Summary of Centre for Adverse Reactions Monitoring reports of MeNZB™ adverse events

Spontaneous reports
19 July 2004 to 30 June 2006

Intensive Vaccine Monitoring Programme
19 July 2004 to 30 September 2005

Prepared by the Centre for Adverse Reaction Monitoring
and the Meningococcal Vaccine Strategy Data Management Group
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List of Abbreviations

CARM:	Centre for Adverse Reactions Monitoring
CMDHB:	Counties Manukau District Health Board
DHB:	District Health Board
GPs:	General Practitioners
HCPs:	Health Care Professionals
HSB:	Health (care) Seeking Behaviour
HSP:	Henoch Schönlein Purpura
IMMP:	Intensive Medicines Monitoring Programme
ISMB:	Independent Safety Monitoring Board
IVMP:	Intensive Vaccines Monitoring Programme
MMR:	measles-mumps and rubella vaccine
NHI:	National Health Index
NIR:	National Immunisation Register
PMS:	Practice Management System
RTI:	Respiratory Tract Infection
SOC:	System Organ Class
SRP:	Spontaneous Reporting Programme
The Programme:	New Zealand's Meningococcal B Immunisation Programme
WHO:	World Health Organisation
WHOART:	WHO Adverse Reaction Terminology

Introduction

Post-marketing safety surveillance forms a key component of New Zealand's Meningococcal B Immunisation Programme (the Programme). The safety monitoring strategy comprises both passive and active monitoring methodologies. Whilst passive monitoring through the Centre for Adverse Reactions Monitoring (CARM) at the University of Otago, Dunedin, has been the cornerstone of New Zealand's national adverse drug reaction programme, as with all passive reporting systems, CARM's Spontaneous Reporting Programme (SRP) has many limitations. Such limitations include under-reporting, differing thresholds for reporting among health care professionals (HCPs) and, until the recent establishment of the National Immunisation Register (NIR), the absence of an accurate denominator.

Despite the fact that New Zealand has a high level of reporting of adverse events compared to other countries which are part of the World Health Organisation's (WHO) International Monitoring Programme for Drug Safety, HCPs were encouraged to lower their threshold for, and be even more diligent about, submitting reports on suspected events potentially linked to immunisation with the meningococcal serogroup B outer membrane vesicle vaccine (MeNZB™) in an attempt to reduce under-reporting. It was envisaged that this 'stimulated' SRP would further strengthen the chances of identifying rare events, whilst also providing some indication of the range of typical post-immunisation reactions.

In addition, the Intensive Vaccine Monitoring Programme (IVMP), an active surveillance strategy, was introduced to overcome some of the shortcomings with the SRP. The primary aims of the IVMP were:

i. To identify the occurrence of any significant event of a nature that may have implications for the continuation of the immunisation programme and
ii. To identify and measure the incidence of clinical conditions ('adverse events') requiring consultation with a HCP in the six weeks following immunisation with the MeNZB™ and/or routine immunisation schedule vaccines.

The safety profile of MeNZB™ was overseen and evaluated by an Independent Safety Monitoring Board (ISMB) composed of national and international advisors.

This report presents MeNZB™ vaccination adverse event data from both the SRP and IVMP.

1. For the SRP, health professionals voluntarily report adverse events in vaccinees of any age to CARM. SRP data are usually reported to the ISMB in the format of a line-listing documenting all adverse events for a particular individual's report, and a tabulation of reactions by System Organ Class (SOC). For this report the SRP data have been analysed in more detail, including the estimation of "rates" of adverse events and reactions by age group, using estimates for the population-at-risk (denominators) derived from the NIR.

2. The IVMP prospectively collects data on a cohort of children aged less than 5 years receiving immunisations in primary care settings. Clinical data routinely recorded in the primary care provider's Practice Management System (PMS) are electronically transferred through a secure health intranet to CARM where all health consultations captured in the six weeks following immunisation are assessed and assigned a degree of causal association with the immunisation.

The ISMB Formal Decision Report 2 (Reporting period 19 July to 28 November 2004) included preliminary IVMP data, primarily to provide an early indication of the adverse event pattern when MeNZB™ vaccinations were first administered in Counties Manukau District Health Board (CMDHB). More comprehensive reports summarising SRP and IVMP data were provided in both December 2005 and April 2006. For this final report, the data analysis period has been extended to 30 June 2006 for the SRP and to 30 September 2005 for the IVMP.

1 MeNZB™ spontaneous adverse event reporting assessments

1.1 Methodology

In the SRP, adverse events are reported to CARM using a standardised reply paid postcard that HCPs complete then post or fax to CARM.

On receipt of an adverse event report the details were entered in an electronic database established especially by CARM for the Programme and:

i. The reasons for each consultation were assessed and, where appropriate, an event term(s) was assigned using standard terms from the WHO Adverse Reaction Terminology (WHOART) dictionary. More than one adverse event may have been recorded for each consultation. The WHOART dictionary organises terms under SOC headings, with sub-hierarchies within each SOC[1].

ii. WHOART terms were further grouped into categories representing related clinical symptoms and signs that may cross SOCs, forming recognised clinical groupings. This 'Event Dictionary' (see Appendix 1) was used for analyses intended to facilitate the recognition of patterns of events or clinical presentations. For example, 'somatic-immune responses' includes the following adverse events: gastro-intestinal, fever, fever-related, general body symptoms and headache.

iii. Event terms were further assessed according to the following criteria based on standard WHO coding and terminology (see Appendix 2):
   - Causality (relationship to vaccine)
     Relationships of 'possible', 'probable' and 'definite' represent degrees of likely causal association, whilst 'unlikely' reflects coincidental events. Unlikely events represent background levels but may contain previously unrecognised signals.
   - Seriousness, ranging from not serious to life-threatening or death. Seriousness refers to an outcome that results in any of: hospitalisation, a life threatening event, intervention to prevent permanent impairment, persisting disability, death or a congenital effect. If no serious outcomes occur then the event is deemed to be not serious.
   - Severity (severe or not severe). Severity refers to the degree/extent of the event as defined by the reporter, or if the event meets predefined criteria such as resulting in hospitalisation, fever ≥ 40^0C, or a local reaction ≥ 10cm in any direction.
   - Outcome, where known

1.2 Overview of spontaneous reports following MeNZB™

From 19 July 2004 to 30 June 2006, over 3.0 million doses of MeNZB™ vaccine were administered, with almost 1.06 million individuals having received at least one dose of this vaccine. Over this same period 2,212 spontaneous reports of events following MeNZB™ vaccination were received by CARM referring to 2,107 unique vaccinees. For only 147 (7.0%) was a routine schedule vaccine given at the same time as MeNZB™. Overall, 1,109 (52.6%) of vaccinee reports were for females. Approximately 12.3% (n=258) were for Mäori, 2.9% (n=62)

[1] WHO letter; 1991(a): MIO/372/2/2

for Pacific, leaving 84.0% (n=1,769) for European/Other. In the New Zealand Census 2001 the ethnicity distribution among 0 to 19 year olds was 22.8%, 10.4%, and 66.8% respectively.
The most frequent individual event terms (irrespective of possible causal association with immunisation) are listed below (Table 1). Local injection site reactions, skin reactions, fever and gastrointestinal symptoms accounted for the most common reports submitted. The proportion of the total reports that these event terms represent are also included in Table 1.

Table 1: Most frequent individual event terms reported to CARM following MeNZB™ vaccination for the period 19 July 2004 to 30 June 2006 when over 3.0 million MeNZB™ doses were administered for all age groups

Event	Number of reports* received to 30 June 2006	Proportion of total reports* (%,n=2212) to 30 June 2006
Local injection site reactions	925	41.8
Skin reactions	804	36.3
Fever	705	31.9
Gastrointestinal symptoms	577	26.1
Headache	250	11.3
Musculoskeletal	165	7.5
Irritability	122	5.5
Syncope/fainting	88	4.0
Sleepiness/Somnolence	81	3.7
Seizure (non-febrile)	33	1.5
Febrile seizure	27	1.2

* Each report may include more than one reaction, therefore the proportion of all reports will total to > 100%.

1.3 Spontaneous reports of a more significant nature

Reports referring to event terms that were of a more significant nature included:

1.3.1 Hypersensitivity-type reports

- Urticaria (n=195)
- Periorbital oedema (n=35)
- Facial oedema (n=21)
- Bronchospasm/chest tightness (n=24)
- Angioedema (n=13)
- Erythema Multiforme (n=13)
- Anaphylactic-type events (n=9)
- Peripheral (limb) oedema (n=9)
- Stevens Johnson Syndrome (n=1)

Urticaria was the most commonly reported hypersensitivity adverse reaction. In 71.3% (n=139) of reports, urticaria occurred within 24 hours of immunisation with nearly half (n=91) of those cases recovering from the event at the time of reporting. Twenty-one (10.7%) of the reports for urticaria also had facial/periorbital oedema, angioedema or bronchospasm.

Six of nine reported anaphylactic-type reactions were not severe reactions, and three were for more significant reactions. One was reported as occurring approximately five hours post immunisation and resulted in overnight admission to hospital for observation. The other two occurred shortly following immunisation, one also presenting with urticaria, and both hospitalised

for observation. It is difficult to establish from the reports whether these events were classic anaphylactic reactions.

1.3.2 Seizures

Of the 33 non-febrile seizures (Table 1) 12 (36.3%) had a history of epilepsy or predisposing factors. In a further 12 reports, the convulsions were brief, often occurring in the context of a likely vasovagal reaction and a further 3 were not considered to be causally related.

Of the 27 febrile seizures (Table 1) three had a history of epilepsy or febrile convulsion, one had evidence of a concurrent infection (tonsillitis) and another three possibly had an upper respiratory tract infection at the time. In one instance the child was reported to be prone to febrile seizures. A further two of the reports occurred following MeNZB™ given concurrently with other routine immunisations, which in both cases, included measles-mumps-rubella (MMR) vaccine. Four reports were not considered to be causally related.

1.3.3 Haematological disorders

- Thrombocytopenia/Idiopathic thrombocytopenic purpura (n=6)

  Three were from one particular hospital clinician. In two reports the duration to onset was 2 and 5 days and the others ranged from 12-36 days. One of the reports occurred following MeNZB™ given concurrently with MMR vaccine. The remaining reports occurred following MeNZB™ only. One of these cases resided in the four most northern DHBs (Northern DHBs) and was captured by the hospital-based safety monitoring that was undertaken in this area.

- Henoch Schönlein Purpura (n=2)

  In one report of Henoch Schönlein Purpura (HSP), the duration to onset was one day and the other 10 days. The latter report of HSP documented a coryzal-like illness at about the same time as immunisation. Neither case lived in the Northern DHBs, and so these cases were not identified as part of the hospital-based safety monitoring.

1.3.4 Notable reports received but not considered to be associated with MeNZB™

- Kawasaki disease (n=2)

  In one child the duration to onset was 34 days and both went on to receive a 2nd MeNZB™ without exacerbation of their Kawasaki Disease. The other case developed Kawasaki Disease 6 days after a second MeNZB™ dose (MeNZB2) but no further information was provided. Both children live outside the four Northern DHBs and were therefore not captured in the hospital-based monitoring data.

- Wegeners Granulomatosis (n=1)

  In this case, symptoms began 2 weeks after a first MeNZB™ dose (MeNZB1) and was confirmed as Wegeners Granulomatosis following a positive biopsy. This case subsequently received MeNZB2 with the parents reporting some exacerbation of symptoms. However, subsequently some uncertainty around the exact diagnosis has been raised.

1.4 Number and crude rate of spontaneous reports by reaction group

Table 2 illustrates the number of reports received by reaction *group* (in contrast to Table 1 which lists individual event terms). For Table 2, the individual reaction terms have been grouped according to common post-immunisation clinical presentations (see Appendix 1 and Section 2.1.3.3 for details). For example, 'somatic-immune responses' includes the following adverse events: gastro-intestinal, fever, fever-related, general body symptoms and headache.

Table 2 also provides a crude "rate" for each of the reaction groups based on the number of vaccinees who received MeNZB™ by age group. This rate should be interpreted with caution as, although the denominator is an estimate measure of vaccinees receiving MeNZB™ obtained from the NIR, the numerator is incomplete as it is based on voluntary reporting and is likely to be subject to variable, and possibly substantial, under-reporting.

For all age groups the highest reaction group rates were for somatic immune responses (Table 2). Hypersensitivity-type events were the second most common events in the < 6 months, 6 to <19 months, and 5 to < 21 years age groups whilst in 19 months to < 5 years the localised events were the second most common events. The third most common events in the 6 to <19 months, and 5 to < 21 years age groups were localised events, with hypersensitivity-type events being the third most common in the 19 months to < 5 years age group. In the < 6 month olds, neurological irritability (persistent, abnormal or high pitched crying and irritability), at 0.43 reports per 1,000 vaccinees was the third most common reaction group.

The individual reaction term 'fever', which falls within the somatic immune responses reaction group, was in itself one of the highest rates for all age groups ranging from 0.46 to 1.44 per 1,000 vaccinees.

Reaction group report rates were generally higher for the 6 to < 19 months, and 19 months to < 5 years age groups compared with the two other age groups. For example, the rate of somatic immune responses was 1.89 and 1.62 per 1,000 in the 6 to < 19 months, and the 19 months to < 5 years age groups respectively, compared with 0.73 and 0.76 per 1,000 in < 6 month olds, and 5 to < 21 year olds.

Table 2: Number and spontaneous reporting rate (per 1,000 MeNZB™ age specific vaccinees) of adverse reaction groups and other selected reaction terms in vaccinees who received a MeNZB™ vaccine

Reaction Groups[1]	0 - <6 months	6 - <19 months	19 months - <5 years	5 to <21 years	Total
Localised events (injection site reactions)	21[2]	80	236	344	681
	0.31[3]	1.12	1.36	0.46	0.64
Somatic immune responses[4]	49	135	281	571	1036
... including	0.73	1.89	1.62	0.76	0.98
Fever	36	103	222	344	705
	0.53	1.44	1.28	0.46	0.66
Headache	0	0	14	236	250
	0.00	0.00	0.08	0.31	0.24
Vomiting	15	43	101	153	312
	0.22	0.60	0.58	0.20	0.29
Vaccine anxiety-type events (vasovagal related events)	12	10	52	210	284
	0.18	0.14	0.30	0.28	0.27
Hypersensitivity-type events	40	118	190	377	725
... including	0.59	1.65	1.09	0.50	0.68
Urticaria	10	20	56	109	195
	0.15	0.28	0.32	0.15	0.18
Convulsions and convulsion-like events ... including	3	9	27	30	69
	0.04	0.13	0.16	0.04	0.06
Convulsion	0	1	10	18	29
	0.00	0.01	0.06	0.02	0.03
Febrile convulsion	1	6	16	2	25
	0.01	0.08	0.09	0.00	0.02
Neurological irritability	29	73	54	5	161
	0.43	1.02	0.31	0.01	0.15
Sleep-related events	6	21	34	38	99
	0.09	0.29	0.20	0.05	0.09
Infections	0	1	5	19	25
	0.00	0.01	0.03	0.03	0.02
Haematological events	2	10	14	29	55
	0.03	0.14	0.08	0.04	0.05
Cardiovascular-related events	12	6	11	29	58
	0.18	0.08	0.06	0.04	0.05
Other (Miscellaneous) events	17	14	42	166	239
	0.25	0.20	0.24	0.22	0.23

1 A vaccinee may have more than one event in each grouping, but is only counted once in each heading.

2 Number of age specific spontaneously reported events.

3 Spontaneous reporting "rate" per 1,000 MeNZB™ age specific vaccinees.

4 A vaccinee may appear in more than one of the specific lower level terms where listed.

1.5 Summary of spontaneous reports following MeNZB™

For the period 19 July 2004 to 30 June 2006, the number of MeNZB™ spontaneous reports received by CARM (n=2,212) was approximately 1.3 times higher than the number received for non-MeNZB™ vaccines for the same age group (n=1,666). However, given the large volume of MeNZB™ doses given (over 3.0 million) compared with an estimate of the volume of routine childhood immunisations given (approximately 300,000 per year given a birth cohort size of around 50,000 children), the rate of reporting MeNZB™ adverse events was comparatively low.

The main pattern of reactions observed for MeNZB™ was that of local reactions (injection site pain/limb pain, injection site inflammation, injection site erythema, injection site mass); somatic immune responses (fever, headache, vomiting and musculoskeletal symptoms) and hypersensitivity (skin reactions – most commonly rashes, less frequently urticaria and much less frequently erythema multiforme; peri-orbital oedema and facial swelling, bronchospasm with occasional anaphylactic-type events).

Patterns of events observed have been in line with those considered to be common or expected adverse events following immunisation occurring with vaccines typically used in immunisation programmes[2] [3]. No significant safety issues have been raised based on spontaneous reports received in this programme. The presence of significant numbers of urticaria reports did lead to review and distribution of advice to vaccinators on administering subsequent MeNZB™ doses following a previous urticarial reaction with MeNZB™. The initial review for reports received to June 2005 noted that whilst urticarial reactions were observed within the first 24 – 48 hours post immunisation, recovery was reported in 47% of recipients. This supported the notion that these later onset urticarial events were likely to be type 3 immune complex reactions and unlikely to progress to a future type 1 anaphylactic event at re-immunisation. Therefore only urticarial events occurring within minutes (type 1, IgE mediated reaction) were recommended to be reason to review further immunisation.

Similar findings were made when the analysis was repeated for reports made to 30 June 2006; 71% of urticaria cases occurred within 24 hours of immunisation with nearly half (n=91) of those cases recovering from the event at the time of reporting. In a previous analysis to 27 March 2006 reported to the ISMB, of 291 hypersensitivity reactions (anaphylactic type reaction angiodema, bronchospasm, urticaria, facial oedema) 162 reactions were in individuals who went on to receive subsequent doses without a recurrence reported.

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[2] *Immunisation Safety Surveillance – Guidelines for managers of immunisation programmes,* 1999, immunisation focus, World Health Organisation, Regional Office for the Western Pacific, Manila.
[3] *Immunisation Handbook 2002,* Wellington: Ministry of Health.

2 MeNZB™ adverse events assessed in the Intensive Vaccine Monitoring Programme (IVMP)

2.1 Methodology

2.1.1 Design of the IVMP

The IVMP prospectively collected data on a cohort of children receiving immunisations in primary care. The primary aims of the IVMP were:

iii. To identify the occurrence of any significant event of a nature that may have implications for the continuation of the immunisation programme and

iv. To identify and measure the incidence of clinical conditions ('adverse events') requiring consultation with a HCP in the six weeks following immunisation with the MeNZB™ and/or routine immunisation schedule vaccines.

Clinical data routinely recorded in MedTech32®, a PMS software package, on all immunisations administered, and all subsequent health consultations at the vaccinee's own practice in the six weeks following an immunisation, are electronically transferred through a secure health intranet to CARM for analysis. The data extraction operated automatically within the PMS with no extra compliance burden for the HCP. At CARM, all health consultation visits in the six weeks following immunisation ('consultations') were assessed and clinical events assigned a degree of causal association with the immunisation.

2.1.1.1 Source of monitoring cohort (sentinel practices)

The IVMP cohort was established from 35 medical centres, known as 'sentinel practices', recruited from across New Zealand. Medical centres were selected if they were using MedTech32® PMS, were willing to participate in the IVMP, and if they were medical centres with a large infant cohort.

Preference was given to practices that would contribute to establishing a cohort that would reflect the ethnic and socio-demographic diversity of the New Zealand population in the age groups being monitored. The Programme first started in Counties Manukau District Health Board (CMDHB) and therefore this area required the most intensive safety monitoring. Because CMDHB has a high Mäori and Pacific population and HCP attendance patterns are known to differ between ethnic groups[4], Mäori and Pacific providers were actively sought for the IVMP, and hence were over-sampled.

2.1.1.2 The monitoring cohort

The New Zealand-wide cohort consists of children registered at a sentinel practice who received an immunisation (routine or MeNZB™) from six weeks up to but not including 19 months of age. In CMDHB the monitoring cohort was also extended to include children aged up to but not including five years of age to supplement the SRP in the area where the Programme first started, providing an additional mechanism to detect early indications of adverse events in the older age group.

Children were recruited at the time they received any immunisation at one of the selected 'sentinel practices'. Immunisations to children registered with the sentinel practices, but given by a different provider, were not monitored.

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[4] *A Portrait of Health: Key results of the 2002/03 New Zealand Health Survey*, 2004, Wellington: Ministry of Health.

All parents/guardians were advised of the IVMP and given an information pamphlet at the time of immunisation. Parents could opt out by asking the practice to withdraw their child from the monitoring programme. Data from these children were not electronically messaged to CARM.

2.1.2 Ethical approval

The IVMP received National Ethics Approval through the Otago Ethics Committee as lead committee. Ethics reference No. OTA/03/09/097.

2.1.3 Data collection and management

2.1.3.1 Data extraction

MedTech32®-designed software extracted routinely entered information relating to each eligible patient's demographic data, immunisations, and consultations (including medications, other provider visits, and referral letters). In addition, existing medical conditions and medications prescribed in the 30 days prior to the immunisation were also extracted. Each patient was uniquely identified using their National Health Index (NHI) number.

2.1.3.2 Data transfer and management

All data were electronically transferred to CARM through a secure health intranet. The data were parsed and stored in appropriate data fields under each patient's NHI. All data were electronically collated by vaccination visit and assessed by a medical assessor at the completion of the six-week period following that visit.

2.1.3.3 Data assessment process

The data assessment process for the IVMP was undertaken using the same procedures as SRP (see section 1.1). In summary, event terms were assigned by a medical assessor using standard terms from the WHOART dictionary and assessed for severity and causality, and the consultation assessed for seriousness and outcome. Event terms were also grouped for analysis into categories representing related clinical symptoms (Appendix 1). Where a vaccinee did not return for any clinical consultation they were deemed by default to have been event free following immunisation.

2.1.3.4 Quality control

Quality control measures included strategies to identify obvious misclassification errors through exception reporting according to pre-specified parameters. This involved line listing review of assessments coded as vaccine related, but generally considered to be unlikely to be associated, which were rechecked and/or corrected (e.g. Injury, Upper Respiratory Tract Infection). Other coding errors searched for review and possible correction included causal events with duration to onset of >7 days, or rare terms. In addition, to determine the reliability (reproducibility) between medical assessors, an experienced medical assessor re-evaluated 200 randomly selected vaccination visits (refer section 2.1.4.6). Although the IVMP operated on the basis of every eligible child being incorporated into the cohort, parents or caregivers were able to opt out of the monitoring programme. When this occurred, the sentinel practice made an appropriate software entry which disabled data transfer for that patient and resulted in an electronic message to the IVMP that a single patient had opted out from the practice. No details of the patient opting out were sent.

2.1.4 Data analysis

2.1.4.1 Definitions

- 'Vaccinee' – any child who received one or more immunisations at any one of the sentinel practices
- 'Vaccination visit' - any visit to the sentinel practice at which one or more immunisations (routine or MeNZB™) were given
- 'Consultation' - any visit in the six weeks following immunisation to the sentinel practice at which the vaccination visit took place
- 'Adverse event' - any clinical condition requiring a consultation in the six weeks following vaccination, irrespective of the relationship with vaccination
- 'Reaction' – an adverse event assessed as being possibly, probably, or definitely related to a vaccination
- Routine vaccination – any vaccine that was part of the New Zealand standard immunisation schedule
- MeNZB™ only vaccination – a vaccination visit where only the MeNZB™ vaccine was received
- Hybrid vaccination – a vaccination visit where any of the Routine and a MeNZB™ vaccine were received

2.1.4.2 Age groupings and time period of analysis

All analyses in this report were conducted in three age groups: less than 6 months old, 6 to less than 19 months old, and 19 months to less than 5 years old. The primary purpose of these analyses was to evaluate the potential risks of adverse events that may be attributable to MeNZB™.

- For children aged less than 6 months, vaccination visits that occurred from 3 February 2005 (Programme start date for this age group) through 30 September 2005 were assessed.
- For children aged 6 months to less than 5 years, vaccination visits were assessed from 19 July 2004 (Programme start date for these ages) to 15 November 2004. This end point was chosen because assessments at the time of analysis had only been completed to this point.

2.1.4.3 Units of observation and Data Extraction

Two units of observation are presented in this report:

(i) By Vaccinee – where the age group, sex and ethnicity of the children immunised were analysed.

(ii) By Vaccination-visit – where events related to a particular vaccination-visit were analysed. (NB: Individual vaccinees could have one or more vaccination visits recorded in the dataset). Analysis 'by vaccination-visit' therefore assumes there is no cumulative risk of adverse effects with repeated vaccination.

Data were extracted from the IVMP database into two separate Microsoft Excel® spreadsheets; one by vaccinee and the other by vaccination-visit. All statistical analyses were performed using SAS v9.1.

2.1.4.4 By Vaccinee Analysis

2.1.4.4.1 Descriptive analysis

Descriptive analyses were conducted to characterise vaccinees by age, sex and ethnicity.

2.1.4.4.2 Cumulative dosing effects

Dose inter-dependence was studied in 'pure' Hybrid and MeNZB™ cohorts (see Appendix 3). This was undertaken to consider whether the risk of experiencing an adverse effect or reaction following MeNZB™ is higher among children who experienced any similar adverse effect / reaction following a previous MeNZB™ dose. However, despite extensive efforts, we were unable to assess the possibility of dose-interdependence, as many issues with respect to the data remain unresolved (refer Appendix 3).

2.1.4.5 By Vaccination Visit Analysis

2.1.4.5.1 Descriptive analysis

The 'by vaccination visit' descriptive analyses were confined to vaccination visits where a dose of MeNZB™ only was administered in each of the three age groups and the relevant time frames (section 2.1.4.2).

2.1.4.5.2 Comparative analysis: MeNZB™ + Routine compared with Routine vaccines in children aged less than six months of age

Comparative analyses were undertaken to evaluate whether MeNZB™ given concurrently with the routine immunisations carries any greater risk of adverse events or reactions as compared to routine only immunisation and to characterise the nature and extent of any effects found.

This analysis was conducted within the less than 6 month age group assessing differences in the magnitude and distribution of risks between two vaccination visit categories, comprising visits during which routine childhood immunisation schedule vaccines were administered alone ('Routine') compared with concurrent administration of routine childhood immunisation schedule vaccines and MeNZB™ ('MeNZB™ + Routine').

For the descriptive and comparative analyses, we used rates and mean numbers of adverse events as summary measures of absolute risk:

- Rates – the number of consultations with ≥ 1 adverse event (or ≥ 1 reaction) in the six weeks following the vaccination visit per 1,000 vaccination visits (note any one consultation can have multiple adverse events e.g. fever, injection site reaction and headache)
- Means – the average number of adverse events (or reactions) per vaccination visit.

No formal tests were performed to assess the presence of statistically significant differences in rates or means between vaccination visit categories due to the fact that individual vaccines could—and did—appear in both of the vaccination visit categories, thereby violating the assumption of independence of events.

2.1.4.6 Reliability of medical assessor judgements

Inter-rater reliability for key judgements made by the medical assessors was calculated using the kappa statistic. Kappa is a chance-corrected index of agreement and reliability of 0.40 or less is considered poor agreement, 0.41 to 0.60 considered moderate agreement, 0.61 to 0.80 good and 0.81 to 1.00 very good agreement[5]. Confidence intervals were also calculated with asymptotic standard error using SAS[6].

[5] Landis JR and Koch GG (1977). The measurement of observer agreement for categorical data. *Biometrics*. 33(1):159-174.

[6] Stokes ME, Davis CS, Koch GG (1995). Categorical data analysis using the SAS system. SAS Institute Inc., Cary NC, USA.

2.2 *Results*

The parents of 10 children opted out of the monitoring via the IVMP system. Although the IVMP has received data on 17,921 vaccinees who have had 52,754 vaccination visits of which 30,369 (57.6% of the total number of vaccination visits) have been assessed, this report is based on the analysis of a subset limited to 10,308 (57.5%) vaccinees and 19,257 (36.5%) vaccination visits (Data flow is shown in Figure 1).

The restriction of the observation period used in all analyses was necessary to ensure that all types of vaccines/vaccine combinations were administered to study participants in each age group during the defined study period. Since the cohort contains vaccinees of a wide spectrum of ages from 6 weeks to 5 years, as well as a multiplicity of permutations of MeNZB serial dose exposures, with and without the co-administration of other vaccines, it has been necessary to further stratify the cohort into a number of logical, but inevitably smaller cohorts to facilitate analysis. As a consequence of this, some sub-cohorts may be considered too small to provide enough precision for the interpretation of the findings. Furthermore, due to potential biases (discussed more completely below) that may have affected the validity of the data, these findings should be interpreted with caution.

Moderate agreement between medical assessors (kappa = 0.55, 95%CI 0.47-0.63) was found for the number of events coded per vaccination visit. Very good agreement (kappa = 0.91, 95%CI 0.85-0.96) was found for the relationship (causality) assessment of event and very good agreement was also found for the severity of event (kappa = 0.97, 95%CI 0.93-1.0).

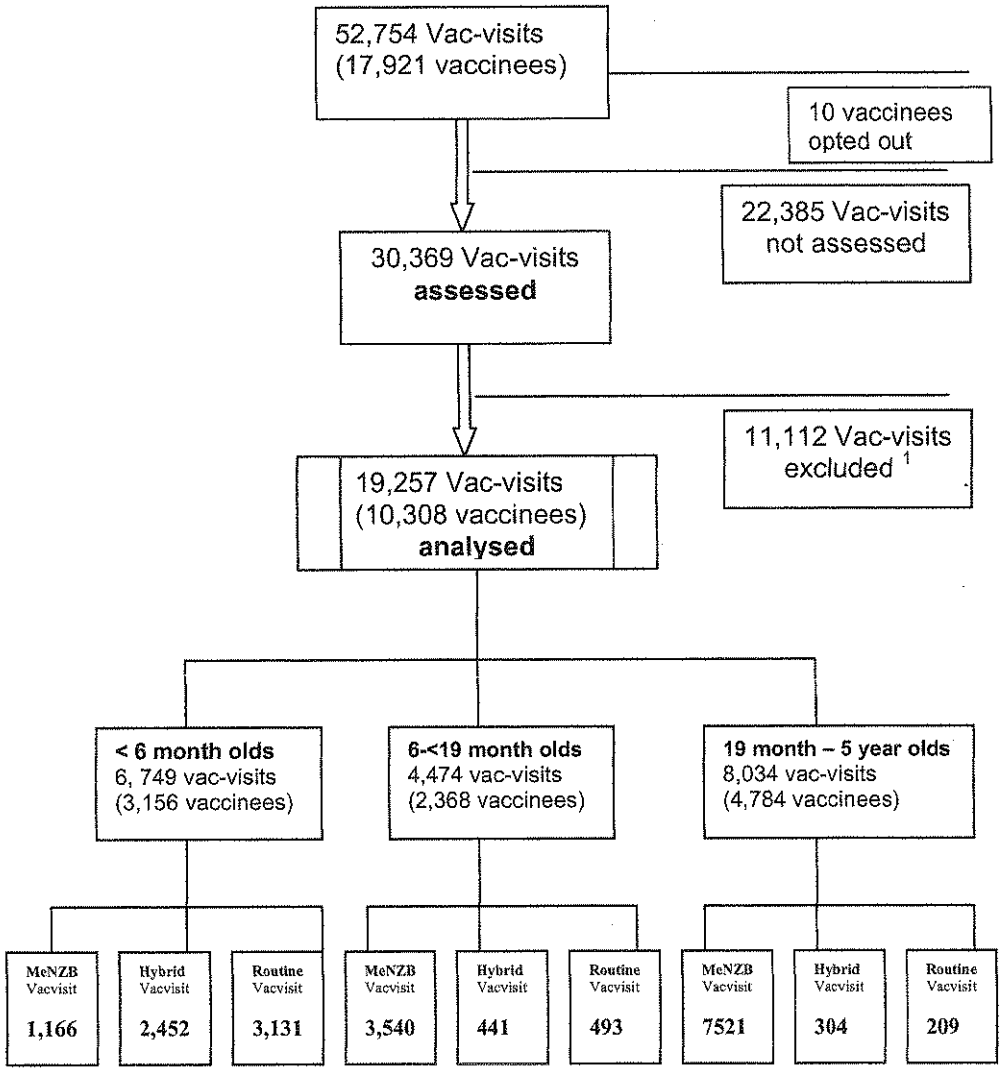

Figure 1: Flow chart of vaccination visits

1 Outside of defined time periods:

- < 6 month olds, 03 Feb. 2005 - 30 Sep. 2005
- ≥ 6 month olds, 19 Jul. 2004 - 15 Nov. 2004

2.2.1 By Vaccinee Analysis

2.2.1.1 Descriptive Analysis

There were 3,156 (30.6%), 2,368 (23.0%) and 4,784 (46.4%) vaccinees respectively in less than 6 months, 6 to <19 months, and 19 month to 5 years old during the relative study periods. There were approximately equal numbers of males and females in all age groups (Table 3).

Table 3 Number (%) of vaccinees, by sex and age group

Sex	< 6 months[1]		6 to < 19 months[2]		19 months to < 5 years[2]		Total	
	Number	Proportion %	Number	Proportion %	Number	Proportion %	Number	Proportion %
Male	1609	51.0	1250	52.8	2429	50.8	5288	51.3
Female	1529	48.5	1109	46.8	2351	49.1	4989	48.4
Unknown	18	0.6	9	0.4	4	0.1	31	0.3
Total[3]	3156	100.0	2368	100.0	4784	100.0	10308	100.0

1. 3 February 2005 to 30 September 2005
2. 19 July 2004 to 15 November 2004
3. Total percentages may not add to 100.0 due to rounding

As practices with high Mäori and Pacific populations were over-sampled, the proportion of vaccinees by Mäori and Pacific children are disproportionately high compared with ethnicity recorded by the New Zealand Population Census. Approximately 28% vaccinees represented in the IVMP dataset were Mäori, 37% for Pacific, and 34% for European/Other/Unspecified (Table 4). This compares with New Zealand Census 2001 figures of 22.8%, 10.4%, and 66.8% for Mäori, Pacific and European/Other/Unspecified, respectively, for those aged under five years.

Table 4 Number (%) of vaccinees, by ethnicity and age group

Ethnicity	< 6 months[1]		6 to < 19 months[2]		19 months to < 5 years[2]		Total	
	Number	Proportion %	Number	Proportion %	Number	Proportion %	Number	Proportion %
ä	744	23.6	661	17.9	1527	31.9	2932	28.4
Pacific	741	23.5	918	38.8	2178	45.5	3837	37.2
European	1284	40.7	445	18.8	383	8.0	2112	20.5
Other	375	11.9	300	12.7	688	14.4	1363	13.2
Unspecified	12	0.4	44	1.9	8	0.2	64	0.6
Total[3]	3156	100.0	2368	100.0	4784	100.0	10308	100.0

1. 3 February 2005 to 30 September 2005
2. 19 July 2004 to 15 November 2004
3. Total percentages may not add to 100.0 due to rounding

2.2.1.2 Cumulative Dosing Effects

The possibility of dose-interdependence was unable to be assessed due to multiple unresolved issues with respect to the data. A discussion of the challenges encountered and solutions explored in extensive efforts to resolve these issues are provided in Appendix 3.

2.2.2 By Vaccination-visit analysis

2.2.2.1 Descriptive analyses: MeNZB™ only vaccination visits in children aged less than five years of age

2.2.2.1.1 Adverse Events

Over 50% of vaccination visits in the two younger age groups and almost 40% of vaccination visits in the 19 month to < 5 year age group resulted in at least one adverse event (Table 5). For both the total adverse events and vaccination visits with at least one adverse event, there seemed to be an inverse gradient between age and the crude overall rate and mean number of adverse events. In all age groups, infections, hypersensitivity-type events, and somatic immune responses were the most frequently recorded types of adverse events (excluding 'other miscellaneous events')(Table 6).

Table 5: MeNZB™ only recipients, number, crude rate (consultations with ≥1 adverse event[3] per 1,000 vaccination visits[4]), and crude means (average number of adverse events/reactions[5] per vaccination visit) of all adverse events and reactions, by age group

	< 6 months[1]		6 to < 19 months[2]		19 months to < 5 years[2]	
	Number	Crude Rate/Mean	Number	Crude Rate/Mean	Number	Crude Rate/Mean
Number of MeNZB™ only vaccination visits	1166	n/a	3540	n/a	7521	n/a
Adverse Events						
Total adverse events (mean)	1273	1.092	3802	1.074	5026	0.668
Visits with ≥1 adverse event (rate)	641	549.74 per 1000 vaccination visits	1873	529.10 per 1000 vaccination visits	2729	362.85 per 1000 vaccination visits
Total severe adverse events (mean)	10	0.086	102	0.029	102	0.014
Visits with ≥1 severe adverse event	10	8.58 per 1000 vaccination visits	78	22.03 per 1000 vaccination visits	80	10.64 per 1000 vaccination visits
Reactions						
Total reactions (mean)	96	0.082	300	0.085	374	0.050
Visits with ≥1 reaction (rate)	58	49.74 per 1000 vaccination visits	211	59.60 per 1000 vaccination visits	247	32.84 per 1000 vaccination visits
Total severe[6] reactions (mean)	0	0.000	17	0.004	25	0.003
Visits with ≥1 severe reaction (rate)	0	0.00 per 1000 vaccination visits	13	3.67 per 1000 vaccination visits	20	3.32 per 1000 vaccination visits

1. 3 February 2005 to 30 September 2005
2. 19 July 2004 to 15 November 2004
3. Adverse event = any clinical condition requiring a consultation in the six weeks following vaccination
4. Vaccination visit = visit to a sentinel practice at which one or more immunisations (routine or MeNZB™) were given
5. Reaction = adverse event assessed as being possibly, probably, or definitely related to vaccination
6. Severe = one or more of: reference to severity in the clinician's notes, hospitalisation, a life threatening event, fever ≥ 40°C, or an injection site reaction ≥ 10cm in any direction

Table 6: MeNZB™ only recipients, number and crude means (average number of adverse events[3]/reactions[4] per vaccination visit) of specific adverse events and reactions, by age group

Reaction groups	< 6 months[1] (n=1166)		6 to < 19 months[2] (n=3540)		19 months to < 5 years[2] (n=7521)	
	Total Adverse Events	Crude Reactions	Total Adverse Events	Crude Reactions	Total Adverse Events	Crude Reactions
Localised events (injection site reactions)	12	12	23	15	48	40
	0.010	0.010	0.007	0.004	0.006	0.005
Somatic immune responses	109	21	637	185	835	226
	0.094	0.018	0.180	0.052	0.111	0.030
Vaccine anxiety-type (vasovagal related events)	2	1	5	2	7	3
	0.002	0.001	0.001	0.001	0.001	0.000
Hypersensitivity-type events ...including	297	36	689	60	949	76
	0.255	0.031	0.195	0.017	0.126	0.010
Urticaria	3	1	20	4	44	10
	0.003	0.001	0.006	0.001	0.006	0.001
Convulsion/convulsion-like events	5	1	3	1	9	2
	0.004	0.001	0.001	0.000	0.001	0.000
Neurological irritability	40	17	35	16	12	4
	0.034	0.015	0.010	0.005	0.002	0.001
Sleep-related events	13	3	11	8	11	1
	0.011	0.003	0.003	0.002	0.002	0.000
Injury	11	0	77	0	241	0
	0.010	0.000	0.022	0.000	0.032	0.000
Infections	600	2	1937	3	2410	2
	0.515	0.002	0.547	0.001	0.320	0.000
Haematological	10	0	40	4	52	8
	0.009	0.000	0.011	0.001	0.007	0.001
Cardiovascular-related events	1	0	3	0	4	1
	0.001	0.000	0.001	0.000	0.001	0.000
Other miscellaneous events	173	3	342	6	448	11
	0.148	0.003	0.097	0.002	0.060	0.002

1. 3 February 2005 to 30 September 2005
2. 19 July 2004 to 15 November 2004
3. Adverse event = any clinical condition requiring a consultation in the six weeks following vaccination
4. Reactions are adverse events assessed as possibly, probably or definitely related to vaccination

2.2.2.1.2 Reactions

In all age groups, fewer than 6% of vaccination visits resulted in at least one reaction (i.e. a rate less than 60 per 1,000 vaccination visits, Table 5). The 6 to < 19 months age group had the highest overall mean number of total reactions (0.085), and the highest crude overall rate of at least one reaction per vaccination visit (59.60 per 1,000 vaccination visits).

With regard to specific reactions, somatic immune responses and hypersensitivity-type events comprised the top two reaction groups in all three age groups (albeit their rank was reversed in <

6 month olds), but the relative ranking of other specific reaction groups differed among the different age groups (Table 6). The 6 to < 19 months age group had the highest mean number of somatic immune response reactions (0.052 reactions per vaccination visits), approximately one and half times higher than the oldest age group (0.030), and around three times higher than the youngest age group (0.018). The crude mean number of hypersensitivity-type reactions was highest in the < 6 months age group (0.031) and lowest in the 19 months to < 5 years age group (0.010).

Although the third most common reaction in the < 6 month age group, overall, the total number of neurological irritability reactions (persistent, abnormal or high pitched crying and irritability) was low (n=17). The mean number of neurological irritability reactions in the youngest age group (0.015) was more than double that of the two older age groups (0.005, 0.001 respectively).

2.2.2.2 Comparative Analyses: MeNZB™ + Routine compared with Routine vaccines in children aged less than six months of age

The comparative analysis examined a total of 5,583 vaccination visits comprising 3,131 (56.1%) Routine and 2,452 (43.9%) MeNZB™ + Routine vaccination visits. For both vaccination visit categories the proportion of visits attended by males and females were similar (Table 7), and the proportion of vaccination visits attended by Mäori or Pacific children were higher than the proportion of the New Zealand Census population for this age group (Table 8, refer section 2.2.1 for Census populations).

Table 7: Number (%) of vaccination visits, 3 Feb 05 to 30 September 05, age less than 6 months, by sex

Sex	MeNZB™ + Routine		Routine		Total	
	Number	Proportion %	Number	Proportion %	Number	Proportion %
Male	1247	50.9	1604	51.2	2851	51.1
Female	1194	48.7	1506	48.1	2700	48.4
Unknown	11	0.5	21	0.7	32	0.6
Total[1]	2452	100.0	3131	100.0	5583	100.0

1 Total percentages may not add to 100.0 due to rounding

Table 8: Number (%) of vaccination visits, 3 Feb 05 to 30 September 05, age less than 6 months, by ethnicity

Ethnicity	MeNZB™ + Routine		Routine		Total	
	Number	Proportion %	Number	Proportion %	Number	Proportion %
Pacific	563	23.0	734	23.4	1297	23.2
Mäori	613	25.0	642	20.5	1255	22.5
European	1010	41.2	1280	40.9	2290	41.0
Other	262	10.7	456	14. 6	718	12.9
Unspecified	4	0.2	19	0.6	23	0.4
Total[1]	2452	100.0	3131	100.0	5583	100.0

1 Total percentages may not add to 100.0 due to rounding

Fundamental to this analysis is the assumption that there is no dose interdependence of adverse effects. Due to limitations in the data, this question remains unanswered (Appendix 3), so the comparative rates of adverse events and reactions should not be relied upon with confidence.

2.2.2.2.1 Adverse Events

Almost half of vaccination visits in both vaccination visit categories resulted in at least one adverse event (Table 9). The crude overall mean number of adverse events was comparable in the two vaccination visit categories (0.956 versus 1.011), as were the crude overall rates of at least one adverse event (478 versus 473 per 1,000 vaccination visits).

Infections were the most frequently recorded adverse event group for both vaccination visit categories (Table 10), followed by hypersensitivity-type events, somatic immune responses, neurological irritability, then haematological events (excluding "other miscellaneous events").

Table 9: Number, rate (consultations with ≥1 adverse event[1] per 1,000 vaccination visits[2]), and crude means (average number of adverse events/reactions[3] per vaccination visit) of all adverse events/reactions, 3 Feb 05 to 30 September 05, age less than 6 months

	MeNZB™ + Routine		Routine	
	Number	Crude Rate/Mean	Number	Crude Rate/Mean
Number of vaccination visits	2452	n/a	3131	n/a
Adverse events				
Total adverse events (mean)	2345	0.956	3165	1.011
Visits with ≥1 adverse event (rate)	1173	478.39 per 1,000 vaccination visits	1480	472.70 per 1,000 vaccination visits
Total severe adverse events (mean)	52	0.021	56	0.018
Visits with ≥1 severe adverse events (rate)	49	20.00 per 1,000 vaccination visits	47	15.01 per 1,000 vaccination visits
Reactions				
Total reactions (mean)	244	0.100	299	0.096
Visits with ≥1 reactions (rate)	135	55.06 per 1,000 vaccination visits	161	51.42 per 1,000 vaccination visits
Total severe[4] reactions (mean)	2	0.001	0	0.000
Visits with ≥1 severe reactions (rate)	2	0.82 per 1,000 vaccination visits	0	0.00 per 1,000 vaccination visits

1. Adverse event = any clinical condition requiring a consultation in the six weeks following vaccination
2. Vaccination visit = visit to a sentinel practice at which one or more immunisations (routine or MeNZB™) were given
3. Reaction = adverse event assessed as being possibly, probably, or definitely related to vaccination
4. Severe = one or more of: reference to severity in the clinician's notes, hospitalisation, a life threatening event, fever ≥ 40°C, or an injection site reaction ≥ 10cm in any direction

Table 10: Number and crude means (adverse events/reactions per vaccination visit) of specific adverse events[1] and reactions[2] within six weeks after vaccination, 3 Feb 05 to 30 September 05, age less than 6 months

Reaction groups	MeNZB™ + Routine		Routine	
	Total Adverse Events	Reactions	Total Adverse Events	Reactions
Localised events (injection site reactions)	16	15	27	21
	0.007	0.006	0.009	0.007
Somatic immune responses	236	81	333	98
	0.096	0.033	0.106	0.031
Vaccine anxiety-type (vasovagal related events)	8	5	10	5
	0.003	0.002	0.003	0.002
Hypersensitivity-type events ...including	537	76	706	89
	0.219	0.031	0.226	0.028
Urticaria	3	0	10	4
	0.001	0.000	0.003	0.001
Convulsion/convulsion-like events	2	0	4	0
	0.001	0.000	0.001	0.000
Neurological irritability	85	40	131	50
	0.035	0.016	0.042	0.016
Sleep-related events	24	12	34	13
	0.010	0.005	0.011	0.004
Injury	22	0	18	0
	0.009	0.000	0.006	0.000
Infections	1098	7	1367	14
	0.448	0.003	0.437	0.005
Haematological	10	1	19	3
	0.004	0.000	0.006	0.001
Cardiovascular-related events	4	2	5	1
	0.002	0.001	0.002	0.000
Other miscellaneous events	303	5	511	5
	0.124	0.002	0.163	0.002

1. Adverse event = any clinical condition requiring a consultation in the six weeks following vaccination
2. Reaction = adverse event assessed as being possibly, probably, or definitely related to vaccination

2.2.2.2.3 Reactions

In both vaccination visit categories, just over 5% of vaccination visits resulted in at least one reaction (i.e. crude rates of 55.06 and 51.42 per 1,000 vaccination visits respectively, Table 9). In addition, there appeared to be little difference in the crude overall mean number of reactions (0.100 for MeNZB™ + Routine, 0.096 for Routine). There were only two reactions assessed as severe, and both occurred following a MeNZB™ + Routine vaccination visit.

The top four reaction groups in both vaccination visit categories were somatic immune responses followed by hypersensitivity-type events, neurological irritability, and localised events (Table 10). The crude mean number of somatic immune responses and hypersensitivity-type events were similar in the MeNZB™ + Routine vaccination visit group and the Routine

vaccination visit group (0.033 cf. 0.031 and 0.031 cf. 0.028). The crude mean number of neurological irritability reactions (0.016) was found to be identical for both vaccination visit categories.

2.3 *Discussion of adverse event reports assessed in the IVMP*

2.3.1 Key findings

The exceedingly low opt-out rate given the size of the cohort provides reassuring evidence for the degree of patient compliance and support for the monitoring programme that is not easily matched by other community based monitoring programmes. In addition it provides confidence that loss to follow-up arising from opt-out attrition is not a factor for this study.

No clinically significant individual events and / or patterns of concern that may have warranted consideration of reviewing the continued roll-out of the programme were retrospectively identified in the IVMP cohorts assessed. The IVMP methodology was designed to overcome reporting bias and barriers that may be present in the SRP through direct access to and review of consultation notes; however, there are important questions about the validity and representativeness of this data set that remain to be fully understood and, if possible, resolved.

The results of the (so-called) "by vaccination" visit analyses presented above suggest a remarkably low rate of MeNZB™ related adverse reactions, both overall and with respect to most specific reaction group types. Similarly, the absolute magnitude and distribution of reactions/reaction group types are in themselves generally unremarkable and consistent with post-immunisation occurrences typically listed for standard immunisation programme vaccines[7]. Fewer than 6% of vaccination visits at which MeNZB™ doses were administered were associated with at least one reaction, regardless of the age of the vaccinee. Furthermore, the occurrence of reactions that were assessed to be clinically severe was rare following administration of MeNZB™.

Considering that the observed adverse events and reactions largely comprise localised events, somatic immune responses and mild hypersensitivity reactions, these findings, particularly in the absence of severe reactions, are consistent with results gleaned from other aspects of the overall MeNZB™ safety monitoring efforts in offering some reassurance about the safety of the MeNZB™ vaccine in the age groups monitored. Nonetheless, even though the relatively high mean number of adverse events for infection-related events (largely upper respiratory tract infections and related episodes) are generally consistent with background levels of such events typical for GP consultations in these age groups, these and other adverse events assessed as unrelated to vaccination may require further scrutiny to determine any possible occult association with MeNZB™ immunisation.

2.3.2 Limitations

New System

The IVMP is based on a sentinel reporter/practice model that has been previously used in other parts of the world in disease surveillance and other related applications[8] [9]. This model offers a

[7] *Immunisation Handbook 2002*, Wellington: Ministry of Health.
[8] Coulter D. *PEM in New Zealand*. Chichester: John Wiley & Sons, 2002

potentially powerful means of obtaining data on clinical encounters at the practice level. Overall, the debut of this system in New Zealand worked reasonably well, imposing only a minimal burden on participating HCPs (after a few technical problems encountered during the start-up phase were resolved) while providing valuable demographic and clinical information on a large number of vaccine-eligible children from throughout New Zealand. However, as with any new system, conceptual and operational problems occurred.

Sample size restrictions

To some extent, this study is limited due to the manner in which the cohort for analysis was extracted which as a consequence of *a priori* age groupings, made the sub-cohort groupings small. The restriction of the observation period used in all analyses was however necessary to ensure that all types of vaccines/vaccine combinations were administered to study participants in each age group during the defined study period.

Representativeness of the sample

The nature of the recruitment process and eligibility criteria for participating GP-practices, including patient recruitment campaigns by some individual practices, may have adversely affected the representativeness of the sample of vaccine-eligible children. Although the extent, and ultimate impact, remains to be fully evaluated, there are strong indications that Pacific and Mäori children were over-represented, and European children under-represented in the IVMP dataset on which these initial analyses were based.

Effects of health seeking behaviour and effects of general practices

In addition, there was evidence of differences in so-called health care seeking behaviour (i.e., wherein MeNZB™ recipients appeared to be more likely to attend their GPs with higher frequency than did recipients of other vaccines). There also appeared to be differences in the number and detail of GP-reporting by vaccine group (i.e., wherein GP practices that were more likely to administer MeNZB™ seemed to report more post-immunisation visits and recorded more clinical details about these consultations). Furthermore, in addition to the possibility of introducing independent biases, these two phenomena appeared to be related.

Partial assessment of immunisation exposure

Another important issue that remains to be resolved is the fact that the complete immunisation exposure for many of the children included in the IVMP database has only been partially assessed for this report. The IVMP data-collection process generated a massive amount of data, which resulted in a backlog of records that required review by the medical assessors at CARM. Thus, until all outstanding immunisation visits are assessed and included in a more complete analysis, there will be some question as to whether the subset of data that was used in generating the foregoing results are a valid and accurate reflection of all vaccinees and vaccination visits.

Factors affecting subsequent analyses

Cumulative dosing effects Not only is the presence of dose-dependence important in informing parents and GPs of such possible effects, but also it largely determines the nature and type of subsequent statistical analyses that must be performed in order to characterise the risk-

[9] Lakshman R, Jones I, Walker D, McMurtrie K, Shaw L, Race G, et al. Safety of a new conjugate meningococcal C vaccine in infants. *Arch Dis Child* 2001;85(5):391-7.

profile of MeNZB™. Specifically, if the risk of an adverse event/reaction is dose-dependent, then the type of analyses of 'vaccination visits' presented earlier in this report will almost certainly yield over-estimates of absolute and relative risk of such adverse events/reactions following MeNZB™.

Other factors There are additional unresolved factors, of which some/all may be co-related, which could affect the determination of the absolute and relative risks of adverse events and reactions that may be attributable to MeNZB™. These include: effects of staggered roll-out of the Programme, differences in the season during which the majority of the different vaccines were administered, differences in health care seeking behaviour by vaccinees, differences in the recording of clinical details by HCPs, and perhaps more importantly the occult 'reactions' included in 'incidents'.

Validity of the by vaccination-visit comparative analysis

Considering that we could not properly assess the possible dose-interdependence of risk of adverse events, the rates/means observed in the by vaccination-visit comparative analysis presented above could at best be a crude over-estimate, and, therefore, cannot be used to inform knowledge at this point. Similarly, we could not fully assess the extent to which the generalizability of the results were affected by the over-representation of Pacific and Mäori children in the data set, the staggered roll-out of the vaccination programme, seasonality effects, differences in health-seeking behaviours by practice and/or ethnic groups, and differences in the recording of clinical details by HCPs affected these findings.

3 Overall conclusions and recommendations

The IVMP is among the first data collection systems of its kind, offering a potentially powerful means of obtaining representative, unbiased data on clinical encounters at the GP-practice level. Findings and analyses to date have shown that it is possible to measure the adverse event profile of vaccines in a reasonably timely fashion. Although further analyses remain to be completed to effectively cope with biases/confounders to obtain valid findings and make sound conclusions, the system has produced initial findings presented in this report that suggest a low reactogenicity profile for the MeNZB™ vaccine in children under 5 years.

The combined findings of the descriptive analyses of data from the SRP and IVMP independently support a low rate of reactogenicity with the MeNZB™. These complementary systems each have unique advantages with the IVMP being designed to measure community level estimates of rates of the more common reactions typically seen in general practice with the added potential of being able to observe occult patterns, whilst the SRP has strengths in harvesting the more unusual or isolated events whilst also serving to support or challenge the profile of IVMP reaction observations. This dual system of event monitoring has demonstrated its value and has the potential to serve as an important strategy to be included in the pharmacovigilance toolbox for future post-marketing vaccine safety surveillance.

Appendix 1: The event dictionary main groupings

- Localised events (injection site reactions)
- Somatic immune responses
  - Gastro-intestinal events
  - fever and fever-related events
  - general body symptoms
  - headache
- Vaccine anxiety-type events (vasovagal related events)
- Hypersensitivity-type events
  - anaphylactic-type reactions
  - angioedema
  - angioedema-like events
  - Urticaria
  - other skin-related events
  - respiratory-related events (excluding respiratory tract infections)
  - eye-related events
- Convulsions and convulsion-like events
  - convulsions
  - convulsion-like episodes
- Neurological irritability
  - Persistent, abnormal or high pitched crying
  - Irritability
- Sleep-related events
- Injury
- Infections
  - Respiratory tract infection (RTI)
  - Non-RTI infection
- Haematological events
  - Purpura and petechial events
  - Lymphadenopathies
  - Other haematological events
- Cardiovascular-related events
- Other disorders
  - Central Nervous system
  - Foetal
  - Gastro intestinal disorders (other than somatic type symptoms)
  - Hearing and vestibular
  - Liver and Biliary
  - Endocrine

- Metabolic and Nutritional
- Miscellaneous terms
- Neonatal and Infancy
- Reproductive disorders (female)
- Reproductive disorders (male)
- Respiratory system (non infection or hypersensitivity disorders)
- Skin & Appendages (other than hypersensitivity type symptoms)
- Urinary system
- Vision
- Musculoskeletal
- Psychiatric

Appendix 2: Standard WHO coding and terminology

The codes are in (brackets).

Causality (Relationship)

Certain (1) – A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Probable (2) – A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.

Possible (3) – A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely (4) – A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Unclassified (5) – A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.

Unclassifiable (6) – A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

Seriousness

Not serious (N)
Hospitalisation (H)
Persisting disability (P)
Life threatening (L)
Died (D)
Congenital (C)
Intervention to prevent permanent impairment (O)

Severity

Severe (1)

Not severe (2)

"A description of the intensity (severity) of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe

headache). Severe is not synonymous with serious, which is based on patient/event outcome or action criteria, usually associated with events that pose a threat to a patient's life or functioning.

Outcome

Recovered without sequelae (A)
Recovered with sequelae (B)
Not yet recovered (F)
Died – due to adverse reaction (D)
Died – drug may be contributory (C)
Died – unrelated to drug (N)
Died Unknown (U)

Appendix 3: Cumulative Dosing Effects (Dose Inter-dependence)

Background

The critical question that remained unanswered in the previous analyses was whether the risk of adverse events or reactions following MeNZB™ are dose-interdependent, i.e., is the risk of experiencing an adverse event or reaction following MeNZB™ higher among children who experienced any similar adverse event / reaction following a previous MeNZB™ dose.

We set out to determine whether the risk of adverse effects or reactions following MeNZB™ is dose-interdependent, and if so, to explore the magnitude and nature of such effects. However, we were unable to assess the possibility of dose-interdependence because of multiple unresolved issues with respect to the data. A discussion of the challenges encountered and solutions explored in extensive efforts to resolve these issues are discussed below.

Methods: Challenges and solutions explored

1. *Ascertainment of a 'pure' cohort*

In order to investigate cumulative dosing effects, a 'pure' MeNZB™ cohort was necessary. This meant that analysis was required to be confined to a subset of vaccinees whose first immunisation was with 'MeNZB™ only'. Such analysis was able to be undertaken in the six month to less than 19 month old age group (study period 19 July to 15 November 2004). However, in the less than six month old group, analysis had to be undertaken in the 'Hybrid only' vaccination grouping (concurrent administration of routine childhood immunisation schedule vaccines and MeNZB™ at a vaccination visit) as very few vaccinees in this age group received 'MeNZB™ only' (study period was between 03 February – 30 September 2005).

Therefore, only those vaccinees whose first 3 recorded vaccines were sequential immunisations of MeNZB™ only in the six to less than 19 month old age group and those whose first 3 recorded vaccines were sequential immunisations of 'Hybrid' in the less than six month old age group were able to be used to investigate dose-interdependence. These are referred to as the 'pure cohorts'.

In addition, the interval between dose one and dose three was restricted to between 12 and 20 weeks for the dose-interdependence analysis, as this would reflect the recommended six week dosing interval for MeNZB™ according to the National Immunisation Schedule advised by the Ministry of Health (More than 83% of vaccinees fell within this restriction in both pure cohorts).

Due to these restrictions, analysis was confined to a small subset of vaccinees; therefore any findings would be limited to the population under study and would not be useful for informing possible effects in the general population.

2. *Lost to follow up*

Secondly, consideration was given to the possible bias effects introduced due to some vaccinees being 'lost-to-follow-up'. In the foregoing analyses, some vaccinees had incomplete MeNZB™ immunisation records in the IVMP system (where less than three sequential doses MeNZB™ were recorded and assessed). Possibilities that account for this loss to-follow up are:

- lost to assessment

These are those vaccinees that did have all three MeNZB™ doses but were lost to assessment either due to the vaccination visits being outside the defined study periods, or because the end of six weeks of monitoring after immunisation was not reached during the study periods, i.e. vaccination visit and consultation information pertaining to these vaccinees was captured and held within the IVMP system, but not assessed due to the exclusion constraints of the study.

- lost to IVMP system

Conversely, those vaccinees who did not return to their practice to receive the second and/or third MeNZB™ dose were lost to the IVMP system. These vaccinees may have received subsequent MeNZB™ doses, but not at one of the study sentinel practices, or may not have received any further MeNZB™ doses.

Those 'incomplete' vaccinees that had vaccination visit details captured within the IVMP system, but outside the original study periods, were identified and became the 'lost to original assessment' group. Further assessments of vaccination visits beyond the study period were undertaken for these defined vaccinees. The remaining incomplete vaccinees where no further vaccination visits could be identified were deemed the 'lost to IVMP system' group.

The unique National Health Index (NHI) number of each vaccinee lost to the IVMP system was matched against records held in the National Immunisation Register (NIR). Vaccinees were thought to be 'lost-to-follow-up', if they did not complete all three doses of 'MeNZB™' according to the NIR. The NIR was established as part of the Meningococcal Immunisation Programme and is a computerised information system that holds details for all MeNZB™ immunisations given to those aged up to 20 years. Using the same NIR-IVMP matching procedure, the lost-to-follow-up rate was also estimated for all vaccinees in the IVMP system.

True lost-to-follow-up, using the IVMP-NIR datasets, seemed to suggest that the prevalence of true 'drop outs' was small and furthermore, that the pattern observed in the IVMP cohorts (using all the vaccinees in the IVMP system) seemed to be consistent with the NZ-wide experience of 90% immunisation coverage rate.

3. *Consideration of biases and confounding factors*

Possible biases and confounding factors were considered as part of the analysis. Confounding factors were predetermined and included age (in days), gender, ethnicity, seasonality and District Health Board (DHB) region. Two additional factors were encountered and considered as follows:

- Effect of Health Seeking Behaviour (HSB)

It became apparent during the dose-interdependence analysis that differences in health seeking behaviour (HSB) between vaccinees was an important contributing factor. As this could not be measured exactly, variables designed to reflect HSB were developed.

Index 1	the ratio of the number of incidents (including 'no events') divided by the number of adverse events at vaccination visit one
Index 2	the ratio of the number of incidents (including 'no events') divided by the number of adverse events at vaccination visit two

The ratios are classified at the cut-off point of 50%. If there is no adverse event at a vaccination visit, the ratio is considered to be less than 50%. If the ratio is greater than 50%, then this was considered to represent some degree of HSB.

Despite extensive efforts to understand the presence and impact of HSB in the dose-dependence study, it was difficult, and may be impractical to develop an independent proxy for HSB.

- Effects of General Practices

It was noted that some General Practices reported more adverse events than others as the consultation notes were more detailed. In an effort to overcome these variations in the recording of consultation details between practices, practices were classified as either those practices with the mean number of adverse events per vaccination visit in the 'scheduled' vaccine immunisations of more than one, or as practices with the mean number of adverse events of less than one.

Future direction for dose-interdependence analysis

Because of the co-related effects of staggered roll-out of the immunisation campaign, seasonality, HSB by vaccinees and differences in recording of clinical details by healthcare professionals, we were unable to assess the possibility of dose-interdependence as many issues with respect to the data remain unresolved. Any future analysis for the presence of dose-interdependence will require these challenges to be overcome. This will be no easy task, but such strategies that remove or reduce the impact of the biases encountered may include:

1) Redefining the cohort: The identification of alternative cohort groupings based on MeNZB™ exposure in the first instance rather than age will allow for alternative analytical strategy starting points. Furthermore, the inclusion of larger numbers in the IVMP cohort for analysis through completing further assessment could be undertaken so that the cohort covers all seasons of a year to minimize the inherent biases due to the correlations between the campaign, DHB region and seasonality.

2) Application of a newly established epidemiological study design, such as the self-controlled case series method[10] [11] [12]. This method is suitable for studying the association between a transient exposure and an (acute) adverse event using risk interval concepts. Only cases are included in the statistical analysis applying conditional Poisson regression model, which can well control fixed variables such as gender, ethnicity, location (DHB region), general practice (if the vaccinee does not switch during the study period), health seeking behaviour, genetics, underlying health states and social-economic status, as the case itself works as its own control. This method also has the potential to control time-varying confounding factors including age and seasonality. Importantly, with high vaccine coverage rates such as that achieved with the MeNZB immunisation programme (close to 90%), this study design is believed to have good power to identify the association between exposure to vaccines and adverse reactions.

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[10] Farrington CP, Nash J and Miller E. Case series analysis of adverse reactions to vaccines: a comparative evaluation. *American Journal of Epidemiology* 1996, 143:1165-1173.

[11] Farrington CP. Control without separate controls: evaluation of vaccine safety using case-only methods. *Vaccine* 2004, 22: 2064-2070.

[12] Whitaker HJ, Farrington CP and Musonda P. Tutorial in Biostatistics: The self-controlled case series method. *Statistics in Medicine* 2006, 25(10): 1768-1797.