Pandemics: emergence, spread and the formulation of control or mitigation policy

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Pandemic emergence and spread

Emergence

Surveillance

Containment

Response & Mitigation
Pandemic emergence and spread

- Emergence
- Surveillance
- Containment
- Response & Mitigation
Emergence

Source: National Institute of Allergy and Infectious Diseases, NIH, USA
SARS 2003

Global alert 13\textsuperscript{th} March 2003

- 8098 probable cases
- 27 countries
- 774 deaths (9.6%)

- Last cases June/July

Sources: WHO and Hollingsworth 2009
Journal of Public Health Policy
HIV/AIDS

• 2.6 million new infections, 1.8 million deaths in 2009
• Main pandemic strain emerged from chimpanzees in West Africa
• Emerged in late 19th/early 20th century
• Expansion may have been due to population changes in early 20th Century
• First noticed in early 1980s
• Asymptomatic transmission for many years prior to developing AIDS

Sources: UNAIDS, Lemey et al Genetics 2004 and references within, image Wikipedia Commons
Ebola haemorrhagic fever

- Intermittent outbreaks of a 10s to 100s of cases
- Very severe symptoms
- High mortality rate (up to 100%)
- Controlled by rapid response including quarantine

Sources: WHO and CDC, image Wikipedia Commons
H5N1 influenza – “bird” flu

Limited outbreaks, Severe symptoms
H1N1 influenza 2009 – “swine” flu

- Worldwide pandemic
- Millions of cases
- Low mortality

Fraser et al Science 2009
Emergence

• Biological factors
  – Ability to infect humans
  – Transmissible in humans

• Human factors
  – Interaction with animals
  – Contact and travel patterns

• Interactions
  – Biological factors which make containment unlikely
**Basic Reproduction number, $R_0$**

- $R_0$: Basic reproduction number
  - average no. of secondary cases generated by 1 primary case in a susceptible population

- $R_t$: Effective reproduction number
  - number of infections caused by each new case occurring at time, $t$

- The key determinant of incidence and prevalence of infection is the basic reproductive number $R_0$.
- Many factors determine its magnitude, including those that influence the typical course of infection in the patient and those that determine transmission between people.

### Chains of transmission between hosts

<table>
<thead>
<tr>
<th>Generation</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number Infected</strong></td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

$R_0$ Basic reproduction number
Repeated crossing from reservoir

- Continued transmission within reservoir
- Multiple opportunities to evolve
- May not be picked up by surveillance
- Increase $R_0$
- Workers in animal markets had previously been exposed to SARS-like viruses

Antia et al Nature 2003
Cluster sizes

- Detecting unusual activity
- Larger cluster size indicates higher $R_0$
- Monitoring identifies how close $R_0$ is to 1

Ferguson et al Science 2004
Emergence

- Biological factors
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\[ R_0 > 1 \]
Symptoms and severity

• Identifiability of symptoms make surveillance easier
• Influenza-like-illness
  – Non-specific
  – Case definition often includes contact with other known cases
  – Need to look for unusual patterns, perhaps in non-standard data sources e.g. excessive paracetamol sales
• High severity makes detection more likely
Surveillance

- Google flu trends
- Use search terms to estimate incidence

- Health Map
- Early warning
- Internet reports
Young die disproportionately in influenza pandemics
Problems with estimating severity: delays

Garske et al, British Medical Journal 2009
Pandemic emergence and spread

Emergence
Surveillance
Containment
Response & Mitigation
Containment

• Contact tracing and quarantine
  – Pre-symptomatic infectiousness

• Local or global spatial containment
  – Epidemic growth rate
  – International travel

• Reducing impact
  – Mitigating impact
Containment: Epidemic curve

- Rate of new infections
- Time

- Establishment
- Exponential growth
- Endemicity

Random effects

Equilibrium, or recurrent epidemics

Ferguson et al Nature 2003
Control of SARS outbreaks

• Lack of pre-symptomatic infectiousness

➢ Increasingly rapid admission to hospital

➢ Infection control in hospitals

Fraser et al PNAS 2004

Riley et al Science 2003
Quarantine

Insufficient control to prevent epidemic

Fraser et al (2004) PNAS

$R_0 = \text{basic reproduction number}$

$\theta = \text{proportion of infections due to asymptomatic infections}$
Hong Kong 2003 SARS outbreak
Rapidly brought under control

Pattern of the epidemic:
stochastic mathematical model - fit to observations

No. of secondary cases generated by each primary case

(Riley, Fraser et al, 2003 Science)
Assume strain emerges in rural SE Asia.

For ‘human-like’ strain, time to peak in the first country affected anywhere from 80-120 days.

Key questions: can we stop spread at this early stage? What resources are required? Can we be sure?

Policies to contain a pandemic at source

Containment = elimination of virus before spread is extensive.

Variety of options; e.g.:

- treatment of cases.
- prophylaxis of household members.
- prophylaxis of schools/workplaces of cases.
- blanket prophylaxis of affected areas.
- Closure of schools/workplaces.
- Reduce travel in and out of affected zones

Delays, detection thresholds and usage limits simulated.

Pandemic influenza – antivirals

• Social + 5km prophylaxis
• 5km quarantine
• Infected
• Recovered
• Treated
• 100 days

International Airline Travel

International Tourist Arrivals, 1950-2004*

Source: World Tourism Organisation

Mean passengers per day
- 300 - 750
- 750 - 1500
- 1500 - 3000
- 3000 - 6000
- 6000 - 12000
International travel SARS 2003

- Global alert 13th March
- Up to 80% reduction in passenger numbers
- Coincident with peak in epidemic
- Continued beyond end of outbreak

Travel restrictions & Internal control

No control of source epidemic

$p = \text{Proportion of travel restricted}$

$R = 0.8, p = 0\%$

$R = 0.8, p = 80\%$

$R = 0.8, p = 99\%$

2003 SARS outbreak

Nature Medicine
## SARS and influenza

<table>
<thead>
<tr>
<th></th>
<th>SARS</th>
<th>Influenza</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic reproductive number $R_0$</td>
<td>2.5</td>
<td>1.8</td>
</tr>
<tr>
<td>Latent period</td>
<td>4 days</td>
<td>1.5 days</td>
</tr>
<tr>
<td>Infectious period</td>
<td>10 days</td>
<td>1.1 days</td>
</tr>
<tr>
<td>Epidemic doubling time</td>
<td>6.5 days</td>
<td>2.3 days</td>
</tr>
<tr>
<td>Pre- or asymptomatic infectiousness</td>
<td>NO</td>
<td>YES</td>
</tr>
</tbody>
</table>

Hollingsworth et al (2007) *Emerging Infectious Diseases*
International travel

• Airborne respiratory infections can rapidly spread globally
• Control of source epidemics is a major factor in limiting global spread of these infections
• Reductions in travel for SARS were too little, too late in absence of internal control
• Influenza is likely to spread globally prior to the introduction of travel restrictions

*Nature Medicine* and several other references at the time.
Global spread and the epidemic in Mexico
Pandemic emergence and spread

Emergence

Surveillance

Containment

Response & Mitigation
Response

• Priority tasks to inform policy
  – Clearly defined case definition
  – Real-time reporting
  – Identifying routes of transmission
  – Identifying etiological agent
  – Design of treatment protocols

• Epidemiological parameter estimation
  – $R_0$, incubation period, epidemic growth rate
  – Example of H1N1 2009 influenza
Parameter estimation: H1N1 Influenza 2009

‘Canaries in the mine’

Fraser et al Science 2009
Size of epidemic in Mexico

Strong correlation allows back-calculation of size of Mexican epidemic.

Best ‘estimate’ – 23,000 (18-32k) (based on interval censored model)  
CFR=0.4%

Worst case (for severity) – 6,000 (based on presence-absence model)  
CFR=1.4%

Fraser et al Science 2009
La Gloria: age-specific attack rates

Consistent with emerging US pattern at the time, though absolute magnitude may differ.

Fraser et al Science 2009
\( R_0 \) from Mexican epi curve

- Derived using renewal equation based method.
- \( R_0 = 1.37 \) (95% Cr.I.:1.24-1.59) for a model with Poisson case counts
- \( R_0 = 1.47 \) (95% Cr.I.:1.21-1.88) for negative binomial (overdispersed) case counts

Fraser et al Science 2009
Planning mitigation strategies

• Mathematical modelling can inform the design of mitigation strategies
  – Scenario building
  – Effect of uncertainties
  – Depends on good quality data

• Insights informed policy in 2009 H1N1 pandemic
Prioritising aims

- Cannot achieve all aims using the same strategy

Minimise peak demand
Minimise total cases

12 week strategy, starting week 5

Hollingsworth et al
PLoS Computational Biology 2010
Uncertainties in pandemic modelling

- Nature of virus (avian- or human-like)
- Transmissibility.
- Where transmission occurs (home, school, workplace, hospital).
- Lethality/risk groups for severe illness.
- The effect of ‘social distance measures’.
- Quality and timeliness of surveillance (ascertainment).
- Logistic constraints.
- .....
Summary

• Emergence
  – Impossible to predict exactly
  – Animal/human interface
  – Depends on both evolution of pathogen and human behaviour

• Containment?
  – Symptoms: type, timing, severity
  – Epidemic growth rate
  – Quality of surveillance

• Mitigation
  – Possible if plans are carefully constructed
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