The changing impact of infections as we go through life and age.

Christopher Whitty

Gresham College 2019

An infection will have a very different course depending on age.

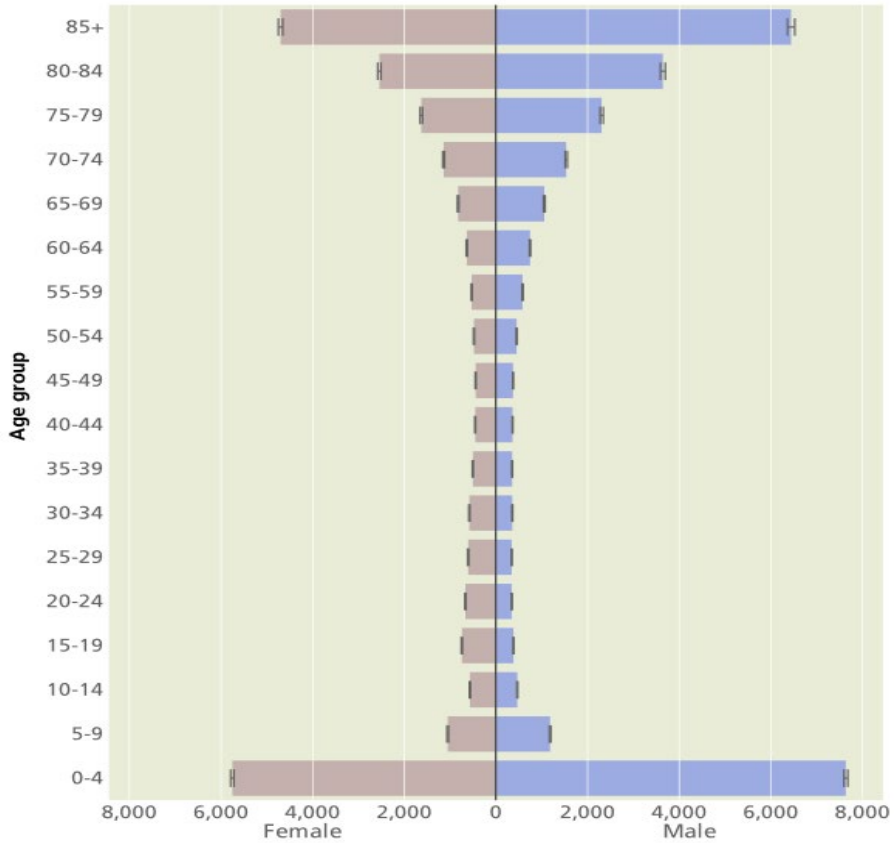
- The probability of acquiring infections varies through our life.
- Some is behavioural, some environmental, biological.
- Most infections are most dangerous in the young and old- but not all.
- The same infection may be trivial at one age but serious at others.
- Or present very differently.
- Infections have been declining as a cause of mortality globally but will increase again as the population ages.

JS Copley. The Copley Family C1777

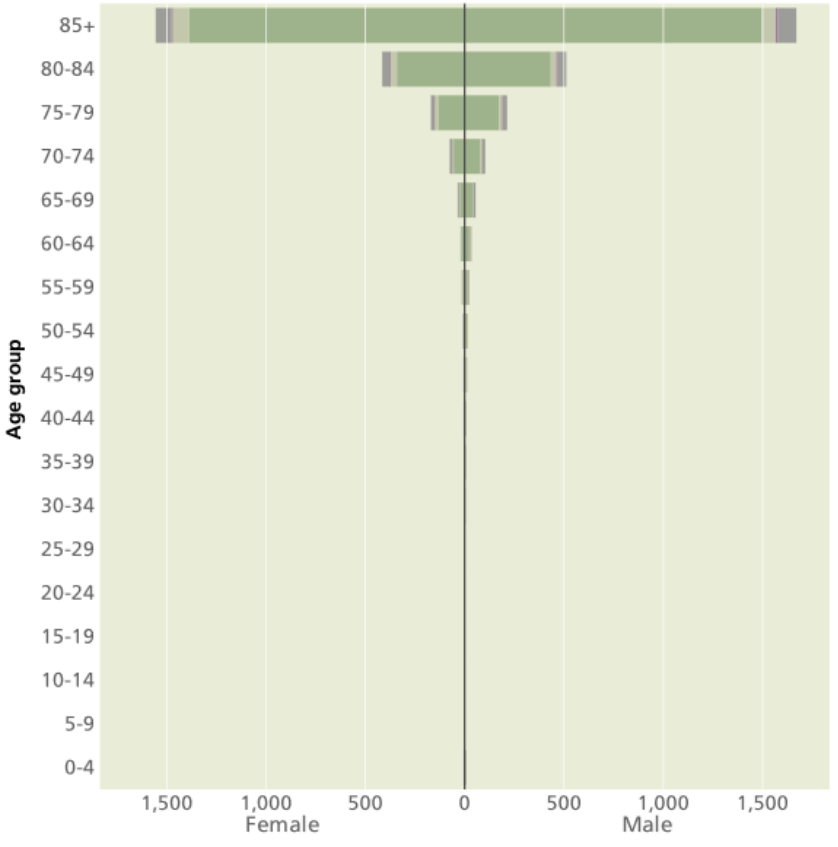
Severe infections commoner in old and young.
In high income settings mortality heavily skewed to older ages.

England data, CMO Report 2012.

Hospital admissions for infections by age, /100,000.



Average annual mortality from infections by age, /100,000.



“At first, the infant,
Mewling and puking in the nurse's arms.”

- Birth is a dangerous business, infections contribute to the risk.
- Infections in the birth canal can be passed on to the baby causing early onset infection (<48 hours), including.

Group B streptococcus (GBS) (58% UK).

E. Coli (18% UK)

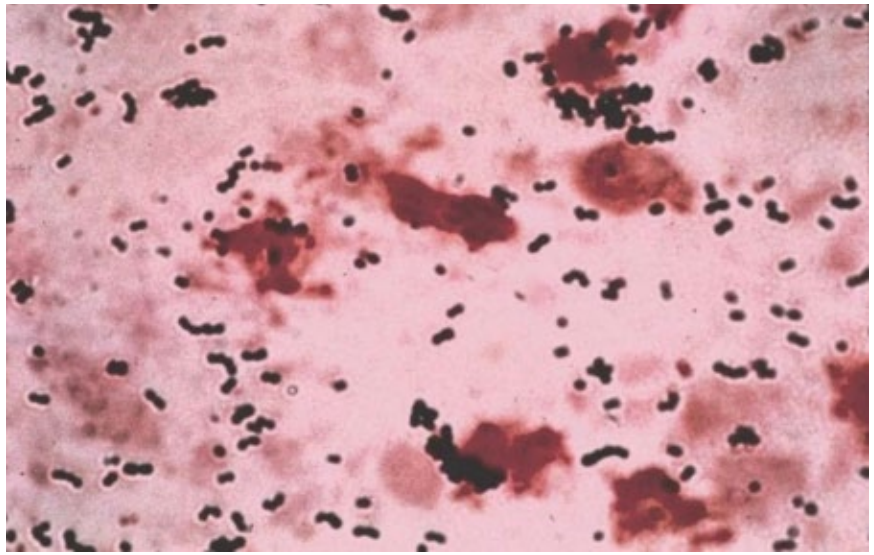
Herpes simplex

- Mixing of blood between mother and child: HIV, Hepatitis B.

Meutia Chaerani - Indradi Soemardjan. Wiki.

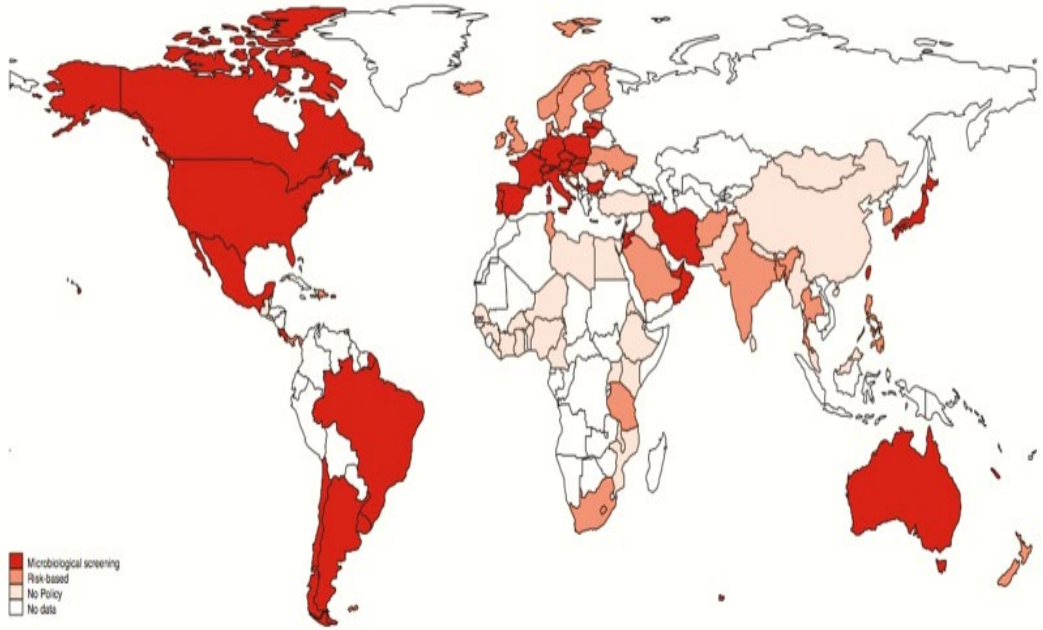
Group B streptococcus (GBS).

- Group B streptococcus is very common. In UK carried by 20-40% of women around the birth canal. Normally does no harm.
- 1/1750 babies develop early onset GBS (first 48h): sepsis, pneumonia or meningitis.
- Most babies with GBS make a full recovery with antibiotics but just over 5% die, 7% have long-term disability. (RCOG data).
- In a typical month 2 babies die from GBS, 3 have disability (out of >56,000 births).
- Higher risk in preterm babies.



Screening for GBS a live controversy.

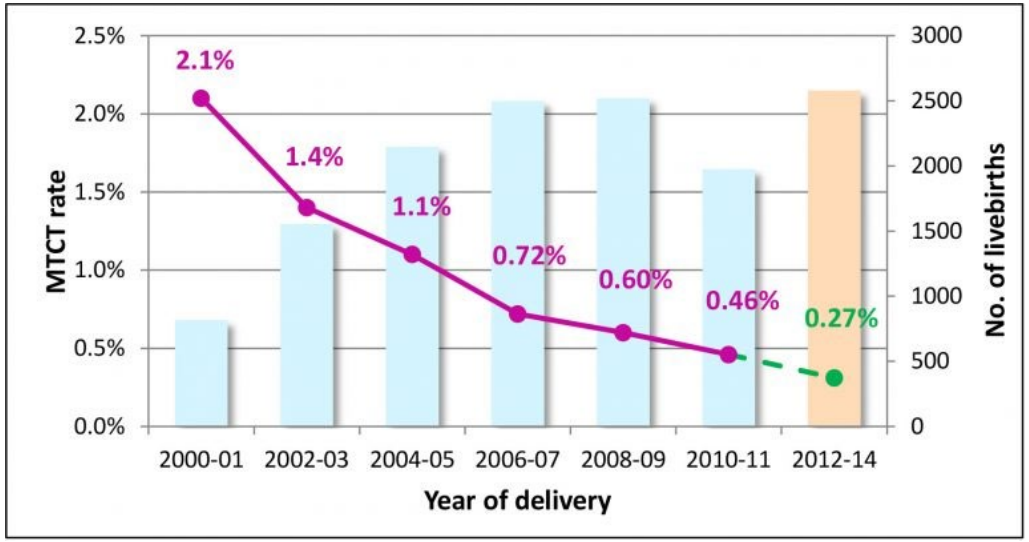
- In UK antibiotics offered to women at high risk, including previous GBS, preterm labour.
- Some countries screen all pregnant women including USA. Some like UK do not.
- If women screen positive they will receive antibiotics (Abx).
- Modelling suggest in UK screening results in 96,260 women/year receiving antibiotics which might prevent 3 EOGBS deaths and 4 cases of severe disability. *(Bevan et al 2019)*
- With screening, between 24,000-32,000 receive Abx to prevent one EOGBS death.
- >99% of antibiotics no positive effect, some risks. We need a trial.



Doare et al CID 2017

Mother-to-child transmission of HIV.

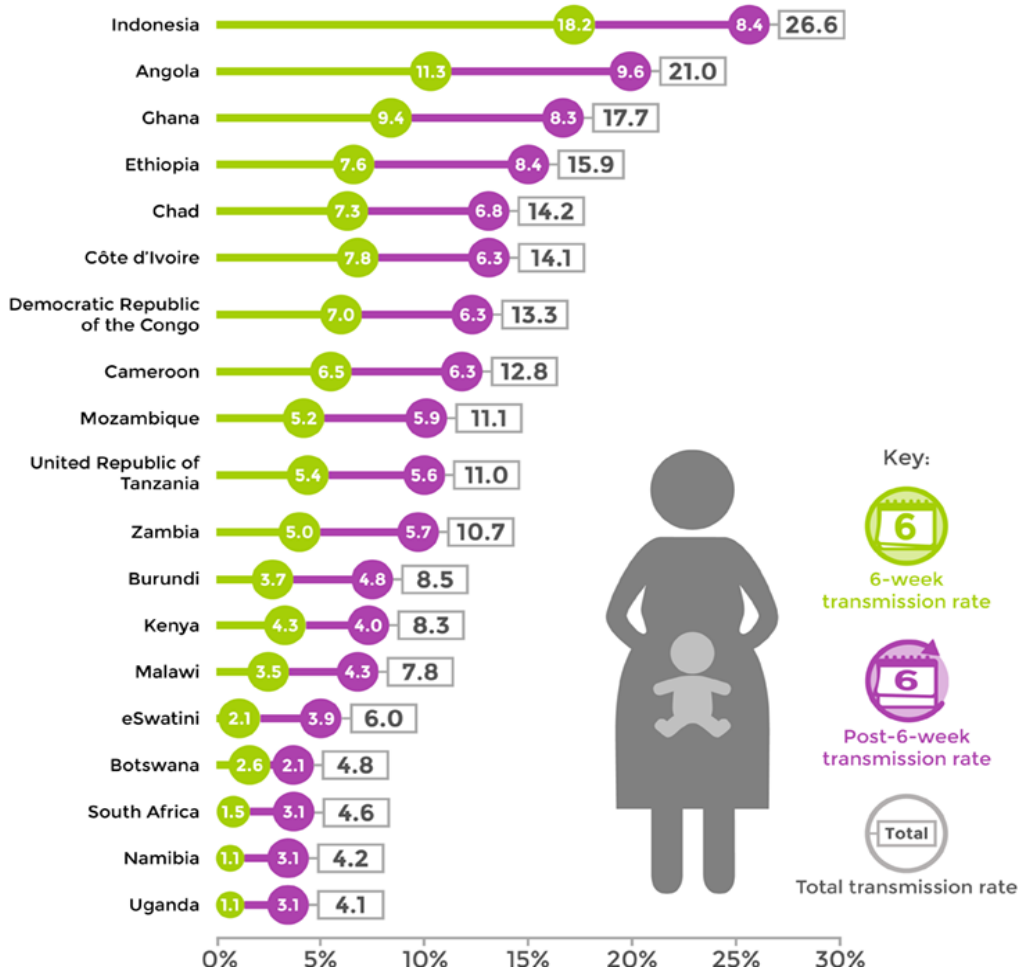
- In the early HIV epidemic 15-45% of children of HIV+ women infected.
- 65% of these were infected at birth; during pregnancy and breastfeeding the remainder.
- In high income settings this is now <1%. Depends on antenatal screening. UK <0.5% transmission.
- Effective antiretrovirals in pregnancy, occasionally caesarean section.



Mother-to-child rates in UK and Ireland (2000 to 2014). <10 yr UK. H Peters 2016.

Globally mother-to-child HIV transmission falling, but a long way to go.

- Around 1.8 million children <15 living with HIV worldwide. 180,000 new HIV infections in children 0-14 in 2017, down from 270,000 in 2010
- Wide variation in transmission rates.
- Uganda 1.1% 6 week transmission, Indonesia 18.2%.
- Green- 6 week transmission (antenatal + birth), purple later.
- *Avert/UNAIDS data.*



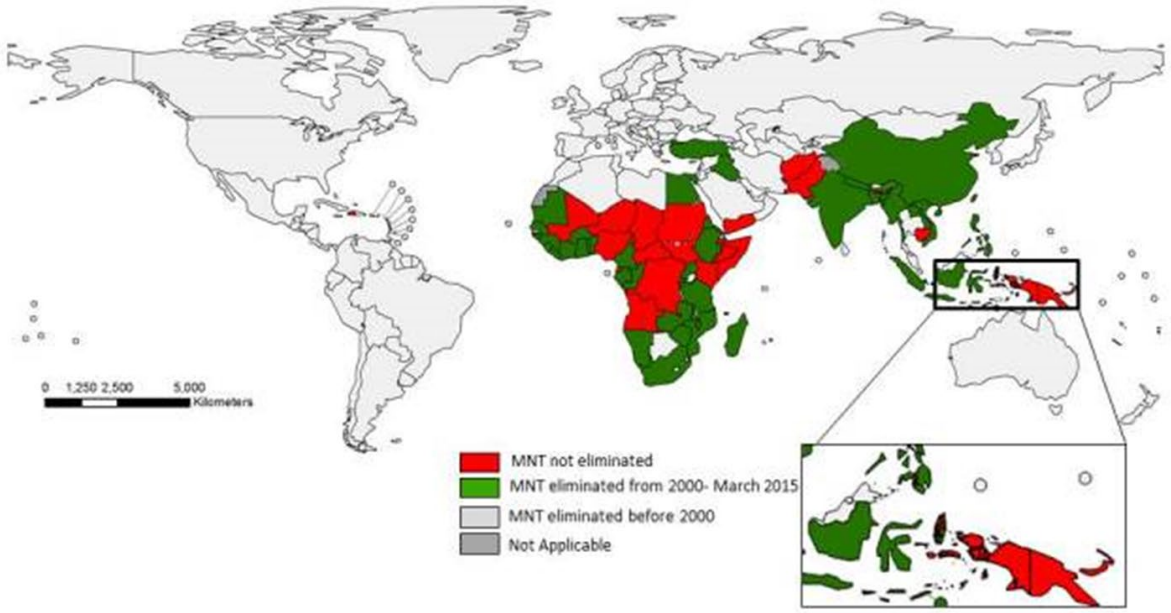
72 hours after birth the serious neonatal infections change.

- In high-income settings strongly associated with prematurity, low birth weight, ventilation, intravenous lines.
- Breastmilk is protective.
- Most common organisms originate from skin, especially staphylococcus.
- Often drug resistant in neonatal intensive care units.

Zerbey Wiki

Neonatal tetanus.

- Was one of the commonest causes of neonatal deaths everywhere.
- Infection occurs with unsafe birthing practices.
- Starts around a week after birth. Over 80% mortality.
- Preventable with maternal immunisation, good midwifery.
- Around 95% reduction since 1980s when over 750,000 children a year died of tetanus before a month old.



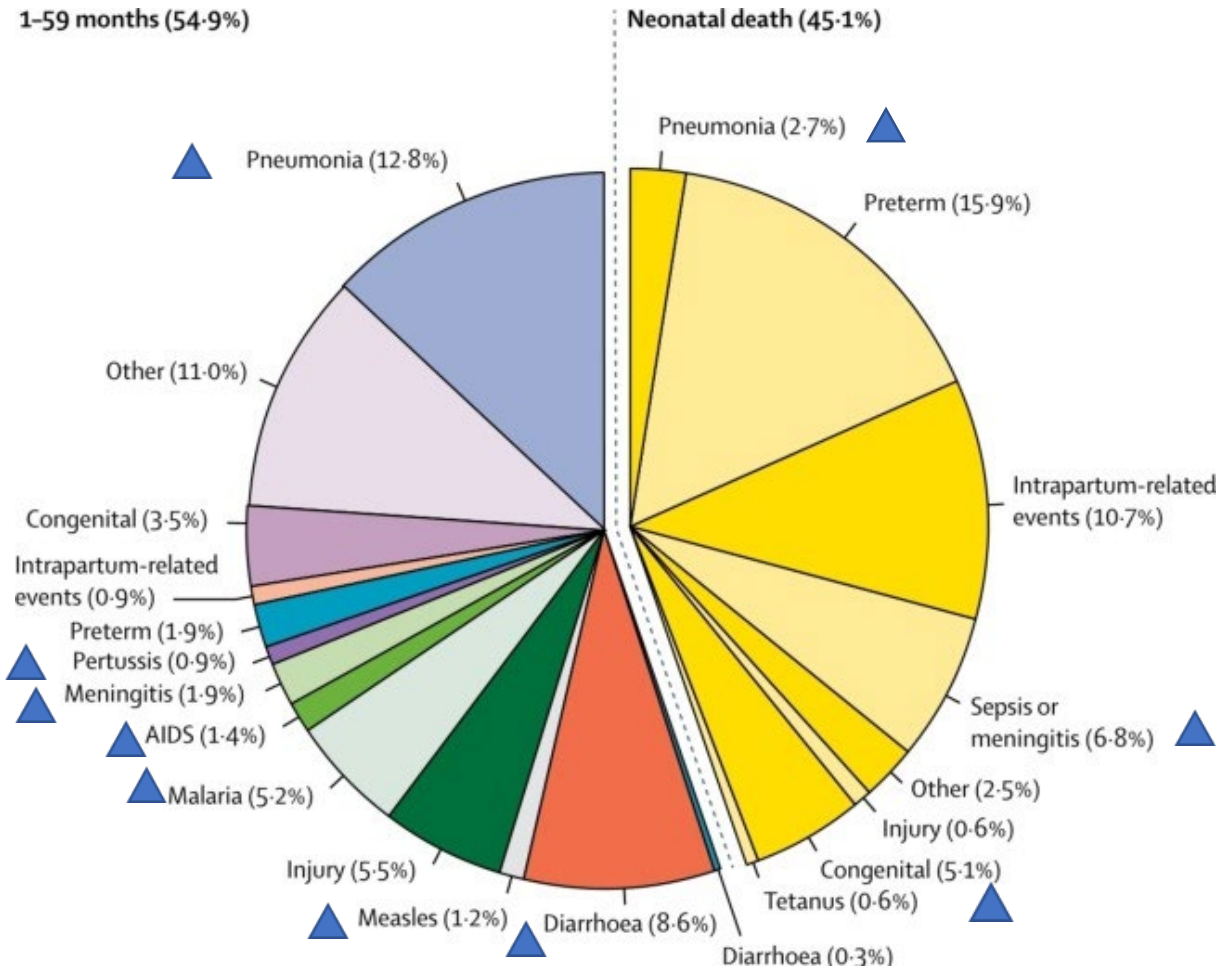
A mother protects her child from infection- but this fades.

- Newborns are very vulnerable to infection- this is reduced by maternal protection.
- Placental transfer of antibodies in the last 3 months of pregnancy.
- What mother is immune to- infection or vaccination.
- This is supplemented by breastmilk.
- The initial breastmilk (colostrum) very rich in antibodies and passive immunity.
- Protection fades within 2 months for many infections, but longer for measles, mumps, rubella (why vaccine at a year).

Attrib. Leonardo da Vinci

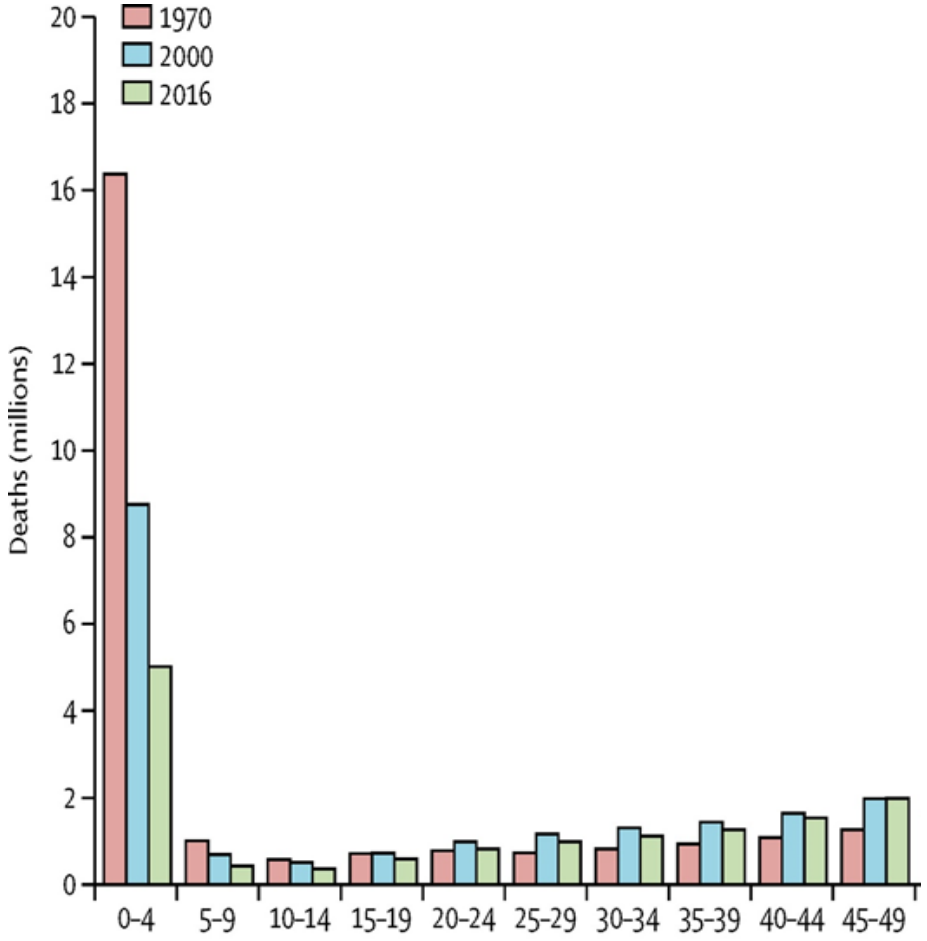
Deaths 1-59 months globally dominated by infections.

- 45% of deaths under 5 occur in the neonatal period: sepsis and meningitis (7%), pneumonia (3%) an important minority.
- After a month globally infections a major part of deaths under 5. *(Liu et al Lancet 2016).*
- Pneumonia around 13%, diarrhoea 9%, malaria 5%.
- Measles, HIV also important.



The 1 month to 5 years period is where sanitation, nutrition and vaccination have had their greatest impact.

- Sanitation and rotavirus vaccine for diarrhoeal disease.
- Measles vaccine, pneumococcal vaccine, whooping cough, diphtheria for respiratory.
- Meningococcus A B C W X, Y, *Haemophilus influenzae* (Hib), mumps, pneumococcus for meningitis.
- Remarkable drops in UK and global child mortality.

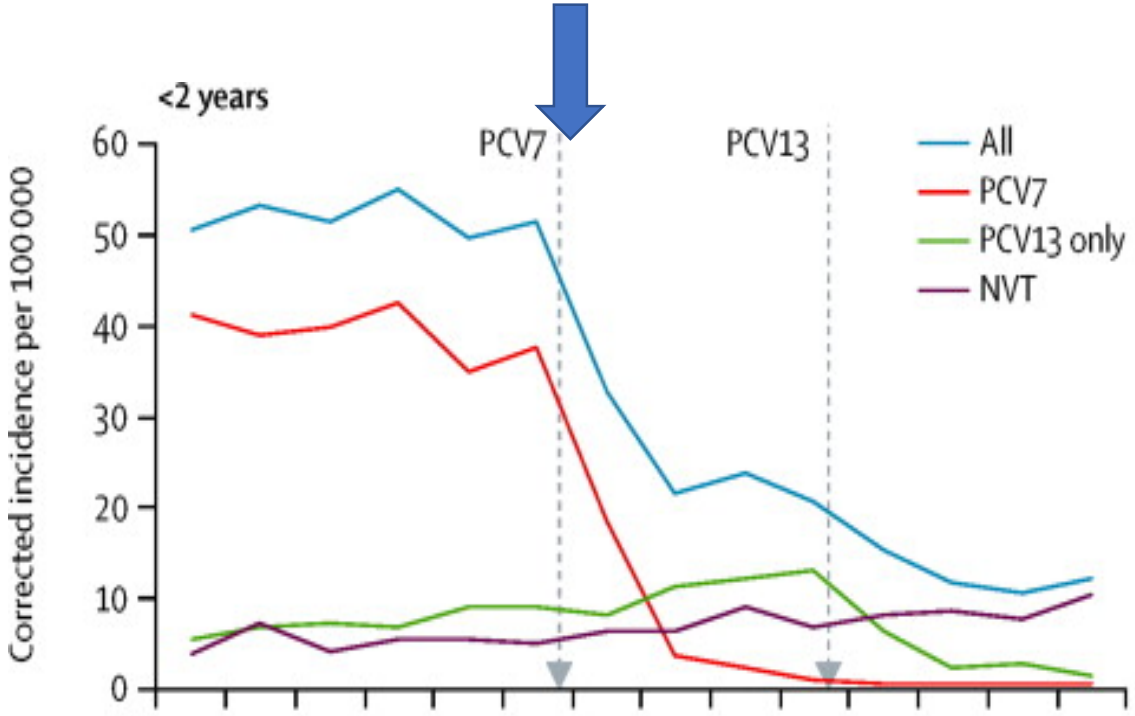


Global Burden of Disease Study 2017

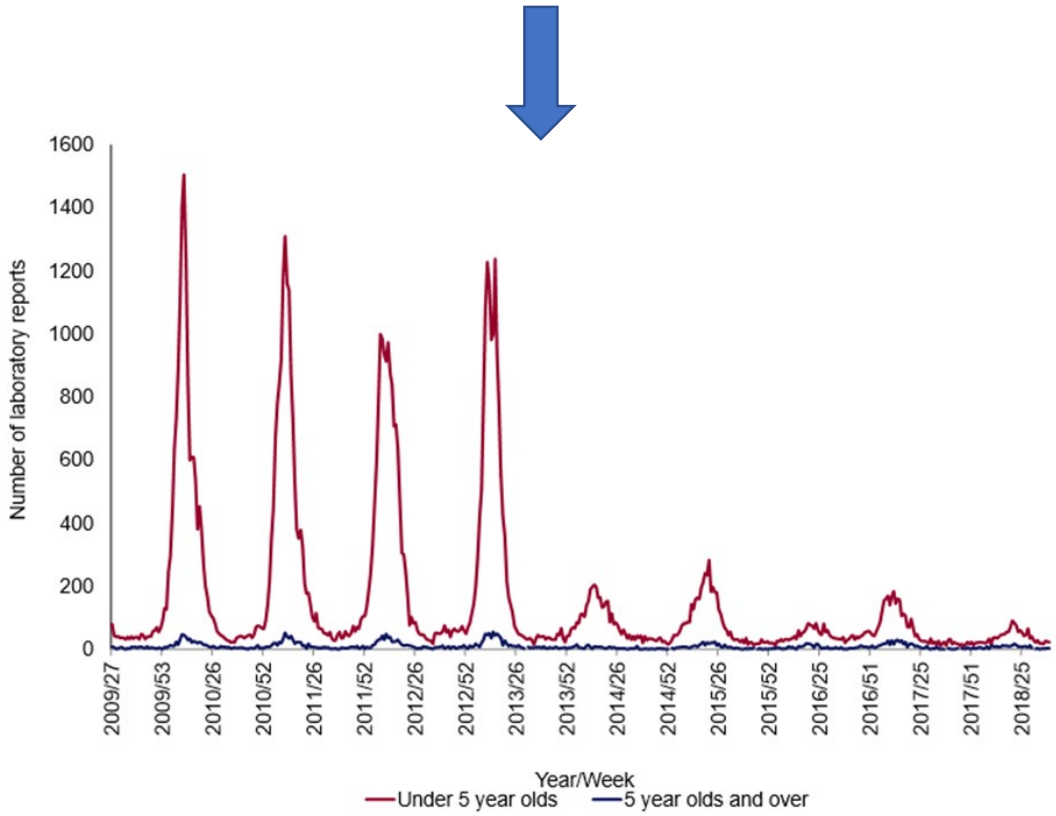
Effect of vaccines in children <5 years in UK. Pneumococcus a major cause of pneumonia, sepsis, meningitis; Rotavirus of diarrhoea.

(PHE E&W data- *Waight P et al Lancet ID 2015*).

Pneumococcal vaccine, age <2, 2000-15.

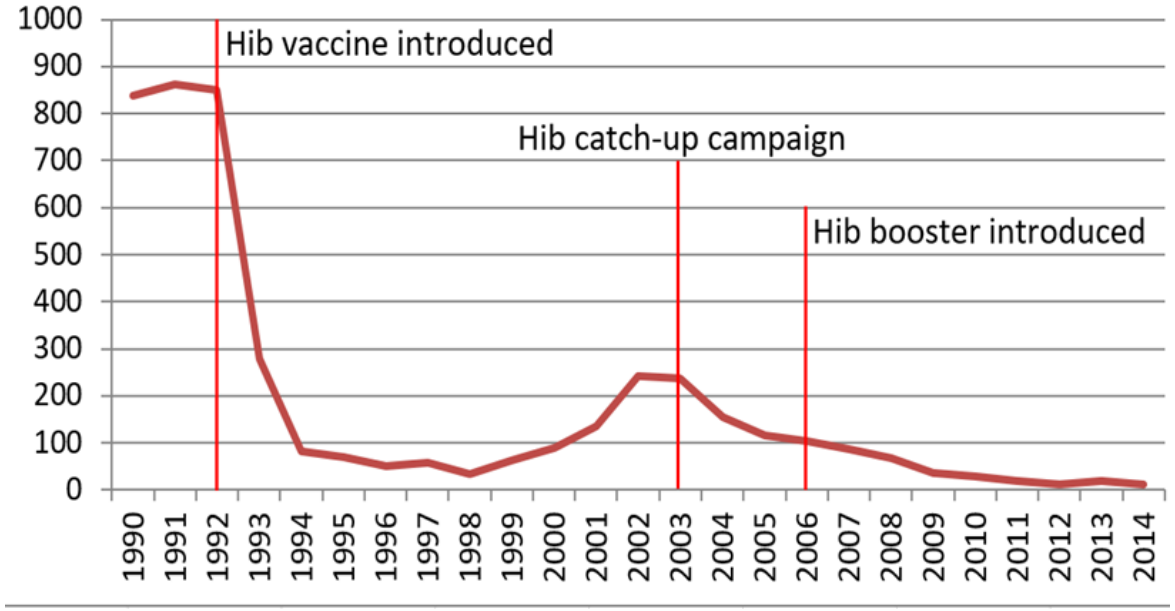


Rotavirus vaccine, <5, 2009-18

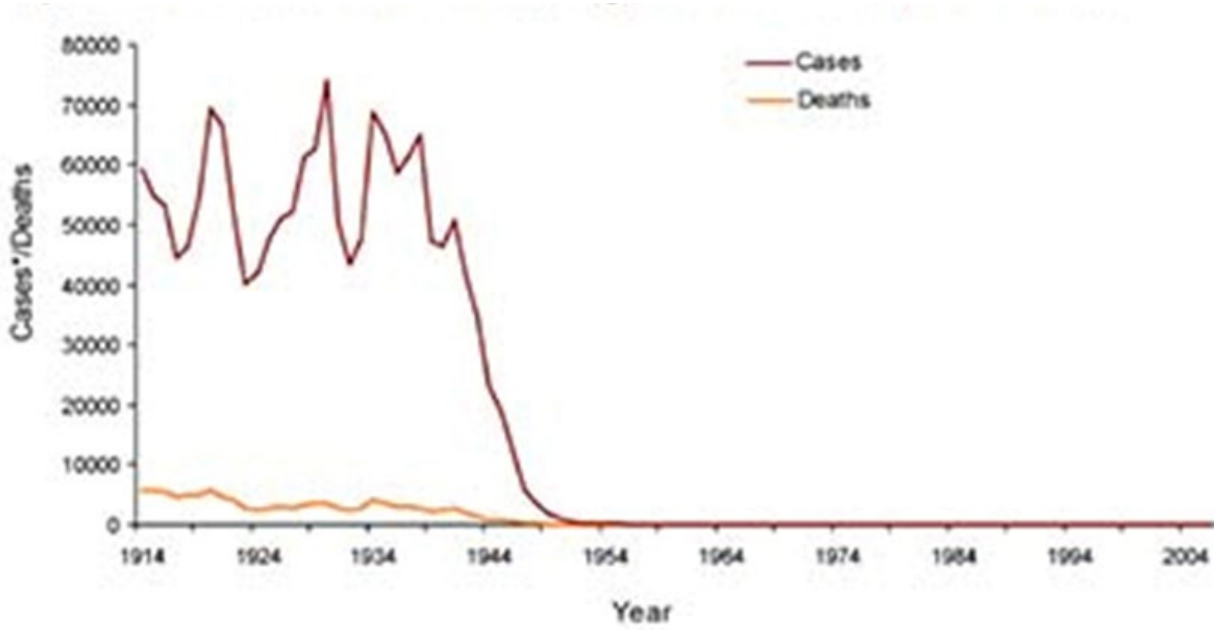


Hib was commonest cause of meningitis under 4 until 1990s, diphtheria a major cause of disease until 1940s.

Hib, 1990-2015

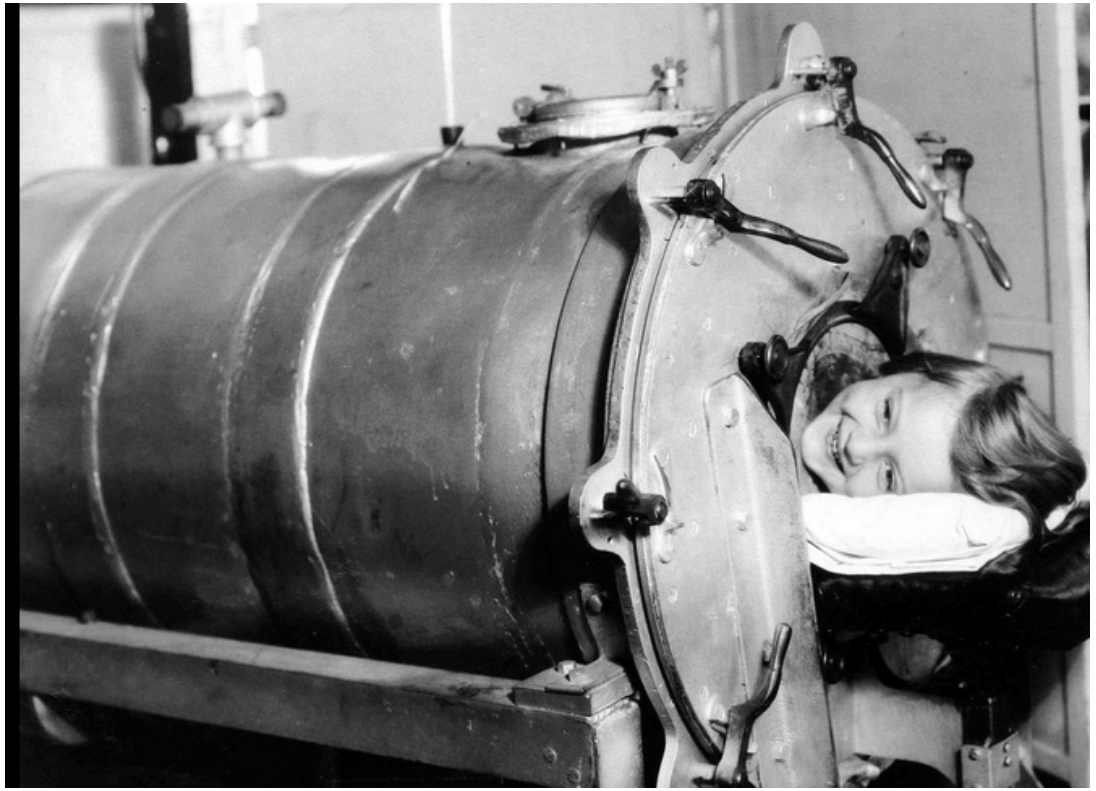


Diphtheria, 1914-2008



Other major infections that killed children in the UK which are now shadows of their former selves.

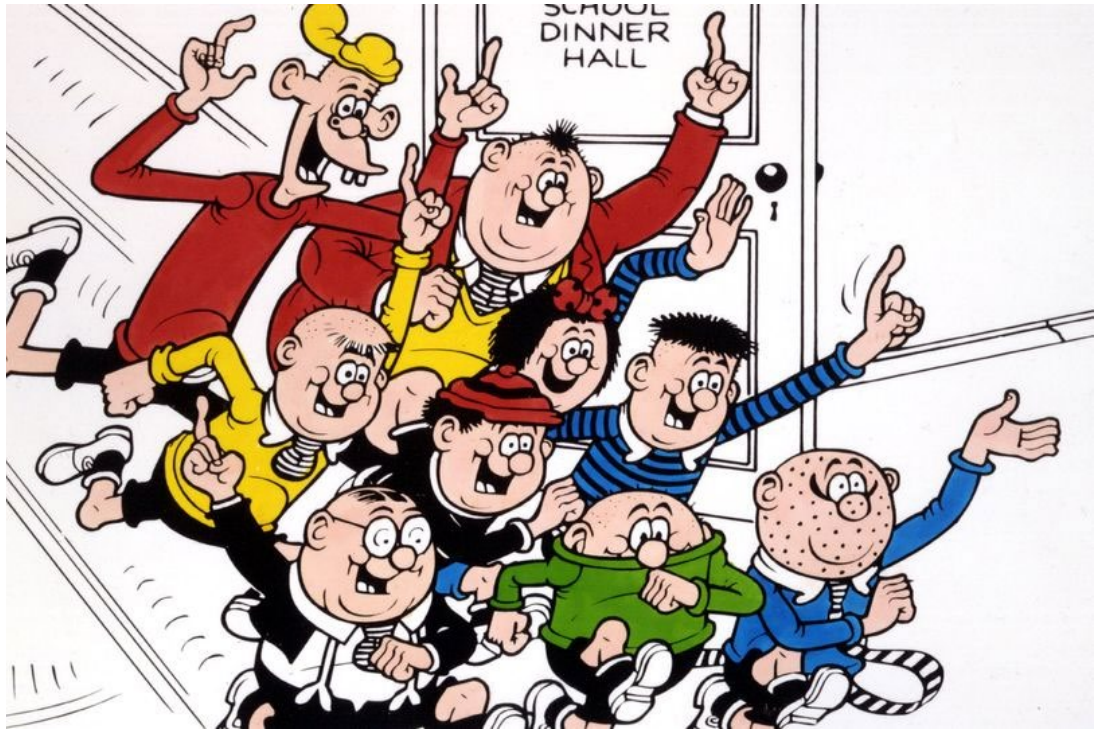
19th C
Cholera
Typhoid
20th C
TB
Rheumatic fever
Polio
Whooping cough
Measles
21st C
Meningococcus A, B, C, W



Polio. Children's Hospital, Boston Mass.

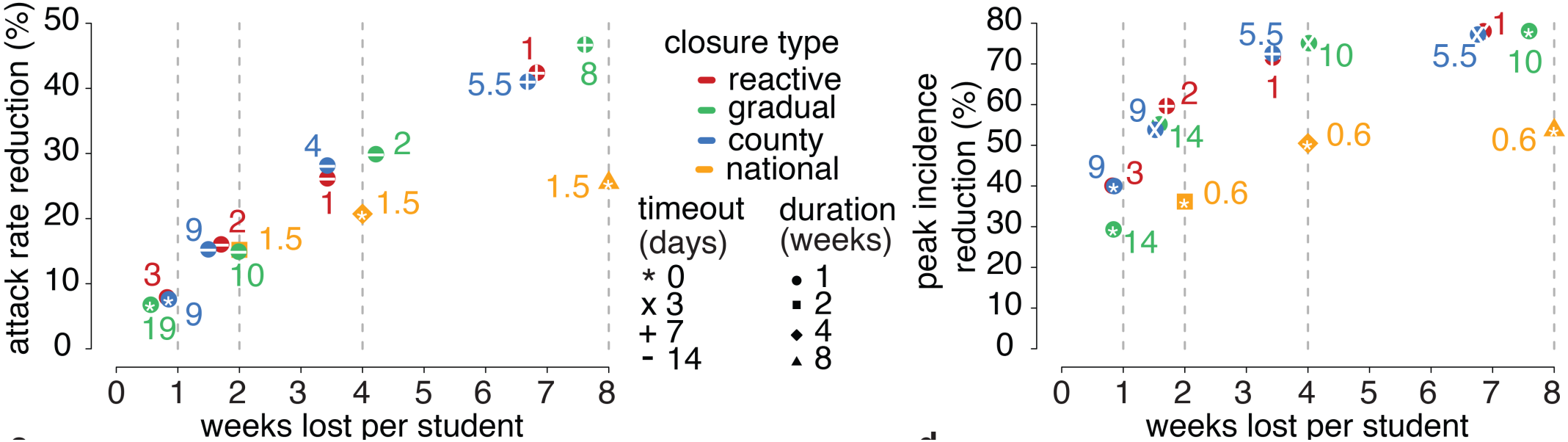
“Then the whining schoolboy, with his satchel
And shining morning face, creeping like snail
Unwillingly to school.”

- This is not to say children do not still get many infections.
- School is one of the best places to catch whatever is going.
- The immune system learns a lot, whether or not the child does…
- The next great opportunity is often university with ‘freshers flu’.



Closing schools in epidemics.
Can reduce the peak, and may reduce the attack rate.
Trade-off between how long closed, how much effect.

A model for influenza in UK. Fumenelli et al 2016.



“And then the lover,
Sighing like furnace…”

- Certain infections are passed on sexually.
- They will occur, if at all, after sexual debut so tend to be diseases of young adults.
- Some are common, but no more than a nuisance, like genital warts.
- Some are unpleasant but rarely dangerous including herpes simplex and gonorrhoea.
- A few can be life-threatening, including HIV, syphilis and cancer-causing papilloma viruses.

The Kiss. A. Rodin 1903.
(P Weissenbacher)

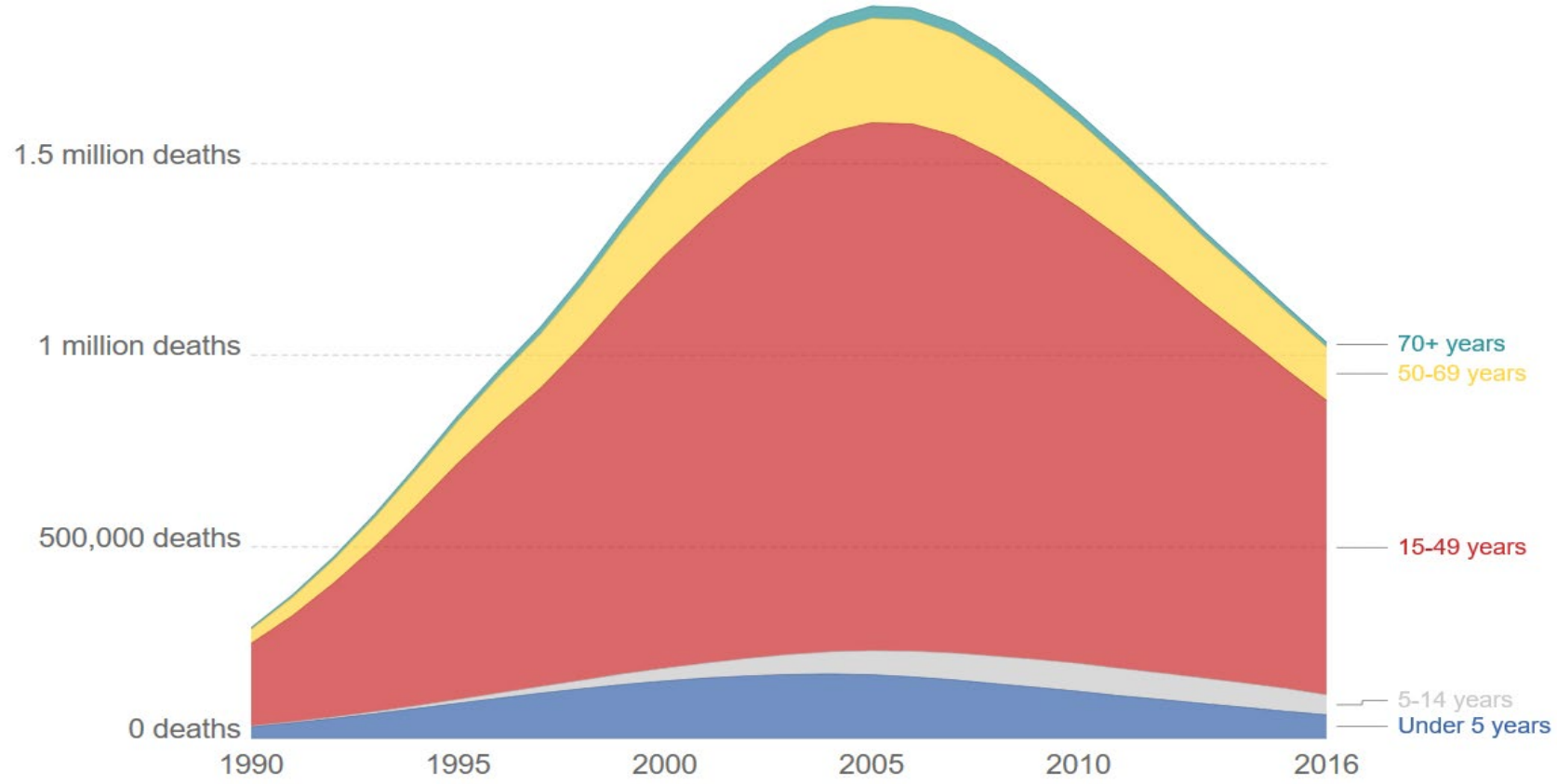
Between the 1980s and 2010s HIV one of the most severe new threats to health in our lifetime spread. 35M deaths to date.

Wikimedia.

From *The Ward* by Gideon Mendel.
Broderip ward, London.

HIV deaths by age. 1990-2017. Around 1.8 million people became newly infected with HIV in 2017.
940 000 people died from AIDS-related illnesses (UNAIDS).

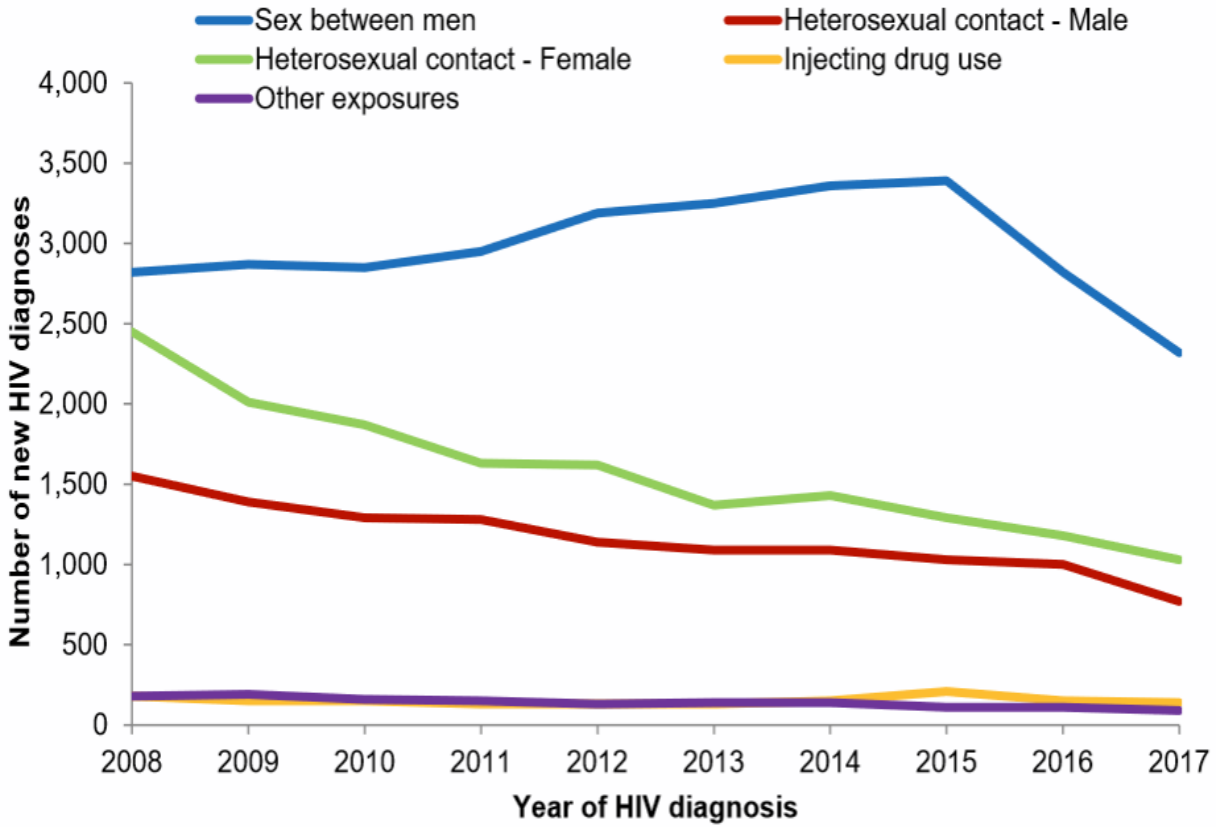
(IHME/Our World in Data)



In high-income countries HIV new cases dropping, deaths rare. UK experience.

- In UK incidence HIV now dropping.
- People with HIV on treatment have a normal life expectancy.
- Both due to effective drugs.
- In both male-male and male-female contact, if people have viral load controlled risk of transmission effectively zero.

Rodger et al Lancet 2019

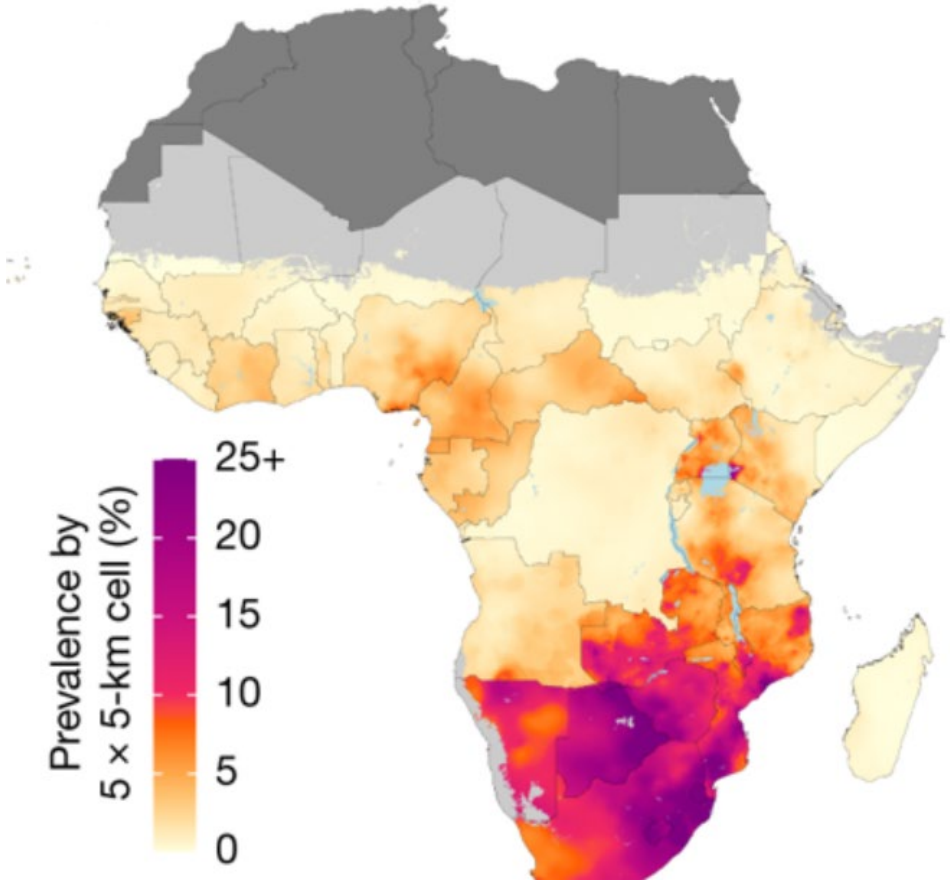


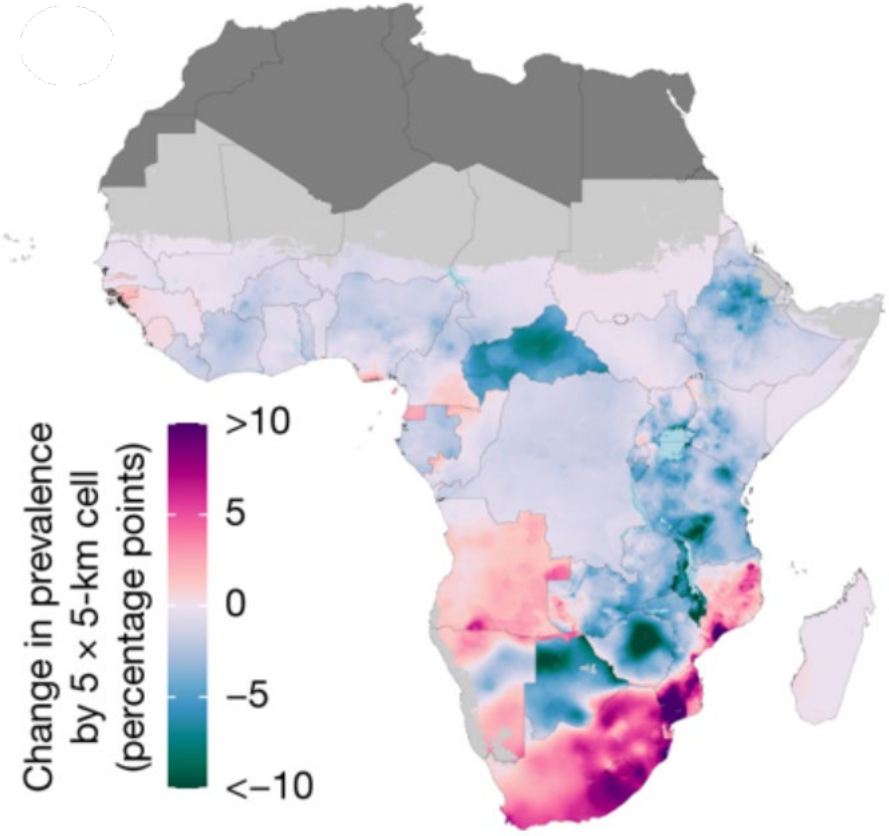
**Adjusted for missing route of exposure*

PHE 2018.

HIV prevalence 2017 (L) and change 2000-17.

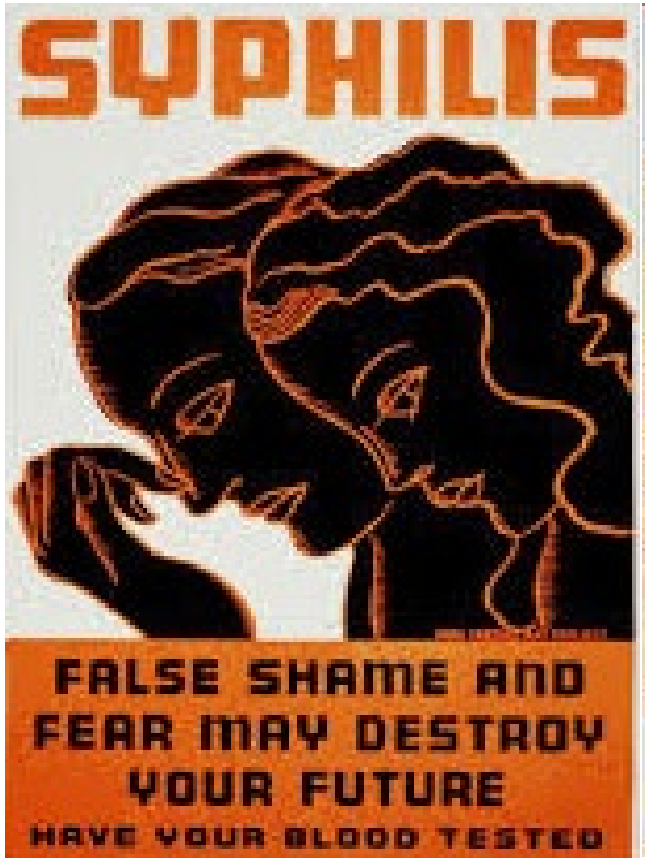
Dwyer-Lindgren L et al GBD Nature 2019.





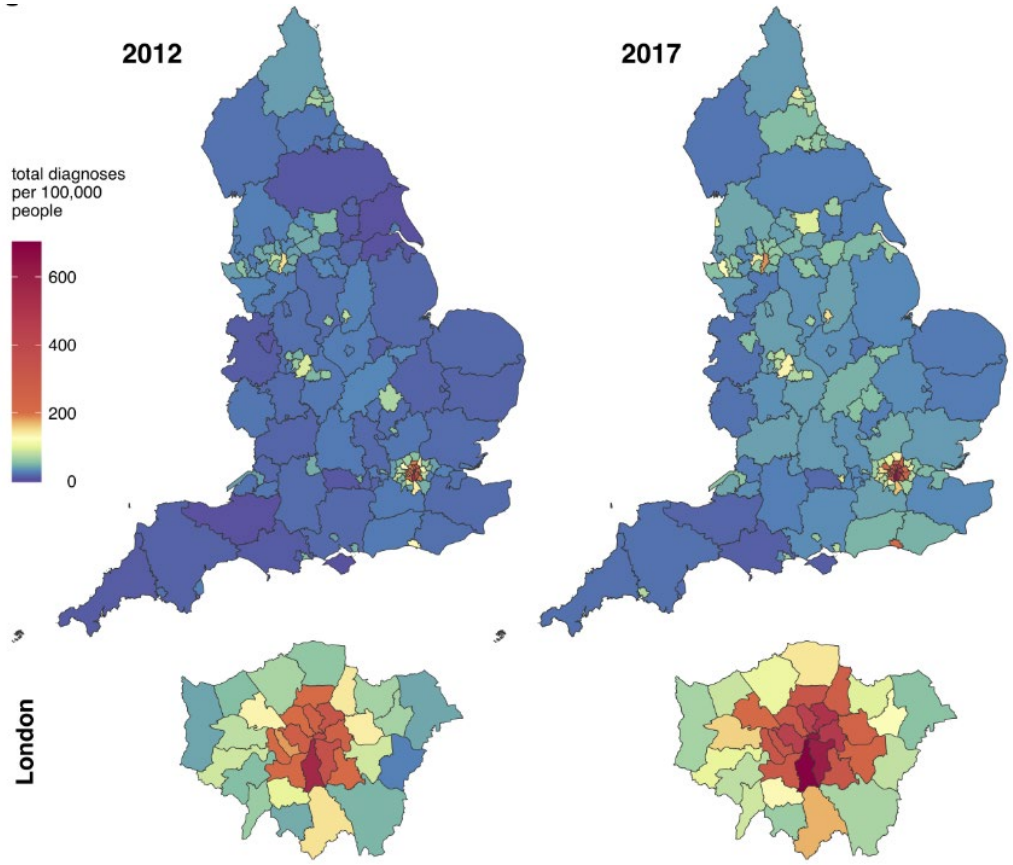
Syphilis.

- When syphilis arrived in Europe around 1495 frequently fatal.
- It spread very rapidly.
- Effects included dementia, mental illness, stroke, heart attack, bone, skin disease.
- Around 10% of adult male Londoners in 1919 had it.
- Penicillin collapsed the epidemic, and prevents complications.



Gonorrhoea

- Much less serious than HIV or untreated syphilis. But unpleasant, occasionally serious.
- Especially around childbirth.
- Quite common; around 35,000 cases a year in UK, 2nd most common reported STI.
- We have a serious problem with multi-drug resistant *N. gonococcus*.
- We are going to need new antibiotics.



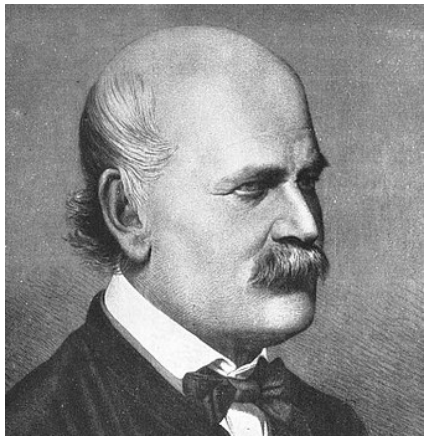
Whittles L et al 2018

Infections in pregnancy.

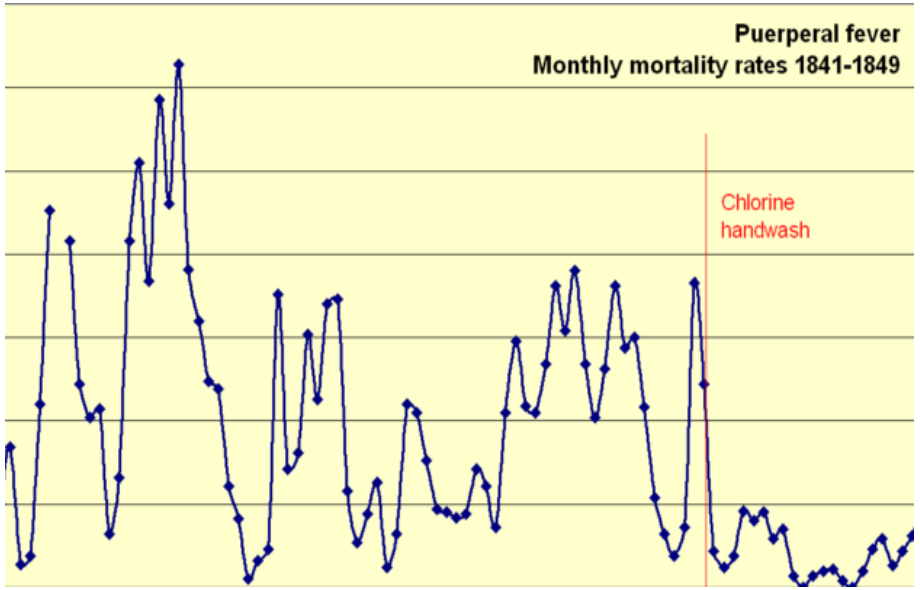
- After birth a serious risk of sepsis.
- A few infections are specific to pregnant women.
- Infections can be significantly more severe for a women in pregnancy.
- Several infections which may be minor for mother can cross the placenta and harm the child.

Gustav Klimpt. Hoffnung I 1903

Infections specific to pregnancy.



- Around 10% of maternal deaths globally are due to infection.
- Puerperal sepsis, bacterial infection soon after birth, most common.
- Poor medical/midwifery practice most common cause.
- Antisepsis, antibiotics key.
- Ignaz Semmelweis, a Hungarian physician demonstrated that hand sepsis by doctors substantially cut infection rates.
- He was committed to an asylum by his medical peers in 1865, and died 2 weeks later (age 47) of sepsis 2^{ry} to mistreatment.



Vienna Maternity Institution 1841–1849

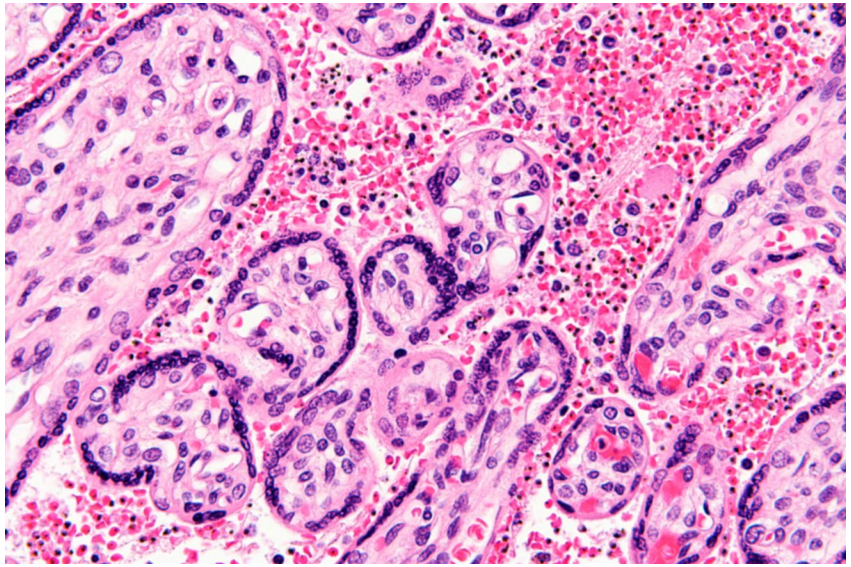
Several infections are more severe if caught in pregnancy, for others pregnant women are more susceptible.

- More severe include:
- Influenza. Vaccination important.
- During the pandemic 1918, maternal mortality was 27% and in the pandemic of 1957 50% of deaths among reproductive-age women occurred in pregnancy.
- Hepatitis E. Around 1% mortality but up to 20% in pregnancy.
- Herpes simplex, malaria.

Pregnancy also makes women more susceptible to certain infections- eg Listeria, probably HIV, malaria.

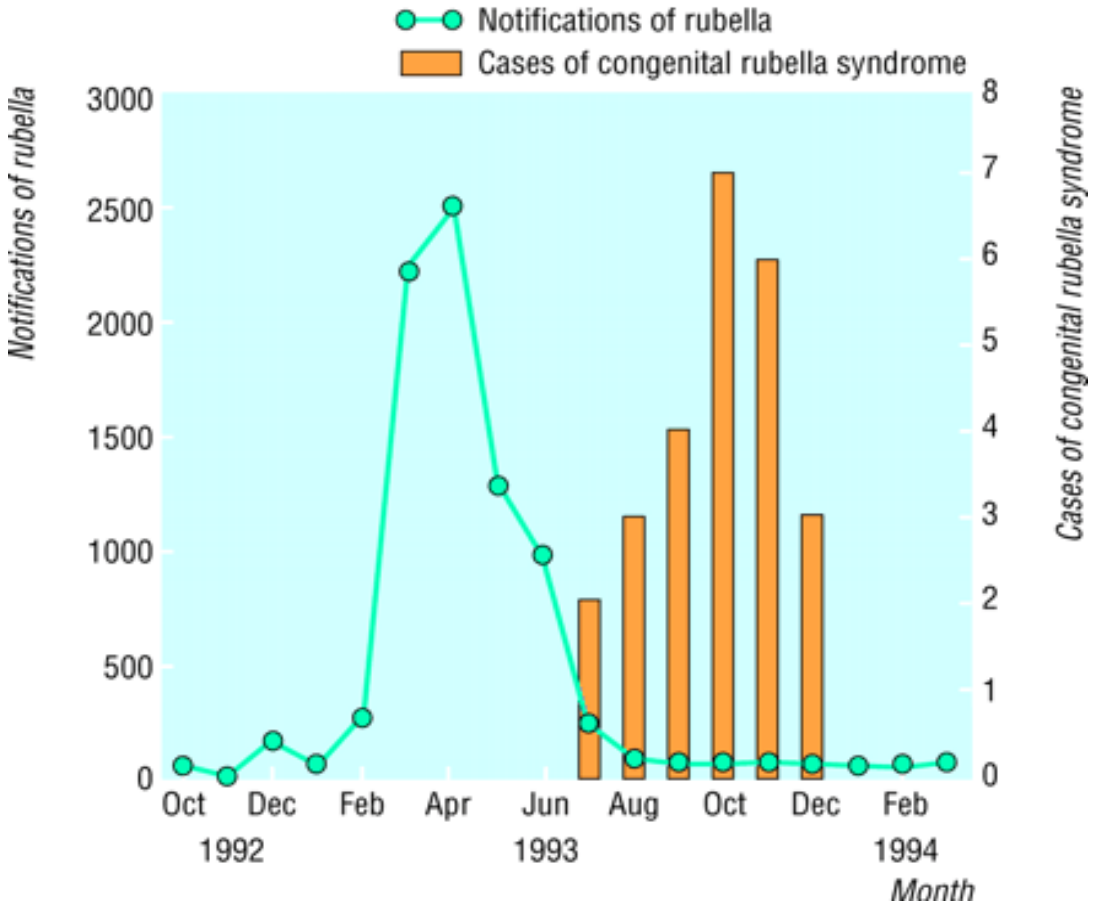
The placenta is a specific target of a few infections. But it mainly protects the baby against infections.

- Globally the most important placental infection is malaria.
- A specific ligand in malaria binds to placentas.
- Placental malaria causes severe anaemia in mothers and small babies.



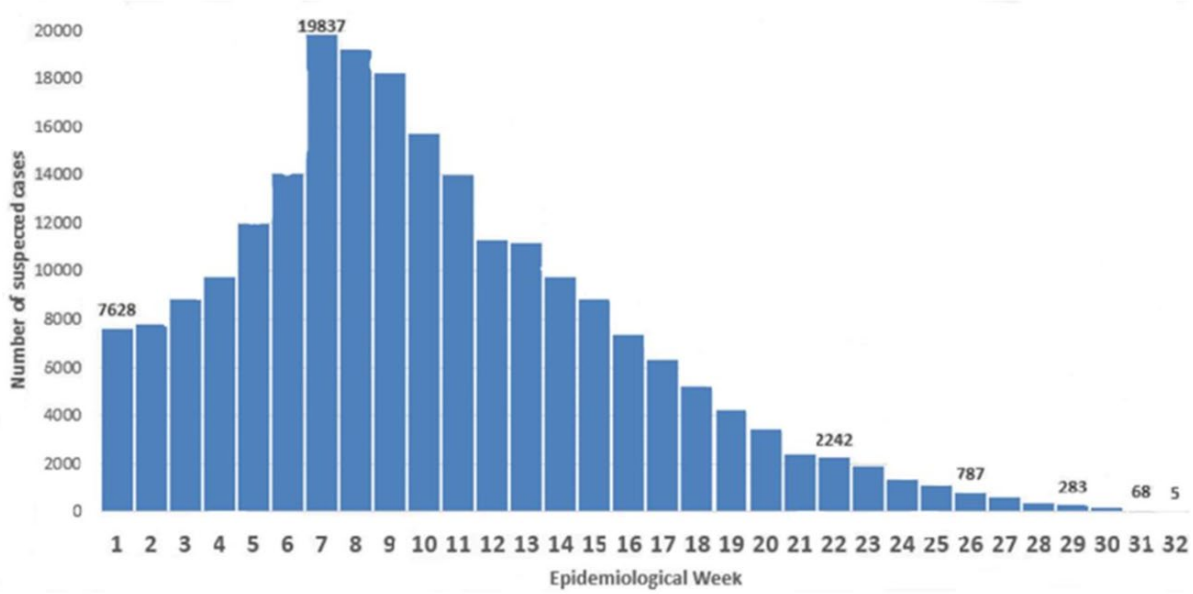
Rubella (German measles) an example of an infection that can cross the placenta and harm the baby in utero.

- Generally a trivial infection except in pregnancy.
- Congenital rubella syndrome can (sometimes) cause loss of the pregnancy or severe abnormalities.
- Highly effective vaccine, now part of MMR.
- A very disrupted vaccine programme can increase average age of infection.
- Other important infections include chickenpox, CMV, toxoplasmosis.



Panagiotopoulos T et al BMJ 1999

Zika: Brazil 2015. Substantial risk of foetal abnormality.



The world of work.

- Infections can be associated with particular work environments, mainly agriculture and healthcare.
- Fungal infections of the lung from working with crops.
- Animal husbandry can expose us to zoonotic diseases.
- Industrial work can damage the body's natural defences especially of the lung. Pneumonia and TB in miners.
- Healthcare workers. Many infections: influenza, TB, SARS, Ebola.

The Gleaners. J-F Millet 1857

Brucellosis. Farmers, vets, dairy workers.

- A disease of cattle, goats, sheep, pigs, camels and other mammals.
- Eliminated in UK in 1979, occasional reintroductions.
- Can cause serious infection in humans.
- Farmers, vets, dairy workers, abattoir workers, microbiologists are at particular risk.
- Still common in Middle East.
- Can catch from unpasteurised milk.

Goat herd milking, Malta.
Sir David Bruce (Wellcome Collection)

TB and pneumonia in miners.

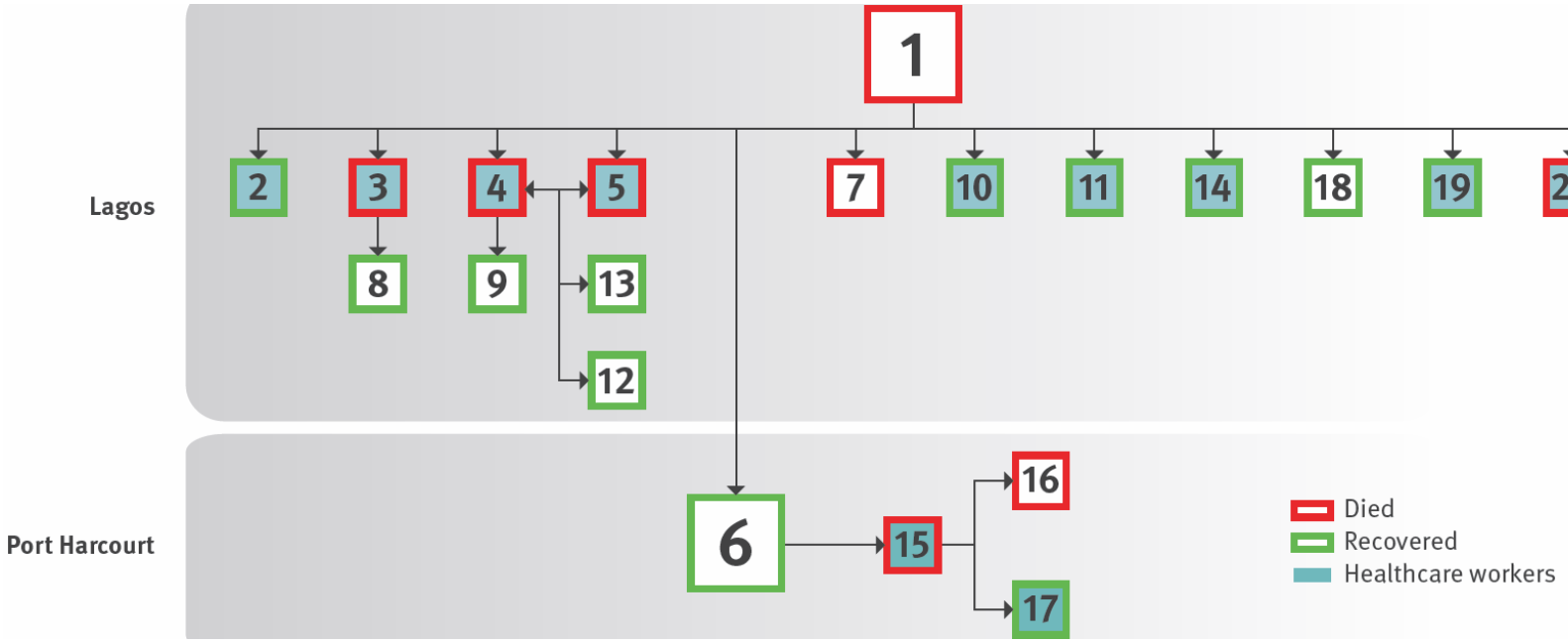
- A strong link between damaged lungs due to silica and other dust, and TB and pneumonia.

- Multiple forms of mining lead to higher rates including coal mining, gold mining, copper mining.

The initial incidence of Ebola in HCWs in West African epidemic estimated around 8-10% per person per year. Over 70% died. There are currently many cases in DRC despite a vaccine.

Ebola virus disease outbreak in Nigeria, July-Sept 2014.

F O Fasina. Eurosurveillance



Sylvain Cherkaoui/Cosmos for MSF

The same infection at different ages can produce a very different disease.

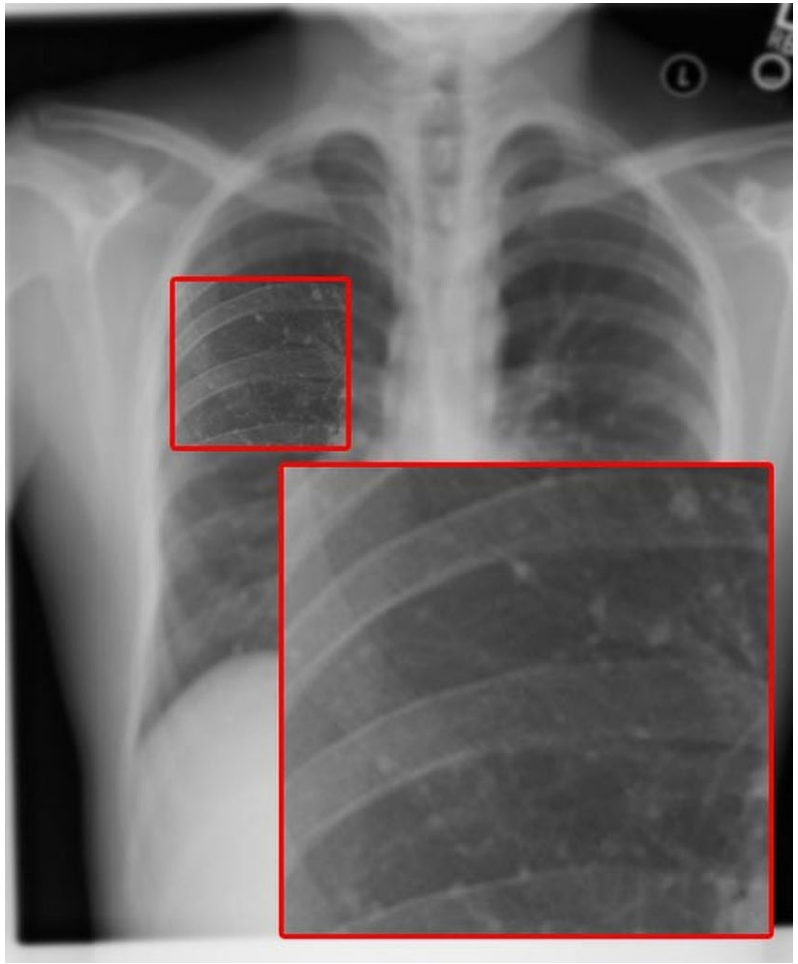
- ‘Childhood diseases’ in adults can be more severe: example include chickenpox, mumps, Hepatitis A, EBV.

- Some diseases can present in multiple ways depending on age- an example is malaria.

G. Jakobodes. *The Favorite*. 1890.

Chickenpox (varicella).

- In children unpleasant, rarely serious.
- Adults complications include varicella pneumonia.
- Adults at significantly higher risk of death (although still very low).
- Pregnant women, immunosuppressed adults greatest risk.



Case courtesy Radswiki, Radiopaedia.org

Mumps.

- Generally relatively mild in children, although rare serious complications including meningitis, meningoencephalitis.
- Once go through puberty severe complications more common.
- In boys/men orchitis (testicular inflammation) 15-40%. In some cases decreased fertility. Mentioned by Hippocrates in 400BC.
- In girls ovarian inflammation less severe.

NHS

Hepatitis A.

- Viral hepatitis, faeco-oral route. Very common. In low-income settings >90% have in childhood.
- Infected children under 6 years of age do not usually experience noticeable symptoms, and only 10% develop jaundice.
- Among older children and adults, infection causes more severe symptoms, with jaundice occurring in more than 70% of cases.

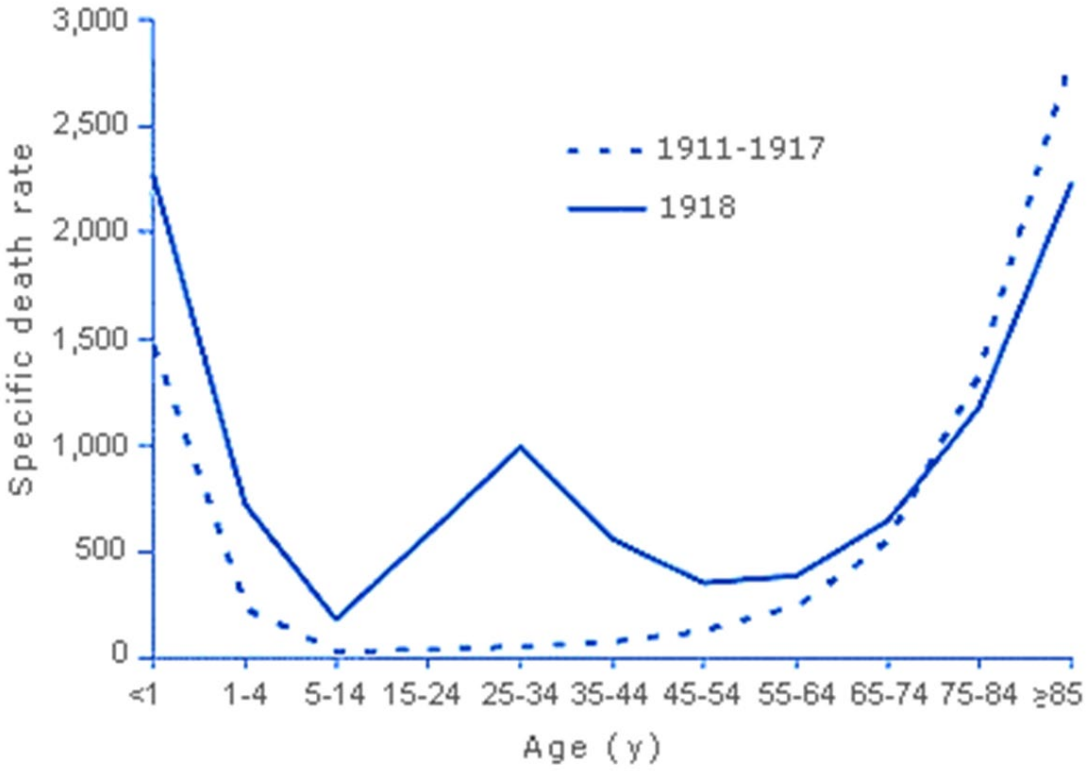
Epstein-Barr virus (EBV, glandular fever, infectious mononucleosis).

- EBV is usually a trivial infection in childhood, conferring immunity.

- Those who first encounter it as young adults can have significant symptoms (‘glandular fever’) in 35-50% of cases. Fatigue can be prolonged.

Gustav Klimt *Der Kuß (The kiss) 1908*

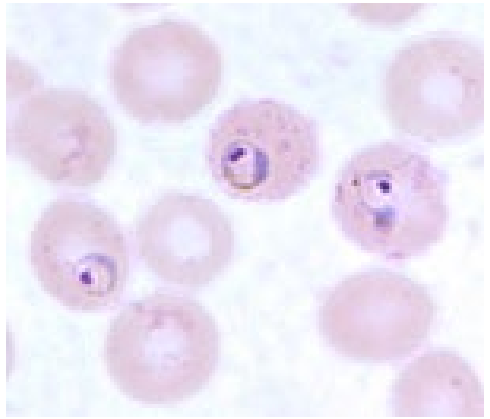
New epidemics can behave differently.



1918 H1N1 influenza and age (CDC).

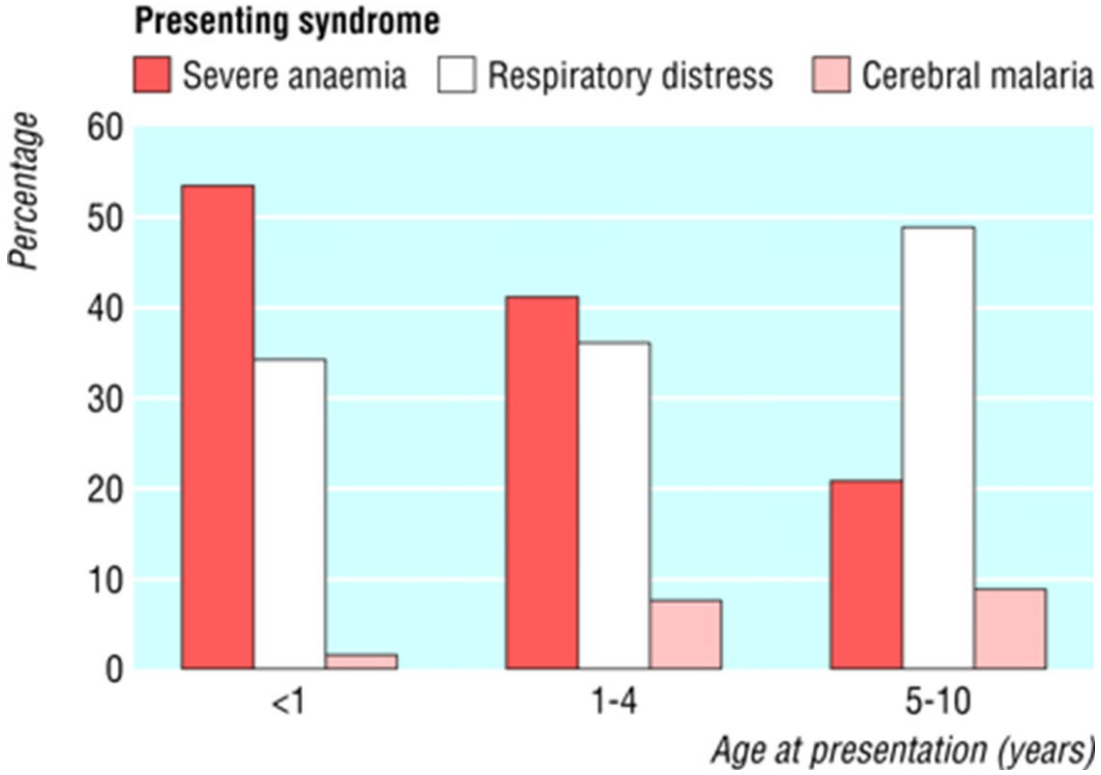
- ‘Flu usually most dangerous in the very young and very old.
- 1918-19 influenza pandemic had a major peak of mortality in young adults.

Severe falciparum malaria by age.



- Same parasite species, same human species.

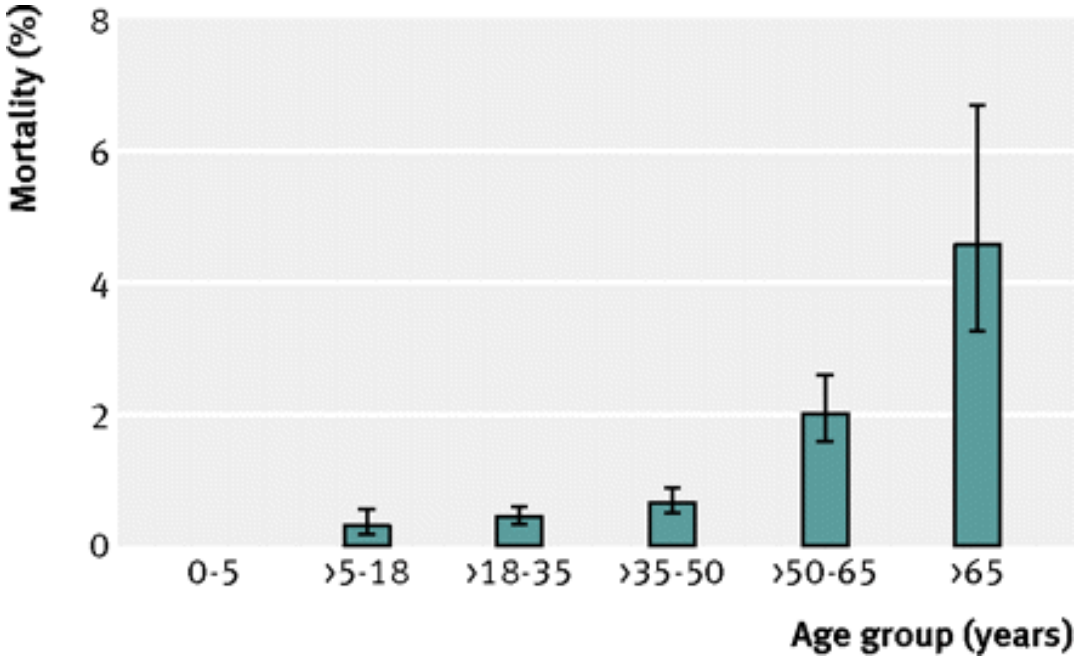
- In very young children: anaemia most common.
- In older children: cerebral malaria, acidosis, bacterial co-infection.
- In adults: cerebral malaria, renal failure, lung injury.



Severe malaria by age: Yemen (al-Taiar et al, BMJ)

Diseases which kill many children in low-income settings can be biologically more dangerous to older adults.
Poverty and age- the two major risk factors for most infections.

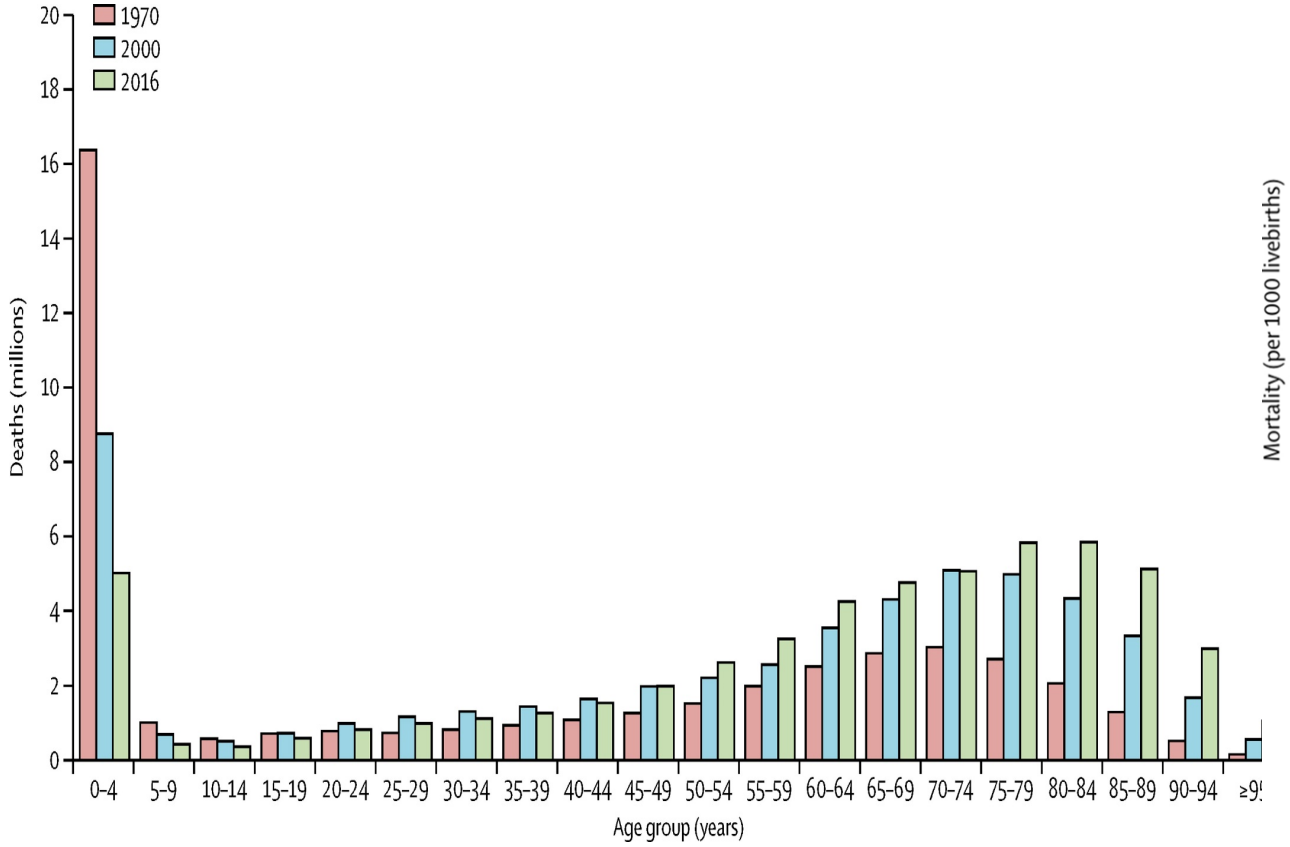
- Malaria kills around 435,000 people a year (WHO 2018).
- Children <5 constitute 61% of the deaths.
- Mortality from malaria in Africa, has fallen by 71% in children under five since 2000.
- In the UK, malaria mortality rates much higher in older adults.

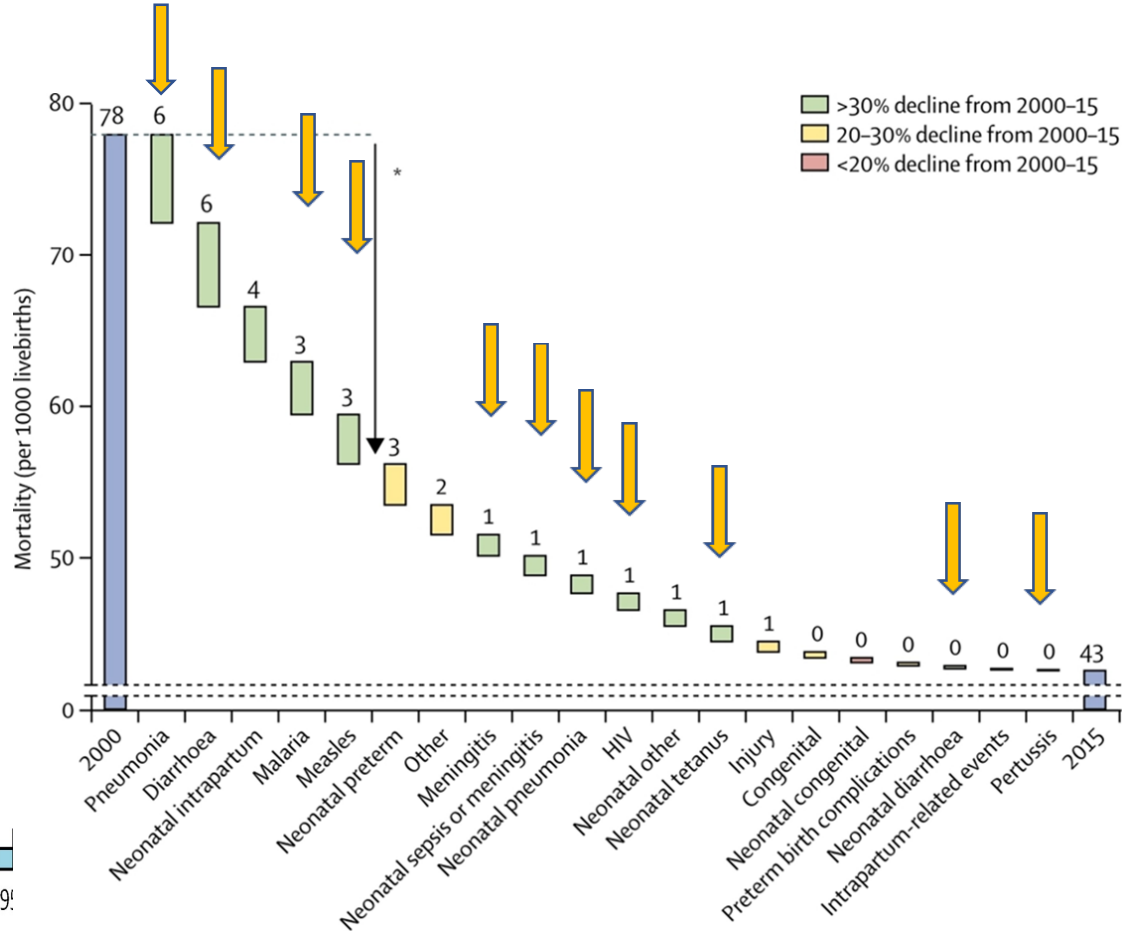


Malaria mortality by age, UK data.
Checkley et al BMJ.

Reduction in child deaths (absolute) by age globally- reduction in infectious diseases a major contribution.

(*Global Burden of Disease Study (GBD), Lancet 2017, Liu et al Lancet 2016.*)

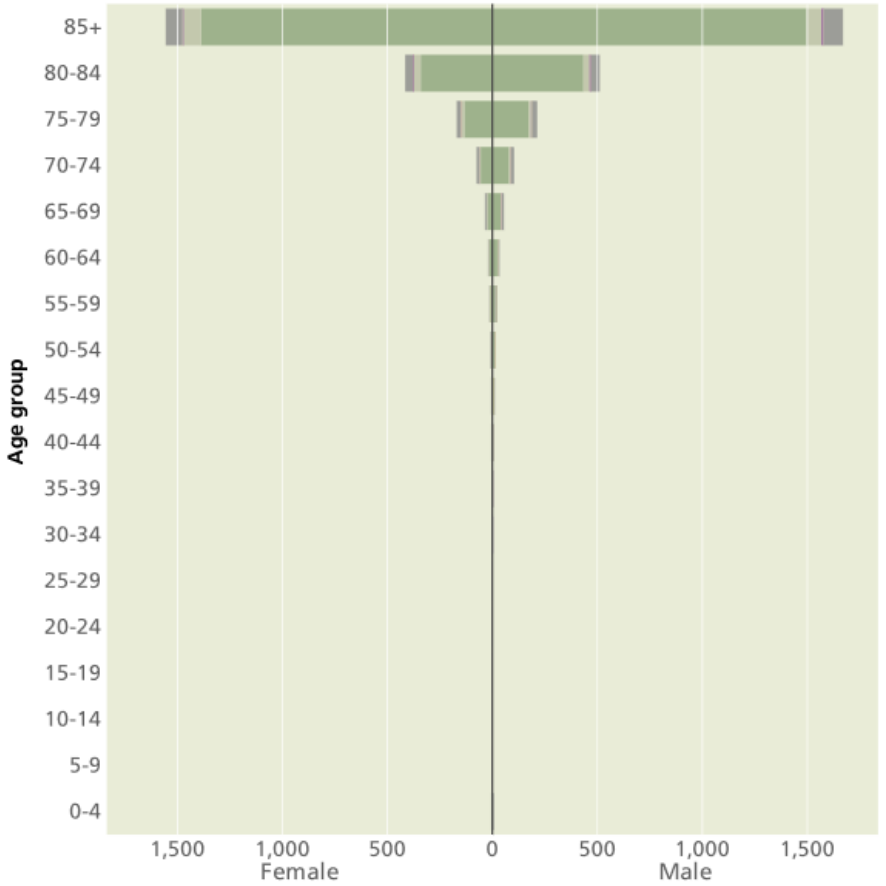




In high income settings mortality from all infections heavily skewed to older ages. The numbers will go up.

- Infections are a significant cause of direct mortality: pneumonia, sepsis, urinary tract infections.
- This will rise as the population >80 rises.
- Infections as an indirect cause of death underappreciated.
- Frequently complicates other conditions of older age.

Average annual mortality from infections by age, /100,000. (CMO)

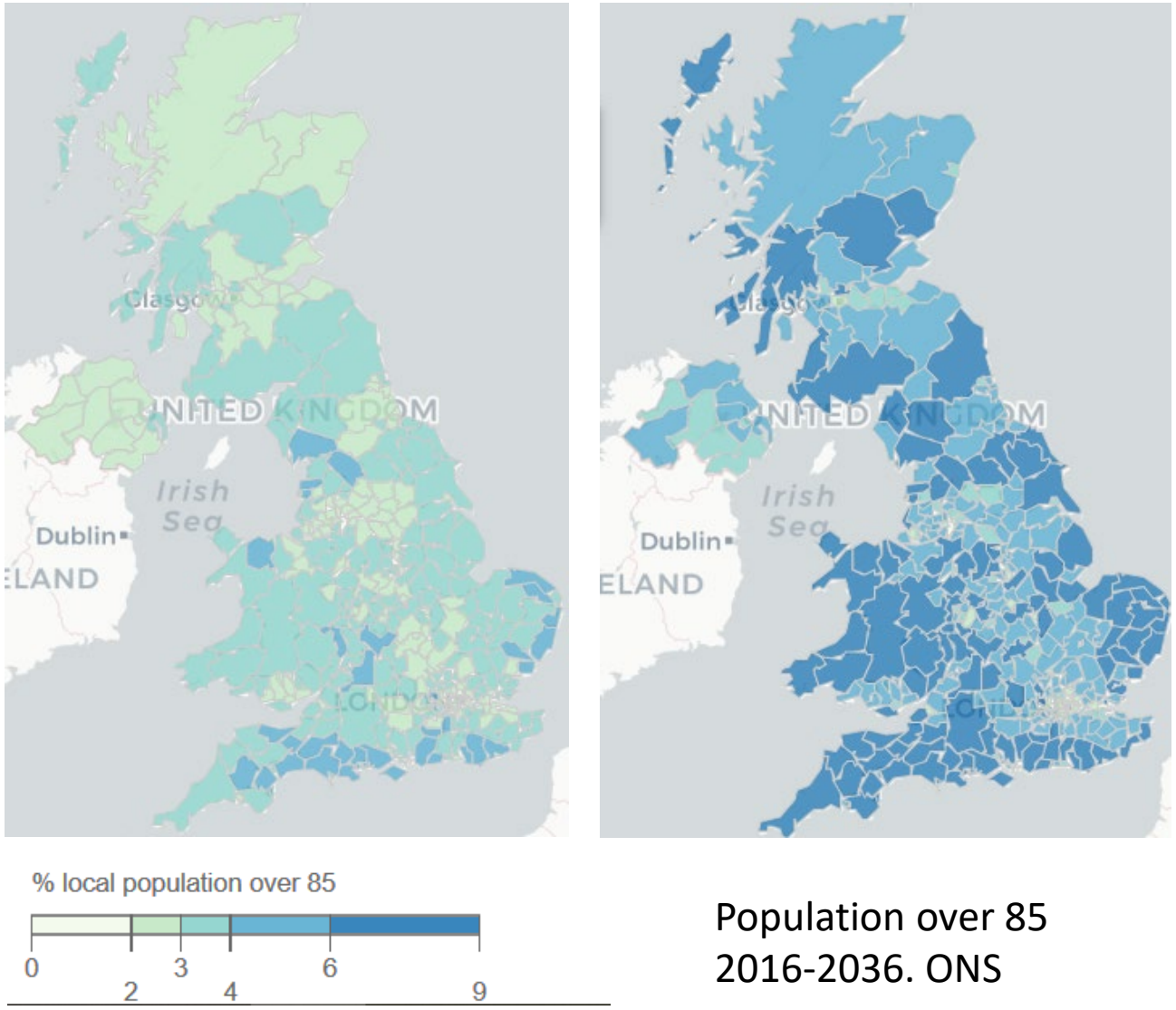


Infections of older age matter, and will matter more…

UK age over 80

(thousands, ONS projections)

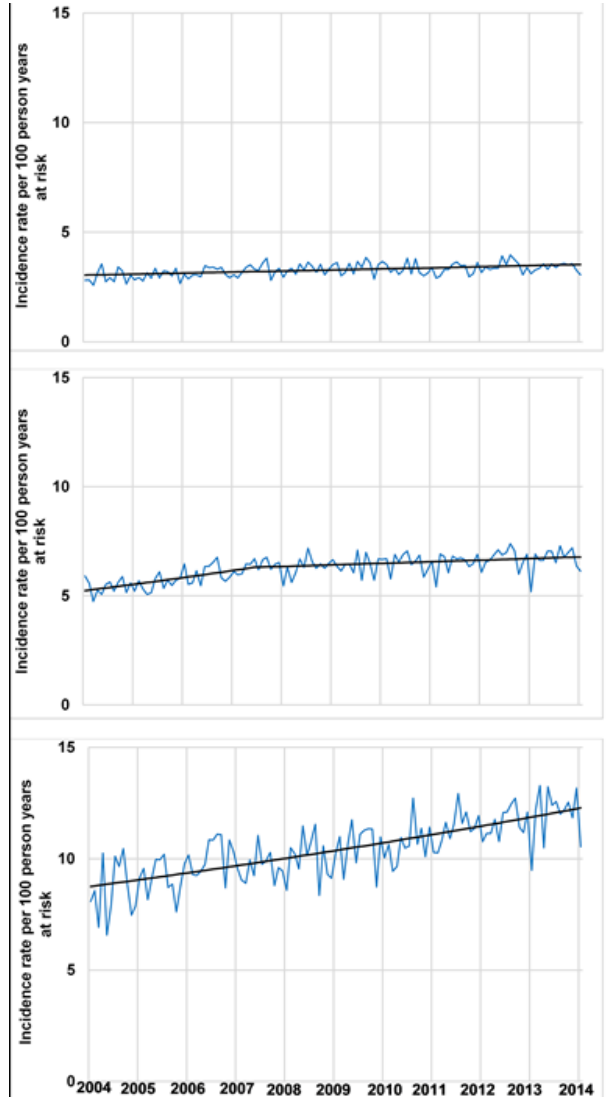
- 2018 3,293
- 2028 4,499
- 2038 5,638
- 2048 7,241



Population over 85
2016-2036. ONS

Urinary tract infections and the elderly. UK data.

- Commonest bacterial infection in those >65. Over 10 years around 20% will have at least 1 infection.
- A wider range of bacteria than younger people, *E. coli* around 50%.
- Higher risk of converting to sepsis as we age.
- UK bloodstream *E. coli* infections rising. 22% increase 2013-17.
- Sepsis has significant mortality- which also increases with age.
- Data 2004-14 from males in UK: incidence / 100 person years. *Ahmed et al PlosOne 2018.*



65-74

75-84

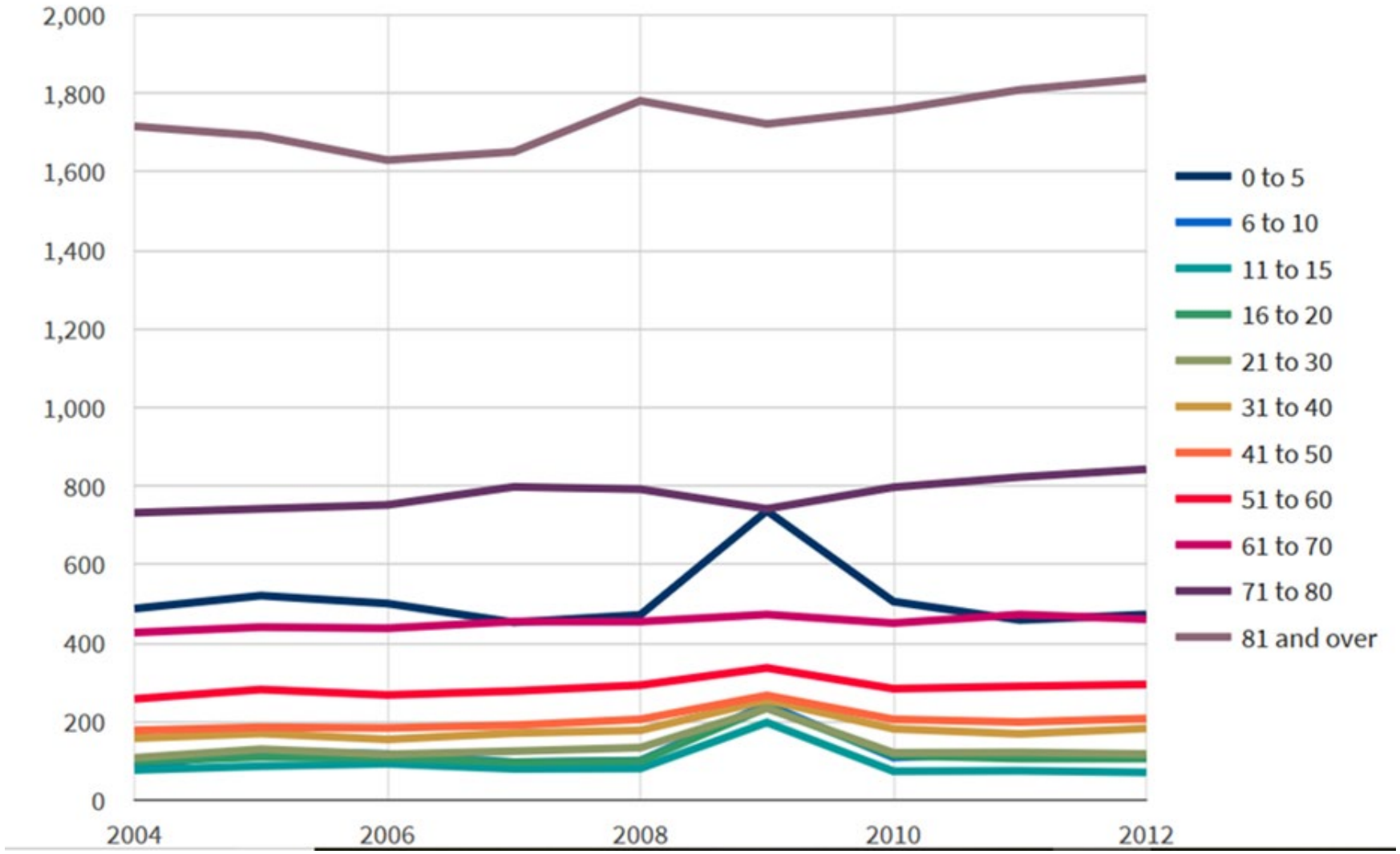
85+

Pneumonia and age. People/100,000 with pneumonia. UK data (BLF).

>80

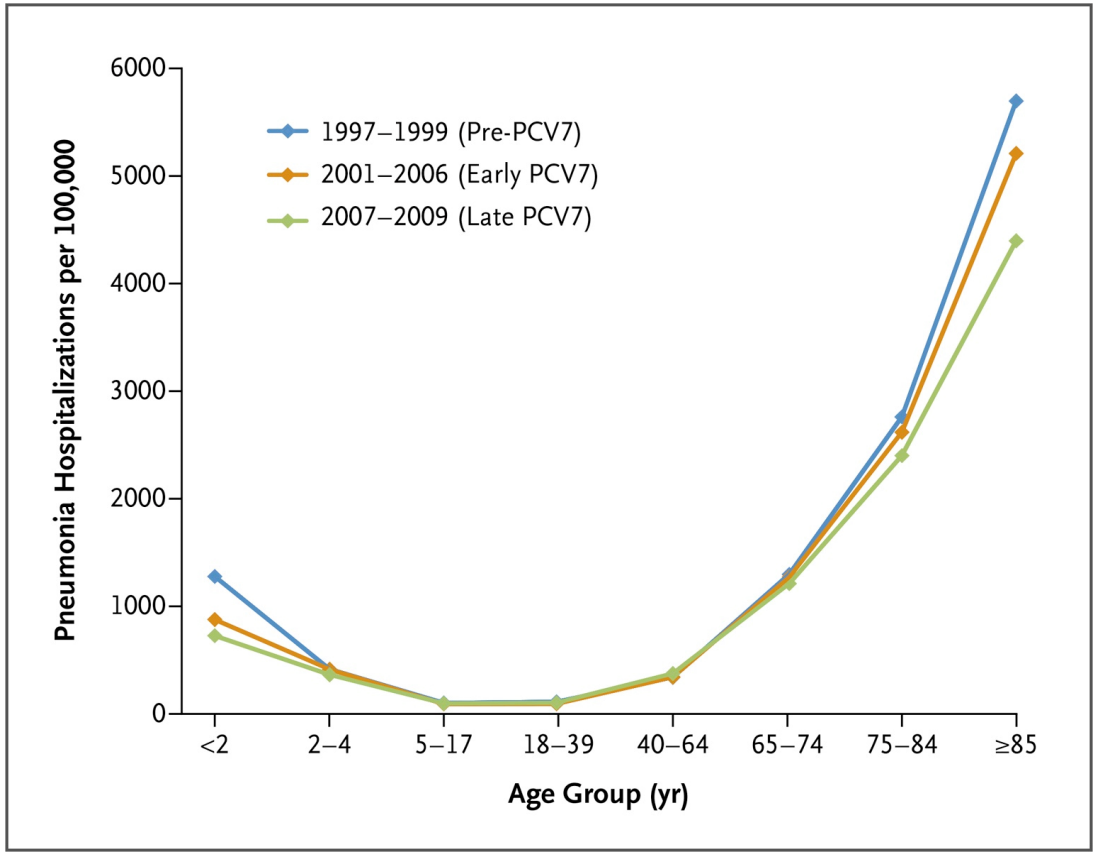
71-80

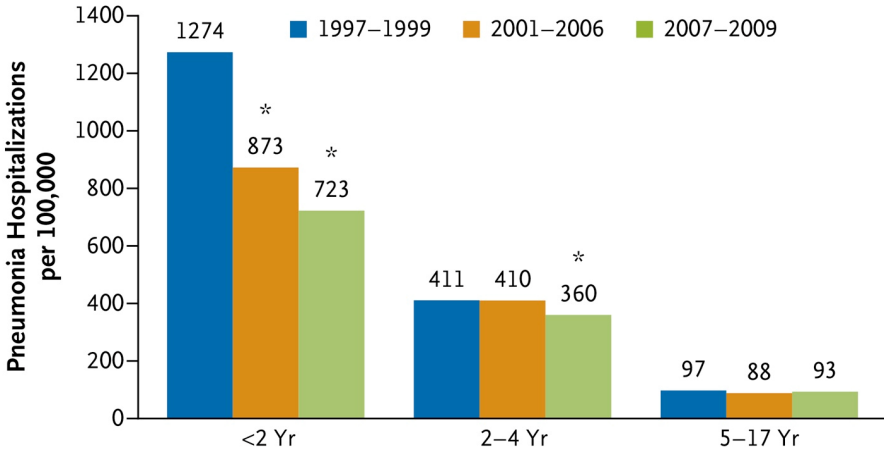
>60, <5

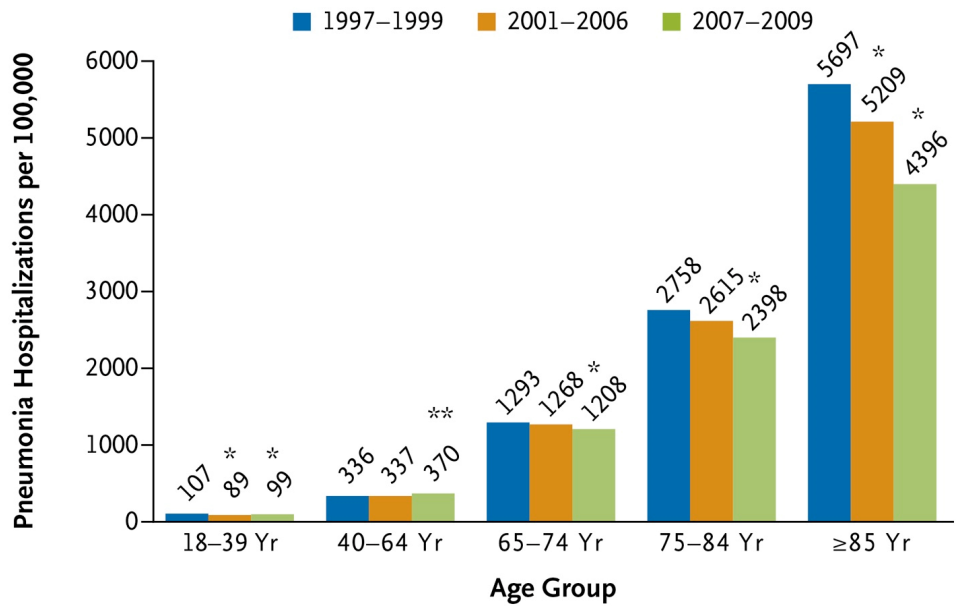


Hospitalisations for pneumonia following PCV7 in USA, by age.

Age <2, 47,000; age >85 73,000 fewer hospitalizations annually.



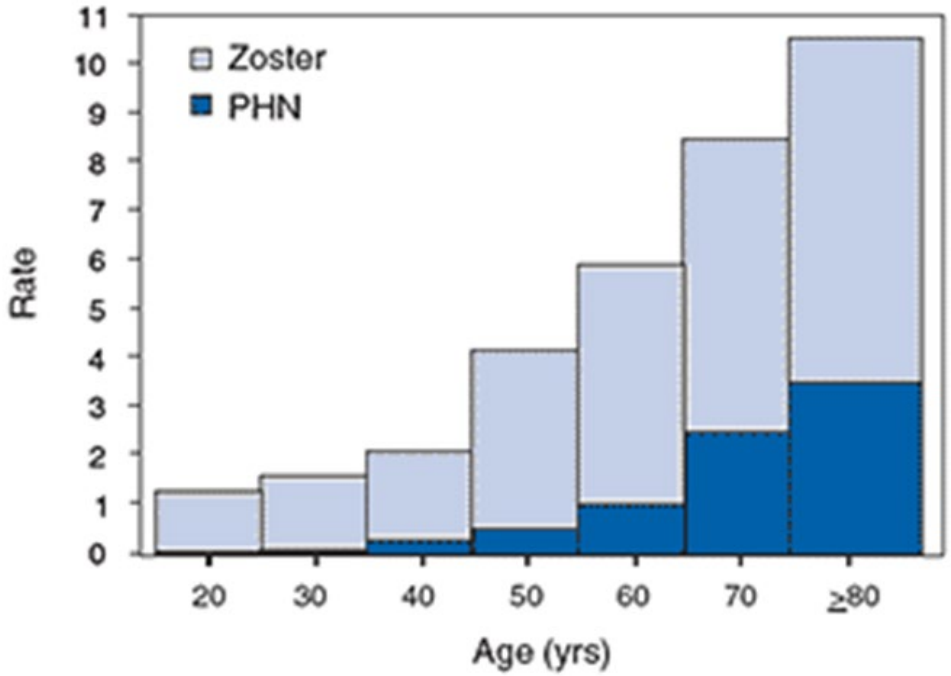




Griffin M et al NEJM 2013.

Shingles incidence by age and new vaccines (US data)

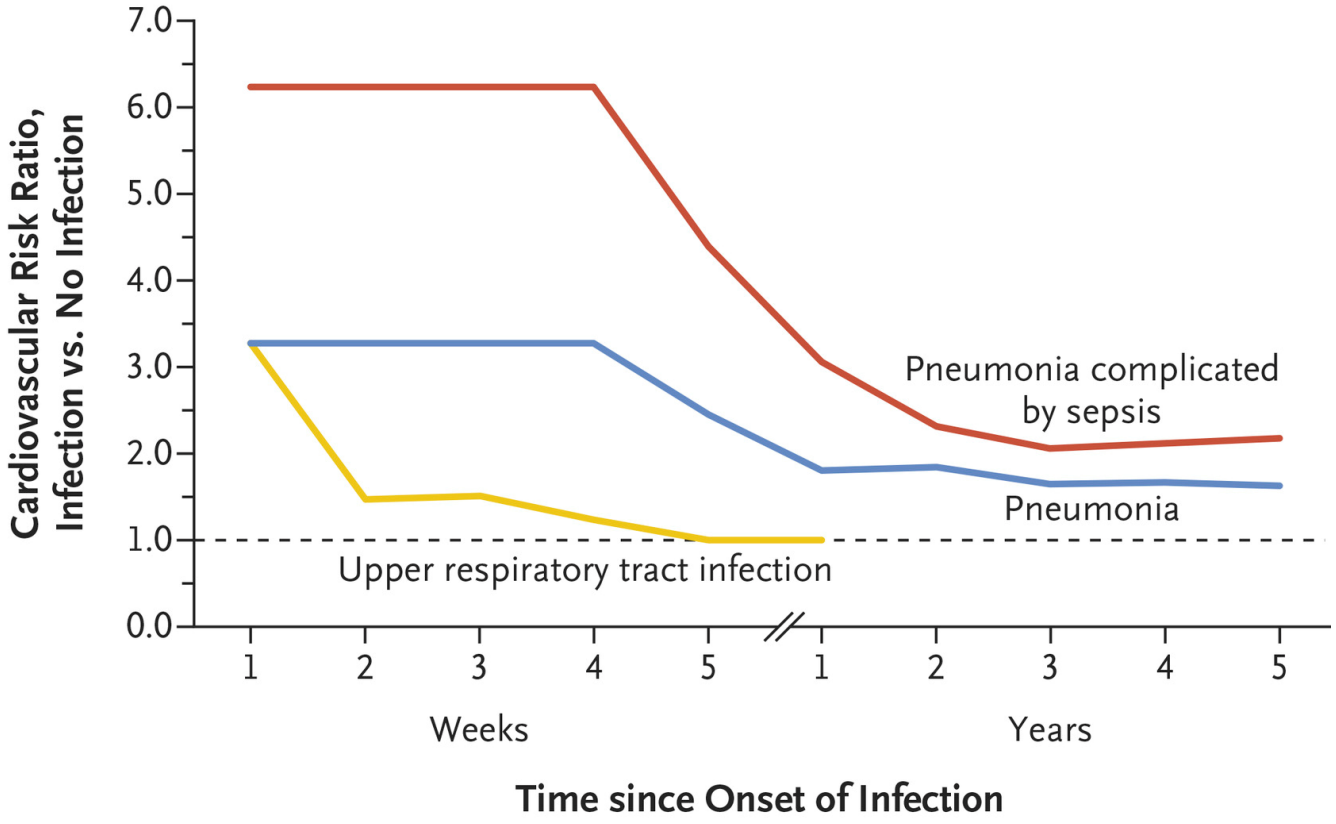
- Around 1/3rd of people develop shingles in their life.
- 15-20% of those affected will develop post-herpetic neuralgia.
- Vaccine for shingles is recommended in older people (>70yrs). Current uptake about 50%.
- Reduces risk of shingles by 50-90%.
- If you get shingles reduces risk of post-herpetic neuralgia.
- Current vaccine live; newer a subunit vaccine.



CDC

Pneumococcal pneumonia increases the risk of heart attack (MI).

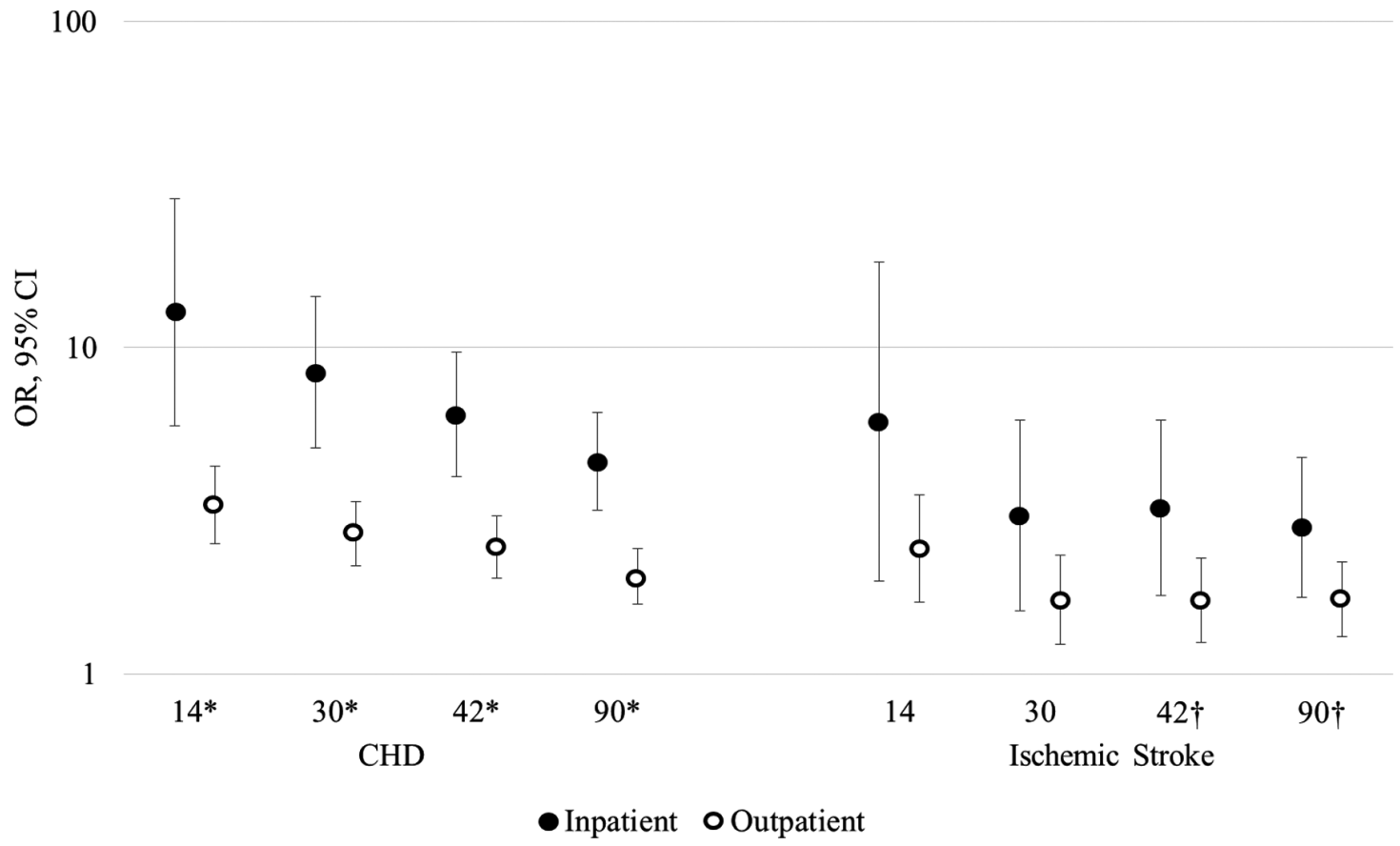
- “Among patients who are hospitalized for pneumococcal pneumonia, the incidence of myocardial infarction is 7 to 8%.”



D. Musher et al NEJM 2019

Accumulating evidence of link between many significant infections and coronary heart disease and stroke.

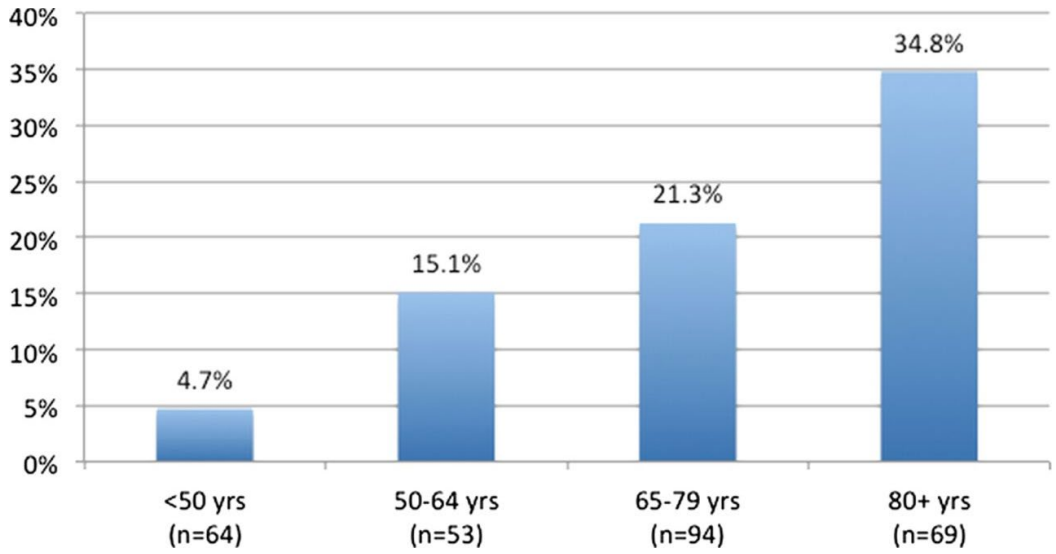
- Risk of coronary heart disease event or stroke by day after infection.
- Urinary tract infection, pneumonia, skin infection, sepsis. *Cowan L et al 2018.*
- There is reasonable evidence for a link between severe shingles and stroke.



Day after infection.

Delirium / acute confusional state with infections.

- In the elderly any infection can cause delirium.
- Very common.
- Confusion, drowsiness, aggression, personality change, can occur.
- Urinary tract infections and pneumonia the most common infectious triggers.
- People usually recover rapidly with antibiotics.
- Cause not fully understood.



Prevalence of delirium in inpatients by age. Ryan et al

Are infections causal or contributory for some people with dementia?

- We know certain infections can cause dementia; historically syphilis, more recently HIV.
- There is still no conclusive proof one way or the other on whether other infections could contribute to some cases of Alzheimer's or dementia with Lewy bodies.
- Current theories include herpesviruses (especially HHV-6A, 7), *P. gingivalis*.
- It would be good if there were a causal link.

NHS Choices

An infections and age- remarkable progress in the young, steady but much slower in older adults.

- The probability of acquiring and being harmed by infections varies throughout our life.
- Most infections are most dangerous in the young, old and pregnant- but not all.
- Remarkable strides forward against infections of infancy and childhood.
- Steady, but much slower, progress against infections in older adults.
- Infections have been declining as a proportion of mortality globally but will increase again as the population ages.

JS Copley. The Copley Family C1777