**From emerging zoonoses to pandemics:
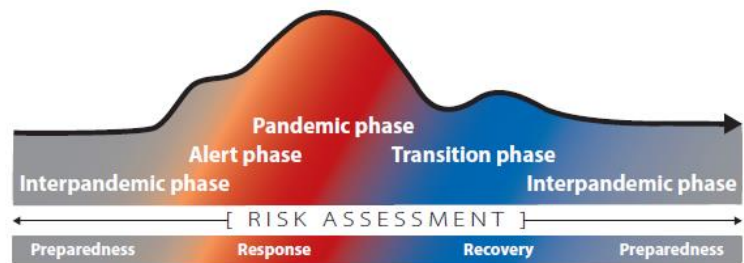what does the future hold?**

Neil Ferguson

WHO Collaborating Centre for Infectious Disease Modelling
MRC Centre for Global Infectious Disease Analysis
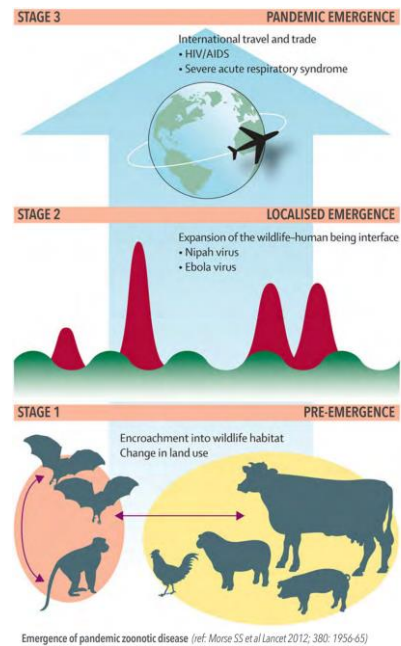Jameel Institute

Imperial College London

1

Topics

- Emergence
  - ➢ Zoonoses
  - ➢ Mechanism
  - ➢ Risk factors
  - ➢ Global change

- Response:
  - ➢ Detection
  - ➢ Characterisation
  - ➢ Control

- Lessons from COVID & outlook

Pandemic phase
Alert phase   Transition phase
Interpandemic phase   Interpandemic phase

[RISK ASSESSMENT]

Preparedness   Response   Recovery   Preparedness

WHO & CDC

2

Emergence

STAGE 3   PANDEMIC EMERGENCE
International travel and trade
• HIV/AIDS
• Severe acute respiratory syndrome

STAGE 2   LOCALISED EMERGENCE
Expansion of the wildlife-human being interface
• Nipah virus
• Ebola virus

STAGE 1   PRE-EMERGENCE
Encroachment into wildlife habitat
Change in land use

Emergence of pandemic zoonotic disease (ref: Morse SS et al Lancet 2012; 380: 1956-65)

Origins of novel infections

- Animals

- Zoonoses

- Some known threats – Influenza, Ebola, Marburg, Nipah…

- But SARS-1 and SARS-2 were unknown

- Risk may be increasing – encroachment on habitats, higher human/livestock densities

- BUT new diseases need to adapt to us to spread from person to person – difficult.
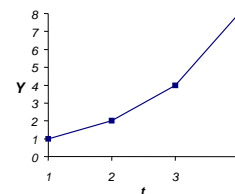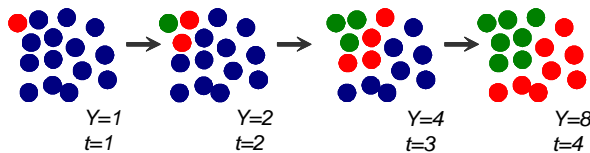
Pandemics

- Pandemic = global epidemic of a new disease

- Starts with a zoonosis mutating to be transmissible
  - Influenza
  - HIV/AIDS
  - Black Death and syphilis
  - SARS-CoV-1 – could have caused a pandemic
  - SARS-CoV-2

- Can profoundly affect society
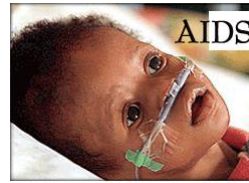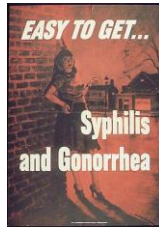
5

Epidemics ABC

- Epidemics spread through contact (e.g. person to person)
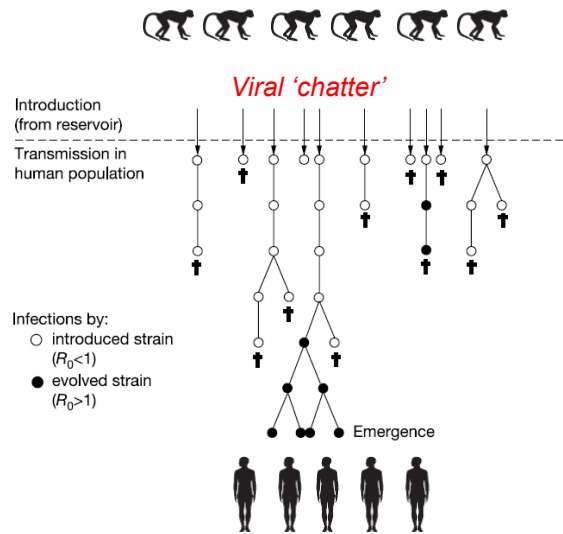- 'Chain reaction' gives exponential growth

- R_0 is the number of secondary cases per case at the start
- Needs to be >1 for an epidemic to take off
- Emerging infections start with $R_0 < 1$, need to evolve to $R_0 > 1$ to cause a human epidemic

6

Process of emergence

- Constant exposure of human populations to animal pathogens

- Only a few breakthrough to cause human epidemics

- Want to predict and detect emergence

- Both hard, but detection easier

Viral 'chatter'

Introduction (from reservoir)

Transmission in human population

Infections by:
- ○ introduced strain $(R_0 < 1)$
- ● evolved strain $(R_0 > 1)$

Emergence

Antia et al. Nature 2003

7

Influenza as an example

- Flu principally a bird virus – e.g. H5N1

- But some mammals can also be infected, with difficulty

- Virus has to adapt (e.g. mutate) to transmit in mammals

- Perhaps easier via intermediate hosts (e.g. pigs)

- Transmissible virus $\Rightarrow$ pandemic (because limited human immunity)
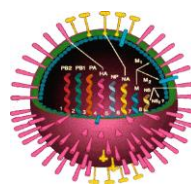
8

H5N1 highly pathogenic avian influenza

Wild birds (Sep-Dec 22)

- First detected in Hong Kong in 1997 – 18 human cases, 6 fatal

- Outbreaks detected in poultry in SE Asia from 2003

- 885 human cases detected globally since 1997, 458 fatal

- Until 2015, spread largely restricted to Asia

- Since then, increasing spread into many European and American wild bird species – 2022-3 worst season yet

https://www.ecdc.europa.eu/en/avian-influenza

Poultry (Sep-Dec 22)

- Occasional spill-over into farmed poultry – resulting in large-scale culls

- Virus has evolved extensively since 1997, via reassortment and mutation – 2.3.3.4b lineage now dominant in Europe

- Infection detected in a range of scavenging mammals, but only a few (mild) human cases recently – evolution?

- A continuing threat to animal and potentially human health
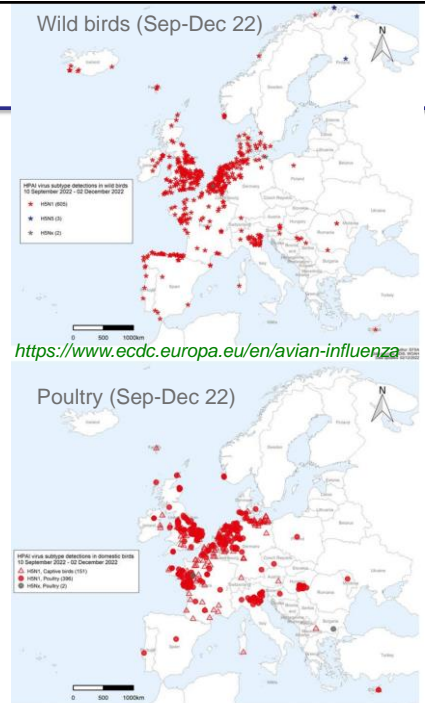
9

H1N1 in 2009

- 2009 pandemic virus had avian, swine and human elements

- May have been circulating for months/years in pigs

Gene Segments, Hosts, and Years of Introduction

2009 A(H1N1)
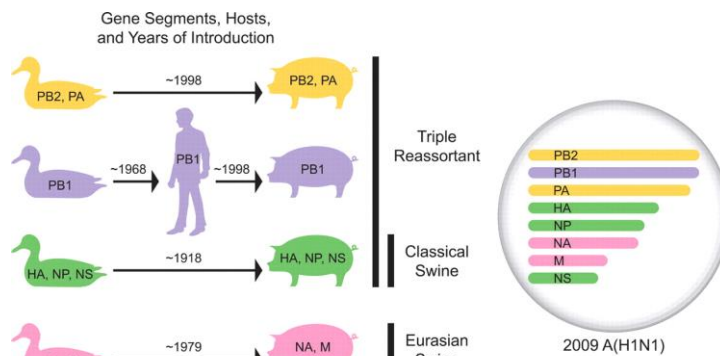
Garten et al, Science 2009

10

Quantifying the risk

- Need to distinguish **frequency** from **severity**

- **Severity** - most emerging infections probably 'mild' (e.g. swine flu) – but need to prepare for low frequency, high severity epidemics

- **Frequency** of emergence depends on:
  - ➤ Human exposure
  - ➤ Evolutionary hurdle for adaptation

- Understanding of both limited
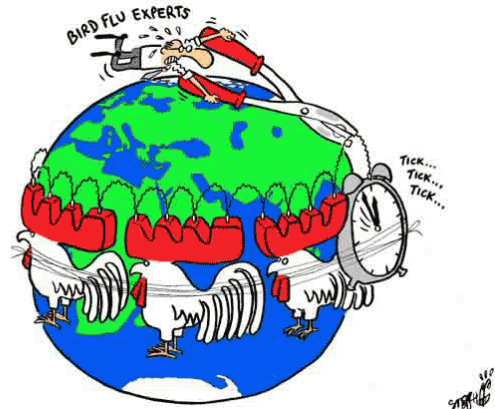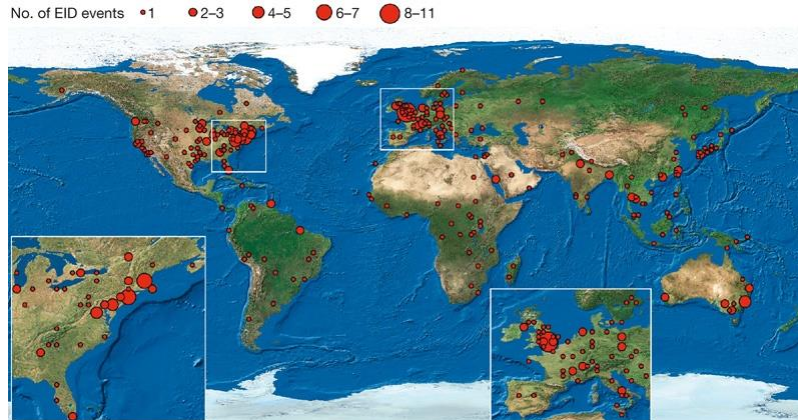

11

Determinants of human exposure

- Human & animal population sizes and density
- Contact with animals – esp. wildlife
- Behaviour
- Infection patterns in animals
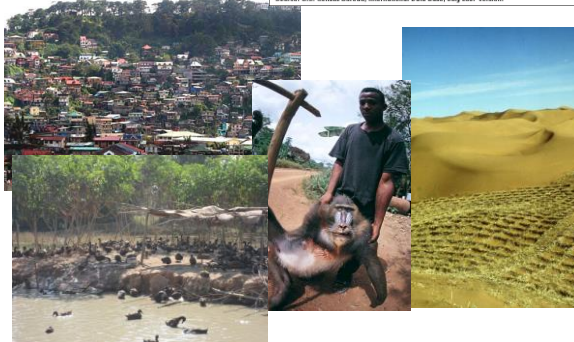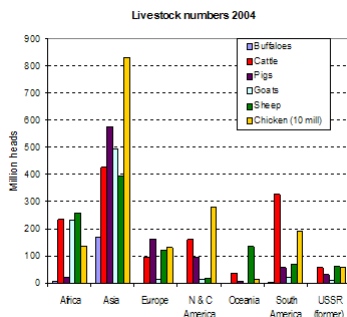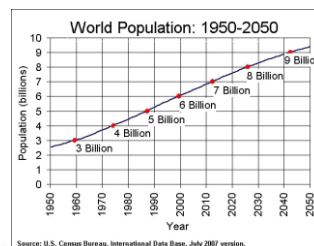
12

Being rigorous

- Easy to hand-wave about increasing risk.
- Much harder to quantify risk, prove hypotheses.
- First start is cataloguing emerging infections.

No. of EID events • 1   • 2–3   ● 4–5   ● 6–7   ● 8–11
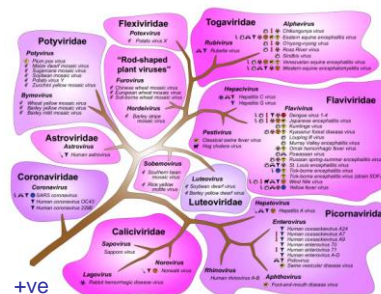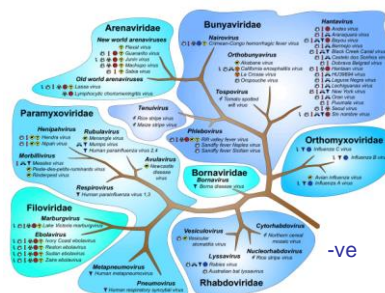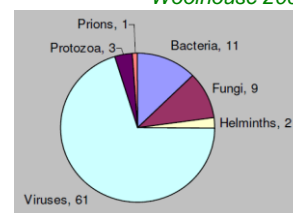

*Jones et al.
Nature 2008*

13

Characteristics of EIDs

- Viruses predominant cause
- Despite there being more bacterial pathogens
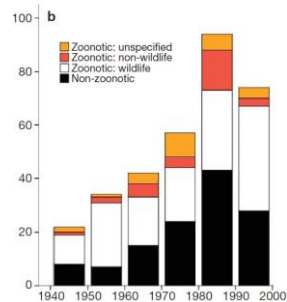- RNA viruses particularly prominent.
  - ➢High mutation rate

Woolhouse 2005

Prions, 1
Protozoa, 3
Bacteria, 11
Fungi, 9
Helminths, 2
Viruses, 61

-ve

+ve

Ecker et al., BMC Microbiol, 2008

14

7

Drivers for changing risk

- EIDs appear to be increasing in frequency
- Correlation between human population density and frequency
- And with wildlife species richness
- Causal relationships unproven though
- Vector-borne diseases have clearer link to climate

Legend:
- Zoonotic: unspecified
- Zoonotic: non-wildlife
- Zoonotic: wildlife
- Non-zoonotic

(x-axis: 1940 1950 1960 1970 1980 1990 2000)

Pathogen type	Zoonotic: wildlife
Number of EID event grid cells	147–156
	b
log(JID articles)	0.34-0.37***
log[human pop. density (persons per km^2)]	0.56-0.64***
Human pop. growth (change in persons per km^2,1990–2000)†	0.09–0.45
Latitude (decimal degrees)	0.002–0.017
Rainfall (mm)	$(0.14-0.06) \times 10^{-3}$
Wildlife host richness	0.008–0.013**
Constant	−9.81 to −8.78***

Jones et al. Nature 2008

15

A changing world

- Rapidly changing world affects EID emergence, spread and impact in multiple ways

Baker et al.
Nature Rev Microb 2022

	Pathogen emergence	Disease dynamics	Global spread
Climatic change	Drives range shifts for reservoir species	Affects transmission and susceptibility	Affects the geographical range of vectors
Technological change			
Transportation	Improved global surveillance		Air transit and high-speed rail affect pace and range of spread
Health care		Vaccination affects dynamics	Improved care reduces burden
Demographic change			
Population growth and land use	Increased contact with reservoir species	Population numbers affect evolution, birth rates affect dynamics	Larger population travelling
Urbanization	Depends on species	Density affects contact rate	Urban population more connected
Ageing	Imunosenescence affects spillover risk	Ageing population increases transmission	Possible larger burden

Fig. 3 | **Effects of climatic, technological and demographic change on disease emergence, dynamics and spread.** The table summarizes select recent global changes (rows) and their impacts on disease emergence, local-scale dynamics and global spread (columns). An example susceptible (S), infected (I), recovered (R) model is shown, where β represents the transmission rate and γ is the recovery rate.
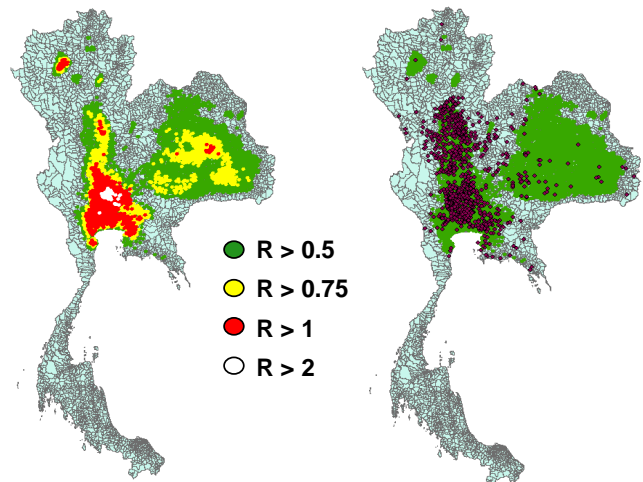
16

8

Dynamics of animal infections

- Sampling will always be sparse, esp. for non-pathogenic infections

- So need to model how transmission varies spatially

- e.g. H5N1 in Vietnam

- Even harder for wildlife populations (e.g. H5N1 in UK now)

- Would like to couple to a model of human exposure.

Modelled risk map for H5N

H5N1 outbreaks in Vietnam

🟢 R > 0.5
🟡 R > 0.75
🔴 R > 1
⚪ R > 2

Walker et al., Plos Comp Biol 2010

17

Genetic risk factors for emergence

- A few known (e.g. use of conserved cellular receptors), especially for flu

- Understanding of the genetic basis of transmissibility weak – experiments hard

- But can examine diversity in multi-host pathogens (e.g. flu)

- Gives data on 'mutational barrier' for species jumps

- Exponentially increasing genetic data and better viral phenotyping leading to faster progress

- Net mutation rate key

- Virus 'sex' (reassortment for flu) offers an evolutionary shortcut

18

9
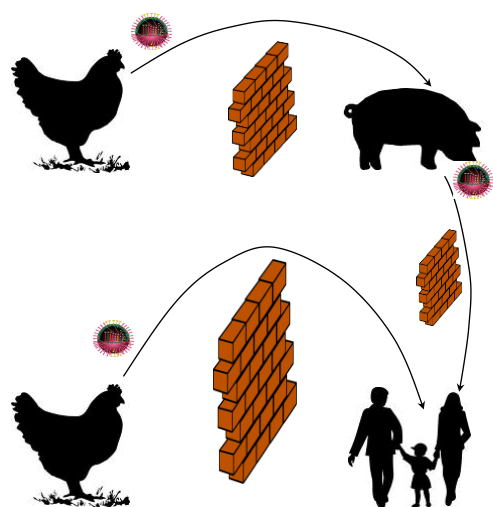
If we know the genetic barrier

- *Can estimate probability of n-point mutant RNA virus arising*

- Need to know (or assume) replication rate, mutation rate, relative fitness …

- e.g. H5N1
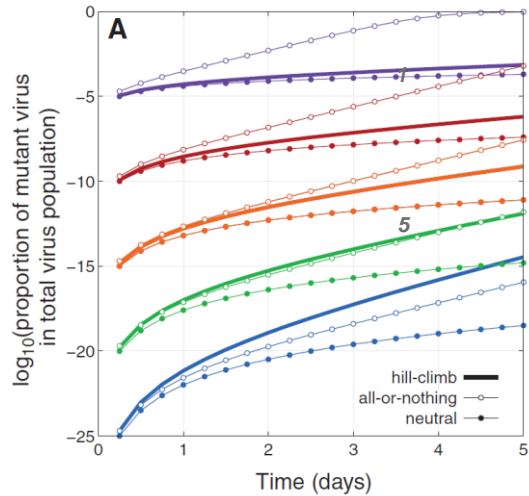
Russell et al. Science 2012

19

The human element

- Also need to understand human exposure:
  - ➢Identify risky behaviours
  - ➢Look for infection in exposed populations
- Growing research area
- But very hard to prove specific risk behaviours for transmission:
  - ➢Rare events
  - ➢Can involve intermediate species (e.g. Nipah)
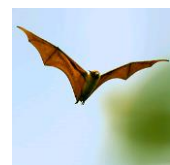

20

Response

21

Approach

- Prior to COVID, many countries shared the same approach:
  - ➢ Prepare
  - ➢ Prevent
  - ➢ Detect
  - ➢ Contain
  - ➢ Mitigate
- COVID hasn't changed the logic, but did highlight implementation and capacity weaknesses
- Focus on "One Health" (human and veterinary) in recent years, though impact as yet unclear

Bedford et al., Nature 2019

22
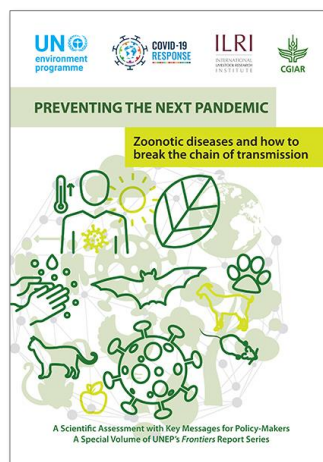
11
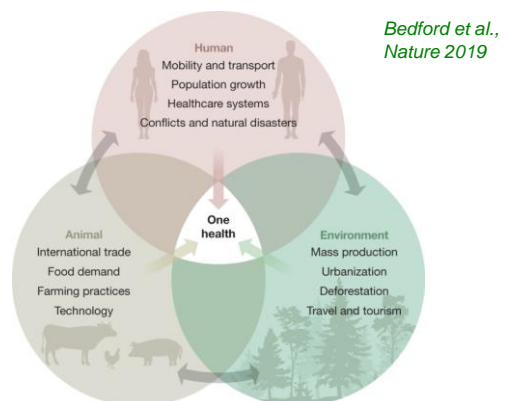
Preparedness

- Investment in systems, capabilities, research:
  - ➤ Surveillance (incl diagnostics & testing)
  - ➤ Research to improve rapid virological and epidemiological assessment
  - ➤ R&D into rapid vaccine/antiviral development and manufacturing
  - ➤ Stockpiling (e.g. PPE, pre-pandemic vaccines)
  - ➤ Health system resilience
- Systems need to be tested
- Pandemic highlighted limitations of investments in preparedness in countries like UK and US
- And identified new priorities ("100 day mission")
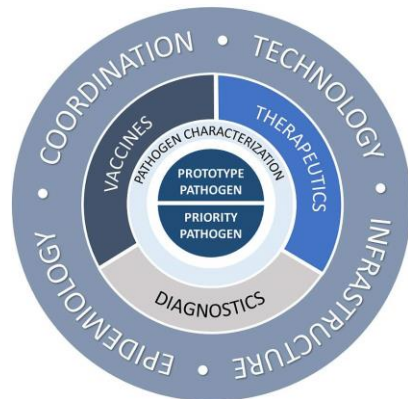
23

Prevention

- Can refer to preventing spill-over or early containment (latter covered later)
- Preventing spill-over requires:
  - ➤ Detecting "worrying" signal in animals
  - ➤ Controlling that virus in animals, *&/or*
  - ➤ Implementing controls to reduce human exposure
- Controls can include:
  - ➤ Animal vaccination/culling
  - ➤ Environmental/economic interventions to shrink animal-human interface
  - ➤ e.g. H7N8 in China – poultry vaccination, ending poultry wet markets
- Much discussed, but implementation hard – both detection of signal and control

UN environment programme · COVID-19 RESPONSE · ILRI INTERNATIONAL LIVESTOCK RESEARCH INSTITUTE · CGIAR

PREVENTING THE NEXT PANDEMIC

Zoonotic diseases and how to break the chain of transmission

A Scientific Assessment with Key Messages for Policy-Makers
A Special Volume of UNEP's *Frontiers* Report Series

Poultry wet market

24

12

Early detection

- Severe infections likely to be picked up earlier (e.g. H5N1 vs H1N1)

- Want to detect *clusters* of (severe) disease

- Community syndromic surveillance key - backed by enhanced genetic diagnostics

- Social media monitoring also valuable

- *e.g.* GPHIN detected SARS in 2002-3, and H5N1 in ducks in China in 2004

- SARS-1 and then H5N1 led to substantial investment diagnostic lab capacity in Asia (backed by genetics)

- Nowhere more so than in China – why SARS-CoV-2 detected & sequenced relatively early


25

Genomic surveillance

- Needed to detect threats and during epidemic to monitor evolution

- Big problem – we probably only know <2% of animal viruses

- Impossible to isolate and identify them all traditionally

- Metagenomics offers the potential to shortcut traditional approaches to identify novel viruses with multiple hosts

- Many research studies in the last decade, but progress slow

- But human viral genomic surveillance grown dramatically in last decade

- Accelerated by COVID pandemic

- Novel approaches: wastewater sampling

Genomic surveillance is monitoring the genetic make-up of pathogens, such as viruses and bacteria, to understand how they behave and how we can control them.
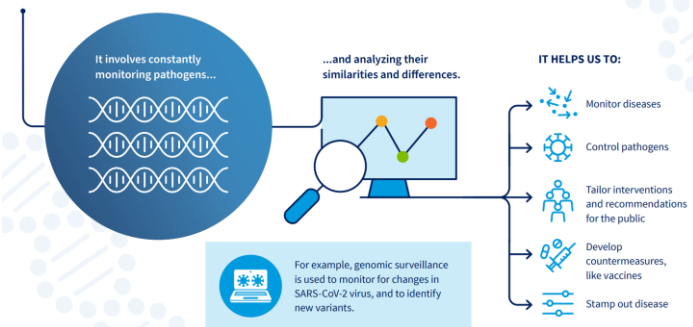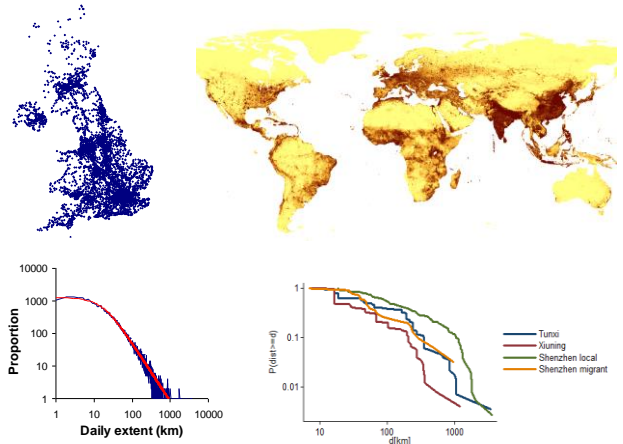
26

Factors determining early human spread

- Transmissibility (is it fully adapted?)

- Social structure/connectivity.

- Mobility of local population.

- Behavioural norms (e.g. re healthcare).
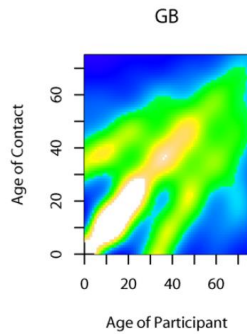
Mossong et al. Plos Med 2007

Containment

- Elimination of the virus from the human population at an early stage

- With non-pharmaceutical interventions (NPIs)

- Feasibility depends on the pathogen

- Probably only possible for severe disease with clear case definition

- e.g. SARS, human H5N1, Ebola

- Impossible when most infections are mild/asymptomatic (e.g. H1N1 in 2009, COVID-19 in 2019/20) – detect outbreak too late

- Effort required increases exponentially with delay – e.g. West Africa Ebola, 2014

- Even for H5N1, need to move fast with intensive measures
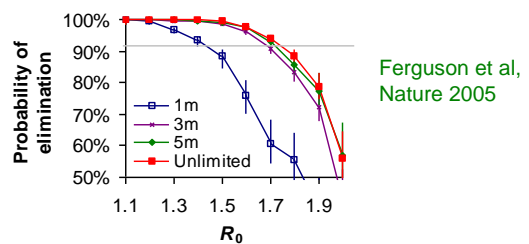
Ferguson et al, Nature 2005
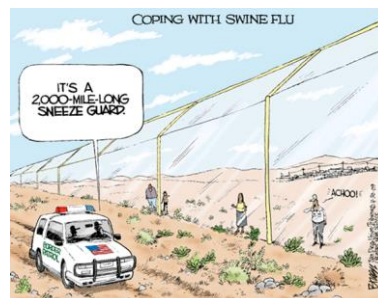
A more severe example – SARS-1

- Was controlled when hospital infection procedures intensified
- Lucky – only sick people transmitted, and universally severe
- Modelling gave epidemiological insight:
  - basic parameters (incubation period, mortality)
  - rate of spread [R=2.7] and impact of controls
  - general insight
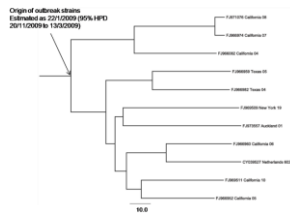

Cases in Hong Kong
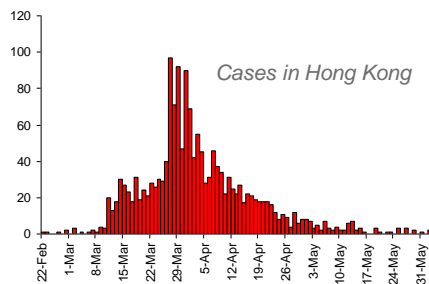
29

Mitigation

- If containment fails
- Key measures:
  - Vaccines
  - Antivirals
  - NPIs
- Problem is the speed of spread
- Key issue: scaling response to level of threat
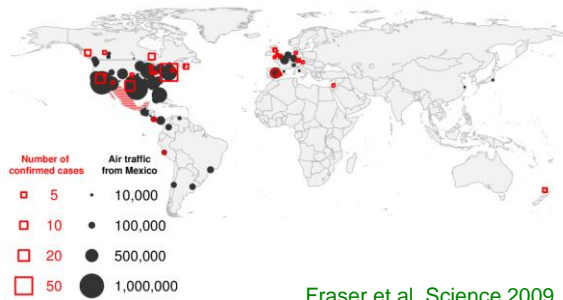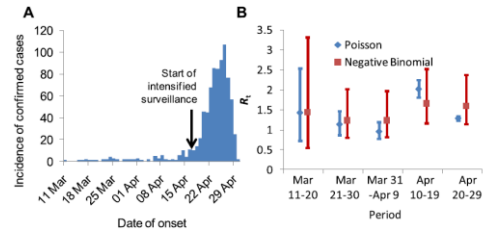- Requires timely characterisation of level of threat

30

Epidemiological characterisation

- How bad is it?

- How far has it got?

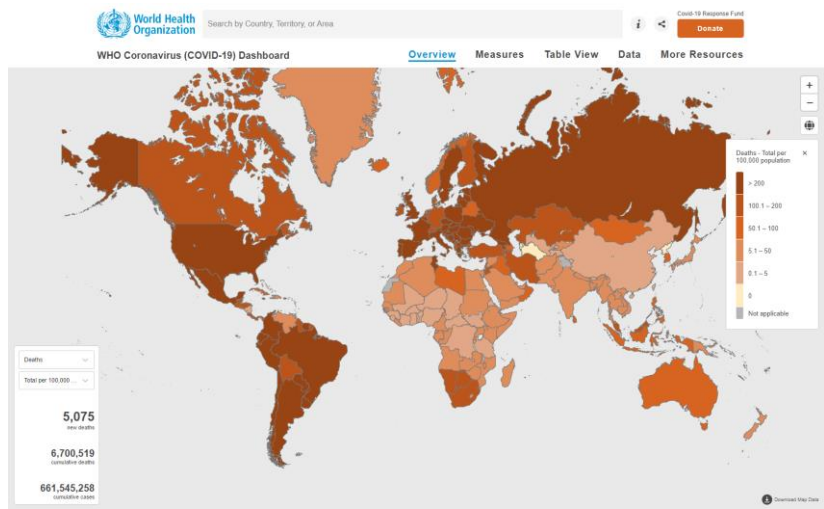- How fast is it spreading?

- What can we do?

*e.g. **2009 H1N1**
– estimated R_0, origin date,
extent of spread and upper
bound on severity within 3
weeks.*

Fraser et al, Science 2009

31

Lessons from COVID-19

32

Experience from COVID-19

- 20 days from first detected case to sequence being available – good compared with past, but room for improvement

- Virus not detected in animals, despite extensive retrospective testing

- Epidemiological assessment took ~8 weeks, notably to obtain reliable estimates of severity – too slow, but hard to improve

- Initial testing capacity was too limited – led to very targeted testing (severe cases, travellers from China), most infections being missed

- Vaccines took 1 year to develop and produce at scale – huge achievement, but still too slow

- Paradigm shift in policy response to a lethal pandemic: suppression adopted by many countries, rather than mitigation

- Rapid viral evolution with large impacts on epidemiology

- Huge health, social and economic impacts, poor affected worst

- Lack of international political coordination, but unpreceded scientific openness and collaboration
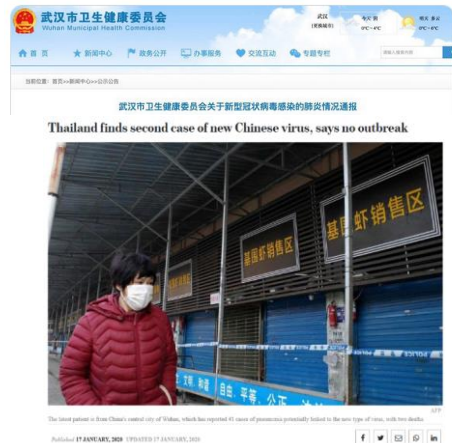
33

Lessons learned: WHO

- Many IGOs/countries have run lessons-learned inquiries

- WHO "Independent panel" 7 recommendation areas:

  1. *Elevate political leadership for global health to the highest levels to ensure leadership, financing and accountability*

  2. *Focus and strengthen the authority and financing of WHO*

  3. *Invest in preparedness now to create fully functional capacities at the national, regional and global level*

  4. *Establish a new agile system for surveillance, validation and alerts*

  5. *Establish a pre-negotiated platform for tools and supplies*

  6. *Raise new international financing for the global public goods of pandemic preparedness and response*

  7. *Put in place effective national coordination for pandemic preparedness and response based on lessons learned and best practice*
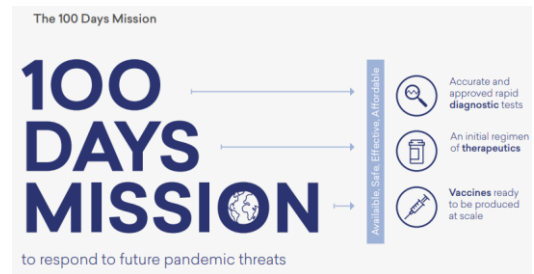

https://theindependentpanel.org/
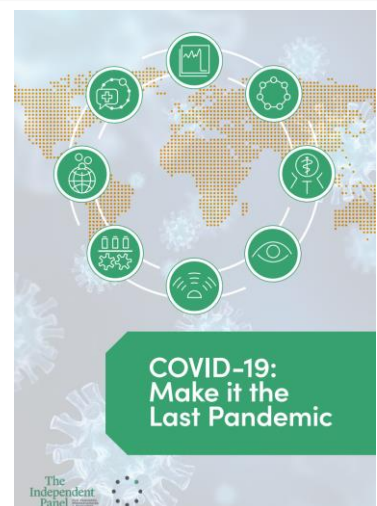
34

Lessons learned: G7

- Focussed on technical challenges rather than social/political/governance
- Key recommendation was for investment and R&D to allow large-scale manufacture and distribution of diagnostics, vaccines, therapeutics within 100 days of an alert
- *i.e.* May 2020 rather than December 2020
- Requires enhanced surveillance, pre-pandemic generation of candidate vaccines, sleeping clinical trial networks, novel manufacturing platforms, financing, …

The 100 Days Mission

100 DAYS MISSION
to respond to future pandemic threats

Accurate and approved rapid **diagnostic** tests

An initial regimen of **therapeutics**

Vaccines ready to be produced at scale

G7, 100 days mission

35

Ongoing priorities

- **Predict:**
  - ➢ Characterise zoonotic pathogens
  - ➢ Identify specific threats
  - ➢ Understand predictors of emergence
- **Prepare**:
  - ➢ Improve animal surveillance
  - ➢ Pre-screen antimicrobial agents
  - ➢ Develop candidate vaccines
  - ➢ Rapid production capacity
- **Detect**:
  - ➢ Innovative surveillance (e.g. wastewater)
  - ➢ Rapid in-country diagnostics (incl. sequencing)
- **Respond**:
  - ➢ Real-time characterisation (virological, clinical, epidemiological)
  - ➢ Real-time clinical research
  - ➢ Healthcare system (and societal) resilience
  - ➢ Improved governance (nationally, regionally and globally)

36