Modelling the transmission of SARS-CoV-2 in the early phases of the COVID-19 pandemic

Ilaria Dorigatti

MRC Centre for Global Infectious Disease Analysis
WHO Collaborating Centre for Infectious Disease modelling

School of Public Health
Imperial College London

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Imperial College London

Christl Donnelly, Constanze Ciavarella, Gina Cuomo-Donnenburg, Lorenzo Cattarino, Katy Gaythorpe, Ettie Unwin, Neil Ferguson & Andrea Crisanti

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Enrico Lavezzo, Elisa Franchin, Luisa Barzon, Claudia Del Vecchio, Lucia Rossi, Riccardo Manganelli, Arianna Loregian, Nicolò Navarin, Davide Abate, Manuela Sciro, Stefano Merigliano, Ettore De Canale, Maria Cristina Vanuzzo, Valeria Besutti, Francesca Saluzzo, Francesco Onelia, Monia Pacenti, Saverio Parisi, Giovanni Carretta, Daniele Donato, Luciano Flor, Silvia Cocchio, Giulia Masi, Alessandro Sperduti, Renato Salvador, Michele Nicoletti, Federico Caldart, Gioele Castelli, Eleonora Nieddu, Beatrice Labella, Ludovico Fava, Matteo Drigo, Alessandra Brazzale, Stefano Toppo, Marta Trevisan, Vincenzo Baldo & Andrea Crisanti

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Case studies

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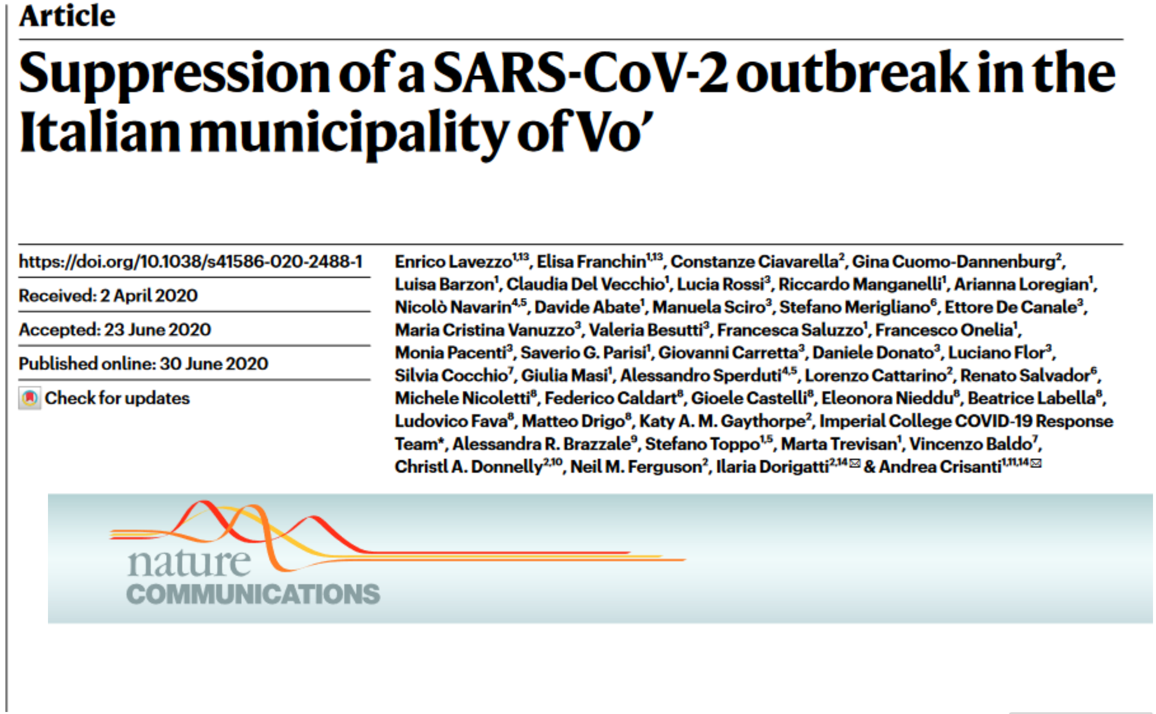

Article

Suppression of a SARS-CoV-2 outbreak in the Italian municipality of Vo'

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Enrico Lavezzo[1,13], Elisa Franchin[1,13], Constanze Ciavarella[2], Gina Cuomo-Dannenburg[2], Luisa Barzon[1], Claudia Del Vecchio[1], Lucia Rossi[3], Riccardo Manganelli[1], Arianna Loregian[1], Nicolò Navarin[4,5], Davide Abate[1], Manuela Sciro[3], Stefano Merigliano[6], Ettore De Canale[3], Maria Cristina Vanuzzo[3], Valeria Besutti[3], Francesca Saluzzo[1], Francesco Onelia[1], Monia Pacenti[3], Saverio G. Parisi[1], Giovanni Carretta[3], Daniele Donato[3], Luciano Flor[3], Silvia Cocchio[7], Giulia Masi[1], Alessandro Sperduti[4,5], Lorenzo Cattarino[2], Renato Salvador[6], Michele Nicoletti[8], Federico Caldart[8], Gioele Castelli[8], Eleonora Nieddu[8], Beatrice Labella[8], Ludovico Fava[8], Matteo Drigo[8], Katy A. M. Gaythorpe[2], Imperial College COVID-19 Response Team*, Alessandra R. Brazzale[9], Stefano Toppo[1,5], Marta Trevisan[1], Vincenzo Baldo[7], Christl A. Donnelly[2,10], Neil M. Ferguson[2], Ilaria Dorigatti[2,14]✉ & Andrea Crisanti[1,11,14]✉

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ARTICLE

https://doi.org/10.1038/s41467-021-24622-7 OPEN

SARS-CoV-2 antibody dynamics and transmission from community-wide serological testing in the Italian municipality of Vo'

Ilaria Dorigatti [1,10]✉, Enrico Lavezzo [2,10]✉, Laura Manuto[2], Constanze Ciavarella [1], Monia Pacenti[3], Caterina Boldrin[3], Margherita Cattai[3], Francesca Saluzzo [2], Elisa Franchin[2], Claudia Del Vecchio[2], Federico Caldart [2], Gioele Castelli [2], Michele Nicoletti [2], Eleonora Nieddu[2], Elisa Salvadoretti[2], Beatrice Labella[2], Ludovico Fava[2], Simone Guglielmo [2], Mariateresa Fascina[2], Marco Grazioli[2], Gualtiero Alvisi[2], Maria Cristina Vanuzzo[3], Tiziano Zupo[3], Reginetta Calandrin[3], Vittoria Lisi[3], Lucia Rossi[3], Ignazio Castagliuolo[2], Stefano Merigliano [4], H. Juliette T. Unwin [1], Mario Plebani[5], Andrea Padoan[5],

ARTICLE

Neutralising reactivity against SARS-CoV-2 B.1.617.2 (Delta) variant by vaccination status and pre-exposure

Enrico Lavezzo, Monia Pacenti, Laura Manuto, Caterina Boldrin, Margherita Cattai, Marco Grazioli, Federico Bianca, Margherita Sartori, Federico Caldart, Gioele Castelli, Michele Nicoletti, Eleonora Nieddu, Elisa Salvadoretti, Beatrice Labella, Ludovico Fava, Maria Vanuzzo, Vittoria Lisi, Maria Antonello, Carmela Grimaldi, Chiara Zulian, Claudia Del Vecchio, Mario Plebani, Andrea Padoan, Daniela Maria Cirillo, Alessandra Brazzale, Giovanni Tonon, Stefano Toppo, Iaria Dorigatti, Andrea Crisanti

DOI: 10.21203/rs.

Abstract

In February an
Vo'. Positive su
neutralisation t
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ARTICLE

Impact of antigen test target failure and testing strategies on the transmission of SARS-CoV-2 variants

Claudia Del Vecchio, Bethan Cracknell Daniels, Giuseppina Brancaccio, Alessandra Brazzale, Enrico Lavezzo, Constanze Ciavarella, Francesco Onelia, Elisa Franchin, Laura Manuto, Federico Bianca, Vito Cianci, Annamaria Cattelan, Ilaria Dorigatti, Stefano Toppo, Andrea Crisanti

DOI: 10.21203/rs.3.rs-1481444/v1

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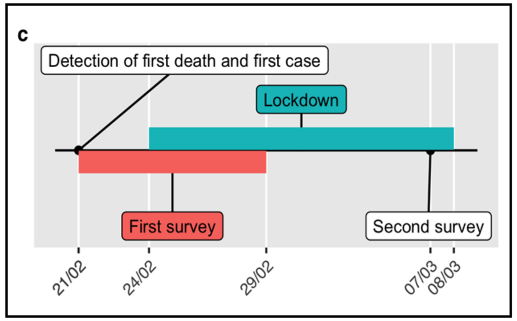
Abstract

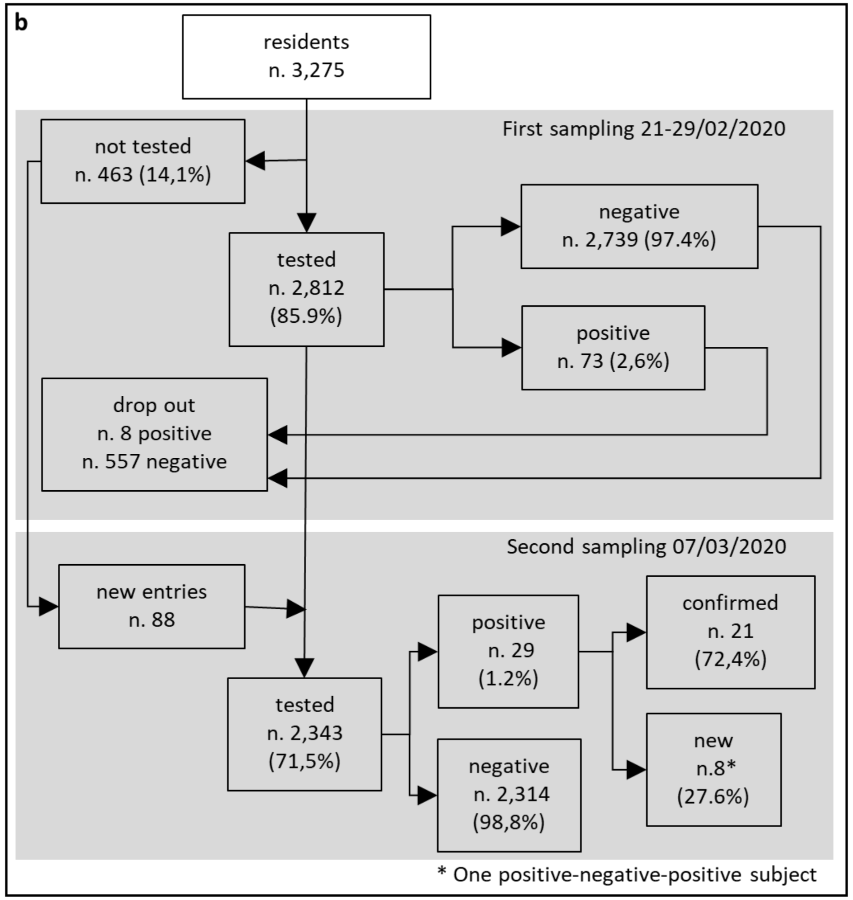
Population testing remains central to COVID-19 control and surveillance, with countries increasingly using antigen tests rather than molecular tests. Here we describe a SARS-CoV-2 variant that escapes N antigen tests due to multiple disruptive amino-acid substitutions in the N protein. By fitting a multistrain compartmental model to genomic and epidemiological data, we show that widespread antigen testing in the Italian region of Veneto favored the undetected spread of the antigen-escape variant compared to the rest of Italy. We highlight novel limitations of widespread antigen testing in the absence of molecular testing for diagnostic or confirmatory purposes. Critically, in the presence of a variant that escapes antigen testing, following up a proportion of negative antigen tests with a molecular test is the optimal testing strategy. Together, these findings highlight the importance of retaining molecular testing for surveillance purposes, also in contexts where the use of antigen tests is widespread.

SARS-CoV-2 transmission in Vo, Italy

- Italy was the first European country to be hit by COVID-19
- First death due to COVID-19 in Italy
  - 21st Feb 2020
  - Vo (Padova) 3,275 residents
- 24th Feb 2020: lockdown for 2 weeks

- Study to assess SARS-CoV-2 prevalence
- Two sequential molecular swab surveys
  - Date sampling and PCR results
  - Demographic & health conditions, contacts, symptoms, date symptoms





residents
n. 3,275

First sampling 21-29/02/2020

not tested
n. 463 (14,1%)

tested
n. 2,812
(85.9%)

negative
n. 2,739 (97.4%)

positive
n. 73 (2,6%)

drop out
n. 8 positive
n. 557 negative

Second sampling 07/03/2020

new entries
n. 88

tested
n. 2,343
(71,5%)

positive
n. 29
(1.2%)

negative
n. 2,314
(98,8%)

confirmed
n. 21
(72,4%)

new
n.8*
(27.6%)

* One positive-negative-positive subject

Lavezzo et al., Nature, 2020

Prevalence & symptoms

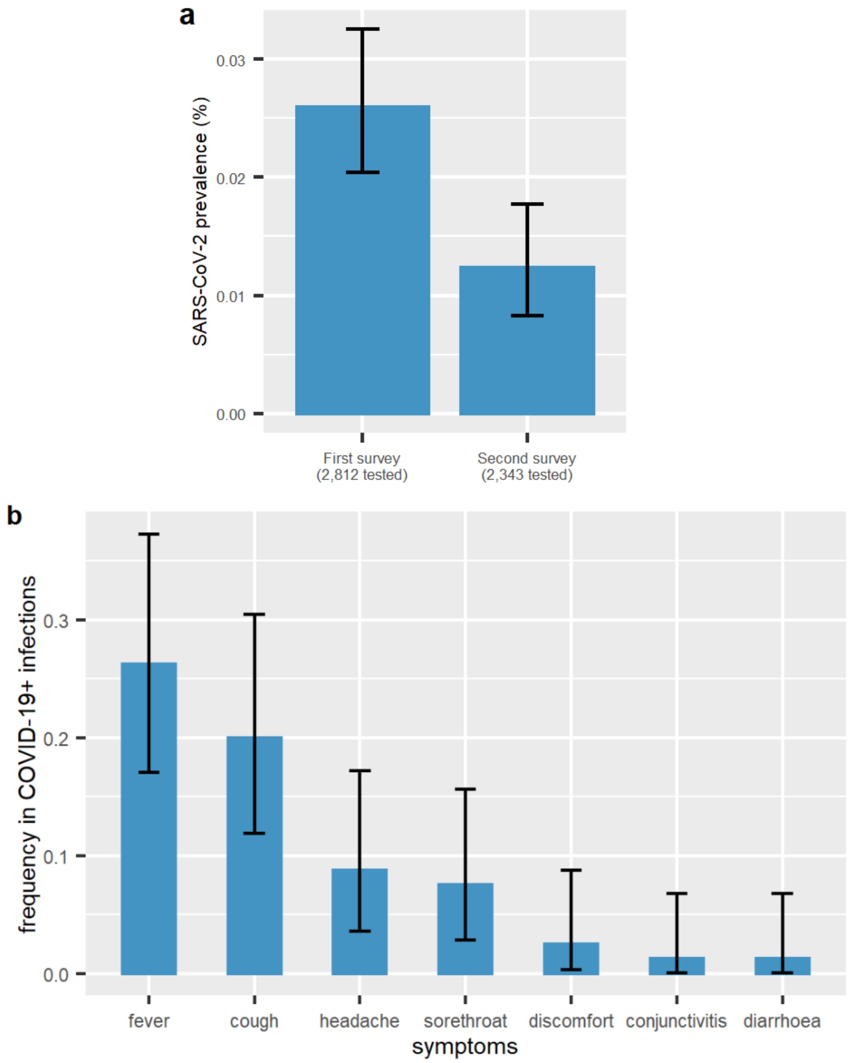
- SARS-CoV-2 infection prevalence
  - 1st survey: **2.6% (95% CI 2.1-3.3%)**
  - 2nd survey: **1.2% (95% CI 0.8-1.8%)**

- Asymptomatic SARS-CoV-2 infection across the two surveys: **42.5% (95% CI 31.5-54.6%)**

	First survey		**Second survey**	
	Total positives	(%)	Total positives	(%)
Symptomatic at the time of sampling*	34	(46.6)	15	(51.7)
Presymptomatic at the time of sampling	10	(13.7)	1	(3.4)
Asymptomatic§	29	(39.7)	13	(44.8)
Total	73		29	

***Defined as the presence of hospitalization and/or fever and/or cough and/or at least two of the following symptoms: sore throat, headache, diarrhoea, vomit, asthenia, muscle pain, joint pain, loss of taste or smell**

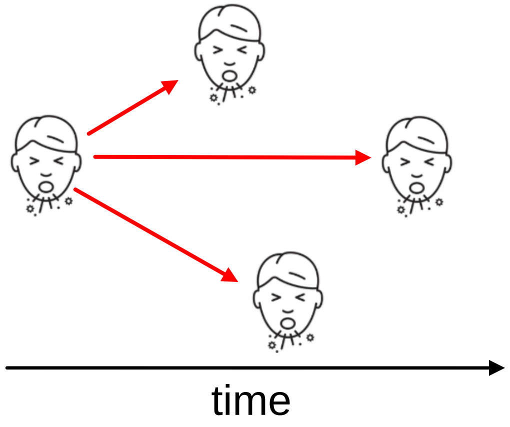
^individuals testing negative for SARS-CoV-2 at the first survey.

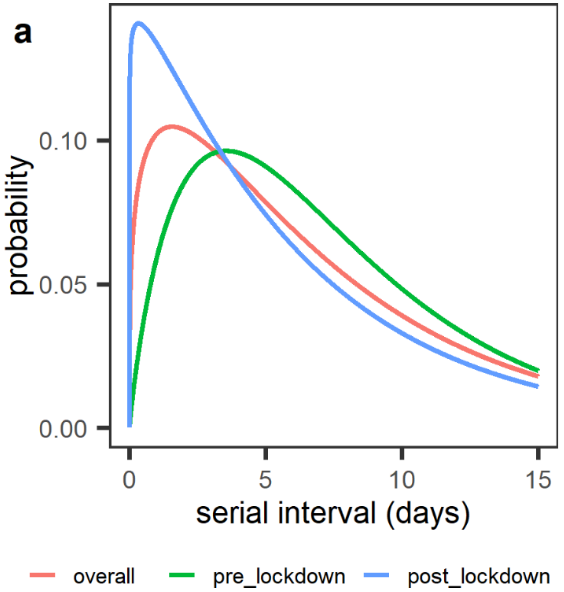


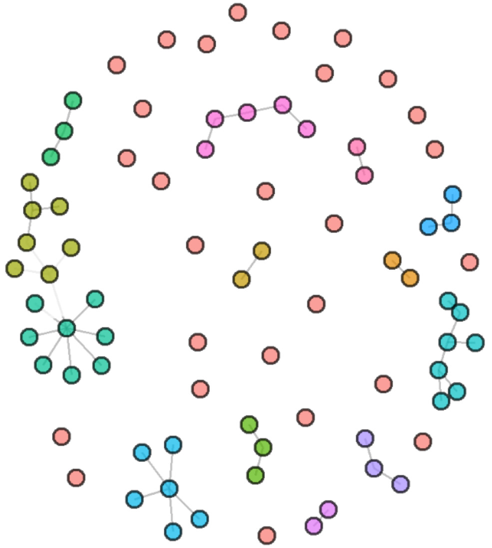
Lavezzo et al., Nature, 2020

Transmission chains

- Serial interval
  - ➢ 7.2 days (95% CI 5.9 – 9.6 days) overall
  - ➢ 7.6 days (95% CI 6.4 – 8.7 days) pre-lockdown
  - ➢ 6.2 days (95% CI 2.6 – 10.7 days) post-lockdown
- Reproduction number
  - ➢ 2.44 (95% CI 1.30 – 3.91) pre-lockdown
  - ➢ 0.41 (95% CI 0.21- 0.64) post-lockdown



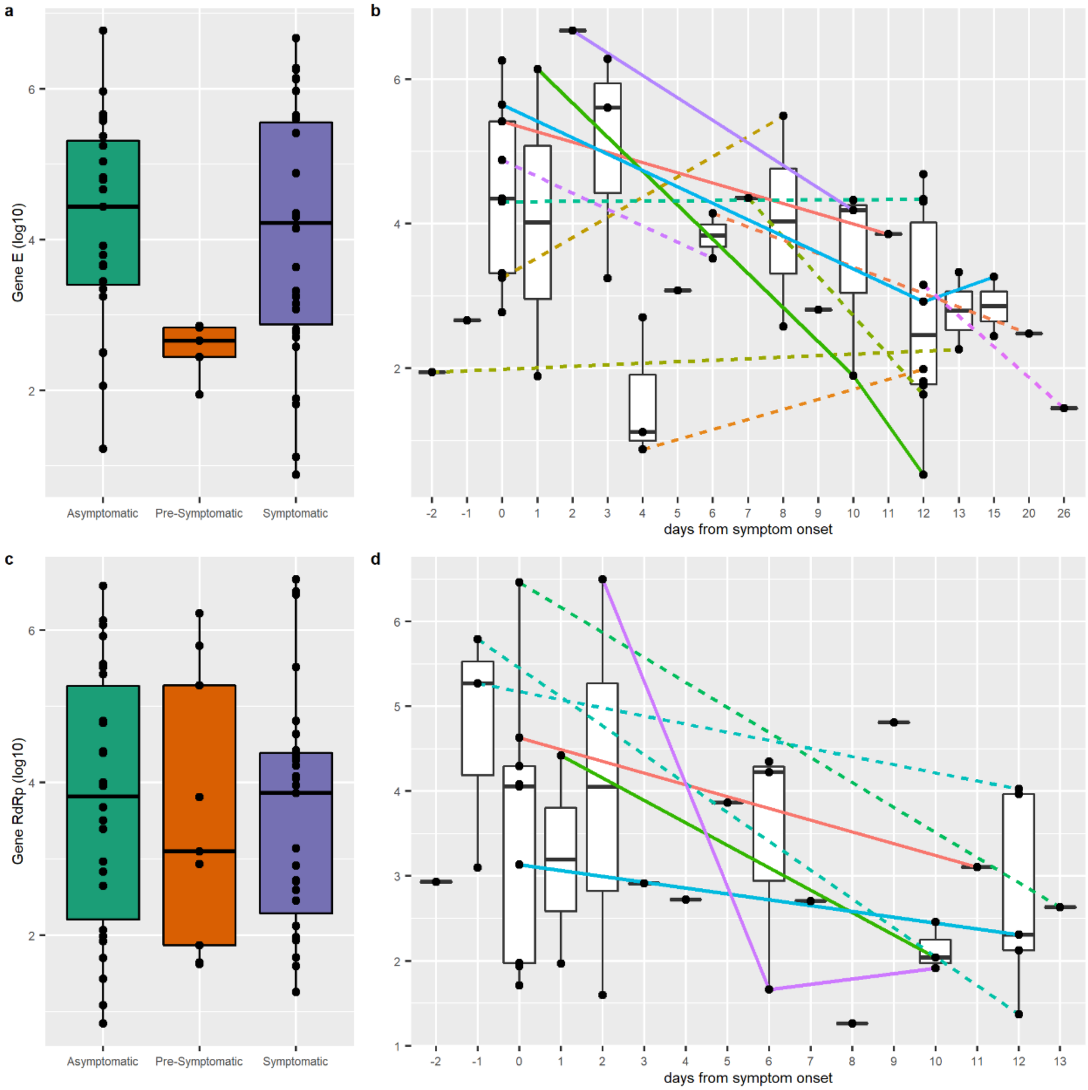




Lavezzo et al., Nature, 2020

Viral load

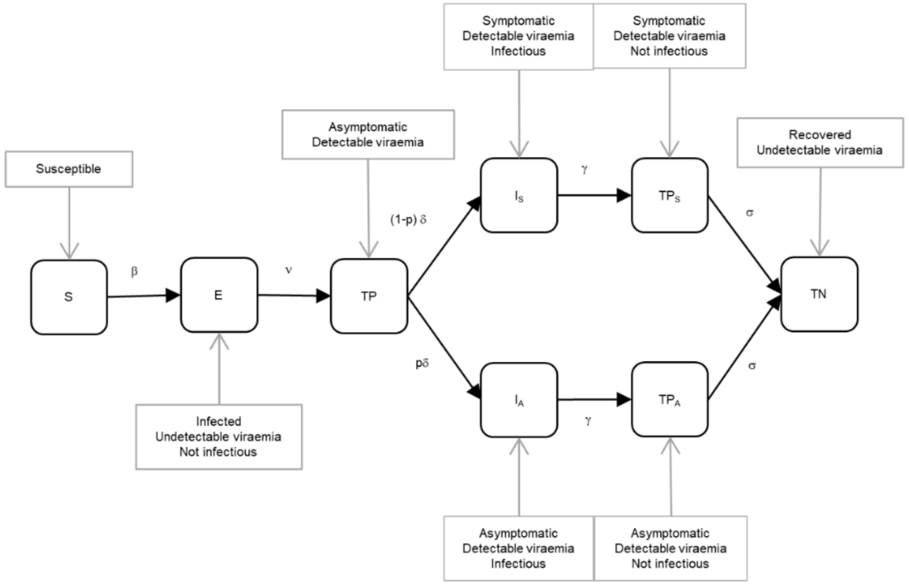
- **No difference in viral load** symptomatic vs asymptomatic infections
- For symptomatic infections, **viral load tends to peak around symptom onset**
    - ➢ Transmission happening before symptoms
- 2 (out of 8) new infections in second survey lived/had contacts with asymptomatic infections
- Living/close contacts with infected family member gives OR 84.5 (95% CI 16.8-425.4) of being infected



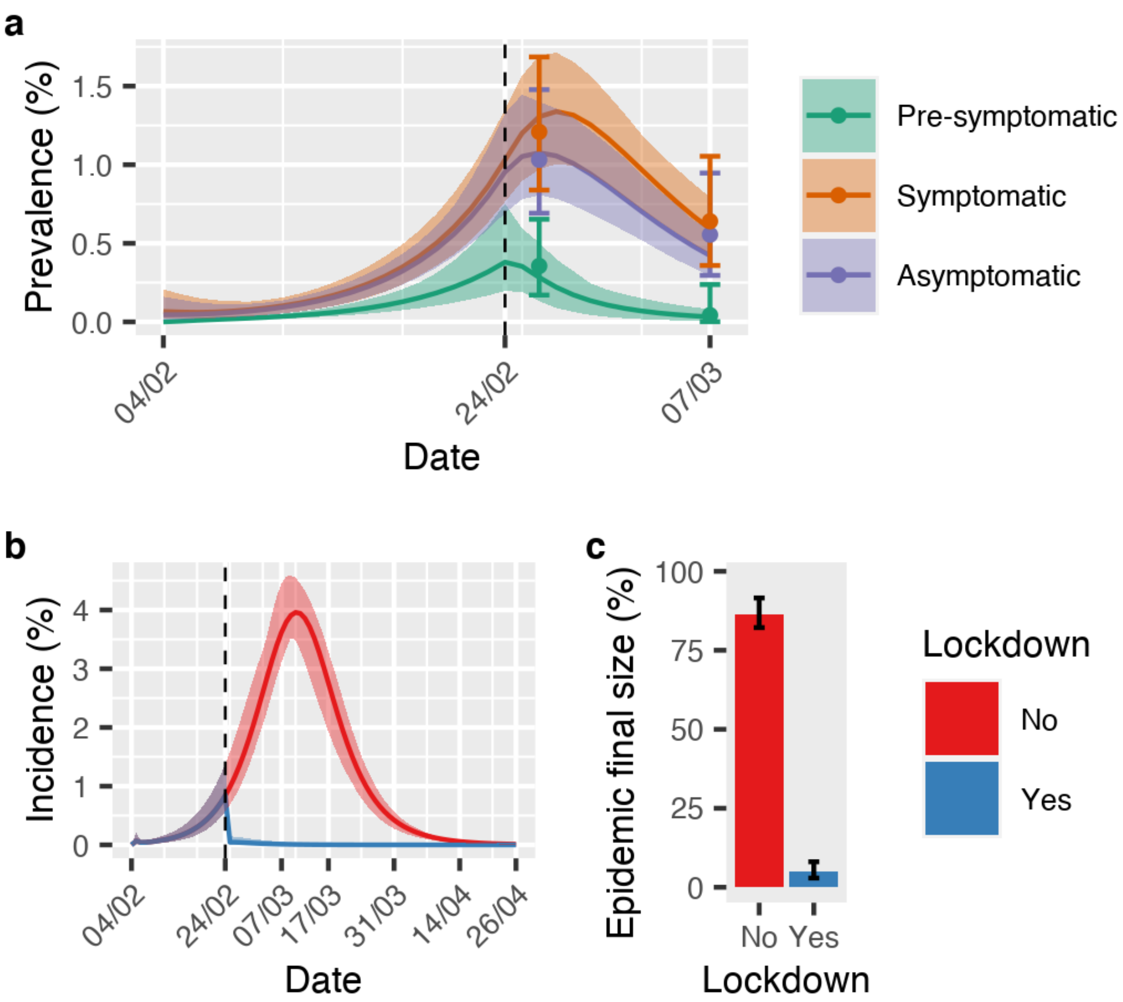
Lavezzo et al., Nature, 2020

Impact of interventions

- By how much did mass testing & lockdown reduce transmission?
  - ➢ Compartmental models



  - ➢ R0 reduced by **82% - 99%**
  - ➢ Final size of epidemic
    With lockdown: **4.9% (range 2.9-8.1%)**
    Without lockdown: **86.2% (range 82.2-91.6%)**

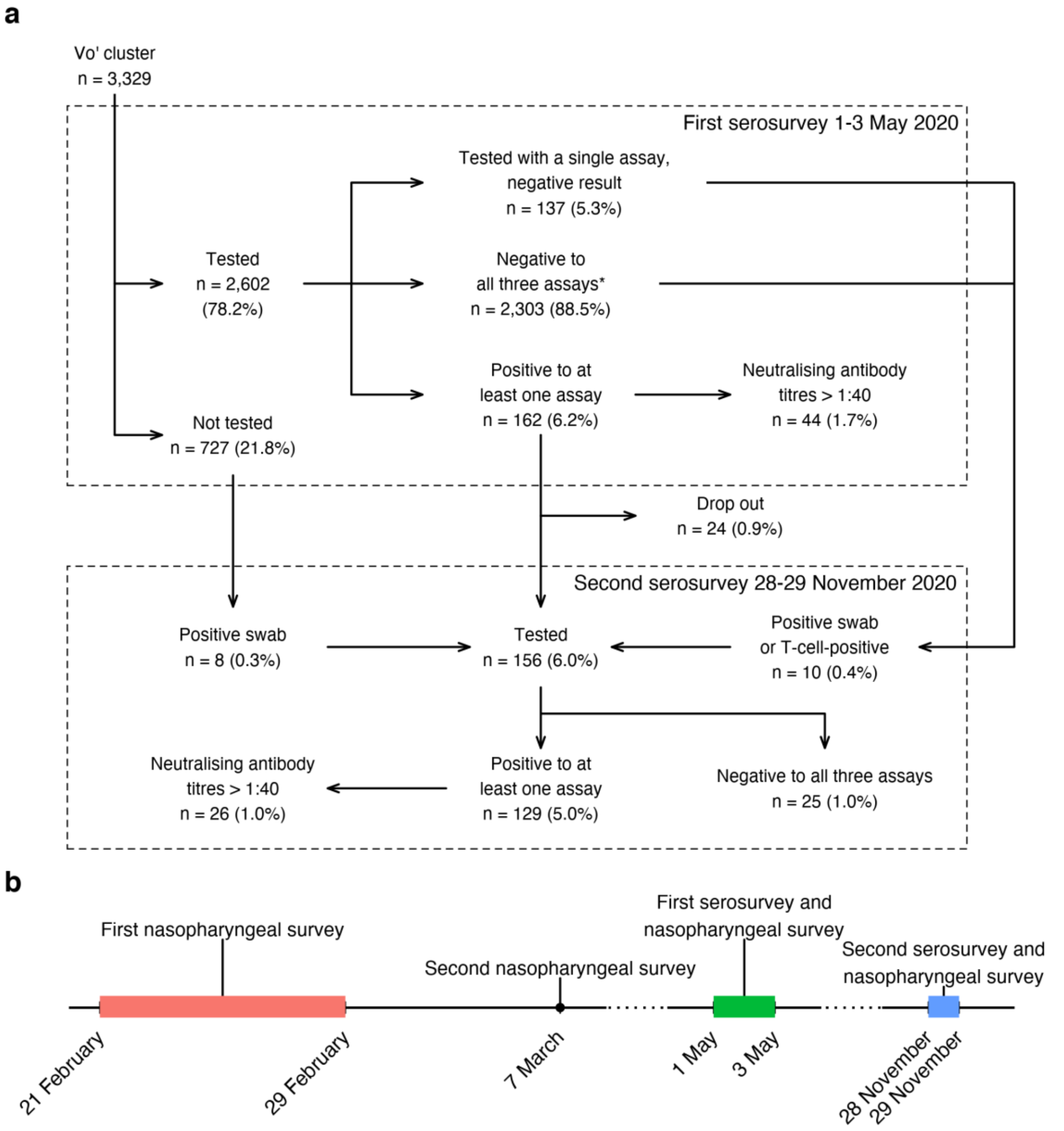


Lavezzo et al., Nature, 2020

Serological surveys (May & Nov 2020)

- **Serological surveys**
  - ➢ May 2020
  - ➢ 2,608 (78%) subjects tested
    - ➢ 2,303 subjects (88.5%) had PCR results Feb/Mar

- Serology to assess past exposure to SARS-CoV-2
  - ➢ 3 assays
    - Abbott (N antigen, IgG antibodies)
    - DiaSorin (S1/S2 antigen, IgG antibodies)
    - Roche (N antigen, total antibodies)
  - ➢ Neutralization assay

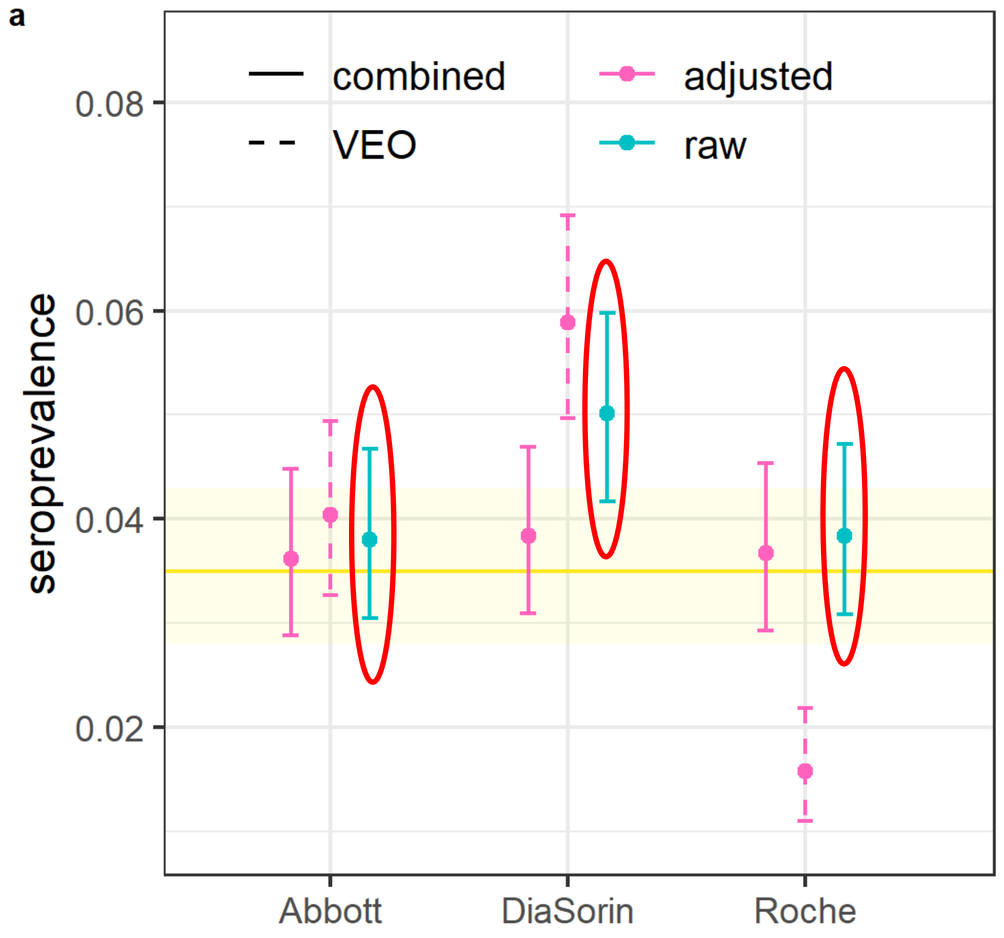


Seroprevalence

- Different assays can give different results
  - ➢ Assay discordance at individual level
  - ➢ Discordant estimates at the population level

	Vo cluster (full dataset)		
	PCR- Feb/Mar* n = 2,097 (%)	PCR+ Feb/Mar* n = 67 (%)	May n = 2,443 (%)
A+D+R+	14 (0.7)	55 (82.1)	76 (3.1)
A+D-R+	2 (0.1)	9 (13.4)	11 (0.5)
A+D+R-	0 (0.0)	0 (0.0)	0 (0.0)
A-D+R+	0 (0.0)	0 (0.0)	1 (0.0)
A+D-R-	6 (0.3)	0 (0.0)	6 (0.2)
A-D+R-	38 (1.8)	0 (0.0)	42 (1.7)
A-D-R+	3 (0.1)	3 (4.5)	6 (0.2)
A-D-R-	2,034 (97.0)	0 (0.0)	2,301 (94.2)

- ➢ raw estimate = positive/tested



Dorigatti et al., Nat Comms, 2021

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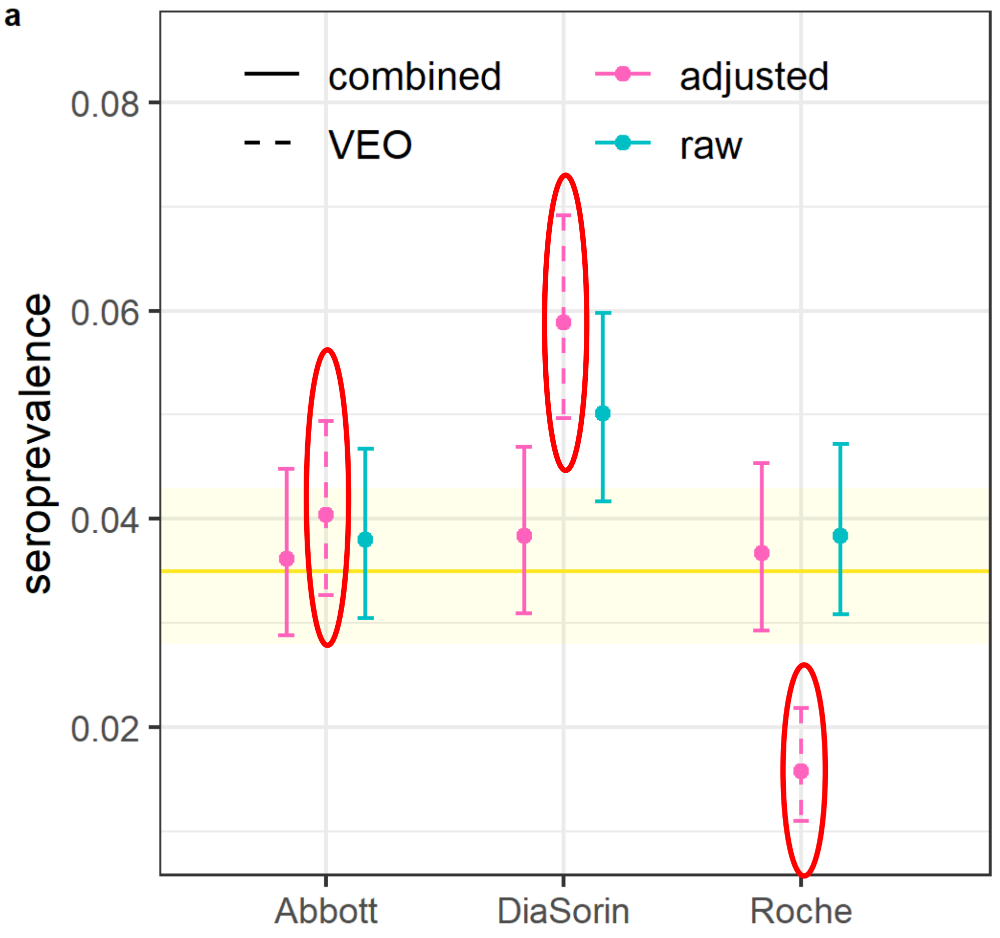
- ➢ raw seroprevalence = positive/tested

- ➢ adjusted seroprevalence

$$\mathrm{serop_{adj}} = \frac{\mathrm{serop_{raw}} + \mathrm{sp} - 1}{\mathrm{se} + \mathrm{sp} - 1}$$



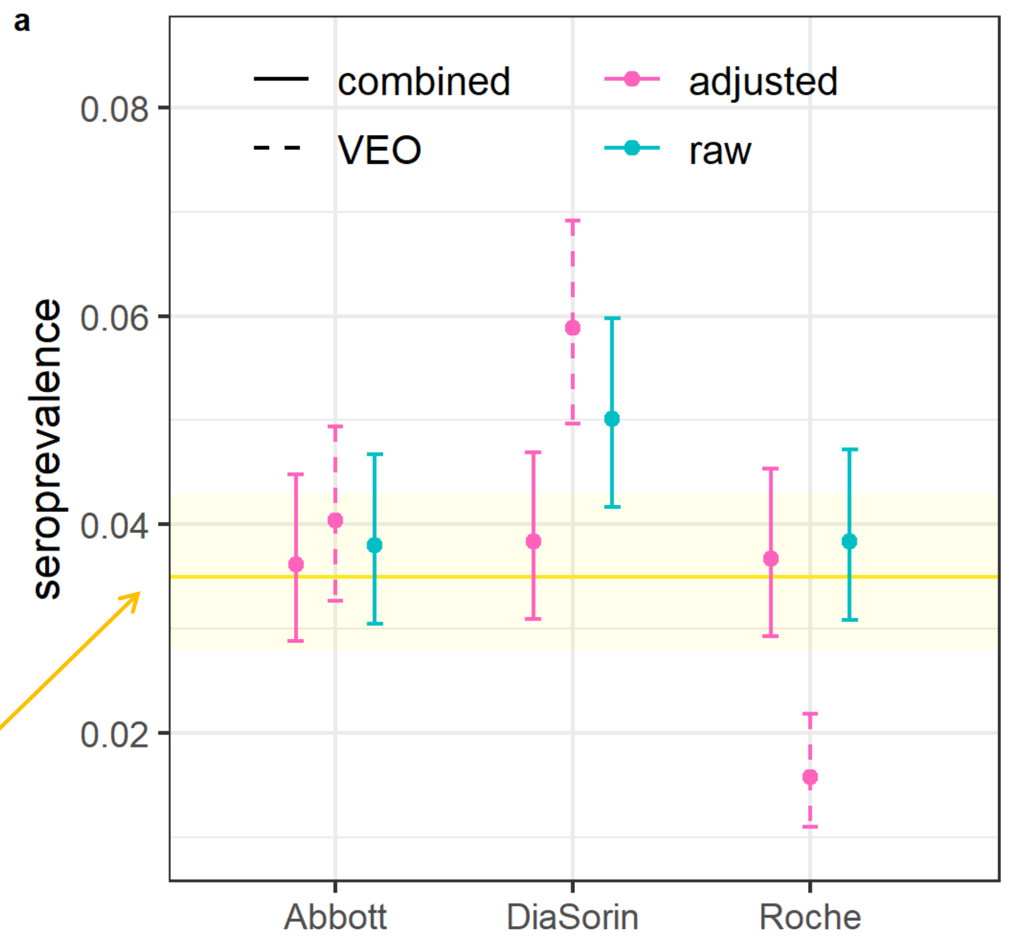
Dorigatti et al., Nat Comms, 2021

Seroprevalence

- Different assays can give different results
  - Assay discordance at individual level
  - Discordant estimates at the population level
- What is the true seroprevalence?
  - Likelihood-based approach

$$P(\mathrm{data}|\mathrm{model}) = \prod_{i\in(A,D,R)} \underbrace{P(P_i^{se},T_i^{se})P(P_i^{sp},T_i^{sp})}_{\text{Validation Experiments Only (VEO)}} \prod_{j\in(+,-)} \underbrace{P(A_jD_jR_j)}_{\text{Result combinations}}$$

$$P(A_+D_+R_+) =$$
$$= P(A_+D_+R_+|infected)\theta + P(A_+D_+R_+|not\ infected)(1-\theta)$$
$$= se_A se_D se_R\theta + (1-sp_A)(1-sp_D)(1-sp_R)(1-\theta)$$

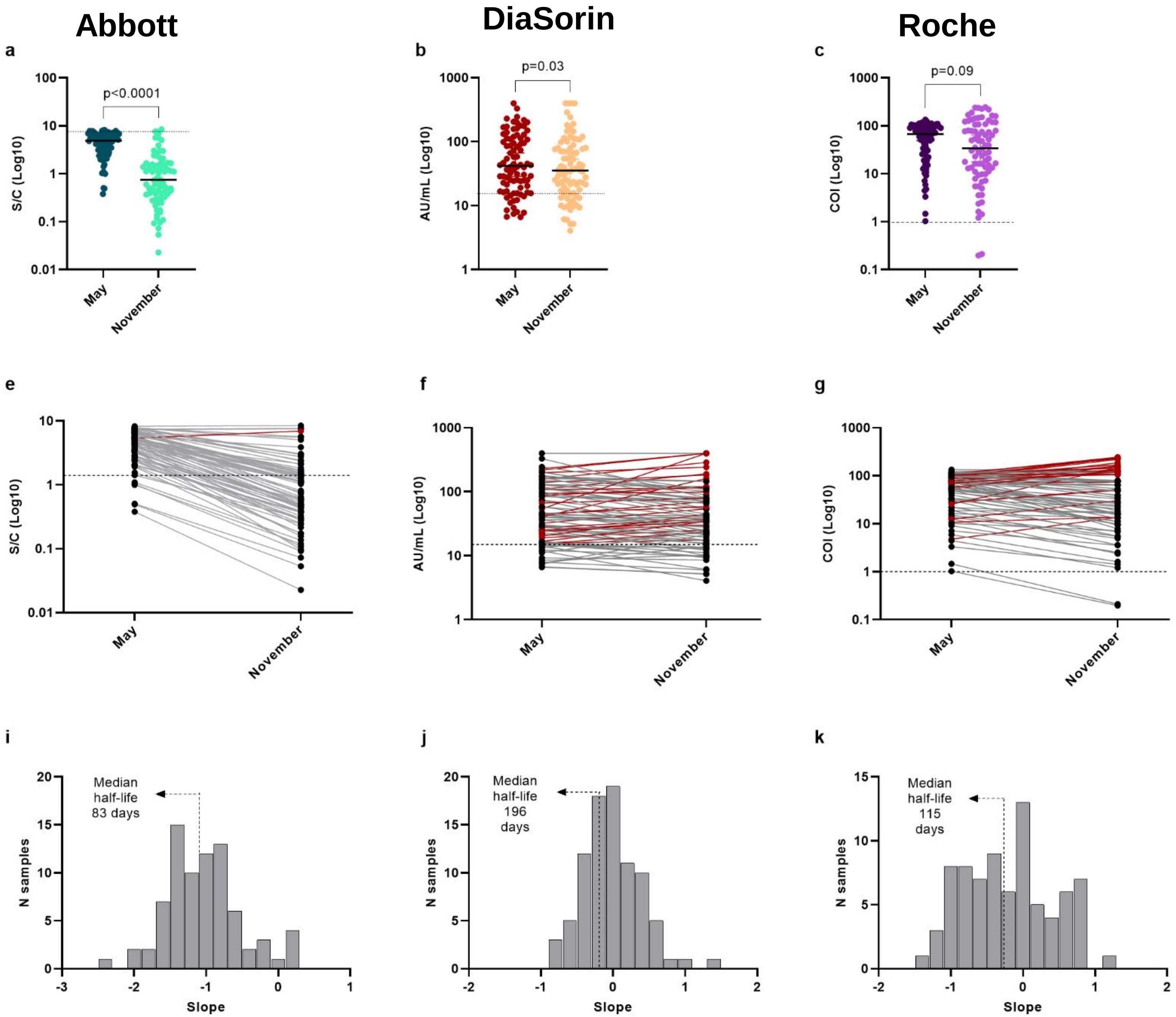


3.5% (95% CrI 2.8%-4.3%)

Dorigatti et al., Nat Comms, 2021

Antibody decay

- Serological survey among positives
    - November 2020
    - 156 subjects
- Antibody decay – positive in May still positive in November
    - Abbott 36% (95% CI 26%-48%)
    - DiaSorin 78% (95% CI 70%-86%)
    - Roche 98% (95% CI 92%-100%)
- Evidence of re-exposures
    - 16 subjects with antibody titres > doubled
    - 56% (95% CI 30%-80%) contacts with PCR+
    - No symptoms experienced



Within-household transmission

- 1,118 households with known infection status of all members

		Household size						
		1	2	3	4	5	6	7
Number of infections	0	329	345	190	167	23	6	2
	1	12	10	9	7	1	0	0
	2	0	5	2	1	1	0	0
	3	0	0	5	1	0	0	0
	4	0	0	0	2	0	0	0

- Applied method developed by Fraser et al, AJE, 2011

$$\binom{s_0}{k} = \frac{\sum_{m=0}^{k}\binom{s_0-m}{k-m}\boxed{F_m^{n,s_0}}}{\Phi_n(s_0-k)^m Q^{(s_0-k)}} \qquad for\ k = 0, \dots, s_0$$

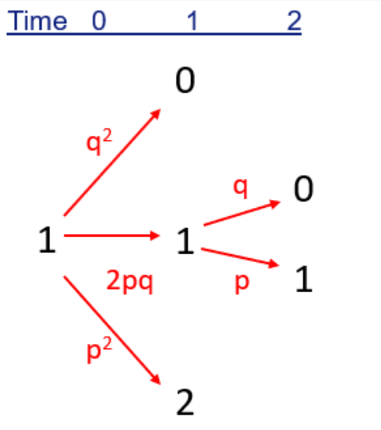
Hazard distribution

$$\Phi_n(x) = q^x = e^{-\beta x}$$

Escape probability from outside the household

Probability that a households of size n with s_0 susceptibles has m infections

Chain-binomial example – household of size 3



Probability	Chain notation	Total infections
q^2	$\{1\}$	1
$2pq^2$	$\{1^2\}$	2
$2p^2q$	$\{1^3\}$	3
p^2	$\{12\}$	

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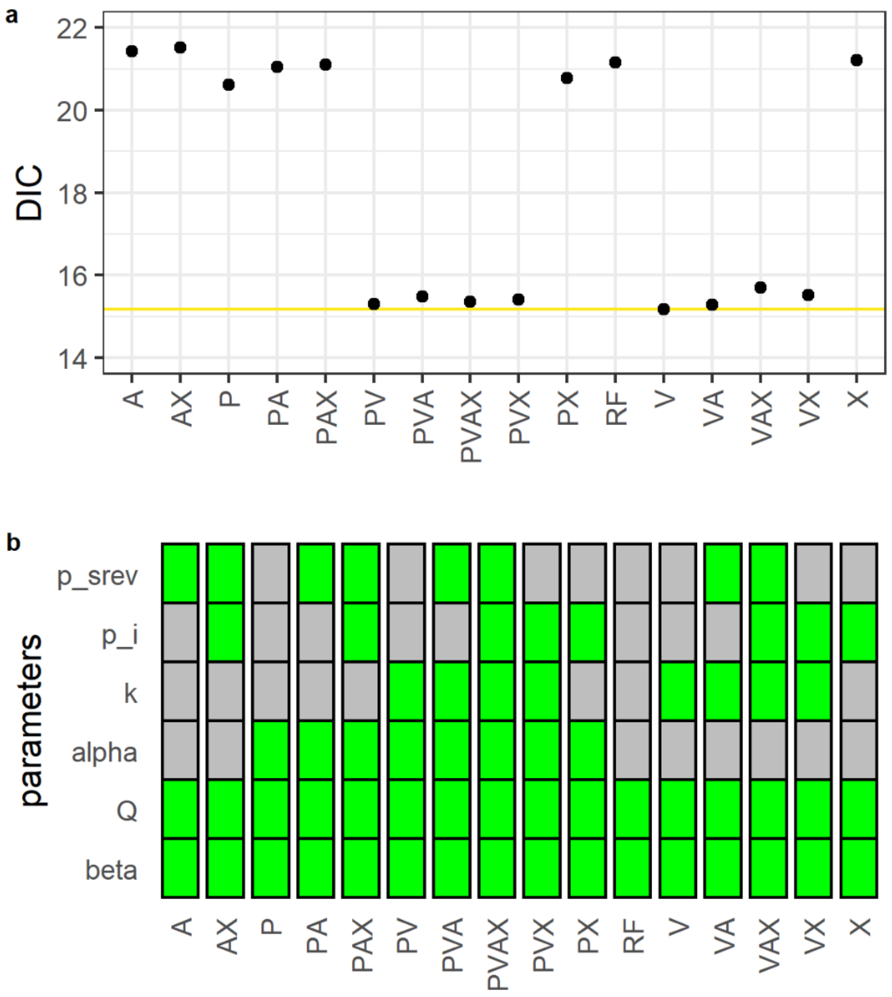
- Applied method developed by Fraser et al, AJE, 2011
  - ➢ Tested different assumptions
    - Overdispersion in number of secondary cases (V)
    - Household size dependency in transmission (P)
    - Proportion of subjects seroreverting (A)
    - Proportion of subjects isolating (X)



Dorigatti et al., Nat Comms, 2021

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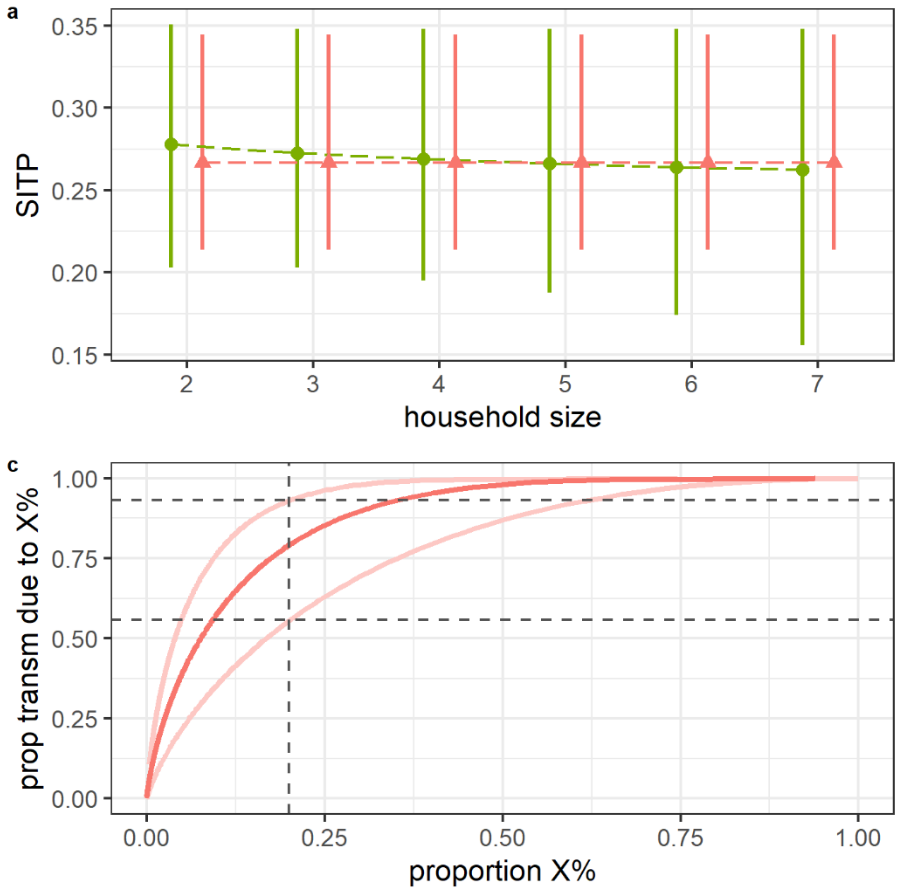
- Applied method developed by Fraser et al, AJE, 2011
  - ➢ Tested different assumptions
    - Overdispersion in number of secondary cases (V)
    - Household size dependency in transmission (P)
    - Proportion of subjects seroreverting (A)
    - Proportion of subjects isolating (X)

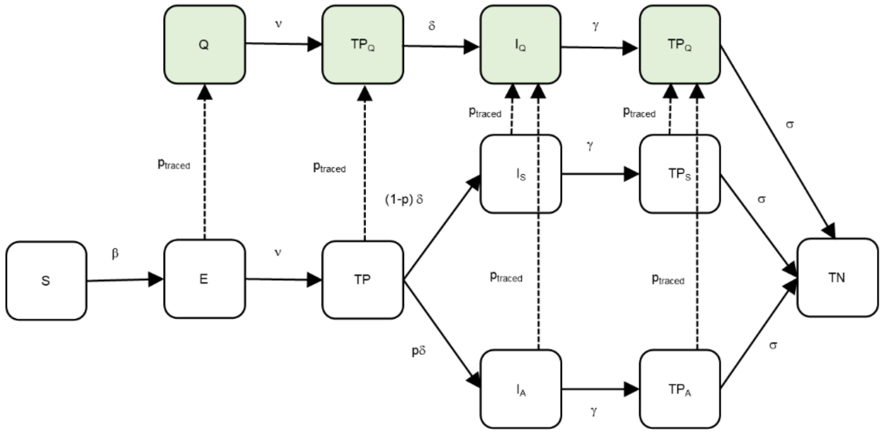
- Preferred models assume overdispersion in offspring distribution
  - ➢ 82% (95% CrI 56% – 95%) transmission due to 20% infections

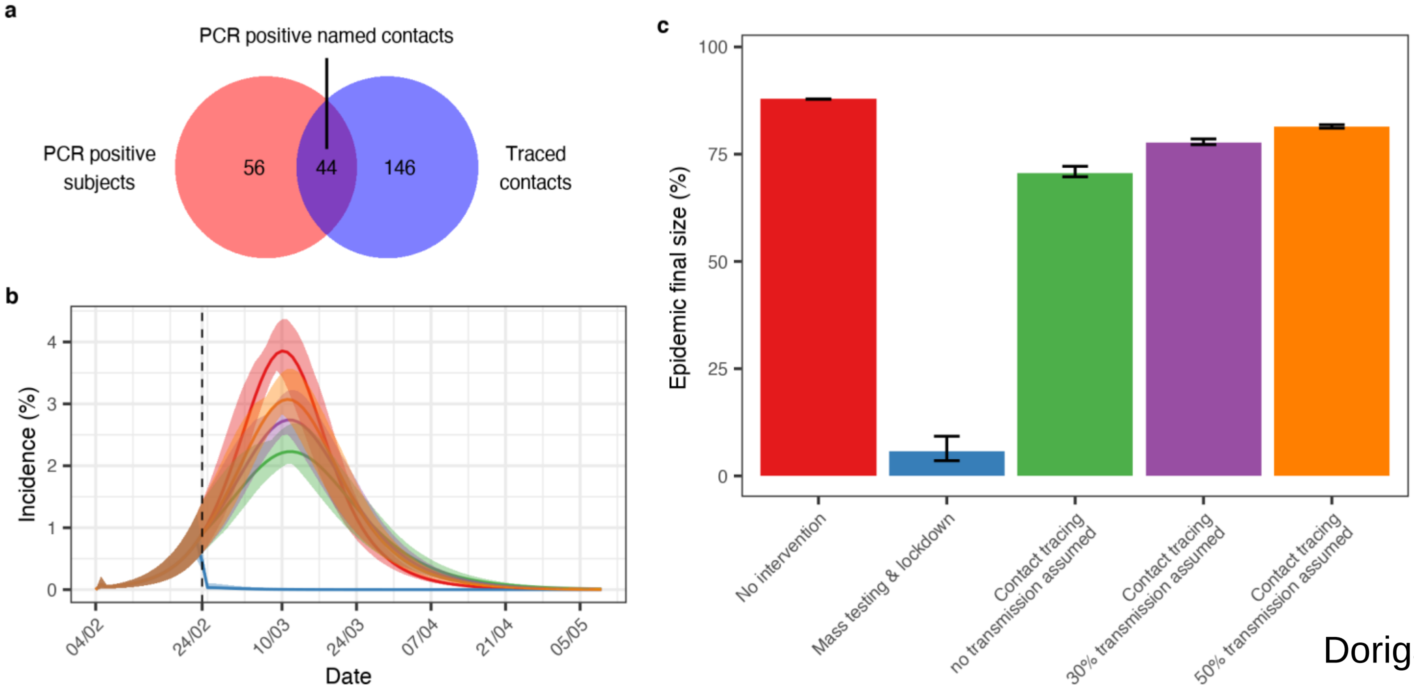


Dorigatti et al., Nat Comms, 2021

Impact of contact tracing

- Contact tracing in Vo
  - ➢ Huge effort to identify patient 0
- Mass testing revealed the infectious status of traced contacts
  - ➢ 44% of traced contacts were positive
- Counterfactual scenario
  - ➢ What would have happened in the absence of mass testing?

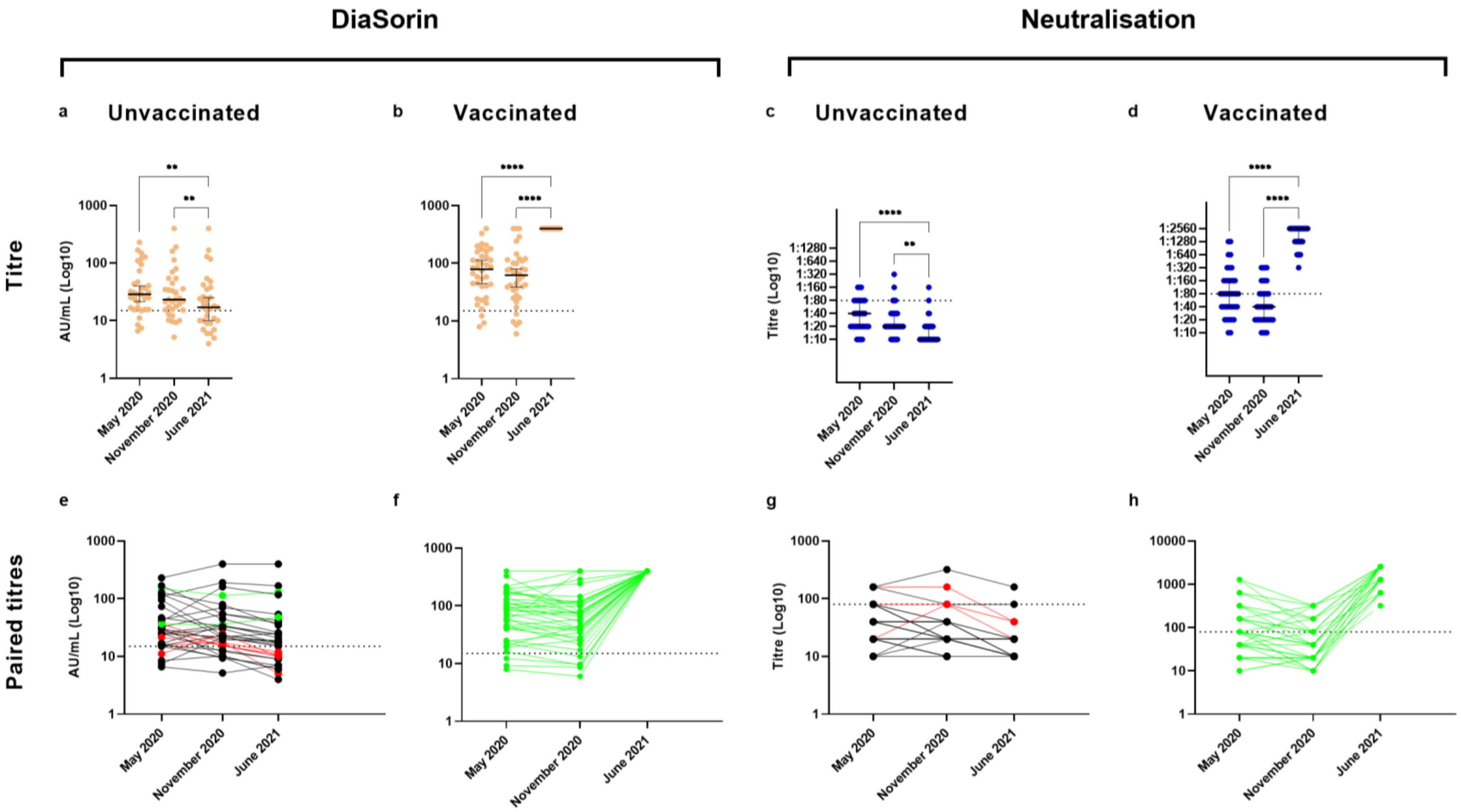




Dorigatti et al., Nat Comms, 2021

Serological survey (June 2021)

- Serological survey
  - ➢ June 2021
  - ➢ 76 subjects
  - ➢ Vaccination



Lavezzo et al., Research Square, 2021

Serological survey (June 2021)

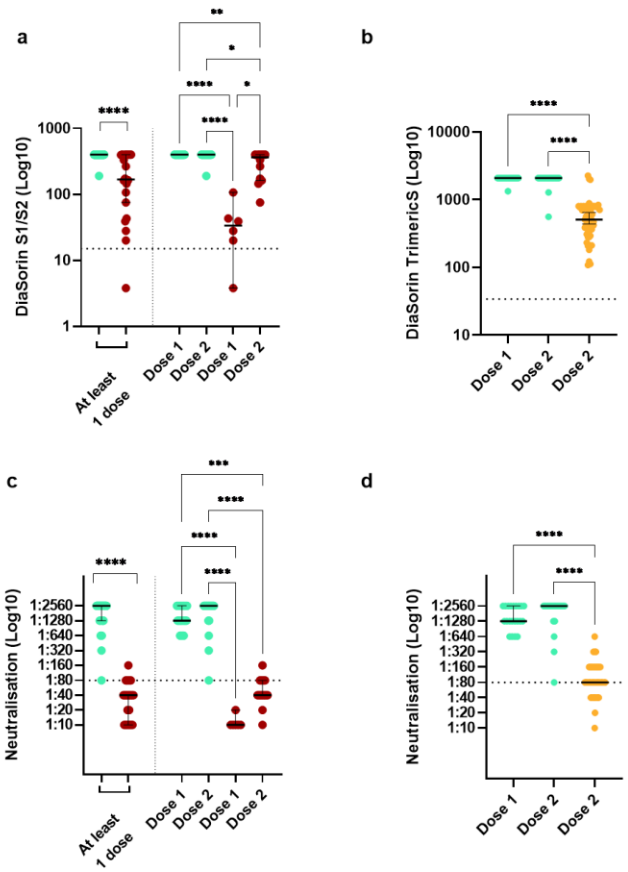
MRC Centre for Global Infectious Disease Analysis

Imperial College London

- Serological survey
  - ➢ June 2021
  - ➢ 76 subjects
  - ➢ Differences by vaccine status

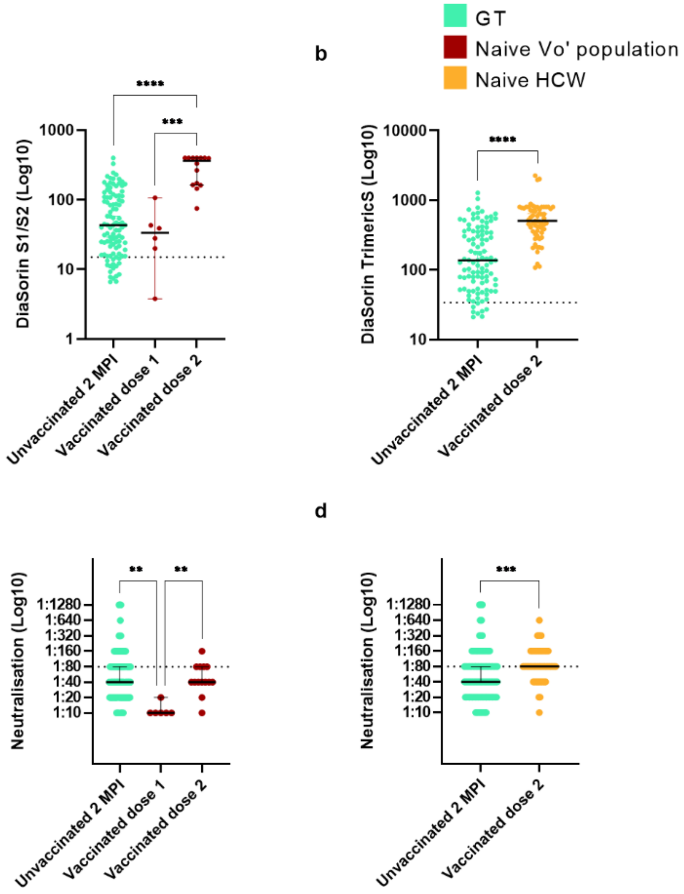
Vaccinated

Hybrid immunity (infection + vaccine) elicits higher Ab responses than vaccination alone



Vaccinated vs unvaccinated

Vaccination (2 doses) elicits higher Ab responses than infection



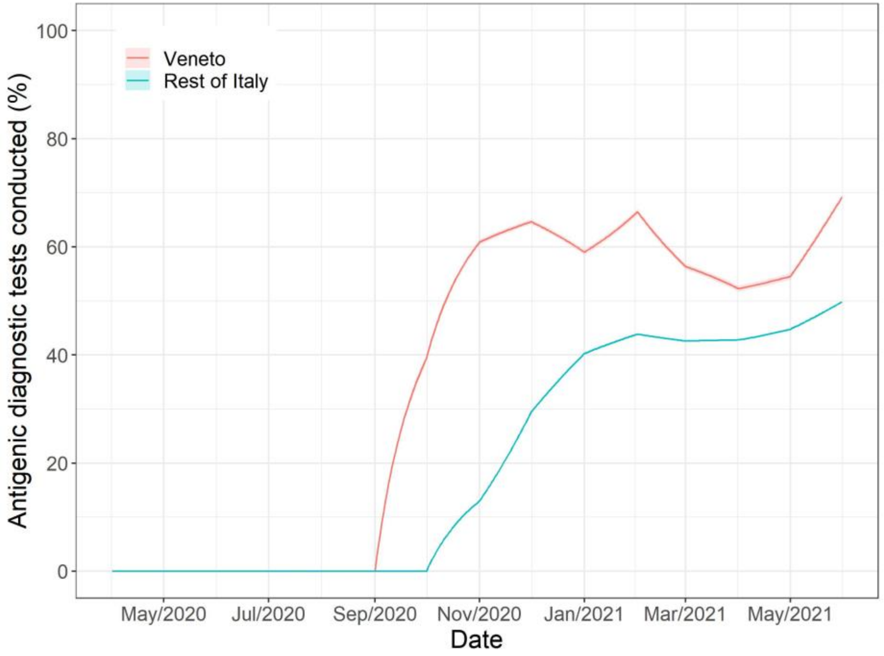
Lavezzo et al., Research Square, 2021

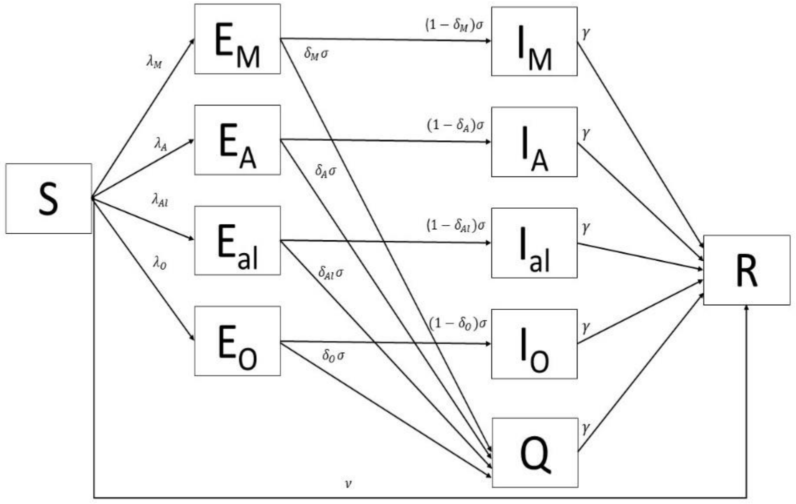
Impact of testing strategies

- Veneto first region to adopt antigen tests at scale

- Hospital-based surveillance study conducted
  - Antigen test escaping variant detected
  - Variant carrying several mutations N antigen
  - Higher peak prevalence in Veneto (20%) than in rest of Italy (10%)

- Did mass use of antigen test promote transmission of antigen test escaping variant?





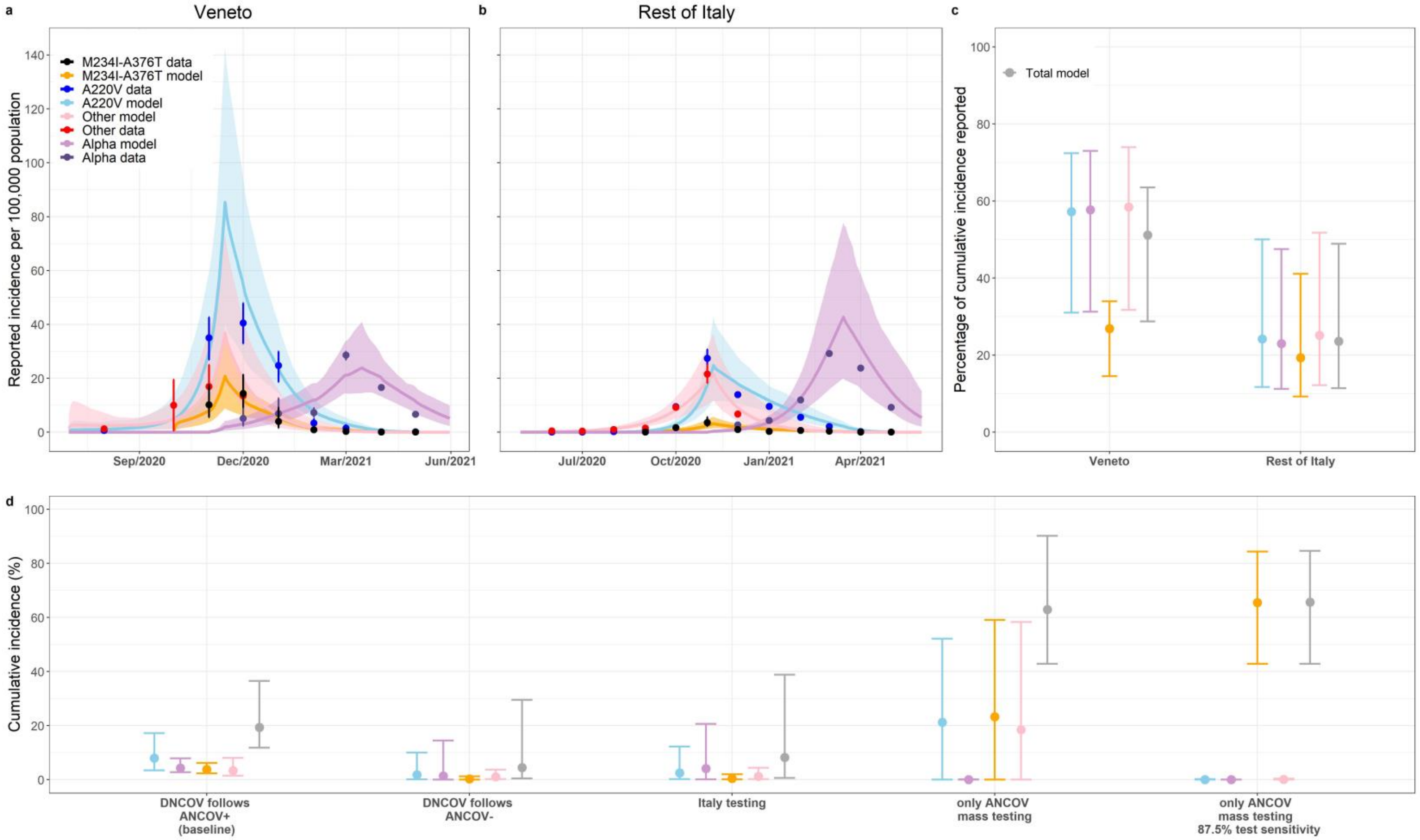
M = antigen escaping variant
A = co-circulating variant
al = Alpha VOC (B117)
O = other variants (combined)

- Data fusion approach
  - Epidemiological data (Protezione Civile)
  - Sequence data (GISAID)

Del Vecchio et al., Research Square, 2022

Impact of testing strategies

- Veneto reported more cases compared to rest of Italy
- Mass use of antigen tests in Veneto promoted transmission of antigen escaping variant

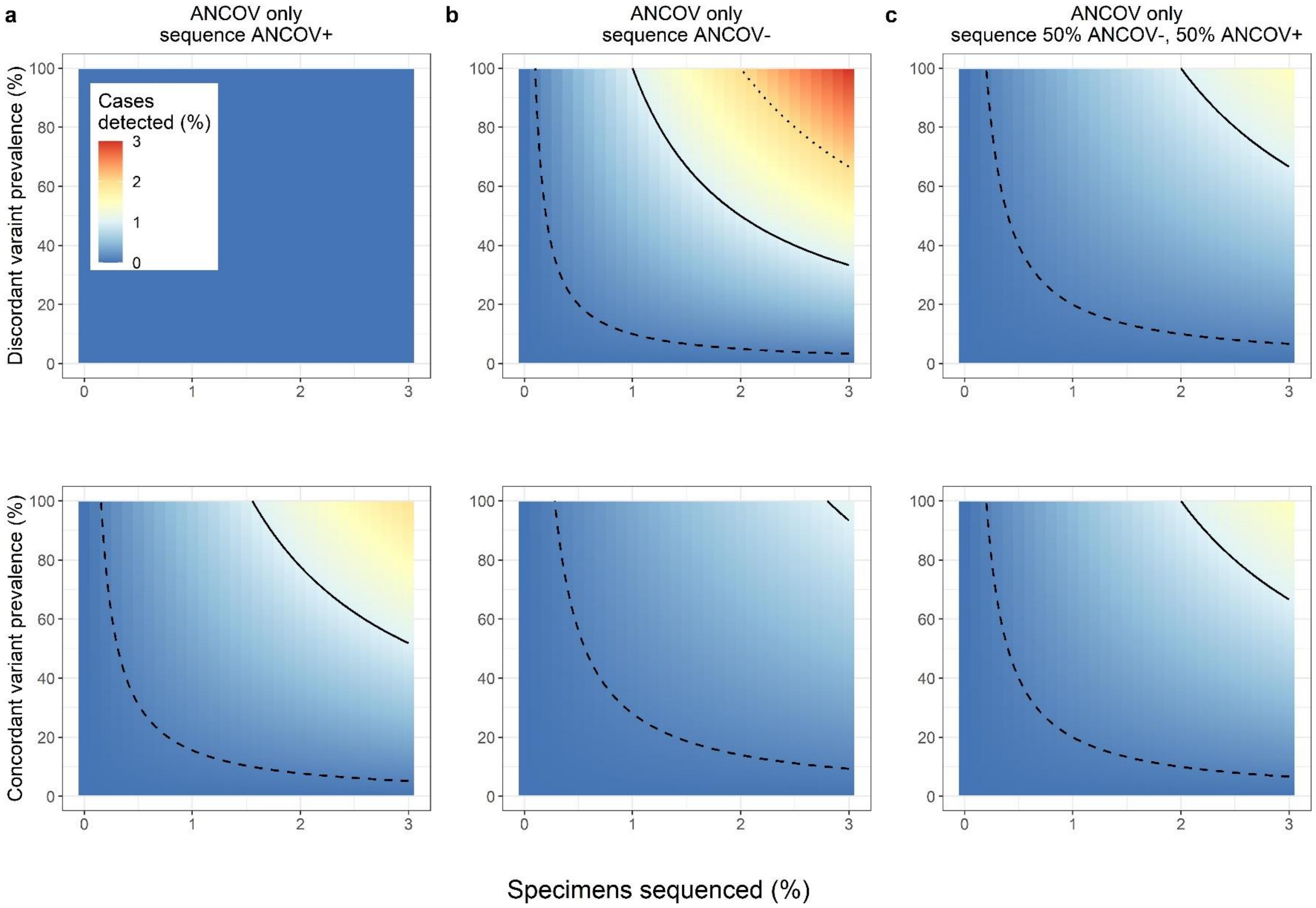


Del Vecchio et al., Research Square, 2022

Impact of testing strategy

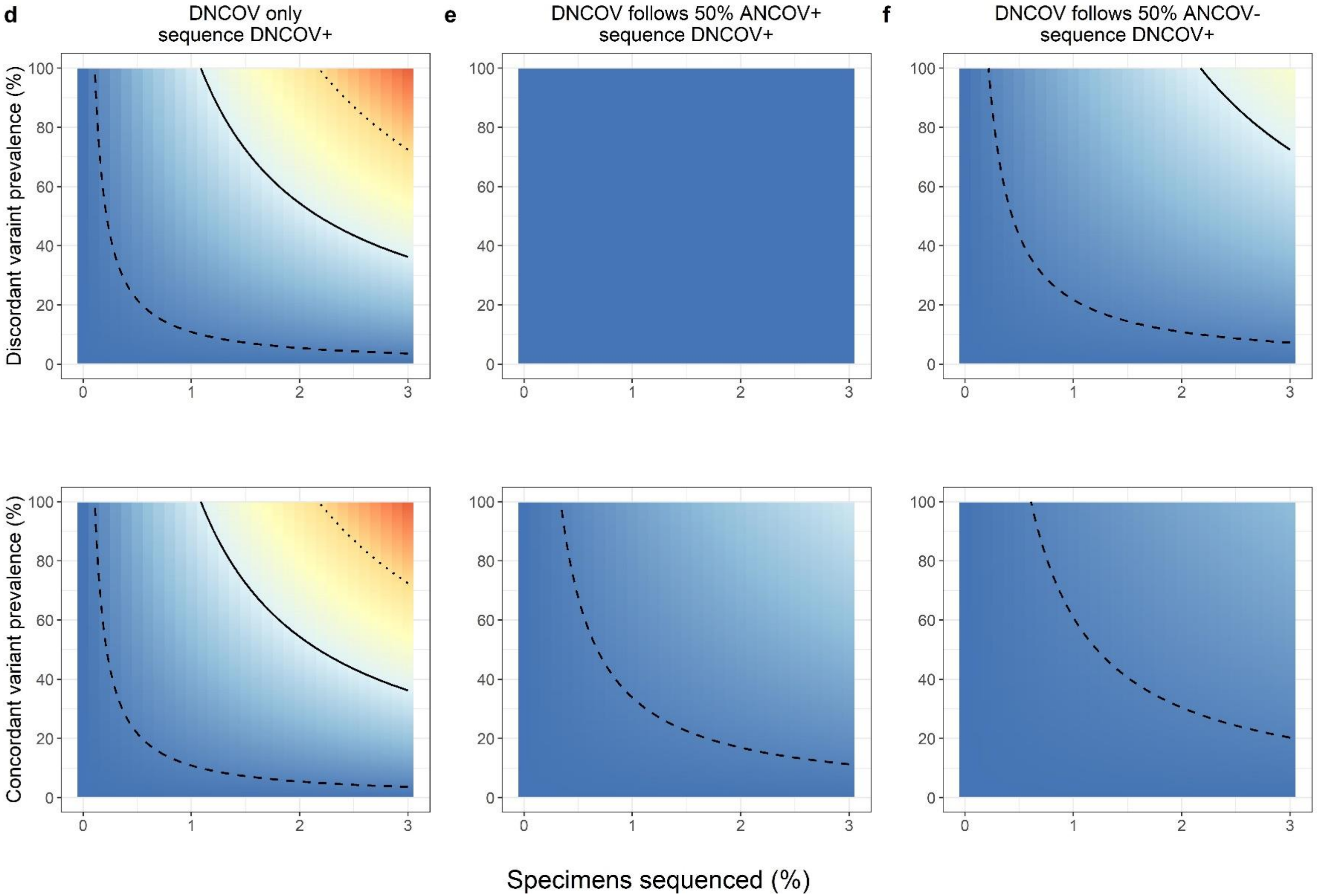
- Proportion of cases detected through sequencing depending on the testing strategy adopted

- If antigen test only strategy
  - Sequencing ANCOV+ completely misses the discordant variant
  - Sequencing ANCOV- captures at most 1/3 concordant variants
  - Sequencing 50% ANCOV+ and 50% ANCOV- is a trade-off



Impact of testing strategy

- Proportion of cases detected through sequencing depending on the testing strategy adopted
- **Molecular test only strategy** provides **unbiased** picture of circulating variants
- Strategies with molecular tests following antigen test not perfect
  - ➢ **Sequencing ANCOV- is essential to capture escaping variants**



Conclusions

- SARS-CoV-2 had spread silently in the population
- 42.5% (95% CI 31.5-54.6%) of infections were asymptomatic
- Mass testing & lockdown significantly reduced transmission
- Contact tracing had a limited impact of the epidemic
- Most of transmission is due to a small proportion of infections
- Antibodies decay (at different rates, depending on the test used)
- Vaccination boosts antibody levels
- Testing strategies based on molecular assays allow to capture actual viral circulation
- Sequencing antigen negative samples is key to detect potentially escaping variants

Thank you!

i.dorigatti@imperial.ac.uk