An epidemiologist's life on the edge (of the science-policy interface)

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Perspectives on epidemics: individuals
Another view: populations

H1N1, 1918-19

SARS, Hong Kong, 2003

Doubling time, attack rate

H1N1, 2009
The bridge: contacts

Variola minor, England, 1966

SARS, Singapore, 2003

Secondary attack rate, offspring distribution, reproduction number, generation time

H1N1, UK, 2009
My academic habitat

http://www1.imperial.ac.uk/publichealth/departments/ide/outbreaks/background/
My background

• Oberlin College: BA Maths 1988
• HSPH: MSc & ScD Biostatistics 1988-1992
• University of Edinburgh
• University of Oxford
  Head of Statistics Unit 1995-2000
• Imperial College London
  Reader then Professor 2000-
Daniel Bernoulli
(1700-1782)

On smallpox inoculation:

“I simply wish that, in a matter which so closely concerns the well-being of mankind, no decision shall be made without all the knowledge which a little analysis and calculation can provide.”
Epidemic as chain reaction:

Governed by $Reproduction\ Number\ R$.

Need $R_0 > 1$ for a large outbreak.
The process of emergence

- Exposure to animal pathogens.
- Only a few break through 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
Being rigorous

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

Jones et al. Nature 2008
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.

Multivariable logistic regression coefficients

<table>
<thead>
<tr>
<th>Pathogen type</th>
<th>Number of EID event grid cells</th>
<th>Zoonotic: wildlife</th>
</tr>
</thead>
<tbody>
<tr>
<td>log(JID articles)</td>
<td>147–156</td>
<td></td>
</tr>
<tr>
<td>log[human pop. density (persons per km²)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human pop. growth (change in persons per km², 1990–2000)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latitude (decimal degrees)</td>
<td>0.09–0.45</td>
<td></td>
</tr>
<tr>
<td>Rainfall (mm)</td>
<td>0.002–0.017</td>
<td>0.34–0.37***</td>
</tr>
<tr>
<td>Wildlife host richness</td>
<td>(0.14–0.06) x 10⁻³</td>
<td>0.56–0.64***</td>
</tr>
<tr>
<td>Constant</td>
<td>0.008–0.013**</td>
<td>0.09–0.45</td>
</tr>
<tr>
<td></td>
<td>−9.81 to −8.78***</td>
<td></td>
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Jones et al. Nature 2008
Role of travel restrictions

- 80% drop in travel to affected countries seen in SARS epidemic – mostly spontaneous.
- Key problem – growth rate of flu pandemic – 10 fold in 7-14 days
- So stopping 90% of travel buys 1-2 weeks, 99% buys 2-4 weeks.
- Very disruptive, expensive.
- So probably only useful while containment is attempted.
SARS 2003

- Was controlled when hospital infection procedures intensified.
- Fortunately 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
Case fatality ratio

• Proportion of cases who eventually die from the disease;
• Often estimated by using aggregated numbers of cases and deaths at a single time point:
  • E.g.: case fatality ratios compiled daily by WHO during the SARS outbreak:
    estimate of the case fatality ratio:
    
    number of deaths / total number of cases.
  • Simple estimates of these reports can be misleading if, at the time of the analysis, the outcome (death or recovery) is unknown for an important proportion of patients.
Proportion of observations censored in the SARS outbreak

We do not know the outcome (death or recovery) yet.

[Ghani et al. AJE, 2005]
Simple methods

- Method 1:

\[ CFR = \frac{D}{C} \]

- Method 2:

\[ CFR = \frac{D}{(D + R)} \]

D = Number of deaths
C = Total number of cases
R = Number recovered
Adapted Kaplan-Meier method

To extrapolate incomplete survivor functions, assume that death/discharge rate at the tail occurs at the same rate as previously:

$$\theta_0 = \frac{\hat{\theta}_0}{\left(\hat{\theta}_0 + \hat{\theta}_1\right)}$$

Proba death at the tail

Proba discharge at the tail
Comparison of the estimates

deaths/(deaths+recoveries)

- Observed case fatality ratio
- Simple estimate 1 (deaths/cases)
- Simple estimate 2
- KM-like method
SARS becoming deadlier: Officials

Friday, April 25, 2003 Posted: 12:41 AM EDT (04:41 GMT)

HONG KONG, China -- As China takes drastic steps to contain the SARS virus, Hong Kong officials say the disease is proving more deadly than first thought.

Global concern is mounting over the rising death rate as authorities clamor to contain the virus, quarantining people, closing schools and installing heat scanners at airports.

Officials in the former British colony of Hong Kong -- the hardest-hit area along with China -- on Thursday revised the death rate from SARS to 7.2 percent from 5 percent.

Death Rate From Virus More Than Doubles, Varying Sharply by Country

By LAWRENCE K. ALTMAN
Published: April 22, 2003

The death rate from severe acute respiratory syndrome has more than doubled, to 5.6 percent, since the epidemic was first detected in mid-March, causing deep concern among health officials.

Although the overall death rate, according to World Health Organization statistics, has hovered around 4 percent in the last three weeks, it has varied widely among the 26 countries, plus Hong Kong, with cases of the disease, known as SARS.
An example: influenza

- Flu principally a bird virus.
- 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 limited human immunity.
- But what is the risk?
What is the epidemic potential of H3N2v?

- H3N2v – new swine variant of influenza A/H3N2 causing cases in people (2011-), associated with animal fairs etc.

- Key questions:
  - Is H3N2v more transmissible in humans than other swine strains?
  - Can H3N2v generate sustained epidemics in humans?

Challenge

Data we would like to have
complete and representative chains of transmission

Data we have
low detection rate
selection bias
incomplete outbreak investigations

In general, we know the source of infection of detected cases.
• From proportion, can estimate length of transmission chain.
• From length of chain, can estimate the reproduction number.
Inferring $R$

![Graph showing the relationship between reproduction number $R$ and case detection rate for different proportions infected by swine.](image)

- **Proportion infected by swine**
  - 1%
  - 0.4%
  - 0.01%

- **Case detection rate**

- **Reproduction number $R$**

- **Y-axis**: Proportion infected by swine
- **X-axis**: Reproduction number $R$
**R** for H3N2v and for other strains

**Other strains:** 81% (17/21) infected by swine

\[ R = 0.2 \ (95\% \ CI: 0.1, 0.4) \]

**H3N2v:** 50% (3/6) infected by swine

\[ R = 0.5 \ (95\% \ CI: 0.2, 0.8) \]

- Significantly <1 if detection rate=0.4%; but not if detection rate=1%.
- Can’t reject the hypothesis of equality (p=0.15).
BSE (Mad Cow Disease)

- First diagnosed in November 1986
- By the end of 1995 there had been over 100,000 clinical cases in British cattle.

![Graph]

Clinical cases peaked in 1992 in Great Britain **despite** a ban on meat-and-bonemeal-containing feed being introduced in 1989.
Backcalculation

Fit the predicted age distribution of case notifications over time to the case reports data using maximum likelihood methods:

\[ c(u|t_0) = \rho(t_0 + u)S(u) \left[ (1 - \pi(t_0)) \int_{a=0}^{u} K(t_0 + a) g(a) f(u - a) da + \pi(t_0) f(u) \right] \]

- Probability that a case gets reported
- Age-related exposure / susceptibility distribution
- Probability that cow is maternally infected
- Density for onset at age \( u \) among those born at \( t_0 \)
- Probability that cow survives to age \( u \)
- Feed risk function
- Incubation period distribution

(to first order in \( K \cdot g \))
BSE Backcalculation Results

Animals slaughtered for human consumption in last year of BSE incubation

10% maternal transmission assumed

OTM ban introduced April 1996

OTMS has by far the largest effect on human risk
A European View

Sichere Insel

Zeichnung: Gotscheber
Conceptual Model for vCJD Epidemic

vCJD cases

- Incubation
  - Dose/age/genotype dependent
  - Survivorship

- Infection
  - Infectivity - by tissue & incubation stage
  - Dose response - linear/non-linear/cumulative
  - Susceptibility heterogeneity

- Consumption patterns
  - Consumption rates - per individual/per product
  - Heterogeneity - by age/time
    - consumers per bovine

- Meat production
  - Tissue types used for food - by time/type of bovine
  - SBO ban effectiveness

- BSE epidemic
  - Estimation of infected animals slaughtered through time
vCJD Incidence

Annual incidence

84 deaths by the end of 2000
vCJD Total Epidemic Size (2000)

95% consistency with marginal time and age distributions
vCJD Incidence

177 deaths to date (as of 7 April 2015)

http://www.cjd.ed.ac.uk/documents/figs.pdf
HEALTH ADVISORY: MERS
Middle East Respiratory Syndrome

Were you in the Middle East recently?

- Watch for fever with cough or difficulty breathing.
- If you get sick within 14 days of leaving, call a doctor.
- Tell the doctor you traveled.

www.cdc.gov/travel
MERS-CoV: scale & severity

• Assessing under-reporting from international cases:
  - 4 non-resident traveller cases returning from Middle East;
  - Given passenger flows from/to Middle East (and if we assume visitors and locals have same risk of infection), how many cases in Middle East?
  - Estimated number of severe cases in Middle East: 940 (290-2,200).

• Assessing selection bias towards more severe cases:
  - Are cases detected by surveillance more severe?
  - Risk of overestimating Case Fatality Ratio (CFR).
  - Comparison of first case in cluster with secondary cases:
    - First case CFR: 74% (49-91%).
    - Secondary case CFR: 20% (7-42%).

Cauchemez et al. Lancet Infect Dis 14: 50-56, 2014. (Published online 13 Nov 2013.)
Sustained transmission in animals, not sustained in humans

Sustained transmission in humans

Human case
Animal case
Detected case

Cross-species transmission
Within-species transmission

Ferguson and Van Kerkhove Lancet 2013
Incubation period and generation time

- **Incubation period**
  - Derived from travel related clusters in the UK, France, Italy, Tunisia.
  - 7 secondary cases with known times of exposures to index case.
  - Mean 5.5 (95% CI: 3.6-10.2) and SD 2.5 (95% CI: 1.2-11.6) days.

- **Generation time (GT)**
  - Lower bound: delay from onset in index case to onset in following case in cluster:
    - Mean: 10.7 (95% CI: 6.5-19.4) days
    - SD 6.3 (95% CI: 3.5-16.9) days
  - Sensitivity analysis GT=7 and 12 days.

- Analysis of human clusters indicated that $R$ – in the absence of controls – was in the range 0.8 to 1.3.
MERS – where are we today?

Figure 1. Epidemic curve of MERS-CoV human cases as of 5 February 2015 (n=971)

http://www.who.int/csr/disease/coronavirus_infections/mers-5-february-2015.pdf?ua=1
CONTAGION
Reporting from Ebola’s front line

PERSON OF THE YEAR
THE EBOLA FIGHTERS
Dr. Jerry Brown
the Liberian surgeon, 46, turned his hospital into a treatment center
Imperial College members of WHO Ebola Response Team

Neil Ferguson
Christl Donnelly
Christophe Fraser
Steven Riley
Pierre Nouvellet
Thibaut Jombert
Maria Van Kerkhove

Tini Garske
Anne Cori
Harriet Mills
Isobel Blake
Ilaria Dorigatti
Gemma Nedjati-Gilani
Wes Hinsley
Ebola Virus Disease in West Africa — The First 9 Months of the Epidemic and Forward Projections

WHO Ebola Response Team*

ABSTRACT

BACKGROUND

On March 23, 2014, the World Health Organization (WHO) was notified of an outbreak of Ebola virus disease (EVD) in Guinea. On August 8, the WHO declared the epidemic to be a “public health emergency of international concern.”

CONCLUSIONS

These data indicate that without drastic improvements in control measures, the numbers of cases of and deaths from EVD are expected to continue increasing from hundreds to thousands per week in the coming months.

*The authors (members of the World Health Organization [WHO] Ebola Response team who contributed to this article) are listed in the Appendix.

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West African Ebola Epidemic after One Year — Slowing but Not Yet under Control

TO THE EDITOR: During the period from early June to mid-September 2014, the epidemic of Ebola virus disease (EVD) in Guinea, Liberia, and Sierra Leone grew exponentially, with national doubling times of between 16 and 30 days. On the basis of case reports through mid-September, and assuming no change in the trajectory of the epidemic, we predicted a cumulative total of 21,000 cases in these three countries by November 2. In fact, the epidemic did change course in September: the increase in case incidence appears to number of confirmed or probable cases of EVD ranged from 77 to 154 per week in Guinea, 73 to 138 in Liberia, and 327 to 537 in Sierra Leone. By December 14, a total of 18,625 confirmed, probable, or suspected EVD cases had been reported in eight affected countries (the three mentioned above, plus Mali, Nigeria, Senegal, Spain, and the United States), with 6971 recorded deaths. The true burden of illness and death is certainly higher, but the changes in epidemic trends between August and December are clear (Fig. 1).
Projections

Figure 1 – WHO Ebola Response Team – NEJM – 24 Dec 2014
Ebola Virus Disease among Children in West Africa

TO THE EDITOR: The epidemic of Ebola virus disease (EVD) in West Africa has caused clinical illness and deaths among persons with reported ages ranging from less than 1 year to more than 100 years. Most published estimates of key epidemiologic parameters have been based on patients of all ages and have thus been dominated by cases in which patients are 16 years of age or older, and as of January 5, 2015, these cases accounted for 79% of the confirmed and probable cases for which age has been reported.

Here we investigate the progression and out-
Acknowledgements – co-authors of Dec NEJM

- Junerlyn Agua-Agum, M.Ph., Archchun Ariyarajah, M.Sc., Bruce Aylward, M.D.

- MRC Centre for Outbreak Analysis and Modelling, WHO Collaborating Centre for Infectious Disease Modelling, Department of Infectious Disease Epidemiology, Imperial College London (I.M.B., A.C., C.A.D., I.D., N.M.F., C.F., T.G., W.H., T.J., H.L.M., G.N.-G., P.N., S.R., M.D.V.K.)
Deadly impacts of Ebola

**EBOLA** – WHO Situation report 5 April 2015

Cases 25,550
Deaths 10,587


“We project that after 6 to 18 months of disruptions, a large connected cluster of children unvaccinated for measles will accumulate across Guinea, Liberia, and Sierra Leone. This pool of susceptibility increases the expected size of a regional measles outbreak from 127,000 to 227,000 cases after 18 months, resulting in **2000 to 16,000 additional deaths** (comparable to the numbers of Ebola deaths reported thus far).”

**MALARIA** – in press... Watch this space!
Common themes

• Hidden events

• Complex systems (e.g. multiple modes of transmission, multiple species, varied healthcare-seeking and risk-taking behaviours)

• Missing data (often far from missing at random)

• Communication of uncertainty

• More mobile, more populous world – diseases spread faster than ever before.

• Statistical/mathematical analysis and modelling can help in:
  ➢ Contingency planning
  ➢ Characterising new threats
  ➢ Informing surveillance design
  ➢ Assessing control policy options
Has the A-team defeated the virus?

The fight against foot and mouth has been spearheaded by a task force of epidemiologists - their weapon is clever software. Roger Highfield reports

“Dream team: (L-r) Prof Roy Anderson, Christl Donnelly and Dr Neil Ferguson”
Mary Creagh (Wakefield) (Lab):

…
The Secretary of State is not in his place, but he referred to Christl Donnelly as a “he” during his statement on Tuesday—Christl is a she.

The Minister of State, Department for Environment, Food and Rural Affairs (Mr David Heath): She is a she.

Mary Creagh: Well, that is a relief. I do not know why the Minister has not told the Secretary of State that, because he is reported in Hansard as saying that she is a he. [Interruption.] He appears not to have read his own Hansard record or corrected it. He obviously has not spoken to the scientists, who faced down the animal rights activists during Labour’s badger cull in order to carry out the Labour Government’s research into culling badgers. We are not talking about some animal rights activists; these are scientists in the field wanting to get the right outcome for farmers and for the nation.
The badger cull - key science questions answered

How many badgers are infected, will enough badgers be culled and is it all worth it? Here is a guide to the recent badger cull

Most badgers aren't infected, is that correct?

The largest study of bovine tuberculosis (TB) in badgers was the randomised badger culling trial, RBCT, which reported in 2007. Nearly 8,900 badgers were culled across large (100 km sq) areas where there was high risk of cattle TB. Their results showed that a significant reduction in TB in cattle was associated with a significant reduction in the prevalence of TB in badgers, although around 75% of badgers were still infected with TB at the end of the trial.

There are concerns that not enough badgers have been culled in order to reduce cattle TB. Photograph: Christopher Mills/Alamy
Dye: Sierra Leone lockdown 'is a statement of political commitment'

The World Health Organization has warned in a new study that the number of Ebola infections could triple to 20,000 by November if efforts to stop the outbreak are not stepped up radically.

“Dr Christopher Dye (left) and Professor Christl Donnelly address a press conference on the Ebola virus”
Key SARS publications


Key Influenza publications


Key BSE/vCJD publications (1)


Key BSE/vCJD publications (2)


Key MERS publications


Key Ebola publications

