COVAX

Pre-/Post Licensure Assessments of COVID-19 Vaccine Efficacy Against Infection & Transmission

With time to address updates from the prior COVAX workshop on Nov 19

Clinical Development & Operations SWAT Team | Thursday December 17, 2020

CEPI

Gavi The Vaccine Alliance

World Health Organization

Workshop Agenda

Time (CET)	Topic	Speaker(s)
15:00 – 15:10	Welcome & Meeting Objectives	Jakob Cramer
Part 1: Correlates of Protection Update		
15:15 – 15:40	Correlates of Protection Update	Peter Dull & Ivana Knezevic
Part 2: What can we learn from pre-licensure trials?		
15:45 – 16:00	SARS-CoV-2 natural course of infection, viral shedding, virus detection and quantification using PCR and rapid diagnostic tests: Current knowledge and gaps	Christian Drosten
16:00 – 16:15	Assessment of SARS-CoV-2 antibody responses in the context of natural infection	Viviana Simon
16:15 – 16:30	Pre-clinical animal studies: evidence from different vaccine platform technologies on infection / duration of viral shedding	William Dowling
16:30 – 16:40	Planned assessments of infection in phase 2/3 trials	Amol Chaudhari
16:40 – 16:50	Experience from using weekly PCRs to detect asymptomatic infections	Andrew Pollard
Part 3: Additional approaches, evidence / post-licensure studies		
16:55 – 17:10	Modelling: impact of vaccine efficacy against disease versus transmission on public health and pandemic curves	Neil Ferguson
17:10 – 17:25	Observational studies: what can we learn from other vaccines?	Natasha Crowcroft
17:25 – 17:35	Statistical approaches to studying transmission	Ira Longini
17:35 – 17:45	Household transmission studies	Adam Finn
17:45 – 17:55	Phase 2b trial design to assess vaccine efficacy against infection, viral load, and secondary transmission	Holly Janes
17:55 – 18:25	Panel Discussion	Moderated by Daniel Feikin
18:25 – 18:30	Wrap Up & Next Steps	Jakob Cramer

Welcome & Meeting Objectives

Jakob Cramer, MD

Head of Clinical Development

Coalition for Epidemic Preparedness Innovations (CEPI)

Context for today's workshop

Part 1:

- Road to Correlate(s) of Protection: Review updates since the last workshop on Nov 19th 2020
- International Standards for serologic assays

Parts 2 and 3:

- "*We need vaccines to control and eventually end this pandemic*"
- Vaccines have demonstrated high efficacy against COVID-19 illness (any severity) based on primary endpoints
- But will vaccines be effective against infection and transmission?
  - Will a vaccine effective against infection also be effective against transmission?
  - Will a vaccine without clear efficacy against infection still be effective against transmission?
- What do we know about SARS-CoV-2 infection / transmission?

Part 2: How can we assess infection (/ transmission) pre-licensure? What should be considered for Ph2/3 clinical trial design?
--> review diagnostic approaches, endpoints, practical experience etc.

Part 3: How can we assess (infection /) transmission post-licensure? What should be considered for post-introduction observational studies? --> post-introduction modelling, lessons learnt form the past, stats/concepts from post-licensure, ...

Part 1:

Correlates of Protection Update

Moderated By:

Peter Dull, MD

Deputy Director,

Integrated Clinical Vaccine Development,

Bill & Melinda Gates Foundation (BMGF)

Correlates of Protection Update

Peter Dull, MD

Deputy Director, Integrated Clinical Vaccine Development (BMGF)

Ivana Knezevic, PhD

Group Lead, Norms and Standards for Biologicals (HPS/MHP/WHO)

Evolution of Phase III studies

As vaccines receive EUA[1] or licensure and are distributed, structure of Phase III trials will necessarily shift

Target: Correlate of Protection accepted by regulators

	Early Wave 1 Start recruitment: Before Nov 2020	Late Wave 1 Start recruitment: Before ~Q2 2021	Wave 2 Start recruitment: ~Q2 2021+
Study Design	• Placebo-controlled efficacy studies • 30k-45k+ subjects enrolled	• Placebo-controlled studies • **?Hybrid approach, able to transition to immunogenicity** • 20-30k+ subjects planned enrollment	• Placebo-controlled for new populations • **<u>Immunological non-inferiority vs. (comparable) EUA'ed/licensed product</u>** • Post-licensure effectiveness required after EUA • **<30,000 subjects enrolled**
Subjects / Sites	• Adults (and adolescents) • Settings of high disease Geographies with strong clinical trial capacities	• **Adults in settings with no EUA'ed or licensed vaccines OR** • **Populations not recommended as priority with available vaccines** • High disease incidence geographies	• **Only low-risk groups (young / healthy)** • **Previously-vaccinated subjects receiving as boost**
Examples	Pfizer, BioNTech, Moderna, Sinovac, AstraZeneca, 中国生物 CNBG, University of Oxford, Janssen, The Gamaleya National Center of Epidemiology and Microbiology, CanSinoBIO	ZF Sw The Biologics Company, CUREVAC, Bharat Biotech, Sanofi, Novavax, Clover Biopharmaceuticals	Biological E. Limited Celebrating Life Every Day, Institute of Medical Biology Chinese Academy of Medical Sciences, Merck, Medicago, SK bioscience, SII, Zydus Cadila, Walvax 沃森生物 Walvax Biotechnology Co., Ltd.

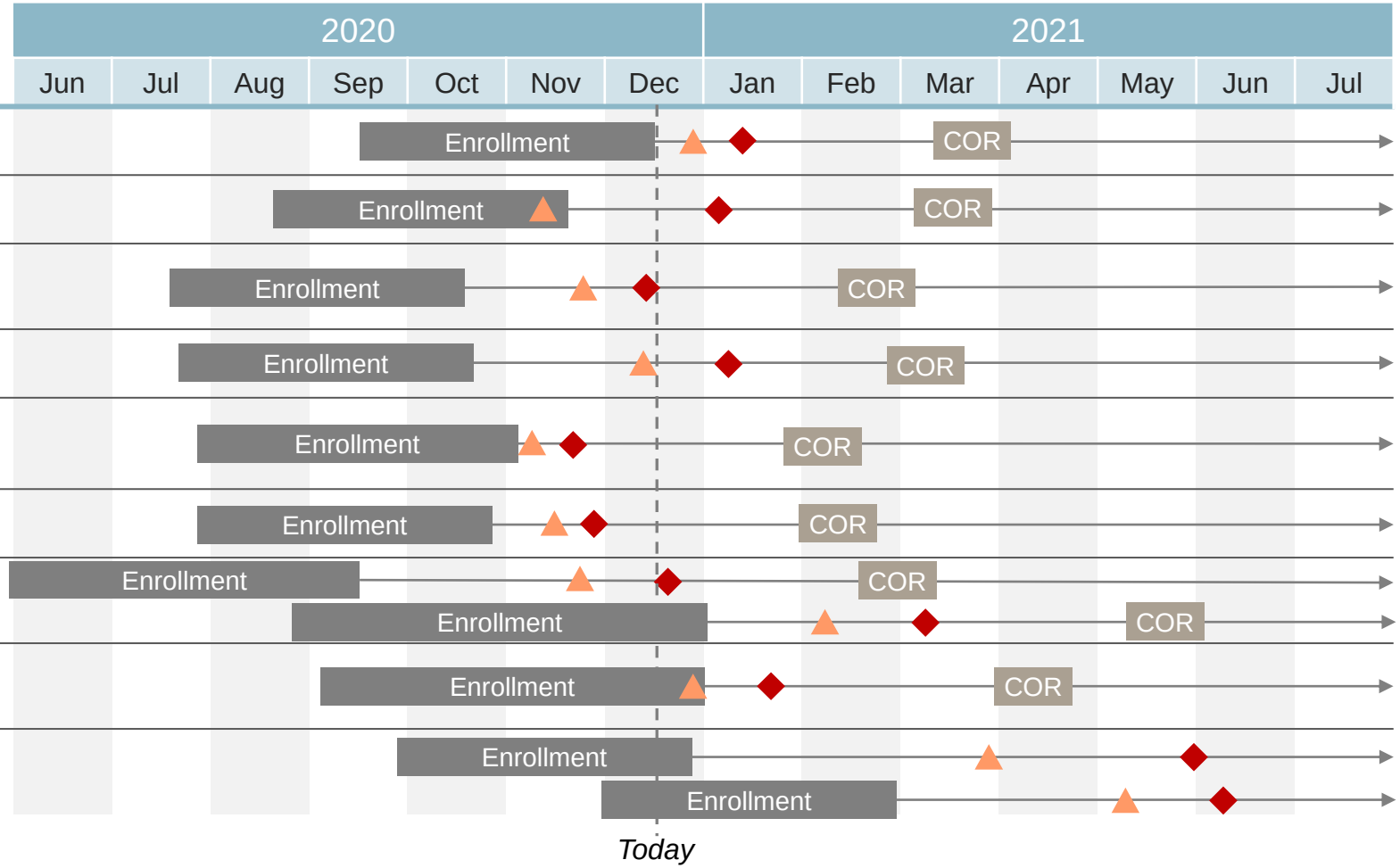
1. Emergency Use Authorization (FDA) used synonymously for national conditional / emergency use approval procedures.

Key changes between eras bolded

Landscape and timing of early Phase III VE trials that may contribute data to correlates analyses

Key
- Interim analysis
- Primary analysis
- COR Potential correlates analysis

Developer	Ph III Sites[1]
CanSino	ARG, MEX, CHL, PAK, RUS
Gamaleya	RUS, BLR, UAE, VEN, IND
Sinopharm	ARG, BHR, EGY, JOR, MOR, PER, UAE
Sinovac	**BRA**, CHI, CHL, IDN, TUR
Pfizer / BioNTech	**USA**, ARG, BRA, GER, RSA, TUR
Moderna	**USA**
Oxford / AZ[2]	**BRA**, **UK**, PER, RSA **USA**
Janssen	USA, ARG, BRA, CHL, COL, MEX, PER, RSA
Novavax	**UK**, MEX, RSA (IIb) **USA**[3]

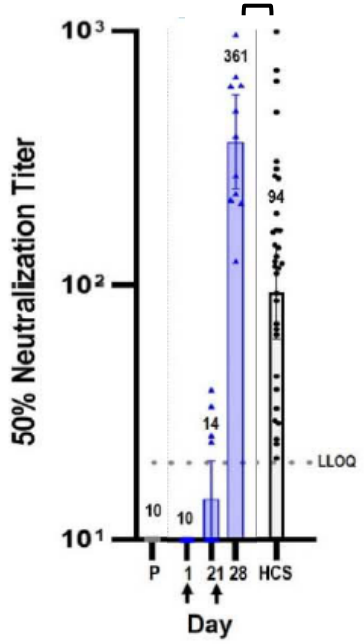
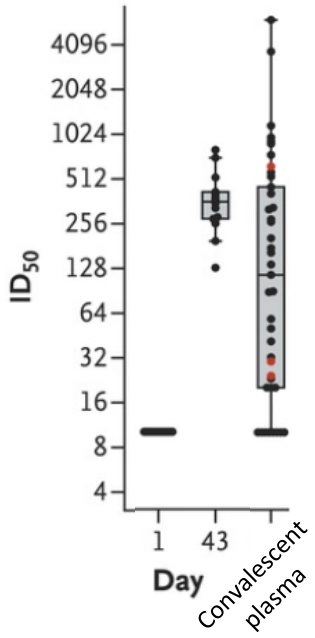
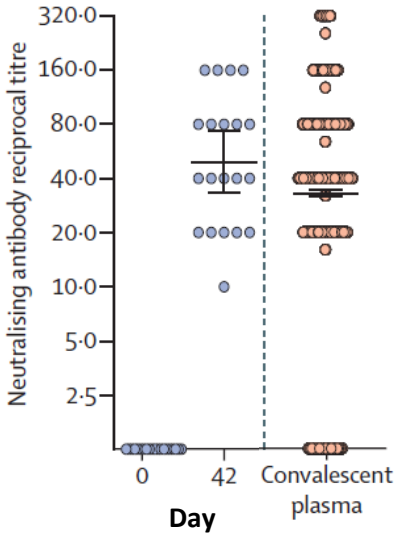
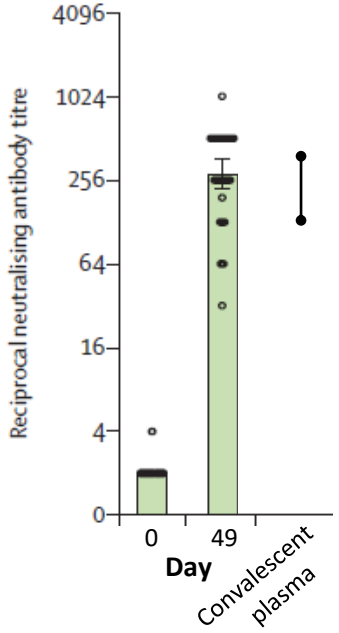
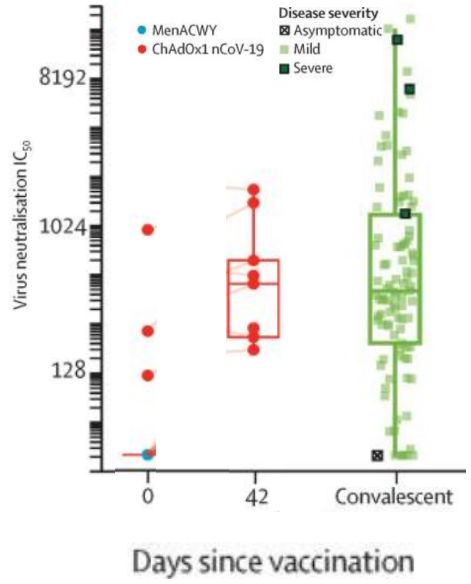


Assumptions:
- 6-month attack rate:
  - US, UK: 2%
  - Others: 5%
- VE: 50%
- Interim analysis: 75 cases
- Primary analysis: 150 cases
- Recruitment / vaccination: 3 mo.
- Follow up for VE endpoint: 2 mo.
- Data mgt & analysis before IA and PA: 1 mo.
- Preparation of correlates report: 2 mo.

1. Where developers are conducting multiple Phase III studies, timeline represents site with predicted earliest readout (bolded), based on public sources (primarily clinicaltrials.gov) and modeled assumptions; 2. Top timeline for Oxford / AZ reflects pooled analysis of Brazil and UK sites, per Phase III interim analysis. 3. Actual start date and study design *TBC*.

Neutralization titers from Phase I/II suggest threshold of protection may be modest across platforms

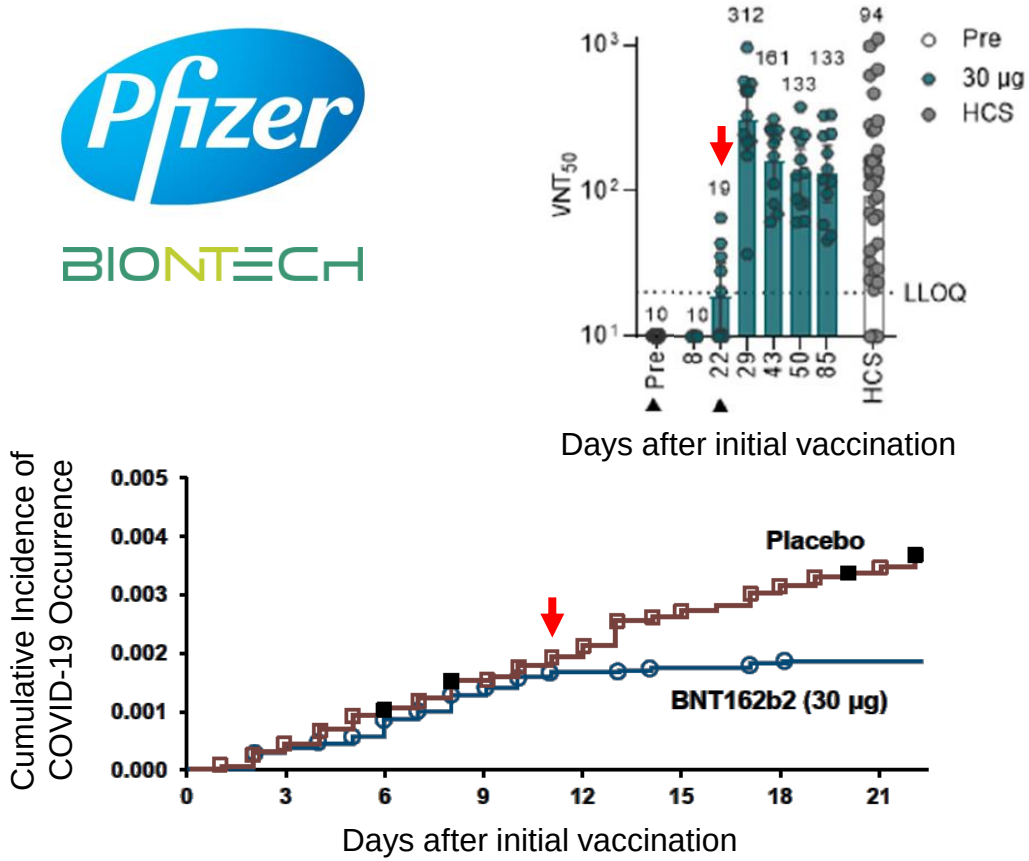
Note: Figures have been cropped / re-labeled as needed to enable comparison; Convalescent sera variably sourced from severe, moderate, mild disease and asymptomatic cases

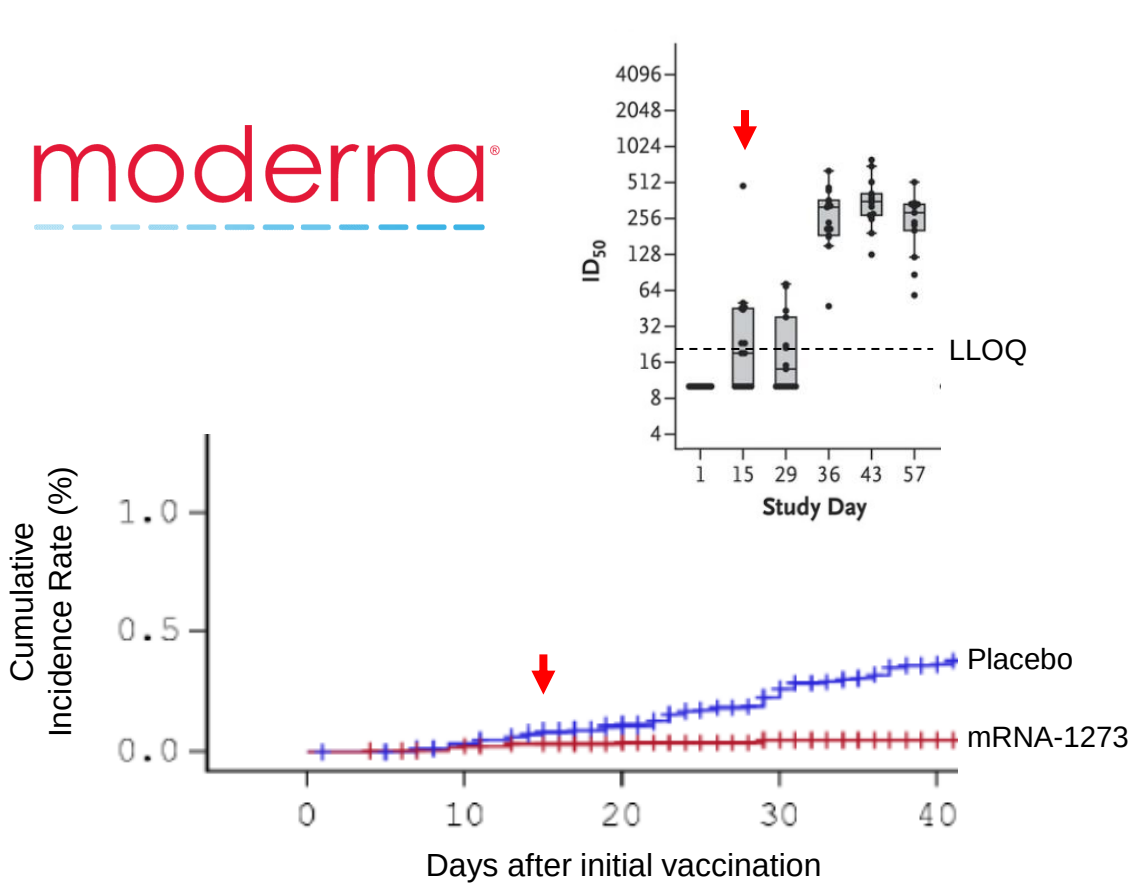
	Pfizer / BioNTech BNT162b2	**Moderna** mRNA-1273	**Gamaleya** Sputnik V	**Sinopharm** BBIP-CorV	**Oxford / Astra Zeneca** ChAdOx1
Neuts relative to convalescents:	3.8-fold **higher**[1]	3.2-fold **higher**[2]	1.5-fold **higher**[3]	Comparable[4]	Comparable[5]
					
Efficacy:	**95%**[6]	**94.1%**[6]	**95%**[7]	**86%**[7]	**62.1% (up to 90%)**[7]

1. wt VNA titers (NT_{50}) in subjects aged 18-55, 7 days following 2nd 30µg dose; HCS: n=38, across full range of disease severity. 2. Lentivirus PsVNA titers (ID_{50}) in subjects aged 18-55, 14 days after 2nd 100µg dose; HCS: n=42, across full range of disease severity. 3. wt MNA titers in subjects aged 18-60, 21 days following rAd5-S boost; HCS: mild and moderate cases only. 4. wt VNA titers (50% CPE) in subjects aged 18-59, 28 days after 2nd 4µg dose; convalescent sera range cited in supplement is plotted here for comparison, severity not specified. 5. Monogram lentivirus PsVNA titers in subjects aged 18-55, 14 days after 2nd $5x10^{10}$vp dose; HCS: n=146 hospitalized patients and 24 asymptomatic HCWs. 6. Primary analysis. 7. Interim analysis

Onset of efficacy following first dose of mRNA vaccines suggests threshold, if neuts are primary driver, may be near assay LLOQ

Efficacy data compiled for FDA review of both Pfizer / BioNTech and Moderna vaccines suggest both products effectively protect subjects between first and second doses, when neutralization titers are still very modest

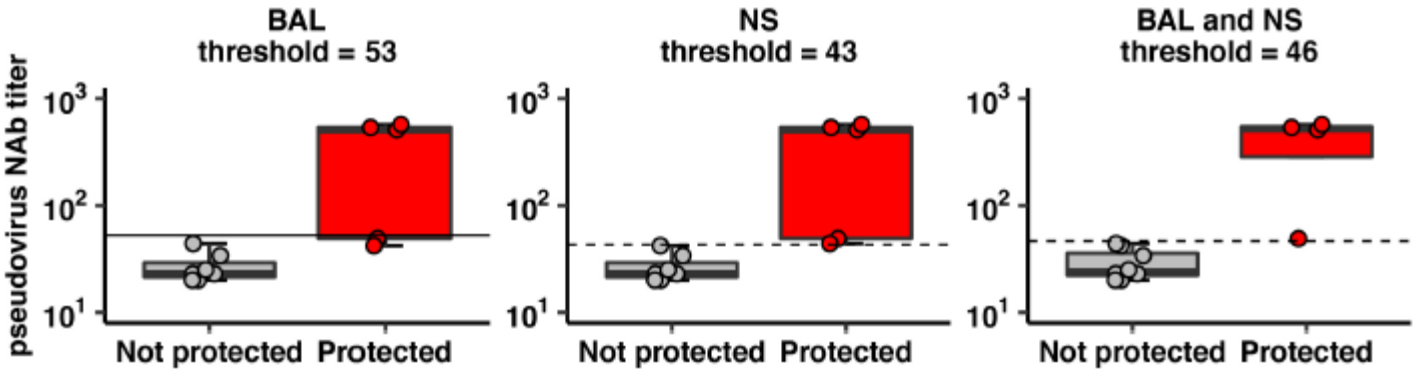




Sources: VRBPAC Meeting Briefing Documents for December 10th and December 17th (Accessed 15 December 2020); Sahin et al. 2020. BNT162b2 induces SARS-CoV-2-neutralizing antibodies and T cells in humans. medRxiv doi: https://doi.org/10.1101/2020.12.09.20245175; Jackson et al. 2020. An mRNA Vaccine against SARS-CoV-2 – Preliminary Report. *NEJM*.

NHP and natural infection studies support evidence that threshold of protection is low for neutralizing titers

Recent non-human primate data



Pseudovirus neutralizing titers of ~50 (adoptively transferred purified IgG) are sufficient to protect naïve macaques from SARS-CoV-2 challenge

Early natural infection study

Modest NAb: **Protected**

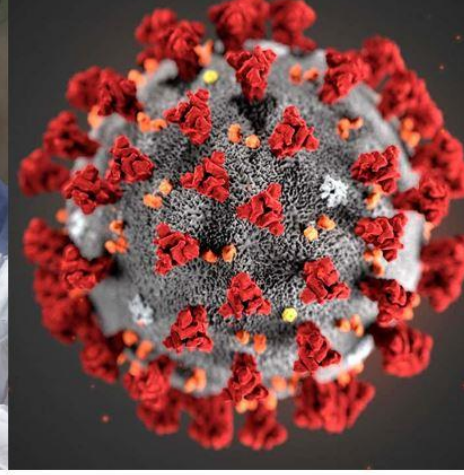
Undetectable NAb: **Susceptible**

RT-PCR result	Neutralization IC_{50}[b]	Neutralization IC_{90}	AUC RBD IgG	AUC Spike IgG	C_T Day 18–21 PCR
Negative	1:174	1:44	15.62	17.15	Negative
Negative	1:161	1:48	10.98	14.27	Negative
Negative	1:3,082	1:458	10.56	14.48	Negative
Negative	Negative	Negative	1.46	4.13	22.91
Negative	Negative	Negative	0.47	2.27	22.84
Negative	Negative	Negative	0.37	2.72	17.57

IC_{50} values ~1:161 by lentivirus PsVNA protected against a SARS-CoV-2 outbreak with an 85.2% attack rate aboard *American Dynasty* fishing vessel

Sources: McMahan, K. et al. Correlates of protection against SARS-CoV-2 in rhesus macaques. *Nature* doi: https://doi.org/10.1038/s41586-020-03041-6 (2020).; Addetia, A. et al. Neutralizing Antibodies Correlate with Protection from SARS-CoV-2 in Humans during a Fishery Vessel Outbreak with a High Attack Rate. *JCM* (2020).



WHO standards for COVID-19: update from WHO ECBS

World Health Organization

Dr Ivana Knezevic, Norms and Standards for Biologicals (WHO/MHP/HPS) and Dr Giada Mattiuzzo, Senior Scientist, NIBSC

17 Dec 2020, workshop on Pre-/Post-Licensure Assessments of COVID-19 Vaccine Efficacy Against Infection and Transmission




Outline of presentation

World Health Organization

- Update on WHO standards for Vaccines and other biologicals
  - Outcomes of 71st, 72nd and 73rd ECBS meetings
  - Written standards
  - Measurement standards
  - Research and Review of Scientific evidence
  - COVID-19 related activities
  - Points for discussion

WHO norms and standards for biologicals

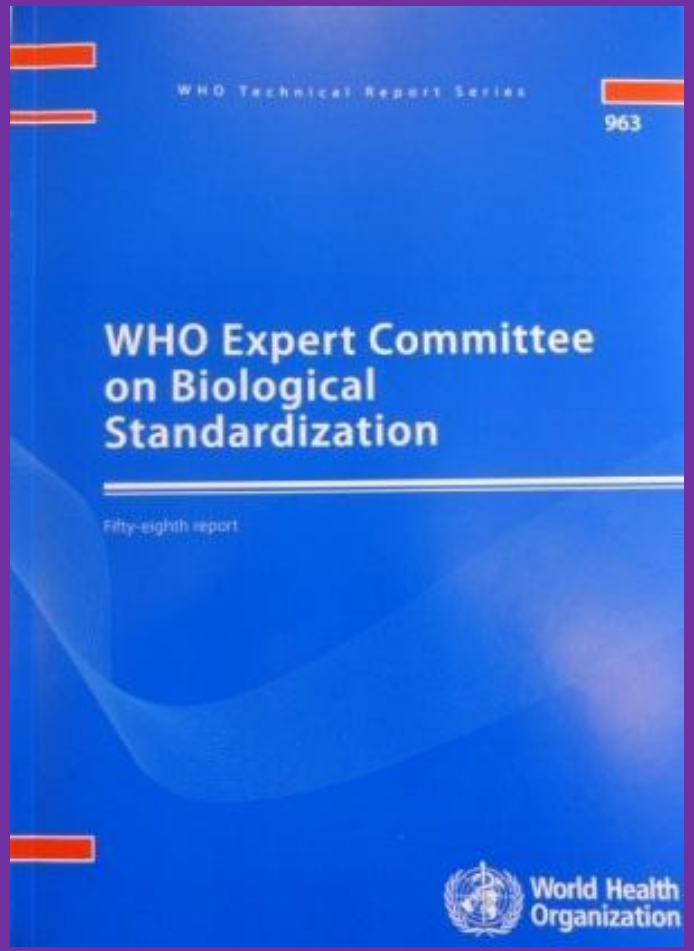
https://www.who.int/groups/expert-committee-on-biological-standardization

Global written standards

Total 103 docs (Recommendations/ Guidelines)
General docs that apply to vaccines & biologicals: 10
General documents that apply to all vaccines: 12
Vaccine specific: 71
BTP specific: 9

Scientific evidence

1) Standardization of assays
2) Further development and refinement of QC tests
3) Scientific basis for setting specifications



Global measurement standards

Measurement standards:
essential elements for development, licensing and lot release

WHO CCs for biological standardization

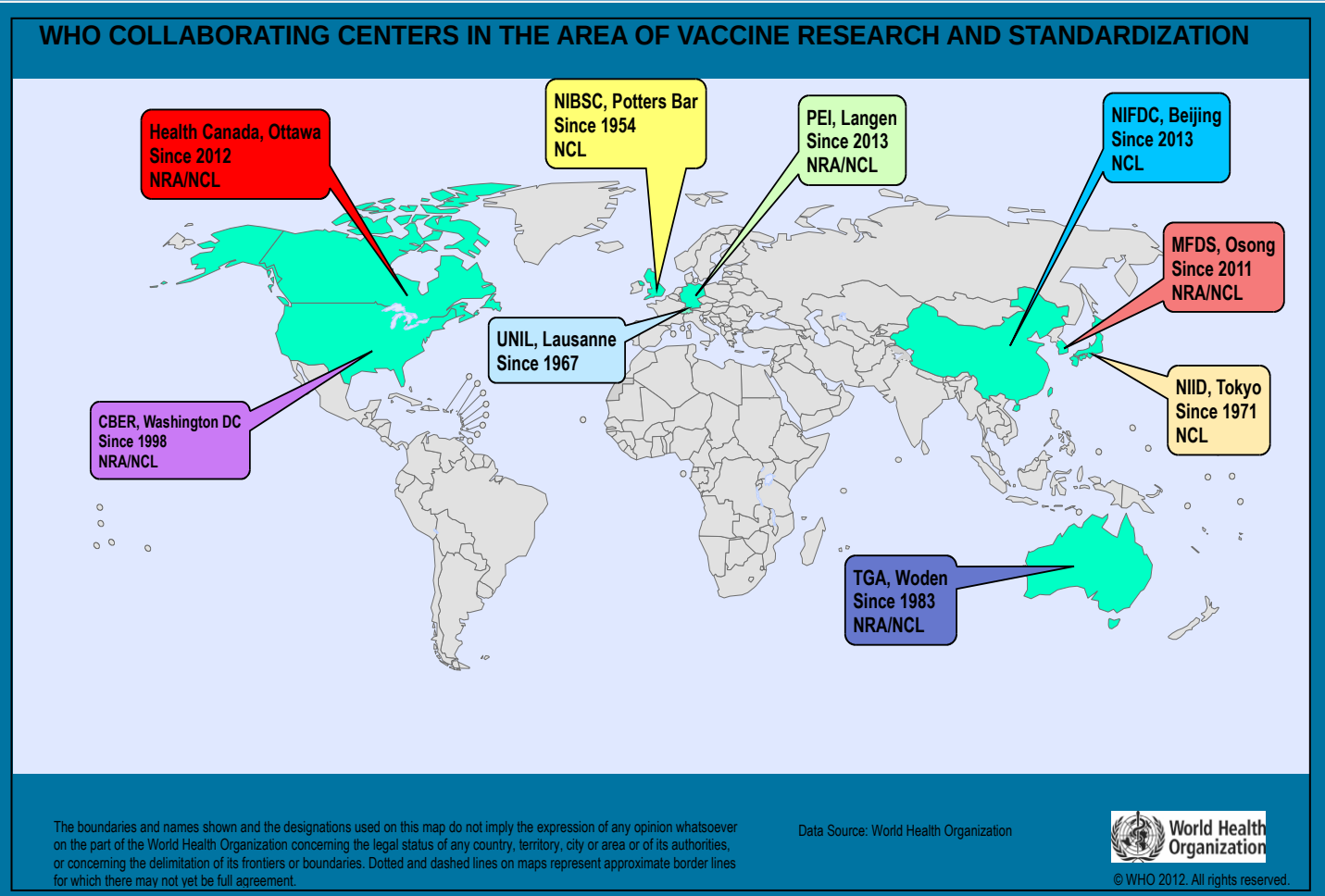
- **Input to COVID-19 related issues in addition to ongoing projects:**
  - Measurement standards (NIBSC) with the input from CCs and other labs
  - Written standards
  - Implementation workshops - postponed

- **Re-designations:**

1. HC – completed in Nov 2020
2. NIFDC, NIBSC and PEI - to be completed in 2021

- WHO CC network for standardization of vaccines – HC offered to host meeting in Sep 2020

- Virtual meetings of CCs – planned for 2021



Ivana Knezevic

Main outcomes of 71st and 72nd ECBS meetings in 2020

World Health Organization

1. ECBS meeting on 24-28 Aug 2020 (focused on COVID-19): published on WHO web site: https://www.who.int/groups/expert-committee-on-biological-standardization:

- Executive Summary posted on WHO web site on 2 Sep 2020

- Guidelines for assuring the quality, safety and efficacy of plasmid DNA vaccines

(direct link: https://www.who.int/publications/m/item/DNA-post-ECBS-1-sept-2020)

2. ECBS meeting on 19-23 Oct 2020 – update on COVID-19 and non-COVID activities:

- 3 written standards established (Recommendations on TCV and EV71 and Guidelines on CRP for Dg)

- 8 new WHO and 3 replacement WHO International reference preparations

- 13 proposals for new or replacement measurement standards

- Review of COVID-19 related activities

- Executive Summary posted on WHO web site on 5 Nov 2020

Main outcomes of 73rd ECBS meeting in 2020

World Health Organization

1. ECBS meeting on 9-10 Dec 2020 (focused on COVID-19): published on WHO web site: https://www.who.int/groups/expert-committee-on-biological-standardization:

- Executive Summary posted on WHO web site on 16 Dec 2020:

https://www.who.int/groups/expert-committee-on-biological-standardization

3 new WHO International reference preparations established

Standards for use in public health emergencies		
SARS-CoV-2 RNA for NAT-based assays	7.40 $\log_{10}$ IU/ampoule	First WHO International Standard
Anti-SARS-CoV-2 immunoglobulin	250 IU/ampoule (neutralizing antibody activity)	First WHO International Standard
Anti-SARS-CoV-2 immunoglobulin panel	[no assigned units]	First WHO International Reference Panel

- Proposal for to develop a standard for SARS-CoV-2 antigens to support the development, assessment and comparability of antigen-based rapid diagnostic tests.

- Update on written standards provided

Measurement standards for COVID-19

World Health Organization

Aim: to facilitate the development, validation and assessment of molecular and antibody assays. This will facilitate the comparability of results from different assays/labs and help harmonize the evaluation of diagnostics, vaccines and other products.

Milestone	Date
Development of measurement standards start	Feb-March 2020
Sourcing of the candidate material	March-May 2020
Agreement to proceed with Measurement standards	April 2020
Formulation of the candidate Standard	June 2020
Collaborative study	July-Oct 2020
Progress report to ECBS meeting	Aug 2020
Data analysis and report published for PC	Oct-Nov 2020
Establishment by ECBS	December 2020

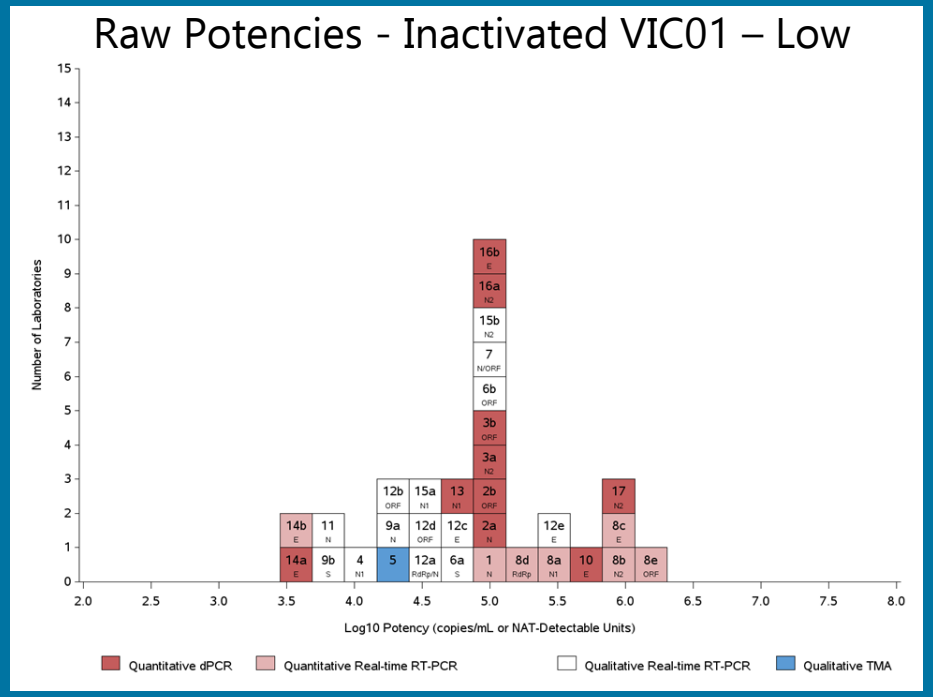
First WHO International Standard for SARS-CoV-2 RNA (20/146)

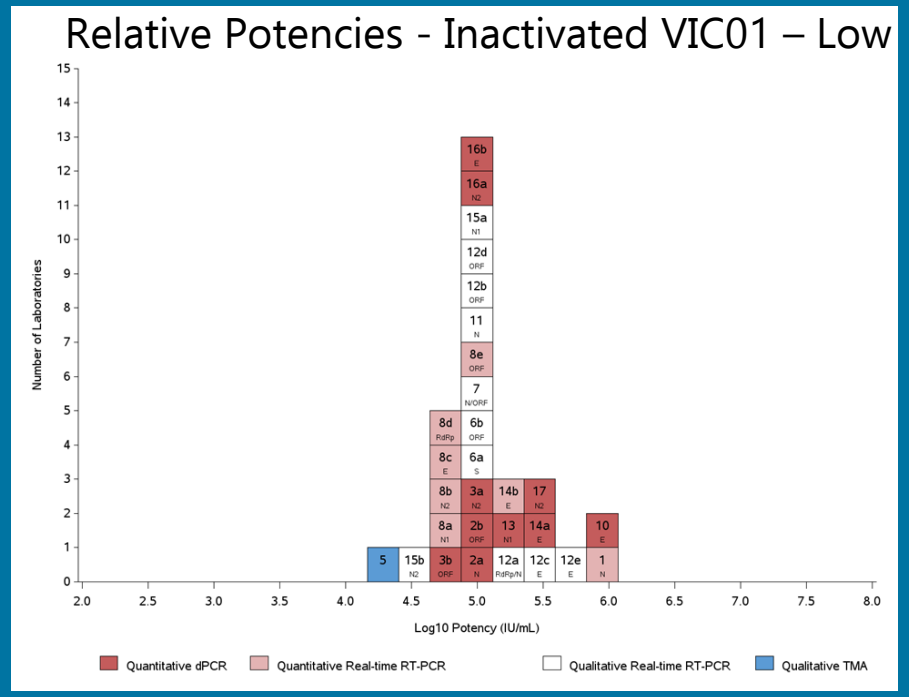
World Health Organization

Intended use: calibration and harmonisation of NAT assay for the detection of SARS-CoV-2 RNA

- Acid/heat inactivated England isolate with an assigned potency of 7.4 Log_{10} IU/ampoule

  Approximately 2500 ampoules available for distribution





NIBSC Confidence in Biological Medicines

First WHO International Standard for anti-SARS-CoV-2 immunoglobulin (20/136)

World Health Organization

Pool of COVID-19 convalescent plasma from 11 donors from UK

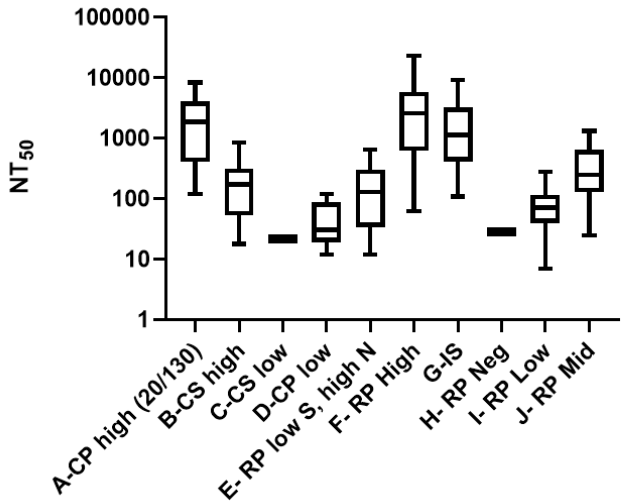
0.25 mL plasma per ampoule, freeze-dried

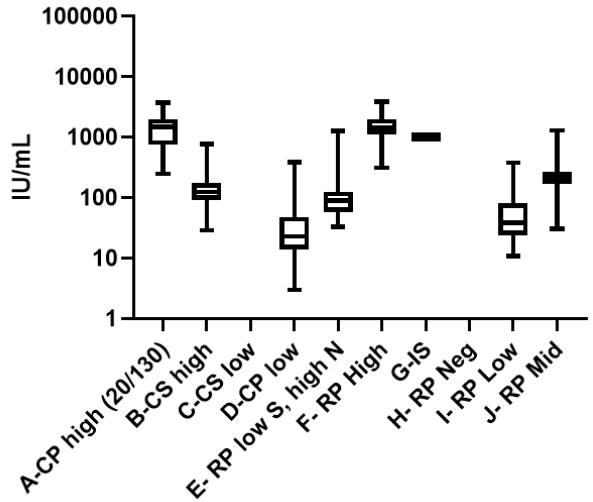
Candidate IS was scored as one of the top three highest titre samples in every assay

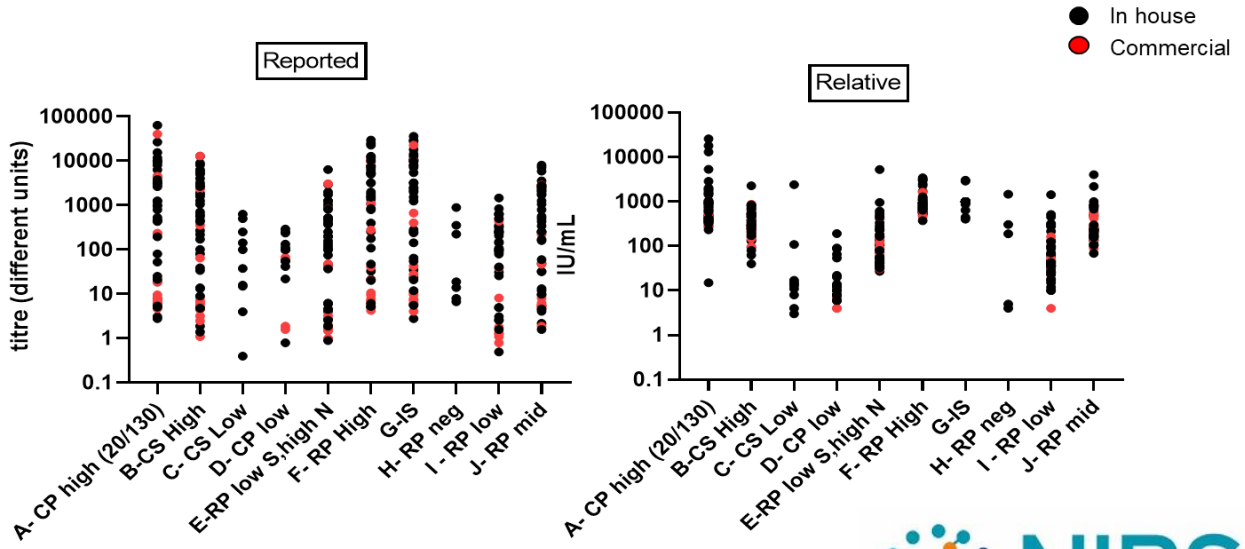
Expression of the titre as relative to the candidate IS reduced inter-laboratory variation in both neutralisation assay and IgG-based ELISA

Assigned potency of 250 IU/ampoule for neutralising antibody activity

But can be used as reference reagent for calibration of assays detecting binding antibody







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NIBSC
Confidence in Biological Medicines

First WHO International Reference Panel for anti-SARS-CoV-2 immunoglobulin (20/268)

World Health Organization

Reference Panel will comprise 4 pools of COVID-19 convalescent plasma and a negative; freeze-dried equivalent of 0.25 mL

High (NIBSC code 20/150)

Mid (NIBSC code 20/148)

Low S, high N (NIBSC code 20/144)

Low (NIBSC code 20/140)

Negative (NIBSC code 20/142)

The candidate Reference Panel samples were ranked similarly in almost all the assays used with very few exceptions

No unitage will be assigned for the Reference Panel, but representative data from CS include in IFU

	High	Mid	low S, high N	low	
	20/150	20/148	20/144	20/140	
Neut Ab	1473	210	95	44	**IU/mL**
anti-RBD IgG	817	205	66	45	**BU/mL**
anti-S1 IgG	766	246	50	46	**BU/mL**
anti-Spike IgG	832	241	86	53	**BU/mL**
anti-N IgG	713	295	146	12	**BU/mL**

CEPI

NIBSC Confidence in Biological Medicines

Distribution of the WHO International Standards for:

SARS-CoV-2 RNA for NAT assay cat no. 20/146

Anti-SARS-CoV-2 immunoglobulin (human) cat no. 20/136

Anti-SARS-CoV-2 immunoglobulin panel cat no. 20/268

Will be available for distribution by beginning of January 2021 at www.nibsc.org

Create an account to avoid delays with the order. Any issues contact Standards@nibsc.org

COVID-19 related activities – brief overview

World Health Organization

1. **Written standards**

- ***WHO, 8 April 2020:*** Application of existing guiding principles to COVID-19 vaccines was made available on WHO biologicals webpage on COVID-19 vaccine standardization: *https://www.who.int/news-room/feature-stories/detail/standardization-of-vaccines-for-coronavirus-disease-covid-19*

- *Guidelines on DNA vaccines (available since Sep 2020)*

- *Regulatory considerations on RNA vaccines and to mAbs for infectious diseases (eg, COVID-19, RSV) - ongoing*

2. **Measurement standards**: International Standards under development by WHO Collaborating Center NIBSC

3. **Research and Review of Scientific evidence**

  - Working Group has been established to investigate potential factors in the observed in vitro genetic instability of SARS-CoV-2 viruses during propagation in different mammalian cell lines. Although this issue is not currently regarded as part of biological standardization activities, it may impact on future WHO guidance on the production and evaluation of COVID-19 vaccines and other biological products.
  - WG on standards and assays as well as on animal models
  - Review of COVID-19 vaccines under development with the aim to identify need for standards and technical assistance

Cross cutting issues in the context of ACT-A

World Health Organization

1. **Vaccine pillar (COVAX):**

- International Standards and input to various WGs set up by WHO and partners
- Input to WHO PQ EUL assessment: WHO standards referred in the criteria for EUL, input to PQ meetings with vaccine manufacturers
- Collaboration between WHO Expert Committee and EAG: ECBS, SAGE and GACVS

2. Dx Pillar:

- Antigen standard, antibody standard and reference panel

3. Tx pillar:

- mAbs under development and application of guiding principles for biotherapeutics to mAbs for COVID-19
- Safe blood supply:
  - WHO interim guidance on maintaining a safe and adequate blood supply during the pandemic, and on the safe collection of CCP – subject of review and update
  - It is essential that virus neutralizing antibody levels are standardized to facilitate consistent treatment. ECBS expressed strong view that that CCP should be calibrated in IU as soon as the antibody standard became available.

Points for discussion

Points for discussion:

1. What kind of standards are most needed for COVID-19 vaccine development?

2. Measurement standards - users to be aware of the need to use IS to calibrate secondary standards for COVID-19: webinars in Q1 and Q2 2021 and Manual for calibration of secondary standards

3. Other issues

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Oslo University Hospital

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Many thanks to:

…team (NSB/TSS/HPS/MHP/WHO)

…members of WHO drafting and Working Groups

…colleagues from Collaborating Centers and Custodian Laboratories

…many individual experts

Further information and contact

Biological standardization website: www.who.int/biologicals

Dr Ivana Knezevic (email: knezevici@who.int)

on behalf of NSB/TSS team

Thank you

World Health Organization

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Switzerland

Dr Ivana Knezevic, WHO

Part 2:

What can we learn from pre-licensure trials?

Moderator By:

Jakob Cramer, MD

Head of Clinical Development

Coalition for Epidemic Preparedness Innovations (CEPI)

SARS-CoV-2 natural course of infection, viral shedding, virus detection and quantification using PCR and rapid diagnostic tests: Current knowledge and gaps

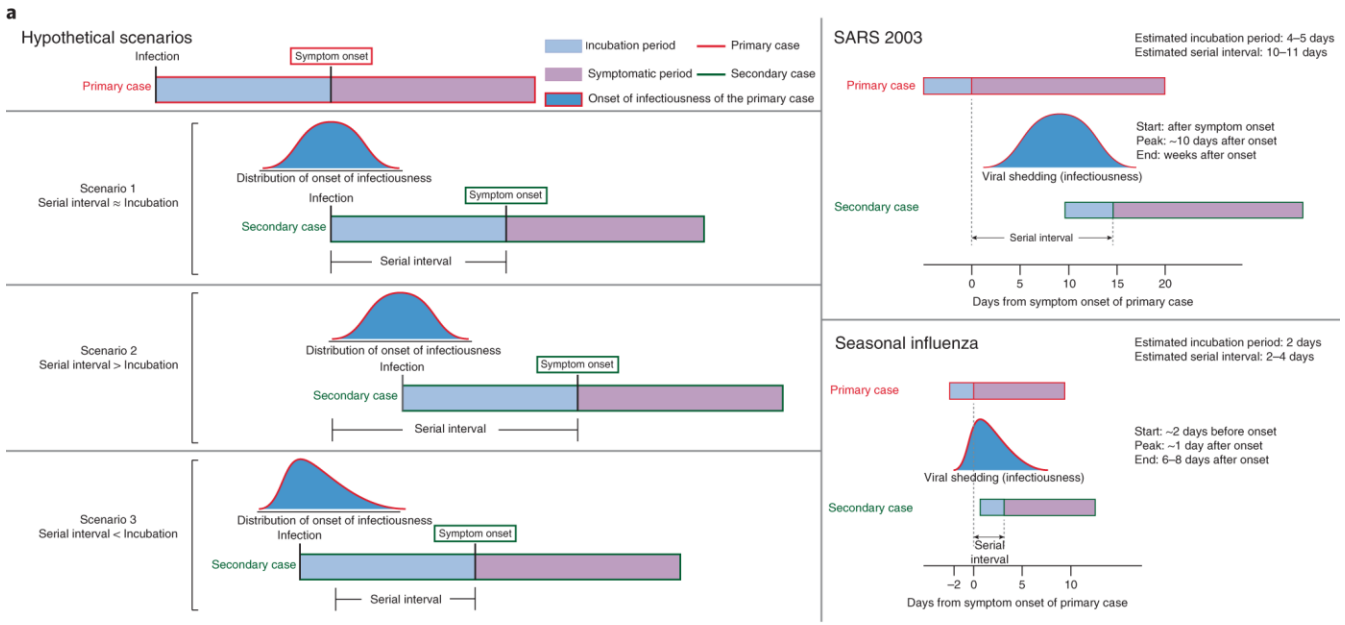
Christian Drosten, MD, PhD
Professor of Virology
Charité, Berlin

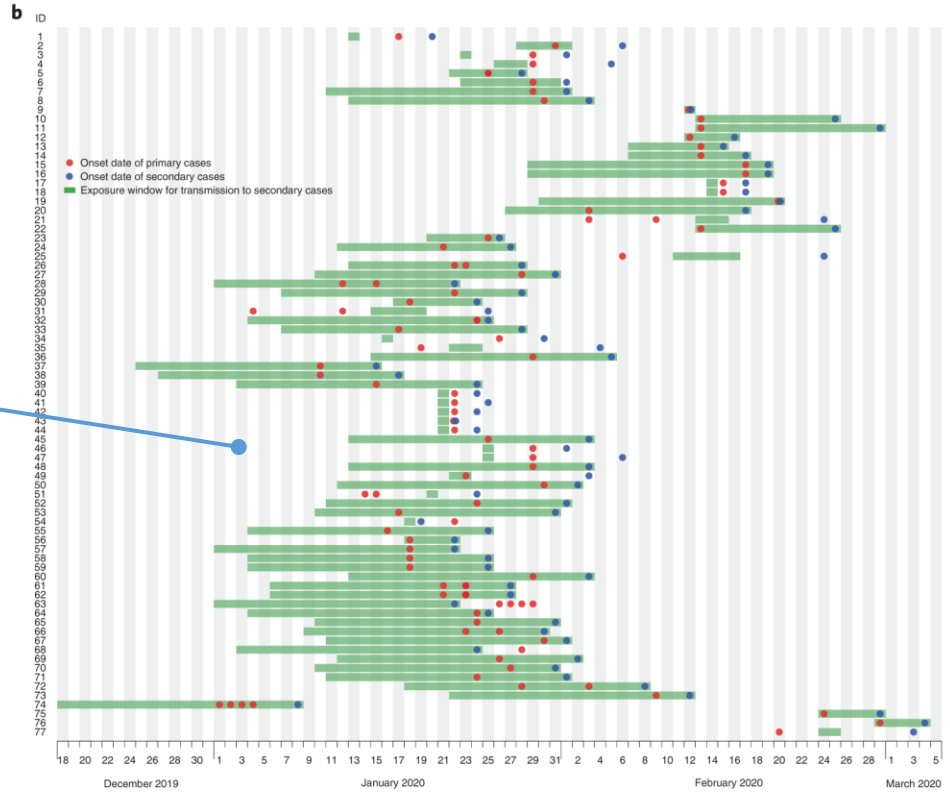
Viral shedding

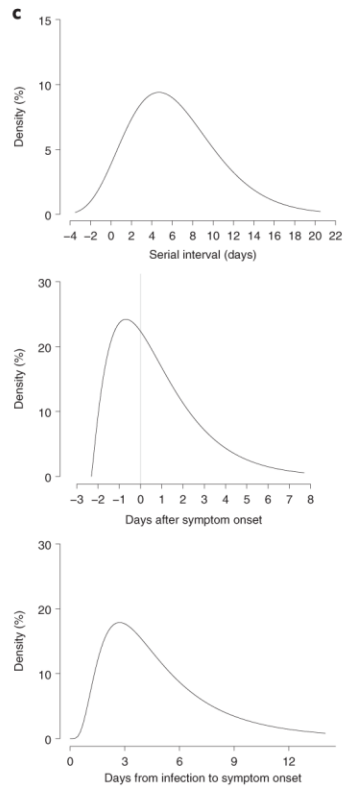
BRIEF COMMUNICATION
https://doi.org/10.1038/s41591-020-0869-5
nature medicine
Check for updates

Temporal dynamics in viral shedding and transmissibility of COVID-19

Xi He[1,3], Eric H. Y. Lau[2,3]✉, Peng Wu[2], Xilong Deng[1], Jian Wang[1], Xinxin Hao[2], Yiu Chung Lau[2], Jessica Y. Wong[2], Yujuan Guan[1], Xinghua Tan[1], Xiaoneng Mo[1], Yanqing Chen[1], Baolin Liao[1], Weilie Chen[1], Fengyu Hu[1], Qing Zhang[1], Mingqiu Zhong[1], Yanrong Wu[1], Lingzhai Zhao[1], Fuchun Zhang[1], Benjamin J. Cowling[2,4], Fang Li[1,4] and Gabriel M. Leung[2,4]

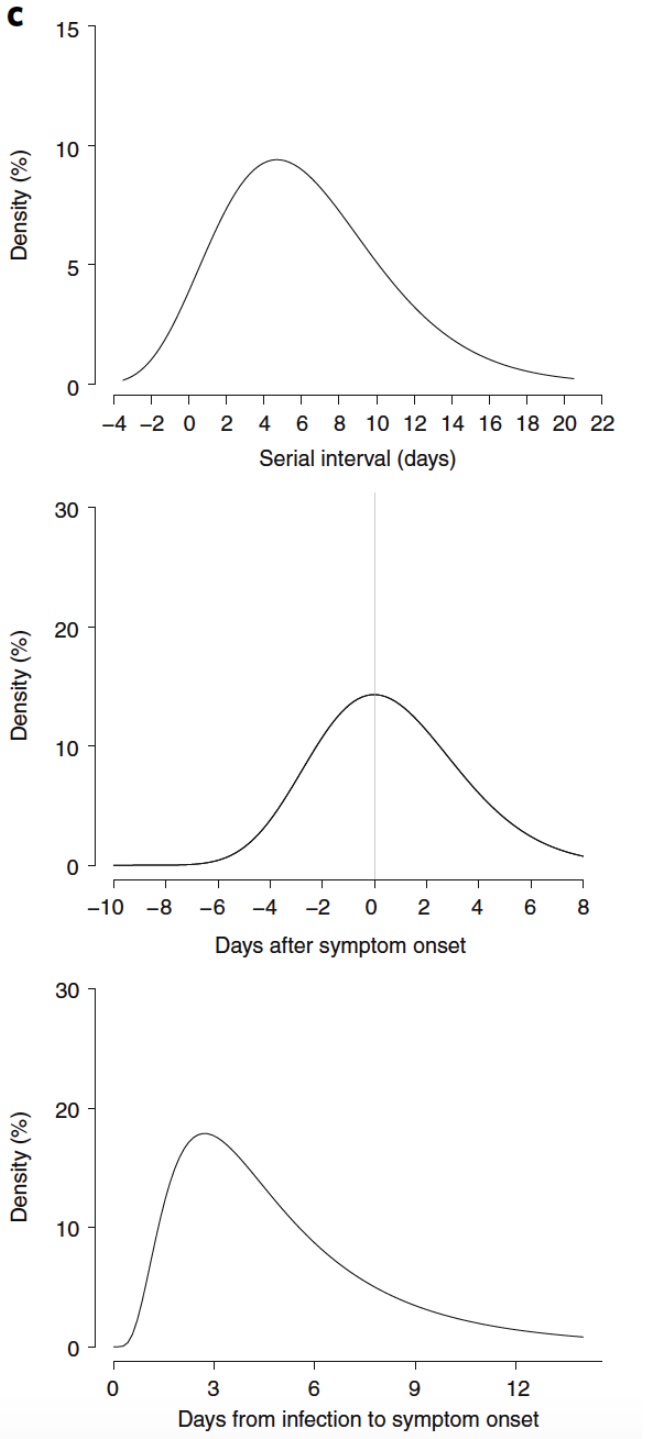






Transmission pairs

He, Nat Med 2020



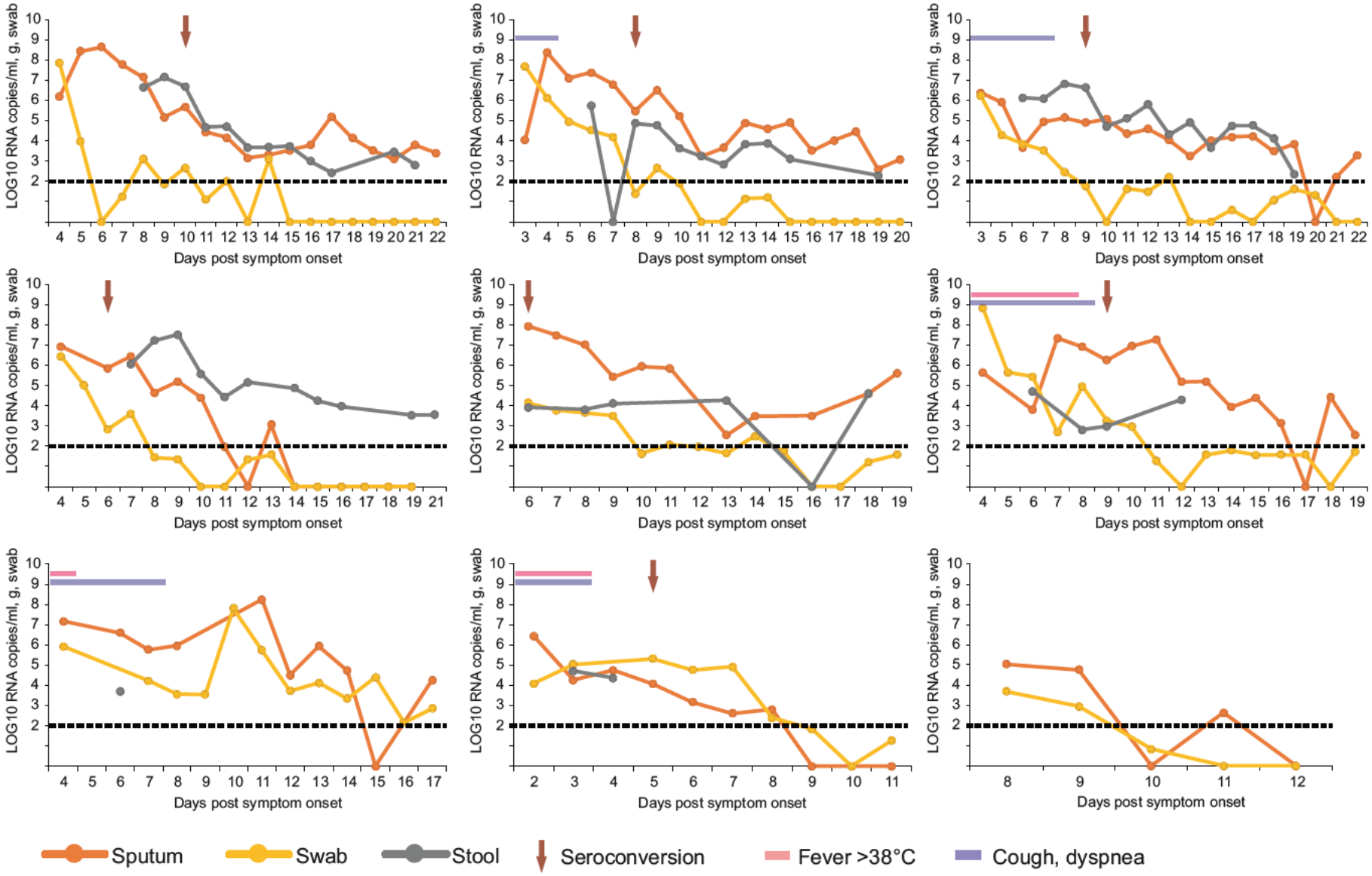
Serial interval

Time of transmission

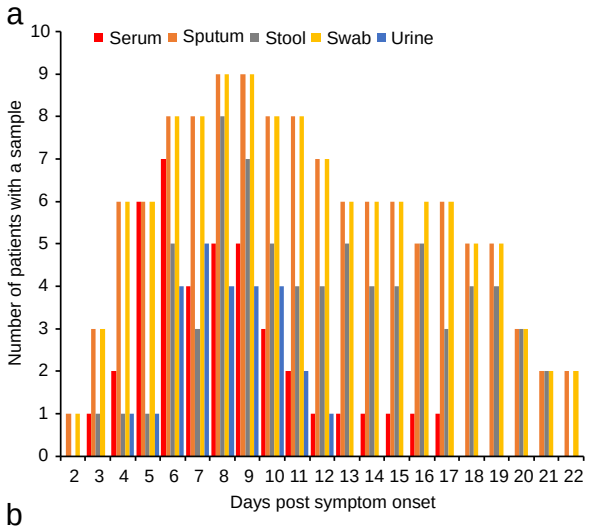
Incubation time

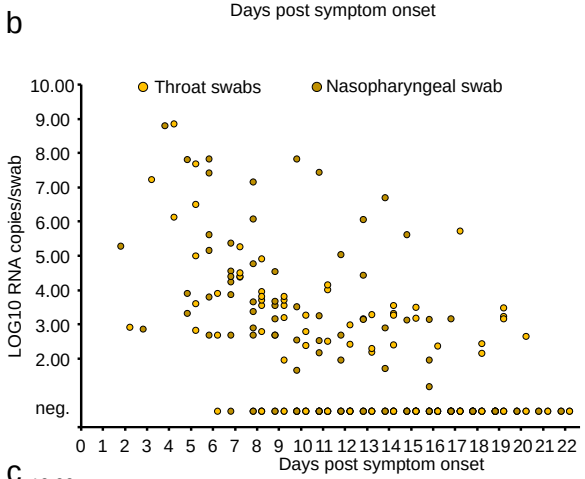
He, Nat Med 2020

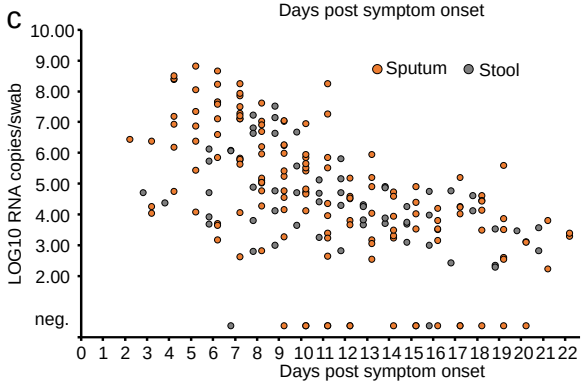
Viral shedding in Munich case cluster

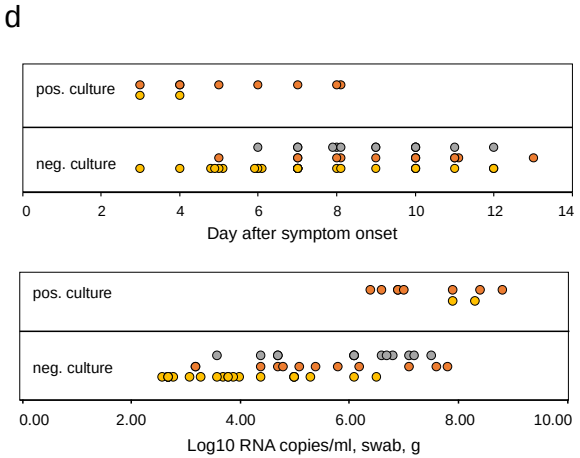


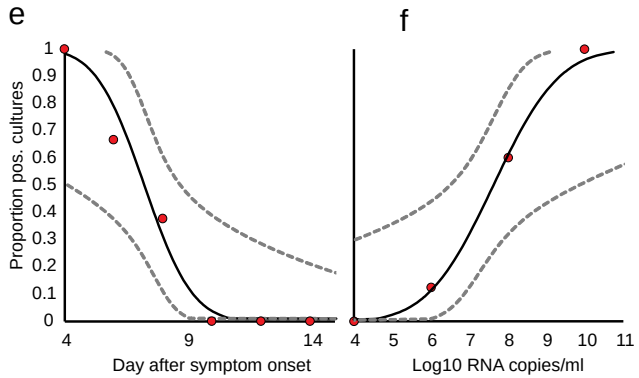
Wölfel, Nature 2020

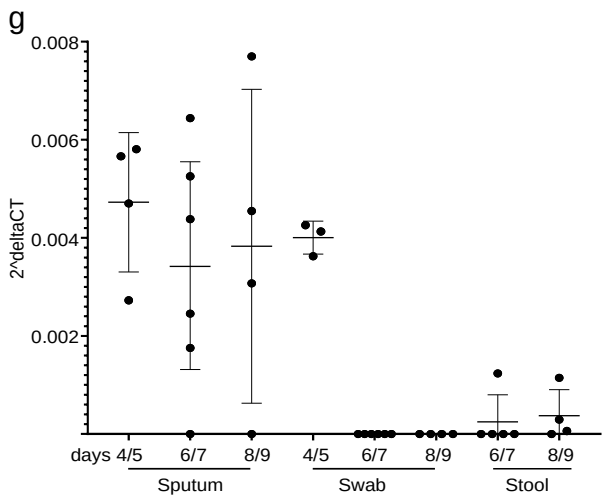


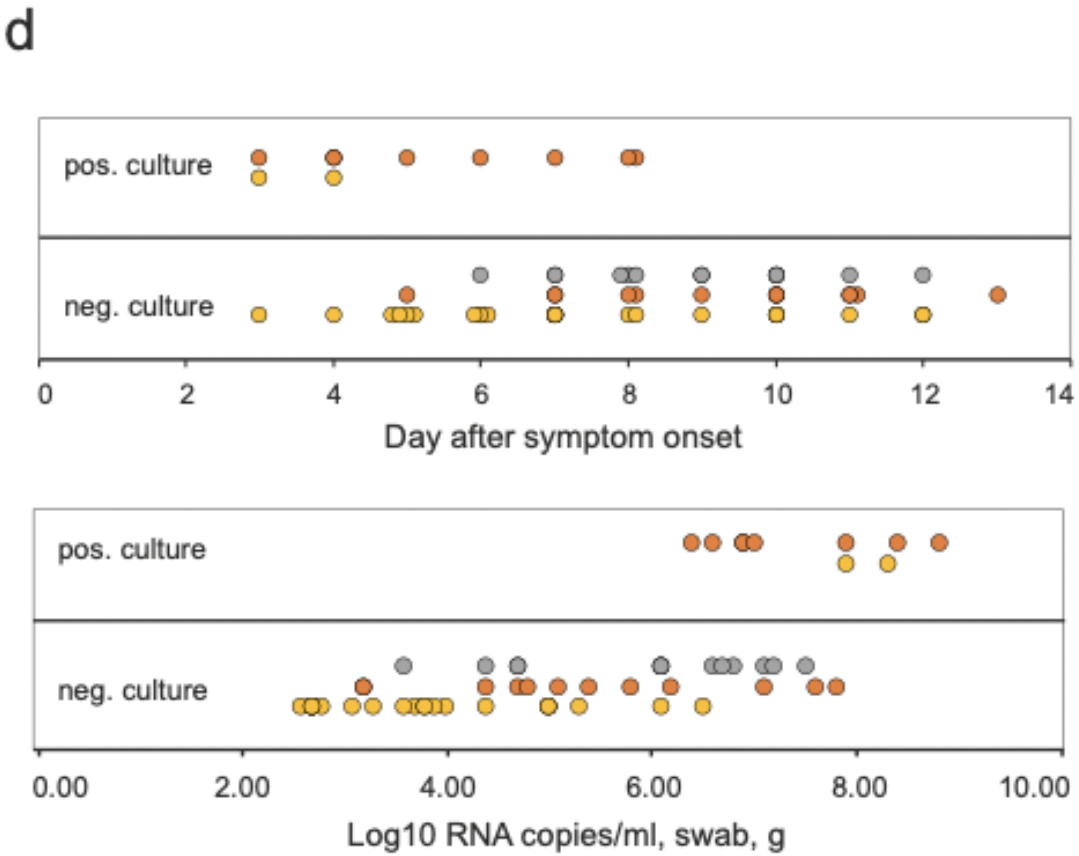






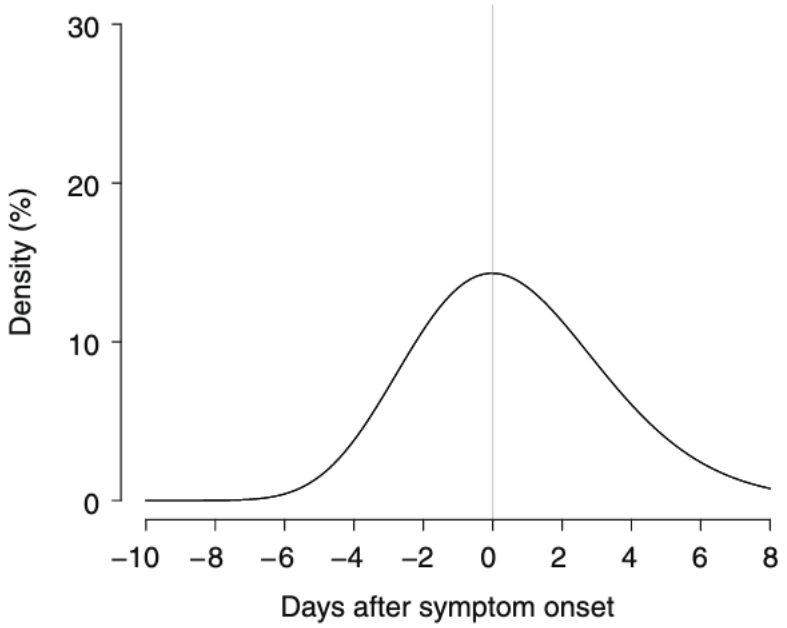






Wölfel, Nature 2020

Transmission vs. cell culture isolation success



Probability of transmission in 77 transmission pairs, mainly from Guangzhou, He et al, Nat Med 2020

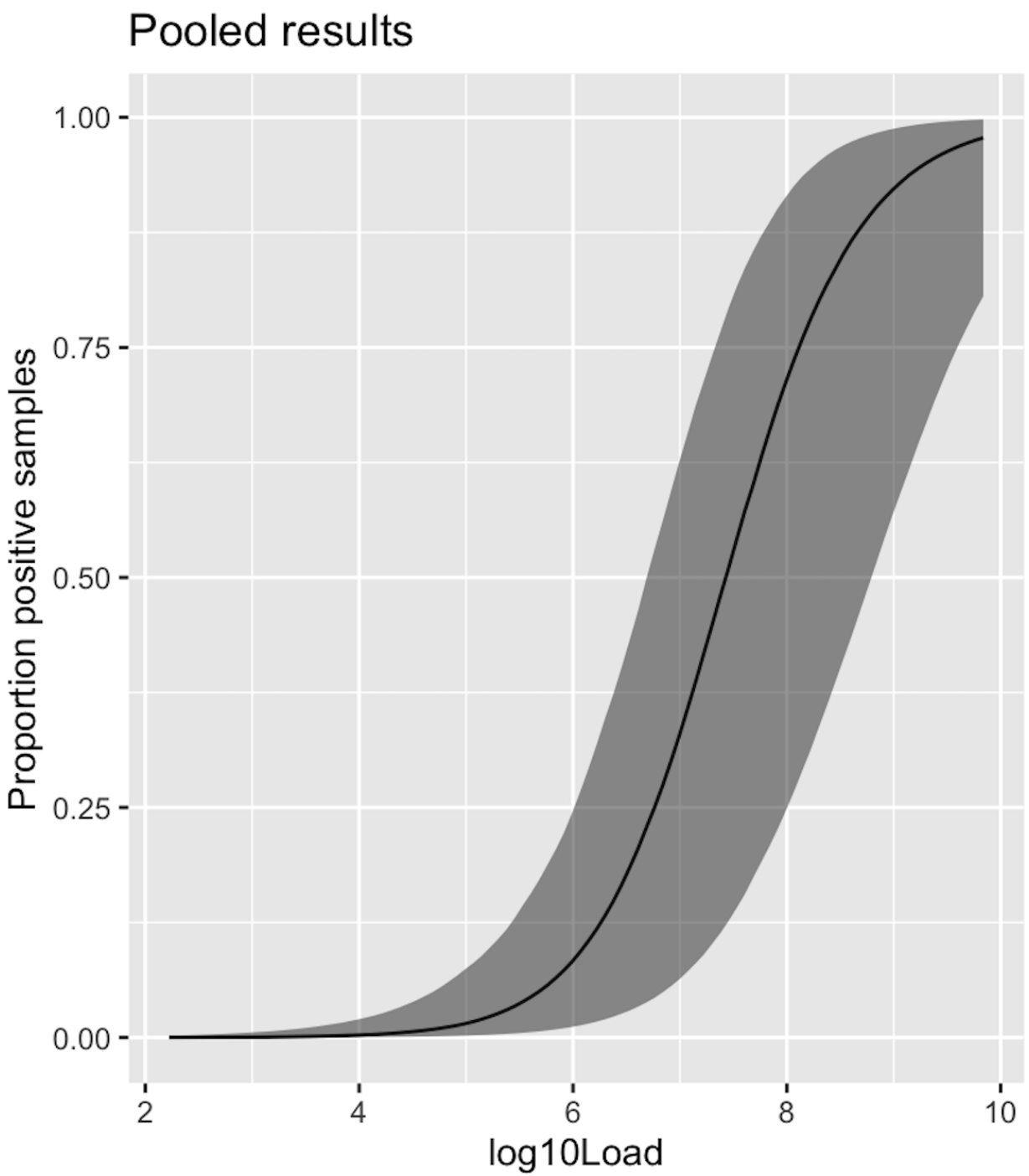
Wölfel et al. (9 patients, early Munich cohort)
Isolation rate goes below 20% (positive cultures / cultures) from ca. day 9 after symptoms onset.

Van Kampen et al. (129 patients, Erasmus MC, Rotterdam)
Isolation rate below 20% from ca. day 8.

Perera et al. (35 patients, Hong Kong)
Isolation rate below 3/11 positive cultures from ca. day 8.

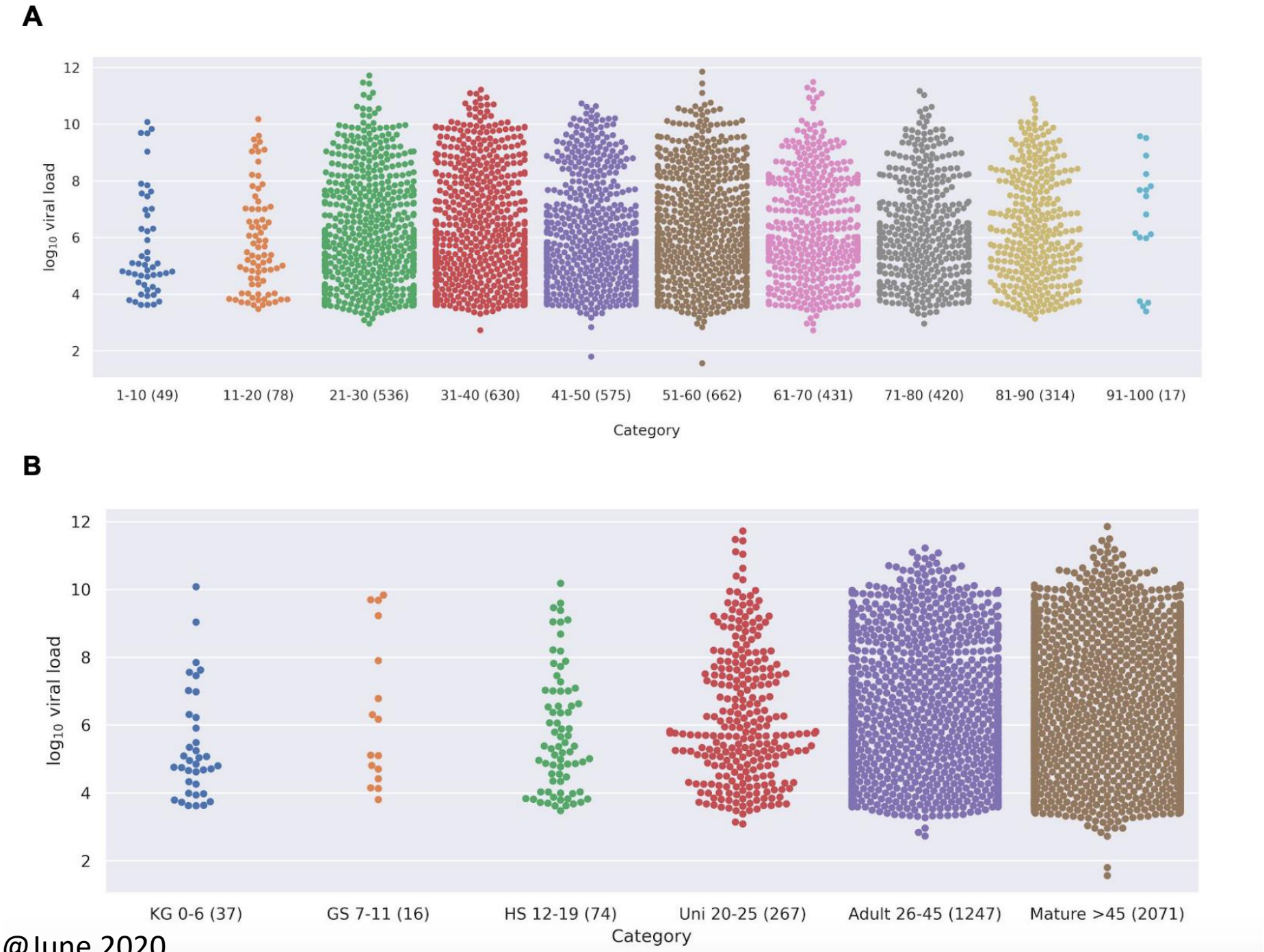
Singanayagam et al. (253 patients, UK)
Isolation rate below 20% from ca. day 8.

Arons et al. (NEJM, 57 Patienten, Seniorenheim, USA)
Isolation successful up to day 9.



Viral load vs cell culture

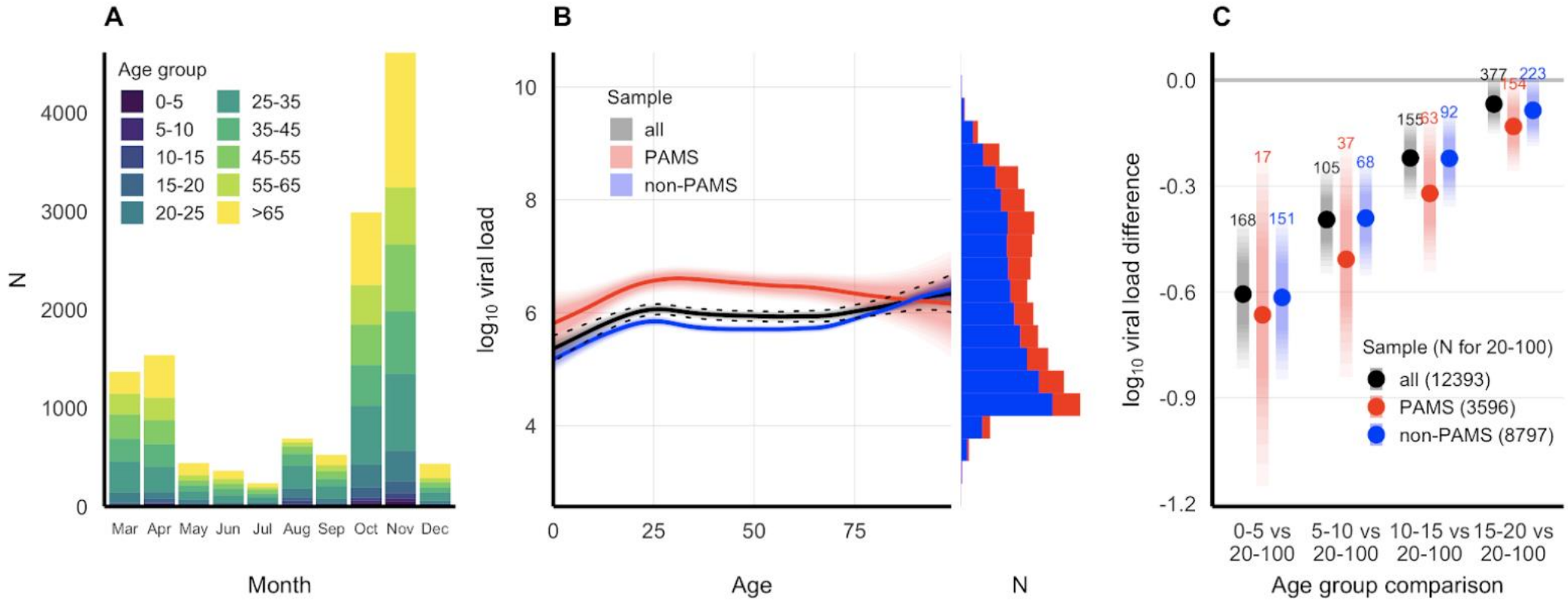
Based on
Perera, EID 2020,
van Kampen MedRxiv 2020,
Wölfel, Nature 2020



Jones, preprint @June 2020

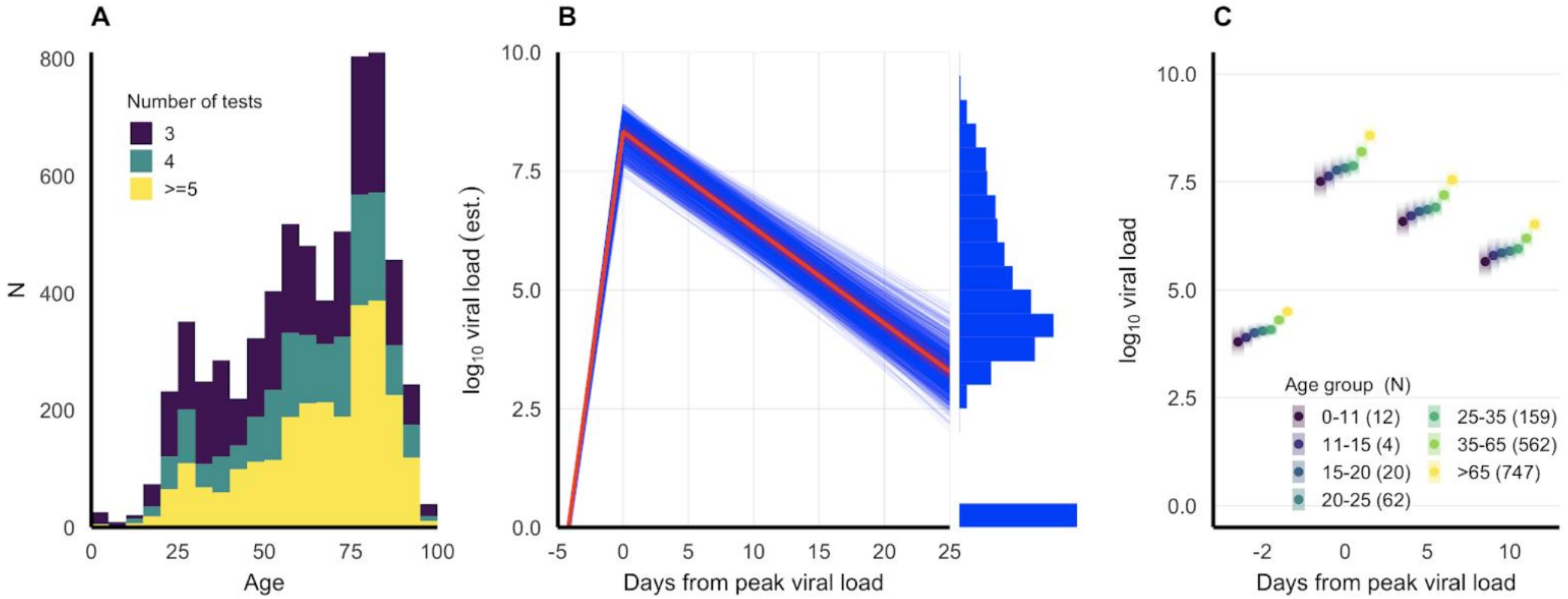
Viral load in first test
Ca. 15,425 positive subjects out of 341,316 tested

PAMS: Pre-, asymptomatic, mildly symptomatic



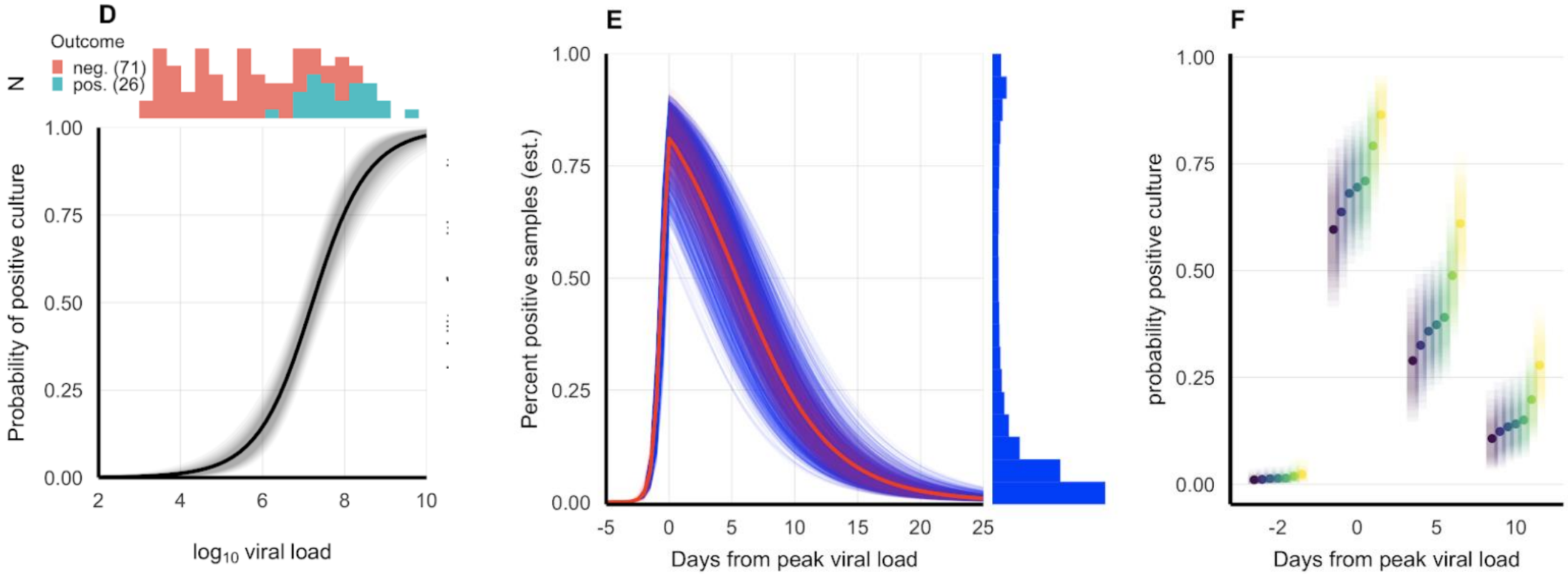
Jones et al., unpublished

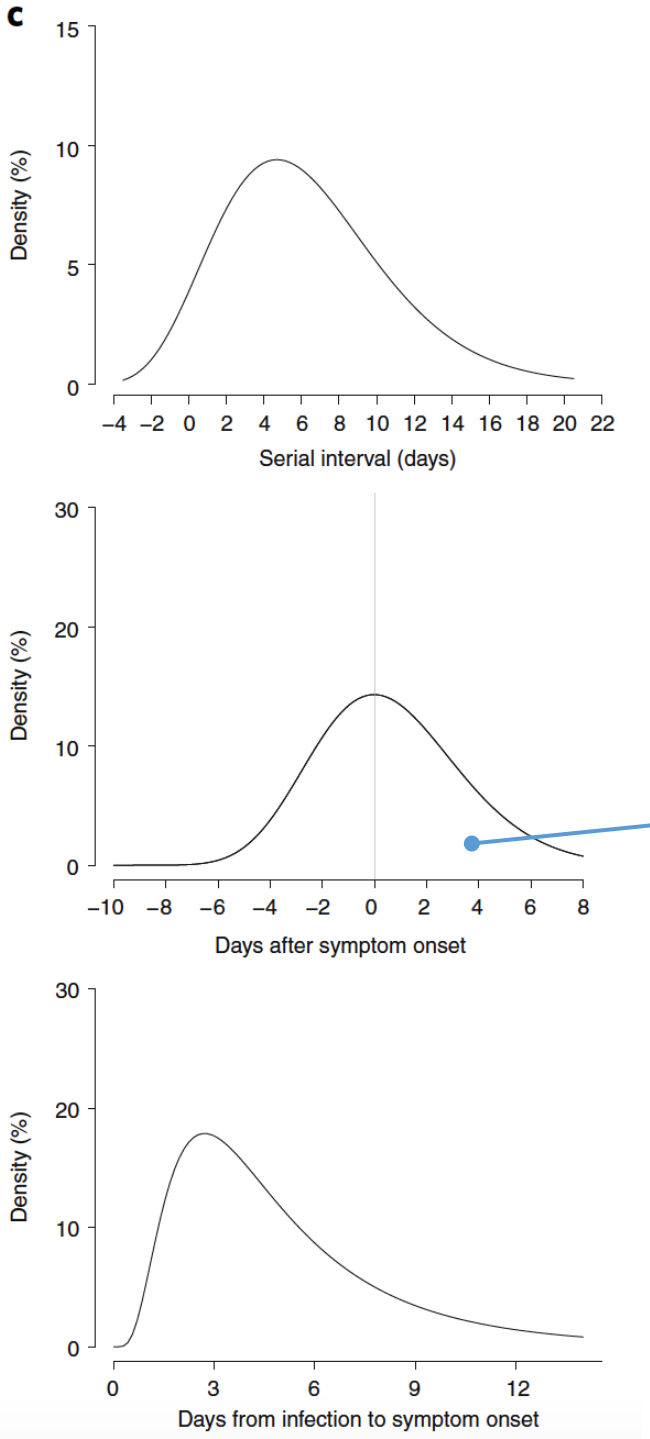
Sychronized viral load courses in multi-tested patients (n = ca. 1900)



Jones et al., unpublished

Probability of successful virus isolation as a lab surrogate of infectivity





Serial interval

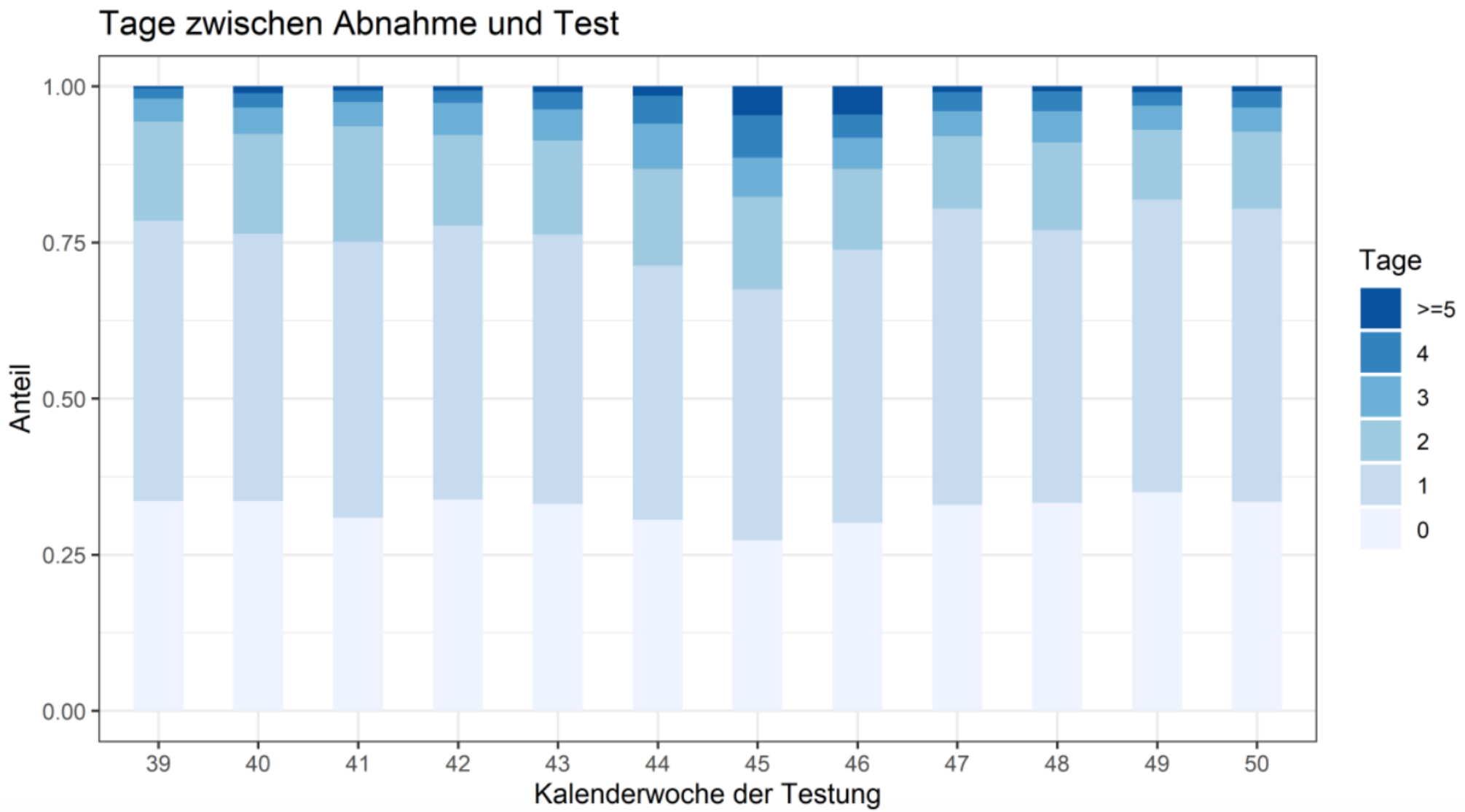
Time of transmission

Empirical time of diagnosis (lab results back)

Incubation time

He, Nat Med 2020

laborbasierte Surveillance SARS-CoV-2, KW39-KW50, Datenstand 15.12.2020



Antigen point of care tests: limits of detection

		Limit of detection[b] Log_{10} SARS-CoV-2 RNA copies per swab		Adjusted limit of detection[d]
Assay[a]	N. of tested samples	50% positive AgPOCT results	95% positive AgPOCT results	95% mean hit rate X 0.125
I	105	5.61 (5.27 - 5.95)	7.45 (6.79 - 8.20)	6.55 copies/swab
II[c]	45	9.51 (8.84 - 12.26)	11.10 (9.71 - 17.01)	10.20 copies/swab
III[c]	105	4.48 (3.41 - 5.32)	7.27 (6.27 - 8.40)	6.37 copies/swab
IV	105	7.60 (7.37 - 7.82)	8.36 (8.00 - 8.76)	7.46 copies/swab
V	105	5.40 (4.99 - 5.77)	7.22 (6.57 - 7.96)	6.32 copies/swab
VI	105	7.19 (6.97 - 7.43)	7.87 (7.52 - 8.23)	6.97 copies/swab
VII	115	5.64 (5.28 - 6.00)	7.68 (6.96 - 8.50)	6.78 copies/swab

[a]I: Abbott Panbio™ COVID-19 Ag Rapid Test; II. RapiGEN BIOCREDIT COVID-19 Ag; III: Healgen® Coronavirus Ag Rapid Test Cassette (Swab); IV Coris Bioconcept Covid.19 Ag Respi-Strip; V: R-Biopharm RIDA®QUICK SARS-CoV-2 Antigen; VI NAL von minden; NADAL COVID19-Ag Test; VII: Roche/SD Biosensor SARS-CoV Rapid Antigen Test

Corman, MedRxiv, 2020

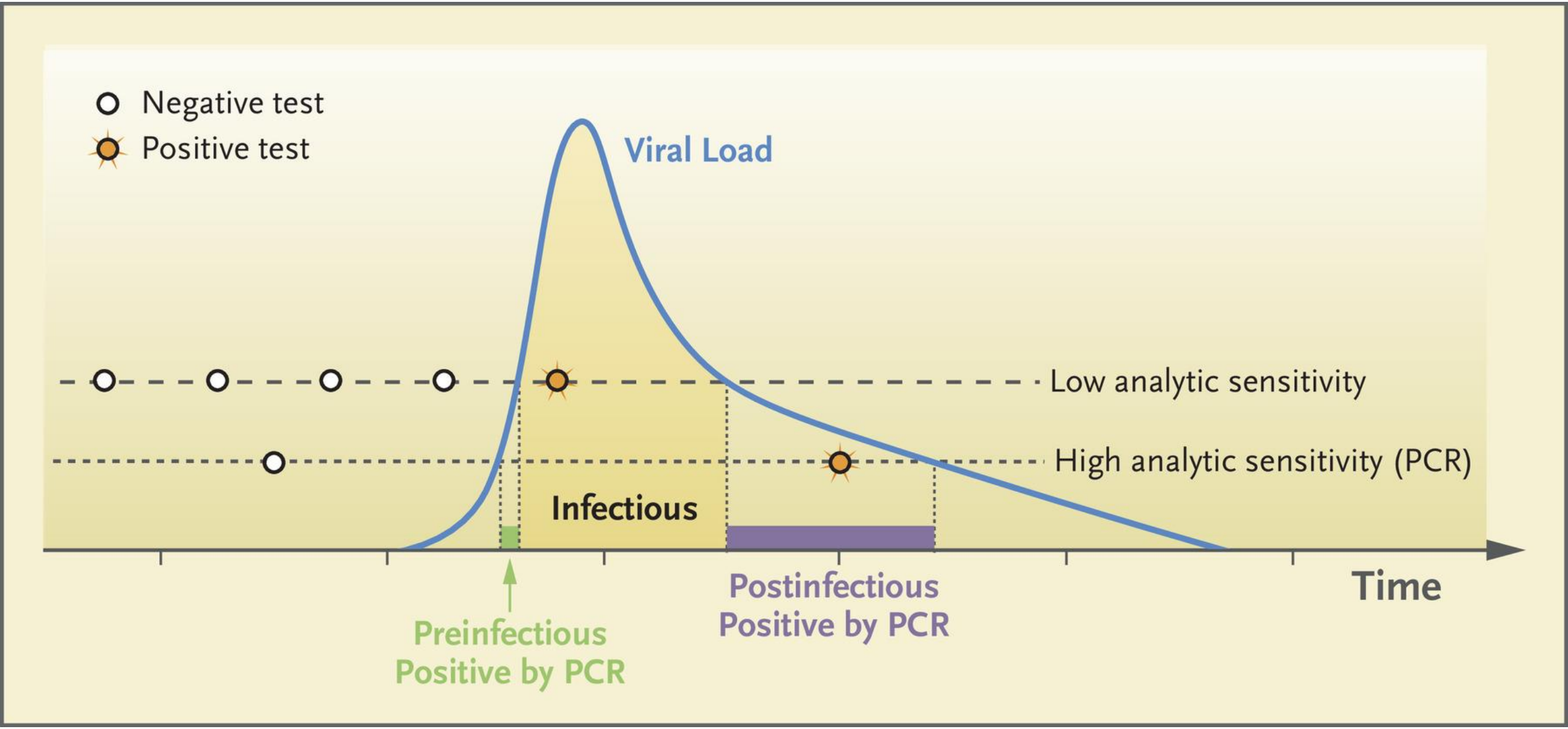
How sensitive are antigen point of care tests towards the end of the first week of symptoms?

A glance at preprints.

Christian Drosten and Victor Corman, Charité – Universitätsmedizin Berlin, Institute of Virology

over the first week of symptoms. The overall impression is that sensitivity toward the end of the first week is only slightly lower than during the first four or five days, with missing data and/or rapid decline of sensitivity during the second week. All studies suggest that sensitivity is mainly determined by viral load (i.e., we could not recognize signs of other influencing factors such as time independent of viral load, although we could not conduct formal analyses).

- https://virologie-ccm.charite.de/fileadmin/user_upload/microsites/m_cc05/virologie-ccm/dateien_upload/20201208-AgPOCT_Preprints.pdf



Mina, NEJM 2020

		AgPOCT assay[a]						
Pathogen	**N**	**I**	**II**	**III**	**IV**	**V**	**VI**	**VII**
Adenovirus	9	-	-	1[b]	-	-	-	-
Bocavirus	9	-	-	-	-	-	-	-
HCoV-NL63	1	-	-	-	-	-	-	-
HCoV-OC43	1	-	-	-	-	-	-	-
Entero/Rhinovirus	9	-	-	1[b]	-	-	-	-
Influenzavirus A H1	10	-	-	2[b]	-	1[c]	-	-
Influenzavirus A H3	9	-	-	2[b,c]	-	1[c]	-	-
Influenzavirus B	1	-	-	-	-	-	-	-
Metapneumovirus	1	-	-	-	-	-	-	-
Parainfluenzavirus 1	8	-	-	3[b]	-	-	-	-
Parainfluenzavirus 2	3	-	-	2[b,c]	-	-	-	-
Parainfluenzavirus 3	10[d]	-	-	1[c]	-	-	-	1[b]
RSV-A	7	1[b]	-	-	-	-	-	-
RSV-B	7	-	-	-	-	-	-	-
Mycopla. pneumon.	8	-	-	-	-	-	-	-
Legion. Pneumophila	7	-	-	-	-	-	-	-
Total	**100**	**1**	**0**	**12**	**0**	**2**	**0**	**1**

Corman, MedRxiv, 2020

AgPOCT[a]	I	II	III	IV	V	VI	VII
False positives	-	-	3[c]	-	5[c]	1	1
Specificity (%)[b]	100	100	91.42	100	82.86	97.12	97.12

[a]I: Abbott Panbio™ COVID-19 Ag Rapid Test; II. RapiGEN BIOCREDIT COVID-19 Ag; III: Healgen® Coronavirus Ag Rapid Test Cassette (Swab); IV Coris Bioconcept Covid.19 Ag Respi-Strip; V: R-Biopharm RIDA®QUICK SARS-CoV-2 Antigen; VI NAL von minden; NADAL COVID19-Ag Test; VII: Roche/SD Biosensor SARS-CoV Rapid Antigen Test;

[b]In 35 subjects, 30 conducting nasopharyngeal swabs and 5 conducting pharyngeal swabs

[c]One person tested false positive in assays III and V

Corman, MedRxiv, 2020

Testing for infectivity

- End of first week = end of transmission (in most patients)
- End of first week = 20% isolation success = 10E6-7 copies per mL
- 10^{6-7} copies per mL = AgPOCT limint of detection
- AgPOCT can provide assessment of infectivity
- Quantitative RT-PCR can provide assessment of infectivity
- Adapted RKI recommendations in place since Dec 2nd, 2020
- Discharge based on viral load $<10^6$, two consecutive samples and known late time in course (particularly ICU patients)

Assessment of SARS-CoV-2 antibody responses in the context of natural infection

Viviana Simon, MD, PhD

Professor of Microbiology and Medicine

Icahn School of Medicine, NY

Assessment of SARS-CoV-2 antibody responses in the context of natural infection

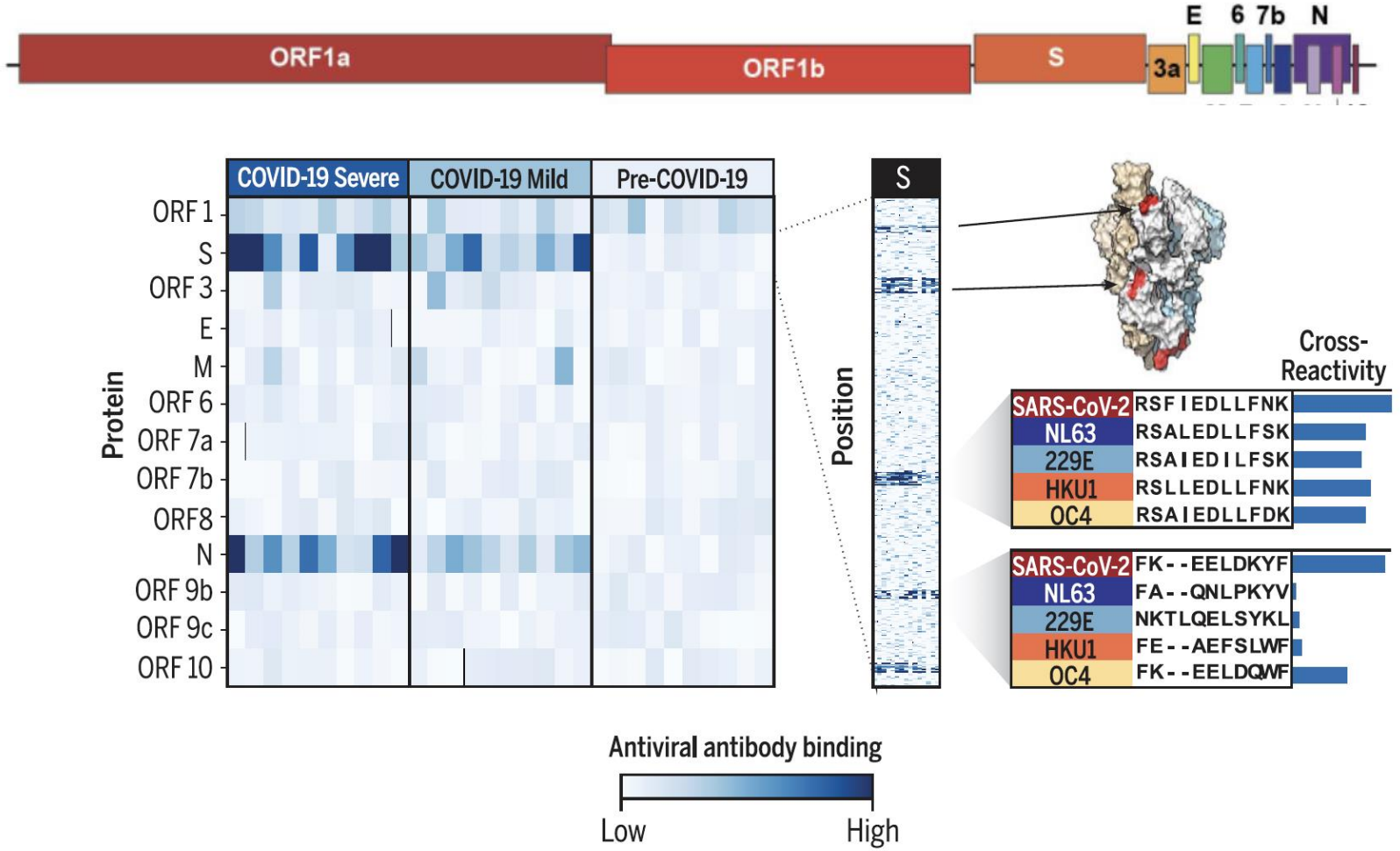
Dec. 17, 2020

Dr. Viviana Simon, Professor, ISMMS

Overview of today's talk

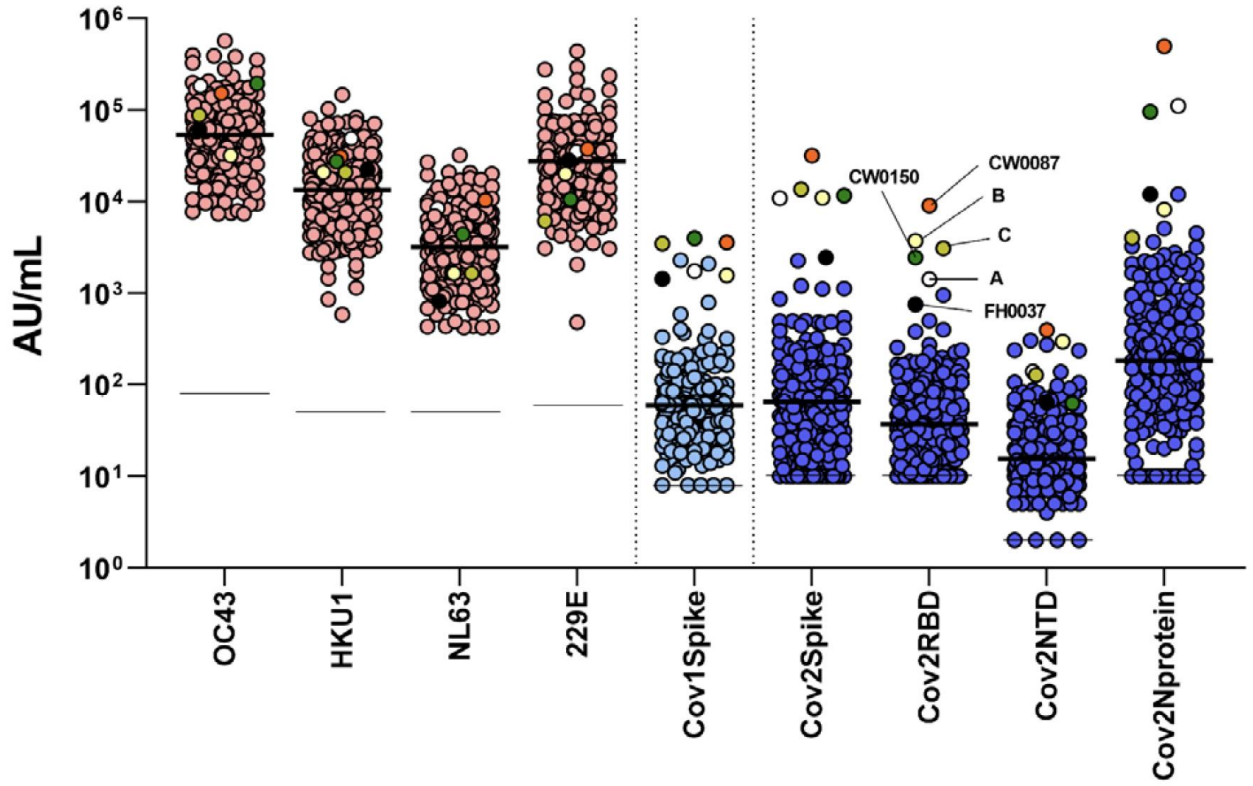
- Intricacy of COVID19 serology
- Comparison of SARS-CoV-2 antibody tests
- Persistence of SARS-CoV-2 antibodies
  - Durability of antibody responses
  - Seroconversion of a City
- Conclusions

Target antigens for SARS-CoV-2 immune responses and vaccines



(Shrock et al., Science 2020)

Multiplex assay to detect antibodies against seasonal coronavirsus, SARS-CoV-1 or SARS-CoV2

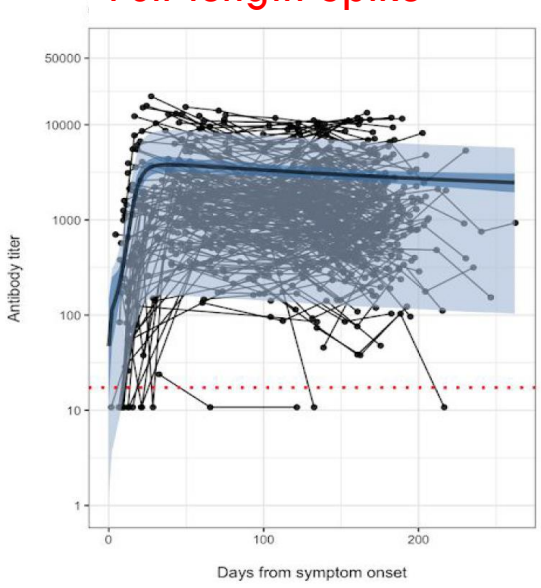


Majdoubi et al., medRxiv preprint doi: https://doi.org/10.1101/2020.10.05.2022020; Oct 7, 2020

Dynamics of antibody responses following infection with SARS-CoV-2

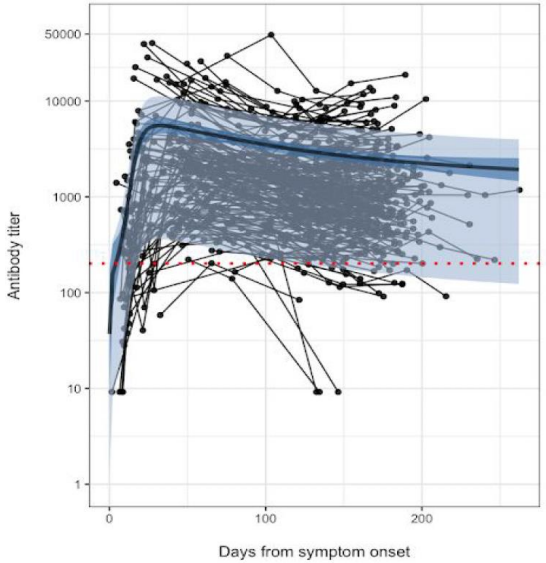
Meso-Scale Discovery assay, 1163 samples from 349 participants, follow-up: 7 months

Full-length Spike



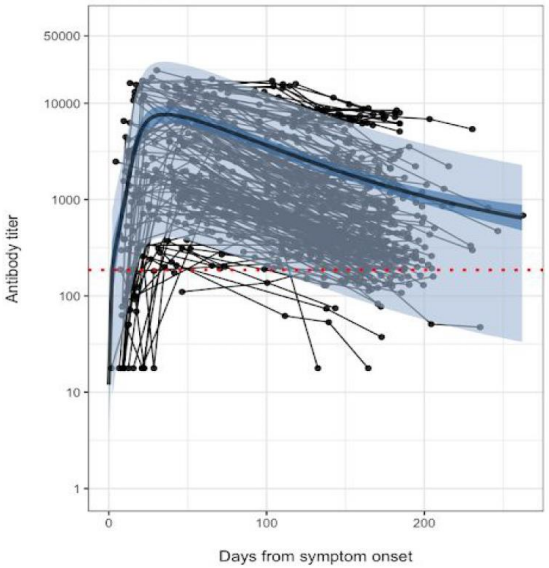
Half-life: 126 days

Spike RBD only



Half-life: 102 days

Nucleoprotein (N)

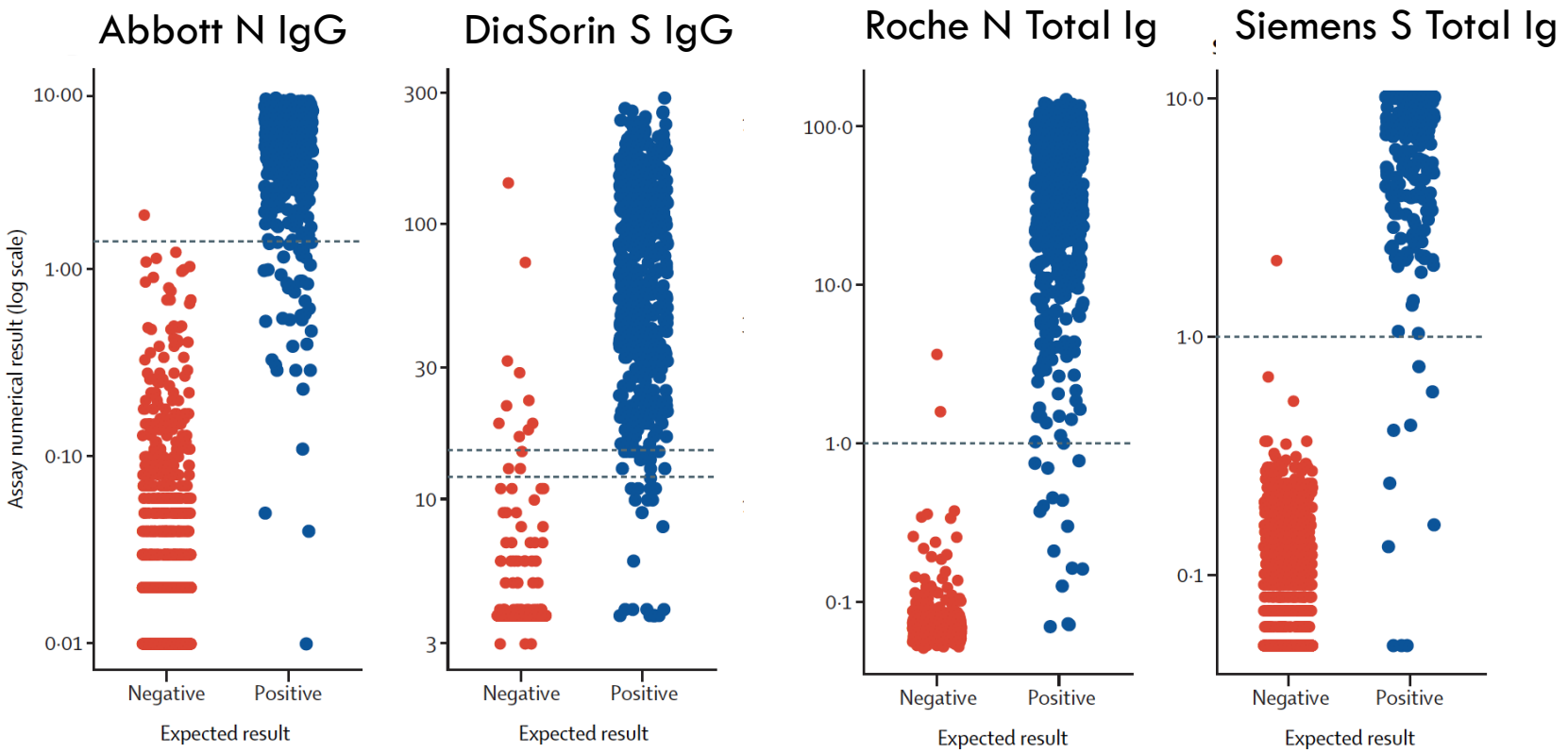


Half-life: 60 days

- Seven months after symptom onset, 75% of participants still had N-antibodies compared to 99% being positive for Spike antibodies

(Grandjean et al., MedRxiv preprint; https://doi.org/10.1101/2020.11.20.20235697; Nov 23, 2020)

A head-to-head benchmark comparison of SARS-CoV-2 immunoassays



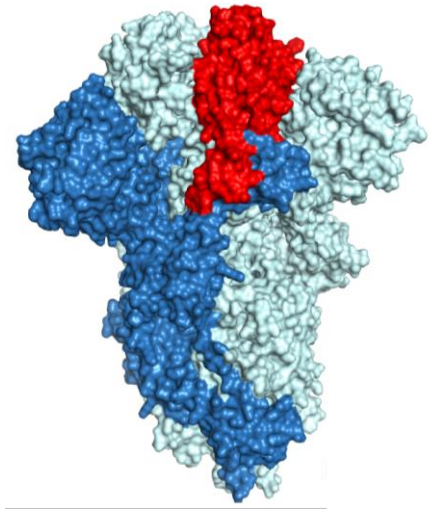
Manufacturers report comparable sensitivity and specificity for each assay.
976 known negative and 536 known positive samples were tested in parallel

(The National SARS-CoV-2 Serology Assay Evaluation Group, Lancet Infectious Disease, 2020)

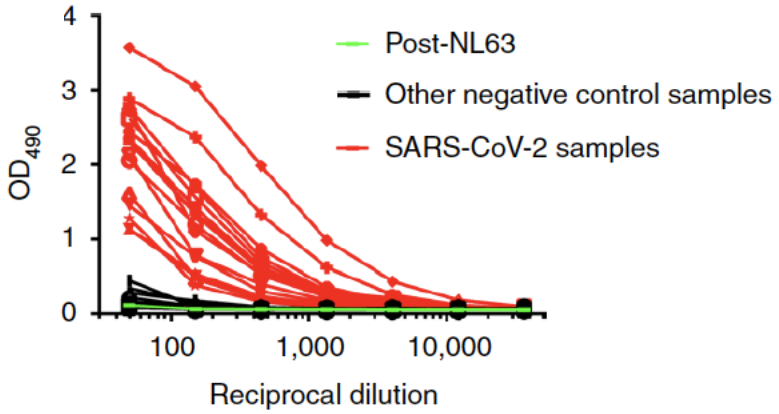
Serology – Spike versus N antibodies

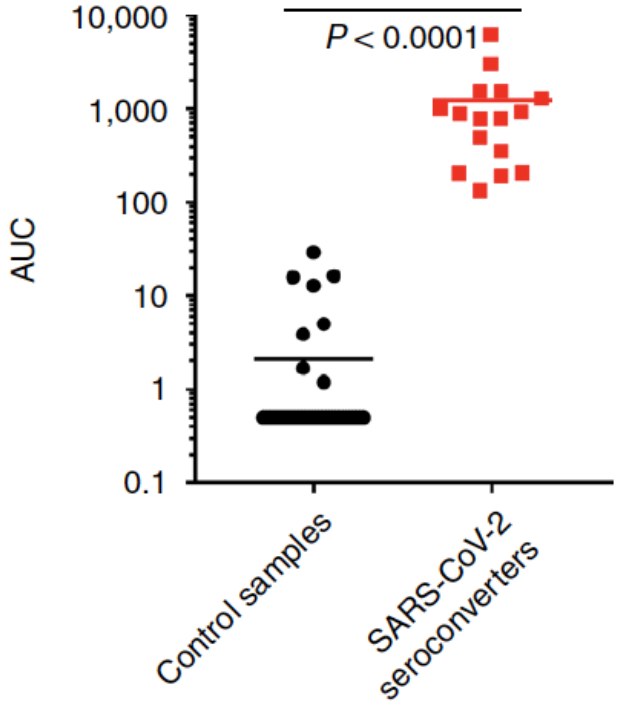
- Antibodies to Spike protein
  - Large protein (1273 aa) = more epitopes
  - External viral protein
  - Neutralizing and non-neutralizing activities
  - Limited cross-reactivity with seasonal coronaviruses
  - Fails to distinguish natural infection from vaccination
- Antibodies to N protein
  - Smaller protein (419aa) = fewer epitopes
  - Internal viral protein
  - Non-neutralizing
  - Cross-reactivity with seasonal coronaviruses
  - "Sero-reversion"
  - Identifies natural infection in individuals that received a Spike vaccinated

A serological assay to detect SARS-CoV-2 seroconversion in humans: Mount Sinai Ab Test



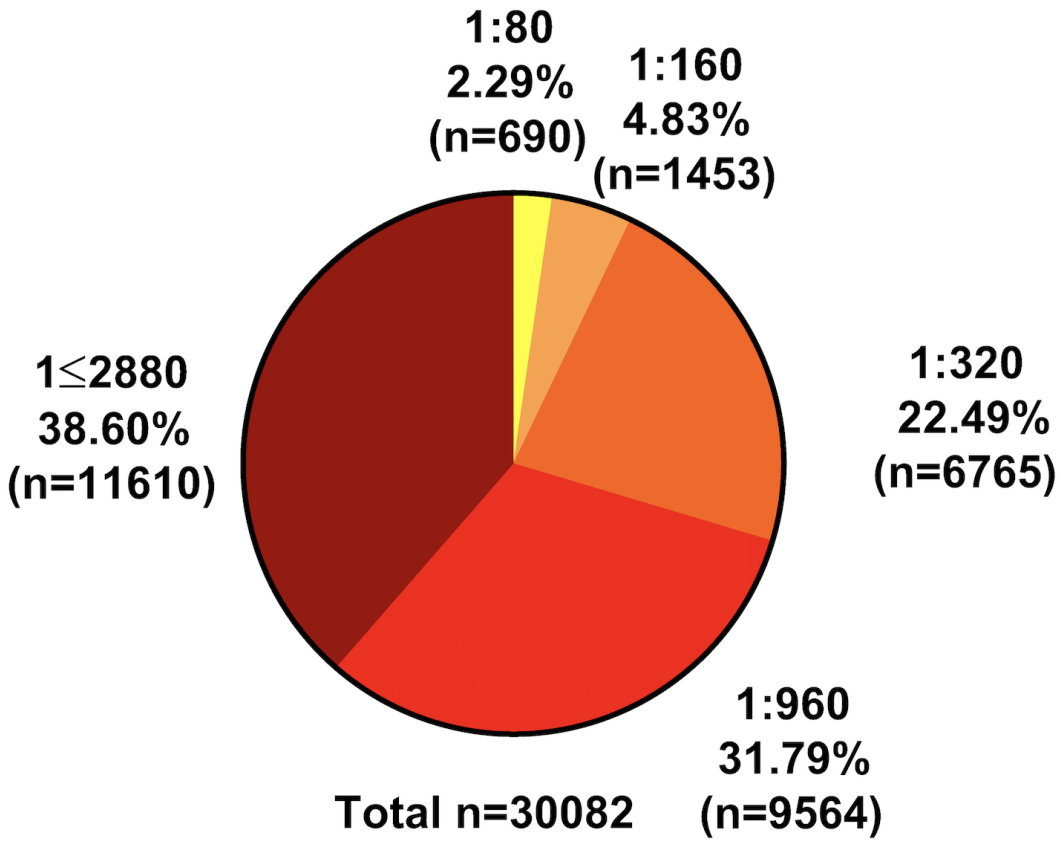
The use of two sequential assays (1. RBD; 2. Full length Spike) reduces the false positive rate and favors high specificity resulting in a sensitivity of 95% and specificity of 100%





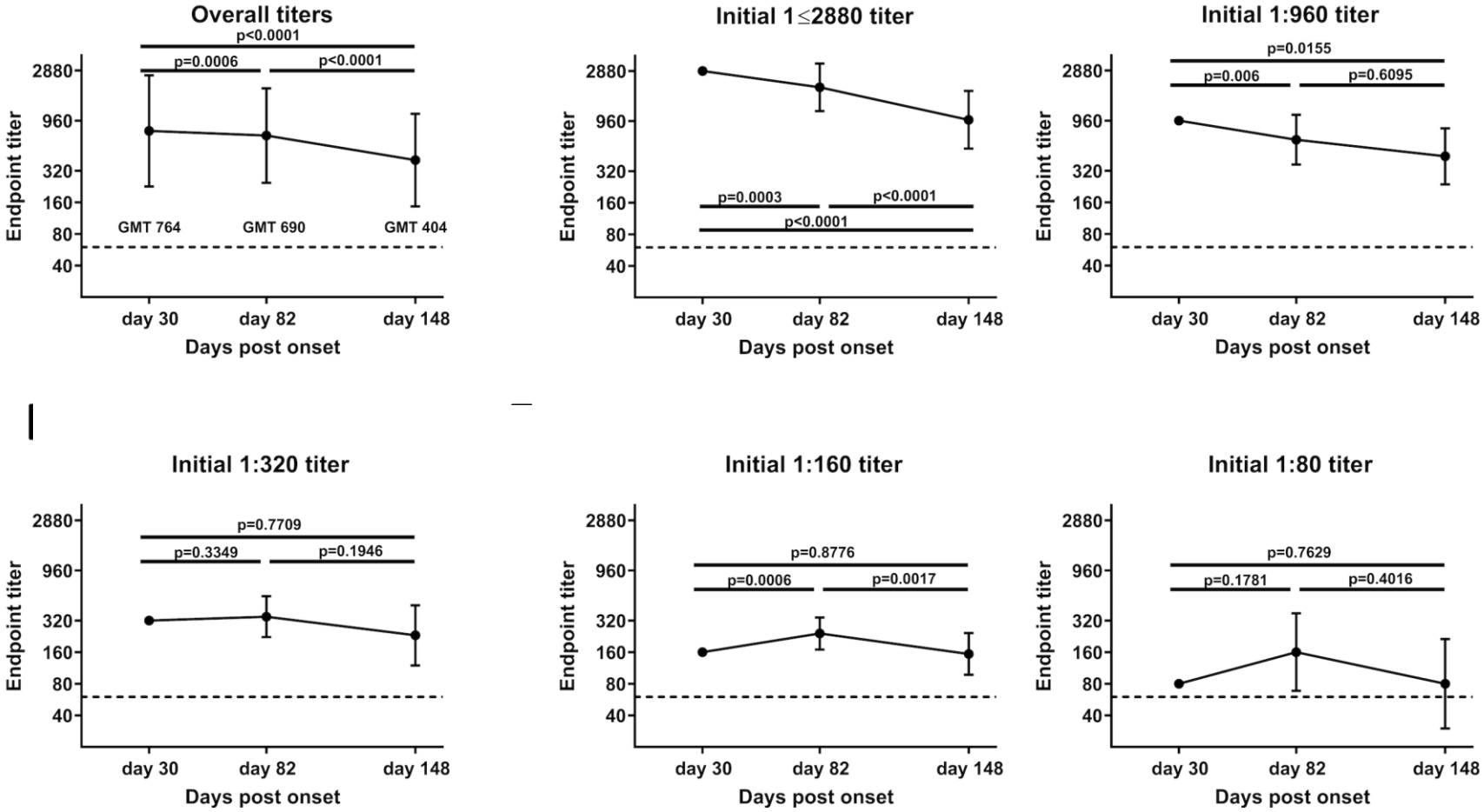
Amanat et al., Nat. Med. 2020

SARS-CoV-2 spike antibody titers in >30,000 individuals (MSSM)



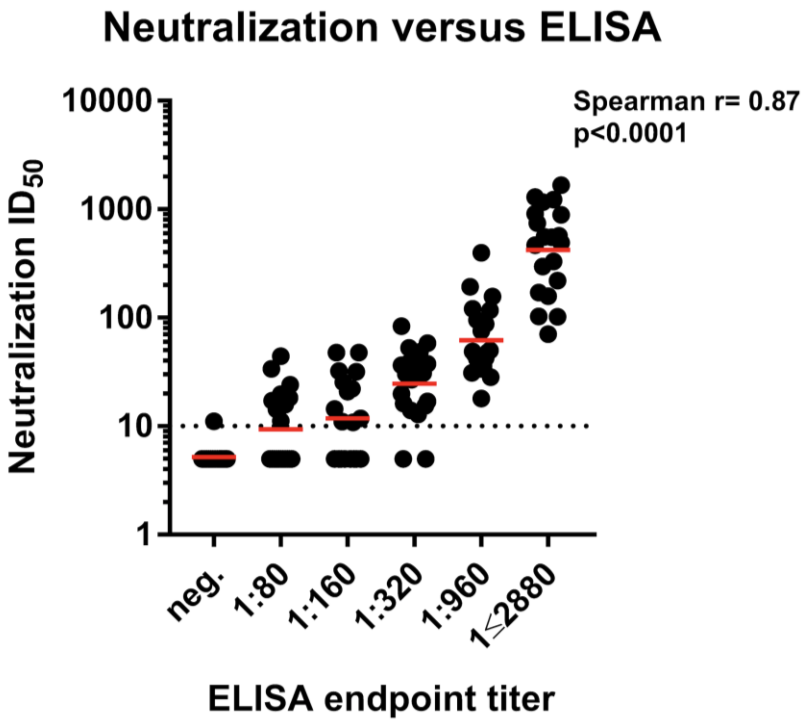
(Wajnberg et al., Science 2020)

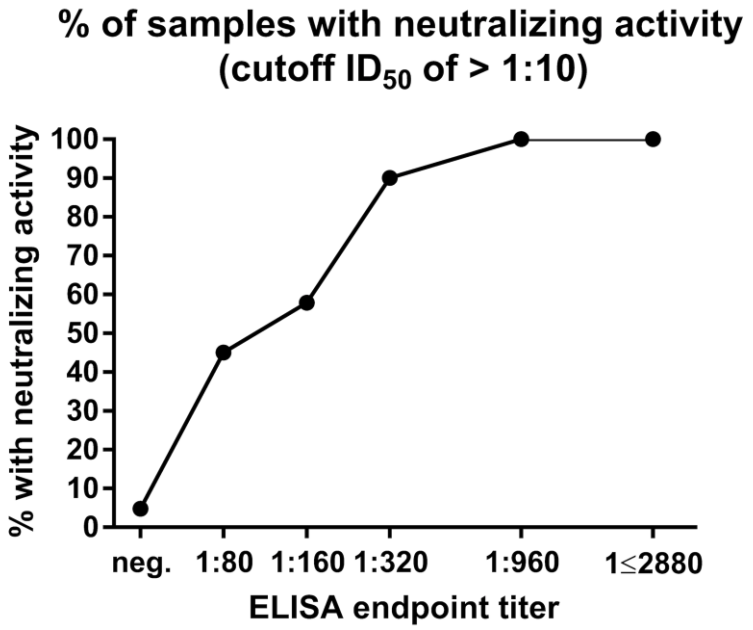
Spike antibodies levels are maintained five months after symptom onset (N=150)



(Wajnberg et al., Science, 2020)

Neutralizing activity of serum samples in relation to antibody titers (MSSM ELISA)



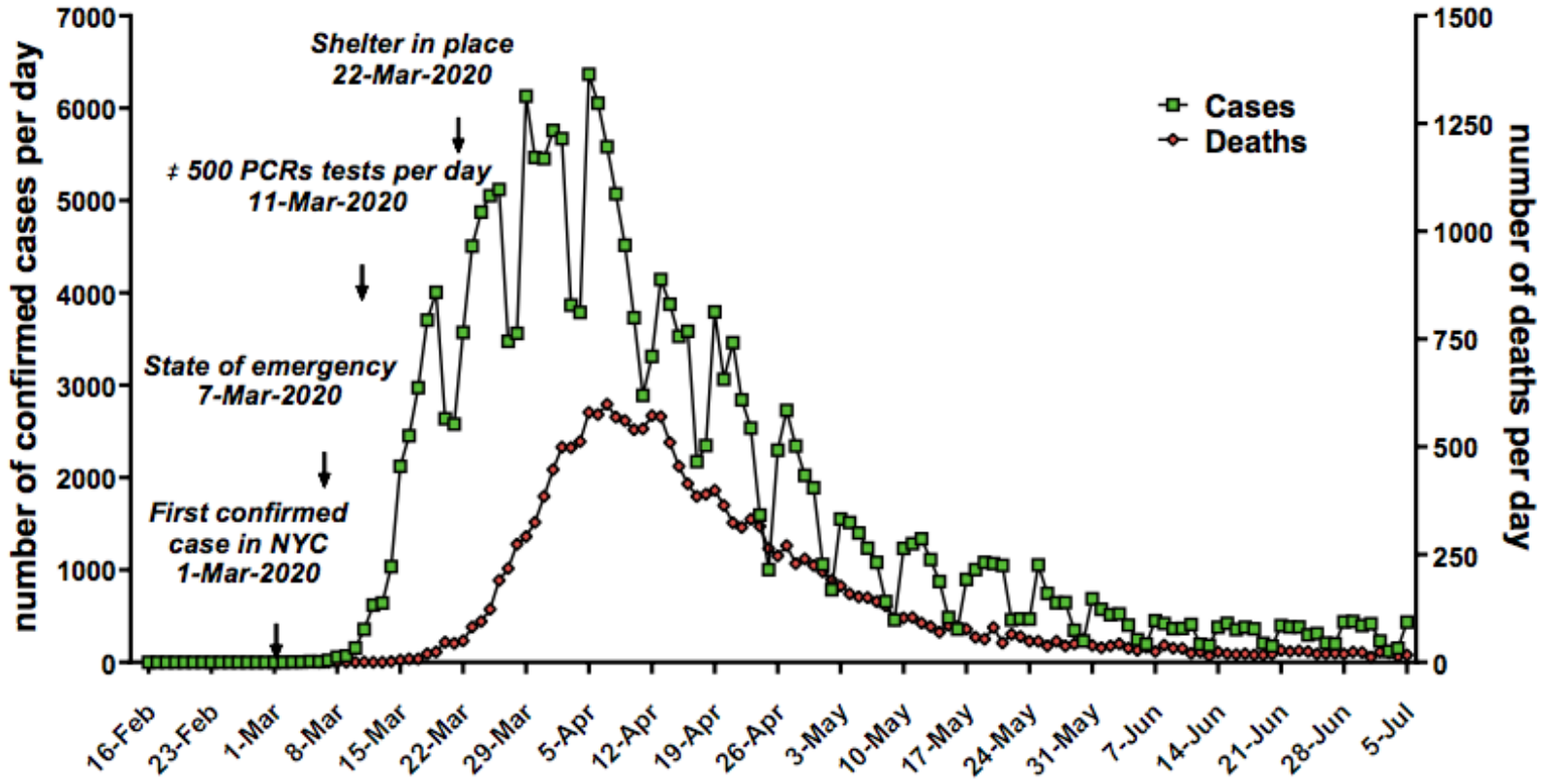


(Wajnberg et al., Science 2020)

Retrospective, repeated cross-sectional analysis of SARS-CoV-2 seroprevalence

- Goal: To determine the true infection rates in NYC in order to assess how close we are to potential 'community immunity'
- We collected >10,000 plasma samples from MSH patients
  - Residual EDTA-anticoagulated blood specimens remaining after standard of care testing (MSH Blood Bank)
  - Samples released 3 weeks after collection
- Two groups
  - 'urgent care' group ('UC', enriched for acute SARS-CoV-2 infections). N=4,101
  - 'routine care' group ('RC', more closely representing the general population). N= 6,590

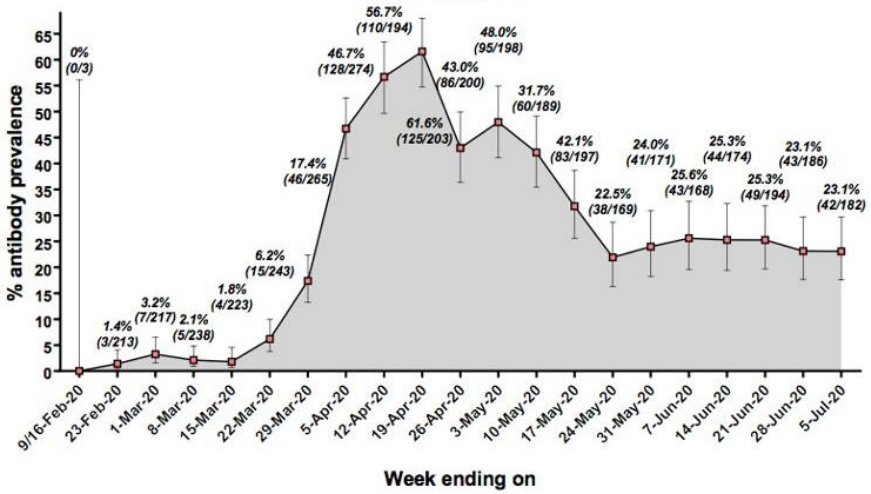
Confirmed cases & deaths in NYC in the early weeks of the SARS-CoV-2 epidemic



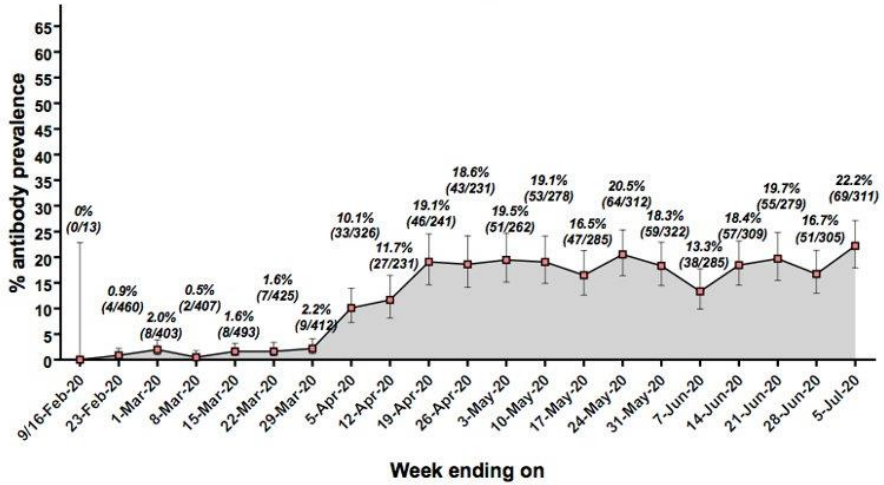
(Stadlbauer et al., Nature 2020)

SARS-CoV2 antibody prevalence in the Urgent Care versus the Routine care groups (Feb 9 to July 5, 2020)

Urgent Care group (+ control)



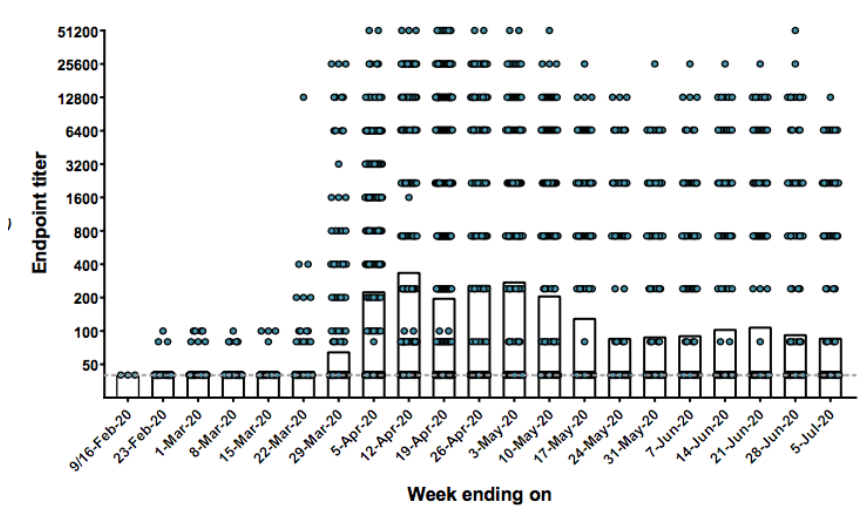
Routine Care group (general population)



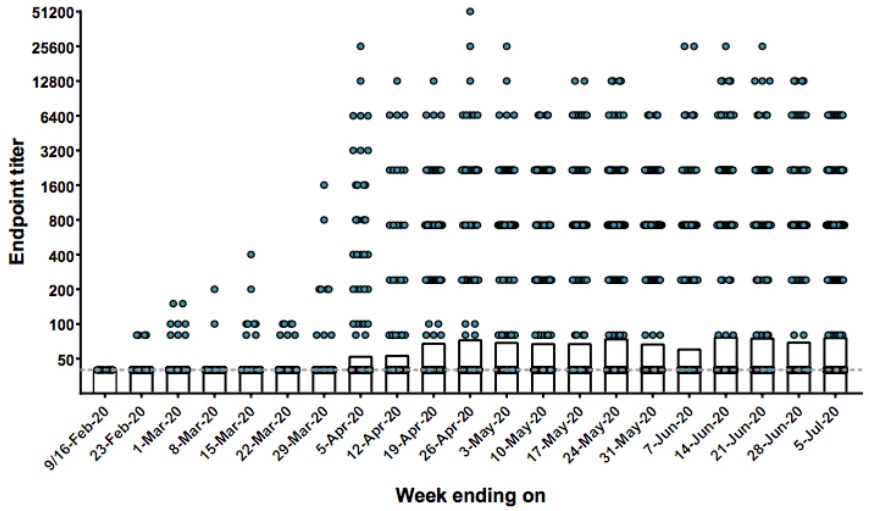
(Stadlbauer et al., Nature 2020)

Full-length spike antibody titers in the Urgent Care versus the Routine care groups (Feb 9 to July 5, 2020)

Urgent Care group (+ control)



Routine Care group (general population)



(Stadlbauer et al., Nature 2020)

Conclusions

- Spike antibodies levels mounted upon natural SARS-CoV2 infection correlate with virus neutralization and remain stable over months
- Seroprevalence data generated before, during and after the first wave of the SARS-CoV2 infections in NYC suggests:
  - The seroprevalence in the RC group (20%) falls significantly below the threshold for potential community immunity
  - Based on the population of NYC (8.4 million), we estimate that app. 1.7 million New Yorkers have been infected with SARS-CoV2
  - Infection fatality rate IFR: 0.97% (2009 H1N1 pandemic: IFR 0.01% and 0.001%!)
- We will continue the seroprevalence study to cover the second wave in NYC as well as the introduction of the vaccines

Serology – vaccination versus infection

- Vaccination
  - Relatively homogenous response (judging from data from the Pfizer and Moderna trials)
  - For the majority of vaccines, there will be a spike only responses (*except inactivated vaccines*)
  - No mucosal sIgA responses (IgG & monomeric IgA maybe found in saliva)
  - Duration: unknown
- Infection
  - Heterogeneous response in general
  - Strong anti-Spike and anti-NP antibody responses
  - Some responses to other proteins like ORF8
  - Mucosal sIgA response
  - Duration: potentially long-lived

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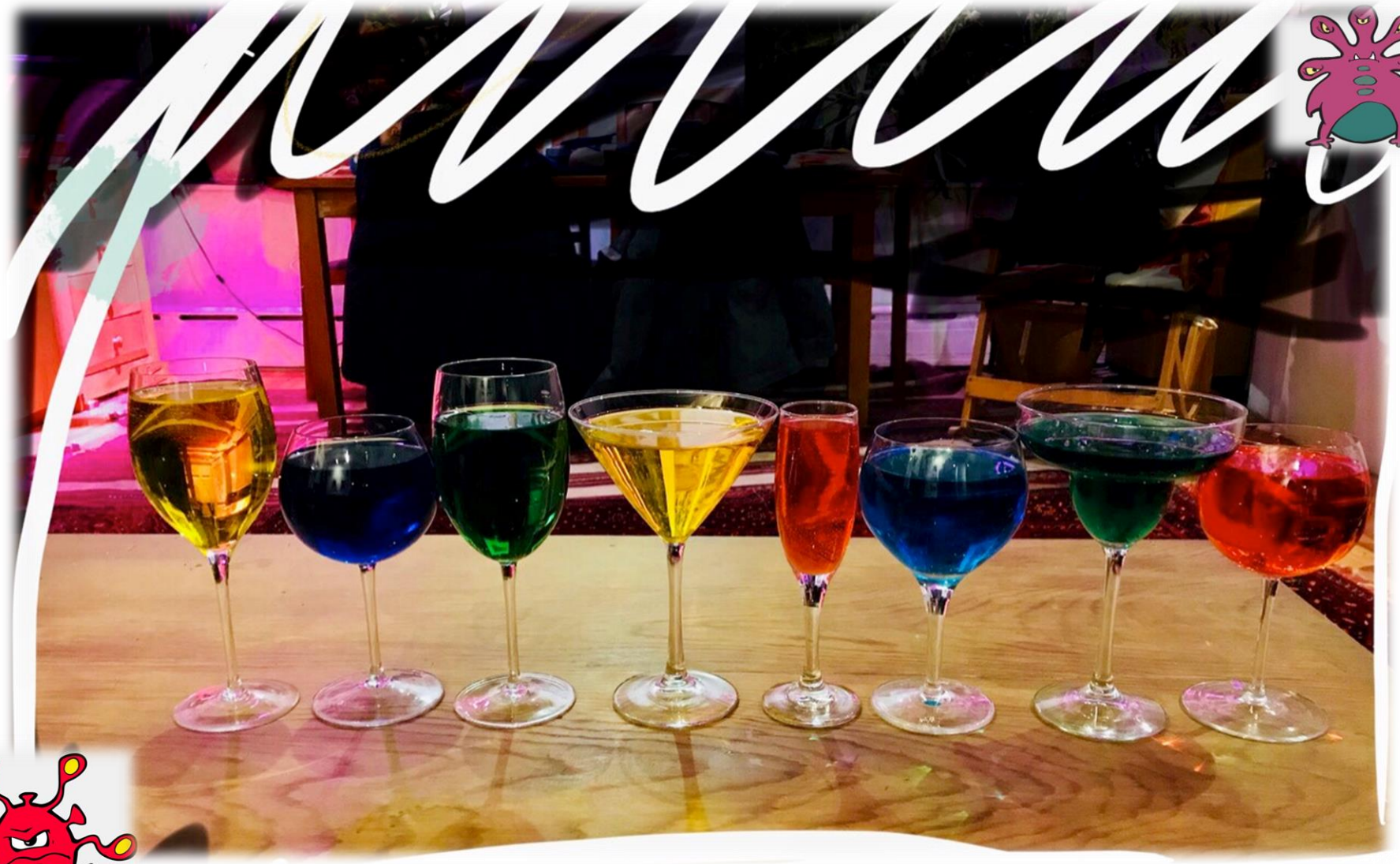


Help crush COVID-19!
Support the Microbiology Department at ISMMS

Pre-clinical animal studies: evidence from different vaccine platform technologies on infection / duration of viral shedding

William Dowling, PhD

Non-Clinical Vaccine Development Leader

CEPI

Pre-clinical animal studies

Evidence from different vaccine platform technologies on infection / duration of viral shedding



William Dowling
Non-clinical vaccine development leader
CEPI

17 December 2020

- SARS-COV-2 models
  - Species
  - Infectious dose
  - Transmission models
  - Re-infection studies
- Vaccine protection studies

SARS-CoV-2 vaccine pre-clinical models

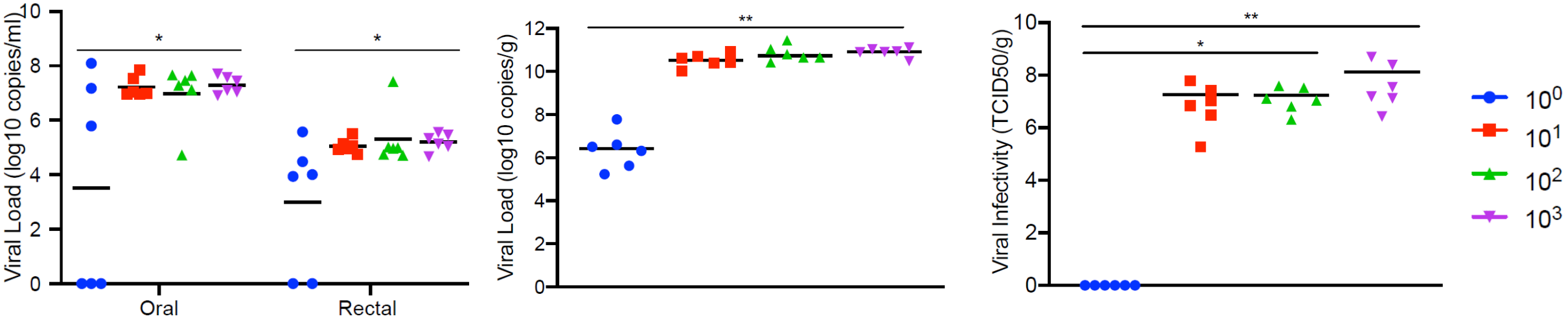
- **Mice** – for SARS-CoV-2, one must change the mouse or change the virus
  - hACE2 (transgenic, knock-in, transient transfection), adapted virus
  - Disease ranges from mild to uniform lethality depending on the approach
- **Ferrets** - infected ferrets show few or no clinical signs but demonstrate high viral shedding and are good transmission models
- **Hamsters** – infected Golden Syrian hamsters demonstrate weight loss and other clinical signs, high viral load in lungs and significant lung pathology
- **NHPs** – AGMs, rhesus macaques and cynomolgus macaques have relatively mild disease, with variable clinical signs, pneumonia by chest x-ray or CT scan , viral shedding, viral load in lung and lung pathology

Infection and viral shedding readouts

- Recovery of live virus – assessed by Plaque assay or CPE based assay
- Genomic RNA by RT-PCR – measures all virus, including the input virus, which may remain for some time, especially at high challenge doses
- Subgenomic RNA by RT-PCR – measures a viral replicative intermediate, so does not count input virus, only replicating virus

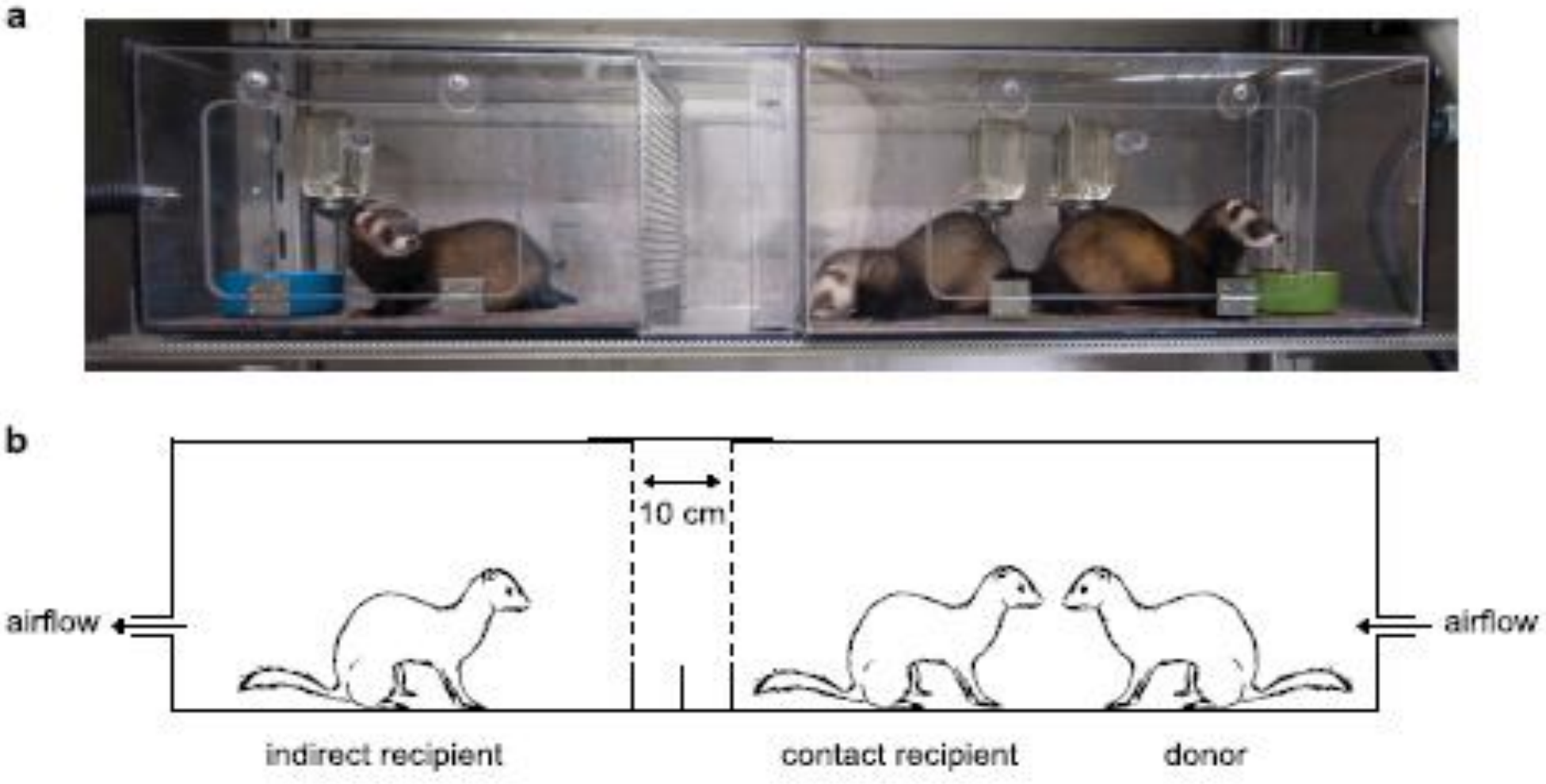
The Infectious dose in animal models is very low

- In initial development of disease models, very high doses were used (10^5 -10^6 PFU or $TCID_{50}$)
- In several models, disease severity was shown to be dose dependent , but very few studies have assessed infectious dose.
- One recent study calculated the ID_{50} to be 5 $TCID_{50}$ in the hamster

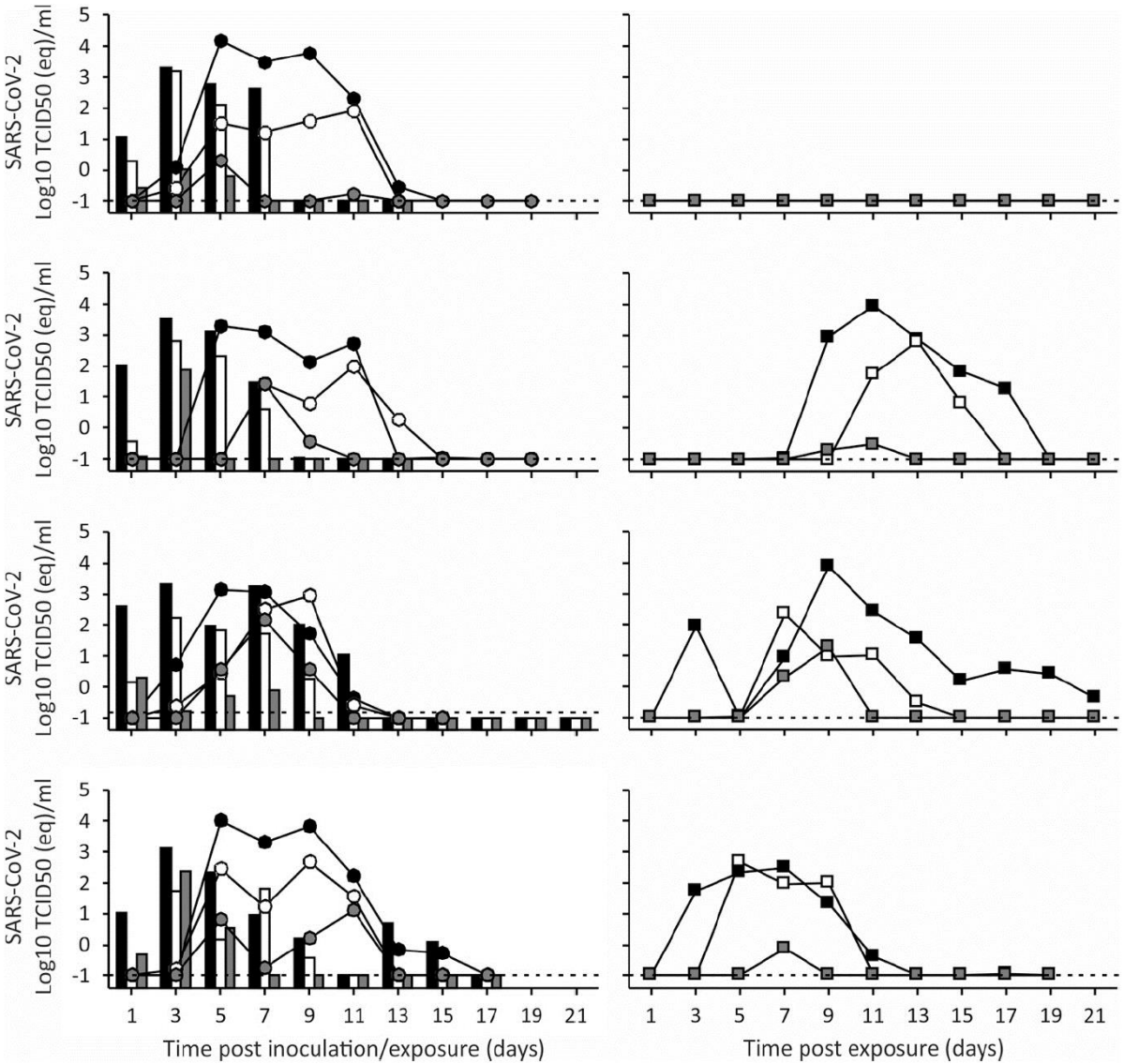


Rosenke et al 2020

SARS-CoV-2 Transmission can occur by direct contact or airborne



Richard et al 2020



SARS-CoV-2 shedding in ferret transmission study

- Throat (black), nasal (white) and rectal (grey) swabs collected from donor ferrets (bars; left panels), direct contact ferrets (circles; left panels) and indirect recipient ferrets housed in separate cages (squares; right panels)
- TCID50 equivalent (eq) were calculated from a standard curve of serial dilutions of the SARS-CoV-2 viral stock.

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Studies in multiple species have demonstrated protection from re-infection

- Rhesus macaque re-infection study :

- Group 1 N=3 $1x10^6$ PFU SARS-CoV-2
- Group 2 N=3 $1x10^5$ PFU SARS-CoV-2
- Group 3 N=3 $1x10^4$ PFU SARS-CoV-2

- All animals re-challenged 35 days post infection

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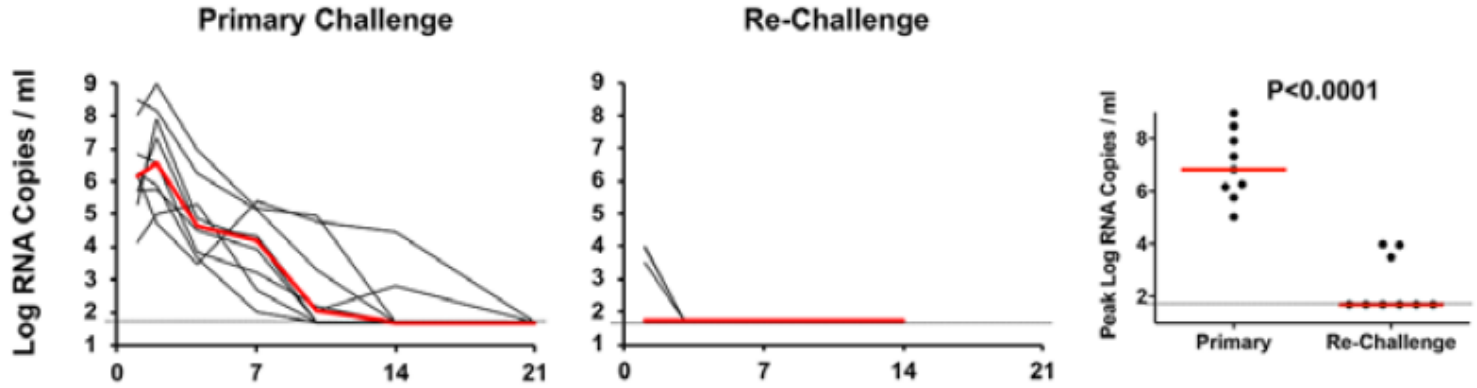
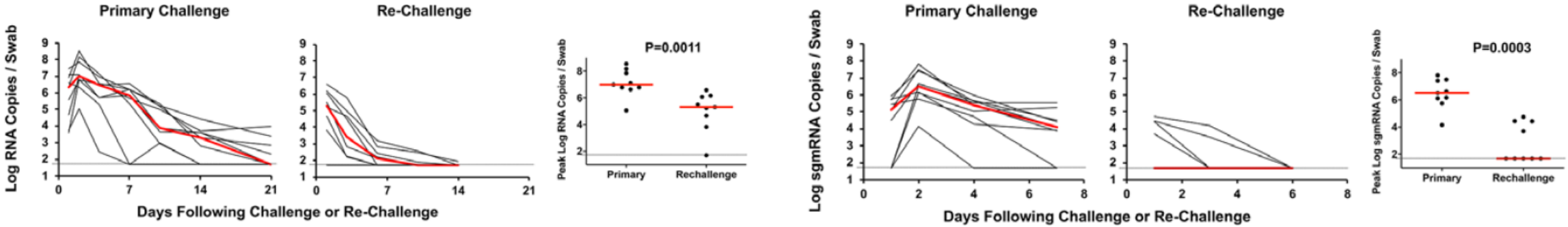
Chandrashekar et al 2020

Rhesus re-infection Study

BAL





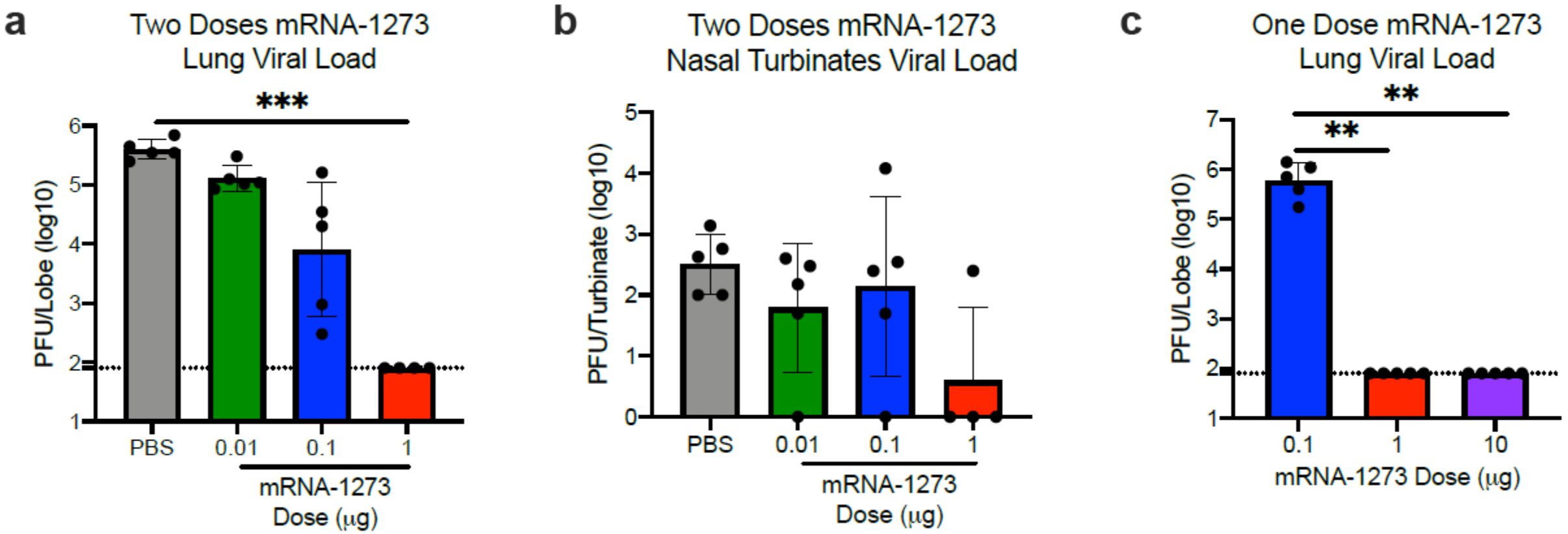
Nasal swabs

Chandrashekar et al 2020

Vaccine protection studies

- Several vaccines demonstrate protection against disease but do not completely protect against viral shedding in the upper respiratory tract, leaving the possibility of viral transmission
- This is seen in multiple vaccine platforms including RNA, viral vectors, subunit protein and whole viral inactivated vaccines
- A few vaccines show lack of shedding in the upper respiratory tract, indicating potential to block transmission

Vaccine Protection: Moderna



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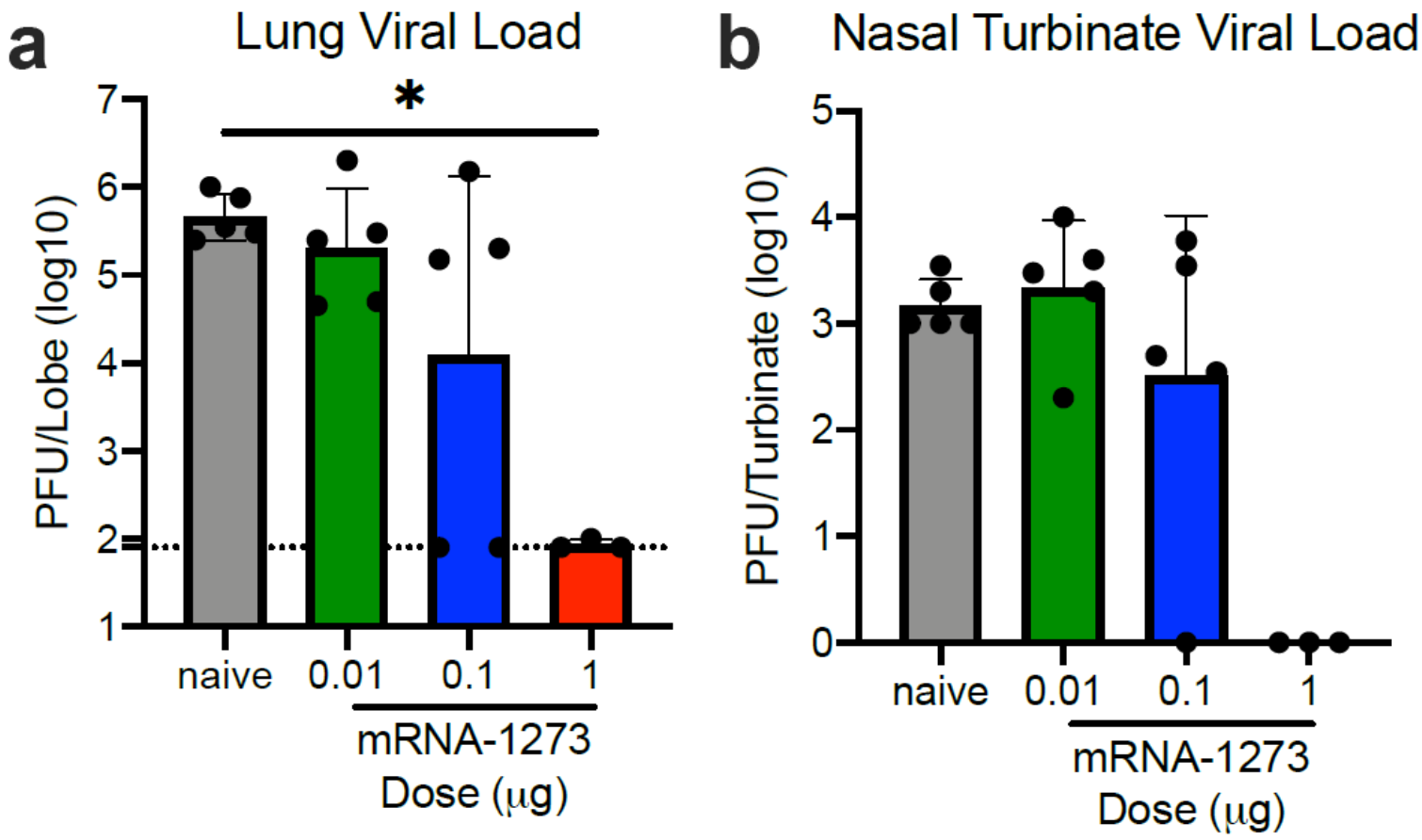
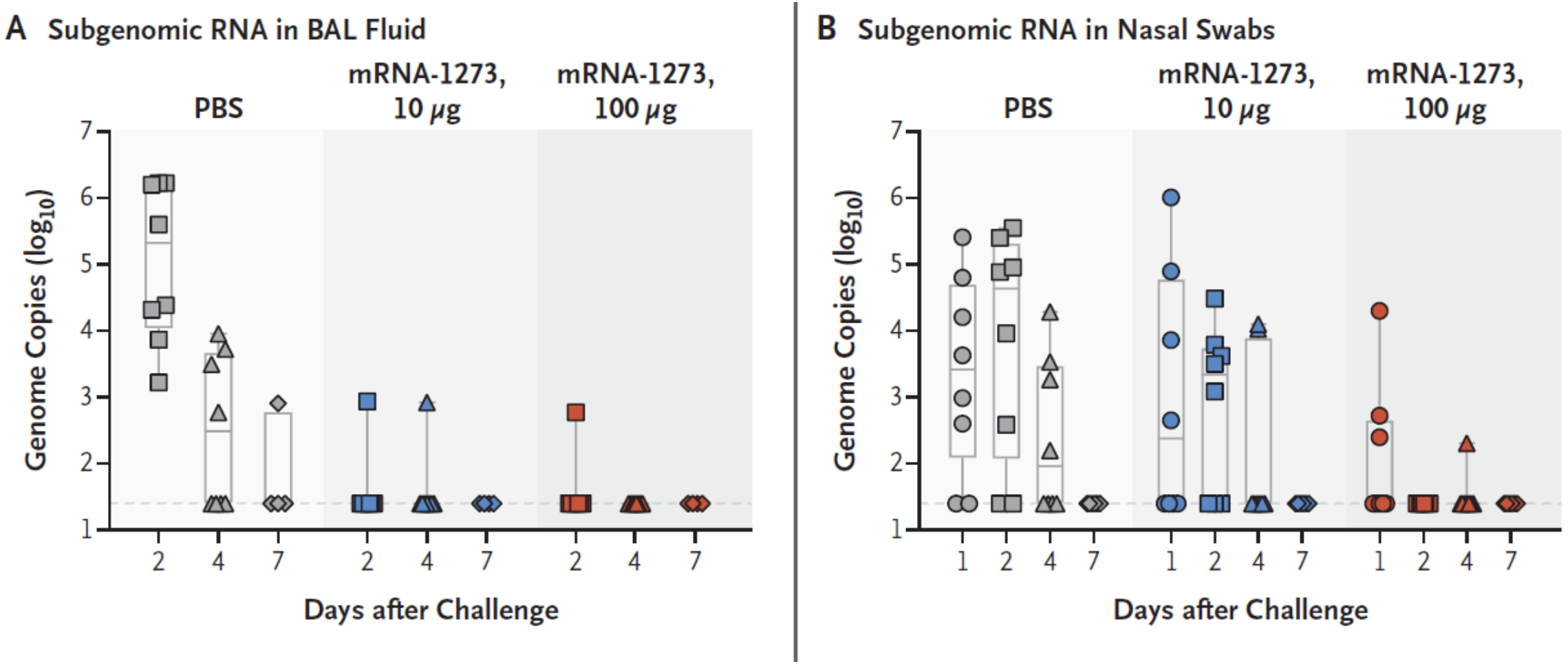
Corbett et al 2020a

Vaccine Protection: Moderna



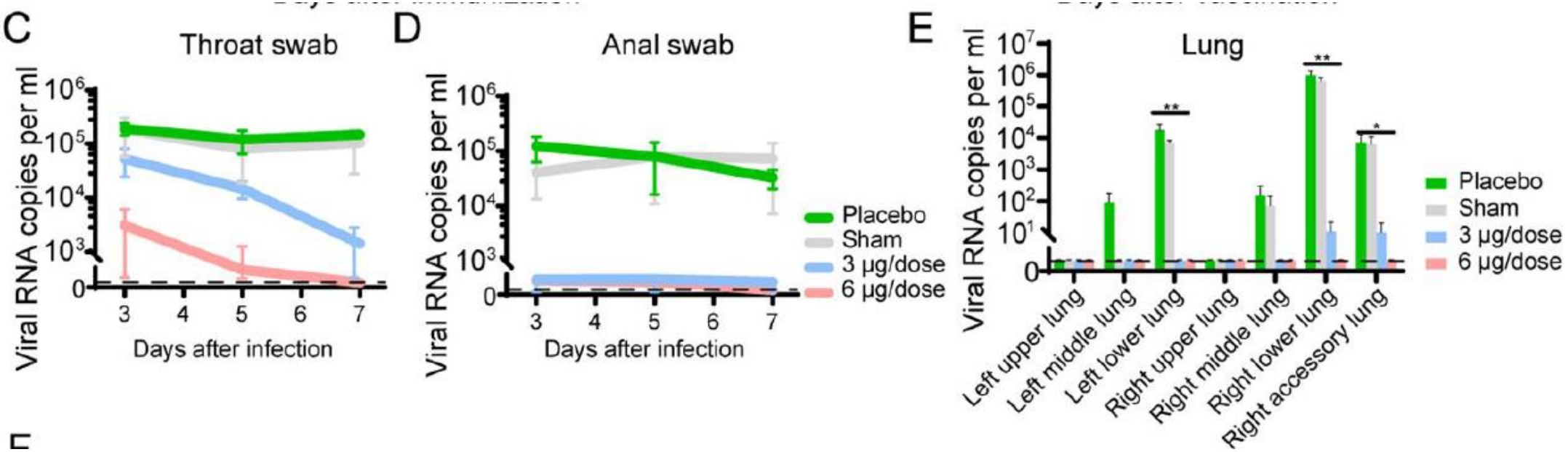
Corbett et al 2020a

Vaccine Protection: Moderna



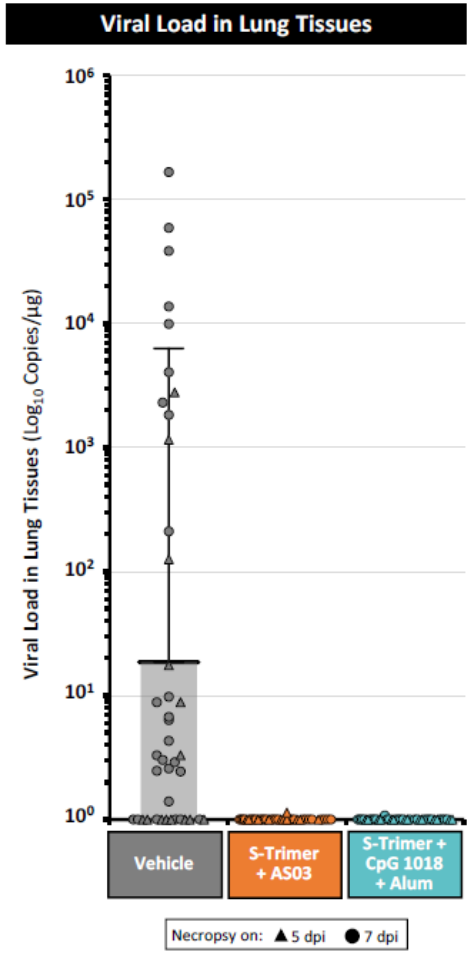
Corbett et al 2020b

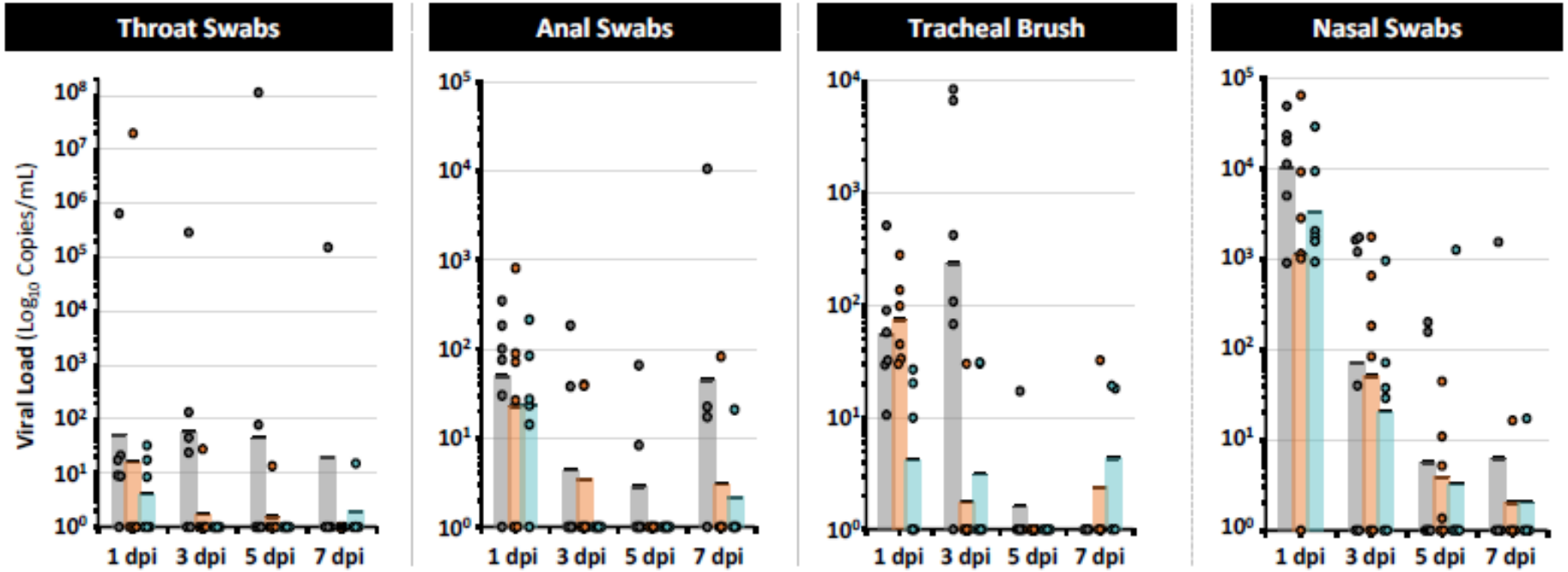
Vaccine protection - Sinovac



Gao et al 2020

Vaccine protection - Clover





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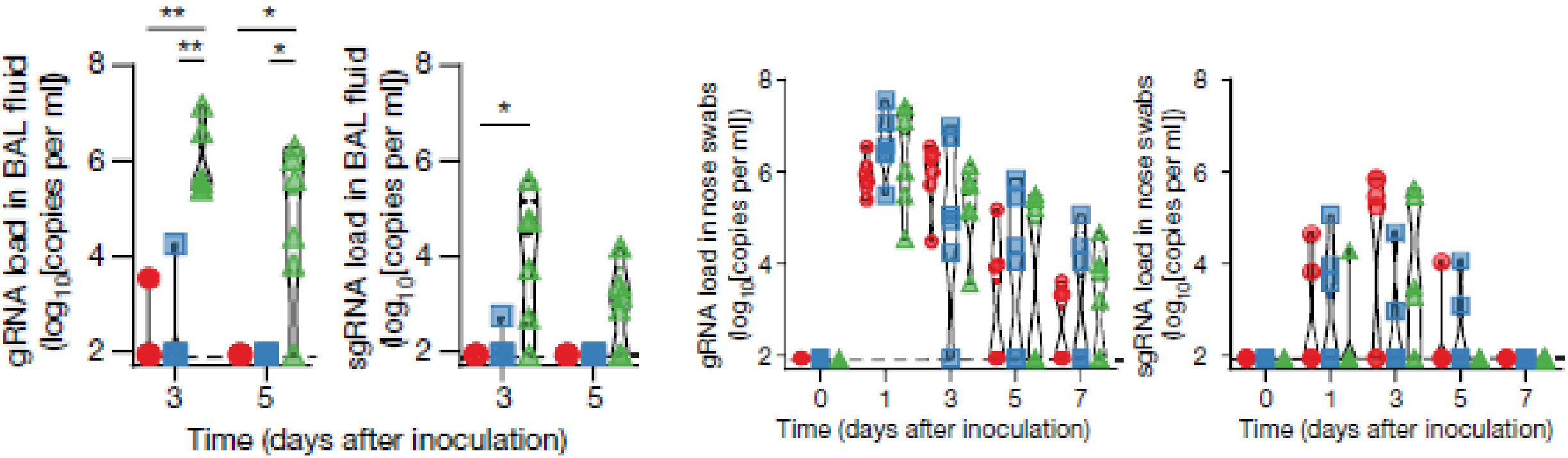
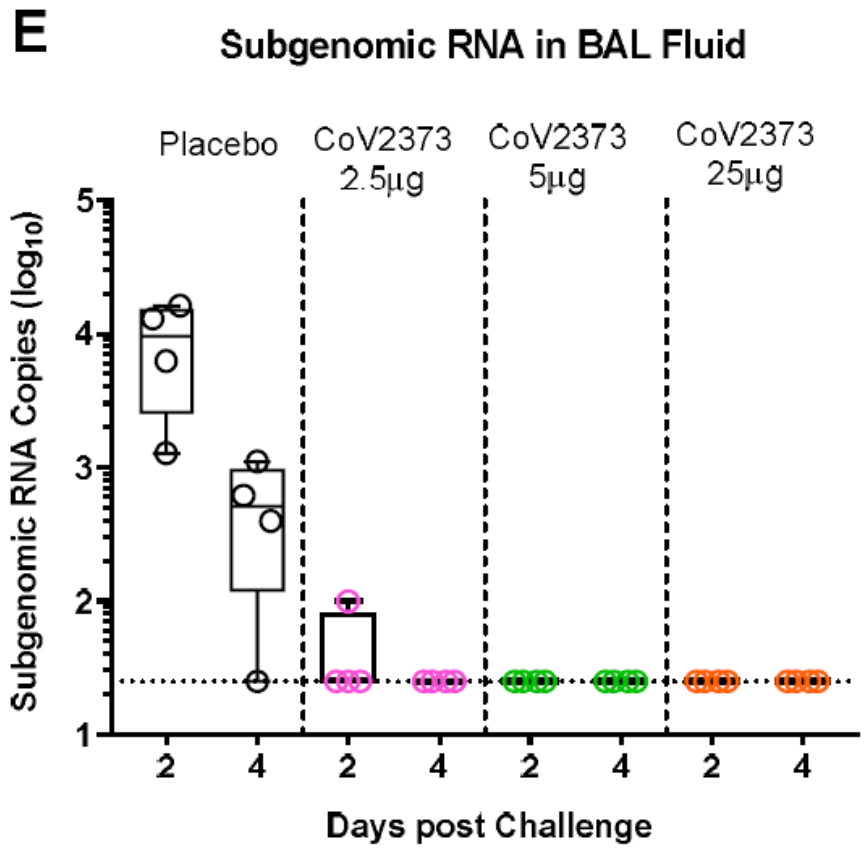
Liang et al 2020

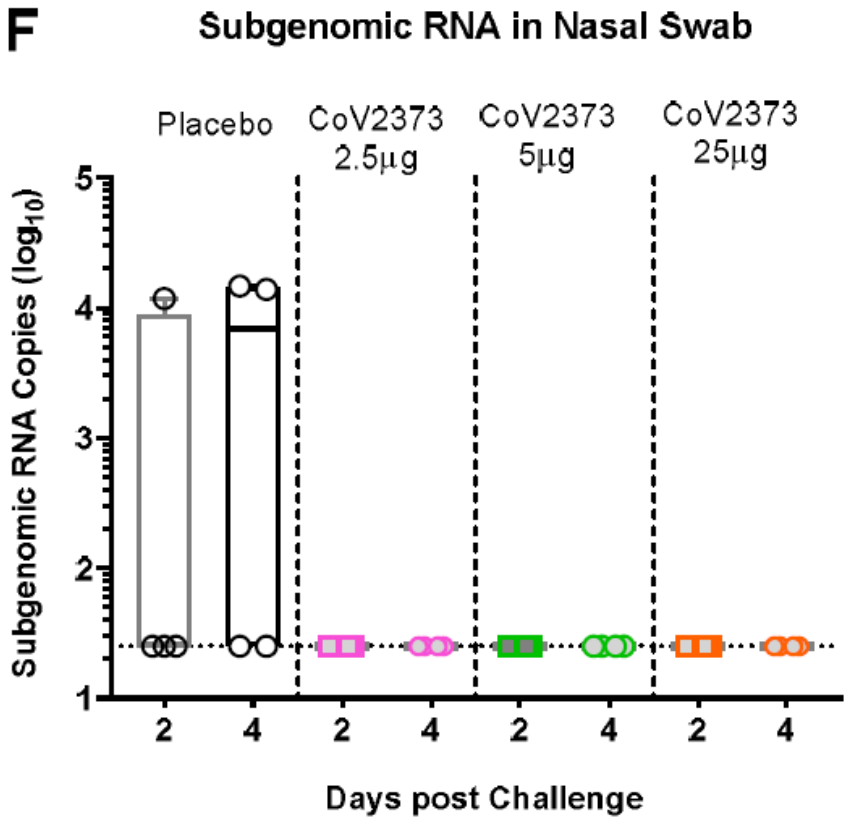
Vaccine protection – AstraZenca/ Oxford



Van Dormalen et al 2020

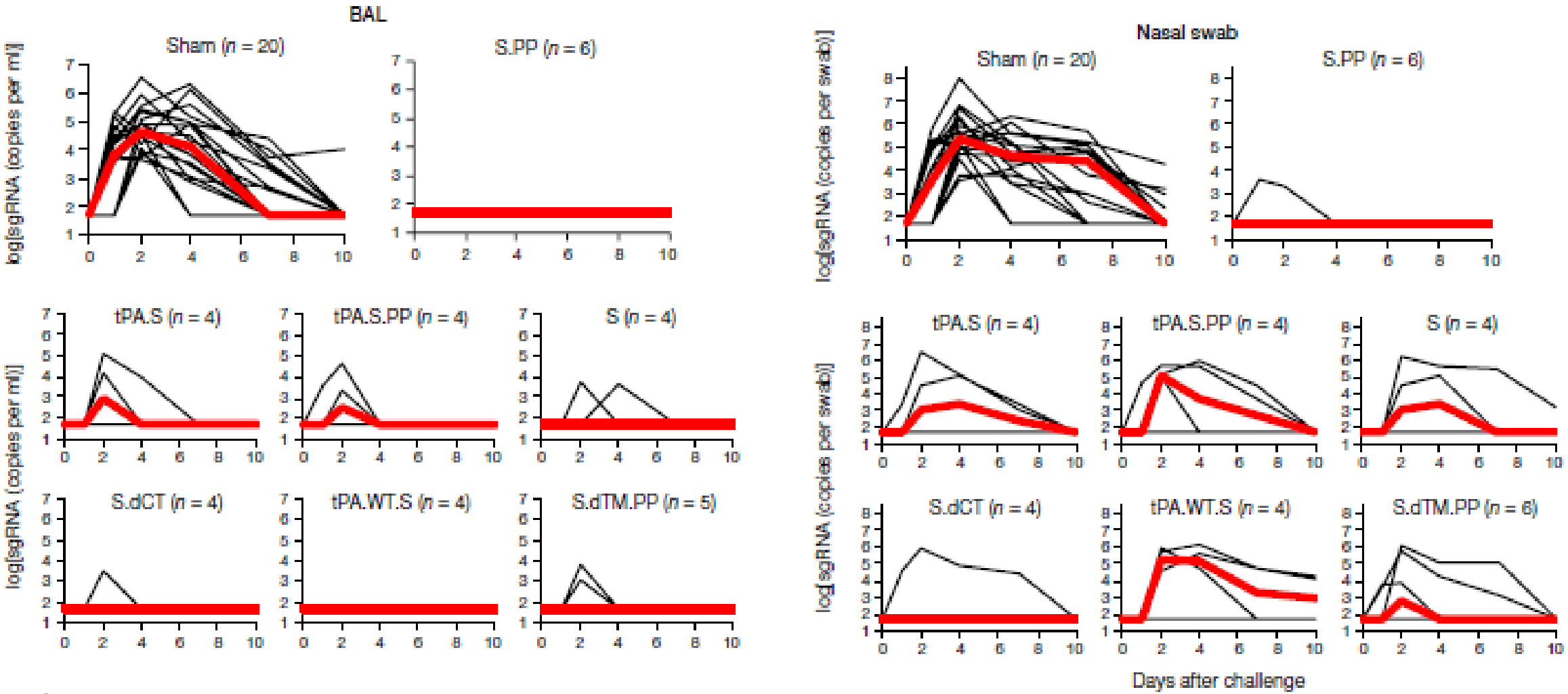
Vaccine protection - Novavax





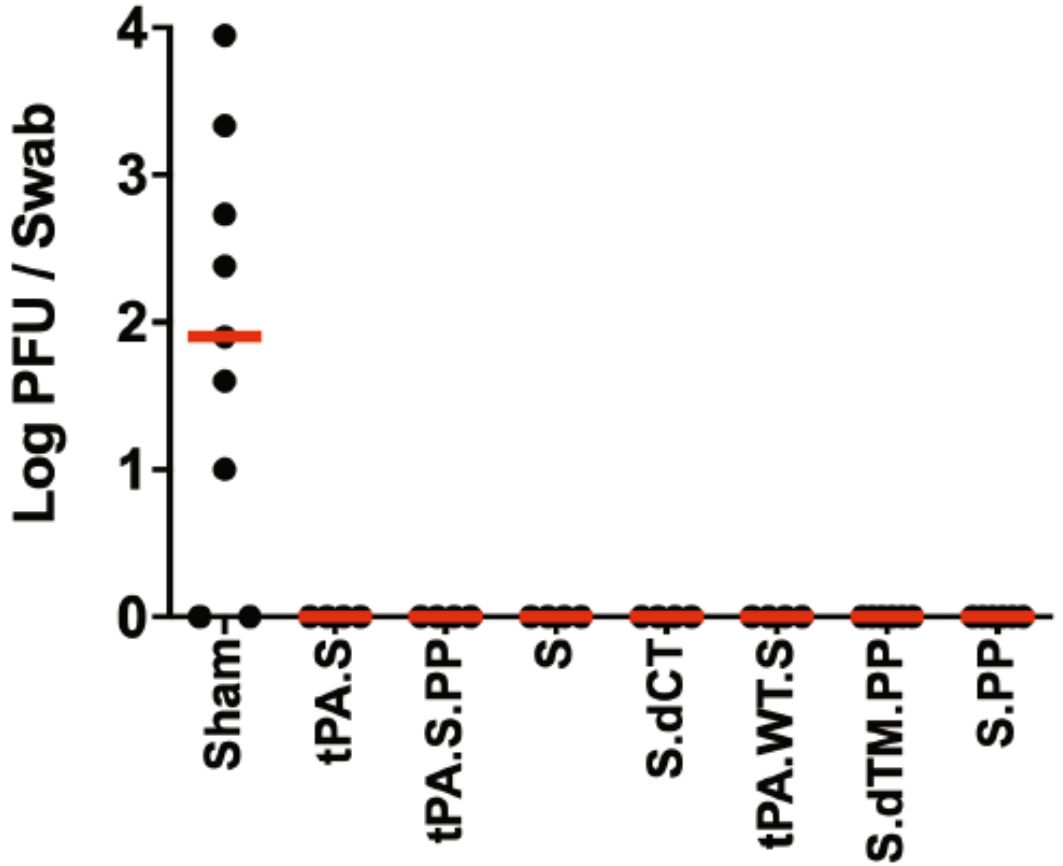
Guebre-Xabier et al 2020

Vaccine protection - Janssen



Mercado et al 2020

Vaccine protection - Janssen



Mercado et al 2020

Summary

- Mice, hamsters, ferrets and NHPs have been used to assess vaccine efficacy and infectious dose appears to be low
- Transmission has been demonstrated by direct contact in several models and by indirect contact/airborne transmission in ferrets
- Transmission from vaccinated animals has not been directly assessed; however, several vaccines protect against disease but do not completely protect against viral shedding in the upper respiratory tract, allowing the possibility of transmission

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Planned assessments of infection in Phase 2/3 trials

Amol Chaudhari, MD
Clinical Development Lead
CEPI

Overview of infection & transmission prevention assessment in ongoing COVID-19 vaccine clinical development programs

Amol Chaudhari, CEPI

17 December 2020

Assessment of infection prevention

Publicly available CT protocols of VE trials

Element	Moderna (US trial)	BNT/Pfizer (US trial)	AZ (US trial)	Janssen (US trial)
Assessed?	Yes	Yes	Yes	Yes
Endpoint#	**Secondary:** SARS-CoV-2 infection in the absence of symptoms defining COVID-19	**Exploratory:** Participants with the immune response for N-protein antibody	**Secondary:** Participants with post-treatment response for N-protein antibodies over time	**Secondary:** Post-vaccination serologic conversion in an N-protein dependent assay
Method	Post vaccination **seroconversion* to N-protein antibodies**			
Analysis population	Baseline seropositive & seronegative ~~both~~	Only baseline seronegative		
Timepoints	D 57 or later	D 28, 180, & 1 Y & 2 Y	D 57, 90, 180, & 1 Y & 2 Y	D 71, 6 M, & 1 Y
Stat test	Cox-proportional hazard	Clopper-Pearson method	Clopper-Pearson method	Poisson regression
Results	Not available publicly	Not available publicly	Not available publicly	Not available publicly

N-protein: Nucleocapsid protein, which is an antigen not contained in above vaccines. Abs specific to SARS-CoV-2 N-protein if detected in trial participants are indicative of natural infection thus allowing distinction from vaccine induced Abs.

 # - Moderna & Janssen protocols also include an endpoint to assess efficacy against symptomatic + asymptomatic infections

**** - Defined as 1) detectable post vaccination serum antibodies in baseline seronegative participants OR***
2) four fold rise in post vaccination titers compared to baseline in baseline seropositive participants

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Assessment of infection prevention

Publicly available CT protocols of VE trials

Element	Novavax (UK trial)	Curevac (multi country)	Butantan (Brazil)
Assessed?	Yes	Yes	Yes
Endpoint#	**Exploratory:** Occurrence of serologic conversion (by serology to SARS-CoV-2 N protein)	**Secondary^:** Occurrence of seroconversion to the N protein of SARS-CoV-2	**Secondary$:** Incidence of symptomatic or asymptomatic infections detected serologically and/or virologically
Method	Post vaccination **seroconversion* to N-protein antibodies**		**RT-PCR** or Four-fold rise in **IgG**
Analysis population	Only baseline seronegative		All trial participants
Timepoints	D 35 & 3M,6M,12 M post dose 2	D 211 and/or D 393	Week 6, 13 & 6M, 9M, 12M
Stat test	Clopper-Pearson method	Relative case reduction	Cox-proportional hazard
Results	Not available publicly	Not available publicly	Not available publicly

 # - Novavax protocol also includes an endpoint to assess efficacy against symptomatic + asymptomatic infections
^ - If primary and severe disease endpoint are not met, it will be considered as exploratory endpoint
$ - Asymptomatic infections are not being looked at separately
**** - Defined as detectable post vaccination serum antibodies in baseline seronegative participants***

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Assessment of infection prevention

Oxford vaccine trials (non-US)[#]

Element	COV002 (UK)	COV005 (S Africa)
Assessed?	Yes	Yes
Endpoint	**Exploratory:** PCR positive SARS-CoV-2 asymptomatic infection	**Exploratory:** VE in preventing asymptomatic SARS-CoV-2 infection (virologically) & VE for seroconversion in N-protein IgG Assay
Method	Virological confirmation (**RT-PCR or other NAAT**) of self-collected swab sample	**RT-PCR or Seroconversion**
Analysis population	All feasible participants^	All participants for virological confirmation Baseline seronegative for serological
Timepoints	Weekly throughout the study.	Day 7, 14, 28, 35, 42, 56, 182, 364
Stat test	Poisson regression model	Poisson regression model
Results*	Yes. VE was reported for : - LD-SD regimen: 58·9% (1·0 to 82·9) - **SD-SD regimen: 3·8% (−72·4 to 46·3)** - Overall : 27·3% (−17·2 to 54·9)	No

**** - Voysey et al. 08 Dec 2020, Lancet.***
 # - The trial in Brazil COV003 did not assess asymptomatic infection
^ - Weekly swab collection was done at only few sites as per feasibility
LD-SD – Low dose followed by standard dose; SD-SD – Two standard doses; NAAT – nucleic acid amplification test

Assessment of infection prevention

Data from clinical trial registries (protocols not available publicly)

	Endpoint for asymptomatic infection	
Developer	**Serology (Anti-N Ab)**	**Virological (PCR/ NAAT)**
Bharat Biotech [NCT04641481]	-	Monthly NP swab for RT-PCR in subset (n=10,000)*
Gamaleya Institute [NCT04530396]	Y	-
Medicago [NCT04636697]	Y	

There are other ongoing efficacy trials of COVID-19 vaccine candidate but information on asymptomatic infection within those programs is not available publicly

**** - Information from a personal communication***

Assessment of transmission prevention

- Efficacy against infection transmission prevention can be assessed via
  - Specially designed studies (e.g household contacts of vaccinees) or
  - Surrogates like viral load or viral shedding in biological samples (e.g. NP swabs, stools)
  - Indirectly through efficacy against infection prevention (a vaccine that completely prevents infection acquisition will also block transmission)

- Little to no public information on plans for special studies to assess transmission prevention among the ongoing COVID-19 vaccine development programs

- Following developers are assessing viral load in efficacy trial of COVID-19 vaccines
  - **AZ/Oxford (UK & US trials), Moderna & Janssen**: Serial viral load in NP swabs via RT-PCR among infected participants

- Viral shedding is being assessed in efficacy trials of AZ/Oxford vaccine candidate in
  - **Stool samples** in UK trial
  - Self or site collected **saliva samples** in US trial

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To summarise….

- Ongoing efficacy trials of COVID-19 vaccine candidates have included asymptomatic infection prevention as secondary or exploratory endpoint

- Major approaches to identify asymptomatic infection include:
  - **Serological** - Seroconversion to non-vaccine antigen (e.g. N-protein)
  - **Virological** – Periodic RT-PCR (or other NAAT) samples from asymptomatic participants
  - **Combination** of serological and virological detection

- Very limited data on VE against infection currently available and it is inconclusive at present. More evidence likely to be available in coming months

- Limited evidence on VE against transmission prevention may also become available through surrogates like viral load and shedding from a few ongoing programs

Experience from using weekly PCRs to detect asymptomatic infections

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Professor of Paediatric Infection and Immunity
University of Oxford

Merryn Voysey, DPhil

Lead Statistician

University of Oxford

Experience using weekly PCRs to detect asymptomatic infections

Dr Merryn Voysey,

Lead Statistician, Oxford Vaccine Group, University of Oxford

Asymptomatic infection

- An estimated 40% of SARS-CoV-2 infections are asymptomatic
- A vaccine with efficacy against asymptomatic infection has the potential to greatly reduce transmission and end the pandemic sooner
- Vaccine efficacy may be lower against asymptomatic infection than for symptomatic COVID-19 for some/all vaccines

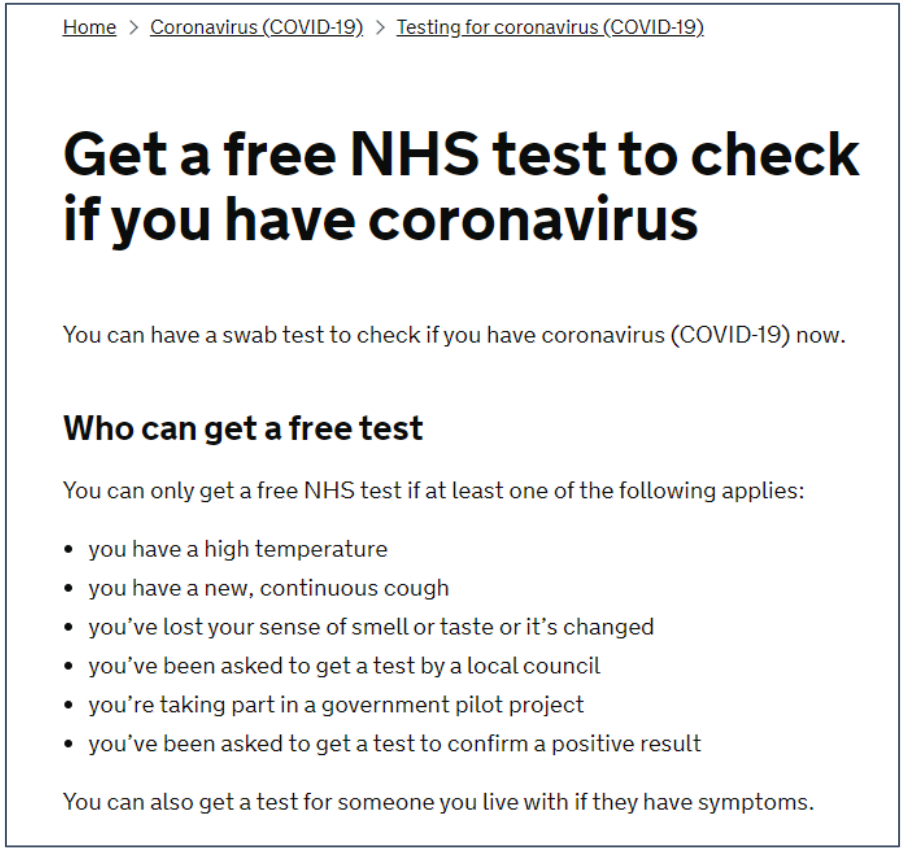
Asymptomatic infection

1. Seroconversion to SARS-CoV-2 N protein
   - Under-detection
     - Short lived N protein antibody responses
     - Assay sensitivity
     - Depends which visits you use for the assessment
   - Timing of infection unknown

2. PCR+ asymptomatic infection
   - No trigger for taking a swab therefore constant swabbing required
   - Logistical nightmare
   - $$$

COV002 study

- Single blind randomised trial of ChAdOx1 nCoV-19 vs MenACWY vaccine (N~10,000) (Voysey et al, Lancet 2020)
- Asymptomatic PCR+ infection secondary endpoint
- UK national system for self-collected nose/throat swab done at home using a kit
- Centralised laboratory for processing



Home > Coronavirus (COVID-19) > Testing for coronavirus (COVID-19)

Get a free NHS test to check if you have coronavirus

You can have a swab test to check if you have coronavirus (COVID-19) now.

Who can get a free test

You can only get a free NHS test if at least one of the following applies:

- you have a high temperature
- you have a new, continuous cough
- you've lost your sense of smell or taste or it's changed
- you've been asked to get a test by a local council
- you're taking part in a government pilot project
- you've been asked to get a test to confirm a positive result

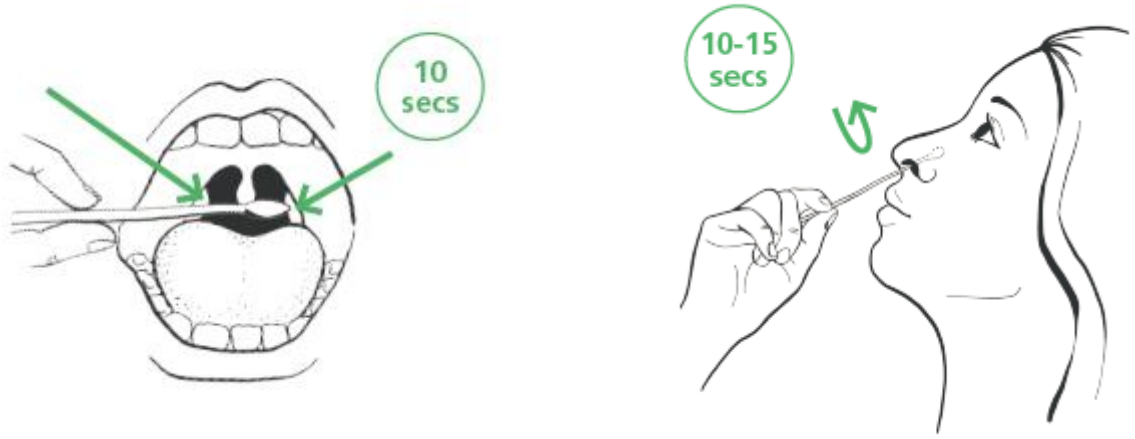
You can also get a test for someone you live with if they have symptoms.

COV002 asymptomatic testing

- Tapping into an already existing NHS system
- NHS swab kits packaged centrally with a unique barcode identifier to separate study swabs from others
- On a weekly basis, participants required to
  - Take swab as per instructions
  - Register the swab online
  - Post to central laboratory using designated post-boxes
- Participants informed of their results directly, via text message, by the NHS, including information on self-isolation

COV002 asymptomatic testing

- Daily data extract from the NHS of all swab results with our barcode (barcodes starting with ‘VAC’)
- Downloaded data matched to participants in the study
- Positive swabs uploaded into study database



Symptomatic or asymptomatic

- Participants not contacted by study team when positive on a weekly self-swab. Participants received information directly from NHS

  - Asymptomatic cases
  - Cases with unknown symptoms

Vaccine efficacy - UK

Cases > 14 days post booster dose	N cases	ChAdOx1 nCoV-19 n/N (%)	Control n/N (%)	VE (95% CI)
Asymptomatic/unknown symptoms	**69**	**29/3288 (0.9%)**	**40/3350 (1.2%)**	**27% (-17%, 55%)**
LD/SD	24	7/1120 (0.6%)	17/1127 (1.5%)	59% (1.0%, 83%)
SD/SD	45	22/2168 (1.0%)	23/2223 (1.0%)	4% (-72%, 46%)
Primary symptomatic COVID-19	**86**	**18/3744 (0.5%)**	**68/3804 (1.8%)**	**73.5% (56%, 84%)**
LD/SD recipients	33	3/1367 (0.2%)	30/1374 (2.2%)	90% (67%, 97%)
SD/SD recipients	53	15/2377 (0.6%)	38/2430 (1.6%)	60% (28%, 78%)

Limitations

- PCR testing for SARS-CoV-2 has improved over time
- Effect of false positives may be important when there is low disease incidence

Next steps

- Correlation with seroconversion to N protein
- Detection/removal of false positives by N protein antibody response post PCR+
- Analysis of shedding time
- Analysis of Ct values

Part 3:

Additional approaches, evidence / post-licensure studies

Moderated By:

Daniel Feikin, MD, MSPH

Department of Immunizations, Vaccines, and Biologicals

(World Health Organization, WHO)

Modelling: impact of vaccine efficacy against disease versus transmission on public health and pandemic curves

Neil Ferguson, PhD

Director, MRC Centre for Global Infectious Disease Analysis

Imperial College, London

Modelling the impact of SARS-CoV-2 vaccines: role of direct vs indirect protection

Neil Ferguson

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

Report 33: **Modelling the allocation and impact of a COVID-19 vaccine**
https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-33-vaccine/

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Joint work involving:

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Imperial College COVID-19 Response Team

Indirect protection

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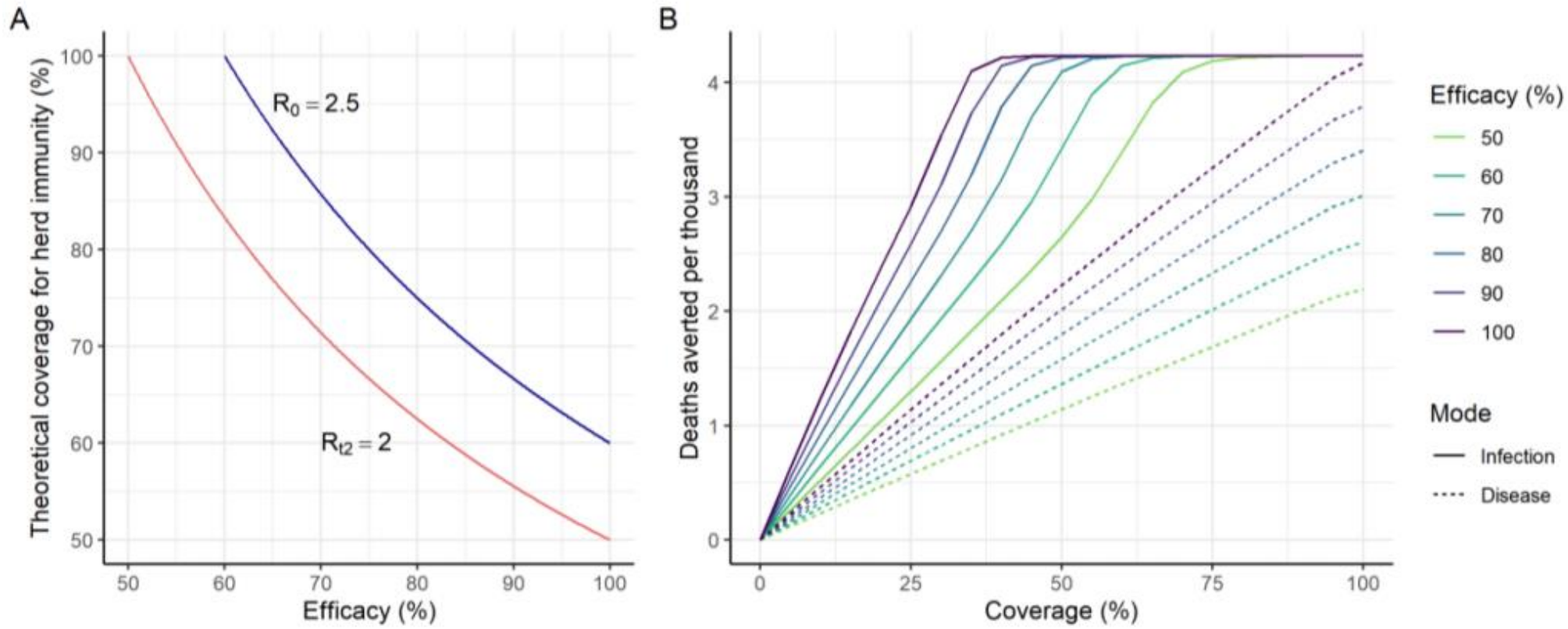
- Protection of unvaccinated people in a population afforded by vaccination of the rest
- Extent depends on vaccine coverage and efficacy against transmission



SARS-CoV-2 Transmission Model

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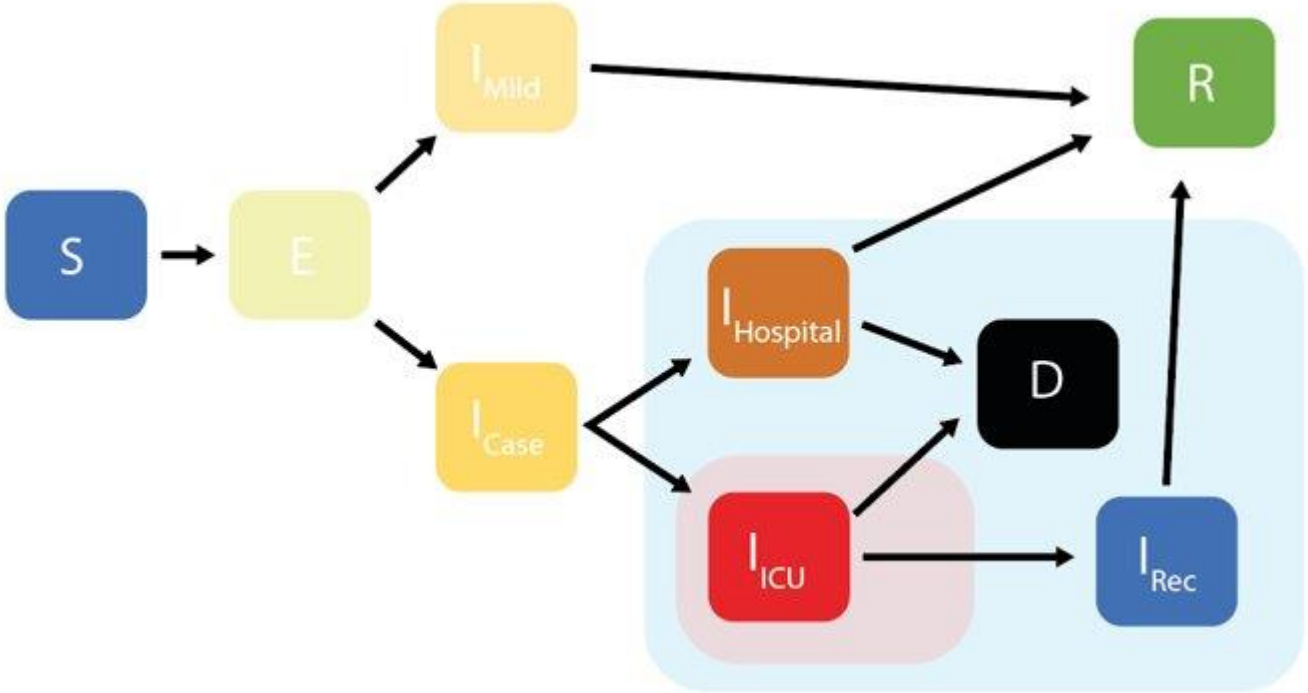
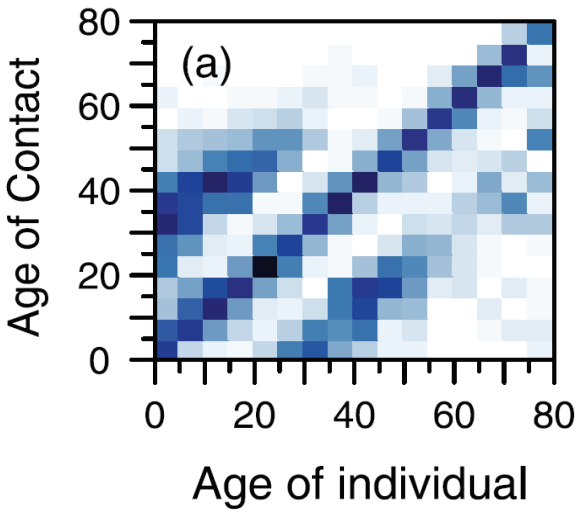
- Age-structured SEIR models (17 five-year age groups) with expanded healthcare component
- Two versions (UK and global) – SIRCOVID and SQUIRE
- Both open source as R package



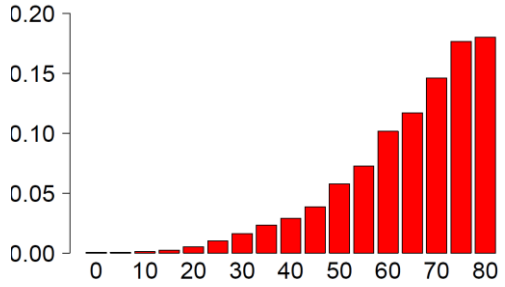
Inputs:

- Epidemiological parameters determining spread and severity
- Demography
- Population contact patterns
- Healthcare capacity

Model features



Patterns of mixing between age-groups: vary by income setting

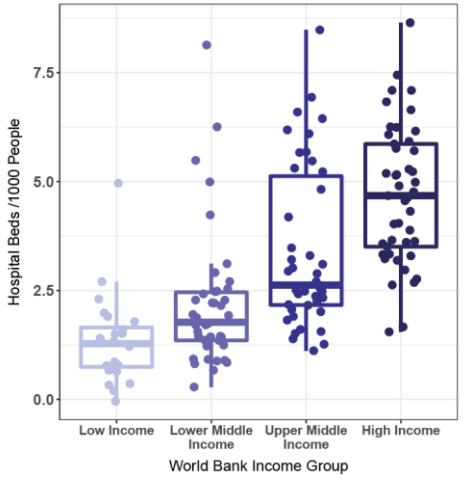


Age-dependent patterns of disease severity.

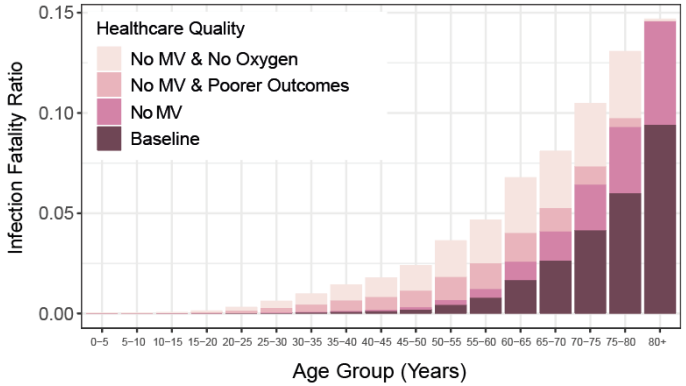
Table S3: Expert Clinical Opinion for Severity Outcomes

Questions
Fatality rate in those who require ICU
1. If require mechanical ventilation (~80% of UK ICU patients) but

Expert clinical consensus opinion on impact of treatment in different settings



Setting-specific healthcare capacity –for both general hospital and ICU beds.



Healthcare capacity-dependent mortality from COVID-19.

Walker PGT, Whittaker C, Watson OJ, *et al.* The impact of COVID-19 and strategies for mitigation and suppression in low- and middle-income countries. *Science* 2020; **422**: eabc0035.

Adding vaccination

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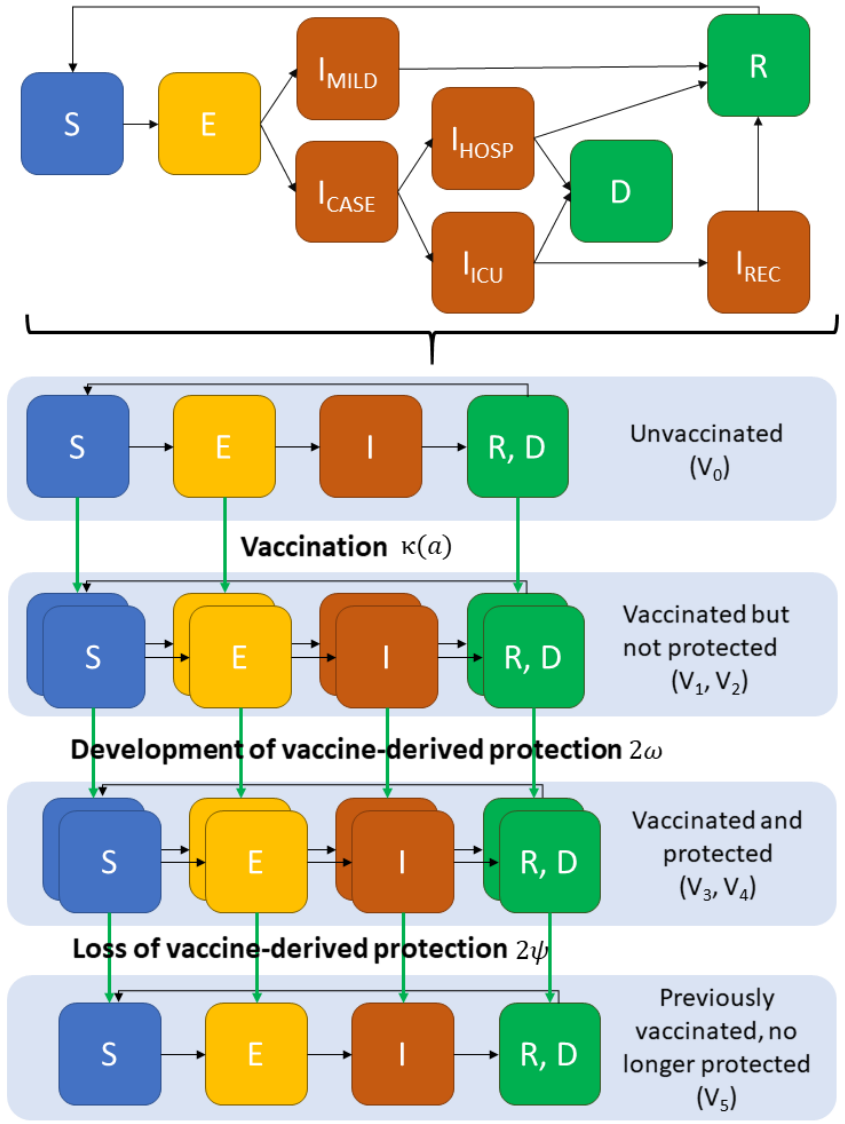
Can capture and explore:

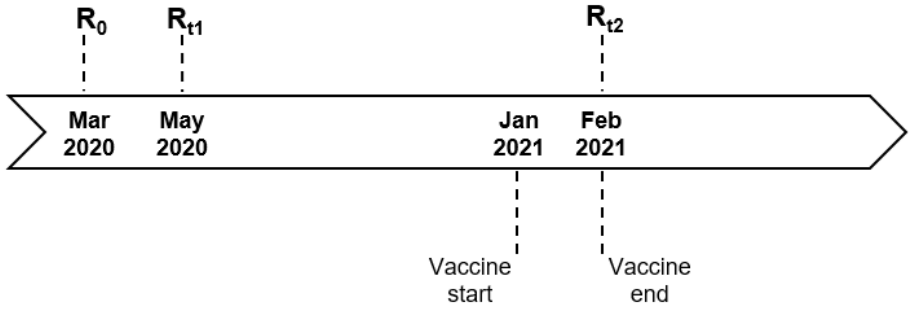
- Vaccine mode of action:
  - anti infection
  - anti disease
- Vaccine efficacy
- Age-varying efficacy (immunosenescence)
- Vaccine age-targeting and prioritisation strategies
- Vaccine coverage
- Duration of vaccine-derived immunity
- Duration of naturally-acquired immunity

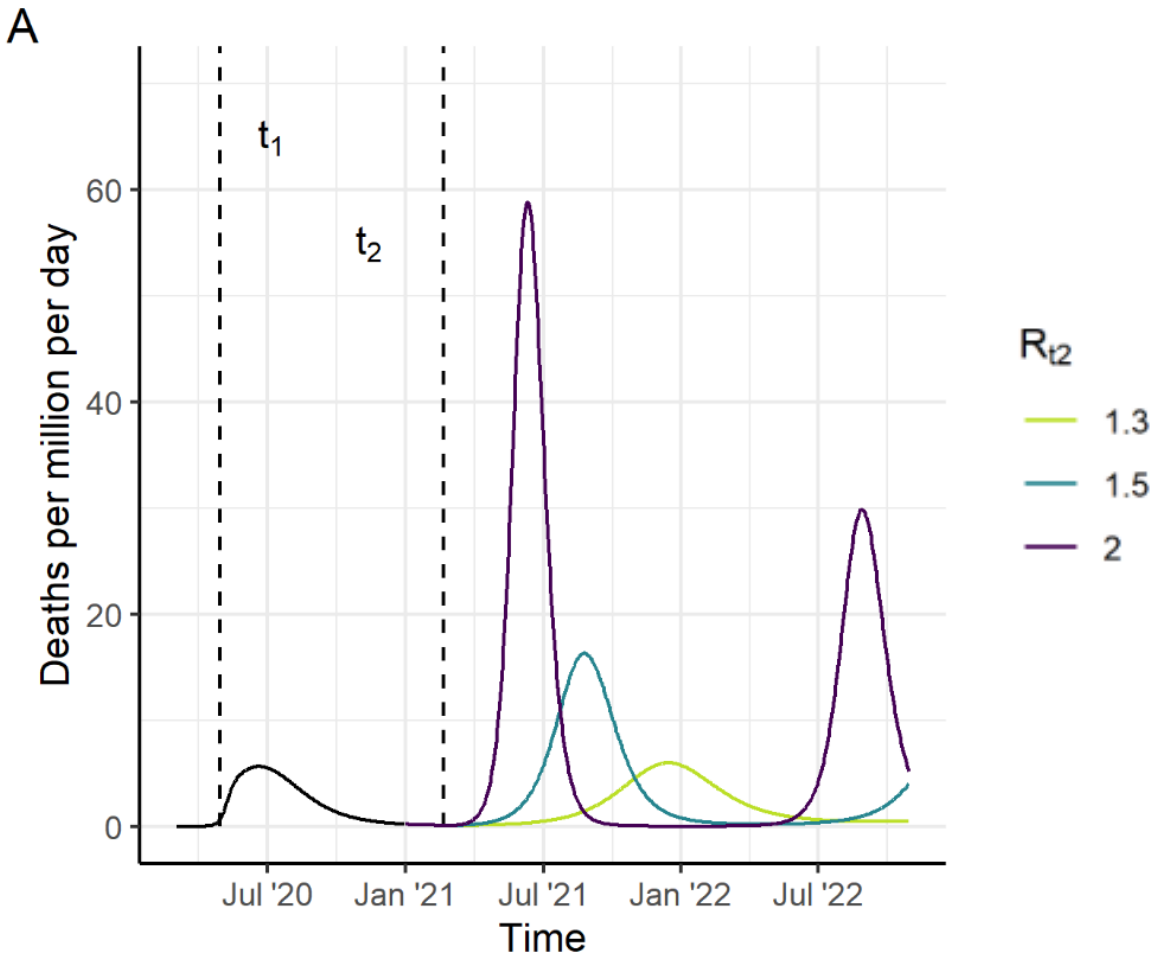


Global scenarios

Varied R_t such that

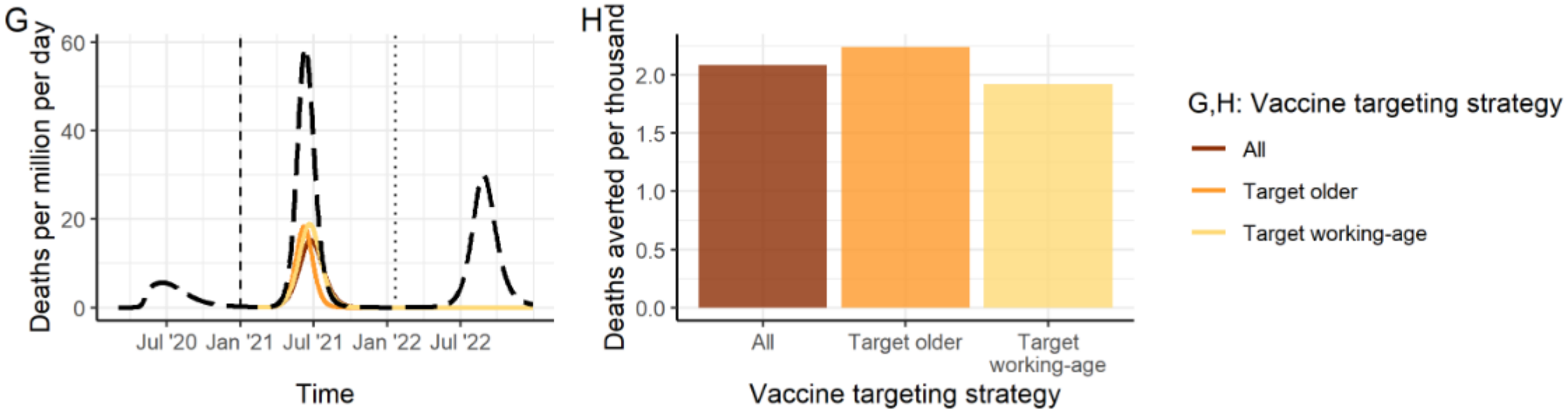
- Initial epidemic wave in March 2020, followed by reduced social contact
- ~10% in Recovered class at end of 2020
- Partial lifting of suppression measures from 2021 when vaccine introduced





Vaccine impact

- If NPIs are lifted at vaccine introduction and that vaccination takes place over a longer time period (one year), vaccine impact will be lower
- A greater public health impact will be obtained by targeting the older ages first rather than the working age population because the overall vaccine coverage during the period in which the epidemic occurs is low



UK modelling

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- Consider protection against disease or against infection
- Assume NPIs are lifted completely at some time point
- Age prioritisation in roll-out
- 4M Pfizer doses in December 2020 (90% efficacy)
- Jan-Mar 2021 – enough doses to vaccinate everyone >50
- 20% Pfizer, 80% AstraZeneca

- Pessimistic scenario:
  - pessimistic vaccine efficacy (AstraZeneca efficacy 65%)
  - pessimistic vaccine uptake (50% uptake in the under 50s)
  - pessimistic post-lockdown transmissibility ($R_{\mathbf{excl\_immunity}}$ = 1.4)
- Reasonable best case, RBC:
  - optimistic vaccine efficacy (AstraZeneca efficacy 90%)
  - optimistic vaccine uptake (75% uptake in the under 50s)
  - optimistic post-lockdown transmissibility ($R_{\mathbf{excl\_immunity}}$ = 1.2)
- "Central" scenario: [*only considered for the full lifting of NPIs scenario*]
  - optimistic vaccine efficacy (AstraZeneca efficacy 90%)
  - pessimistic vaccine uptake (50% uptake in the under 50s)
  - pessimistic post-lockdown transmissibility ($R_{\mathbf{excl\_immunity}}$ = 1.4)

UK modelling: schedule

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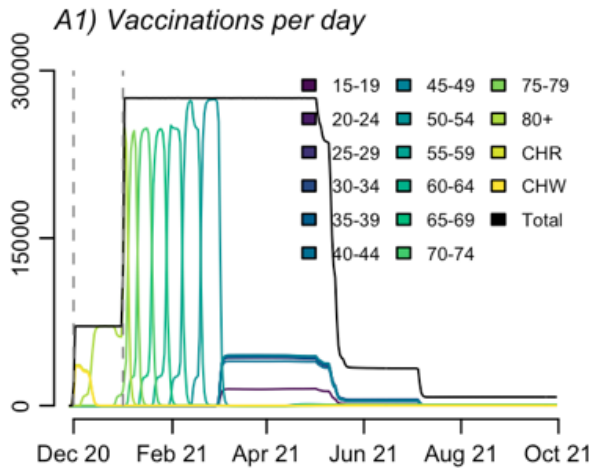
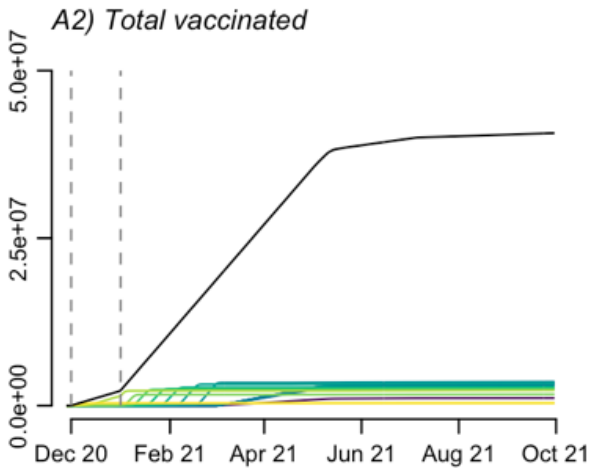
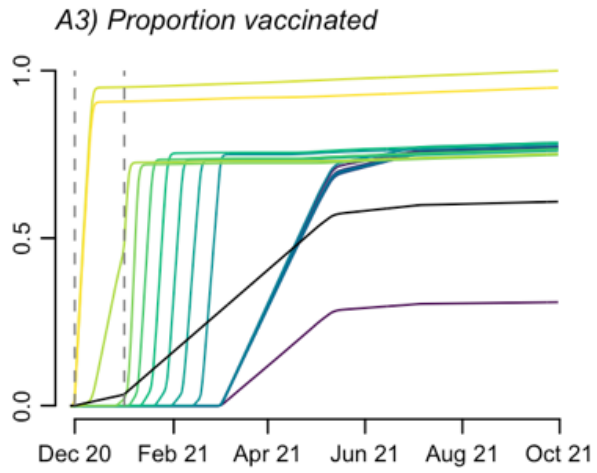
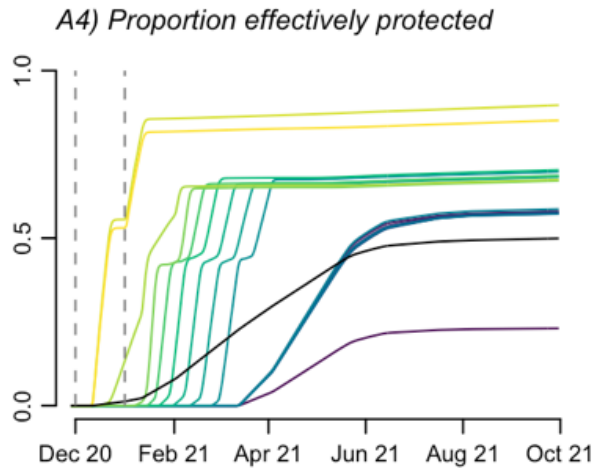
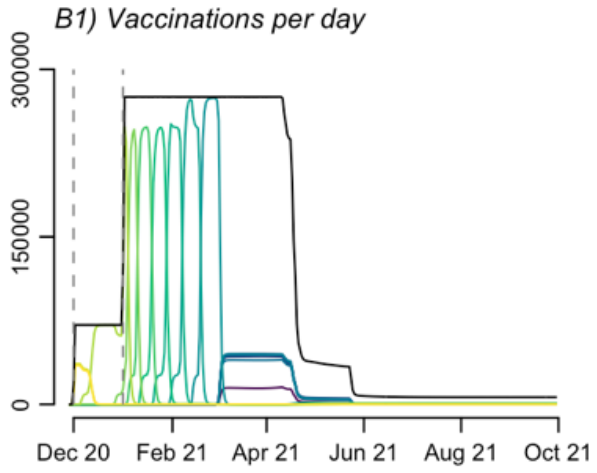
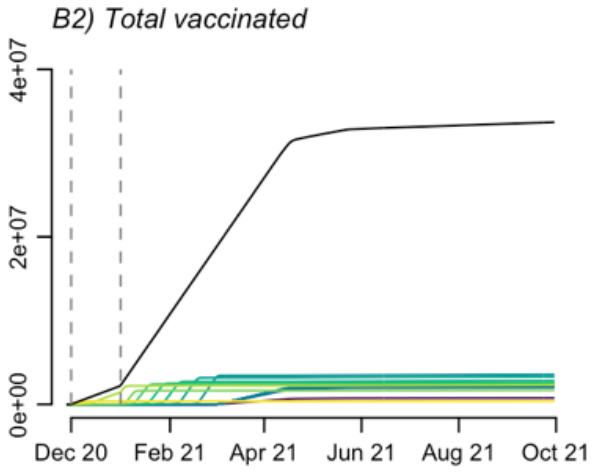


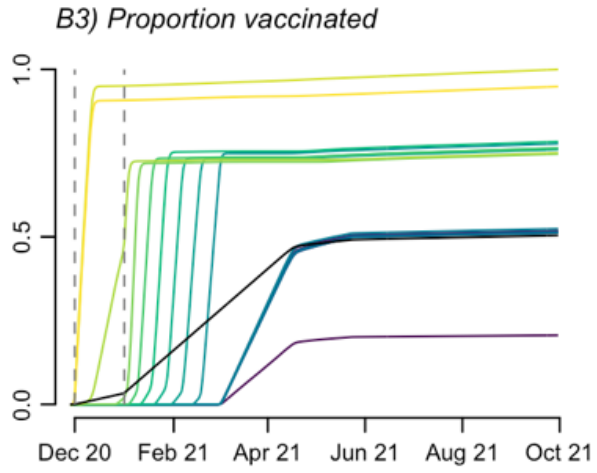


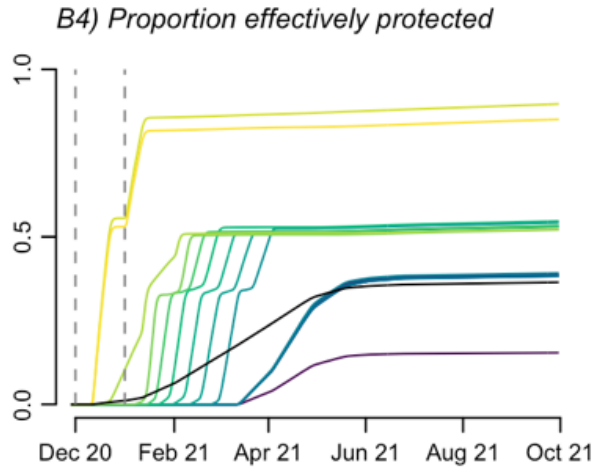


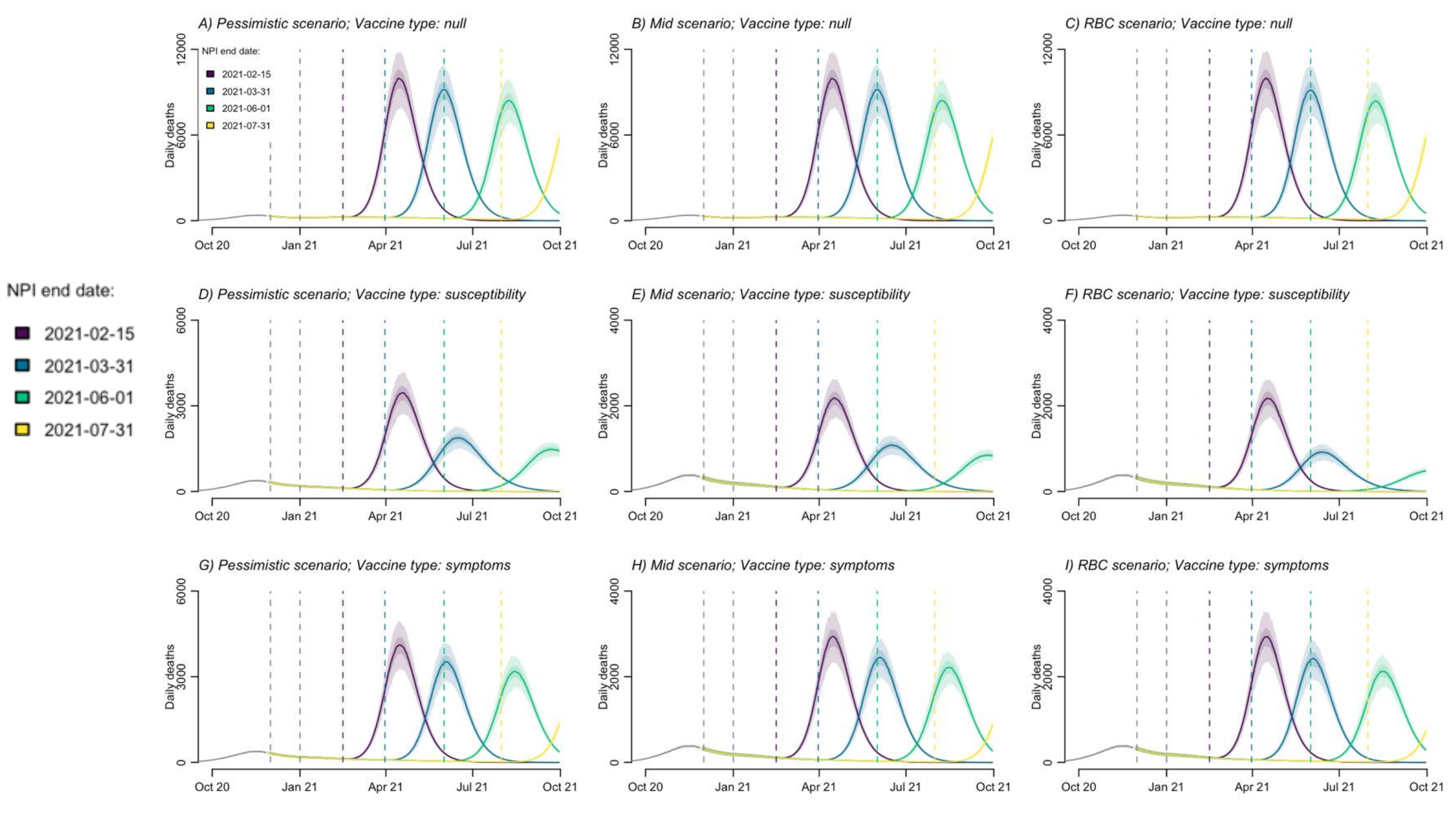








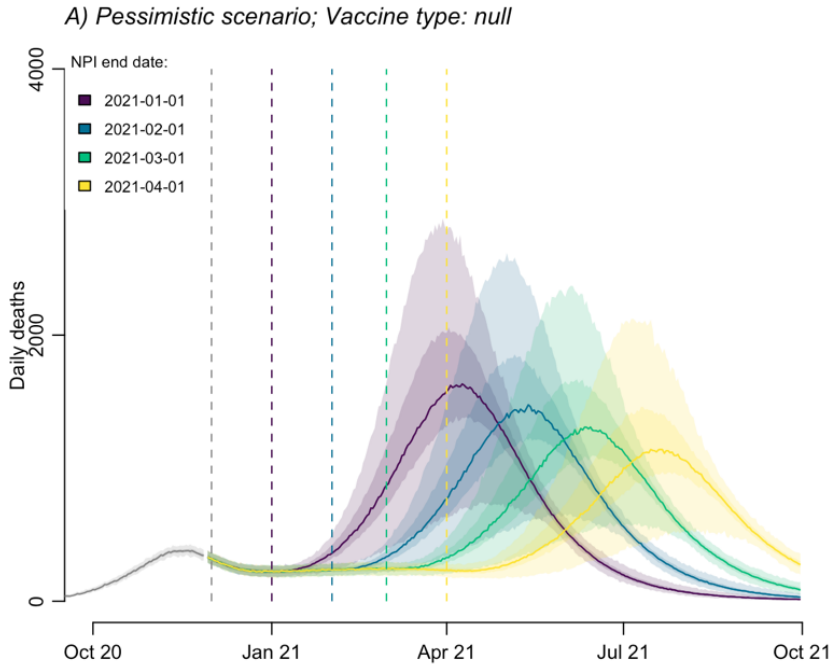


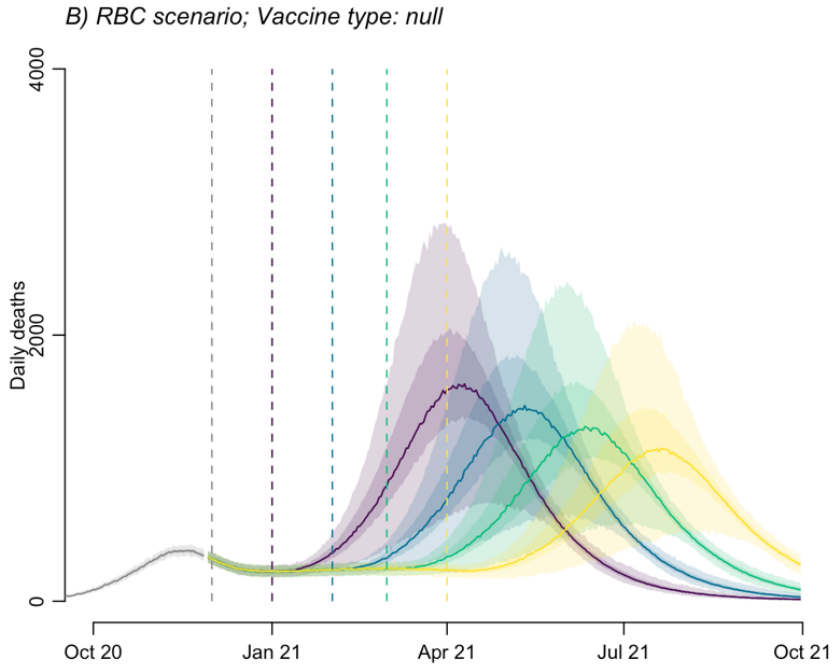

A) Pessimistic scenario; Vaccine type: null
B) Mid scenario; Vaccine type: null
C) RBC scenario; Vaccine type: null
D) Pessimistic scenario; Vaccine type: susceptibility
E) Mid scenario; Vaccine type: susceptibility
F) RBC scenario; Vaccine type: susceptibility
G) Pessimistic scenario; Vaccine type: symptoms
H) Mid scenario; Vaccine type: symptoms
I) RBC scenario; Vaccine type: symptoms
NPI end date:
2021-02-15
2021-03-31
2021-06-01
2021-07-31
Daily deaths
Oct 20
Jan 21
Apr 21
Jul 21
Oct 21

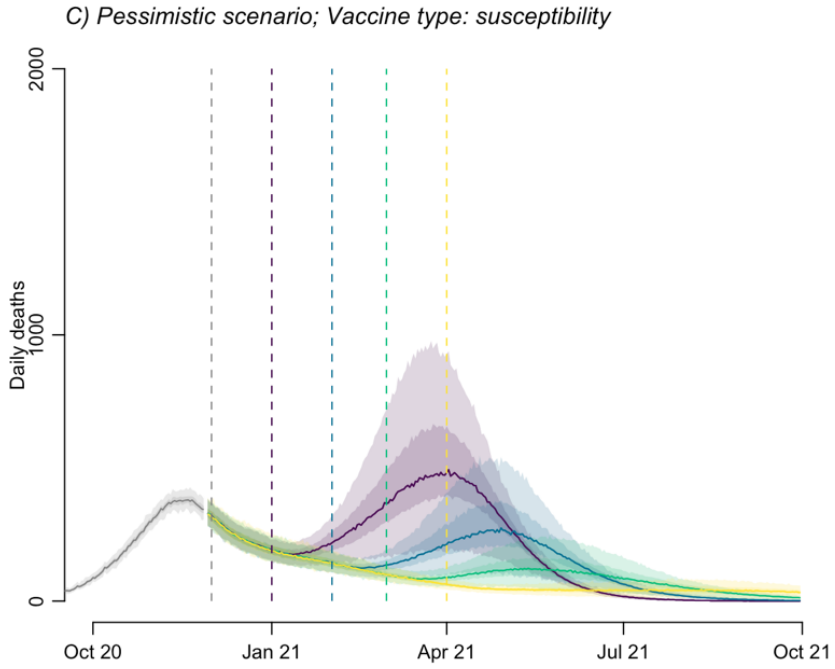
Partial lifting (R=1.4)

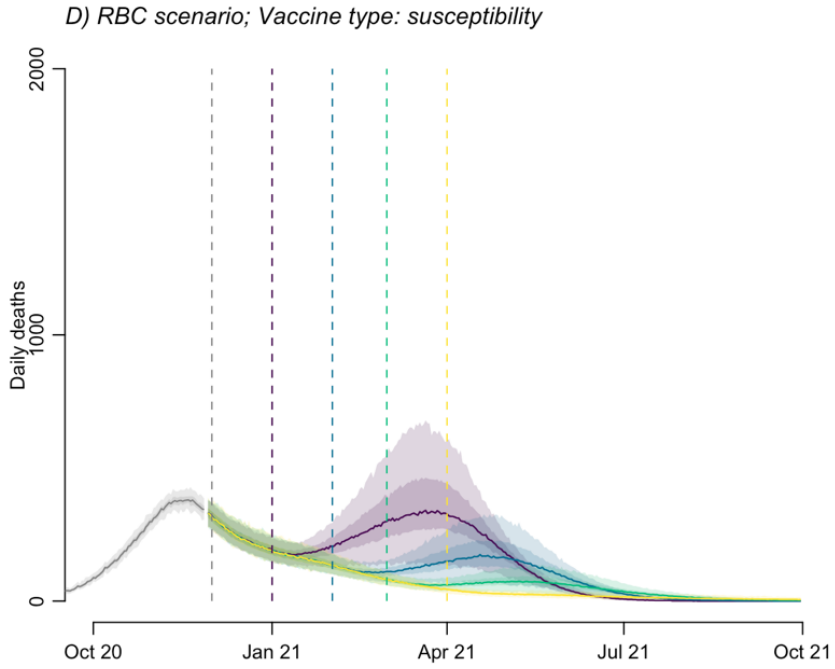
NPI end date:

- 2021-01-01
- 2021-02-01
- 2021-03-01
- 2021-04-01

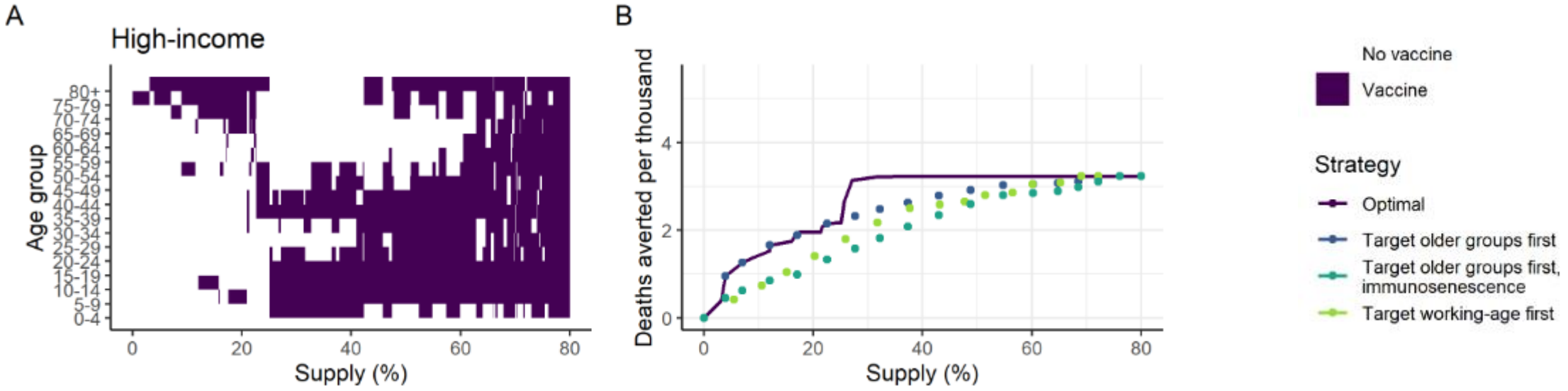






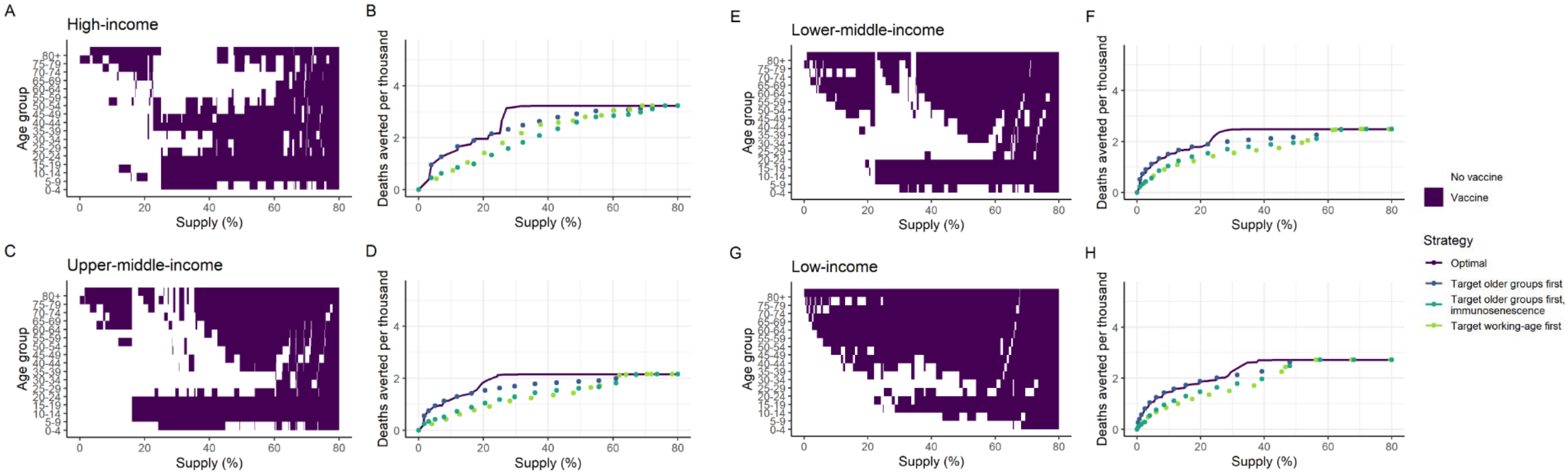


Vaccine allocation: within-country



- With limited dose supply (<20% coverage) all income groups target direct protection of the highest risk groups (elderly) first
- At higher coverage a strategy targeting herd-impact is chosen – this provides indirect protection to the high risk groups by suppressing transmission
- Switching point between two strategies is dependent on demography and contact patterns, as well as NPIs, vaccine characteristics and rollout timescales

Vaccine allocation: within-country



- Switching point between two strategies is dependent on demography and contact patterns, as well as NPIs and vaccine characteristics

Vaccine allocation: global optimised

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Strategy	Total deaths averted per million global population	Total deaths averted per 100 fully vaccinated
Optimised	1609	1.373

Next best solutions:

Strategy	Total deaths averted per million global population	Total deaths averted per 100 fully vaccinated
Countries are allocated doses relative to population size, with individuals 65 years and older targeted first	1257	1.131
Countries are allocated doses relative to size of population 65 years and older, with that age group targeted first	1317	1.178

Within this global optimal allocation we see both strategies seen in the within-country allocation:

1. The most common = direct protection of the high risk groups (elderly)
2. Less common = indirect protection of high risk groups by herd impact

Summary

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- Indirect protection likely to be key to returning to “normal”
- Even with 75-80% coverage with a vaccine which gives 90% efficacy against disease, ongoing transmission can cause very high mortality in the remaining 20% in the absence of efficacy against transmission or NPIs
- Even if vaccines offer high (eg 90%) efficacy against infection/transmission, high coverage in the general population will be necessary to stop transmission, given R_0=3+
- Even in high income countries, significant NPIs will therefore need to remain in force for at least Q1-2 20201
- There are some circumstances (if efficacy against infection/transmission is high) where targeting vaccination at key transmitters (young adults) can in theory be optimal
- However, vaccinating the oldest first is optimal when available stocks are low, or doses are delivered over the course of months-years
- Global allocation by country size is not far from optimal (by population over 65 a little more so)

Ongoing work

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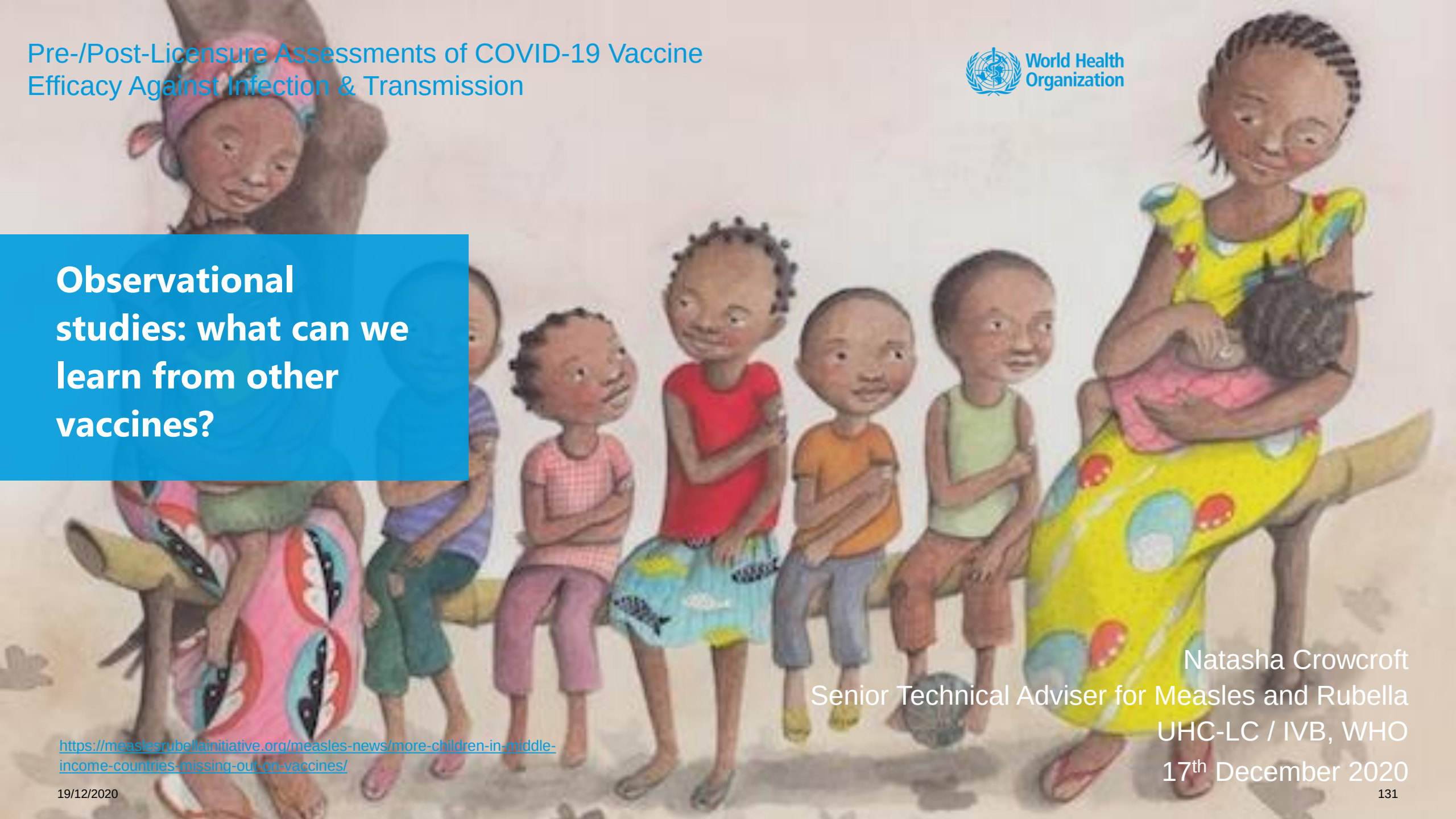
- Updating parameter ranges as trial information becomes available
- More detailed UK modelling exploring rate at which social distancing measures may be able to be relaxed
- Additional analyses, building on country-specific model fitting to numbers of deaths (European Centre for Disease Control) and Google mobility data (https://mrc-ide.github.io/global-lmic-reports/)
  - Static country reports
  - Interactive web tool
- Ongoing work estimating the combined epi-econ impact of Covid19, NPIs and role of vaccination
- Still gaining understanding of protective immunity following COVID-19 disease
- Likely that multiple, different vaccines will be implemented globally and within countries

Observational studies: what can we learn from other vaccines?

Natasha Crowcroft, MD
Senior Technical Adviser
World Health Organization (WHO)

World Health Organization

Observational studies: what can we learn from other vaccines?



https://measlesrubellainitiative.org/measles-news/more-children-in-middle-income-countries-missing-out-on-vaccines/

Natasha Crowcroft
Senior Technical Adviser for Measles and Rubella
UHC-LC / IVB, WHO

17th December 2020

Outline

- Background on pertussis and measles
- Examples from studies of pertussis vaccine effectiveness against transmission and measles vaccine failure
- Conclusions

Pertussis

Inactivated/subunit vaccine: high initial effectiveness, protection wanes

Vaccine modified disease **transmits**; infectivity is related to severity of symptoms

High coverage leads to **moderate** herd effects

No agreed correlate of protection

Measles

Live measles vaccine: highly effective and long duration of protection.

Vaccine modified disease **very rarely transmits**, does not contribute to epidemiology

High coverage leads to **strong** herd effects

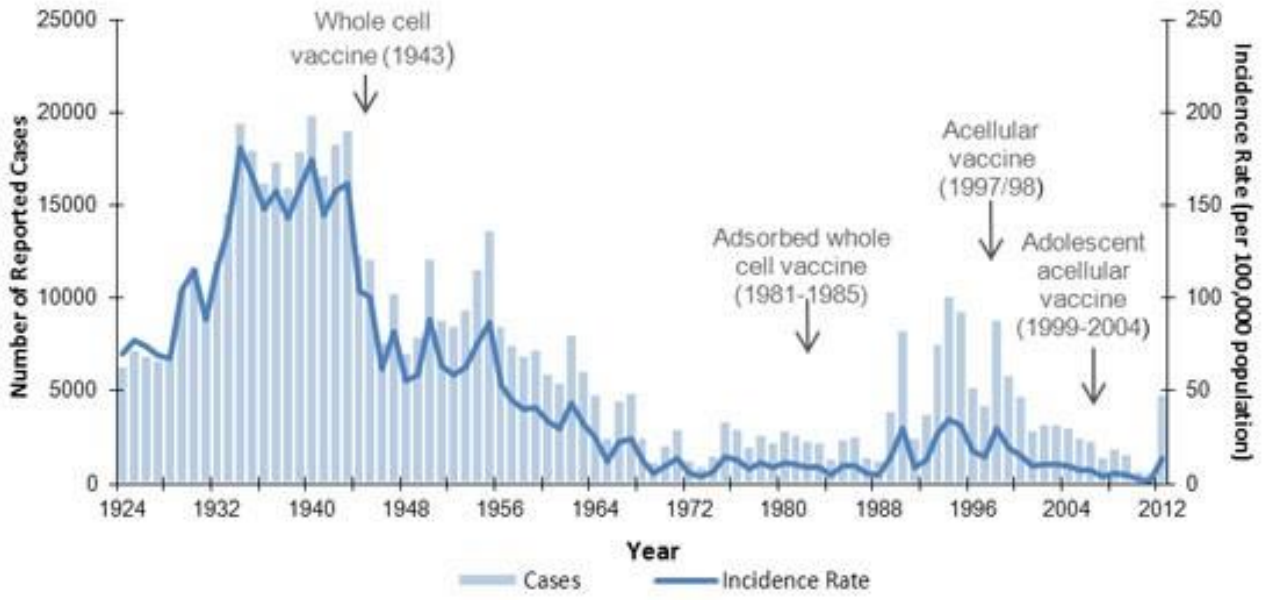
Agreed correlate of protection

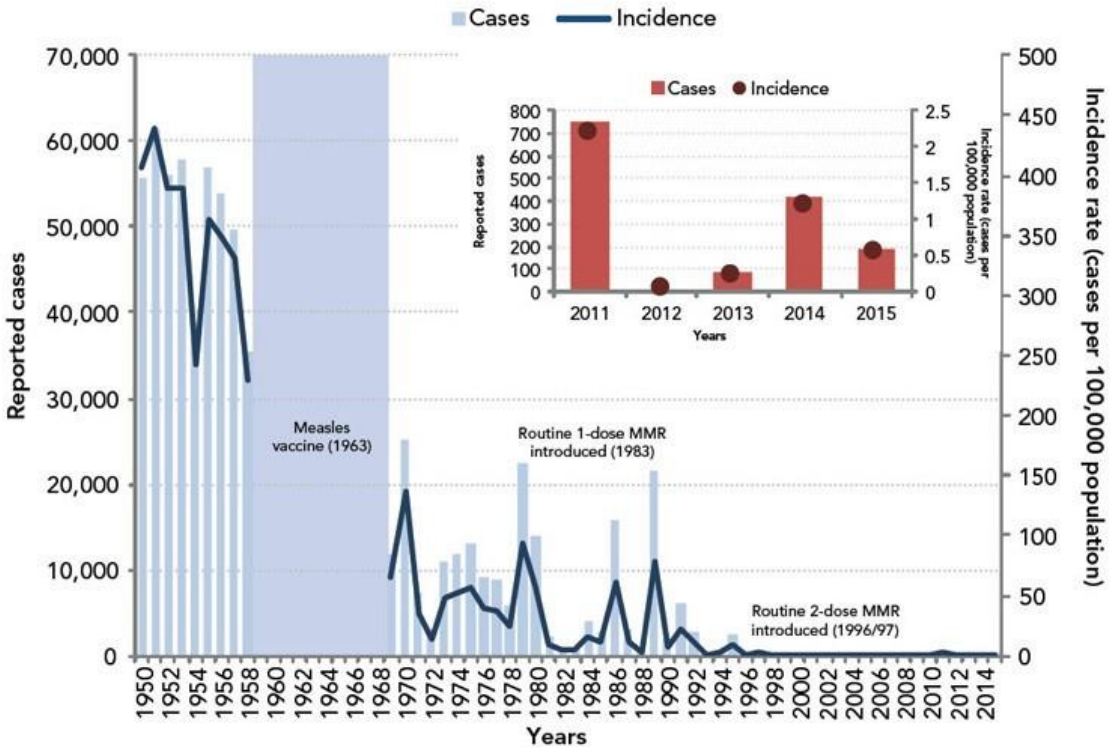
https://www.who.int/wer/2015/wer9035.pdf?ua=1

*Bolotin et al)JID 2020 https://academic.oup.com/jid/article/221/10/1576/5610904

Epidemiology shows indirect effects due to reduced transmission: Good surveillance is essential

Pertussis epidemic cycles indicate ongoing transmission despite immunization





Measles vaccination alters age distribution, interrupts transmission

https://www.canada.ca/en/public-health/services/immunization/vaccine-preventable-diseases/pertussis-whooping-cough/health-professionals.html
https://www.canada.ca/en/public-health/services/diseases/measles/health-professionals-measles.html
https://www.who.int/immunization/sage/meetings/2014/april/1_Pertussis_background_FINAL4_web.pdf?ua=1
https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-015-0382-8

Household studies of pertussis infectivity build on routine reporting, requires agile research team

Households with a case of pertussis in Brazil. Interview and nasopharyngeal swab from every family member with h/o cough in past 21 days. Cases confirmed by culture or clinical case definition.

Estimated whole cell pertussis VE against transmissibility by comparing the secondary attack rate when the primary case was fully vaccinated with the secondary attack rate when the primary case was > 5 years old, unvaccinated or partially vaccinated.

Baptista et al Ped Infect Dis J 2006

VE to reduce case bacteriologic positivity

63.1% (40.7 to 77.0)

VE of reducing transmission to contacts

61.6% (12.8 to 83.1)

Prospective longitudinal cohort studies require community-based platform to study transmission

Active population surveillance in a sub-Saharan rural community of 30 villages

Multiple case definitions based on clinical, laboratory and epidemiological criteria

Key case definition ≥21 days cough with paroxysms and positive culture, serology or epi-link

Secondary case definitions – with or without 28 day cut-off

Using key case definition for secondary cases within 28 days

VE=85% (46-95)

Any secondary case

VE=67% (20-85)

Préziosi and Halloran Vaccine 2003

High vaccine effectiveness: Study vaccine failures and breakthrough measles infections

Outbreak investigations important for understanding the role of vaccine failures

No evidence of onward transmission. Sundell N et al. Measles outbreak in Gothenburg urban area, Sweden, 2017 to 2018: low viral load in breakthrough infections. Euro Surveill. 2019

A one-dose vaccinated case resulted in outbreak of 678 cases. Potentially a primary vaccine failure. De Serres G et al. Largest measles epidemic in North America in a decade--Quebec, Canada, 2011 J Infect Dis. 2013

Transmission by a 3-dose vaccinated adult to to 8 others. Avramovich E et al. Measles Outbreak in a Highly Vaccinated Population - Israel, July-August 2017. MMWR Morb Mortal Wkly Rep. 2018

Quantitative PCR correlate of infectiousness. Seto J et al. Detection of modified measles and super-spreader using a real-time reverse transcription PCR in the largest measles outbreak, Yamagata, Japan, 2017 in its elimination era. Epidemiol Infect. 2018;146(13):1707-13.

Specialist expertise is needed to understand how vaccines fail – microbiology and immunology

All-or-none vaccines (Primary vaccine failure): age-appropriate severity

Waning (Secondary vaccine failure): protection declines exponentially

Vaccine modified disease: Milder illness in vaccinated

Leaky vaccines: Each exposure carries an equal risk of infection for everyone, no change in severity, may look like waning after multiple exposures

Exposure threshold: VE in high infectious dose lower than low infectious dose

Breakthrough infection: a confirmed case in an individual with history of vaccination and/or positive IgG levels

Failure to prevent transmission of infection: multiple potential models

Immunology of pertussis transmission

Cell-mediated immunity is critical for protective immunity

Impact of acellular (aP) versus whole cell (wP) pertussis vaccine on transmission in the baboon model:

Both Th1 and Th17 memory responses are needed to produce sterilizing mucosal immunity against pertussis

Canadian Immunization Research Network study protocol available for human household pertussis study with detailed immunology follow up

Pinto MV and Merkel TJ. J Infect. 2017 Jun;74 Suppl 1:S114-S119; Bolotin et al CMAJ Open 2017 http://cmajopen.ca/content/5/4/E872.long ; https://www.adelaidezoo.com.au/bouncing-baby-baboon/

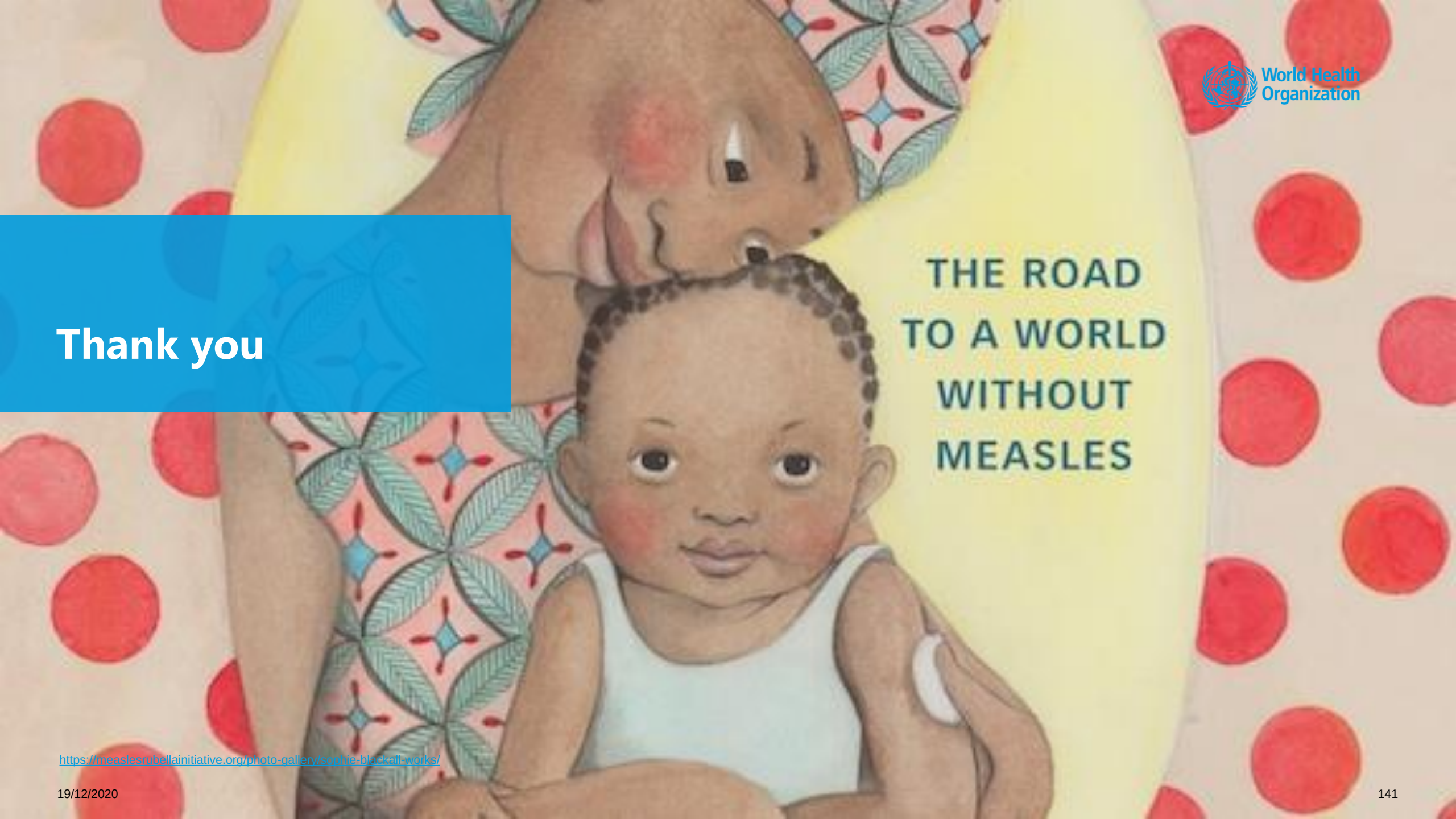
Lessons from experience of pertussis and measles

Mass immunization programmes leave **epidemiological signatures** in surveillance data of impact of vaccines on interrupting transmission. Modelling is an essential tool for interpreting the signature.

Household studies, longitudinal prospective community based cohort studies and outbreak investigations have yielded important insights on impact of vaccines on transmission. Case definitions, secondary case definitions, ascertainment and laboratory diagnostic methods are important considerations.

Surveillance, microbiological and immunological data are essential for understanding why and how vaccines succeed or fail to prevent transmission. Appropriate **specimen collection** is needed to understand the model of failure.

Thank you



https://measlesrubellainitiative.org/photo-gallery/sophie-blackall-works/

Statistical approaches to studying transmission

Ira Longini, PhD

Professor of Biostatistics

University of Florida / WHO

Statistical approaches to studying transmission

Design and analysis of studies to measure the impact of vaccination on transmission on both the individual and population level

Ira Longini
Professor
Department of Biostatistics
Emerging Pathogens Institute
University of Florida

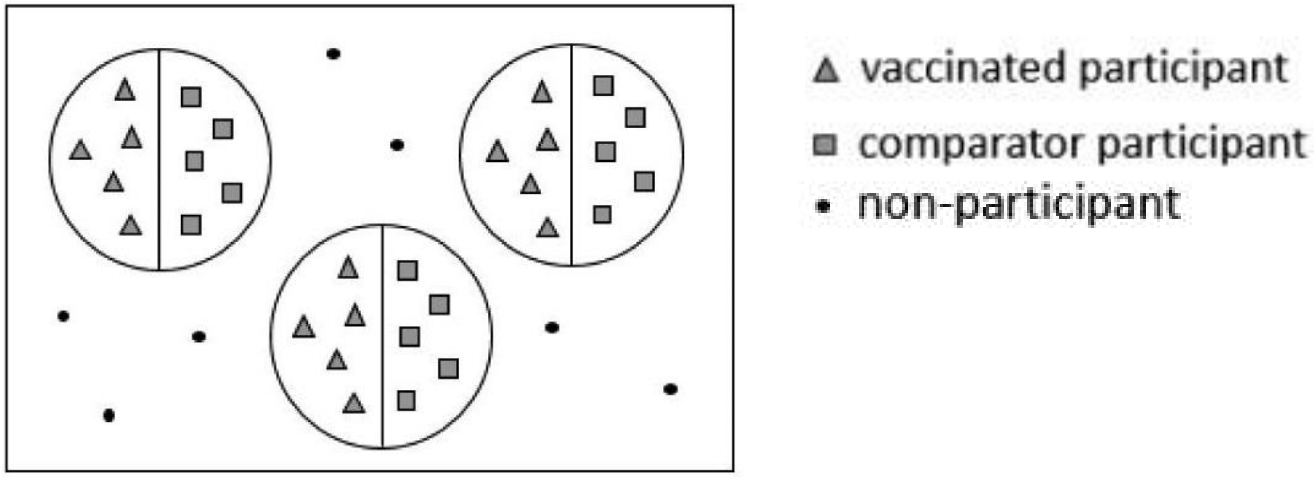
Consultant to WHO

Measures of vaccine effectiveness against transmission

- Based on the ratio definition of VE,
  - λ_V transmission rate involving vaccinated
  - λ_U transmission rate involving unvaccinated
  - $VE = 1 - \frac{\lambda_V}{\lambda_U}$
- Transmission in clusters
  - Individual level
    - Smaller clusters such as households, compounds, contact rings or tracing of contacts
  - Population level
    - Larger clusters such as villages, towns, regions of cities

Individual level study design of vaccine effectiveness against transmission

Distribute vaccine or comparator (or nothing) within cluster



Vaccinated and unvaccinated people are exposed to each other

Individual level estimator of vaccine effectiveness against transmission

- Vaccine efficacy for transmission to others, VE_I
- Secondary attack rate from a vaccinated person to others
  - $SAR_{V\bullet}$
- Secondary attack rate from an unvaccinated person to others
  - $SAR_{U\bullet}$
- $VE_I = 1 - \frac{SAR_{V\bullet}}{SAR_{U\bullet}}$,
  - Other measures: $VE_S = 1 - \frac{SAR_{\bullet V}}{SAR_{\bullet U}}$, $VE_T = 1 - \frac{SAR_{VV}}{SAR_{UU}}$
- Statistics are based on risk ratios, multivariate analogs

Example

ELSEVIER

Vaccine 21 (2003) 1853–1861

Vaccine

www.elsevier.com/locate/vaccine

Effects of pertussis vaccination on transmission: vaccine efficacy for infectiousness

Marie-Pierre Préziosi [a,b,*], M. Elizabeth Halloran [b]

[a] *Niakhar Project, Institut de Recherche pour le Développement, Dakar, Senegal*

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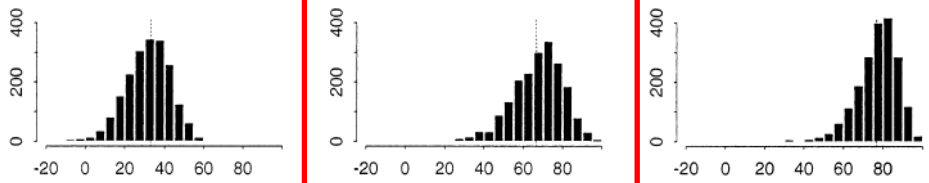
Children vaccinated with three doses of a whole-cell or an acellular pertussis vaccine in compounds. VE_S , VE_I , and VE_T estimated.

Bootstrap estimates



VE_S = 33% VE_I = 85% VE_T = 77%

VE_I = 85% (95% CI: 46–95%)

The vaccine reduce the probability of transmission from vaccinated children to other children by 85% in the compound

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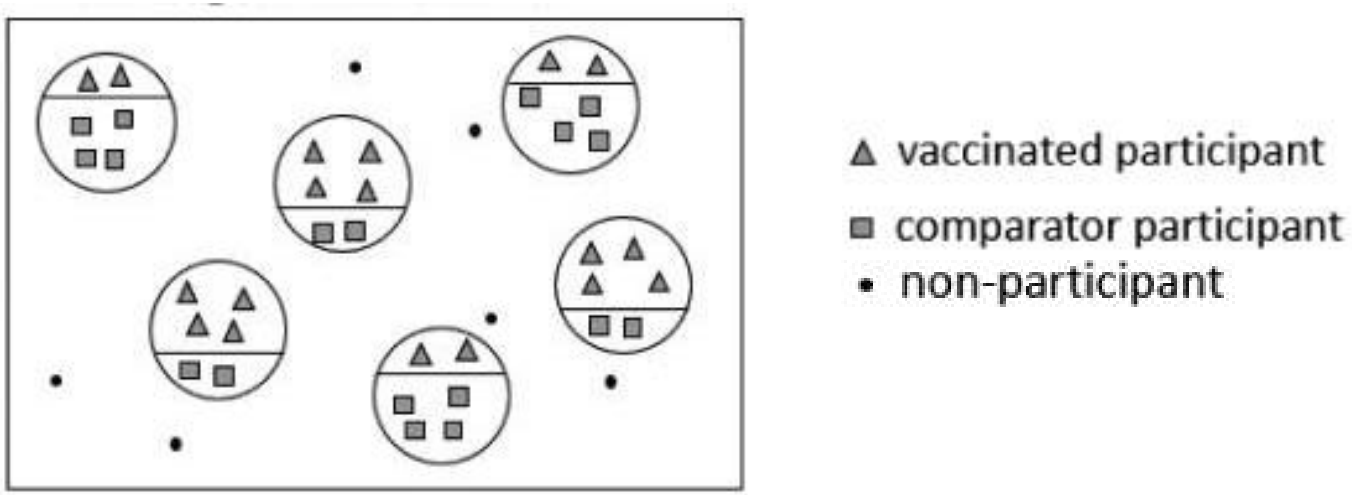
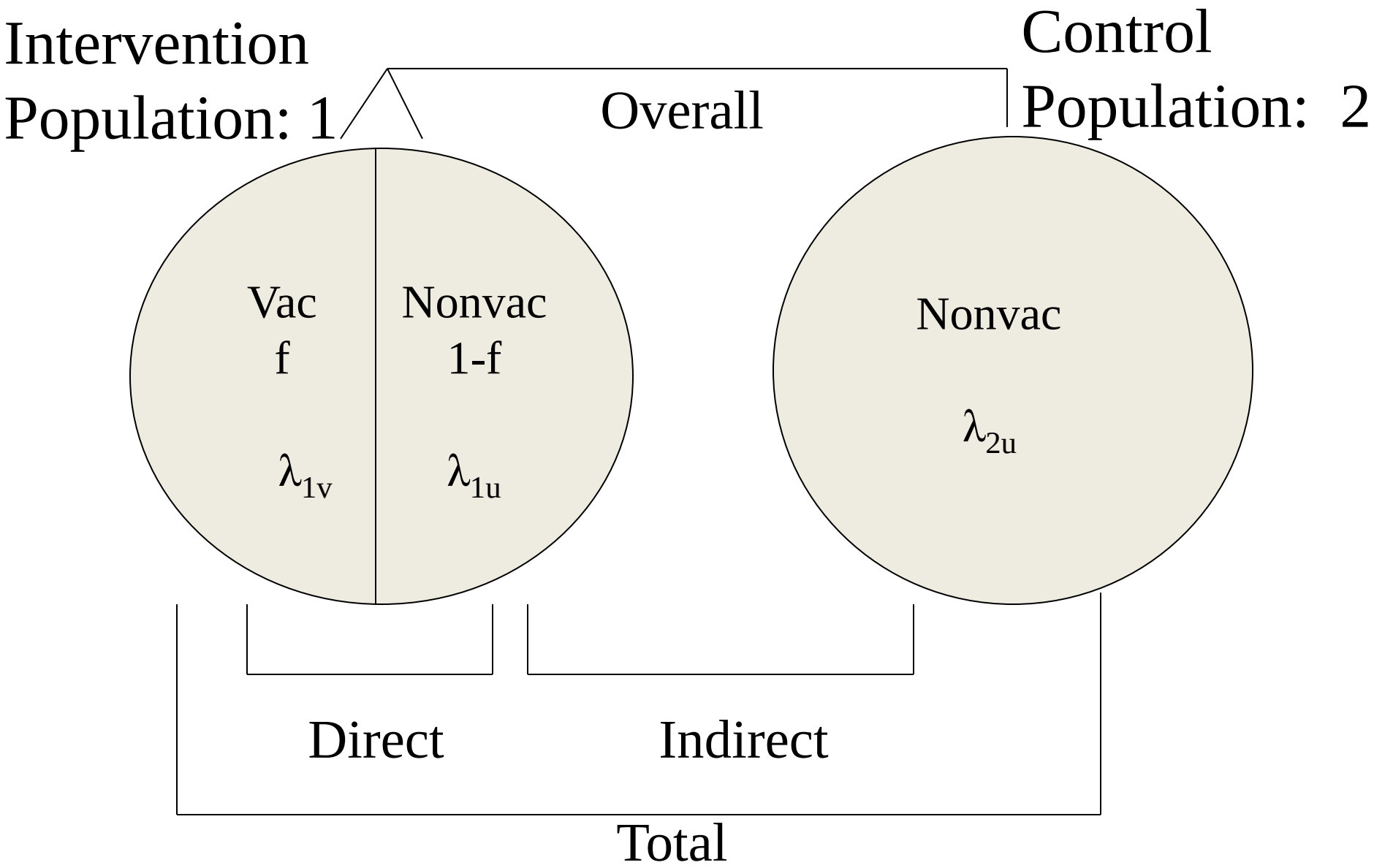
Population level study design of vaccine effectiveness against transmission

Distribute vaccine and comparator (or nothing) within clusters and across clusters with different levels of coverage



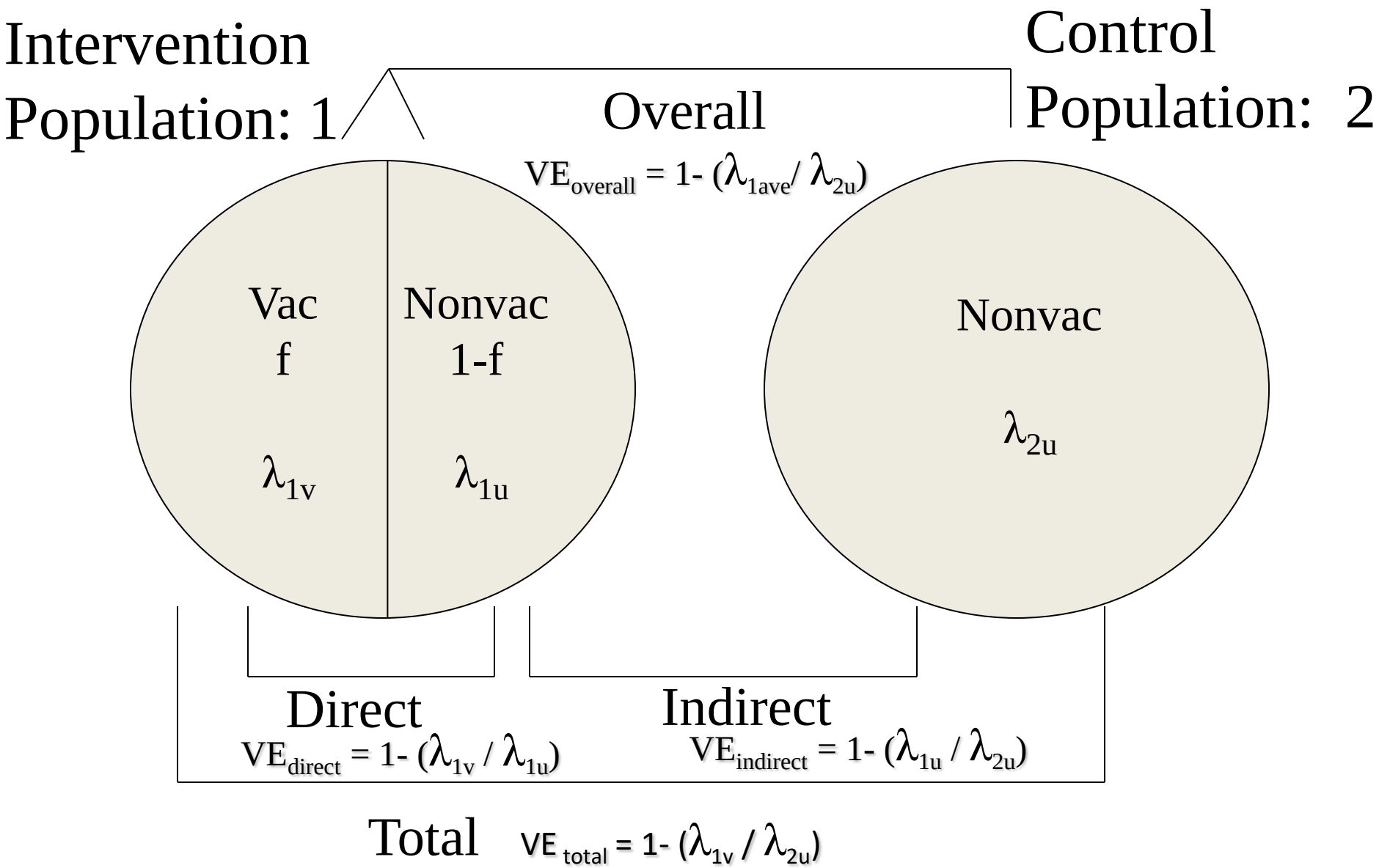
Vaccinated and unvaccinated people are exposed to each other within clusters

Vaccine Effectiveness



Source: Halloran, M.E., Longini, I.M. and Struchiner, C.J.: *The Design and Analysis of Vaccine Studies. Springer, New York*, 387 pp. (2009).

Vaccine Effectiveness



Source: Halloran, M.E., Longini, I.M. and Struchiner, C.J.: *The Design and Analysis of Vaccine Studies. Springer, New York*, 387 pp. (2009).

Statistical methods

- Vaccine effectiveness measures are estimated via the rate ratios: $VE = 1 - \frac{\lambda_V}{\lambda_U} = VE = 1 - RR.$
- The RR is computed through event-history modeling, e.g., survival models, agent-based models
- We are interested in the indirect, overall and total vaccine effectiveness that all functions of reductions in transmission due to vaccination and herd immunity effects

Example

PLOS MEDICINE

OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

Controlling Endemic Cholera with Oral Vaccines

Ira M Longini Jr., Azhar Nizam, Mohammad Ali, Mohammad Yunus, Neeta Shenvi, John D Clemens

Published: November 27, 2007 • https://doi.org/10.1371/journal.pmed.0040336

Reanalysis of oral cholera vaccine trial in Matlab, Bangladesh as a double randomized cluster randomized trial. Clustering unit was the **bari** (patrilineal collection of dwellings in a compound)

THE LANCET

CLINICAL PRACTICE | VOLUME 335, ISSUE 8684, P270-273, FEBRUARY 03, 1990

Field trial of oral cholera vaccines in Bangladesh: results from three-year follow-up

J.D Clemens, MD • D.A Sack, MD • J.R Harris, MD • F van Loon, MD • J Chakraborty • F Ahmed, MD • et al.

Show all authors

Published: February 03, 1990 • DOI: https://doi.org/10.1016/0140-6736(90)90080-O

VE_S = 58%; p<0·01

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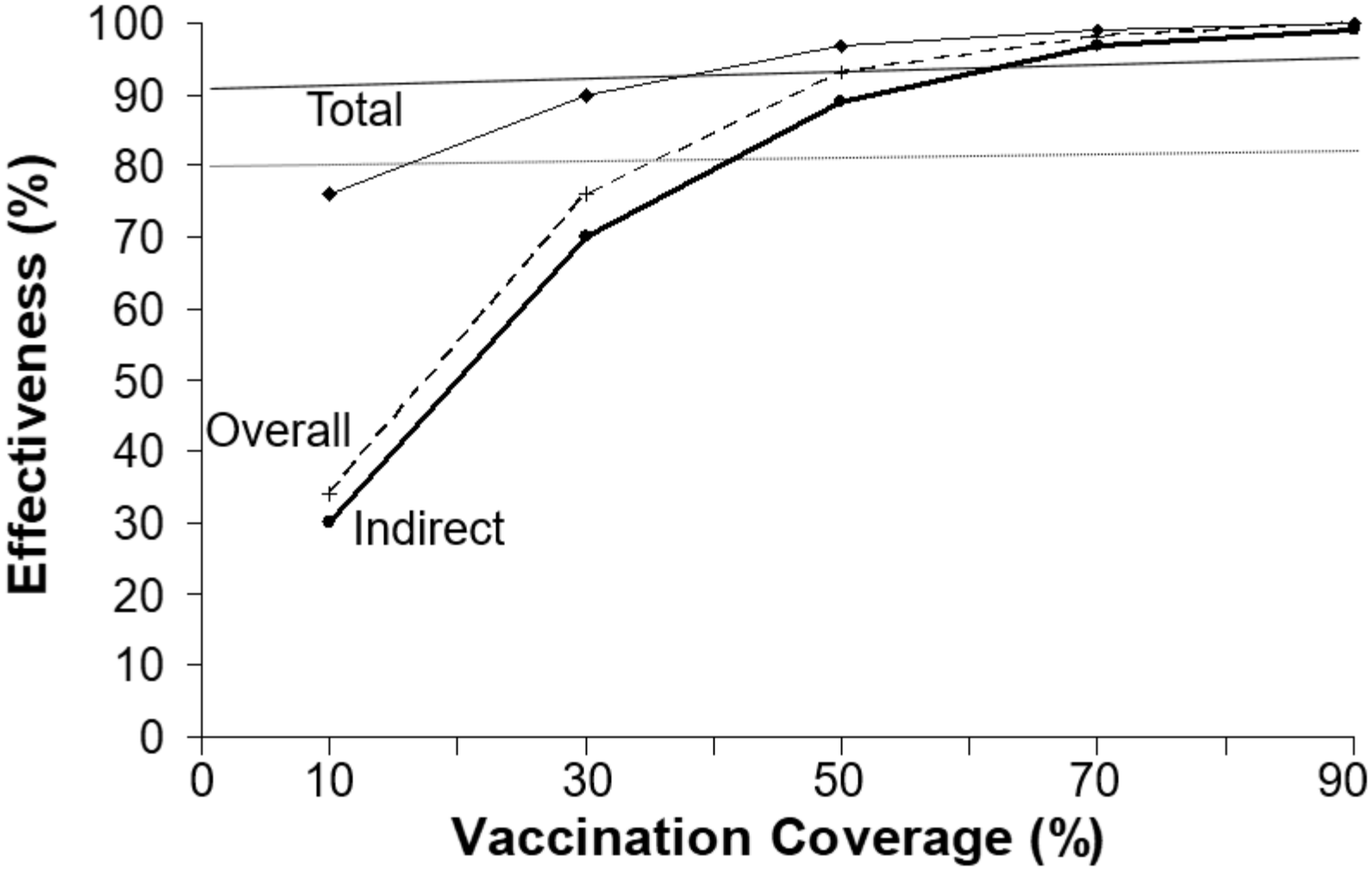
Estimated effectiveness measures: Oral cholera vaccines



Longini, *et al.*, Controlling endemic cholera with oral vaccines. *PloS Med* **4** (11) 2007: e336 doi:10.1371/journal.pmed.0040336.

Conclusion

- Studies can be randomized or observational
- Individual level studies in transmission groups provide estimates of the VE_I
  - Households or other small mixing groups
  - Contact studies
- Larger-scale population level studies prove estimates of the vaccine impact on transmission
  - Cluster randomize studies, including stepped wedge
  - Clustered observational studies

Thank you

Household transmission studies

Adam Finn, PhD
Professor of Paediatrics
University of Bristol

Bristol Children's Vaccine Centre

Can we measure vaccine impact on transmission by studying family transmission?

Adam Finn

@adamhfinn

17th Dec 2020

Pre-/Post-Licensure Assessments Workshop

Thx to Peter Dull, David Vaughn, Danny Feikin, Jamie Lopez Bernal, Gina Murphy, Ping Li, Igor Smolenov

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Ways to study impact on transmission include:

- Cluster randomised trials
- Staggered implementation studies either in time or location or both
- Studying onward transmission to close contacts of vaccine failures vs unvaccinated controls eg families or households

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1. Surveillance

- Need to ascertain not only symptomatic PCR+ blinded study subjects but also
- Asymptomatic infections in real time
  - Self sampling and PCR analysis (costly, slow, sensitive – probably)
  - Self administered rapid tests (cheap, quick, less sensitive but maybe fairly good predictor of infectiousness

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2. Enrollment

- Need to contact families/household immediately (what is a household?)
- ??Exclude families with previous/past history of COVID
- Obtain informed consent from all/adequate number of members
- Deliver materials and train them to obtain samples while obtaining initial set

University of BRISTOL

3. Samples

- Saliva – preferred. Non invasive and well tolerated. Self sampling done easily and well for good volumes. Good for PCR and AB detection. But maybe less sensitive than swab for PCR
- ?Swab – [NP], anterior N, throat, both
- ?Blood – venous, capillary, suction device?

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4. Sampling

- Frequency - ?twice weekly
- Duration – ?three weeks

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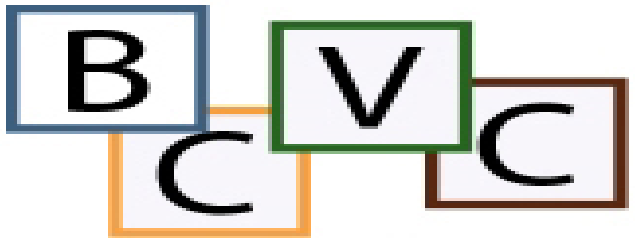
Secondary cases

- Antibody negative on first (?and second) sample (do you exclude whole family or just individual?)
- If PCR+(s) virus already circulating
- Become PCR positive during sampling period or seroconvert
- NB can deduce timing/chronology of infections to an extent – but NOT who infected who reliably – secondary cases may really be "tertiary" cases or infected from outside

Readout

- Proportion of susceptible family/household contacts of the index cases who become cases during the observation period comparing vaccine failures' contacts with those of unvaccinated controls
- Likely to be – if anything – under estimated



Power

- How many infections in vaccinated group and in control group?
- How many susceptible contacts?
- Transmission rate from controls?
- Size of reduction in this rate from vaccinees you want to be able to detect

So, can it be done?

	Vaccine	Control
Number of any COVID cases (assuming true VE of ~65%)	31	69
Number of asymptomatic cases, assuming 1/2 symptomatic and asymptomatic cases, and a 50% efficacy against asymptomatic infection Sensitivity: 1:1	69	138
Total number of SARS-CoV-2 cases in the study	100	207
% of study population included in the HHS (50%) Sensitivity: 20%-30% and 40%	50	103
Average size of household (4) Sensitivity: 3	50x4=200	103x4=412
Proportion of families with study subject as the index case (50%) Sensitivity: 30%, 40%, 60%, 70%	100	206
Transmission rate	20-30-40%	50%
Number of secondary cases	20-30-40	103
Transmission difference that can we detected with 80% power?	See plots below	

Thanks to: Ping Li, Igor Smolenov

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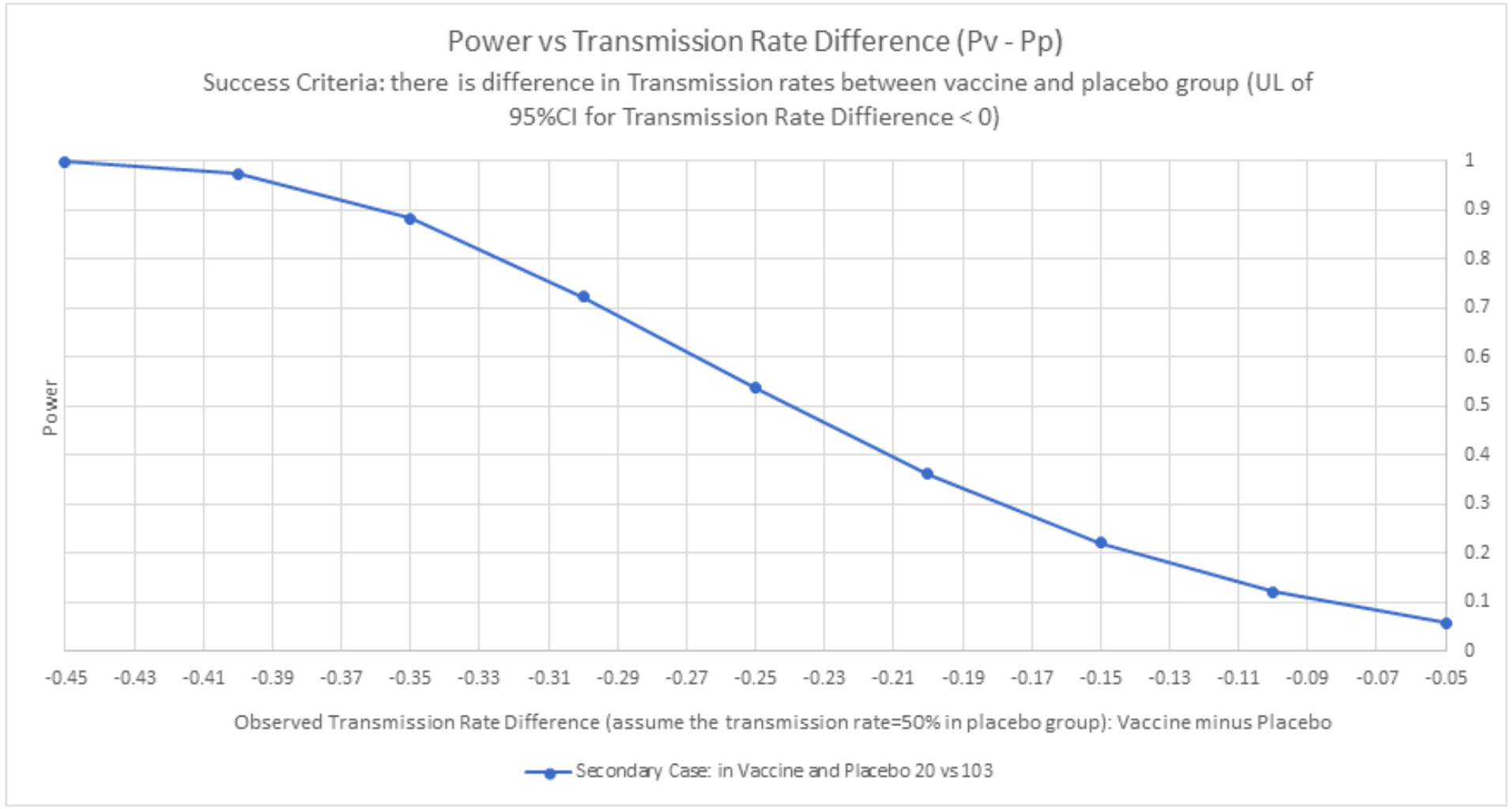
If 50% to 20%: 80% power



Phase 2b trial design to assess vaccine efficacy against infection, viral load, and secondary transmission

Holly Janes, PhD

Professor of Biostatistics

Fred Hutchinson Cancer Research Center

Evaluating COVID-19 Vaccine Efficacy on Infectivity to Infer Population Vaccine Effects

Holly Janes
Fred Hutchinson Cancer Research Center (FHCRC)

In close collaboration with Elizabeth Brown (FHCRC)
Audrey Pettifor (UNC Chapel Hill) and Katy Stephenson (Harvard U)

FRED HUTCH

Proposed Phase 2b Trial to Evaluate Vaccine Effects on Infectivity

Main Study Cohort

Arm	Sample Size	Day 1	Day 29
Vaccine 1*	7,000	Dose 1	Dose 2
Vaccine 2*	7,000	Dose 1	Dose 2
Placebo	7,000	Placebo	Placebo

21,000 **University students** randomized 1:1:1, stratified by residence

- Vaccine coverage (University-wide and residence-specific) and baseline SARS-CoV-2 seropositivity controlled operationally

Close Contact Cohort

Contact of SARS-CoV-2 Infected Ppt in Main Study Arm	Sample Size
Vaccine 1*	~150+
Vaccine 2*	~150+
Placebo	~300+

Close contacts of study participants diagnosed with SARS-CoV-2 infection

+ under 50% VE and with 3.5% incidence. *Actual number of contacts is random* -- depends on incidence, vaccine efficacy, and contact network

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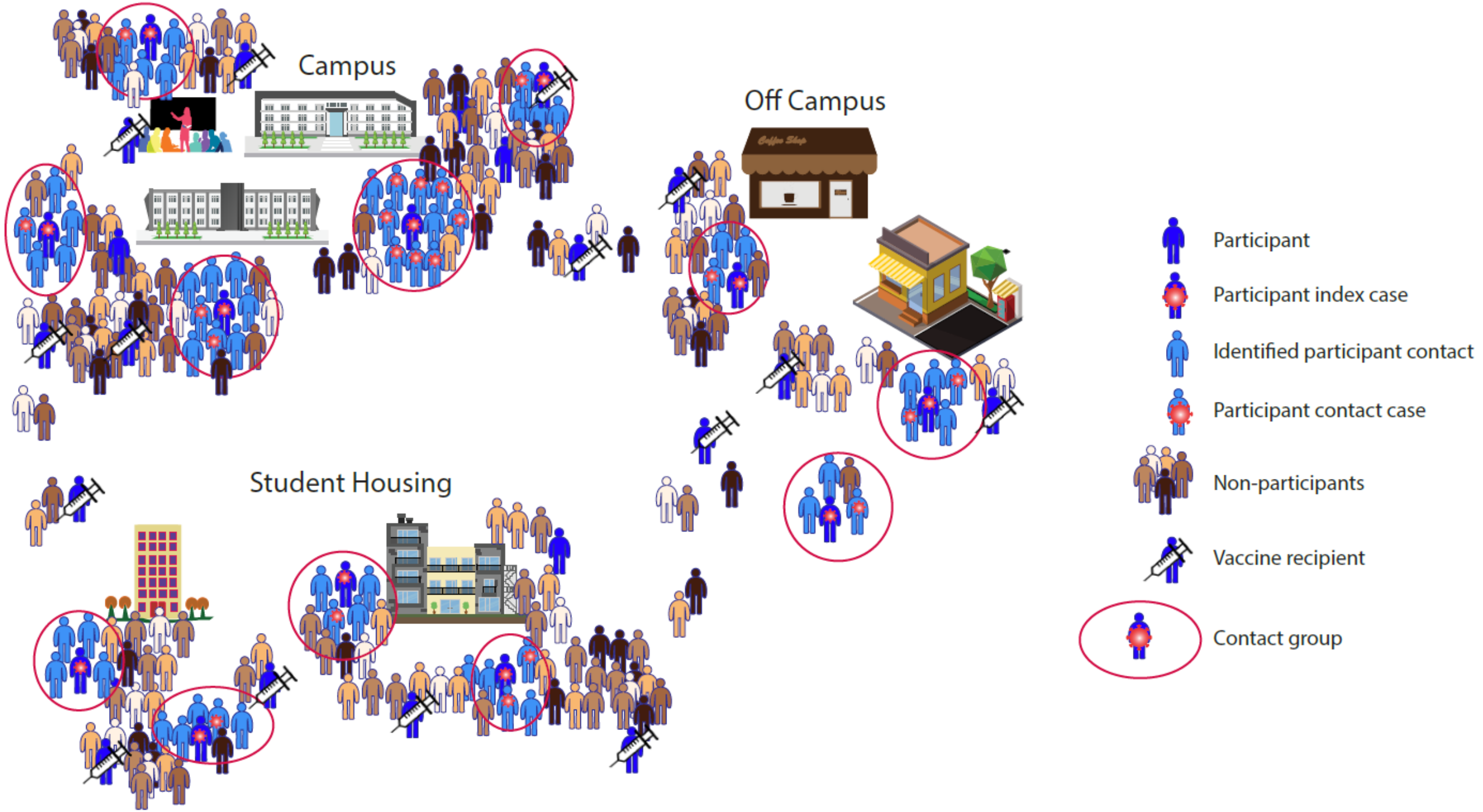
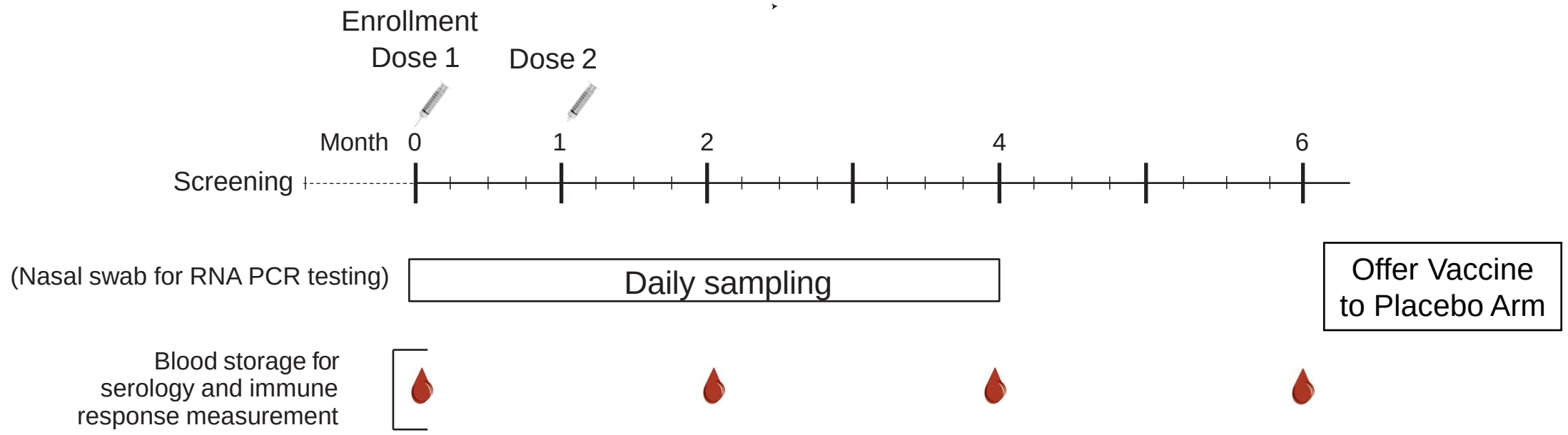
* prioritizing mRNA and adjuvanted protein vaccines given evidence of protection in NHP studies

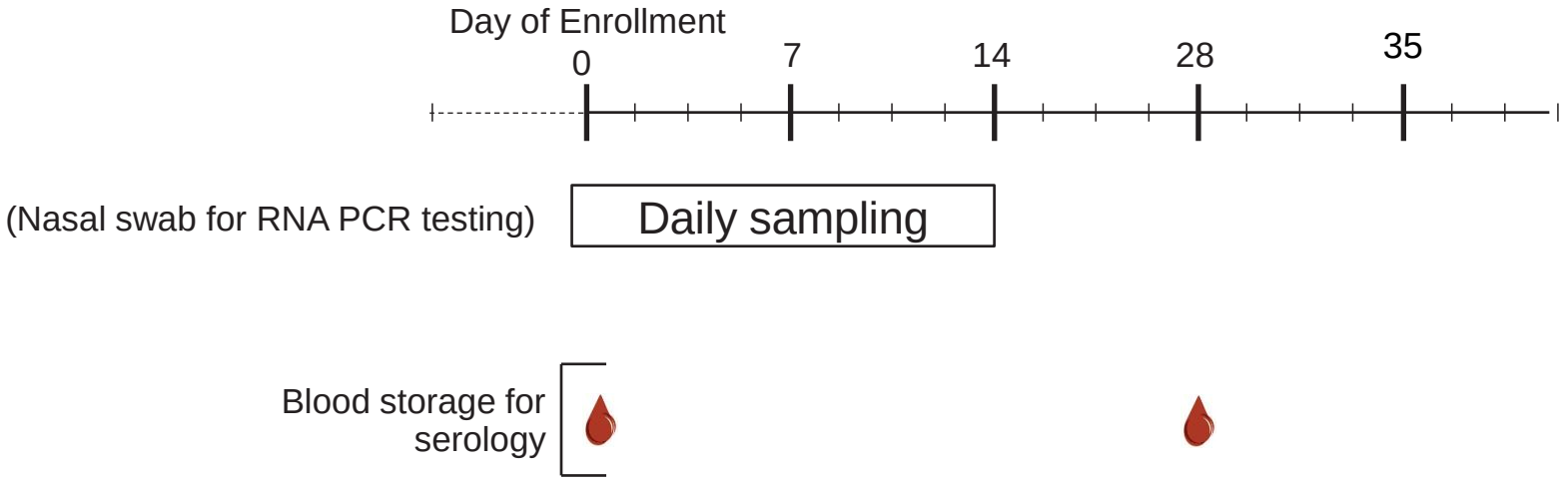

Campus
Off Campus
Student Housing
Participant
Participant index case
Identified participant contact
Participant contact case
Non-participants
Vaccine recipient
Contact group

Sampling Schedule for Main Study Participants



- 4 months self-collection of daily swabs for PCR diagnosis of SARS-CoV-2 infection
- For SARS-CoV-2 infected participants, daily signs/symptoms through resolution

Sampling Schedule for Close Contacts of Study Participants with Positive SARS-CoV-2 PCR



- 14 days self-collection of nasal swabs for PCR diagnosis of infection
- Day 0 and 28 serology to capture past infection and missed incident infections

Primary Objectives and Endpoints

- To evaluate **efficacy against SARS-CoV-2 infection**, each vaccine vs. placebo
  - SARS-CoV-2 PCR positivity based on nasal swab*
- To evaluate **magnitude and duration of viral shedding** among participants with incident SARS-CoV-2 infection, each vaccine vs. placebo
  - Peak log10 viral load and other shedding summaries, based on nasal swab*
- To evaluate differences in **safety parameters** between vaccine and placebo recipients
  - Reactogenicity and AEs

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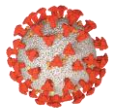
* 14+ days post-dose 2, among per-protocol participants baseline seronegative for SARS-CoV-2

Key Secondary Objectives

- Vaccine efficacy against **secondary transmission**
- Vaccine effects on viral load and secondary transmission, separately for **symptomatic vs. asymptomatic SARS-CoV-2 infections**
- Vaccine efficacy against **seroconversion**
- Vaccine efficacy against **COVID-19**
- **Immune correlates** of COVID-19 disease, viral load kinetics and transmission risk

Each vaccine vs. shared placebo

- **Comparative efficacy** of vaccine regimens



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Sample Size Rationale

- N = 7,000 per arm ensures high prob. 150 primary endpoint infections accrue for each (vaccine, placebo) pair within 20 weeks under **3.5%** placebo SARS-CoV-2 incidence¥
- 150 primary endpoint infections (50 in vaccine group) ensures 90% power to evaluate all primary and key secondary objectives:

Each vaccine vs. placebo

  - Detect 50% VE against infection (rejecting H_0: VE ≤ 0%)
  - Detect 1-log10 reduction in mean peak viral load among infections
  - Detect 39-49% reduction in mean number of secondary transmission events under 25% VE against infection

  - Compare VE against infection between arms, e.g 60% vs. 83% VE against infection
  - Evaluate immune correlates of infection and viral load, esp. combining vaccine arms

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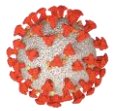
¥ With 80% probability, assuming 6-week accrual, 10% baseline seropositive, VE = 50%, 5% LTFU, 98% per-protocol. Primary endpoint events are 14-days post-second vaccination in the per-protocol set. 1-sided 0.025-level log-rank test.

Methods for Evaluating Vaccine Efficacy

- VE against SARS-CoV-2 infection
  - Cox proportional hazards regression
  - Supported by network simulations that establish operating characteristics in the context of minimal 'interference'
- Vaccine effect on viral load
  - Compare mean viral load conditional on SARS-CoV-2 infection, and unconditional (uninfected get a '0')
  - Various measures of viral load: peak, AUC, time to VL > 10^5 copies/mL
- Vaccine efficacy against secondary transmission
  - Compare mean no. 'potential transmission events' (uninfected get a '0') using proportional means model
  - Inferred from questionnaires, dx timing, viral load, serology, viral sequences and determined by expert adjudication committee

Secondary analyses will leverage causal inference methods to formally accommodate interference



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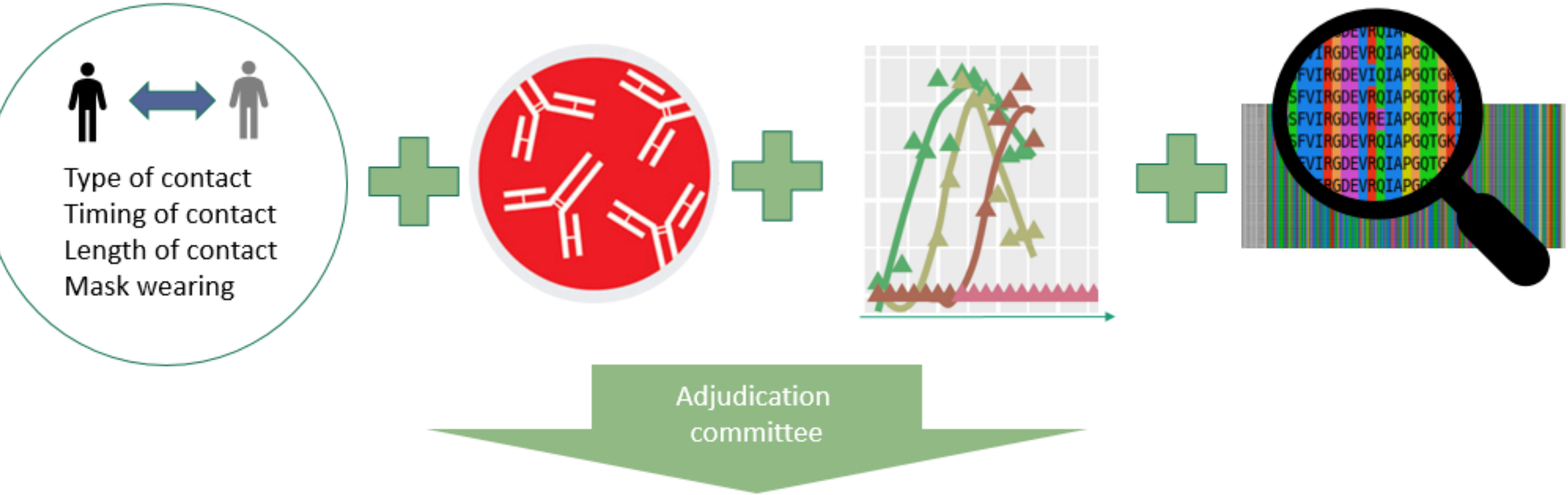
Linking transmissions



Potential transmission?

Why study infectiousness in phase 2b study, instead of deferring for phase 4?

- Policymakers and public need answers now to inform policy and individual actions:
  - Who to vaccinate given vaccine scarcity
  - When/where to mandate vaccination
  - Whether vaccine recipients must still mask and isolate if infected
- Short window of opportunity for gold standard trial, before licensure and wide vaccine availability
- Most rigorous assessment of whether vaccines reduce infectiousness (vs. observational and cluster-randomized stepped-wedge studies)
- Aids bridging to new populations: vaccine effect on viral load bridges more readily than VE against secondary transmission which is context-specific
- Provides data to validate viral load as surrogate of infectiousness
- Potentially identifies immune correlates of SARS-CoV-2 infection and shedding which may differ from disease, aiding licensure of future vaccines with effects on these endpoints
- Defines sensitivity of serology to detect all SARS-CoV-2 infections captured via daily PCR testing

Panel Discussion

Moderated By:

Daniel Feikin, MD, MSPH

Department of Immunizations, Vaccines, and Biologicals

World Health Organization (WHO)

Discussion Panel Members and Example Questions

Panel Members

- **Gagandeep Kang**
  Christian Medical College, Vellore, India
- **Ole Wichman**
  Robert Koch Institute, Germany
- **Peter Smith**
  London School of Hygiene & Tropical Medicine

+ Presenters from Parts 2 & 3

Potential Discussion Questions

1. Might we expect vaccines to exhibit more protection against infection and transmission than naturally acquired COVID-19 infection?
   - Which types of vaccines might better protect against infection and transmission?
2. How might evidence of VE against prevention of infection and/or transmission affect vaccine policy recommendations?
   - Might this evidence affect policy recommendations differently in different geographic settings (e.g., based on differing epidemiology and burden of COVID-19 morbidity and mortality.)
3. How related are VE against infection and transmission?

Wrap Up & Next Steps

Jakob Cramer

Head of Clinical Development

Coalition for Epidemic Preparedness Innovations (CEPI)

Closing remarks

- Thank you all for your participation and engagement today
- Workshop report distributed shortly to summarize today's conversation
- We will continue to share resources at the website here: https://epi.tghn.org/covax-overview/clinical/
- Workshops will continue in 2021 – please provide ideas and suggestions (see website above)
  - F/U on CoP
  - Vaccine Safety / pharmacovigilance
  - Follow up from previous workshops and more 'hot topics'
- The COVAX Clinical SWAT Team plans to continue sharing learnings across developers as we pursue our common goal – a global supply of safe and effective vaccines
- **SEASONAL GREETINGS!**

Clinical Development & Operations SWAT Team