UK COVID-19 response: testing, surveillance, management and vaccines

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Disclosures

Public sector grants

LifeArc	2020-date
CW+ Charity	2017-date
NIHR	2013-date

Industry grants, scientific advice, and honoraria

Sumitovant	2021-date
Kent Pharma	2021-date
Pulmocide	2021-date
Shionogi	2021-date
Umovis Lab	2020-date
Pfizer	2018-date
Eumedica	2015-date
bioMérieux	2013-date

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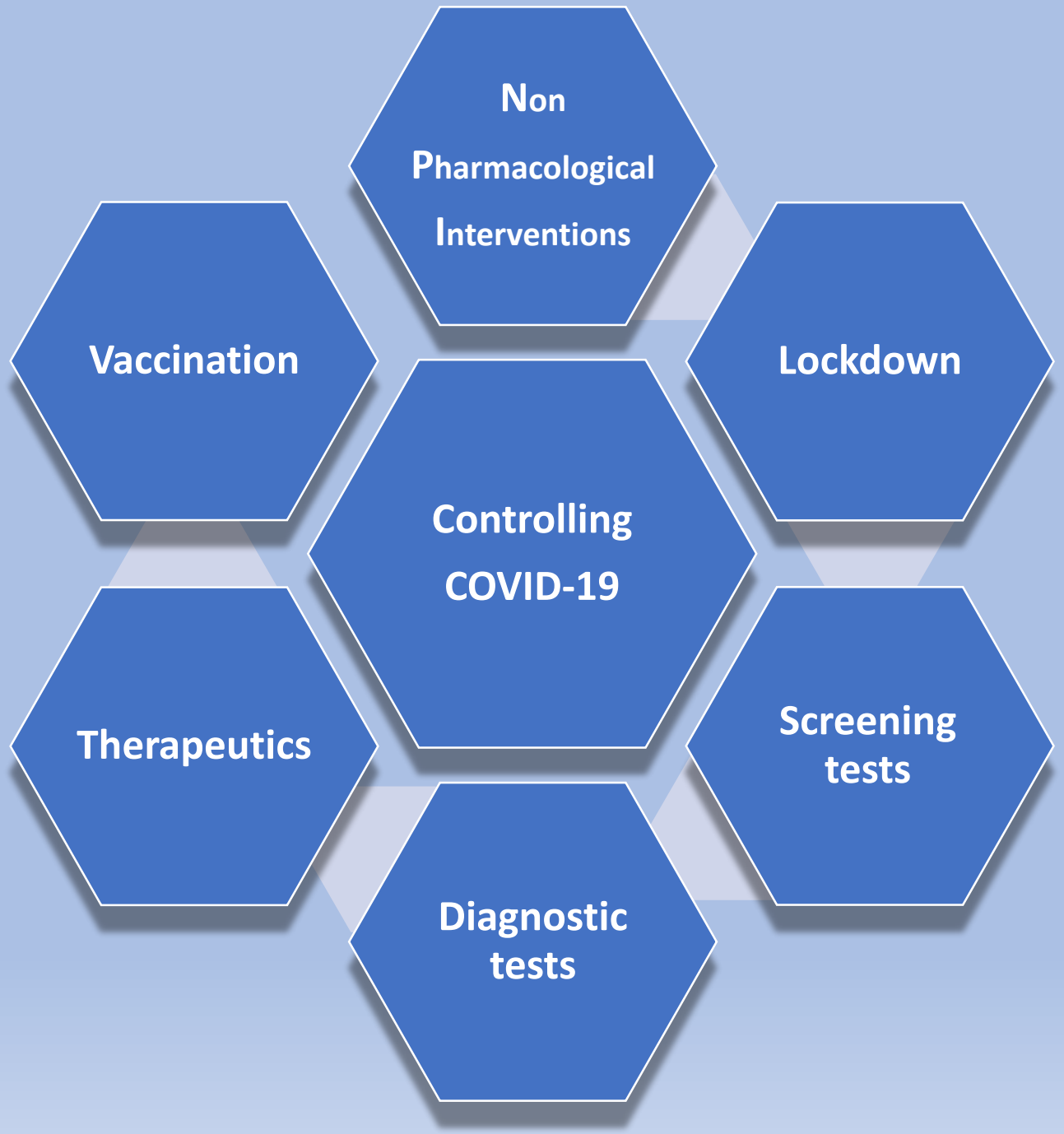
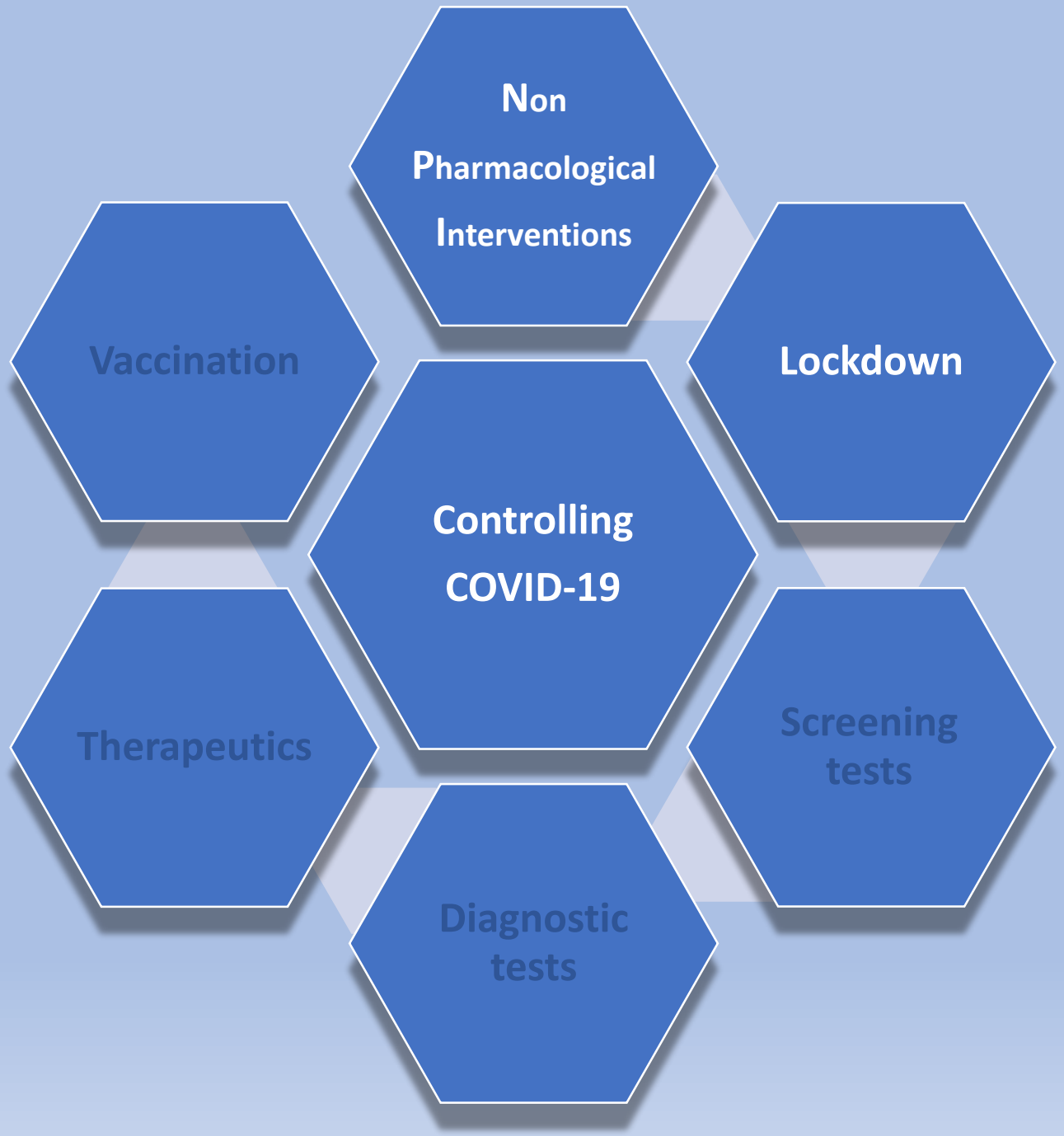
UK COVID-19 response: testing, surveillance, management and vaccines

- Review response to COVID-19
- Learning from international variations in public health interventions
- Review in- and out-patient COVID therapy and referral pathways
- Reflect on the post COVID-19 pandemic era


Non Pharmacological Interventions
Vaccination
Lockdown
Controlling COVID-19
Therapeutics
Screening tests
Diagnostic tests


Non Pharmacological Interventions
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Hand hygiene: Persisting contamination

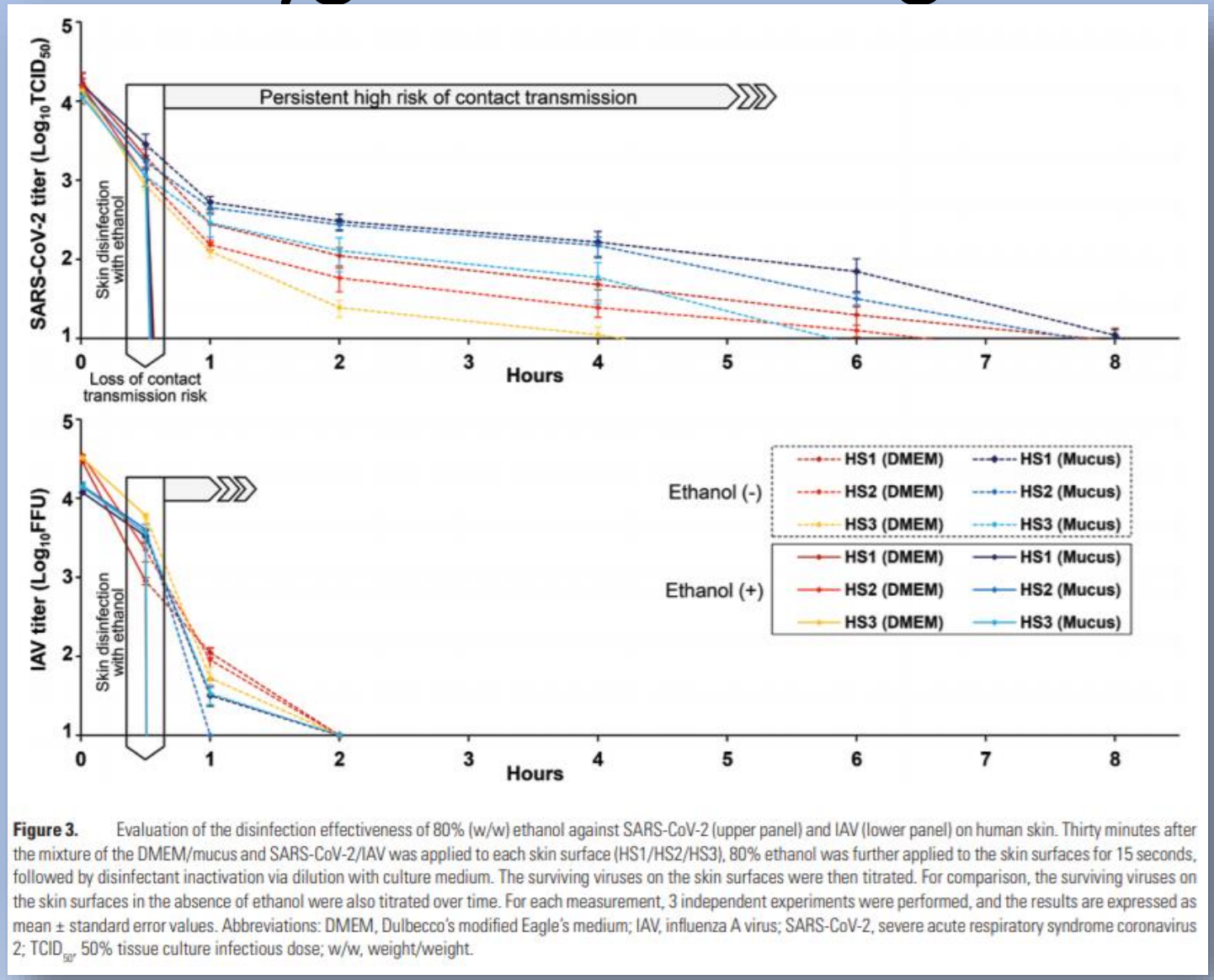
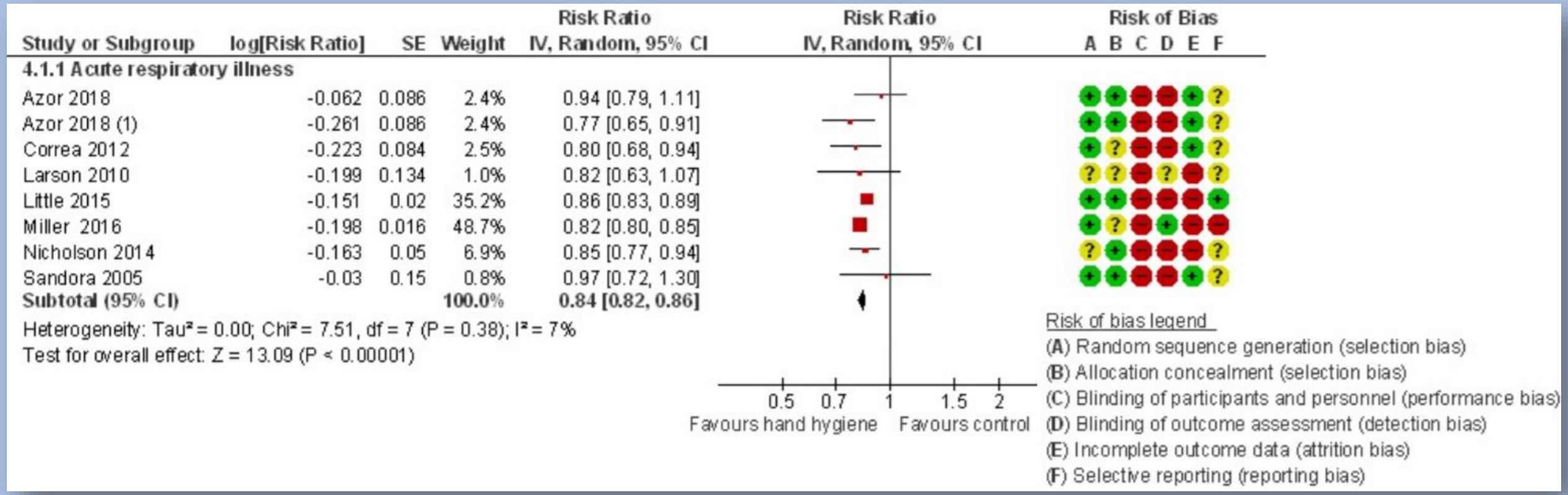


Figure 3. Evaluation of the disinfection effectiveness of 80% (w/w) ethanol against SARS-CoV-2 (upper panel) and IAV (lower panel) on human skin. Thirty minutes after the mixture of the DMEM/mucus and SARS-CoV-2/IAV was applied to each skin surface (HS1/HS2/HS3), 80% ethanol was further applied to the skin surfaces for 15 seconds, followed by disinfectant inactivation via dilution with culture medium. The surviving viruses on the skin surfaces were then titrated. For comparison, the surviving viruses on the skin surfaces in the absence of ethanol were also titrated over time. For each measurement, 3 independent experiments were performed, and the results are expressed as mean ± standard error values. Abbreviations: DMEM, Dulbecco's modified Eagle's medium; IAV, influenza A virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; $TCID_{50}$, 50% tissue culture infectious dose; w/w, weight/weight.

Hirose et al.
CID. 2021;[InPress]

Hand hygiene: impact on acute respiratory illness



Al-Ansary et al.
Pre-print: https://doi.org/10.1101/2020.04.14.20065250

Hand hygiene: Controversy

THE LANCET
Infectious Diseases

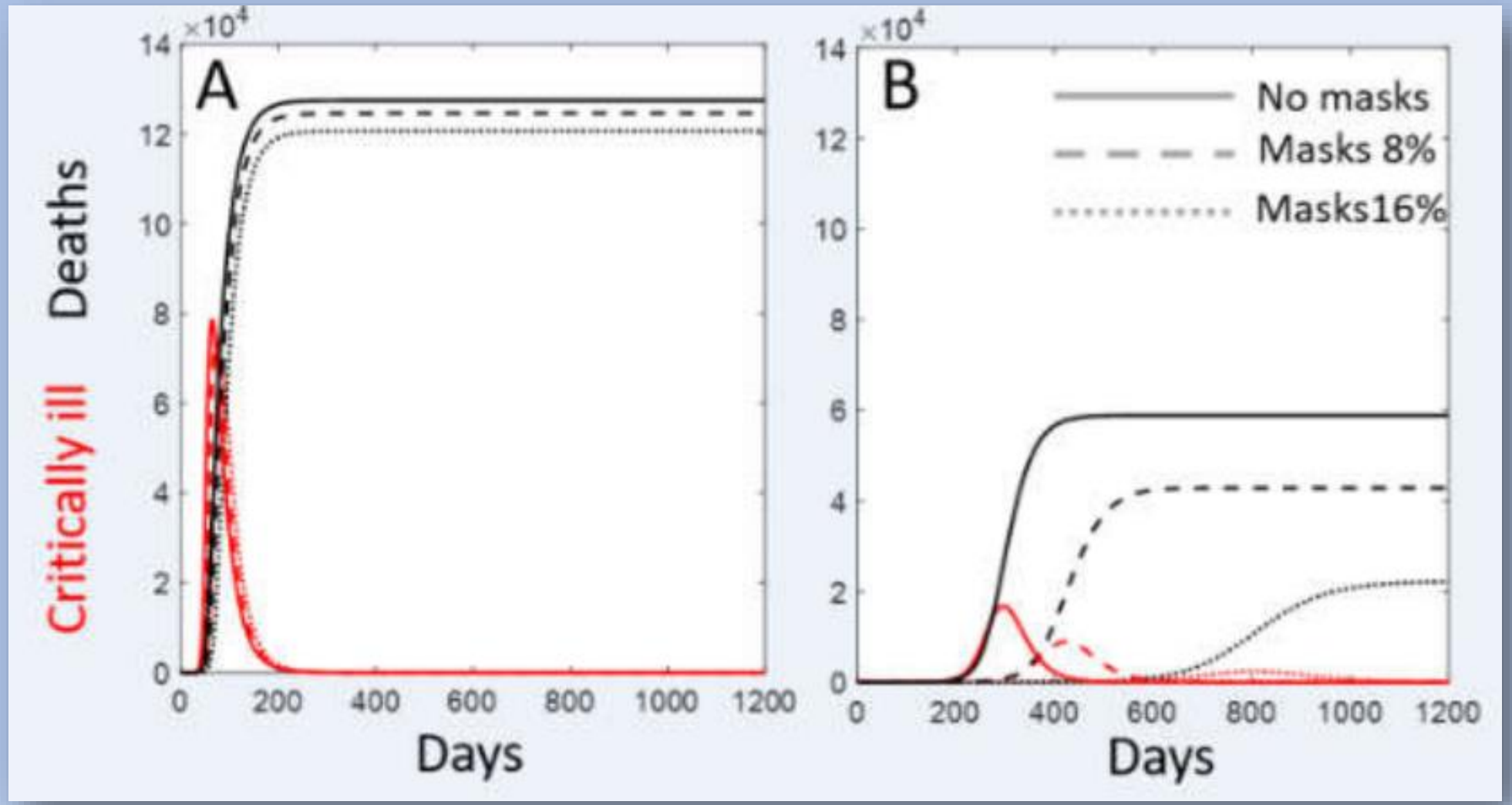
COMMENT | VOLUME 20, ISSUE 8, P892-893, AUGUST 01, 2020

Exaggerated risk of transmission of COVID-19 by fomites

Emanuel Goldman

Published: July 03, 2020 • DOI: https://doi.org/10.1016/S1473-3099(20)30561-2

Masks: Anticipated effect

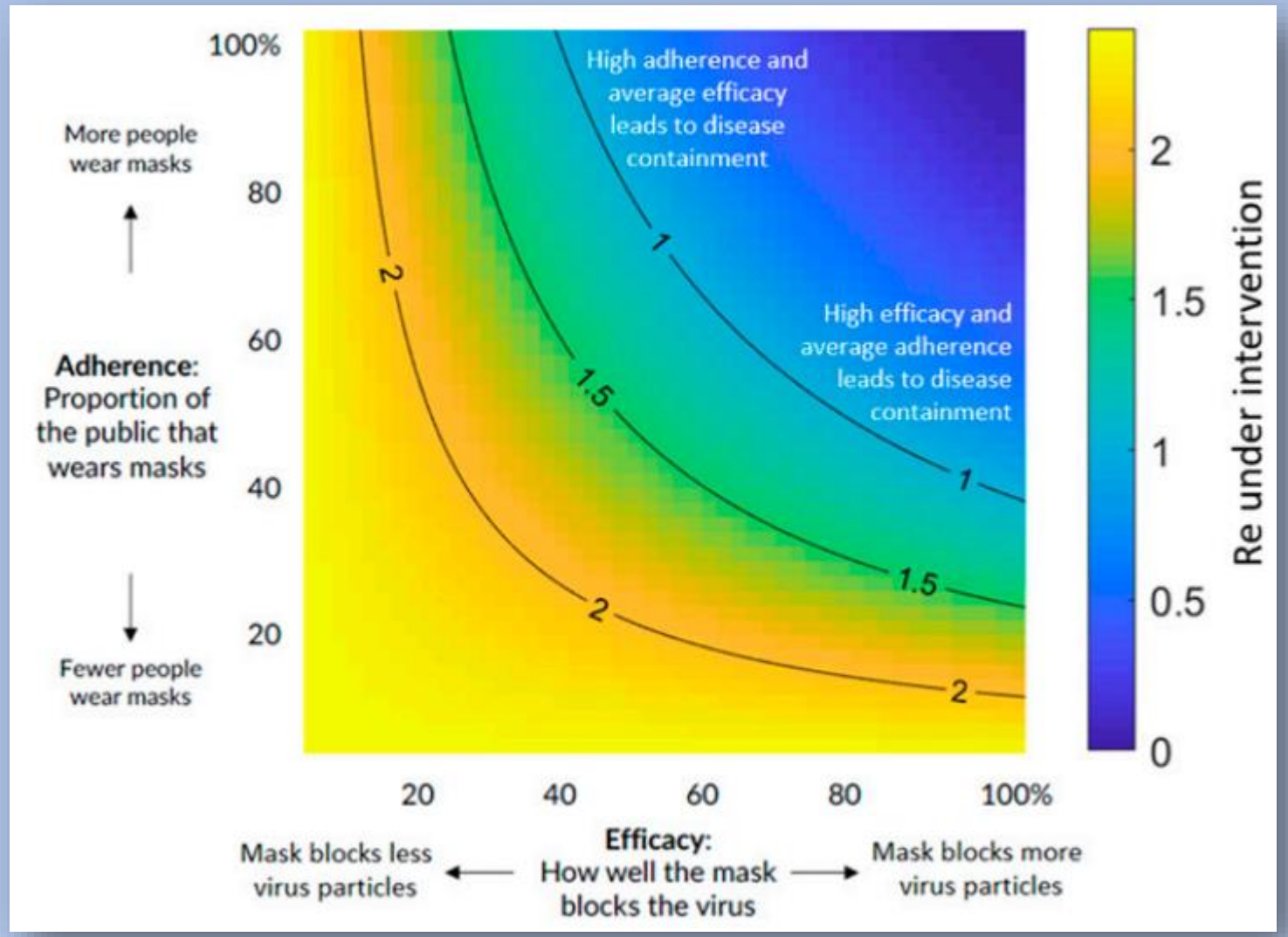


A= R_0 2.2

B=R_0 1.3

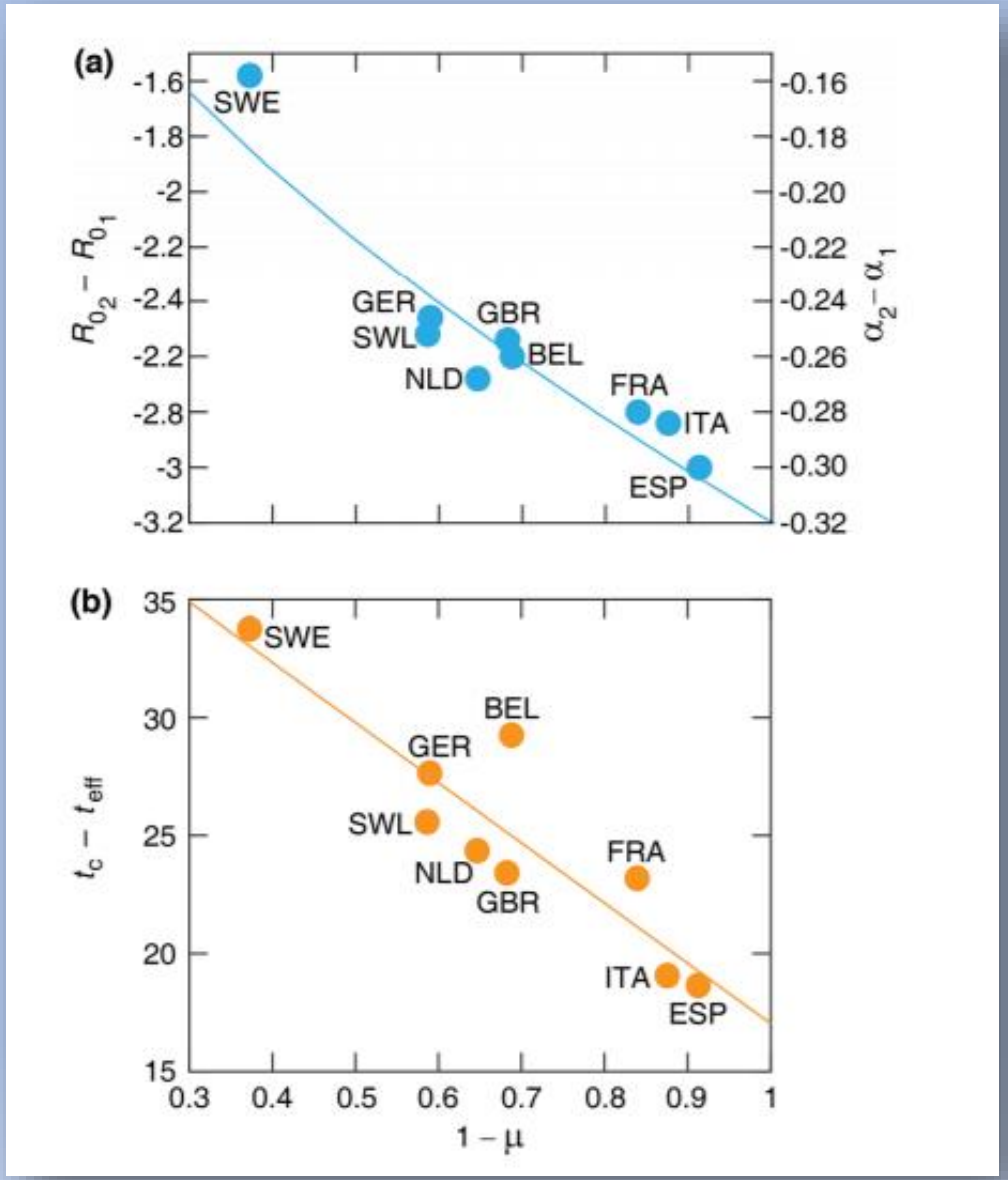
Howard et al.
PNAS. 2021;118(4):e2014564118

Masks: Evidence review



Howard et al.
PNAS. 2021;118(4):e2014564118

Social distancing: impact from mobile phone data

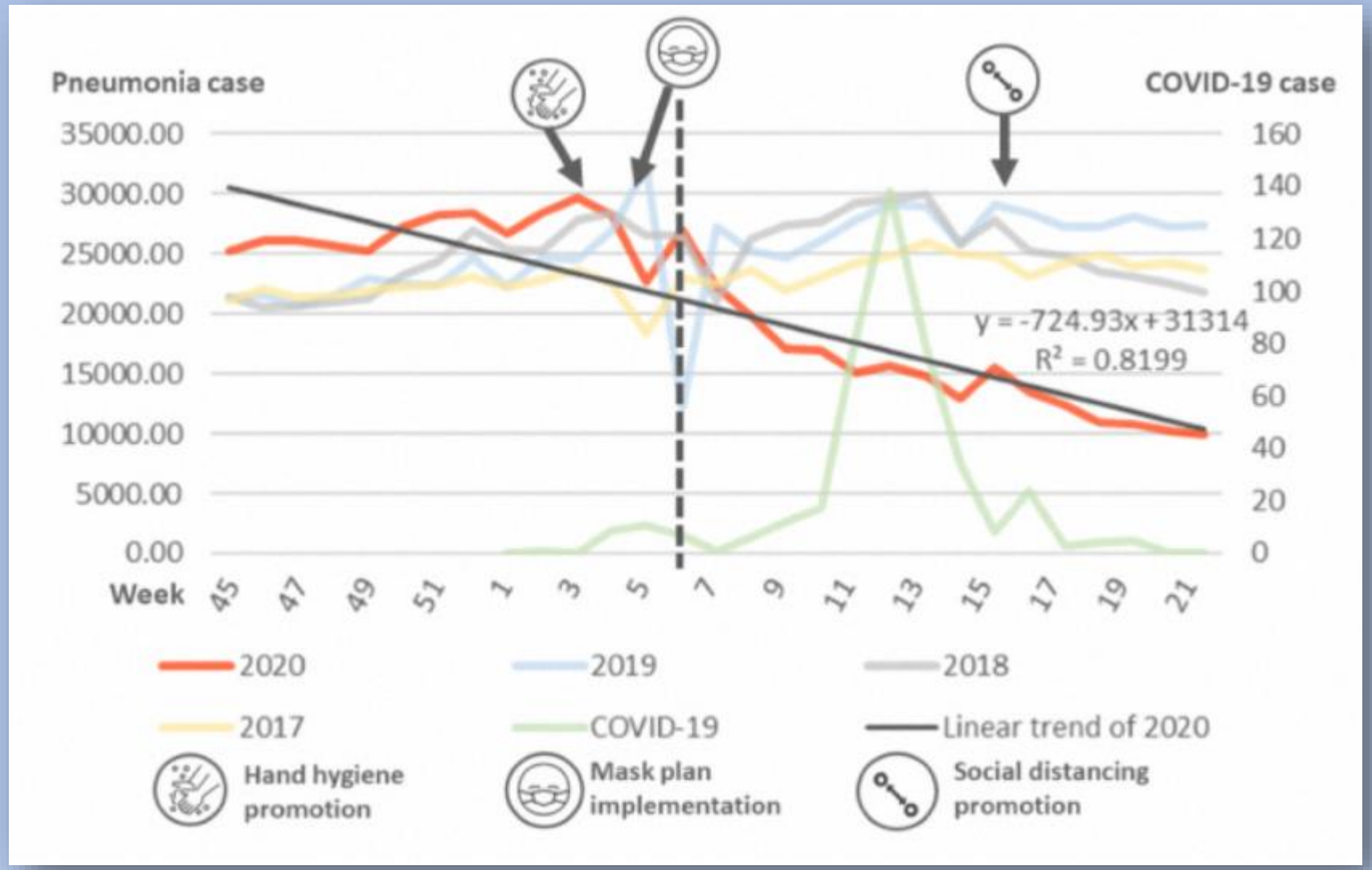


R_o

Elapsed time between epidemic peak and effective lock-down

Khataee et al.
Nature Sci Rep. 2021;11:1661.

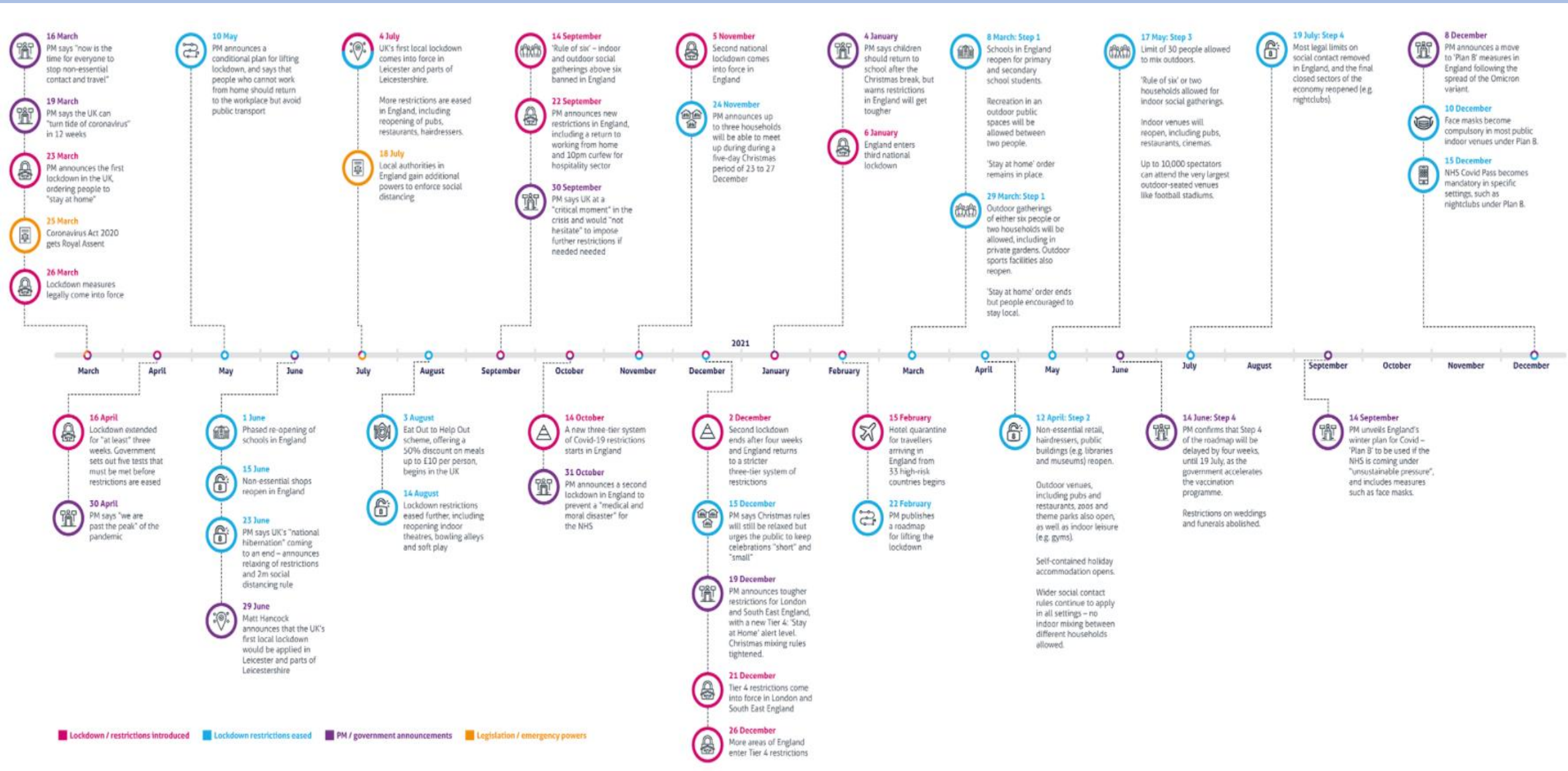
Hands, face, space: sequential impact



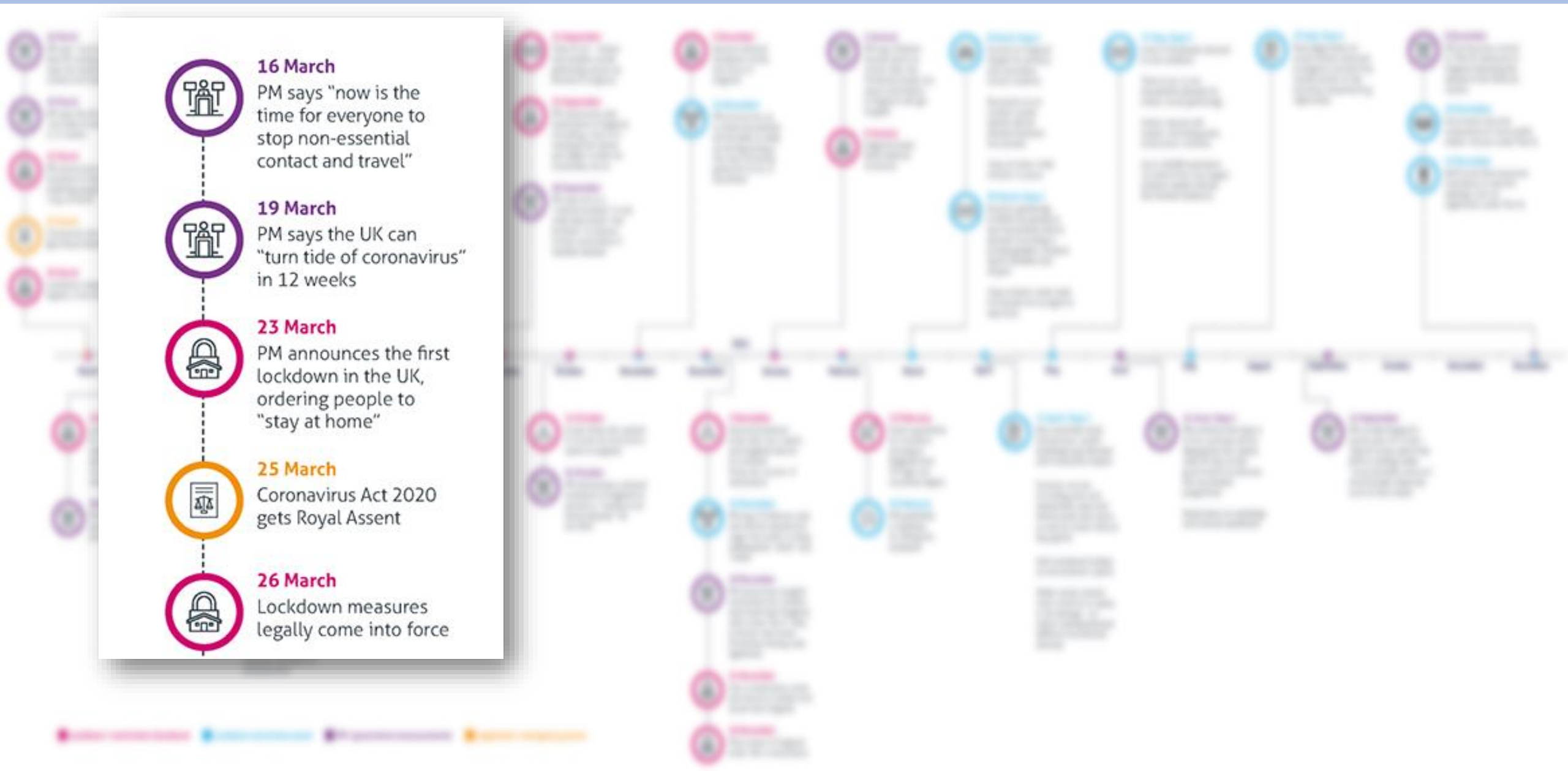
Chiu et al.
JMIR. 2020;22(8):e21257.

Hands, face, space: variable concordance

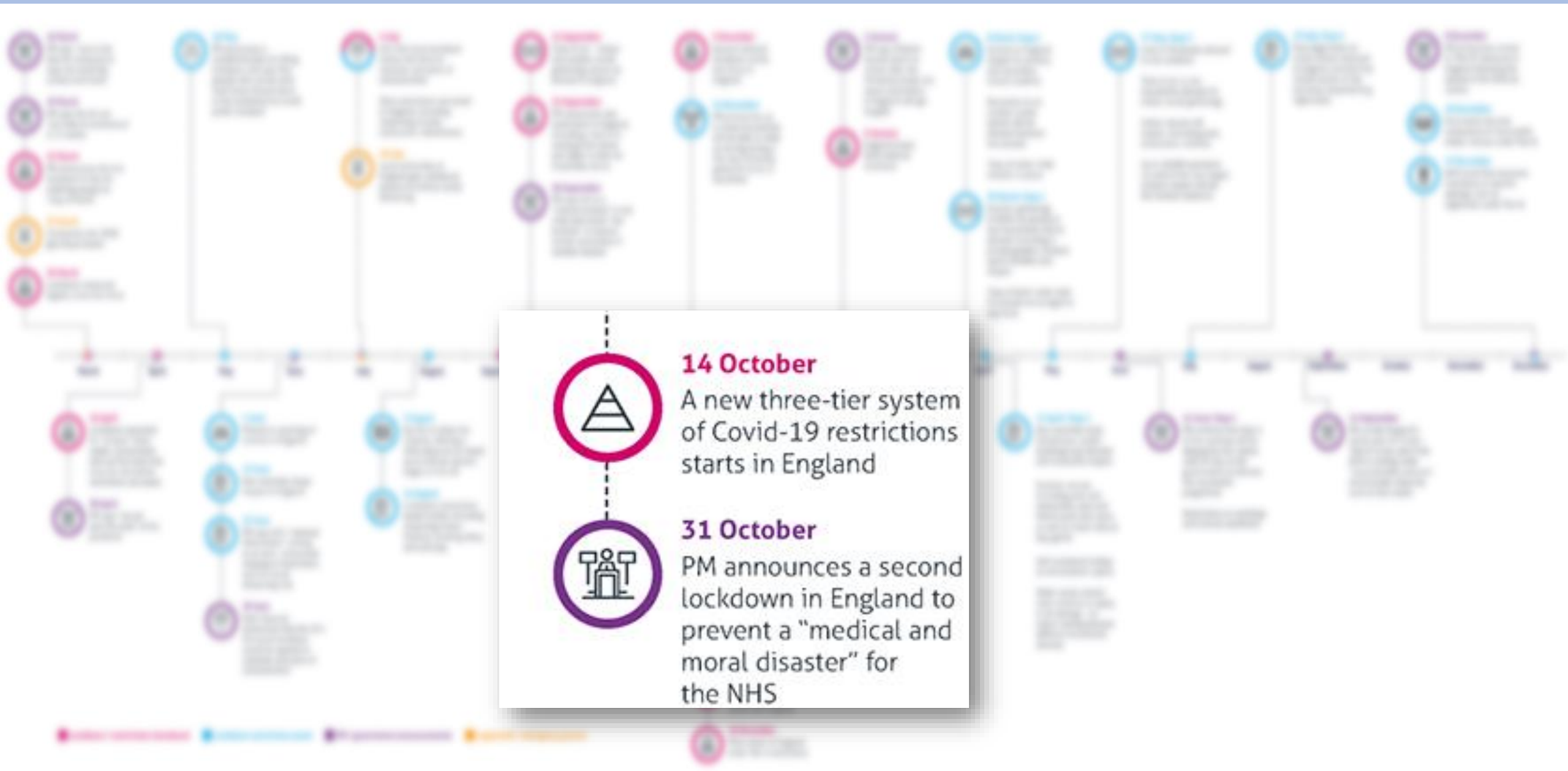
NPI & Lockdowns: UK timeline



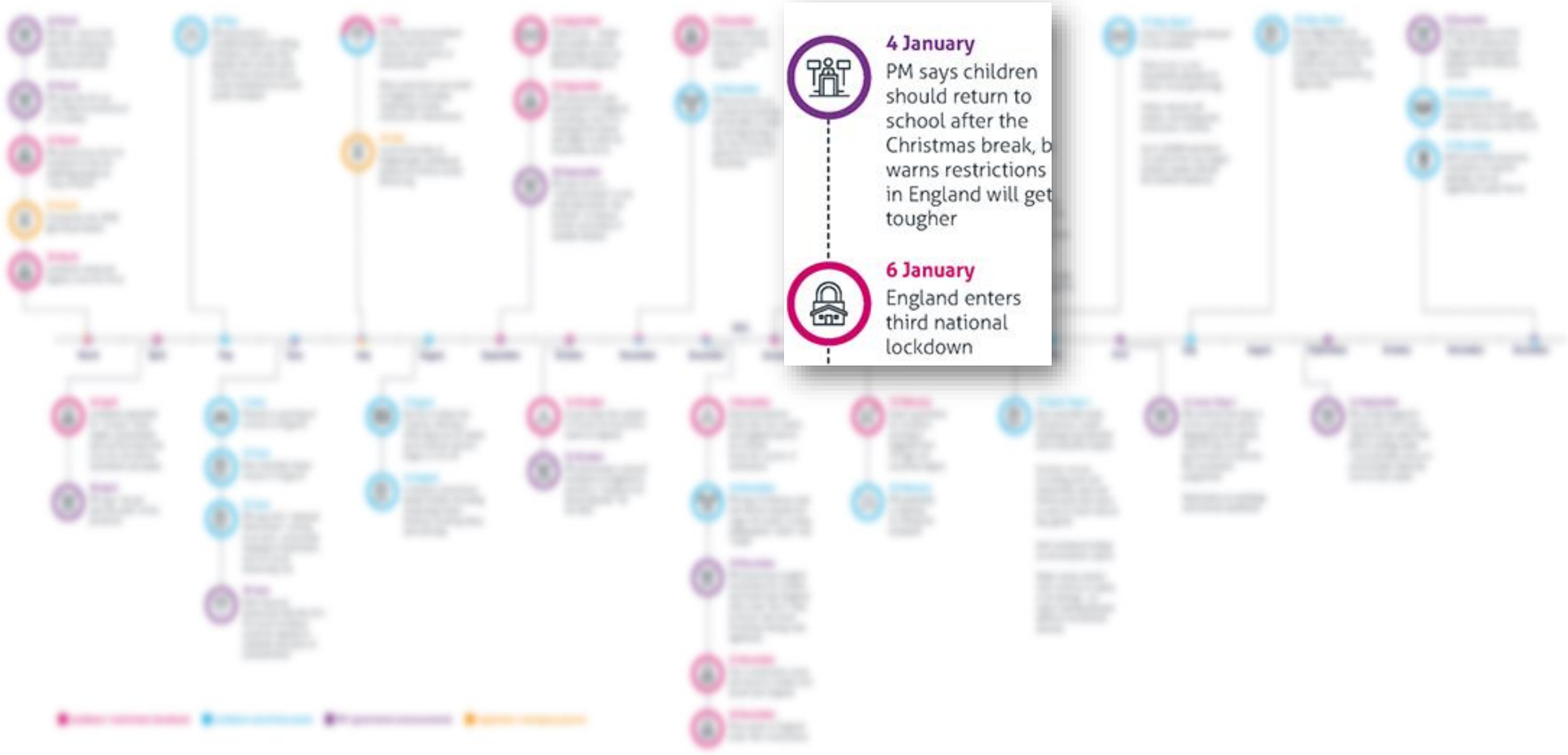
NPI & Lockdowns: UK timeline



NPI & Lockdowns: UK timeline



NPI & Lockdowns: UK timeline



NPI & Lockdowns: UK timeline

8 December

PM announces a move to 'Plan B' measures in England following the spread of the Omicron variant.

10 December

Face masks become compulsory in most public indoor venues under Plan B.

15 December

NHS Covid Pass becomes mandatory in specific settings, such as nightclubs under Plan B.

NPI & Lockdowns: UK timeline

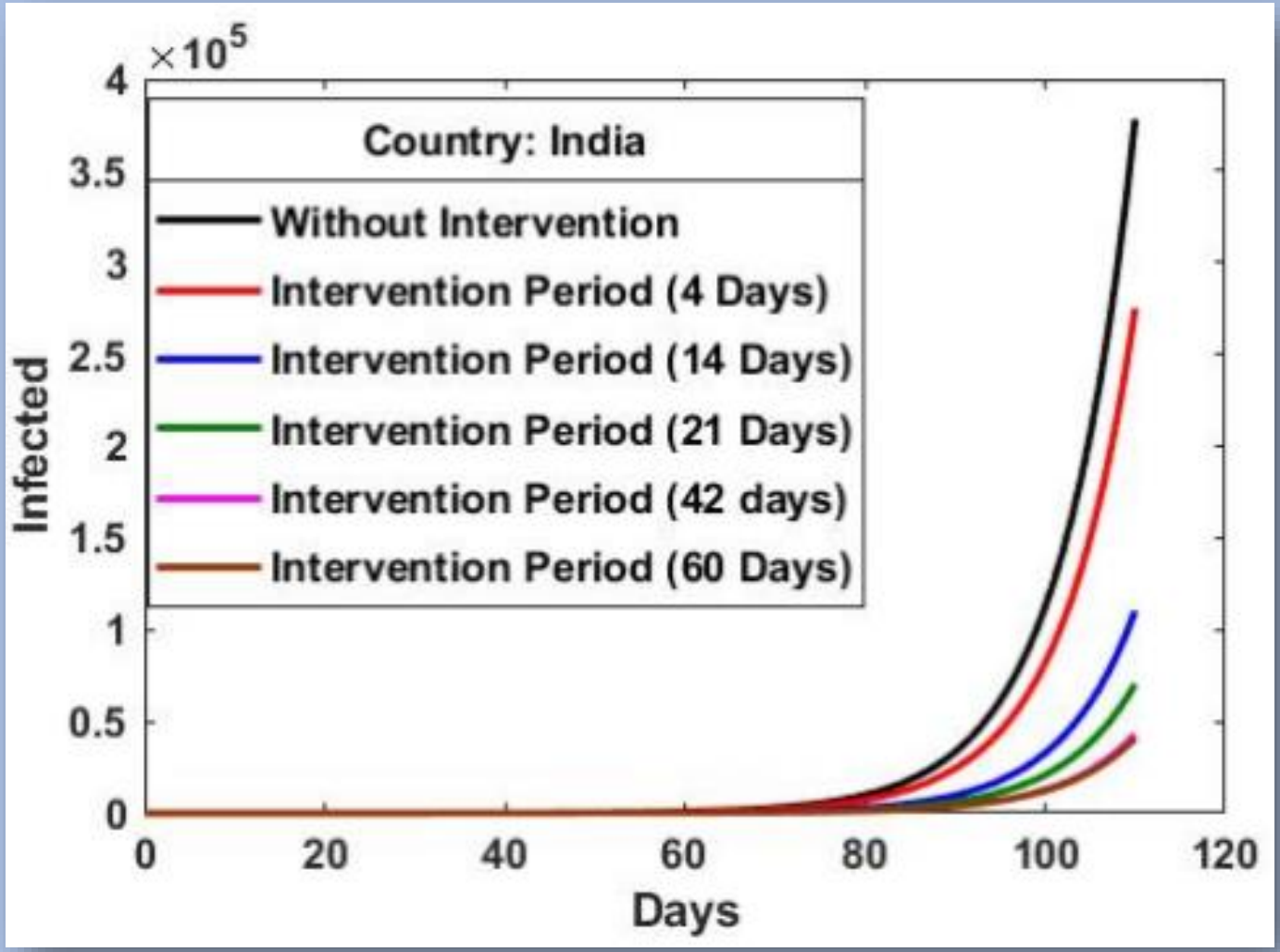
NOW

ALL

GONE

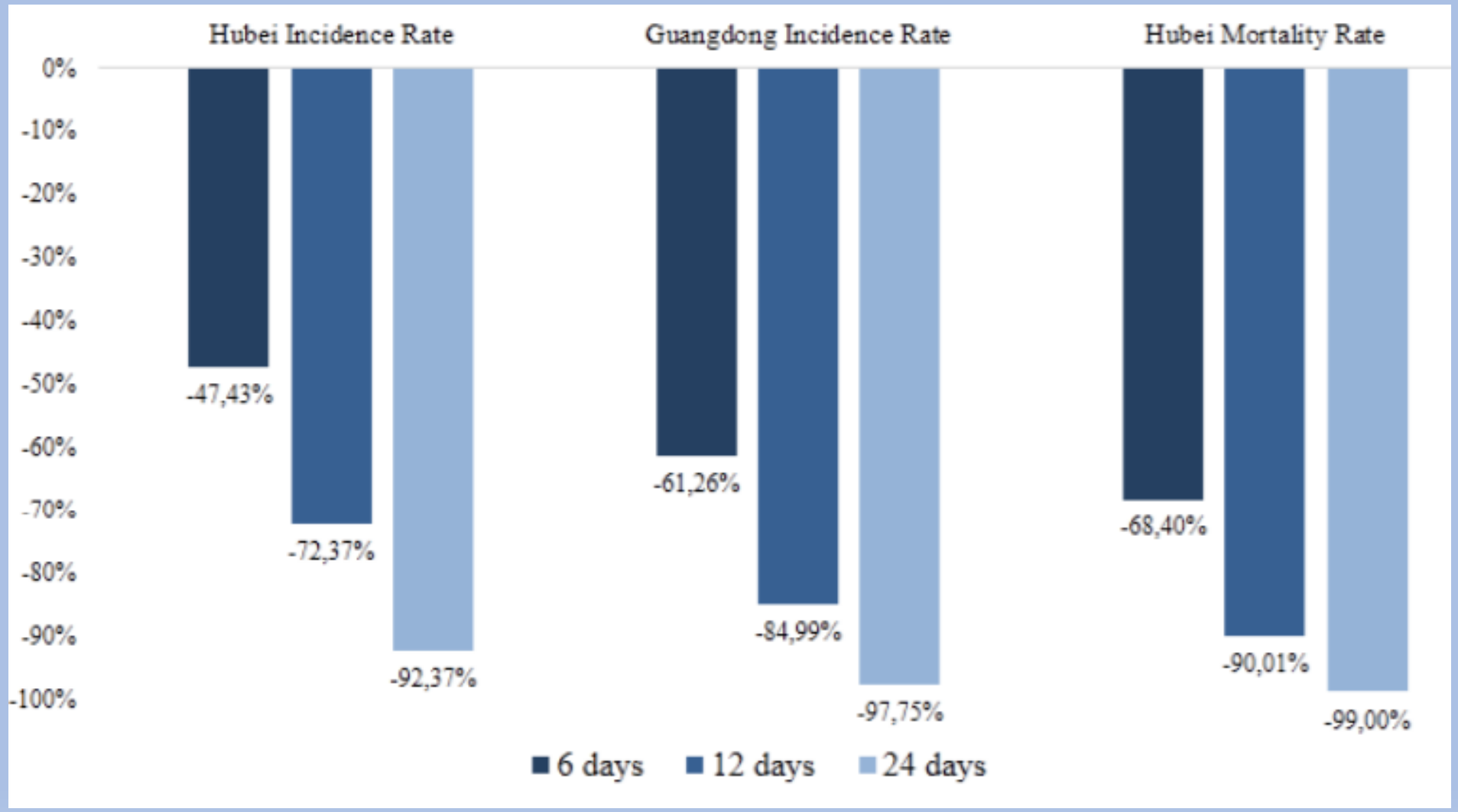
…

Lockdown: India: determining duration



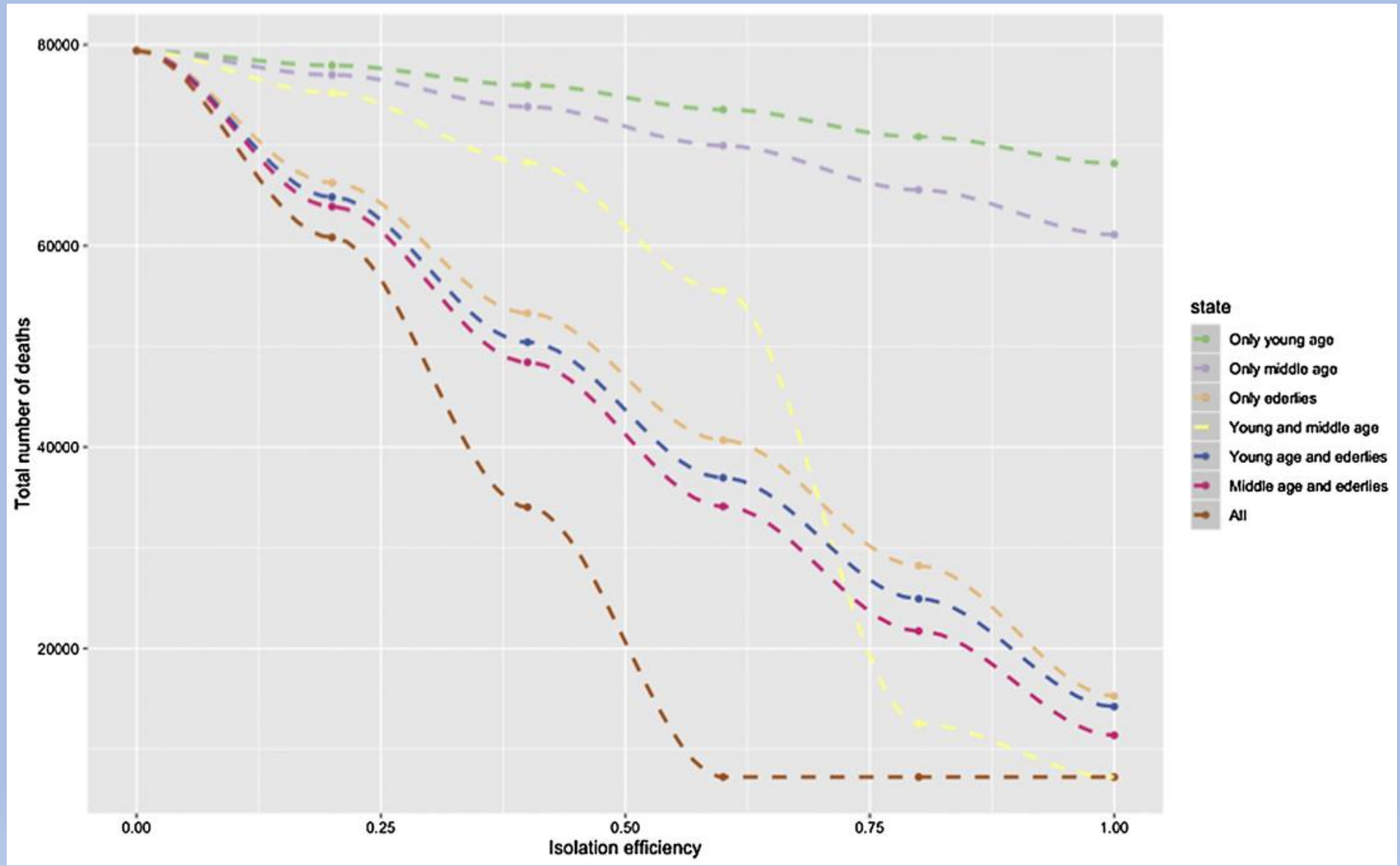
Ambikapathy et al.
JMIR PH Surv. 2020;6(2):e19368

Lockdown: China: determining duration



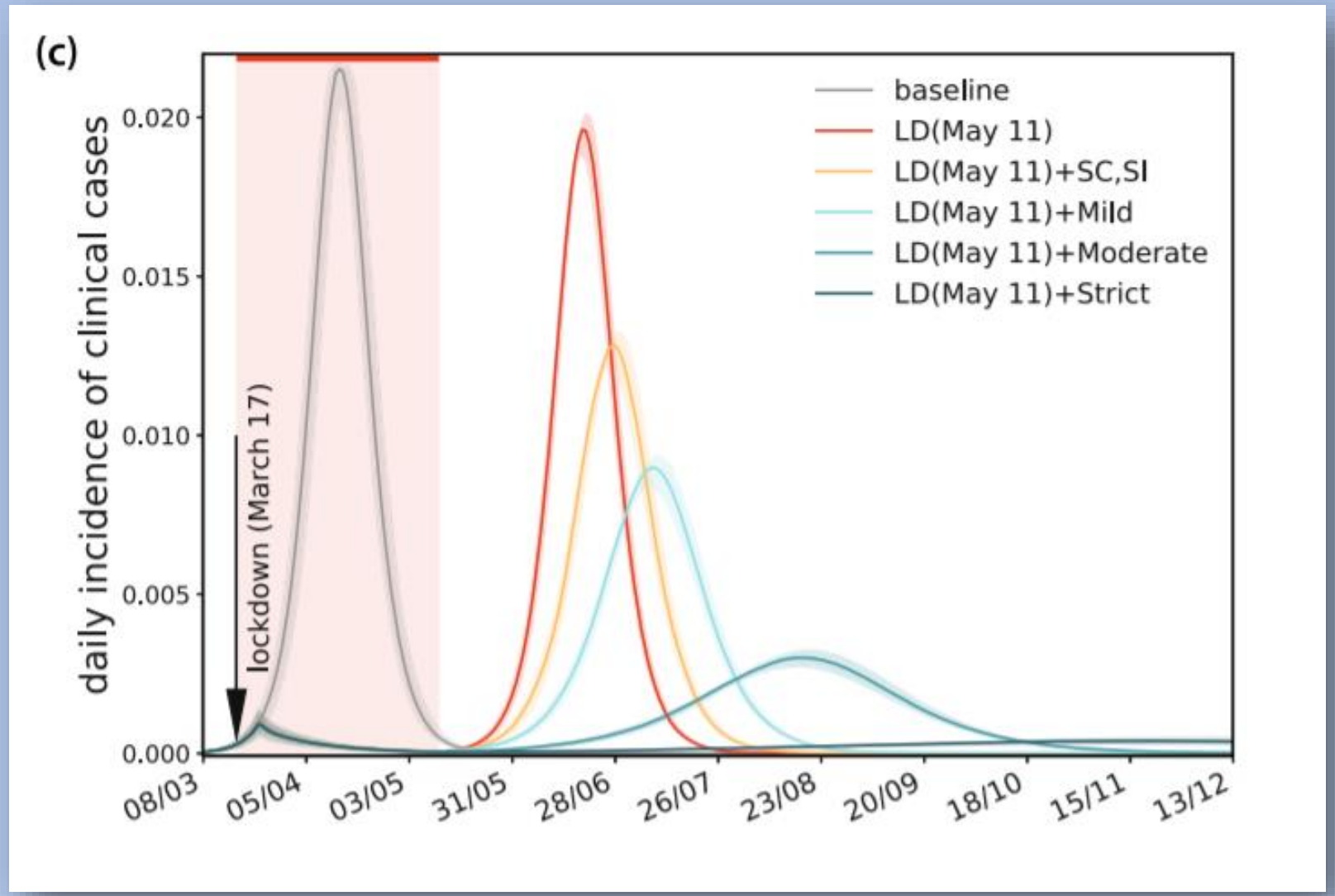
de Figueiredo et al.
Bull WHO. 2021;[InPress]

Lockdown: France: age group specific lockdowns



Roche et al.
Epidemics. 2020;33:100424

Lockdown: France: exiting lockdowns

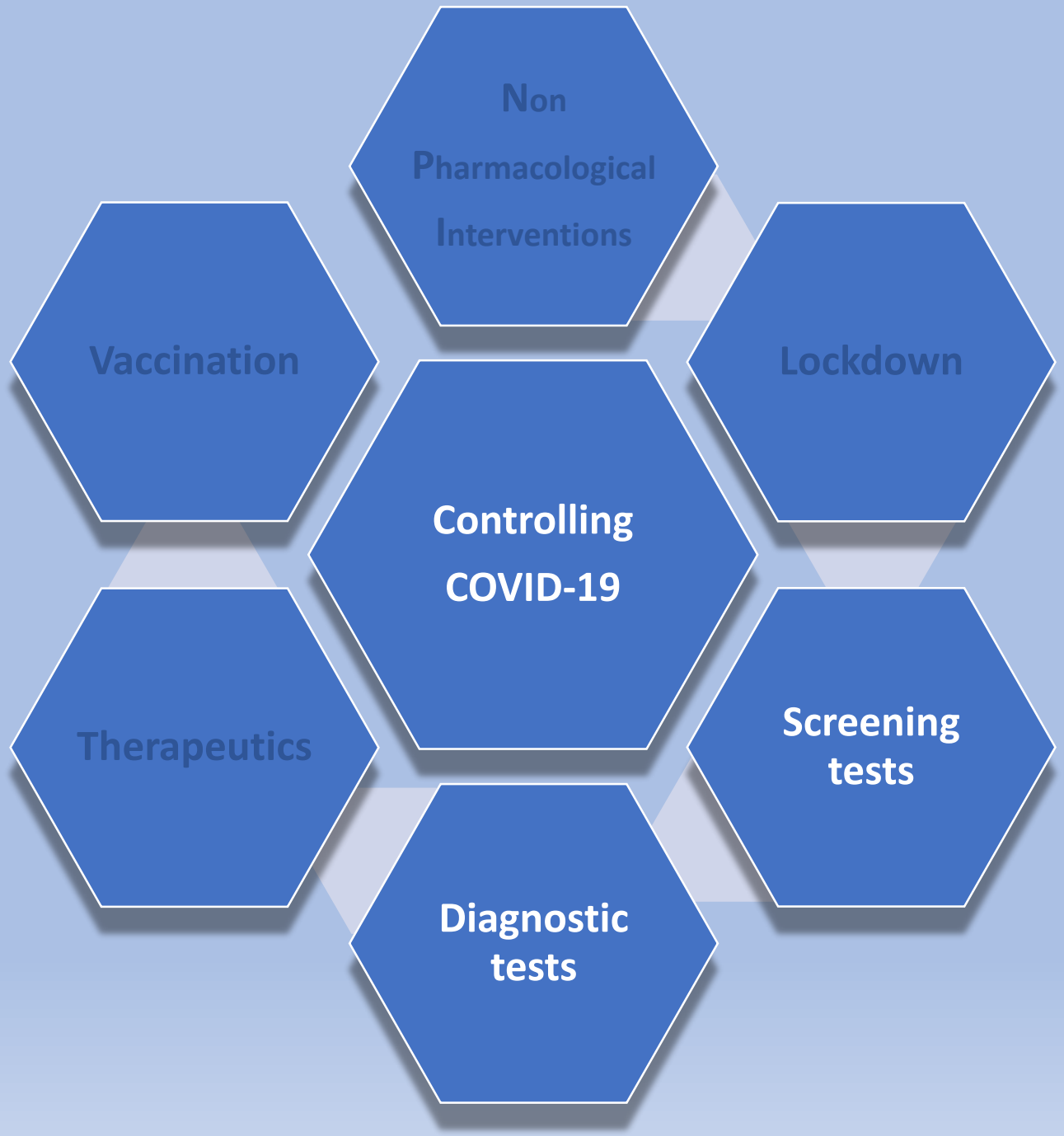


Domenico et al.
BMC Medicine 2020;18:240

Lockdown: ?future

	School closure	Telework (individuals not going to work)	Senior isolation	Closure non-essential activities	Case isolation
Lockdown	Yes; 100% contacts of children on transports removed	70% [39]	Yes, with 90% contact reduction	Yes, 100% closure	No
Set of strict interventions	Yes; 100% contacts of children on transports removed	50% [38]	Yes, with 75% contact reduction	Yes, 100% closure	No
Set of moderate interventions	Yes; 50% contacts of children on transports removed	50% [38]	Yes, with 75% contact reduction	Yes, 50% closure	No
Set of mild interventions	Yes; contacts of children on transports are not removed	25%	Yes, with 75% contact reduction	No	No
School closure and senior isolation	Yes; contacts of children on transports are not removed	As in baseline	Yes, with 75% contact reduction	No	No
Lockdown + case isolation	Yes; 100% contacts of children on transports removed	70% [39]	Yes, with 90% contact reduction	Yes, 100% closure	Yes, for 50%, 75% of cases
Set of strict interventions + case isolation	Yes; 100% contacts of children on transports removed	50% [38]	Yes, with 75% contact reduction	Yes, 100% closure	Yes, for 25%, 50%, 75% of cases
Set of moderate interventions + case isolation	Yes; 50% contacts of children on transports removed	50% [38]	Yes, with 75% contact reduction	Yes, 50% closure	Yes, for 50% of cases
Set of mild interventions + case isolation	Yes; contacts of children on transports are not removed	25%	Yes, with 75% contact reduction	No	Yes, for 50%, 75% of cases

Domenico et al.
BMC Medicine 2020;18:240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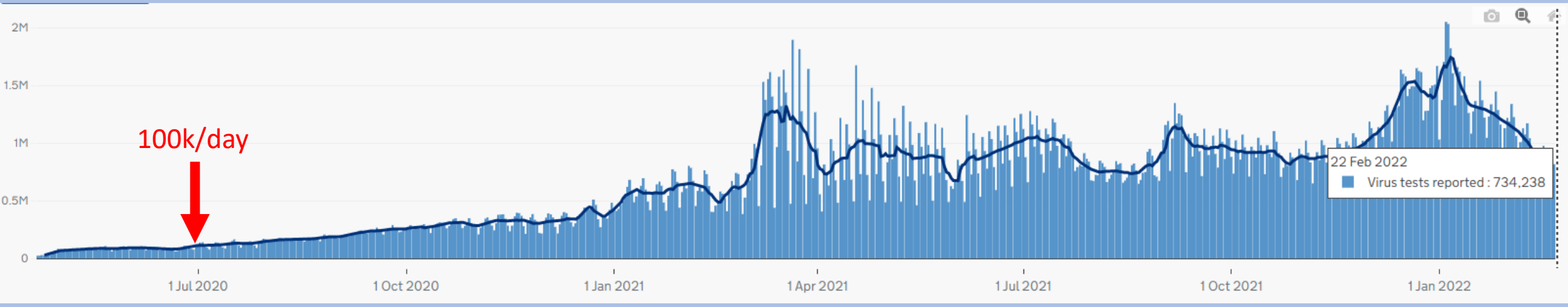
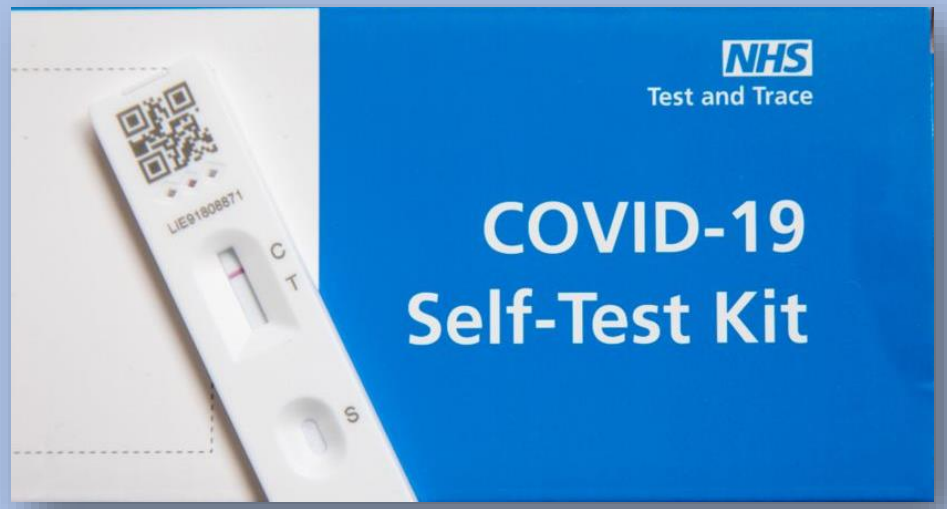
Diagnostics: COVID tests per day



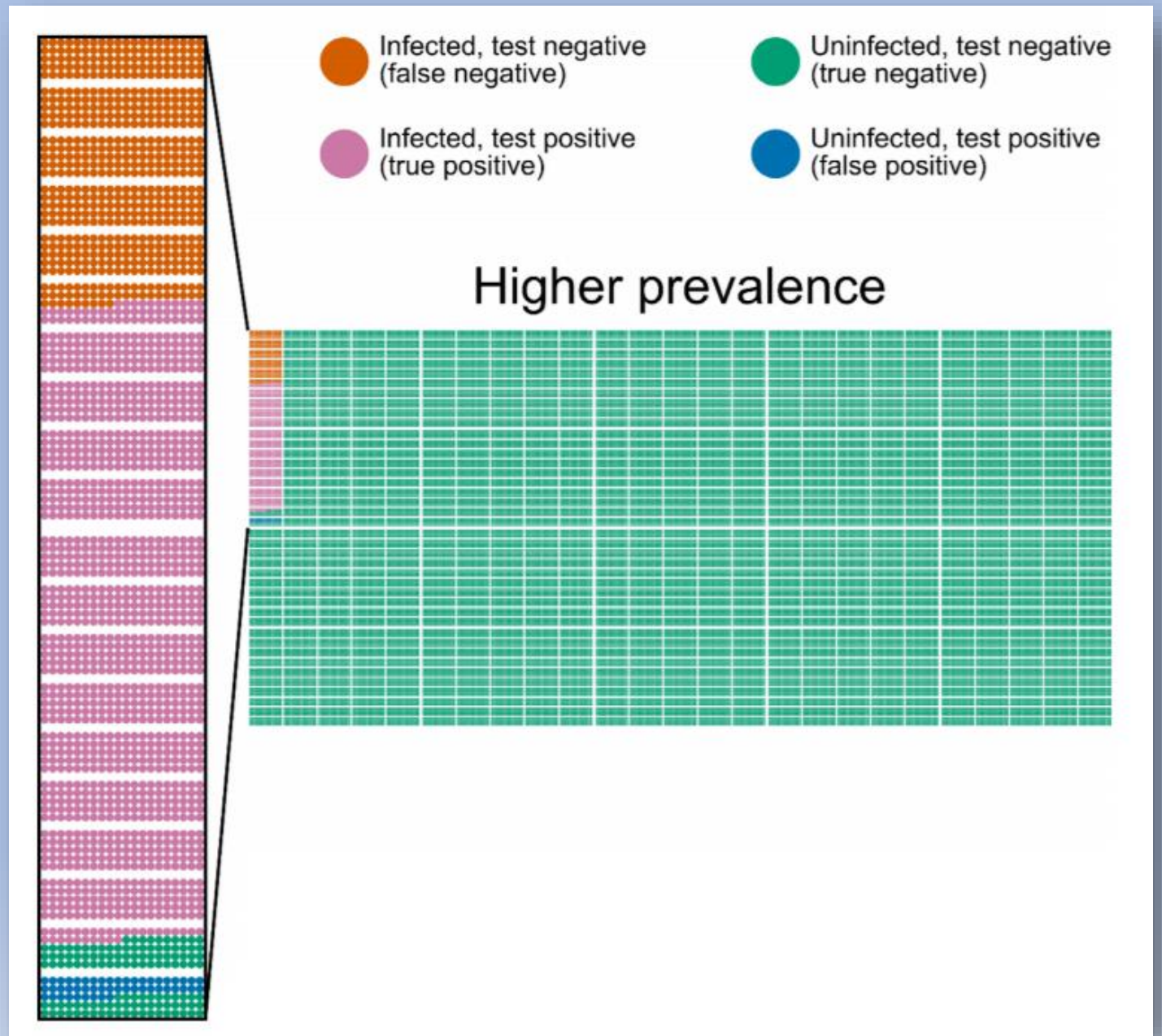
UK HSA
2022. UK Gov

Screening & testing: right tools for the right job



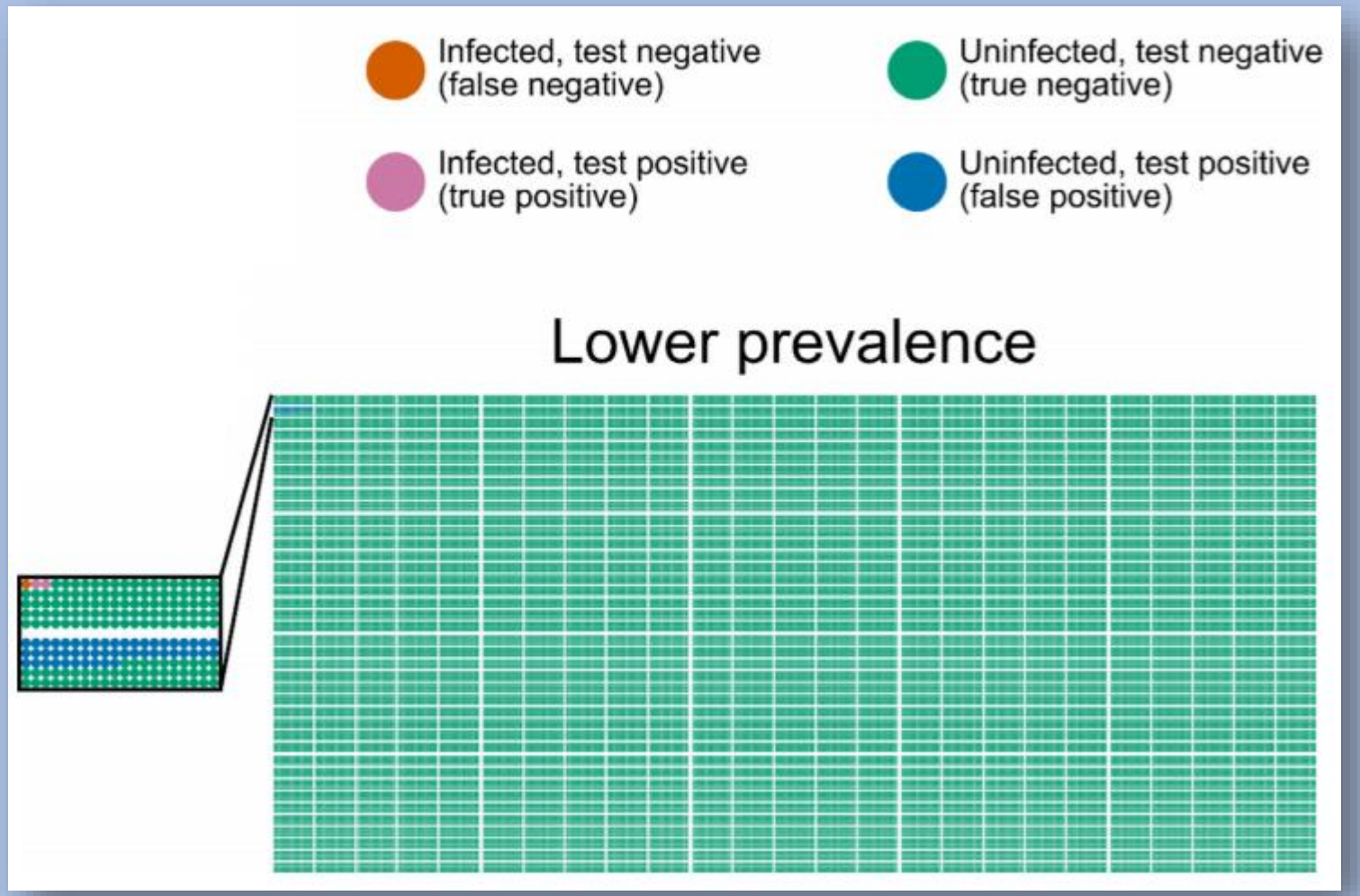
Vs.

Screening: Utility in high prevalence



Skittrall et al.
Lancet RH:E 2021;1:1000002

Screening: Utility in low prevalence



Skittrall et al.
Lancet RH:E 2021;1:1000002

Diagnostics:molecular

Remaining issues

(i) Human 'sample adequacy' controls

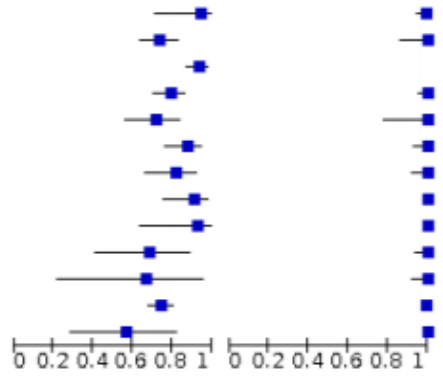
(ii) Determination of VOC in real-time

(iii) Multiplexing for other RTI viruses (flu etc)

Dinnes et al.
Cochrane 2021;3:CD013705.

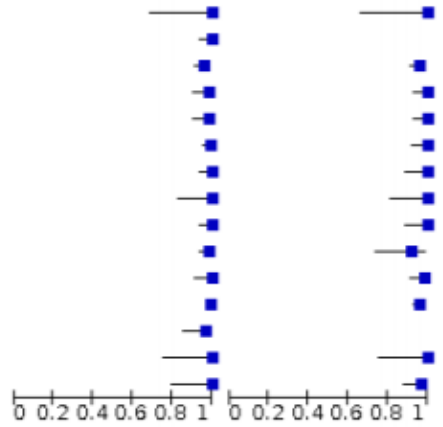
Abbott - ID NOW (Isothermal PCR)

Study	TP	FP	FN	TN	IFU compliant	Sensitivity (95% CI)	Specificity (95% CI)
Ghofrani 2020	16	1	1	95	No	0.94 [0.71, 1.00]	0.99 [0.94, 1.00]
Smithgall 2020 [A]	65	0	23	25	No	0.74 [0.63, 0.83]	1.00 [0.86, 1.00]
Rhoads 2020	90	0	6	0	No	0.94 [0.87, 0.98]	Not estimable
Moore 2020	94	0	25	79	No	0.79 [0.71, 0.86]	1.00 [0.95, 1.00]
Mitchell 2020	33	0	13	15	No	0.72 [0.57, 0.84]	1.00 [0.78, 1.00]
Zhen 2020 [A]	50	0	7	50	No	0.88 [0.76, 0.95]	1.00 [0.93, 1.00]
SoRelle 2020	32	0	7	44	No	0.82 [0.66, 0.92]	1.00 [0.92, 1.00]
Cradic 2020(a)	30	0	3	151	No	0.91 [0.76, 0.98]	1.00 [0.98, 1.00]
Cradic 2020(b)	12	0	1	169	Unclear	0.92 [0.64, 1.00]	1.00 [0.98, 1.00]
Lephart 2020 [A]	11	0	5	59	Yes	0.69 [0.41, 0.89]	1.00 [0.94, 1.00]
Jin 2020	4	0	2	46	Yes	0.67 [0.22, 0.96]	1.00 [0.92, 1.00]
Harrington 2020	139	2	47	336	Yes	0.75 [0.68, 0.81]	0.99 [0.98, 1.00]
Thwe 2020	8	0	6	147	Yes	0.57 [0.29, 0.82]	1.00 [0.98, 1.00]



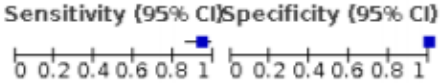
Cepheid - Xpert Xpress (Automated RT-PCR)

Study	TP	FP	FN	TN	IFU compliant	Sensitivity (95% CI)	Specificity (95% CI)
Goldenberger 2020	10	0	0	9	No	1.00 [0.69, 1.00]	1.00 [0.66, 1.00]
Chen 2020a	55	0	0	0	No	1.00 [0.94, 1.00]	Not estimable
Hou 2020	147	5	6	127	No	0.96 [0.92, 0.99]	0.96 [0.91, 0.99]
Stevens 2020	53	0	1	50	No	0.98 [0.90, 1.00]	1.00 [0.93, 1.00]
Zhen 2020 [B]	57	0	1	50	No	0.98 [0.91, 1.00]	1.00 [0.93, 1.00]
Wong 2020	118	0	1	43	No	0.99 [0.95, 1.00]	1.00 [0.92, 1.00]
Wolters 2020	58	0	0	30	No	1.00 [0.94, 1.00]	1.00 [0.88, 1.00]
Dust 2020	20	0	0	18	Unclear	1.00 [0.83, 1.00]	1.00 [0.81, 1.00]
Jokela 2020	60	0	0	30	Unclear	1.00 [0.94, 1.00]	1.00 [0.88, 1.00]
Smithgall 2020 [B]	87	2	1	23	Unclear	0.99 [0.94, 1.00]	0.92 [0.74, 0.99]
Moran 2020	42	1	0	60	Unclear	1.00 [0.92, 1.00]	0.98 [0.91, 1.00]
Loeffelholz 2020	219	11	1	250	Unclear	1.00 [0.97, 1.00]	0.96 [0.93, 0.98]
Broder 2020	34	0	1	0	Yes	0.97 [0.85, 1.00]	Not estimable
Lieberman 2020	13	0	0	13	Yes	1.00 [0.75, 1.00]	1.00 [0.75, 1.00]
Lephart 2020 [B]	16	2	0	56	Yes	1.00 [0.79, 1.00]	0.97 [0.88, 1.00]



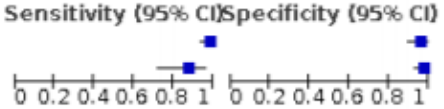
DNANudge - COVID Nudge (Automated RT-PCR)

Study	TP	FP	FN	TN	IFU compliant	Sensitivity (95% CI)	Specificity (95% CI)
Gibani 2020	67	0	4	315	Yes	0.94 [0.86, 0.98]	1.00 [0.99, 1.00]



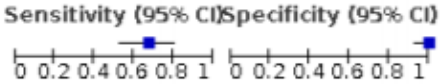
DRW - SAMBA II (Automated RT-PCR)

Study	TP	FP	FN	TN	IFU compliant	Sensitivity (95% CI)	Specificity (95% CI)
Assennato 2020	87	3	1	81	Unclear	0.99 [0.94, 1.00]	0.96 [0.90, 0.99]
Collier 2020	29	3	4	113	Yes	0.88 [0.72, 0.97]	0.97 [0.93, 0.99]



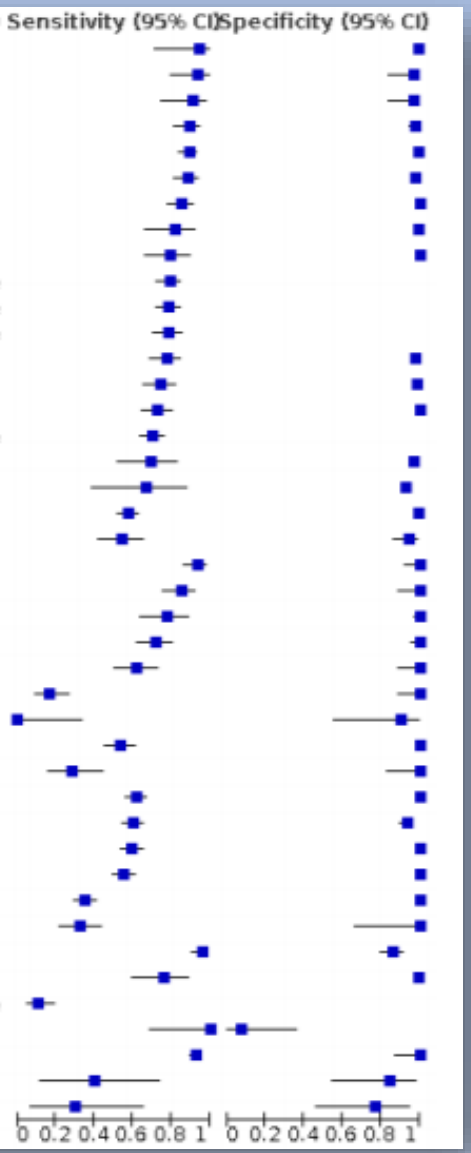
Mesa Biotech - Accula (other molecular)

Study	TP	FP	FN	TN	IFU compliant	Sensitivity (95% CI)	Specificity (95% CI)
Hogan 2020	34	0	16	50	No	0.68 [0.53, 0.80]	1.00 [0.93, 1.00]



Diagnostics: antigen: symptomatic

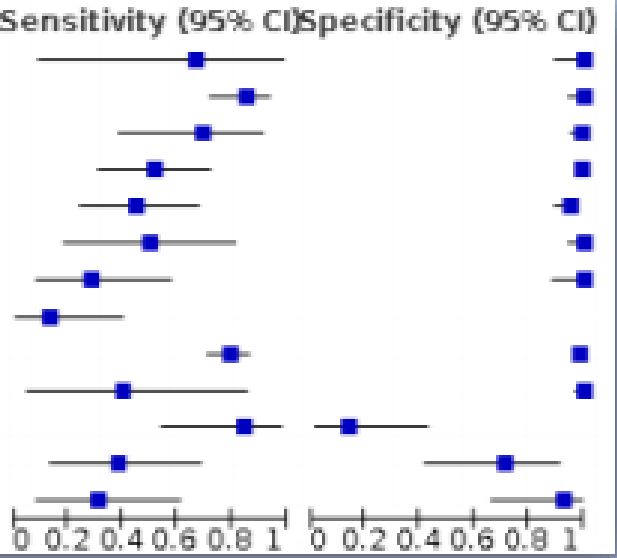
Study	TP	FP	FN	TN	Setting	Sensitivity (95% CI)	Specificity (95% CI)
Van der Moeren 2020(a)	16	2	1	332	COVID-19 test centre	0.94 [0.71, 1.00]	0.99 [0.98, 1.00]
Porte 2020b [A]	30	1	2	31	COVID-19 test centre	0.94 [0.79, 0.99]	0.97 [0.84, 1.00]
Porte 2020b [B]	29	1	3	31	COVID-19 test centre	0.91 [0.75, 0.98]	0.97 [0.84, 1.00]
FIND 2020a	91	8	11	290	COVID-19 test centre	0.89 [0.82, 0.94]	0.97 [0.95, 0.99]
FIND 2020c (CH)	170	1	21	337	COVID-19 test centre	0.89 [0.84, 0.93]	1.00 [0.98, 1.00]
FIND 2020c (BR)	94	7	12	287	COVID-19 test centre	0.89 [0.81, 0.94]	0.98 [0.95, 0.99]
FIND 2020b	106	0	18	411	COVID-19 test centre	0.85 [0.78, 0.91]	1.00 [0.99, 1.00]
Kruger 2020(c)	32	7	7	972	COVID-19 test centre	0.82 [0.66, 0.92]	0.99 [0.99, 1.00]
Albert 2020	43	0	11	358	COVID-19 test centre	0.80 [0.66, 0.89]	1.00 [0.99, 1.00]
Fenollar 2020(a)	144	0	38	0	COVID-19 test centre	0.79 [0.72, 0.85]	Not estimable
PHE 2020(d) [Lab tested]	156	0	42	0	COVID-19 test centre	0.79 [0.72, 0.84]	Not estimable
Van der Moeren 2020(b)	98	0	27	0	COVID-19 test centre	0.78 [0.70, 0.85]	Not estimable
FIND 2020d (BR)	93	7	27	326	COVID-19 test centre	0.78 [0.69, 0.85]	0.98 [0.96, 0.99]
FIND 2020e (BR)	87	4	30	355	COVID-19 test centre	0.74 [0.65, 0.82]	0.99 [0.97, 1.00]
Gremmels 2020(a)	99	0	37	1185	COVID-19 test centre	0.73 [0.65, 0.80]	1.00 [1.00, 1.00]
PHE 2020(d) [HCW tested]	156	0	67	0	COVID-19 test centre	0.70 [0.63, 0.76]	Not estimable
FIND 2020d (DE)	27	20	12	617	COVID-19 test centre	0.69 [0.52, 0.83]	0.97 [0.95, 0.98]
Kruger 2020(a)	10	49	5	663	COVID-19 test centre	0.67 [0.38, 0.88]	0.93 [0.91, 0.95]
PHE 2020(c) [non-HCW tested]	214	5	158	1299	COVID-19 test centre	0.58 [0.52, 0.63]	1.00 [0.99, 1.00]
Billaud 2020	40	4	34	69	Contacts	0.54 [0.42, 0.66]	0.95 [0.87, 0.98]
Porte 2020a	77	0	5	45	Hospital A&E	0.94 [0.86, 0.98]	1.00 [0.92, 1.00]
Weitzel 2020 [D]	68	0	12	31	Hospital A&E	0.85 [0.75, 0.92]	1.00 [0.89, 1.00]
Linares 2020	39	0	11	133	Hospital A&E	0.78 [0.64, 0.88]	1.00 [0.97, 1.00]
Cerutti 2020	75	0	29	81	Hospital A&E	0.72 [0.62, 0.80]	1.00 [0.96, 1.00]
Weitzel 2020 [A]	49	0	30	30	Hospital A&E	0.62 [0.50, 0.73]	1.00 [0.88, 1.00]
Weitzel 2020 [C]	13	0	65	31	Hospital A&E	0.17 [0.09, 0.27]	1.00 [0.89, 1.00]
Weitzel 2020 [B]	0	1	9	9	Hospital A&E	0.00 [0.00, 0.34]	0.90 [0.55, 1.00]
PHE 2020(a)	95	0	83	940	Hospital in-patient	0.53 [0.46, 0.61]	1.00 [1.00, 1.00]
Veyrenche 2020	13	0	32	20	Hospital in-patient	0.29 [0.16, 0.44]	1.00 [0.83, 1.00]
Fourati 2020 [E]	182	0	113	337	Laboratory-based	0.62 [0.56, 0.67]	1.00 [0.99, 1.00]
Fourati 2020 [B]	175	23	116	314	Laboratory-based	0.60 [0.54, 0.66]	0.93 [0.90, 0.96]
Fourati 2020 [D]	177	0	120	337	Laboratory-based	0.60 [0.54, 0.65]	1.00 [0.99, 1.00]
Fourati 2020 [C]	163	0	132	337	Laboratory-based	0.55 [0.49, 0.61]	1.00 [0.99, 1.00]
Fourati 2020 [A]	103	0	189	337	Laboratory-based	0.35 [0.30, 0.41]	1.00 [0.99, 1.00]
Scohy 2020	25	0	52	9	Laboratory-based	0.32 [0.22, 0.44]	1.00 [0.66, 1.00]
Courtellemont 2020	97	20	4	127	Mixed	0.96 [0.90, 0.99]	0.86 [0.80, 0.91]
Young 2020	29	1	9	212	Mixed	0.76 [0.60, 0.89]	1.00 [0.97, 1.00]
Nagura-Ikeda 2020	10	0	78	0	Mixed	0.11 [0.06, 0.20]	Not estimable
Schildgen 2020 [C]	10	12	0	1	Unclear	1.00 [0.69, 1.00]	0.08 [0.00, 0.36]
Alemany 2020	388	0	31	27	Unclear	0.93 [0.90, 0.95]	1.00 [0.87, 1.00]
Schildgen 2020 [B]	4	2	6	11	Unclear	0.40 [0.12, 0.74]	0.85 [0.55, 0.98]
Schildgen 2020 [A]	3	3	7	10	Unclear	0.30 [0.07, 0.65]	0.77 [0.46, 0.95]



Dinnes et al.
Cochrane 2021;3:CD013705.

Diagnostics: antigen: asymptomatic

Study	TP	FP	FN	TN	Setting	Sensitivity (95% CI)	Specificity (95% CI)
Gremmels 2020(a)	2	0	1	34	COVID-19 test centre	0.67 [0.09, 0.99]	1.00 [0.90, 1.00]
Shrestha 2020	40	0	7	66	Contacts	0.85 [0.72, 0.94]	1.00 [0.95, 1.00]
Gupta 2020	9	1	4	113	Contacts	0.69 [0.39, 0.91]	0.99 [0.95, 1.00]
Billaud 2020	13	1	12	289	Contacts	0.52 [0.31, 0.72]	1.00 [0.98, 1.00]
Fenollar 2020(b)	10	7	12	130	Contacts	0.45 [0.24, 0.68]	0.95 [0.90, 0.98]
Linares 2020	5	0	5	62	Hospital A&E	0.50 [0.19, 0.81]	1.00 [0.94, 1.00]
Scohy 2020	4	0	10	31	Laboratory-based	0.29 [0.08, 0.58]	1.00 [0.89, 1.00]
Nagura-Ikeda 2020	2	0	13	0	Mixed	0.13 [0.02, 0.40]	Not estimable
Alemany 2020	93	5	24	365	Screening	0.79 [0.71, 0.86]	0.99 [0.97, 1.00]
Cerutti 2020	2	0	3	140	Targeted screening	0.40 [0.05, 0.85]	1.00 [0.97, 1.00]
Schildgen 2020 [C]	11	12	2	2	Unclear	0.85 [0.55, 0.98]	0.14 [0.02, 0.43]
Schildgen 2020 [B]	5	4	8	10	Unclear	0.38 [0.14, 0.68]	0.71 [0.42, 0.92]
Schildgen 2020 [A]	4	1	9	13	Unclear	0.31 [0.09, 0.61]	0.93 [0.66, 1.00]



Remaining issues

(i) What is the cost-utility

(ii) Can we optimise use (technique or assay)

Dinnes et al.
Cochrane 2021;3:CD013705.

Diagnostics: antibodies

World Health Organization

WHO/BS/2020.2403
ENGLISH ONLY

EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION
Geneva, 9 - 10 December 2020

Establishment of the WHO International Standard and Reference Panel for anti-SARS-CoV-2 antibody

Giada Mattiuzzo[1]# , Emma M. Bentley[1], Mark Hassall[1], Stephanie Routley[1], Samuel Richardson[1], Valentina Bernasconi[2], Paul Kristiansen[2], Heli Harvala[3], David Roberts[3], Malcom G Semple[4] , Lance CW Turtle[4], Peter JM Openshaw[5] and Kenneth Baillie[6] on behalf of the ISARIC4C Investigators, Lise Sofie Haug Nissen-Meyer[7], Arne Broch Brantsæter[8], Helen Baxendale[9], Eleanor Atkinson[10], Peter Rigsby[10], David Padley[11], Neil Almond[11], Nicola J. Rose[1], Mark Page[1] and the collaborative study participants*

Now a consensus on:

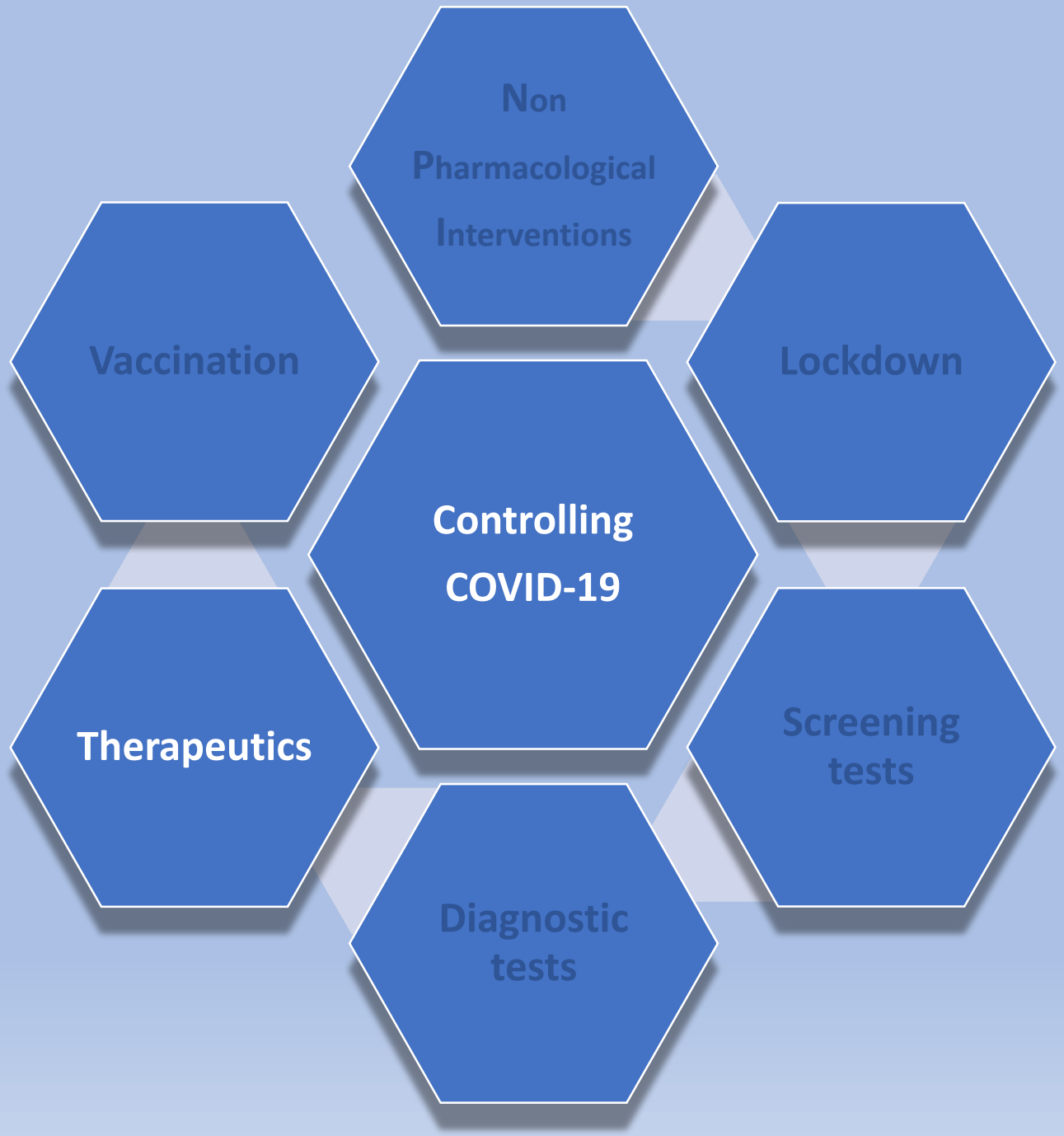
(i) International units

Still no consensus on:

(i) Whether quantification correlates with immunity

(ii) Inter-platform equivalence

(iii) Role of T cells


Non Pharmacological Interventions
Vaccination
Lockdown
Controlling COVID-19
Therapeutics
Screening tests
Diagnostic tests

Therapeutics

COVID-19 rapid guideline: Managing COVID-19

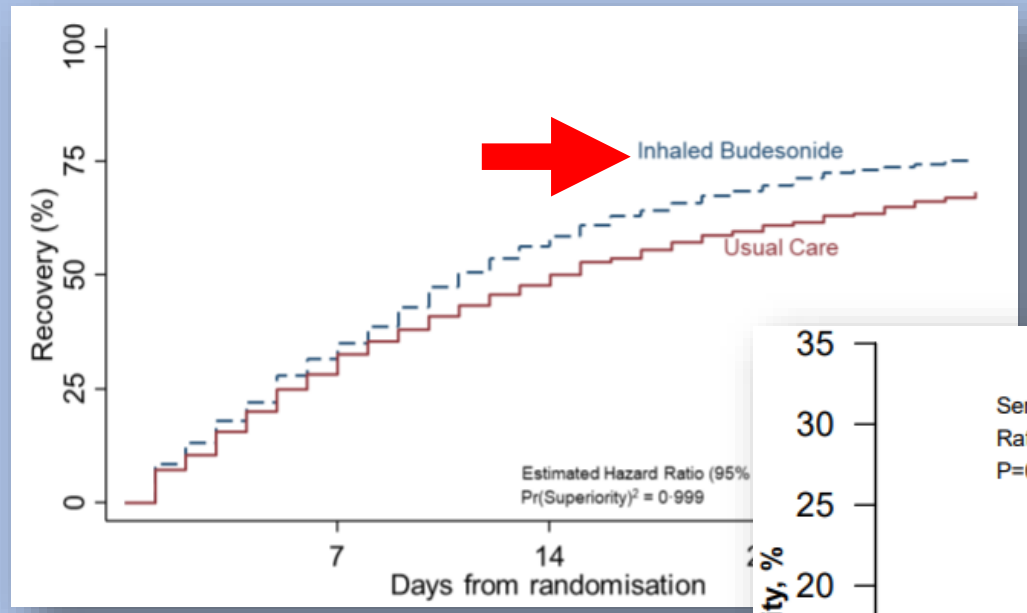
Main editor

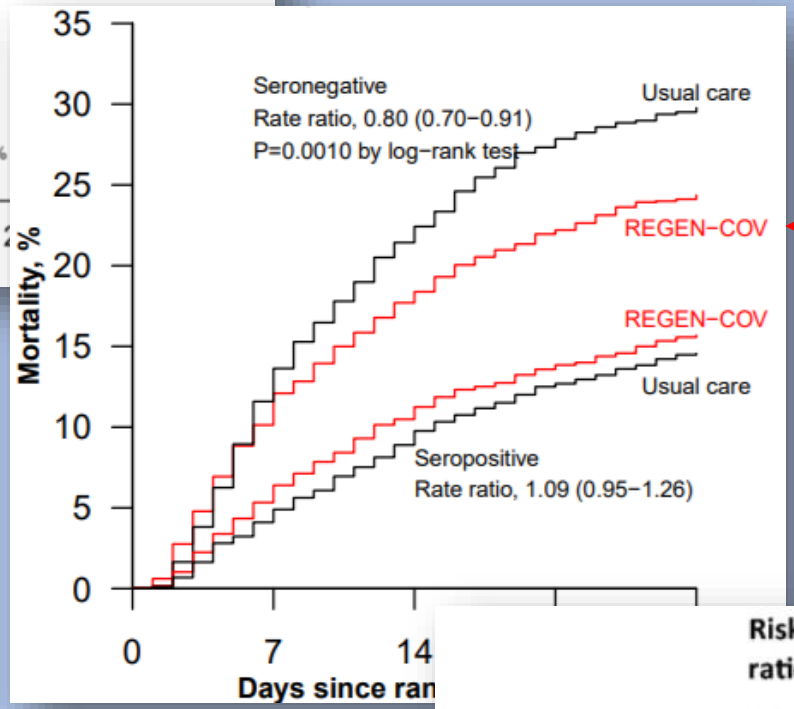
NICE

Publishing, version history and subscription

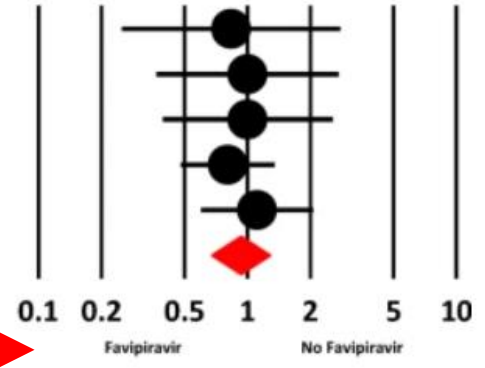
21.0 published on 23.02.2022

Therapeutics





	Risk ratio	Lower limit	Upper limit	p-Value
Lou, 2020	0.833	0.252	2.755	0.765
Udwadia, 2020	1.000	0.369	2.712	1.000
Ivashchenko, 2020	1.000	0.395	2.534	1.000
Chen, 2020	0.805	0.483	1.340	0.403
Zhao, 2020	1.111	0.604	2.045	0.735
	0.930	0.671	1.289	0.664



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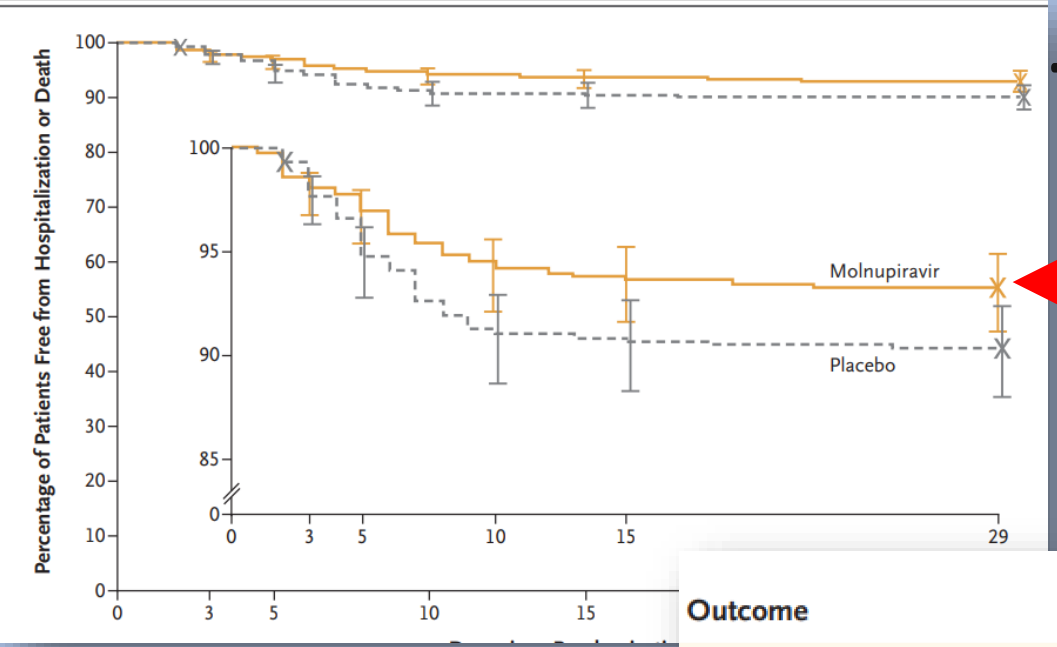
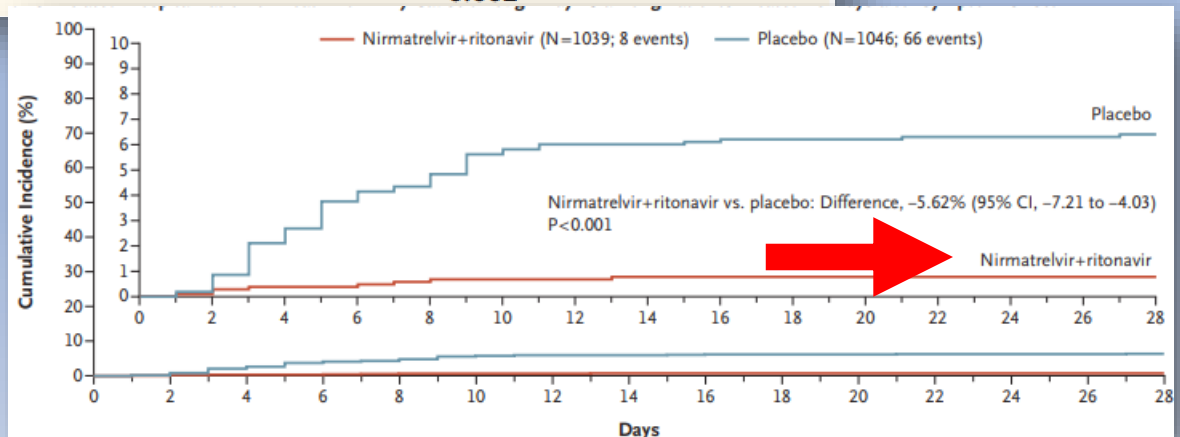


Outcome	Sotrovimab (N = 291)	Placebo (N = 292)
Primary outcome		
Hospitalization for >24 hr for any cause or death from any cause — no. (%)	3 (1)	21 (7)
Hospitalization for >24 hr for any cause	3 (1)	21 (7)
Death from any cause	0	1 (<1)†
Alive and not hospitalized — no. (%)	284 (98)	270 (92)
Relative risk reduction (97.24% CI)	85 (44–96)	—
P value	0.002	—



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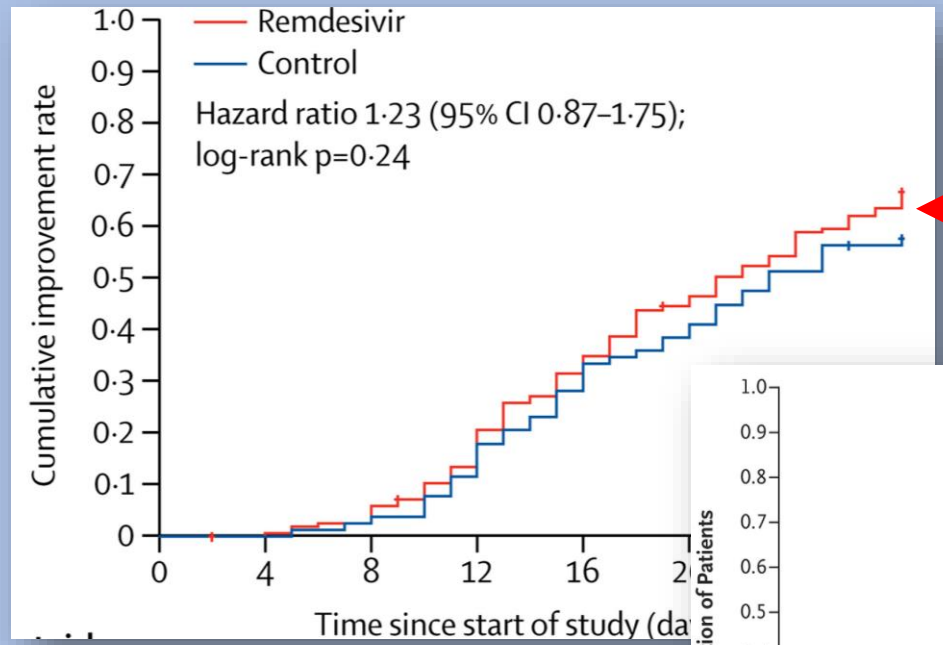
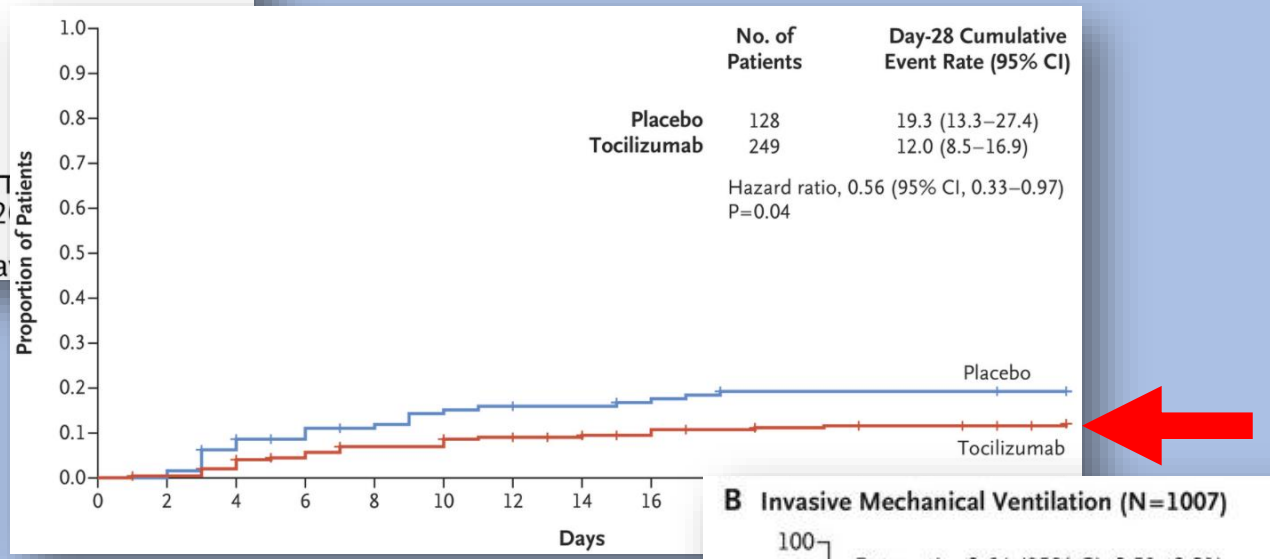
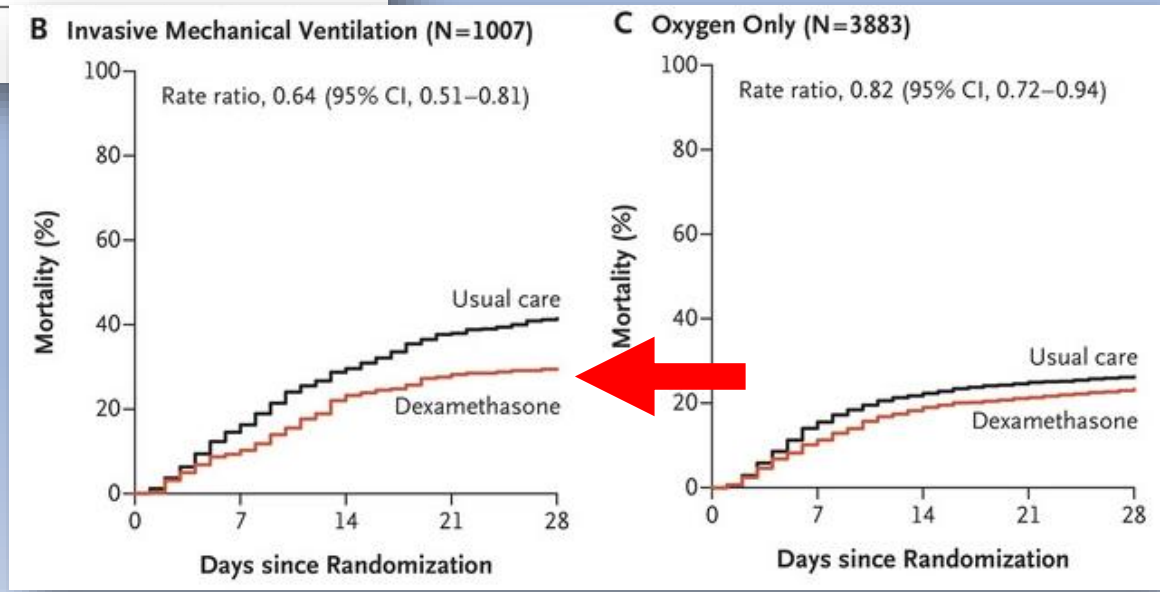
Therapeutics







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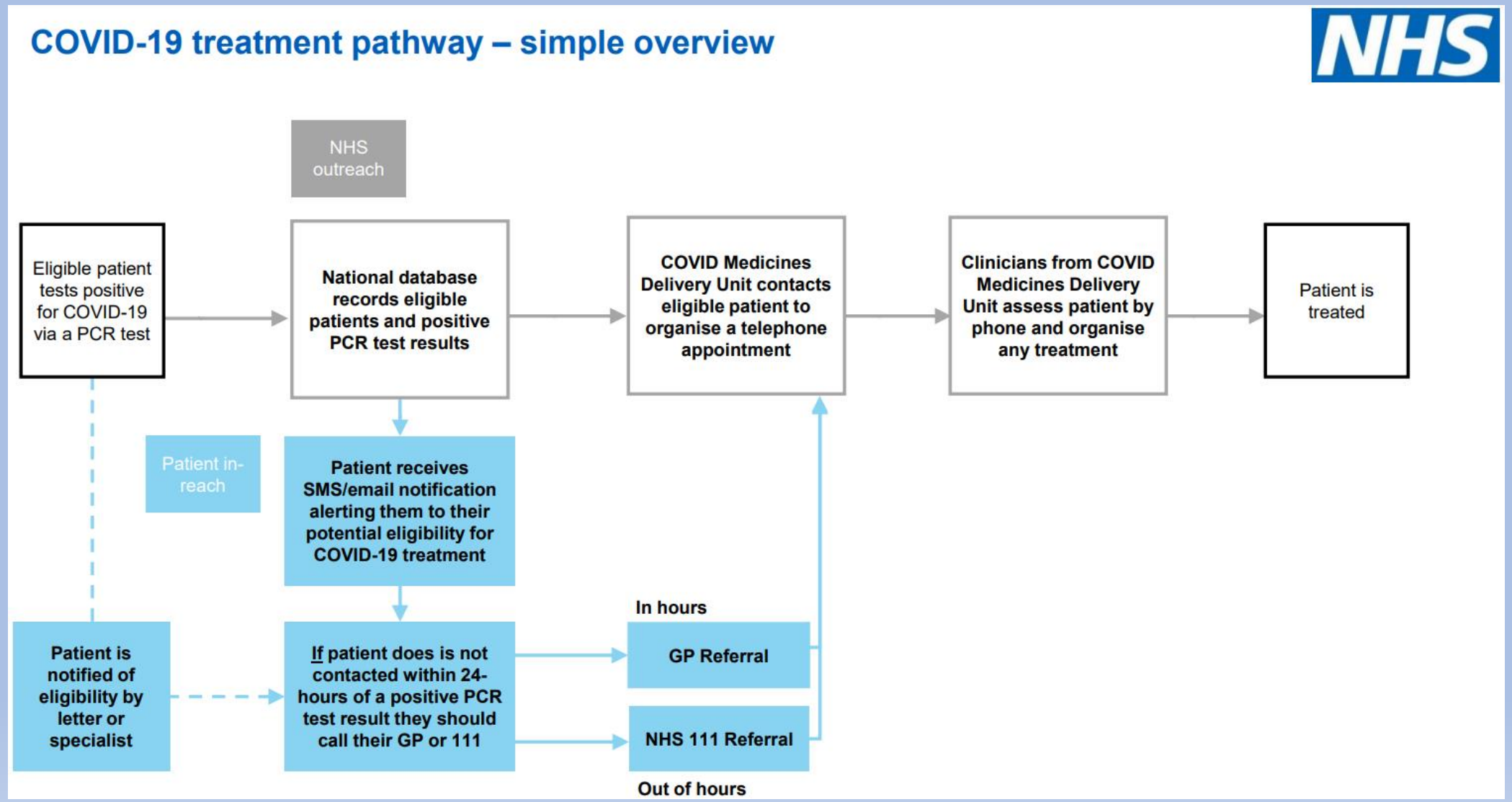
CMDU


COVID-19 treatment pathway – simple overview
NHS
NHS outreach
Eligible patient tests positive for COVID-19 via a PCR test
National database records eligible patients and positive PCR test results
COVID Medicines Delivery Unit contacts eligible patient to organise a telephone appointment
Clinicians from COVID Medicines Delivery Unit assess patient by phone and organise any treatment
Patient is treated
Patient in-reach
Patient receives SMS/email notification alerting them to their potential eligibility for COVID-19 treatment
In hours
Patient is notified of eligibility by letter or specialist
If patient does is not contacted within 24-hours of a positive PCR test result they should call their GP or 111
GP Referral
NHS 111 Referral
Out of hours

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Patient cohorts considered at highest risk from COVID-19 and to be prioritised for treatment with nMABs

Eligibility criteria

Patients must meet all of the eligibility criteria and none of the exclusion criteria. Pre-hospitalised patients are eligible to be considered if:

- SARS-CoV-2 infection is confirmed by polymerase chain reaction (PCR) or lateral flow testing within the last 5[$] day AND
- Onset of symptoms of COVID-192 3 within the last 5[$] days AND
- A member of a 'highest' risk group (see appendix 1)

[$] patients may be considered for IV/PO therapy up to 7 days of symptoms / diagnosis if clinically appropriate

Patients who have received an nMAB within a post-exposure prophylaxis (PEP) or pre-exposure prophylaxis (PrEP) trial (such as the PROTECT-V trial) who meet the eligibility criteria of this policy can still receive treatment with an nMAB.

Exclusion criteria

- Require hospitalisation for COVID-19
- Require supplemental oxygen (above baseline requirements)
- Children aged under 18 years should be referred via paediatric pathway

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Patients with renal disease	• Renal transplant recipients (including those with failed transplants within the past 12 months), particularly those who:
	  ○ Received B cell depleting therapy within the past 12 months (including alemtuzumab, rituximab [anti-CD20], anti-thymocyte globulin)
	  ○ Have an additional substantial risk factor which would in isolation make them eligible for nMABs or oral antivirals
	  ○ Not been vaccinated prior to transplantation
	• Non-transplant patients who have received a comparable level of immunosuppression
	• Patients with chronic kidney stage (CKD) 4 or 5 (an eGFR less than 30 ml/min/1.73m2) without immunosuppression

HIV/AIDS	• Patients with high levels of immune suppression, have uncontrolled/untreated HIV (high viral load) or present acutely with an AIDS defining diagnosis • On treatment for HIV with CD4 <350 cells/mm3 and stable on HIV treatment or CD4>350 cells/mm3 and additional risk factors (e.g. age, diabetes, obesity, cardiovascular, liver or renal disease, homeless, those with alcohol-dependence)
Solid organ transplant recipients	All recipients of solid organ transplants not otherwise specified above
Rare neurological conditions	• Multiple sclerosis • Motor neurone disease • Myasthenia gravis • Huntington's disease

Patients with liver disease	• Patients with cirrhosis Child's-Pugh class B and C (decompensated liver disease). • Patients with a liver transplant • Liver patients on immune suppressive therapy (including patients with and without liver cirrhosis) • Patients with cirrhosis Child's-Pugh class A who are not on immune suppressive therapy (compensated liver disease)
Patients with immune-mediated inflammatory disorders (IMID)	• IMID treated with rituximab or other B cell depleting therapy in the last 12 months • IMID with active/unstable disease on corticosteroids, cyclophosphamide, tacrolimus, cyclosporin or mycophenolate. • IMID with stable disease on either corticosteroids*, cyclophosphamide, tacrolimus, cyclosporin or mycophenolate. • IMID patients with active/unstable disease including those on biological monotherapy and on combination biologicals with thiopurine or methotrexate
Immune deficiencies	• Common variable immunodeficiency (CVID) • Undefined primary antibody deficiency on immunoglobulin (or eligible for Ig) • Hyper-IgM syndromes • Good's syndrome (thymoma plus B-cell deficiency) • Severe Combined Immunodeficiency (SCID) • Autoimmune polyglandular syndromes/autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED syndrome) • Primary immunodeficiency associated with impaired type I interferon signalling • X-linked agammaglobulinaemia (and other primary agammaglobulinaemias) • Any patient with a secondary immunodeficiency receiving, or eligible for, immunoglobulin replacement therapy

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Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Alpha 1-adrenoreceptor antagonist	alfuzosin	↑ alfuzosin	Co-administration contraindicated due to potential hypotension *[see Contraindications (4)]*.
Analgesics	pethidine, propoxyphene	↑ pethidine ↑ propoxyphene	Co-administration contraindicated due to potential for serious respiratory depression or hematologic abnormalities *[see Contraindications (4)]*.
Antianginal	ranolazine	↑ ranolazine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions *[see Contraindications (4)]*.
Antiarrhythmics	amiodarone, dronedarone, flecainide, propafenone, quinidine	↑ antiarrhythmic	Co-administration contraindicated due to potential for cardiac arrhythmias *[see Contraindications (4)]*.
Antiarrhythmics	bepridil, lidocaine (systemic)	↑ antiarrhythmic	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics if available.
Anticancer drugs	apalutamide	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.
Anticancer drugs	abemaciclib, ceritinib, dasatinib, encorafenib, ibrutinib, ivosidenib, neratinib, nilotinib, venetoclax, vinblastine, vincristine	↑ anticancer drug	Avoid co-administration of encorafenib or ivosidenib due to potential risk of serious adverse events such as QT interval prolongation. Avoid use of neratinib, venetoclax or ibrutinib. Co-administration of vincristine and vinblastine may lead to significant hematologic or gastrointestinal side effects. For further information, refer to individual product label for anticancer drug.
Anticoagulants	warfarin rivaroxaban	↑↓ warfarin ↑ rivaroxaban	Closely monitor INR if co-administration with warfarin is necessary. Increased bleeding risk with rivaroxaban. Avoid concomitant use.
Anticonvulsants	carbamazepine[a], phenobarbital, phenytoin	↓ nirmatrelvir/ritonavir ↑ carbamazepine ↓ phenobarbital ↓ phenytoin	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Antidepressants	bupropion trazodone	↓ bupropion and active metabolite hydroxy-bupropion ↑ trazodone	Monitor for an adequate clinical response to bupropion. Adverse reactions of nausea, dizziness, hypotension, and syncope have been observed following co-administration of trazodone and ritonavir. A lower dose of trazodone should be considered. Refer to trazadone product label for further information.
Antifungals	voriconazole, ketoconazole, isavuconazonium sulfate itraconazole[a]	↓ voriconazole ↑ ketoconazole ↑ isavuconazonium sulfate ↑ itraconazole ↑ nirmatrelvir/ritonavir	Avoid concomitant use of voriconazole. Refer to ketoconazole, isavuconazonium sulfate, and itraconazole product labels for further information.
Anti-gout	colchicine	↑ colchicine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment *[see Contraindications (4)]*.
Anti-HIV protease inhibitors	amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, saquinavir, tipranavir	↑ protease Inhibitor	For further information, refer to the respective protease inhibitors' prescribing information. Patients on ritonavir- or cobicistat-containing HIV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or protease inhibitor adverse events with concomitant use of these protease inhibitors *[see Dosage and Administration (2.4)]*.
Anti-HIV	didanosine, delavirdine, efavirenz, maraviroc, nevirapine, raltegravir, zidovudine bictegravir/ emtricitabine/ tenofovir	↑ didanosine ↑ efavirenz ↑ maraviroc ↓ raltegravir ↓ zidovudine ↑ bictegravir ↔ emtricitabine ↑ tenofovir	For further information, refer to the respective anti-HIV drugs prescribing information.

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Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Anti-infective	clarithromycin, erythromycin	↑ clarithromycin ↑ erythromycin	Refer to the respective prescribing information for anti-infective dose adjustment.
Antimycobacterial	rifampin	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance. Alternate antimycobacterial drugs such as rifabutin should be considered *[see Contraindications (4)]*.
Antimycobacterial	bedaquiline rifabutin	↑ bedaquiline ↑ rifabutin	Refer to the bedaquiline product label for further information. Refer to rifabutin product label for further information on rifabutin dose reduction.
Antipsychotics	lurasidone, pimozide, clozapine	↑ lurasidone ↑ pimozide ↑ clozapine	Co-administration contraindicated due to serious and/or life-threatening reactions such as cardiac arrhythmias *[see Contraindications (4)]*.
Antipsychotics	quetiapine	↑ quetiapine	If co-administration is necessary, reduce quetiapine dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations.
Calcium channel blockers	amlodipine, diltiazem, felodipine, nicardipine, nifedipine	↑ calcium channel blocker	Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with PAXLOVID. If co-administered, refer to individual product label for calcium channel blocker for further information.
Cardiac glycosides	digoxin	↑ digoxin	Caution should be exercised when co-administering PAXLOVID with digoxin, with appropriate monitoring of serum digoxin levels. Refer to the digoxin product label for further information.
Endothelin receptor Antagonists	bosentan	↑ bosentan	Discontinue use of bosentan at least 36 hours prior to initiation of PAXLOVID. Refer to the bosentan product label for further information.

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Ergot derivatives	dihydroergotamine, ergotamine, methylergonovine	↑ dihydroergotamine ↑ ergotamine ↑ methylergonovine	Co-administration contraindicated due to potential for acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system *[see Contraindications (4)]*.
Hepatitis C direct acting antivirals	elbasvir/grazoprevir, glecaprevir/pibrentasvir ombitasvir/paritaprevir/ritonavir and dasabuvir sofosbuvir/velpatasvir/voxilaprevir	↑ antiviral	Increased grazoprevir concentrations can result in ALT elevations. It is not recommended to co-administer ritonavir with glecaprevir/pibrentasvir. Refer to the ombitasvir/paritaprevir/ritonavir and dasabuvir label for further information. Refer to the sofosbuvir/velpatasvir/voxilaprevir product label for further information. Patients on ritonavir-containing HCV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or HCV drug adverse events with concomitant use *[see Dosage and Administration (2.4)]*.
Herbal products	St. John's Wort (*hypericum perforatum*)	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance *[see Contraindications (4)]*.
HMG-CoA reductase inhibitors	lovastatin, simvastatin	↑ lovastatin ↑ simvastatin	Co-administration contraindicated due to potential for myopathy including rhabdomyolysis *[see Contraindications (4)]*. Discontinue use of lovastatin and simvastatin at least 12 hours prior to initiation of PAXLOVID.
HMG-CoA reductase inhibitors	atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Consider temporary discontinuation of atorvastatin and rosuvastatin during treatment with PAXLOVID.

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Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Hormonal contraceptive	ethinyl estradiol	↓ ethinyl estradiol	An additional, non-hormonal method of contraception should be considered.
Immunosuppressants	cyclosporine, tacrolimus, sirolimus	↑ cyclosporine ↑ tacrolimus ↑ sirolimus	Therapeutic concentration monitoring is recommended for immunosuppressants. Avoid use of PAXLOVID when close monitoring of immunosuppressant serum concentrations is not feasible. Avoid concomitant use of sirolimus and PAXLOVID. If co-administered, refer to individual product label for immunosuppressant for further information.
Long-acting beta-adrenoceptor agonist	salmeterol	↑ salmeterol	Co-administration is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Narcotic analgesics	fentanyl methadone	↑ fentanyl ↓ methadone	Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl is concomitantly administered with PAXLOVID. Monitor methadone-maintained patients closely for evidence of withdrawal effects and adjust the methadone dose accordingly.
PDE5 inhibitor	sildenafil (Revatio®) when used for pulmonary arterial hypertension	↑ sildenafil	Co-administration contraindicated due to the potential for sildenafil associated adverse events, including visual abnormalities hypotension, prolonged erection, and syncope *[see Contraindications (4)]*.
Sedative/hypnotics	triazolam, oral midazolam	↑ triazolam ↑ midazolam	Co-administration contraindicated due to potential for extreme sedation and respiratory depression *[see Contraindications (4)]*.

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Sedative/hypnotics	midazolam (administered parenterally)	↑ midazolam	Co-administration of midazolam (parenteral) should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered. Refer to the midazolam product label for further information.
Systemic corticosteroids	betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, methylprednisolone, mometasone, prednisone, triamcinolone	↑ corticosteroid	Increased risk for Cushing's syndrome and adrenal suppression. Alternative corticosteroids including beclomethasone and prednisolone should be considered.

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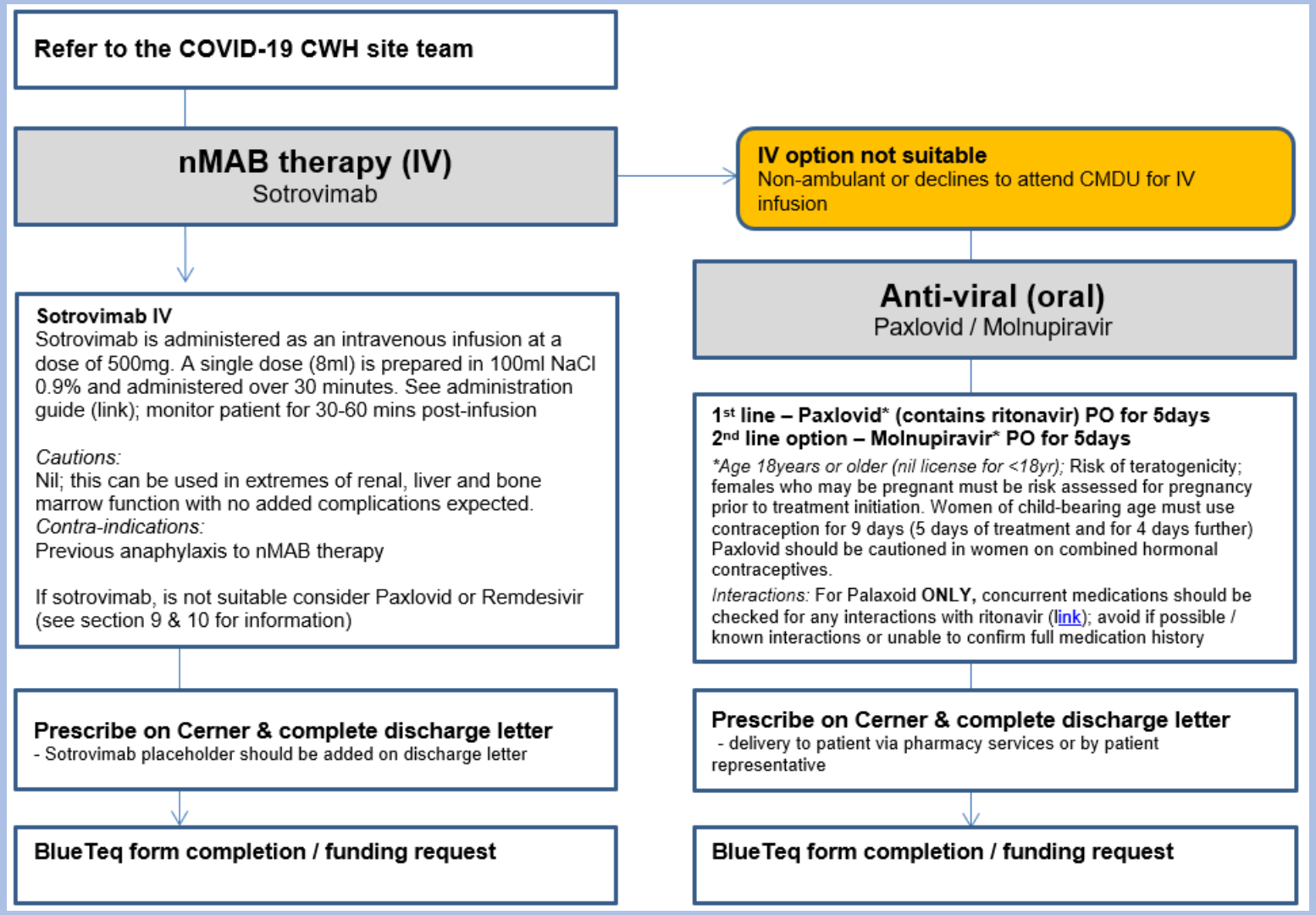

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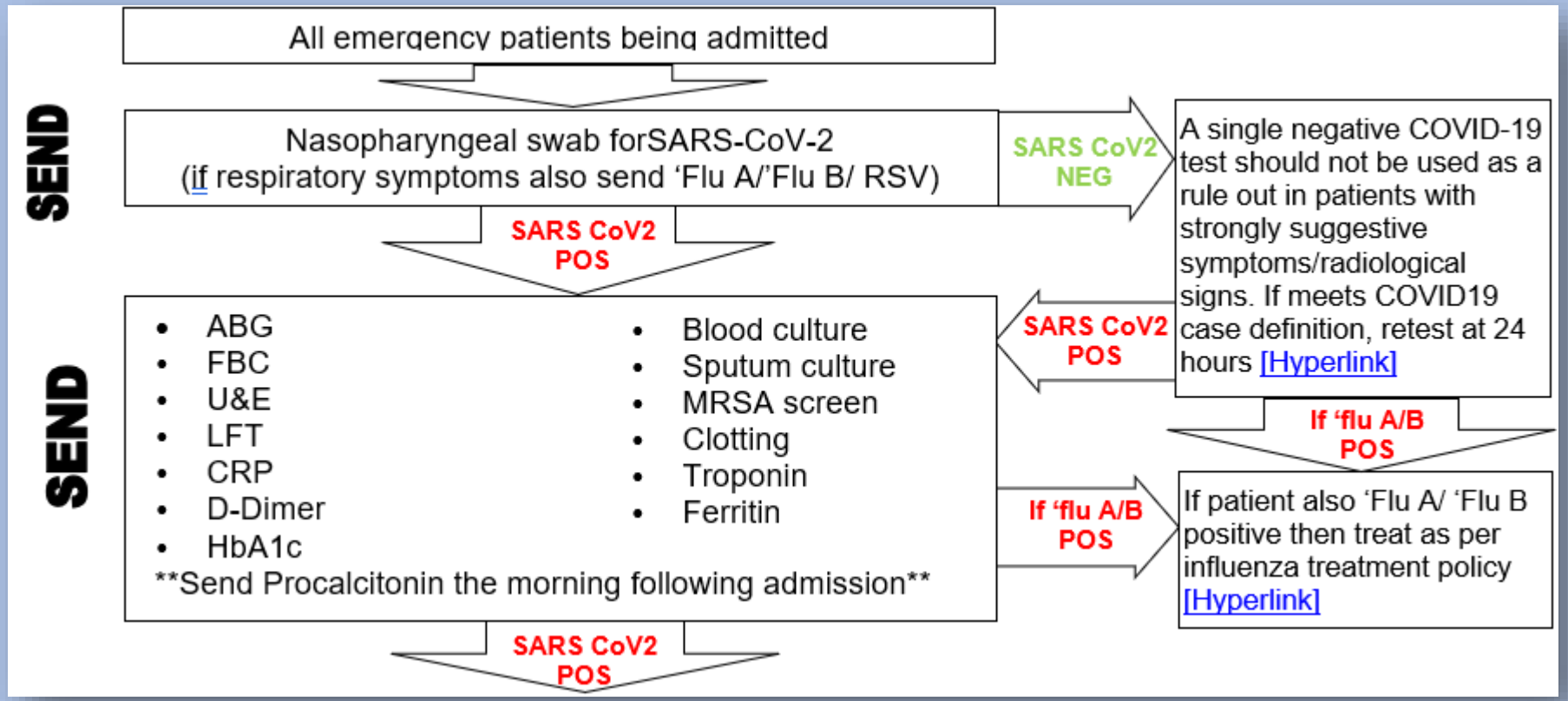
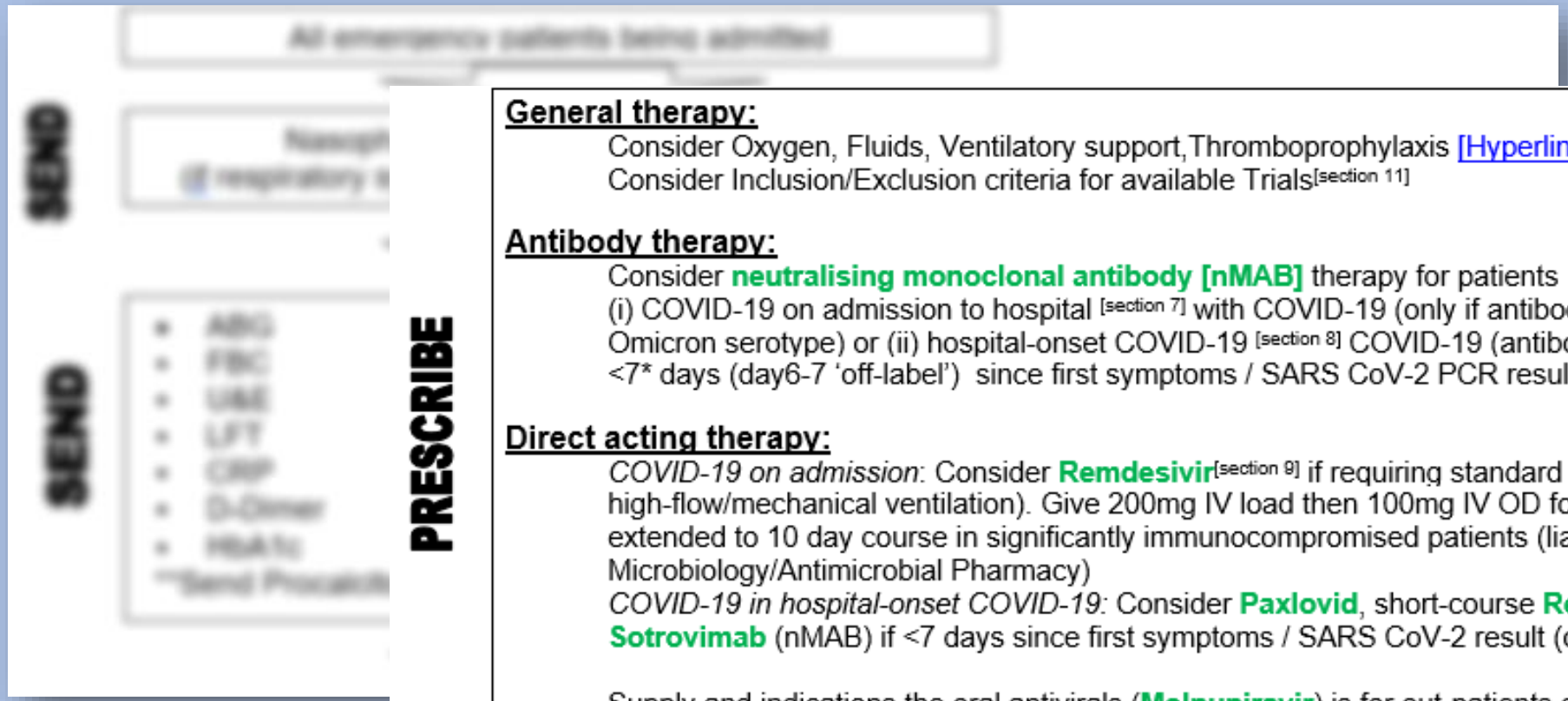
Inpatient Therapeutics



Inpatient Therapeutics



General therapy:

Consider Oxygen, Fluids, Ventilatory support,Thromboprophylaxis [Hyperlink].
Consider Inclusion/Exclusion criteria for available Trials[section 11]

Antibody therapy:

Consider **neutralising monoclonal antibody [nMAB]** therapy for patients
(i) COVID-19 on admission to hospital [section 7] with COVID-19 (only if antibody negative and non-Omicron serotype) or (ii) hospital-onset COVID-19 [section 8] COVID-19 (antibody status not relevant) if <7* days (day6-7 'off-label') since first symptoms / SARS CoV-2 PCR result for all **HIGH-risk** patients

Direct acting therapy:

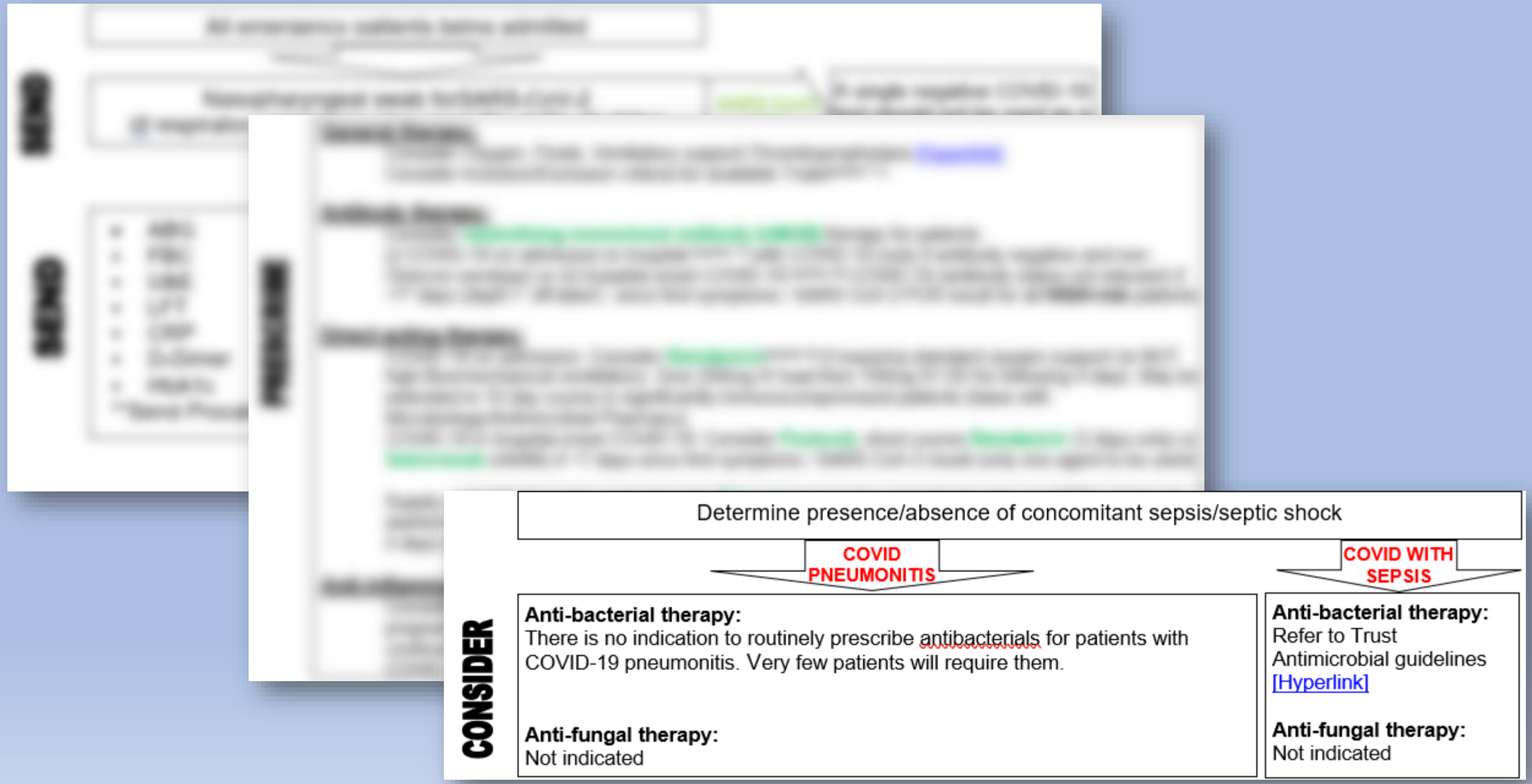
COVID-19 on admission: Consider **Remdesivir**[section 9] if requiring standard oxygen support (ie NOT high-flow/mechanical ventilation). Give 200mg IV load then 100mg IV OD for following 4 days. May be extended to 10 day course in significantly immunocompromised patients (liaise with Microbiology/Antimicrobial Pharmacy)
COVID-19 in hospital-onset COVID-19: Consider **Paxlovid**, short-course **Remdesivir** (3 days only) or **Sotrovimab** (nMAB) if <7 days since first symptoms / SARS CoV-2 result (only one agent to be used)

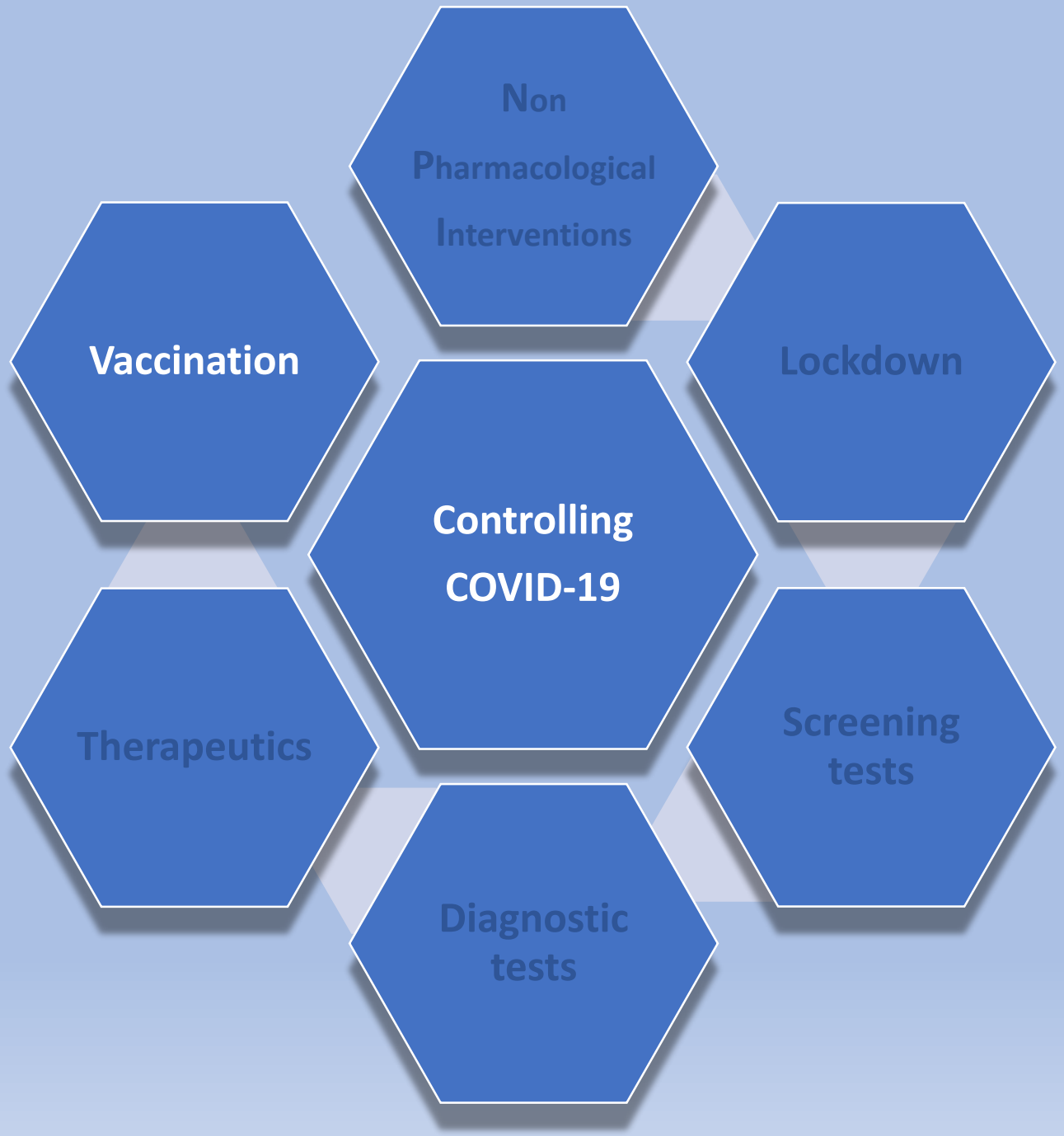
Supply and indications the oral antivirals (**Molnupiravir**) is for out-patients only via CMDU. Antivirals started in CMDU (e.g. Paxlovid, remdesivir or molnupiravir) can be continued if patient admitted within 5 days or switched to Remdesivir FIVE day course.

Anti-inflammatory therapy:

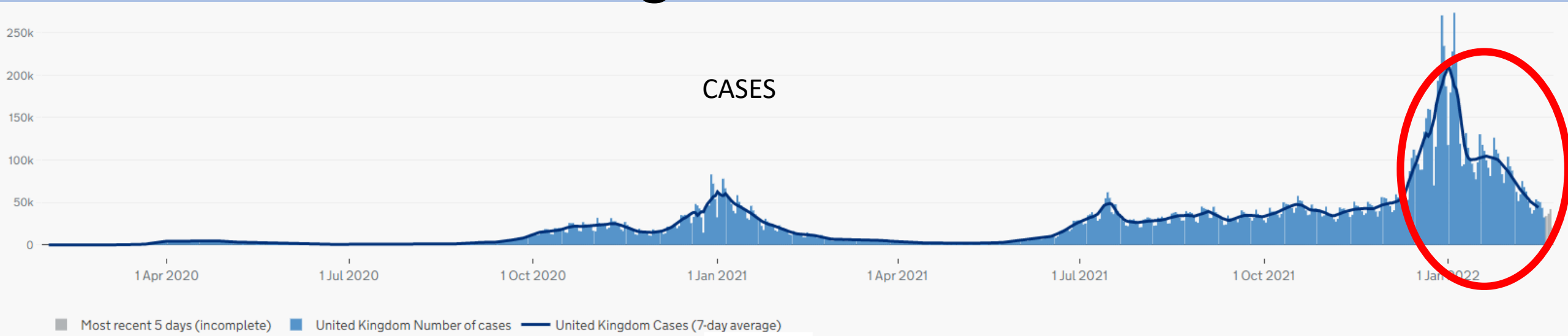
Consider **Dexamethasone** if requiring oxygen support (any). Give 6mg PO/IV OD for up to 10 days. If pregnant use **hydrocortisone** 80mg IV BD or **prednisolone** 40mg PO OD for up to 10 days. ONLY continue steroids on discharge if clinically indicated **and** under the care of a hospital-supervised virtual COVID ward. Monitor blood glucose [Hyperlink]. Refer to local dosing guidance for paediatrics.

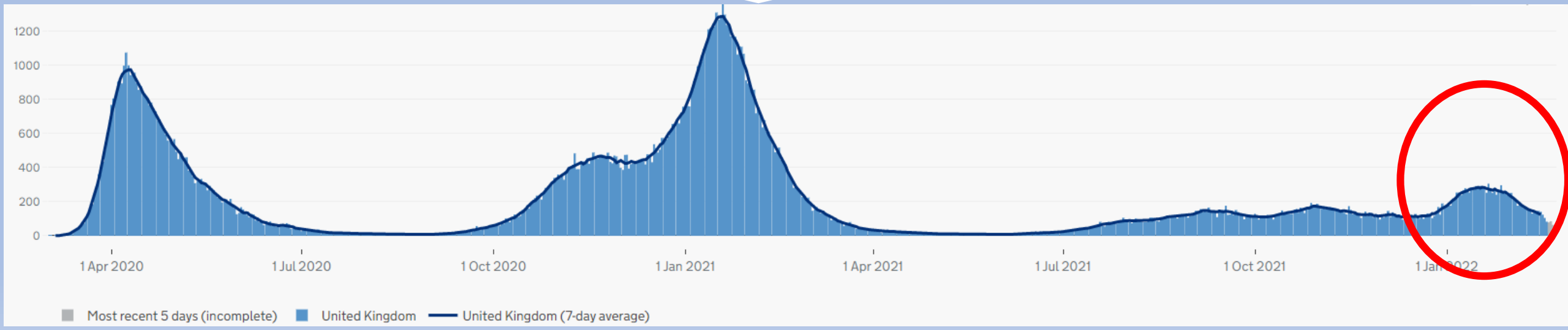
Inpatient Therapeutics




Non Pharmacological Interventions
Vaccination
Lockdown
Controlling COVID-19
Therapeutics
Screening tests
Diagnostic tests

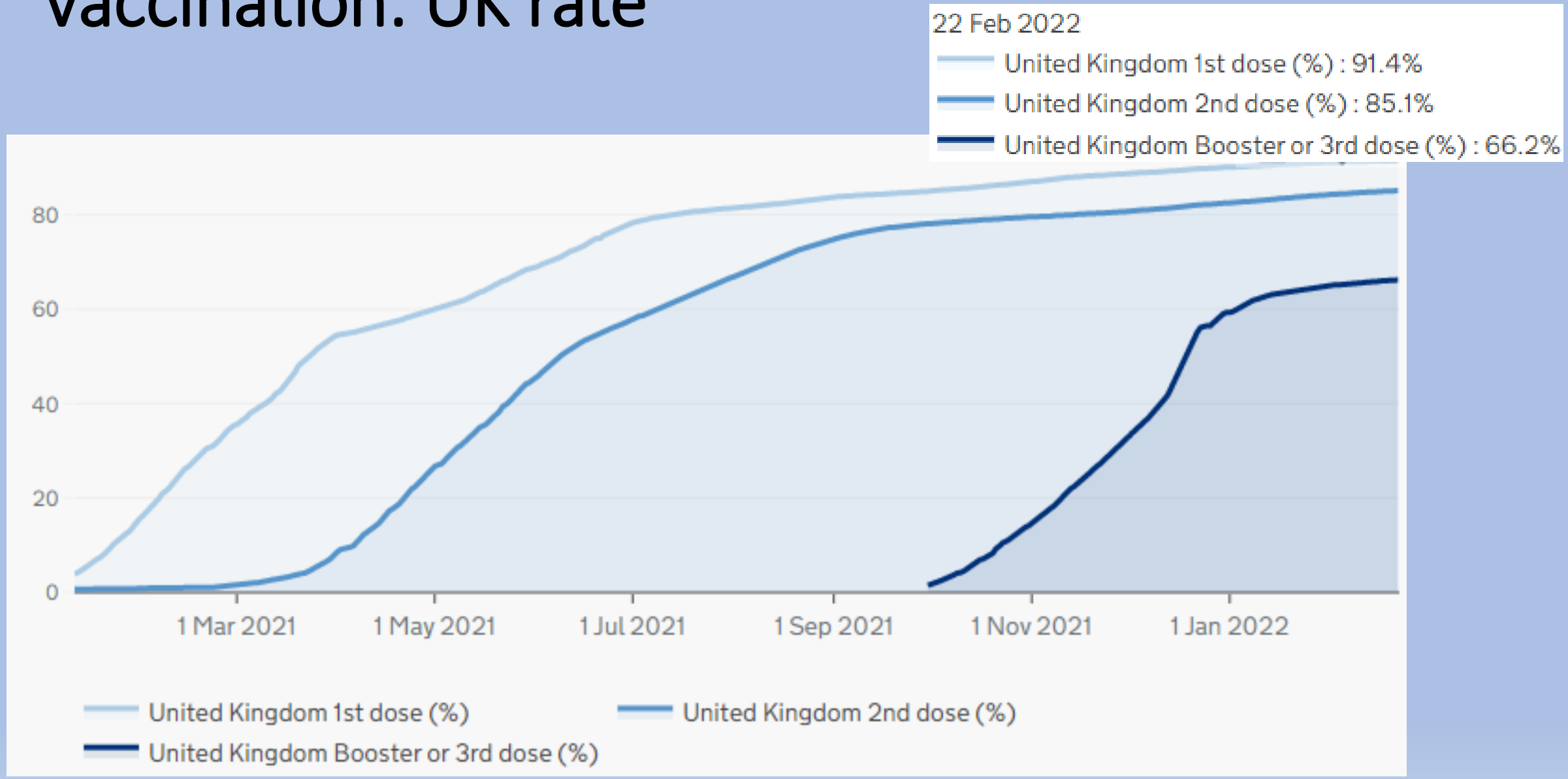
Vaccination: Breaking the link between cases and death





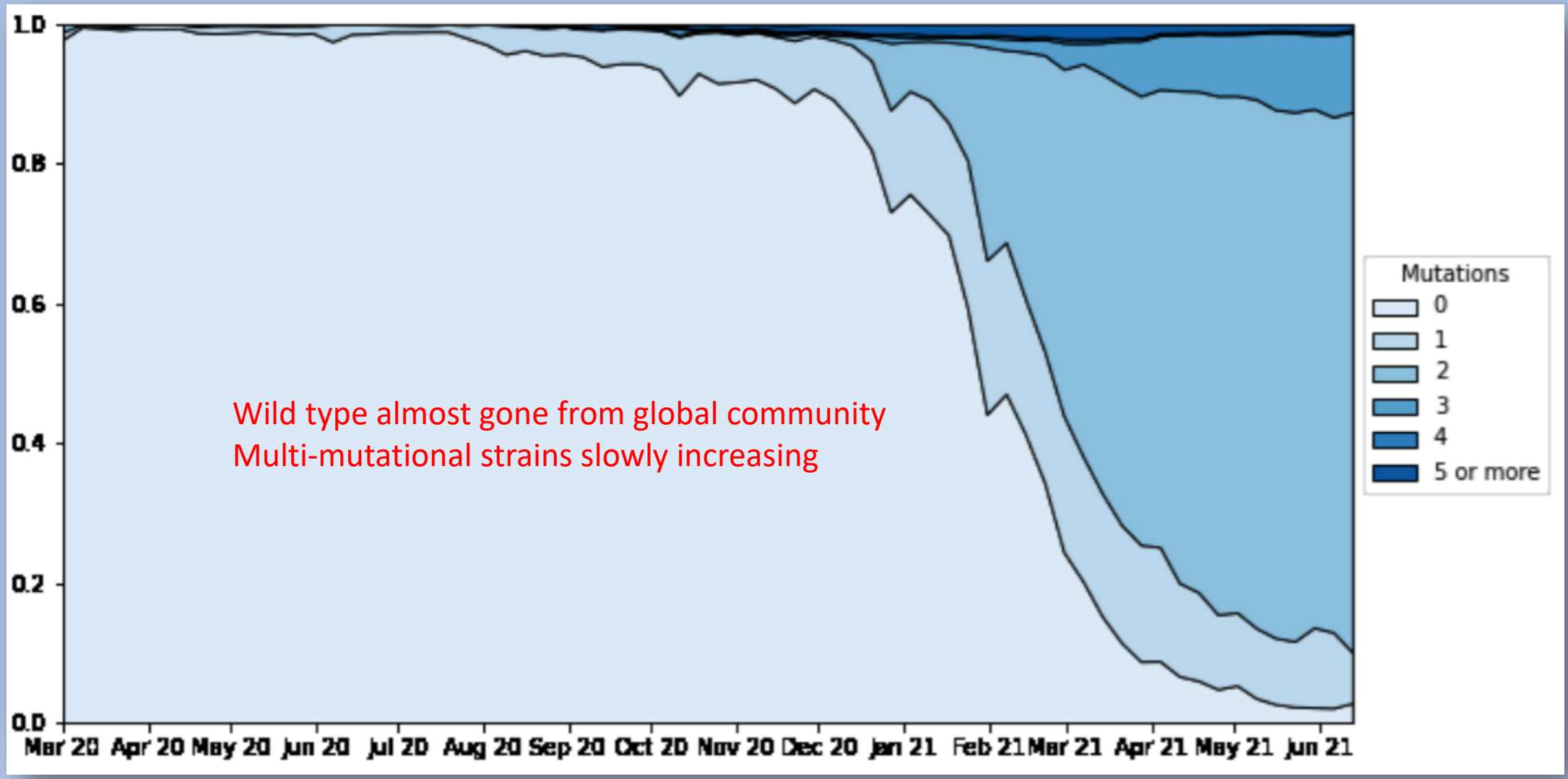
UK HSA
2022. UK Gov

Vaccination: UK rate



UK HSA
2022. UK Gov

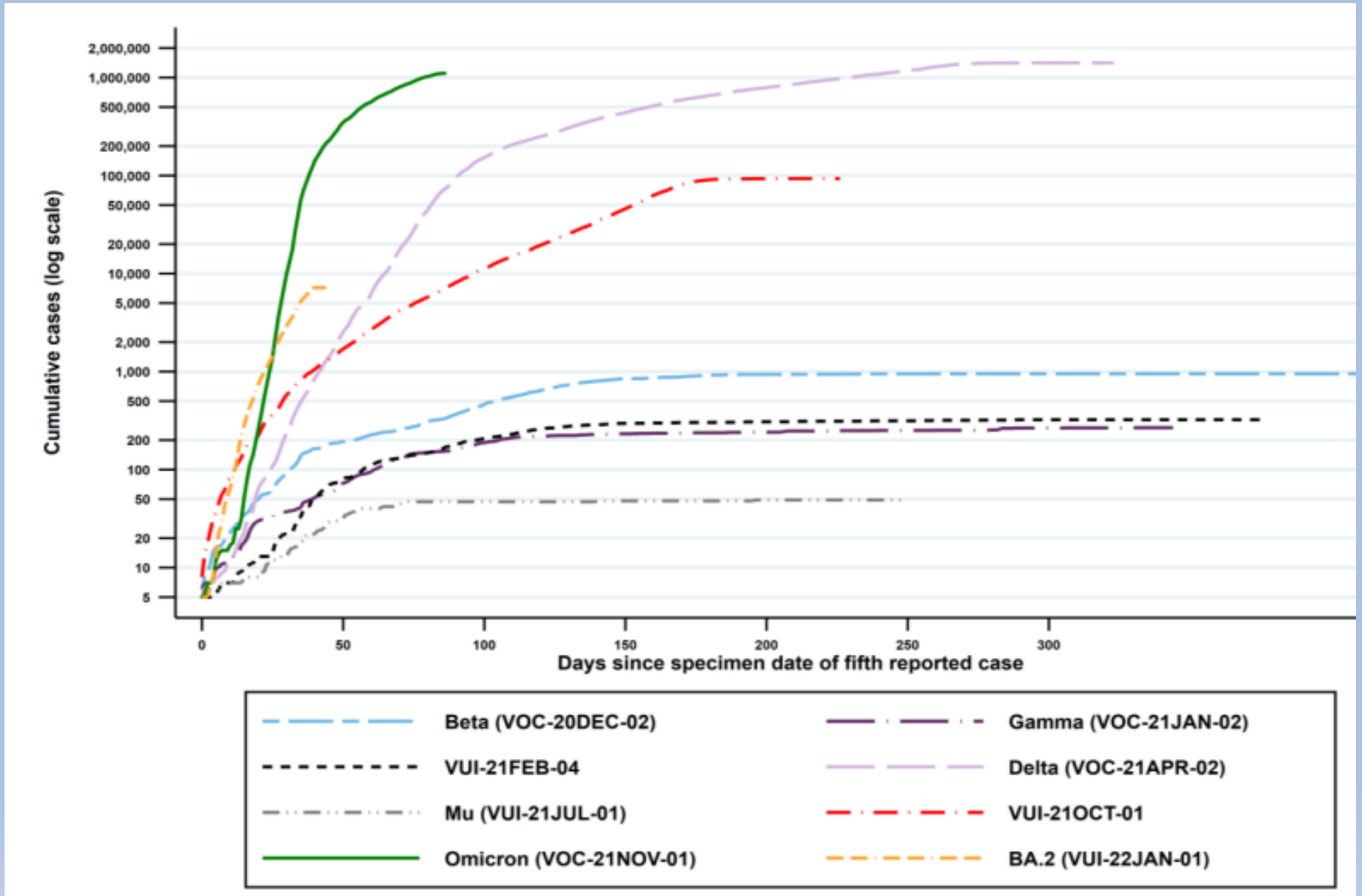
VOC: compound mutations



PHE

July 2021. UK GOV

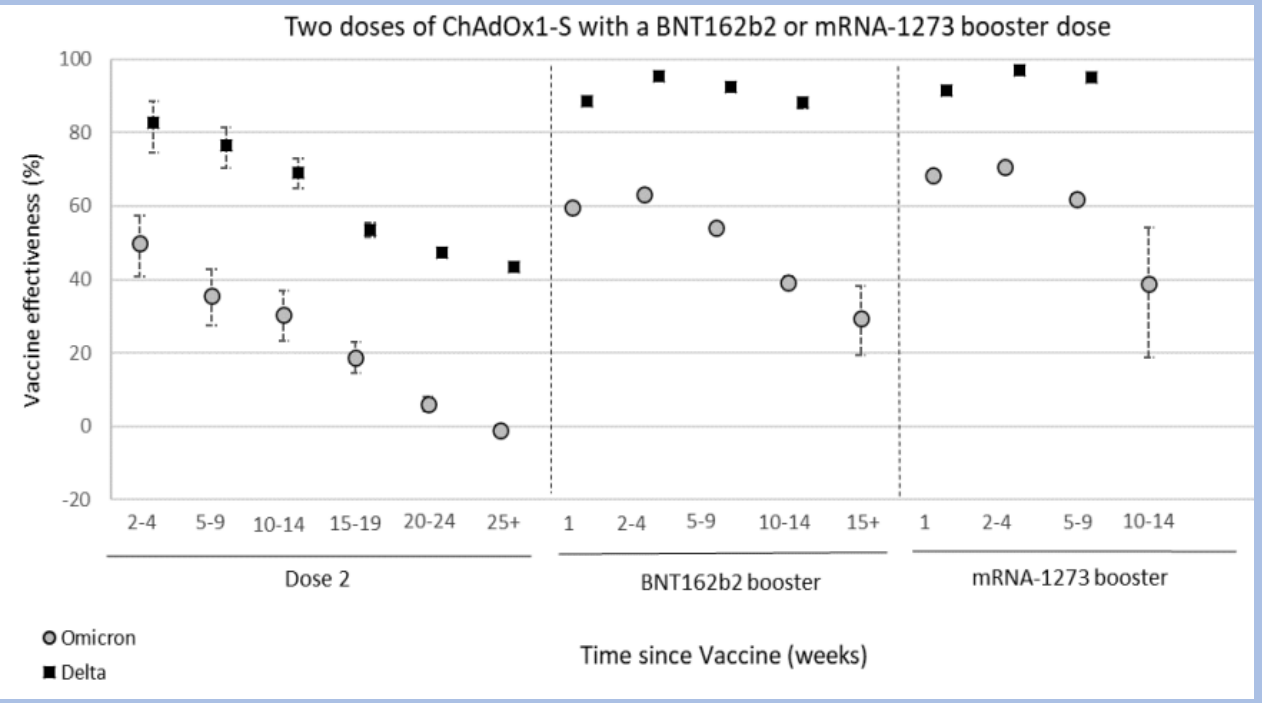
VOC: UK penetration

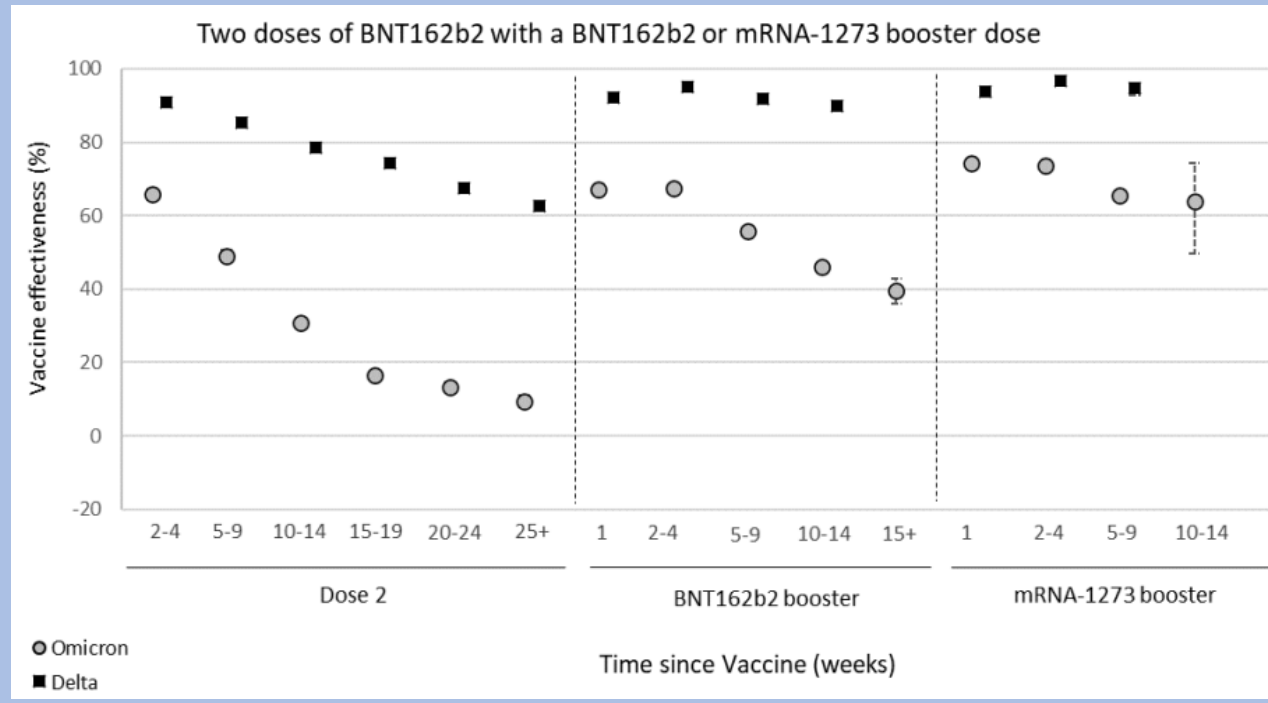


UK HSA

2022. UK GOV

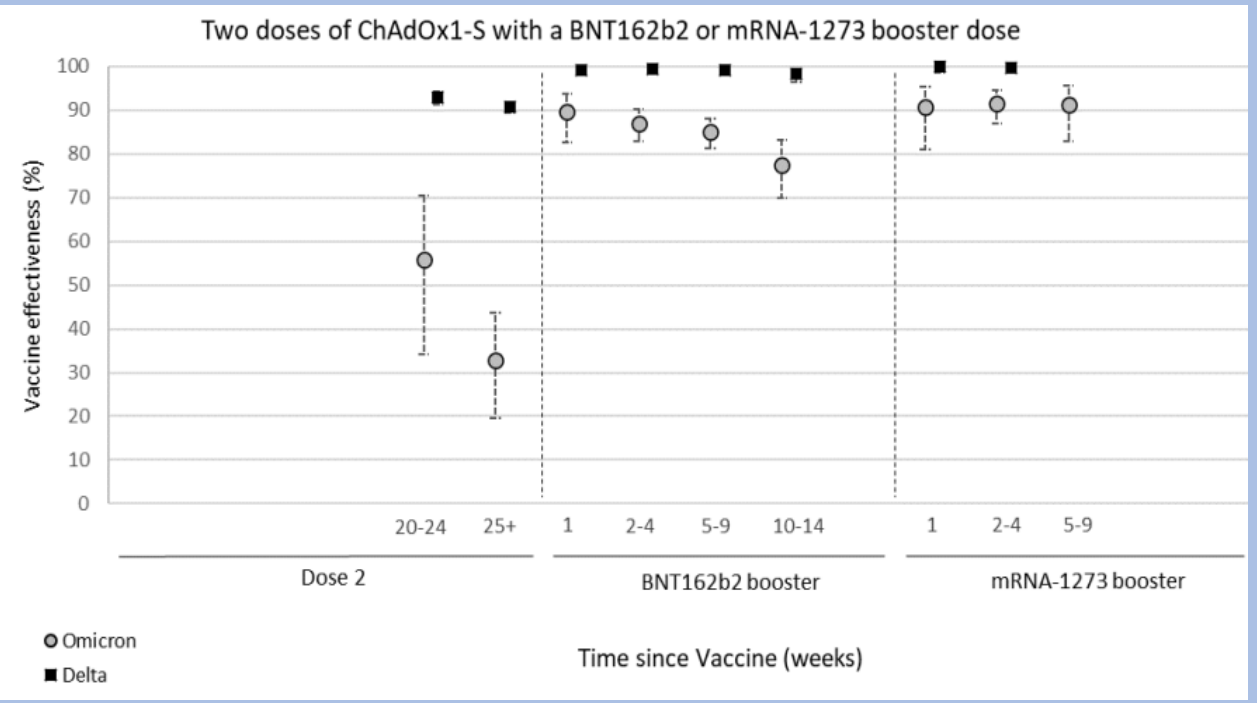
VOC: impact on vaccine effectiveness: symptomatic disease

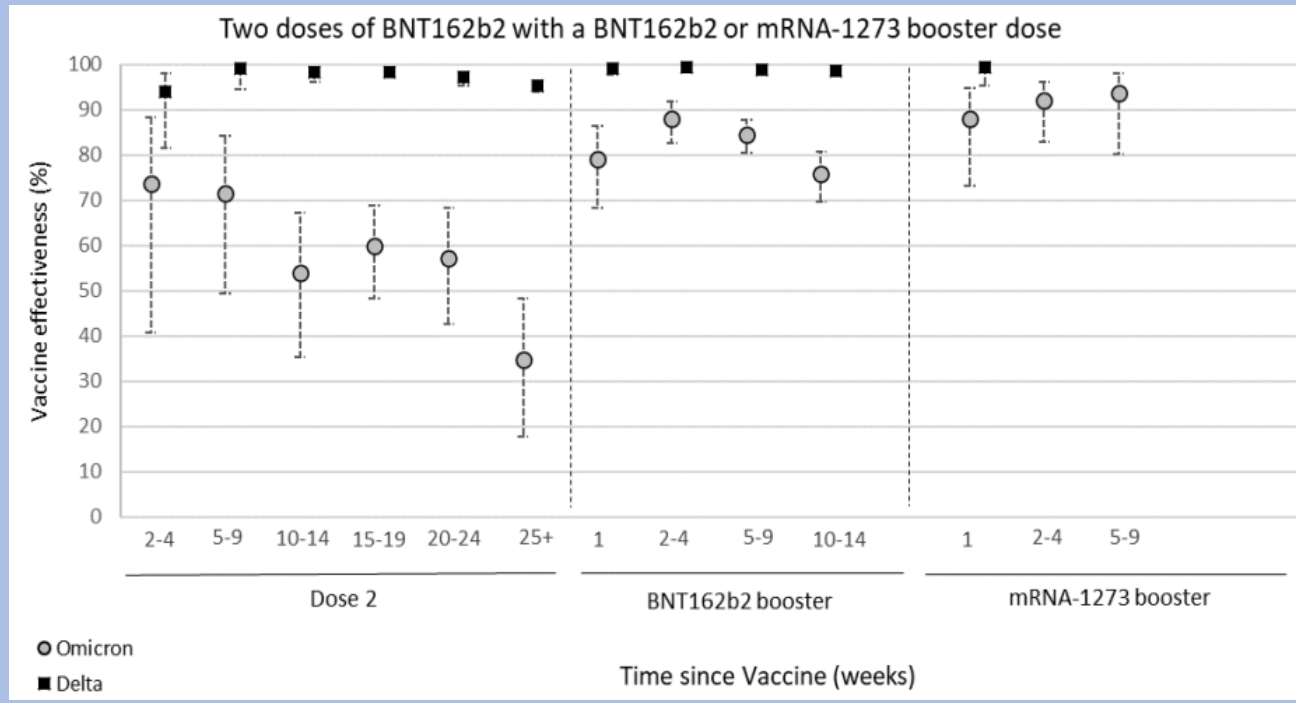




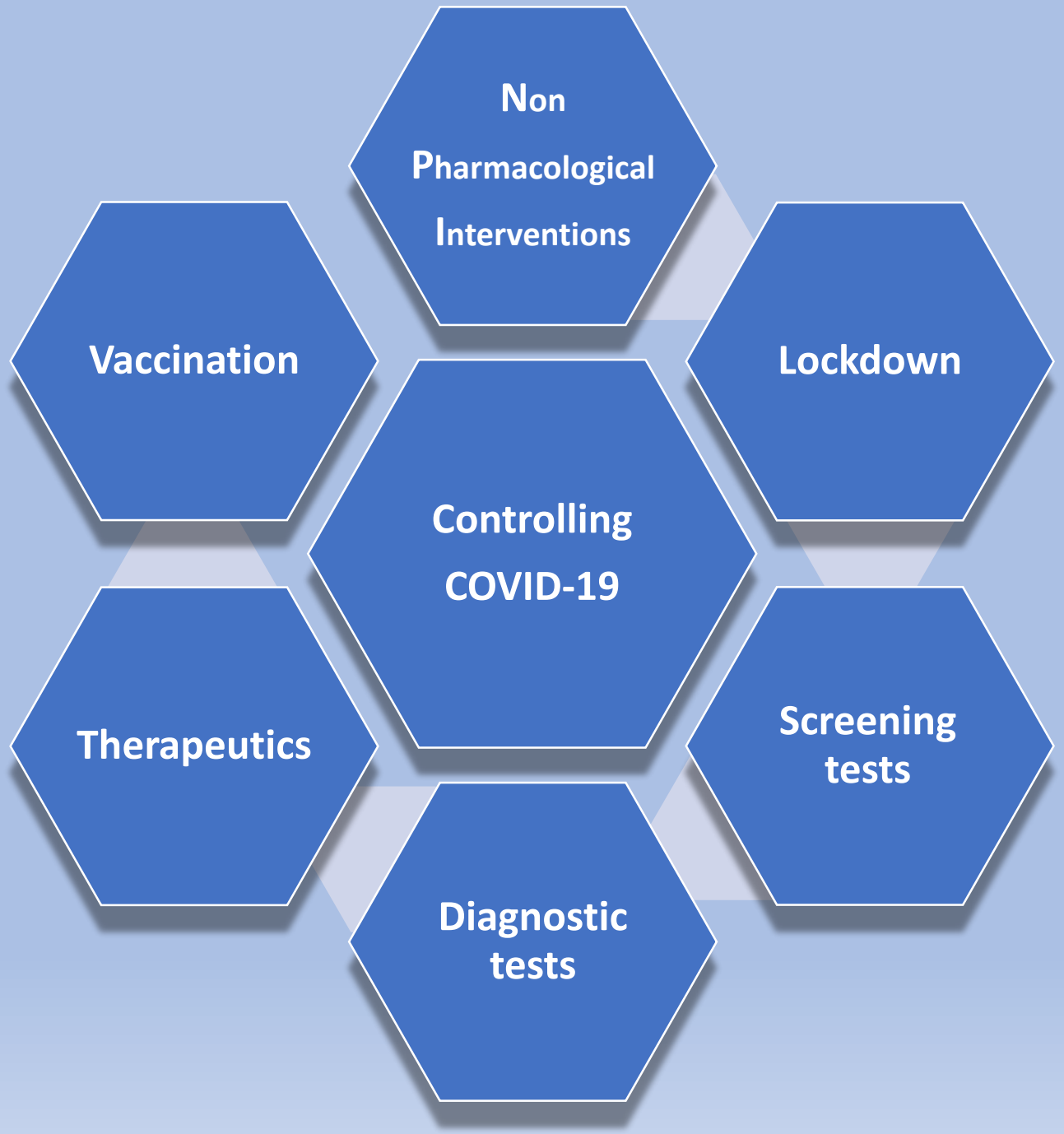
UK HSA.
2022. UK GOV

VOC: impact on vaccine effectiveness: hospitalisation





UK HSA.
2022. UK GOV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UK COVID-19 response: testing, surveillance, management and vaccines

- Review response to COVID-19
- Learning from international variations in public health interventions
- Review in- and out-patient COVID therapy and referral pathways
- Reflect on the post COVID-19 pandemic era