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INFECTIONS AND THE BRAIN

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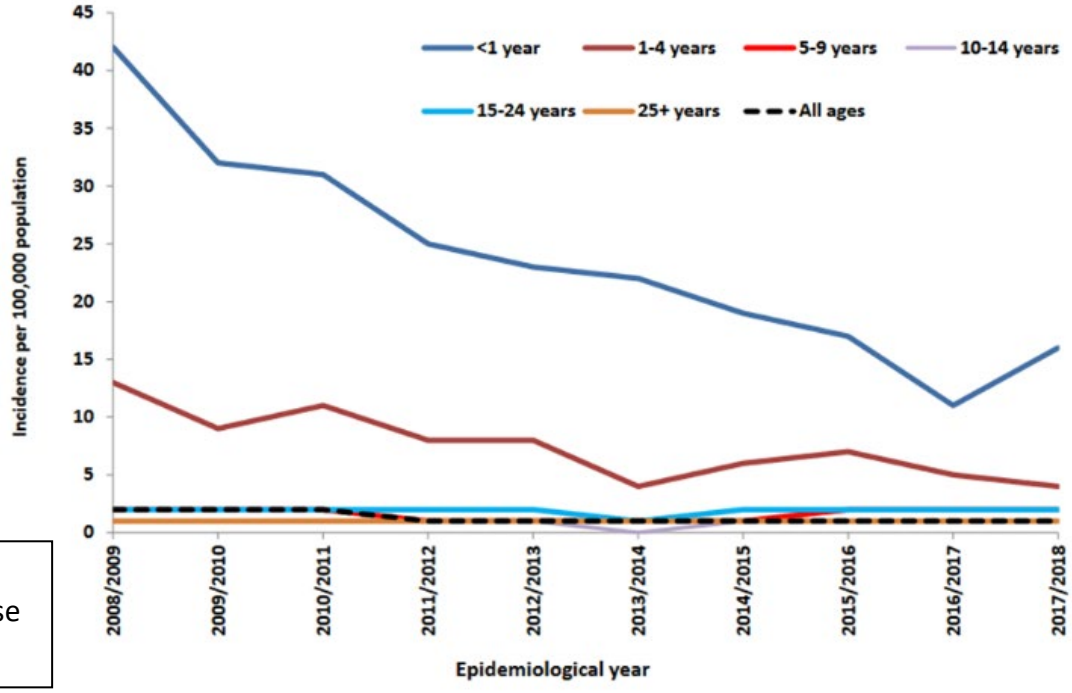
The brain is our most complex and extraordinary organ. Thought, movement, sensation, memory, emotion and controlling the basic functions of life all start in the brain. Inevitably this means that any damage to the brain can be serious, and sometimes catastrophic. The brain is protected both by the immune system and by multiple physical layers. Despite that some infections do get into the brain and cause reversible or permanent damage. Infections of the surroundings of the brain (particularly meningitis) and serious infections of the body a long way from the brain can affect its function. The brain achieves its many parallel processes by being highly specialised. If the infection of the brain is localised, the effect on brain function may also be localised with the rest of the brain functioning normally. The brain is affected by many infections; most are preventable, especially by vaccines, or treatable. This talk will cover meningitis, encephalitis, parasitic infections, localised infections and generalised effects of infections on the brain.

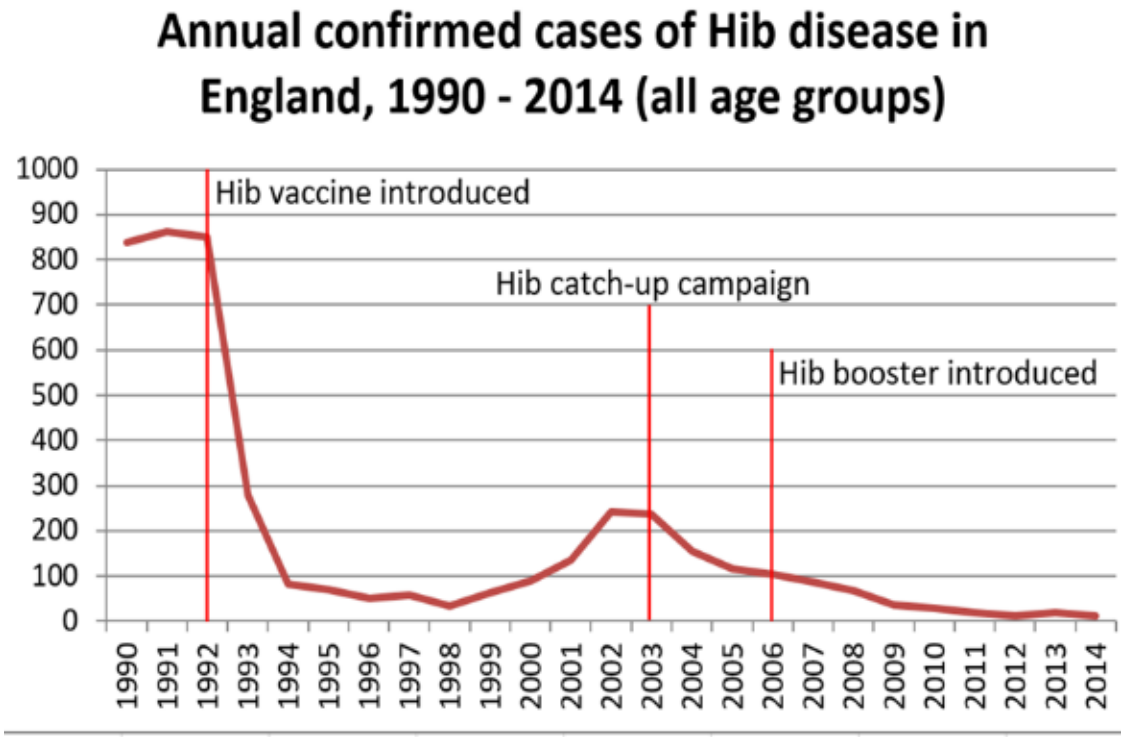
Meningitis is a common serious infection of the brain in both developing and developed countries. It can be caused by bacterial, viral, fungal and tuberculosis infections. The infection is of the surroundings of the brain, and usually does not directly invade the brain itself. The classical symptoms of meningitis are headache, significant neck stiffness, photophobia (light causing pain), and fever. Diagnosis in most cases is by a lumbar puncture. Whilst untreated bacterial meningitis has high mortality, treated early bacterial meningitis can have a quick and full recovery, and viral meningitis often has very limited impact. Severe cases with disability or death do still occur in all countries and are common in several parts of the world and in all countries in the immunosuppressed.



Incidence of invasive meningococcal disease England, 2008-2018.

At least to this point in history the most important bacterial meningitis is meningococcal meningitis. Is carried by around 10% of adults in the nose or throat. When it does invade, onset can be very rapid and untreated there is a very high mortality of around 50%. There are six major types (ABC WXY); we now have vaccines that are effective in almost all settings. The incidence varies by age and geography. Globally the most important of these is Meningococcus A. This used to cause massive epidemics particularly in West Africa, but these large outbreaks have been virtually eliminated by the introduction of an effective vaccine, although significant numbers of cases still occur. After Men A vaccine introduction there was a 71% decline in the risk of meningitis in the most affected part of Africa. In UK, Europe and the USA meningococcus types B and C disease predominate. There is been a substantial reduction first in Men C and in other forms more recently due to widespread vaccination programs.

The second major cause of bacterial meningitis is pneumococcal meningitis. This affects particularly young children (less than two years) and those over 65 years. There is a high mortality from treated meningitis and around one in five survivors have significant disability. The introduction of routine immunisation for the 13 most common strains of pneumococcus in infants and a vaccine for the over 65's is leading to a reduction in invasive pneumococcal disease. 30 years ago, the most common bacterial meningitis in children was *Haemophilus influenzae* b (Hib). The introduction of Hib vaccine first in high-income countries and now globally has led to a massive reduction in cases, deaths and disability.



A number of rarer bacterial infections occur, particularly in new-borns and people who are severely immunosuppressed (eg AIDS). In new-borns the main cause of meningitis is now group B Streptococcus. Finding a vaccine for this is a priority. Globally other groups are very important. Meningitis due to tuberculosis is one of the most serious forms of the infection. Now rare in wealthier countries it remains a significant risk in less wealthy countries and additionally in those who have HIV. HIV is also a risk for a number of forms of bacterial and fungal infections, in particular cryptococcal meningitis. Before effective drugs for HIV were widely available the outlook was bleak. Now these are much rarer and can usually be treated.

Viral meningitis is usually a relatively mild infection, and is less common since the MMR vaccine, as around one in 10 cases were due to mumps previously. By contrast viral encephalitis, which causes inflammation of the brain, can be very serious. There are between 4,000 and 6,000 cases in the UK a year. The cause is unknown in most of these but *Herpes simplex* (cold sore) virus is the most common identified. In encephalitis the brain becomes inflamed leading to drowsiness, confusion, difficulty communicating, fits and in severe cases unconsciousness and occasionally death. Survivors can often have significant long-term disability. One of the most common viral causes of encephalitis used to be measles which is almost entirely preventable by vaccination. 1-3 in 1,000 children will develop encephalitis with measles infection; of these 10 to 15% will die and a further 25% left with permanent neurological damage. There are also post infectious encephalitis forms. Discouraging parents from having their children vaccinated against measles is a deeply stupid thing to do.

Whilst the effect on the brain of the forms of encephalitis we have talked about so far are in evolutionary terms an accident, for rabies it is a central part of its transmission mechanism. Globally there are up to 59,000 human cases a year with a great majority coming from dog bites. Death within 10 days of symptoms is virtually inevitable and it is a terrible way to die. The virus once it invades the brain causes affected mammals to salivate and become highly aggressive including biting; this leads to transmission. Rabies vaccination of domestic dogs reduced rabies to very small numbers in Europe and North America and this has been backed up by vaccine on baited foods to control rabies in wild mammals. Post bite vaccination is highly effective if started early.

Globally several major forms of viral encephalitis are transmitted by mosquitoes, ticks and other insects. These include Japanese B encephalitis in Asia, Eastern Equine Encephalitis in the USA, tickborne viral encephalitis across Europe and Asia. Ticks can also cause encephalitis and neurological symptoms due to bacteria, of which Lyme disease is the most well-known. A century ago a spirochete bacterium that has some structural similarities, syphilis, was a very major cause of meningo-encephalitis in the UK. The neurological form 'general paresis' was very common and accounted for between 12 and 25% of diagnoses in public psychiatry institutions. It causes grandiose ideas, personality change, dementia and eventually paralysis. Whilst syphilis is still present (and common in part of the world) neurological syphilis which usually comes on many years after initial infection is now exceptionally rare as most people are given antibiotics prior to onset.

Several parasites have particular predilection for the brain. The most dramatic, but extremely rare one is the 'brain eating parasite', the amoeba *Naegleria fowleri*, generally caught from swimming in warm untreated freshwater. Much more common and important around the world is cerebral malaria. There are over 200 million cases of malaria a year with over 400,000 deaths and cerebral malaria is a major cause of these. Since year 2000 malaria mortality rates have fallen by over 60%. Whilst the major pillars of control of encephalitis and most meningitis is vaccination, for malaria preventing infected mosquito bites and drug treatment has been the key. Another important insect borne parasite, also controlled by vector control and treatment, is African sleeping sickness (human African trypanosomiasis). Passed on by tsetse flies, historically there have been devastating epidemics killing up to 2/3 of some populations. In 1995 the World Health Organisation estimated over 300,000 cases. By 2017 less than 2,000 cases were reported, mainly in areas of recent conflict where health services break down.

Less severe, but globally extremely common as a parasitic infection of the brain is cysticercosis, caught from the pork tapeworm. WHO estimates 2-8 million people have it, and it is probably the leading cause of adult onset epilepsy globally. Humans catch it from eating food (not pork) contaminated by human faeces. An animal husbandry to keep pigs away from humans, meat inspection, treating human cases and treating and vaccinating pigs are the key to control. Several other parasites can get into human brains; an example of a particularly serious one is hydatid disease, a sheep/dog tapeworm which infects humans accidentally that can cause large parasites that behave quite like brain tumours in the brain. A smaller parasite, the mouse-cat parasite toxoplasmosis, quite commonly affects human brains mainly from infected cat faeces. It usually only becomes a serious medical

problem if people are immunosuppressed for example with AIDS. Toxoplasmosis is another infection which appears to control the brain to make it more likely to be passed on; mice and rats it infects start to behave much less cautiously and are therefore more likely to be eaten by cats completing the cycle. The effects of the infection on the workings of the human brain are controversial.

Bacteria also can cause a space occupying mass. The commonest of these, although fortunately still very rare, is brain abscess. It can occur due to local infections particularly from teeth or sinuses, but this is much rarer since antibiotics. Structural abnormalities of the heart and immunosuppression are also risks. It may well need surgery to drain it. Tuberculosis also can cause mass lesions in the brain. Abscesses and other infections causing mass effects in the brain can cause fitting as well as headaches and local effects which clinically often mimic brain tumours.

The most common way infections affect the brain in high-income countries is however indirect. In the elderly, and in some younger people, any infection can cause delirium. Delirium includes confusion, aggression, personality change and drowsiness. Up to 2 in 10 hospital patients may have it, and it is even more common in those with dementia, including early dementia. Bacterial urinary tract infections and pneumonia are the most common infectious triggers. There is a good chance that people make a rapid and full recovery on antibiotics, although it can sometimes trigger a step down in function. There does seem to be an increased risk of dementia following an episode of delirium. The way that infections cause delirium is not fully understood and in contrast to most of the previous effects of infection in the brain which are decreasing as medicine and development advances, it is likely to increase both in the UK and globally as the population ages. At the other end of the age spectrum infections remain one of the major causes of acquired brain injury in children and until recently meningitis accounted for around 13% and encephalitis around 5% of children needing neurological rehabilitation.

Overall however the outlook for most of the major causes of infection damaging the brain is very good, in both high income and developing country settings. There have been considerable strides forward in many vaccine preventable diseases including meningococcal meningitis, pneumococcal meningitis, Hib meningitis, measles encephalitis, Japanese B encephalitis and rabies. We have effective countermeasures to reduce malaria, sleeping sickness and many parasites affecting the brain. Given the high mortality in some of those infections and the substantial impact that an infection of the brain can have on someone for the rest of the lives this is very encouraging.