

Re-vaccination of 421 children with a past history of an adverse vaccine reaction in a special immunisation service

Michael Gold, Helen Goodwin, Sue Botham, Margaret Burgess, Margot Nash, Ann Kempe

Abstract

Background—In Australia an adverse event following immunisation (AEFI), with the exception of anaphylaxis and encephalopathy, is no longer considered an absolute contraindication to continuing vaccination with the suspect vaccine. Despite these recommendations there is a paucity of information on the re-vaccination of such children.

Aims—To describe the re-vaccination of a large number of children with a past history of an AEFI.

Methods—A review of children attending special immunisation services in three Australian tertiary care paediatric centres.

Results—During the review 970 children attended of whom 469 had experienced a past AEFI. Of these, 293 had experienced minor while 176 children had experienced significant neurological or allergic reactions. The majority (421/469) were re-vaccinated, with only one child having a significant neurological event; this was transient and resolved spontaneously.

Conclusions—Re-vaccination of children who have a past history of an AEFI appears safe. A special immunisation service should be part of a comprehensive immunisation programme.

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Concerns about vaccine safety are of crucial importance to parents and vaccine providers, particularly in countries where vaccine preventable disease (VPD) is uncommon.¹ Vaccines are not devoid of risk, and minor adverse reactions following childhood vaccination, especially vaccines containing pertussis antigens, are common.² Fortunately serious adverse reactions are rare and the risk of morbidity from such reactions is far less than that which may occur following a VPD. Ironically while concerns have been increasing about vaccine safety, the contraindications to re-vaccination, in children who experience an adverse reaction, have been reduced. In Australia and the USA, anaphylaxis and encephalopathy are now considered the only conditions that are an absolute contraindication to re-vaccination with the suspect vaccine.^{3–6} In these countries an adverse event following immunisation

(AEFI) such as a severe local reaction, high fever, screaming, convulsion, or hypotonic hyporesponsive episode (HHE) is no longer considered an absolute contraindication. Despite these recommendations it is likely that many children who have experienced such reactions do not complete their immunisation schedule. In Australia pertussis vaccine was frequently omitted from the immunisation schedule, prior to the introduction of acellular pertussis vaccine, and this was reflected in the widespread use of a combined diphtheria-tetanus vaccine.⁵ This is of concern given the recent epidemic of pertussis in Australia with at least 10 668 cases notified in 1997.⁷

In the late 1980s special immunisation services (SIS) were established in the UK to review and promote the vaccination of children with an existing medical disorder, egg allergy, or those with a perceived contraindication to vaccination or a past history of an AEFI.^{8–9} Within Australia a SIS was first established in 1994.¹⁰ However, these earlier services have reported only small numbers of children and do not reflect the current practice of offering continuing vaccination, including acellular pertussis vaccine, to those children who have experienced serious reactions which were then regarded as contraindications. Similar SIS have been established in three tertiary care paediatric hospitals in Australia. The aim of this report was to describe the re-vaccination of a larger number of children who have attended these services with a past history of an AEFI.

Methods

This was a retrospective review of children attending the SIS in South Australia (Women's and Children's Hospital, Adelaide), New South Wales (New Children's Hospital, Sydney), and Victoria (Royal Children's Hospital and Monash Medical Centre, Melbourne). The overall period of review was from October 1996 to March 1999. The routine childhood immunisation schedule in place at the time was for diphtheria, tetanus, and pertussis (DTP), *Haemophilus influenzae* type b (HiB), and oral polio (OPV) vaccines to be administered at 2, 4, and 6 months of age. Measles, mumps, and rubella (MMR) vaccine was administered at 12 months of age followed by booster doses of DTP and HiB at 18 months. Between 4 and 5 years of age DTP and OPV were administered. In August 1997 a three component acellular containing pertussis vaccine (Infanrix; Smith-Kline Beecham, Melbourne) was licensed for

South Australian Immunisation Coordination Unit, Communicable Disease Control Branch, Department of Human Services, PO Box 6, Rundle Mall, Adelaide 5000, South Australia
M Gold
H Goodwin
S Botham
M Burgess
M Nash
A Kempe

Correspondence to:
Dr Gold
email: mgold@
medicine.adelaide.edu.au

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Table 1 Details of previous adverse event following immunisation and vaccine(s) associated with the event in 469 children attending the SIS

| Previous adverse reaction | Vaccines associated with reaction | | | | | | | Total (% of total) |
|--|-----------------------------------|-----------------------------------|----------------|-----|-------|----------------|-----|--------------------|
| | DTPw +/- Hib, OPV, Hep B | DTPa +/- Hib, OPV, Hep B | Hib +/- OPV | MMR | Hep B | CDT +/- OPV | BCG | |
| Fever, local reactions, screaming, other* | 274 | 10 | 3 | 2 | 1 | 3 | | 293 (63%) |
| HHE | 75 | 5 | 1 | | | | | 81 (17%) |
| Convulsions | 38 | | 1 | 2 | 1 | | | 42 (9%) |
| Skin rash | 21 | 6 | | 2 | 6 | | | 35 (8%) |
| Anaphylaxis | 2 | | | 3 | | | | 5 (0.5%) |
| Apnoea | 4 | | | | 1 | | | 5 (0.5%) |
| Serious other† | 6 | | | 1 | | | 1 | 8 (2%) |
| Total | 420 | 21 | 5 | 10 | 9 | 3 | 1 | 469 (100%) |

*Other includes lethargy, vomiting, diarrhoea, and drowsiness.

†Serious other: one case each of monoparesis, hepatitis, BCG abscess, cerebral haemorrhage, encephalopathy, thrombocytopenia, bronchospasm without anaphylaxis, episode of cyanosis.

DTPw and a, diphtheria, tetanus, and whole cell/acellular pertussis; Pa, monovalent acellular pertussis; CDT, diphtheria, tetanus; Hib, *Haemophilus influenzae* B; OPV, oral polio vaccine; MMR, measles, mumps, and rubella; Hep B, hepatitis B; BCG, Bacille Calmette Guérin.

use in Australia and by 1999 this vaccine replaced the use of whole cell pertussis vaccine. However, from August 1997 children who presented with an AEFI, to the SIS, associated with DTPw (whole cell pertussis) were offered re-vaccination with DTPa (acellular pertussis) if this was appropriate.

Each SIS was promoted locally as a service for children with a prior history of an AEFI or an underlying medical disorder which may have precluded immunisation. Children attending were referred by a health professional (consultant paediatrician, or medical or nurse practitioner). The following features were common to all services. Firstly, all children were reviewed by a paediatrician with a special interest and expertise in immunisation. Secondly, vaccines were administered according to guidelines detailed in the National Health and Medical Research Council Australian Immunisation handbook.⁴ Re-vaccination with the suspect vaccine was considered to be contraindicated if the presenting event was anaphylaxis or encephalopathy (for vaccines containing pertussis, measles, mumps, or rubella antigens). All other children were offered re-vaccination with the suspect vaccine if these vaccines were due, the child was not acutely unwell with a fever (body temperature above 38.5°C), and neither the child (for MMR and OPV) nor any household contacts (for OPV) were immunosuppressed. Parental valid consent was obtained following a discussion of the risks and benefits of re-vaccination. Thirdly, each child was observed following vaccination. Those considered at high risk were observed in hospital for a period of between four and eight hours. In a minority of cases children were admitted for overnight observation. Lastly, parents of those children who were immunised were telephoned between 24 and 72 hours after vaccination and questioned about any symptoms their child had developed. In Adelaide and Melbourne parents were also contacted seven days after vaccination, while in Sydney this only occurred if an AEFI was reported during the first telephone contact. At follow up a standard telephone questionnaire was adminis-

tered in Melbourne while parents were asked to report any adverse events at the remaining two sites.

Data were collated from each service, including the total number of patients attending, their ages and sex, the proportion of those with an AEFI, the nature of the AEFI and vaccines associated with the reaction, the vaccines administered in the SIS, and the outcome of vaccination in the service. The presenting AEFIs were divided into local reactions, fever (of any degree), irritability, screaming (unspecified), vomiting, or diarrhoea. These reactions often occurred concurrently and were analysed together. Reactions such as convulsions (within seven days of a vaccine), HHE, skin rash (usually urticarial and not associated with thrombocytopenia, anaphylaxis, or vaccine viraemia), or anaphylaxis were considered primary reactions regardless of any other symptoms reported. HHE was defined as a sudden event occurring within 48 hours of vaccination characterised by hypotonia, hyporesponsiveness, and pallor in the absence of a known cause such as a convulsion.¹¹ An AEFI was recorded to the vaccines administered in the SIS if the parents reported any symptoms in the seven day period post-vaccination.

Results

During the period of review 970 children attended the three SIS of whom 469 (48%) had experienced a prior AEFI, with the remainder having an underlying medical disorder (including egg anaphylaxis) which led to concerns regarding immunisation. Of those presenting with an AEFI, 55% were boys, with a median age 24 months (range 1 to 183 months), often indicating a considerable delay in the interval between the AEFI and review. Table 1 presents details of the vaccines associated with each AEFI. Of the 469 children with an AEFI, 293 (63%) had a history of a local reaction, fever, irritability, screaming, vomiting, or diarrhoea post-vaccination. The remaining 176 (37%) children presented with HHE, convulsions, skin rash (usually urticarial and not associated with thrombocytopenia, anaphylaxis, or vac-

Table 2 Details of vaccines administered to 421 children, with a past history of an adverse event following immunisation, attending the SIS

| Previous adverse reaction | Vaccines administered in Special Immunisation Service | | | | | | | | | % of affected immunised |
|---|---|-------------------------------|-----------------------------|-----------------|-----|--------------------|-----|-------|-------|-------------------------|
| | DTPw +/- Hib, OPV, Hep B, MMR | DTPa +/- Hib, OPV, Hep B, MMR | PA +/- Hib, OPV, Hep B, MMR | CDT/ADT +/- Hib | OPV | Hib +/- OPV, Hep B | MMR | Hep B | Total | |
| Fever, local reactions, screaming, other* | 17 | 163 | 68 | 3 | 2 | 6 | 7 | 2 | 269 | 92 |
| HHE | 2 | 54 | 12 | 3 | | | 1 | | 72 | 89 |
| Convulsions | 1 | 20 | 8 | 1 | | | 4 | 1 | 35 | 83 |
| Skin rash | 6 | 14 | 4 | 1 | | 2 | 3 | 3 | 33 | 94 |
| Anaphylaxis | | | | | 2 | | 1 | | 3 | 60 |
| Apnoea | | 3 | 1 | | | | | | 4 | 80 |
| Other serious† | | 3 | 1 | | 1 | | | | 5 | 63 |
| Total | 26 | 257 | 94 | 8 | 5 | 10 | 16 | 6 | 421 | 90 |

*Other includes lethargy, vomiting, diarrhoea, and drowsiness.

†Serious other: one case each of monoparesis, hepatitis, thrombocytopenia, bronchospasm without anaphylaxis, episode of cyanosis.

DTPw and a, diphtheria, tetanus, and whole cell/acellular pertussis; Pa, monovalent acellular pertussis; CDT, diphtheria, tetanus; Hib, *Haemophilus influenzae* B; OPV, oral polio vaccine; MMR, measles, mumps, and rubella; Hep B, hepatitis B; BCG, Bacille Calmette Guerin.

cine viraemia), anaphylaxis, apnoea, or a number of miscellaneous symptoms. In 420/469 (90%) children the AEFI was associated with administration of DTPw vaccine. In these children DTPw was given alone or in combination with Hib, OPV, or hepatitis B (Hep B) vaccines. The remaining 48/469 (10%) of AEFIs were associated with the administration of DTPa, MMR, Hib, OPV, Hep B, and CDT (combined diphtheria and tetanus) vaccines.

Following clinical review 421/469 (90%) children were vaccinated in the SIS. Table 2 shows details of the vaccines administered to each child, for each presenting AEFI. Of the 421 children vaccinated, 257 received DTPa and 94 a monovalent acellular pertussis vaccine with or without diphtheria, tetanus, Hib, MMR, OPV, or Hep B vaccines. Forty eight (10%) children were not vaccinated following clinical review. However, in seven of these children (five with anaphylaxis, one with encephalopathy, one with thrombocytopenia) further vaccination with the suspect vaccine was contraindicated or not due, and in 18 children no further doses of the suspect vaccine were due. The parents of only 13 children refused the recommended vaccinations or failed to reattend the service to receive them.

Of the 421 children vaccinated, 350 (83%) experienced no subsequent AEFI. Seventy children (17%) experienced fever and/or a local reaction and/or lethargy within the seven day period post-vaccination. One of these 70 children required hospital admission four days following vaccination with an acellular pertussis vaccine. This child was subsequently diagnosed as having a lobar pneumonia which improved following intravenous penicillin. Only one of the 421 children vaccinated in the SIS experienced a significant AEFI and is likely to have experienced an HHE following re-vaccination. This child attended the SIS because he experienced fever, pallor, and irritability with screaming at 2 months of age following his first DTPw vaccine. At 4 months of age and following review in the SIS he was vaccinated with DTPa, Hib, and OPV vaccine. Approximately five hours after the vaccination

he became pale and hypotonic. This resolved spontaneously and no hospital admission was required. Subsequent to this event the child received a further DTPa vaccine without sequelae.

Of particular interest was the re-vaccination of children who presented with significant neurological reactions (HHE, convulsions, apnoea). In all 101 of the 130 children (78%), those who experienced these reactions post-vaccination with a pertussis containing vaccine were re-vaccinated with either a whole cell or acellular pertussis containing vaccine. All but five of these children received DTPa and none of these children experienced a recurrence of a significant AEFI.

Discussion

Communicating to parents the relative risks and benefits of vaccination is essential when deciding whether to vaccinate a child.¹² In children who have experienced an AEFI it is difficult for vaccine providers and parents to make this risk-benefit assessment when considering re-vaccination with the suspect vaccine. Although the benefits from immunisation may be easily defined, an assessment of risk is difficult. Firstly, there is a paucity of information about the risk of an AEFI recurring in such children. Secondly, a poor understanding of the pathogenesis of many AEFI, the lack of identifiable risk factors in individual children, and the uncommon occurrence of significant AEFI further complicates such assessments. Clinical vaccine studies and post-marketing surveillance provide an indication of the frequency of adverse reactions in the general population. They do not define the risk of recurrent reactions in children who have experienced an AEFI. The information presented in this report may help vaccine providers and parents to determine more accurately the risk of re-vaccinating children who have experienced an AEFI.

The majority of children who were seen in these services presented with fever, a local reaction, and/or screaming although a number had experienced a significant neurological

reaction (HHE, convulsions, apnoea, monoparesis, and encephalopathy). The whole cell pertussis component of the DTPw vaccine was thought to be associated with the majority of these reactions as the reactogenicity of this vaccine is well documented. Successful re-vaccination, with a vaccine containing acellular pertussis vaccine, occurred in most of these children. These findings further support a recent study from the Netherlands which investigated the risk of recurrence of HHE following repeat vaccination with a whole cell pertussis vaccine.¹³ In this study 84 children with a past history of HHE received 236 doses of whole cell pertussis vaccine, with no child experiencing a recurrence. However, recurrences of HHE have been documented following re-vaccination with whole cell pertussis vaccine and it has been suggested that re-vaccination should be avoided.¹⁴ The findings of our study suggest that acellular pertussis vaccine is a safe alternative in those children who have experienced significant neurological reactions following a whole cell pertussis vaccine. This is consistent with recent surveillance data from South Australia which show that minor and serious reactions and reactions requiring medical and hospital review were three times less common with a three component acellular pertussis vaccine than with a whole cell pertussis vaccine.¹⁵ In Australia DTPa has now replaced DTPw, and it remains to be seen if children presenting with AEFIs associated with DTPa administration can be successfully re-vaccinated using this vaccine.

It is clear that this cohort of children is a selective sample as the services did not capture all children who experienced an AEFI. In Australia vaccine coverage for three doses of pertussis-containing vaccines is estimated to be around 80%, which is considered suboptimal and lower than rates in the UK and the USA.¹⁶ The exact rate of AEFIs in Australia was not known nor was it known how many children with AEFIs were referred to a SIS and subsequently assessed. Ideally, the service would need to review a larger sample of children who experience an AEFI and determine the outcome of re-vaccination. Nevertheless, the vast majority of children attending these services in whom vaccination was indicated, were successfully re-vaccinated. This indicates that the parents attending the services were highly motivated to continue or complete their child's immunisation schedule. Further research is required to ascertain what factors determine which parents presented for review and whether this sample is representative of all children who have experienced an AEFI.

We consider that an SIS should be an essential component of an immunisation programme. Firstly, an SIS facilitates the continued immunisation of children who have experienced an AEFI. It was the anecdotal impression of the authors that many of these children would not have continued with the immunisation schedule or sought catch up

vaccination were it not for the SIS. This delay would increase the risk of vaccine preventable disease in these children and their communities. The SIS allowed the parents time to discuss the relative risks and benefits of re-vaccination with the suspect vaccine. In addition, parents were reassured that, if need be, their child could be observed and managed in hospital post-vaccination. Secondly, an SIS can be used to enhance the post-marketing surveillance of AEFI, thereby ensuring vaccine safety. The SIS should encourage parents and vaccine providers to refer children who have experienced a significant AEFI where further advice is needed by the parent and/or the vaccine provider. Clinical review in the SIS further clarifies the true nature of such reactions. Thirdly, the service conveys an important message to parents, vaccine providers, and the general community that AEFI do occur, are taken seriously by health providers, but rarely contraindicate further doses. This is of particular importance in counteracting the false claims of anti-immunisation groups which have a particular focus on AEFI.¹⁷ Lastly, an SIS should enhance current research regarding the clinical management and investigation of children with AEFI. The potential public health and individual benefits of an SIS need to be considered in planning a comprehensive immunisation programme.

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