# Epidemics with two levels of mixing 

Frank Ball
Frank.Ball@nottingham.ac.uk

## University of Nottingham

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## Outline of talk

- Background on homogeneously mixing SIR (susceptible $\rightarrow$ infective $\rightarrow$ removed) epidemic models
- General two-level-mixing SIR epidemic model
- Special cases
- households model
- overlapping groups model
- great circle model
- network model with casual contacts
- Threshold behaviour and final outcome of global epidemic
- general results
- applications to special cases
- numerical illustrations
- Vaccination in Households SIR model
- Concluding comments


## General deterministic epidemic



$$
\begin{aligned}
& (x(0), y(0), z(0))=(N, a, 0) \\
& \beta=\text { infection rate } \\
& \gamma=\text { removal rate }
\end{aligned}
$$

- SIR (susceptible $\rightarrow$ infective $\rightarrow$ removed)
- $\frac{d x}{d t}=-\beta x y, \frac{d y}{d t}=\beta x y-\gamma y, \frac{d z}{d t}=\gamma y$
- $\frac{d y}{d t}>0 \Longleftrightarrow \beta x y-\gamma y>0 \Longleftrightarrow x>\gamma / \beta$
- Epidemic takes off $\Longleftrightarrow N>\gamma / \beta \Longleftrightarrow R_{0}=N \beta / \gamma>1$
(Kermack and McKendrick (1927))


## General deterministic epidemic



## General stochastic epidemic



$$
\begin{aligned}
& X(0)=N \\
& Y(0)=a \\
& Z(0)=0
\end{aligned}
$$

Transition
$t \quad t+\Delta t$


Probability

$$
\beta x y \Delta t+o(\Delta t)
$$

$$
\gamma y \Delta t+o(\Delta t)
$$

(Bartlett (1949))

## General stochastic epidemic



$$
\begin{aligned}
& X(0)=N \\
& Y(0)=a \\
& Z(0)=0
\end{aligned}
$$

- Final size $T=N-X(\infty)$ — number of susceptibles ultimately infected
- Let $P_{j}=\mathrm{P}(T=j)(j=0,1, \ldots, N)$. Then

$$
\sum_{j=0}^{i}\binom{N-j}{N-i}\left(1+\left(1-\frac{i}{N} R_{0}\right)\right)^{a+j} P_{j}=\binom{N}{i} \quad(i=0,1, \ldots, N)
$$

(Whittle (1955))

## Final size



Final size distribution for general stochastic epidemic with 1 initial infective and 50 initial susceptibles

## Threshold behaviour

- Consider epidemic with initially few infectives and many susceptibles
- If $R_{0} \leq 1$, then
- Only minor outbreaks occur
- Size of outbreak distributed according to total progeny of approximating branching process, $Z$ say, in which all contacts lead to an infection
- If $R_{0}>1$,
- $\mathrm{P}($ major outbreak $)=1-\mathrm{P}(Z$ goes extinct $)>0$
- Size of minor outbreak distributed according to total progeny of $Z$, conditional upon extinction
- Size of major outbreak satisfies a central limit theorem with mean given by deterministic model


## Basic reproduction number $R_{0}$

- $R_{0}=$ "the expected number of secondary cases produced by a typical infected individual during its entire infectious period, in a population consisting of susceptibles only" (Heesterbeek and Dietz (1996))
- Major outbreak can occur $\Longleftrightarrow R_{0}>1$
- If proportion $c$ of susceptibles is vaccinated with a perfect vaccine, $R_{0}$ is reduced to $R_{v}=(1-c) R_{0}$, so, if $R_{0}>1$,
$R_{v} \leq 1 \Longleftrightarrow c \geq 1-R_{0}^{-1}$ —critical vaccination coverage
(Smith (1964))


## Multitype general deterministic epidemic

- $m$ types of individual, labelled $1,2, \ldots, m$, reflecting e.g. age, vaccine status, geographical location.

$$
\begin{aligned}
& \frac{d x_{i}}{d t}=-x_{i} \sum_{j=1}^{m} \beta_{j i} y_{j}, \\
& \frac{d y_{i}}{d t}=x_{i} \sum_{j=1}^{m} \beta_{j i} y_{j}-\gamma_{i} y_{i}, \\
& \frac{d z_{i}}{d t}=\gamma_{i} y_{i} \quad(i=1,2, \ldots, m),
\end{aligned}
$$

with $\left(x_{i}(0), y_{i}(0), z_{i}(0)\right)=\left(N_{i}, a_{i}, 0\right)$

- Analogues of all previous results hold BUT threshold behaviour requires $N_{i} \rightarrow \infty(i=1,2, \ldots, m)$, i.e. that the population is LOCALLY LARGE


## Non-locally-large models

- Spatial models
- percolation
- structure too rigid for human populations
- Network models
- Multi-level mixing models
- metapopulation/households models
- Complex simulation models
- more realistic but can be computationally expensive and difficult to interpret


## General two-level-mixing epidemic model



$$
\begin{aligned}
& \text { Population } \\
& \mathcal{N}=\{1,2, \ldots, N\}
\end{aligned}
$$

- SIR (susceptible $\rightarrow$ infective $\rightarrow$ removed)
- Infectious periods $I_{1}, I_{2}, \ldots, I_{N}$ iid $\sim I$ (arbitrary but specified)
- Infection rates (individual $\rightarrow$ individual)
- local $\lambda_{i j}^{L}$
- global $\lambda_{G} / N$
- Latent period


## Households model


$m$ households, each of size $n$
$N=m n$

- $\lambda_{i j}^{L}= \begin{cases}\lambda_{L} & \text { if } i \text { and } j \text { belong to same household } \\ 0 & \text { otherwise }\end{cases}$
- Unequal-sized households.
(Bartoszyński (1972), Becker and Dietz (1995), Ball, Mollison and Scalia-Tomba (1997))


## Overlapping groups model



- $m_{\alpha}$ households, each of size $n_{\alpha}, m_{\beta}$ workplaces, each of size $n_{\beta}$, so $N=m_{\alpha} n_{\alpha}=m_{\beta} n_{\beta}$
- $\lambda_{i j}^{L}= \begin{cases}\lambda_{\alpha}^{L} & \text { if } i \text { and } j \text { belong to same household } \\ \lambda_{\beta}^{L} & \text { if } i \text { and } j \text { belong to same workplace } \\ 0 & \text { otherwise }\end{cases}$
(Ball and Neal (2002), cf. Andersson (1997))


## Great circle model


(Ball, Mollison and Scalia-Tomba (1997), Ball and Neal $(2002,2003)$ )

## Networks with casual contacts



- 'independent' random graph of possible local contacts with specified degree distribution $p_{k}=\mathrm{P}(D=k) \quad(k=0,1, \ldots)$
- $\lambda_{i j}^{L}= \begin{cases}\lambda_{L} & \text { if } i \text { and } j \text { are neighbours } \\ 0 & \text { otherwise }\end{cases}$
(Diekmann et al. (1998), Ball and Neal (2002), (2008), Kiss et al. (2006); Newman (2002))


## Directed graph of potential local contacts


$i \rightarrow j$ if and only if $i$, if infected, contacts $j$ locally.
Given infectious periods $I_{1}, I_{2}, \ldots, I_{N}, \mathrm{P}(i \rightarrow j)=1-\mathrm{e}^{-\lambda_{L} I_{i}}$ independently for distinct $(i, j)$.

## Local infectious clump $\mathcal{C}_{i}^{N}$


$\mathcal{C}_{i}^{N}=\{j \in \mathcal{N}: i \rightsquigarrow j\}$, where $i \rightsquigarrow j$ if and only if there exists a chain of directed arcs from $i$ to $j$, and $C_{i}^{N}=\left|\mathcal{C}_{i}^{N}\right|$.

## Local infectious clumps


$\mathcal{C}_{i}^{N}=\{j \in \mathcal{N}: i \rightsquigarrow j\}$, where $i \rightsquigarrow j$ if and only if there exists a chain of directed arcs from $i$ to $j$, and $C_{i}^{N}=\left|\mathcal{C}_{i}^{N}\right|$.

## Threshold parameter $R_{*}$

- As $N \rightarrow \infty$, process of infected clumps tends to a branching process having offspring random varaible $R \sim \operatorname{Poisson}\left(\lambda_{G} A\right)$, where $A=\sum_{j \in \mathcal{C}} I_{j}$
- Global epidemic occurs if and only if this branching process does not go extinct
- $R_{*}=\mathrm{E}[R]=\lambda_{G} \mathrm{E}[A]=\lambda_{G} \mathrm{E}\left[\sum_{j \in \mathcal{N}} I_{j} 1_{\{j \in \mathcal{C}\}}\right]=$
$\lambda_{G} \sum_{j=1}^{N} \mathrm{E}\left[I_{j}\right] \mathrm{P}(j \in \mathcal{C})=\lambda_{G} \mu_{I} \mathrm{E}[C]$
- $\mathrm{P}($ global epidemic $)>0 \Longleftrightarrow R_{*}>1$


## Local susceptibility set $\mathcal{S}_{i}^{N}$


$\mathcal{S}_{i}^{N}=\{j \in \mathcal{N}: j \rightsquigarrow i\}$ and $S_{i}^{N}=\left|\mathcal{S}_{i}^{N}\right|$.

## Final outcome of global epidemic

- Suppose $N$ is large and there are few initial infectives. Let $z$ be the expected proportion of the population who are infected by the epidemic. Then
$\pi=\mathrm{P}($ typical susceptible avoids global infection $)=\exp \left(-\frac{\lambda_{\mathrm{G}}}{N} N z \mu_{\mathrm{I}}\right)=\exp \left(-\lambda_{\mathrm{G}} z \mu_{\mathrm{I}}\right)$ and

$$
\begin{align*}
1-z & =\mathrm{P}(\text { typical susceptible avoids infection by epidemic }) \\
& =\mathrm{P}(\text { typical local susceptibility set avoids global infection }) \\
& =\sum_{k=1}^{\infty} \mathrm{P}(S=k) \pi^{k}=f_{S}(\pi)=f_{S}\left(\mathrm{e}^{-\lambda_{\mathrm{G}} z \mu_{\mathrm{I}}}\right) \tag{1}
\end{align*}
$$

- $R_{*}=\lambda_{G} \mu_{I} \mathrm{E}[C]=\lambda_{G} \mu_{I} \mathrm{E}[S]$
- $\quad R_{*} \leq 1 \quad z=0$ is the only solution of (1) in $[0,1]$
$R_{*}>1$ unique second solution $\hat{z} \in(0,1)$, giving mean 'size' of global epidemic
- Fully rigorous proof and central limit theorem for final size of global epidemic is available using Scalia-Tomba (1985) embedding technique


## Great circle model



- $\mathcal{S}_{i}=\{i\} \cup \mathcal{S}_{L} \cup \mathcal{S}_{R}$
- $p_{L}=\mathrm{P}(i$ infects $i+1$ locally $)=1-\mathrm{E}\left[\mathrm{e}^{-\lambda_{L} I}\right]$
- $\mathrm{P}\left(S_{L}=k\right)=\mathrm{P}\left(S_{R}=k\right)=\left(1-p_{L}\right) p_{L}^{k}$ ( $k=0,1, \ldots$ )
- $S_{L}$ and $S_{L}$ are independent, so

$$
\mathrm{P}(S=k)=\left(1-p_{L}\right)^{2} p^{k-1}(k=1,2, \ldots)
$$

- $\mathrm{E}[S]=2 p_{L}^{-1}-1$


## Households model

Consider household of $n$ individuals, labelled $1,2, \ldots, n$, and let $\mathcal{S}$ be the local susceptibility set of individual 1.


$$
\text { Let } P_{j}^{(n)}=\mathrm{P}(S=j) \quad(j=1,2, \ldots, n)
$$

$q_{k}=\mathrm{E}\left[\mathrm{e}^{-k \lambda_{L} I}\right]$ be the probability that a given set of $k$ susceptibles avoids local infection from a given infective

$$
P_{j}^{(n)}=\binom{n-1}{j-1} P_{j}^{(j)} q_{j}^{n-j} \quad(j=1,2, \ldots, n)
$$

$$
\sum_{j=1}^{k} P_{j}^{(k)}=1 \quad \Longrightarrow \quad \sum_{j=1}^{k}\binom{k-1}{j-1} P_{j}^{(j)} q_{j}^{k-j}=1
$$

$$
\Longrightarrow \quad \frac{\sum_{j=1}^{k}\binom{n-k}{n-j} P_{j}^{(n)}}{q_{j}^{n-k}}=\binom{n-1}{k-1} \quad(k=1,2, \ldots, n)
$$

- Triangular system of linear equations for $\mathrm{P}(S=j) \quad(j=1,2, \ldots, n)$


## Overlapping groups model



Workplace

Household

- Construct local susceptibility set $\mathcal{S}$ of typical individual $i$ via a two-type branching process in which individuals beget only the opposite type and the offspring of a type $\alpha(\beta)$ individual are the individuals in its workplace (household) susceptibility set.
- If $\mu_{\alpha}\left(\mu_{\beta}\right)$ is the mean size of a household (workplace) susceptiblity set, then

$$
\mathrm{E}[S]= \begin{cases}\frac{\mu_{\alpha} \mu_{\beta}}{\mu_{\alpha}+\mu_{\beta}-\mu_{\alpha} \mu_{\beta}} & \text { if }\left(\mu_{\alpha}-1\right)\left(\mu_{\beta}-1\right)<1 \\ \infty & \text { otherwise }\end{cases}
$$

## NETWORK - Configuration model

- Population $\mathcal{N}=\{1,2, \ldots, N\}$
- $D=$ degree of typical individual

$$
p_{k}=\mathrm{P}(D=k) \quad(k=0,1, \ldots) \quad \text { specified } \quad \mu_{\mathrm{D}}=\mathrm{E}[D]
$$

- $D_{1}, D_{2}, \ldots, D_{N}$ iid copies of $D$, conditioned on
$S_{N}=D_{1}+D_{2}+\cdots+D_{N}$ being even
- Attach $D_{i}$ half-edges to individual $i(i=1,2, \ldots, N)$
- Pair up the $S_{N}$ half-edges uniformly at random to form the network

$$
\text { IMPERFECTIONS — sparse if } \sigma_{\mathrm{D}}^{2}=\operatorname{var}(D)<\infty
$$

(Bollobás (2001))

## Networks with casual contacts

- Let $\tilde{D}=$ degree of typical neighbour of typical individual in the network and $\mu_{\tilde{\mathrm{D}}}=\mathrm{E}[\tilde{D}]$. Then

$$
\mathrm{P}(\tilde{D}=k)=k p_{k} / \mu_{\mathrm{D}} \quad(k=1,2, \ldots) \text { and } \mu_{\tilde{\mathrm{D}}}=\frac{\operatorname{var}(D)+\mu_{\mathrm{D}}^{2}}{\mu_{\mathrm{D}}} .
$$

- Size of typical local susceptibility set $S^{N} \xrightarrow{\text { a.s. }} S$ as $N \rightarrow \infty$, where $S$ is the total size of a branching process having offspring law $\operatorname{Bin}\left(D, p_{\mathrm{L}}\right)$ for the initial individual and $\operatorname{Bin}\left(\tilde{D}-1, p_{\mathrm{L}}\right)$ for all subsequent individuals

$$
\mathrm{E}[S]= \begin{cases}1+\frac{\mu_{\mathrm{D}} p_{\mathrm{L}}}{1-\left(\mu_{\tilde{\mathrm{D}}}^{-1) p_{\mathrm{L}}}\right.} & \text { if }\left(\mu_{\tilde{\mathrm{D}}}-1\right) p_{\mathrm{L}}<1 \\ \infty & \text { otherwise }\end{cases}
$$

## 'Deterministic' households model


$m$ households of size $n$, labelled $1,2, \ldots, m$.
Let $x_{i}(t)$ and $y_{i}(t)$ be the number of susceptibles and infectives in household $i$ at time $t$.

$$
\begin{aligned}
\frac{d x_{i}}{d t} & =-\left(\lambda_{L} y_{i}+N^{-1} \lambda_{G} \sum_{j=1}^{m} y_{j}\right) x_{i}, \\
\frac{d y_{i}}{d t} & =\left(\lambda_{L} y_{i}+N^{-1} \lambda_{G} \sum_{j=1}^{m} y_{j}\right) x_{i}-\gamma y_{i} \quad(i=1,2, \ldots, m),
\end{aligned}
$$

- Basic Reproduction number $R_{0}=\left(\lambda_{G}+n \lambda_{L}\right) / \gamma$
- Proportion of susceptibles ultimately infected, $\hat{z}_{\text {det }}$ given by largest root in $[0,1]$ of $1-z=\exp \left(-R_{0} z\right)$


## Households and great circle models

Households, $\mathrm{R}_{\star}=1$.


Great circle, $R_{\star}=1$.


Households, $z, \lambda_{G}=0.75$.



Critical values of $\left(\lambda_{\mathrm{L}}, \lambda_{\mathrm{G}}\right)$ so that $R_{*}=1$ and final outcome $\hat{z}$ when $I \sim \operatorname{Exp}(1)$.

## Overlapping groups model, varying $\lambda_{\beta}^{L}$




Critical values of $\left(\lambda_{\alpha}^{L}, \lambda_{G}\right)$ so that $R_{*}=1$ and final outcome $\hat{z}$ when $I \sim \operatorname{Exp}(1)$

## Overlapping groups model, varying $n_{\beta}$




Critical values of $\left(\lambda_{\beta}^{L}, \lambda_{G}\right)$ so that $R_{*}=1$ and final outcome $\hat{z}$ when $I \sim \operatorname{Exp}(1)$

## Networks with casual contacts



Histograms of size of 10,000 simulated epidemics per parameter combination, for a constant-degree network with $D \equiv d, I \equiv 1$ and other parameters as shown.

## Illustration of CLT



Histogram of size of 10,000 simulated global epidemics in a population of size $N=10,000$ when $D \equiv 8, \lambda_{\mathrm{G}}=0$ and $p_{\mathrm{L}}=0.2(I \equiv 1$ and $\left.\lambda_{\mathrm{L}}=-\log 0.8\right)$, with asymptotic normal approximation superimposed.

## Networks with casual contacts



Critical values of $\left(\lambda_{\mathrm{L}}, \lambda_{\mathrm{G}}\right)$ so that $R_{*}=1$ when $I \equiv 1$. [Expected number of potentially infectious contacts made by an infective is $\lambda_{\mathrm{G}}+d \lambda_{\mathrm{L}}$.]

## Networks with casual contacts



Asymptotic proportion of population infected by global epidemic, $\hat{z}$, for constant-degree and scale-free $\left(\mathrm{P}(D=k) \propto k^{-2.466956}(k=3,4, \ldots)\right)$ networks with $\mu_{\mathrm{D}}=8$ when $I \equiv 1$.

## Households SIR epidemic model


$m_{n}$ households of size $n(n=1,2, \ldots)$
total no. of households $m=\sum_{n=1}^{\infty} m_{n}$
total no. of individuals $N=\sum_{n=1}^{\infty} n m_{n}<\infty$

- SIR (susceptible $\rightarrow$ infective $\rightarrow$ removed)
- Infectious period $\sim T_{I}$, having an arbitrary but specified distribution
- Infection rates (individual $\rightarrow$ individual)
(i) local (within-household) $\lambda_{L}$
(ii) global (between-household) $\quad \lambda_{G} / N$
- Latent period
(Bartoszyński (1972), Becker and Dietz (1995), Ball, Mollison and Scalia-Tomba (1997))


## Threshold parameter $R_{*}$



- $R_{*}=$ mean number of global contacts emanating from a typical single-household epidemic

$$
R_{*}=\sum_{n=1}^{\infty} \tilde{\alpha}_{n} \mu_{n}\left(\lambda_{L}\right) \lambda_{G} \mathrm{E}\left[T_{I}\right],
$$

where

$$
\begin{aligned}
\tilde{\alpha}_{n}=\frac{n m_{n}}{N} & =\mathrm{P}(\text { randomly chosen person lives in a household of size } n) \\
\mu_{n}\left(\lambda_{L}\right) & =\text { mean size of single (size-n) household epidemic with } 1 \text { initial infective }
\end{aligned}
$$

- $\mathrm{P}($ global epidemic $)>0 \Longleftrightarrow R_{*}>1$
(Ball, Mollison and Scalia-Tomba (1997), Becker and Dietz (1995))


## Vaccination

- For $n=1,2, \ldots$ and $v=0,1, \ldots, n$, let
$x_{n v}=$ proportion of size- $n$ households that have $v$ members vaccinated
$\mu_{n v}=$ mean number of global contacts emanating from a single-household epidemic in a household in state $(n, v)$, initiated by an individual chosen uniformly at randomly being contacted globally
- Post-vaccination

$$
R_{v}=\sum_{n=1}^{\infty} \tilde{\alpha}_{n} \sum_{v=0}^{n} x_{n v} \mu_{n v}
$$

- Vaccination coverage

$$
c=\sum_{n=1}^{\infty} \tilde{\alpha}_{n} \sum_{v=0}^{n} \frac{v}{n} x_{n v}
$$

- Determination of optimal vaccination scheme (e.g. to reduce $R_{v}$ to 1 with minimum vaccination coverage) is a linear programming problem, whose solution can be constructed explicitly.
(Becker and Starczak (1997), Ball and Lyne (2002, 2006))


## Calculation of $\mu_{n v}$

- $x_{n v}=$ proportion of size- $n$ households that have $v$ members vaccinated
$\mu_{n v}=$ mean number of global contacts emanating from a single-household epidemic in a household in state $(n, v)$, initiated by an individual chosen uniformly at randomly being contacted globally
- $\mu_{n v}$ depends on model for vaccine action.
- For an all-or-nothing model, in which vaccinees are rendered immune independently with probability $\epsilon$, otherwise the vaccine has no effect

$$
\mu_{n v}=\sum_{k=0}^{v} \underbrace{\binom{v}{k} \epsilon^{k}(1-\epsilon)^{v-k}}_{(1)} \underbrace{\frac{n-k}{n}}_{(2)} \underbrace{\mu_{n-k}\left(\lambda_{L}\right)}_{(3)} \lambda_{G} \mathrm{E}\left[T_{I}\right]
$$

(1) $\mathrm{P}(k$ vaccinations are successful)
(2) P (globally contacted individual is susceptible)
(3) Mean size of single-household epidemic

## Variola Minor, Sao Paulo, 1956

- Data comprise final numbers infected in each of 338 households. Household size varied from 1 to 12 (mean $=4.56$ )
- Each individual labelled vaccinated or unvaccinated

$$
\begin{array}{ll}
773 \text { unvaccinated } & -425 \text { infected (58\%) } \\
809 \text { vaccinated } & -85 \text { infected (11\%) }
\end{array}
$$

- Fit households SIR model with non-random vaccine response, assuming infectious period $T_{I} \equiv 1$, using pseudolikelihood method of Ball and Lyne (2010) to obtain the estimates

$$
\hat{\lambda}_{L}=0.3821, \hat{\lambda}_{G}=1.4159, \hat{a}=0.1182, \hat{b}=0.8712
$$

## Comparison of vaccination strategies



## Concluding comments

- General framework for determining threshold behaviour and final outcome of stochastic SIR epidemics with two levels of mixing.
- Local (e.g. household) structure matters!
- Significant impact on threshold and final outcome.
- Consequent impact on performance of vaccination schemes.
- Explicit calculation is possible only in a few special cases - need to find other local structures which are both practically relevant and mathematically tractable.
- Can relax symmetries and/or consider multitype epidemics.
- Non-SIR models
- SIS households and great circle
- SIR households with demography? FADE OUT


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