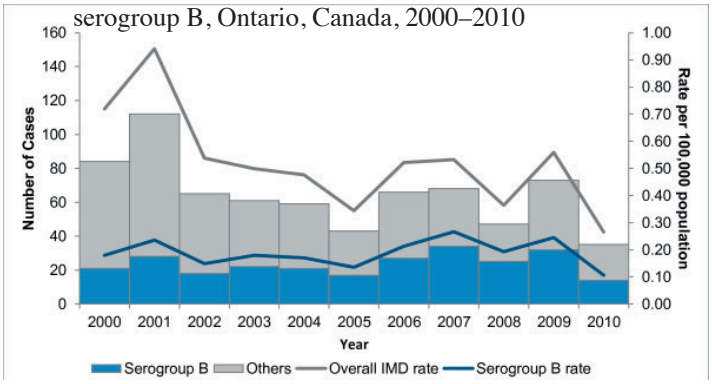
Section 4: The Strange Case of Bexsero®

Bexsero® was approved for use in Canada in January of 2014 and first sold in Canada in February that year according to Health Canada's ***Summary Basis of Decision (SBD) to Accept Bexsero***. In the SBD Health Canada informs us, "Protection by the vaccine **was inferred** from immune responses against the four antigens of the vaccine." This statement means efficacy for this vaccine has not been proven.

Furthermore, a Canadian study ***Epidemiology of serogroup B invasive meningococcal disease in Ontario, Canada***, published in 2012 concerning the incidence of the meningitis B strain cases in Ontario calls it a **rare disease**—256 cases in Ontario in 10 years. Note also the fall-off in incidence of IMD (all serogroups of meningitis) in Figure 1 from the report.

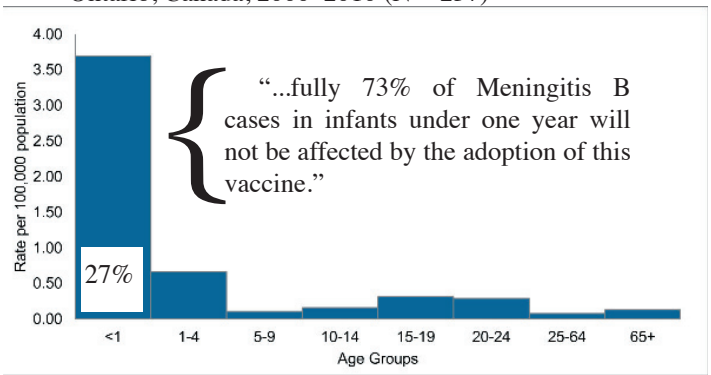
Fig 1: Number and incidence (per 100,000) of IMD and by serogroup B, Ontario, Canada, 2000–2010



Source: http://www.biomedcentral.com/1471-2334/12/202/figure/F1

The report also states the vaccine cannot protect infants under 6 months of age: "Because the vaccine will not protect very young infants, fully 73% of Meningitis B cases in infants under one year will not be affected by the adoption of this vaccine." Note in Figure 3 below those infants under 1 year of age is the largest group affected by Meningitis B, yet only 27% would be protected. (Notes added to figure.)

Fig 3: Annualized age-specific incidence for serogroup B IMDa, Ontario, Canada, 2000–2010 (N = 257)



Source: http://www.biomedcentral.com/1471-2334/12/202/figure/F3

The report also states: "Given that novel meningococcal B vaccines are based on sub-capsular proteins rather than polysaccharides, and there are **no published efficacy or effectiveness studies on these vaccines**, we do not yet know whether these vaccines would result in herd immunity as observed from MCCV and other bacterial conjugate vaccines." [Emphasis added]

The report also discusses the concept of Number Needed to Vaccinate (NNV) to prevent one case of the disease. In their own words:

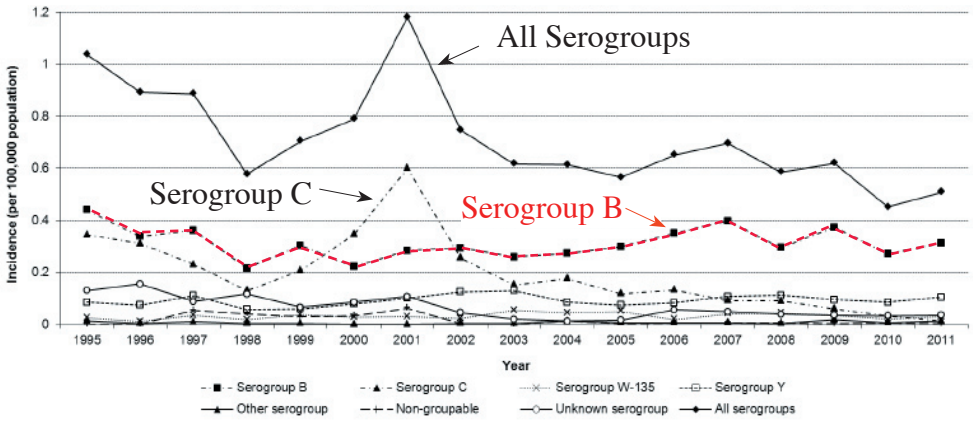
> "Our crude NNV to prevent a single case of disease is high, in excessive of 30,000 infants, yet this is conservative as it assumes that all cases under one year would be vaccine preventable. For the calculation we used a vaccine effectiveness of between 70 and 80%, yet this is an assumption as the true value is not known. As noted in our results, approximately 70% of our infant cases occurred among infants under 6 months of age and these cases may not be vaccine preventable depending on age at vaccination and duration of time to mount an immune response. In a phase IIb clinical trial, Gossger and co-authors [15], found that a schedule of three doses of Novartis' novel multicomponent meningococcal B vaccine (4CMenB) given to infants at 2, 4, and 6 months of age, and in an accelerated schedule at 2, 3, and 4 months of age were necessary to achieve optimal immunogenicity. This would suggest that disease in infants less than 6 months of age, using a 2, 4, and 6 month schedule, which is typical in Canada, may not be vaccine preventable. Using this assumption the revised NNV would increase to over 120,000 infants. Although applying the number needed to treat concept to vaccines is not new, there is no agreed upon NNV threshold for vaccine decision-makers. "

The NNV number is also used in calculations for cost effectiveness of vaccination programs expressed in Quality of Life Years (QALY). Articles can be referenced **here on NNV** and **here on its use in QALY** calculations.

In conclusion the report states, "our findings suggest that decisions regarding publicly funding serogroup B meningococcal vaccines will be difficult and may not be based on disease burden alone."

This prediction is proved true in the findings of the March 2014 PHAC report titled *The Recommended Use*

Figure 1 - Incidence of IMD (per 100,000 population) in Canada by serogroup and year, from 1995 to 2011[8]



Source: http://publications.gc.ca/site/eng/search/search.html?st=1&ssti=1&ast=&cnop=1&cnst=978-1-100-23515-8&e=1&_e=on&f=1&_f=on&_adoof=on

Notes to Figure 1:
Serogroup C incidence has waned significantly since introduction of the MCCV vaccine.

Serogroup B 2007–2011
- Average Incidence: .33 per 100,000 (1 case per 300,000)
- Average number of Cases: 111 per year
- Lowest Fatality rate at 6%
- Average of 7 deaths per year
- 61% of Serogroup B cases occurred within first 6 months of life, yet Bexsero® offers no protection to that age group.

of the Multicomponent Meningococcal B (4CMenB) Vaccine in Canada (**Archived here**). (The European Medicine Agency **Assessment Report on Bexsero®** published in 2012 when it was accepted for use in Europe has the studies referred to in the PHAC Recommended Use report.)

The good news is the report recommends NOT including this vaccine in the current immunization schedule. As stated in the conclusion on page 66:

> "Given the current available information on the burden of IMD in Canada, as well as the lack of evidence and the range of uncertainty of the underlying assumptions, particularly those concerning the predicted level of strain susceptibility [efficacy], **duration of protection** [effectiveness], impact on meningococcal carriage and herd immunity [effectiveness], and potential adverse effects of vaccination at the population level [safety], a recommendation for the implementation of a routine immunization program for meningococcal serogroup type B in Canada cannot be made at this time."

That is quite a long list of deficiencies of data. The report is extensive and covers safety, effectiveness and efficacy concerns which are too extensive to cover here individually.

Figure 1 and Table 1 from this report are reproduced above. They show the disease burden of Serogroup B meningitis in Canada. Notes have been added from the report itself.

On the subject of NNV and Cost Effectiveness of a new vaccination program for meningococcal B, the extremely high NNV and other factors from the Ontario report produce an outrageous cost for such a program.

Table 2 - Summary of the epidemiology of invasive meningococcal disease in Canada by serogroup in 2011, and between 2007-2011[8]

Serogroup	2011		2007 to 2011			
	Number of cases	Incidence (cases per 100,000 population)	Average annual number of cases (range)	Average annual incidence (cases per 100,000 population)	Median age (years)	Case fatality ratio
A	0	0	0.2 (0 to 1)	0	16	0.0%
B	108	0.31	111 (92 to 131)	0.33	16	6.0%
C	4	0.01	19 (4 to 30)	0.06	44.5	15.3%
W-135	10	0.03	11.2 (7 to 14)	0.03	38	8.5%
Y	36	0.10	33.8 (29 to 37)	0.10	47	12.1%
Other	4	0.01	3 (1 to 6)	0.01	34	0%
Non-groupable	1	0	1.6 (1 to 2)	0	28	10.0%
Unknown	12	0.04	12.8 (11 to 16)	0.04	16.5	8.2%
All serogroups	175	0.51	192.4 (154 to 229)	0.57	20	8.2%

Keep in mind that a widely accepted cost-effectiveness number is $50,000/QALY. On page 50 of the PHAC Report we read the following:

> "The most unfavourable cost-effectiveness ratios are those from the Ontario analysis. In the baseline model, the differential cost of the program per QALY is an estimated **$55.6 million CAD for one cohort** … For the cost-effectiveness ratio to be below $40,000 or $50,000 per QALY the incidence of meningococcal infections would have to be multiplied by 10, or the cost of the vaccine would have to be almost nil to be cost-effective." [Emphasis added]

Little wonder this vaccine was not added to the immunization schedule!

Bexsero® was licensed in Canada with strings attached. Namely, that population studies be done to access safety and effectiveness. These **studies are ongoing** and no doubt account for a portion of the increased adverse event reports in the full year of 2014.

Of the 93 serious reports in 2014, 38 listed Bexsero® as the suspect vaccine. That's 41% of the serious reports linked to this one vaccine. To put this in perspective, there are 40 vaccines on the database. The next highest count of serious AERs in 2014 for a single type of vaccine was for pneumonia vaccines at 9 reports.

Bexsero® is a vaccine that received **priority review status** with neither effectiveness nor efficacy studies and it's for a **rare** disease (low disease burden) which cannot provide protection to the highest incidence group (infants under 6 months old).

The main question that arises is why the Canadian population is being used as test subjects with a government funded vaccine and whether they are being told of this circumstance. This link to **the program in Quebec** is not reassuring on the latter point.

While the PHAC report is a bit reassuring, plans continue to eventually move this vaccine into the immunization schedule, as the report also makes clear. The government must track Bexsero® adverse events with great care. The benefit/risk ratio may turn out to be similar to that of the untested PENTA vaccine used in the 1990's and the HINI Swine Flu vaccine in 2009/10.