Pigs didn't Fly, but Swine Flu

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In 2009, the world experienced the first influenza pandemic for thirty years. Identified in Mexico in March, the novel swine flu quickly spread across the globe and was declared a public health emergency by the World Health Organization at the end of April. In the UK, the epidemic differed from regular flu epidemics in that it occurred during the summer rather than the winter. Using a relatively simple system of differential equations, we try to understand how changes in human behaviour and social mixing influenced the epidemic.

1 The 2009 swine flu epidemic

The little town of La Gloria, nestled in the hills to the east of Mexico City, is a fairly unremarkable place. With a population of a little over 2,000, many of whom commute to the city during the week, and a large pig farm a few miles away, it had little to bring it to the world's attention. Until, that is, March 2009, when a new strain of flu was identified in the Americas [1]. The new virus contained elements of human, avian and swine influenzas, and appeared to have originated in Mexico. The nearby pig farm, the links to Mexico City, and the fact that about 600 residents reported respiratory symptoms, led to La Gloria being suggested as the place where it all began.

Whether or not swine flu really started in La Gloria, it quickly became a global problem. Mexico was initially hardest hit, and from there the new virus began to spread; by the end of April it was in the UK, carried by returning holidaymakers, and before long it had reached every part of the globe. Health authorities around the world swung into action: public health campaigns were launched, schools closed, supplies of Tamiflu were made ready and vaccines ordered.

About a million people in England[1] were infected; one of us (EBP) managed to avoid it, but the other (KTDE) wasn't so lucky. He doesn't know who he got it from, but he knows that he passed it on to his partner, who made the mistake of bringing him tea and sympathy as he coughed and spluttered in bed for a couple of days. For mathematical modellers, who spend most of their time creating simulations of epidemics, this practical experience of swine flu in action provided a useful, if unwelcome, dose of reality.

2 Epidemic modelling

In 1927, two scientists working in Edinburgh called William Kermack and Anderson McKendrick published 'Contribution to the mathematical theory of epidemics'. Under this unassuming title, their paper described the now well-known Susceptible-Infected-Recovered (SIR) model for describing a novel pathogen spreading in a population [2]. In searching for a mechanism to explain when and why an epidemic terminates, they made a key observation that: *'In general a threshold density of population is found to exist, which depends upon the infectivity, recovery and death rates peculiar to the epidemic. No epidemic can occur if the population density is below this threshold value.'*

The realisation that the number of *unaffected*, rather than infectious, people governed epidemic dynamics had profound consequences for controlling disease outbreaks. For instance, the necessary level of vaccine coverage is determined by calculating the minimum number of susceptible individuals required for an epidemic; cross this threshold and there is the potential for an outbreak. The insights of Kermack and McKendrick were the first steps towards understanding disease dynamics, but the real world is much more complex and interesting. The 2009 swine flu epidemic demonstrated the importance of population structure, in addition to population size, for describing the progression of a disease through a population.

3 Modelling swine flu in the UK

During the early stages of the epidemic, the UK government tried to contain swine flu, advising people neither to go to work nor to visit their GP if they had flu-like symptoms. By July, however, with high rates of infection in children and young adults, the strategy changed from 'containment' to 'treatment'. London and the West Midlands experienced the epidemic before other regions, with several big outbreaks in schools. The summer epidemic wave died out in August but was rekindled in the autumn, resulting in a second surge in cases. By December (coincidentally, the usual start of the flu season) there were few cases left and the epidemic had run its course (see Figure 1).

When describing an epidemic mathematically, most modellers will start with a set of differential equations similar to those of Kermack and McKendrick. Individuals are modelled as either S: susceptible to being infected, I: infectious or R: recovered and immune, and a system of ODEs is derived to capture the change in the proportion of individuals in each of the infection states over time

$$\begin{aligned} \mathrm{d}S(t)/\mathrm{d}t &= -\beta S(t)I(t) \\ \mathrm{d}I(t)/\mathrm{d}t &= \beta S(t)I(t) - \gamma I(t) \\ \mathrm{d}R(t)/\mathrm{d}t &= \gamma I(t). \end{aligned} \qquad \textbf{[Model 1]}$$

In the early stages of a novel outbreak, much effort goes into estimating the rates by which people move through the infection states. The recovery rate, γ, is often approximated by the inverse of the average infectious period, measured in the first few detected cases. The transmission rate, β, is the daily rate at which a single infectious person produces new infections, which in practice can be hard to estimate, especially if many infections are mild and go undetected. β captures both the physical process of meeting someone and the biological process of transmitting infection. In Model 1, we have assumed that everyone is in contact with each other, such that there are $\beta S(t)I(t)$ new infections per unit time at time t.

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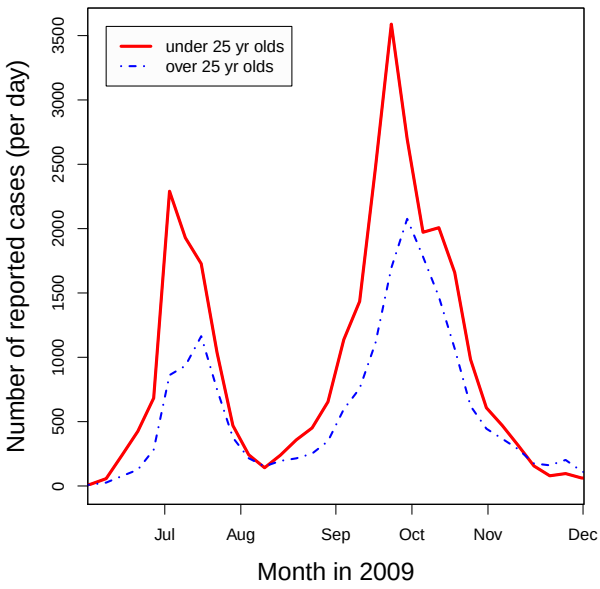

Figure 1: The 2009 swine flu epidemic in England. The solid line shows cases in the under 25s and the broken line is cases in the over 25s.

The initial conditions are determined by the immunological status of the population with respect to the invading pathogen. In an epidemic caused by a new strain, we might assume that the majority of the population is susceptible and a small proportion (ϵ) are infectious

$$S(t=0) = 1-\epsilon,$$
$$I(t=0) = \epsilon,$$
$$R(t=0) = 0.$$

An epidemic grows in size if $\mathrm{d}I(t)/\mathrm{d}t > 0$. Assuming that there are infectious individuals in the population ($I(t) > 0$), we find that we must have $S(t=0) > \gamma/\beta$. The parameter, $R_0 := \beta/\gamma$, is called the *basic reproductive number* of a disease and is defined as the average number of new infections produced by an average infectious person in an otherwise susceptible population. It is precisely this population threshold, $S(t) > 1/R_0$, that Kermack and McKendrick described as a necessity for an epidemic.

From the early stages of the swine flu epidemic, R_0 was estimated as $\approx$ 1.3 and the recovery rate was estimated as $\gamma \approx 1/2$ days^{-1} [1, 3]. Mutliplying $I(t)$ by the population of England ($\approx$ 50 million) gives the number of infectious cases in the population at time t. The number of new infections per day is scaled by the fraction of cases that seek medical attention (estimated at 0.1 by [3]). Taking the initial proportion of infectious individuals as $I(t=0) = 1 \times 10^{-6}$, Figure 2 compares the model with the number of reported cases. The epidemic curve in Figure 2 was produced using SIR Model 1 with swine flu-like parameters ($\gamma = 0.1$, $R_0 = 1.3$, reporting rate $= 0.1$ and $S + I + R = 50$ million [3]). The data are shown for comparison only; the model was not fitted to the data.

The epidemic produced by the standard SIR model clearly does not reproduce the dynamics observed in England. Most notably, the SIR curve has one turning point, whereas the real epidemic curve has three. In fact, it looks as if treating the epidemic as two separate epidemics might be a better idea. To try this, we could solve Model 1 for the first epidemic wave and use the final state as the initial conditions for the second epidemic wave. At the peak of the first wave, we know $\mathrm{d}I/\mathrm{d}t = 0$ with $I \neq 0$, and find that $S(t) = 1/R_0$. As the second wave started just a few weeks later, we assume recovered individuals remain immune and that demographic changes (births and deaths) were negligible, and use the final state of the first wave to provide bounds on the initial conditions for the second

$$S^{(2)}(t=0) < 1/R_0,$$
$$I^{(2)}(t=0) = \epsilon,$$
$$R^{(2)}(t=0) > 1 - 1/R_0 - \epsilon.$$

But... under these conditions the second epidemic wave could never take off because $SR_0 < 1$ and $\mathrm{d}I/\mathrm{d}t < 0$! Therefore, two independent epidemics is not a satisfactory solution unless the virus significantly mutated. Alternatively, we must revisit how the transmission was modelled to begin with.

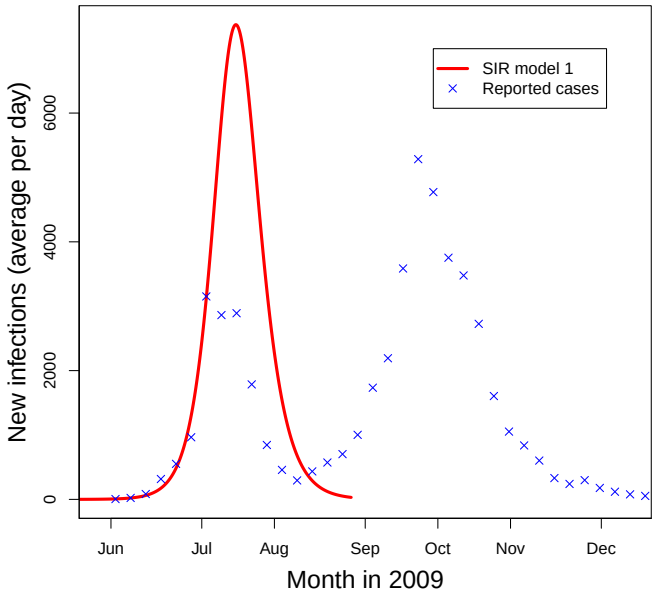

Figure 2: The epidemic curve produced by SIR Model 1 with swine flu-like parameters. The actual number of reported cases is shown for comparison.

4 The importance of social mixing for explaining the two epidemic waves

As mentioned above, the transmission rate of Model 1, β, encompasses multiple processes. If we assume that the biological processes of transmission and recovery are not changing, then it must be the contact process, or social mixing, that is changing.[2]

The peak of the summer epidemic wave occurred at the end of July, corresponding to the week in which most schools in England broke up for their summer holidays, suggesting that it was not a lack of susceptibles that caused the decline in the epidemic, but rather altered contact rates that resulted in a change in β to fall below the epidemic threshold such that the effective reproductive number $R_{\text{eff}} < 1/S(t)$ [4].

A further consequence of contact patterns is seen in the different rates of infection in adults and children. From surveys, we know

that school-aged children have almost twice as many social interactions as adults, which suggests that infectious children typically generate more new infections than adults [5, 6]. Further, the vast majority of social contacts are between people of a similar age, so the infection is concentrated in children. Visualising the transmission network, we have a densely connected subgraph comprised of children loosely connected to a less well-connected group of adults, forming a network similar to Figure 3.[3] This network simulation was generated using social network parameters obtained from the UK flusurvey. The links in the network represent potential transmission routes, for influenza these are social contacts.

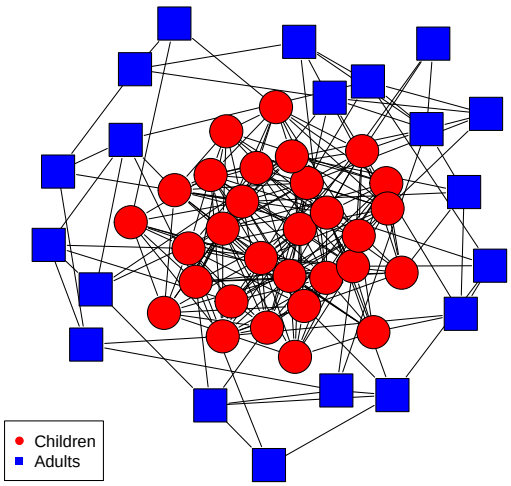

Figure 3: An age-structured population in which children (red circles) have more connections than adults (blue squares).

We can improve upon Model 1 by incorporating both age-related differences in contact rates and changes over the summer holidays. We partition the population into adults and children and call upon the contact survey to parameterise a mixing matrix $\mathscr{M} = \{m_{ij}, \text{ for } i,j = c,a\}$, which defines the average number of contacts within and among children, c, and adults, a. The new model, incorporating changes over the holidays, is defined for $i = c, a$ as

$$\begin{aligned} \mathrm{d}S_i/\mathrm{d}t &= -\sum_{j=c,a} \tau m_{ji}(t) S_i I_j \\ \mathrm{d}I_i/\mathrm{d}t &= \sum_{j=c,a} \tau m_{ji}(t) S_i I_j - \gamma I_i \qquad \textbf{[Model 2]} \\ \mathrm{d}R_i/\mathrm{d}t &= \gamma I_i \end{aligned}$$

where τ is the (biological) transmission rate and

$$\mathscr{M}(t) = \mathscr{M}_1 = \begin{pmatrix} 20 & 4 \\ 4 & 8 \end{pmatrix} \qquad \text{if } t \in \text{term time}$$

$$\mathscr{M}(t) = \mathscr{M}_2 = \begin{pmatrix} 4 & 2 \\ 2 & 4 \end{pmatrix} \qquad \text{if } t \in \text{school holidays.}$$

The values in matrices $\mathscr{M}_1$ and $\mathscr{M}_2$ are taken from the online contact survey at `http://www.flusurvey.org.uk` [6]. Model 2 reproduces two main features of the epidemic in Britain: the two peaks caused by changing contact patterns over the summer and the trailing epidemic in adults from their fewer social interactions (Figure 4).

A simple extension to the standard SIR model in which the population is separated into children and adults is shown below. The two epidemic peaks are achieved by allowing contact rates to drop during the summer holidays (indicated by the shaded region). Other parameters are taken from [3] and the flusurvey [6]: $\gamma = 0.5$, $R_0 \approx 1.3$ and a reporting rate of 0.1 in a population of 20 million children and 40 million adults. The actual number of reported cases is shown for comparison; the model was not fitted to the data.

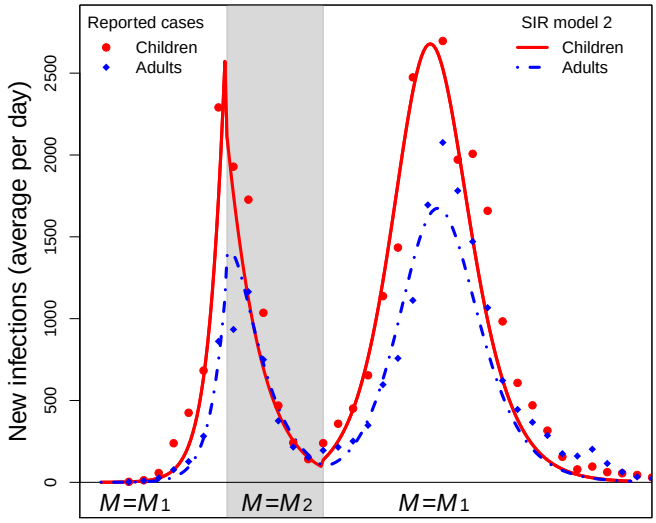

Figure 4: The epidemic curve produced by SIR Model 2, which incorporates a drop in social contacts during the holidays.

5 Defining R_0 for a heterogeneous population

How can R_0 be interpreted in Model 2 and how does it differ from in Model 1? In Model 2, an infectious child generates $\tau m_{cc}/\gamma$ new infectious children and $\tau m_{ca}/\gamma$ infectious adults. Similarly, an infectious adult will result in $\tau m_{ac}/\gamma$ infectious children and $\tau m_{aa}/\gamma$ infectious adults. We define the *next generation matrix*, $\mathscr{G} = \{G_{ij}\}$, which tracks the number of new infections generated in group j by infectious individuals in group i

$$\mathscr{G} = \frac{\tau}{\gamma} \begin{pmatrix} m_{cc}S_c & m_{ca}S_a \\ m_{ac}S_c & m_{aa}S_a \end{pmatrix}.$$

Say the epidemic starts with one infectious child, and $S_a = S_c \approx 1$, and that we knew τ/γ to be $1/10$. Then, in the next generation of infection there would be 2 further infectious children and 0.4 infectious adults. In the third generation, there would be $4 + 0.16$ infectious children and $0.8 + 0.32$ infectious adults, and so on…

second generation: $$\begin{pmatrix} 2 & 0.4 \\ 0.4 & 0.8 \end{pmatrix} \begin{pmatrix} 1 \\ 0 \end{pmatrix} = \begin{pmatrix} 2 \\ 0.4 \end{pmatrix}$$

third generation: $$\begin{pmatrix} 2 & 0.4 \\ 0.4 & 0.8 \end{pmatrix} \begin{pmatrix} 2 \\ 0.4 \end{pmatrix} = \begin{pmatrix} 4.16 \\ 1.12 \end{pmatrix}.$$

As the total number of infections grows in each generation, 2.4, 5.28, 11.328, 24.12, 51.2102, 108.6628, …, the average number of secondary cases per infectious person converges to R_0: 2.20,

2.15, 2.13, 2.1236, 2.1219, ... This inter-generation scaling is the maximum eigenvalue of the next generation matrix:

$$R_0 = \frac{\tau}{2\gamma}\left(m_{cc} + m_{aa} + \sqrt{4m_{ac}m_{ca} + (m_{cc} - m_{aa})^2}\right),$$

which equals 2.121 for our example epidemic. The corresponding eigenvector describes the distribution of cases in the next generation of infection. The high contact rate between children, such that $m_{cc} \gg m_{aa} > m_{ca}$, means that the overall population R_0 is dominated by these contacts. Furthermore, Model 1 will only produce similar dynamics to Model 2 in the limited case when $m_{ij} = \bar{m}$ for all i and j.

6 Regional variation across England

An effect of mixing patterns is also hinted at in the geographical spread of swine flu in England (Figure 5). The epidemic took off earlier in London and the West Midlands, after which other regions followed. The age distribution might go some way to explaining this pattern. London and the West Midlands have a higher proportion of people under 25 years of age than the country average, whereas the South West has a higher proportion of people over 50 years of age. This may affect the number of contacts between adults and children and, hence, have an impact on how quickly the epidemic spreads in each of the regions. Figure 5 compares the early observed exponential growth rate of swine flu ($\approx \gamma(R_0 - 1)$) against the maximum eigenvalue of the contact matrix within each region. While some of the epidemic patterns are captured, there are also some other effects, such as differences in surveillance, the definition of a contact and network structure beyond raw number of contacts, that might be important for describing transmission.

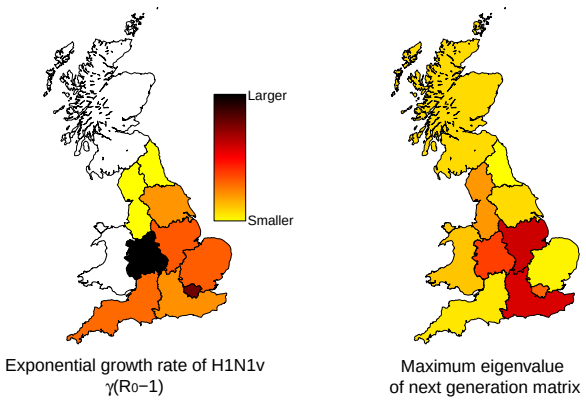

Figure 5: The dominant eigenvalue for the mixing matrices obtained by region, and the exponential growth rate of swine flu in England.

7 The next stages in epidemic modelling

Mathematical epidemic modelling has come a long way since Kermack and McKendrick's groundbreaking work in the 1920s. Modern computing power has allowed researchers to develop massively complex models, containing billions of unique, interacting individuals. But, as we have seen, even simple models can go a long way towards explaining observed epidemic patterns. Simple or complex, these models will be governed by the answers to a few key questions: how long does an infection last? How quickly does it spread? How does it get from person to person? Good data – from surveys, from surveillance, and from field epidemiology, are needed to answer these questions.

We don't know what new diseases the future holds: before swine flu arrived, new forms of flu had been forecast, but it was expected that these would be avian influenza emerging from South East Asia, not swine flu from the Americas. Whatever it is that's lurking around the corner, when it first emerges modelling will play a vital role in predicting its impact.

8 Afterword

The contact data in this paper were produced from the UK flusurvey (`http://www.flusurvey.org.uk`) hosted at the London School of Hygiene and Tropical Medicine. Our research group in the Centre for Mathematical Modelling of Infectious Diseases at LSHTM is interested in how human behaviour and contact patterns affect disease dynamics and epidemics. The flusurvey is run every year during the flu season to collect data about influenza activity, healthcare usage, vaccine choices and contact patterns. We encourage all interested to participate! If you don't have symptoms then the survey takes seconds (but 'susceptible' individuals are vital for correctly estimating force of infection βSI!). Visit `http://www.flusurvey.org.uk` for more information about our work, influenza, epidemics and mathematical modelling. ❑

Notes

1. We show data for England only because of the different surveillance systems in other parts of Great Britain.
2. The precise nature of an epidemiologically relevant 'contact' can be difficult to define. A contact depends on the disease: HIV is transmitted via contact of bodily fluids; malaria is transmitted via mosquito contact; flu is transmitted via aerosol contact. However, aerosol contact can be a slippery notion in itself. How close do you need to be to 'make contact' with someone? Do you need to converse? Or touch? Does length of time matter? We use *conversational* (face-to-face) and *physical* (handshake, kiss, etc.) contact as measurable quantities, but the proof of the model is in its prediction. See reference [5] for more details on measuring social contacts.
3. This contact network was generated using data collected from the online contact survey at `http://www.flusurvey.org.uk` – see Section 8 for further details.

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Biographies

Ellen Brooks-Pollock is a research fellow at the London School of Hygiene and Tropical Medicine. As well as flu modelling, she is interested in tuberculosis (TB) transmission. During her PhD at the University of Warwick, she studied the spatial spread of bovine TB via cattle movements, and as a postdoc at Harvard she worked on the transmission of drug-resistant TB in humans. She started reading *Mathematics Today* in 2003 after receiving an IMA student prize!

Ken Eames trained as a mathematician before turning his hand to epidemiological modelling. Before moving to the London School of Hygiene and Tropical Medicine in 2008, he worked in mathematics and biological sciences in Cambridge and Warwick. His research focus has primarily been on modelling infections and other processes taking place within social networks; when the swine flu pandemic hit he moved into data collection, running internet based surveillance and surveys of changing patterns of social mixing. In his spare time he sings noisily and plays cricket with limited success.