Vaccine adverse events reported in New Zealand 1990-95

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Abstract

Aim: New Zealand monitors vaccine safety through vaccinator reports of adverse events following immunisation. The rate of reporting for the commonly used vaccines during 1990-95 are presented. During this time new vaccines were added to the immunisation schedule, enabling comparison of reporting rates.

Method: The number of events were obtained from the CARM database, and a rate calculated based on estimated vaccine use.

Results: Injection site reaction with adult tetanus-diphtheria vaccine was most commonly reported (68/100,000); a rate five times higher than with tetanus vaccine. There were also more reported reactions from Diphtheria-Tetanus-Pertussis-Haemophilus influenzae type b (DTPH) than DTP vaccine, with 'abnormal crying' the commonest reaction reported after 29/100,000 doses of DTPH and 3/100,000 doses of DTP. The next commonest reaction for DTPH was injection site reaction (25/100,000) which compares to 17/100,000 doses of DTP. For the other inactivated vaccines, more reports were made for fever following Hib (16/100,000), than for hepatitis B (2/100,000) or influenza (1/100,000). The most common reports following Measles-Mumps-Rubella (MMR) vaccine were rash (17/100,000), fever (12/100,000), and injection site inflammation (5/100,000). There were very few reports following polio vaccine, with rash, fever and headache all reported at less than 1/100,000 doses.

Conclusion: Although only a proportion of events are reported, the picture presented here confirms the overall safety of vaccines and the value of the adverse event monitoring system. Monitoring vaccine adverse events is an essential part of the immunisation programme.

Disclaimer: Osman Mansoor is an advisor for the Ministry of Health. However, the views expressed in the article are those of the authors and do not necessarily reflect those of the Ministry.

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Introduction

Immunisation prevents disease, but can cause adverse events. While the balance of risks and benefits is strongly in favour of immunisation, it remains important to monitor
vaccine adverse events. In New Zealand, the National Toxicology Group's Centre for Adverse Reactions Monitoring (CARM) receives reports of adverse events following immunisation, and is a member of the World Health Organization (WHO) collaborating programme for international monitoring. This voluntary reporting system has been in place since 1965 and one of its goals is the detection and appropriate response to possible hazards.

The numbers of adverse events reported for each vaccine are included in CARM's annual report which is sent to all medical practitioners. In these reports, the numbers of events but not their rate has been reported. Comparison of reported events between vaccines and over time need to take into account number of doses used. The estimated rate of reported events is reported for the period 1990-95.

The immunisation schedule changed in 1994. *Haemophilus influenzae* type b (Hib) vaccine was added to the schedule both on its own and as tetravalent DTPh (Diphtheria-Tetanus-Pertussis-Hib) replacing triple (DTP) vaccine. Also, adult tetanus-diphtheria (Td) vaccine replaced tetanus vaccine. The comparative event reporting rates are presented for the old and new vaccines.

**Method**

The CARM database provided the numbers of the most commonly reported and serious adverse events reported for each vaccine for the years 1990 to 1995 inclusive, or after their addition to the schedule. The WHO Adverse Reaction Terminology was used.

The number of vaccines administered had to be estimated. For most vaccines this was based on estimated coverage. As there are no coverage estimates for monovalent Hib, tetanus, Td and influenza vaccines, the number of vaccines issued or sold (influenza) were the basis of the estimate. To avoid underestimating the rate, minimal estimates were used.

For early childhood immunisation, 80% coverage of the birth cohort rounded to 60,000 children was estimated based on the 1992 coverage survey and 1994 immunisation benefit claim data. For Measles-Mumps-Rubella (MMR) vaccine (which replaced measles vaccine in November 1990), a second dose was added for 11 year old children in 1992. MMR vaccine replaced the rubella vaccine for girls which had achieved 98% coverage. There are no national statistics on MMR coverage, but anecdotal reports are that coverage has been lower, so 90% coverage of 55,000 children was estimated.

For the vaccines where use was based on issues or sales, 20% wastage was assumed.

**Results**

Injection site reaction (ISR) after Td vaccine was the most commonly reported adverse event (68 reports per 100,000 doses). This compares with a rate of 14/100,000 for tetanus vaccine from 1990-93. Events associated with Td are given in Table 1. The reported frequency of fever (2/100,000) with tetanus was also about five times lower than after Td, but rash (1/100,000) was reported at the same rate.
Table 1. Events reported after Td vaccine, 1994-1995

<table>
<thead>
<tr>
<th>Event</th>
<th>Number</th>
<th>Rate per 100,000 doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISR inflammation</td>
<td>170</td>
<td>68.11</td>
</tr>
<tr>
<td>Fever</td>
<td>25</td>
<td>10.02</td>
</tr>
<tr>
<td>Nausea &amp; Vomiting</td>
<td>19</td>
<td>7.61</td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
<td>6.01</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>15</td>
<td>6.01</td>
</tr>
<tr>
<td>Malaise</td>
<td>15</td>
<td>6.01</td>
</tr>
<tr>
<td>Myalgia</td>
<td>11</td>
<td>4.41</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8</td>
<td>3.21</td>
</tr>
<tr>
<td>Lethargy/Fatigue</td>
<td>8</td>
<td>3.21</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>7</td>
<td>2.80</td>
</tr>
<tr>
<td>Influenza type symptoms</td>
<td>6</td>
<td>2.40</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4</td>
<td>1.60</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>1.20</td>
</tr>
<tr>
<td>Delirium</td>
<td>2</td>
<td>0.80</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>2</td>
<td>0.80</td>
</tr>
<tr>
<td>Urticaria</td>
<td>2</td>
<td>0.80</td>
</tr>
<tr>
<td>Muscle contractions involuntary</td>
<td>2</td>
<td>0.80</td>
</tr>
<tr>
<td>Ataxia</td>
<td>1</td>
<td>0.40</td>
</tr>
<tr>
<td>Hallucination</td>
<td>1</td>
<td>0.40</td>
</tr>
<tr>
<td>Neuritis</td>
<td>1</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Figure 1 compares the reports for DTP and DTPH vaccine. Injection site reactions, abnormal crying (inconsolable crying for three or more hours), fever, rash, and irritability were the most commonly reported with both vaccines. For most events there was a higher reporting rate for DTPH. "Pallor" and "abnormal crying" were reported 10.7 and 8.3 times more often with DTPH than DTP, respectively. Injection site abscesses were only reported following DTP.

Figure 1. Events reported after DTP and DTPH vaccines, 1990-95

ISR = injection site reaction
Figure 2 compares the reporting rate for Hib with the other non-toxoid, inactivated vaccines: influenza and hepatitis B. The reported frequency of most events was higher for Hib.

**Figure 2. Events reported after influenza, hepatitis B, and Hib vaccines, 1990-95**

Note: For influenza vaccine, there were also 11 reports (1.1 per 100,000) of myalgia, five reports (0.5 per 100,000) of influenza type symptoms, and one each of anaphylaxis, pericarditis and polyarthritis.

Figure 3 compares the reporting rate for the live vaccines: Measles-Mumps-Rubella (MMR) and oral polio (OPV). Since OPV is scheduled to be given at the same time as other vaccines, adverse events are more likely to be attributed to the injected vaccine.

**Figure 3. Events reported after MMR and Oral Polio vaccines, 1991-95**

**ISR = injection site reaction**
Discussion

Adverse event monitoring is an important aspect of immunisation programmes. Vaccinators are advised to report adverse events, particularly serious or unexpected reactions, following immunisation. This requirement is now one of the Immunisation Standards in the Ministry of Health's Immunisation Handbook. The handbook also includes a list of specific serious adverse events which should be reported. Despite this requirement, the reporting of adverse events remains essentially voluntary. In Sweden reporting adverse events is legally required, but the reporting rate is lower than in New Zealand which has the highest spontaneous reporting rate for medicines and vaccines in the world [Unpublished WHO data].

The term 'adverse event' has been used to depict an untoward event temporally associated with immunisation, that might or might not be caused by the vaccine or immunisation process. A reaction is an event caused by the vaccine. The spectrum of vaccine reactions are well known and many are predictable responses to the antigenic stimuli and/or adjuvant, such as injection site inflammation and fever.

As with any such reporting programme, the results presented here suggest that only a minority of adverse events are reported. The reaction rates are lower than those found in studies where vaccinees are followed up. For example, hypotonia was only reported after about 1 per 100,000 doses of either DTP or DTPH compared to a rate of 57 per 100,000 in the largest study. The lower rate is likely to be because descriptions of hypotonic-hyporesponsive episodes (HHE) vary considerably, and inadequate details may result in the event being coded as pallor or some other reaction.

A double-blind placebo trial of MMR vaccine in twins found considerably lower reaction rates than commonly reported, suggesting that many of the reactions (eg, fever) attributed to MMR are in fact due to other viral infections, and not the vaccine. That study found rash in 1.6% and high fever in 1.4% compared with our reporting rate of 17/100,000 and 12/100,000, respectively.

Despite inherent under-reporting, it is apparent that a representative sample of reports are received which provide valuable insight into the overall picture, with clustering of a particular problem serving as a potential signal. It is apparent there were no serious safety issues during the monitoring period. Allergic reactions can occur with any vaccine, but anaphylaxis is rare. The reporting rate for anaphylaxis after MMR (0.29/100,000) is similar to the Finnish experience with only two cases of anaphylaxis following 3 million doses (0.15/100,000), but lower than the 1 per 100,000 reported in the 1994 British campaign where 92% of schoolchildren received measles-rubella vaccine. The close match between these numbers suggests better reporting for more serious adverse events.

The new vaccines (DTPH and Td) generated more adverse event reports than the vaccines they replaced. One possibility is that vaccinators are more likely to report the reactions to a new vaccine. This effect can be seen in the comparison between Hib and hepatitis B vaccines (Figure 2).

With DTPH, while the number of reports increased, the overall pattern of reactions remained similar (Figure 1). The report profile of events following Hib vaccine suggest that the difference is not simply due to the Hib component. However, the reported rate of fever with Hib vaccine is similar to DTPH and may contribute to the higher rate with DTPH than DTP. These data contrast with controlled trials which have shown no increase in reactivity with the addition of Hib vaccine to DTP.

Sterile abscesses were only reported following DTP. This may have been related to the freezing of part of the batch in 1991. Freezing of DTP vaccine not only inactivates it
but also leads to more local reactions. The reports of sterile abscesses were during the
time of use of that batch.

The change from tetanus to Td was associated with a wider range of new adverse events,
as well as an increase in the rate of predictable local reactions and fevers. The addition of
the diphtheria component was not expected to lead to any increase in adverse events.
The Institute of Medicine's extensive review of adverse events was unable to identify any
serious reaction causally related to diphtheria toxoid, with the exception of Guillain-
Barré Syndrome in immunocompromised individuals. Furthermore, studies have not
shown significant differences in reaction rates between tetanus and Td.

The reactions associated with Td prompted discussion of this issue in a Public Health
Commission circular letter to health professionals in June 1995. The total number of
reports have remained low, and reactions transient. The balance of risks from potential
return of diphtheria versus vaccine adverse events favours continuation of Td
immunisation.

The voluntary reporting system has generated an important and representative profile of
the adverse events associated with immunisation. This information should be useful for
vaccinators and all health professionals by providing insight into the more common
adverse events and their reported rate. Despite its limitations the system provides a
mechanism for identification of significant safety issues. The increase of reports
associated with new vaccines also suggest that change is associated with increased
reporting. The main limitations are the low reporting rates, and the inability to separate
coincidental events following immunisation from reactions caused by immunisation. The
low reporting rates allow for a large relative increases reporting reactions (eg, doubling).
This means that an increase in reports are not necessarily due to more reactions, but
could represent improved reporting. There have been continuing messages to vaccinators
over the past few years on the importance of reporting, and it is likely that reporting
rates are improving over time, in tandem with the increasing interest in immunisation
over the past decade.

Voluntary reporting systems have been used in the USA to confirm the safety of
simultaneous administration of vaccines. The authors of the USA study concluded that
large linked databases are the ideal method of monitoring adverse events. Recent studies
from Canada and England have effectively linked immunisation and health databases
to monitor adverse events. For one rare adverse event, the English study found the linked
records to provide a five fold higher rate than from voluntary reporting.

New information technology enables the development of systems to provide improved
surveillance of adverse events through linked databases. If resources permit,
immunisation information systems may be built with the capacity for linkage to facilitate
future monitoring of adverse events. Until such a system can establish its feasibility,
affordability, and superiority, the current system provides good monitoring of the
immunisation programme. Vaccinators are reminded of the importance of reporting
clinically significant events following immunisation.

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