UNIVERSITY OF LIVERPOOL

MODELLING SYMPTOM PROPAGATION IN PATHOGENS INFECTING VIA THE RESPIRATORY TRACT

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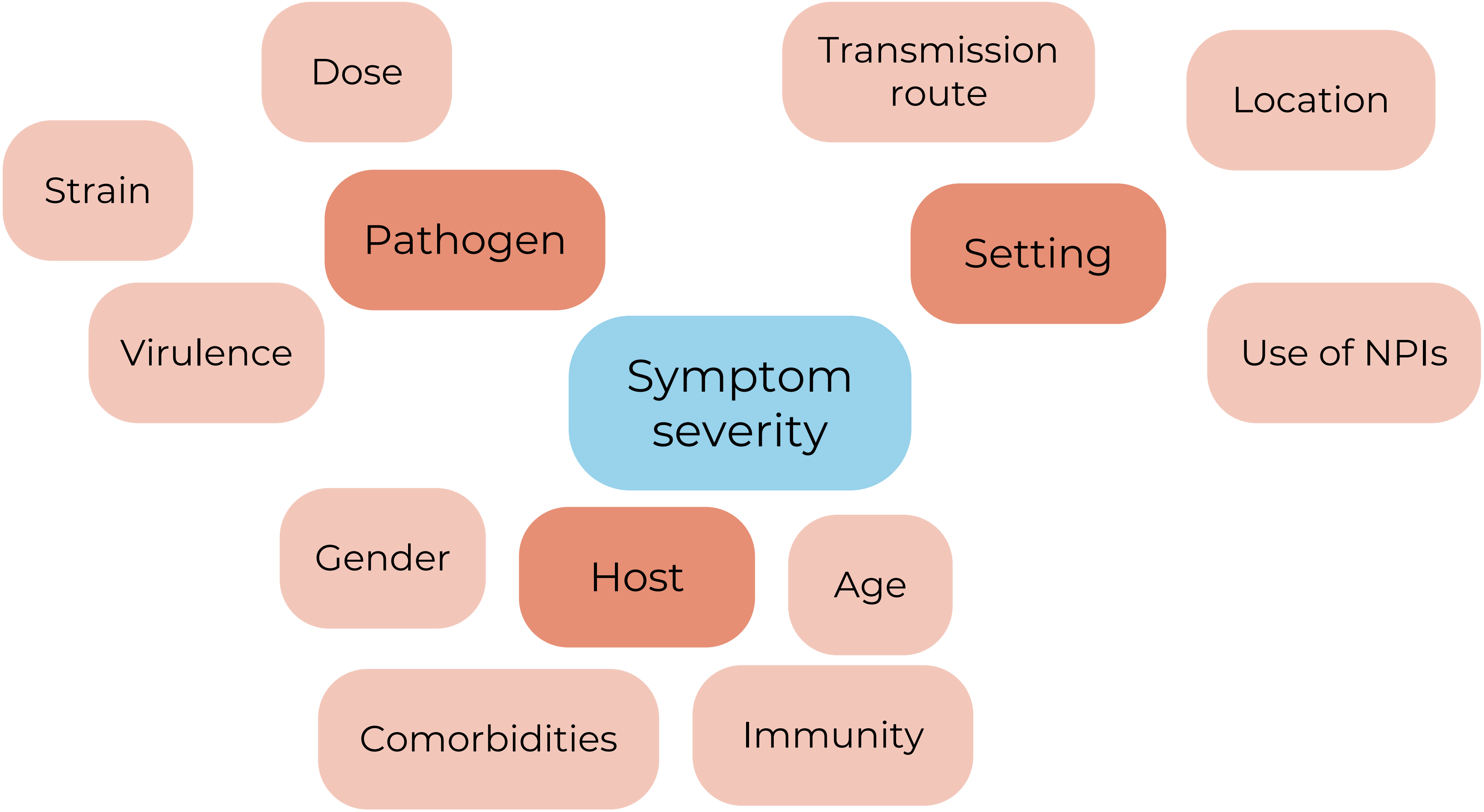
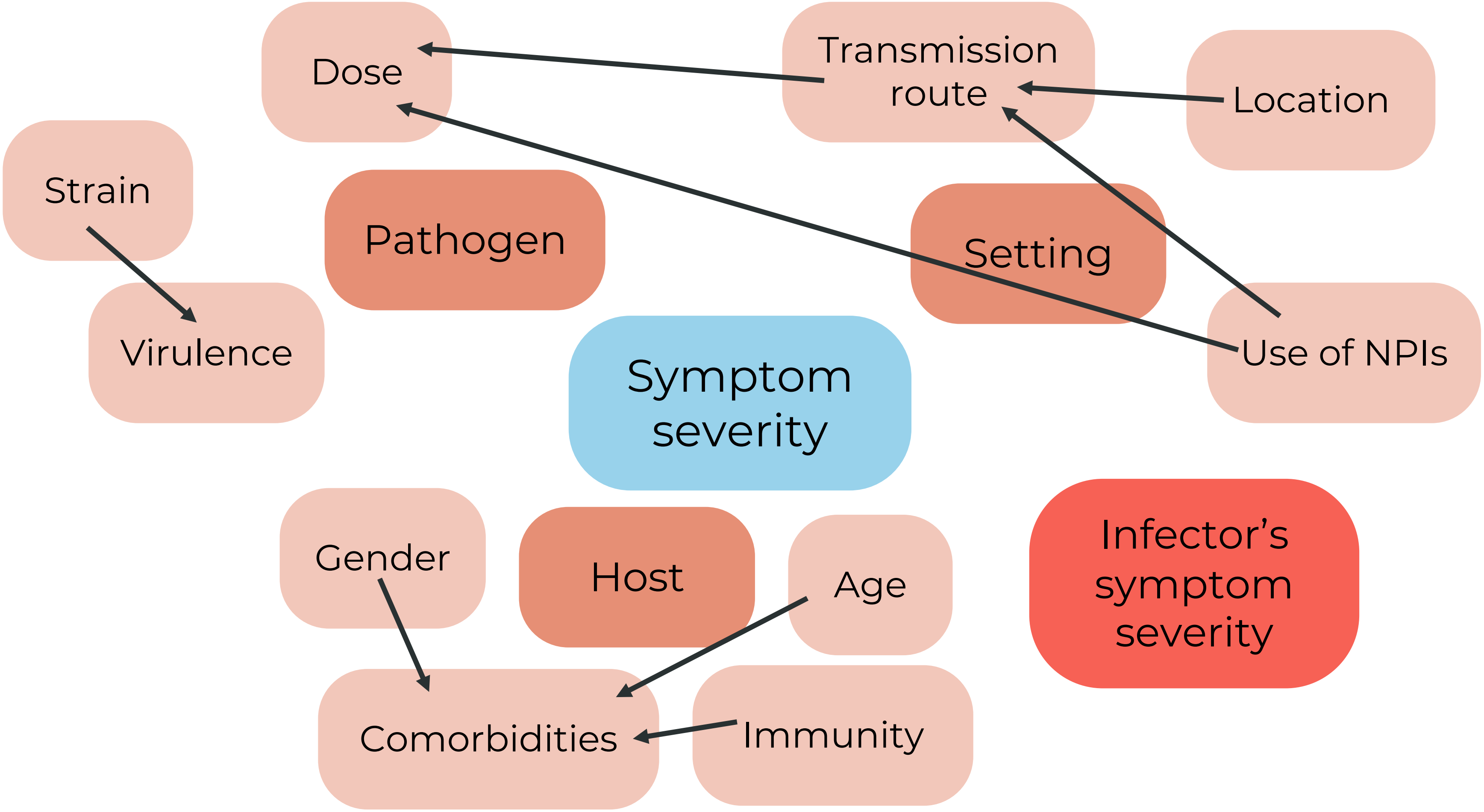
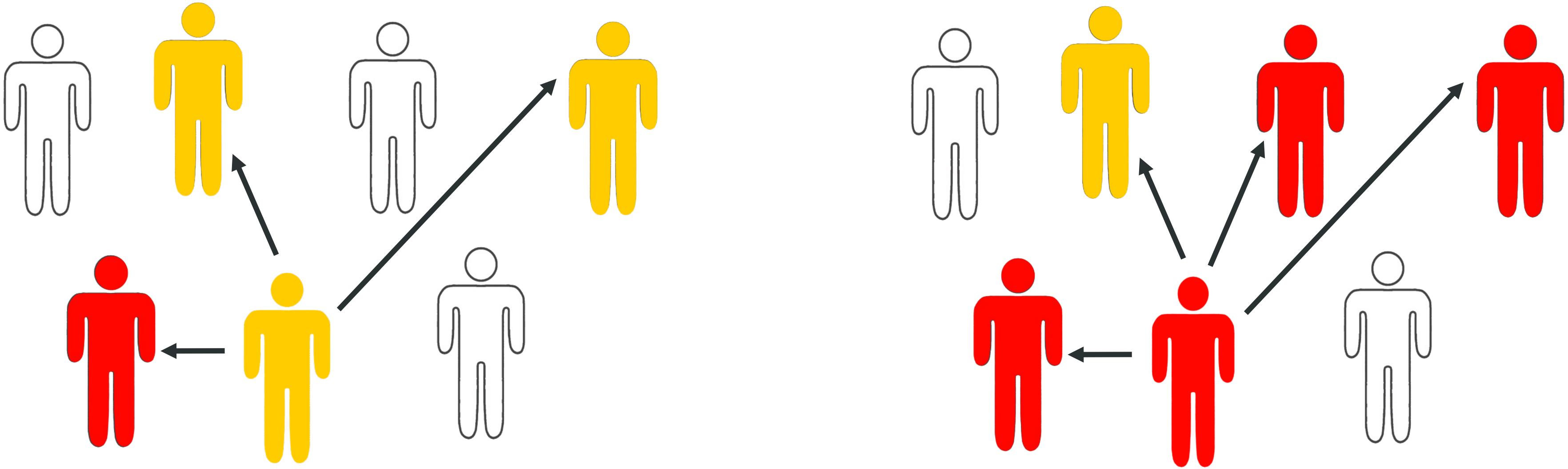
Co-supervisors: Matt Keeling (University of Warwick), Rebecca Mancy (University of Glasgow)
External partners: Tom Finnie (UKHSA), Fergus Cumming (FCDO)


Dose
Transmission route
Location
Strain
Pathogen
Setting
Virulence
Symptom severity
Use of NPIs
Gender
Host
Age
Comorbidities
Immunity

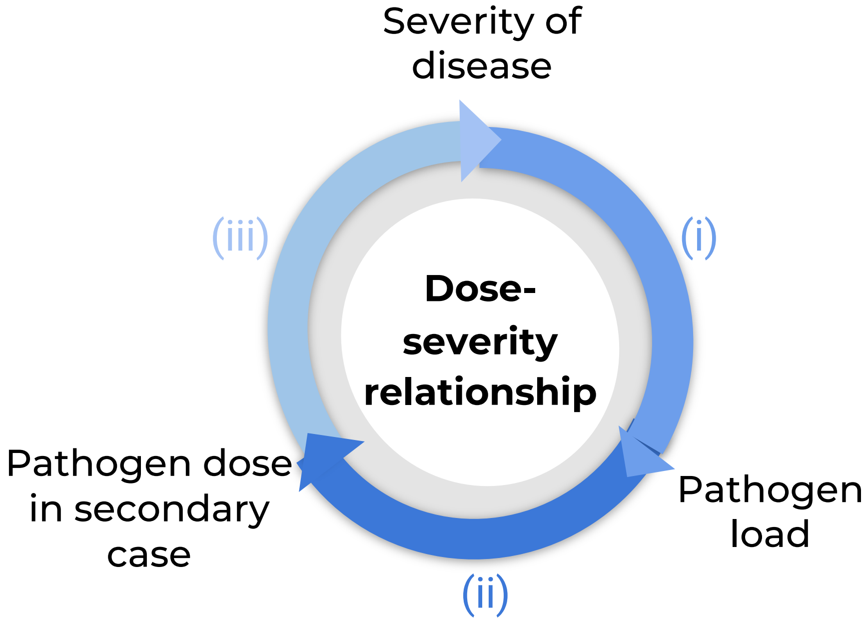

Dose
Transmission route
Location
Strain
Pathogen
Setting
Virulence
Use of NPIs
Symptom severity
Gender
Host
Age
Infector's symptom severity
Comorbidities
Immunity

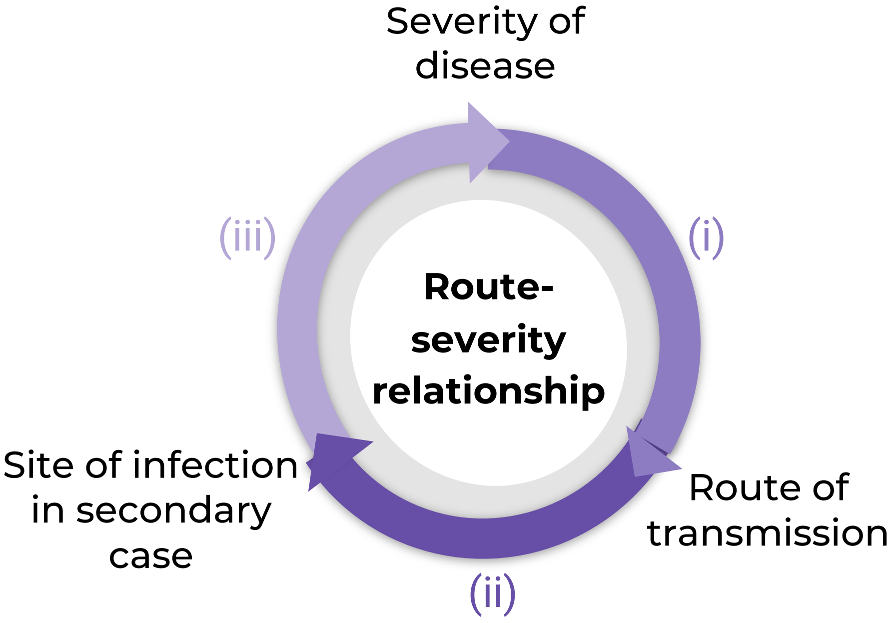
What is symptom propagation?

Symptom propagation occurs when the symptom set of an infected individual depends on the symptom set of the individual from which they acquired infection



Biological background





Study aims

Modelling paper

Literature review

1. Pathogens with symptom propagation traits

What is the evidence (supporting and non-supporting) for different pathogens infecting via the respiratory tract for the presence of symptom propagation mechanisms?

2. Modelling symptom propagation

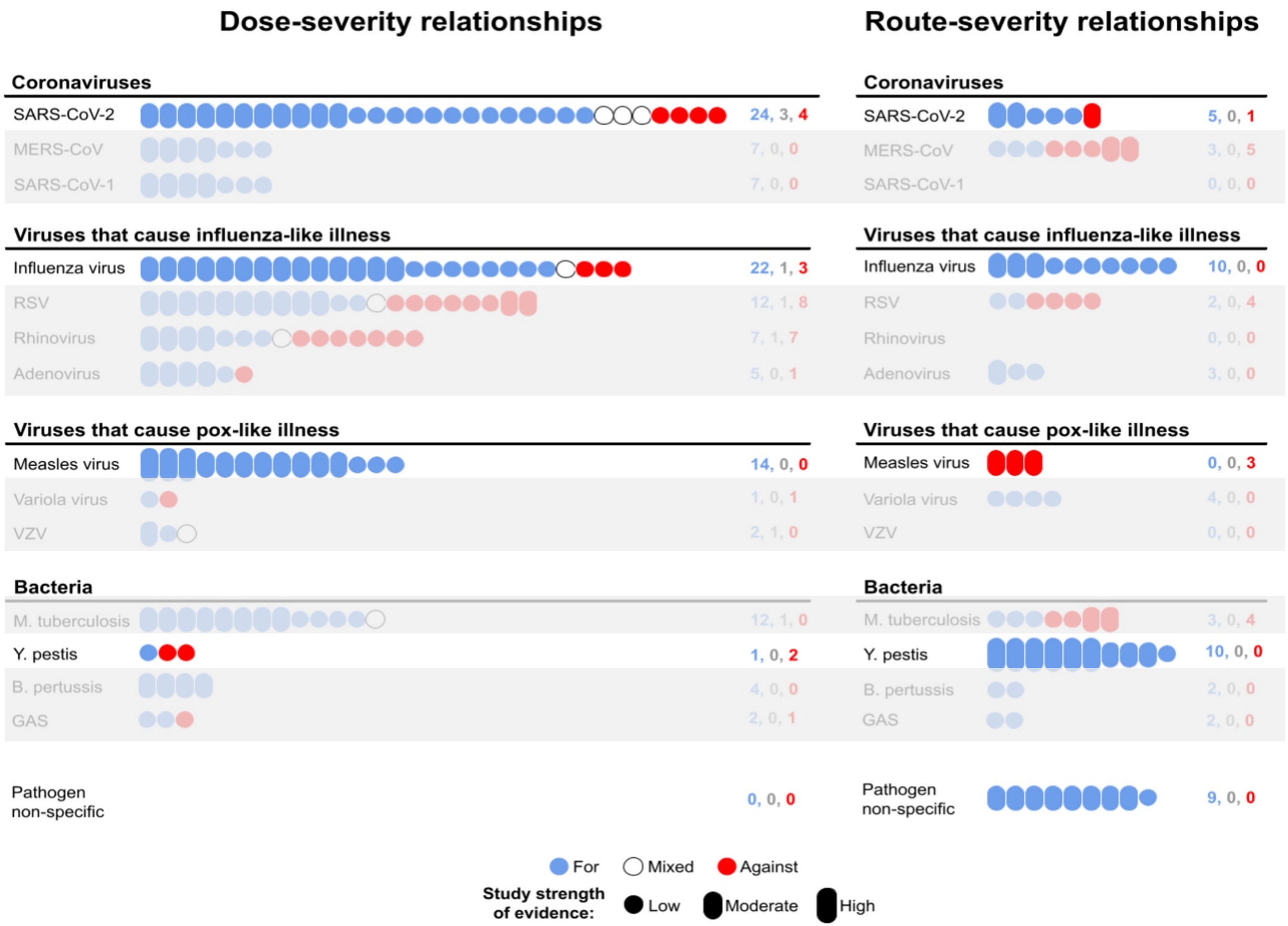
How can we include symptom propagation in models of infectious disease transmission?

3. Modelling interventions

How does symptom propagation affect isolation & vaccination strategies?

1. Pathogens with symptom propagation traits

What is the evidence (supporting and non-supporting) for different pathogens infecting via the respiratory tract for the presence of symptom propagation mechanisms?



Literature review

Dose-severity relationships for Influenza

Literature review

OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

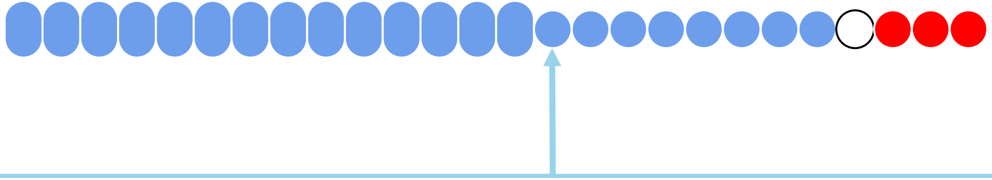
Clinical correlation of influenza and respiratory syncytial virus load measured by digital PCR

Diego R. Hijano, Jessica Brazelton de Cardenas, Gabriela Maron, Cherilyn D. Garner, Jose A. Ferrolino, Ronald H. Dallas, Zhengming Gu, Randall T. Hayden

Published: September 3, 2019 • https://doi.org/10.1371/journal.pone.0220908

Dose-severity relationships for Influenza

Literature review



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RESEARCH ARTICLE

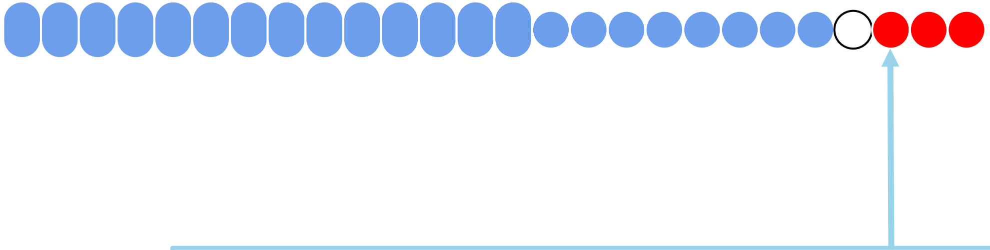
Exhaled Aerosol Transmission of Pandemic and Seasonal H1N1 Influenza Viruses in the Ferret

Frederick Koster, Kristine Gouveia, Yue Zhou, Kristin Lowery, Robert Russell, Heather MacInnes, Zemmie Pollock, R. Colby Layton, Jennifer Cromwell, Denise Toleno, John Pyle, Michael Zubelewicz, Kevin Harrod, [...], Yung-Sung Cheng
[view all]

Published: April 3, 2012 • https://doi.org/10.1371/journal.pone.0033118

Dose-severity relationships for Influenza

Literature review



RESEARCH ARTICLE | BIOLOGICAL SCIENCES

Infectious virus in exhaled breath of symptomatic seasonal influenza cases from a college community

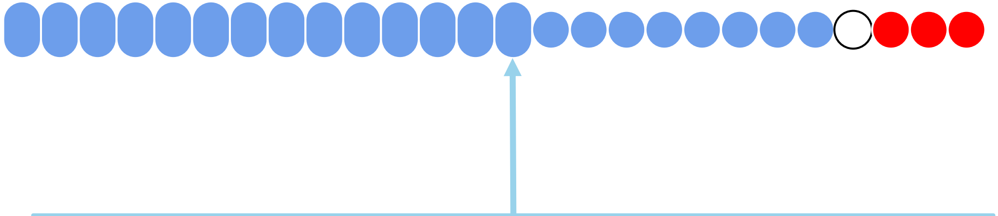
Jing Yan, Michael Grantham, Jovan Pantelic, +5, and EMIT Consortium Authors Info & Affiliations

Edited by Peter Palese, Icahn School of Medicine at Mount Sinai, New York, NY, and approved December 15, 2017 (received for review September 19, 2017)

January 18, 2018 | 115 (5) 1081-1086 | https://doi.org/10.1073/pnas.1716561115

Dose-severity relationships for Influenza

Literature review



JOURNAL ARTICLE

A Dose-finding Study of a Wild-type Influenza A(H3N2) Virus in a Healthy Volunteer Human Challenge Model

FREE

Alison Han ✉, Lindsay M Czajkowski, Amanda Donaldson, Holly Ann Baus, Susan M Reed, Rani S Athota, Tyler Bristol, Luz Angela Rosas, Adriana Cervantes-Medina, Jeffery K Taubenberger ... Show more

Clinical Infectious Diseases, Volume 69, Issue 12, 15 December 2019, Pages 2082–2090,
https://doi.org/10.1093/cid/ciz141

Published: 16 February 2019 **Article history** ▾

Route-severity relationships for Influenza

Literature review

JOURNAL ARTICLE

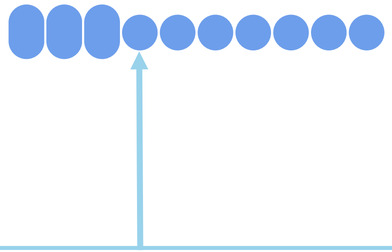
Exposure to Influenza Virus Aerosols During Routine Patient Care

Werner E. Bischoff, Katrina Swett, Iris Leng, Timothy R. Peters Author Notes

The Journal of Infectious Diseases, Volume 207, Issue 7, 1 April 2013, Pages 1037–1046,
https://doi.org/10.1093/infdis/jis773
Published: 30 January 2013 **Article history** ▾

Route-severity relationships for Influenza

Literature review



Restricted access | Research article | First published July 1966

Human Influenza Resulting from Aerosol Inhalation

Robert H. Alford, Julius A. Kasel, Peter J. Gerone, and Vernon Knight (-1) View all authors and affiliations

Volume 122, Issue 3 | https://doi.org/10.3181/00379727-122-31255

Dose-severity relationships for SARS-CoV-2

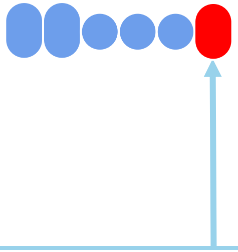
Literature review

On the SARS-CoV-2 "Variolation Hypothesis": No Association Between Viral Load of Index Cases and COVID-19 Severity of Secondary Cases

Mattia Trunfio[1*] Bianca Maria Longo[1] Francesca Alladio[1] Francesco Venuti[1] Francesco Cerutti[2] Valeria Ghisetti[2] Stefano Bonora[1] Giovanni Di Perri[1] Andrea Calcagno[1]

Route-severity relationships for SARS-CoV-2

Literature review



Articles

Viral emissions into the air and environment after SARS-CoV-2 human challenge: a phase 1, open label, first-in-human study

Jie Zhou PhD [a] †, Anika Singanayagam PhD [b] †, Niluka Goonawardane PhD [a], Maya Moshe MSc [a], Fiachra P Sweeney MSc [a], Ksenia Sukhova MSc [a], Ben Killingley MD [d], Mariya Kalinova MD [e], Alex J Mann MSc [e], Andrew P Catchpole DPhil [e], Prof Michael R Barer PhD [f], Prof Neil M Ferguson DPhil [c], Prof Christopher Chiu PhD [b], Prof Wendy S Barclay PhD [a]

Scoping literature review: Conclusions

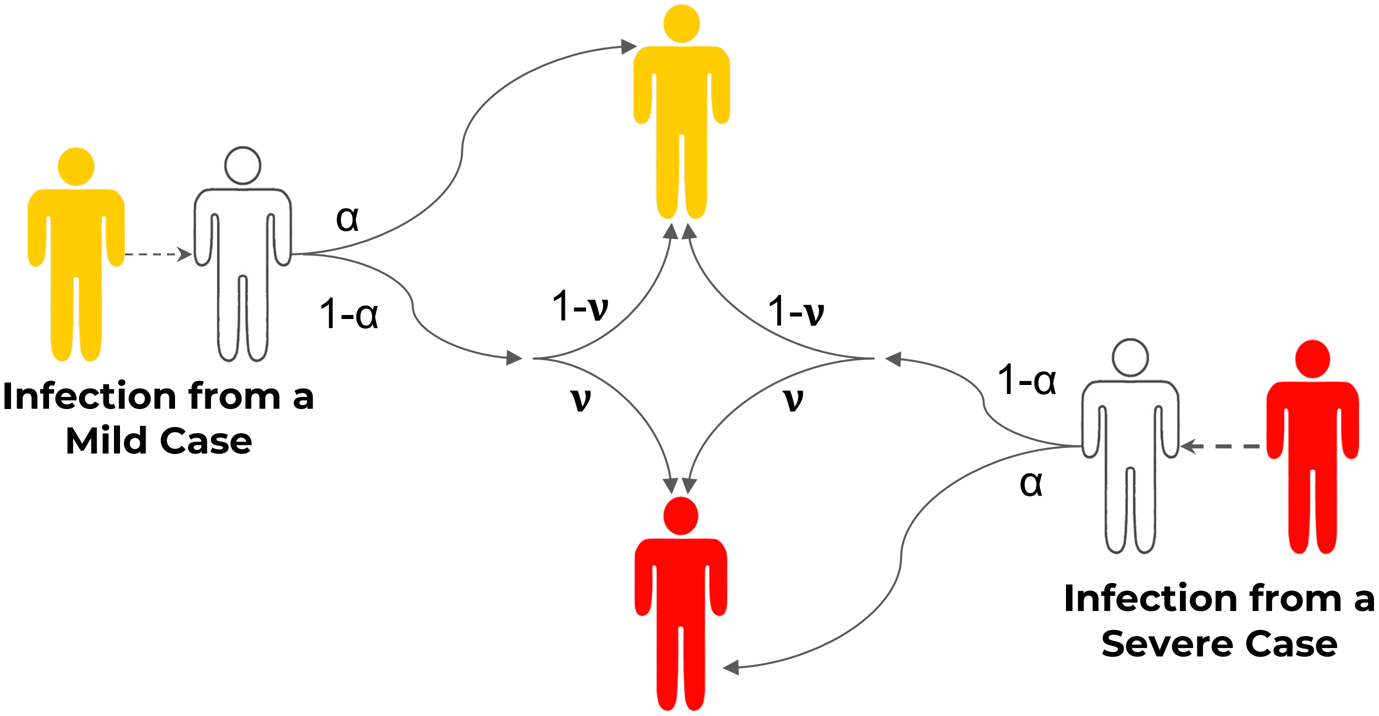
Literature review

- The **relationship between severity, LRT infection and aerosol transmission** provide support for the idea that both mechanisms of symptom propagation can act for some pathogens (e.g. influenza).
- Symptom propagation is highly **pathogen specific**.
- Further studies **investigating LRT viral load** would be helpful to confirm the role of dose-severity relationships with LRT involvement.
- Work required to **quantify the epidemiological impact** of symptom propagation and its strength.

2. Modelling symptom propagation

How can we include symptom propagation in models of infectious disease transmission?

Modelling symptom propagation




Modelling paper

Model equations

Modelling paper

S
$$\frac{dS}{dt} = -\lambda_M S - \lambda_S S$$

E
$$\frac{dE_M}{dt} = (\alpha + (1-\alpha)(1-\nu))\lambda_M S + (1-\alpha)(1-\nu)\lambda_S S - \epsilon E_M$$
$$\frac{dE_S}{dt} = (1-\alpha)\nu\lambda_M S + (\alpha + (1-\alpha)\nu)\lambda_S S - \epsilon E_S$$

I
$$\frac{dI_M}{dt} = \epsilon E_M - \gamma_M I_M$$
$$\frac{dI_S}{dt} = \epsilon E_S - \gamma_S I_S$$

R
$$\frac{dR_M}{dt} = \gamma_M I_M$$
$$\frac{dR_S}{dt} = \gamma_S I_S$$

$$\lambda_M = \frac{\beta_M I_M}{N}$$
$$\lambda_S = \frac{\beta_S I_S}{N}$$

Expectations about epidemiological impacts

01 Larger proportion of infections should be severe

02 Potential to under- or overestimate intervention effectiveness

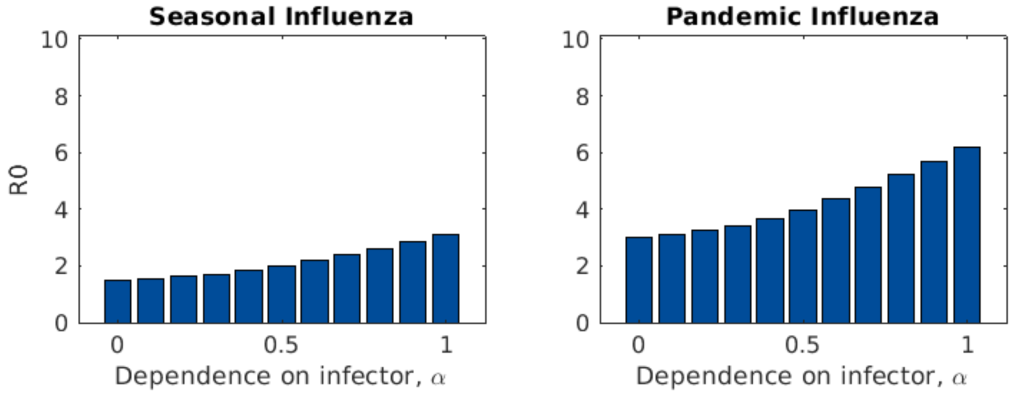
03 Could mean that we choose the wrong intervention strategy

R_0 analysis

Modelling paper

- We consider two disease parameterisations: seasonal influenza (R_0 = 1.5 when α = 0); pandemic influenza (R_0 = 3.0).

Since R_0 increases with α, these parameterisations are not realistic for stronger symptom propagation.

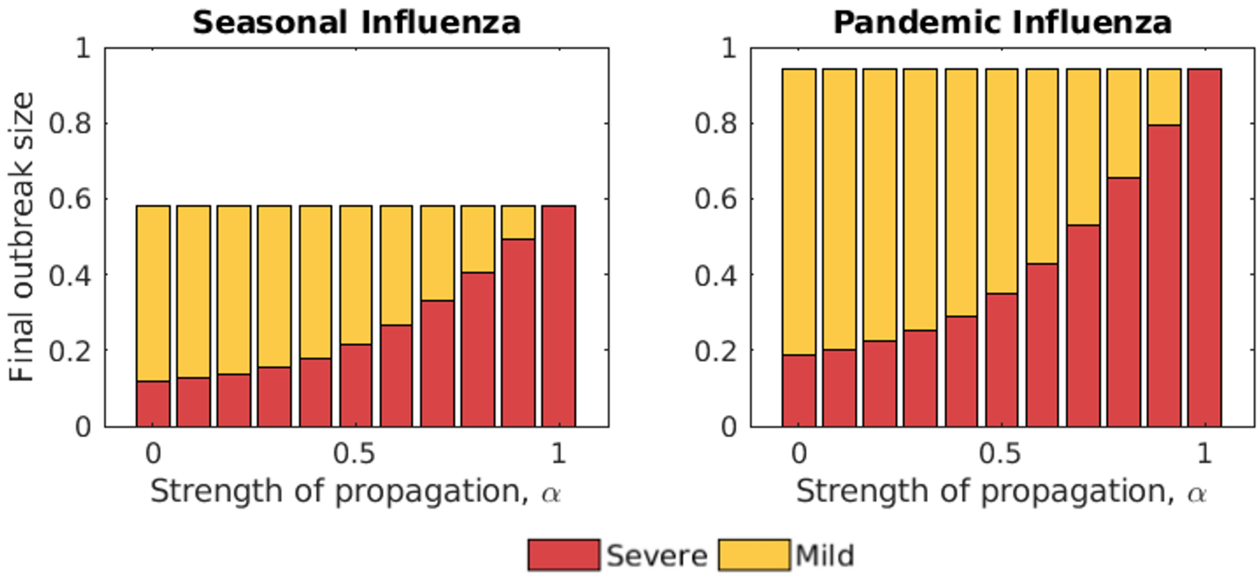


Final outbreak size

Modelling paper

When we fix R_0 the final outbreak size is constant across values of α.

The proportion of cases that are severe also increases.

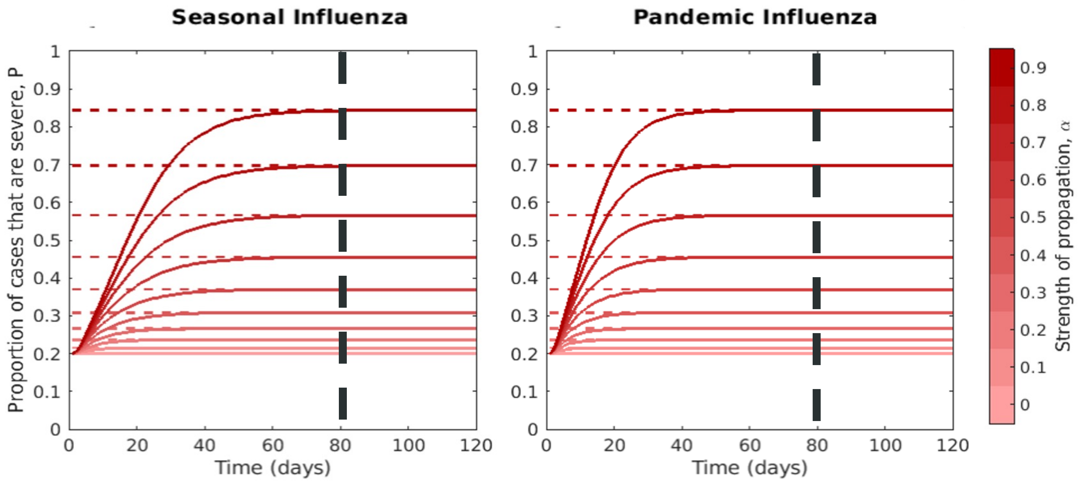


The proportion of cases that are severe, P

Modelling paper

- If $\gamma_S = \gamma_M$, then the proportion of cases that are severe tends to a fixed value (shown by the red dashed lines).

P reaches the fixed value within 80 days for all strengths of symptom propagation.

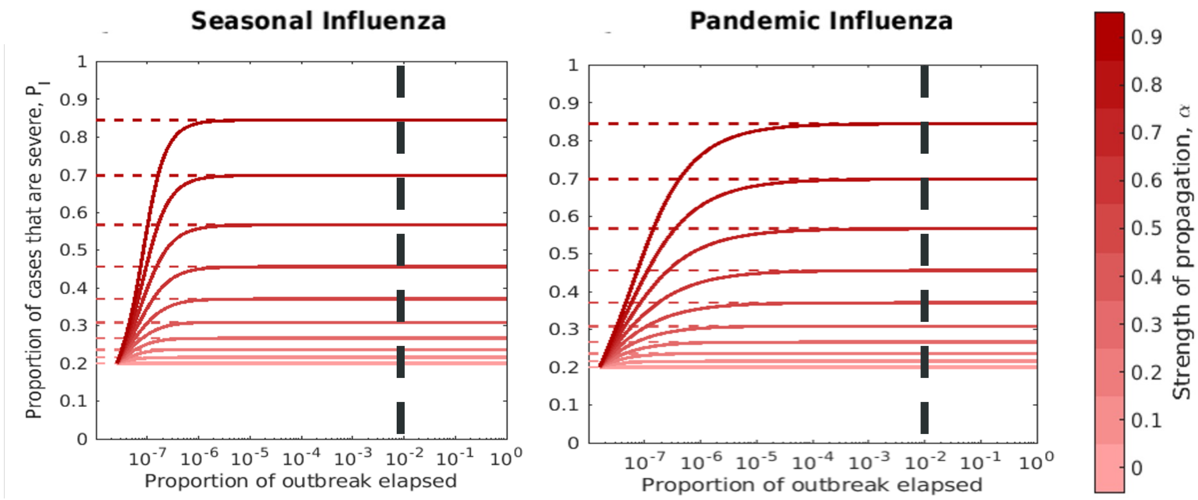


The proportion of cases that are severe, P

Modelling paper

- If $\gamma_S = \gamma_M$, then the proportion of cases that are severe tends to a fixed value (shown by the red dashed lines).

P reaches the fixed value by the time 1% of cases have occurred for all strengths of symptom propagation.

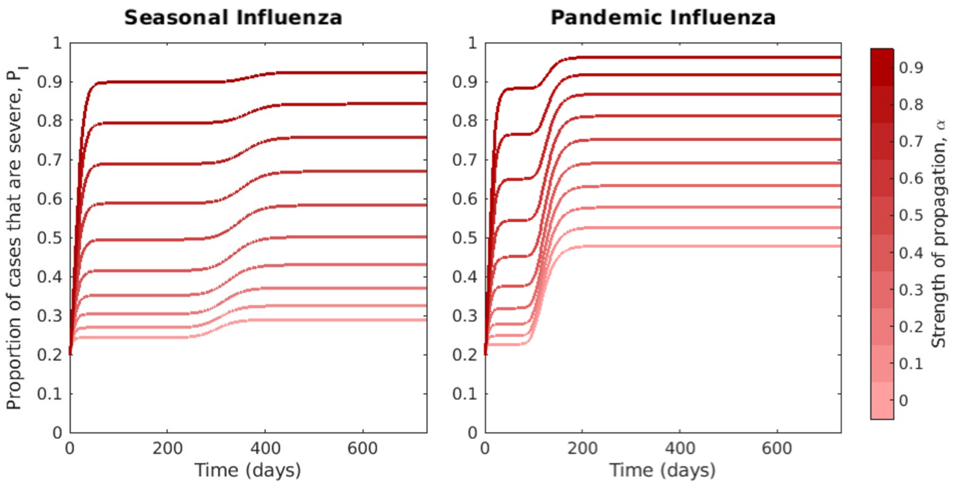


The proportion of cases that are severe, P

Modelling paper

- If $\gamma_S \neq \gamma_M$, then the proportion of cases that are severe varies over time.

P reaches a plateau in the early stages of the outbreak and then increases to a higher plateau in the late stages.



3. Modelling interventions

How does symptom propagation affect isolation strategies?

Isolation scenarios

Literature review

We compared between two isolation strategies:

1. Isolating **mild AND severely infected** individuals
2. Isolating **only severely infected** individuals

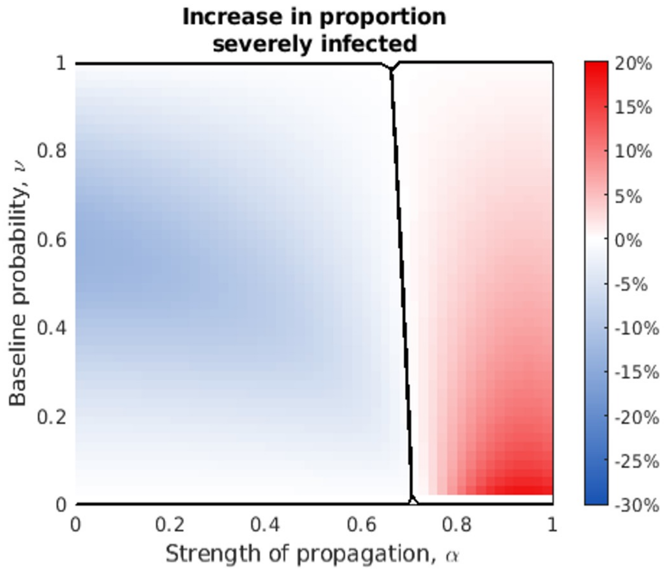
For each strategy, the probability of an infected individual eligible for isolation being successfully isolated was **0.5**.

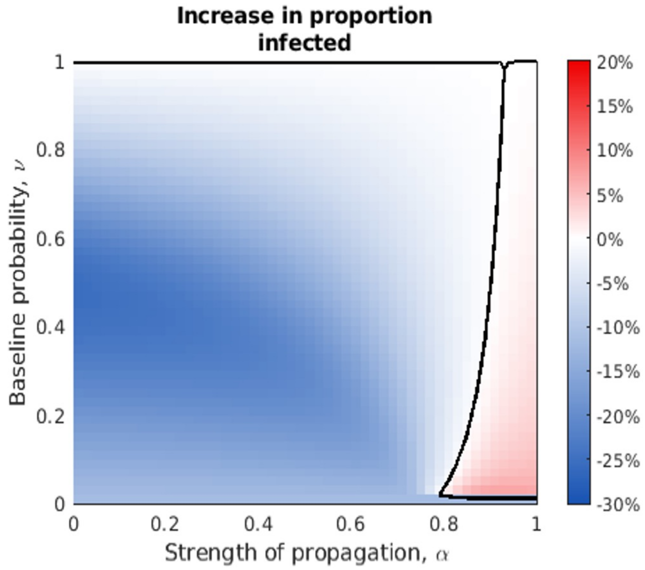
28

Isolation case-study

Literature review

- Red regions: isolating mild+severe cases leads to an overall increase in case numbers

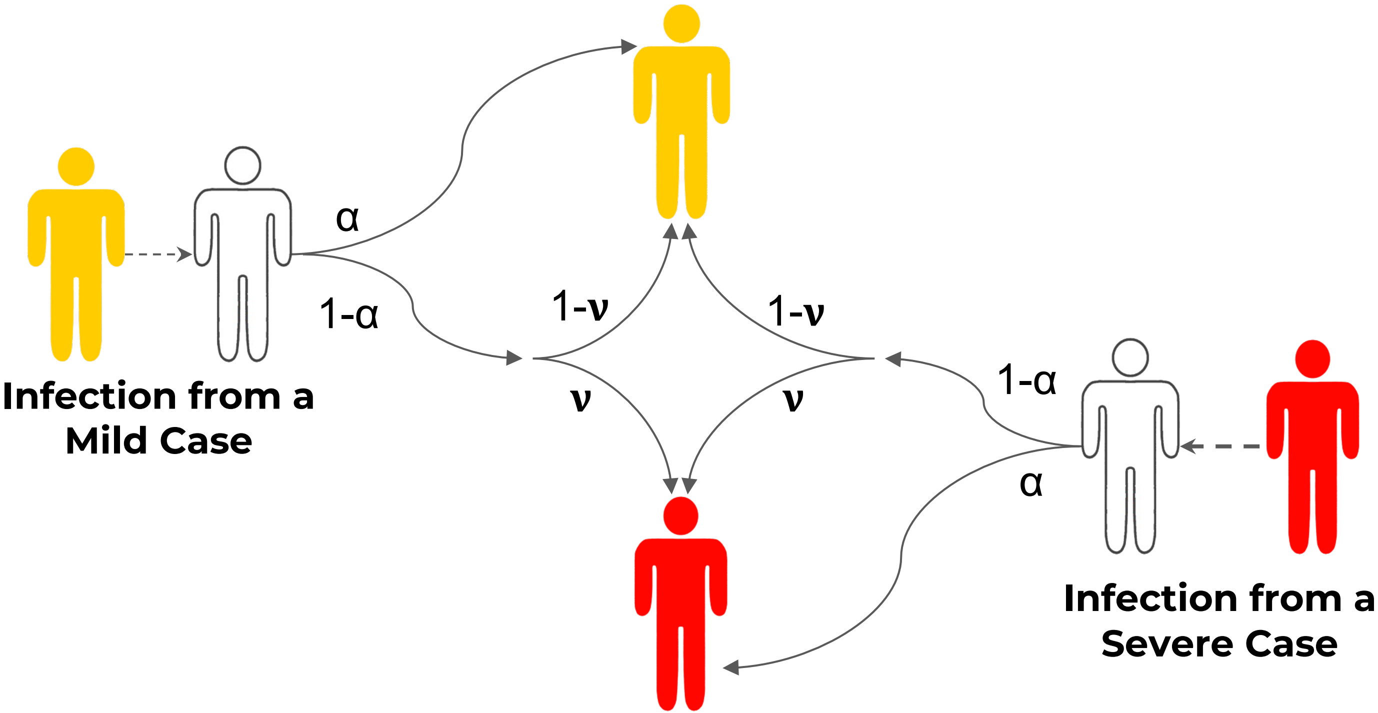




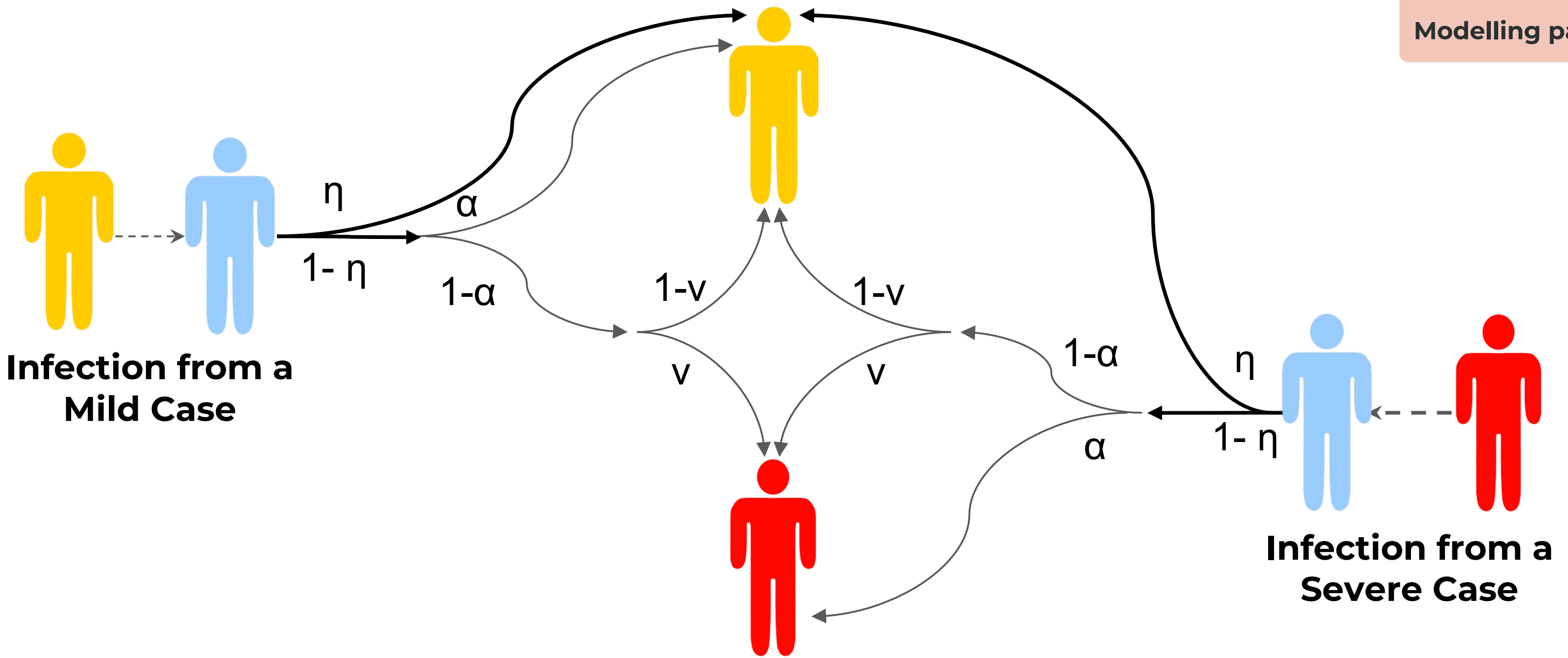
3. Modelling interventions

How does symptom propagation affect the effectiveness of vaccination strategies?

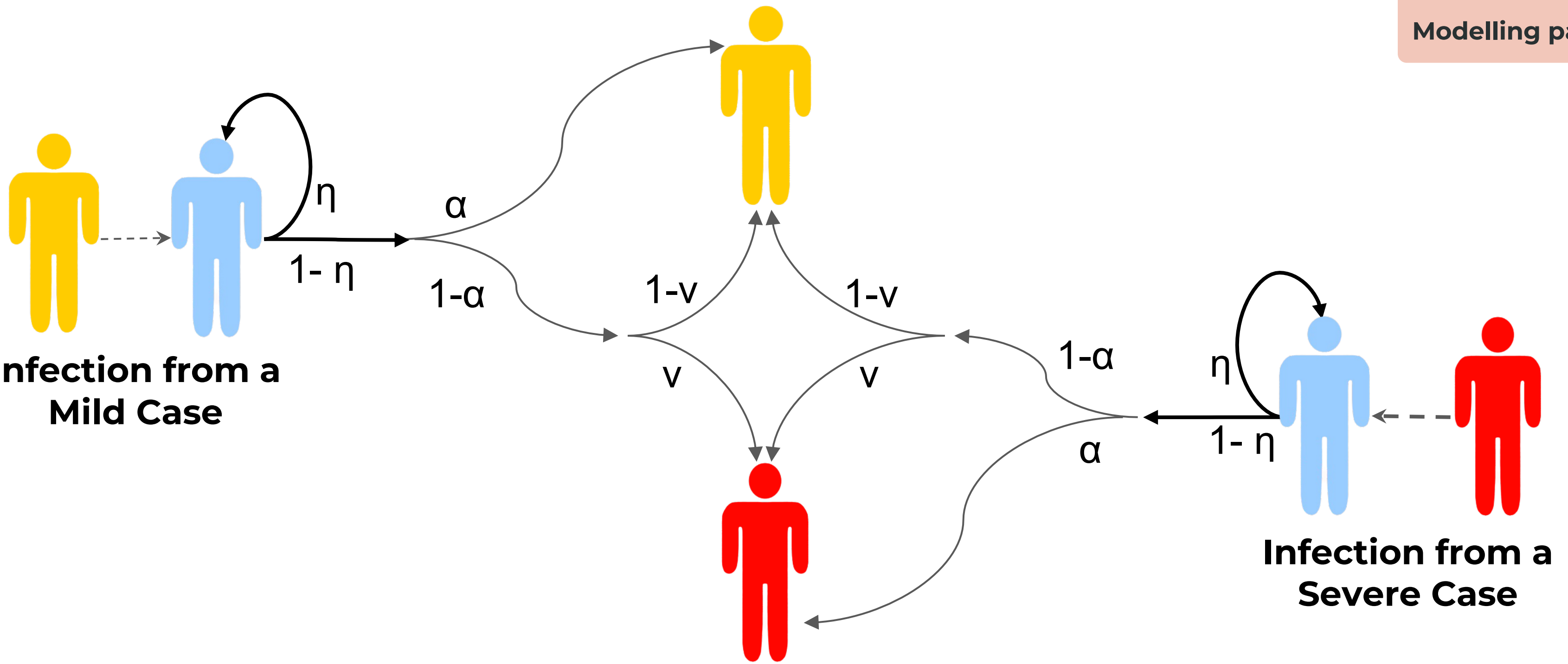
Modelling symptom propagation



Symptom-attenuating vaccine (SA)



Infection-blocking vaccine (IB)



Exploring the effect of varying α on the proportion of the population infected

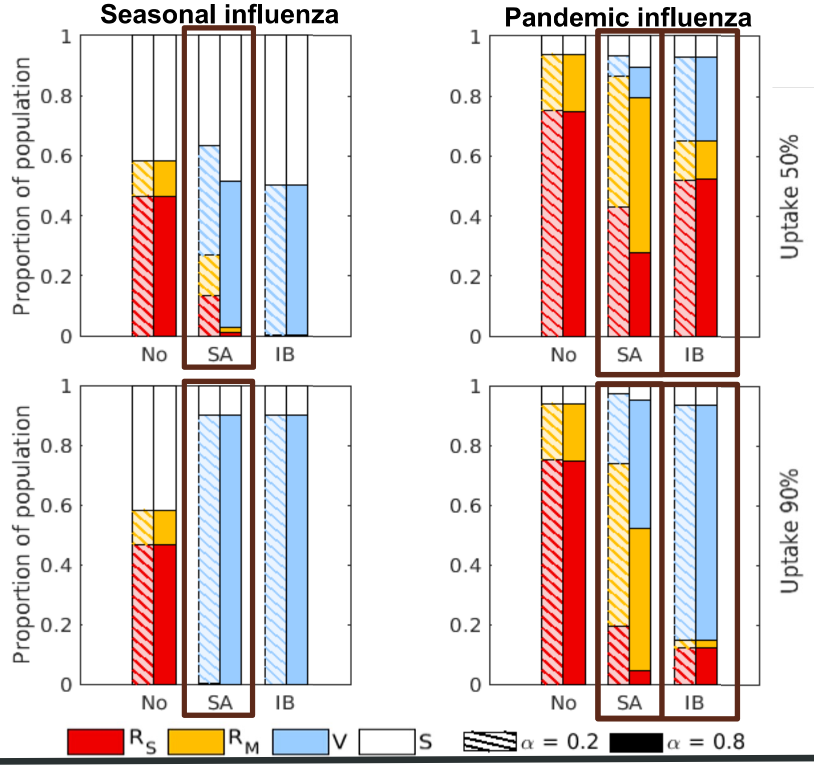
Modelling paper

Final proportion of the population in each disease status compartment for α: 0.2 (hashed) and 0.8 (solid)

SA vaccines are more effective when symptom propagation is stronger.

For pandemic influenza and high uptake, which of SA and IB is more effective at reducing severe cases depends on α.

Which intervention is preferable can depend on whether you care about reducing all cases or only severe cases.



Symptom-attenuating versus infection-blocking vaccines

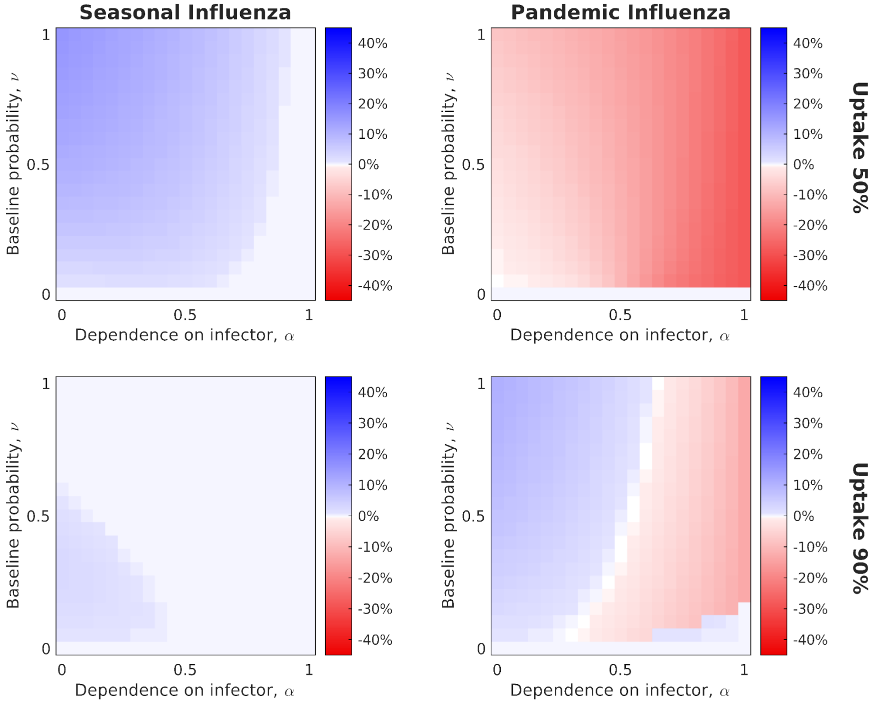
Modelling paper

Blue regions denote parameter values for which IB vaccines are more impactful (in reducing severe cases).

Red regions denote parameter values for which SA vaccines are more impactful (in reducing severe cases).

For low uptake (top row), which vaccine is more effective only depends on the disease parameterisation.

For high uptake and pandemic influenza, which vaccine is more effective depends on α.



Modelling study: Conclusions

Modelling paper

- Modelling shows that symptom propagation can affect **epidemiological outcomes:**
  - The total number of cases
  - The proportion of cases that are severe

- Under strong symptom propagation, interventions that **reduce symptom severity** are **more effective** at reducing total and severe cases.

- The **strength of symptom propagation** has the potential to determine the most effective **intervention type**.

Future work

Future work will be increasingly **computational** and will focus on:

- **Parameter inference:** Inferring the value of α from data to quantify the extent of symptom propagation.
    - Synthetic data studies
    - Real-world application to individual-level data for SARS-CoV-2
- **Structured populations:** Epidemiological modelling to investigate
    - e.g. implications of clustering of severe cases
    - e.g. stochastic simulations on a network

Acknowledgements

Lead author: Phoebe Asplin (University of Warwick)

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Literature review

INTERFACE

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Review

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Cite this article: Asplin P, Mancy R, Finnie T, Cumming F, Keeling MJ, Hill EM. 2024 Symptom propagation in respiratory pathogens of public health concern: a review of the evidence. *J. R. Soc. Interface* **21**: 20240009. https://doi.org/10.1098/rsif.2024.0009

Symptom propagation in respiratory pathogens of public health concern: a review of the evidence

Phoebe Asplin[1,2,3], Rebecca Mancy[5,6], Thomas Finnie[7], Fergus Cumming[8], Matt J. Keeling[2,3,4] and Edward M. Hill[2,3]

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[4]School of Life Sciences, [5]School of Biodiversity, One Health and Veterinary Medicine, and [6]MRC/CSO Social and Public Health Sciences Unit, University of Glasgow, Glasgow, UK
[7]Data, Analytics and Surveillance, UK Health Security Agency, London, UK
[8]Foreign, Commonwealth and Development Office, London, UK

Modelling paper

PLOS COMPUTATIONAL BIOLOGY

RESEARCH ARTICLE

Epidemiological and health economic implications of symptom propagation in respiratory pathogens: A mathematical modelling investigation

Phoebe Asplin[1,2,3]*, Matt J. Keeling[2,3,4], Rebecca Mancy[5,6], Edward M. Hill[2,3]*

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