# Preparing for the next pandemic? Don’t leave pregnant women behind

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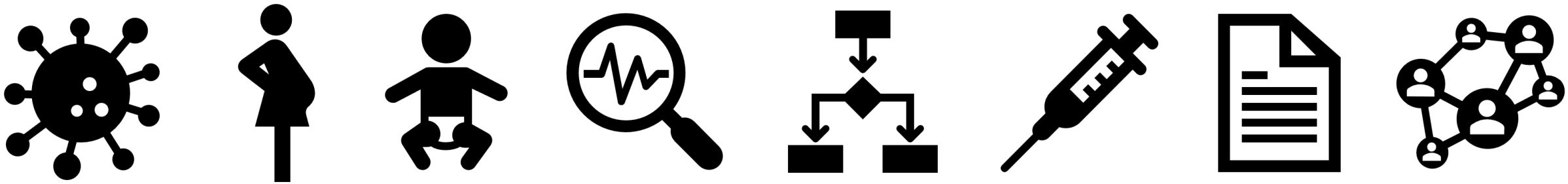
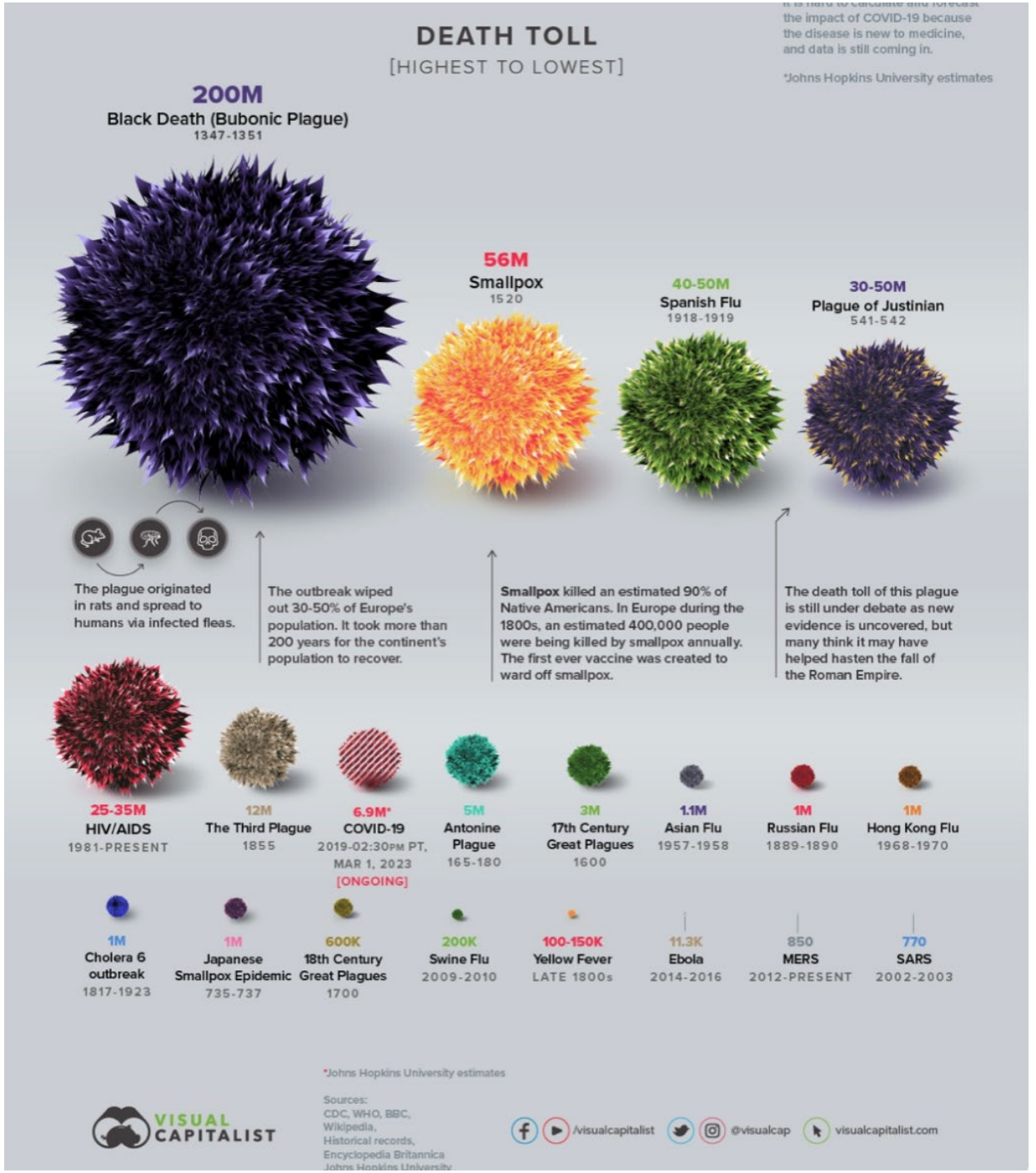


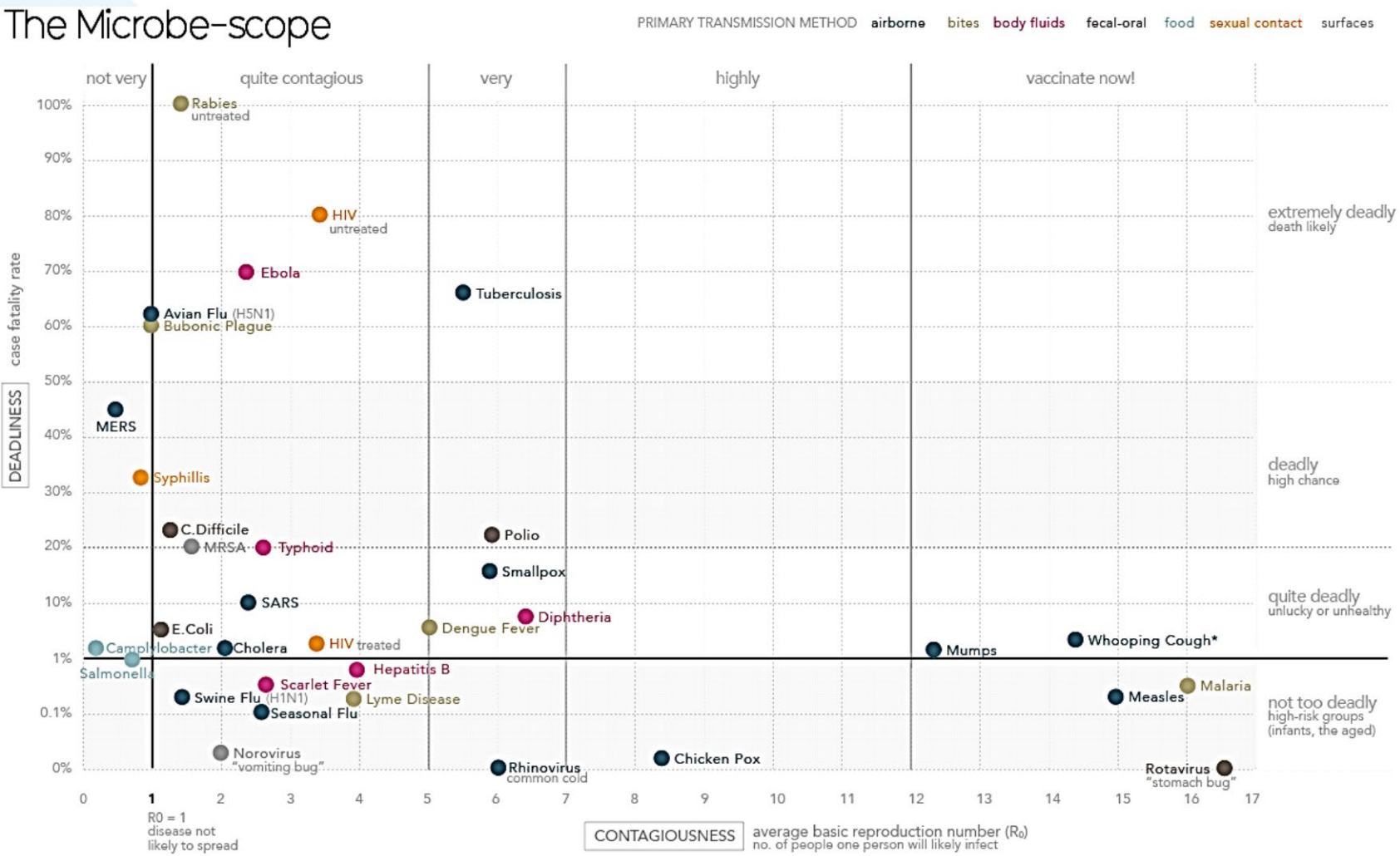
# Deaths by pandemic

[DEATH TOLL AS A PERCENT OF THE POPULATION]

| Pandemic | % of Population | Death toll | Population Est. | Year of Est. |
|---|---|---|---|---|
| Black Death | 51.0% | 200M | 0.39B | 1300 |
| Plague of Justinian | 19.1% | 40M | 0.21B | 500 |
| Smallpox | 12.1% | 56M | 0.46B | 1500 |
| Antonine Plague | 2.6% | 5M | 0.20B | 200 |
| Spanish Flu | 2.5% | 45M | 1.82B | 1919 |
| The Third Plague | 1.0% | 12M | 1.26B | 1850 |
| HIV/AIDS | 0.7% | 30M | 4.46B | 1981 |
| COVID-19 | 0.09% | 6.9M | 8.00B | 03/01/202 |



# Infection fatality rate AND Ro drives worry




## Level of Worry

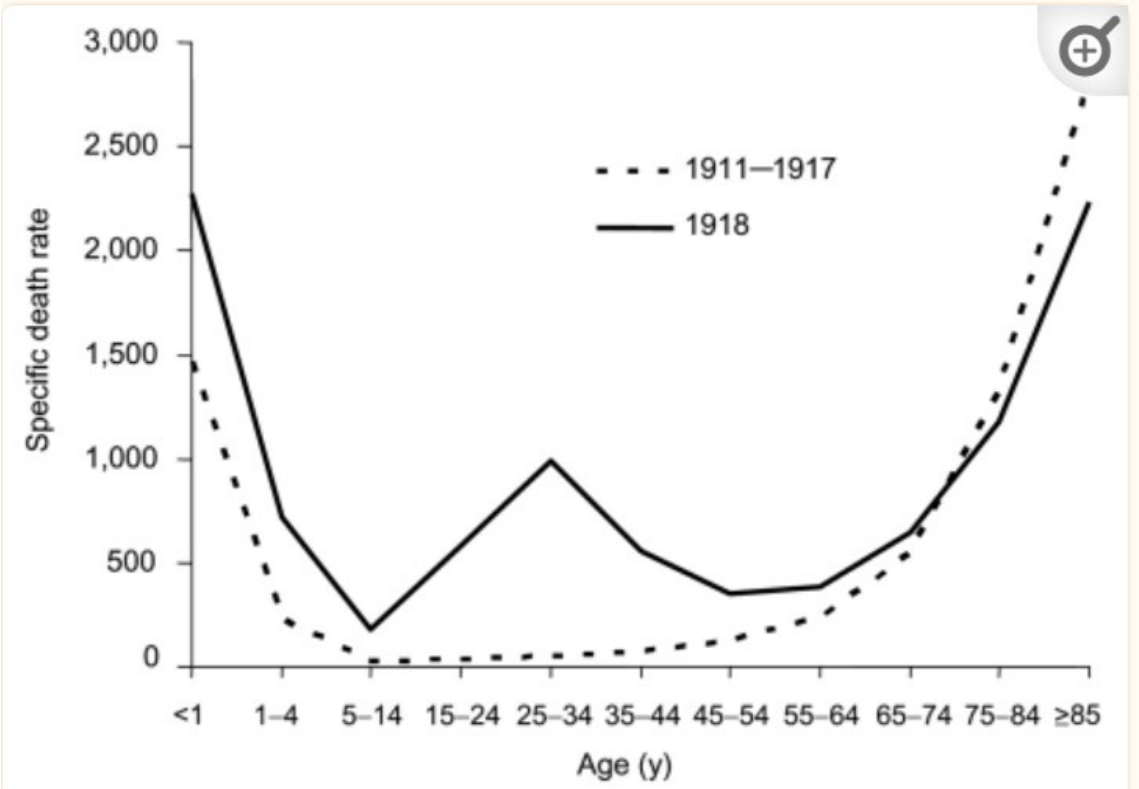
| | |
|---|---|
| High transmission Low Mortality | **High transmission High mortality** |
| Low transmission Low mortality | Low transmission High Mortality |

David McCandless v1.02 / Oct 2014
InformationisBeautiful.net

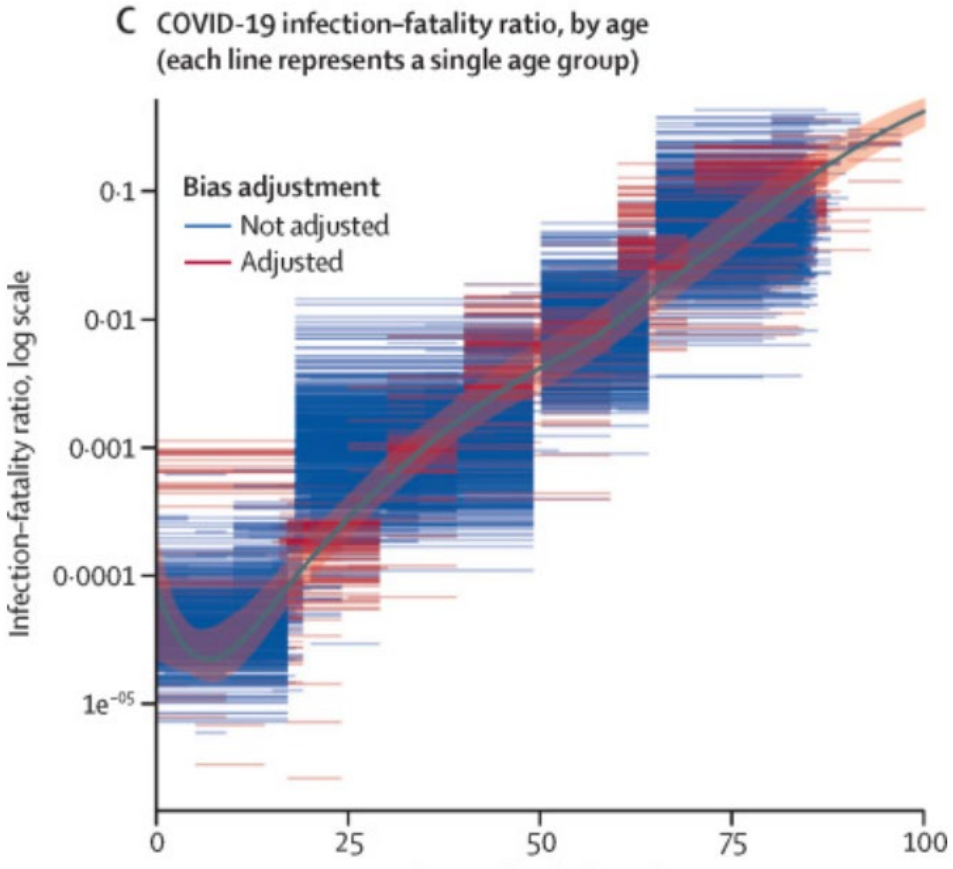
sources: Centers for Disease Control, World Health Org, CIDRAP, studies
fatality rate for health adult in developed nation, * = infants

data: bit.ly/KIB_Microbescope
part of KnowledgeisBeautiful

# Difference between 1918 flu and 2020 COVID-19

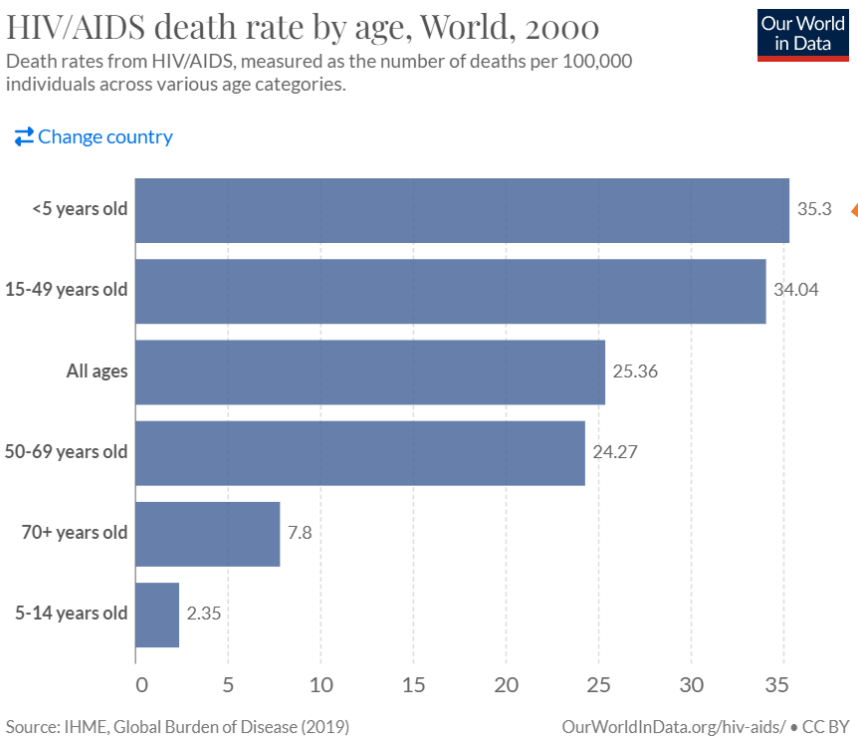


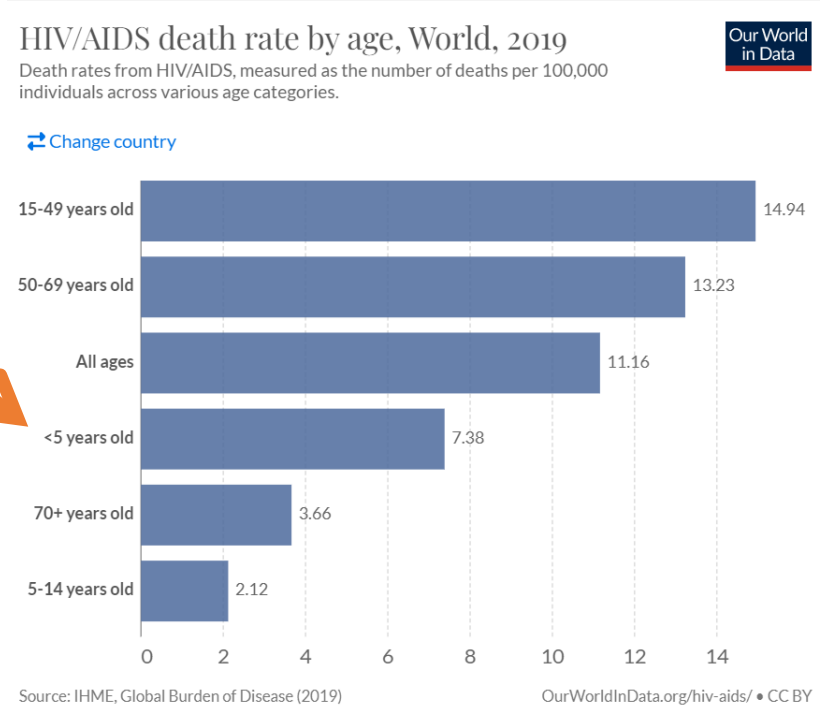

1918 Influenza: the Mother of All Pandemics - PMC (nih.gov)

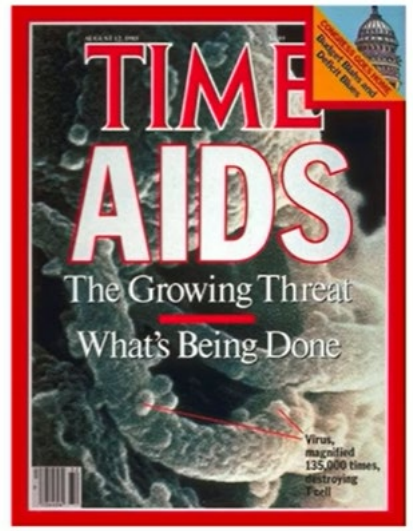



Variation in the COVID-19 infection–fatality ratio by age, time, and geography during the pre-vaccine era: a systematic analysis - The Lancet

# Changes in HIV mortality over time



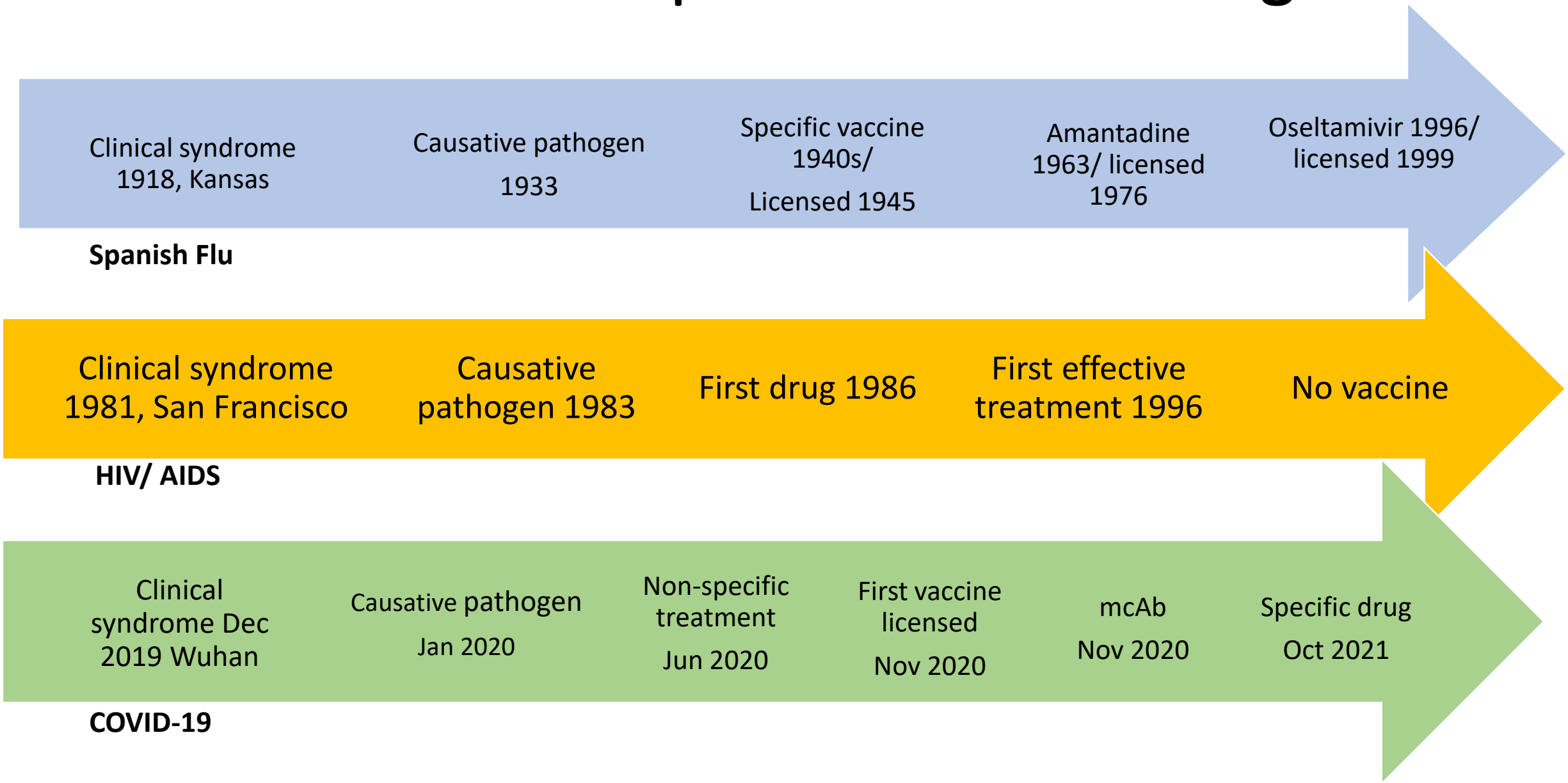



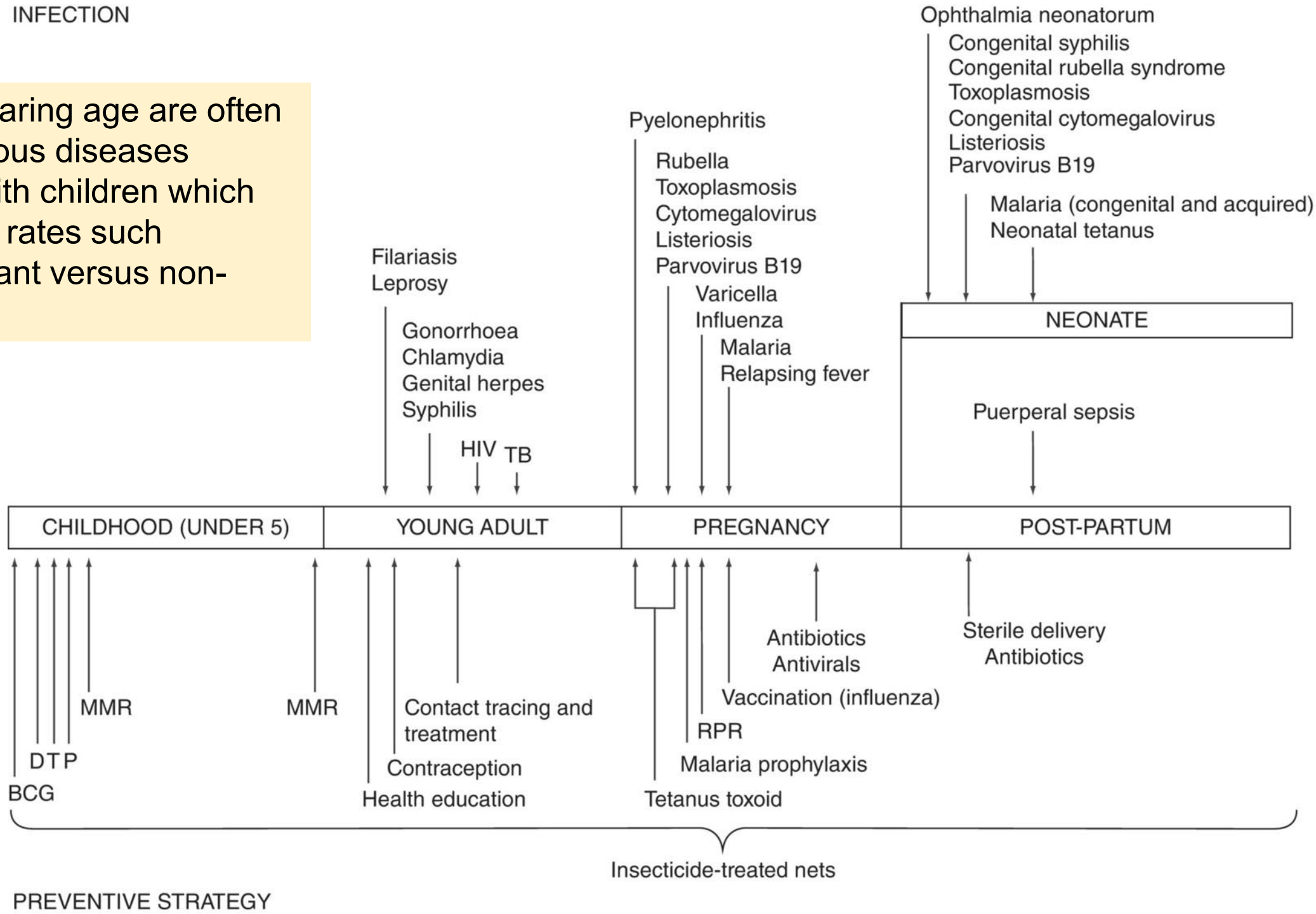

Time, 1985

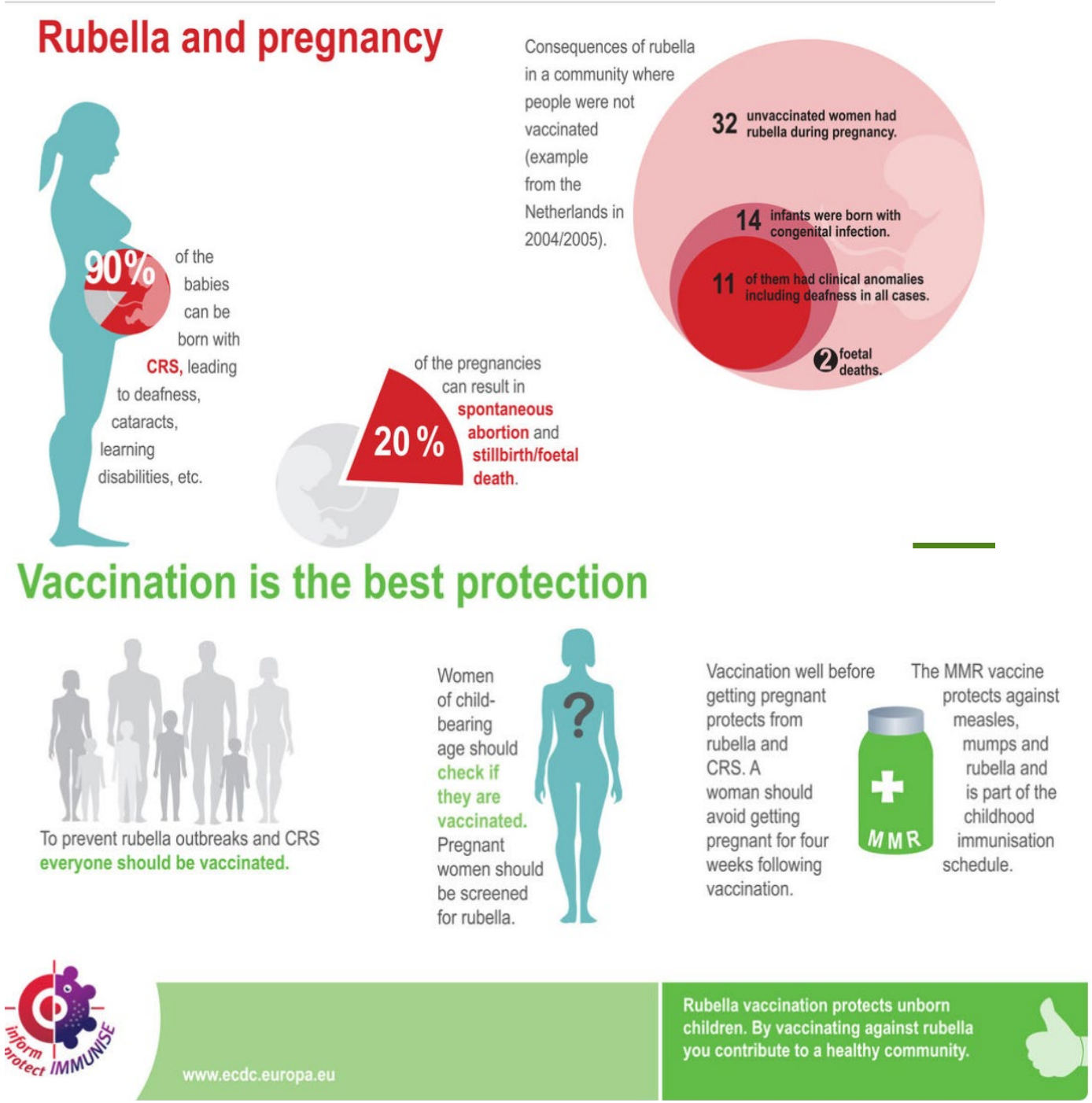
Public health and communication campaigns
Testing to identify cases
Understanding who is at greatest risk
Randomised controlled trials, MTCT, PrEP

# From identification to pharmaceutical mitigation



Women of childbearing age are often exposed to infectious diseases through contact with children which can lead to higher rates such diseases in pregnant versus non-pregnant women

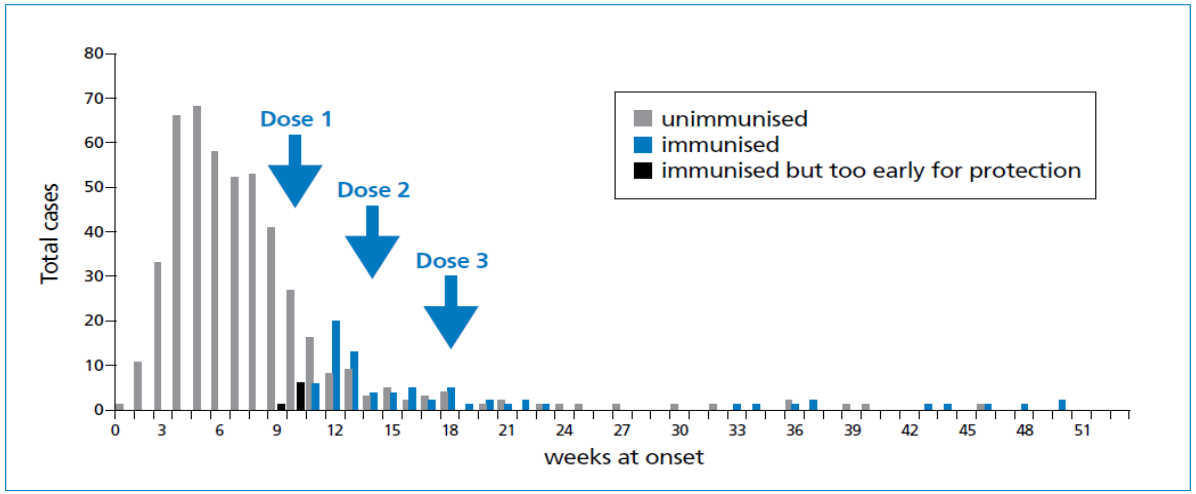




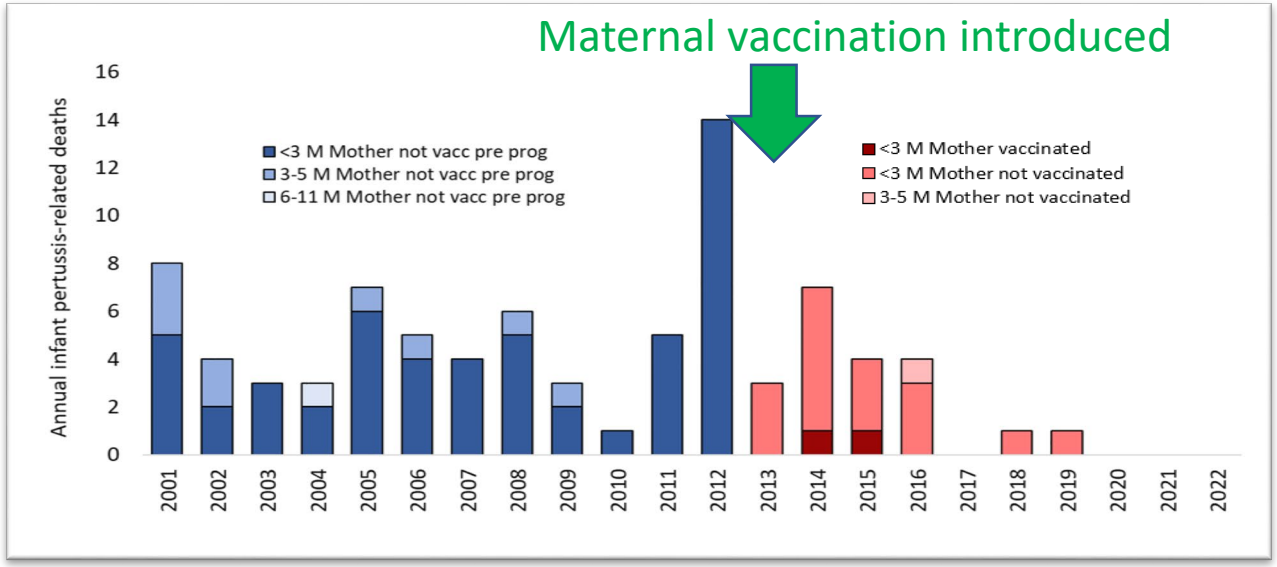

# Measles

- Measles in pregnancy alters body's immune tolerance to foetus and increases spontaneous abortion
- Measles infection associated with preterm delivery, foetal death and in some rare cases, congenital infections
- During a recent measles outbreak in Italy (2017–2018) 25% of infected pregnant women delivered prematurely
- Vaccine is live attenuated vaccine - contraindicated during pregnancy – prior to pregnancy or immediately post
- Immunoglobulins can be given to pregnant women or neonates (within 6 days of exposure) to reduce the severity of the disease

# Infant deaths due to pertussis in England




Confirmed cases in infants aged under one year, by week of age at onset (2011- August 2012). Protection is assumed to accrue within the two weeks following immunisation.




Pertussis immunity wanes over time—adolescent and adult family members are likely reservoirs of the disease

Neonates have a higher risk of severe complications and death than older infants

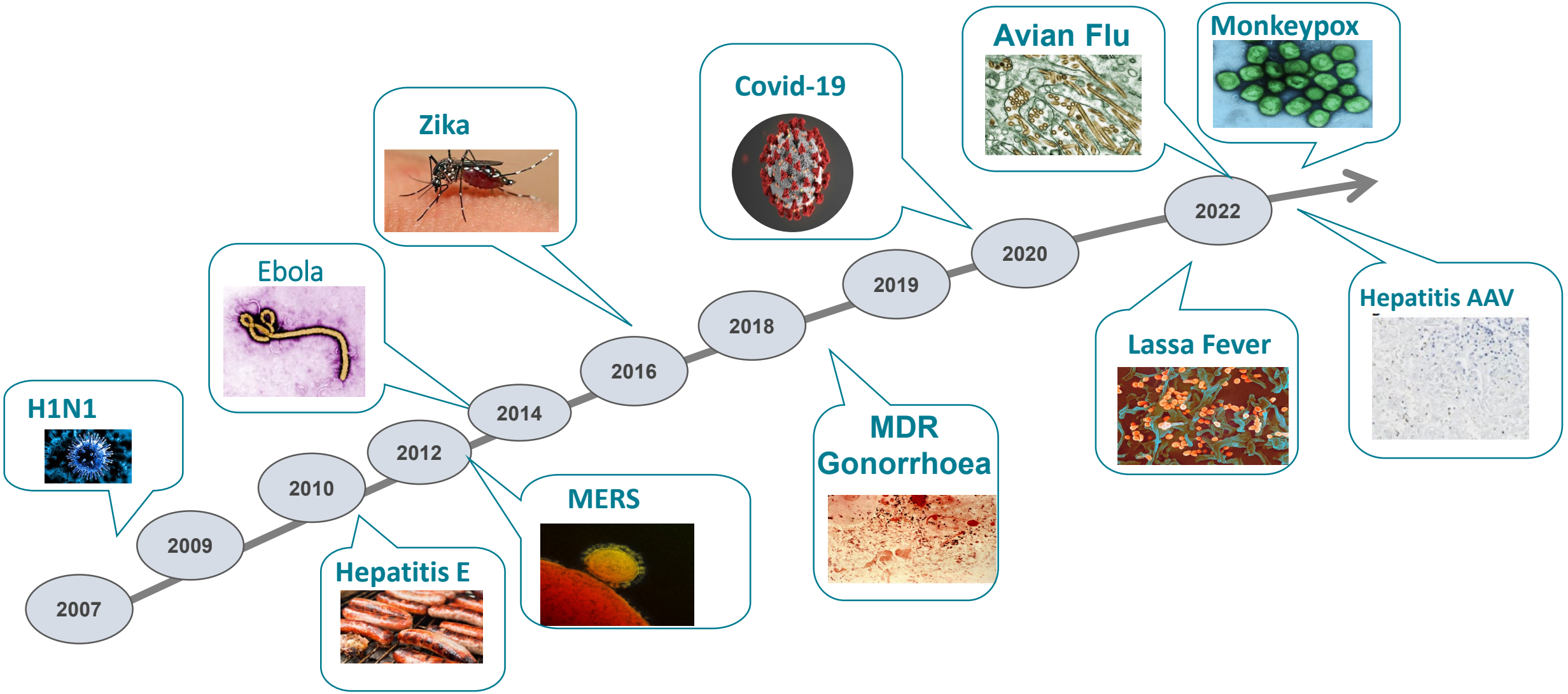
An estimated 1,400-4,300 infant hospitalisations and 41-170 infant deaths averted between 2012-2017

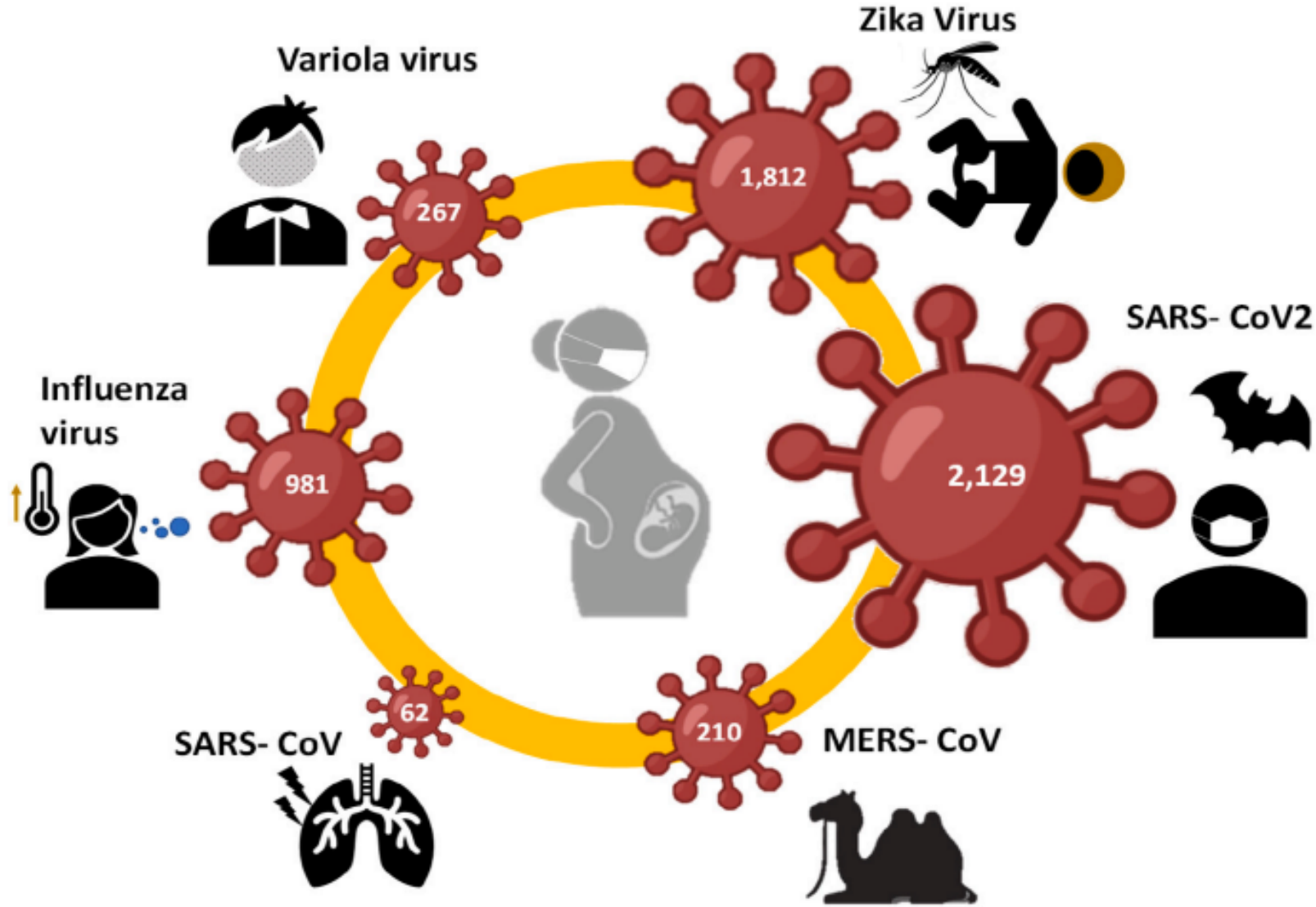
Vaccination during pregnancy gives approximately **90% protection against pertussis disease** and **97% protection against death** from pertussis in the first 2 months of life.

Sandmann et al. CID 2020, Amirthalingam et al 2022

# UK health security landscape 2007 – 2022

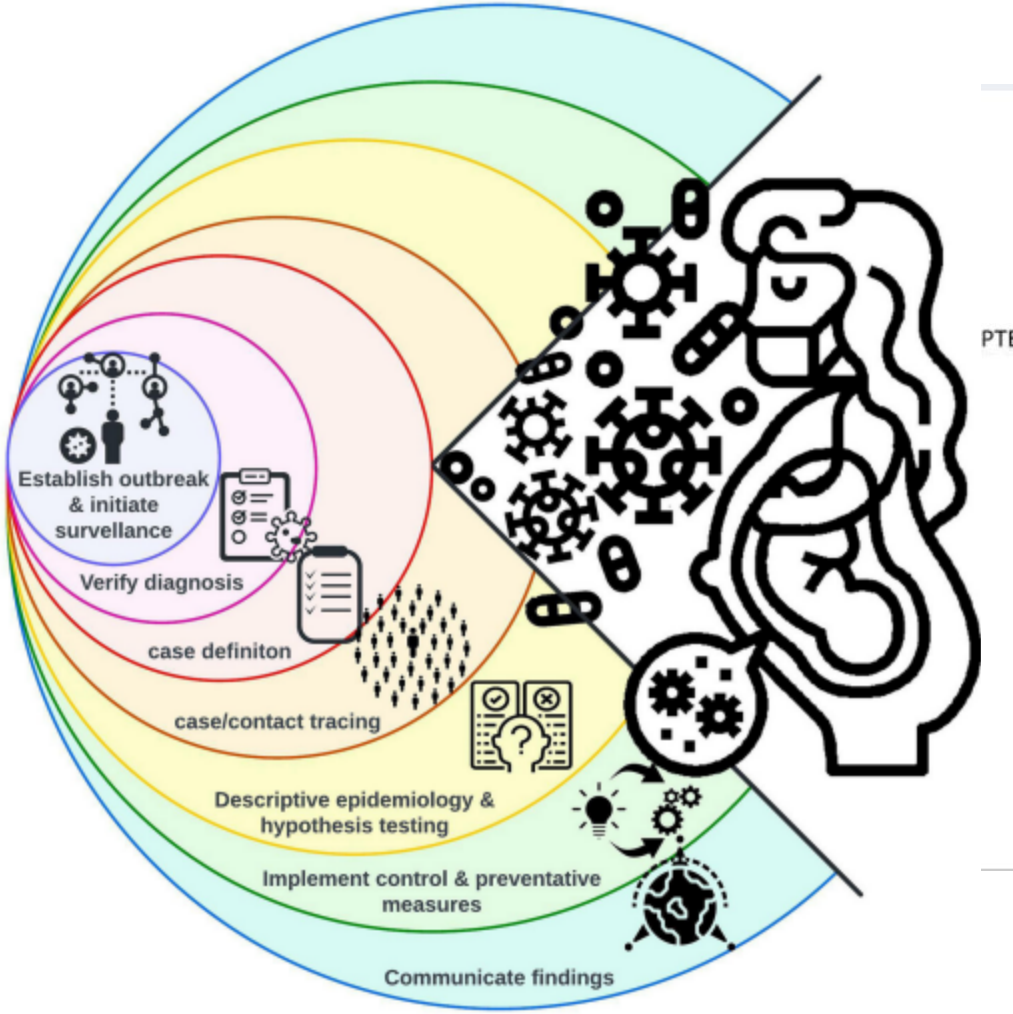
*We deal with around 10,000 incidents a year*

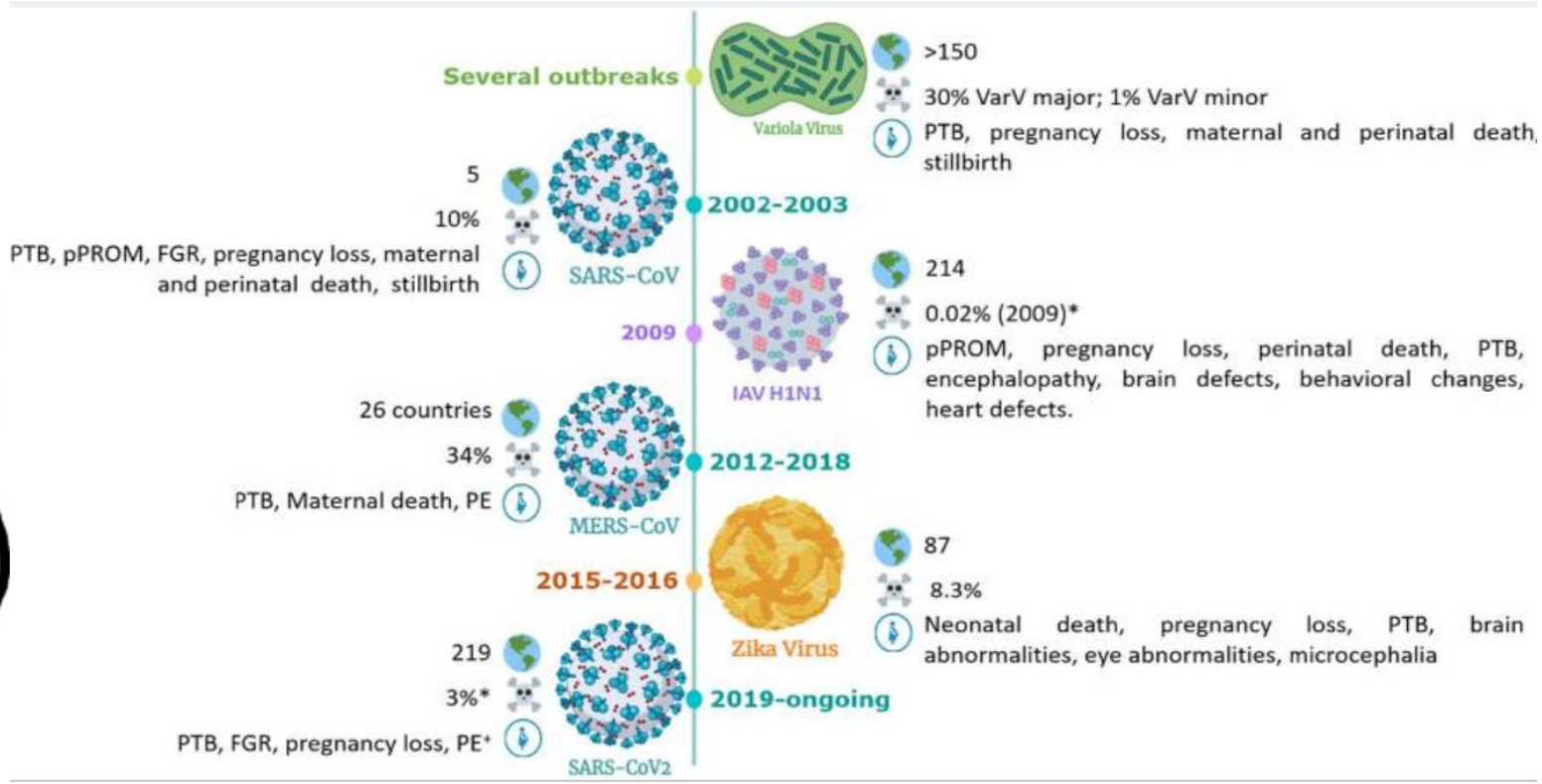





Selected pandemic viruses for this review. Infographic of number of publications reported in PubMed concerning the respective virus in pregnancy.

# Pregnancy and Epi/Pandemics




[Pregnancy and pandemics: Interaction of viral surface proteins and placenta cells - PMC (nih.gov)]

# How long does it take to establish perinatal outcome

| Emerging infection | Start date | Time to establishment of perinatal outcome |
|---|---|---|
| H1N1 flu pandemic | April 2009 | 11 months |
| Cholera, Haiti | Oct 2010 | 22 months |
| Lassa Fever, Ghana | Oct 2011 | - |
| MERS Co-V, Middle East | Sept 2012 | - |
| H7N9 flu, China | Mar 2013 | 40 months |
| Ebola virus, West Africa | Aug 2014 | 40 months |
| Zika virus, the Americas | Aug 2015 | 5 months |
| Chikungunya, Pakistan | Feb 2016 | 38 months |
| Monkeypox, Nigeria | Feb 2017 | - |
| Nipah virus, India | Apr 2018 | - |
| COVID-19 pandemic | Dec 2019 | 6 months |

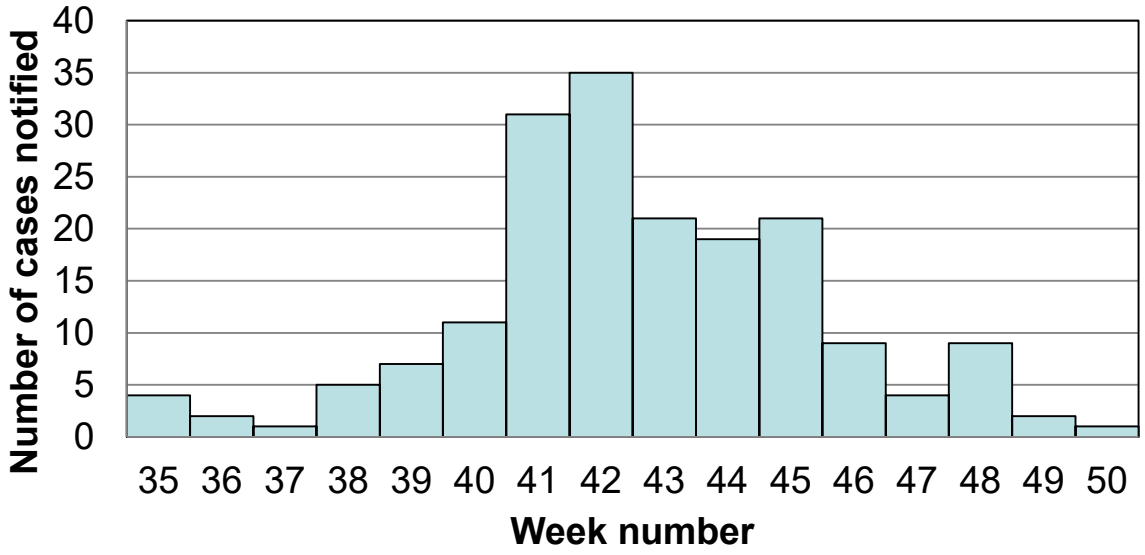
# What are the urgent research studies

| Question | How |
|---|---|
| Clinical presentation and spectrum of disease | **Patient cohorts [FFX, ISARIC, UKOSS]** |
| Definition of a case [sx, asx] and contact | **Patient cohorts [FFX, ISARIC, UKOSS]** |
| Risk factors for infection | **Cohorts, Case control studies** |
| Risk factors for severe illness or death | **Cohorts, Case control studies** |
| Causative agent | Lab studies [Koch's postulates] |
| Optimal diagnostic tests/ use cases | Diagnostic validation studies and trials |
| Duration of transmission [e.g. viral shedding] | Prospective cohorts with repeated sampling |
| Effective treatments [direct and indirect] | ***RCT/ Adaptive trial design*** |
| Prevention [vaccines and non-pharm interventions] | ***RCT/ Adaptive trial design*** |
| Monitoring of changes in pathogen | Genomics, Cohort studies |
| Health care workers risk factors for infection | Cohort studies |
| Psychosocial and societal consequences | **Qualitative and Quantitative surveys** |

jogh-10-011001.pdf (nih.gov)

# UK Obstetric Surveillance System (UKOSS)

- Monthly prospective case collection from obstetrician, midwife, obstetric anaesthetist and risk midwife (individualised by hospital)
- Cohort or case control studies conducted as well as descriptive studies
- Rolling programme of studies
- Central data collection




Pregnant women hospitalised with confirmed H1N1v

| Treated within two days | Admitted to ITU (n,%) | Not admitted to ITU (n,%) | Adjusted Odds Ratio (95% CI) |
|---|---|---|---|
| **Yes** | 12 (26) | 119 (68) | 0.1 (0.1-0.3) |
| **No** | 34 (74) | 55 (32) | 1 |

Antivirals for H1N1

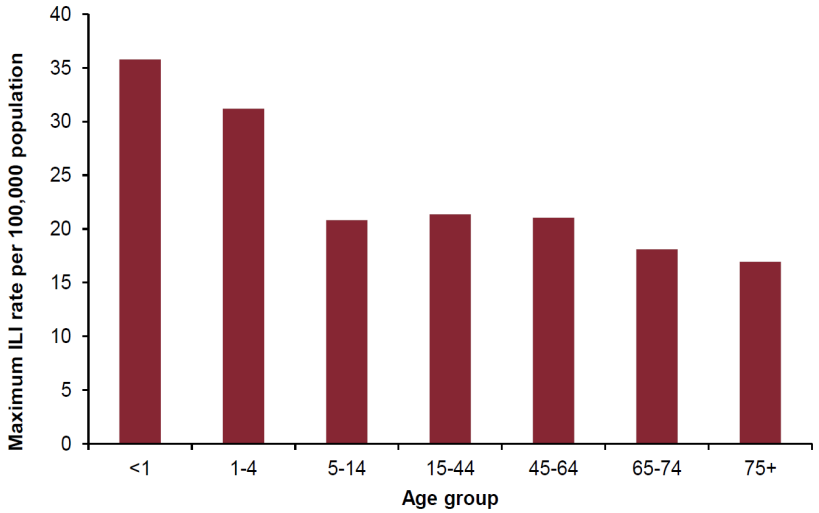
# Pregnant women representation in general studies is low

- Largest study  - data collected from 26 January 2020 to 7 April 2021 on 483,929 people hospitalised with COVID-19 in 1,609 sites in 54 countries
- Analysis reported on 142,540 patients (60,977 female, 81,325 male) median age 70 [IQR 56-82]), admitted at 620 sites in 47 countries.
- 1030 individuals (0.7%) were 177 pregnant women
- Lower odds of death, lower ICU admission than non-pregnant…
- But no sub-analysis within the pregnant women

Ten months of temporal variation in the clinical journey of hospitalised patients with COVID-19: an observational cohort (medrxiv.org)

# Obsetetic and Paediatric surveillance via UKOSS and UKHSA

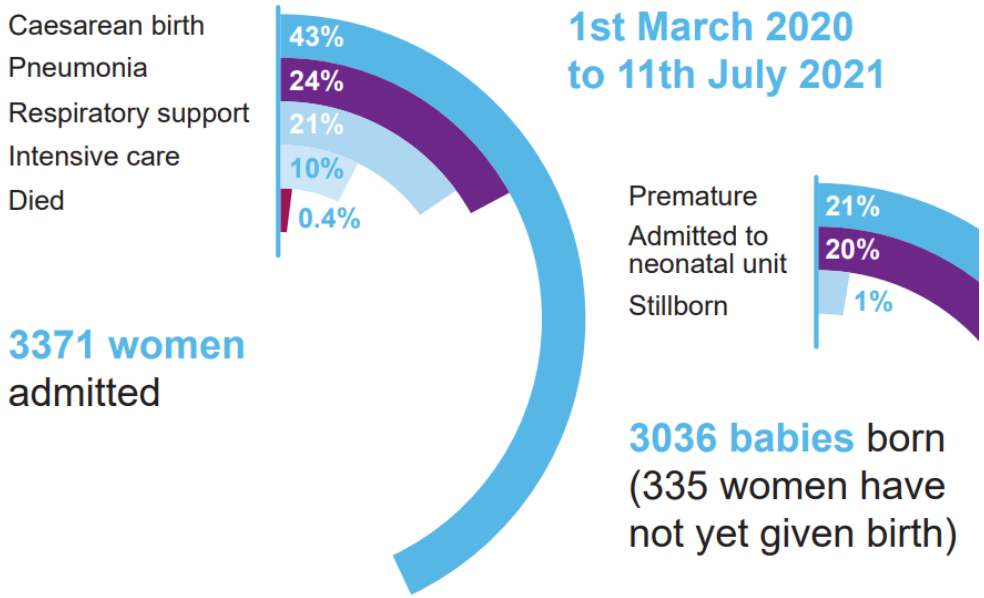
- UKOSS surveillance of 2009/H1N1 influenza showed a significant association with poor pregnancy outcomes
- Perinatal mortality higher among infants born to infected women (39 per 1,000 total births vs uninfected women 7 per 1,000 total births)
  - Explained by an increase in the stillbirth rate (27 per 1,000 vs 6 per 1,000 total births)
  - Infants of infected women more likely to be born prematurely
- 23% of infants born to infected women admitted to neonatal ITU (median 12 days)



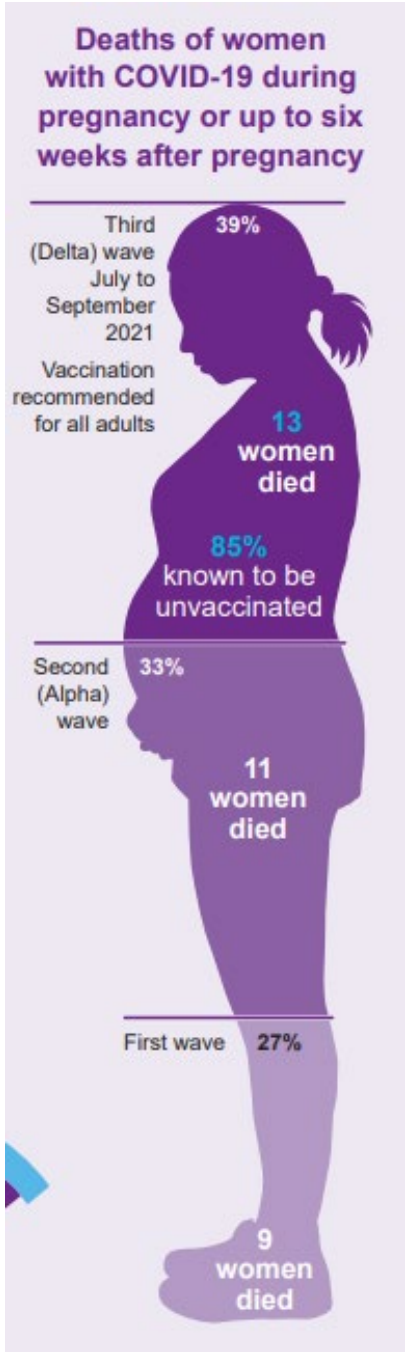

**Weekly GP influenza-like illness peak rates by age group in 2019 to 2020, England (RCGP)**

- Infants under the age of six months have the highest rate of GP consultations and hospitalisations for influenza in the UK
- There is no influenza vaccine that is currently licensed for children aged less than six months
- the only way that children in this age group can benefit from the influenza vaccine is via the transplacental transfer of antibodies following maternal vaccination

## Outcomes of COVID-19 for pregnant women and their babies after admission to hospital with symptoms




- Risk of hospital admission increased from 6.7% in 1st trimester to 10.7% in 2nd and 33.5% in 3rd trimester
- Extended perinatal mortality for women who gave birth within 28 days of diagnosis of Covid was 22.6 per 1000 births (14 stillbirths/ baby deaths) vs pandemic background of 5.6 per 1000 births and 4.3 per 1000 in vaccinated women
- 77% of infections, 91% hospital admissions, 98% of critical care admissions and all baby deaths were in unvaccinated women

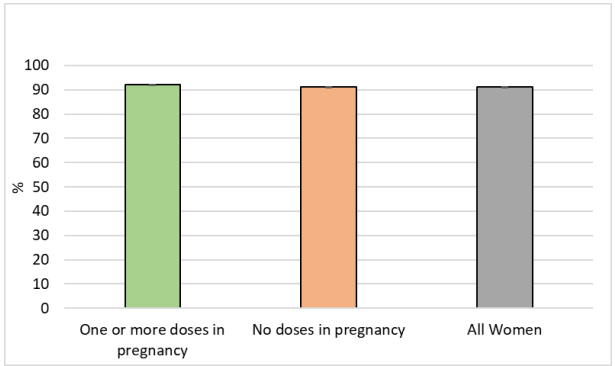


# COVID vaccine in pregnancy

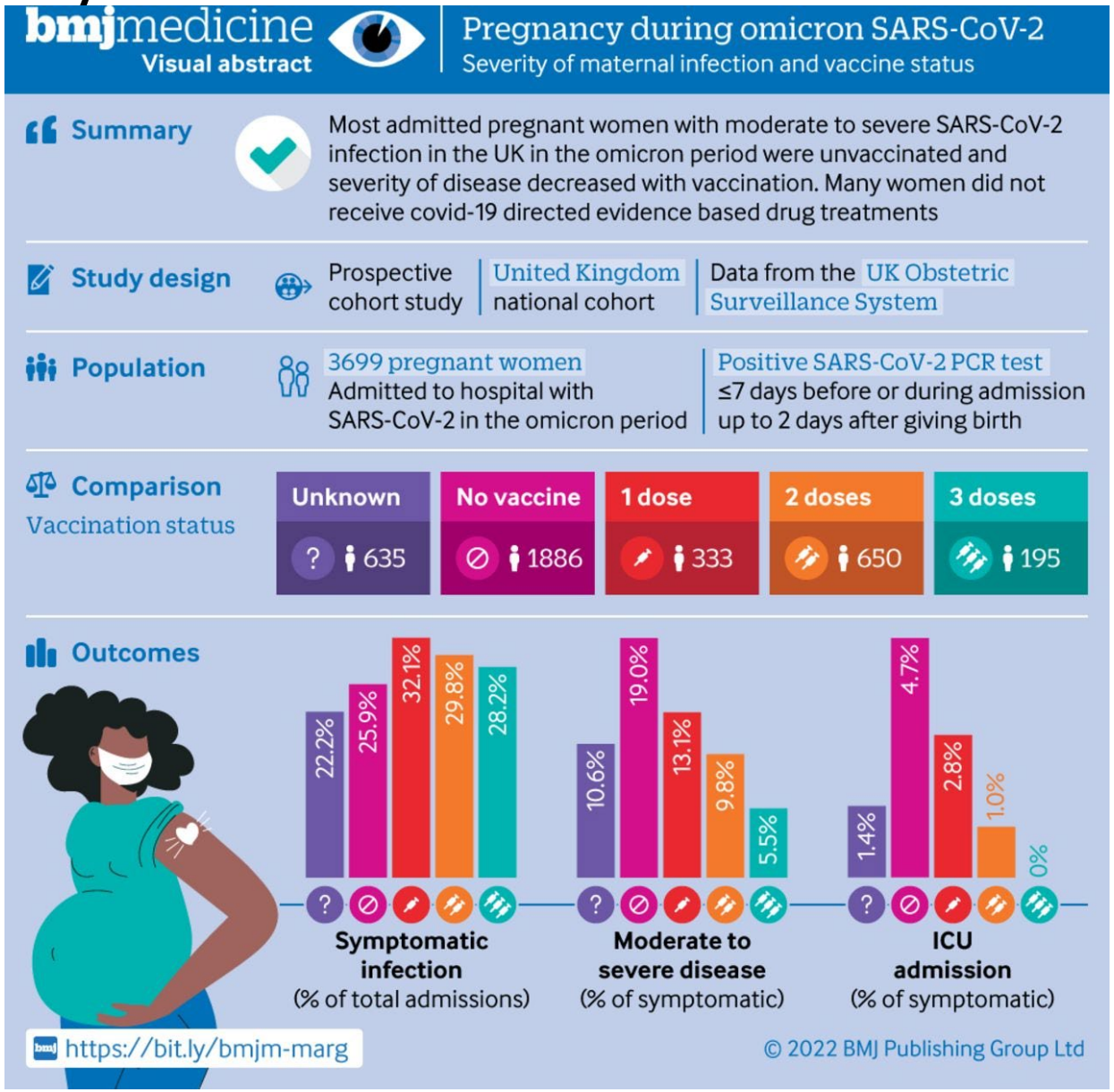
- Systematic review and meta-analysis of 81,000 women vaccinated in pregnancy and 255,000 unvaccinated pregnant*women found COVID-19 vaccination during pregnancy was associated with
  - Lower risk of NICU admission (OR, 0.88; 95% CI, 0.80-0.97) and
  - Lower risk of intrauterine fetal death (OR, 0.73; 95% CI, 0.57-0.94)
  - Lower risk of maternal SARS-CoV-2 infection (OR, 0.46; 95% CI, 0.22-0.93)

- Evidence from 23 studies including 117,552 COVID-19 vaccinated pregnant people**, almost exclusively with mRNA vaccines were safe
  - associated with a reduction in maternal infections and stillbirth
  - no evidence of a higher risk of adverse outcomes including miscarriage, earlier gestation at birth, placental abruption, pulmonary embolism, postpartum haemorrhage, maternal death, intensive care unit admission, lower birthweight Z-score, or neonatal intensive care unit admission

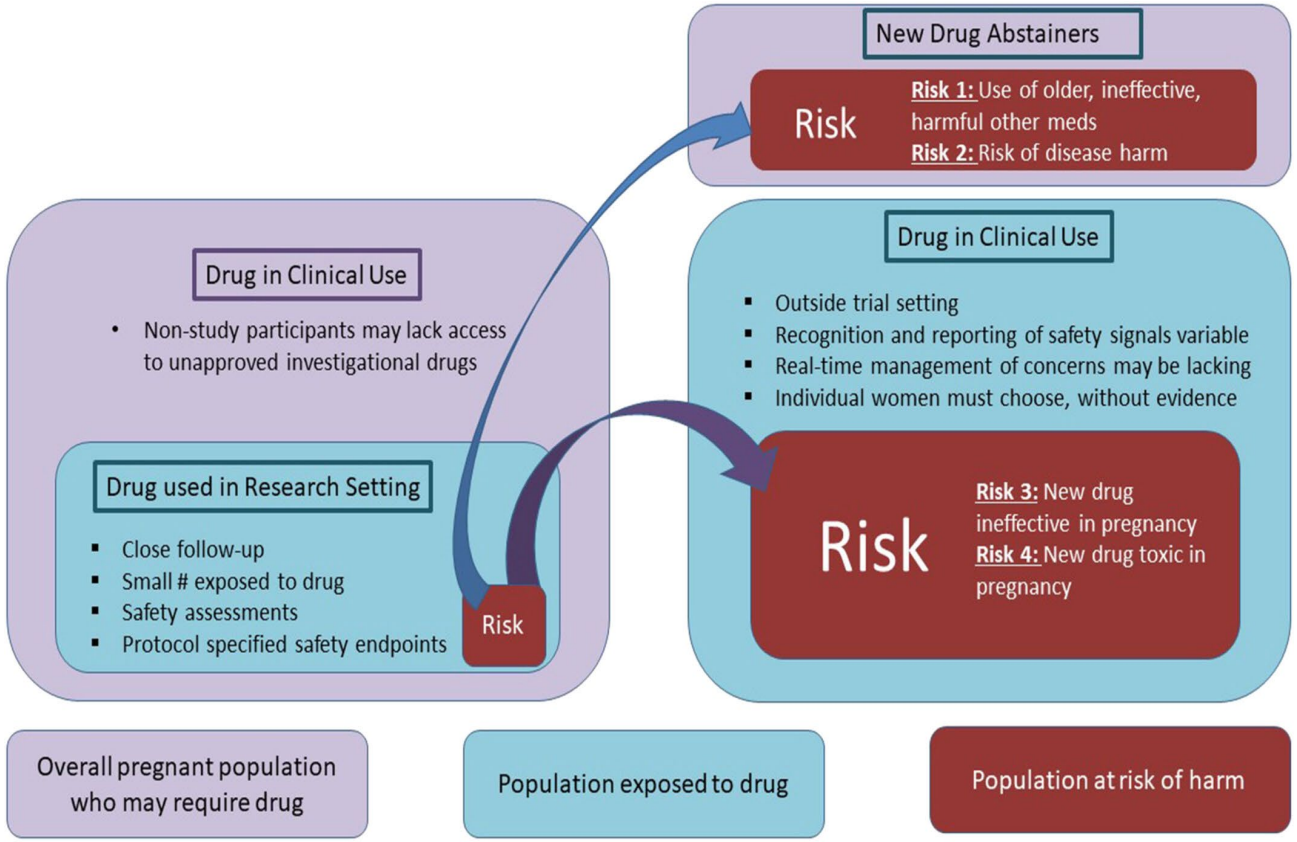
Women giving birth January 2021 to November 2022 to live-born babies at term without low birthweight




Engjom et al BMJ Medicine 2022;1:e000190
Watanabe et al JAMA Pediatr. 2022
Prasad et al Nature Communications 2022



# Ethical issues in pregnancy




**Scenario 1: Ebola Virus Disease Therapeutics (Urgent Gap-Filling Research)**

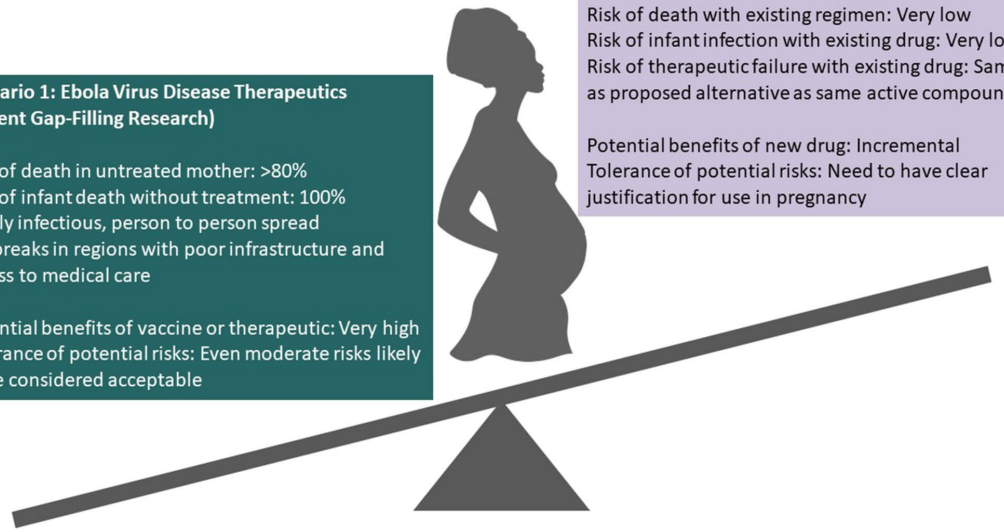
Risk of death in untreated mother: >80%
Risk of infant death without treatment: 100%
Highly infectious, person to person spread
Outbreaks in regions with poor infrastructure and access to medical care

Potential benefits of vaccine or therapeutic: Very high
Tolerance of potential risks: Even moderate risks likely to be considered acceptable

**Scenario 2: Alternative formulation of existing safe and effective drug. Example: antiretroviral tenofovir ("Me-Too" Research)**

Risk of death with existing regimen: Very low
Risk of infant infection with existing drug: Very low
Risk of therapeutic failure with existing drug: Same as proposed alternative as same active compound

Potential benefits of new drug: Incremental
Tolerance of potential risks: Need to have clear justification for use in pregnancy



Brit J Clinical Pharma, Volume: 88, Issue: 1, Pages: 7-21, First published: 14 May 2021, DOI: (10.1111/bcp.14914)

# Clinical Trials and Pregnancy

## Justice

Fairness in distribution of benefits and burdens

Key questions

- Are there systematic disparities in the medical evidence base for pregnant women vs other groups?
- What factors affect the fairness/unfairness of excluding or delaying involvement of pregnant women in research?

## Non-Maleficence

"First, do no harm": Act to Avoid or Minimize Harms

Key questions

- Do existing laws and regulations suffice to minimize harm?
- Does the lack of evidence put populations at risk of harm?
- What factors make study- related harm a case of wrongful malfeasance vs unfortunate injury?
- Are there harms to pregnant women from prohibiting or delaying their participation in research?

## Autonomy

Opportunity and Capability of Individuals to Make Informed Decisions About Themselves

Key questions

- Does sufficient data exist to support comparably autonomous health choices on the part of pregnant women vs other groups?
- Does lack of data mean a pregnant woman's autonomy is curtailed?
- Is autonomy of a pregnant woman to participate in research less protected than that of a non-pregnant woman?
- Should a person be permitted to choose a higher risk option?
- How can a woman's autonomy be balanced with the fetus' inability to choose?

## Beneficence

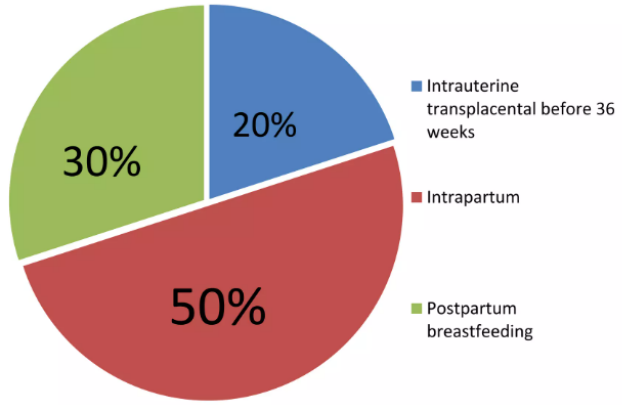
Act with the Intent & Effect of Providing Benefits

Key questions

- What is the consequence of untreated or undertreated disease?
- Are there known risks, to either mother or fetus, of the drug?
- Is there an alternative evidence-based treatment option?
- How much benefit may accrue to pregnant women from early vs delayed inclusion in research

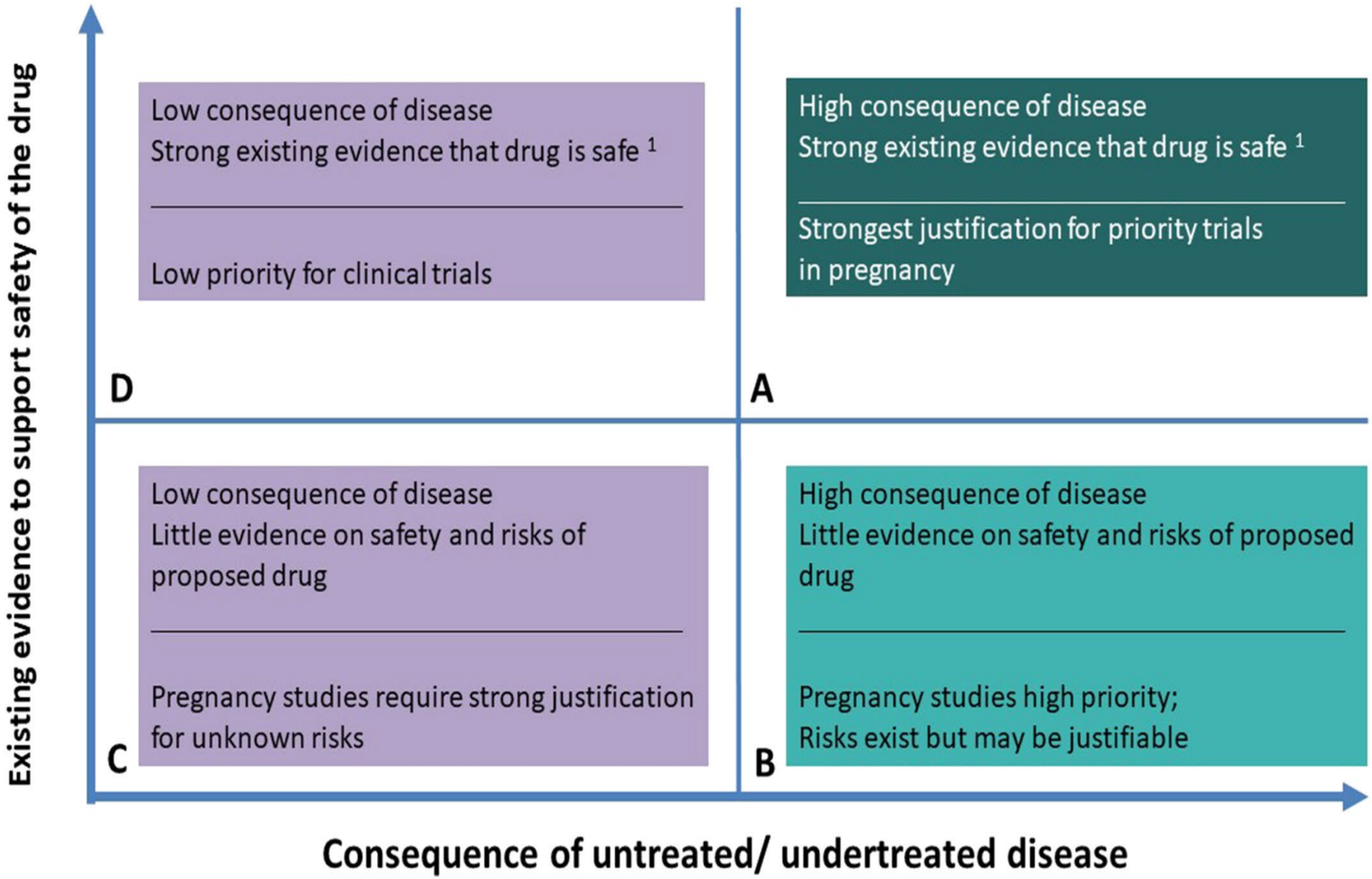
# HIV has led the way

- Advocated for the earlier and routine inclusion of pregnant or potentially pregnant women in such studies
- Provided guiding principles for the design and analysis of high quality pharmacokinetic studies
- Provided an ethical framework on which to underpin trials
- 2016 systematic review of all pharmacokinetic studies in pregnancy identified 198 studies exploring 121 different medications; 25% were HIV drug trials
- ARV were given to mothers with HIV to protect the infant from up to a 30% risk of acquiring HIV in utero or peripartum & 50% mortality by age 2 years without treatment, rather than to improve the mothers' health.
- Risk and benefit reflected the substantial risk to the infant of not treating the mother
- Strong advocacy from affected communities
- Strong partnerships and stakeholder relationships prioritising the generation of evidence

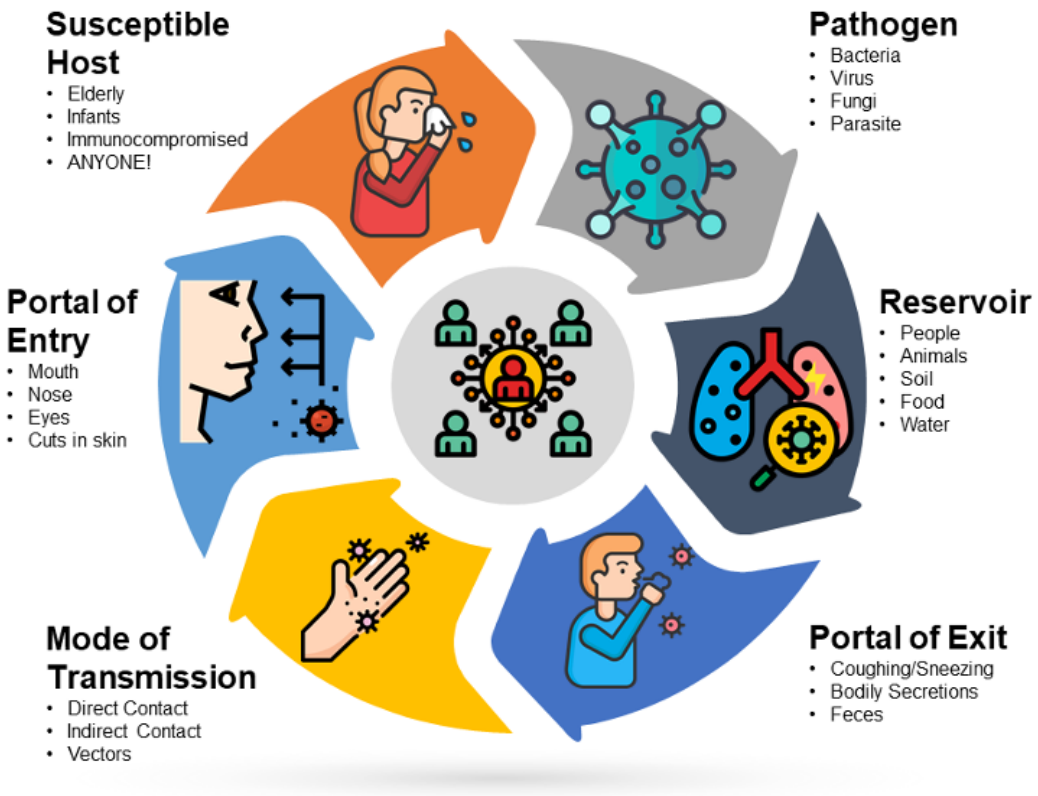



Timing of MTCT of HIV

Fairlie et al. Inclusion of pregnant women in antiretroviral drug research: what is needed to move forwards? *J Int AIDS Soc*. Sep 2019
Eke et al. Optimizing Pharmacology Studies in Pregnant and Lactating Women Using Lessons from HIV: A Consensus Statement. *Clin Pharmacol Ther*. 2020.
Pariente et al. Pregnancy-Associated Changes in Pharmacokinetics: A Systematic Review. *PLoS Med*. 2016

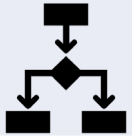

Existing evidence to support safety of the drug
Low consequence of disease
Strong existing evidence that drug is safe [1]
Low priority for clinical trials
D
High consequence of disease
Strong existing evidence that drug is safe [1]
Strongest justification for priority trials in pregnancy
A
Low consequence of disease
Little evidence on safety and risks of proposed drug
Pregnancy studies require strong justification for unknown risks
C
High consequence of disease
Little evidence on safety and risks of proposed drug
Pregnancy studies high priority;
Risks exist but may be justifiable
B
Consequence of untreated/ undertreated disease

# Transmission routes and mitigations essential




1. Reduce contact with saliva and urine from babies and young children – CMV, MMR, Pertussis
2. Avoid unpasteurized (raw) milk, smoked salmon– Listeria,
3. Do not touch or change dirty cat litter – Toxoplasma
4. Stay away from wild or pet rodents and their droppings – LCMV
5. Get tested for sexually transmitted infections – HIV, Hepatitis, Syphilis
6. Pre-pregnancy and in pregnancy vaccines
7. Avoid people who have an infection/ fever – chickenpox, rubella
8. Ask your doctor about group B strep
9. Protect yourself from vector borne diseases [Zika, Chikungunya, Malaria) – think about where you travel to
10. Wash your hands with soap and water –
    - Bathroom, nappies
    - Preparing food
    - Gardening/ soil
    - Handling pets
    - Saliva, spit
    - Sick people

# Key Points

| | |
|---|---|
| | There will always be new infectious diseases threats causing epidemics and pandemics |
| | Infectious diseases will continue to have a disproportionate impact on pregnant women and neonates |
| | Systematic surveillance set up in advance will allow rapid detection of the impact on pregnancy |
|  | Clinical trials should consider including pregnant women where the infection impacts on pregnancy or paediatric outcome |
| | Vaccines have the greatest impact on reducing the effect of infectious diseases in pregnancy |
| | Ethical frameworks for inclusion of pregnant women have been developed but they are still underutilised |
| | Advocacy and stakeholder engagement is required in advance of epidemics and pandemics |

# Epidemics and Pandemics - what have we learnt

**Structured approach essential**

- Understand who is affected
- Understand who needs hospital care
- Understand who dies
- Understand the transmission routes and when it occurs
- Develop pharmaceutical interventions - treatments and vaccines
- Equity consideration

**Until then**

- Identify cases rapidly
- Manage force of transmission - contact tracing and measures for contacts
- Reduce risk of transmission by understanding routes, NPIs
- Ensure healthcare delivery protected
- Protect those at greatest risk for severe outcomes

New and existing health threats are constantly emerging

We must continue to improve our response and ensure equity at the heart of everything we do.