65.8	<0.001
Reciprocal titer — median (95% CI)	1176 (910 to 1176)	≥1448 (≥1448 to ≥1448)	NS
<b>Type 3</b>			
Response to birth dose			
Seroconversion — %	0.8	16.8	0.006
Reciprocal titer — median (95% CI)	576 (362 to 910)	910 (724 to 910)	NS
Response to challenge dose at 30 days			
Seroconversion — %§	3.5	10.8	0.02
Reciprocal titer — median (95% CI)	512 (14 to ≥1448)	576 (288 to 1176)	NS
Cumulative response at 60 days			
Seroconversion — %	4.3	25.8	0.004
Reciprocal titer — median (95% CI)	455 (28 to ≥1448)	567 (288 to 910)	NS

\* The median reciprocal titer was calculated only for subjects who underwent seroconversion. NS denotes not significant.

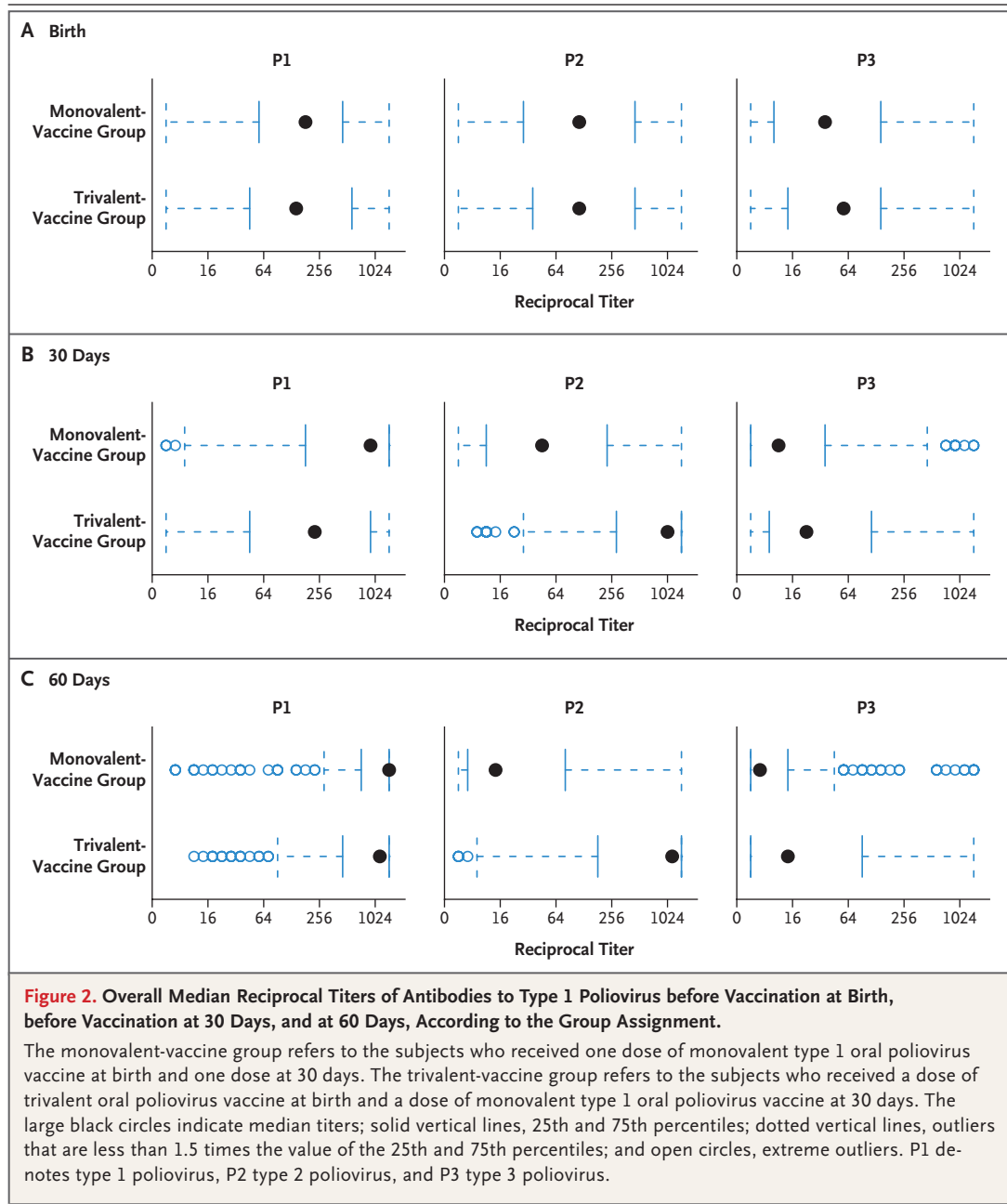
† Subjects in the monovalent-vaccine group received one dose of monovalent type 1 oral poliovirus vaccine at birth and one dose at the 30-day visit.

‡ Subjects in the trivalent-vaccine group received a dose of trivalent oral poliovirus vaccine at birth and a dose of monovalent type 1 oral poliovirus vaccine at the 30-day visit.

§ The denominator for seroconversion in response to the dose at 30 days excludes the subjects who underwent seroconversion in response to the birth dose.

trivalent oral poliovirus vaccine in inducing a type-specific seroconversion; second, vaccination with monovalent type 1 as compared with trivalent oral poliovirus vaccine significantly decreases subse-

quent excretion of type 1 oral poliovirus after a challenge with the monovalent vaccine; and third, vaccination with the monovalent vaccine after initial vaccination with the trivalent vaccine appears



to be as effective in closing the type 1 immunity gaps as vaccination with the monovalent vaccine in previously unvaccinated infants or in those who have undergone initial vaccination with the monovalent vaccine.

One of the reasons that this monovalent vaccine is significantly more immunogenic in inducing a type-specific antibody response than the trivalent vaccine may be that this monovalent vaccine has a higher potency than previous mono-

valent vaccines used in the United States and other industrialized countries in the 1960s<sup>21</sup> (i.e.,  $\geq 1,000,000$  CCID<sub>50</sub>, vs. 200,000 CCID<sub>50</sub>). The higher potency was selected on the basis of a review of previous trials in developing countries<sup>21</sup> and as part of the regulatory approval strategy to remove the unnecessary Sabin strains from the trivalent oral poliovirus vaccine while maintaining all other requirements for the formulation of the trivalent oral poliovirus vaccine.

**Table 3. Excretion of Types 1, 2, and 3 Poliovirus in Stool Specimens Obtained before and after a Challenge Dose of Monovalent Type 1 Oral Poliovirus Vaccine at the 30-Day Visit, According to Study Group.\***

Poliovirus Excretion	Monovalent-Vaccine Group (N=231)†	Trivalent-Vaccine Group (N=190)‡	P Value
	<i>no./total no. (%)</i>		
<b>Type 1</b>			
Before challenge	29/231 (12.6)	11/190 (5.8)	0.03
After challenge			
At 7 days	59/228 (25.9)	78/188 (41.5)	0.001
At 14 days	50/224 (22.3)	54/184 (29.3)	NS
At 21 days	28/222 (12.6)	28/183 (15.3)	NS
At 28 days	18/220 (8.2)	24/182 (13.2)	NS
<b>Type 2</b>			
Before challenge	12/231 (5.2)	39/190 (20.5)	<0.001
After challenge			
At 7 days	8/228 (3.5)	9/188 (4.8)	NS
At 14 days	3/224 (1.3)	3/184 (1.6)	NS
At 21 day	5/222 (2.3)	6/183 (3.3)	NS
At 28 days	1/220 (0.5)	5/182 (2.7)	NS
<b>Type 3</b>			
Before challenge	4/231 (1.7)	24/190 (12.6)	<0.001
After challenge			
At 7 days	2/228 (0.9)	10/188 (5.3)	0.02
At 14 days	2/224 (0.9)	4/184 (2.2)	NS
At 21 days	2/222 (0.9)	3/183 (1.6)	NS
At 28 days	1/220 (0.5)	2/182 (1.1)	NS

\* NS denotes not significant.

† Subjects in the monovalent-vaccine group received one dose of monovalent type 1 oral poliovirus vaccine at birth and one dose at the 30-day visit.

‡ Subjects in the trivalent-vaccine group received a dose of trivalent oral poliovirus vaccine at birth and a dose of monovalent type 1 oral poliovirus vaccine at the 30-day visit.

Excretion on day 7 after the challenge was significantly reduced in the monovalent-vaccine group. Resistance to excretion after exposure may be the most important mechanism for interrupting the remaining chains of poliovirus transmission.

Low socioeconomic status, defined as fewer years of formal maternal education, was a risk factor for failure to undergo seroconversion to type 1 poliovirus in the monovalent-vaccine group but not in the trivalent-vaccine group for types 1, 2, and 3. Low socioeconomic status has been identified in several studies of trivalent oral poliovirus vaccine as a risk factor for failure to undergo seroconversion after a full series with trivalent oral poliovirus vaccine.<sup>6,17</sup>

The seroconversion rate with monovalent type 1 oral poliovirus vaccine in our study was similar to that in previous studies conducted in developing countries. In these studies, seroconversion rates of 50 to 70% were reported with monovalent type 1 oral poliovirus vaccines of various potencies.<sup>21,31-36</sup>

In our study, none of the serious adverse events that were reported among the study subjects during the follow-up period were attributed by the investigators or by the data and safety monitoring board to the receipt of either of the study vaccines. The number of deaths was consistent with expectations based on infant mortality rates in Egypt.

An important limitation of this study is that

we restricted enrollment to newborns. However, we chose to study the vaccine in newborns because infants in developing countries receive multiple doses of trivalent oral poliovirus vaccine, typically starting with a dose administered at birth or shortly thereafter. The study of newborns allows an evaluation of monovalent type 1 and trivalent oral poliovirus vaccines before the subjects are potentially exposed to poliovirus. However, newborns have the highest levels of maternally derived antibodies, which are known to interfere with seroconversion.<sup>37</sup> Therefore, our findings with respect to the immunogenicity of monovalent type 1 oral poliovirus vaccine are probably biased toward the lower ranges of immunogenicity as compared with those we might have observed after administration of the vaccine in slightly older infants ( $\geq 1$  month of age).

In conclusion, our data confirm the potential contribution of supplemental doses of monovalent type 1 oral poliovirus vaccine to accelerate the

interruption of the final chains of poliovirus transmission and eventually achieve the goal of global eradication of poliomyelitis.<sup>2</sup>

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