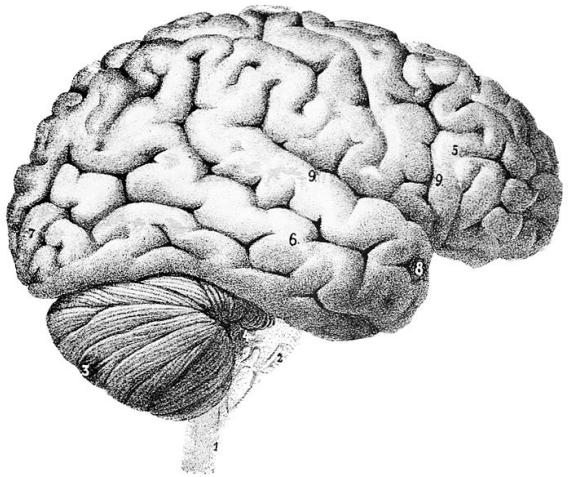
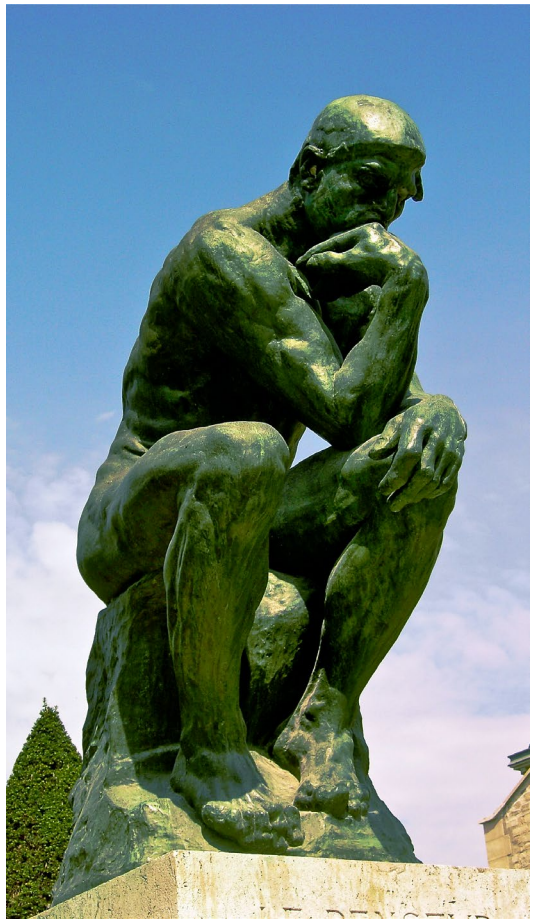
Infections and the brain.

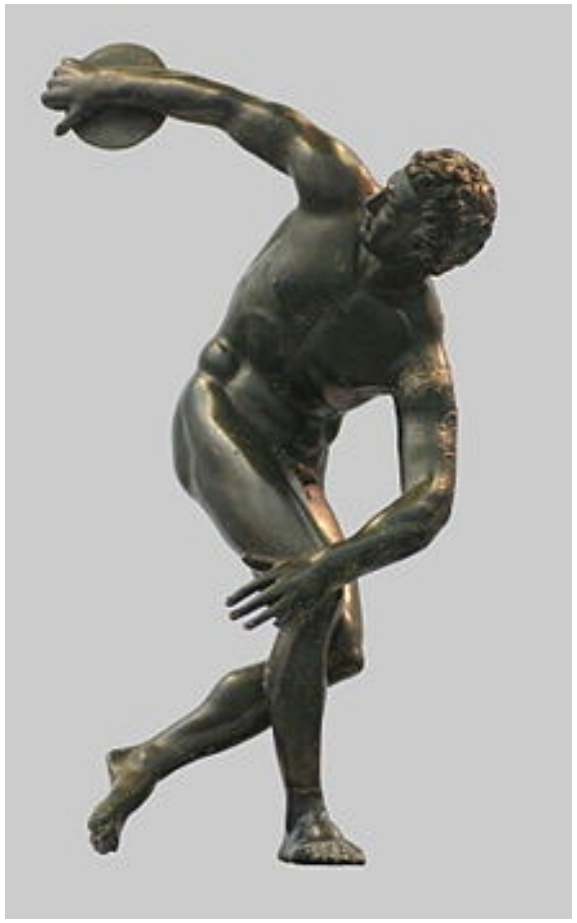


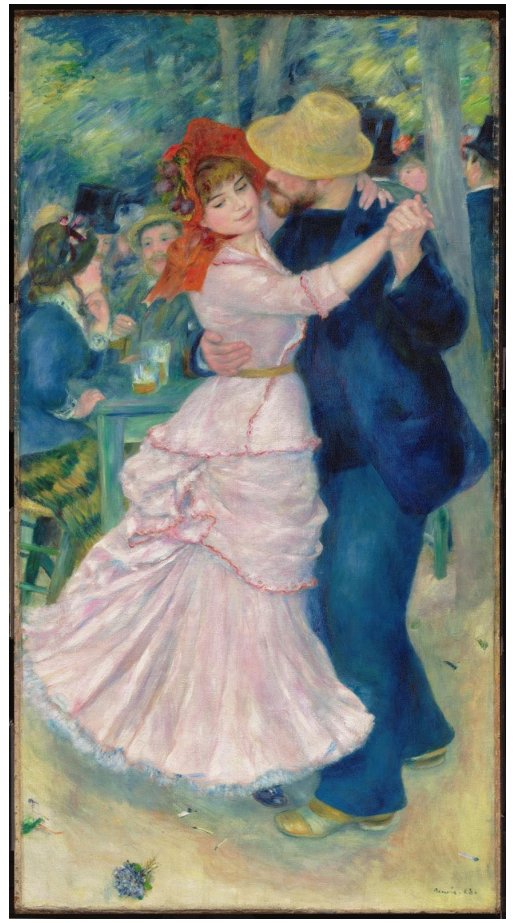
Christopher Whitty

Gresham College 2018

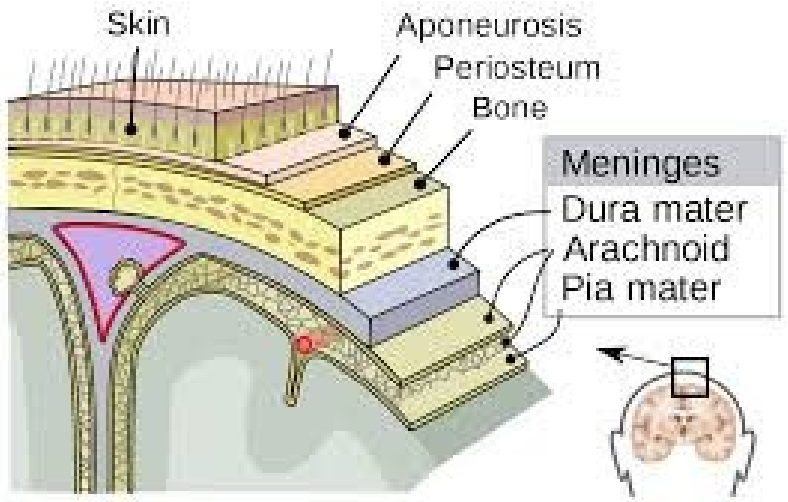
The brain- our most complex and extraordinary organ.
Thought, movement, sensation, memory, emotion…

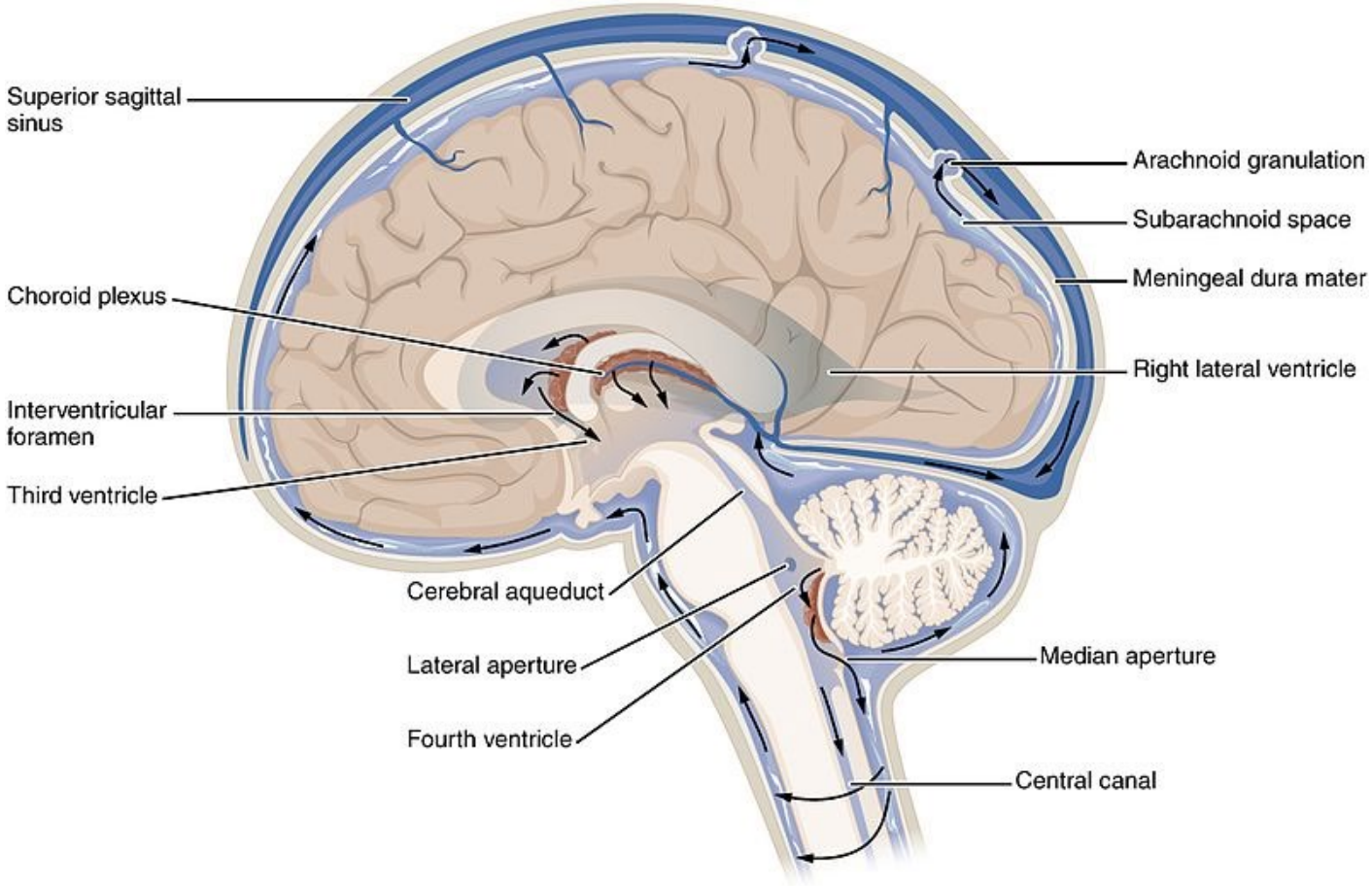




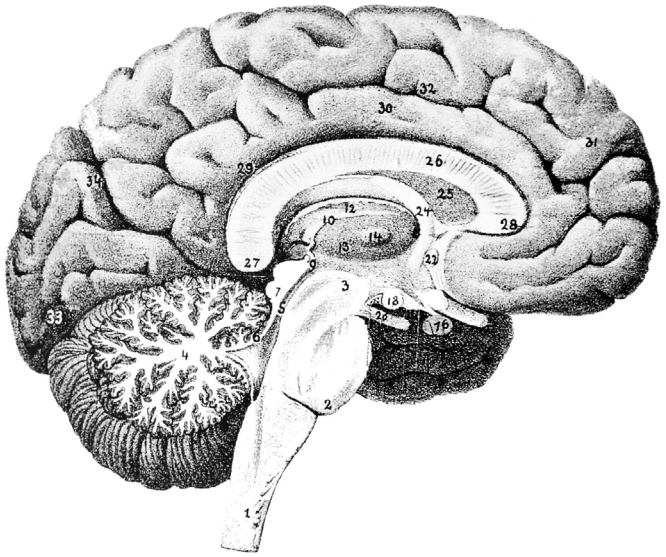


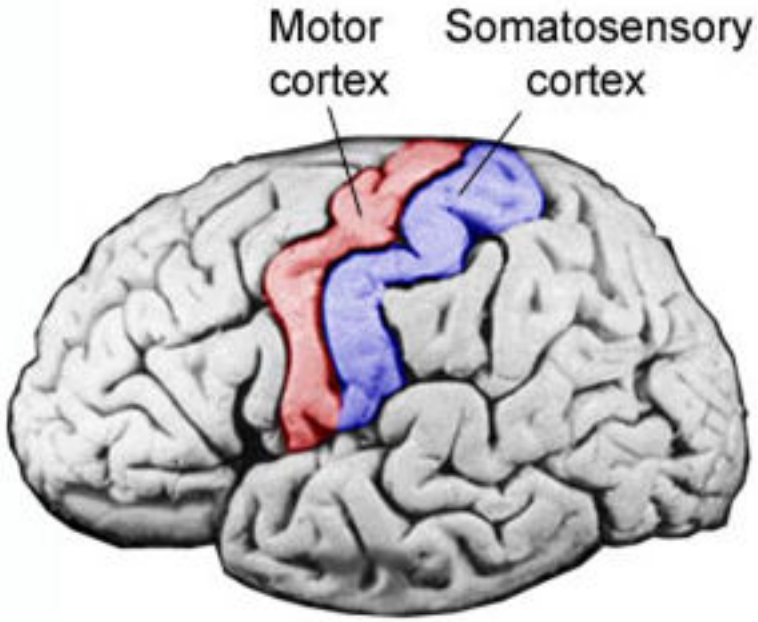
The brain is protected from infection by multiple layers. Infections including meningitis may not get into brain tissue.

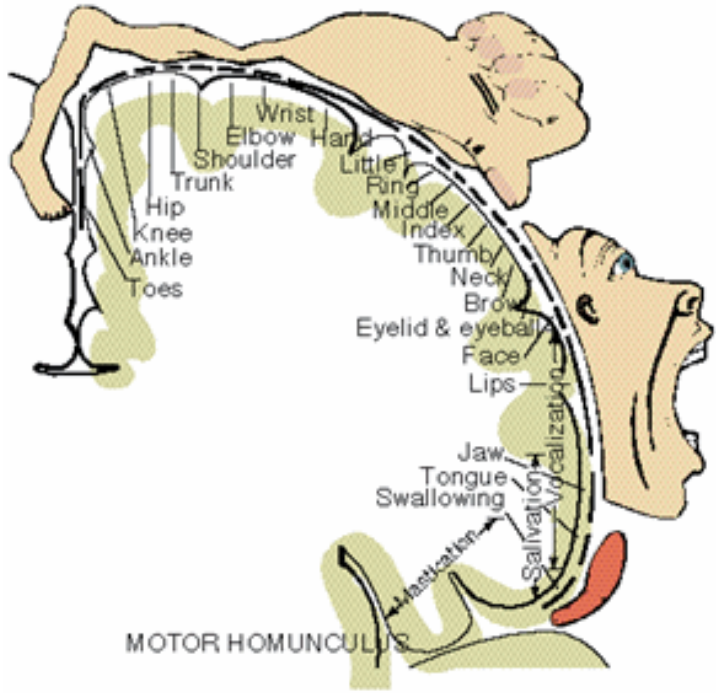




The brain is highly specialised.
If the infection is localised, the effect may be localised.







The brain is affected by many infections. Most are preventable or treatable.

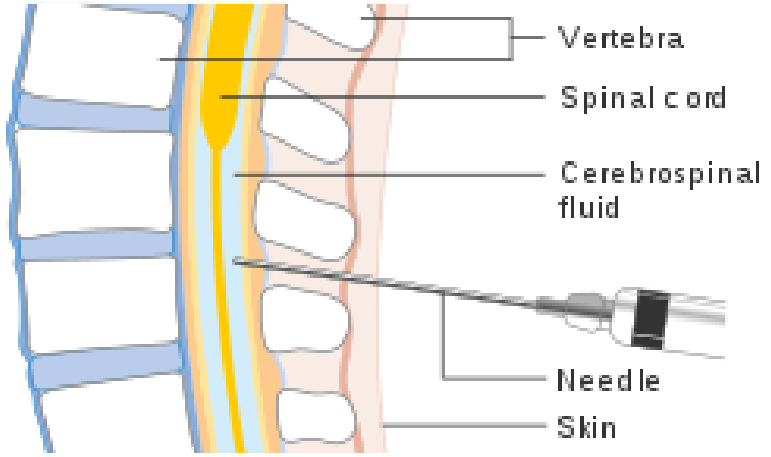
This talk will cover:

- Meningitis.
- Encephalitis.
- Parasitic infections.
- Localised infections.
- Generalised effects of infections on the brain.

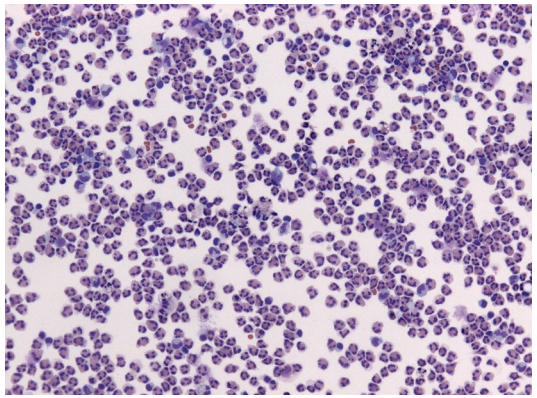
Edward Jenner 1749-1823

Meningitis- infection of the meninges surrounding the brain. Bacterial, viral, fungal, tuberculosis, (parasitic).

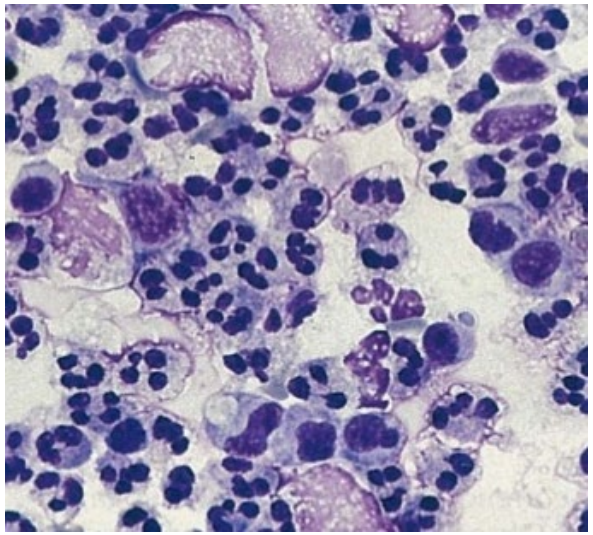
- Headache
- Neck stiffness
- Photophobia (light painful)
- Fever
- Diagnosed by lumbar puncture.

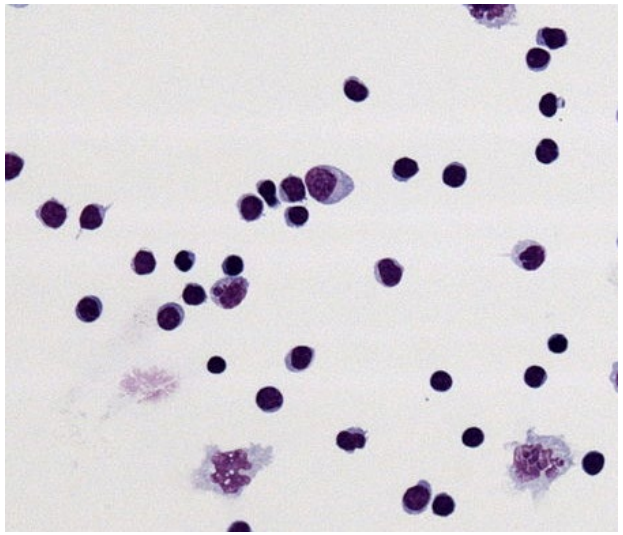


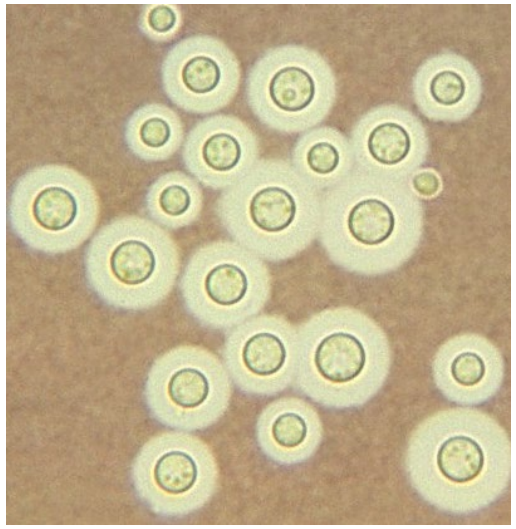
- Viral meningitis, and bacterial meningitis treated early can have a quick and full recovery.



Cerebrospinal fluid (CSF) in meningitis.







Wikimedia

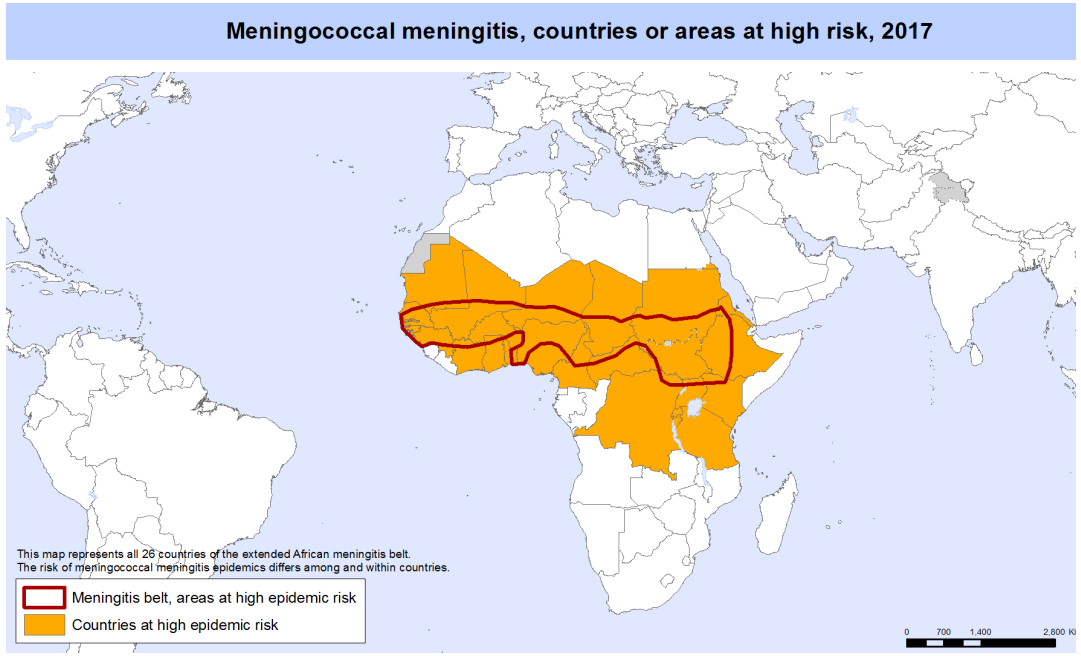
Bacterial meningitis. Meningococcus.

- Carried by around 10% of adults in nose or throat.
- Can cause meningitis, septicaemia, or both.
- Rapid onset (hours).
- Untreated very high mortality (~ 50%).
- Antibiotic sensitive.
- Meningococcus A, B, C, W, X, Y.
- Incidence varies by age and geography.
- Effective vaccines available.

Charlotte Cleverley-Bisman- survived with many disabilities. Her family campaigned to increase vaccine uptake.

Globally the most important Meningococcus A.
1996-7 >250,000 cases.
Around 30,000 cases a year in meningitis belt 2017.

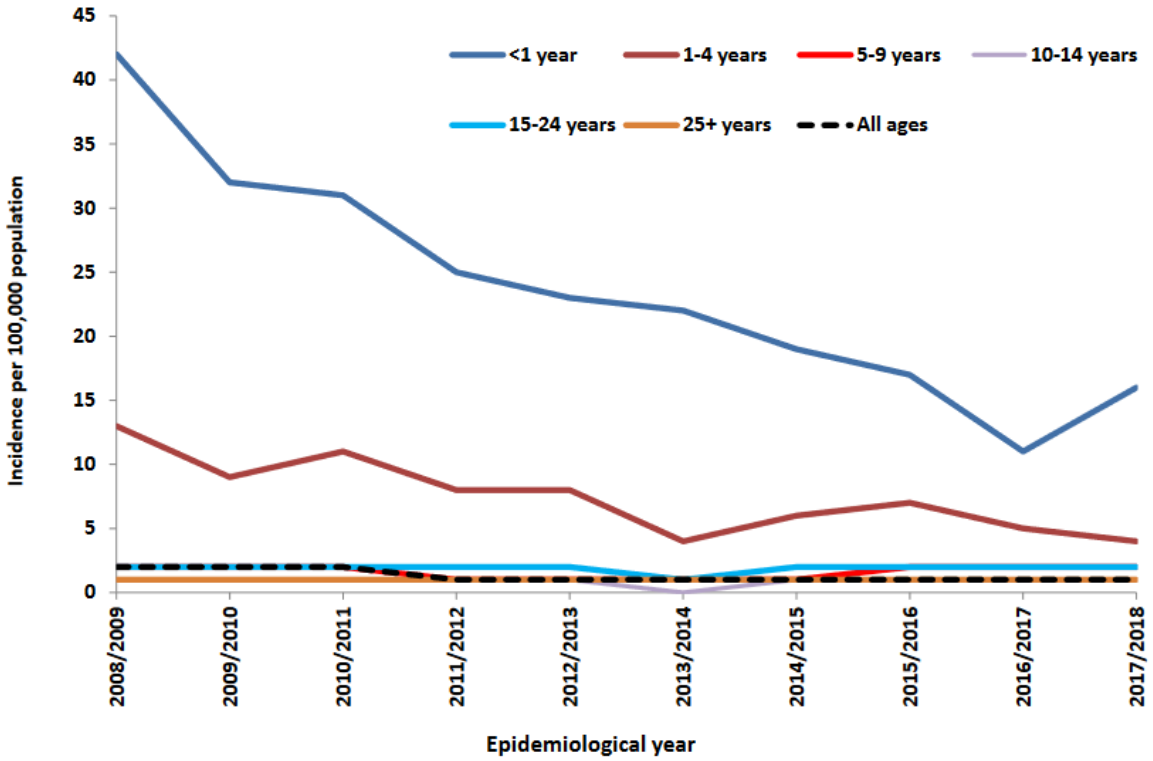
- Used to be massive epidemics in West Africa.
- Meningococcus A outbreaks have been virtually eliminated by introduction of vaccine.
- After Men A vaccine introduction, there was a 71% decline in risk of meningitis.
- Meningococcus C and W still occur: vaccines available.



WHO

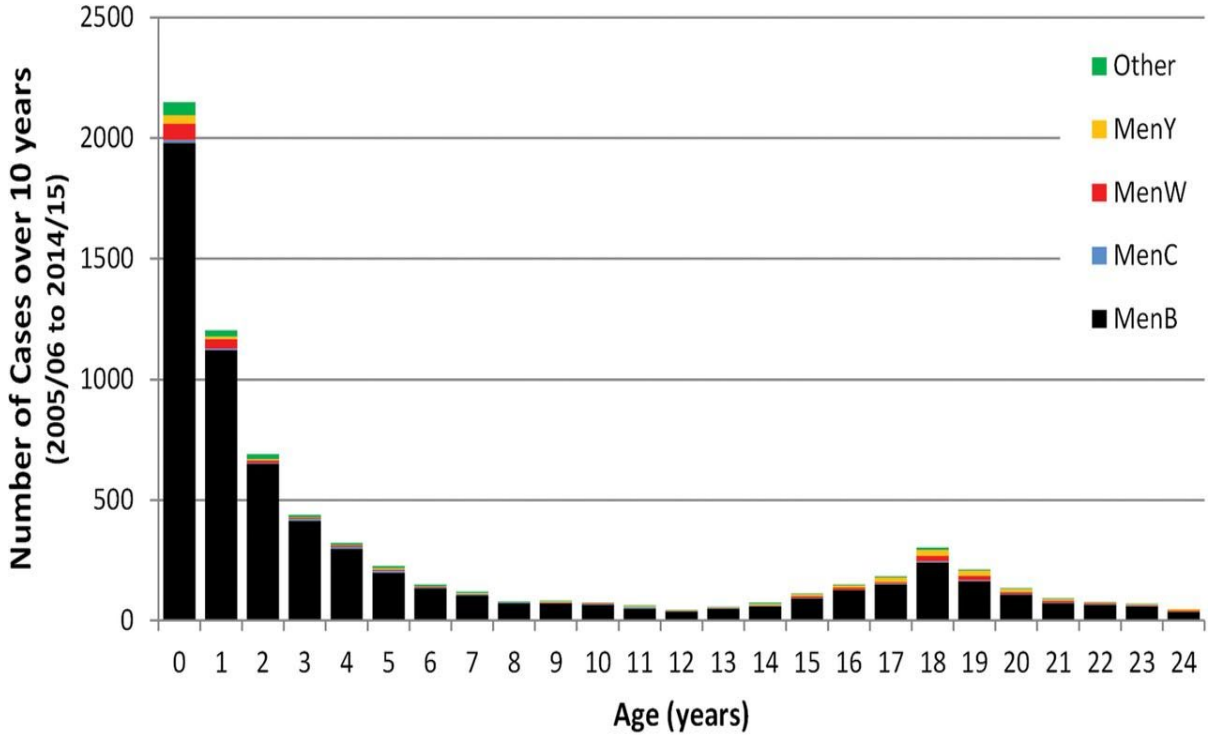
In UK, Europe and USA Meningococcus B, C cause most disease.

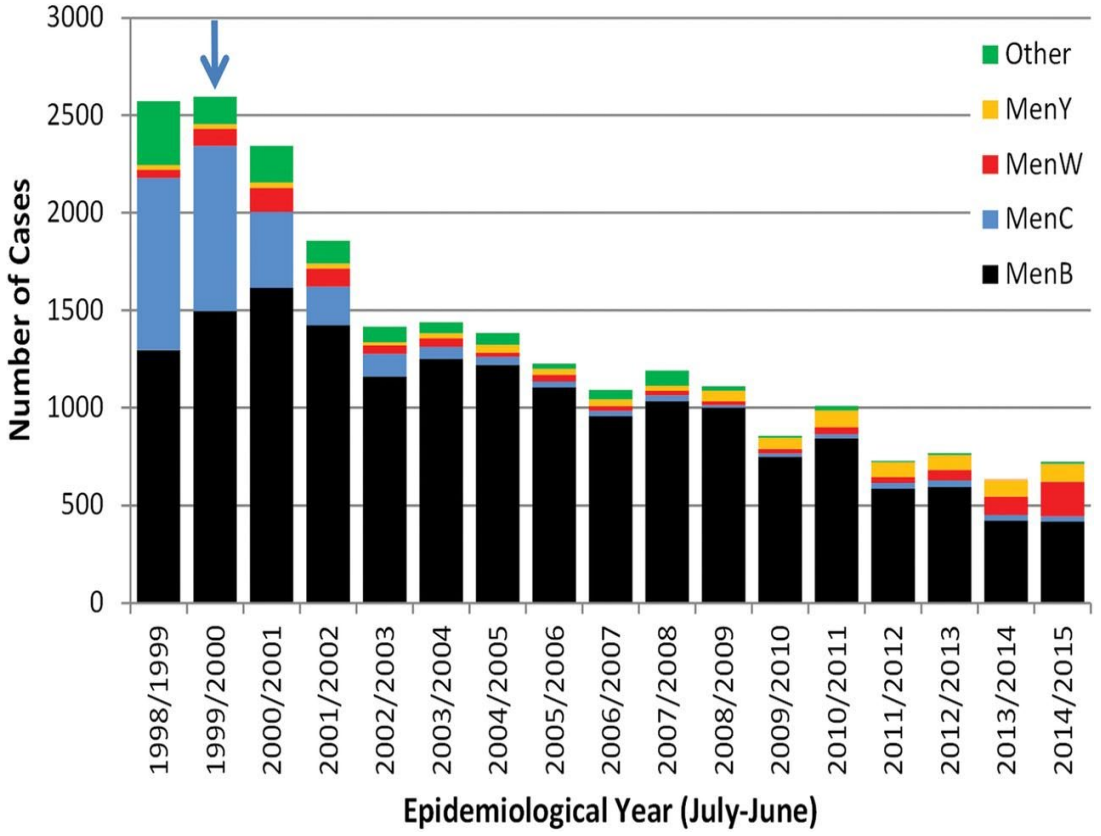
- Reduction in invasive meningococcal disease from 2,595 (1999/2000) to 755 (2017/18).
- Most cases in children under 5, a small second peak in teenagers.
- MenC vaccines available UK and Ireland since around 2000. Reduced by 96%.
- Since 2015 infants in England offered Meningococcal B vaccines. Most cases under 1.
- Since 2015 teenagers offered MenACWY at 14 due to W outbreak.



Incidence of invasive meningococcal disease England, 2008-2018. PHE.

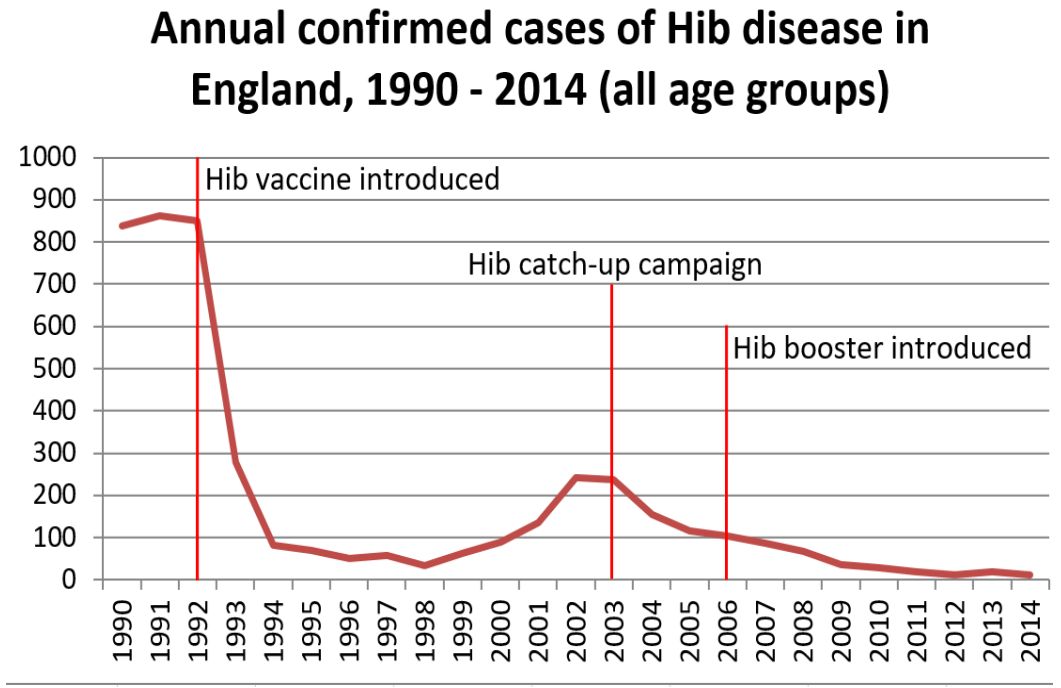
Age distribution of invasive meningococcal disease 2005-2015, and type over time in England. *PHE data, Ladhani et al.*





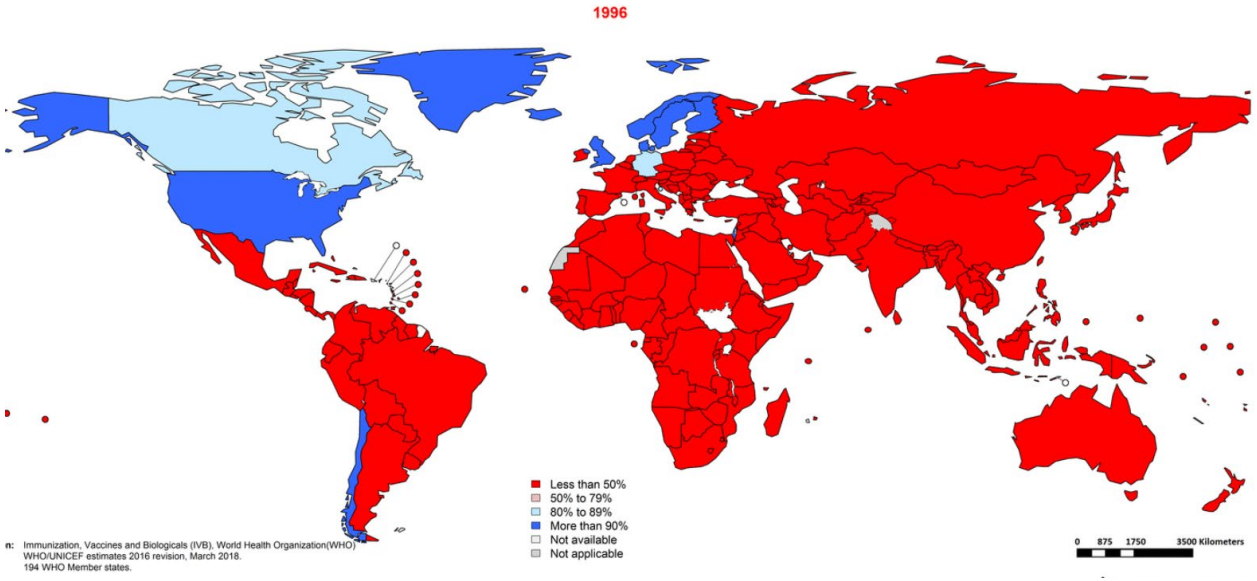
Bacterial meningitis in children- *Haemophilus influenzae* b (Hib).

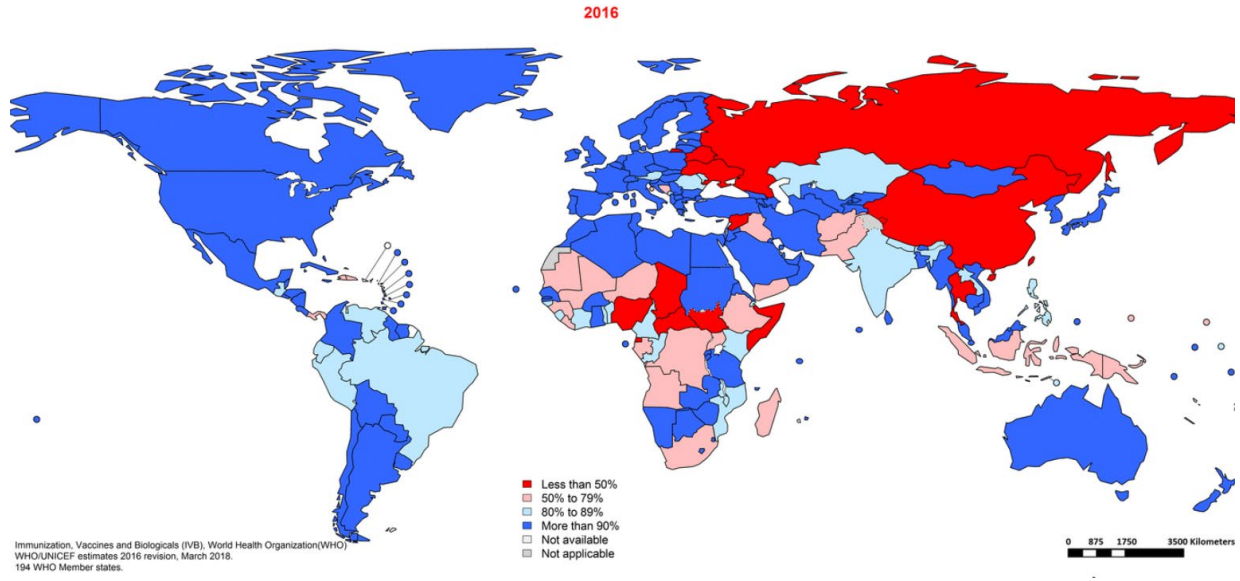
- Was the commonest cause of meningitis in children <4.
- 1:20 died, 1:5 left with serious neurological disability.
- Hib vaccine introduced in UK and Ireland 1992. Reduced incidence >90%.
- In 1991 759 reported cases of invasive Hib in children <5 in England. By 2014, there only 2 confirmed cases in this age group.
- Also reduces carriage.



PHE data.

Hib vaccination, 1996-2016 (WHO). <50% 50-79% >90%





Pneumococcal meningitis.

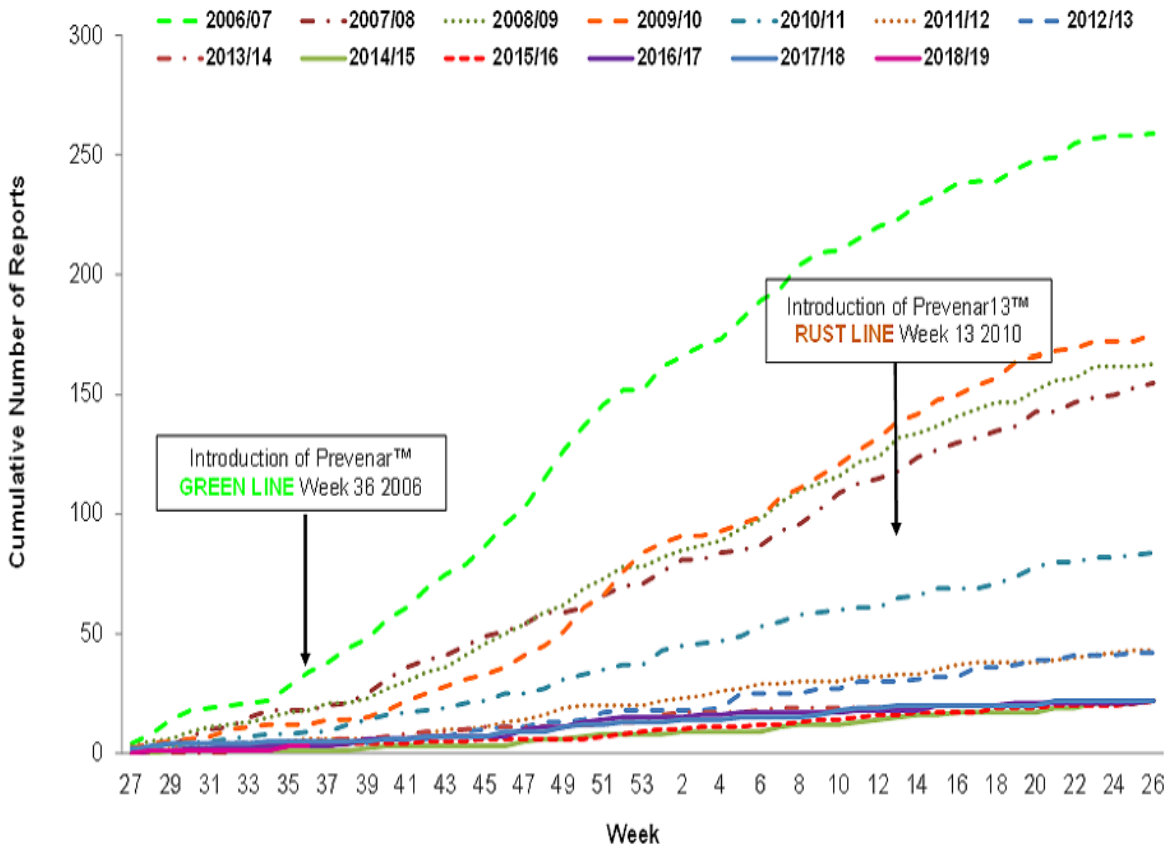
- Young children (<2) and >65 years.
- The pneumococcus is carried in the throats of many adults and over half of pre-school children.
- It can cause various diseases; meningitis is rare but serious. 2nd most common in UK.
- High mortality for untreated pneumococcal meningitis, and around 1:5 survivors have significant disability.
- Routine immunisation for 13 most common strains in infants. Vaccine for over-65s.

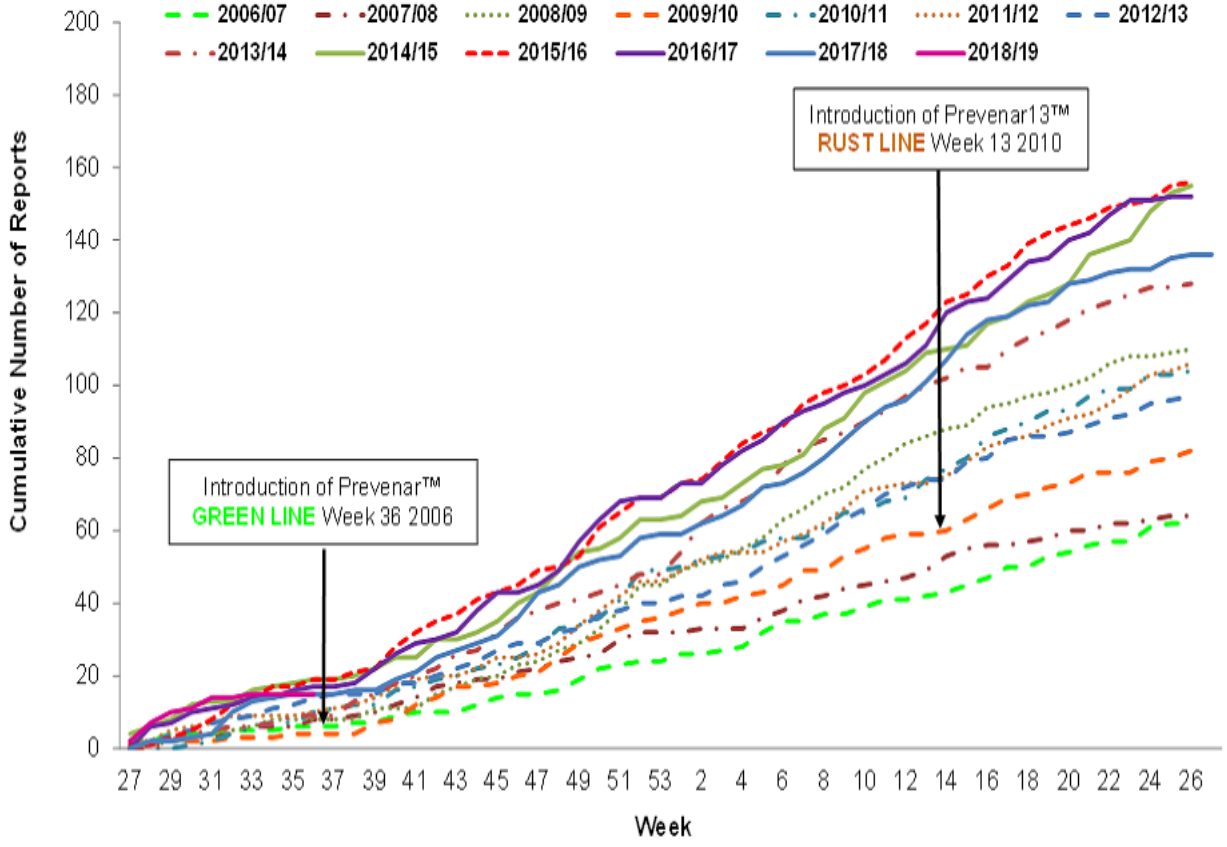
Guido Reni 1635

Invasive pneumococcal disease, children <2: 2006-2018.

7-valent vaccine introduced 2006, 13 valent introduced 2010 (PHE).

L- serotypes covered by the vaccine. R- serotypes not covered.





Rarer bacterial meningitis. In wealthier countries generally in newborns and immunosuppressed.

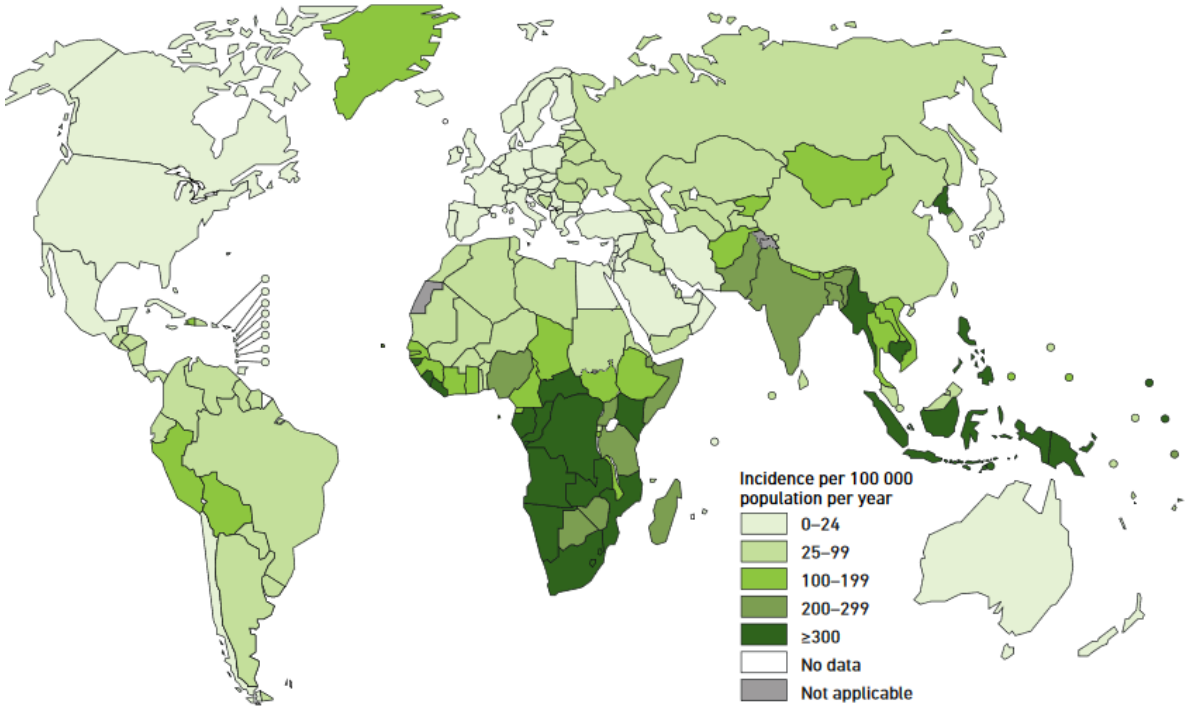
- Group B Streptococcus (GBS). Main cause of meningitis in newborns in UK.
- 20 –30 % of pregnant women carry GBS bacteria in the bowels or birth tract; 99% of babies born to mothers who carry GBS are perfectly healthy.
- *E. coli* K1. 20% of meningitis in newborns, <3% others.
- Listeria. Now very rare. Unpasteurised milk products in pregnancy.
- Salmonella. Very rare. Pet reptiles.

Cheeses. Tzahy Lerner

Pet water dragon. Fazyk

TB meningitis: the most dangerous form of tuberculosis.

- In wealthier countries TB meningitis is now very rare.
- When the NHS was founded there were 2,000 cases a year in in England and Wales- now around 100 a year (2.2% of TB).
- Children under 4, and HIV positive adults most at risk.
- BCG vaccine provides 75% protection in UK context.
- A major burden in less wealthy countries, especially those with high HIV rates.
- TB drug resistance a serious threat.

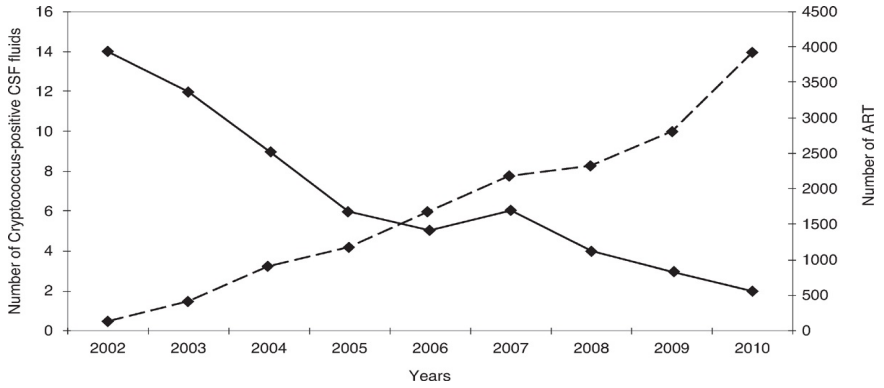


Incidence of TB 2017. WHO estimates.

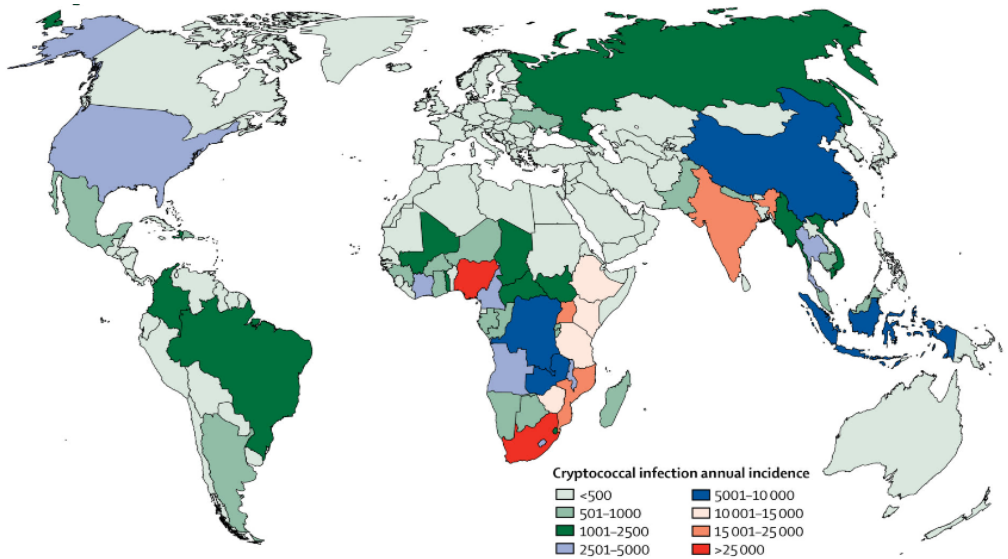
HIV and meningitis.

- People with AIDS (advanced HIV disease) have substantially increased rates of meningitis.
- Cryptococcal (fungal).
- Pneumococcal.
- TB meningitis.

- In pre antiretroviral days outlook bleak. Now much rarer, can usually be treated.
- HIV causes, or allows, multiple other neurological infections.



Bamba et al. Cryptococcal meningitis in W Africa.
Rajasingham et al. Incidence of cryptococcal infection.



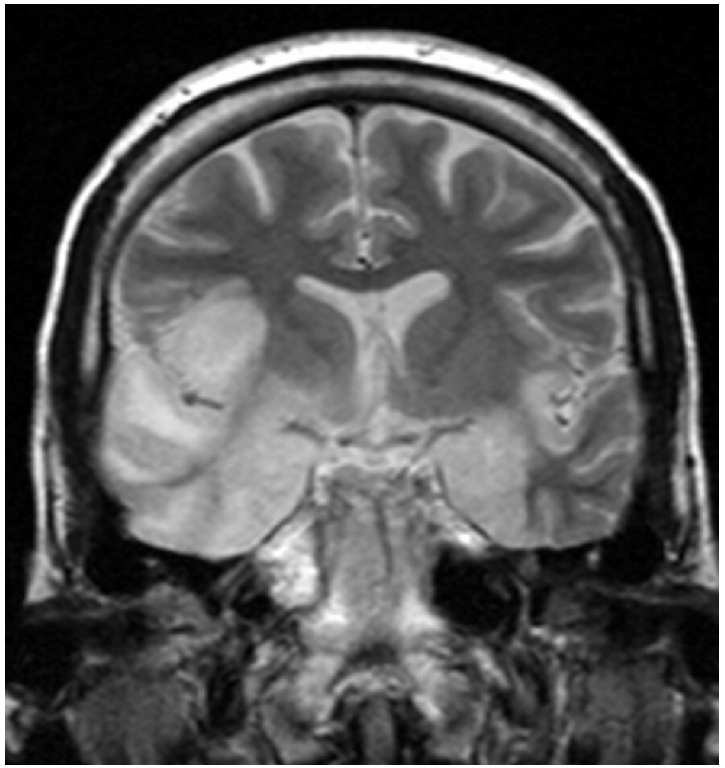
Viral meningitis.

- Generally mild, and lasts less then 14 days.
- Occasional, generally mild, neurological after-effects.
- No treatment other than analgesia.
- Around 1:4 cases of viral meningitis were mumps prior to MMR.
- Several other viruses can cause it, mainly ones associated with gut infections in children (enteroviruses), HSV, measles.

Child with mumps. CDC

Viral encephalitis- inflammation of the brain.

- Several common infections can rarely cause encephalitis (brain inflammation).
- Around 4-6,000 cases in the UK a year.
- Common causes:
  - Herpes simplex (cold sore virus).
  - Varicella (chickenpox virus).
  - Measles, rubella in unvaccinated.
  - HIV, EBV, CMV.



HSV encephalitis. Dr. L Dawes.

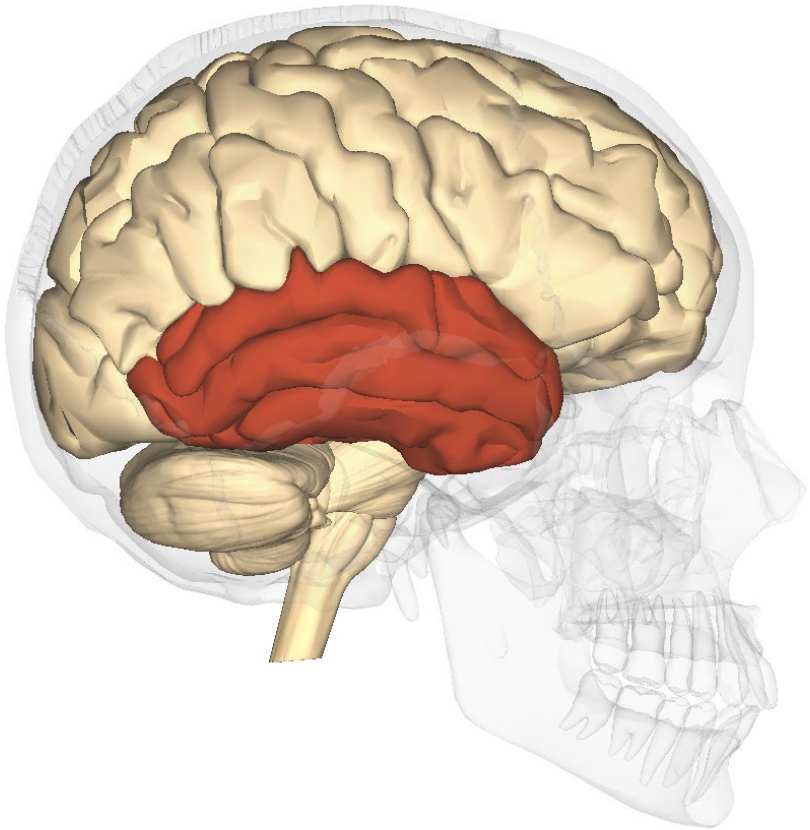
Herpes simplex encephalitis.

Commonest identified cause in UK: around 20%.

Rare: 0.2–0.4/100 000 population.

Typically affects the temporal lobe of the brain. Following ‘flu-like symptoms:

- Drowsiness, unconscious.
- Confusion, difficulty communicating.
- Fits.
- Currently no vaccine.
- Drug treatment (acyclovir). If started early (48 hours) reduces mortality from around 70-80% to 10-20%.
- Around 20% of survivors have serious long-term damage. 55% have good outcome.



Wikimedia

Measles encephalitis- almost entirely preventable.

- 1-3 in 1,000 children will develop encephalitis with the measles infection. 10–15% of these will die, a further 25% will be left with permanent neurological damage.
- 1 in 1,000 children with measles will develop post-infectious encephalitis.
- 1 in 25,000 children will develop subacute sclerosing panencephalitis (SSPE), up to years later (usually fatal).
- 1-2 in 1,000,000 children will develop encephalitis from measles vaccination (less than the incidence of all types of encephalitis).

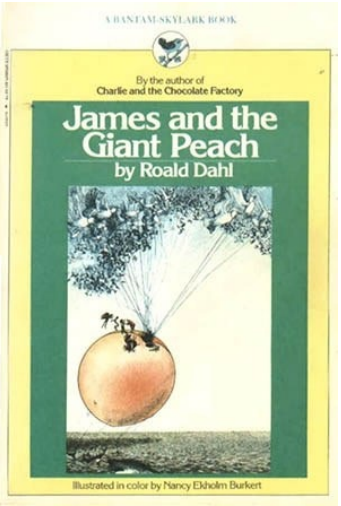
CDC

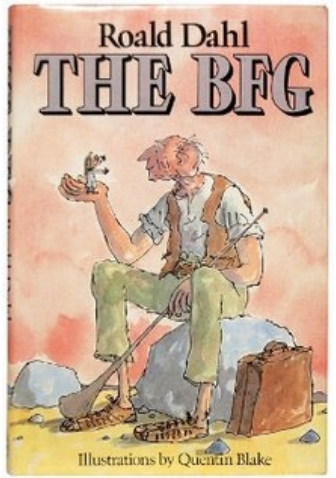
Roald Dahl's letter to parents.

"Olivia, my eldest daughter, caught measles when she was seven years old. As the illness took its usual course I can remember reading to her often in bed and not feeling particularly alarmed about it.

Then one morning, when she was well on the road to recovery, I was sitting on her bed showing her how to fashion little animals out of coloured pipe-cleaners, and when it came to her turn to make one herself, I noticed that her fingers and her mind were not working together and she couldn't do anything. "Are you feeling all right?" I asked her. "I feel all sleepy, " she said.

In an hour, she was unconscious. In twelve hours she was dead. The measles had turned into a terrible thing called measles encephalitis and there was nothing the doctors could do to save her."



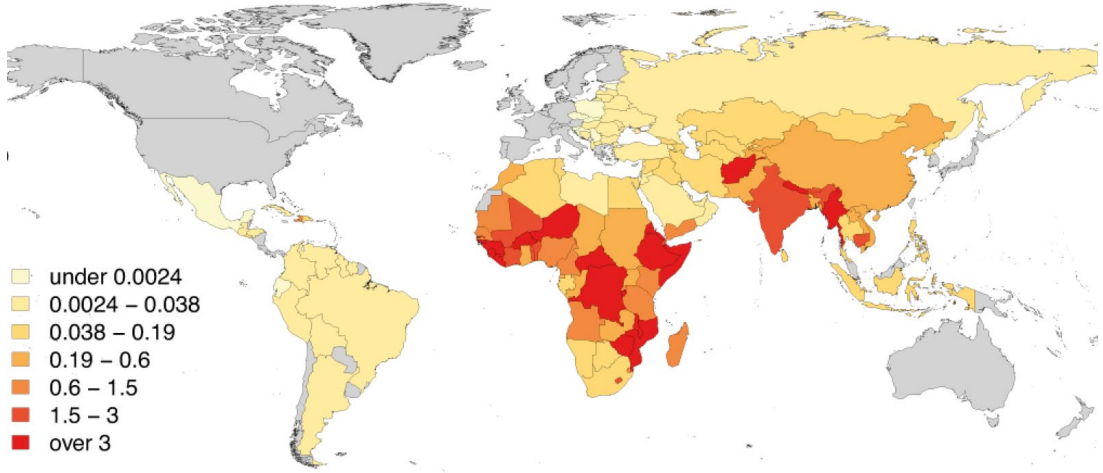


Rabies.

- Up to 99% of human cases from dog bites. Globally up to 59,000 cases a year (WHO).
- Bats more important in Americas since dog rabies controlled. Small numbers.
- Death within 10 days of symptoms is virtually inevitable.
- A terrible disease. People die in pain and terror if not sedated.
- The virus causes affected mammals (including humans) to salivate, and become aggressive.

Rabies prevention.

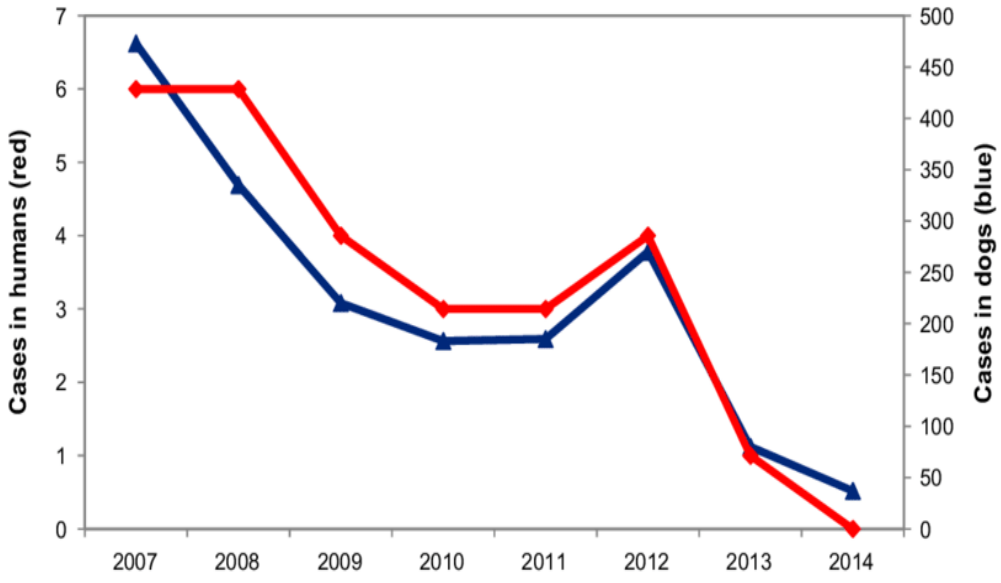
- Rabies vaccination of domestic dogs has reduced rabies to very small numbers in Europe and North America.
- Vaccine on baited foods (eg chicken heads) has helped control rabies in wild mammals.
- Post-bite vaccination (within 10 days) also effective.

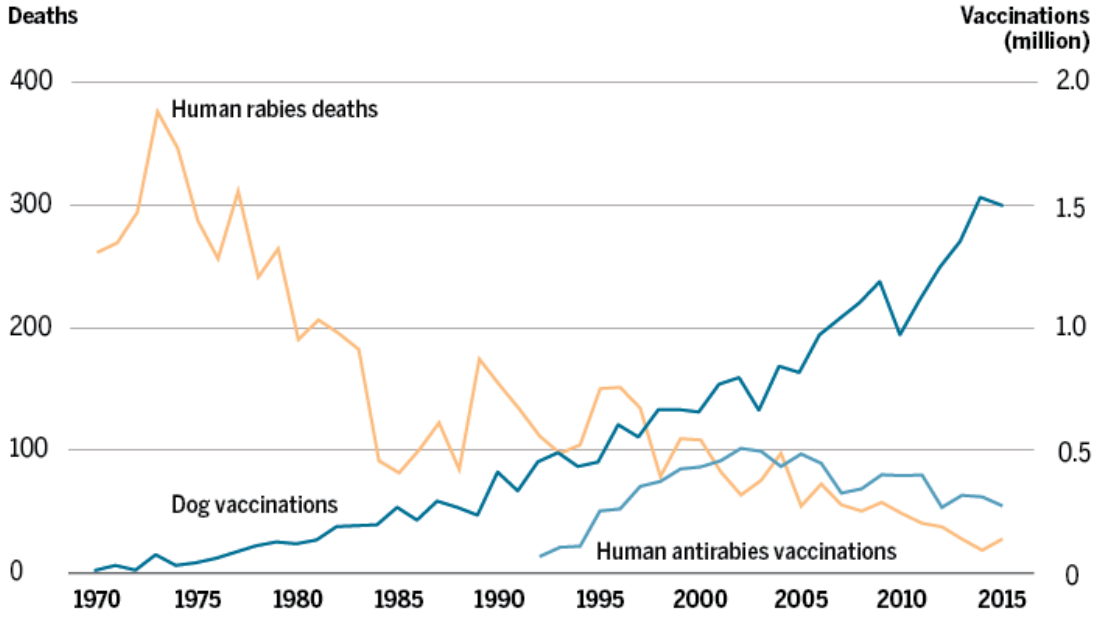


Deaths per 100,000 population.

WHO 2017

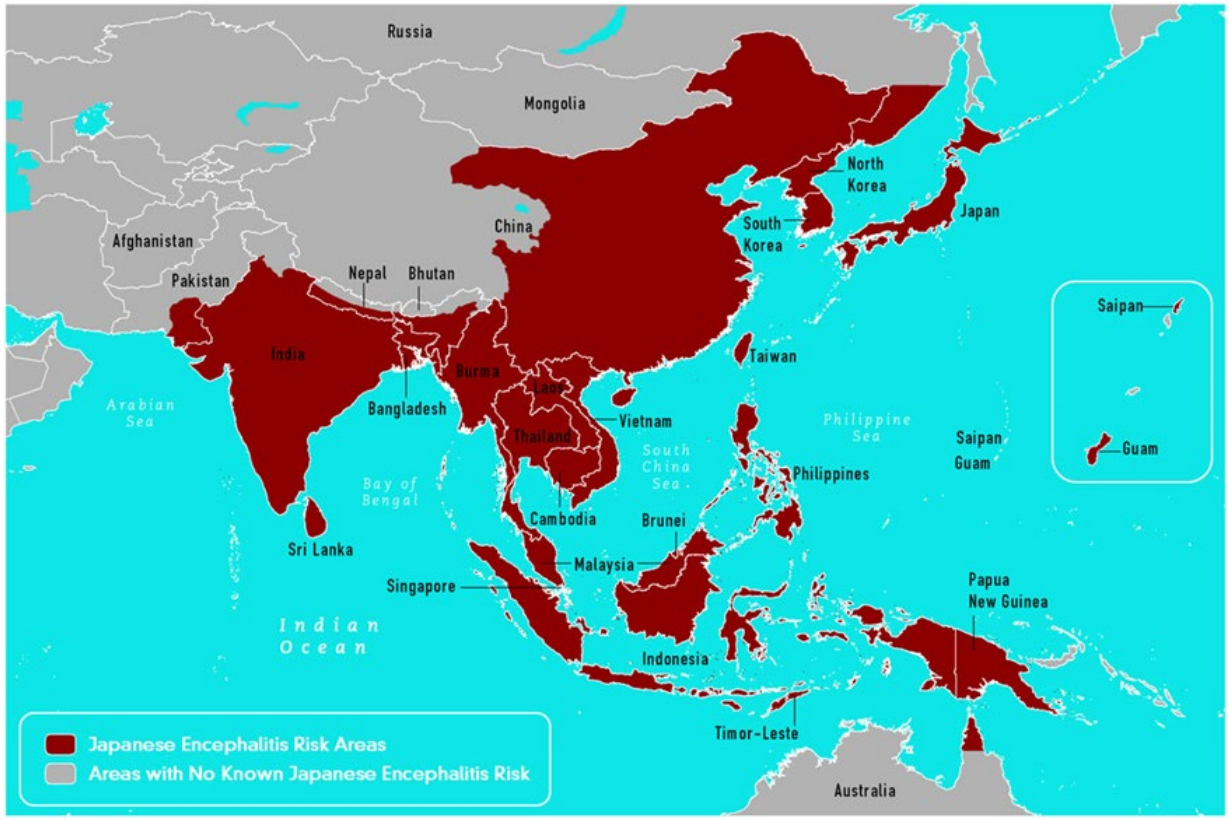
Effects of dog vaccination on rabies rates.
KwaZulu Natal (L), Sri Lanka (R).



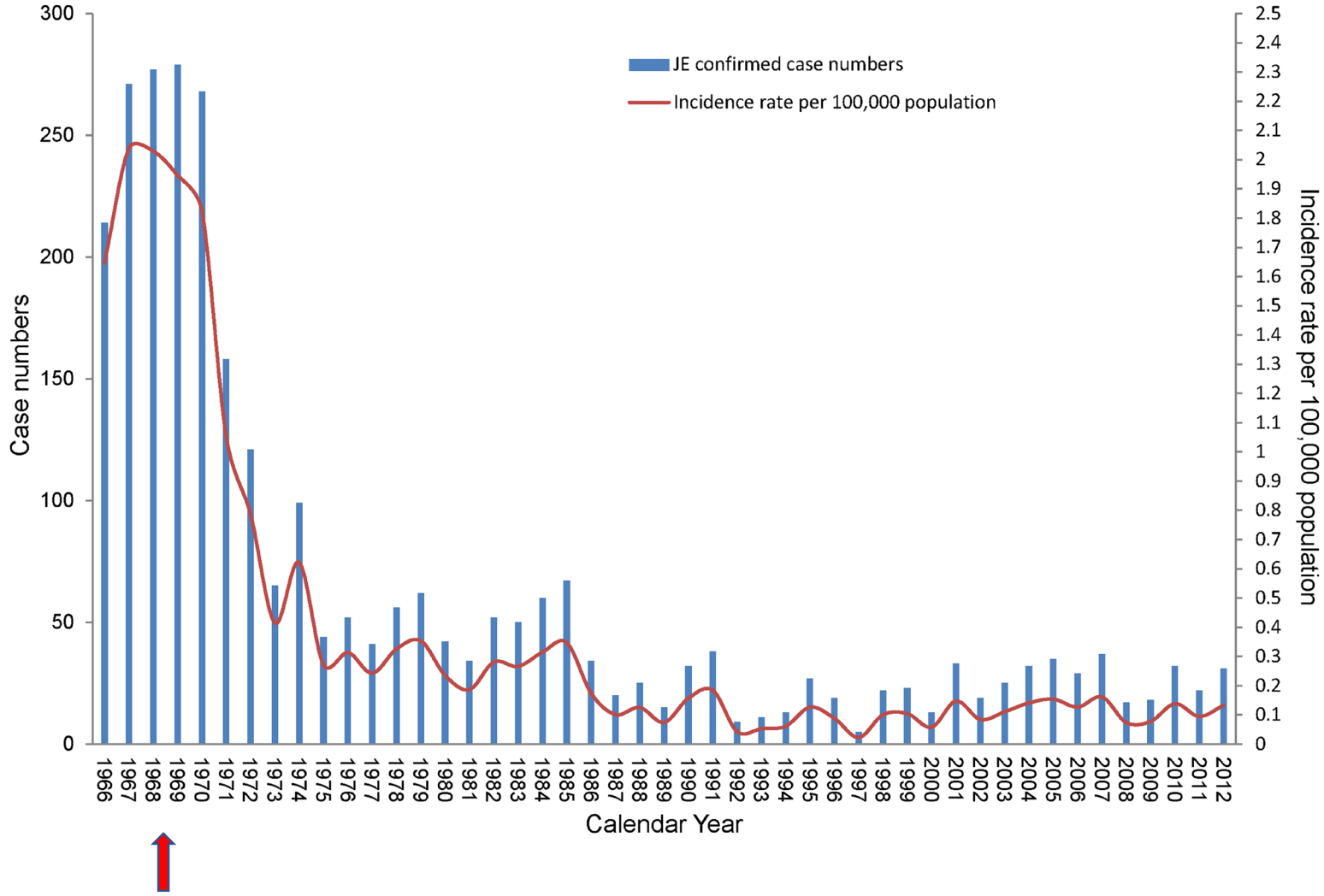


Mosquito-borne viral encephalitis.
Japanese B Encephalitis.

- Most infections no symptoms, but can be severe.
- Up to 68,000 cases.
- Commonest cause of encephalitis in Asia.
- Culex mosquito: wild waterfowl and pigs as reservoir.
- Highly effective vaccines.



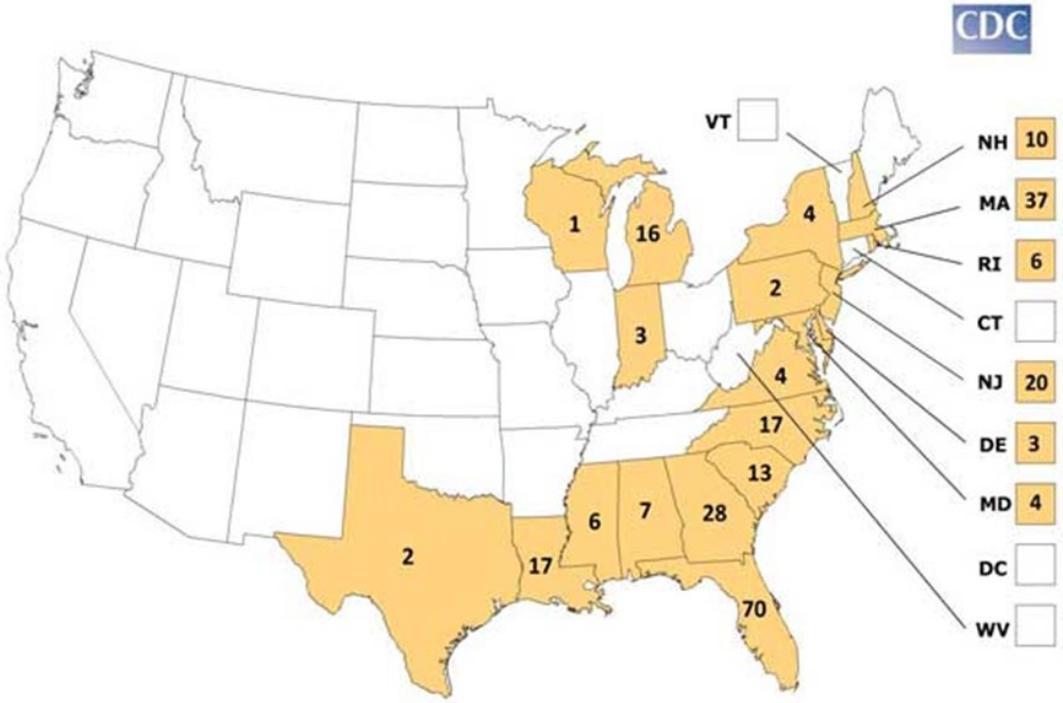
Taiwan introduced a Japanese B vaccine programme in 1968.



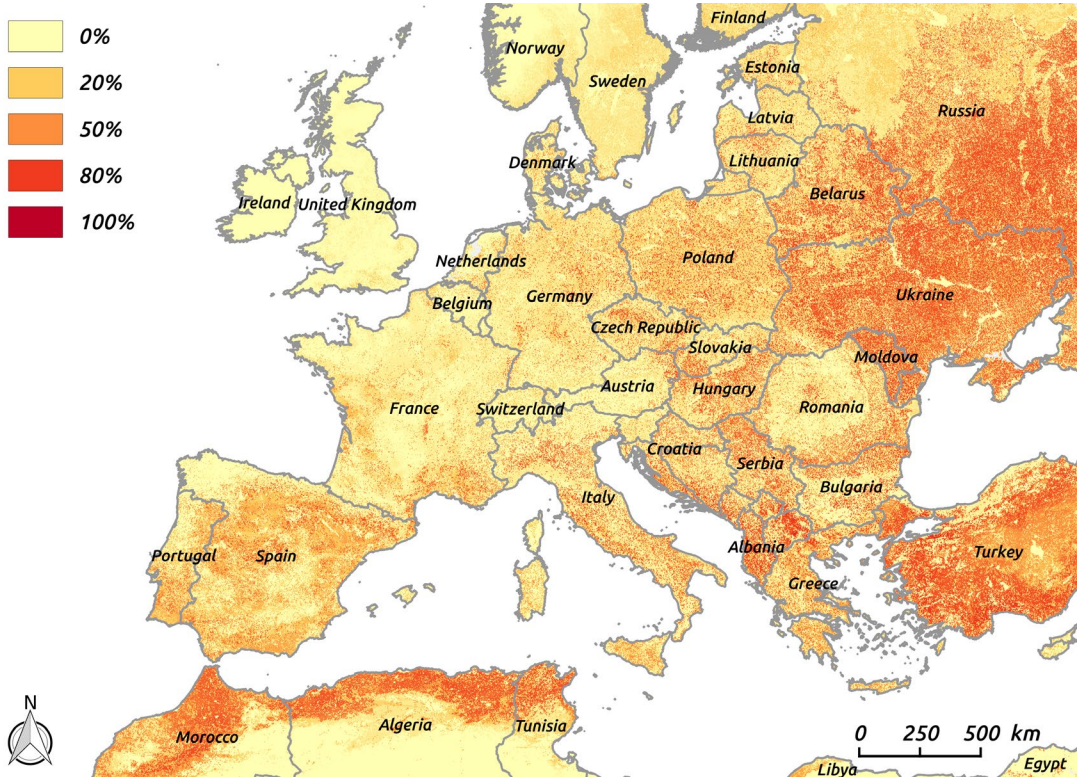
Li-Ching Hsu et al 2014

Other examples of rarer mosquito-borne encephalitis.

Eastern Equine Encephalitis USA



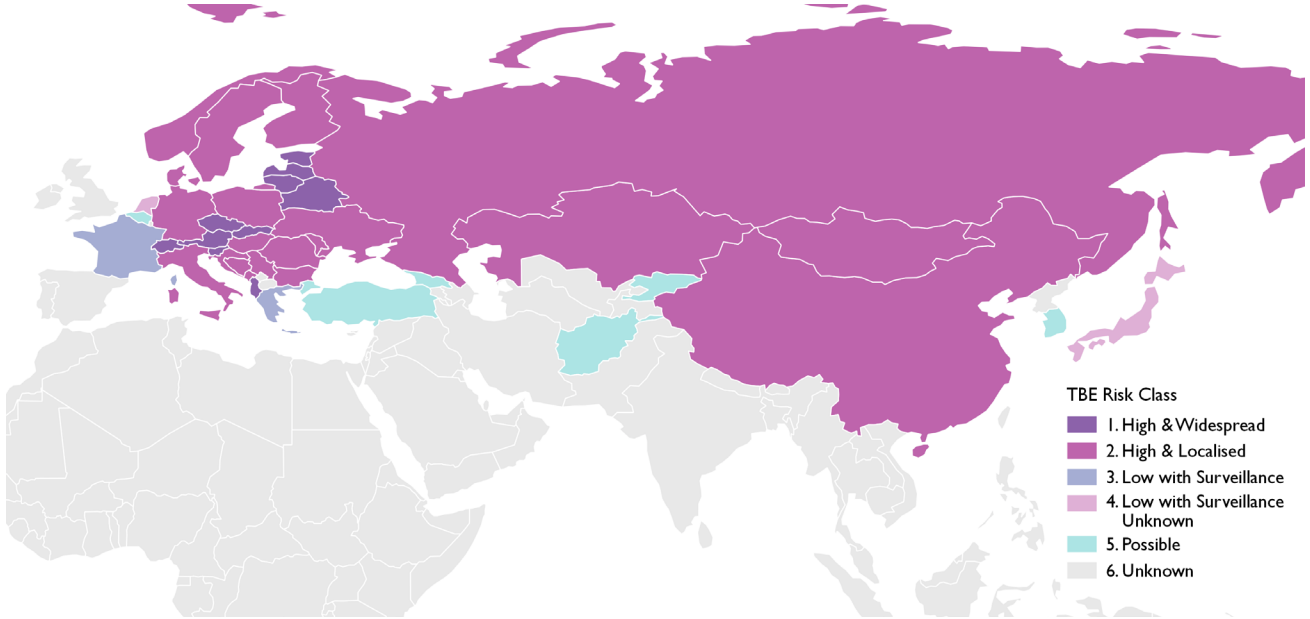
West Nile Virus- bird-mosquito suitability in Europe.



Durand et al 2017

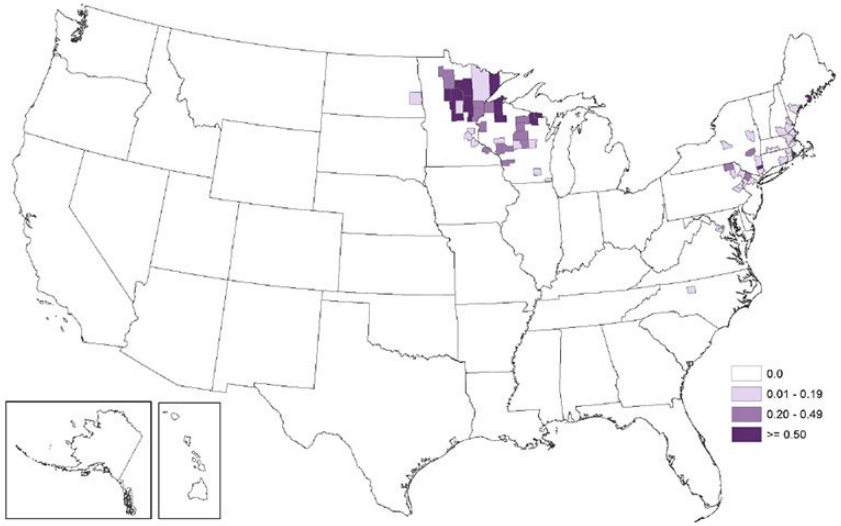
Tick-borne viral encephalitis.

Tick-borne encephalitis.
A highly effective vaccine.



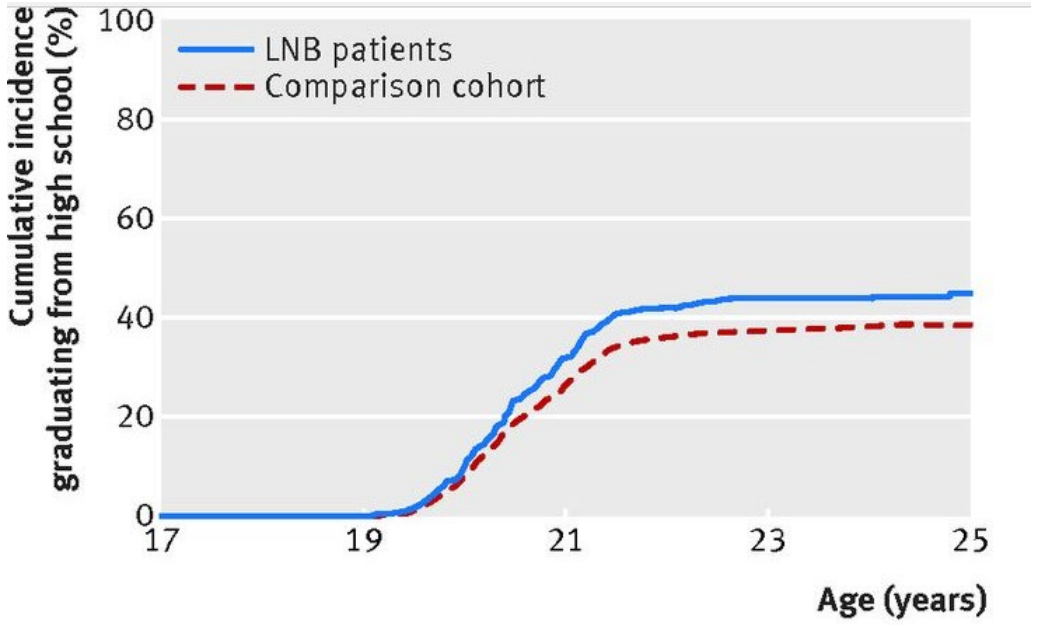
NaTHNaC.

Powassan virus



Neuroborreliosis (neurological Lyme). Tick-borne spirochete bacteria.

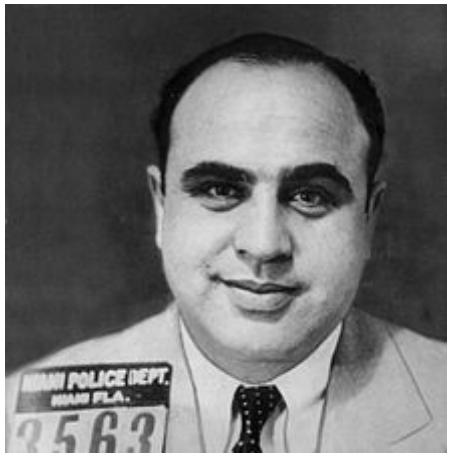
- Lyme disease can cause neurological inflammation in a minority.
- Rare in most of the UK, more common in parts of Europe and northeastern USA.
- Can be difficult to diagnose. In most cases antibiotic treatment very effective.
- Controlled studies suggest outlook usually good. For example recent study of 2,067 people proven neuro Lyme and 20,670 general Danish population.
- Almost identical hospitalisations, employment, income, disability, children.



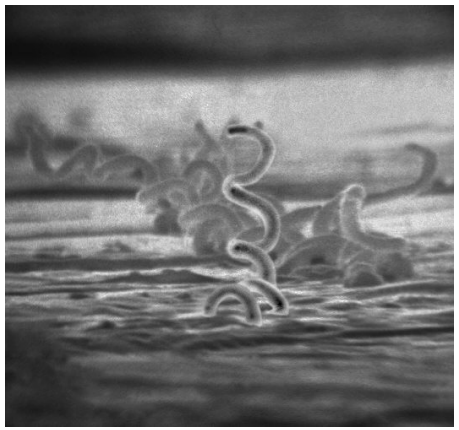
Obel et al, *BMJ* 2018

Neurological syphilis- general paresis / ‘general paralysis of the insane’.

- Meningo-encephalitis and brain atrophy in tertiary syphilis- around 7% of untreated cases.
- Was very common- 12-25% of diagnosis in public psychiatry institutions.
- Occurs 10-30 years after initial infection.
- Grandiose ideas, personality change, dementia, paralysis.
- Now exceptionally rare as most people given antibiotics prior to onset.
- Was initially treated with vivax malaria.
- Penicillin transformed the outlook- now very rare.



Al Capone, neurosyphilis patient.



Treponema pallidum (CDC)

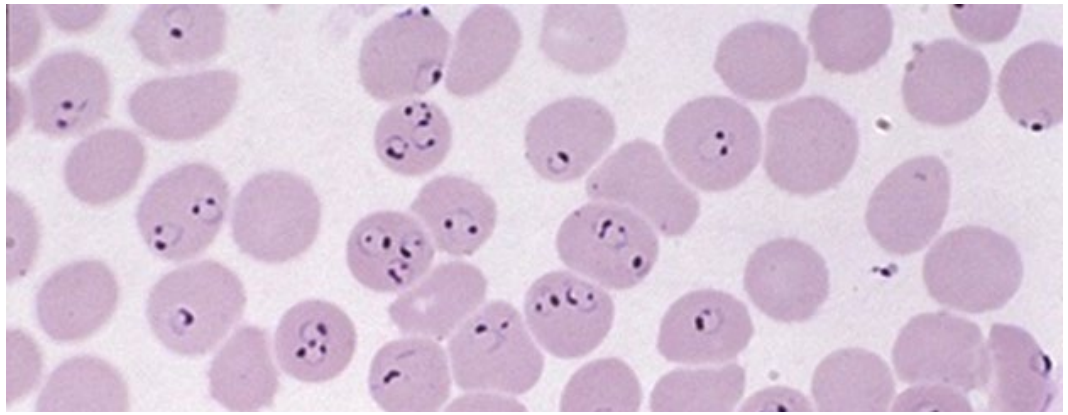
‘Brain eating parasite’: rare, but real.

- Meningoencephalitis due to amoeba *Naegleria fowleri.*
- Enters nose when swimming in warm untreated freshwater.
- Destroys brain tissue.
- Very rare. 34 cases in USA in 10 years.

CDC

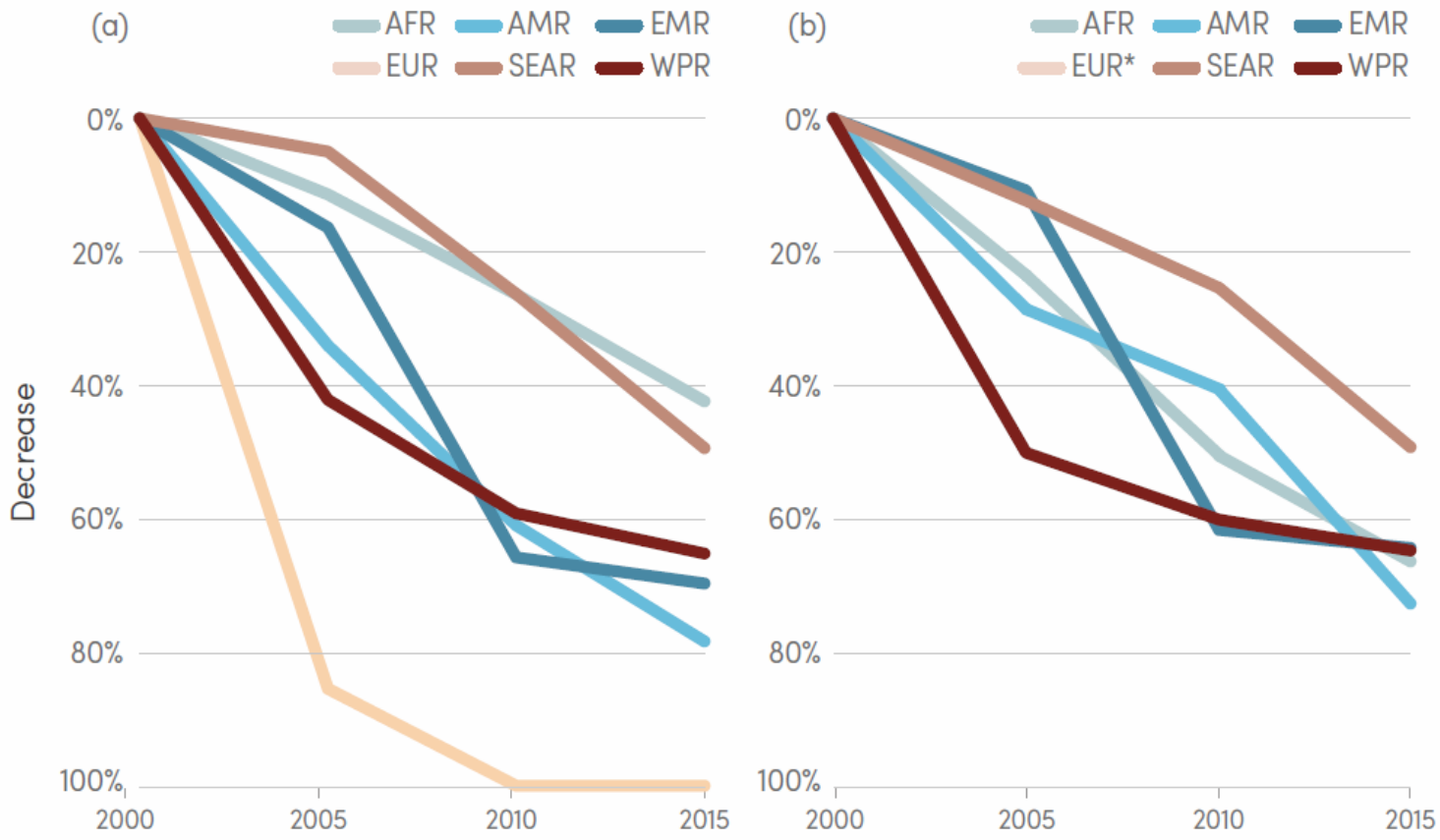
Cerebral falciparum malaria.

- The most important parasite affecting the brain is falciparum malaria.
- 216 million cases of malaria in 2016 (2018 data).
- 445,000 deaths, cerebral malaria a major cause.
- Most who die are children (77%), poor and African (91%). Some in UK.
- Since 2000, malaria mortality rates have fallen by 62% overall, and by 69% among children <5.



To stop deaths from cerebral malaria: prevent people being bitten by anopheles mosquitoes, and treat fast with effective drugs.

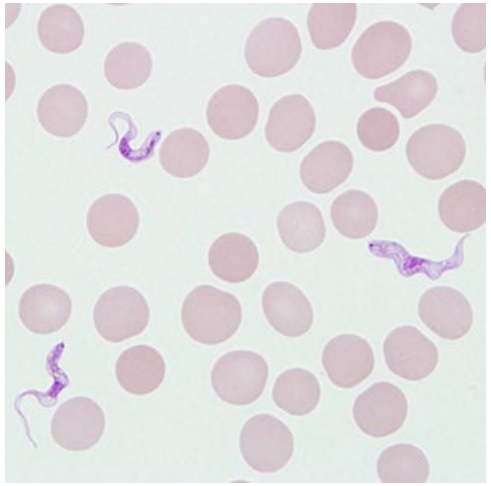
Decrease in incidence (L) and mortality by WHO region. *WHO 2015.*



AFR, African Region; AMR, Region of the Americas; EMR, Eastern Mediterranean Region; EUR, European Region; SEAR, South-East Asia Region; WPR, Western Pacific Region

African sleeping sickness.

- Was a major cause of mortality in Africa.
- Parasite (trypanosomiasis) passed on by tzetse fly.
- Infection of West African form led to invasion of the brain. Death was slow but inevitable.
- Personality change, sleep inversion.



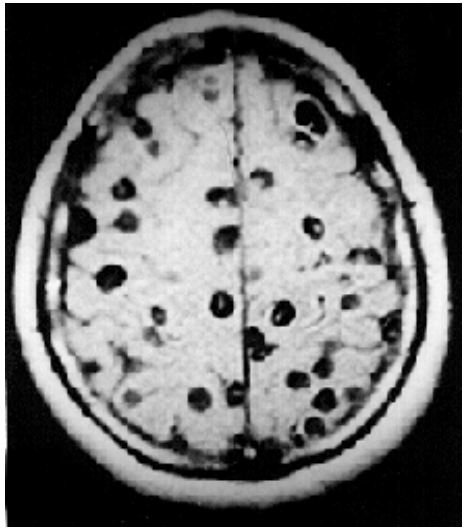
CDC

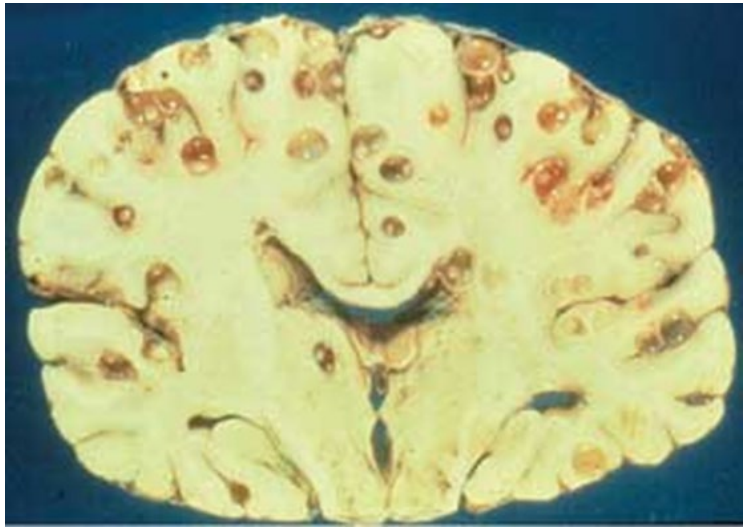
There has been a substantial reduction in cases, due to a combination of early treatment and tsetse fly control.

- Historically devastating epidemics, killing up to 2/3rds of some populations.
- In 1995 WHO estimated over 300,000 cases.
- 17,616 in 2004.
- 9,875 cases in 2009.
- 1,447 new cases reported to WHO in 2017.

C. Borgemeister

Cysticercosis. 2-8 million people have it (WHO).
Probably the leading cause of adult-onset epilepsy globally.

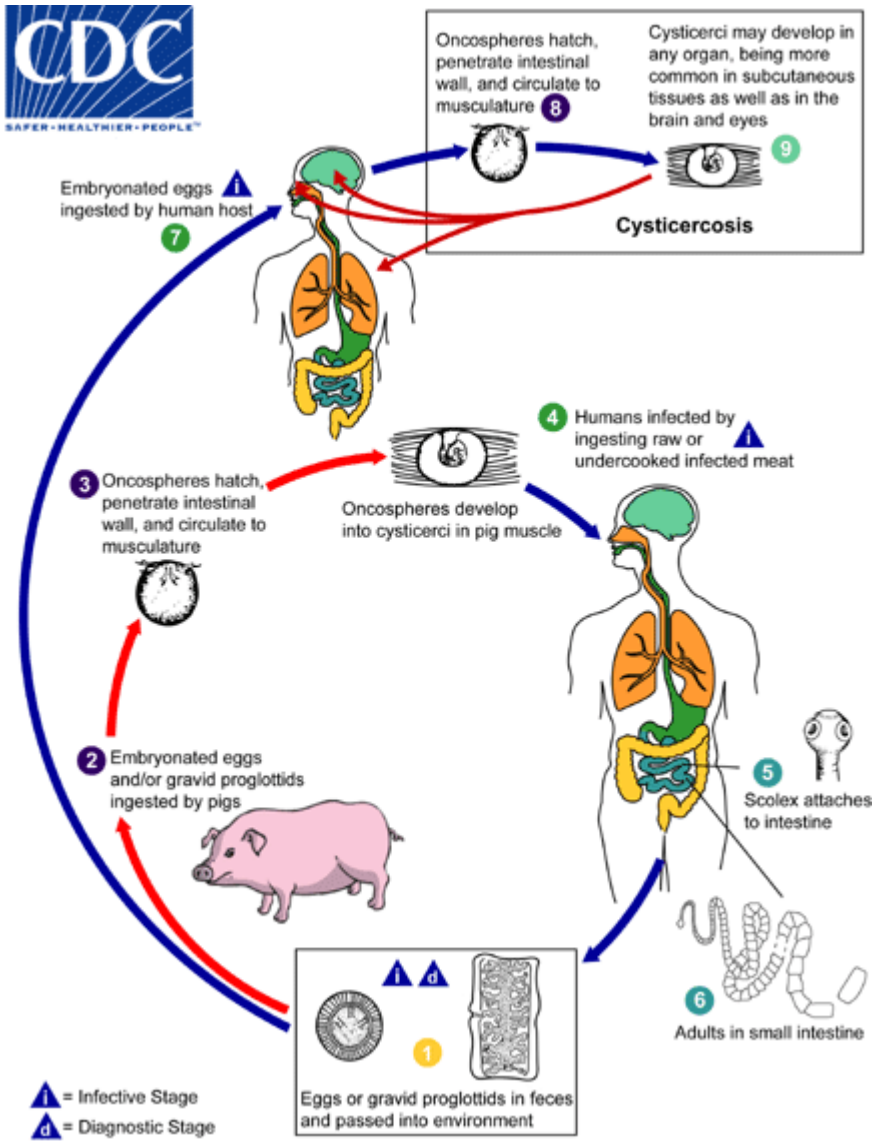




Cystercicosis- pork tapeworm.

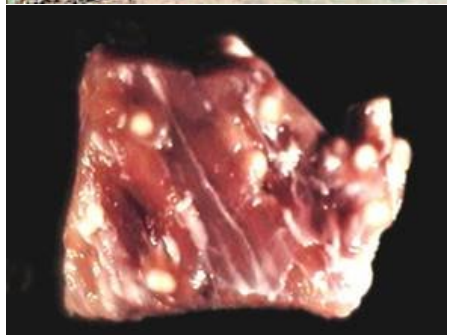
Taenia soleum

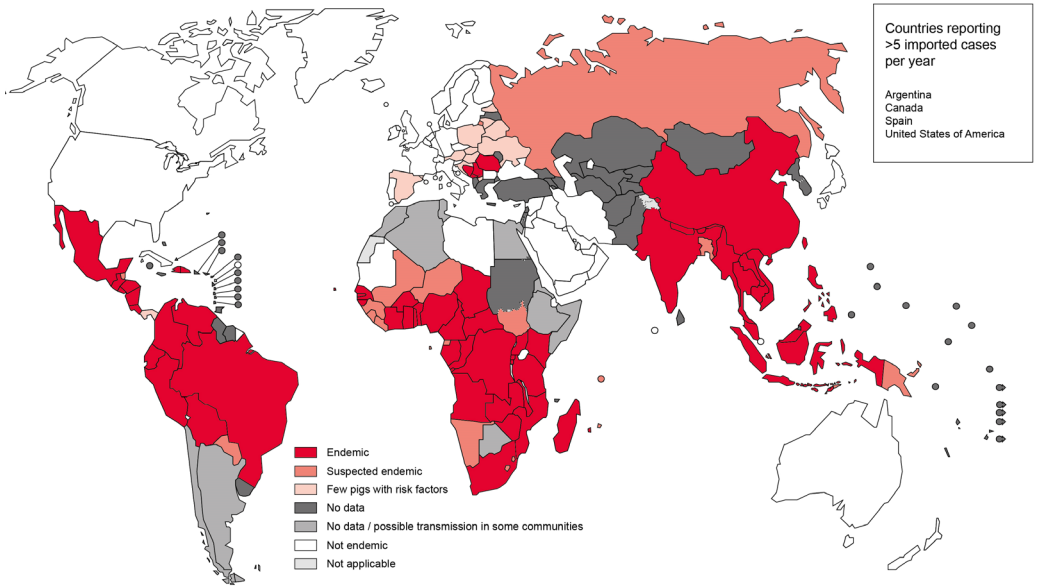
- Pigs eat food contaminated with eggs from human faeces.
- Eggs hatch in the pig intestine circulate to muscle.
- A person eats undercooked meat.
- Tapeworm develops into adult human in the intestines. Shed eggs.
- If humans eat water or food contaminated with eggs they can infect brain.



It’s a wide-spread problem, and needs a multi-pronged approach.

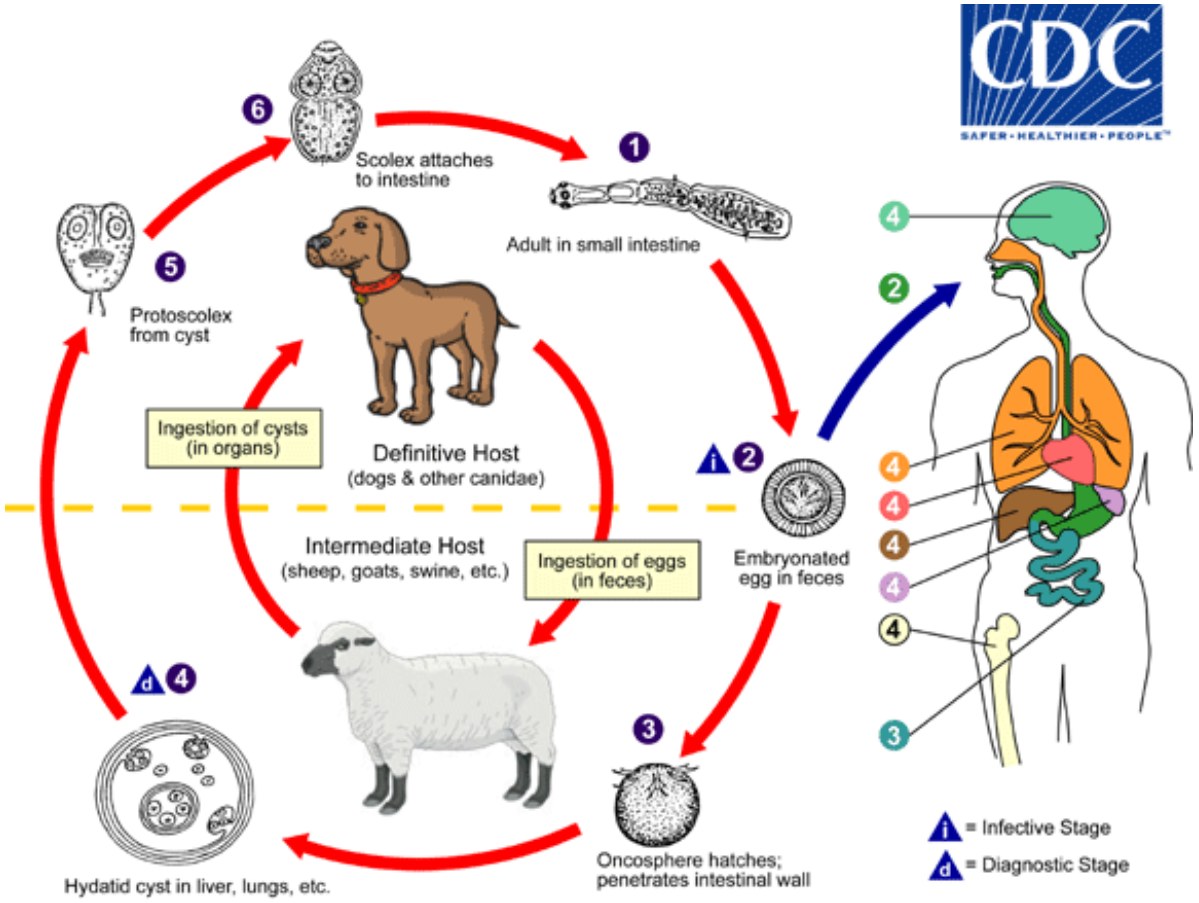
- Sanitation and hygiene.
- Animal husbandry.
- Meat inspection.
- Identify and treat human tapeworm cases.
- Drug treatment of pigs.
- Vaccine for pigs?

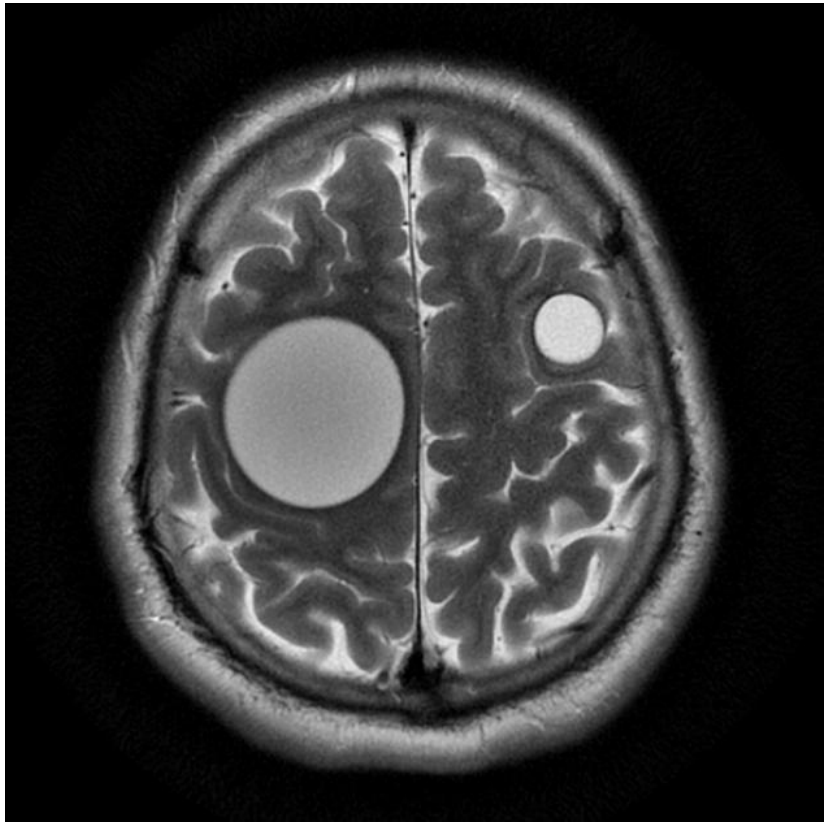




WHO

Hydatid disease of the brain: sheep/dog cycle.

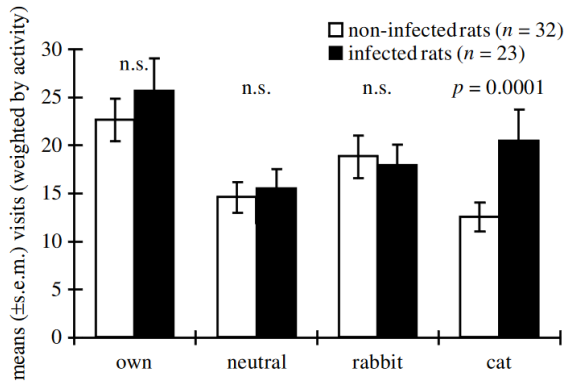




Courtesy of Dr Roberto Schubert, Radiopaedia.org

Toxoplasma gondii- manipulates animal behaviour.

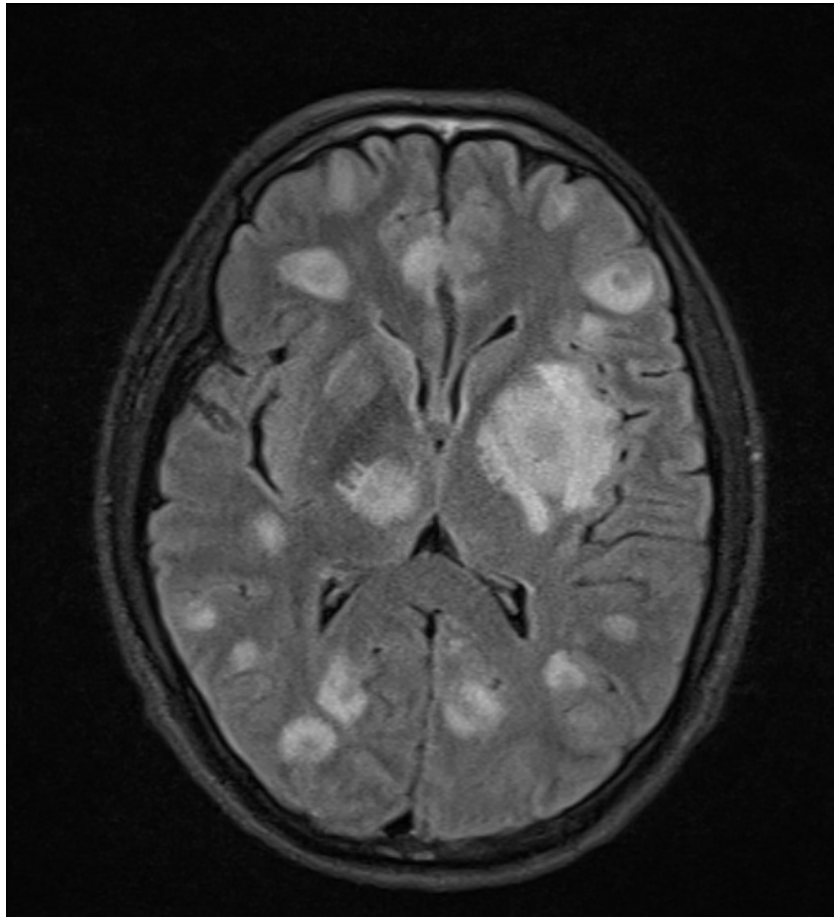
- Cat-mouse/rat cycle.
- Humans mainly infected from cat faeces, some from infected meat.
- In rodents infects the brain; several lines of evidence alters behaviour.
- Reduces aversion to cat odours, increases activity, decreases anxiety.
- Effects on human brains controversial. Some evidence of association with lower IQ and schizophrenia.



Number of visits by rates to areas with cat urine.
Berdoy M et al. *Proc. R. Soc. Lond. B 2000*

Toxoplasmosis in immunosuppressed people.

- High proportion of people infected- 23-33% in the UK.
- Generally does little or no harm (occasional temporary symptoms).
- In badly immunosuppressed people (AIDS, transplant) can cause serious problems in the brain.
- Fitting common.
- Can be treated.



Dr Ian Bickle, Radiopaedia.org

Worms caught from eating undercooked exotic foods can travel through the brain.

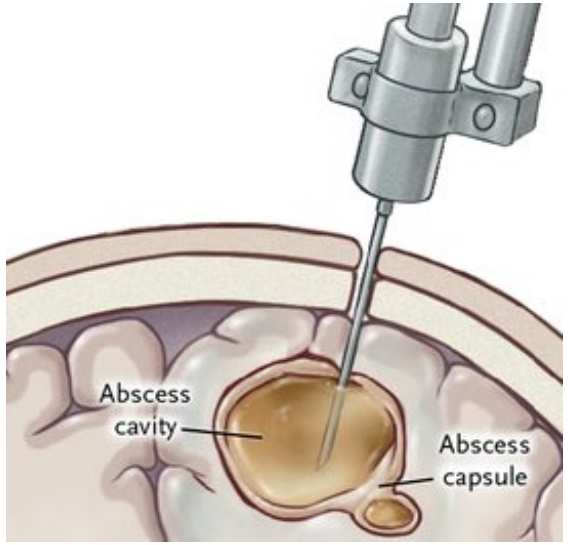
Godlesscook.com, Wikimedia commons

Brain abscesses. Rare: 0.4-0.9/100,000

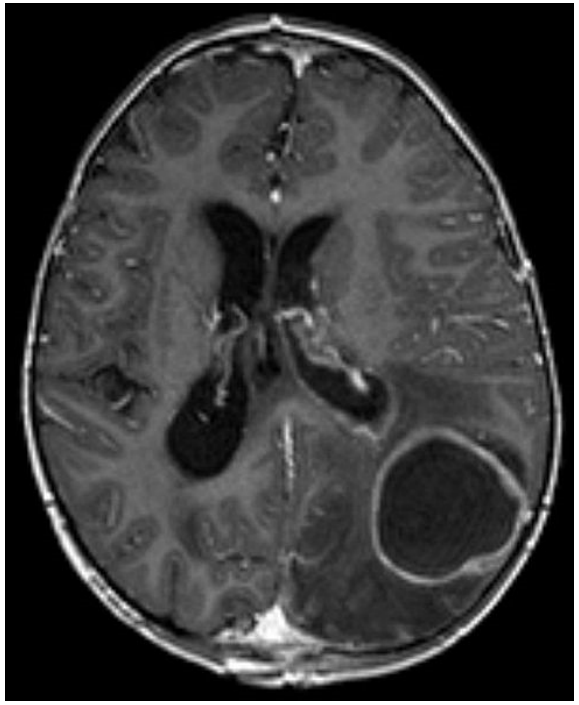
- Local infection (tooth, sinuses).
- Immunosuppressed.
- Heart structural abnormality.

- Headache
- Local effects
- Fits

- Bacterial, fungal, TB.
- May need surgery.



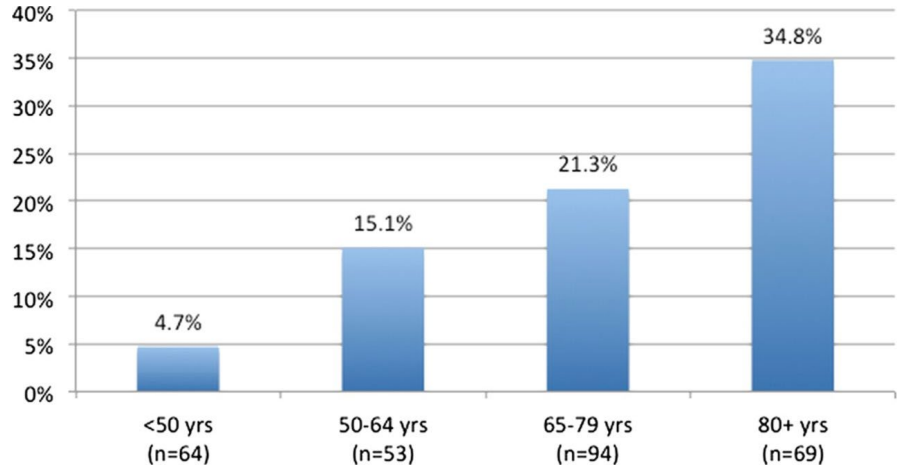
Brower et al. NEJM



Hellerhoff, Wikimedia.

Delirium / acute confusional state with infections.

- In the elderly and in some younger people any infection can cause delirium.
- Very common. 2:10 hospital patients may have delirium, infection a major cause.
- Confusion, drowsiness, aggression, personality change, can occur.
- Urinary tract infections and pneumonia the most common infectious triggers.
- Not an infection of the brain- and people usually recover rapidly with antibiotics.
- Cause not fully understood.

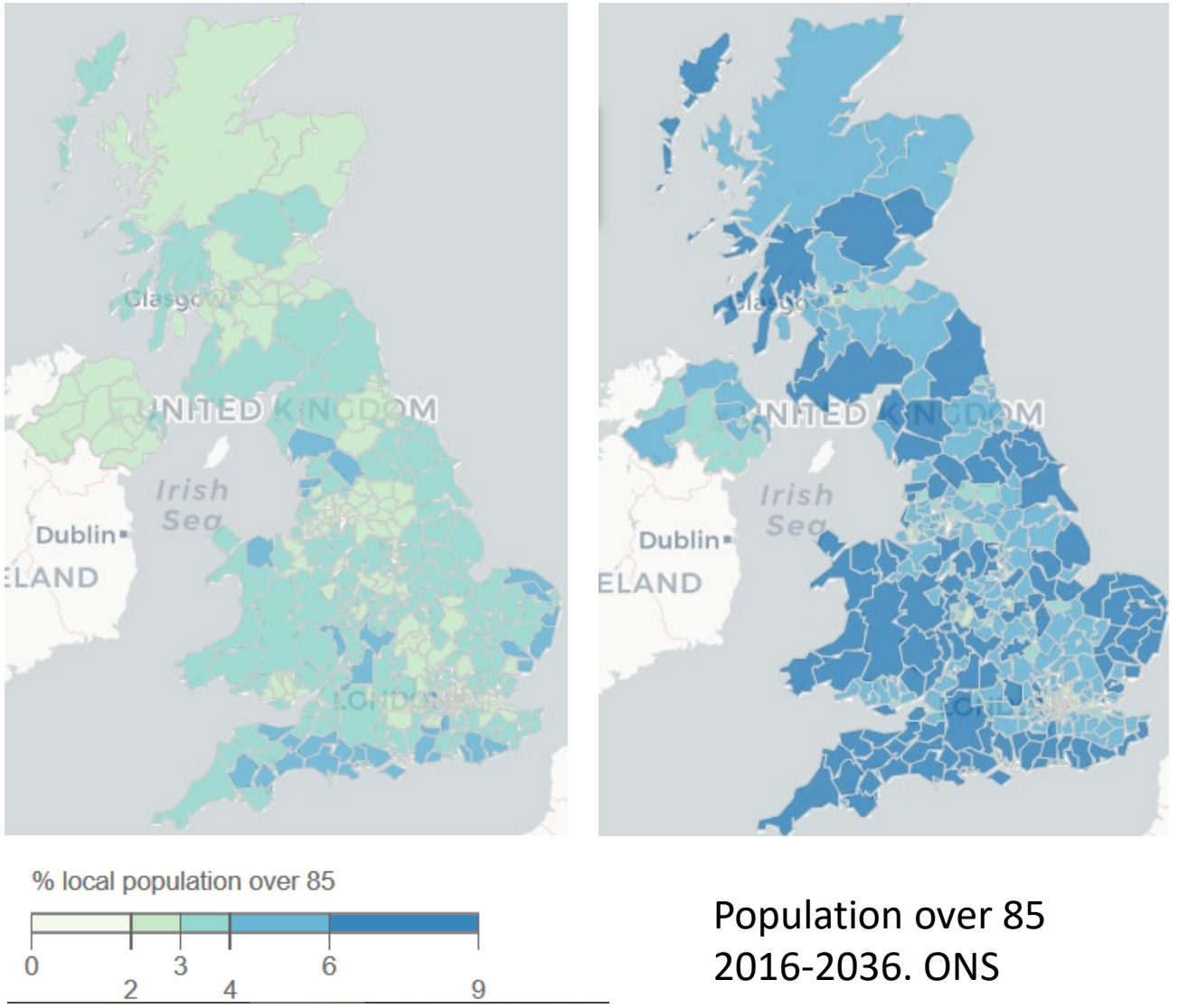


Prevalence of delirium in inpatients by age. Ryan et al

Infections of older age matter, and will matter more…

UK age over 80
(thousands, ONS)

- 2018 3,293
- 2028 4,499
- 2038 5,638
- 2048 7,241



Population over 85
2016-2036. ONS

Infections are one of the leading causes of acquired brain injury.

Others include

- Trauma
- Stroke
- Lack of oxygen
- Tumours
- Drugs and toxins

For children in the UK, meningitis accounts for around 13% and encephalitis for around 5% of those needing rehabilitation.

-Around 100 a year. (Hayes et al 2016)

Rehabilitation after ABI. The Children's Trust.

We are making substantial progress in many forms of recently common, serious infection in the brain.

- Meningococcal meningitis*
- Hib meningitis*
- Pneumococcal meningitis*
- HIV associated meningitis
- Measles encephalitis*
- Jap B encephalitis*
- Rabies*
- Malaria
- Sleeping sickness
- Many parasites