

The legacy of MeNZB and possible implications for COVID-19 vaccination

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ABSTRACT

It is now over a decade since the meningococcal B vaccine, MeNZB, was in routine use in New Zealand. From July 2004 until June 2008 it was administered in a three-dose schedule to over a million individuals, aged six weeks to 20 years, to provide protection against the epidemic strain of group B Meningococci. The cost of the campaign, including the development of the vaccine was substantial, in excess of \$200M, but it contributed to a reduced incidence of meningococcal infections along with a reduction in morbidity and mortality. The campaign led to the development of a national immunisation register (NIR), which is still in existence today. As well as considering the legacies of the MeNZB vaccination programme, this paper examines whether there are any lessons to be learned, specifically concerning active vaccine safety monitoring, which may be important if, and when, a COVID-19 vaccine is developed and a national immunisation campaign instituted.

It is now over a decade since MeNZB was in routine use in New Zealand. Starting in July 2004, it was administered in a three-dose schedule to over a million individuals, aged six weeks to 20 years, to provide protection against the epidemic strain of group B Meningococci. This strain, P4.B1.4, was responsible for a substantial epidemic of meningococcal disease which commenced in 1990 and peaked in 2001, with over 600 cases, a rate of 17.4/100,000 population.¹ The routine administration of MeNZB ceased in June 2008, at which time it was only being given to infants. The decision to cease routine administration was made because the disease incidence had reduced significantly, and it was realised the duration of protection was quite brief.² The cost of the campaign, including the development of the vaccine, was in excess of \$200M.³ Was the campaign, including the search for and investigation of the tailor-made vaccine, MeNZB, worth the effort?

One way of considering this is to examine the legacy of MeNZB.

There are two expected legacies: a contribution to a reduction in meningococcal B incidence and the establishment of the National Immunisation Register. There

were two unexpected legacies: a reduction in the incidence of gonococcal infection in recipients of MeNZB, and the inclusion of the MeNZB, Por A outer membrane protein antigen as one of the components in 4CMenB, a vaccine now licensed in New Zealand and in routine use in the UK. It is inevitable that there will be many similarities between a COVID-19 vaccination campaign and the MeNZB campaign. Therefore, the MeNZB experience has the capacity to inform the delivery, administration and safety monitoring of a possible COVID-19 vaccine campaign in New Zealand.

Did MeNZB contribute to reduction of disease?

In the clinical studies, three doses of MeNZB achieved the pre-determined correlate of protection in all age groups except infants, for whom a four-dose schedule was required.² The vaccine came into use in 2004 at a time when the epidemic, which peaked in 2001, was declining.² Such epidemics often decline in an erratic manner with increases and decreases in annual incidence, even though the overall trend is to decline. However, with the introduction of MeNZB the decline was steady and sustained.⁴ Holst et al

suggested that the epidemic decline, which commenced in 2001 would have continued without MeNZB though at a slower rate.⁵ Arnold et al estimated vaccine efficacy at 77% (95% CI 62–85), and they suggested that 208 cases were avoided to the end of 2008.⁶ Further, applying observed case fatality rates for the epidemic, an estimated 5.6 deaths (95% CI 2.9–10.0) were avoided. Based on published data on sequelae of meningococcal disease, they estimated 21 cases with serious sequelae were avoided (approximately 10% of cases, interval estimate 16–27 cases).⁶ These data suggest that MeNZB vaccine contributed to the decline in the epidemic. Further, since 2008 the rate of meningococcal disease, though varying from year to year, is within the expected background rate of 1–3/100,000 population. At present, group B causes the bulk of the cases followed by groups W and Y.⁷ Although the epidemic strain continues to circulate, there has been no significant increase in disease caused by it.⁷ So perhaps the first legacy of MeNZB is a contribution to the sustained reduction in disease caused by the target strain. However, this was at considerable cost,³ and some authors have suggested its introduction should have occurred earlier.²

National Immunisation Register

The second legacy, and perhaps the most important, is the establishment of the National Immunisation Register (NIR). The vaccine licence application was made with a small safety data set, with information on only 3,300 doses being available.¹ Accordingly, to enable the vaccine licence application to Medsafe to succeed, careful post-licensure safety monitoring was essential. Several methods of monitoring were planned and implemented, including hospital-based monitoring for “pre-selected events”, “other serious and/or unusual events,” and “all events that occurred within seven days of vaccination”.⁸ All deaths within three months of receipt of MeNZB were monitored. In addition to the routine passive safety monitoring by the Centre for Adverse Reaction Monitoring (CARM), there was an enhanced monitoring system, the Intensive Vaccine Monitoring Programme, which reviewed all medical records for a period of six weeks following vaccination from a selected group of general practices.⁹ All these systems required timely

and accurate data of vaccine receipt, and to enable this, it was essential to establish a national immunisation register (the NIR).¹⁰ Using this electronic system, vaccine receipt was recorded and available to be sought within 24 hours. One of the key features was that the NIR uses the National Health Index number (NHI), which is used for an individual's contact with the health system and is allocated shortly after birth. Considerable effort is taken to ensure that the NHI data are accurate and that duplicate numbers are minimised.¹¹ The NHI is used for all contacts with the health system. Without the NIR and the NHI the comprehensive safety monitoring would not have been possible, and the vaccine could not have been licensed. All data was assessed by an Independent Safety Monitoring Board who concluded “that the combined results of the monitoring undertaken during the period of the programme provide confidence regarding the safety of the vaccine”.⁸

The NIR remains in use today and provides regular reports. In conjunction with the NHI it enables the accurate monitoring of vaccine coverage and the identification of those who have not received a vaccine dose so that the individual can be followed up and offered vaccination. The NIR is clearly an important legacy of the MeNZB campaign. However, it is now 16 years old and has been recently described as “old, slow and struggling”.¹² Its software will require a substantial upgrade to enable its use in monitoring the delivery of a future vaccine. Such an upgrade is essential for the delivery of a vaccine against COVID-19, which is likely to be offered to the whole population of New Zealand.

These two parts of the legacy were anticipated but there were also some unexpected benefits.

Reduction in gonococcal infections

Neisseria gonorrhoea is a very similar organism to *Neisseria meningitidis* and so it is perhaps not surprising that there might be some cross protection from a vaccine which protects against *Neisseria meningitidis*. Candidate vaccines against gonorrhoea have not proved successful in clinical trials.¹³ However, it has been observed that in the immediate period after the use of the outer membrane vesicle vaccines against group B meningococci in

Cuba, Norway and New Zealand there has been a transient reduction in gonococcal infections.¹⁴ This has recently been studied by Petousis-Harris et al in a retrospective case control study in New Zealand.¹⁴ They compared the likelihood of being diagnosed with gonococcal disease by sexual health clinics in those who had received MenNZB compared to those who had not received the vaccine. For primary analysis, cases were those with laboratory confirmed gonococcal infection only and controls were those with laboratory confirmed chlamydia infection only.¹⁴ There were 10 times as many controls as cases for analysis.¹¹ Vaccination status was determined from the National Immunisation Register and it was found that those vaccinated were less likely to suffer gonococcal infection with an adjusted overall estimate of protection of 31% (95% CI 21–39). There was a non-significant decline in effectiveness when the period 2004–2009 was compared with 2010–2014; MenNZB was used from 2004 until 2008. The authors speculated that the licensed vaccine Bexsero, which contains the same PorA, outer membrane protein, as MenNZB, may also provide some protection against gonococcal infection, though this clearly would require study.¹⁴ Any protection would probably not persist to young adulthood in those who had received the vaccine in infancy. It was also suggested that a vaccine with this level of protection against gonococcal infection could have a significant impact on its incidence if the protection afforded was reasonably sustained.¹² A reduction in hospitalisation for gonorrhoea has also been observed following the administration of MenNZB. The estimate of vaccine effectiveness against hospitalisation is 24% (95% CI 1–42).¹⁵

4CMenB—Bexsero

This vaccine, now licensed in New Zealand, contains four antigens; three of its antigens are recombinant proteins—factor H-binding protein [FHbp], neisserial heparin-binding antigen [NHBA] and neisseria adhesin A [NadA]. The fourth antigen is the New Zealand PorA [P1.4].¹⁶ The vaccine has been offered to infants in a three-dose schedule (8 and 16 weeks and 12 months) in the UK since 2015. A review of the experience with this vaccine over three years has recently been published.¹⁷ The coverage

with the vaccine has been high, with 87.9% receiving all three doses by age two years. The estimate of efficacy was derived by comparing the incidence during three years of vaccine use, with the expected incidence estimates based on the previous four years prior to vaccine use and disease trends in unvaccinated children under age five, who were not eligible to receive the vaccine. When the vaccine was first introduced, there was a limited catch up: opportunistic catch-up vaccination was offered to those aged 12 and 16 weeks at their routine vaccination visits. This meant that many children under age five would not have been vaccine eligible. The estimate of vaccine efficacy against all Group B meningococcal disease was 59.1% (95% CI 31.1–87.2) and protection was sustained for two years.¹⁷ However, the vaccine is not expected to protect against all strains of group B meningococci. The Meningococcal Antigen Typing System (MATS) was developed to predict strain coverage of 4CMenB and this system estimated 73% strain coverage in England and Wales, prior to introduction of the vaccine.^{18,19} When cases where protection was not expected, using MATS, were excluded, the estimated effectiveness of three doses of the vaccine against susceptible group B strains increased to 71.2%. Accordingly, the fourth MenNZB legacy is a contribution to a licensed meningococcal vaccine against group B meningococcal disease, which is efficacious and in routine use in one country at least.

Potential implications for a COVID-19 vaccination programme

On the assumption that a vaccine against COVID-19 is developed and found to be effective and safe in clinical trials, it presumably will be widely offered in New Zealand. Healthcare, border and other essential workers are likely to have priority, followed by high-risk groups, including those with co-morbidities and those aged over 60 or 65 years. If the immune response in the older age group is poor in comparison to younger age groups, it may be necessary to have widespread vaccination of children and younger adults to reduce the likelihood of exposure to infection to those in the older age group. It has been noted, however, that there may be reluctance to receive the vaccine in a significant minority of the population.²⁰

When such a vaccine is introduced to New Zealand, and offered to a large proportion of the population, the introduction will have to be very carefully managed. This will require clear communication with information about the efficacy and safety of the vaccine to be used and, in particular, the safety monitoring which will be occurring internationally. There may be several different vaccines used worldwide and it is possible that the safety data on the vaccine to be administered in New Zealand may be limited at the time of introduction. Alternatively, there may be a paucity of safety data on a target age group, for example, those aged >65 years. With the vaccine being offered to a substantial proportion of the New Zealand population, coincidental adverse events following vaccination will occur. Some of these events will be serious. Even if there is a substantial safety data base on the vaccine to be used in New Zealand and continued international monitoring, there is the possibility that a cluster of serious adverse events following immunisation (AEFI) could occur in New Zealand and receive widespread publicity. Would the passive monitoring system in current use have the capacity to assess such a cluster and, if appropriate, reassure the public? Further, would the acceptance of the vaccine in this country be improved by having effective active monitoring in place to supplement the passive monitoring system? I suggest that active monitoring of a COVID-19 vaccine, even if only for the purpose of public confidence, merits serious consideration.

If active adverse event monitoring is introduced, then a further, and possibly

final, legacy of MeNZB may be a model of how such vaccine safety monitoring could be conducted in this country. The most effective system of assessing serious adverse events in a timely manner is probably hospital-based monitoring using the NHI number and upgraded NIR to track events of sufficient severity to merit hospital attendance/admission following vaccination.⁸ An effective NIR will be required to determine vaccination status, including timing, of individuals suffering such events. This means that delivery of each and every dose of the vaccine would have to be recorded on an upgraded National Immunisation Register. Using the NHI, hospital attendance could be matched to vaccination records to assess specified events following vaccination within a pre-specified timeframe. In addition, it may be appropriate to re-establish the Intensive Vaccine Monitoring Programme using GP records following vaccination.⁹ In my opinion, planning for the monitoring of COVID-19 vaccine safety should begin soon. The critical requirement is that the NIR must be capable of accurately and comprehensively recording the receipt of a COVID-19 vaccine to the entire New Zealand population. In addition to the current passive monitoring system, I recommend that an active monitoring system, specific for COVID-19 vaccination, be designed and implemented in New Zealand. However, it is important to remember that planning for the safety monitoring of MeNZB took approximately three years. Even with the guidance that the MeNZB safety monitoring experience could provide, urgent consideration is required.

Competing interests:

Nil.

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