Clinical Assessor's Report on MeNZB (*N. meningitidis* group B, strain NZ98/254, outer membrane vesicle vaccine)

Assessor:

Summary Estimates of Efficacy and Effectiveness

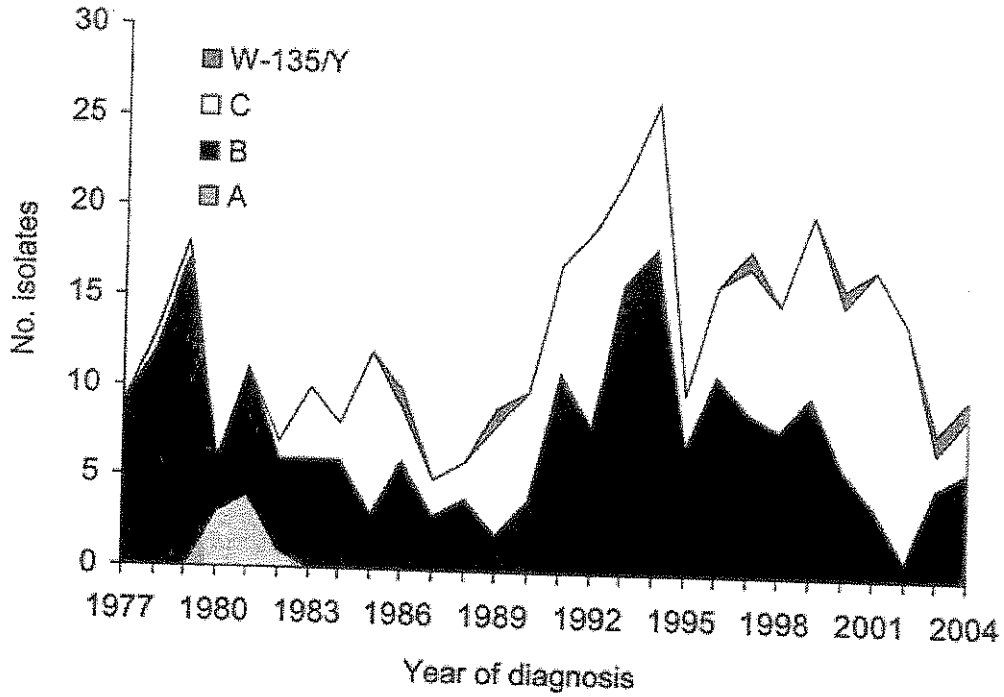
This assessor's report concentrates on the efficacy and effectiveness data. There were complete data provided for the studies which had been submitted earlier. These have been reviewed before, and they do not materially add to the data already considered for the provisional licensure application.

There are no clinical efficacy data available because of the decision to proceed without phase III randomised controlled studies. All of the analysis therefore focuses on post roll-out surveillance data of various sorts.

Laboratory and Notification Surveillance Data

The main data provided with respect to effectiveness were surveillance figures extracted from the ESR annual report http://www.moh.govt.nz/moh.nsf/pagesmh/4872/$File/epidemiology-meningococcal-disease-2005.pdf , which show a clear decline in meningococcal cases since 2001. What is not clear is how much is due to vaccination, and how much is due to the natural decline in the epidemic. Comment is made that the rate of decline is greater than that seen in Norway where vaccination was not used. It is not clear to me how that is relevant, when considering the differences in the populations, climates and socioeconomic factors between the two countries.

By way of comparison, a recent article in Emerging Infectious Diseases http://www.cdc.gov/ncidod/eid/vol12no07/05-1624.htm shows the decline in meningococcal disease in Iceland (graph below). The group B disease shows relatively rapid declines, in spite of the absence of a vaccine. This is provided for context: the whole effectiveness assessment appears to rely on the slope of decline in incidence, and I would regard international comparisons to be subject to many confounders.



Another major confounder is the increase in laboratory confirmation rates in Auckland: the overall confirmation rate of meningococcal disease increased from 55.3% in 2004 to 81.3 in 2005 (table 2 below). It was stated that "the number of cases from this DHB confirmed by PCR alone has only increased by one to a total of four cases", suggesting that meningococcal disease was over-diagnosed on presumptive grounds in the past. This is important when one considers that Auckland significantly contributes to the total number nationally.

Table 2: Meningococcal disease, basis for diagnosis, 2001-2005[1]

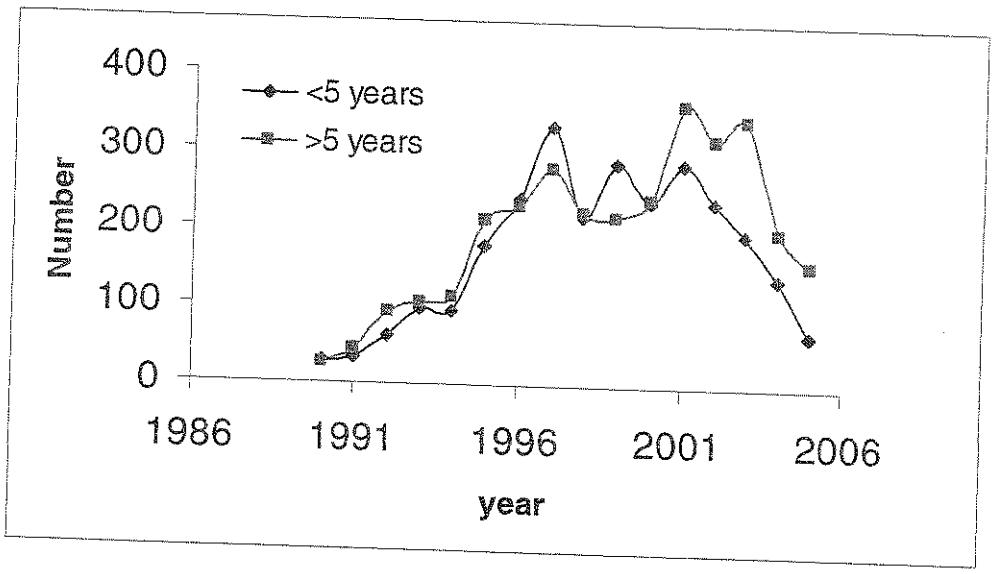
Basis for diagnosis	2001		2002		2003		2004		2005	
	No.	%	No.	%	No.	%	No.	%	No.	%
Isolation of *N. meningitidis* from blood and/or CSF or any other sterile site	319	49.1	229	41.1	242	44.7	180	52.6	130	57.0
PCR test	159	24.5	177	31.8	142	26.2	93	27.2	70	30.7
Gram-negative diplococci in CSF	11	1.7	7	1.3	4	0.7	0	0.0	0	0.0
Confirmed –subtotal	**489**	**75.2**	**413**	**74.1**	**388**	**71.7**	**273**	**79.8**	**200**	**87.7**
Clinical criteria and a positive throat swab	4	0.6	4	0.7	6	1.1	3	0.9	0	0.0
Clinical criteria	157	24.2	140	25.1	147	27.2	66	19.3	28	12.3
Probable –subtotal	**161**	**24.8**	**144**	**25.9**	**153**	**28.3**	**69**	**20.2**	**28**	**12.3**
Total	**650**	**100**	**557**	**100**	**541**	**100**	**342**	**100**	**228**	**100.0**

1 Each case is represented only once in the table.

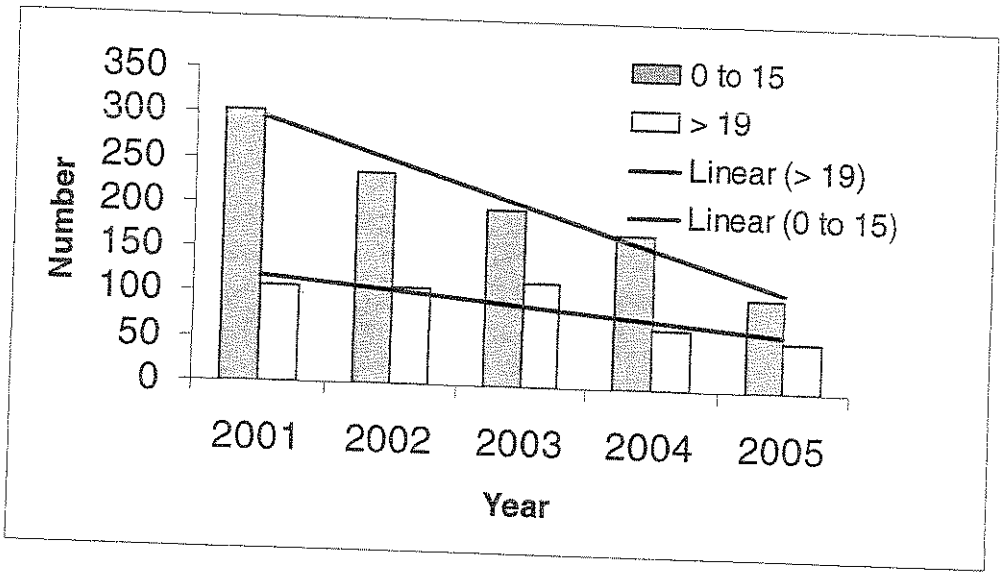
This table originates from the MOH website, and was not provided in the application, which is disappointing.

The data in the application was quite selectively presented, and concentrated on two age groups: the over and under 5 year-olds. The data from the ESR reports are presented below, in a graph which I constructed myself from the data. There is a clear decline in both groups, but

the over 5 yr-olds will obviously include vaccinated and non vaccinated individuals. This would at best suggest herd immunity if there is a vaccine-driven fall in the incidence of meningococcal disease.



I have constructed a graph which attempts to separate those likely to be well covered (< 15 yr-olds) from those who will not have received vaccination. It can be seen from both graphs that there is a fall in both groups over a 4 year period, and it would be hard to describe an effect of vaccination beginning in 2004.



These figures describe notified cased, presumably both confirmed and probable.

Vaccine breakthrough data

The breakthrough data for 41 children with breakthrough disease are presented in a single table. This table is not easily understood without denominator data: ie the rates per 100,000 vaccinated children, according to whether they had one, two or three doses. I imagine this data would be difficult to collect, but estimates could perhaps be made.

In the methods it is stated that causes of immune deficiency were looked for in the vaccine breakthrough cases, but no information is given for how this assessment was made.

Poisson Analysis

Poisson analysis data were presented with the conclusion that effectiveness was calculated at 80% (58-91%). There was a reasonably lengthy section describing the method, but the actual results were very briefly presented. This reviewer is concerned that more details were not given describing the analysis, and whether independent statistical review was obtained to validate the interpretation. Considering that this is the only quantitative assessment of effectiveness, I consider that it would be useful to be provided with the full report from the Vaccine Effectiveness Peer Review Group. This would be consistent with the approach taken with the IMB.

Case Control study

There are no data available.

Seroprevalence surveys

The seroprevalence studies suggest a vaccine effect within the limits of the method, which looked at unlinked sera.

The graph (Figure 12) which shows falling numbers of cases from surveillance against rising antibody levels from the seroprevalence study is an interesting use of data. It should be presented as part of a more complete discussion on confounders, and discussion regarding the appropriateness of pooling of data from different studies.

It would have been interesting to know what the IgG levels were at presentation for the breakthrough cases, when available.

Throat carriage rates

The data presented are not related to any other comparable studies and as such cannot be easily interpreted.

Summary of Efficacy/Effectiveness Data.

It is axiomatic that there are no phase III controlled studies to give a precise indication of efficacy. The data presented therefore is less convincing and has to rely on national surveillance data.

I would appreciate an expert opinion on how vaccine effect can be separated from natural decline in disease incidence. In particular would the high incidence areas be expected to experience a fall in new cases ahead of low prevalence areas? It seems intuitive that they would, but this fall has been ascribed to earlier vaccine roll out in high incidence areas.

The only "precise" figure that is presented originates from the Poisson Regression model. This figure is so critical, that it merits its own folder, describing in detail the methods, the

limitations and discussion. It is unacceptable to this reviewer to have such critical information glossed over. One would expect the graphical representation of the surveillance data to be more convincing, with clear changes in the slopes relating to vaccine introduction. In my experience Poisson merely provides a statistic to what seems clear on a graph.

Safety data

Post roll-out data are presented in addition to the safety and reactogenicity data provided for each study. This reviewer does not intend presenting an in-depth reiteration of data presented to the VSC. The safety monitoring has been precisely and carefully carried out, and I am satisfied that no unacceptable safety issues have been exposed to date.

Conclusions

The information provided is insufficient to make this reviewer confident that the clear decline in meningococcal disease incidence is mainly due to MeNZB effectiveness. The strength of evidence required for full licensure does not appear to be provided.

The MeNZB team should be congratulated for their passion and vision, and it is fantastic that the rates of meningococcal disease have fallen so much. Unfortunately, at this stage I recommend to the VSC that MeNZB is fully licensed, on the basis that is not possible to confidently demonstrate efficacy or effectiveness.

not - confirmed as missing until.
by
28/9/2006