

Causality Assessment of Serious Neurologic Adverse Events Following the bOPV National Vaccination Campaign in Israel

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ABSTRACT: **Background:** During 2013–2014 Israel experienced a continuous circulation of wild poliovirus type 1 (WPV1) but with no clinical cases. WPV1 circulation was gradually terminated following a national vaccination campaign of bivalent oral poliovirus vaccine (bOPV) for 943,587 children < 10 years. Four cases of children with neurological manifestations that appeared following bOPV vaccinations were reported during the campaign: three of Guillain-Barré syndrome (GBS) and one of acute disseminated encephalomyelitis (ADEM).

Objectives: To present an analysis of these cases, the rapid response and the transparent publication of the results of this analysis.

Methods: The clinical, laboratory and epidemiological data of these four patients were available during the analysis. In addition, data regarding the incidence of GBS and ADEM during previous years, and reported cases of acute flaccid paralysis (AFP) and the incidence of *Campylobacter jejuni* enteritis were collected from the Epidemiology Department of the Israel Ministry of Health.

Results: The incidence of GBS among bOPV-vaccinated children was not higher than among bOPV-unvaccinated children. For all the cases reviewed the “incubation period” from vaccination to the event was longer than expected and other more plausible causes for the neurologic manifestations were found. There is no evidence in the literature of a causal relationship between bOPV and ADEM.

Conclusions: There was no association between the bOPV vaccine and the reported neurological manifestations. We believe that our experience may assist other public health professionals when confronting a similar problem of alleged side effects during a mass medical intervention.

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KEY WORDS: bivalent oral poliovirus vaccine (bOPV), Guillain-Barré syndrome (GBS), acute disseminated encephalomyelitis (ADEM), *Campylobacter jejuni*, neurological effect

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During 2013 and the beginning of 2014 Israel experienced continuous circulation of wild poliovirus type 1 (WPV1) but with no clinical cases. WPV1 circulation was gradually terminated following a national vaccination campaign of bivalent oral poliovirus vaccine (bOPV) administered to 943,587 children < 10 years old [1,2]. Four cases of children with neurological manifestations – three with Guillain-Barré syndrome (GBS) and one with acute disseminated encephalomyelitis (ADEM) that appeared following bOPV vaccinations – were reported during the campaign. These reports attracted broad media attention and threatened to compromise the entire vaccination campaign. As a result, a rapid response was generated aimed at bringing the scientific data to the public as soon as possible.

PATIENTS AND METHODS

The data of the four patients were available during the analysis. The patients’ medical records were reviewed and findings from the different laboratories were collected. Data regarding the specific dates of bOPV vaccination were also recorded. In addition, data on the incidence of GBS and ADEM during previous years, on reported cases of acute flaccid paralysis (AFP), and on the incidence of *Campylobacter jejuni* enteritis were collected from the Epidemiology Department of Israel’s Ministry of Health.

RESULTS

The clinical, laboratory and epidemiological data are summarized in Table 1. According to the Ministry of Health data, during 2007–2012 an average of 18 children < 10 years old in Israel developed GBS per year, and another 18 children < 10 years in Israel developed ADEM [Table 2]. In 2013, 12 confirmed cases of Guillain-Barré were reported in children < 10 years old. Nine cases occurred among children who had not received bOPV

Table 1. Clinical and epidemiological data of the children with neurological manifestations

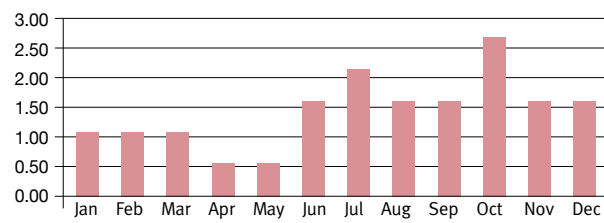
Case #	Age	Medical diagnosis	Interval between OPV vaccination and neurological event	Probable infectious neurological trigger	Poliovirus laboratory results	Lapse between infectious trigger and neurological symptoms	Poliovirus vaccination status (IPV)
1	5 yrs	GBS	23 days	Diarrheal disease. <i>Campylobacter</i> was detected in stool (positive culture and PCR)	Negative PCR in stool	7 days	Full for age (4 doses)
2	6 yrs	GBS	45 days	Respiratory disease. Negative culture and negative <i>Campylobacter</i> PCR in stool	Negative PCR in stool	10 days	Full for age (4 doses)
3	3 yrs	GBS	38 days	Viral febrile illness with acute tonsillitis (non-streptococcal)	Negative PCR in stool	21 days	Full for age (4 doses)
4	11 mo	ADEM	32 days	Febrile illness accompanied by rash and vomiting	Negative PCR in CSF	6 days	Full for age (3 doses)

OPV = oral poliovirus vaccination, IPV = inactivated polio vaccine, GBS = Guillain-Barre virus, PCR = polymerase chain reaction, ADEM = acute disseminated encephalomyelitis, CSF = cerebrospinal fluid

Table 2. Guillain-Barre syndrome (GBS) and acute disseminated encephalomyelitis (ADEM) in children < 10 years old in Israel, 2007–2012

Event/Year	2007	2008	2009	2010	2011	2012
Infectious ADEM	10	5	6	4	19	16
Non-infectious ADEM	10	5	1	6	10	18
ADEM (Total)	20	10	7	10	29	34
Guillain-Barré syndrome	21	22	18	12	20	17

Figure 1. Incidence of acute flaccid paralysis per 100,000 population < 15 years, monthly rate, 2013

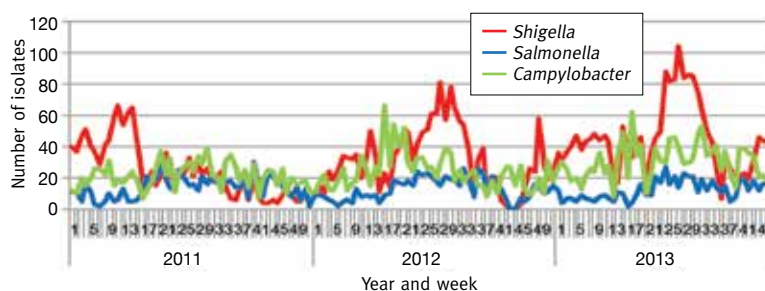


vaccines during the campaign. During the entire vaccination campaign 943,587 children aged < 10 years (79% of the eligible target population) were vaccinated with bOPV. At the time of the analysis (August 2013) the vaccination rate was 50–80% of the eligible target population according to the Ministry of Health’s Epidemiology Department.

The monthly incidence of acute flaccid paralysis (AFP) per 100,000 population < 15 years old during 2013 is shown in Figure 1, demonstrating the increased vigilance toward the occurrence of AFP during the vaccination campaign (since August 2013) and indicating that rates of AFP cases including GBS were less likely to be ignored.

National data regarding the isolation of bacterial pathogens in stool samples processed in the laboratories of Maccabi Health Services (the second largest health fund in Israel) are shown in Figure 2, demonstrating the increased incidence of *Campylobacter* isolation during the second half of 2013 even though the annual sum of cases was similar to that of previous years.

Figure 2. Incidence of Enterobacteriaceae (*Salmonella*, *Shigella* and *Campylobacter*) infections in 2011–2013, Maccabi Health Services



Based on these data we concluded that there was no association between the bOPV vaccine and the reported neurological manifestations. This conclusion was disseminated among health professionals and received broad media coverage, which helped prevent obstruction of the national vaccination campaign.

DISCUSSION

The present analysis was conducted to examine the possible association of the above-mentioned neurological manifestations of bOPV vaccination. Undoubtedly, a retrospective analysis at the end of the campaign was expected to be more accurate and comprehensive. However, waiting for such an analysis (and possibly even withholding bOPV vaccination until the conclusion of such an analysis) might have compromised the vaccination campaign while the parents were waiting for more rapid and conclusive answers.

For causality assessment of possible adverse events following vaccine administration, several questions must be addressed:

- Whether an event occurred following the vaccination at a greater rate than the background incidence
- Was the interval between the vaccination and the event compatible with the expected “incubation period”
- Is there a biologic mechanism that could potentially explain how the vaccine might have caused the adverse event

- Were there other possible causes for the adverse effect (e.g., infectious illness)
- Are there previous reports in the literature regarding the association between the vaccine and specific adverse effects.

In answer to the above:

- **GBS and ADEM rates compared to their background incidence.** Consideration should be given to the likelihood that the neurological events could have occurred purely by chance through assessment of their background rate. In 2013, 13 confirmed cases of GBS were reported in children < 10 years old. Nine cases occurred among children who had not received bOPV vaccines during the campaign. This finding is particularly striking since the routine AFP surveillance was enhanced during this period [Figure 1] and because the incidence of *C. jejuni* infections (an important causal factor for GBS) in Israel has been as high as in previous years. In addition, the GBS incidence among bOPV-vaccinated children was not higher (in fact was even lower) than the incidence in bOPV-unvaccinated children in the same age group (0.5/100,000 as compared to 1.3/100,000) (Source: Epidemiology Department of the Israel Ministry of Health).
- **Interval between the vaccination and the neurological events.** The timing of the suspected adverse effect in relation to vaccine administration is critical. Furthermore, the event should occur within a defined window of risk following vaccine administration. ADEM is an inflammatory demyelinating disease of the central nervous system and has an estimated annual incidence of 0.8/100,000 [3]. Infection is the most frequent etiology, and post-vaccination ADEM accounts for less than 5% of all the ADEM cases [4]. Typically, there is a latency of 3–14 days (within 1 day to 3 weeks of immunization) between a febrile illness or vaccination and the onset of neurological symptoms [5]. It has also been noted to occur more frequently after primary vaccination than after revaccination [6,7]. In our case, ADEM showed a plausible time relationship with the preceding febrile illness that occurred 6 days earlier. Therefore, due to long latency (32 days after bOPV), causality for the vaccine is much less likely. bOPV was given 23, 32 and 45 days before GBS onset. However, GBS was preceded by a gastrointestinal and respiratory infection (one and two cases, respectively) – the most common triggers – within the prior 3 weeks.
- **Biologic mechanism that could potentially explain the adverse event.** The pathophysiological mechanism by which the vaccine causes disease must make biological sense. It is obvious that the neurological events were not due to a direct effect of the live attenuated poliovirus. bOPV strains were not isolated from fecal and spinal fluid samples in any of the cases. One proposed mechanism for GBS and ADEM

is that an antecedent infection evokes an immune response, which in turn cross-reacts with nervous system components because of the sharing of cross-reactive epitopes (molecular mimicry) [6]. All the patients received repeated doses (at least three) of inactivated polio vaccine (IPV) without any sequelae in the past. Therefore, it seems unlikely that a booster dose will activate immune damage that could have been activated several times previously.

- **Other possible causes for the adverse effects.** The etiology of GBS is not completely understood; however, a number of gastrointestinal and respiratory infectious triggers have been identified, *Campylobacter* being the most common. Molecular mimicry and cross-reactive immune responses to *C. jejuni* lipo-oligosaccharides precipitate the development of GBS [8]. A study from Sweden estimated that the risk for developing GBS during the 2 months following a symptomatic episode of *C. jejuni* infection was approximately 100-fold higher than the risk in the general population, with GBS developing in an estimated 0.03% of patients with *C. jejuni* enteritis [9]. In the last decade, the annual incidence of *Campylobacter* spp. infection in Israel increased from 31.04 to 90.99 cases/100,000 population, a yearly increase of 10.24% [10]. One patient with GBS in the present series had a *C. jejuni* infection, which is well known as a triggering factor in the etiology of GBS (proven by stool culture and polymerase chain reaction). All GBS cases had a preceding infection, unrelated to bOPV occurring days before the onset of the neurological illness. The preceding febrile illness that occurred before ADEM onset is also a suggestive trigger.
- **Association between the OPV and neurological events reported in the literature.** GBS and ADEM have been associated with vaccines. A recent review of studies examining associations between various vaccines, GBS and ADEM found that, with rare exceptions, these associations have been temporal only, with little evidence from most vaccines to support a causal association [11]. Recent evidence from large epidemiological studies and mass immunization campaigns in different countries found no correlation between oral polio vaccines and GBS [12,13]. A nationwide OPV vaccination campaign in Finland in 1985 raised the question of a relationship between OPV and GBS, but in-depth analysis of the data showed that the increase in GBS occurred before the vaccination campaign started [14]. There is no evidence in the literature of a causal relationship between bOPV and ADEM. We conclude that there was no association between the bOPV vaccine and the neurological manifestations based on the rate of the neurological events among vaccinees, their clinical presentations and a review of the literature. Moreover, for all the cases reviewed, other more plausible causes for the neurological manifestations have been found,

or the interval between the vaccination and the event was incompatible with the expected “incubation period.”

In conclusion, we believe that our experience in performing a timely analysis in response to the communication crisis during a national health campaign may assist other public health professionals when faced with a similar problem of alleged side effects during a mass medical intervention.

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