

L8, Covid-19 analyses

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Herd immunity (Britton, Ball, Trapman, 2020+2021)

Classical result: Critical vaccination coverage (= herd immunity level) when immunity/vaccination is uniformly distributed equals

$$V_c = 1 - \frac{1}{R}$$

But last year (before vaccine arrival) first wave was stopped by mitigation/suppression (and summer effects)

Infected people (later immune) are not uniformly distributed – more immunity among socially active and highly susceptible!

This should lead to a **smaller overall immunity level** required for herd immunity!!

Scientific task: Investigate and quantify this effect

A model for COVID-19 allowing for heterogeneities

SIR epidemic with four types of heterogeneities:

- **Age cohorts:** with mixing and community fractions taken from empirical study (Wallinga et al, 2006)
- **Variable social activity:** assumed independent of other heterogeneities
- **Variable susceptibility:** assumed independent of other heterogeneities
- **Variable infectivity:** assumed independent of other heterogeneities

Simple model for social activity, susceptibility and infectivity:

50% have medium level, 25% have low (=half this level) and 25% have high (=double this level)

A model for COVID-19 allowing for heterogeneities, cont'd

Model of heterogeneity quite arbitrary but:

no left or right tails, and coefficient of variation = 0.48

Age-distribution gives a next generation matrix including mixing features, age-differences and population fractions (6 age-groups)

"On top" of this individuals are categorized according to social activity, susceptibility and infectivity independently

First result: **Variable infectivity has no effect** (on deterministic model)

Model: Deterministic Multitype epidemic: $6 * 3 * 3 = 54$ types

R_0 = largest eigenvalue to $54*54$ next generation matrix

Final size equations exist

Including prevention and vaccine-induced immunity

Preventive measure assumption: **all** contact rates are reduced with the same factor p (restrictive assumption!)

Suppose a fraction \hat{i} are immunized from (uniform) vaccination

Effective reproduction number

$$R_E = R_0(1 - \hat{i})(1 - p)$$

Same expression as homogeneous case!

\implies Same herd immunity level $\hat{i}_{Vac} = 1 - 1/R_0$

and same $p_{Min}^{(Vac)} = 1 - 1/(R_0(1 - \hat{i}))$ as in homogeneous case

where p_{Min} = minimal amount of preventive measures to avoid an outbreak

Including prevention and disease-induced immunity

Suppose instead that a fraction \hat{i} are immune from a suppressed or mitigated outbreak

Then immunity is not uniformly distributed: socially active and highly susceptible individuals are over-represented

\implies This immunity is more "effectively distributed"

$$\implies R_t < R_0(1 - p)(1 - \hat{i})$$

so $\implies \hat{i}_{Dis} < 1 - 1/R_0$

and $p_{Min}^{(Dis)} < p_{Min}^{(Vac)} = 1 - 1/(R_0(1 - \hat{i}))$

\implies The minimal effect of preventive measures is lower

- if immunity comes from disease spreading vs vaccination
- if acknowledging heterogeneities vs homogeneous model

Herd immunity levels (B+B+T *Science* 2020)

$\rho_{Min} = 0 \implies$ Herd-immunity.

Tabell: Disease-induced herd immunity level \hat{i}_{Dis} and vaccine-induced herd immunity level $\hat{i}_{Vac} = 1 - 1/R_0$, for $R_0 = 2.0, 2.5$ and 3.0 . Levels correspond to percentages.

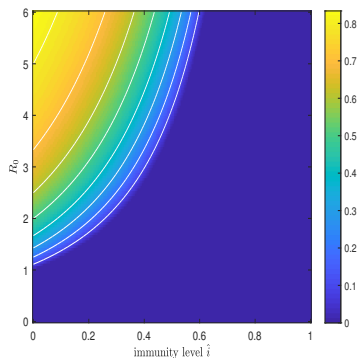
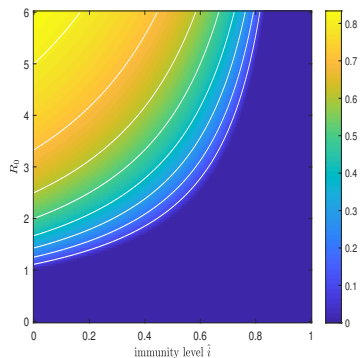
Population structure	$R_0 = 2.0$		$R_0 = 2.5$		$R_0 = 3.0$	
	\hat{i}_{Dis}	\hat{i}_{Vac}	\hat{i}_{Dis}	\hat{i}_{Vac}	\hat{i}_{Dis}	\hat{i}_{Vac}
Homogeneous	50.0	50.0	60.0	60.0	66.7	66.7
Age structure	46.0	50.0	55.8	60.0	62.5	66.7
Activity structure	37.7	50.0	46.3	60.0	52.5	66.7
Age & Activity structure	34.6	50.0	43.0	60.0	49.1	66.7

Herd immunity level is lower than earlier believed! (Unclear exactly how much lower!!)

Heatmap of minimal preventive measure p_{Min} (BTB, 2021)

Left: Vaccine-induced immunity and/or homogeneous model

Right: Disease-induced immunity + heterogeneous model



Example: $R_0 = 2.5$, $\hat{i} = 25\%$: $p_{Min}^{(Vac)} = 47\%$ and $p_{Min}^{(Dis)} = 29\%$

Illustration: Country estimates of R_0 taken from Flaxman et al (2020) and tweaked within country from country specific analyses

Region	R_0	Deaths/100k	\hat{i} (%)	$p_{Min}^{(start)}$ (%)	$p_{Min}^{(Dis)}$	$p_{Min}^{(Vac)}$
Madrid	4.7			78.7		
Cataluna	4.5			77.8		
Lombardy	3.4			70.6		
Lazio	3.4			70.6		
New York	4.9			79.6		
Wash D.C.	2.5			60.0		
Stockholm	3.9			74.4		
Copenhagen	3.5			71.4		
Oslo	3.0			66.7		

Illustration: Immunity estimates taken from case fatality numbers September 2020 and assuming the **same** $ifr = 0.5\%$ in all regions.

Region	R_0	Deaths/100k	\hat{i} (%)	$p_{Min}^{(start)}$ (%)	$p_{Min}^{(Dis)}$	$p_{Min}^{(Vac)}$
Madrid	4.7	145	29.0	78.7	58.3	70.0
Cataluna	4.5	77.4	15.5	77.8	68.9	73.7
Lombardy	3.4	168	33.6	70.6	34.7	55.7
Lazio	3.4	16.2	3.2	70.6	68.6	69.6
New York	4.9	169	33.8	79.6	54.4	69.2
Wash D.C.	2.5	89.4	17.9	60.0	40.8	51.3
Stockholm	3.9	102	20.4	74.4	59.7	67.8
Copenhagen	3.5	20.0	4.0	71.4	69.0	70.2
Oslo	3.0	11.4	2.3	66.7	65.1	65.9

Conclusions

Vaccine-induced immunity is less efficiently distributed compared with disease-induced immunity

⇒ more individuals need to be immunized with vaccination to obtain herd immunity (assuming equal immunity from disease and vaccine)

⇒ more preventive measures needed (for a fixed overall immunity level) if immunity comes from vaccination compared to disease-induced immunity

(The exact size differences need to be investigated further – we use a toy model)

Important result, but **NOT** an argument for aiming for disease-induced herd immunity **OR** to skip vaccination!

Definition of generation time

The **generation time** G describes the time between an individual getting infected and infecting others

G is a random variable, affected by: latent period, incubation period, length of infectious period, infectivity over time, ...

Given an epidemic model the **generation time distribution** (GTD) $p_G(t) = P(G = t)$ can often be computed

Knowledge of GTD is important because it is used when estimating the daily reproduction number R_t from (reported) incidence $I(t); t = 1, \dots, t_{obs}$:

Based on (reported) incidence and knowledge about GTD $p_G(\cdot)$, R_t can be **estimated** from the (Euler-Lotka) equation:

$$I(t) = R_t \sum_k I(t-k)p_G(k), \quad t = 1, \dots, t_{obs}$$

GTD changes when preventive measures are adopted

Favero, Scalia Tomba and Britton (2022)

During covid-19 pandemic preventive measure have been enforced and we have changed behaviour:

1. Social distancing in general
2. Self-isolation upon symptoms
3. Screening - testing
4. Contact tracing diagnosed cases

All of these reduce the daily reproduction number R_t (the average number of infections made by an infected now)

But some also change the timing when infections happen, so changes the GTD

A model to investigate effect of prevention on GTD

Contact process:

$$C = \{C(t)\}_{t \geq 0} \text{ with } C(t) = \begin{cases} C_1, & \text{if } t \leq \tau \\ C_2, & \text{if } t > \tau \end{cases}$$

C_1 : base contact rate (r.v)

C_2 : reduced contact rate (r.v)

τ : reduction-time (r.v) e.g. onset or detection

Different definitions of τ , C_1 , C_2 , allow modelling contacts in several scenarios, with or without interventions

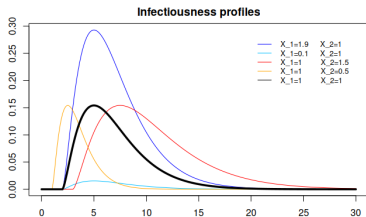
Infectiousness process:

$X = \{X(t)\}_{t \geq 0}$: probability of infection at time t (given a contact)

e.g. $X(t) = p \mathbb{I}_{[0,1]}(t)$ (SIR)

Our focus: $X(t) = X_1 h(X_2 t)$,
 h deterministic function, X_1, X_2 r.v.'s

Infectivity proc: $\lambda(t) = C(t)X(t)$



Effects of various preventions:

Infectivity function: $\beta(t) = E(C(t)X(t))$

Basic reproduction number: $R_0 = \int_0^\infty \beta(t)dt$

Generation time density (GTD): $f_G(t) = \beta(t)/R_0$

Various preventions (all reduce R but):

Overall **contact-reduction:** $C \rightarrow \rho C$ (no effect on GTD!)

Face masks: $X(\cdot) \rightarrow \rho X(\cdot)$ (no effect on GTD!)

Isolation of symptomatic/confirmed: $C_2 \rightarrow \rho C_2$ (reduces GTD!)

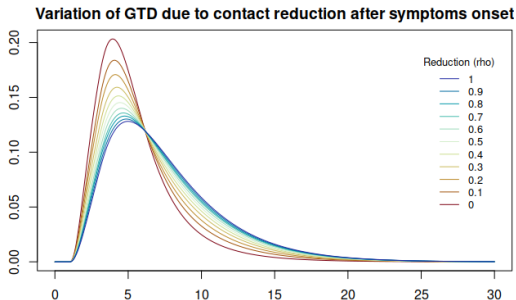
Screening: $\tau = \min\{T_{Sympt}, T_{scrc}\}$ (reduces GTD!)

Contact tracing: $\tau = \min\{T_{Sympt}, T_{CT}\}$ (reduces TGD!)

Effects on GTD depends on model assumptions and is quite complicated, in particular contact tracing

Illustration: Isolating symptomatic individuals

$$\tau = T_S \quad C_2 = \rho C_1 \quad X(t) = X_1 h(tX_2)$$



ρ	R	$R^{(1)}$	$R^{(2)}$	mean gen. time (mgt)
1	3.76	1.64	2.11	8.24
0.9	3.54	1.64	1.90	8.11
0.8	3.33	1.64	1.69	7.96
0.7	3.12	1.64	1.48	7.79
0.6	2.91	1.64	1.27	7.60
0.5	2.70	1.64	1.06	7.38
0.4	2.49	1.64	0.84	7.12
0.3	2.39	1.64	0.63	6.81
0.2	2.07	1.64	0.42	6.44
0.1	1.85	1.64	0.21	5.98
0	1.64	1.64	0	5.41

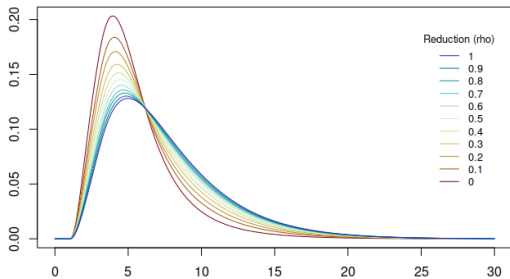
Asymptomatic cases: about 1/3

Example: $\rho : 0.5 \rightarrow 0.1$ implies R reduced by 31% and mgt by 19%

Illustration: Isolating symptomatic individuals

$\tau = T_S$ $C_2 = \rho C_1$ $X(t) = X_1 h(tX_2)$ MGT = mean generation time

Variation of GTD due to contact reduction after symptoms onset



ρ	R	$R^{(1)}$	$R^{(2)}$	MGT
1	4.54	1.73	2.81	7.57
0.9	4.26	1.73	2.53	7.48
0.8	3.98	1.73	2.25	7.38
0.7	3.70	1.73	1.97	7.28
0.6	3.42	1.73	1.69	7.15
0.5	3.14	1.73	1.41	6.99
0.4	2.86	1.73	1.13	6.82
0.3	2.57	1.73	0.84	6.59
0.2	2.29	1.73	0.56	6.31
0.1	2.01	1.73	0.28	5.96
0	1.73	1.73	0	5.48

Asymptomatic cases: about 1/3

Example: $\rho : 0.5 \rightarrow 0.1$ implies R reduced by 36% and mgt by 15%

Covid example and effect on bias

Combining preventions (added isolation, screening and CT) where we have "guessed" suitable values reduces

$$R = 3.9 \rightarrow R = 1.45 \text{ (reduction by 62\%)}$$

$$E(G) = 7.4 \rightarrow E(G) = 5.8 \text{ days (reduction by 22\%)}$$

Inferring R_t

Suppose we observe (increasing) incidence $\{I(t)\}$ for this situation ($R_t = 1.45$ and mean gen-time $E(G) = 5.8$)

If we use this new correct GTD and apply Euler-Lotka estimating equations we get $\hat{R}_t \approx 1.45$ as it should

However, if we instead used the original/old GTD with mean 7.4 days (as most do!!!) we would get $\hat{R}_t \approx 1.75$, so biased by more than 20%

R_t -estimates that use early GTD-estimates are **biased from above** (or more accurately "biased away from 1")

Over-all summary

General advice: Complement more advanced statistical analysis with simple model analysis. If similar conclusions: reassuring. If very different: mistake or understanding needed

Some important messages

- Prior (partial) immunity makes big difference for estimates
- Inference for emerging epidemics is hard
- Heterogeneities usually makes R_0 larger but not necessarily bigger outbreak!

Important but not treated:

- Changing behaviour over time
- Selection bias
- Asymptomatics and other under-reporting