

# Meningitis UK's Search **4** a Vaccine the story so far ...



On 1st November 1982, 14-month-old Spencer Dayman, normally a happy, lively little boy, was weak and listless when he awoke from his midday nap. It wasn't until some hours later, when his anxious parents took Spencer into hospital, and the doctors noticed a small pink rash on his stomach, that he was diagnosed with meningitis and meningococcal septicaemia. Spencer was treated in Intensive Care as his body struggled to cope with the disease that rapidly overwhelmed him. His heart stopped once and the doctors were able to restart it, but a few hours later it failed again and he stopped breathing. Just 24 hours after being admitted to hospital, Spencer lost his battle against meningococcal disease.

Since losing Spencer, his father, Steve Dayman, has become a leading figure in the fight against meningitis. In 1999 he founded Meningitis UK, a charity devoted to searching for a vaccine against meningitis and helping to fund research and raise awareness about the deadly disease.

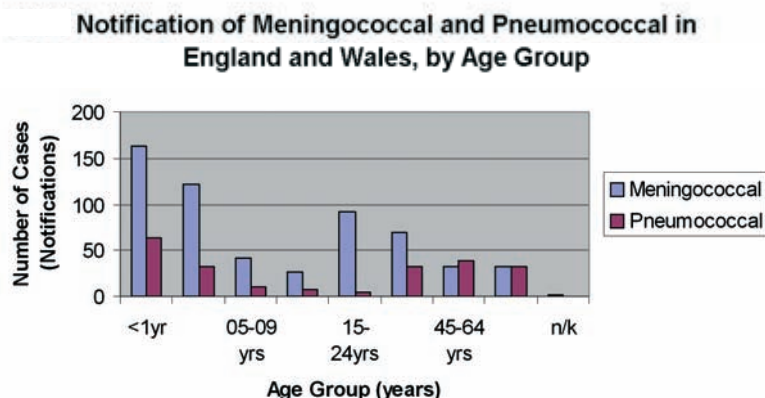


## Meningitis and septicaemia

Meningitis and septicaemia affect over 2,000 people in the UK each year. The disease occurs most frequently in young children, young adults aged between 16 - 24 years old, and the elderly. It is seasonal, with a marked increase in cases in the winter months. There are currently vaccines against certain forms of the disease, but we still have no protection against the most dangerous form - Meningitis B. Despite rapid diagnosis and treatment with antibiotics, 1 in 10 patients die. Those who do survive are often left with physical impairments such as deafness or partial paralysis. In some cases, damage to tissues is so severe that patients must undergo limb amputation or are left with permanent brain damage.

Meningitis (an infection of the lining of the brain and spinal cord) and septicaemia (infection of the blood) can be caused by both viruses and bacteria, which vary in the severity of disease they cause. Bacterial meningitis is the most dangerous, and the most common agent is the bacterium *Neisseria meningitidis* which causes 150 deaths per year in the UK.

## Prevalence of Bacterial Meningitis (without septicaemia) by Age Group



Source: NOIDS England & Wales Final Midi Report for 2005 (Table 3 - Final totals for 2005 by sex and age-group)



## Symptoms

Meningitis and septicaemia can kill in just four hours. That's barely long enough to recognise the symptoms and get to a hospital in time. A major problem is that the symptoms are often mistaken for the common flu. By the time the patient is diagnosed it can be too late to save them. Usually the first symptoms of meningitis and septicaemia are classic flu-like symptoms, a fever and headache, often accompanied by nausea and vomiting, or aching joints.

Signs of meningitis also include stiffness in the neck and an aversion to bright light, whilst the clearest symptom of septicaemia is a pinprick rash which can be identified by the simple 'Tumbler Test'. This is where a glass tumbler is pressed against the suspected rash. If the rash does not disappear under the pressure, it is likely to have been caused by septicaemia, and the patient requires urgent medical attention. However, many patients show these more specific symptoms too late or not at all, which makes the disease very difficult to diagnose.

### Do the Tumbler Test

Most people with meningococcal septicaemia develop a rash of tiny red 'pin prick' spots, which can rapidly develop into purple bruising. If the rash does not fade when a glass is pressed against it, it could be meningococcal septicaemia. On dark skin, check for the rash on lighter parts of the body, e.g. inner eyelids or fingertips.

#### Important

Someone who becomes unwell rapidly should be examined particularly carefully for the meningococcal septicaemia rash.

#### Other symptoms in babies may include:

- Blotchy skin, quite pale or turning blue
- Tense or bulging soft spot (fontanelle) on the baby's head
- Poor feeding
- High pitched cry/irritable (especially when being held)



Rash on dark skin

**NOT EVERYONE GETS ALL OF THESE SYMPTOMS AND THEY CAN APPEAR IN ANY ORDER**

Meningococcal Septicaemia		Meningitis
Rash	<input type="checkbox"/>	
Leg pain	<input type="checkbox"/>	
Cold hands & feet	<input type="checkbox"/>	
Floppy child/ difficulty supporting own weight	<input type="checkbox"/>	<input type="checkbox"/>
Fever, vomiting or diarrhoea	<input type="checkbox"/>	<input type="checkbox"/>
Confusion & drowsiness	<input type="checkbox"/>	<input type="checkbox"/>
Difficulty breathing	<input type="checkbox"/>	
Abdominal/joint/ muscle pain	<input type="checkbox"/>	
Abnormal skin colour	<input type="checkbox"/>	
Severe headache		<input type="checkbox"/>
Stiff neck		<input type="checkbox"/>
Dislike of bright light		<input type="checkbox"/>
Body stiffens/jerky movements		<input type="checkbox"/>

## The bacterium - how it causes disease

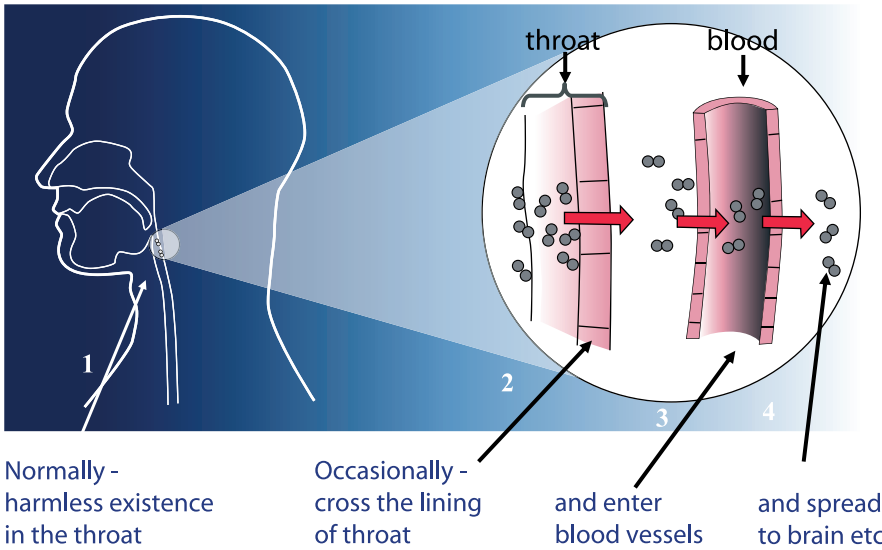
*N. meningitidis* is not a rare bacterium. It is found living in up to 40% of the population, colonising the cells lining the nose and throat. In these cases the bacterium lives in balance with its human host and does not cause disease. It is passed between people by coughing and sneezing, which release tiny droplets containing bacteria into the air, and also more directly by kissing. In some cases, however, the bacteria go beyond colonisation, and invade the body to cause a serious and life-threatening disease. This crucial invasion process is still not fully understood and much of the research funded by Meningitis UK is devoted to discovering the exact mechanisms used by the bacteria to gain entry into the body.

*N. meningitidis* is known as the meningococcus because it is round in shape and coccus means spherical. It often exists in pairs, as *diplococci*. The surface of the bacterial cell is constantly changing as it encounters and responds to the environment around it. Many different proteins and protective carbohydrates, including a thick sticky capsule, allow it to interact with the human host. When a meningococcal strain begins to cause disease it attaches intimately to the host cells, triggering signals inside the cell that cause it to fold up and over the bacteria, engulfing it. In this, and other ways, the bacteria start to burrow deep into the tissues of the nose and throat until they reach the bloodstream.



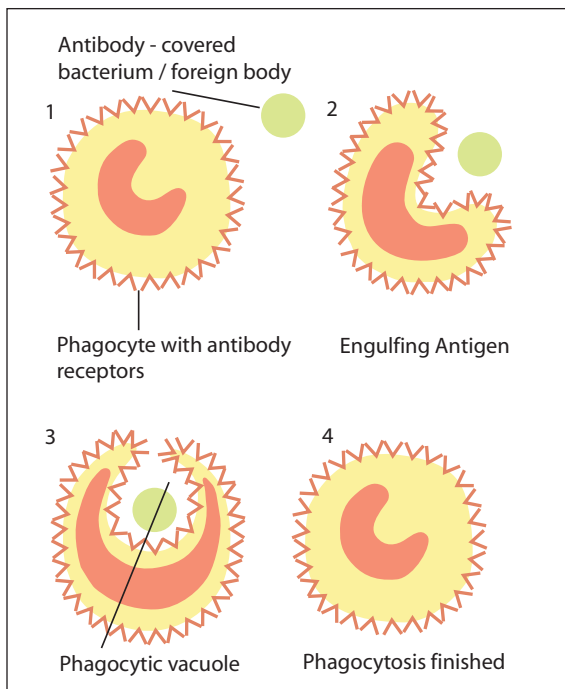
Meningococcal bacteria grow in pairs called diplococci often surrounded by a capsule coat. Over a million of these would fit on the head of a pin.

## Stages in the course of meningococcal disease



For the bacteria, our circulatory system of interconnecting blood vessels is like a high-speed motorway, allowing them to spread rapidly to every organ and tissue in the body. The bloodstream is also the focus of the human immune response, our defence against disease. The bacteria shed part of their cell wall into the blood, where it acts as a toxin, triggering an immune response.

The toxin is detected by white blood cells, neutrophils and macrophages, which patrol the blood vessels. They are the first to respond, engulfing and destroying the invading bacteria (phagocytosis). As they do so, they release chemical signals into the blood, recruiting more white blood cells to the battle. At the same time, a cascade of blood molecules swarm onto the surface of the bacteria, building up on top of each other to form a biological needle that bursts the bacterium like a balloon. This process is called the Complement System, and is our body's primary killing mechanism for fighting infection by *N. meningitidis*. At the onset of this battle between bacterium and immune system, the patient will start to display classic flu-like symptoms, which rapidly worsen as the bacteria multiply and spread further throughout the body.

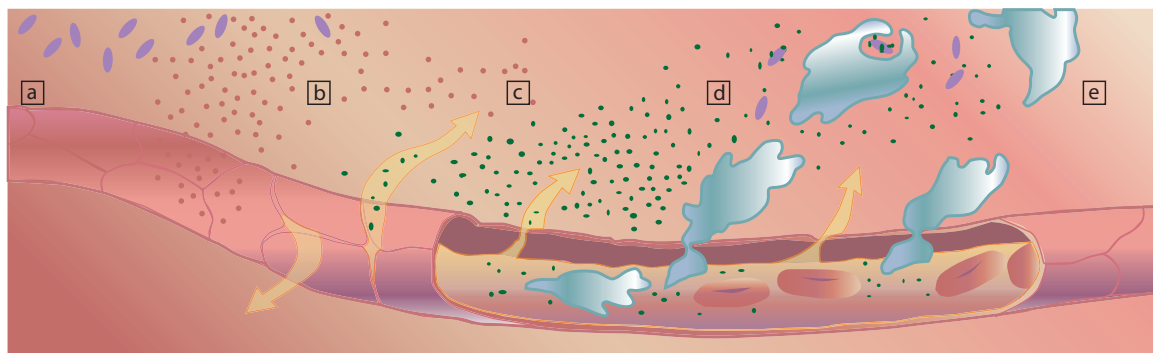


The process of phagocytosis where the bacteria are engulfed by macrophages (white blood cells).

## Immune evasion - bacterial survival tactics

The bacteria are able to spread in this way because they have developed extremely clever ways of protecting themselves against the immune system. They decorate their outer surface to camouflage themselves, copying the decoration on the outside of human cells, and even stealing molecules from the blood so that the immune system cannot detect them. Proteins on the bacterial surface manipulate the white blood cells, altering their normal behaviour and sending out signals to recruit yet more cells which start to cause damage to tissues in their voracious hunt for bacteria. This process is called an inflammatory response, and when it gets out of hand, it can be life-threatening. Meanwhile, the invading bacteria continue to multiply. A blood test at this point will show a dangerously high level of bacteria in the blood.

### Acute inflammation (inflammatory response)



a. Bacteria invade a tissue. They kill cells or release harmful metabolic by-products.

b. The substances released by bacteria and by damaged or killed body cells accumulate in the tissue.

c. The substances make the tissue's small blood vessels more permeable. Plasma proteins escape into the tissue.

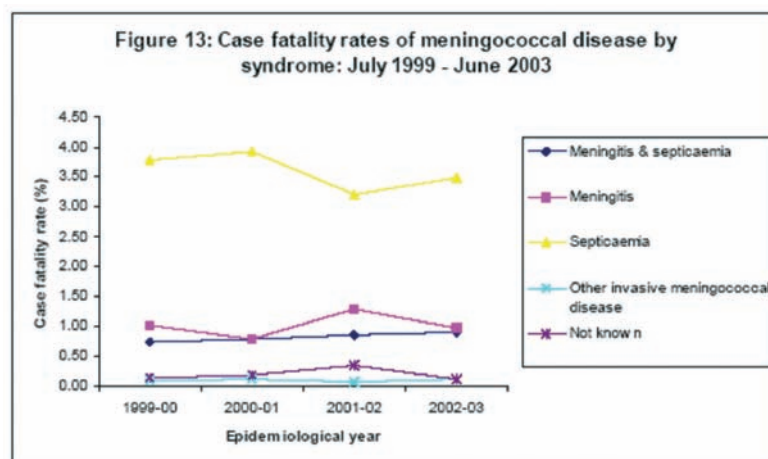
d. Some plasma proteins attack bacteria. Others create chemical gradients that facilitate migration of phagocytes to the tissue. Still others repair tissue damage (as by clotting mechanisms).

e. Phagocytic white blood cells engulf bacteria.

Reference: Starr, Cecie and Taggart, Ralph, Biology: The Unity and Diversity of Life, 7th Ed. Wadsworth Publishing Co. Belmont, CA. 1995. Fig. 40.3, pg. 679

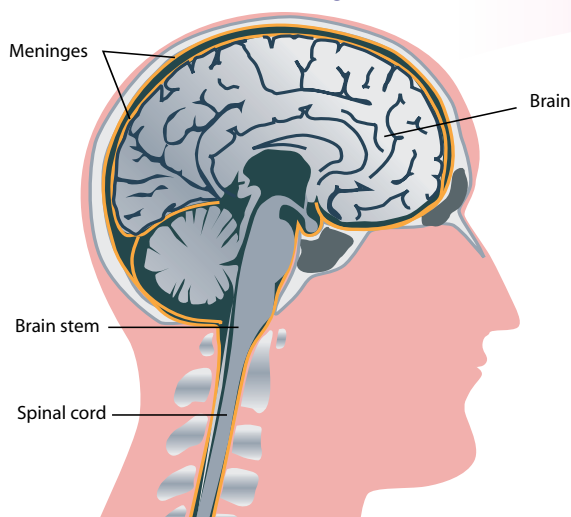
This condition is called septicaemia. It develops when the bloodstream is simply overwhelmed by the sheer number of bacteria. By now the patient may be showing signs of the telltale rash, along with severe fever. Their vital organs struggle to cope, and eventually shut down. Meningococcal septicaemia results in more deaths than any other form of infection by *N. meningitidis*. It is also this form of the disease that results in patients requiring life-saving amputations.

### High Mortality Rate of Meningococcal Septicaemia (without Meningitis)



Source: HPA Enhanced Surveillance of Meningococcal Disease National Annual Report: July 2002-June 2003

## The Meninges



In some cases, the bacteria are also able to force their way through the lining of the central nervous system to infect the cells lining the brain and spinal cord, the meninges. They multiply in the cerebrospinal fluid, the liquid that bathes the brain and spinal cord. Meningitis occurs as a result of swelling in the meninges, and in the brain itself, and the pressure of the swelling often causes the patient to lapse into a coma before their body is forced to give up its battle.

## The immune response - developing natural immunity

Our bodies are continually under attack from bacteria in the environment. Some are harmless, whilst others are more dangerous and likely to cause disease. When we are exposed to a bacterium for the first time, our immune system is naïve - it recognises the bacteria as foreign but must start building a defence against it from scratch. Certain white blood cells, collectively known as Antigen-Presenting Cells (APC), engulf the bacteria and degrade them into bite-size chunks that are then combined with special proteins and displayed on the surface of the APC. These chunks of protein, carbohydrate and lipid are known as antigens, and many are unique to the bacterium.

Another type of white blood cell, the B-cells, are attracted to the antigens and are specialised to produce complementary antibodies that bind perfectly to the antigen like a key in a lock. Antibodies are then mass-produced and released into the bloodstream, where they stick to the invading bacteria like iron filings to a magnet. This has the effect of lighting it up like a beacon, and the killing cells of the immune system can lock onto them and target them for destruction. Once this process has happened once, the cells retain a memory of the antibodies they have produced. If the same bacteria infect the body again, those antibodies are waiting in the wings to be reproduced and prevent disease. This is why people only suffer from some diseases, like chicken pox, once in their lifetime.

## Antibodies bind to antigens like a key in a lock

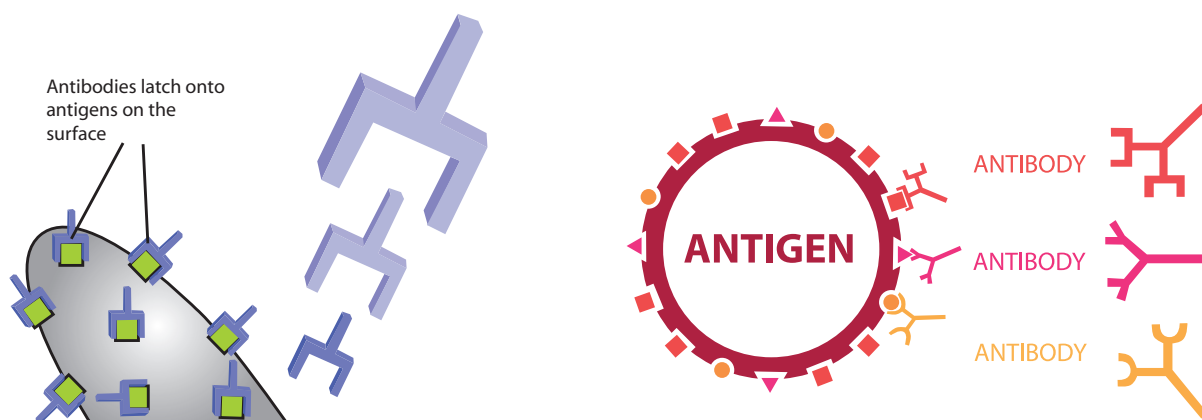


Image source: Association of the British Pharmaceutical Industry.  
Reproduced with kind permission. [www.abpischools.org.uk](http://www.abpischools.org.uk)

## What is a vaccine?

Vaccines exploit this natural process of antibody production by introducing key antigens of certain disease-causing bacteria to the body. Antibodies are produced in response but as it is not a real infection, there is no disease. If the body is later infected by that bacterium, antibodies are already present, the immune response is rapid and the vaccinated person does not contract the disease. Thus, vaccination acts as an early warning system, priming the immune system for future infections.



Vaccines are also very important in reducing the number of people who carry the disease. Many diseases are most commonly carried by people of certain ages or backgrounds. Provided immunisation is achieved for a certain percentage of these people, carriage rates are decreased. This extends protection over the rest of the population, removing the need to immunise everybody. This is known as 'herd immunity' and is crucial for keeping people protected. If vaccination levels in the carrier groups drop below the threshold though, there is a serious risk of outbreaks of the disease.

## Meningitis vaccines

There are two main types of vaccine that have been designed against bacteria that cause meningitis.

- **Polysaccharide vaccines** are relatively simple vaccines. They exploit the long strings of sugars and carbohydrates (polysaccharides) on the outer surface of all bacteria. The nature of the polysaccharide coating, which often forms a 'capsule', varies between different species and strains and it is therefore a very useful antigen to design a vaccine against. A piece of the polysaccharide is taken from the bacterium and used to immunise people.
- **Conjugate vaccines** are more complex. Many bacterial polysaccharides, such as the *N. meningitidis* capsule, do not cause a strong enough immune response to protect the immunised person against disease, particularly in the long term. In these cases, another, more 'immunogenic' protein will be included. The presence of this protein, usually a de-toxified toxin, triggers a more effective immune response, causing more antibodies to be produced.

There are already a number of vaccines against meningitis-causing bacteria that have been very successful. In 1992 the Hib conjugate vaccine against the bacterium *Haemophilus influenzae* was introduced into the UK, resulting in a 90% decrease in cases.

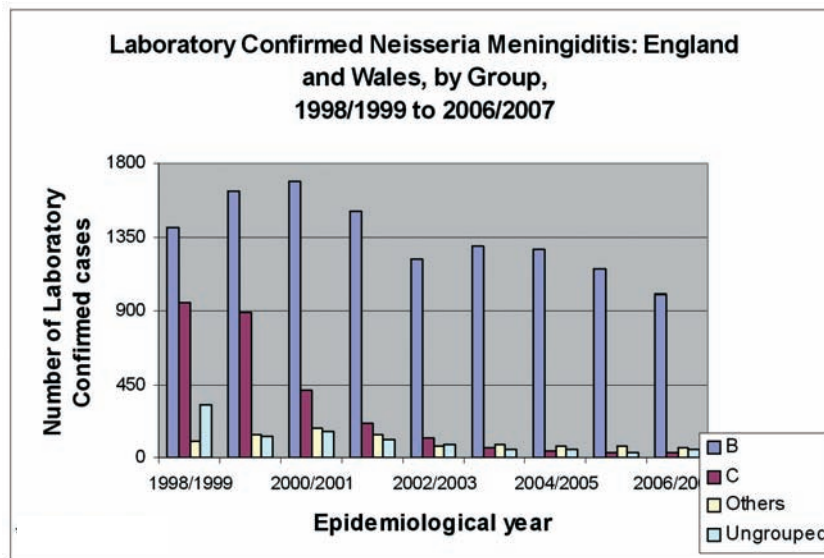
Routine vaccination is also performed against the bacterium *Streptococcus pneumoniae*, the 'pneumococcus'. There are 90 different subtypes, of which just seven cause over 80% of pneumococcal disease. Both polysaccharide and conjugate vaccines are available.

- **Pneumococcal Polysaccharide Vaccine (PPV)** provides relatively short-term protection against 23 subtypes of the bacterium (accounting for 96% of pneumococcal disease in the UK). Since 2005, PPV has been recommended for all adults over the age of 65. It may also be given to others who are deemed to be particularly at risk, for example those who suffer from diabetes, heart disease, or have a compromised immune system due to HIV or chemotherapy. PPV is not suitable for children under two.
- **Pneumococcal Conjugate Vaccine (PCV)** protects against the seven most common forms of *S. pneumoniae*. The polysaccharide components are combined with a non-toxic form of the Diphtheria toxin protein to provide longer lasting protection. Since 2006, PCV has been used to immunise children aged from two months to five years, and may be combined with PPV for children over five who have health conditions that put them at higher risk of disease. Within a year of its introduction, PCV is estimated to have prevented 300 cases of childhood pneumococcal disease, such as meningitis.
- A new version of PCV, currently known as Wyeth's PCV13, which protects against 13 subtypes is currently performing very well in clinical trials.

Vaccines against certain types of *N. meningitidis* are also available. The capsule of each type of the meningococcus - A, B, C and so on - are all slightly different and so result in different antibodies. This means that someone who has been vaccinated against all the Meningitis C types, for example, will be protected against Meningitis C but not against the other types of the bacterium. The protection afforded by the original polysaccharide vaccines waned rapidly, and did not cover young children. Therefore, all meningococcal vaccines are now conjugate vaccines.

- The **MenC** conjugate vaccine protects against Meningitis C. There are three MenC vaccines, all of which use the Diphtheria toxin as a conjugate, and are considered to be interchangeable. MenC is given to babies aged 3 to 4 months, and is available for everyone under 25. Since its introduction in 1999 cases of disease caused by type C meningococcus have dropped by over 95%.

### Decrease in Meningococcal Group C

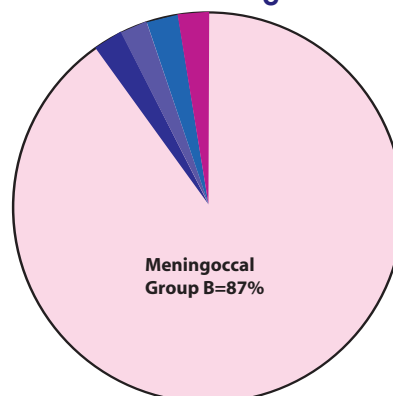


Source: PHLS Meningococcal Reference Unit (provisional data for 2006/2007)

- The **Hib/MenC** vaccine is also available, and protects against infection from both *H. influenzae* and *N. meningitidis*. This vaccine is given as a booster to children at 12 months following standard vaccination with the individual Hib and MenC vaccines
- The **Quadrivalent MenA/C/W/Y** or the **bivalent A/C** vaccine are recommended for people travelling to certain parts of Africa and Asia, where the A, W and Y strains are still prevalent. People travelling for the Hajj Mecca are now legally required to be immunised with a vaccine against Meningitis W. These vaccines offer protection for up to five years, but are not effective in young children.

The last few decades have seen a great deal of progress in vaccines against meningitis. However, there is still no vaccine against the most common type - Meningitis B.

### Current Prevalence of Meningococcal Group B



Source: HPA Meningococcal Reference Unit 2006/07

## Meningitis B

Meningitis B employs particularly cunning ways to avoid the immune system, which in turn present serious challenges for the scientists trying to design a vaccine against it. The capsules of Meningitis B bacteria are decorated with sugar molecules that perfectly mimic molecules found on our own human cells. This means that the bacteria are not recognised as foreign when they are in the body. They effectively slip under the radar of the immune system, camouflaged to look like the host cells.

This clever trick makes vaccine design difficult because the capsule is no good to use as an antigen. Therefore, scientists have been searching for new, different antigens on the surface of Meningitis B bacteria that could be developed as potential vaccine targets. To make things even more difficult for them, Meningitis B continually changes the proteins displayed on its outer surface. It makes constant alterations, choosing from an enormous library of potential combinations. This means that the scientists must look for an antigen that remains the same so that antibodies against it will still work against all the different variations.

A number of potential MenB vaccines are in the pipeline. These vaccines are using not one, but many MenB proteins in an attempt to protect against this variable bacterium. In some cases, scientists have used proteins found on small bubbles of membrane that exist on the outside of the bacterium. Others are targeting specific groups of well-characterised proteins. Researchers are also looking at whether the non-disease causing sister bacterium, *Neisseria lactamica*, could hold the key to producing an effective vaccine against MenB.

## Immunisation schedule for babies in the UK

The current immunisation protocol for babies and young children in the UK has been in place since 2006.

Age of immunisation	Vaccine
2 months	DTaP / IPV + PCV
3 months	DTaP/IPV/Hib + MenC
4 months	DTaP/IPV/Hib + MenC + PCV
12 months	Hib / MenC
13 months	MMR + PCV

DTaP/IPV/Hib is a single vaccine that protects against diphtheria, tetanus, pertussis, polio and Hib.

MMR protects against measles, mumps and rubella

The immunisation website is [www.immunisation.nhs.uk](http://www.immunisation.nhs.uk). It is a very detailed site, which has downloadable leaflets and should answer any questions you might have.

## Meningitis UK funded projects

Meningitis is often incredibly difficult to detect, particularly since the symptoms are so similar to those of common colds and flu. Because of this, we firmly believe that prevention is the only way to eradicate the disease. Our sole focus at Meningitis UK is the eradication of meningitis and its associated diseases. Although there are currently vaccines against some forms of meningitis, there is still no vaccine to protect against all forms of the disease. Our fundraising aims to support the scientists who are working to make this goal a reality.

Meningitis UK is closely involved with a number of current projects, and helps to fund the research that is pushing towards a vaccine to eliminate disease caused by Meningitis B. Our Search 4 a Vaccine Campaign, launched in 2007, aims to raise £7million for research into a Meningitis B vaccine. Our scientists believe this is possible within the next few years provided the funds are available to support the breakthroughs that are already being made. So far, we have invested over £2million into this life-saving research.

*We would like to thank Dr Anne Corbett for her kind input into this research document.*