



The Development of the NZ Meningococcal B Vaccine

Why has it taken so long to develop this vaccine?

Why can't my children have the Meningococcal Vaccine now?

What is in it and how has it been tested?

There are a number of reasons why the vaccine is not available to all young people yet....

1. Developing a vaccine takes time
2. Testing a vaccine takes time
3. Making a vaccine takes time
4. Making a vaccine in sufficient quantity and consistent quality for all - takes time



.....And good things take time

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Developing the NZ Meningococcal Vaccine:

Our Meningococcal B vaccine is not entirely new. It is a variant on another vaccine, which has been extensively tested. There have been three Meningococcal B vaccines with similar constituents, and used in other countries such as Cuba, Norway and Chile for epidemics such as ours. However their epidemic strains of meningococci were different to the NZ one, and hence, while the vaccine was produced using similar methods, the strain used to make the NZ vaccine had to be changed.

In the beginning... the ESR (Environmental and Scientific Research) sent 25 different samples of the New Zealand strain of Meningococcal B to Norway. These were isolates from New Zealand children who had caught the specific epidemic strain of meningococcal disease.

The scientists in Norway selected one of these samples of meningococci as a candidate for a vaccine based on several factors. They ensured that the isolate selected could produce a good selection of proteins, called antigens that would induce a protective immune response.

This sample provided the seed stock (that which would be used to grow all the bacteria needed for production of the vaccine). These bacteria were grown in a nutrient rich broth that contained sugar, essential amino acids and essential elements such as iron and potassium (NB there was no substance of bovine origin). The bacteria and the nutrient were then placed in a big fermenter which is akin to a highly complex thermos, keeping the conditions optimal including gas mixtures and temperature, encouraging good growth of the meningococcal bacteria. The conditions of this process are strictly controlled to ensure every step is carried out with machine-like precision.

Once the seed bacteria have multiplied many times they are killed with a detergent that acts by breaking the cell wall into many fragments, most of which then re-aggregate into vesicles (Outer Membrane Vesicles) – much like detergent breaks up grease and oil.

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This detergent is sodium deoxycholate, a compound made from carbon, oxygen, hydrogen and sodium (salt) and is a normal by-product of bile metabolism.

Those vesicles that are the best components for the vaccine are separated out by centrifugation (spun at a very high speed until all fragments are separated into layers according to weight). The characteristics of these fragments are known well as they have been intensively studied for their immune generating properties.

The selected fragments are purified by ultra filtration and then added to the other constituents that make up the vaccine. The other major component necessary is the adjuvant, which acts to boost the immune response to the fragments of bacteria. The adjuvant in this vaccine is aluminium, which is used in many other vaccines. The other ingredient is histadine, which is an essential amino acid.

Now the vaccine is ready for testing.



The vaccine is tested initially in mice and rabbits.

Testing the vaccine

- The parent vaccine has been intensively studied and trials have been conducted on more than 100,000 people. As well there have been more than 65 million people vaccinated with this type of vaccine so the safety profile is well established.
- Checking that a vaccine is safe is paramount. Initially it is assessed in clinical trials starting with small numbers of healthy adults. These are called phase I trials and for the NZ vaccine there were 75 participants.
- Providing these trials go well they are extended to other age groups. Safety and the ability of the vaccine to protect are both closely assessed. These are called Phase II trials and have now been completed successfully for the NZ variant with almost 4000 doses in over 1300 young people. Recruiting volunteers for the trials took a long time, almost 2 years. Based on the results of the Phase II trials

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and the quality data of the manufacturing process, Medsafe (the New Zealand Independent licensing body) has given approval to extend the availability of the vaccine to the population most at risk of disease. This is the first phase of the roll out and is occurring now in South Auckland.

- During the roll out the vaccine continues to be assessed in the target population for safety and its ability to protect against disease.

Ongoing Safety:

The initial rollout process will be very closely monitored in the following ways for safety.

- Voluntary reporting of adverse events following immunisation by health care professionals and parents. Reports go to the Centre for Adverse Reaction Monitoring (University of Otago) as for other vaccines. Health professionals are actively encouraged to look out for and report any possible safety concerns.
- Any admissions to hospital and emergency department consultations in approximately 100,000 vaccinees under 5 years of age and 100,000 vaccinees over 5 years of age will be monitored. The National Immunisation register will be matched against the hospital data to see if there has been a consultation within a certain period after vaccination.
- All hospital admissions and emergency department consultations in those aged 0-19 years in Northern NZ will be reviewed daily to identify pre selected rare conditions that may be potentially linked to immunisation. These are looking for any possible link between vaccination and these events. In depth investigations will occur for serious or unexpected cases.
- Ongoing data matching of hospital discharge data and immunisation data will occur so that any event or disease that may be of possible concern can be linked back to immunisation status. This gives the ability for follow up of any concerns that may arise in the longer term.
- The Health Research Council of New Zealand has set up an Independent Safety Monitoring Board to regularly review and advise the Ministry of Health on all available data.

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Ability to Protect:

The ability of the vaccine to protect against disease (efficacy) must be assessed early in the trial process. Blood is taken from vaccinees and the ability of the antibodies made in response to the vaccine to kill the meningococcal bacteria is assessed. Data from other similar vaccines indicates that if a reasonable proportion of those vaccinated mount an immune response to the vaccine, measured in this way, a high proportion of vaccine recipients are likely to be protected.

The true test of the vaccine is in the field, in the population in whom it has been designed to protect. It requires many people to be vaccinated and then exposed to the disease to determine the true efficacy of a vaccine, simply by observing the difference in vaccination status in cases of disease. It is expected that there will be very few cases of the NZ strain meningococcal B disease among those recipients of the vaccine. Because there is such a high incidence of meningococcal disease in South Auckland it should not be long before the real efficacy of the vaccine is known.

Making the vaccine

The facility in Italy that makes this vaccine also makes many other vaccines such as influenza and meningococcal group C vaccines. As with any manufacturing processes all the necessary ingredients, components and the production facility must be ordered and available. In general there is up to an 18-month wait to book manufacturing time for vaccines.

Consistent production:

It is of paramount importance that all batches of vaccine are consistently the same as the batch used in the clinical trials as this is the "recipe" that has been shown to be both safe and effective. To give you a flavour of the complexity of this process consider baking a cake...

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When you have a favorite cake recipe, perfected over many trial and errors, it is possible to turn it out time and time again. However try changing that recipe to make a cake big enough for 1000 people. You have to get the same amount of fruit and flour per slice as your original small recipe. You must also contend with how to cook such a monstrous cake to perfection, even though it will not fit in your own oven. This is no small task and the judges will be voting, they will count how many raisins, cherries and almonds in each slice – and this must be the same as the original recipe. Now try making it for 150,000 people...

To grant consent to market a medicine such as meningococcal vaccine Medsafe have to be convinced that the production of every batch will be consistent and every dose will be the same so that the immune response as was seen in the clinical trials will also be seen in the rollout.

All of this takes a large amount of time. When all the initial trials have been completed and the results analysed the vaccine manufacturer must make some more vaccine and this must be booked approximately 18 months in advance.

It is not just a matter of having enough money to pay for the vaccine; it is a matter of getting the science right, reliably and repeatedly right. If the vaccine is not safe or effective we have to go back to the drawing board while the epidemic rages on.

Development of a new vaccine from the first production to marketing authorisation takes many years, usually 8-10. In this case, based on the information from the parent vaccine, the time has been shortened to 2-3 years. However it is important to monitor the roll out in South Auckland very closely in order to pick up any possible important signals, which could inform the rest of the national rollout.

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Key messages:

- Development of this vaccine has been fast compared to other vaccines because we were able to modify an existing vaccine.
- Testing this vaccine has also been fast compared to other vaccines because we already know much about the parent vaccine.
- It is important that monitoring the effect of the vaccine continues when it is first used simply because it is the first use of this vaccine anywhere.
- Making this vaccine takes time because it is so important to get the formulation exactly right each time a batch is made and the bacteria have to be carefully nurtured and grown before they can be chopped up and used for vaccine. Only so much can be grown at once.
- No amount of money thrown at this vaccine would make it happen any faster.

WE HAVE TO GET THIS RIGHT FIRST TIME!

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