

Meningococcal B Vaccine (MeNZB™) Safety Monitoring Plan

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Data Management Group**

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1 Introduction

Post-licensure safety monitoring of MeNZB™ vaccine is being conducted during a structured rollout of vaccine to the eligible population as outlined in the “Strategy to control the New Zealand epidemic of serogroup B meningococcal disease by vaccination”¹. As such it is not a clinical trial and accordingly this safety monitoring plan comprises mainly a description of data flows from various sources and the processes through which critical data will be collected. It describes how the data will be presented to the Independent Safety Monitoring Board (ISMB) for its consideration. The ISMB will review and approve the overall safety monitoring plan prior to commencement of the vaccine rollout, and will regularly receive reports summarizing the safety monitoring data and results throughout the early stages of the rollout (described in more detail below). Based on these reports, the ISMB will make recommendations to the Ministry of Health regarding the conduct of the safety monitoring activities, and the overall management of the MeNZB™ vaccination programme. Any recommendation to the Ministry of Health should be copied to Medsafe, the New Zealand Medicines Regulatory Authority and Chiron Vaccines the company manufacturing the vaccine.

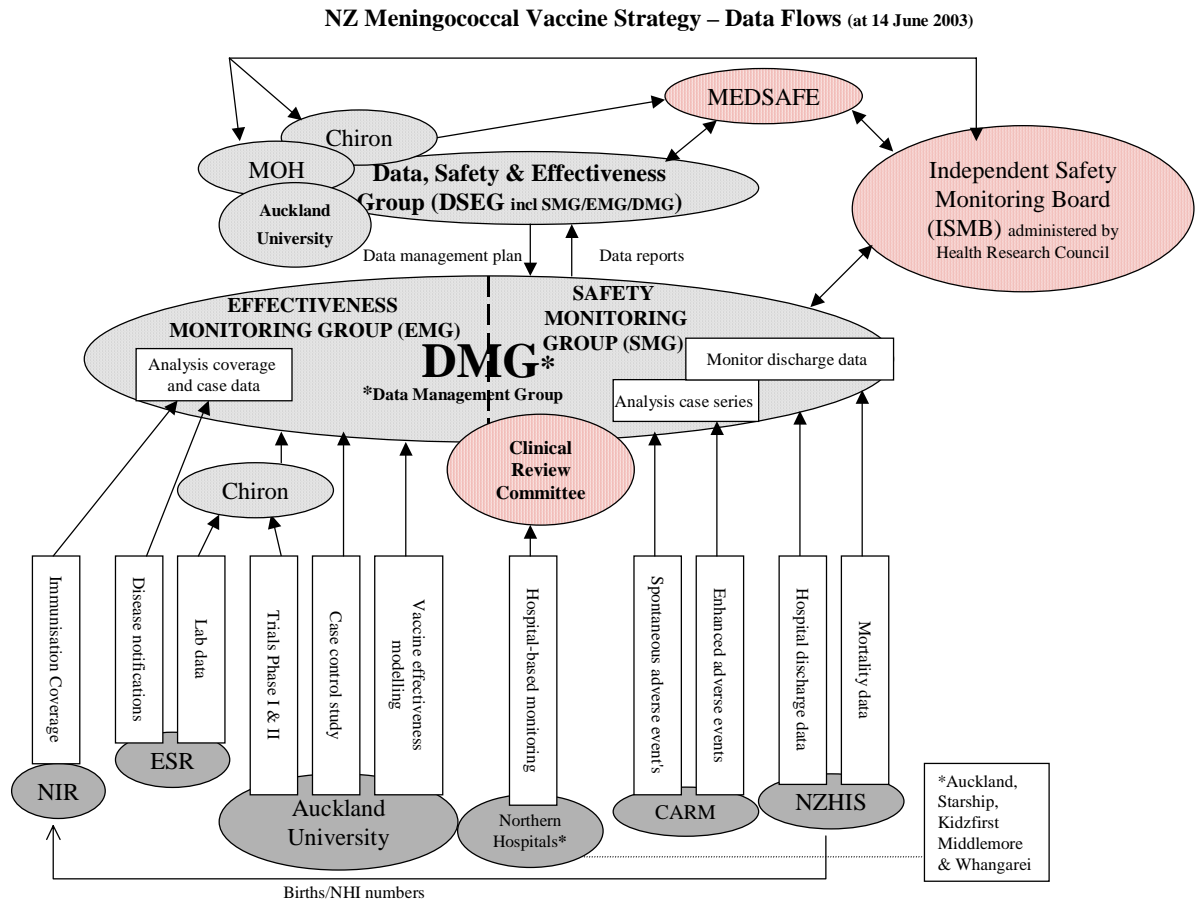
Data will be collected from several sources and the handling of data from each will be described. The Data Management Group (DMG) established by the Ministry of Health is the key group involved. The DMG is supervised and guided by Data Safety and Effectiveness Group (DSEG), a group charged with assessing the effectiveness and safety of MeNZB vaccine and established by the Meningococcal Management Team (MMT), the consortium of the Ministry of Health, Chiron Vaccines and the University of Auckland. However, the DMG will answer primarily to the ISMB. The relationships and data sources of the DMG are illustrated in figure 1. One of the roles of the DMG will be to detect duplicate reporting of single cases and to decide which source will be the principal information source for each case, with cross referencing to other sources.

The structure of this document is as follows. Firstly there is a description of the proposed vaccine rollout in relation to safety monitoring and the proposed decision points to be adjudicated by the ISMB. Secondly the steps from the pilot to countrywide rollout are described. Thirdly data from the main sources, to be collated and analysed by the DMG will be discussed in detail covering data flows and proposed analyses. The data sources are:

- Hospital-based monitoring - Rare event
All event
- Centre for Adverse Event Monitoring (CARM)
Routine passive
Intensive Vaccine Monitoring programme (IVMP)
- Hospital discharge data
- National immunisation register (NIR)
- Meningococcal surveillance data
- Rates of adverse events following routine childhood vaccines

Finally a consideration of other analyses, which may be required in specific circumstances, and a suggested framework for the assessment of causality, are included.

Figure 1: Meningococcal Vaccine Strategy data flows



2 Rollout

One of the most important considerations in establishing the safety monitoring plan is the structure of the rollout and the proposed decision points to be adjudicated by the ISMB. This is described below and greater detail is also covered in the “Strategy Document”¹.

The first use of the vaccine will be in a high-risk area of south Auckland, the first stage roll-out area. Available safety data one week after a predetermined number of doses have been administered (see below) will be collated for presentation to and assessment by the ISMB. If these data are judged satisfactory the rollout will be extended to the rest of New Zealand, whilst vaccine delivery in the first stage area is completed. It is anticipated that the licence will permit a rollout structured as follows:

- The 1st stage rollout commences in those aged 6 months to 19 years in high-risk areas of Auckland; viz. Counties Manukau District Health

Board (CMDHB) and the eastern corridor of Auckland DHB (ADHB). It is likely that the initial use of vaccine will be in school children followed by preschool children, though this is not a requirement of the safety monitoring.

- During the 1st stage rollout, graduated vaccine delivery will occur with approximately 5,000 (maximum 7,500) of those aged 5-19 years receiving vaccine in the first week, increasing to 25,000 in the 4th to 6th weeks of the campaign. A similar gradation will occur in the 6 month to 4 year old age group in whom vaccination may commence concurrently.
- “Real-time” safety data from hospital-based monitoring for serious adverse events for all 6 months to 19 year old vaccinees will be available throughout the first stage rollout.
- Following vaccination of the first 12,000 aged 5-19 years (including 5,000 aged 5-10 years), 8,000 aged 16 months to 5 years (at least 1000 per year of age cohort) and 2,500 aged 6-15 months, available data following dose 1 will be collated and presented to the ISMB.
- If such data are considered satisfactory the 2nd stage of the rollout can commence, initially covering the rest of Auckland and Northland where hospital based surveillance will operate for those aged less than 5 years.
- Licensure and delivery of vaccine to those aged under 6 months will depend upon presentation to Medsafe of data from the clinical trial in this age group, and safety data from older age groups. Similar safety monitoring is proposed for the less than 6 months age group.

The key elements of the safety monitoring are -

- During the 1st stage rollout to all ages and the greater Auckland and Northland countrywide rollout to those aged less than 5, safety data from hospital-based monitoring will be overseen and reviewed for quality, completeness, and indications of possible vaccine-associated adverse events by the DMG each day.
- If necessary such data will be reported to the chair of the ISMB who, at any time, can call a full meeting of the ISMB.
- Routine weekly summary reports, during the 1st stage rollout and the early part of the 2nd stage, will be presented to the ISMB by the DMG. Clarification of data on individual cases can be sought from the DMG and/or Clinical Review Committee (CRC), which will be responsible to ensure consistent reporting from all sites and that as far as is possible the investigation of rare cases is consistent between cases and sites.
- Data from all available sources will be collated, analysed and presented to the ISMB by the DMG one week after the predetermined points described above.
- The ISMB will inform the Ministry of Health of its opinion on the safety of the vaccine and if satisfactory the 2nd stage of the rollout can commence.
- Real-time hospital-based monitoring for defined serious adverse events and monitoring of all hospital admissions and emergency department consultations in vaccinees in the week following vaccination will occur

throughout the 1st stage rollout. At least 100,000 vaccinees aged > 5 years will be monitored during this phase of the campaign (see Table1).

- During the 2nd stage rollout, hospital-based monitoring for defined serious adverse events and monitoring of all hospital admissions in vaccinees in the week following vaccination will be established for a cohort of at least 100,000 of those aged less than 5 years. This will occur in all the Auckland DHB's with the addition of Northland DHB.
- Data generated by the New Zealand Pharmacovigilance Centre (NZPhvC, formerly CARM) will be available as well.
- The ISMB can assess and provide a report on the data at any stage of the rollout and advise the MoH on the continuation of the vaccination programme. Their advice will be simultaneously sent to Medsafe, the New Zealand Medicines Regulatory Authority, and the Pharmacovigilance division of Chiron Vaccines (CV), who manufacture MeNZB™.
- Clearly if at any stage the ISMB (or CV Pharmacovigilance) recommends to the MoH that the rollout cease, Medsafe will be informed of this advice.

Table 1: Hospital-based monitoring during 1st stage rollout and Auckland/ Northland-wide rollout

Hospital	South Auckland Rollout		Auckland/Northland Rollout	
	5-19 yrs	<5 yrs [#]	5-19 yrs	< 5 yrs
Middlemore/Kidzfirst	ED consults & admissions	ED consults & admissions	Nil	Admissions
Auckland/Starship	Admissions*	Admissions	Nil	Admissions
Whangarei	Nil	Nil	Nil	Admissions

* If the south Auckland rollout overlaps the Auckland/Northland 5-19 year age group rollout, monitoring of Auckland hospital admissions in the 5-19 year age group will continue (approx 6 months)

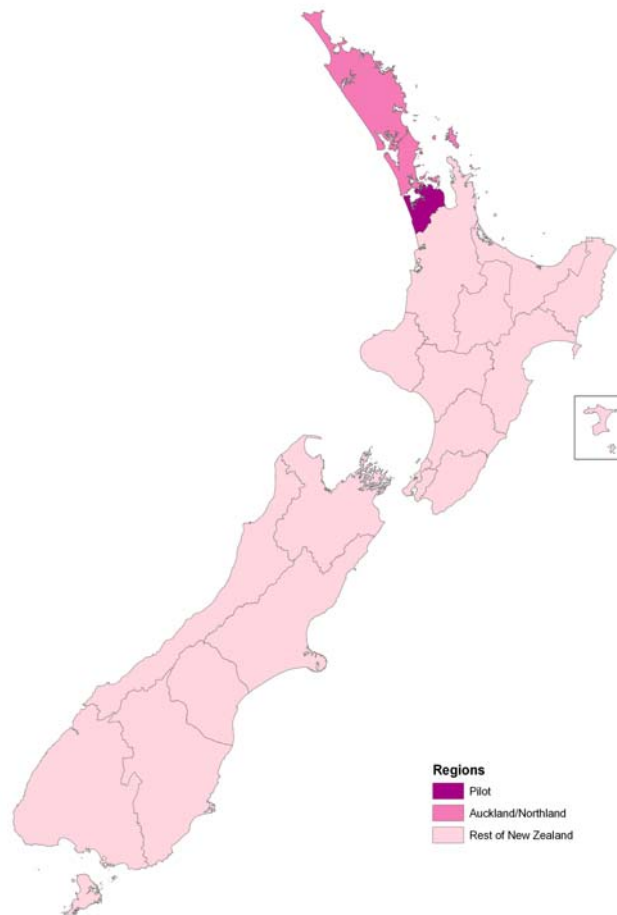
[#] Vaccinations for the age groups 16 months to < 5yrs, 6mths to < 16mths, and < 6 months may start at different times.

3 ISMB Formal Decision Points

The safety monitoring is being structured in such a way that if the hospital-based monitoring, or any other data source, detects a cluster of serious events following vaccination the ISMB can be consulted, assess all available information on such events and consider whether to advise that the Ministry of Health on what further action, if any, is required including to cease vaccination. This can occur at any stage of the vaccination campaign until

such time as full licensure is granted and/or the ISMB retires. Summarised safety data in tabular form, with appropriate statistical interpretation, will be presented weekly to the ISMB. It will be the responsibility of the chair to decide whether such data justifies discussion by all ISMB members, though clearly any member can request such a discussion. In addition there are several formal decision points at which the ISMB will meet (see below).

Vaccine use will be slow and progressive, and thresholds have been established for expanding the vaccination programme. The estimates of the minimum detectable risk of adverse events (see below) from which these thresholds derive are based on vaccination target levels (i.e., projected number of vaccinees and doses administered) which are up to 50% of those children eligible to receive MeNZB™ in an area. Initially those aged 6 months to 19 years residing in south Auckland will be vaccinated, though the rollout is likely to commence in school aged children. For those aged greater than 5 years the threshold of 12,000 vaccinees has been established and if the safety data are judged satisfactory then vaccination can extend to those aged 5-19 years in the rest of the country. This is supported by the substantial safety data available on the parent Norwegian vaccine. For those aged less than five the initial threshold will permit an extension of the vaccination campaign to the rest of Auckland and Northland, where hospital based monitoring for this age group will be established (see map). Following assessment of further safety data from this area, including the first stage rollout area, vaccination can be extended to the rest of the country if the data are judged satisfactory.



It is important to note that licensure for those aged under six months is anticipated, at best, six to eight months after the initial licence; thresholds for this age group are considered in paragraphs 3.1.2.2 and 3.1.2.3. It is also important to note that the size of the cohorts falls with age and, as the age bands narrow, but that the percentage of the eligible cohort increases with declining age and declining age band. In general data on younger children will be supported by substantial amounts of data from the monitoring of older children. The establishment of the size of the threshold cohorts was based on a combination of pragmatic considerations, relating to what level of vaccine delivery could be achieved in a reasonable time frame, and sensible safety thresholds. To some extent therefore, these thresholds are arbitrary.

There are several formal decision points the first two of which are stop/go points. Data will be collated and presented to the ISMB for consideration -

1. one week after administration in the first stage roll-out of
 - A. 12,000 first doses to those aged 5 – 19 years, with at least 5,000 to those aged 5-10 years to allow extension of vaccination to the rest of the country for this age cohort ,
 - B. 8000 first doses to those aged 16 months to 4 years, with at least 1000 per eligible age cohort, to allow extension of vaccination to the rest of Auckland and Northland for this age cohort.

- C. 2,500 first doses to those aged 6 -15 months to allow extension of vaccination to the rest of Auckland and Northland for this age cohort.
2. One week after administration in Counties Manukau, Auckland Waitemata and Northland District Health Boards of
 - A. 30,000 first doses to those aged 16months – 4 years to allow extension for this age group to the rest of the country
 - B. 7,500 first doses to those aged 6 – 15 months to allow extension for this age group to the rest of the country.
 3. One month after 100,000 third doses are administered to those aged over 5 years.
 4. One month after 100,000 third doses are administered to those aged under 5 years
 5. Six monthly during the vaccination campaign.

At these predetermined points the DMG will present all available data to the ISMB for its consideration. It is anticipated that the ISMB will meet at these times to consider these data. The sources from which it is expected data will be available at each point are listed below.

- | | |
|-----------------|--|
| Points 1 and 2. | Hospital-based rare event monitoring
CARM – Passive reporting - preliminary data only.
IVMP – preliminary data
Background Hospitalisation data
Routine childhood vaccine adverse event data
NIR data – progress of vaccination campaign |
| Point 3. | Hospital-based rare event monitoring
100,000 aged > 5 years post dose 3
30,000 aged < 5 years post dose 3
up to 70,000 under fives following dose 1 from Northland and rest of Auckland
All event hospital-based monitoring
CARM – Passive reporting
IVMP
Background Hospitalisation data
Routine childhood vaccine adverse event data
NIR data – progress of vaccination campaign
Institute of Environmental Science and Research (ESR) surveillance data |
| Point 4 | Hospital-based rare event monitoring under age 5
100,000 post dose 3
update on other data sources listed for point 2 above |

Point 5 Six monthly during the vaccination campaign. Assuming the pilot rollout starts May 2004, the first report will be November 2004 and could coincide with point 2. It is Possible point 3 will coincide with the 2nd six monthly report around May 2005.

3.1 Steps from pilot to countrywide use

There are two key steps in widening the use of MeNZB™ vaccine. The first, from clinical trials to pilot rollout, will be dependent on Medsafe granting a license. The second step from an area where hospital-based monitoring is in place to the rest of the country, where there is no hospital-based monitoring, will occur after consideration of available safety data by the ISMB. These steps are required for each age group and are now considered for each age group in detail. It is possible that the licence for some of these age groups may be granted simultaneously.

For those aged under five there is an additional step; the initial use of the vaccine will be in CMDHB with hospital-based monitoring for admission and Emergency Department (ED) attendance including the widest range of conditions. Subsequent use of vaccine will involve an extension to Auckland, Waitemata and Northland DHB's where hospital-based monitoring for hospital admission and for a narrower range of conditions will be in place. Safety data from this monitoring will be assessed prior to extension of the campaign to areas without hospital-based monitoring.

3.1.1 5-19 year olds total cohort for hospital-based monitoring N = 100,000

As with all age groups the initial use of the vaccine in the first stage rollout will involve a "stagger" i.e. smaller numbers being vaccinated in early weeks than in later weeks. In addition there will be a period of several weeks, following vaccination of the initial target number during which the following steps will occur;

- data collation for hospital-based monitoring - one week
- data analysis and presentation to ISMB by DMG - three weeks
- ISMB clarification and decision – two weeks
- Total time 6 weeks.

Therefore for 5-19 year olds during the first three weeks approximately 5,000 per week (no more than 7,500) will be vaccinated. One week after 12,000 (including at least 5,000 aged 5-10) have received vaccine – probably end of week 4 - data will be collated and presented to the ISMB. These data will give reasonable certainty that an event occurring at a rate of up to as rarely as 1 in 4,000 population will be observed.

By the time the ISMB has undertaken its first formal review to allow extension of the campaign to the wider Auckland area and Northland at least a further 6 weeks of vaccine delivery with hospital-based monitoring will have occurred in

CMDHB. This means that data from hospital-based rare event reporting from ~80,000 vaccinees aged 5-19 who will have received their first dose will have been presented weekly to the ISMB chair (see table 2).

*3.1.2 6 week –4 years total cohort for hospital-based monitoring
N = 100,000*

It is possible that the initial licence granted will only permit vaccination of those aged 16 months to 19 years with licensure extending to younger age groups as data from the clinical trials in these age groups are presented to Medsafe. The ages of those enrolled in the clinical trials determine the age groups considered in this document. With those aged 4 years and under there is the additional step in the extension of the vaccination campaign, described above (see sections 3 & 3.1).

*3.1.2.1 16 month – 4 year olds CMDHB cohort
N ~ 25,000*

Immunisation for those aged 16 months to 4 years will commence, as for all other age groups, in CMDHB where hospital-based monitoring for admissions and ED attendance is established. During the first three weeks of the campaign up to 3000 children per week in this age group will be vaccinated. One week after 8000 (at least 1000 per year age band) have received their first dose, data will be presented to the ISMB. If data are satisfactory then the campaign can be extended to the rest of Auckland, Waitemata and Northland where hospital-based monitoring for those aged less than 5 is in place.

These data will give reasonable certainty that an event occurring at a rate as rarely as 1 in 2,500 population will be observed. This higher rate than for those aged 5 -19 is justified on the basis that this extension is to another area with hospital-based monitoring covering hospital admissions, (but not ED department attendances and excluding petechial rashes see section 4.1).

By the time the ISMB has undertaken its first formal review to allow extension of the campaign to the wider Auckland area and Northland a further 6 weeks of vaccine delivery with hospital-based monitoring will have occurred in CMDHB. This means that data from hospital-based rare event reporting from ~20,000 vaccinees aged 16 months to 5 years, who will have received their first dose, will have been presented weekly to the ISMB chair.

The step from Auckland, Northland, Waitemata and Counties Manukau to the rest of the country will only occur after a minimum of 30,000 (~50% of eligible cohort) children in this age group from this area have been monitored for one week following the first dose allowing reasonable certainty that an event which occurs at a rate as rarely as 1 in 10,000 population will be observed. This is expected to have occurred by the end of January 2005. By this time many of the eligible 25,000 children in this age group in CMDHB will have received 3 doses as well as up to 45,000 from the other three DHB's who will have received one dose. See table 2.

3.1.2.2 *6-15 month olds CMDHB cohort*
N ~ 5000

Immunisation for this age group will commence, as for all other age groups, in CMDHB where hospital-based monitoring for admissions and ED department attendance is established. During the first three weeks of the immunisation campaign in this age group up to 1000 children per week will be vaccinated. One week after 2500 (~50% of eligible cohort) have received their first dose the data will be presented to the ISMB. If data are judged satisfactory then the campaign can be extended to the rest of Auckland, Waitemata and Northland where hospital-based monitoring for those aged less than 5 is in place. These data will give reasonable certainty that an event occurring at a rate as rarely as 1 in 800 population will be observed. This higher frequency than for older age groups is justified on the basis that this extension is to another area with hospital-based monitoring covering hospital admissions and that data on an adjacent older age groups have been collected.

The step from Northland, Auckland, Waitemata and Counties Manukau to the rest of the country will only occur after 7,500 (~50% of eligible cohort) children in this age group from this area have been monitored for one week following the first dose allowing reasonable certainty that an event occurring as rarely as 1 in 2,500 population will be observed. These data will be supported by data on up to 5,000 children aged 6 –15 months, ~25,000 children aged 16 months to 4 years and ~100,000 children aged 5-19 years who have received 3 doses of vaccine in the pilot rollout area. This is expected to occur by approximately 6 months after vaccination commences to this age group in CMDHB. See table 2

3.1.2.3 *6 week – 5 month olds CMDHB cohort*
N ~ 2,700

The stagger in this age and the progression from CMDHB to wider Auckland and Northland and then to the rest of the country is similar to that for the 6 –15 month age group i.e. monitoring of 1,250 (~50% eligible cohort) vaccinees in CMDHB prior to extension to greater Auckland and Northland and 4,000 (~50% of eligible cohort) vaccinees prior to extension to the rest of country. These will allow reasonable certainty that events occurring at rates as rarely as 1 in 400 and 1 in 1,300 population, respectively, will be observed. These data will be supported by data on up to 80,000 children aged 6 month to 4 years including up to 30,000 aged 6 months to 2 years who have been monitored for hospitalisation for one month following 3 doses of MeNZB vaccine. Furthermore the IVMP established by CARM will be in place to monitor events following immunisation for a cohort of approximately 5,000 infants and children aged 18 months and under, countrywide (see table 2).

Table 2: Doses monitored to enable ISMB decision to extend rollout

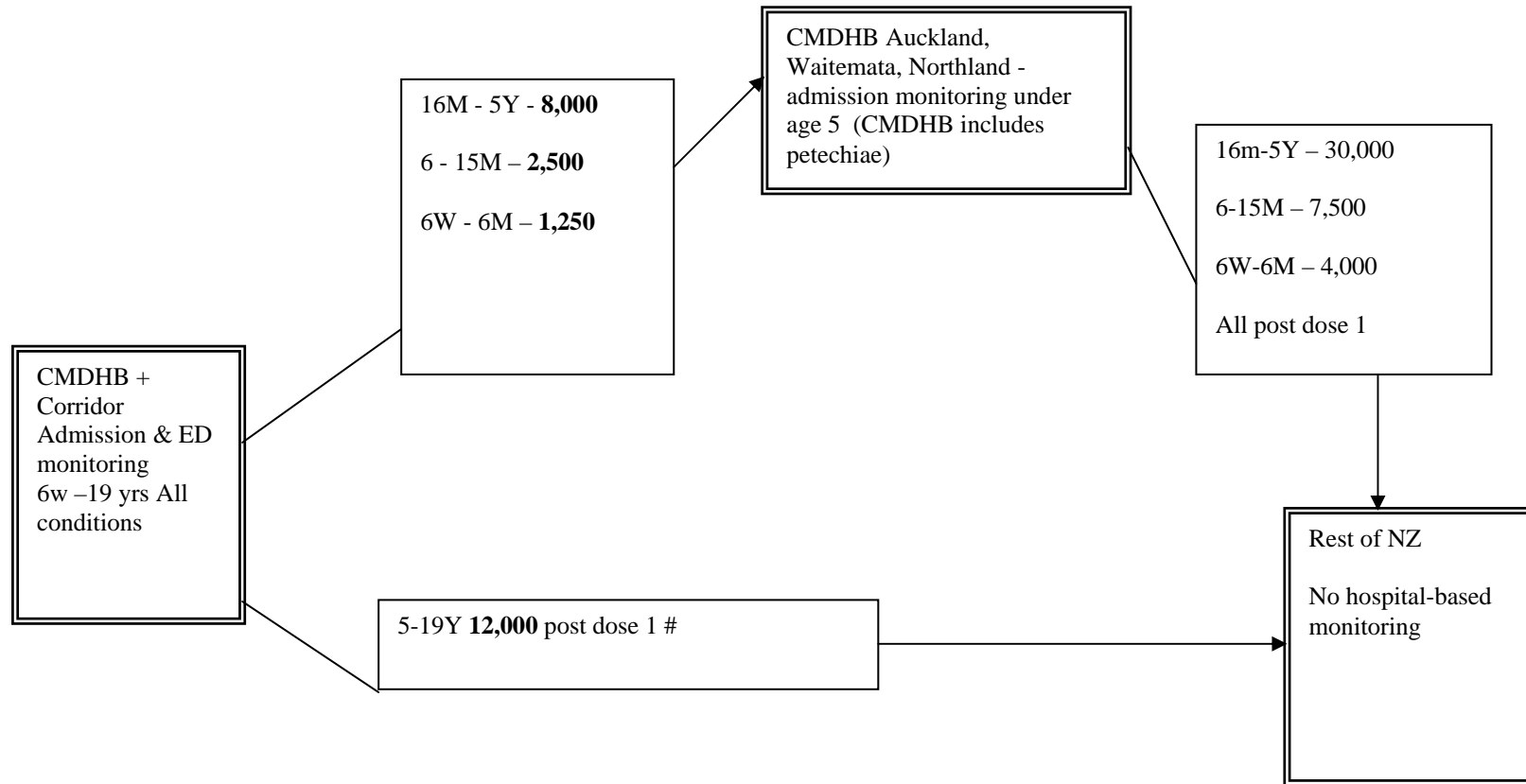
Age group	Doses delivered in South Auckland Rollout	Decision One* (~ 9 weeks from pilot start)	Doses delivered in Auckland Waitemata Northland & CMDHB's	Decision Two# (~ 9 weeks from Auckland/Nland rollout start for each cohort)
5-19 yrs	12,000	Can vaccinate in DHBs without real time hospital monitoring		
16 months – 4yrs	8,000	Can vaccinate Auckland/Northland wide area with real time hospital admission monitoring	30,000	Can vaccinate in DHBs without real- time hospital admission monitoring
6 months – 15 months	2,500		7,500	
< 6 months	1,250		4,000	

* By the time the ISMB Decision One is made for each cohort, the majority of South Auckland vaccinees for that age cohort will have received their first dose, with hospital-based adverse event monitoring in place.

By the time the ISMB Decision Two is made, the majority of Auckland/Northland vaccinees for that age cohort will have received their first dose, and the majority of South Auckland vaccinees will have received their third dose, with hospital-based adverse event monitoring in place.

See also figure 2, which displays these steps in diagrammatic format.

Figure 2: Diagram to illustrate thresholds for extending vaccination campaign from areas with to areas without hospital-based monitoring.



At this decision point ~80,000 vaccinees will have been subject to rare event hospital-based monitoring for 1 week post vaccination

3.2 *Number of observed events*

Historical data on related vaccines indicate that no serious safety concerns are expected. As the number of vaccinees increases without a specified event being detected, there is reasonable certainty that the specified event does not occur at a frequency greater than one in approximately one third of the total number of vaccinees observed. I.e., if 90,000 individuals have received vaccine and been observed for a week and no cases of flaccid paralysis, for example, have occurred then one can be 95% certain that the rate of flaccid paralysis with onset within one week of receipt of the vaccine is less than one in 30,000. It is proposed therefore, that a spreadsheet will be produced which indicates the expected number of vaccinees at specific points during the vaccination campaign and the corresponding rates at which we can be reasonably certain that events do not occur; then, after the vaccine rollout commences, the actual number of vaccinees/doses administered, and the concomitant rates of expected rates of adverse events, can be monitored over time using this same format.

4 *Data Sources - Data flows*

4.1 *Hospital-based monitoring - rare events*

This is the most important monitoring system for the detection and evaluation of immediate onset events. It is based on the Canadian IMPACT system² but conducted in real time. Nurse monitors will be appointed in the district hospitals in Counties Manukau, Auckland, Waitemata and Northland DHB's to detect predefined cases of interest. A pilot has been established in CMDHB and screening and case definitions and case report forms have been developed. The system will be thoroughly tested and be capable of detecting defined serious events. An operations manual for the system is being written. Validation of case detection will be carried out with an independent assessment of whether all cases of interest were detected. More specifically it is proposed that, prior to the rollout, all the clinical records of at least one week's attendees be examined independent of the nurse monitors to ensure no cases of interest were omitted. The results of this validation will be used to design a regular audit of the monitoring system during the roll-out. See also below under all - event monitoring, section 4.2.

In Counties Manukau all hospital admissions and ED consultations and in Auckland hospital all admissions in those aged 0-19 years vaccinated during the pilot rollout will be reviewed to identify pre-selected rare conditions that may be linked to immunisation. In addition to specified events various "catch-all" categories have been defined (see below). The starting point is the event, with checks to see if the person suffering the event had been immunised within the preceding days, weeks, or months, by matching against the NIR. A clinical review committee will evaluate all cases identified through the hospital-based systems that meet criteria for seriousness or unexpectedness, and will identify signals for in depth investigation. In each hospital the nurse monitors will be supervised by a clinician, usually a consultant paediatrician or

physician. In addition to detecting cases of interest their main role is to complete case report forms from the clinical records and forward them to the DMG.

The supervising paediatricians/physician in CMDHB and Auckland DHB, a public health physician from Auckland, a third senior paediatrician from another area of New Zealand, as chair, will form the Clinical Review Committee (CRC). In addition a paediatric neurologist and a haematologist will be corresponding members, whose advice can be sought as appropriate. The role of the CRC is to ensure consistency of reporting from each site and that as complete clinical information as possible is obtained on all cases of interest particularly those that are most severe. This includes serious cases occurring in non-vaccinees.

As mentioned previously, all events involving ED attendance and admission will be monitored in CMDHB during the pilot rollout, whilst in ADHB hospitals admissions only will be monitored (and petechial rashes excluded). When one month has elapsed after 100,000 of those aged > 5 years have received their third vaccine dose the monitoring in ADHB hospitals will be modified to cover hospital admissions only in those aged less than 5 years. At this stage it is anticipated that approximately 30,000 vaccinees aged less than 5 years will have been vaccinated in the pilot rollout. For Northland hospital admission monitoring will be conducted only for those aged less than 5 years and for all conditions excluding petechial rashes.

This hospital-based monitoring will continue until 100,000 of those aged under five have received all three injections and one birth cohort has received vaccine as part of the routine childhood programme. If a booster dose is required for any children, the period of time monitoring is in place may be extended.

An Operating Manual will define the time frames around reporting of events to the DMG. If informed of a case of, for example, flaccid paralysis in a vaccinee, the DMG will seek clarification including whether any similar cases have occurred in vaccinees or non-vaccinees at any of the hospitals undertaking surveillance. The system is designed so that, as it is the event which is the trigger and the vaccination status is determined later, events occurring in those who have not been vaccinated will be detected and investigated and can assist in the assessment of causality to be undertaken by the ISMB.

The hospital-based nurse monitors will forward complete case report forms to the DMG for entry on to a database. Each adverse events case will be assigned a unique case number. Other than for neurological events, case report forms will be forwarded to the DMG by the on-site nurse monitors when completed unless previously requested. Weekly updates (or daily if requested) of neurological case report forms will be forwarded routinely. The previous report form(s) will be checked for consistency, discarded and replaced by the updated form.

The DMG will collate, tabulate and forward these data weekly to the ISMB, in an agreed format, adding a breakdown from the NIR detailing the progress of the vaccination campaign— i.e. number vaccinated by age and area. ESR surveillance data will be submitted as well to provide information on the impact of the vaccination campaign on the incidence and distribution of meningococcal disease.

Case report forms will be forwarded to the ISMB as requested. The ISMB can request more clinical information on each case of interest either from the DMG or the CRC.

At present the DMG does not propose to add the laboratory data from cases of interest to its database. Such results will be available in paper form attached to the case report forms. However, if the ISMB requests it, such data could be entered electronically for subsequent statistical analyses and/or for other specific purposes.

To assist the ISMB assess the significance of events occurring in vaccinees, data on the occurrence of events of interest in those who have not been vaccinated will be available from participating hospitals. Estimates of the expected frequency of such events derived from historical data (over the prior 5 - 10 years) will be provided. These estimates will be obtained from the hospital discharge database for most events. The limitations of such historical data, e.g. changes in coding practice, inappropriate coding etc. are acknowledged. See Section 5 below for further detail.

4.2 Hospital-based monitoring of ALL events

This system will operate during the South Auckland first stage rollout and be conducted in hospitals in CMDHB and ADHB during that rollout for all aged less than 19 and for those aged less than five years during the second stage rollout in hospitals in ADHB, Waitemata DHB and Northland DHB. It will monitor hospital admissions and ED consultations in approximately 150,000 vaccinees aged 0-19 years in CMDHB and a further approximately 65,000 vaccinees aged less than 5 years in the other northern DHB's.

In this surveillance activity, the starting point is the vaccinee. The participating hospitals will send a weekly list of ED attendees and admissions identified by National Health Index (NHI) number to the DMG. The list will be matched against the NIR to identify those vaccinees who have attended hospital in the week following MeNZB™ vaccination. The matched list will be returned to the respective nurse monitors to ensure that no vaccinee has been omitted from the rare event surveillance.

When available, usually 2 months following discharge, the discharge diagnoses codes (ICD10) on vaccinees who attended hospitals serving the pilot rollout area (CM and Auckland DHB's) within 7 days of vaccination will be obtained from New Zealand Health Information Service (NZHIS). This will be

compared with the rare event monitoring data to assist in the validation of those data.

4.3 NZPhvC (CARM) – Passive reporting

CARM will receive reports of adverse events following vaccination. These passive reports are subject to all the difficulties of interpretation acknowledged in the literature³. Nevertheless, New Zealand sustains a high rate of passive reporting⁴ and in the early stages of the campaign the rate of reporting will be boosted by stimulating reports in CMDHB first stage rollout area. An information pack, which explains the safety data from the clinical trials and the historical safety data on the Norwegian vaccine and encourages reporting, will be sent to all health professionals prior to the rollout of the vaccine in an area. The information pack will contain a supply of standard adverse reaction reporting cards. Health professionals will be encouraged to report such events in the usual way to CARM, whether or not they consider them related to vaccination. The purpose is simply to increase the number of reports received in the early part of the campaign so that any “signals” which require more detailed investigation may be detected as early as possible.

A summary of reports received will be prepared at specified points during the vaccination campaign and forwarded to any health professional who reports an adverse event.

4.4 NZPhvC (CARM) Active reporting – IVMP

The primary role of the IVMP will be to provide information on infants and children who receive vaccination as part of the routine childhood vaccination schedule. The information obtained through IVMP will be supportive to the data obtained through real-time hospital monitoring (which will be the key stop/go data during the epidemic control phase of the vaccination programme), and to inform the decision to continue to include MeNZB™ as part of the routine childhood immunisation programme. This system utilises event reporting following vaccination with MeNZB™ and other concurrently administered vaccines for a cohort of ~5,000 children under the age of 19 months. General Practitioner's, in 20 - 30 sentinel group practices throughout New Zealand, utilising fully computerised medical records will be recruited to take part in this monitoring system. An annual birth cohort of ~ 3,000 infants will be enrolled in this programme. Information on immunisations in infants at the sentinel group practices will be electronically transferred to CARM and will form the denominator for the monitoring cohort. Data on health events for the six weeks following immunisation and subsequent immunisation data will be electronically transferred to CARM. This will reduce the additional work by sentinel group practices and reduce the processing requirements for CARM. Serious events will be followed up with the health care professional by CARM and/or the DMG. A pilot of this programme has been conducted in Otago. The final evaluation report of this pilot is attached in Appendix 1.

In the south Auckland rollout general practices from that area will send clinical records following vaccination to CARM for all aged less than 5 years in their populations. To date, 12 general practices have been recruited, including three practices in south Auckland, and will start sending data to CARM from early in 2004. The cohort of children covered by the enrolled practices is approximately 1,500. CARM will assess, summarise, tabulate and forward these data weekly to the DMG, following the initial six weeks post vaccination period.

4.5 Background hospitalisation data

Hospitalisations data on those aged less than 20, identified by specific ICD codes will be collated over the last 10 years and presented to the ISMB as background on the occurrence of serious events which may be detected by the hospital monitoring system (see Appendix 2). Data will be presented by DHB and age or as requested by the ISMB. The following ICD 10 codes will be used. The corresponding ICD 9 codes may be used for analysis including years prior to 1998.

Acute flaccid paralysis

- G61 Inflammatory polyneuropathy (includes GBS-G61.0)
- G37.3 Polyneuropathy due to other toxic agents
- G62.2 Other specified polyneuropathies
- G62.8 Polyneuropathy, unspecified
- G62.9 Acute transverse myelitis in demyelinating disease of the central nervous system

Anaphylaxis

- T78.0 Anaphylactic shock due to adverse food reaction
- T78.2 Anaphylactic shock unspecified
- T78.4 Allergy, unspecified
- T78.8 Other adverse effects, not elsewhere classified
- T80.5 Anaphylactic shock due to serum
- T88.6 Anaphylactic shock due to adverse effect of correct drug or medicament properly administered

Encephalitis

- G04 Encephalitis, myelitis and encephalomyelitis
- G05 Encephalitis, myelitis and encephalomyelitis in diseases classified elsewhere
- A81.0 Creutzfeldt-Jakob disease
- A86 Unspecified viral encephalitis
- G92 Toxic encephalopathy
- G93.4 Encephalopathy unspecified
- G93.8 Other specified disorders of the brain
- G93.9 Disorder of the brain, unspecified
- T80.6 Other serum reactions (Complications following infusion, transfusion and therapeutic injection)

Thrombocytopenia

- D69.3 Idiopathic thrombocytopenic purpura
- D69.5 Secondary thrombocytopenia
- D69.6 Thrombocytopenia, unspecified

Seizures

- R56 Convulsions, not elsewhere classified
- G41 Status epilepticus

General

- T50.9 (Poisoning by) Other and unspecified drugs, medicaments and biological substances
- Y58.9 (Poisoning by) Other and unspecified bacterial vaccines

4.6 Adverse events following routine childhood vaccines

To further assist the ISMB assess the significance of adverse events following MeNZB™ vaccine the frequency of events following comparable vaccines will be derived from the literature. Whole cell and acellular pertussis vaccines will be used as comparators. (See Appendix 3)

4.7 National Immunisation Register NIR

Data will be obtained weekly from the NIR defining vaccination status by age and date of vaccination. These data will be used to confirm immunisation status of those identified by the rare event monitoring system and to ascertain vaccinees who have been seen at hospital in the seven days following vaccination. It will be also used to confirm the immunisation status of any individual who is the subject of an adverse event report.

NIR data will be used to plot the progress of the vaccination campaign. It will be capable of reporting by DHB those who have been vaccinated by age, ethnicity, doses of MeNZB™ vaccine received (i.e., 1, 2 or 3 doses), batch number, site of vaccination, provider, and date of vaccination. Such data should be available from the NIR within 24 hours of receipt of the vaccine so that those who have suffered serious adverse events can have their vaccine status determined accurately.

4.8 ESR Meningococcal Surveillance data

These data have been collected and validated during the course of the epidemic and published annually. To enable the ISMB to assess the risk of adverse events in relation to the risk of meningococcal disease these data will be reviewed over the last 5-6 years to produce estimates for various age groups of the annual risk of acquiring meningococcal disease caused by the vaccine strain.

5 Data Analysis

5.1 Hospital-based monitoring – rare events

It is intended that as complete clinical information as possible, derived from chart reviews, will be available on all cases of interest, whether in vaccinees or non-vaccinees, so that appropriate causal attribution can occur. Standard epidemiological techniques— e.g., to compare rates in vaccinees and non-vaccinees or rates within and without specific time windows following vaccination—, will be used to analyse these data. If vaccine coverage is very high then clearly most events will occur in vaccinees. Our null hypotheses for most events being monitored is that MeNZB™ vaccine will not cause an increase in the frequency of the event above the background rate derived from historical hospital discharge data. However, it is anticipated that some events, for example, anaphylaxis, may occur following MeNZB™ vaccine and in this case the vaccine could increase its incidence. In this circumstance our hypothesis would be that the vaccine caused anaphylaxis at a rate of, for example, less than 1 in 100,000 vaccinees/doses

Specific additional analyses can be requested by the ISMB. The DMG will conduct routine analyses – numbers and rates of events in vaccinees and non-vaccinees by age group, sex, ethnicity, time period following vaccination etc. The DMG will be the source of raw data to other eligible groups (e.g. Chiron Vaccines), who may wish to conduct further analyses on specific areas of concern.

To assist the ISMB assess the significance of events detected by this system, comparison with background rates (described in section 5.5) and with rates following other vaccines (section 5.6) will be presented.

Although no ethnic disparity in the occurrence of adverse events is expected it will be possible to compare the occurrence of events between ethnicities if required.

The epidemiologic case definitions (see appendix 4) for most events include specific time windows (incubation period, latent period) in which a case following vaccination can occur; e.g. for anaphylaxis the time window in which its occurrence can be considered related to vaccination is 24 hours. However for acute flaccid paralysis and encephalopathy in the absence of a clear standard for an underlying biologic mechanism and related latent period (or at least pre-clinical interval) that could be applied to an epidemiologic case definition it is proposed to analyse the occurrence of these two events using the time windows 7, 30, 60 and 90 days following vaccination.

5.2 Hospital-based monitoring of ALL events

The DMG will tabulate and present these data to the ISMB monthly following the initial delay until the discharge diagnosis has been coded and forwarded to the Ministry of Health. In general, cumulative data will be presented. The

data will be analysed by week of immunisation, age, ethnicity and DHB. Broad categorisation of conditions, e.g. respiratory illness, will be used in the initial analyses though it will be possible to analyse these data by individual ICD code, subject to the limitation of small numbers of cases. As individual vaccination status at any time will be available from the NIR, comparison of admission rates in vaccinees, non-vaccinees and those who have been vaccinated but outside the hypothesised post vaccination window will be conducted. It is anticipated that these data may generate signals for further investigation.

It is possible that hypotheses may arise during the vaccination campaign; for example, that MeNZB vaccine causes an increase in the occurrence of attacks of asthma requiring attendance at hospital in the week following vaccination. These data will at least provide a basis on which such a claim can be initially investigated. A comparison of the rate at which hospitalisation for asthma in the week following vaccination occurs with the rate in those who have not been vaccinated in the prior 7 days and/or during other time periods may, or may not, support the hypothesis.

5.3 CARM - Passive reporting

CARM will report weekly to the DMG. The weekly report will relate to the week ten days prior (e.g. Reports received at CARM between 1st February and 7th February will be reported to the DMG on 17th February). Data will be presented in a tabular form indicating age, sex, ethnicity, batch and type of event. Clinical details on Adverse Events Following Immunisation (AEFI) involving hospitalisation will be forwarded to the DMG. For the purpose of prioritising reports, those which involve a systemic reaction and/or hospitalisation will have priority for assessment. At present CARM reports defined serious events, e.g. deaths, serious neurological events, to Medsafe within 24 hours of receipt by CARM. This will continue for reports involving MeNZB™, and these reports will also be forwarded to the DMG

CARM will match the NHI number of the reports received by CARM and the DMG to ascertain duplicate reporting. A joint decision will be reached to determine which reporting source should have priority. E.g. if the CRC were investigating a case of interest which had been reported to CARM then the investigation would be undertaken by the CRC and results forwarded to CARM.

If CARM is informed of a case of a serious neurological problem (to be clearly defined *a priori*) following vaccination then the DMG will be informed of that case within 24 hours of receipt of the initial report by CARM.

These data reported through CARM can only provide “signals” which may require further investigation. It is acknowledged that under-reporting is the norm, that events occurring closer in time to immunisation are more likely to be reported, that information is not collected in a structured way, may be incomplete and insufficient for causality assessment. In a later section of this

document our approach to investigating “clusters” is described. See section 6.2.1.

5.4 *CARM - Active reporting – IVMP*

The clinical records forwarded electronically will be assessed by CARM staff and entered on a database utilising standard adverse event coding practices. Data will be capable of analysis by age, sex, ethnicity, vaccine(s) received, time following vaccination and reason for consultation. It is intended that cumulative data will be sent monthly to the DMG, two weeks following the conclusion of the monthly monitoring period.

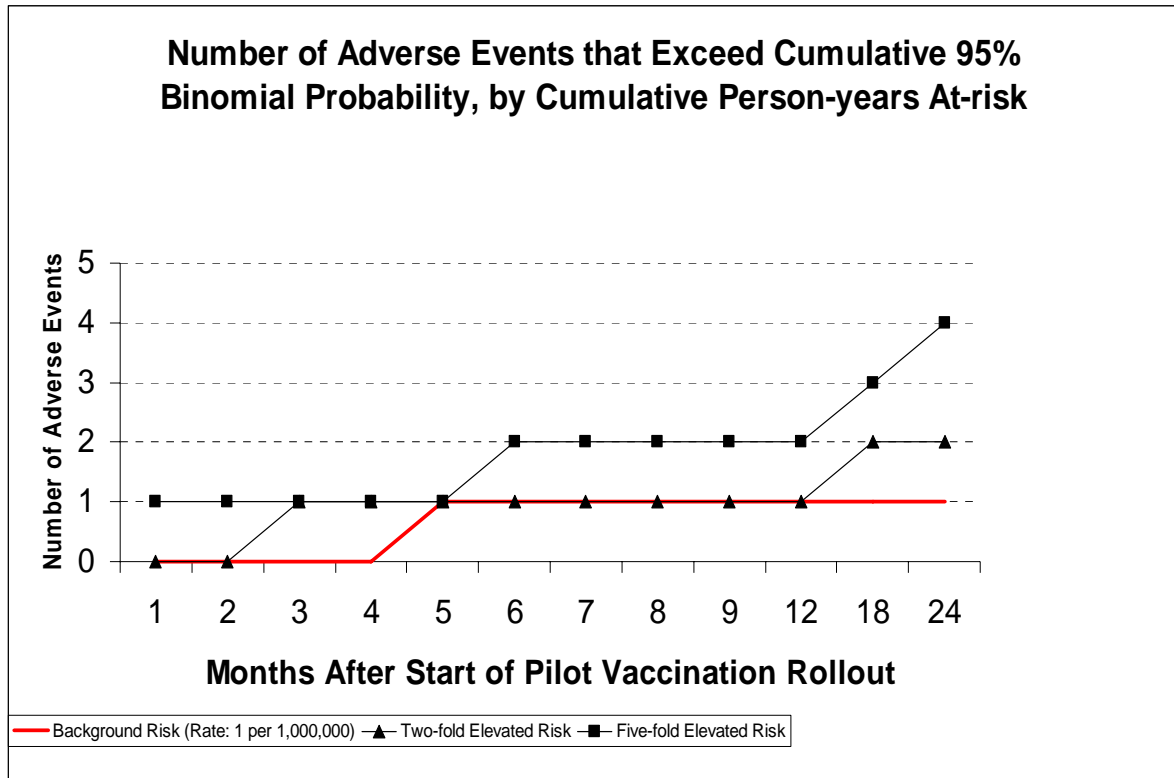
Although this monitoring is active, reporting will be retrospective. Firstly the clinical records will not be assessed by CARM until 6 weeks after the immunisation event. Secondly, the data will be entered, assessed and analysed and it is anticipated this will take several weeks. Thirdly, it is likely the data will be slow to accumulate, but will become more relevant as the cohort and events accumulated increase in size. Thus, as stated previously, the information obtained through IVMP will be supportive to the data obtained through real-time hospital monitoring (which will be the key stop/go data during the epidemic control phase of the vaccination programme), and to inform the decision to continue to include MeNZBTM as part of the routine childhood immunisation programme.

For these data there exist an established denominator and therefore rates of events following vaccination can be derived. However the number of vaccinees and vaccination episodes will be relatively small, given the cohort of ~ 5,000 vaccinees annually each receiving three vaccine doses, equivalent to 30,000 vaccination episodes over two years.

5.5 *Background hospitalisation data*

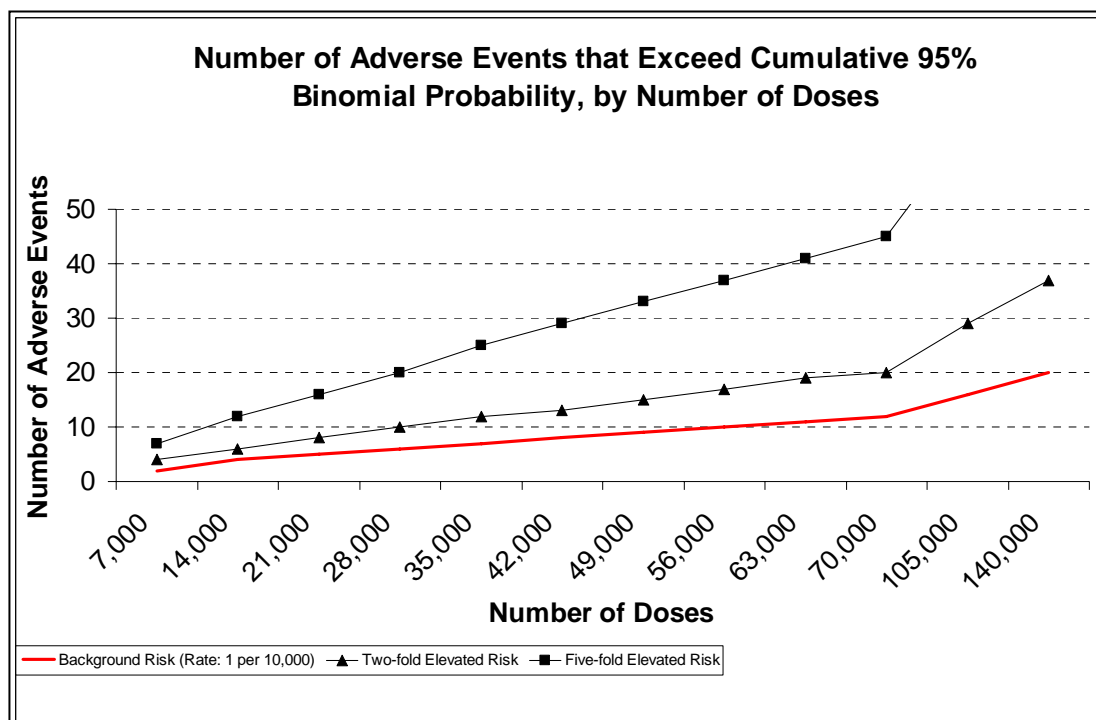
Background rates will be determined from the last 5-10 years of hospitalisation data, if necessary by age group. For some conditions (e.g., seizures) estimation of expected rates may be based on events seen at the DHB where monitoring is taking place. Using this rate, we will be able to demonstrate the expected occurrence of a specific adverse event graphically. The number of expected adverse events will be plotted against time with, for example, the upper bound of the 95% confidence interval of the expected rate being indicated. Two or more times this rate as a threshold, (or the actual rate) for consideration by the ISMB, can also be plotted – see sample graph below which reflects an assumed background rate of 1 per 1,000,000 events. By comparing the actual cumulative number of adverse events that are detected through the above described surveillance system with pre-determined thresholds, the DMG can alert the ISMB if previously agreed thresholds are exceeded. It is important to note that the null hypothesis being tested is that the vaccination will not raise the detected background rate of the event in question. Thus, all events whether related to vaccination or not will be counted. It is envisaged that if the background rate of events is

exceeded by an agreed margin, further investigation and analysis as described in section 6 could occur as directed by the ISMB. It is anticipated Poisson regression will be one of the key methods used to assess whether the background rate of events following the introduction of MeNZB™ differs from historical rates over the past 5-10 years. On the advice of the ISMB confidence intervals derived from standard deviation will be calculated as well as those derived from binomial probability.



5.6 Adverse events following routine childhood vaccines

Published data concerning the rates of events following routine childhood vaccines will be used to derive “expected” / “acceptable” rates of events following immunisation with MeNZB™ vaccine. Where expected rates of adverse events following vaccination have been defined a graph similar to that discussed above will be produced plotting the detected events against the number of vaccinations administered. The graph will indicate, for example, when the upper bound of the 95% confidence interval of the expected rate (acceptable level of risk) has been exceeded (see following graph). It is envisaged that if the threshold level of risk of these selected adverse events is exceeded further investigation and analysis as described in section 6 could occur as directed by the ISMB.



5.7 National Immunisation Register

The NIR provides denominator data of vaccine doses administered and describes the progress of the vaccination campaign using a standard report. It will also be used to determine vaccination status on cases of interest and if necessary for matching with the hospital discharge database.

Approach to the ascertainment of vaccination status

The accurate ascertainment of vaccination status is critical for the post-licensure monitoring of vaccine safety. It is intended that a comparison of rates of events in vaccinees and non-vaccinees be presented by the DMG to the ISMB and, if vaccination status cannot be reliably ascertained, this comparison will not be possible. It is therefore important that the vaccination status, particularly of those who suffer rare events is independently confirmed, as the NIR is new and will be largely untested when the rollout commences. The safety monitoring team propose to take the following approach to the confirmation of vaccination MeNZB™ status.

1. The National Immunisation Register (NIR) is the key tool for the ascertainment of vaccination status. It is accepted that if information on a vaccinee is recorded on the NIR, either indicating vaccination or indicating refusal to be vaccinated, then there is a high probability that this information is accurate. However, as the NIR is not being “pre-populated” for the meningococcal vaccination campaign, for an individual who has not been vaccinated no record will appear on it.
2. The NIR team are proposing sufficient internal audits of their system to ensure that once vaccination information is inserted on the School Based Vaccination System (SBVS) or on a practice management

system (PMS) with electronic messaging to the NIR that such data will appear accurately on the NIR. The NIR team will provide a description of such audits.

3. The NIR team cannot take responsibility for vaccinators to either fail to or incorrectly enter vaccination status on the SBVS or PMS.
4. For those general practices in which information transmission is paper based or for outreach providers, the possibility of failure to or incorrectly enter information is greater. However it is still probable that information recorded on the NIR, indicating that an individual is vaccinated or has declined vaccination, will be correct.
5. The most important question is how reliable an indication of not having being vaccinated is the absence of information on the NIR.
6. A crude audit can be performed by ensuring that regular returns are obtained from all vaccinators and the numbers of doses of vaccine distributed reasonably correspond to provider returns to the NIR allowing for vaccine which might be stored prior to use.
7. It is proposed to conduct an audit of the recording of vaccination status on the NIR. The questions to be answered by this audit are
“For all vaccine-eligible children (defined by specific time, place, and age characteristics), can we rely on the MeNZB™ vaccination status data contained in the NIR? And, conversely, for all vaccine-eligible children (defined by specific time, place, and age characteristics), can we reliably interpret the absence of a vaccination record on the NIR as an indication that that child has not been vaccinated with MeNZB™?”

The DMG will oversee the conduct of an audit of a representative random sample of those who are eligible for vaccination in CMDHB. This will ideally be conducted at, at least two, time points; towards the end of the first six weeks of the first stage roll-out and towards the end of the first stage rollout. A detailed proposal is under development.

In addition the Safety Monitoring Team proposes the following approach to the ascertainment of vaccination status.

This will be considered under the following headings.

Rare Event Monitoring

- A. Encephalitis, AFP, Thrombocytopenia, Death, rare and unusual events.
- B. Anaphylaxis and HHE
- C. All other conditions

All Event Monitoring

A. Encephalopathy , AFP, Thrombocytopenia*, Death, rare and unusual events.

For this group of conditions, which occur relatively infrequently, accurate ascertainment of vaccination status is critical. We propose to accept as accurate the information recorded on the NIR. We consider such information will be accurate for the reasons outlined

above. However for those for whom no information appears on the NIR the following algorithm will be followed:-

Does the individual reside, attend a primary care provider or attend school in an area eligible for vaccination?

If No - accept they are not vaccinated.

If Yes or uncertain - ask the clinician involved in their care to check on vaccination status.

Is vaccination status recorded in the clinical records?

If yes - please ascertain source of information

If not documentary or no record - please check with primary care provider or school based vaccination system to ascertain immunisation status.

* excludes oncology related thrombocytopenia.

B. Anaphylaxis and HHE

For these vaccine related events we would expect accurate information on vaccination status to be recorded in the clinical records. This will be compared to information recorded on the NIR. If the information is not consistent between the two sources we would ask the clinician involved to ascertain vaccination status.

C. All other conditions

For all other conditions, seizures will be taken as an example. Too many seizures occur to individually ascertain vaccination status. Therefore the data obtained from the NIR will be used in analyses making the assumption that the absence of information on the NIR equates with not being vaccinated. Rates of seizures in vaccinees and non vaccinees will be compared with each other and historical rates. Sensitivity analyses, with differing assumptions around the vaccination status of those recorded as not having been vaccinated, may be carried out. Rates in vaccinees will be compared to rates of seizures following other vaccines. If the rates of seizures are consistent in vaccinees, non vaccinees and with historical rates then no further action will be taken. However if the rates are inconsistent and it is important to precisely ascertain vaccination status a project will be conducted to accurately ascertain the status of a representative random sample of those who suffer seizures

All event Monitoring

This project uses hospital discharge data which will not be available till sometime has elapsed after the vaccination programme has commenced. It is anticipated that as experience with the NIR is gained its accuracy will improve. Other projects as described above will estimate the level of inaccuracy of the NIR which can be taken into account when analysing these data.

5.8 ESR Meningococcal Surveillance data

These data will be analysed to determine the annual risk of all meningococcal disease and that caused by the vaccine strain by age group. This will be

calculated over the last 5 years and will cover those aged < 1, 1 – 4 years, 5 - 9 years, 10 – 14 years and 15 – 19 years. A range of rates will be calculated for each age group deriving ethnic and in some cases area specific rates, providing the denominator numbers are not too small.

5.9 *Limitations of these data*

5.9.1 Chance

It is important to note that for rare events which occur early in the vaccination programme the role of chance will be difficult to assess and the statistical appraisal of risk may be of very low statistical power. Indeed as has been seen for events which have a true rate of 1 in 1,000,000 the occurrence of a single such event in the early stages of the vaccination campaign would exceed the upper bound of 95% confidence interval of that frequency and could signal a problem with the vaccine. See graph in section 5.5 above. It is important to recognise that it may be unethical to stop the campaign prematurely on the basis of emerging trends from a small number of events as such findings may be transient and within expected rates when a larger sample has accumulated. An example from a trial investigating the potential of clofibrate to reduce coronary mortality illustrates this point⁵. On three occasions during the first 30 months of the trial the mortality reduction in the clofibrate group attained significance at the $P = 0.05$ level. However the guidelines for stopping required a higher level of significance⁶. The trial continued, eventually demonstrating no reduction in mortality in the clofibrate group.

It is therefore proposed that a small number of events, as defined by the ISMB, early in the vaccination campaign should not result in any action other than intensified surveillance and/or investigation, and possibly slowing of delivery of vaccine.

5.9.2 Bias

In the data obtained from hospital based monitoring there are potential sources of bias. Selection bias may occur if those who suffer an event following immunisation are more likely to attend hospital than those who suffer the same event but have not been immunised. It is possible that the publicity surrounding MeNZB™ immunisation and the information given to those who are immunised may encourage their presentation at hospital because “we thought you wanted to know”. However events which precipitate attendance at hospital do so because of their inherent nature and severity. Attendance at hospital involves expense in terms of travel and time, though in CMDHB there is a tendency to use the ED for primary care. Whilst it is possible that a factor in the decision to attend hospital will be because of a recent immunisation, it is not considered that this source of bias will to be of significance.

For the IVMP selection bias, or at least diminished representativeness, is possible in that only GP's using Medtech 32 and fully computerised clinical

records will be enrolled. With this group there may be a bias towards those in the higher socio-economic groups and of European ethnicity. However the NZPhvC team are making considerable efforts (to date successful) to enrol general practices whose population includes considerable numbers of those of Maori and Pacific ethnicity. There is also no reason to suspect that MeNZB™ vaccine is more likely to cause adverse events in those of differing ethnic or socio-economic backgrounds and accordingly this source of bias is not considered significant.

For the routine passive reporting system selection bias is anticipated. The publicity surrounding the vaccination campaign will include a general encouragement to report. It is likely this will be reinforced by the anti-immunisation lobby. It has been reported elsewhere⁷ that there is “over-reporting of serious events coincidentally associated with the timing of immunisation, particularly for newer vaccines and among children”. However the main purpose of the passive reporting system is to detect signals for further investigation. It cannot attribute causality, nor assess frequency.

Observational / information bias could occur in the hospital based monitoring system. Because the method of detecting and assessing events differs from the method of obtaining the comparative background data it is possible that an overestimate of the rate of some events could occur. An underestimate is unlikely as case ascertainment for events is well developed and the validity of case finding will have been established. Overestimation can be assessed, at least in part, by comparing the hospital based monitoring data with the hospital discharge diagnoses on the same cases when those data are available. This assumes that the discharge diagnosis will not be altered by the monitoring system. We believe it is unlikely that the process of case detection used in the hospital based monitoring project will interfere with discharge diagnosis categorisation, other than to increase its precision in a small number of cases. The nurse monitors are completing case forms on all cases, irrespective of vaccine status, and simply reviewing what has already been written in case notes. It is possible for some events, e.g. encephalopathy, more investigations will be done with the intention of establishing an aetiological diagnosis: but this simply increases diagnostic precision. Furthermore there will be no contact between the monitoring system and those involved in coding.

This same type of bias is not anticipated for either the passive reporting system or the IVMP. Under both systems the assessment of events is standardised and the NZPhvC is very experienced in adverse event assessment. For the IVMP all clinical events within six weeks of immunisation will be assessed. It will not be possible for anyone to influence which events will be assessed.

5.9.3 Confounding

In the hospital based programme confounding could occur if those most likely to suffer (or not suffer) an event following vaccination were also more (or less)

likely to be vaccinated; this has been referred to as “confounding by contraindication”⁸. This may have occurred in studies indicating that Sudden Infant Death Syndrome (SIDS) is less likely in those who have been vaccinated. The explanation may simply be that the risk factors for SIDS are the same as those for failure to be vaccinated and as a result those who suffer SIDS are less likely to be vaccinated, giving a false impression of the “protective” effect of vaccination. At present it is not possible to state whether or not such confounding could apply for individual events in this programme but this will have to be assessed in any analysis, or at least considered in interpreting any results from the various above-described surveillance activities.

6 Other Analyses

6.1 Situations requiring further analyses

It is envisaged that further analyses will be required under the following circumstances:

- *Unusual clusters* – More than the expected numbers of an event have occurred in a designated place over a specified time period.
- *New hypotheses* – e.g. a case report or case series indicates that a syndrome/disease may occur following vaccination. This may occur with conditions not readily detected by our surveillance systems because of long latency or in those in which hospitalisation does not normally occur e.g. autism, chronic fatigue syndrome, attention deficit hyperactivity disorder etc.
- *Systematic review* In the longer term, e.g. 3-5 five years after the vaccination programme has commenced, a systematic review of all the safety databases, established during the vaccination campaign, should occur to ascertain, where possible, estimates of absolute and relative risk of adverse events in vaccinees compared to non-vaccinees.

6.2 Methodologies

In the circumstances described above it is anticipated that the following general approach will be taken:

1. Develop a case definition. For certain conditions the case definitions could be established prior to vaccination commencing e.g. chronic fatigue syndrome, Autism, attention deficit hyperactivity disorder (see below)
2. Institute case finding – the methods used will depend upon the condition of concern.
3. Apply the case definition.
4. Assess and confirm vaccination status of cases who fulfil the case definition

5. Apply the analytic methodology deemed most appropriate e.g. case control, case series analysis, Poisson regression etc.

For the purpose of such studies it is the intention of the safety monitoring team to propose case definitions for chronic fatigue syndrome, autism spectrum disorder and attention deficit hyperactivity disorder (ADHD) prior to the start of the use of MeNZB™ vaccine (see Appendix 4). NB This is in addition to the case definitions already established for the hospital rare event monitoring system.

6.2.1 Cluster definition and investigation

A systematic, integrated approach is needed for responding to clusters of adverse events potentially related to MeNZB™ vaccination. To meet these needs, the DMG will develop and put into place an internal management system to assure prompt investigation of clusters. Such a system will include the establishment of a locus of responsibility and control contained in written operating procedures and supported by dedicated resources, and a process for involving the ISMB and MMT.

Appendix 5 contains a draft manual that will guide the investigation of AEFIs. The approach is an adaptation of the generic model suggested by the US Centers for Disease Control and Prevention for investigating clusters of health events, and comprises a four-stage process:

- initial ascertainment of cases and summarization of relevant data,
- assessment,
- feasibility study, and
- etiologic investigation.

6.3 Deaths outside hospital

It is expected that deaths occurring within or presenting to hospitals will be detected by the hospital-based monitoring system. It is important that deaths occurring outside hospital are also detected, particularly those occurring as a result of SIDS.

Under the New Zealand Health and Disability Act (2000), the Child Youth and Mortality Review Committee (CYMRC) reviews and reports to the Minister of Health on the deaths of children and youths, with a view to reducing the number of deaths.

There exists a legal requirement for all deaths to be notified to the Registrar of Births Deaths and Marriages within three days. These records are forwarded to the CYMRC database on a weekly basis.

The CYMRC has created a MVS Mortality Review Committee, with the MVS DMG staff acting as the Committee's agents. This step enables DMG timely access to all records held on the CYMRC database.

The epidemiology of SIDS is clearly established in New Zealand⁹. It is likely that a case or cases of SIDS will occur by chance following vaccination with MeNZB™ vaccine. To assist in assessing the significance of SIDS occurring in a close temporal relationship to MeNZB™ vaccination the approach outlined in section 5.5 will initially be undertaken followed, as warranted, by the conduct of more intensive epidemiologic investigation.

7 Assessment of causality

The DMG proposes the following framework for assessing causality for events following MeNZB™. This is based on the IOM framework for assessing causality derived from their report “Adverse effects of Pertussis and Rubella Vaccines”¹⁰ and should be agreed by the ISMB.

Three questions need to be asked in causality assessment¹⁰

1. Can the vaccine cause an adverse event?
2. If so how frequently does it do so?
3. Did the vaccine cause a particular case of an adverse event?

This latter question concerns the attribution of causality in individual cases and “the judgement in a specific case would depend on the circumstances concerning that case alone, in isolation about a causal relationship in general”.¹⁰

The ISMB is charged with answering the first two of these questions for adverse events which occur during the term of their appointment whilst MeNZB vaccine is being delivered in New Zealand prior to full licensure. The assessment of causality in individual cases may be required and if so is likely to be conducted by the Accident Compensation Commission.

Assessments of whether vaccines can cause specific adverse events, and if so, how frequently, are fraught with difficulty, particularly for rare events. We feel the most reasonable approach is that taken by the Institute of Medicine (IOM) in its various assessments of vaccine adverse events. The IOM committee used six general considerations when assessing causality as follows¹⁰

Strength of association - usually expressed in epidemiologic studies as the magnitude of the measure of the effect e.g. relative risk or odds ratio.

Dose-response relation – If such a relationship exists, i.e. in the context of MeNZB vaccine is an event more likely after further exposures, this tends to strength the inference that the association is causal.

Temporally correct association – The exposure should precede the event and in a time frame consistent with the “incubation period” of the event. If the exposure occurs after the onset of the event or in a time period well in

advance of the event such that the length of the “incubation period” is unlikely then this indicates that the exposure is unlikely to cause the event.

Consistency of association – If an event is associated with MeNZB vaccine in several different populations and in several different time periods and age groups this would support causality.

Specificity of Association – This indicates the degree to which the exposure predicts the frequency or magnitude of the event. In an extreme example if the event only occurs after MeNZB vaccination i.e. is a new syndrome then causality is strongly inferred. However, although possible, this is unlikely to occur with MeNZB vaccination.

Biological Plausibility – Does the association fit with current biologic or medical knowledge? Alternatively is there a plausible mechanism by which MeNZB could cause the event being investigated.

We recommend that this is the framework under which the ISMB considers causality of events following MeNZB vaccination. It is anticipated that the ISMB will debate and decide upon the framework it will use to assess causality at its first meeting and to assist in this process a discussion around causality assessment is attached in appendix 6.

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Appendix 1: Executive summary from IVMP report of trial in Dunedin

The Intensive Vaccines Monitoring Programme (IVMP) was piloted in two Dunedin medical centres from 28 July 2003 until 26 September 2003. The programme was successfully implemented in the two practices.

Software installation and data transfer

The CARM-IVMP upgrade to MedTech32 delivered the required data in an appropriate format. The data was transferred seamlessly through HealthLink on a daily basis. There were some minor issues around the installation and setup of the CARM-IVMP upgrade to MedTech32 and the HealthLink mailbox. Provision will be made in the nationwide monitoring for practices to bring in expert IT assistance where there are difficulties around installation.

Immunisation monitoring card

The immunisation monitoring card that was used in the pilot to facilitate other providers to report the details of consultations for IVMP cohort patients did not result in any other provider reports. As a result of the limited success of the monitoring card in generating other provider reports, this will not be used in the main monitoring. Instead, the emphasis will be on obtaining information on other provider visits through the practice management software by recruiting practices that provide after hours services or where information on other provider visits is entered into the practice management software and where this is not the case, by asking practice nurses that they ask parents about other provider visits at the next immunisation.

IVMP application and assessment

The application to capture, store and make the data available for assessment worked as anticipated. The data obtained from practices was adequate to undertake standard adverse event assessment.

Reporting

The standard reports based on the six week monitoring period were prepared using the pilot data. The required reports can be prepared using the data collected. As complete coverage of other provider visits is not possible given the practical limitations, a document outlining the extent of information that will be collected on other provider visits will be prepared and made available to the users of the data.

Recommendation

That the Intensive Vaccines Monitoring Programme is implemented in 20-30 medical centres around New Zealand

Appendix 2: Reviews of rates of events over the last 10 years

This appendix is a separate document.

Appendix 3: Rates of specified events following routine childhood vaccines

The purpose of this appendix is to present the frequency of various events which have followed other vaccines, notable acellular and whole cell pertussis vaccines, to provide a background against which the occurrence of such events which may follow MeNZB™ can be assessed. The upper bound of the 95% confidence interval of these rates, or the rate itself as determined by the ISMB will be plotted on the graph illustrated in section 5.6 above. This will enable the DMG to track the likely frequency of monitored events and alert the ISMB chair when a pre-determined frequency has been exceeded.

Rates have been derived for the following events

Seizures

Following whole cell pertussis vaccine the rate of seizure has been estimated as 1 in 12,500 doses¹, 1 in 1,750 doses² and 1 in 3,926 doses³.

Following acellular pertussis vaccine the rate of seizure has been assessed as 1 in 19,496 doses⁴ and 1 in 15,912 doses³.

The IMPACT monitoring system in Canada has demonstrated a 79% decrease in the frequency of febrile seizures following acellular pertussis vaccine when compared to whole cell pertussis vaccine { David Scheifele, Scott Halperin – personal communication}. A 70% reduction has been observed the Vaccine Adverse Event Reporting System⁵

The rate of seizure following DTwP approximates 1 in 2,000 whilst the rate of seizure following DTaP approximates 1 in 20,000. It is therefore proposed that seizures following MeNZB™ vaccine be compared with three incidence rates: 1 in 2,000, 1 in 10,000 and 1 in 20,000, approximating to the rates of seizures following DTP, DTaP vaccine and an intermediate rate. The upper bound of the 95% confidence interval of these rates should be graphically displayed as shown in section 5.6. The threshold for alerting the ISMB should be a rate which exceeds 1 in 10,000.

Hypotonic Hyporesponsive Episodes (HHE)

Following whole cell pertussis vaccine these have been reported at a rate of 1 in 1,750 vaccinees². IMPACT reports a 67% decrease in the incidence of HHE following the introduction of acellular pertussis vaccine {David Scheifele, Scott Halperin – personal communication} and this is consistent with the reduction seen with VAERS reporting⁶

The HHE rate following DTwP vaccine approximates to 1 in 2,000 whilst for DTaP it approximates to 1 in 10,000. It is therefore proposed that HHE following MeNZB™ vaccine be compared with three incidence rates 1 in /2,000, 1 in 5,000 and 1 in 10,000 approximating to the rates of HHE following

DTP, DTaP vaccine and an intermediate rate. The upper bound of the 95% confidence interval of these rates should be graphically displayed as shown in section 5.6. The threshold for alerting the ISMB should be a rate which exceeds 1 in 5,000.

Persistent Inconsolable Crying

This is not one of the conditions which will be detected by the hospital based monitoring programme but it is likely to be reported to the Centre for Adverse Reaction Monitoring. Persistent inconsolable crying lasting for 3 hours within 3 days of vaccination occurred at a rate of 1 in 113 vaccinees for DTwP as reported by Uberall et al³. The rate decreased with increasing number of doses and presumably age. The rate was 4.4 fold less in the DTaP recipients³. In Cody's study² infants who appeared to have "truly unusual high pitched cry within 48 hours of immunisation did so at a rate of 1 in 900.

Injection site limb pain following MeNZB™ vaccine occurs at quite a high rate. Assuming that in infants pain is the cause of persistent inconsolable crying, then the rate at which this could be anticipated is likely to be between 1 in 100 and 1 in 1,000 vaccinees with the former rate being more likely after the first vaccine and the rate decreasing with increasing doses and age. As this event is not likely to involve hospitalisation reporting of it will be through the passive reporting system and the IVMP.

Thrombocytopenia

The rate of thrombocytopenia occurring after MMR is reported as 1 in 24,000 doses¹. A further British study reported an incidence of 1 in 29,000 doses of MMR vaccine⁷. Thrombocytopenia occurring within 30 days after immunisation of Canadian children is "rare and usually benign resolving within 1 month in most children". 80% follows MMR vaccine with the occurrence after DTwP or DTaP containing vaccines being described as rare. Further the mean interval between immunisation and onset for DTwP or DTaP containing was 6.7 days (range 1-24) compared to 16.4 (range 6-30) for MMR.

It is therefore proposed that the occurrence of thrombocytopenia with onset within 30 days after MeNZB™ vaccine be compared with rates of 1 in 50,000 and 1 in 30,000. The upper bound of the 95% confidence interval of these rates should be graphically displayed as shown in section 5.6. The threshold for alerting the ISMB should be a rate which exceeds 1 in 30,000.

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Appendix 4: Case definitions for events following MeNZB™ vaccination

Introduction

The purpose of this appendix is to *a priori* define the case definitions which will be used in an epidemiologic investigation designed to determine the role of MeNZB™ in the causation of an adverse event. During an epidemic control campaign in which 3,000,000 doses of vaccine are administered to 1,000,000 recipients aged < 20 in New Zealand adverse events following vaccination will occur. Individuals will wish to know whether such events are likely to have been caused by MeNZB™, and public and professional concern that the vaccine causes serious adverse events will arise. To answer these questions clinical and epidemiological investigations will be required. For the latter, case definitions, to define the numerator and population denominators to allow the calculation of rates are essential components. In section 1 of this document the general approach to screening criteria, case definitions and the definition of denominators for the calculation of rates of events is outlined.

Specified events which result in hospitalisation will be detected by the hospital based monitoring system as described in the safety monitoring plan. The case definitions, including screening definitions, for these events form section 2 of this appendix.

It is likely that unanticipated events which cause concern will occur. Some of these events may not involve hospitalisation nor have a specific diagnostic test associated with them. Whilst it is not known what events may occur following vaccination and give rise to concern, there are a number of conditions where this can be anticipated. When such concern arises the available information will be presented to the ISMB seeking their advice on whether a formal epidemiologic investigation needs to be conducted (see cluster investigation protocol). To reduce the potential for bias *a priori* case definitions for those events which can be anticipated will be established and submitted to the ISMB for approval. When a hypothesis arises for which a case definition has not been determined *a priori*, then establishing an appropriate definition, to be agreed by the ISMB, will be the first task to be undertaken in the investigation, as outlined in paragraph 6.2 of the safety monitoring plan. Case definitions for several anticipated conditions are proposed in section 3 of this appendix.

1. General Approach

When concern has arisen that an event may be caused by MeNZB™ and an investigation is required three key *a priori* steps must be undertaken. These are the definition of -

- Sensitive screening criteria,
- A specific case definition,
- The population at risk.

1.1 Screening criteria

The purpose of this definition is to ensure as complete case finding as possible and accordingly it must be sensitive. It is not anticipated that all cases detected using such criteria would fulfil the specific case definition and so form part of the numerator for the purpose of calculating rates. In general it is anticipated that such screening criteria would include for example all cases diagnosed as such in the hospital discharge data base or, from another data source, all “doctor diagnosed conditions”.

1.2 Clinical case definition

Cases detected using the screening criteria would then be subject to review to ascertain whether they met the specific case definition, established *a priori*. Cases that did so would form the numerator for the calculation of rates. It is possible that in some instances, e.g. sensitivity analyses, rates would also be calculated using alternative less specific, more sensitive case definitions.

1.3 Epidemiological case definition

Cases which fulfil the case definition and occur in the predetermined time windows after MeNZB™ vaccination fulfil the epidemiological case definition.

1.4 Population at risk.

In general the progress of the rollout will establish the population at risk. For example if the vaccine has only been given to those aged 5 and older then that will establish the age group of those at risk. If at the time when the concern has arisen only those in the greater Auckland area have been eligible to receive vaccine, then the population at risk will be those residing in greater Auckland. The age group at risk will also be established by the condition; e.g. the age group for Sudden Infant Death Syndrome (SIDS) is up to one year of age whilst for acute flaccid paralysis it will be all aged less than 20.

The National immunisation register will define the number of vaccinees at any stage of the campaign and enable the calculation of rates in vaccinees. These rates may be compared to rates in non vaccinees in the population at risk, though it is anticipated, as described in the safety monitoring plan, that historical rates or rates in the rest of New Zealand who have not yet been vaccinated may require to be used for comparison. It is also possible that a case-control approach may be used in which the vaccination status of cases (with a disease) will be compared to the vaccination status of matched controls (without the disease).

The time during which the population at risk is exposed will also depend on the date of commencement of vaccination in the area in question. This will enable rates to be established using person years at risk.

2 Screening and case definitions for hospital based surveillance

It is important to note that case report forms for the events defined below are completed if the screening criteria are met. The case definition is applied only after the case report form is completed. The vaccination status will be ascertained by the data management group using the National Immunisation Register. This means that the nurse monitors who complete the case report forms use only the screening criteria. The case definition is applied by the Clinical Review Committee (see terms of reference).

2.1 Acute Flaccid Paralysis

Screening Criteria

Acute flaccid paralysis or sensory dysfunction in one or more limbs, or a bulbar paralysis.

Clinical Case Definition

Acute flaccid paralysis or sensory disturbance in one or more limbs, or a bulbar paralysis (includes all motor cranial nerves); **NOT** explained by trauma, toxins, drugs, spinal cord compression (haematoma, abscess, tumour), systemic illness, metabolic disturbance or psychogenic causes. Includes:

- acute transverse myelitis
- demyelinating disease such as Guillain-Barre Syndrome (post infectious polyneuritis) which typically includes symmetrical muscle weakness, worse over the distal portions of the extremities, areflexia and an isolated raised CSF protein
- polyneuropathies

Epidemiological Definition

Meets clinical case definition and occurs after MeNZBTM vaccination.

2.2 Anaphylaxis

Screening Criteria

Severe allergic reaction leading to signs of circulatory failure (decreased level of consciousness, hypotension, tachycardia) with or without bronchospasm and/or laryngospasm/laryngeal oedema.

Clinical Case Definition

Severe allergic reaction usually occurring within 24 hours of MeNZBTM vaccination (most often within 30 minutes) leading to signs of circulatory failure (decreased level of consciousness, hypotension, tachycardia) with or without flushing, urticaria, angio-oedema, airway obstruction; and **NOT** attributed to other causes of shock or an allergic reaction following exposure to any other allergen (e.g. drugs, food, insect bite or sting).

Epidemiological Definition

Meets clinical case definition.

2.3 Encephalopathy [Includes acute encephalitis, toxic encephalopathy, acute disseminated encephalomyelitis,]

Screening Criteria

A major illness with sudden onset with either of the following:

- i. distinct alteration in level of consciousness **and/or** mental status (behaviour and/or personality) for \geq 24 hours
- ii. seizures **and** new focal neurological signs that persist for \geq 24 hours

Clinical Case Definition

A major illness occurring characterised by either of the following;

- i. distinct alteration in level of consciousness **and/or** mental status (behaviour and/or personality) for \geq 24 hours
- ii. seizures **and** new focal neurological signs that persist for \geq 24 hours and **NOT** explained by the presence of trauma, haemorrhage, infection, drugs, toxins or fluid, electrolyte or metabolic disturbance, or psychiatric illness:

Epidemiological Definition

Meets clinical case definition and occurs after MeNZB™ vaccination

2.4 Hypotonic-hyporesponsive episode (HHE)

Screening Criteria

Sudden onset of an episode occurring within 48 hours of any vaccination (usually < 12 hours) lasting from 1 minute to several hours with all the following features - limpness, reduced responsiveness and pallor / cyanosis - in a child < 10 years.

Clinical Case Definition

Sudden onset of an episode occurring within 48 hours of MeNZB™ vaccination (usually < 12 hours) lasting from 1 minute to several hours with all the following features - limpness, reduced responsiveness and pallor / cyanosis - in a child < 10 years. The event is **NOT** due to anaphylaxis, convulsion or post-ictal state, simple faint or other syncopal episode in child older than 2 years.

Epidemiological Definition

Meets clinical case definition

2.5 Petechial/Purpuric Rash

Screening Criteria

The appearance of a petechial or purpuric rash.

Clinical Case Definition

The appearance of a petechial or purpuric rash (more than 3 lesions) and **NOT** attributed to thrombocytopenia, meningococcal disease, other infection (particularly viral), vasculitis (eg Henoch Schonlein purpura), raised venous pressure (eg coughing, vomiting) or allergy (eg eczema, contact irritation).

Epidemiological Definition

Meets clinical case definition and occurs within 7 days of MeNZB™ vaccination

2.6 Seizures/Convulsions

Screening Criteria

Onset of a seizure accompanied by a disturbance in level of consciousness and motor manifestations.

Clinical Case Definition

Occurrence of a seizure with loss of consciousness with motor manifestations; and **NOT** otherwise categorised as acute encephalopathy or HHE; and **NOT** explained by intoxication, hypoxia or vasovagal episode, CNS infection, shunt obstruction, head trauma, cerebral haemorrhage, stroke, neoplasm, or fluid, electrolyte or metabolic disturbance, or psychogenic cause. Fever ($T > 38^{\circ}\text{C}$) may or may not be present.

Epidemiological Definition

Meets clinical case definition and occurs within 72 hours of MeNZB™ vaccination

2.7 Thrombocytopenia

Screening Criteria

A platelet count of less than $50,000 \times 10^9/\text{L}$.

Clinical Case Definition

A platelet count of less than $50,000 \times 10^9/\text{L}$ and **NOT** explained by other conditions such as malignancy, haematological disorders, acute or chronic infection, or drugs. Apart from spontaneous bruising, mucosal bleeding, petechiae or purpura, the physical examination and the blood film must be otherwise normal.

Epidemiological Definition

Meets clinical case definition and occurs within 8 weeks of MeNZB™ vaccination

2.8 Death

Screening Criteria

Any death.

Clinical Case Definition

Any death after MeNZB™ vaccination.

Epidemiological Definition

Meets clinical case definition.

2.9 Unusual event**Screening Criteria**

Unusual event with cause otherwise undefined.

Clinical Case Definition

Unusual event with cause undefined after MeNZB™ vaccination.

Epidemiological Definition

Meets clinical case definition.

3. Case definitions - Other events**3.1 Chronic Fatigue Syndrome.**

We propose to use the surveillance case-definition proposed by the International Chronic Fatigue Syndrome Study Group [Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann Intern Med* 1994; 121; 953-959.].

In short, “prolonged fatigue” is defined as self-reported, persistent fatigue lasting 1 month or longer; “chronic fatigue” is defined as self-reported persistent or relapsing fatigue lasting 6 or more consecutive months.

However, the presence of prolonged or chronic fatigue requires clinical evaluation to identify underlying or contributing conditions that require treatment. The Study Group suggested that the following items should be included in the clinical evaluation:

1. A thorough history that covers medical and psychosocial circumstances at the onset of fatigue; depression or other psychiatric disorders; episodes of medically unexplained symptoms; alcohol or other substance abuse; and current use of prescription and over-the-counter medications and food supplements.
2. A mental status examination to identify abnormalities in mood, intellectual function, memory, and personality. Particular attention should be directed toward current symptoms of depression or anxiety, self-destructive thoughts, and observable signs such as psychomotor retardation. Evidence of

a psychiatric or neurologic disorder requires that an appropriate psychiatric, psychological, or neurologic evaluation be done.

3. A thorough physical examination.
4. A minimum battery of laboratory screening tests including complete blood count with leukocyte differential; erythrocyte sedimentation rate; serum levels of alanine aminotransferase, total protein, albumin, globulin, alkaline phosphatase, calcium, phosphorus, glucose, blood urea nitrogen, electrolytes, and creatinine; determination of thyroid-stimulating hormone; and urinalysis.

In clinical practice, no additional tests, including laboratory tests and neuroimaging studies, were recommended for the specific purpose of diagnosing chronic fatigue syndrome. Rather, tests should be directed toward confirming or excluding other etiologic possibilities, such as multiple sclerosis. In these cases, additional tests or procedures should be done according to accepted clinical standards. Examples of specific tests that do not confirm or exclude the diagnosis of chronic fatigue syndrome include serologic tests for Epstein-Barr virus, retroviruses, human herpesvirus 6, enteroviruses, and *Candida albicans*; tests of immunologic function, including cell population and function studies; and imaging studies, including magnetic resonance imaging scans and radionuclide scans (such as single-photon emission computed tomography and posi-tron emission tomography) of the head.

3.2 Autistic Disorder and Attention Deficit / Hyperactivity Disorder.

For these disorders we propose to use the definitions from DSM IV. These are appended below.

DSM IV Diagnostic criteria for 299.00 Autistic Disorder.

- A. A total of six (or more) items from (1), (2) and (3), with at least two from (1), and one each from (2) and (3):
 1. qualitative impairment in social interaction, as manifested by at least two of the following:
 - marked impairment in the use of multiple nonverbal behaviours such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction.
 - failure to develop peer relationships appropriate to developmental level.
 - a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (eg by a lack of showing, bringing, or pointing out objects of interest)
 - lack of social or emotional reciprocity.
 2. qualitative impairments in communications as manifested by a least one of the following:

- delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
 - in individuals with adequate speech, marked impairment in the ability to initiate or sustain conversation with others.
 - stereotyped and repetitive use of language or idiosyncratic language
 - lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level.
3. restricted repetitive and stereotyped patterns of behaviour, interests, and activities, as manifested by at least one of the following:
- encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus.
 - apparently inflexible adherence to specific, non-functional routines or rituals.
 - stereotyped and repetitive motor mannerisms (eg hand or finger flapping or twisting, or complex whole-body movements)
 - persistent preoccupation with parts of objects.
- B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play.
- C. The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder.

DSM IV Diagnostic criteria for Attention-Deficit/Hyperactivity Disorder

- A. Either (1) or (2):
1. six (or more) of the following symptoms of **inattention** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Inattention

- Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities.
- Often has difficulty sustaining attention in tasks or play activities
- Often does not seem to listen when spoken to directly
- Often does not follow through on instructions and fails to finish school work, chores or duties in the workplace (not due to oppositional behaviour or failure to understand instructions)
- Often has difficulty organising tasks and activities
- Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)

- Often loses things necessary for tasks or activities (eg toys, school assignments, pencils, books or tools)
 - Is often easily distracted by extraneous stimuli
 - Is often forgetful in daily activities
2. Six (or more) of the following symptoms of **hyperactivity-impulsivity** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity

- Often fidgets with hands or feet or squirms in seat
- Often leaves seat in classroom or in other situations in which remaining seated is expected.
- Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
- Often has difficulty playing or engaging in leisure activities quietly
- Is often “on the go” or often acts as if “driven by a motor”
- Often talks excessively

Impulsivity

- Often blurts out answers before questions have been completed
 - Often has difficulty awaiting turn
 - Often interrupts or intrudes on others (eg butts into conversations or games)
- B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.
- C. Some impairment from the symptoms is present in two or more settings (e.g. at school [or work] and at home).
- There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.
 - The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (eg Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

3.3 Sudden Infant Death Syndrome (SIDS).

For this disorder we propose to use the definition of the Centers for Disease Control as described in the references below.

The sudden death of an infant under one year of age which remains unexplained after a thorough case investigation including the performance of a complete autopsy, examination of the death scene and a review of the clinical history.

References for SIDS

1. Centers for Disease Control Guidelines for death scene investigation of sudden unexplained infant deaths: recommendations of the Interagency panel on Sudden Infant death Syndrome. MMWR 1996;45 (no RR-10):2.
2. Willinger M James L Catz c Defining the Sudden Infant Death Syndrome (SIDS): deliberations of an expert panel convened by the National Institute of Child Health and Human Development} *Pediatr pathol* 1991;11:677-84.

Appendix 5: Cluster Investigation Protocol

DRAFT (26 November 2003)

Guidelines for Investigating Clusters of Adverse Events Potentially Related to Receipt of New Zealand's meningococcal B vaccine (MeNZB™)

OVERVIEW

A systematic, integrated approach is needed for responding to clusters of adverse events (AEs) potentially related to the administration of New Zealand's meningococcal B vaccine (MeNZB™). Public health investigators in the Data Management Group (DMG) in the New Zealand Ministry of Health (MoH) must have epidemiologic and statistical expertise and should develop an investigation approach that optimises the chance of identifying the nature and magnitude of any excess risks attributable to MeNZB™. In addition, investigators and their managers must also recognise the social dimensions of these clusters, develop and maintain critical community relationships, and undertake courses of action that do not excessively deplete resources. Public health investigators and managers should understand how risks are perceived by the community, the potential influence of the news media on those perceptions, and the potential ramifications of reported clusters for the MeNZB™ programme and, possibly, for the routine childhood vaccination programme.

To meet these needs, the DMG should put into place an internal management system to assure prompt investigation of clusters. Such a system requires the establishment of a locus of responsibility and control contained in written operating procedures and supported by dedicated resources, and a process for involving the Independent Safety Monitoring Board (ISMB). Any information given to the ISMB will also be available to the MoH (which is responsible for the vaccination programme), Medsafe (the medicine regulatory authority), and Chiron Corporation (the manufacturer of the vaccine). In turn, any advice from the ISMB to the MoH will also be provided to Medsafe and Chiron.

The World Health Organization's Expanded Programme On Immunisation has prepared a manual to guide the development and management of surveillance programmes for AEs following immunisation (AEFIs) that includes guidelines for investigating AEFIs [1]. The approach presented herein, based on the same principles, is an adaptation and expansion of the generic model suggested by the US Centers for Disease Control and Prevention [2] for investigating clusters of health events. This approach comprises a four-stage process:

- initial ascertainment of cases and summarisation of relevant data,
- assessment,
- feasibility study, and
- aetiologic investigation.

Each step provides opportunities for collecting data and making decisions. Although this approach may not always be followed sequentially, it will provide a systematic plan with points at which the decision may be made to terminate or continue the

investigation. Of course, although a systematic approach is vital, the DMG will have to be flexible.

INTRODUCTION

Purposes and Caveats

The purpose of these guidelines is to describe a systematic approach to the evaluation of clusters of AEs, with reference to epidemiologic and statistical source materials.

At the outset, it is important to note several limitations that are likely to affect investigations of clusters of AEs potentially associated with MeNZB™, including:

- In many cluster investigations, a geographic or temporal excess in the number of cases cannot be demonstrated.
- Even if an excess of a specific AE is confirmed, the likelihood of establishing a definitive cause-and-effect relationship between the health event and vaccination is slight.
- A cluster may be useful for generating hypotheses but is not likely to be useful for testing hypotheses—i.e., the issues raised by a cluster frequently cannot be definitively addressed by the investigation; rather, they will almost certainly require an alternative epidemiologic approach.
- From a public health perspective, the perception of a cluster in a community may be as important as, or more important than, an actual cluster. In dealing with cluster reports, the general public is not likely to be satisfied with complex epidemiologic or statistical arguments that deny the existence or importance of a cluster. Therefore, achieving rapport and trust with a concerned community is critical to a satisfactory outcome, and this rapport often depends on a mutual understanding of the limitations and strengths of available methods.

Definition of Clusters

As used in these guidelines, the term "cluster" is an unusual aggregation, real or perceived, of health events that are grouped together in time and space; of note, even one case of a rare, serious AE (sometimes also called a "trigger event") could constitute a cluster.

MANAGING INVESTIGATIONS OF CLUSTERS: SKILLS AND KNOWLEDGE REQUIRED

The investigation of a perceived cluster of adverse health effects should not be viewed simply as an epidemiologic or statistical exercise that occurs in isolation. Appropriate response to possible clusters demands that the social complexities be recognised and, in addition, requires the possession and application of skills and knowledge that extend well beyond epidemiologic and statistical tools. These additional skills include a sensitivity to the psychology of the situation, an understanding of the principles of risk perception, a recognition of the functions of news media, and an awareness of potential impacts on the MeNZB™, as well as other, vaccination programmes.

Scientific Tools

The investigation of clusters may be best viewed as public health surveillance activity (i.e., the ongoing collection, analysis, and dissemination of information important to public health practice). It is not a primary mechanism for investigating aetiologic relationships. Thus, the investigators may be looking more at patterns (spatial, temporal, or both) in data than searching for specific associations between agent and disease [3]. As discussed in Appendix A, various statistical techniques may be used to detect and characterise such patterns—none of which is consistently the technique of choice or the most appropriate. The investigator should select the epidemiologic or statistical approach to be used according to the circumstances under study (e.g., the nature of the condition, the type of data available on cases, the availability of appropriate denominator data, etc.). In addition to knowing how to apply the selected method, the investigator will need to know its limitations, assumptions, and tendency to give false-positive or false-negative results (and under what conditions it is prone to do so). Finally, the investigator should determine the statistical power of any planned study to detect an increased number of cases.

Psychological Factors

Investigators of clusters should understand the various ways in which individuals and communities respond to stressful situations and react to uncertainties [4]. Investigators also should be able to recognise the source of community suspicions (e.g., of deliberate delay and cover-ups) and demands (e.g., for the unrealistic allocation of resources and timelines). Finally, investigators must be aware of and responsive to the fact that a perceived problem must be resolved responsibly and sympathetically, even if no underlying community health problem or cluster of disease truly exists.

Risk Communication

After the DMG has initially estimated the degree of risk inherent in the situation under investigation, this information should be given to the ISMB, the MoH, Medsafe, and Chiron. The MoH's communication team should also be consulted at this stage and asked to advise whether the information should be given to the community-at-large and, if so, in what form. To facilitate discussion and decision-making, the risk should be quantified in terms familiar to the general public and put in perspective through comparison with risks associated with other vaccines and/or with other familiar activities [5].

In addition, the risk perceived by community members does not necessarily parallel the estimates of risk that are produced by mathematical or scientific assessments [6]. This divergence may be more than a failure to communicate the true risk or a failure of the community to understand. Rather, it likely represents a factoring of other aspects of the situation into the reactions of community members [6]. In dealing with the community's perceptions of risk, it is always important that it be balanced with a similar characterisation of the benefits of vaccines (in general) and MeNZB™ (in particular).

News Media

Public health officials (i.e., investigators and public health managers) must understand the factors that influence the various news media in their selection and presentation of stories (e.g., the desire for a pictorial/visual component, the presence of conflict or

controversy, the presence of strong emotive content, and the availability of target for blame) [7]. Similarly, public health officials must recognise that the news media tend to simplify complex, technical explanations, thereby losing subtle distinctions or qualifications. Thus, public health officials should distill the messages they wish to convey and present them in the way they are most likely to be transmitted without confusion or distortion. Public health officials must be prepared to stress key points; provide background necessary for better understanding; and be straightforward regarding what is fact, what is speculation, and what is not known. Most of all, public health officials must remain cooperative and responsive, and seize the initiative in providing needed information to the news media and the general public, before distortion and discord have been introduced into the public exchanges.

ORGANISATIONAL REQUIREMENTS

The multifaceted MeNZB™ Vaccine Safety Monitoring Plan is organised to provide the DMG with prompt reports of cases of AEs, in particular those involving hospitalisation. In designing a response to such events, the DMG must ensure that the process can proceed smoothly from one level of action to the next and that it can terminate an investigation effectively when resolution is reached.

The following organisational components are recommended to assure smooth and timely public health responses:

- a locus of responsibility and control—i.e., an individual with stature in the agency to serve as the identifiable point of responsibility;
- a set of written operating procedures for evaluating clusters (an outline for such a protocol is provided below);
- dedicated, trained professional staff and adequate financial and logistical resources; and
- a process for involving responsible groups (e.g., the ISMB and the MoH) and individuals (e.g., the AE cases, the cases' parents, the attending physicians to whom the AE cases originally presented).

GUIDELINES FOR A SYSTEMATIC APPROACH

This section outlines a four-stage approach for managing a cluster investigation. The four stages may be viewed as a series of filters that lead to appropriate responses to a potential problem. The issue of increased frequency of occurrence of AEs should be separated from the evaluation of potential aetiology, and an assessment of the feasibility of performing aetiological studies should be made before any actual study is begun.

Furthermore, it is important that the ISMB is informed of progress and agrees to further assessment at all stages of an investigation. It will be their responsibility to advise the MoH on the conduct of the vaccination campaign whilst the investigation is taking place (specifically, whether the vaccination should continue as planned, whether delivery of vaccine should be slowed or delayed, whether delivery of vaccine

should be stopped, or whether surveillance for the event in question (and associated events) should be heightened).

Stage 1. Initial Ascertainment of AEs and Summarisation of Relevant Data

Purpose: To detect putative vaccine-associated AE cases.

Procedures: The initial detection of potential AEs will usually be obtained through the routine, ongoing analysis of surveillance data collected as described in the MeNZB™ Vaccine Safety Monitoring Plan; however, these guidelines should also apply to situations in which the apparent cluster is brought to the attention of public health officials directly from health care providers or parents. In either situation, depending on the specific nature and number of suspected AEs, it may be necessary to collect additional information from medical charts and/or interviews with health care providers, cases, cases' parents, and vaccination programme staff.

- A. Gather and summarise the initial data that define the epidemiologic and characteristics (i.e., person, place, and time characteristics) of the cluster, such as: number and types of suspected AE(s) cases; cases' sex, age (or birthdate, age at diagnosis, age at death), and race; geographic area of concern, time period of concern, etc.
- B. Collect and summarise clinical information on cases, such as: date of and basis for diagnosis, relevant medical histories, clinical/vital status of cases, MeNZB™ (and other) vaccination status and timing, etc.
- C. Develop an initial case-definition, based on the epidemiologic/demographic and clinical information described above or use an *a priori* case-definition, if it's appropriate.
- D. Obtain identifying information on persons affected: name, address (or approximate geographic location), telephone number, contact person (i.e., parents or guardian) and preferred method for contact, and the attending physician's contact information.
- E. Assess community perceptions, reactions, and needs.
- F. Notify the ISMB chairperson about the suspected cluster and keep the ISMB informed regarding the progress of ongoing investigations and their outcomes, and solicit advice and guidance regarding future plans for and the conduct of the ongoing investigations.
- G. Notify the Director of the Meningococcal Vaccine Strategy, MoH about the suspected cluster and keep them informed about plans for ongoing investigations and their outcomes.
- H. Notify the MoH's communication team about the suspected cluster and keep them informed about the progress of ongoing investigations and their outcomes.

Outcomes:

- Initial examination of these preliminary data may suggest that further evaluation is needed (i.e., detection of *a priori*-identified AEs without plausible alternative aetiology, apparent excess occurrence of AEs, and plausible temporal association with MeNZB™ vaccination) → proceed to Stage 2.

- Initial examination of these preliminary data may suggest that further evaluation is not needed (e.g., plausible alternative aetiology(ies) identified for detected AEs, no apparent excess occurrence of AEs, no apparent temporal association with vaccination) → prepare a summary report for the ISMB and, on their advice, cease the investigation.

Stage 2. Assessment

It is important to separate whether an excess of AEs has actually occurred and whether the excess can be linked aetiologically to MeNZB™ vaccination; the first issue usually has precedence, and it may or may not lead to evaluation of the second issue.

In evaluating whether an excess has occurred, three separate steps should be taken:

1. *preliminary evaluation of excess occurrence* to assess quickly from the available data whether an excess may have occurred;
2. *verification of the diagnoses* to assure that a biological basis exists for further investigation; and
3. *expanded evaluation* for the purpose of obtaining a more detailed description of the cluster through case-finding, interaction with health care providers and, possibly, the general community, and descriptive epidemiology.

In addition, the investigators should refamiliarise themselves with the relevant scientific literature at this point of the investigation and, possibly, seek consultation with other investigators and experts. These activities are often interrelated and may occur in parallel or, in some circumstances, it may be appropriate to start the assessment process with *verification of the diagnoses* (although this is usually a more expensive and time-consuming step) before proceeding with the *preliminary evaluation of excess occurrence*.

Stage 2a. Preliminary evaluation of excess occurrence

Data from the routine surveillance systems, possibly with augmentation from other sources, are used to perform an initial calculation of observed versus expected occurrence.

Purpose: To provide a quick, rough estimate of the likelihood that an excess of potential public health importance has occurred.

Procedures:

- A. Determine the appropriate geographic area and the time period in which the cluster will be studied.
- B. Determine which cases will be included in the preliminary analysis. Because this stage does not involve case verification, all cases will be assumed to be real. However, some cases may need to be excluded from this preliminary analysis because they occurred outside the designated geographic area or not during the designated time period, or because the AE case differs clinically from that of other cases. A helpful step in sorting through these issues may be to tabulate frequencies of all AEs and to look at related descriptive statistics for each of these factors.

- C. Determine an appropriate reference population. Occurrence rates (or other statistics) calculated for the cluster should be compared with those for a reference population (e.g., from another area and/or using historical data) in order to identify an excess number of cases.
- D. If the number of cases is sufficiently large to obtain meaningful rates and if an appropriate denominator is available (e.g., number of children in the vaccine programme target area or number of children enrolled in a school district), calculate occurrence rates, standardised morbidity/mortality ratios, or proportional mortality ratios. Compare the calculated statistic with that for the reference population to assess statistical significance. Chi-square tests and Poisson regression are also commonly used techniques for comparing proportions.
- E. If the number of cases is not large enough to obtain meaningful rates, or if denominator data are not available, use one of the statistical tests developed to assess space, time, or space-time clustering (see Appendix A).

Outcomes:

- If this preliminary evaluation suggests a statistically significant excess occurrence → proceed to Stage 2b.
- If this preliminary evaluation shows no statistically significant excess but the overall evidence suggests an occurrence of potential biologic and public health importance that is plausibly associated with vaccination (e.g., based on extant evidence in the medical literature or based on the clinical judgment of the ISMB members) → decide if further assessment is warranted. (Note: A decision to proceed further at this point should not be based solely on an arbitrary criterion of statistical significance.)
- If this preliminary evaluation suggests no statistically significant excess and the overall evidence does not suggest potential biologic and public health importance that is plausibly associated with vaccination → prepare a summary report for the ISMB and, on their advice, cease the investigation.

Stage 2b. Verification of the diagnoses

Purpose: To confirm the diagnoses.

Even if it appears that an excess exists, it is important to verify the diagnoses of all “cases” according to a clear, consistently applied case-definition; if cases are not clearly defined or if they were inconsistently diagnosed, the “cluster” may simply represent a mixture of different outcomes, likely without a common aetiology. Depending on the circumstances and the stage of the investigation, this case-definition may be one that has been defined *a priori*, one that is based on epidemiologic/demographic and clinical information collected as part of ongoing surveillance activities and/or this investigation, or one that is based on some combination thereof.

Procedures:

- A. Verify the diagnosis by contacting the attending physicians and by referring to the appropriate health-event registry (e.g., AE surveillance reports and/or medical charts). Verification is often a multi-step process, involving initial contact with the attending physicians to obtain permission to examine the

- cases' medical records, as well as possibly the case, or their family members or friends.
- B. If possible, obtain copies of relevant pathology reports, laboratory or other diagnostic tests, and medical examiner's reports.
 - C. Obtain clinical/laboratory reevaluations, if needed.

Outcomes:

- If cases are verified and an excess is confirmed → proceed to Stage 2c.
- If some of the cases are not verified but the data are still suggestive of an excess occurrence and/or the overall evidence suggests an occurrence of potential biologic and public health importance that is plausibly associated with vaccination → seek ISMB advice and decide if further assessment is warranted.
- If some (or all) of the cases are not verified, and/or an excess is clearly not substantiated, and/or the overall evidence does not suggest an occurrence of potential biologic and public health importance that is plausibly associated with vaccination → prepare a summary report for the ISMB and, on their advice, cease the investigation.

Stage 2c. Expanded evaluation

Purpose: To design and perform a more thorough investigation to confirm if an excess has actually occurred and to describe the epidemiologic characteristics of the cluster.

The expanded evaluation differs from Stage 1 in that additional case-finding is undertaken and relevant information is verified in order to better define the characteristics of the cluster. This expanded evaluation will almost certainly require a field investigation.

This expanded evaluation begins with a written protocol that outlines the costs and provides information on data collection, the methods to be used, and the plan of analysis. The main product should be a detailed description of the cluster.

Procedures:

- A. Reconsider the initial case-definition, based on additional information collected so far, to determine if greater sensitivity (i.e., decreasing the number of false-negatives) or greater specificity (i.e., decreasing the number of false-positives) is desired at this stage of the investigation.
- B. Determine the most appropriate temporal and geographic (community) boundaries.
- C. Ascertain all potential cases within the defined space-time boundaries.
- D. Identify the appropriate databases for both numerators and denominators, and their availability and quality.
- E. Identify statistical and epidemiologic procedures to be used in describing and analyzing the data.
- F. Perform an in-depth review of the medical literature, and consider the epidemiologic and biologic plausibility of the purported association (by detailed review of the medical literature, possibly with the assistance of the ISMB and/or experts outside the DMG).

- G. Assess the likelihood that an AE-vaccination relationship may exist, paying special attention to the number and timing of MeNZB™ doses received in relation to onset/diagnosis of the AE.
- H. Assess community perceptions, reactions, and needs.
- I. Complete the proposed descriptive investigation.

Involvement of the ISMB is of particular importance during this step. Because the occurrence evaluation may vary considerably in size and content, consensus on the appropriate level of effort will enhance the credibility and facilitate acceptance of the results.

Outcomes:

- If an excess is confirmed and the evidence for epidemiologic and biologic plausibility is compelling → proceed to Stage 3.
- If an excess is confirmed but no relationship to vaccination is apparent and/or the overall evidence does not suggest an occurrence of potential biologic and public health importance → prepare a summary report for the ISMB and, on their advice, cease the investigation.
- If an excess is not confirmed → prepare a summary report for the ISMB and, on their advice, cease the investigation.

Stage 3. Feasibility Study

Purpose: To determine the epidemiologic and logistical feasibility of performing an epidemiologic study of the association of the AE and MeNZB™ vaccination.

At this stage, all of the options for geographic and temporal analysis should be considered, including the use of cases that were not part of the originally defined “cluster”, expanding or using a different case-definition (most likely one that is more specific and less sensitive), and expanding or using a different geographic locale or time period.

Procedures:

- A. Determine the hypothesis(es) to be tested.
- B. Consider the appropriate study design (see Appendix B for a brief discussion of the relative strengths and limitations of different methodologic approaches), with attendant costs, methodologic/logistical challenges (e.g., a consideration of sample size, the appropriateness of using previously identified cases, the geographic area and time period concerned, and the selection of comparison/control subjects), and likely outcomes of the various alternative study designs.
- C. Determine the statistical power of the selected study design to detect meaningful differences.
- D. Review the detailed medical literature on what is known about the hypothesised association of MeNZB™ and the identified AE(s), and determine what data should be collected on cases and comparison/control subjects, including previously or newly performed clinical and laboratory measurements.

- E. Specify detailed collection and verification of information on the sequence and timing of MeNZB™ vaccinations for both cases and comparison/control subjects.
- F. Review the detailed medical literature with particular attention to other known and putative causes, confounders, and effect modifiers of the outcome(s) of concern; specify detailed collection of information on these putative factors (including other vaccinations).
- G. Delineate the logistics of data collection, processing, and quality control/assurance.
- H. Develop an appropriate plan of data analysis.
- J. Assess the resource implications and requirements of both the study and the epidemiologic and policy/programme implications of alternative findings that may result from this investigation.
- K. Assess community perceptions, reactions, and needs.

Outcomes:

- If the feasibility study suggests that an aetiologic investigation is logistically feasible and affordable, and that the likely benefits justify the effort → proceed to Stage 4.
- If the feasibility study suggests that little will be gained from an aetiologic investigation, or that such an aetiologic investigation is logistically impossible/improbable, is too expensive, or is not likely to affect existing policies or programmes (i.e., regardless of the results of the investigation) → prepare a summary report for the ISMB and, on their advice, cease the investigation. (Note: In some circumstances the ISMB, MMT, MoH, Chiron, general public, or news media may demand further investigation regardless of cost or public health merit. Thus, the effort devoted to community relationships, news media contacts, and interactions with the ISMB will be critical for achieving an optimal public health outcome.)

Stage 4. Aetiologic Investigation

Purpose: To perform an aetiologic investigation of a potential MeNZB™-associated AEs.

The primary purpose of the study is to attempt to generate knowledge regarding the broader epidemiologic and public health issues that the cluster raised—not merely to explain a specific cluster. In this context, this step is a standard epidemiologic study, for which all the preceding effort has been preparatory.

Procedures:

Using the feasibility study as a guide, develop a formal study protocol, obtain necessary human subjects review clearances, and implement the study.

Outcomes:

The results of an aetiologic investigation are expected to contribute to epidemiologic and public health knowledge. Regardless of whether these results offer support for or against the existence of an association between MeNZB™ vaccination and specified AE, the ISMB, should consider these findings in the context of an overall assessment of the likely causal nature of this association and its public health impact, and advise

the MoH (in consultation with Chiron and Medsafe) regarding the management of the MeNZB™ vaccination programme.

COMMUNICATION OF RESULTS

There will be a continuing need to for the ISMB, assisted by the DMG, to communicate the results of ongoing and completed investigations to the MoH, Chiron, Medsafe, as well as to a variety of interested parties, including public health managers, health care providers, members of the general public and the news media, and the public health and scientific communities. The presentation and level of detail will, of course, vary widely, depending on the intended audience. In all these settings, however, investigators should describe what was done, what was found, and what can be done about it in a scientifically objective, defensible fashion that clearly distinguishes between what is fact, what is speculation, and what is not known.

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APPENDIX A

A BRIEF REVIEW OF STATISTICAL AND EPIDEMIOLOGIC TECHNIQUES FOR DETECTING CLUSTERS OF HEALTH EVENTS

The approach taken to investigate a suspected cluster of health events depends on the nature of the cluster, the data available, and the questions being asked, including the following:

- Do the health events cluster in space or time alone, in space and time simultaneously, or in neither?
- What are the spatial and temporal boundaries of the cluster?
- What are the characteristics of the health events—e.g., acute or chronic disease, long or short latency period, and known or unknown aetiology?
- What data are available for the health event—e.g., case counts, disease rates, or data on each event, such as place of residence and time of onset of disease or death?
- What data are available to describe the population-at-risk?

A number of problems are encountered in the study of clusters. The health events being investigated (often morbidity or mortality) are usually rare, and increases of these events tend to be small and may occur over a long time period. Another issue that complicates the investigation—especially with regard to the perceived credibility of its results—is that most/some clusters occur by chance. A further complicating factor is that information on the population-at-risk or on the expected rates is often not available. The choice of a geographic area that is too small or too large, or of a time period that is too short or too long, may result in insufficient statistical power to indicate a cluster; conversely, arbitrarily drawing time/space boundaries to encompass known cases may introduce the “Texas Sharpshooter Effect”, in which an apparent excess may merely be the result of bias introduced in drawing these boundaries. Many of the articles referenced at the end of this Appendix contain informative discussions about issues that can compromise application of statistical methods in investigations of clusters, and how they might be avoided, or at least mitigated.

Standard statistical and epidemiologic techniques for assessing excess risk can often be used to evaluate reported clusters. Tabulating frequencies of the health event and examining related descriptive statistics is a useful first step in the evaluation. If the number of cases is sufficiently large and population data are available, examination of rates (possibly age-, race-, and sex-adjusted), standardised morbidity/mortality ratios, or proportional mortality ratios may determine whether there is an excess number of events. If the number of health events is too small to show meaningful rates, pooling across geographic areas or time may be possible. Combinatorial methods are often used for small amounts of data. Other commonly used statistical approaches include Chi-square tests of observed versus expected frequencies (based on the Poisson distribution for low-frequency data) and Poisson regression (used for comparison of rates). Confidence intervals may be calculated for point estimates.

Whether the rate for a geographic area or time period is excessive may be determined by comparing it with rates of other areas or times. If a temporal cluster is being assessed, the occurrence in that time period can be evaluated in the context of

previous or subsequent periods. If a spatial cluster is being assessed, the occurrence in the geographic area can be compared with that in adjacent areas (e.g., a census area unit with surrounding census area units) or with other areas of similar size (e.g., a district health board [DHB] with other DHBs); alternatively, the rate for an area can be compared with that of a larger area (e.g., the rate for a city with that of the surrounding DHB). In either situation, the referent population must be chosen carefully to ensure its appropriateness when such comparisons are made. Mortality and morbidity data for referent populations may be available from vital statistics systems or registries; population denominators may be available from recent census data or enrolment lists (e.g., from schools).

If the above standard approaches cannot be used in an investigation of clusters because the number of health events is too small, data on the population-at-risk are unavailable, or space-time clustering is suspected, numerous statistical tests are available for use in detecting spatial, temporal, and space-time clusters. Although some of these tests may not be familiar to investigators and may require the preparation of more data than required by standard techniques, many of the tests are relatively simple to understand and use. Numerous methods for studying clusters have been reviewed [A1, A2]. A more extensive listing, along with brief descriptions and critiques, of some of these techniques have been presented elsewhere [A3].

Most of these tests use data on individual cases of health events, although a few employ aggregated data such as frequency counts or rates. Information generally required for each case is location of the case (often the place of residence) and date of onset of the disease (or injury) or of death. Most of the tests based on aggregated data assume that the number of health events that occur in an area and/or time period follows a Poisson distribution. The tests do not usually require knowledge of the distribution of the population-at-risk. Instead, they may assume that the population-at-risk remains constant over time, and they offer special considerations for differing population sizes. The reporting rate for the health event is also assumed to be constant.

The assumption of minimal population shifts over time is frequently violated. More subtly, subgroups of the population with different levels of risk may not remain constant over the time period of interest. Violations of these assumptions can lead to spurious results. An additional problem is encountered when investigators study the occurrence of health events over a long period—i.e., the problem posed by migration. Migration tends to decrease the chance of detecting clustering; however, certain tests account for non-uniformity of or changes in the population [A4-A6]. As an alternative, adjustments for the size of the population-at-risk (to account for population changes during the study period) can be made before testing.

Other approaches in use or under investigation for the analysis of clusters include the quality control measure known as the cumulative sum, or “cusum”, technique [A7], the sets technique [A8], nearest-neighbour procedures [A9, A10], and nonlinear and Bayesian time series methods. Normal-theory confidence intervals and bootstrap-prediction intervals for detecting frequencies of disease occurrence above those expected have been explored [A11].

Because of the diverse and complicated nature of clusters, there is no obvious preferred test for assessing all of them. Investigators are advised to perform several related tests and to report the results that are most consistent with validated assumptions.

Appendix A References

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APPENDIX B

A BRIEF DESCRIPTION OF THE RELATIVE STRENGTHS AND WEAKNESSES OF EPIDEMIOLOGIC STUDY DESIGNS FOR ASSESSING AETIOLOGY

As with the available epidemiologic and statistical techniques for assessing clusters of health events discussed in Appendix A, there is no consistently preferred methodologic approach for assessing aetiologic associations. Each of the generic approaches described below has inherent strengths and weaknesses, as discussed. It is left to the investigator to choose the appropriate study design to optimise the likelihood of yielding meaningful, generalisable results, taking into account the hypothesis(es) to be tested; the availability, appropriateness, and quality of the data; and the relative merits of each methodologic approach (discussed below).

A *prospective cohort study* (i.e., in which participants would be enrolled into the study based on their receipt of MeNZB™ at the time of the study, then evaluated during a specified time period for the occurrence of selected outcomes in the future) is probably the most expensive approach available and would take the longest time to complete, but would provide many of the advantages of a randomised, controlled clinical trial, thereby mitigating some of the concerns about the introduction of selection or ascertainment biases. However, given the current high risk of exposure to *N. meningitidis* in New Zealand, there are clear and compelling ethical proscriptions about withholding MeNZB™ from at-risk persons. Thus, despite its methodologic advantages, the use of a prospective cohort study approach should not be considered in this setting.

A *retrospective cohort study* (i.e., in which participants would be enrolled into the study based on their MeNZB™ vaccination status and history at some point in the past, then followed for a specified period time, which may also have occurred in the past, for the occurrence of selected AEs) has many of the methodologic and statistical advantages of a prospective cohort study; in addition, efforts to find eligible study participants could also serve as an effective means of identifying unvaccinated persons and referring them for MeNZB™ vaccination. Using this approach, we would be able to mitigate exposure misclassification errors by using the most complete vaccination histories available from the NIR (or other vaccination records). Similarly, we would be able to mitigate misclassification errors and potential biases due to insensitive, inconsistent, and differential (with respect to vaccination status) ascertainment of a variety of outcomes-of-interest by using standardised case-finding efforts and by applying standardised case-definitions and diagnostic criteria to all participants in a controlled and blinded (with respect to MeNZB™ vaccination status) fashion. Furthermore, because the determination of vaccination status would be based on historical records and the ascertainment of selected AEs could be completed in a timely fashion (determined by the suspected induction period of the selected AE), we would be able to have results of completed statistical analyses within weeks or months after the commencement of the study. Finally, the data from this study could be used to directly estimate absolute and excess rates of risk for a variety of selected AEs that may be generalisable to other populations, depending on the representativeness of the sampling frame used. The most compelling limitation of this approach—which may

be insurmountable—is that the statistical power to detect excess risks, if they indeed exist, would be severely limited in the case of rare AEs (i.e., even if the entire New Zealand population were enrolled in such a study, there may simply not be enough AEs observed to yield adequate statistical power), and to a lesser extent, the cost to perform such a large study.

The *case-series* approach is a modified cohort method, wherein cases are self-matched (i.e., they serve as their own controls, comparing rates of occurrence of selected AEs for different time periods before and after vaccination within each participant's observation/follow-up period), thereby avoiding the need and expense to identify and select comparison/control subjects, as well as eliminating some forms of ascertainment and selection bias. In addition, this method eliminates confounding due to factors that are potentially associated with both the outcome-of-interest and avoidance of vaccination. The statistical power of this approach is slightly lower than that of the cohort approach, and would be even lower as the induction/latency period lengthens and/or if overall vaccination coverage is low. To avoid bias and misclassification errors in case-series analyses, the mechanism of case-ascertainment must be independent of vaccination history and diagnostic criteria must be clear and consistently applied, as with all the other methods described above. The data from this type of study may be used for estimating rates of excess risk that are generalisable to other populations, depending on the representativeness of the sampling frame used, but cannot be used for estimating absolute rates of risk for selected AE endpoints. The cost and the time-to-completion for a case-series analysis should at least be comparable to that of case-control studies—and could be even less expensive and quicker, because most of the relevant data should already be available. (For example, a crude analysis using hospital discharge data matched with the immunisation database could be performed relatively quickly and inexpensively; of course, additional costs would be incurred and additional time would be required if, for example, review of case notes were required to verify cases against the study case-definition and/or it were necessary to collect additional clinical and/or demographic information on study participants.)

A *case-control study* (i.e., in which participants are enrolled into the study based on whether they have an AE or other disease endpoint-of-interest, then their history of MeNZB™ vaccination is compared to noncases' history of MeNZB™ vaccination) would have greater statistical power to detect differences for the same sample size as any of the approaches discussed herein, although this seeming advantage would be diminished if most potential study participants (i.e., the cases and controls) have been vaccinated with MeNZB™. Furthermore, given the likely rarity of the most important AEs, the identification and selection of an adequate number of cases with the selected clinical outcome(s)-of-interest would be problematic; and, if we desired to examine more than a single outcome, we would need to assemble several “case” groups—thereby increasing the complexity and cost of such a study. Furthermore, cases may be subject to misclassification errors and potential bias due to insensitive, inconsistent ascertainment and diagnosis of outcomes-of-interest and faulty, incomplete recall, thereby complicating the interpretation of the results of such a study. Finally, the data collected in this type of study could normally not be used to directly generalise absolute rates of risk for selected AE outcome(s), but might be

used to estimate rates of excess risk for selected AEs that should be generalisable to other populations, depending on the representativeness of the sampling frame used.

A *cross-sectional analysis* of populations that include some proportion of persons who have and have not been vaccinated with MeNZB™ would be the easiest and least costly to perform, but it would have the lowest statistical power for the same sample size as the other study designs described above—and the statistical power would diminish further as vaccination coverage increases. In addition, such an analysis would be prone to biases and inexact outcome measures that would limit the validity and reproducibility, and hence the usefulness, of the results. Nonetheless, because the determination of vaccination status would be based on historical records, we would be able to have results of completed statistical analyses within weeks or months after the commencement of the study, at a minimal cost. As with cohort studies, the data from this study might also be useful for estimating absolute and excess rates of risk for selected endpoints that may be generalisable to other populations, depending on the representativeness of the sampling frame used.

Appendix 6: Consideration of potential frameworks for causality assessment

1. Context

MeNZB™ is a tailor-made vaccine to be used for epidemic control specifically against the New Zealand strain of *N. Meningitidis* group B. It is probable that it will be included in the childhood vaccination schedule for the foreseeable future.

Post-licensure safety monitoring of MeNZB™ is being conducted for several reasons.

- To support provisional Licencesure of MeNZB™. The licence to distribute MeNZB™ will be granted under section 23 on the Medicines Act which allows the distribution of a medicine in New Zealand following the presentation of much less data than would be required for a licence under section 21 (full licence).
- To obtain a licence under section 21. For section 23 safety data on ~1200 participants in clinical trials will be presented. To obtain a licence under section 21 substantially more safety data are required.
- This is the first widespread use of this vaccine anywhere in the world, although substantial safety data are available on similar vaccines.
- Adverse events following receipt of MeNZB™ will occur. It is important that data are available to assist in assessing the significance of such events.

There is an implicit assumption that minor adverse events following vaccination occur commonly, whilst severe events occur rarely. Whilst this may very well be true of MeNZB™, and data from the related Norwegian and Cuban vaccines support this assertion, it is not **known** to be true for MeNZB™. Given that data will only be available from ~1200 recipients when the first stage roll-out commences events which occur relatively frequently, say 1/1000, cannot be excluded. Therefore, the most important purpose of the safety monitoring strategy is to detect and define the rate of any serious event caused by MeNZB™ as early as possible during the rollout.

New Zealand is somewhat limited in the certainty with which the rate of occurrence of rare events can be excluded simply on the basis of its small population, ~ 4,000,000. The target populations for those who will be subject to hospital based monitoring are 100,000 aged 5-19 year and 100,000 aged 0 - 4 years, i.e. 300,000 vaccine doses in each age group. This means that for each age group, following the period of observation, there will be 95% certainty that an event involving hospitalisation which occurs at the rate of 1/100,000 after any vaccine dose will be detected.

The target population for MeNZB™ vaccination is all aged 0 -19 years that number ~ 1,000,000. For this group, for whom hospital discharge diagnosis can be reviewed, there will be 95% certainty that an event involving hospitalisation which occurs at the rate of 1/1,000,000 after any vaccine dose will be observed. To give a feel for the certainty with which the rate of an event may be determined, the following table shows the 95% confidence intervals, assuming Poisson distribution, around events occurring at a frequency of 1/10,000 – 1/1,000,000 in a population at risk of 1,000,000.

Rate	No. of events observed in Population at risk = 1M	95% confidence limits expressed as integers
1/1,000,000	1	0 – 6
1/500,000	2	0 – 7
1/100,000	10	4 – 21
1/50,000	20	11 – 32
1/10,000	100	81 – 122

One of the key difficulties which will face the ISMB will be to distinguish between events which follow, (temporal relationship), from those which are caused by, (causal relationship), MeNZB™. “Causal inference based on mere coincidence of events constitutes a logical fallacy known as *post hoc ergo propter hoc* (Latin for after this therefore on account of this). This fallacy is exemplified by the inference that the crowing of a rooster is necessary for the sun to rise because sunrise is always preceded by the crowing”¹. Many events are bound to occur within in a few days of receipt of MeNZB™ vaccination. For some it will be easy to dismiss a causal relationship with MeNZB™ vaccine, e.g. road traffic accident, for others such as the onset of flaccid paralysis it will be much more difficult. The ISMB should therefore consider determining an *a priori* framework for the assessment of causality.

2. Framework

The Safety Monitoring Team has proposed the following framework for causality assessment. It is based on the framework proposed by the Immunisation Safety Review Committee of the Institute of Medicine² (IOM), which in its turn is based on the set of criteria proposed by Hill in 1965³. The IOM Immunisation Safety Review Committee used six general considerations when assessing causality as follows²

Strength of association - usually expressed in epidemiologic studies as the magnitude of the measure of the effect e.g. relative risk or odds ratio.

Dose-response relation – If such a relationship exists, i.e. in the context of MeNZB vaccine is an event more likely after further exposures, this tends to strengthen the inference that the association is causal.

Temporally correct association – The exposure should precede the event and in a time frame consistent with the “incubation period” of the event. If the exposure occurs after the onset of the event or in a time period well in

advance of the event such that the length of the “incubation period” is unlikely then this indicates that the exposure is unlikely to cause the event.

Consistency of association – If an event is associated with MeNZB vaccine in several different populations and in several different time periods and age groups this would support causality.

Specificity of Association – This indicates the degree to which the exposure predicts the frequency or magnitude of the event. In an extreme example if the event only occurs after MeNZB vaccination i.e. is a new syndrome then causality is strongly inferred. However, although possible, this is unlikely to occur with MeNZB vaccination.

Biological Plausibility – Does the association fit with current biologic or medical knowledge? Alternatively is there a plausible mechanism by which MeNZB could cause the event being investigated.

These criteria have been criticised by Rothman and Greenland¹. Their criticisms can be summarised as follows

Strength of association - although this may be reasonably taken in some situations to indicate a causal relationship a weak association, which could more readily be explained by undetected biases does not necessarily mean that the relationship is not causal. Strong associations which are not causal can occur if significant confounding exists.

Dose-response relationship – described by Rothman and Greenland as Biologic gradient. This is criticised on two bases. Firstly, there may be a threshold and all doses are above the threshold. An alternative name for this is “the crocodile analogy” – once a crocodile gets to 2.5 metres it can kill you. Therefore it does not matter if it is 3, 4, or 5 metres; one should have equal fear of all crocodiles over 2.5 metres. Secondly, the dose response curve may be J shaped of which the relationship between alcohol consumption and mortality is an example. An additional example from vaccinology of a dose response relationship which does not become stronger with increasing numbers of doses is seen with rotavirus vaccine where the incidence following dose 2 was much less than dose 1 and following dose 3 the risk is negligible.

Temporality – that the exposure has to precede the effect is accepted by Rothman and Greenland.

Consistency - Lack of consistency does not necessarily rule out a causal association as such an association may occur only in specific population groups or specific circumstances.

Specificity - Rothman and Greenland use a different meaning of specificity to that used by the IOM. They use it to mean that the exposure can only cause a single effect, and concludes that when used as such it is wholly invalid.

Biological plausibility - this is criticised on the grounds that because no known biological mechanism is known at present, it does not mean that one yet to be discovered exists.

The IOM Safety Review Committee has used a similar “weight of evidence” approach in 1994⁴ and 2001⁵. In its most recent report⁶ the Committee did not use this approach because “it was not asked to evaluate exposure to Anthrax Vaccine Adsorbed (AVA) as a cause of specific health outcomes. Rather, the committee was asked to provide an overall evaluation of the anthrax vaccine’s safety”.

The Canadian Advisory Committee on Causality Assessment has published its criteria for assessing causality⁷. This committee was set up to specifically assess individual adverse event reports following the administration of vaccines in Canada, whether reported from the passive or active monitoring systems. To facilitate the process, a standard evaluation instrument known as the causality assessment form was developed.

To make a judgement “complete” reports are required. Those submitted by the active reporting system, on which the New Zealand hospital based safety monitoring for MeNZB™ is based, are “the most complete”. In establishing how to assess causality the committee considered the range of methods described by Amery⁸. However these methods relate to adverse events following drugs rather than vaccines and are not directly transferable to an assessment of safety following vaccination. The Canadian causality assessment form has the following characteristics.

Section 1 covers the reason for reporting, the diagnosis, its severity and whether the committee agreed with the assessment of the reporter.

Section 2 covers the information which may bear on the causality of the event and is divided into nine sections

- 2.1 Frequency of occurrence of adverse event
- 2.2 Similar events known to occur with other diseases
- 2.3 Event is known to be related to this vaccine
- 2.4 Event is explained by the biological properties of the vaccine
- 2.5 Vaccine-event interval compatible with the onset
- 2.6 The patient had similar symptoms in past
- 2.7 Concomitant or preceding drug therapy
- 2.8 Concomitant or preceding condition
- 2.9 Other contributing factors

Section 3 relates to the causality assessment using the different classes of probability used by WHO, see below.

Section 4 permits a brief summary of the case to be written

Section 5 permits recommendations for improving immunisation delivery.

Section 6 considers whether the case could be useful for educational purposes

Section 7 considers whether the case could be useful for publication.

The WHO causality assessment criteria.

Very likely/ certain	Clinical event with a plausible time relationship to vaccine administration and which cannot be explained by concurrent disease or other drugs or chemicals.
Probable	Clinical event with a reasonable time relationship to vaccine administration and is unlikely to be attributed to concurrent disease other drugs or chemicals
Possible	Clinical event with a reasonable time relationship to vaccine administration but which could also be explained by concurrent disease, other drugs or chemicals
Unlikely	Clinical event whose time relationship to vaccine administration makes a causal connection improbable, but which could plausible be explained by underlying disease or other drugs or chemicals.
Unrelated	Clinical event with an incompatible time relationship to vaccine administration and which could be explained by underlying disease or other drugs or chemicals
Unclassifiable	Clinical event with insufficient information to permit assessment and identification of the cause.

The Anthrax Vaccine Expert Committee reviewed the safety of anthrax vaccine by reviewing the events reported to the Vaccine adverse Event Reporting System in the USA⁹. This group used a very similar approach to that of the Canadians. A medical reviewer “developed a preliminary opinion concerning the causal relationship between the AVA and the reported AE(s) taking into consideration 1) cumulative information on the consistency of association in different groups, sexes or ages with inactivated vaccines generally and AVA specifically, 2) the specificity to AVA aloe (e.g. did the subject have a concurrent or predisposing illness or did he/she receive other vaccines or medications at the same time as AVA?). 3) The temporal relationship of the AE to the receipt of AVA and 4) biological plausibility (i.e. is there a clear physiological basis for thinking that an AE could have been

caused by AVA or have successive doses of vaccine repeatedly induced particular AE's?).

Subsequently this assessment along with the initial VAERS report and any other available clinical information was reviewed by the committee. "a Delphic approach was used to achieve expert consensus concerning the causal relationship between each reported AE and AVA"¹⁰

Lange et al¹¹ in a description of a comprehensive surveillance system for adverse events following AVA indicate that to assess causality data on biological plausibility, specific temporal relationships, medical histories, comorbidities, behavioural and other illness and injury risk factors, concurrent vaccinations and variations in healthcare access, usage and reporting are required.

3. Conclusion

All the above methods of causality assessment have similar characteristics which are reflected in the IOM criteria. It is recommended that the ISMB decide on their approach to assessing the causality of events following MeNZB™ taking into account the frameworks described in this document.

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