The effects of population heterogeneities on spread of infection

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Background: Salmonella transmission in a dairy herd



Y. Xiao, D. Clancy, N.P. French, R.G. Bowers (2006), Math. Biosci.

Salmonella transmission in a dairy herd



Major outbreak probability versus various model parameters. Dashed line is for structured model, solid line for homogeneous model with R_0 matched.

- Population partitioned into k groups
- Group *i* consists of N_i individuals, with $N_1 + \cdots + N_k = N$
- Each group *i* infective contacts each group *j* susceptible at rate

$$\beta_{ij} = \frac{\beta}{N} \times \lambda_i \times \pi_{ij} \times \mu_j$$
 (irreducible)

- β : overall scaling factor
- λ_i : infectivity
- μ_j : susceptibility
- π_{ij} : mixing matrix

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Separable model

- Model with $\beta_{ij} = \frac{\beta}{N} \lambda_i \mu_j$ is called separable, or sometimes proportionate mixing
- Model of E. Kenah, J.M. Robins (2007), J. Theo. Biol., 'Network-based analysis of stochastic SIR epidemic models with random and proportionate mixing'

Graphs from Yates et al.



Major outbreak probability versus R₀
(a) Hetero infectivity (combined with hetero mixing)
(b) Hetero susceptibility (combined with hetero mixing)

Initial conditions

• Cattle model: Initial infective in group 2 (weaned calves)

• Yates et al: Initial infective in group *i* with probability $\mu_i f_i$ $f_i = N_i / N_i$ proportion of total population in group *i*

• Alternatively, initial infective in group *i* with probability *f_i*

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Separable model, randomly chosen parameter values



Minor outbreak probability versus R_0 , with initial infective in group 1, with hetero infectivity and susceptibility Green line for homogeneous model.

Notation:

T = infectious period, $\psi(\theta) = E[\exp(\theta T)]$

 G_{ij} = Number of group *j* offspring of group *i* parent

$$\phi_i(\mathbf{s}) = E\left[\prod_{j=1}^k s_j^{G_{ij}}\right] = \psi\left(-\beta \sum_{j=1}^k \lambda_i \pi_{ij} \mu_j f_j \left(1-s_j\right)\right)$$

$$q_i = \phi_i(\mathbf{q}) \text{ for } i = 1, 2, \dots, k$$

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If the distribution ν , specifying the group of the initial infective, is a left-eigenvector of the next-generation-mean matrix, corresponding to the dominant eigenvalue R_0 , then the major outbreak probability is bounded above by the homogeneous population (matched according to R_0 value).

(Similar to N. Becker, I. Marschner (1990), Lect. Notes Biomath.)

- Interpretation of the eigenvector: In the case of a major outbreak, with successive generations the proportion of all infectives which belong to group *i* converges to ν_i.
- So not a very natural initial condition, except in special cases.

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Special cases

In general:
$$\beta_{ij} = \frac{\beta}{N} \times \lambda_i \times \pi_{ij} \times \mu_j$$
 and $f_i = N_i/N$

1. Separable case: $\beta_{ij} = \frac{\beta}{N} \lambda_i \mu_j$. Then it's natural to assign the initial infective to group *i* with probability $\mu_i f_i$, and this is the appropriate eigenvector.

2. Hetero mixing: If $\beta_{ij} = \frac{\beta}{N} \pi_{ij}$ with $\sum_i \pi_{ij} = 1$ and $f_j = 1/k$ for all *j*, then the uniform distribution is the appropriate eigenvector.

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Separable model $\beta_{ij} = (\beta/N) \lambda_i \mu_j$



Major outbreak probability versus R_0 Two groups, hetero susceptibility, varying hetero infectivity. Infectious period: Solid = Constant, Dashed = Exponential

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- Latent period
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SIR model, infection followed by lifelong immunity

- Final size: N_i^* = number of group *i* individuals ever infected
- Vector $(N_1^*, N_2^*, \dots, N_k^*)$ is asymptotically multivariate normal
- Mean proportions $\tau_i = E[N_i^*/N_i]$ asymptotically satisfy

$$\tau_i = 1 - \exp\left(-\frac{\beta}{N}\sum_{j=1}^k \tau_j f_j \lambda_j \pi_{ji} \mu_i\right)$$
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- Total final size $= N \sum_{i} \tau_{i} f_{i}$ (asymptotic mean)
- Covariance $[\boldsymbol{\lambda}, \boldsymbol{\mu}] = \sum \lambda_i \mu_i f_i (\sum \lambda_i f_i) (\sum \mu_i f_i)$
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Total outbreak size versus R_0 Two groups, hetero susceptibility, varying hetero infectivity. Solid line shows homogeneous case

SIS model, infection followed by immediate return to susceptibility

- Assume infectious periods exponentially distributed, then in large population limit can approximate Markov process with deterministic ODE system.
- x_i = proportion of group *i* infected
- Endemic equilibrium point x satisfies

$$x_i = \beta (1 - x_i) \sum_{j=1}^k x_j f_j \lambda_j \pi_{ji} \mu_i$$
 for $i = 1, 2, ..., k$

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In the separable case,

$$x_i = \frac{D\mu_i}{1+D\mu_i}$$
 for $i = 1, 2, \dots, k$

where *D* solves (uniquely for $R_0 > 1$)

$$\beta \sum_{j=1}^{k} \frac{\lambda_j \,\mu_j \,f_j}{1 + D\mu_j} = 1$$

A. Nold (1980), Math. Biosci.

- Overall endemic prevalence level = $N \sum_{i} x_i f_i$
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Endemic prevalence level versus R_0 Two groups, hetero susceptibility, varying hetero infectivity. Solid line shows homogeneous case

- For the above SIS model, disease extinction occurs within finite time with probability 1.
- Before extinction, state of process settles to a quasi-stationary distribution, which can be evaluated as eigenvector of truncated transition rate matrix.
- Mean time to extinction, starting from quasi-stationarity, is quasi-stationary probability that there is only 1 infective present multiplied by recovery rate of that 1 infective.

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Log (expected persistence time) versus R_0



Hetero infectivity, combined with hetero mixing Black = homogeneous, Blue = hetero infectivity only

Log (expected persistence time) versus R_0



Hetero susceptibility, combined with hetero mixing Black = homogeneous, Blue = hetero susceptibility only

- Quasi-stationary distribution can be approximated by a multivariate normal distribution centred at the deterministic endemic equilibrium level.
- Some indication of likely time-to-extinction is given by the Coefficient of Variation of the total number of infectives present under the normal approximation

$$CV = \frac{SD}{Mean}$$

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$$CV = \frac{SD}{Mean}$$

• Variance matrix S is the $k \times k$ matrix satisfying

 $JS + SJ^T + G = 0$

where J is Jacobian of the ODE system at endemic equilibrium and G is local variance matrix of approximating k-dimensional Ornstein-Uhlenbeck process.

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It appears that:

- With hetero infectivity, *CV* is minimised in homogeneous case (so persistence time maximised)
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Conclusions

- Heterogeneity often seems to reduce spread, whether measured by major outbreak probability; outbreak size; endemic prevalence; persistence time
- Sufficient conditions for this to be true depend on particular measure of spread
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Related models

• Above results keep number of groups k fixed, and suppose each group is large.

What happens if groups stay small (households), and consider limit $k \to \infty$?

 Compare with J.C. Miller (2007), Phys. Rev. E, SIR network model, homogeneous infectivity maximises probability of major outbreak, homogeneous susceptibility maximises outbreak size.

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References

11			

ANDERSSON, H. (1992)

A threshold limit theorem for a multitype epidemic model.

Research report no. 165, Institute of Actuarial Mathematics and Mathematical Statistics, Stockholm University.



ANDREASEN, V. (2011)

The final size of an epidemic and its relation to the basic reproduction number. *Bull. Math. Biol.*



BALL, F.G. AND CLANCY, D. (1993).

The final size and severity of a generalised stochastic multitype epidemic model. *Adv. Appl. Probab.* **25**, 721–736.



BECKER, N. AND MARSCHNER, I. (1990)

The effect of heterogeneity on the spread of disease. *Lect. Notes Biomath.* **86**, 90–103.



KENAH, E. AND ROBINS, J.M. (2007).

Network-based analysis of stochastic SIR epidemic models with random and proportionate mixing. J. Theo. Biol. 249, 706–722.



MILLER, J.C. (2007).

Epidemic size and probability in populations with heterogeneous infectivity and susceptibility. *Phys. Rev.* E **76**, 010101.

References



NOLD, A. (1980)

Heterogeneity in disease-transmission modelling. *Math. Biosci.* **52**, 227–240.



XIAO, Y., CLANCY, D., FRENCH, N.P. AND BOWERS, R.G. (2006)

A semi-stochastic model for Salmonella infection in a multi-group herd. *Math. Biosci.* **200**, 214–233.

YATES, A., ANTIA, R. AND REGOES, R.R. (2006)

How do pathogen evolution and host heterogeneity interact in disease emergence? *Proc. Roy. Soc. B* **273**, 3075–3083.