NUS National University of Singapore | Saw Swee Hock School of Public Health

The role of modelling in the Covid pandemic

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SOME *A PRIORI* PATHOMETRIC EQUATIONS.

BY

SIR RONALD ROSS, K.C.B., F.R.S.

In the second edition of my book on the *Prevention of Malaria* (Murray, 1911) I published a considerable amount of work (which had occupied me for a long time) on what may be called pathometry—that is, the mathematical study of epidemiology. In these studies I followed the *a priori* method: in other words, I *assumed* a knowledge of the fundamental laws governing the time-to-time variations of disease in a population of living creatures; formed the corresponding difference- and differential-equations; and then sought by solving these to ascertain the more remote laws which should govern the variations if my assumptions were correct. My work was concerned chiefly with insect-borne diseases; but on page 678 I gave brief, but not quite complete, integrated equations on the general theme, these equations being obtained on the supposition that the total population remains constant during the considered period of time. A year ago, however, I was able to remove this restriction by integrating the original differential equations even when the population varies, and I have now found a simplification which enables us to state the equations in forms which are easy to analyse and which will be readily understood by any one who has some knowledge of the calculus. Thus put, they give us an elegant (though tentative) mathematical theory both of epidemic and endemic communicable diseases.

The theory is of course based upon certain probable assumptions; but its utility lies in this very point, because it enables us to test these assumptions by comparing the resulting curves with those derived from observation or statistics—a verification which cannot otherwise be obtained. My full paper on the subject is more suitable for mathematical than for medical publications; but you may possibly consent to publish the following very brief statement for the information of some epidemiologists who, I believe, will be interested in it. I will first give the identities and equations and will then add a short explanation.

$$1.\quad v = n - m + i - e$$

$$2.\quad V = N - M + I - E$$

$$3.\quad K = c - (v - V)$$

$$4.\quad I_{\cdot} = I - (N + r)/K$$

$$5.\quad \frac{dx}{dt} = Kx(I_{\cdot} - x)$$

$$6.\quad \frac{dP}{dt} = vP - (v - V)Px$$

$$7.\quad x = x_0 \frac{I_{\cdot}}{x_0 + (I_{\cdot} - x_0)\epsilon^{-KIt}}$$

$$8.\quad P = P_0 \epsilon^{vt}\left(\frac{x}{x_0}\epsilon^{-KIt}\right)^{\frac{v-V}{K}}$$

$$9.\quad KIt = \log_{\epsilon}\frac{I_{\cdot} - x_0}{x_0} - \log_{\epsilon}\frac{I_{\cdot} - x}{x}$$

$$10.\quad f = cx(I - x)$$

$$11.\quad \frac{df}{dt} = cKx(I_{\cdot} - x)(I - 2x)$$

$$12.\quad \frac{d^2f}{dt^2} = cK^2x(I_{\cdot} - x)\left\{I_{\cdot} - 2(2I_{\cdot} + I)x + 6x^2\right\}$$

Here t denotes the time, measured from the beginning of the inquiry; P_0 is the total population at the beginning of the inquiry (when $t = o$), and P is the total population at the end of the time t. The symbols n, m, i, e denote respectively the nativity, mortality, immigration, and emigration rates per unit of time (hour, day, or week, etc.) of the unaffected population, and v is the sum of these. The capitals of the same letters in (2) denote the same rates among those of the population who are affected by the considered disease. All these quantities are taken as being constant during the inquiry,[1] but the constants of the affected population, especially the mortality, will often be different from those of the unaffected population, and V will generally be smaller than v. The symbol r denotes the proportion of the affected population who recover in unit of time, or rather who become unaffected—that is, lose infectivity and also acquired immunity. The symbol x denotes the proportion of the total population P who are affected by the disease and living at the end of the time t, and x_0 is this proportion at the beginning of the inquiry when $t = o$. The symbol f denotes the current proportion of new cases to total population at the time t, and, when multiplied by P, gives the current number of new cases—that is, the curve generally shown in statistics of epidemics.

I call the important constant c the *infection rate*; and these equations are based on the assumption that each affected individual infects or reinfects c other individuals in unit of time, and that c is a constant. But some of the individuals to whom he thus gives the infection may be affected already, and we must allow for this. The actual number of affected individuals at the time t will be xP; and by supposition these will infect or reinfect cxP individuals; but of these only the ones which are not affected at the time t will be *new* cases. The actual number of new cases, F, will then be given by the proportion,

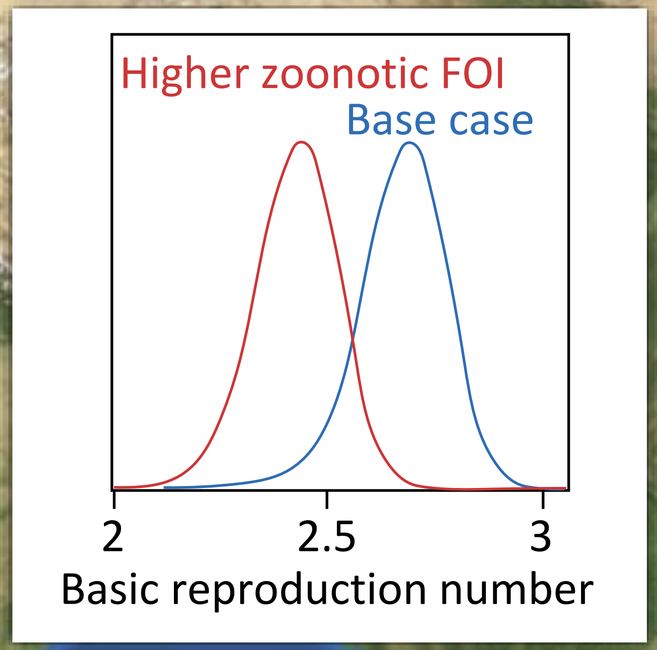
$$F : cxP :: (P - xP) : P$$

that is $F = cxP(I - x)$. But $f = F/P$; therefore finally we get the equation (10). This equation may, however, be also deduced from the fundamental differential equations (5) and (6) described in my book. The magnitude of c, as of the other constants, will, of course, depend on the unit of time taken. It is always positive, but must not be so small as to render KI negative.

The Curve of Affected Individuals, x, is an S-shaped curve beginning at x_0 when $t = o$, and approximating to a limit I when t is large. Its tangential, $\frac{dx}{dt}$, is a symmetrical bell-shaped curve with a maximum which $= \frac{1}{4}KI^2$ when $x = \frac{1}{2}I$ and $KIt = \log_{\epsilon}\frac{I_{\cdot} - x_0}{x_0}$. The Curve of New Cases, f, is especially important as it should agree when multiplied by P with observed curves if our assumptions are sound. It begins at a small value when x_0 is small and $t = o$, and then rises more or less rapidly, reaching its maximum, $\frac{1}{4}c$, when $x = \frac{1}{2}$ and then falling again and approximating to a limit which $= cI(I - I)$ when t is large. In this case (Type I) it has an irregular bell shape, but one which tails away more gradually than it rises. But if I is not greater than $\frac{1}{2}$, x never exceeds the value $\frac{1}{2}$ and consequently f loses this bell shape and becomes an S-shaped curve (Type II) which constantly rises towards the limit $cI(I - I)$. The former would appear to be the curve of true epidemic outbreaks, and the latter of slowly increasing endemic maladies. In both cases the value of f when t is large expresses and explains the endemic persistence of the disease in a locality.

The curve f is also much modified if (as usual) the reversion factor r does not come into play until months or years after infection, in which case f will at first approximate very closely to the curve $\frac{dx}{dt}$ and then tail off more slowly. Moreover, the infection rate, c, may be changed by local conditions, as for instance those of climate and season, which may favour or disfavour the transference of infection from individual to individual. It is impossible to examine these and other consequences of the equations except at considerable length; but I should add that the functions are usually easy to manage in finite terms, and seem to me, judging from general knowledge both of epidemic and endemic diseases, to be likely to agree with the facts.

So far as I know, these are the first attempts to obtain *a priori* equations on the subject; but it is interesting to compare them with results obtained *a posteriori*—that is, by trying to fit functions to observed curves of epidemics. Dr. John Brownlee has published some able papers on this part of the subject. In one paper[2] he says that the late Dr. Farr had found long ago that the second difference of the logarithm of epidemic curves is a constant. From this Dr. Brownlee deduces for epidemics a normal curve of probability (Type IV), *which is also a bell-shaped curve*, and he proceeds to fit this, with considerable success, to many epidemics. As a result he appears to conclude (page 516) that an epidemic depends on the acquisition by the infecting organism "of a high grade of infectivity at the point where the epidemic starts, this infectivity being lost from that period, till the end of the epidemic." In a



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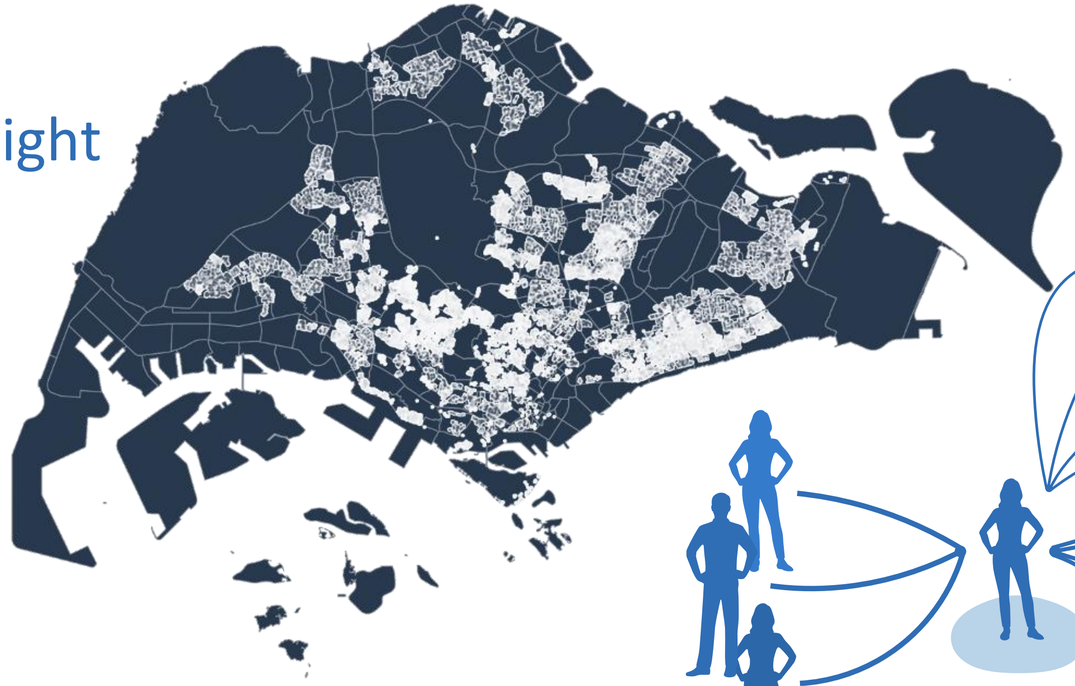
Wu et al (2020)
Lancet 395:689-697

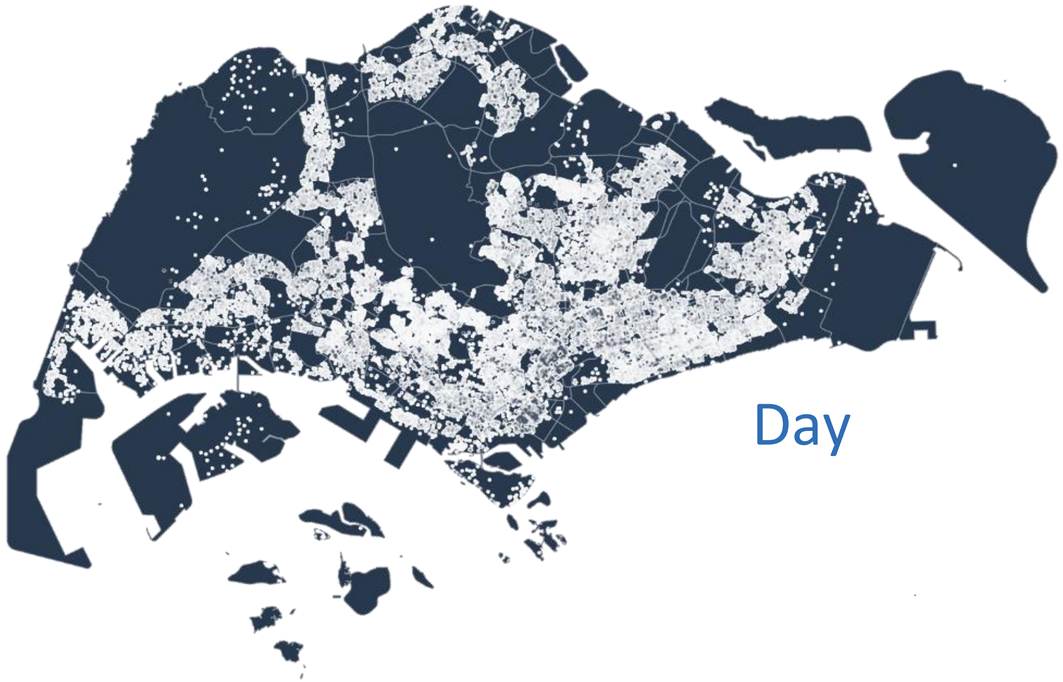
Example 1: Early measures to control the pandemic

Work by Joel Koo, Bo Dickens, Minah Park,
Sun Yinxiaohe, Sun Haoyang, Lim Jue Tao, Clarence Tam,
Annelies Wilder-Smith, Sharon Quaye, Rachael Pung, Vernon Lee, Louis Chai

Data-driven simulation model

Night



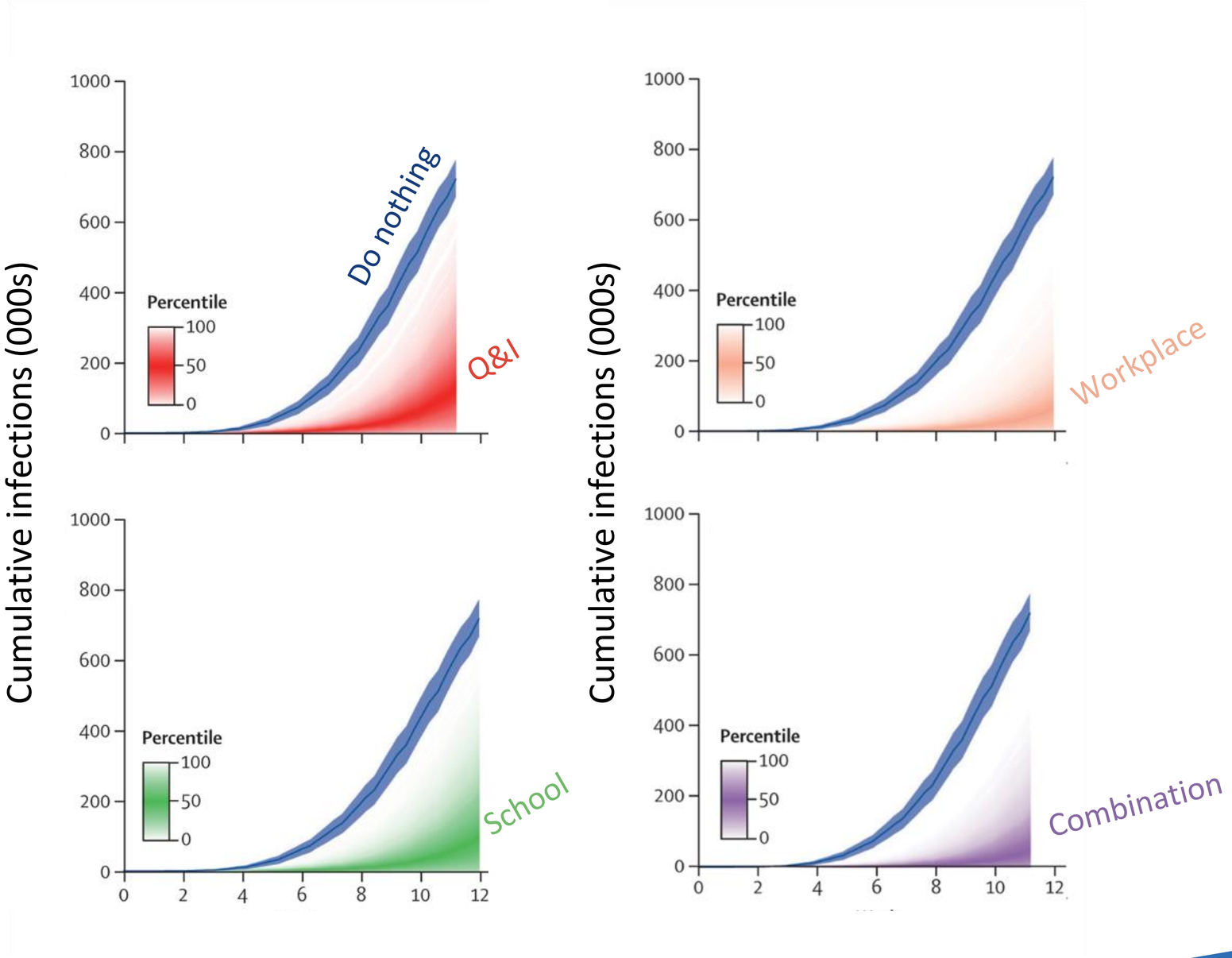


Day

Developed a highly detailed individual-based representation of Singapore using many data sources, developed for a flu pandemic and reworked based on early Chinese studies

Schools, businesses, business sectors, hospitals, public housing, private housing, age profile, household structure, distance home to work, etc for the resident population

How critical a comprehensive approach is

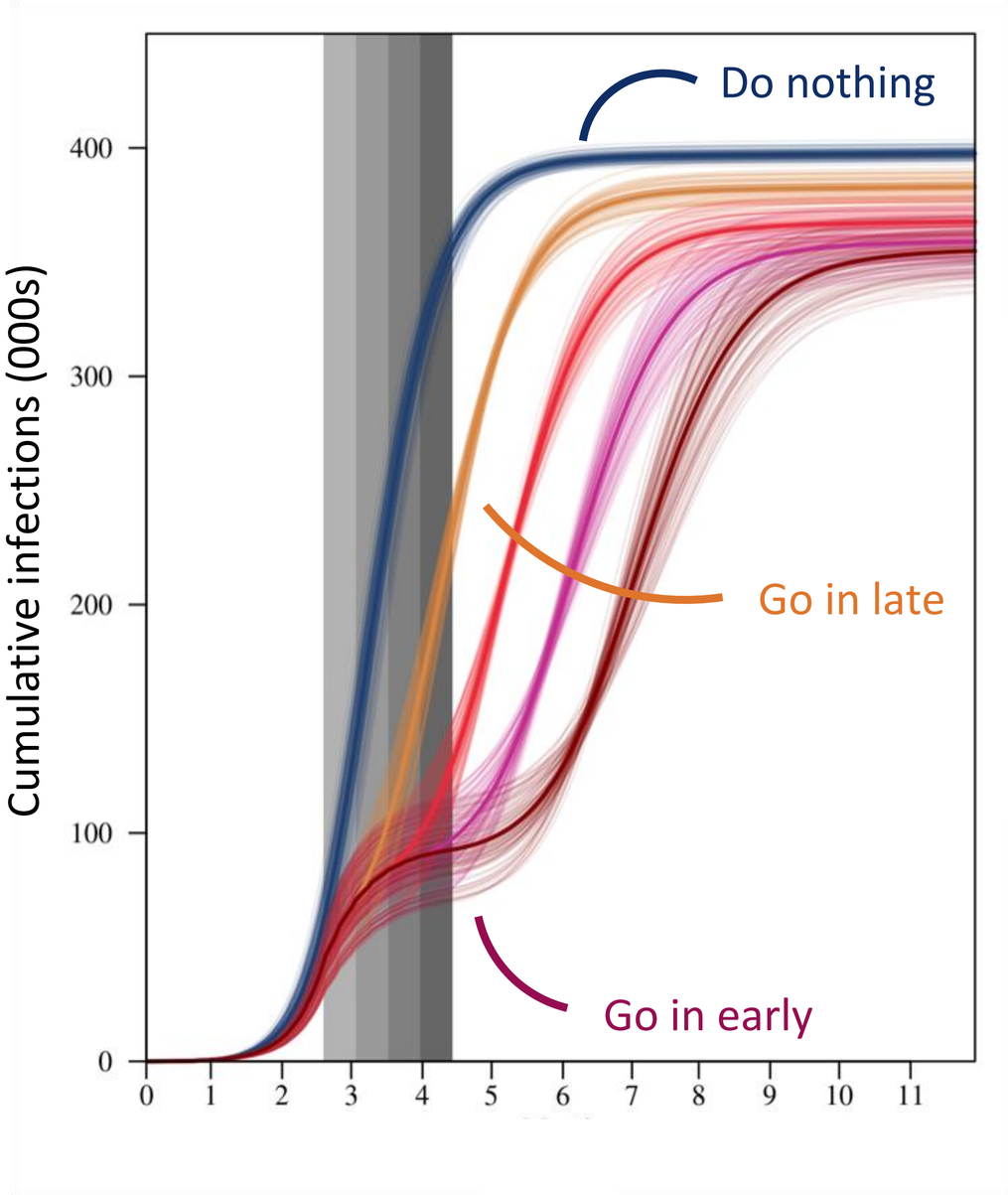


Koo et al (2020)
Lancet Inf Dis

Just quarantine and isolation, or just workplace distancing, or just school closure: not enough to prevent spread once imported

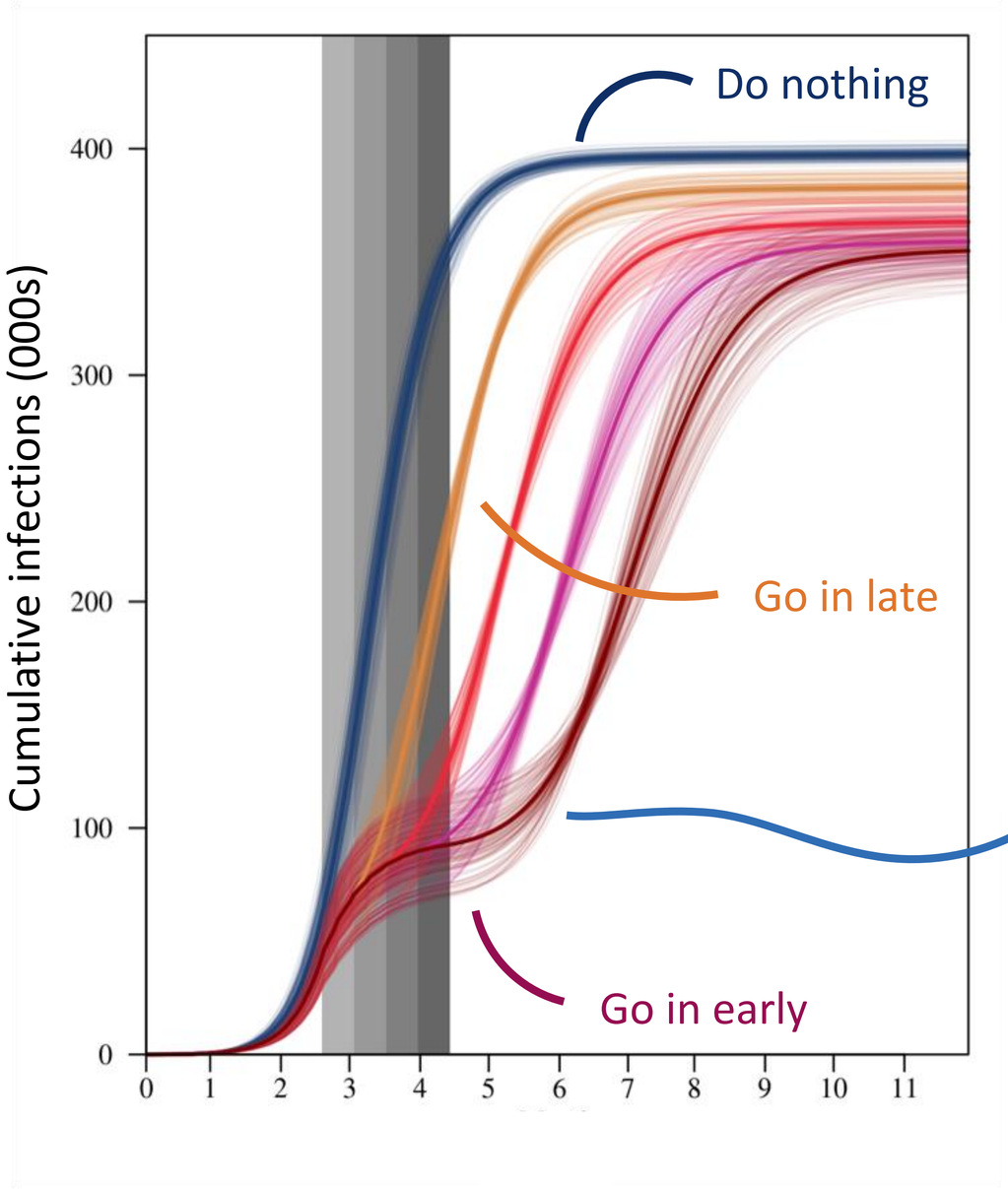
Advocated for a combination of strategies to buy time

How critical the timing of lockdown is



Dickens et al (2020)
Lancet West Pac

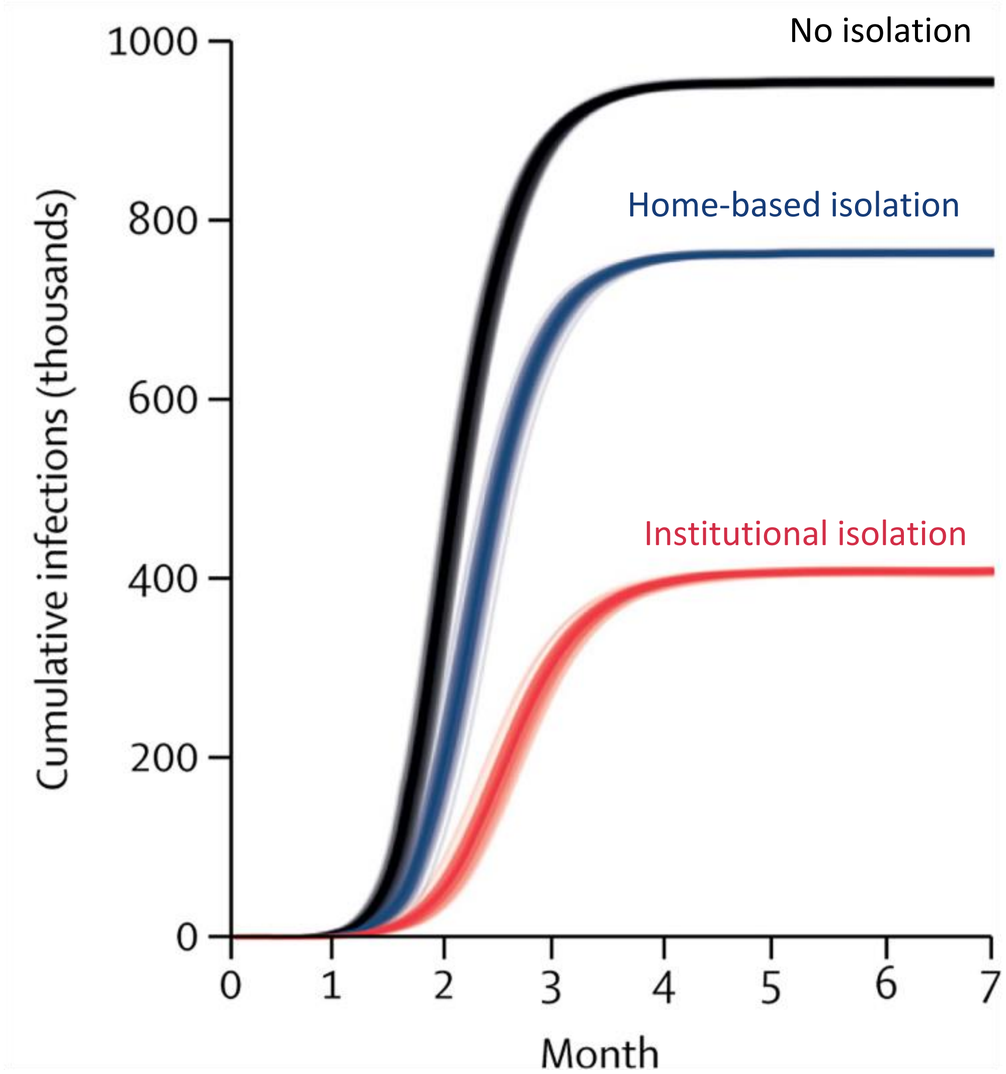
How critical the timing of lockdown is



Lockdown has to be followed by something else if cases >0 or border open or herd immunity isn't reached or the epidemic will resurge after lockdown

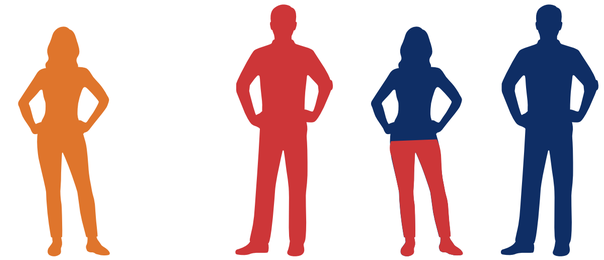
Dickens et al (2020)
Lancet West Pac

How critical institutional isolation is

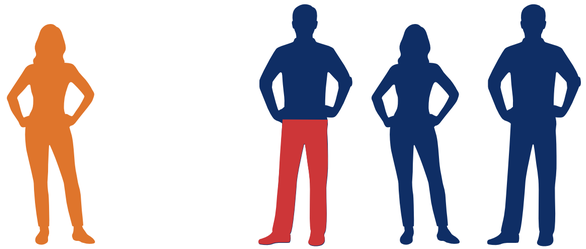


Dickens et al (2020) Lancet 395:1541–2

In HH of :



1.3 secondary infections (US)



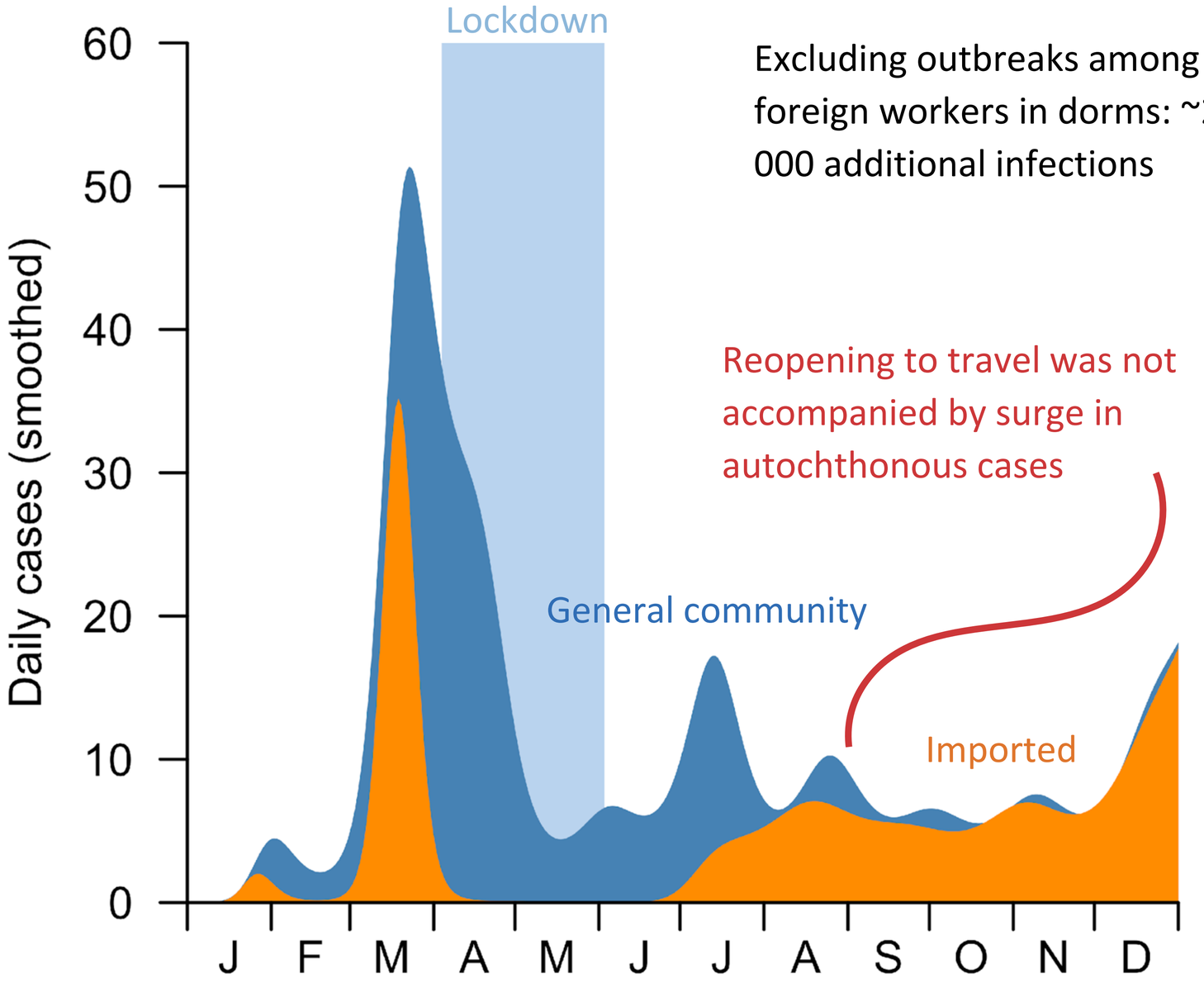
0.4 secondary infections (CH/SG)

Ng et al (2020) Lancet Inf Dis 10.1016/S1473-3099(20)30833-1

Lewis et al (2020) Clin Inf Dis ciaa1166

Dickens et al (2020) Lancet 395:1541–2

For the most part, it worked… in 2020

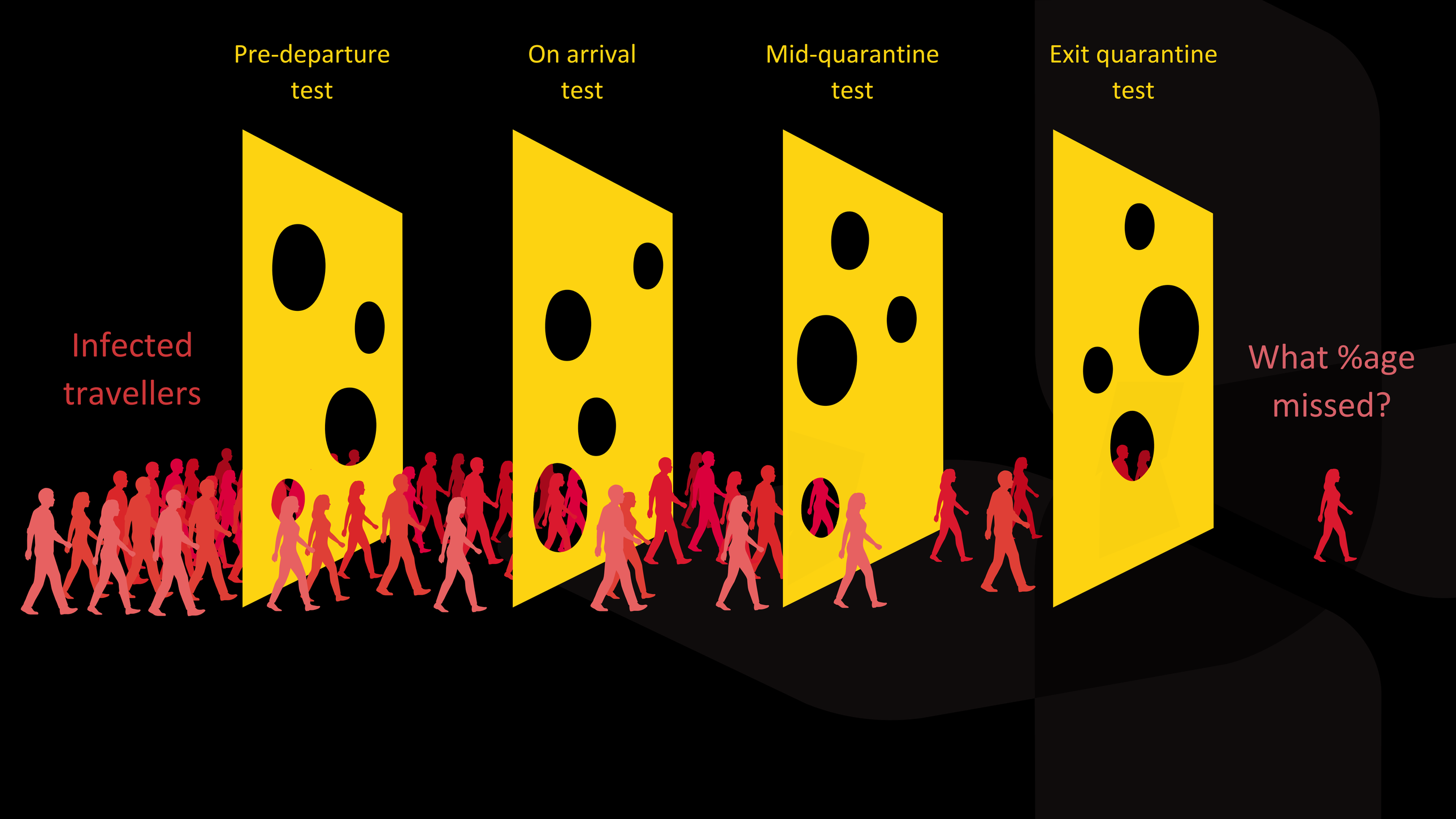


Excluding outbreaks among foreign workers in dorms: ~200 000 additional infections

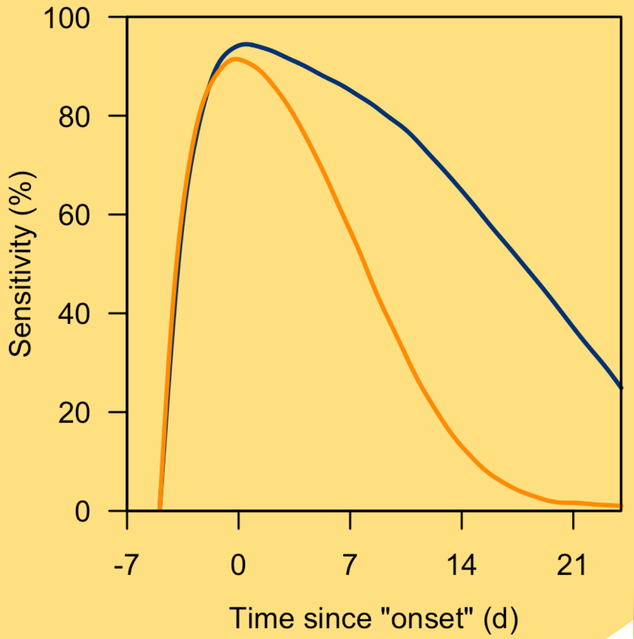
Example 2: Border control

Note: this work is funded in part by Becton Dickinson, a medical device company which develops PCR and antigen tests.

Work by Bo Dickens, Joel Koo, Lim Jue Tao,
Sun Haoyang, Hannah Clapham, Annelies Wilder-Smith,
Minah Park, Sun Yinxiaohe, Zeng Zitong, Sharon Quaye, Wee Hwee Lin


Pre-departure test
On arrival test
Mid-quarantine test
Exit quarantine test
Infected travellers
What %age missed?

Disparate data sources



Risk in source country

Pre-test	Test on arrival	Quarantine	Mid-test	Exit test
None	PCR	None	None	None
PCR	Ag	Q3	D3	PCR
Ag		Q5	D5	Ag
		Q7	D7	
		Q10	D10	
		Q14		
		Q21		

On arrival
PCR
Quarantine exit
PCR

	Prevalence	2%	1%	0.5%	0.15%
	Infected travellers (/10 000)	200	100	50	15
Quarantine	% missed	N missed			
3d	17%	33	17	8	2
7d	7%	15	7	4	1
10d	4%	7	4	2	1
14d	2%	3	2	1	0

Prevalence is of infection within the last 14d

On arrival
PCR
Quarantine exit
PCR

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On arrival
PCR
Quarantine exit
PCR

	Prevalence	2%	1%	0.5%	0.15%
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Quarantine	% missed	N missed			
3d	17%	33	17	8	2
7d	7%	15	7	4	1
10d	4%	7	4	2	1
14d	2%	3	2	1	0

Prevalence is of infection within the last 14d

On arrival
Antigen
Quarantine exit
Antigen

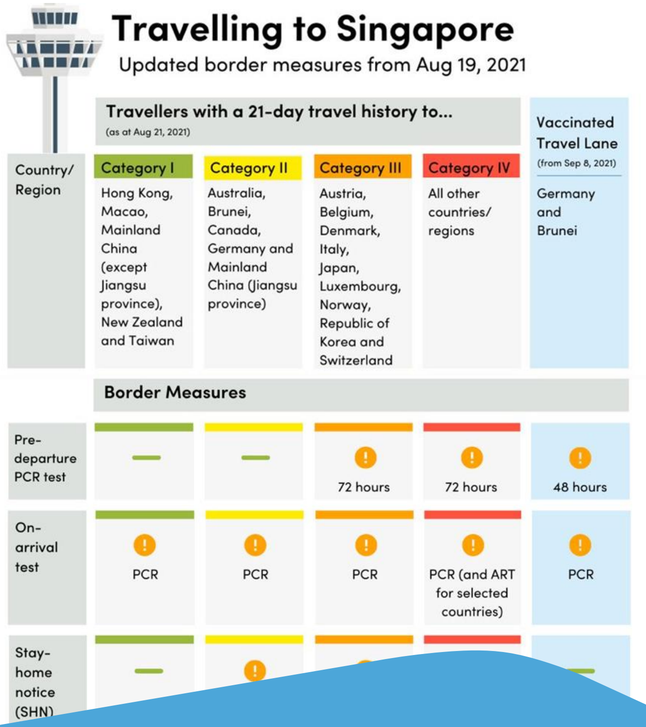
	Prevalence	2%	1%	0.5%	0.15%
	Infected travellers (/10 000)	200	100	50	15
Quarantine	% missed	N missed			
3d	17%	34	17	9	3
7d	8%	15	8	4	1
10d	4%	8	4	2	1
14d	2%	5	2	1	0

Prevalence is of infection within the last 14d

Border policies work

- In a low Covid strategy, amount of spillovers from travel can be calibrated through good use of testing and quarantine
- Although Ag tests are not as sensitive as PCR tests, that difference is markedly reduced as part of a bundle of tests and quarantine: use the most practical rather than most sensitive test
- This approach requires policy makers have a risk budget: How many missed travellers am I willing to accept to get 10 000 travellers into the country?
- For lower risk ports of departure you can substantial reduce quarantine length with minimal additional risk to destination

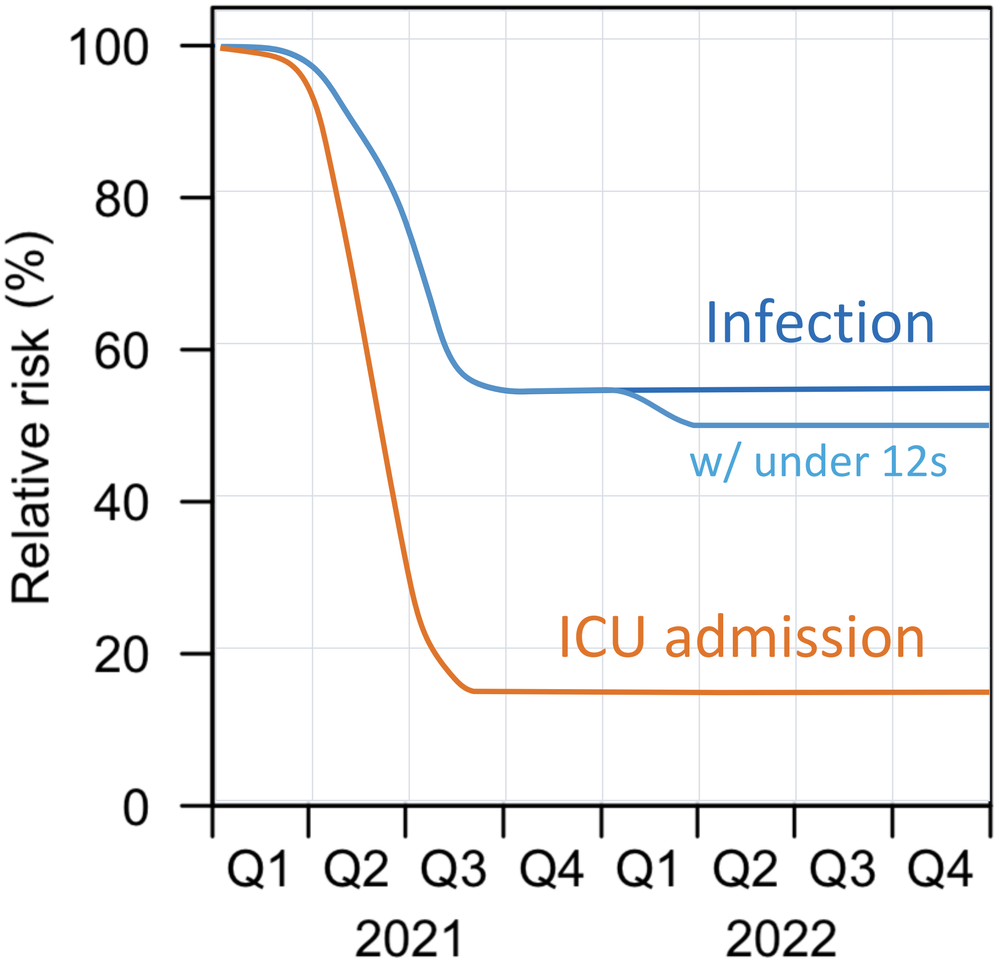
Dickens et al (2021).
J Travel Med taab088.



Example 3: The journey to endemicity

Work by Goh Fang Ting, Bo Dickens,
Hannah Clapham, Vernon Lee, Rachael Pung

Vaccination has brought substantial benefits, but…



- Accounting for age-specific severity and prioritisation for older age groups, risk of severe disease dropped markedly since early 2021
- But risk of infection fell by less even before accounting for any waning
- Vaccinating children will bring little additional herd immunity

We can’t completely avoid the pandemic…

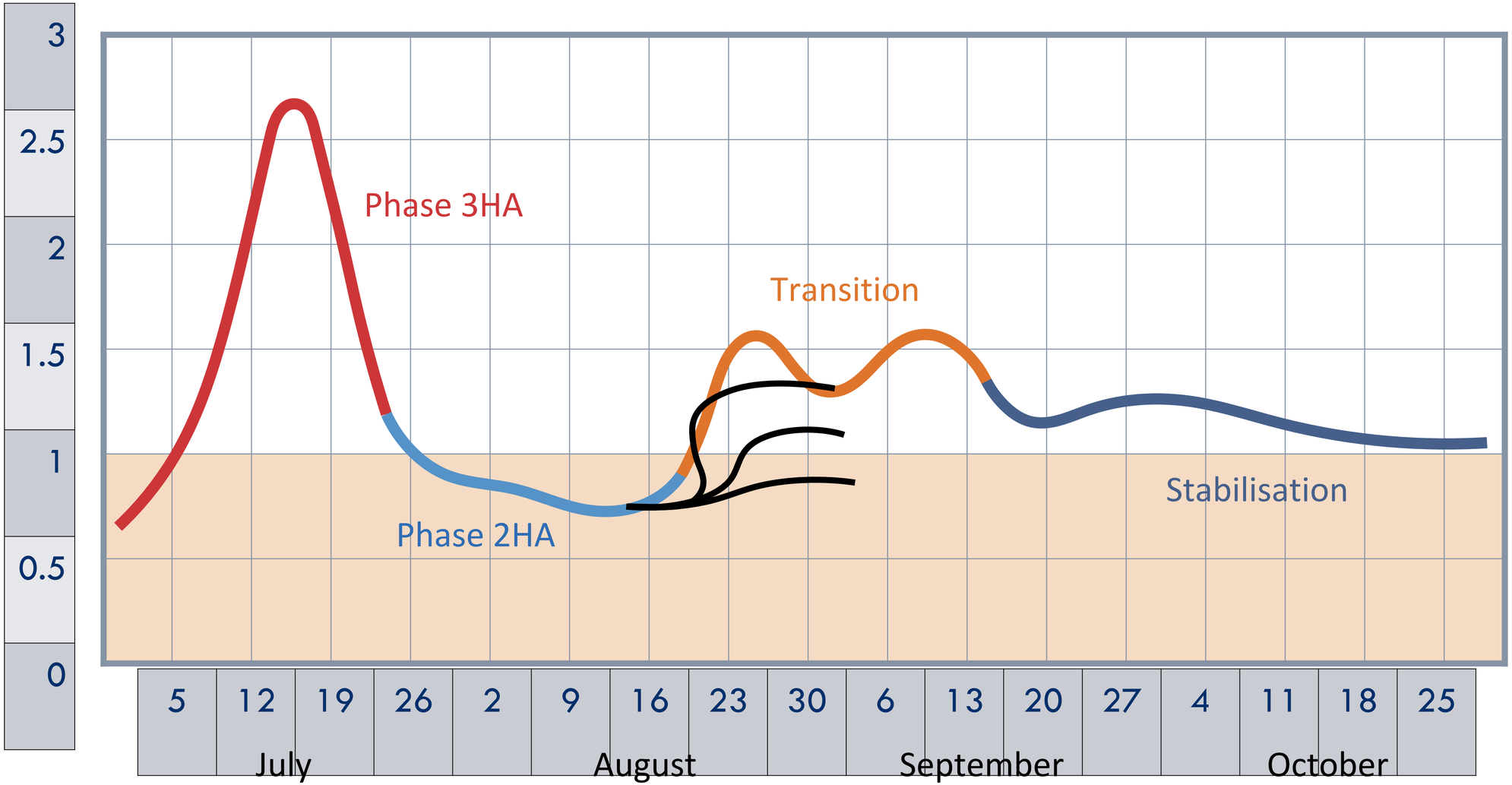
- If is 5–8, and the against infection is 0.4–0.6 then even complete vaccination is not enough for herd immunity without additional measures

Temporary suppression of to buy time for vaccination through control measures

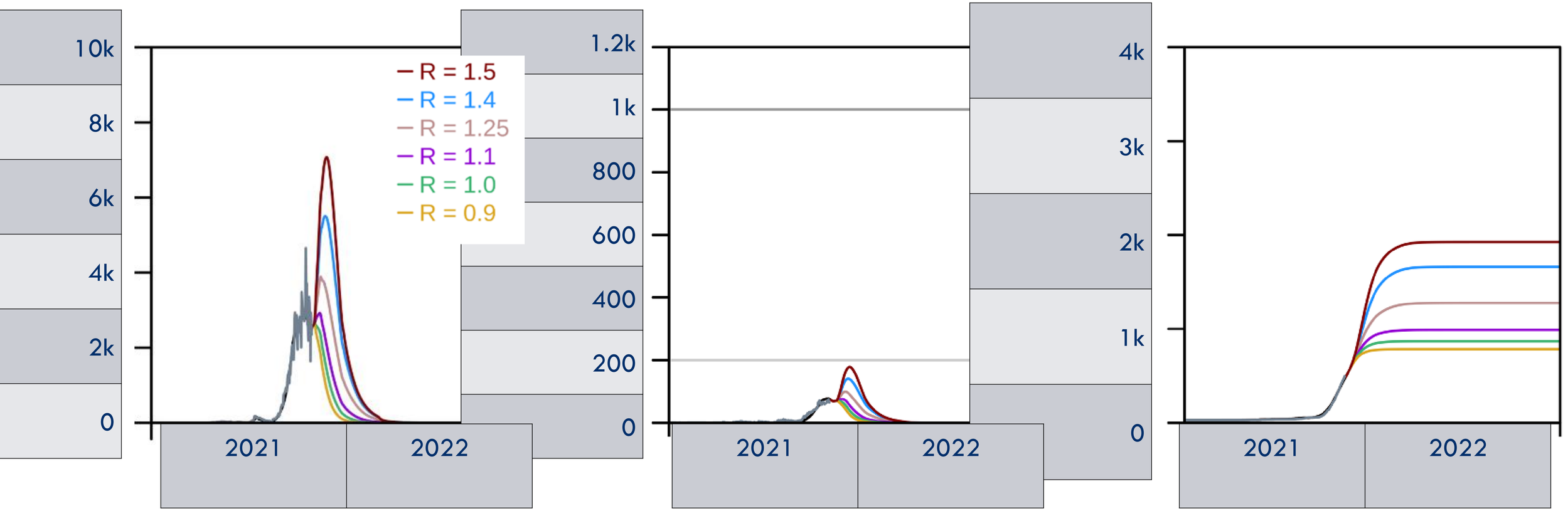
Development of population immunity through ‘letting go’ the control measures
(or to put faith in boosters)

Long term suppression of through immunity

Impact of policies on transmissibility



Projections show how sensitive the results are to



If herd immunity when 29% infected

If herd immunity when 12% infected

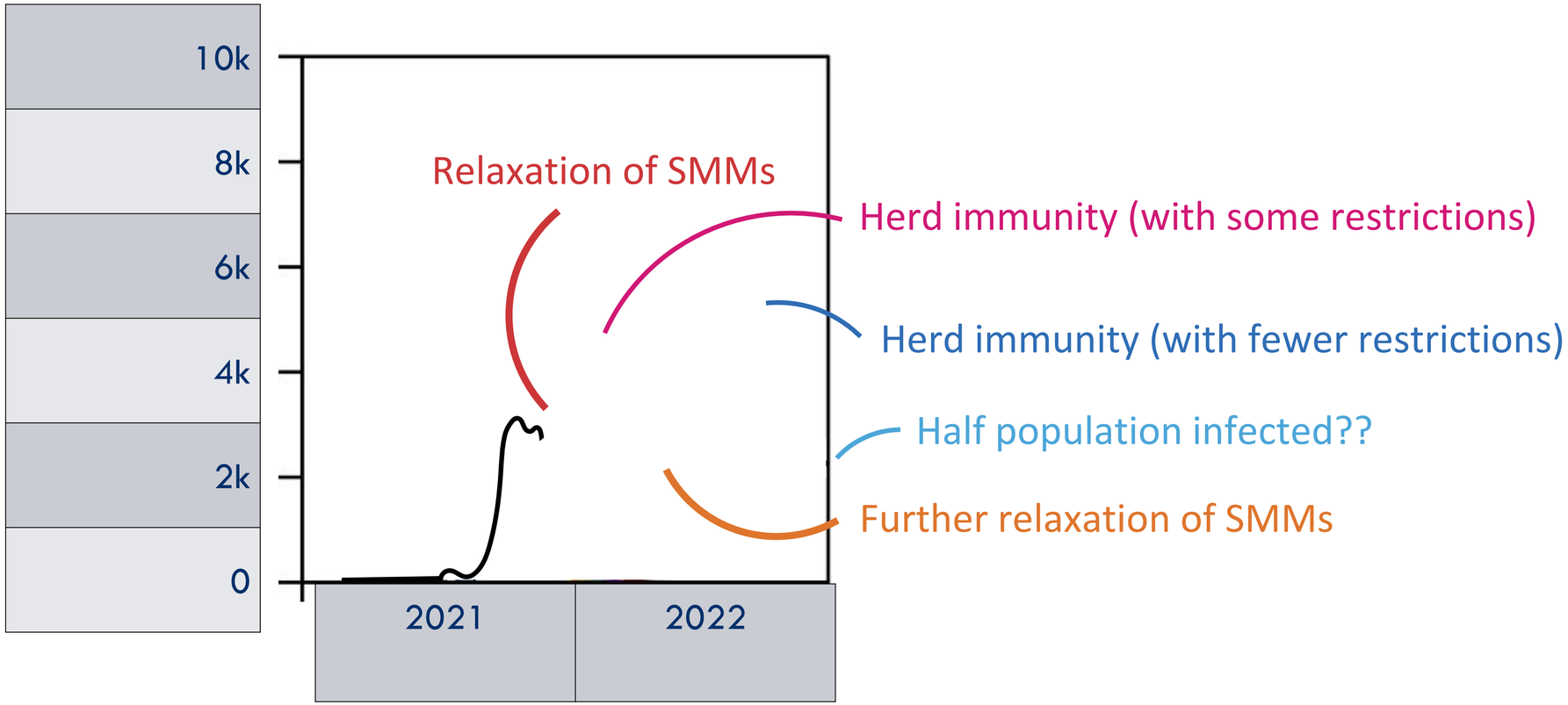
If herd immunity when 6% infected

and wave ends when 54% infected

and wave ends when 34% infected

and wave ends when 17% infected

Projections show how sensitive the results are to



As immunity builds, more and more SMMs can be relaxed, until endemic state is reached

Thanks to:

- Funding from the National Medical Research Council, the Ministry of Education, the National University of Singapore, and Becton Dickinson
- My fabulous team and collaborators
- National Medical Research Council for the invitation

NUHS National University Health System

National University Hospital

Ng Teng Fong General Hospital

Alexandra Hospital

Jurong Community Hospital

National University Polyclinics

Jurong Medical Centre

National University Cancer Institute Singapore

National University Heart Centre Singapore

National University Centre for Oral Health Singapore

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