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Commentary

Safety monitoring of COVID-19 vaccines – Lessons learned from the 1976 national influenza immunization program about detecting rare vaccine-related severe adverse events in emergency mass-vaccination programs ☆

Alan Kendal

Community Health Consultant, Blaine, WA, USA

1. Linkage of A/New Jersey/76 - containing influenza vaccines with Guillain-Barré syndrome (GBS)

In 1976, a National Influenza Immunization Program (NIIP) was established with Congressional and Presidential support to mitigate a possible pandemic. This followed the isolation of novel influenza viruses in January and February from recruits training at Fort Dix, New Jersey [1] that were shown at the CDC to antigenically resemble the strain implicated in the severe 1918 influenza pandemic [2]. The NIIP required expedited production, testing and use of vaccines containing the A/New Jersey/76 (A/NJ/76) virus before the following fall/winter.

Four manufacturers produced test lots of vaccines of varying potencies, whose optimum safety and immunogenicity profiles were determined in multi-center trials coordinated by the National Institutes of Health [3]. Consolidated results were used to set the composition of vaccines, approved by the Food and Drug Administration, and subsequently administered to over 40 million US residents between Oct 1 and Dec 16, 1976 [4,5].

By December 2, two states reported to CDC small clusters (total 7 cases) of Guillian Barré syndrome (GBS) among influenza A/NJ/76 vaccinees, a severe adverse event (SAE) not previously attributed to influenza vaccines [4,5]. GBS is characterized by sometimes life-threatening progressive muscle weakness or paralysis caused by immunological damage to nerves, that has been reported following some bacterial and viral infections [5]. CDC initiated active surveillance in 11 states, showing GBS incidence increased during the NIIP, largely with onsets 2–3 weeks post-vaccination [5].

During 1976, the A/NJ/76 strain did not spread within the U.S. [4], so there was no health benefit from the NIIP. Vaccination with A/NJ/76 was stopped by CDC leadership, with concurrence of the Assistant Secretary for Health [4]. Active surveillance for GBS was extended to the entire nation.

The background rate of GBS in the national study was 1.3 cases per million per 6-week period among unvaccinated adults 18 years and older, compared to 10.1 during the 6-week period after vaccination (i.e., an extra 8.8 GBS cases per million vaccinees) [5]. Over 20% of the 479 GBS cases among vaccinated adults for whom the information was available required respiratory support, and 6% (32) died from the total 529 reported cases among vaccinated adult [5].

No laboratory or clinical markers distinguished background GBS cases from vaccine-linked cases. Accordingly, only the following epidemiological criteria were available to establish the presumptive existence of GBS as an influenza A/NJ/76 vaccine-caused injury:

- the increased incidence of GBS began within 6-weeks after A/NJ/76 vaccination, for all, or almost all, vaccine-related cases evaluated in several studies, including the CDC national study and the evaluations in MI and MN [5,6]
- Onset of symptoms of GBS clustered over time, particularly in the second and third weeks after vaccination
- histories of any acute illness within four weeks before GBS onset among cases were markedly less frequent in vaccinated (32.8%) compared to unvaccinated (61.8%) patients – this suggested that vaccinations were replacing the usual infectious disease causes of GBS [5]

Earlier in 1976, stimulated by the summer outbreak of Legionnaire's Disease, the US Government had accepted liability for injuries that might be caused by the A/NJ/76 vaccine, other than due to manufacturer's negligence [4]. A small increased risk of GBS could not be excluded statistically for a few weeks beyond the 6 weeks in the CDC national study. This may have caused legal uncertainty as to awarding injury compensation in a few GBS cases with onset from 6 weeks to about 10 weeks post vaccination. Legal research would be needed to ascertain if, and how often, this issue arose.

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E-mail address: apkenda@gms-ppa.net

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2. Re-evaluation of GBS risk from A/New Jersey/76 containing vaccines.

Largely because of concerns that risk estimates might have been overestimated by biased diagnosing or reporting of GBS cases in vaccinated persons, an independent risk assessment was done [6]. Neurologists, blinded to patients' vaccination status, reviewed records of all patients hospitalized with GBS during October 1, 1976 through January 31, 1977 in Michigan and Minnesota. For the 6-week period post-vaccination, the risks of GBS attributable to the influenza vaccinations were 8.6 (Michigan) and 9.7 (Minnesota) per million adults vaccinated [6], resembling the 8.8 excess cases in CDC's national study [5].

3. Evaluating adverse event risks for multiple related vaccines.

During 1976, four vaccine manufacturers produced monovalent vaccine against A/NJ/76 influenza, and (to also protect against the latest seasonal strain of influenza A), bivalent vaccine containing A/NJ/76 and A/Victoria/75 antigens. Two manufacturers' vaccines contained purified whole virus, the other two ("split" or "subunit" vaccines), chemically disrupted virus. The 95% confidence limits of the relative risk for post-vaccination GBS of vaccines from the 4 different manufacturers overlapped [5], suggesting the GBS risk was NOT linked to a specific manufacturer or product type (whole virus, split virus). The commonality among these vaccines of the A/NJ/76 influenza virus antigens implied that this was the component triggering rare abnormal immune responses in some patients leading to GBS.

4. Likelihood of seeing a rare SAE in clinical trials.

To illustrate the potential for rare SAE's to be seen during clinical trials, using rates of GBS seen in 1976 it was estimated there is only a 41% chance of seeing even one case of such a rare SAE in a trial that vaccinated 60,000 adults and followed them for 6 weeks, approximating the situation applicable to the largest trials of vaccines against COVID-19.

5. Risk-benefit of vaccination when a rare SAE exists.

In early 1977 the US Secretary of Health, Education and Welfare approved re-starting immunization with bivalent influenza vaccines of people at increased risk of serious influenza disease, even though the vaccines included A/NJ/76 antigen, to protect against the seasonal influenza that *was* causing outbreaks [8]. In 2009, a mass vaccination program occurred against a pandemic variant of influenza A (H1N1), which circulated widely, causing considerable morbidity and mortality. A vaccine-attributable risk was found of about 1.6 cases of GBS per million vaccinees [7], but clearly the benefits of the vaccine outweighed this risk.

6. Relevance of experiences with the 1976 NIIP to the COVID-19 pandemic

Several adverse event monitoring systems were in place or initiated when SARS-CoV-2 vaccination began. Unlike 1976, in 2021 they use active mass collection of data, from systems with unavoidable sample biases, data size limitations, or variable use over time after vaccination. Thus, urgent epidemiological evaluation of events temporally linked to vaccination will often be essential to avoid needless concerns about inevitable coincidental SAEs (https://www.cdc.gov/mmwr/volumes/70/wr/mm7008e3.htm).

The following key lessons learned from the NIIP in 1976 about rare SAE's may be helpful:

A: Unlike influenza mass vaccination programs in 1976 and 2009, rapid increases in mass vaccination to counter the COVID-19 pandemic will include vaccine(s) made with widely different and often new technologies [9], and may evolve to include vaccines updated with new pandemic variants. This will require constant vigilance to quickly evaluate if any further SAE's seen post-vaccination are coincidental or not, as different vaccines come into use. Furthermore, if a post-vaccination SAE is suspected among SARS-CoV-2 vaccinees, but is due to something not common among all vaccines, it will likely take longer to recognize than if it is due to a common feature in multiple types of the vaccine. Statistical confidence in there being low risks from vaccination may thus vary between different COVID-19 vaccines used at different rates.

B: Linking a potential rare SAE to any SARS-CoV-2 vaccine may also be more challenging if, like GBS in 1976, the onset begins later and is spread over a longer interval than rare allergic reactions already reported following vaccination with the SARS-Cov-2 vaccines first authorized in mass programs, as well as some other existing vaccines.

C: Statistical data about both the earliest and the latest times post-vaccination when an SAE linked to the vaccine can occur could be important in dealing with possible vaccine injury claims. The Public Readiness and Emergency Preparedness Act that defines US Government indemnification of pandemic vaccine manufacturers was declared, (effective as of February 4, 2020), to include medical countermeasures against COVID-19 [10].

In summary, GBS was suggested as a possible consequence of the A/NJ/76 vaccine, based on rapid investigations in eleven states after physicians reported a few temporally-associated cases. The association was concerning enough after a rapid study in a subset of states to pause immunizations as the A.NJ/76 virus was not spreading. But a national active study was needed to provide statistical evidence justifying a permanent halt to mass vaccination. An independent follow-up study was done later, finally overcoming skepticism about the newly identified influenza vaccine-GBS linkage.

From such experiences in 1976, one of the most important purposes of SAE surveillance around use of SARS-CoV-2 vaccines appears to be continually updating and sharing statistical estimates of the apparent low risk - high benefit from being vaccinated. To preserve public confidence in the analysis, and thus the mass vaccination program, regular evaluation of the strengths and weaknesses of the surveillance for SAEs in the USA is desirable. It also seems desirable to consider supplementing national SAE surveillance in the USA by the regular planned sharing of data with international partners using similar vaccines as in the USA, but who benefit from national integrated health care systems and records that the USA lacks – e.g. the UK.

Declaration of Competing Interest

The author declares having no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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