Infections and the nerves.

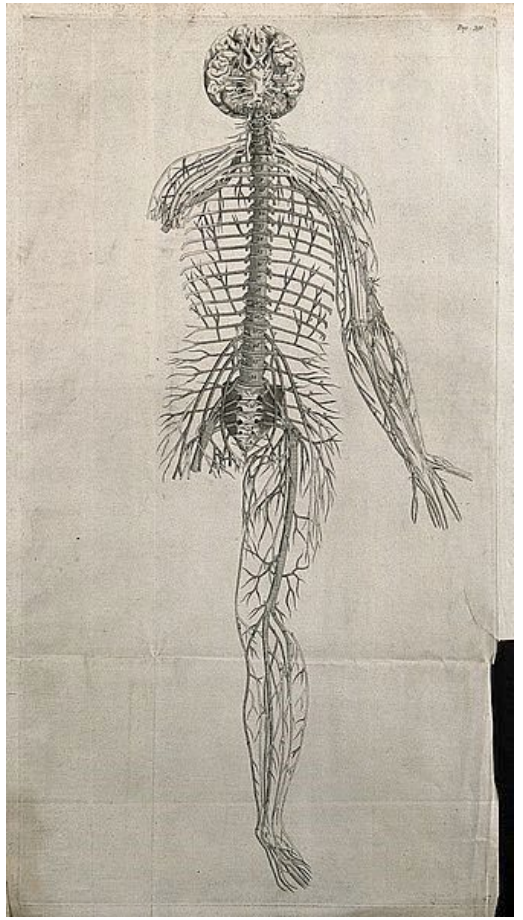
Christopher Whitty

Gresham College 2019

The brain thinks, but the peripheral nervous system is needed for the body to sense, and to act.

- The motor system. Controls and regulates movement.
- The sensory system. Touch, pain, temperature, hearing, sight, taste, smell, stretch.
- The autonomic nervous system. Basic functions, flight and fight.
- The spinal cord. More than just a nerve highway.

- Infections can affect all, or just one of these.



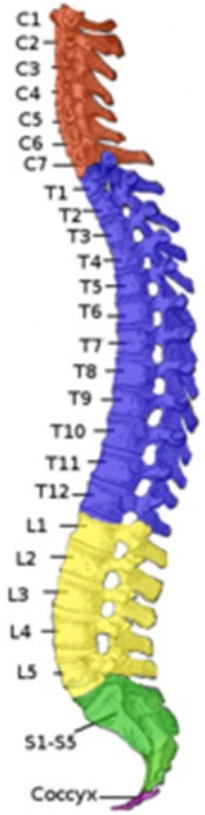
J. Wandelaar, 1726, after a woodcut of 1543.

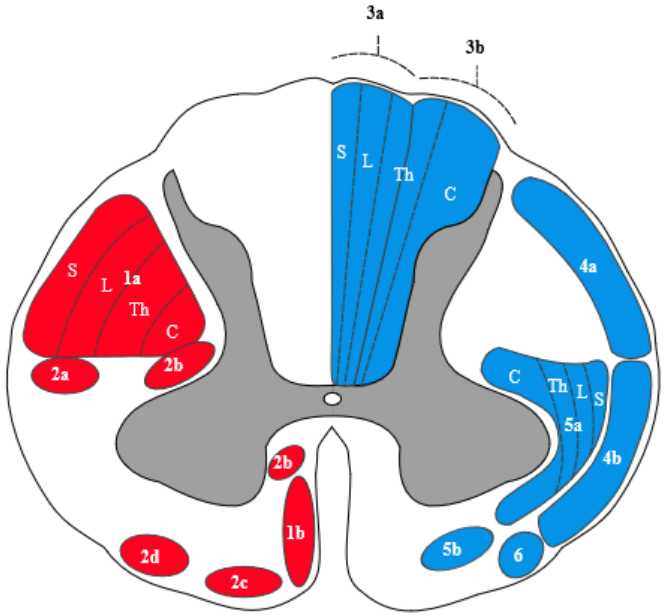
Infectious can damage nerve function by several routes. Generally prevention is better than cure.

Include:

- Produce nerve toxins. Mainly motor system.
- Direct invasion of nerves.
- Activate the immune system, which damages nerves.
- Physical damage due to pressure (esp. spinal cord).

The basic anatomy of the spinal cord and peripheral nerves.

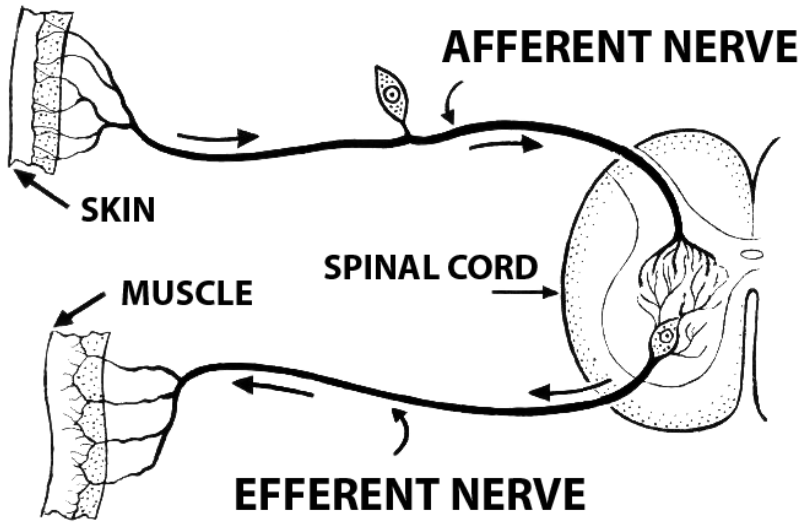




Sensory- ascending

Motor- descending.

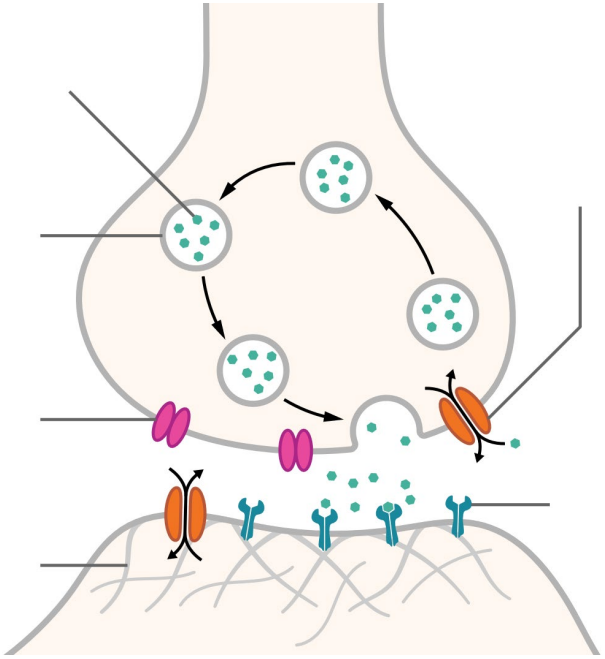
Sensory



Motor

At every stage neurotransmitters.

- Two important ones for the peripheral nervous system and spinal cord:
- Acetylcholine (ACh)- includes motor nerves and autonomic system.
- GABA- an inhibitory neurotransmitter.



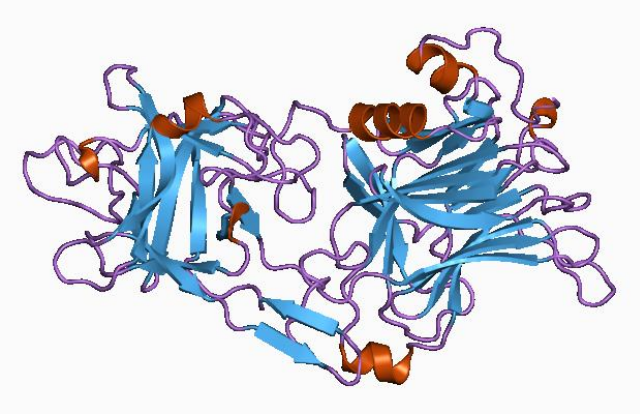
Tetanus- nerve toxin causing spasm.

- Adults and newborn.
- The bacteria *C. tetani* which causes it lives in soil and animal dung. Can infect puncture wounds.
- Agriculture, childbirth in non-sterile settings and unclean surgery common risks.
- Forms a small abscess- often not noticed by the person infected.
- Produces a potent toxin which is the dangerous part.

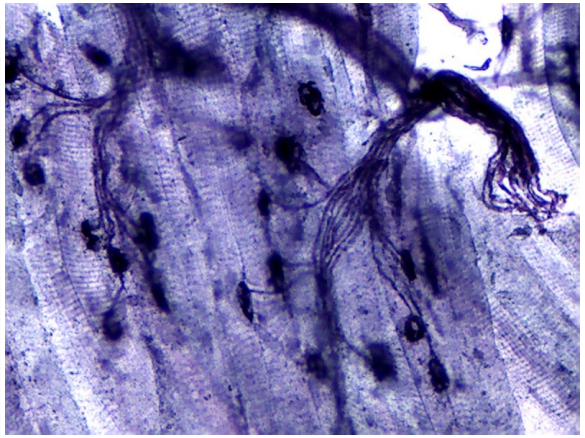
V. Van Gogh; Harley MS.

The mechanism of action of tetanus toxin.

- The main tetanus toxin, tetanospasmin, is taken up by the nerve motor end plate.
- It is transported up to the spinal cord / central nervous system.
- Here it binds irreversibly to the inhibitory nerves which balance movements and prevent spasms stopping GABA release.
- The result is uncontrollable spasms.



Tetanospasmin toxin.



Motor end plates.
Hlj55567516

Tetanus progression.

- After the injury, a delay as the toxin moves to CNS.
- Then spasms begin, initially in the jaw (shortest motor nerves).
- Progress to generalised spasms.
- Even after treatment has started the disease will progress.
- Plateau phase of around 2 weeks, then slow recovery.

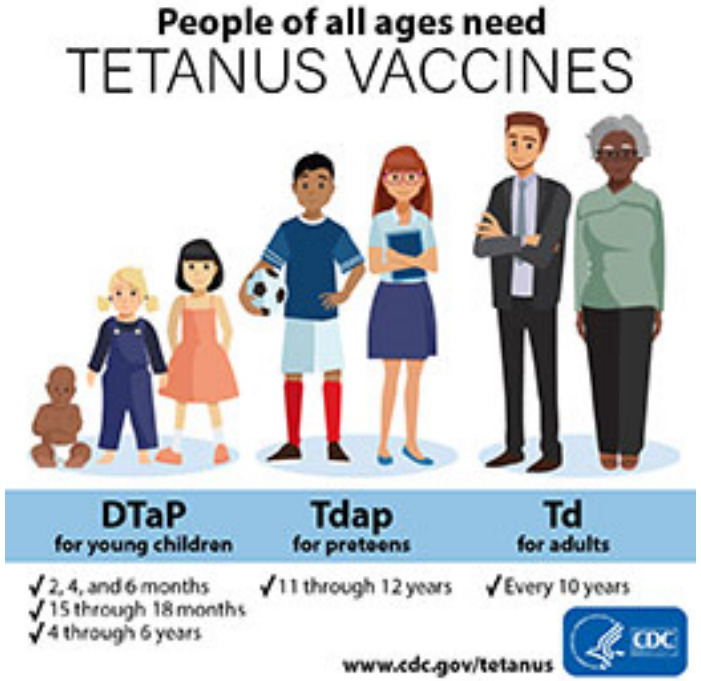
A soldier with tetanus.
Sir Charles Bell, 1809.

Treatment of tetanus.

- Treatment includes:
- -antibiotics (to stop production)
- -antitoxin (to mop up toxin)
- -muscle relaxants
- May need tracheotomy, intensive care.
- Feeding difficult.
- High mortality in low-resource settings- up to 80% in adults, up to 100% in neonates.

Vaccine for tetanus and other toxin-mediated damage.

- The toxin is inactivated (*toxoid*), and then adsorbed. Developed 1938, introduced widely in 1950s.
- Vaccine is highly effective.
- Does not stop infection- but stops toxin damage. No herd effect.
- Vaccinate mothers to protect newborns. Good birthing practice also essential.
- Usually given with diphtheria and pertussis vaccine (DTaP).



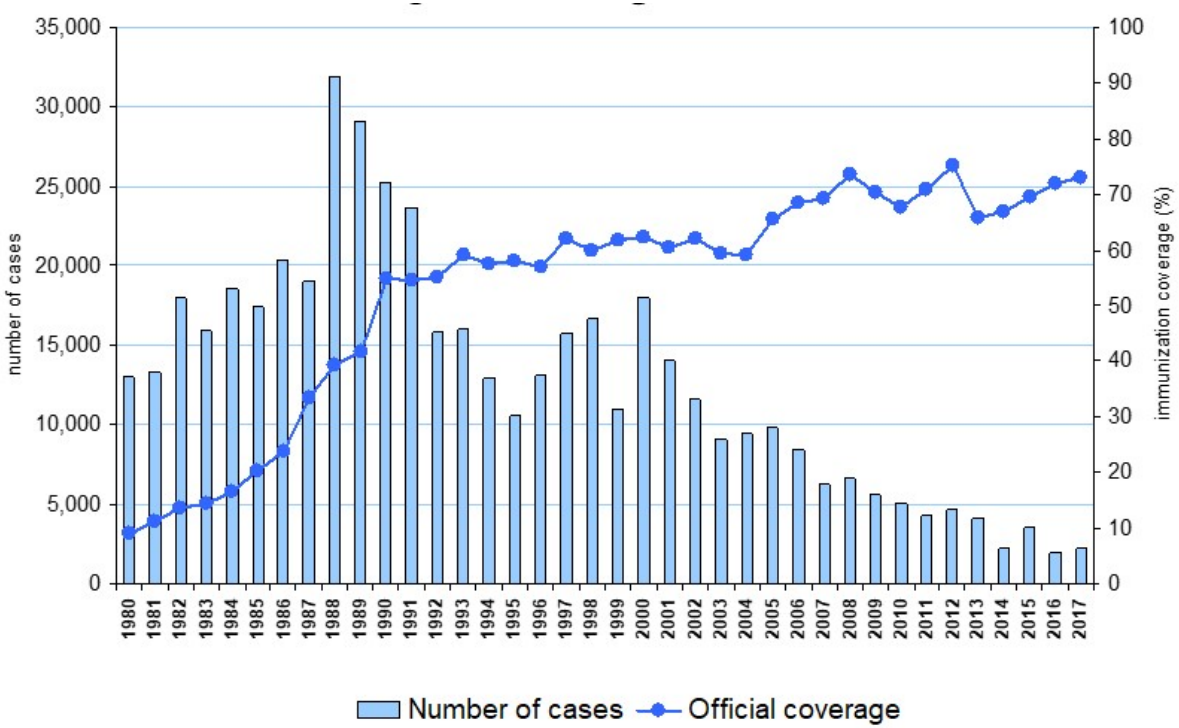
US poster (CDC).

St Kilda, 1880s.

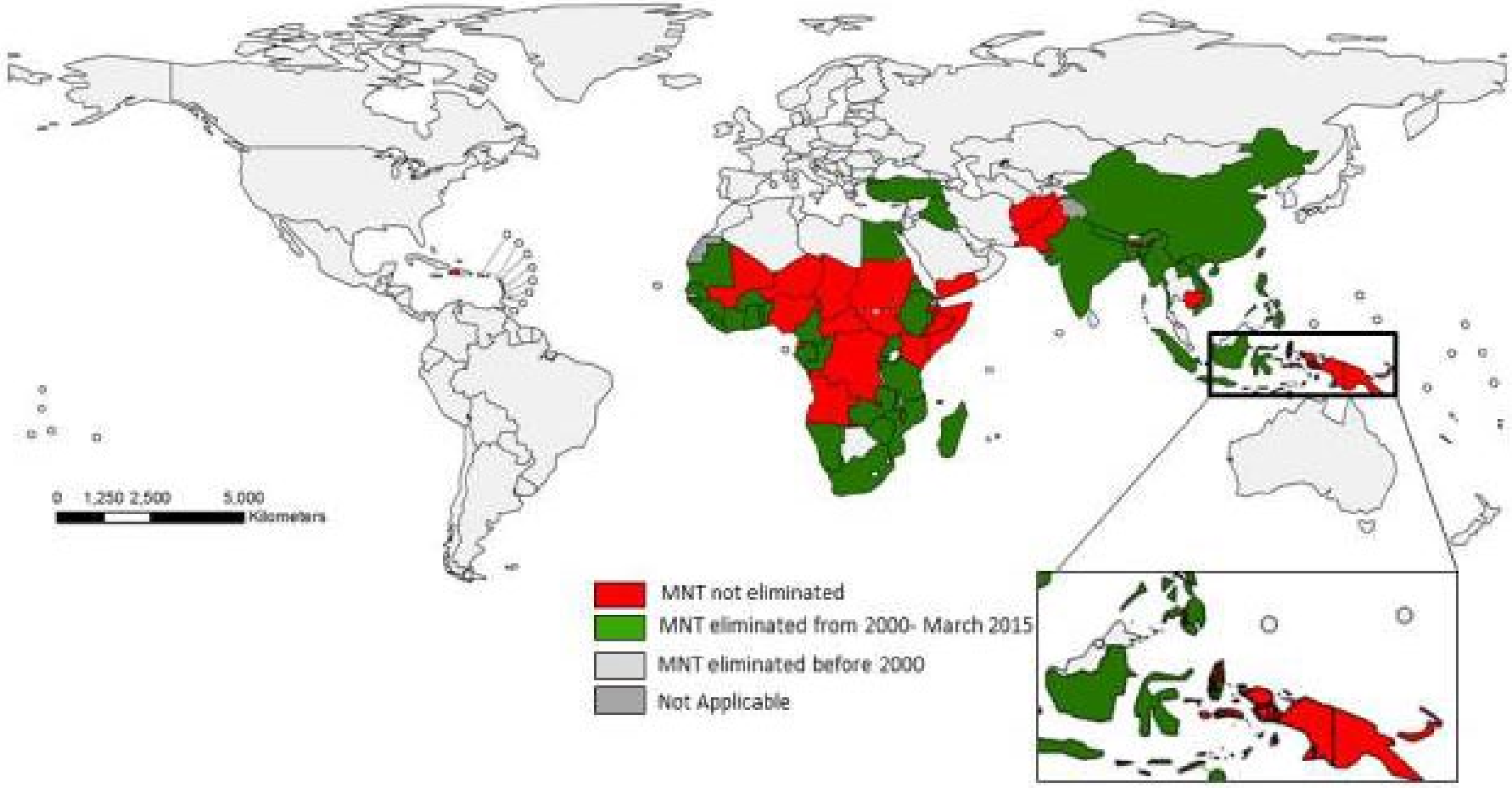
Neonatal tetanus.

- In rural communities without expert midwifery high infant mortality- up to 50% recorded.
- In some settings tetanus can the the majority of these. Mortality almost 100%.
- Recent rapid drops in developing world.
- Was common in rural UK and USA.
- Clean childbirth and maternal vaccination almost eliminate it.

Global neonatal tetanus- WHO.

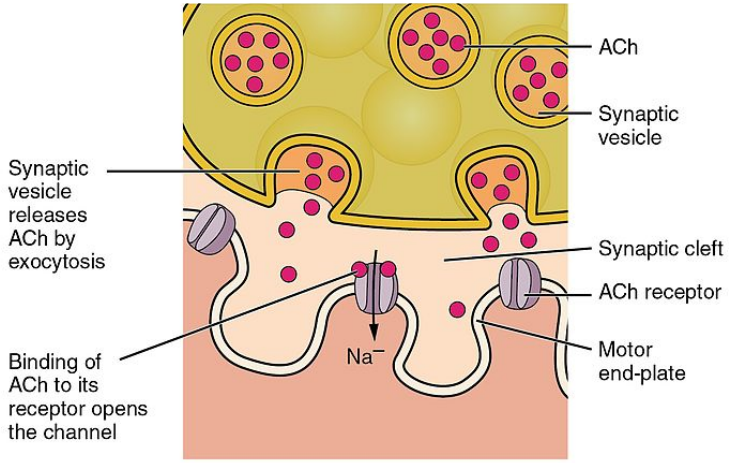


36 countries eliminated maternal and neonatal tetanus (MNT) between 2000 and 2015 (WHO).
49,000 newborn children in 2013, 94% reduction from 1988 when an estimated 787,000 infections. (UNICEF/WHO). <1/1000 live births in every district.



Botulinum. The most potent toxins known.

- Fortunately very rare- around 1000 cases a year globally.
- *C. botulinum* bacteria toxins A-G. A, B, E (F) in humans.
- Inhibits the release of acetylcholine (ACh), the key neurotransmitter to muscle.
- Spores in soil. Can produce toxins in certain low-oxygen settings.
- Infants <6m- in the gut (eg after honey).
- Foods. Poorly canned foods, hooch.
- Wounds- injecting drug users.



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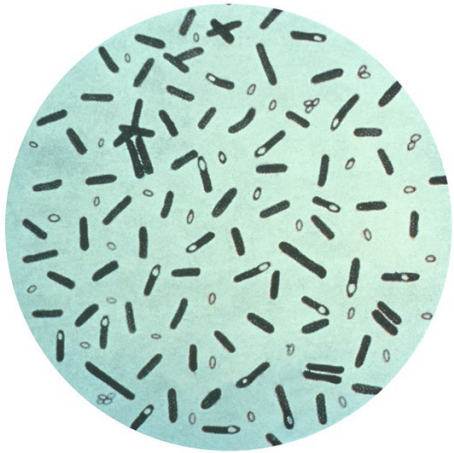


C. botulinum. CDC.

Medical responses to, and uses of, botulinum toxin.

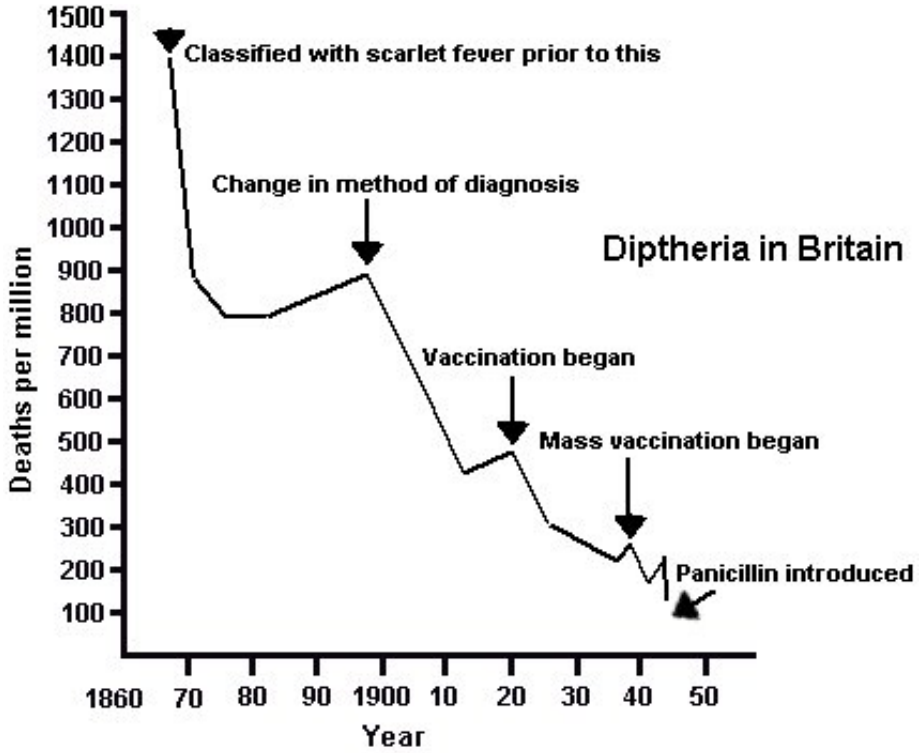
- Botulinum toxin causes flaccid paralysis, initially of face and then breathing.
- Treatment is antitoxin (antibodies) and respiratory support.
- Recovery after about 8 weeks.
- Medical uses in muscle spasm and migraine.
- Cosmetic use as botox. Highly dilute. 1 gram of botulinum toxin could kill over 1 million people.

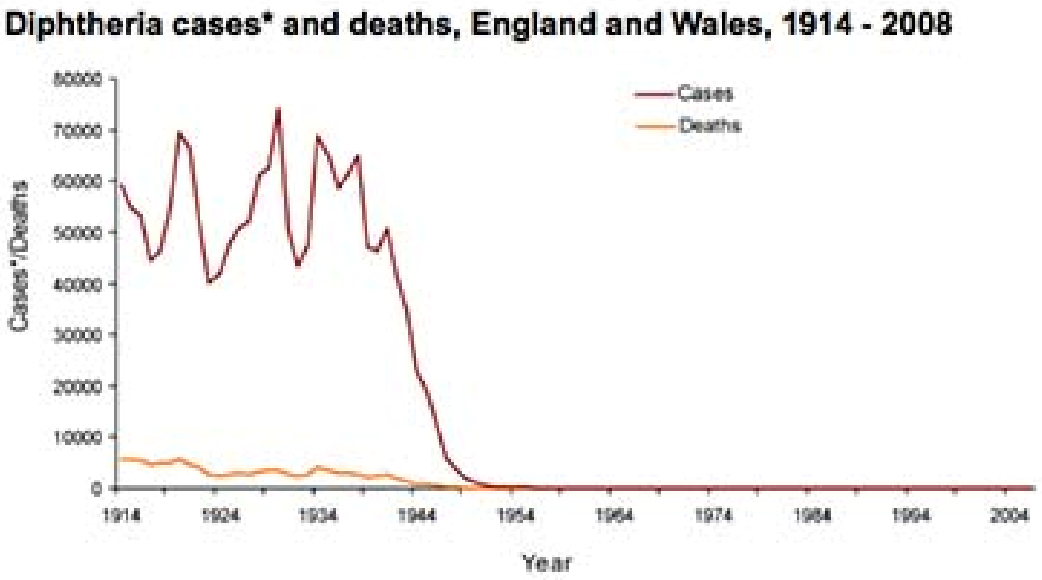
Dr. Braun.

Diphtheria toxin- affects nerves by damage.

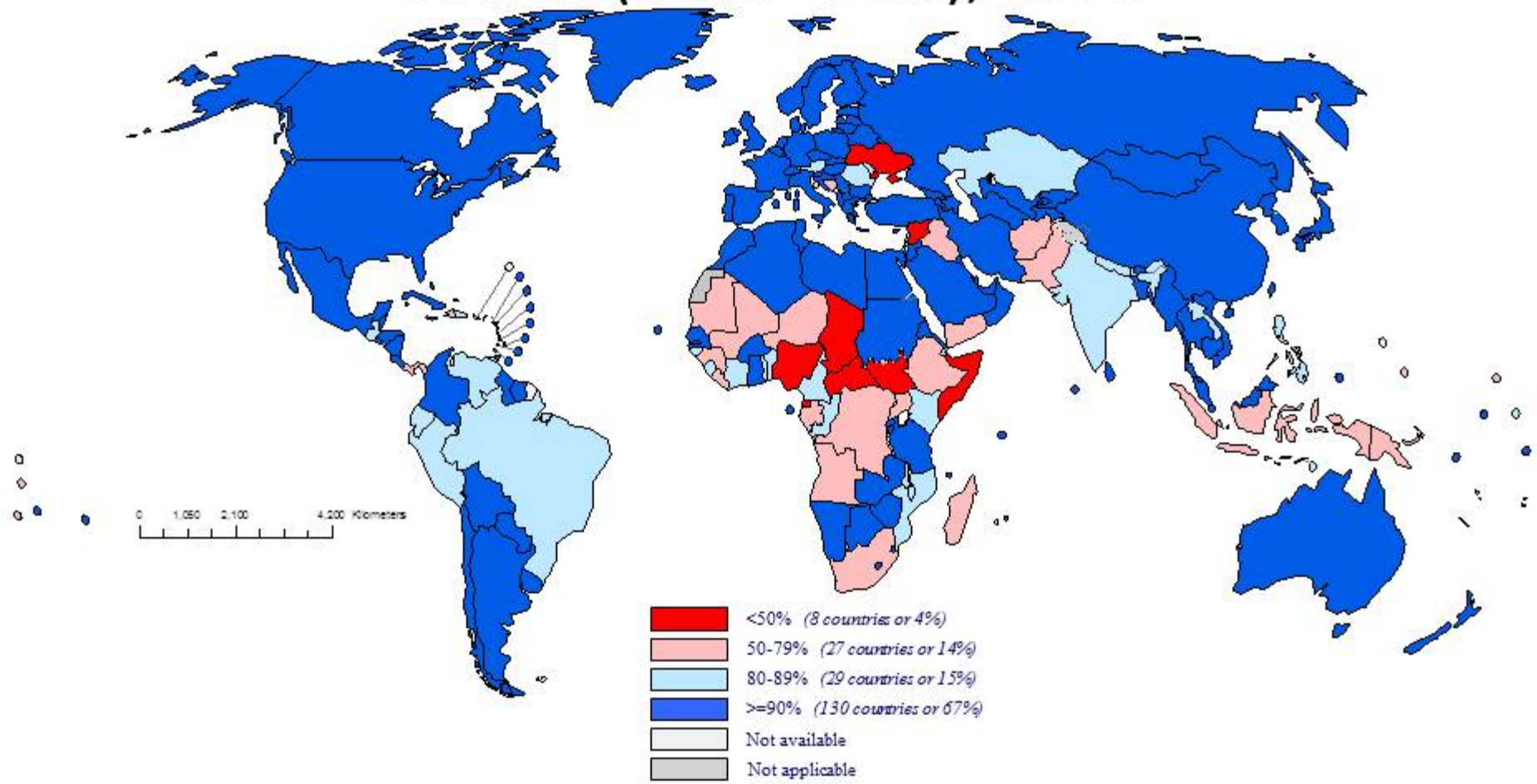
- Diphtheria used to be a major cause of death in the UK.
- A common throat bacteria, only some strains produce toxin.
- Local and general effects due to toxins. Nerve inflammation.
- Usually affects motor nerves.
- Palate often affected, but various peripheral nerves.
- Generally nerves make a full recovery if the patient survives (most now do).

Diphtheria in the UK. Improved living conditions, better treatment (antibiotics), vaccination.





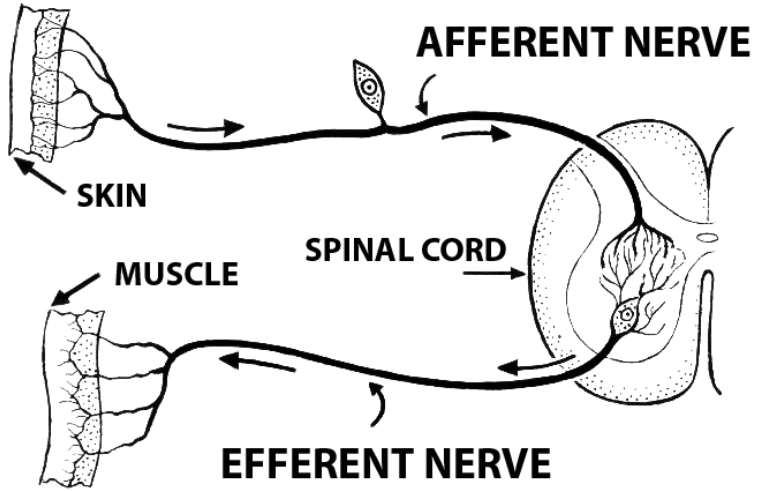
Immunization coverage with DTP3 vaccines in infants (from <50%), 2016

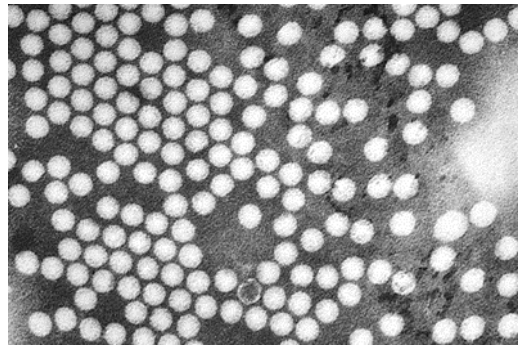


Polio

Polio is a direct viral infection of the motor nerves.

- Polio virus an enterovirus- faeco-oral.
- Multiplies in motor nerves, killing them, causing temporary or permanent paralysis in <1% cases.
- Major outbreaks, especially in children, including in Europe and Americas until vaccines.
- WHO estimates 10-20 million polio survivors worldwide.

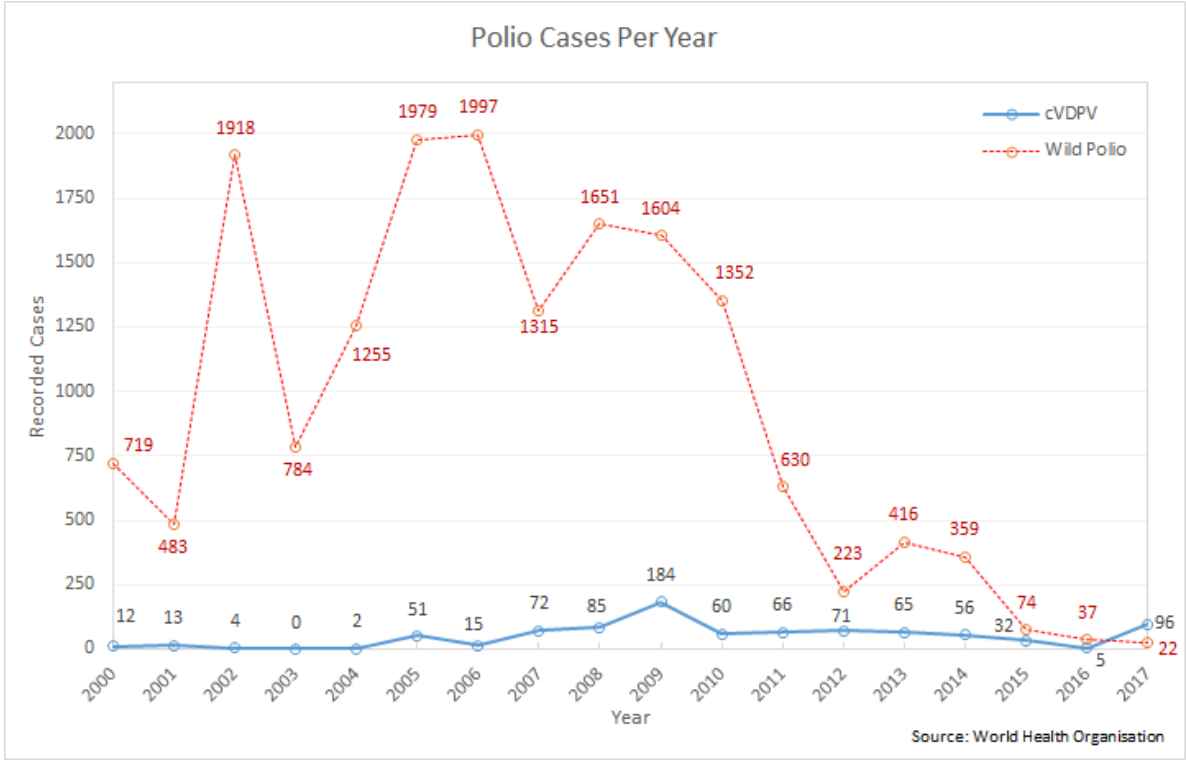




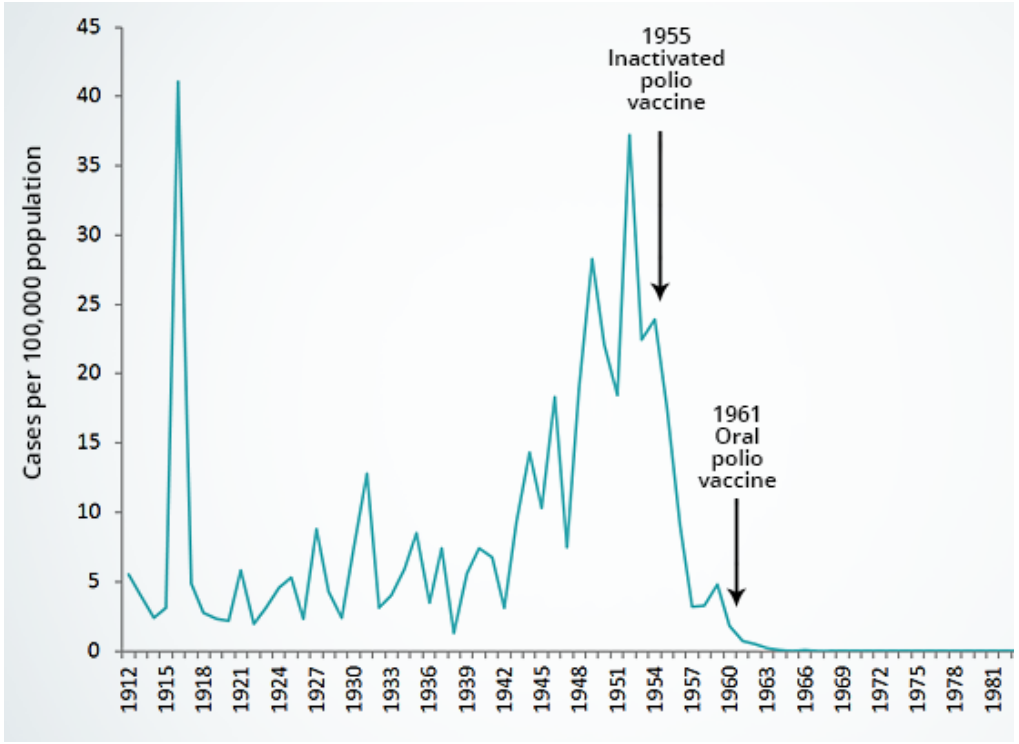
CDC/ Fred Murphy, Sylvia Whitfield

Two polio vaccines- attenuated oral and inactivated injection.

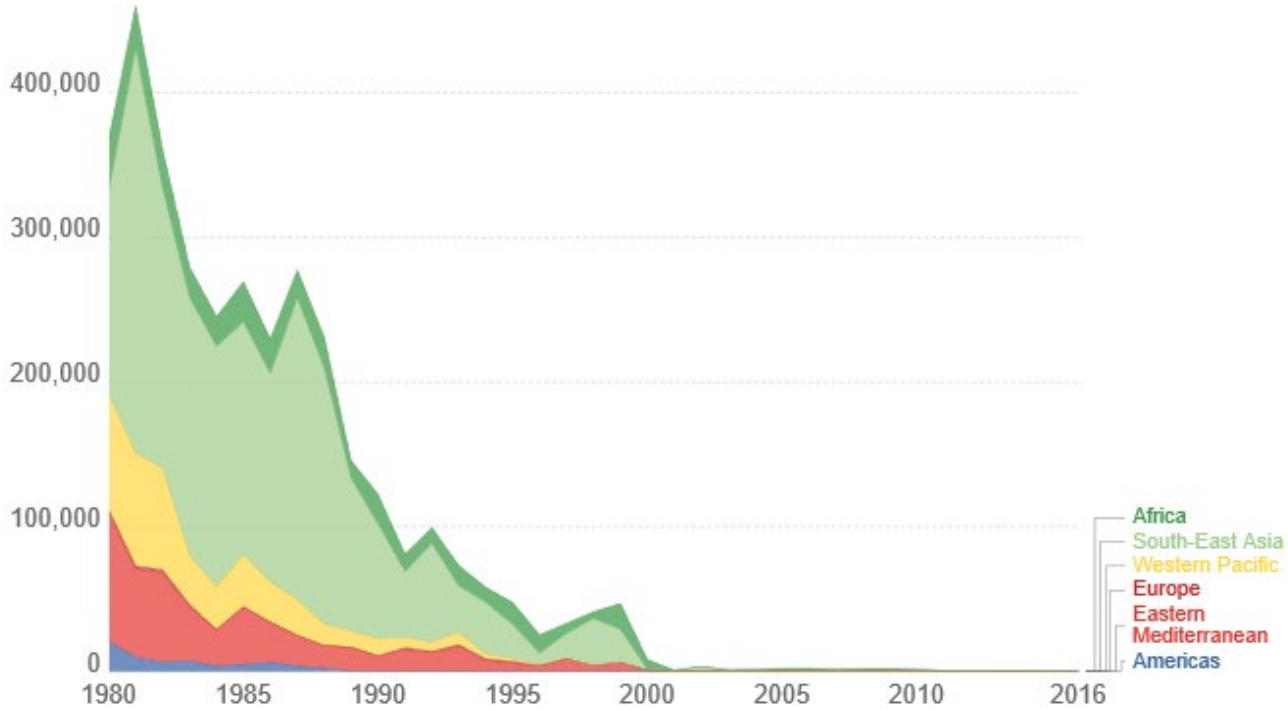
- Jonas Salk inactivated vaccine- 1950s.
- Albert Sabin oral attenuated to the 3 polio strains. Replicates in the gut, but not nerves.
- Pro oral: easy to give, acceptable, good immunity, some spread possible.
- Con oral: very rarely (about three per million doses) can cause paralysis.



Polio cases in the US 1912-1980, and globally 1980-2017.

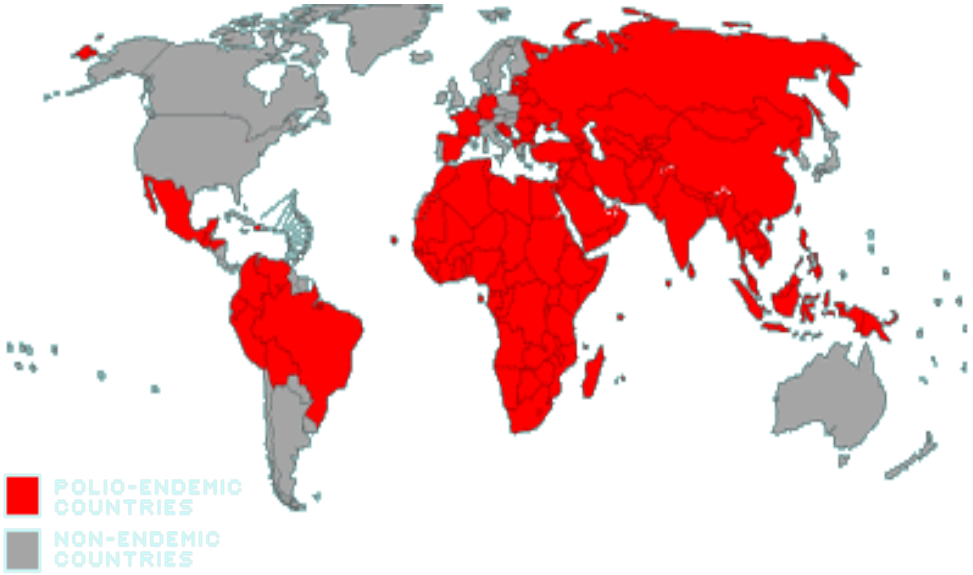


US Census Bureau- cases/100,000

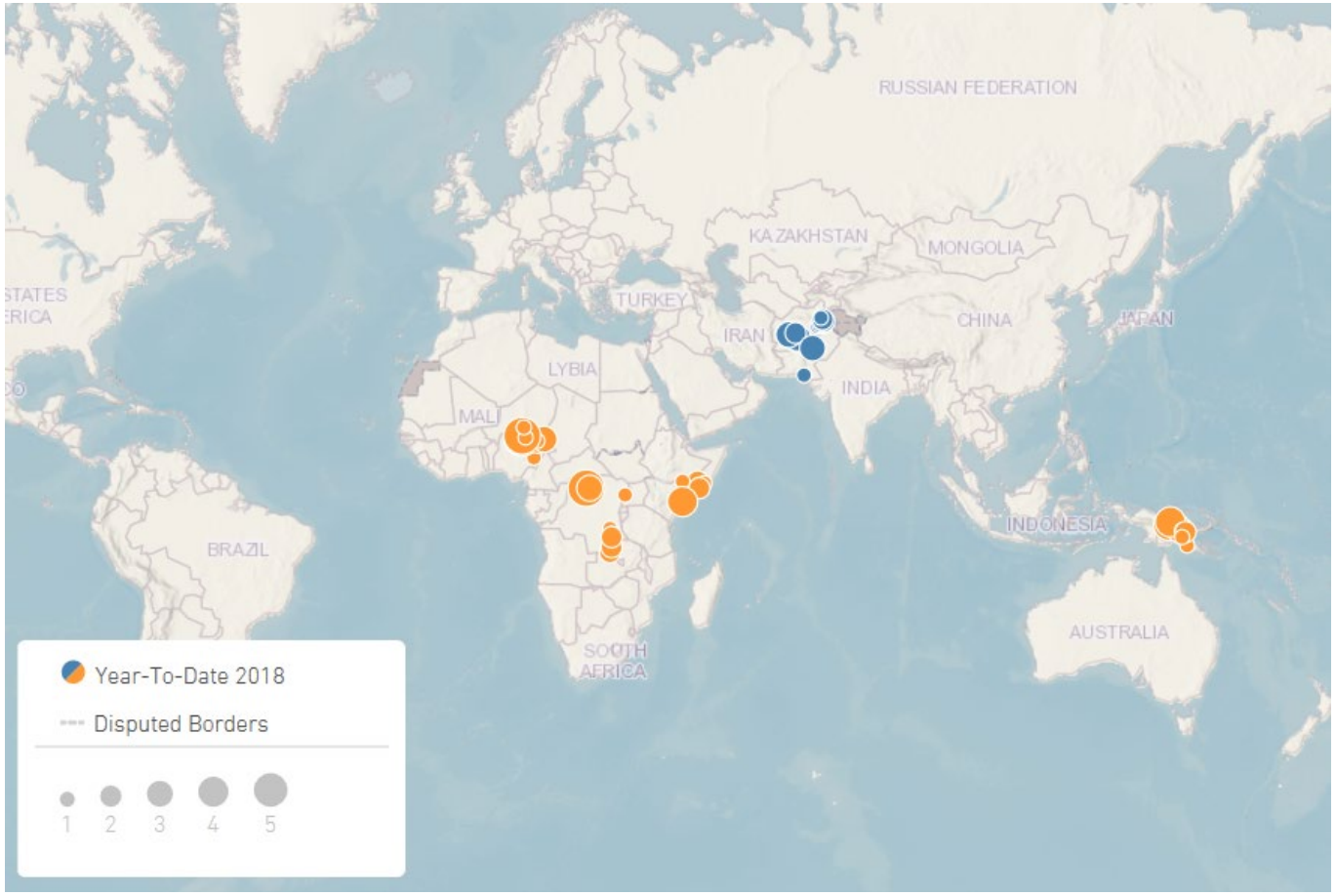


Number of estimated paralytic polio cases globally. Our World in Data / WHO / Tebbens

350,000 wild cases in 1988; 29 in 2018 (WHO). Eradication tantalisingly close.



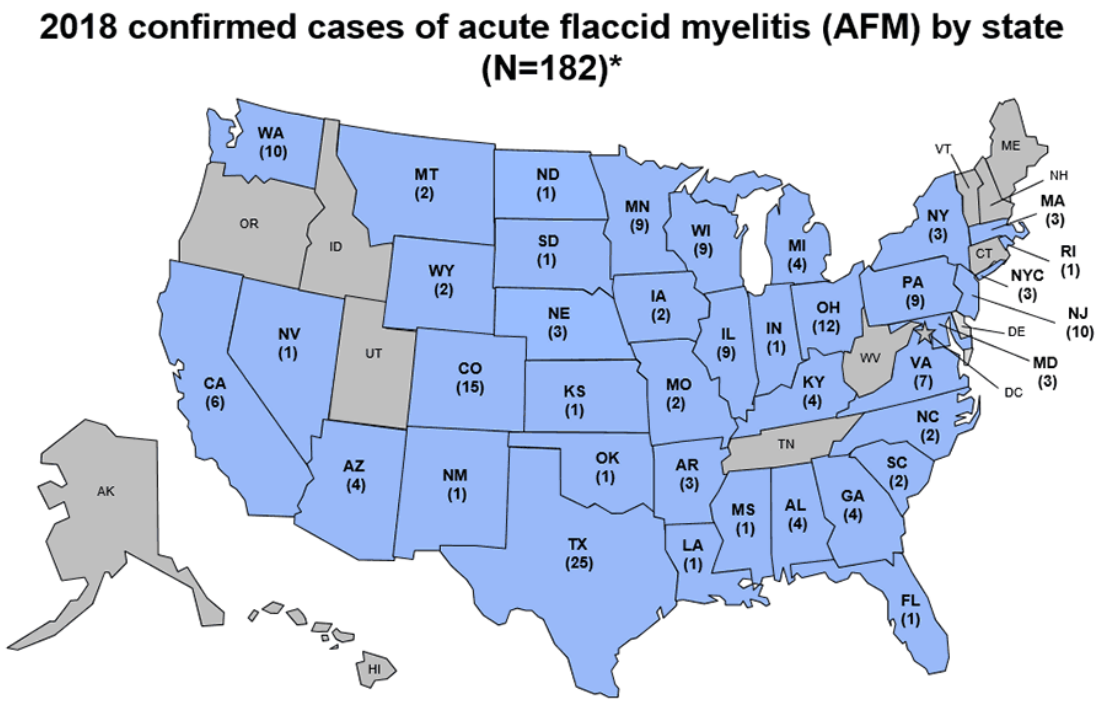
1988



29WPV 99cVDPV

Polio is the most dangerous enterovirus that causes flaccid paralysis, but not the only one. Others very rare.

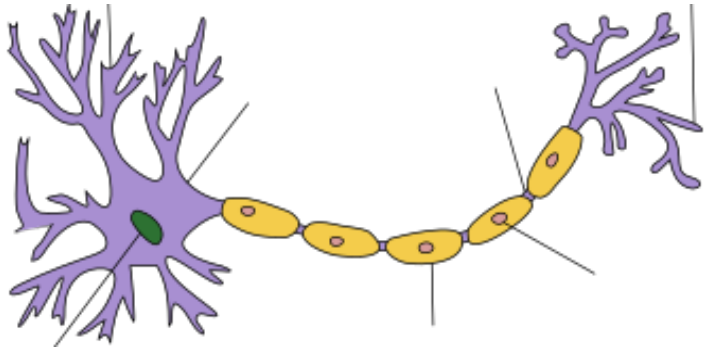
- Acute flaccid paralysis / acute flaccid myelitis cases continue to occur. A small spike in UK in 2018 (28 cases, PHE).
- Tend to be seasonal, especially autumn.
- Can come on after a virus-like infection.
- May be some link to the enterovirus EV-D68 which causes a respiratory infection.



US data- CDC

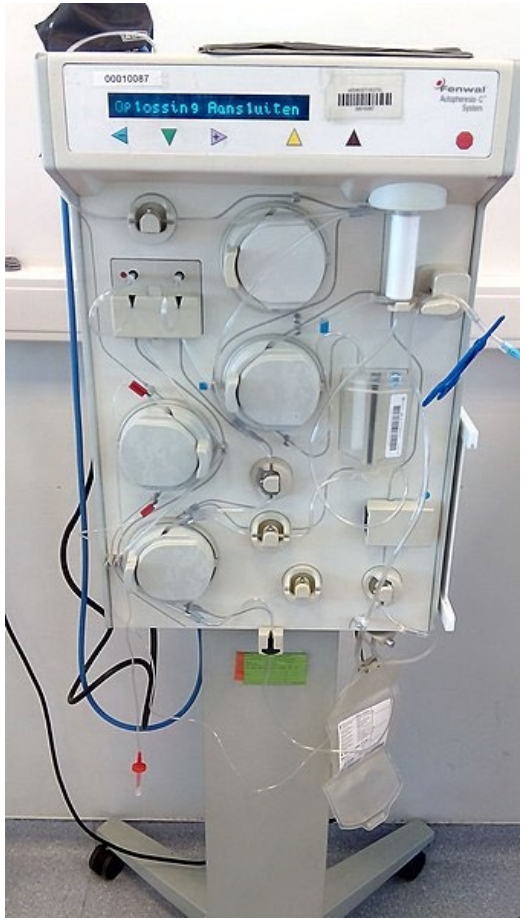
Guillain-Barré syndrome. An immune response to infection.

- (Rarely) occurs after various infections. An immune response to prior infection.
- Known triggers include the gut bacteria campylobacter, and viruses including CMV and Zika.
- Very rarely, some vaccines have been implicated (eg 1976 influenza vaccine)
- Damages the myelin sheath of the nerve, or more rarely the axon.
- Occurs more commonly in adults than children, and males than females.
- 1-2 cases per 100,000 people per year.



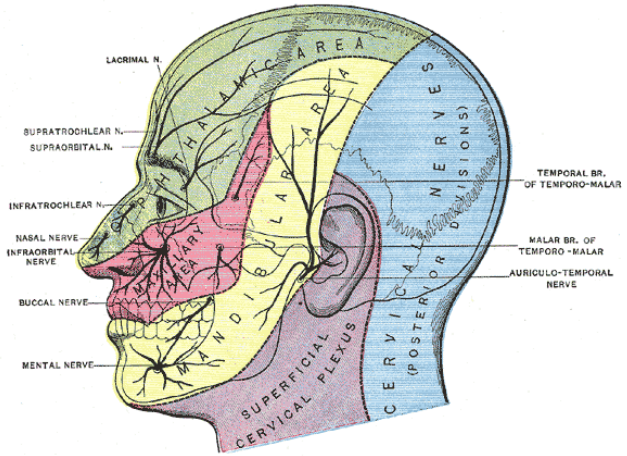
Course of GBS disease.

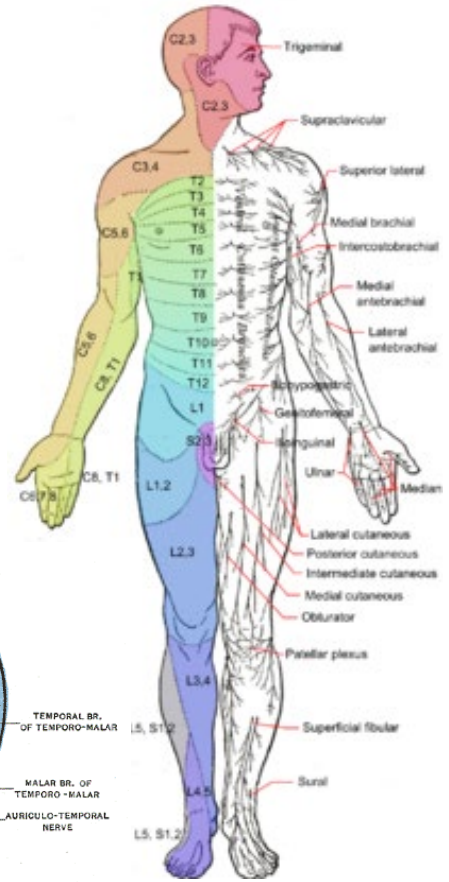
- Typically comes on 3-6 weeks after infection, takes 1 day-2 weeks to reach maximum severity.
- Ascending, symmetrical weakness common.
- Sensory (pain, tingling) and motor systems, but the motor ones are the life-threatening ones.
- Treatment- immunoglobulins or plasmapheresis.
- Around 5% mortality. Respiratory weakness serious.
- Most make a good (but slow) recovery.



Sensory nervous system; a place for viruses to hide. Herpes zoster (varicella zoster virus) and shingles.

- After an initial chickenpox infection.
- The virus stays latent in sensory nerve roots.
- It can reactivate, especially when immune system less effective.
- Painful at the time.
- Can leave severe long-term pain.



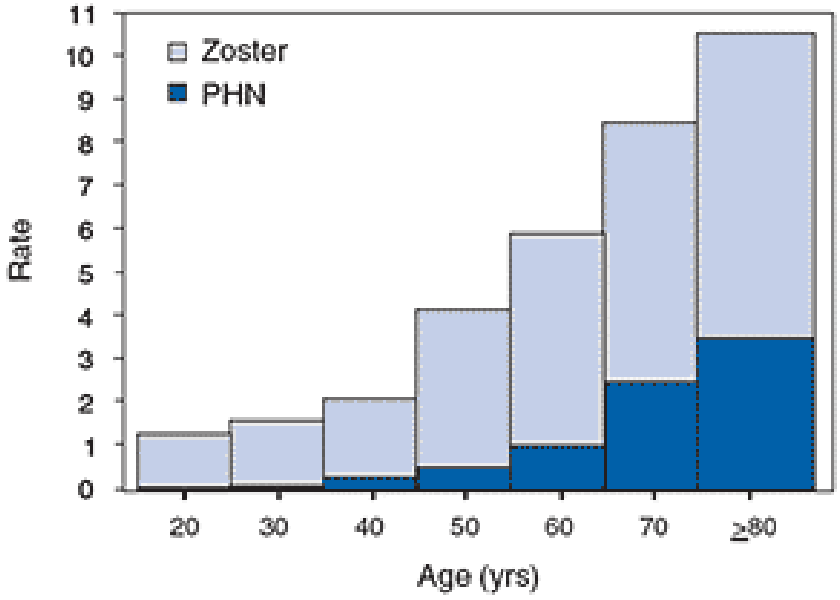


Wikimedia

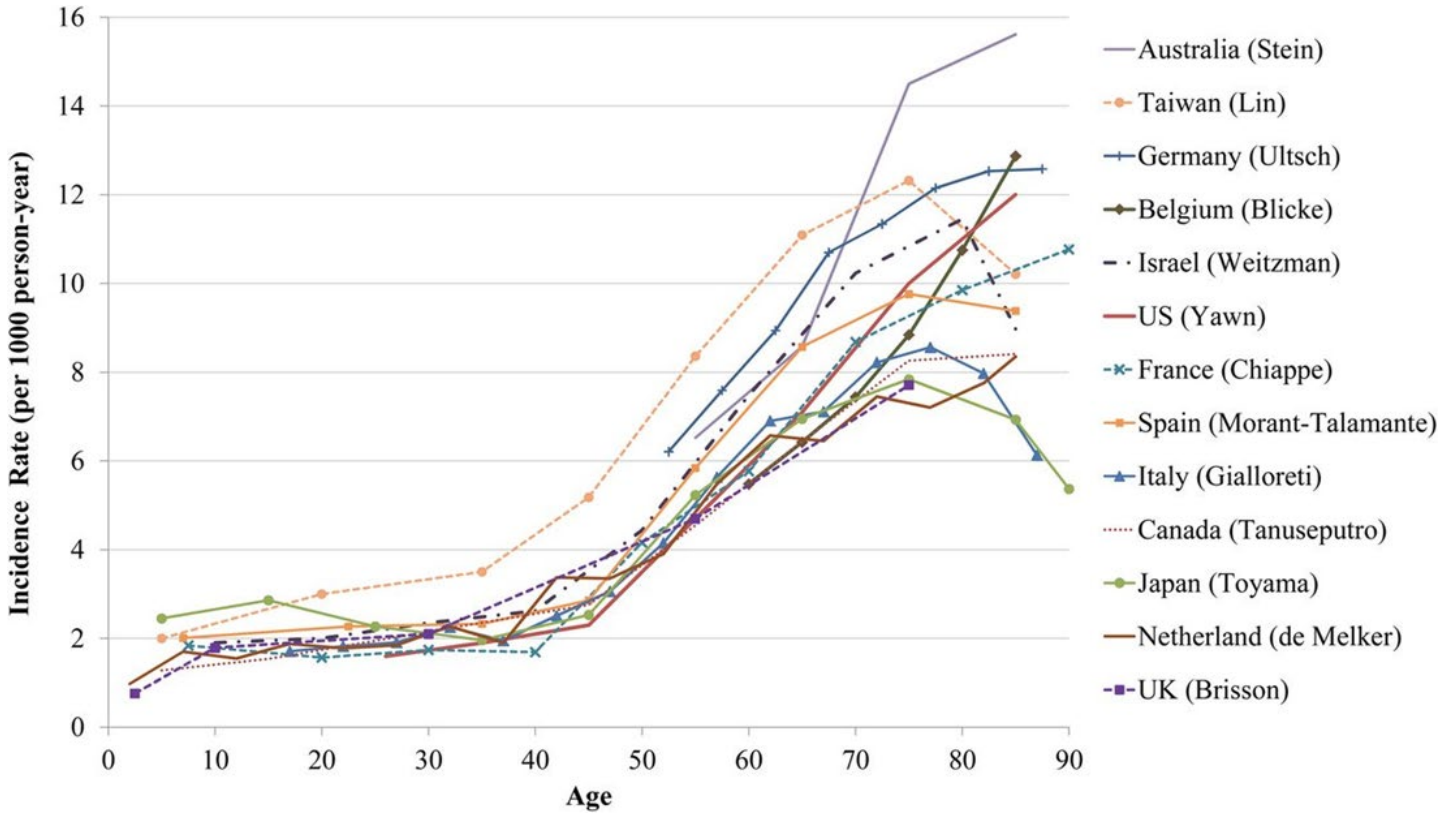
Shingles- prevention.

- Around 1/3rd of people develop shingles in their life.
- 15-20% of those affected will develop post-herpetic neuralgia.
- Primary vaccine for *chickenpox* not recommended in the UK (is in some countries).
- Vaccine for *shingles* is recommended in older people (>70yrs). Current uptake about 50%.
- Reduces risk of shingles by 50-90%.
- If you get shingles reduces risk of post-herpetic neuralgia.
- Current vaccine live; newer a subunit vaccine.

Shingles incidence by age (US and global data)

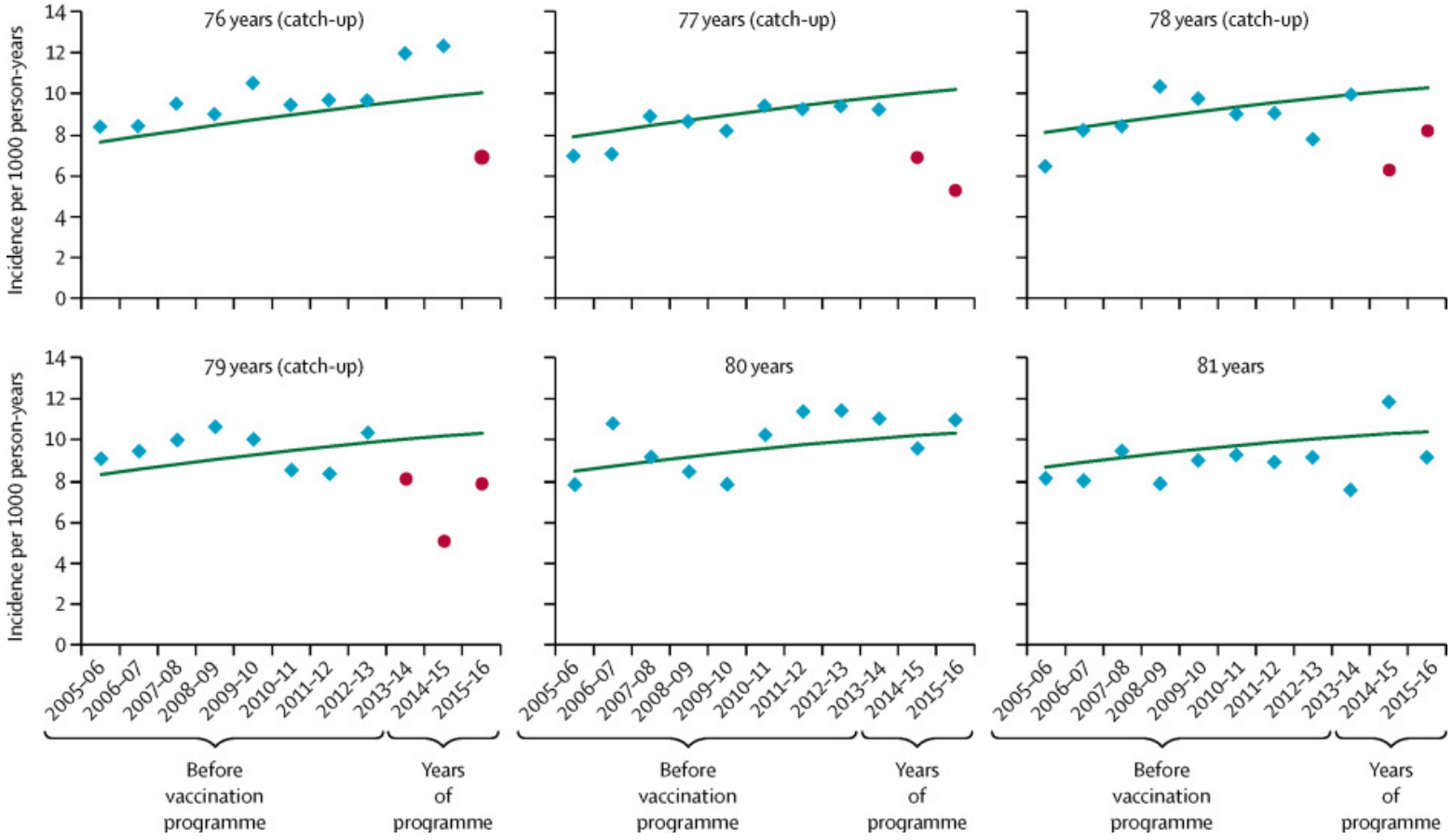


CDC

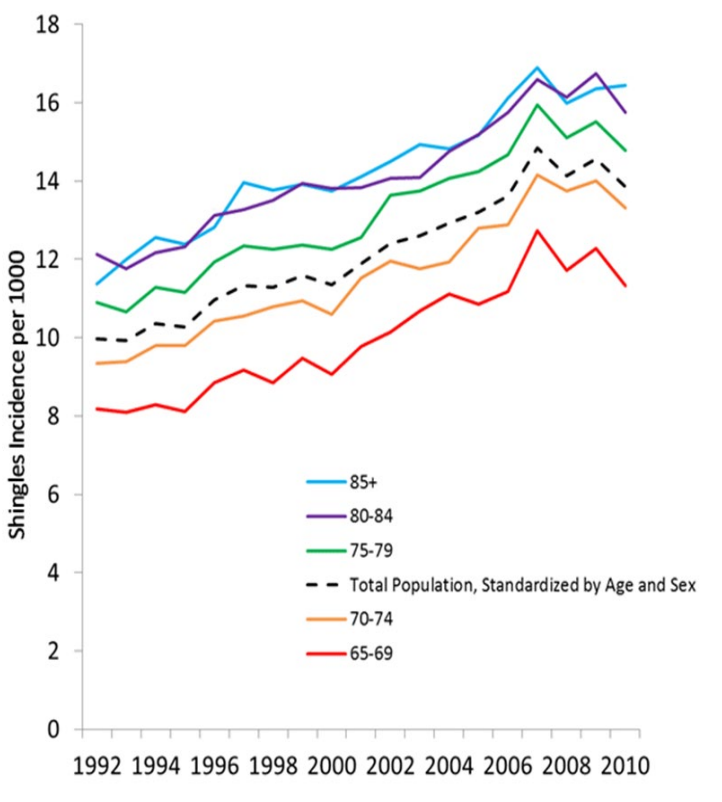


Kawai et al, BMJ Open

Shingles incidence over time- UK (L) and US data.



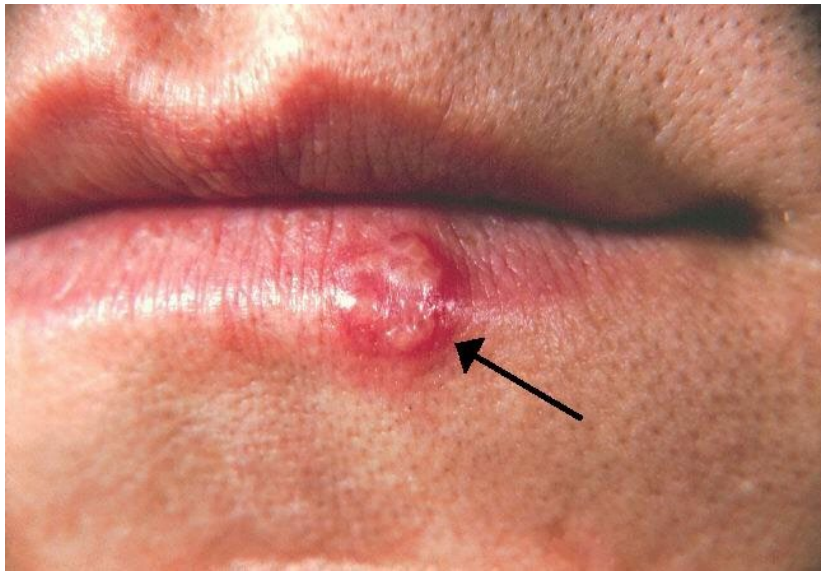
G Amirthalingam et al Lancet PH 2017



US data

Herpes simplex: HSV1 (coldsore) and HSV2 (genital).

- Primary (first) infection can be unpleasant, especially genital.
- Then lie dormant in sensory nerves (ganglia).
- HSV-2 can recur several times a year. Usually asymptomatic. Infected for life.
- Around 12% in 14-49 year old US residents, lower in UK.
- No vaccine. Drugs (e.g. acyclovir) can reduce severity.



Leprosy (Hansen's disease)- extreme destruction of the sensory nerves. Extreme stigma.

- Mycobacteria.
- Historically one of the most feared, and stigmatised, diseases.
- 10s of millions of cases as late as the 1960s.
- Remains a significant public health problem in a few countries.
- Very difficult to catch, from nasal secretions.
- Incubation period many years.
- Non-infectious after first treatment.

Leprosy is a spectrum, depending on immune system.

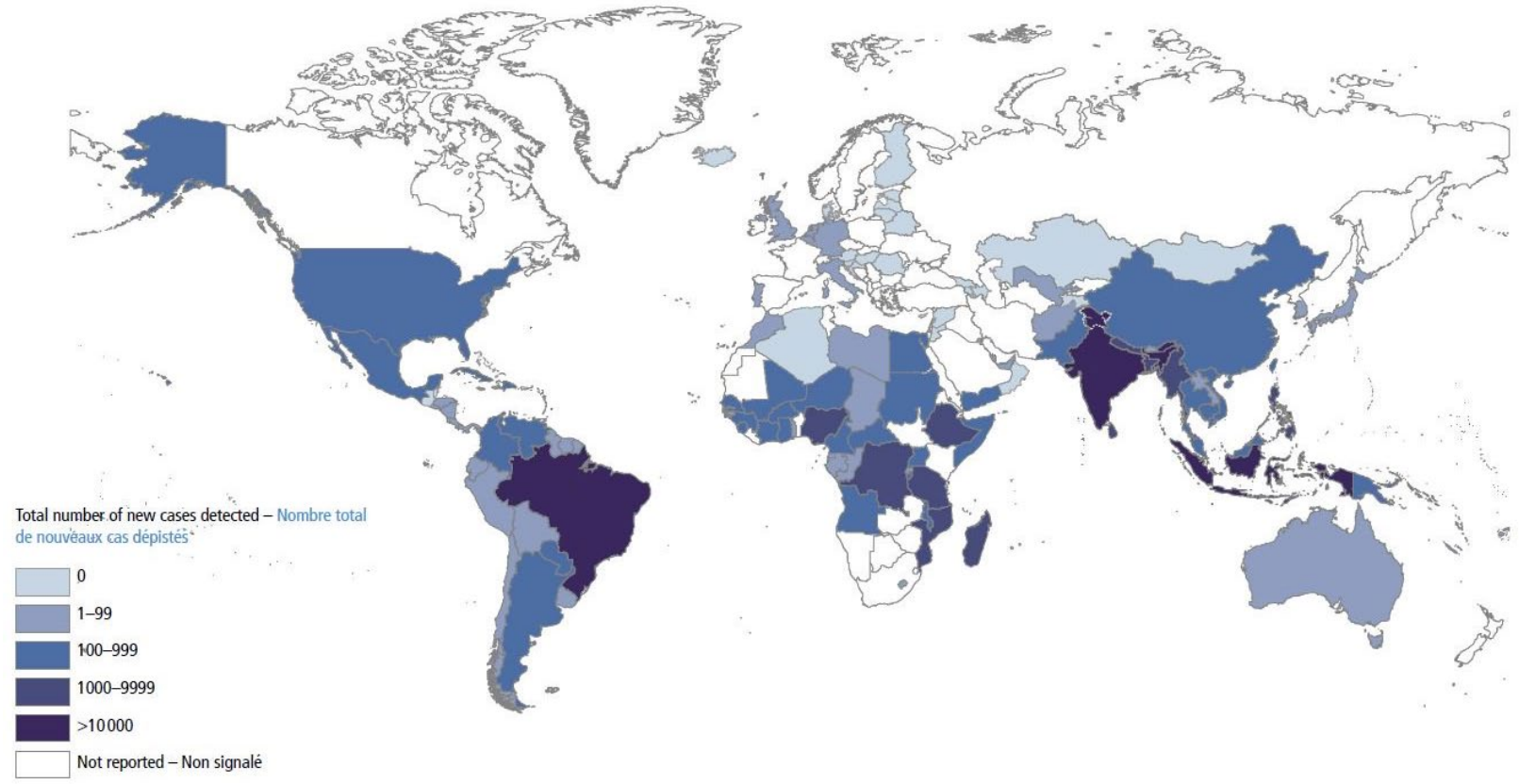
WHO, Wiki

Leprosy- once sensation goes, damage is common.

- If a few localised anaesthetic patches and thickened nerves the outlook is good.
- If generalised destruction of the sensory nerves, especially of hands, feet, repeated injury and infection.
- Eventually fingers and toes may be lost.
- The infection can be stopped (killed)- but the damage to nerves does not reverse.

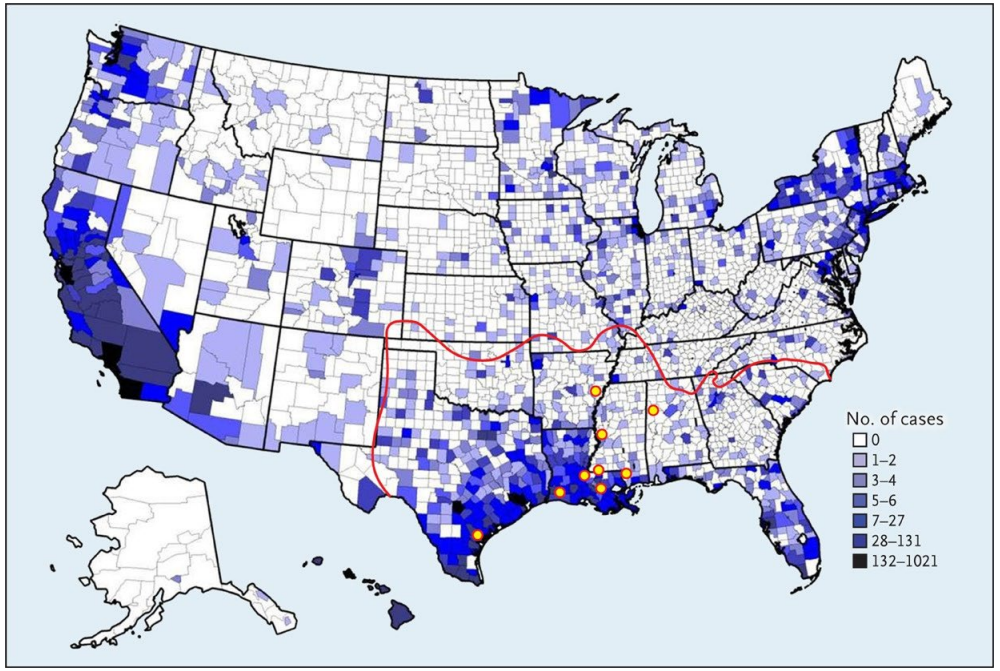
New leprosy in 2016 (WHO).

- Globally > 200,000.
- Around 19,000 children were diagnosed: >50 a day.
- 2 to 3 million people living with disease-related disabilities globally.



Leprosy in the USA and UK.
Introduced to Americas from Europe and Africa.

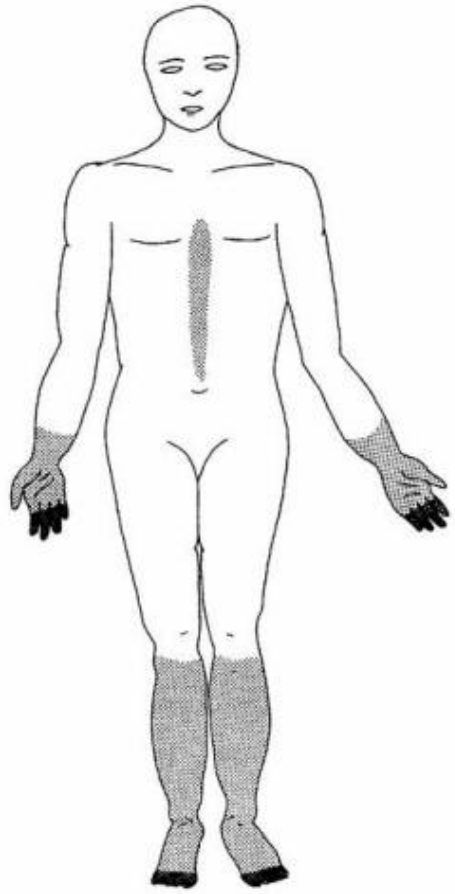
- Last indigenous case of leprosy in the UK 1952 (family member), but a few imported cases still happen.
- Most US cases now (around 150 a year) imported.
- But around 1/3rd no known travel or contact.
- 9-banded Armadillo may be a reservoir.
- Stigma remains a serious problem.



Truman et al NEJM

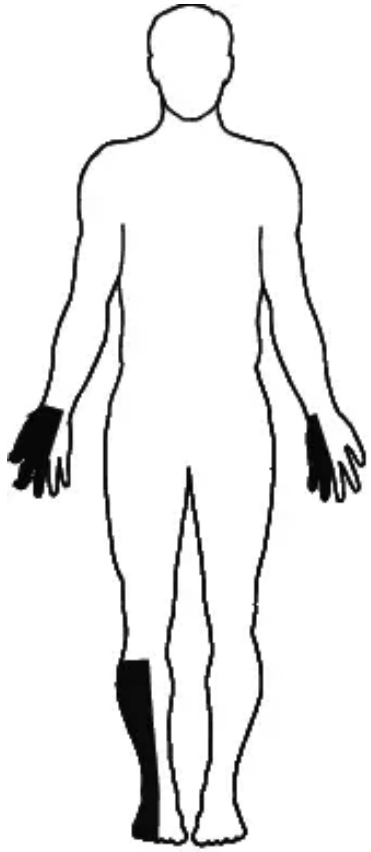
HIV neuropathy.

- Affects sensation in a glove-and-stocking distribution.
- Peripheral neuropathies affect the longest nerves most.
- Tingling, odd sensation.
- Mild cases common. Generally resolve with HIV treatment.
- Severe cases occur especially in advanced HIV.
- Some (generally older) HIV drugs can also damage the nerves.



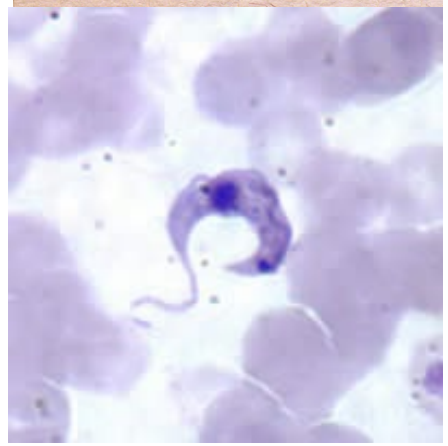
Mononeuritis multiplex.

- Occasionally individual nerve trunks can be affected with others spared.
- May be combined motor and sensory.
- Many causes (eg diabetes) but infection one of them.
- HIV, Hepatitis C, Lyme, leprosy all rare causes.



The autonomic nervous system.

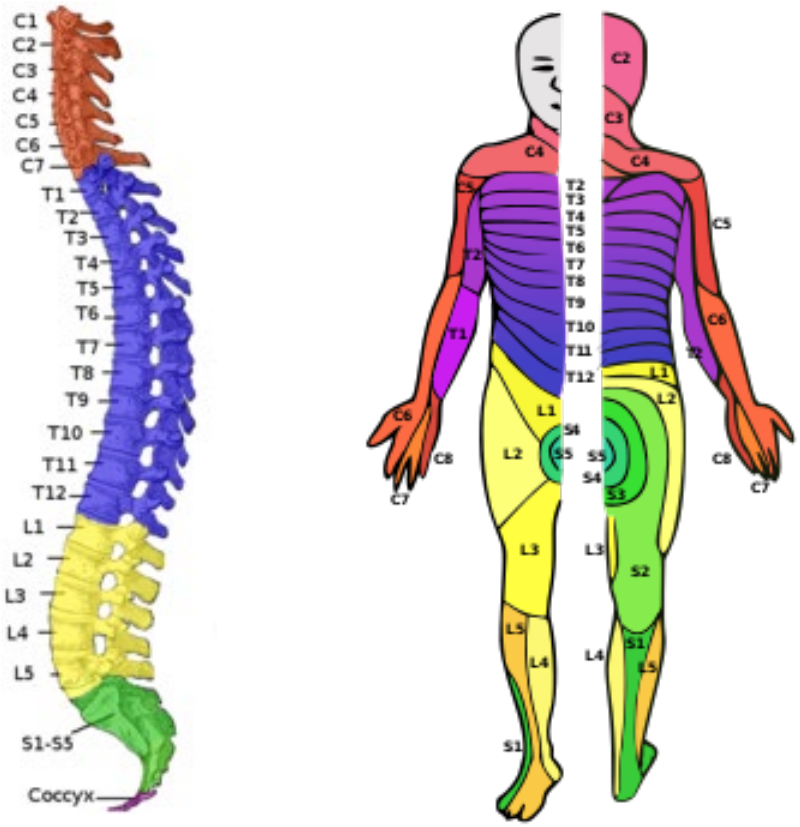
- Effects on heart rate, blood pressure, gut.
- Minor autonomic dysfunction common.
- Significant dysfunction can occur in severe tetanus, diphtheria, leprosy, Guillain–Barré, HIV, rabies.
- Chagas (*T. cruzi*) disease in Latin America affects the heart. Autonomic nerve function may be a major part.
- Passed on by reduviid bug, congenital, (transfusion).
- Global prevalence dropped from 18m in 1991 to <6m today.



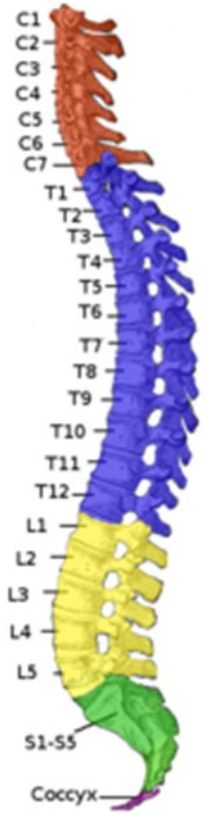
Adapted from C Bern

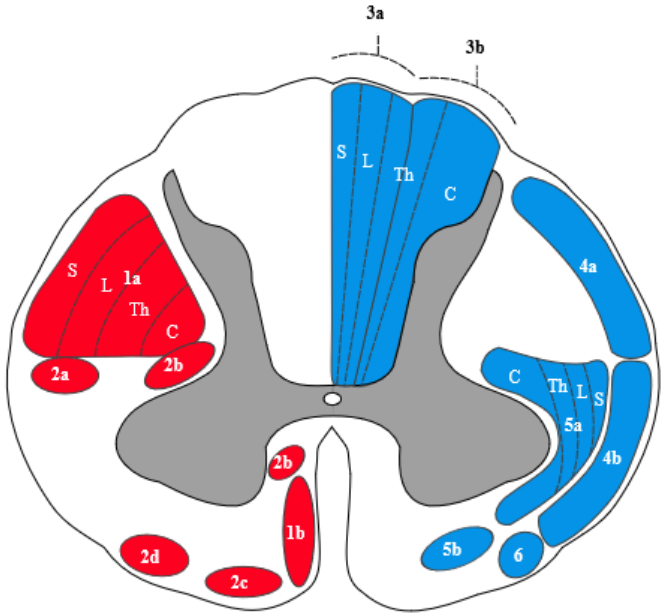
The spinal cord.

- The effects of infection affecting the spinal cord depend on the level it occurs.
- Function reduced at and below the damage.
- The higher the level, the greater the potential functional impact.



The basic anatomy of the spinal cord and peripheral nerves.

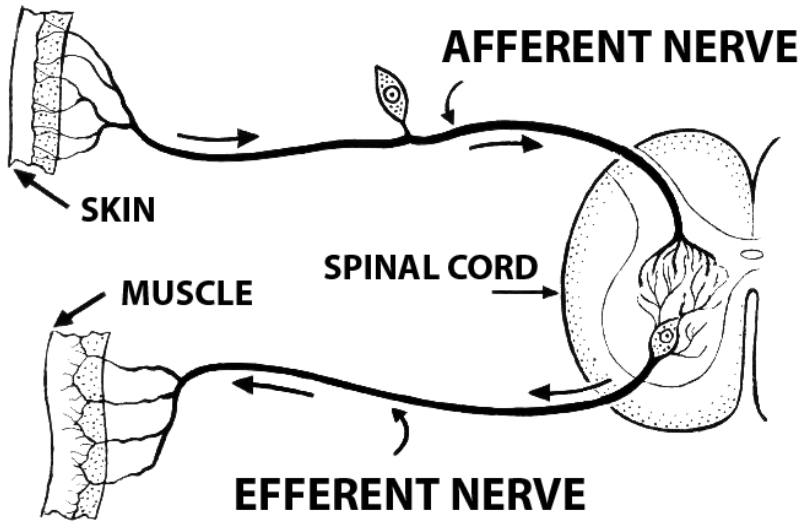




Sensory- ascending

Motor- descending.

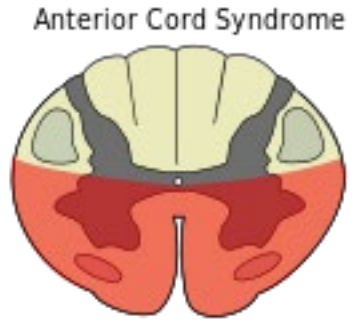
Sensory

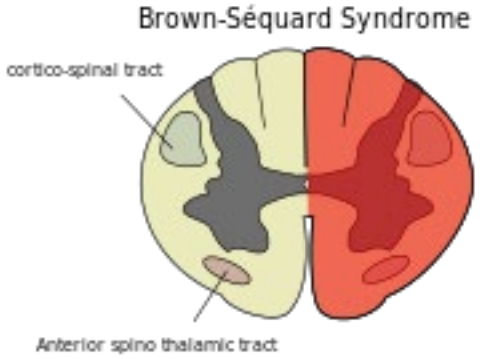


Motor

Complete and incomplete spinal cord effects.

- If across the whole cord, loss of motor, sensation, bladder control.
- Anterior cord (front, often from vertebrae), motor function, pain sensation, and temperature sensation are lost; sense of touch and proprioception (sense of position) intact.
- If one side: on same side the body loses motor function, proprioception, touch; on opposite side loss of pain and temperature sensation.





Spinal infections: tuberculosis of the spine (Pott's disease)

- Found in Egyptian mummies.
- Used to be common in the UK.
- Destruction of the vertebrae.
- Pressure on the spinal cord.
- Treatment- TB drugs, sometimes surgery.
- Prevention: reduce poverty, BCG, early detection.
- Now relatively rare.

Benoît Prieur

Hani Salam, Radiopaedia

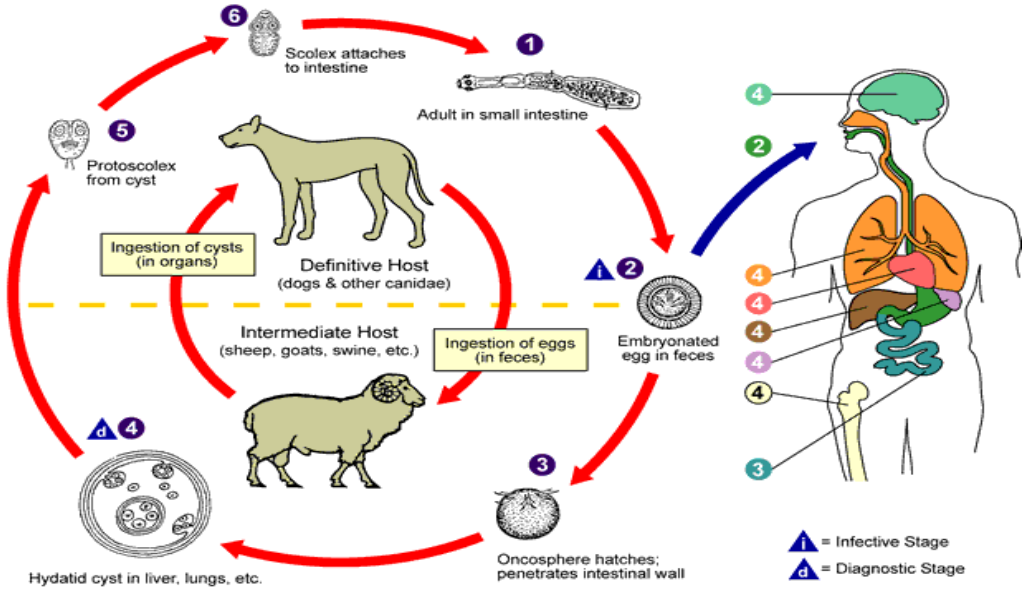
Bacterial infection of disk or spine.

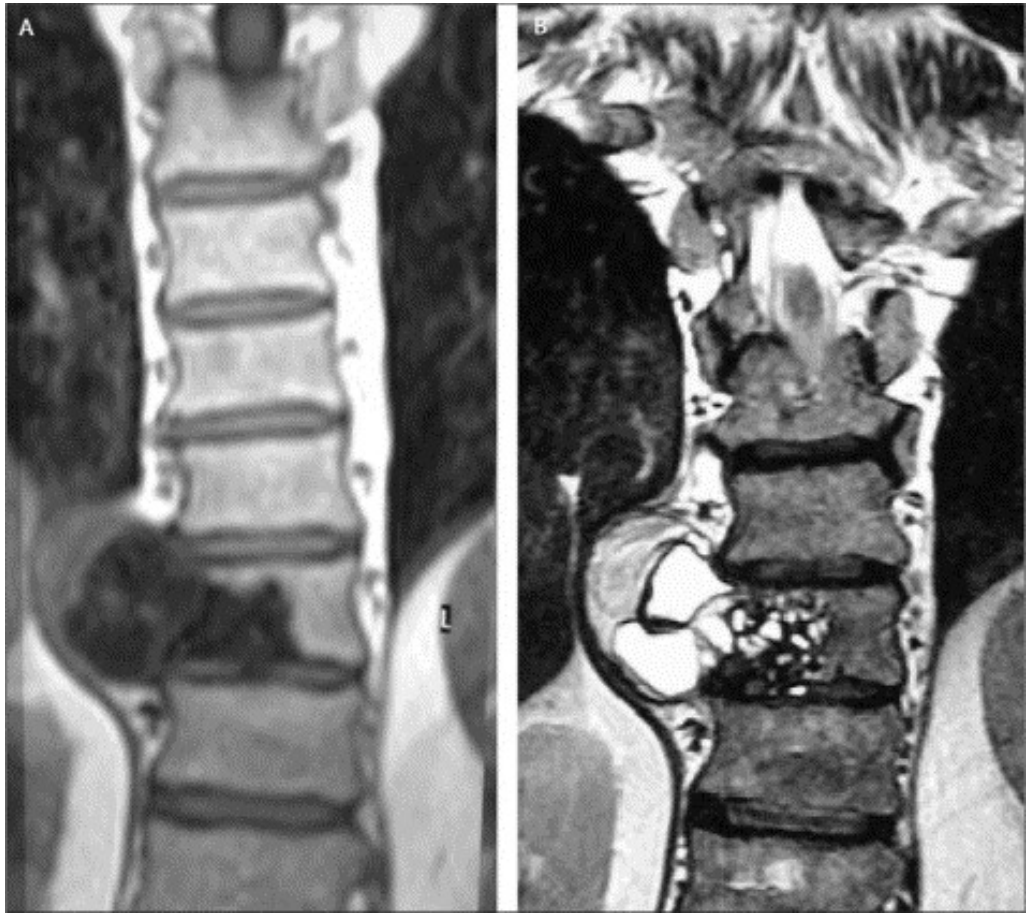
- Damage may be to the vertebrae, disc or both.
- A few bacteria such as staphylococcus cause most disease.
- Intravenous lines, intravenous drug use major risks.
- Treatment antibiotics.
- Occasionally surgery or radiological drainage.

James Heilman

Frank Gaillard, Radiopaedia

Parasitic disease of spine- hydatid. Sheep-dog cycle.

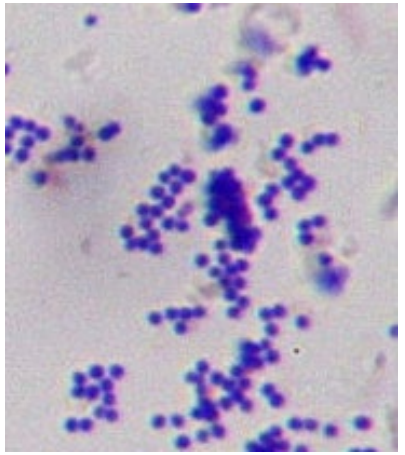


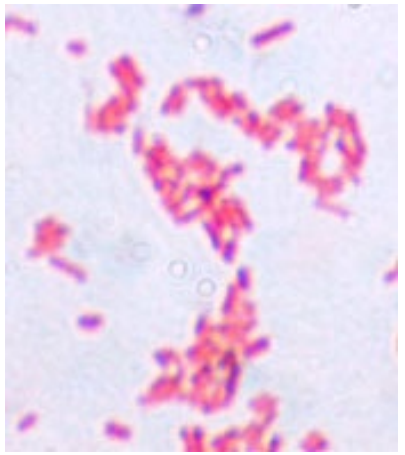


C A Logroscino et al 2005

Abscess in soft tissue pressing on spinal cord.

- Spread from blood (or procedures).
- Bacterial most common.
- Occasionally tuberculosis, fungal.
- Treatment is antibiotics / antimicrobials and sometimes drainage.





Dr Roberto Schubert, Radiopaedia

Rare parasitic causes: spinal cysticercosis and schistosomiasis.

- Cysticercosis caught by ingesting eggs from humans infected by pork tapeworm.
- Cysts mainly in muscle and brain, but occasionally spinal cord.

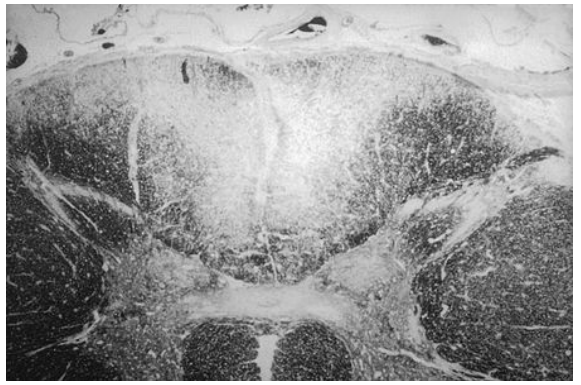
- Schistosomiasis caught from swimming in fresh water with relevant snails. Mainly in Africa.

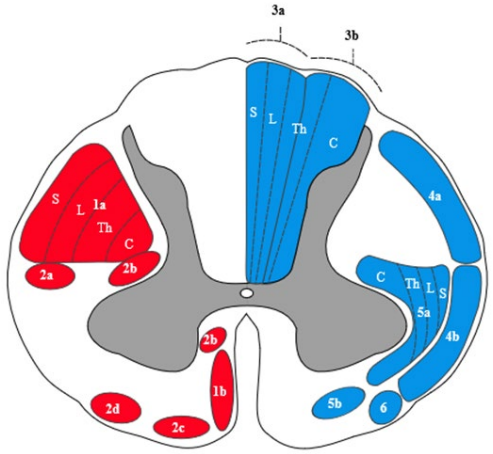
J Lin et al BMJ Cases 2010

Bruce Wetzel/. Harry Schaefer NCI

Tabes dorsalis- tertiary syphilis of the spinal cord.

- Used to be common in the UK- Sir Arthur Conan-Doyle did his doctorate on it.
- Years after the initial syphilis infection demyelination of the dorsal columns of the spinal cord (nearest the back).
- Affects sensations, especially touch and position sense (proprioception), and reflexes.
- Staggering, wide-based gait. Worse in dark.
- Prevented by antibiotics early in infection.





Sensory Motor

CDC/Susan Lindsley

Acute transverse myelitis (ATM)- viral infections.

- 1-5/ million get transverse myelitis per year. Infections one trigger.
- Inflammation of the spinal cord in one, or a number of, places.
- With viruses and vaccination probably an immunological reaction rather than infection.
- Can affect the whole cord width, or only some columns.
- May resolve, or leave permanent damage.
- Herpes viruses (VZV, HSV), CMV, enteroviruses, measles, mumps, HIV, Influenza A most common worldwide.
- Various tropical viruses (dengue, Zika, West Nile).

Bacterial infections causing transverse myelitis.
Many causes, all very rarely cause ATM. Usually curable.

Include:

- TB.
- Campylobacter.
- Paratyphoid.
- Leptospirosis.
- Scrub typhus.
- Lyme disease.
- Brucellosis, Q fever.
- *Chlamydia psytichi*.

Infectious can damage nerve function by several routes. Many of these are preventable, or treatable.

Include:

- Produce nerve toxins. Tetanus, botulinum, diphtheria.
- Direct invasion of nerves by infections. Polio, leprosy, shingles, syphilis.
- Activate the immune system, which damages nerves. Guillain-Barre syndrome, transverse myelitis.
- Physical damage due to pressure (esp. spinal cord).

Infectious diseases affecting the nerves are some of the most debilitating and feared, but many retreating.

Most of the worst are substantially reduced in scale and impact, including:

- Tetanus
- Polio
- Leprosy
- Diphtheria
- Neurological syphilis.

Risks from others like shingles are reducing, if more slowly.

A smaller but important group remain.

2 children with polio.
CDC/Charles Farmer