*Presidenza del Consiglio dei Ministri*

**COMITATO TECNICO-SCIENTIFICO**
**Ex O.C.D.P.C. 3 febbraio 2020, n. 630, come modificata dalla O.C.D.P.C. 17 marzo 2021, n. 751**

**Verbale n. 27** della riunione tenuta presso il Dipartimento della Protezione Civile il giorno 11 giugno 2021

| | Presente | Assente |
|---|---|---|
| Franco LOCATELLI (coordinatore) | X | |
| Silvio BRUSAFERRO (portavoce) | in videoconferenza | |
| Sergio FIORENTINO (segretario) | X | |
| Sergio ABRIGNANI | in videoconferenza | |
| Cinzia CAPORALE | in videoconferenza | |
| Fabio CICILIANO | X | |
| Donato GRECO | in videoconferenza | |
| Giuseppe IPPOLITO[1] | in videoconferenza | |
| Alessia MELEGARO | in videoconferenza | |
| Giorgio PALÙ | in videoconferenza | |
| Giovanni REZZA[2] | in videoconferenza | |

Ordine del giorno, di cui alla nota di convocazione del 10 giugno 2021:

**1**. Audizione del Sig. Ministro delle infrastrutture e della mobilità sostenibili, Prof. Enrico Giovannini;

**2.** Aggiornamento situazione epidemiologica nel Paese;

**3.** Varie ed eventuali.

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La seduta inizia alle ore 12,45.

[1] Collegato in videoconferenza dalle ore 12,55.
[2] Collegato in videoconferenza dalle ore 13,50.

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È collegato in videoconferenza il Sig. Ministro delle infrastrutture e della mobilità sostenibili, Prof. Enrico Giovannini

Il Coordinatore ringrazia della sua presenza il Sig. Ministro, cui cede la parola per illustrare le ragioni della richiesta di incontro del CTS.

Il Sig. Ministro ringrazia il Comitato, non solo per il lavoro che svolge e le responsabilità che assume nell'interesse del Paese, ma anche per avere prontamente calendarizzato questo incontro nel quale condividere le ipotesi di soluzione ad alcune problematiche del trasporto pubblico che è opportuno affrontare per tempo, in vista della "ripresa" di settembre. Tra queste, il Sig. Ministro ricorda che il CTS aveva suggerito separatori tra i sedili, cosa che alcuni esercenti hanno fatto, mentre altri stanno definendo con INAIL i materiali utilizzabili. Nel trasporto aereo e in quello ferroviario ad alta velocità, per quanto riguarda i treni di NTV, sono stati installati i filtri HEPA, mentre sui convogli di Trenitalia ciò non è ancora avvenuto. Più in generale, potrebbe rendersi opportuno valutare la sicurezza dei filtri al grafene, meno costosi dei filtri HEPA e, dunque, potenzialmente utilizzabili su più larga scala, anche nel trasporto locale. Nel settore marittimo, il CTS si è già espresso sui collegamenti con le isole minori, autorizzando l'elevazione del limite di affollamento dei mezzi all'80% della capienza, in presenza di rigorose condizioni supplementari. Sul trasporto pubblico locale, il Paese ha fatto un grosso investimento per consentire agli enti locali di dotarsi di mezzi supplementari. Ulteriori fondi sono stati messi a disposizione per preparare la ripresa di settembre, in vista della quale si è data attuazione anche alla norma che impone di nominare un *mobility manager* nelle realtà con più di cento addetti. Si prevede d'introdurre incentivi per spostare la domanda di trasporto verso orari lontani da quelli di punta. Accanto a tutte queste misure, volte a conseguire l'obiettivo prioritario della riduzione del tasso di affollamento dei mezzi di trasporto pubblico, è necessario conoscere, con un anticipo tale da consentire un'adeguata

programmazione del trasporto pubblico locale, se, per la ripresa di settembre, si possano autorizzare, e a quali condizioni, indici di affollamento superiori a quelli attualmente vigenti. Ciò, fermo restando che ogni eventuale decisione sarebbe prontamente rivista in caso di mutamento in peggio dello scenario epidemiologico.

Il Coordinatore ringrazia nuovamente il Sig. Ministro dell'attenzione rivolta al lavoro del CTS, confermando che lo scenario epidemiologico testimonia attualmente una condizione di bassa circolazione e incidenza, come confermano anche i dati più recenti, che oggi stesso il Comitato è chiamato ad analizzare. Le valutazioni sulle condizioni del trasporto saranno svolte, dal CTS, alla stregua della situazione attuale, ma occorrerà, comunque, tenere presente che non vi sono certezze assolute circa il fatto che, anche in ragione della diffusione di varianti, non vi possa essere una ripresa del contagio.

Si apre una discussione sui temi sollevati dal Sig. Ministro, nel corso della quale i componenti del CTS confermano che lo scenario epidemiologico in miglioramento rende potenzialmente attualizzabili le indicazioni relative al trasporto, senza tuttavia consentirsi cali di tensione, dovendosi in particolare prestare attenzione alla eventuale diffusione di varianti del ceppo virale (tra queste, una certa preoccupazione desta la variante c.d. Delta, che è in espansione nel Regno Unito, ma anche in Finlandia e in Belgio). In quest'ottica, essenziali saranno le attività di tracciamento e, a tal fine, sarà importante promuovere, in tutti i casi in cui ciò sia possibile, l'utilizzo della prenotazione. L'adeguamento delle condizioni igieniche dei mezzi di trasporto è obiettivo da perseguire indipendentemente dal fenomeno del Covid-19 e, d'altra parte, la ripresa del trasporto pubblico, a discapito di quello privato (verso il quale molti cittadini hanno preferito orientarsi in questa fase), contribuisce essa stessa ad obiettivi di salute pubblica, limitando gli effetti ambientali e gli eventi avversi dovuti a incidenti. Le più recenti linee guida prodotte in ambito internazionale sembrano

concentrarsi più sulle misure di protezione e di igienizzazione, che non sull'aspetto dell'affollamento dei mezzi di trasporto.

Rispondendo alle sollecitazioni di alcuni membri del Comitato, il Sig. Ministro rappresenta che lunedì si disporrà di una ricerca commissionata dal Ministero all'ISTAT sulle scelte dei cittadini in materia di trasporto per il periodo delle vacanze, rendendosi disponibile a condividere il testo. All'attenzione del Dicastero vi è già il lavoro fatto dalle reti delle Università per lo sviluppo sostenibile sulle scelte di trasporto degli studenti, dei docenti e del personale tecnico degli atenei. Il Ministero chiederà all'ISTAT un'ulteriore indagine sulle scelte di trasporto della cittadinanza per la ripresa di settembre. Quanto ai tempi del parere, sarebbe opportuno poterne disporre per la fine di giugno o per i primi mesi di luglio.

Il Coordinatore, nel salutare il Sig. Ministro, assume a nome e con il consenso dei componenti del Comitato, l'impegno di rendere il parere nei tempi richiesti.

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A questo punto il Sig. Ministro, con i suoi collaboratori, interrompe il collegamento in videoconferenza.

Il CTS condivide che, sui temi sollevati, sarà opportuno richiedere il coinvolgimento del Dott. Sergio Iavicoli e, per suo tramite, dell'INAIL. Tutti i componenti approvano la proposta. Il Dott. Iavicoli verrà contattato nei prossimi giorni per esplorarne la disponibilità a fornire la sua preziosa e qualificata competenza nell'ambito specifico. FL

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Si passa, quindi, all'esame dl **punto n. 2** dell'ordine del giorno.

TRASMISSIONE DATI EPIDEMIOLOGICI EX ART. 19-*BIS* DEL DECRETO-LEGGE 28/10/2010, N. 137, CONVERTITO, CON MODIFICAZIONI, DALLA LEGGE 18/12/2020, N. 176

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Il Coordinatore da atto che il CTS ha acquisito i dati epidemiologici relativi al periodo 31/05/2021–06/06/2021, trasmessi dall'Istituto Superiore di Sanità (ISS) inerenti al sistema di monitoraggio del rischio e della resilienza dei servizi sanitari istituito dal Ministero della Salute ed elaborati dalla cabina di regia di cui al DM Salute 30/04/2020.

Il CTS prende atto che, dagli aggiornamenti dei dati epidemiologici di ISS e dal monitoraggio del rischio della cabina di regia di cui al DM Salute 30/04/2020, viene rilevata un'ulteriore riduzione dell'incidenza cumulativa a 7 giorni a livello nazionale, che ha raggiunto, sulla scorta di dati elaborati dal Ministero della Salute riferiti al periodo di 04/06/21-10/06/2021, il valore di **25 casi/100.000 abitanti** rispetto ai 32 casi/100.000 abitanti nella settimana precedente. In particolare, altre 5 Regioni (Emilia Romagna, Lazio, Lombardia, Piemonte e Puglia) e 1 PA (Trento), oltre alle 7 Regioni della scorsa settimana, per la terza settimana consecutiva hanno un valore inferiore a 50 casi/100.000 abitanti e mostrano una percentuale di occupazione di posti letto in area medica e nelle terapie intensive inferiore ai valori soglia. Nessuna Regione o PA mostra un valore superiore a 50 casi/100.000 abitanti.

**Nel periodo 19 maggio – 1 giugno 2021, l'Rt medio calcolato sui casi sintomatici è stato pari a 0,68 (range 0,67– 0,69), identico a quello della settimana precedente, e sotto l'uno anche nel limite superiore**. Tutte le Regioni/PPAA sono classificate a rischio basso secondo il DM del 30 Aprile 2020 tranne una, Sardegna, a rischio moderato. Tutte le Regioni/PPAA hanno un Rt medio inferiore a 1 nel limite inferiore del range e, quindi, una trasmissibilità compatibile con uno scenario di tipo uno.

Si osserva una ulteriore diminuzione nel numero di nuovi casi non associati a catene di trasmissione (4.992 vs 7.424 la settimana precedente). La percentuale dei casi rilevati attraverso l'attività di tracciamento dei contatti è stabile (40,3% vs 40,1% la

scorsa settimana). Stabile anche la percentuale dei casi rilevati attraverso la comparsa dei sintomi (38,6 vs 38,6%).

Infine, il 21,0% è stato diagnosticato attraverso attività di screening.

**Nessuna Regione/PPAA supera la soglia critica di occupazione dei posti letto in terapia intensiva o area medica**. Il tasso di occupazione in terapia intensiva è 8%, sotto la soglia critica, con una diminuzione nel numero di persone ricoverate che passa da 1.033 (31/05/2021) a 688 (08/06/2021). Il tasso di occupazione in aree mediche a livello nazionale scende ulteriormente (8%). Il numero di persone ricoverate in queste aree passa da 6.482 (31/05/2021) a 4.685 (08/06/2021). Due Regioni (Puglia e Sardegna) riportano allerte di resilienza, nessuna riporta molteplici allerte.

Complessivamente, l'incidenza sull'intero territorio nazionale è in ulteriore diminuzione, e nella totalità dei territori regionali ha raggiunto livelli tali da consentire una gestione basata sul contenimento, ovvero sull'identificazione dei casi e sul tracciamento dei loro contatti. La stima dell'indice di trasmissibilità Rt medio calcolato sui casi sintomatici è stabilmente al di sotto della soglia epidemica e la pressione sui servizi ospedalieri è in ulteriore diminuzione e largamente al di sotto della soglia critica in tutte le Regioni/PA.

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È fondamentale che la popolazione continui a rispettare tutte le misure raccomandate di protezione individuale e distanziamento in tutte le occasioni di contatto con persone al di fuori del proprio nucleo abitativo per ridurre il rischio di contagio. Si ricorda che è obbligatorio adottare comportamenti individuali rigorosi e rispettare le misure igienico-sanitarie predisposte relative a distanziamento e uso corretto delle mascherine. Si ribadisce la necessità di rispettare le misure raccomandate dalle autorità sanitarie compresi i provvedimenti quarantenari dei contatti stretti dei casi accertati e di isolamento dei casi stessi.

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**Il CTS sottolinea ancora una volta l'importanza di progredire rapidamente con la campagna vaccinale, rispettando le priorità identificate in funzione del criterio di fragilità per fascia anagrafica o per patologia concomitante.**

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A questo punto il Coordinatore, rilevato come il Comitato disponga di tutti gli elementi di informazione e di giudizio necessari, propone di completare l'analisi delle questioni esaminate nella scorsa seduta del CTS e di assumere le conseguenti determinazioni.

Prima che sia avviata la discussione, la Componente Cinzia Caporale desidera richiamare l'attenzione del Comitato sulla situazione che si è determinata a seguito del suo abbandono, per scadenza del mandato, della carica di Presidente del Comitato etico dell'Istituto nazionale per le malattie infettive «*Lazzaro Spallanzani*» di Roma. Sebbene l'O.C.D.P.C. n. 751 del 2021 la individui nominativamente tra i Componenti del CTS, la circostanza che, nell'art. 1 di tale ordinanza (che ha sostituito l'art. 2 dell'O.C.D.P.C. n. 630 del 3 febbraio 2020), sia indicato che la scelta è operata anche «*in considerazione del ruolo istituzionale ricoperto*», potrebbe far ritenere – secondo una possibile, benché controvertibile, interpretazione – che sia venuto meno il titolo di partecipazione al CTS. La Dott.ssa Caporale rappresenta di avere tempestivamente informato il segretario del CTS il quale, per parte sua, conferma di avere immediatamente comunicato la circostanza al Capo del Dipartimento della protezione civile e al Segretario Generale della Presidenza del Consiglio dei ministri, per ottenerne un definitivo chiarimento sull'interpretazione della questione e, ove necessario, la formalizzazione dei conseguenti provvedimenti. Il CTS, esaminata la questione, considerata anche la necessità di non deprivare il Comitato dell'essenziale apporto dell'esperto nelle materia bioetiche, ciò che finirebbe anche per alterare l'equilibrio che si era opportunamente perseguito all'atto della composizione del CTS,

non ravvisa ragioni affinché la Componente Cinzia Caporale debba oggi astenersi e – pur condividendo l'esigenza che tale stato di cose trovi conferma in atti formali degli organi competenti – chiede, pertanto, alla Componente medesima di continuare a partecipare alla discussione e alle votazioni.

Il CTS riprende l'analisi delle questioni già preliminarmente esaminate nella seduta del 9 giugno 2021, nella quale sono interventi il Sig. Ministro della salute, On.le Roberto Speranza, il Commissario straordinario per l'emergenza COVID-19, Gen.le Francesco Paolo Figliuolo, il Capo del Dipartimento della protezione civile della Presidenza del Consiglio dei ministri, Ing. Fabrizio Curcio e il Direttore Generale dell'Agenzia Italiana del Farmaco, Dott. Nicola Magrini.

La prima questione concerne la possibilità di aggiornare, in senso più stringente, l'attuale raccomandazione relativa all'utilizzo del vaccino Vaxzevria (Vaccino a vettore adenovirale di scimpanzé prodotto da AstraZeneca), **approvato sia dall'EMA sia dall'AIFA per i soggetti al di sopra dei 18 anni e già oggi preferenzialmente raccomandato per soggetti di età uguale o superiore a 60 anni**. Questa riflessione trova il suo razionale alla luce del mutato scenario epidemiologico in senso favorevole e di alcuni recenti eventi avversi cronologicamente e, verosimilmente, anche eziologicamente, collegati alla somministrazione di questo tipo di vaccino. La mutata situazione epidemiologica ha determinato una rivalutazione del rapporto benefici-rischi per le fasce di età meno a rischio di forme gravi di COVID-19.

Il CTS è stato anche chiamato a esprimersi in merito alla possibilità di completare il processo di vaccinazione, per i soggetti che hanno ricevuto la prima dose del Vaccino Vaxzevria, attraverso la somministrazione di vaccino a mRNA, se del caso anche fornendo una indicazione in tal senso.

Già nella seduta del 7 giugno u.s. il CTS aveva condiviso alcune conclusioni preliminari.

Quanto alla prima questione, occorre preliminarmente considerare e valorizzare l'evoluzione in senso favorevole dello scenario epidemiologico. Le valutazioni formulate dal CTS nella seduta dello scorso 12 maggio si fondavano su un'analisi pubblicata in data 23 aprile 2021 da EMA, relativa al rapporto benefici/potenziali rischi di trombosi in sedi inusuali associati a trombocitopenia (VITT – *vaccine-induced thrombotic thrombocytopenia*) nel contesto di diversi scenari di circolazione virale. All'epoca, la circolazione virale nel Paese era inquadrabile in uno scenario intermedio, mentre al momento lo stesso è riferibile a uno scenario di circolazione limitata.

Relativamente alla seconda questione – benché i) tutti gli studi registrativi per i vari vaccini siano stati condotti utilizzando due dosi dello stesso vaccino; ii) non siano stati pubblicati, allo stato, studi che includono un elevato numero di soggetti; iii) e non siano disponibili studi randomizzati in cui il braccio di controllo è rappresentato da due somministrazioni del vaccino Vaxzevria – si può affermare, sulla base delle evidenze di cui si dispone, che la descritta vaccinazione "eterologa" trova un suo solido razionale immunologico e biologico e non appare essere sconsigliabile né sul fronte della sicurezza (reattogenicità), né su quello della immunogenicità. Infatti, i dati attualmente disponibili derivanti da studi condotti in diversi Paesi Europei (vedi allegato[3]) indicano la capacità di questo approccio di indurre buona risposta

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[3] V. Robert H Shaw RH et al, Heterologous prime-boost COVID-19 vaccination: initial reactogenicity data. www.thelancet.com Vol 397 May 29, 2021: 2043-6 (Published Online May 18, 2021 https://doi.org/10.1016/ S0140-6736(21)01158-2, corrected version first appeared at thelancet.com on May 21, 2021 https://doi.org/10.1016/ S0140-6736(21)01115-6.

Borobia MA et al. Reactogenicity and immunogenicity of BNT162b2 in subjects having received 1 a first dose of ChAdOx1S: initial results of a randomised, adaptive, phase 2 trial (CombiVacS). https://ssrn.com/abstract=3854768. Presentato anche come

ISCIII. A Phase 2, Randomised, Multicenter, Adaptive Trial to Evaluate the safety and immunogenicity of one dose of COMIRNATY® in subjects that had received one dose of VAXZEVRIA® EudraCT 2021-001978-37

Groß R et al.Heterologous ChAdOx1 nCoV-19 and BNT162b2 prime-boost vaccination 2 elicits potent neutralizing antibody responses and T cell reactivity

medRxiv preprint doi: https://doi.org/10.1101/2021.05.30.21257971;

anticorpale e un profilo di reattogenicità nel complesso accettabile e non dissimile da quello osservato somministrando due dosi dello stesso tipo di vaccino.

Il CTS, preso atto delle informazioni e valutazioni riferite dal Sig. Ministro della Salute, dal Commissario straordinario e dal Direttore generale di AIFA nella seduta del 9 giugno 2021, dopo approfondita discussione, condivide le seguenti conclusioni:

- il rapporto rischi/benefici connesso all'utilizzo del vaccino Vaxzevria è influenzato, in maniera determinate, dallo scenario epidemiologico in atto, come è stato messo in evidenza dal documento dell'EMA del 23 aprile 2021, già valorizzato dal CTS nella seduta dello scorso 12 maggio;

- lo scenario epidemiologico del Paese ha, fortunatamente, avuto un'evoluzione in senso positivo, da un livello di incidenza intermedio a basso, in misura anche maggiore di quella prevedibile poche settimane fa. Viene precisato che il documento di Risk Assessment dell'ECDC (revisione 15 del 10 giugno 2021) colloca l'Italia al terzo posto tra i Paesi europei nell'ambito di quelli a più basso rischio (dopo 2 paesi insulari quali Islanda e Malta, e primo tra i Paesi non insulari sotto osservazione (totale 30 paesi in Europa). Nel merito, si veda al proposito il documento disponibile all'indirizzo: https://www.ecdc.europa.eu/sites/default/files/documents/RRA-15th-update-June%202021.pdf);

- i fenomeni tromboembolici sono meno frequentemente osservati dopo somministrazione della seconda dose (secondo stime provenienti dal Regno Unito sono pari a 1,3 casi per milione, valore che corrisponde a meno di 1/10 dei già rari fenomeni osservati dopo la prima dose). Secondo quanto riferito dal Direttore

Behrens G et al. Humoral and cellular immune response against SARS-CoV-2 variants following heterologous and homologous ChAdOx1 nCoV-19/BNT162b2 vaccination. Research Square DOI: https://doi.org/10.21203/rs.3.rs-580444/v1

Generale di AIFA, a oggi, in Italia, non sono stati registrati casi di VITT dopo la seconda somministrazione di Vaxzevria. Queste evidenze suggeriscono come il tasso d'incidenza riportato dopo la seconda dose sia inferiore a quello osservato dopo la prima dose;

- il cambiamento di scenario epidemiologico in considerazione del basso livello di circolazione virale e della prevalente disponibilità di vaccini a mRNA, tenuto conto del principio di massima cautela e del principio di equità che richiede di assicurare a tutti i soggetti pari condizioni nel bilanciamento benefici/rischi, consente di attualizzare le indicazioni vigenti, e, pur rimandando alla competenza e responsabilità delle Autorità amministrative a ciò preposte, **di rafforzare la raccomandazione per l'uso della prima dose del vaccino Vaxzevria nei soggetti di età superiore a sessanta anni**, nei quali il beneficio derivante dalla vaccinazione supera i potenziali rischi collegati allo sviluppo di fenomeni VITT associati alla vaccinazione (si vedano al proposito i due seguenti documenti:

https://www.ema.europa.eu/en/documents/chmp-annex/annex-vaxzevria-art53-visual-risk-contextualisation_en.pdf

https://wintoncentre.maths.cam.ac.uk/coronavirus/using-italian-data-illustrate-potential-harms-and-benefits-astrazeneca-vaccine/?s=09

il secondo dei quali facente riferimento a stime effettuate in funzione di dati ottenuti in Italia). **La strategia vaccinale raccomandata per la somministrazione della prima dose nei soggetti di età inferiore ai 60 anni è rappresentata dai vaccini a mRNA** per i quali, a oggi, non sono stati riportati fenomeni VITT correlabili alla loro somministrazione;

- per quel che riguarda la seconda dose, è raccomandato continuare la somministrazione con il vaccino Vaxzevria per i soggetti di età superiore a sessanta

anni. Sotto i sessant'anni di età, pur essendo, come sopra ricordato, i fenomeni trombotici assai meno frequentemente associabili alla somministrazione della seconda dose, in ottemperanza a **un principio di massima cautela** ispirato a prevenire l'insorgenza di fenomeni VITT in soggetti a rischio estremamente basso di sviluppare patologia COVID-19 grave, nonché in ottemperanza del principio di equo trattamento sopra richiamato, **si ritiene raccomandabile l'utilizzo di un vaccino a mRNA nei soggetti di età inferiore ai 60 anni. La somministrazione della seconda dose a mRNA dovrebbe avvenire – sulla base di studi disponibili – a una distanza compresa tra le 8 e le 12 settimane dalla somministrazione della prima dose di Vaxzevria.**

- il già citato documento di EMA, prodotto in data 23 aprile per supportare le autorità nazionali nel decidere come utilizzare al meglio il vaccino Vaxzevria nei rispettivi territori, è focalizzato solo per questo tipo di vaccino e contestualizza il rischio di VITT e decesso per COVID, rispetto a fasce di età e tassi di infezione (https://www.ema.europa.eu/en/documents/chmp-annex/annex-vaxzevria-art53-visual-risk-contextualisation_en.pdf). Per quel che riguarda l'altro vaccino a vettore adenovirale, un panel di esperti dei CDC (*Centers for Disease Control and Prevention*) americano ha recentemente raccomandato, dopo un'iniziale sospensione, di ricominciare negli Stati Uniti la somministrazione del vaccino Janssen. Alcuni membri di questo panel hanno anche proposto che l'FDA includa un *warning* per le donne al di sotto dei 50 anni di età. Più precisamente, i dati disponibili presso i CDC al momento della ripresa della campagna negli USA riportavano 7 eventi per milione nelle donne di età compresa tra 18 e 49 anni e un tasso di 0,9 per milione di vaccinazioni tra le donne di età pari o superiore a 50 anni. Per le donne dai 50 anni in su e per gli uomini di tutte le età, l'evento avverso è ancora più raro. Pur tenendo conto delle analogie esistenti tra il vaccino Vaxzevria e il vaccino Janssen, per quanto riguarda sia le piattaforme che la tipologia di eventi tromboembolici riportati nella letteratura, lo

stato attuale delle conoscenze (che fanno propendere per un rischio associato all'adenovirus), il numero di poco superiore al milione di dosi a oggi somministrate nel Paese e la rarità, anche in ambito Europeo, delle segnalazioni di VITT a oggi disponibili, **non permettono di trarre valutazioni conclusive rispetto al rapporto beneficio/rischio relativo al vaccino Janssen**, connotato dal vantaggio della singola somministrazione, peculiarità che può risultare di particolare beneficio in determinate categorie di popolazione. Il vaccino Janssen viene raccomandato, anche alla luce di quanto definito dalla CTS di AIFA, per soggetti di età superiore ai 60 anni. Qualora si determinino specifiche situazioni in cui siano evidenti le condizioni di vantaggio della singola somministrazione ed in assenza di altre opzioni, il vaccino Janssen andrebbe preferenzialmente utilizzato, previo parere del Comitato etico territorialmente competente. L'eventuale evidenza, nel contesto nazionale e internazionale, di fenomeni tromboembolici dopo vaccino Janssen dovrà essere oggetto di attento e costante monitoraggio attraverso le procedure di farmacosorveglianza e vaccino-vigilanza, in maniera tale da offrire, nel breve futuro, la possibilità di formulare più compiuto parere su questo vaccino all'acquisirsi di ulteriori evidenze rispetto all'eventuale incidenza di fenomeni VITT e all'evolversi della situazione epidemiologica.

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Alla luce delle considerazioni riportate, che determinano un aggiornamento delle valutazioni formulate dal CTS nella seduta dello scorso 12 maggio, il CTS raccomanda che le Regioni ogniqualvolta promuovano eventi Open Day che sensibilizzano alla vaccinazione anti-SARS-CoV-2, rispettino le indicazioni per fasce d'età, rendendo quanto più possibile l'approccio alla vaccinazione omogeneo sul territorio nazionale.

I documenti richiamati mediante link alle pagine internet sono allegati al presente processi verbale.

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*Presidenza del Consiglio dei Ministri*

**COMITATO TECNICO-SCIENTIFICO**
**Ex O.C.D.P.C. 3 febbraio 2020, n. 630, come modificata dalla O.C.D.P.C. 17 marzo 2021, n. 751**

Alle ore 16,00, in assenza di altri argomenti sui quali concentrare l'attenzione, il Coordinatore dichiara chiusa la seduta.

| | Presente | Assente |
|---|---|---|
| Franco LOCATELLI (coordinatore) | X | |
| Silvio BRUSAFERRO (portavoce) | in videoconferenza | |
| Sergio FIORENTINO (segretario) | X | |
| Sergio ABRIGNANI | in videoconferenza | |
| Cinzia CAPORALE | in videoconferenza | |
| Fabio CICILIANO | X | |
| Donato GRECO | in videoconferenza | |
| Giuseppe IPPOLITO | in videoconferenza | |
| Alessia MELEGARO | in videoconferenza | |
| Giorgio PALÙ | in videoconferenza | |
| Giovanni REZZA | in videoconferenza | |

Verbale approvato dopo condivisione via e.mail da parte di tutti i Componenti.

IL COORDINATORE

Franco Locatelli

IL SEGRETARIO VERBALIZZANTE

Sergio Fiorentino

# IMPATTO DELL'EPIDEMIA COVID-19 SULLA MORTALITÀ TOTALE DELLA POPOLAZIONE RESIDENTE. ANNO 2020 E GENNAIO-APRILE 2021

Il sesto Rapporto prodotto congiuntamente dall'Istituto nazionale di statistica (Istat) e dall'Istituto Superiore di Sanità (Iss) presenta una sintesi delle principali caratteristiche di diffusione dell'epidemia Covid-19 e del suo impatto sulla mortalità totale del 2020 e un'analisi dettagliata della nuova fase epidemica che, nel primo quadrimestre 2021, si caratterizza anche per la progressiva diffusione della vaccinazione Covid-19.

Contestualmente vengono diffusi dall'Istat i dati sui decessi giornalieri per tutti i comuni aggiornati fino al mese di marzo 2021. La base dati di mortalità giornaliera, che l'Istat ha reso disponibile per il monitoraggio tempestivo dei decessi, è consolidata a distanza di 45 giorni rispetto alla data di evento mediante l'integrazione delle notifiche di cancellazione per decesso di fonte anagrafica (ANPR e comuni) con i dati sui deceduti risultanti all'Anagrafe tributaria.[1] Nel Report si fornisce inoltre una stima anticipatoria a livello regionale, a soli 15 giorni di ritardo data, relativamente ai decessi per il complesso delle cause avvenuti nel mese di aprile 2021.

L'Istituto Superiore di Sanità ha il compito di coordinare la Sorveglianza Nazionale integrata Covid-19, attraverso l'ordinanza 640 della Presidenza del Consiglio dei Ministri – Dipartimento della Protezione Civile del 27/2/2020 (Ulteriori interventi urgenti di protezione civile in relazione all'emergenza relativa al rischio sanitario connesso all'insorgenza di patologie derivanti da agenti virali trasmissibili).

La sorveglianza raccoglie i dati individuali dei soggetti positivi al Covid-19, in particolare quelli anagrafici, il luogo di domicilio e residenza, alcuni dati di laboratorio, informazioni sul ricovero e sullo stato clinico (indicatore sintetico di gravità della sintomatologia), nonché sulla presenza di alcuni fattori di rischio (patologie croniche di base) e sull'esito finale (guarito o deceduto).

I dati, relativi a tutti i casi di Covid-19 diagnosticati microbiologicamente (tampone naso-faringeo positivo a SARS-Cov-2) provenienti dai laboratori di riferimento regionali, vengono raccolti dalle Regioni/Province Autonome attraverso una piattaforma web dedicata e sono aggiornati quotidianamente da ciascuna Regione[2].
I dati commentati nel Rapporto sono in continua fase di perfezionamento. La scelta di assumere come riferimento il periodo gennaio-aprile 2021 consente di effettuare l'analisi dell'impatto dell'epidemia Covid-19 sulla mortalità totale della popolazione residente su una base dati il più possibile consolidata[3].

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[1] Per le informazioni sulla qualità e copertura dei dati di mortalità si veda la Nota Metodologica allegata al Rapporto. La base dati è consultabile al seguente link https://www.istat.it/it/archivio/240401

[2] Si precisa che i dati della Sorveglianza Nazionale integrata Covid-19 dell'ISS non sono perfettamente allineati con il flusso della Protezione Civile e del Ministero della Salute che riportano dati aggregati inviati giornalmente dalle regioni http://opendatadpc.maps.arcgis.com/apps/opsdashboard/index.html#/b0c68bce2cce478eaac82fe38d4138b1

[3] Data di estrazione della base dati della Sorveglianza Integrata 26 maggio 2021, data di consolidamento della base dati Istat del 17 maggio 2021.

# SINTESI DEI PRINCIPALI RISULTATI

- In Italia, dall'inizio dell'epidemia con evidenza di trasmissione (20 febbraio 2020) fino al 30 aprile 2021 sono stati segnalati al Sistema di Sorveglianza Integrato 4.035.367 casi positivi di Covid-19 diagnosticati dai Laboratori di Riferimento regionale (data di estrazione della base dati della Sorveglianza Integrata 26 maggio 2021), di cui 1.867.940 nei primi 4 mesi del 2021, il 46% del totale. Sempre dall'inizio dell'epidemia, nel Sistema di Sorveglianza Nazionale integrato Covid-19 dell'ISS, sono stati registrati 120.628 decessi di persone positive al Covid-19 con data di evento entro il 30 aprile 2020.

- L'analisi del primo quadrimestre 2021 documenta, rispetto al 2020, un ulteriore calo in termini percentuali dei contagi registrati nella popolazione molto anziana (80 anni e più) ed un abbassamento dell'età dei casi segnalati. Questo è un segnale di come la campagna di vaccinazione, le raccomandazioni e la prevenzione messa in atto abbiano dato esiti postivi nel ridurre la trasmissione di malattia nella fascia anziana della popolazione, ma è anche una conseguenza dell'aumentata capacità diagnostica e delle attività di contact tracing che hanno facilitato l'identificazione di casi tra la popolazione più giovane, più frequentemente paucisintomatici o asintomatici.

- Alla data del sette giugno 2021 in Italia sono state somministrate 38.178.684 dosi di vaccino per la prevenzione dell'infezione da SARS-CoV-2, con un totale di 13.028.350 di persone che hanno ricevuto il ciclo completo (24,01% della popolazione over 12 anni). Il secondo rapporto dell'ISS sull'impatto della vaccinazione Covid-19 nella popolazione italiana ha evidenziato una riduzione progressiva del rischio di infezione da SARS-CoV-2, di ricovero e di decesso. Per quest'ultimo è stata osservata una riduzione del rischio di circa il 95% a partire dalla settima settimana dopo la somministrazione della prima dose di vaccino.

- Come già nei precedenti Rapporti congiunti Istat-Iss, l'evoluzione della mortalità totale del 2020 e del 2021 è stata confrontata, a parità di periodo, con la media dei decessi del quinquennio 2015-2019. Nel 2020 il totale dei decessi per il complesso delle cause è stato il più alto mai registrato nel nostro Paese dal secondo dopoguerra: 746.146 decessi, 100.526 decessi in più rispetto alla media 2015-2019 (15,6% di eccesso).

- Considerando le variazioni nei tassi standardizzati di mortalità, ottenuti rapportando i decessi alla popolazione a parità di struttura per età, la mortalità ha registrato nel 2020 un aumento del 9%, a livello nazionale, rispetto alla media del quinquennio 2015-2019; le regioni che riportano aumenti significativamente più alti della media nazionale sono il Piemonte, la Valle D'Aosta, la Lombardia e la Provincia autonoma di Trento. Le Regioni del Centro e del Mezzogiorno non mostrano variazioni rilevanti.

- Analizzando la diffusione del virus nei primi mesi del 2021 le Province con il maggior tasso di incidenza sono state quelle del versante Nord-orientale: Bologna, Gorizia, Forlì-Cesena, Udine, Rimini, Bolzano/Bozen. Molto bassa appare l'incidenza in alcune province della Sardegna (Sud Sardegna, Oristano, Sassari), in alcune Province della Calabria (Catanzaro, Cosenza, Crotone) e della Sicilia (Ragusa, Enna, Agrigento).

- Rispetto all'intero anno 2020, nei primi quattro mesi del 2021 l'impatto dei decessi per Covid-19 sui decessi totali è aumentato soprattutto nelle regioni del Centro e del Mezzogiorno; questo accade sia perché è aumentata la capacità di rilevazione dei decessi Covid-19 da parte delle Regioni sia per lo scenario di diffusione del virus che è notevolmente mutato interessando le regioni del Centro e del Mezzogiorno, le quali avevano registrato una scarsa presenza del virus nella prima ondata (marzo-maggio 2020).

- La stima del contributo dei decessi Covid-19 alla mortalità generale conferma come l'impatto sia più marcato nel genere maschile. Si evidenzia inoltre come la fascia di età in cui si riscontra un'incidenza

maggiore di decessi Covid-19 sui decessi totali sia la 65-79 anni, in questa classe un decesso su 5 è attribuibile al Covid-19.

- Da marzo 2021 si cominciano ad osservare gli effetti positivi della campagna vaccinale che ha prioritariamente puntato a proteggere la popolazione più fragile. Se da un lato l'eccesso di decessi di marzo 2021, rispetto al dato medio dello stesso mese del periodo 2015-2019, continua ad essere attribuibile per quasi il 90% ai morti di 65 anni e più, d'altro canto rispetto al picco di decessi di marzo 2020 il calo più importante si deve soprattutto alla classe 80+; il crollo dei decessi di questa classe di età rispetto a marzo 2021 spiega il 70% della diminuzione dei decessi totali osservata tra marzo 2021 e marzo 2020; un altro 26% è dovuto alla minore mortalità della classe 65-79 anni.
- Un confronto internazionale, basato su dati ufficiali, è al momento possibile solo attraverso i dati pubblicati da Eurostat relativi all'eccesso di mortalità mensile dei paesi dell'Unione Europea: l'Italia ha condiviso con la Spagna il primo drammatico incremento dei decessi a partire dal mese di marzo 2020. Tale incremento è comunque diminuito a partire dal mese di maggio 2020 fino al mese di ottobre quando si è verificata una nuova fase di rapida crescita dei decessi. Nel mese di dicembre e nei primi mesi del 2021 l'eccesso di mortalità in Italia è stato al di sotto della media Europea per poi risalire leggermente nel mese di marzo 2021.
- I confronti Internazionali basati sul solo dato dell'eccesso hanno di sé dei forti limiti in quanto non tengono conto della diversa struttura per età delle popolazioni. È solo attraverso la standardizzazione per fasce di età che si evidenziano le vere differenze in termini di mortalità fra paesi. Uno studio recente pubblicato sulla rivista British Medical Journal che ha mostrato gli eccessi in diversi paesi standardizzando per età, ha evidenziato come l'eccesso di mortalità nel nostro Paese è risultato inferiore a quello registrato in altri paesi Europei, tra i quali Spagna, Belgio e Regno Unito, e negli Stati Uniti.

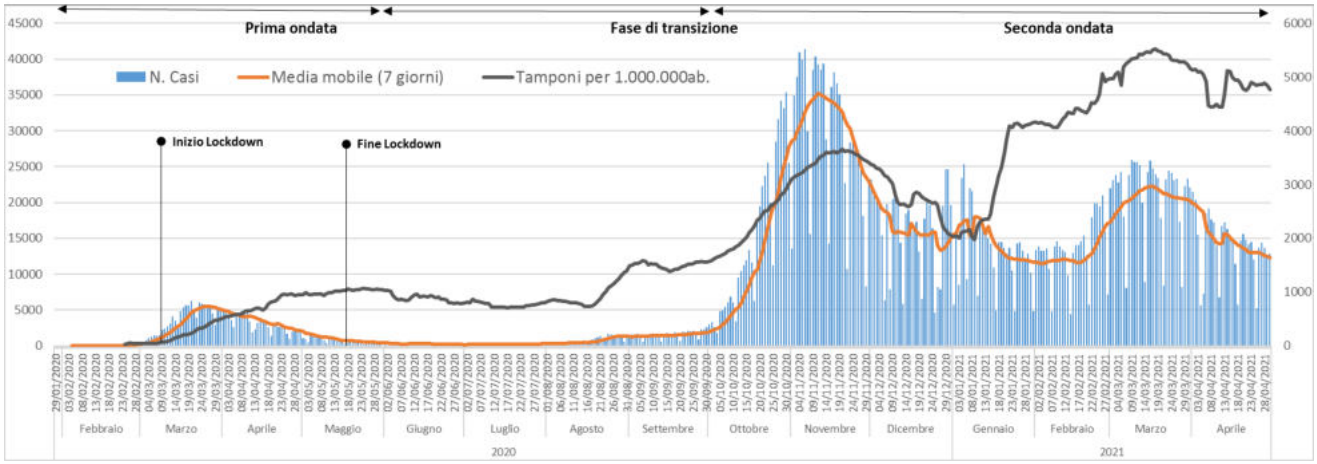
## Lo scenario di diffusione dell'epidemia di Covid-19 nell'anno 2020 e nel primo quadrimestre del 2021

In Italia, dall'inizio dell'epidemia con evidenza di trasmissione (20 febbraio 2020) fino al 30 aprile 2021 sono stati segnalati al Sistema di Sorveglianza Integrato 4.035.367 casi positivi di Covid-19 diagnosticati dai Laboratori di Riferimento regionale (data di estrazione della base dati della Sorveglianza Integrata 26 maggio 2021), di cui 1.867.940 nei primi 4 mesi del 2021, il 46% del totale.

Rispetto alla prima ondata epidemica (definita tra inizio marzo e fine di maggio 2020) è molto cambiata la capacità diagnostica dell'infezione, grazie all'aumento della possibilità di eseguire tamponi molecolari e alla ricerca attiva di casi secondari che è stata messa in atto da Regioni e Provincie Autonome. È stato stimato, grazie anche all'indagine di sieroprevalenza sul SARS-CoV-2 condotta da Istat e Ministero della Salute[4] che nella prima ondata il rapporto tra i casi notificati e i casi reali fosse almeno di 1 a 6.

[4] Cfr https://www.istat.it/it/archivio/246156

**Figura 1. Numero di casi di Covid-19 per data di prelievo/diagnosi e numero di tamponi** *(per milione di abitanti)*. **Italia, febbraio 2020 –aprile 2021**




*Fonte: Iss, Sistema di sorveglianza integrata Covid-19*

La Figura 1 mostra l'andamento del numero di casi di Covid-19 segnalati in Italia per data di prelievo/diagnosi. La curva epidemica indica che l'impatto della seconda ondata, in termini di numero complessivo di casi giornalieri notificati, è decisamente più elevato di quello della prima ondata, per via dell'aumentata capacità diagnostica e delle attività di contact tracing, che hanno permesso di individuare numerosi soggetti asintomatici o paucisintomatici. Si osserva inoltre come durante la seconda ondata la curva abbia subito una flessione nei primi mesi dell'anno per poi ricrescere a fine febbraio anche se in maniera più contenuta rispetto al momento di picco registrato in Italia ad inizio settembre (il massimo relativo si è avuto in corrispondenza del 6 novembre con 41.373 casi segnalati).

Da evidenziare è il progressivo aumento dei tamponi effettuati sulla popolazione: la capacità diagnostica nella prima fase dell'epidemia è stata limitata e pertanto l'esecuzione di test molecolari è stata riservata ai casi più gravi di malattia, mentre già a partire da mese di ottobre il numero di tamponi è cresciuto notevolmente fino a raggiungere una media giornaliera di 5.071 per 1.000.000 abitanti nel mese di marzo e aprile 2021 (nel periodo marzo-aprile 2020 la media giornaliera era di 473 tamponi per 1.000.000 abitanti).

## Sempre più giovane l'età dei casi segnalati

Considerando le caratteristiche demografiche dei casi, nel primo quadrimestre2021 si conferma un numero leggermente più elevato di persone di sesso femminile (51%, nell'intero 2020 52%); per quanto riguarda l'età il 12% dei casi hanno meno di 14 anni, il 17% hanno una età compresa tra i 15 e i 29 anni, il 52% tra i 30 e i 64 anni, il 20% oltre i 65 anni.

Appare evidente, dunque, un ulteriore calo in termini percentuali dei contagi registrati nei primi quattro mesi del 2021 della popolazione più anziana ed un abbassamento dell'età dei casi segnalati: la classe di età 0-49 ora rappresenta il 58% dei casi segnalati rispetto al 52% dell'intero anno 2020. La classe di età mediana dei casi confermati di infezione da SARS-CoV-2 nei primi 4 mesi del 2021 è scesa a 40-44 anni, mentre per quelli segnalati entro il 31 dicembre 2020 era 45-49 anni.

Se si considera in particolare la classe di età degli over 80 anni i casi diagnosticati nel primo quadrimestre 2021 sono il 7%, inferiori rispetto alla percentuale del 2020 che era intorno al 10%.

Questi risultati sono da un lato il segnale di come la campagna di vaccinazione, le raccomandazioni e la prevenzione messa in atto abbiano dato esiti postivi nel ridurre la trasmissione di malattia nella

fascia di età più fragile della popolazione, dall'altro sono anche una conseguenza dell'aumentata capacità diagnostica che ha facilitato l'identificazione di casi tra la popolazione più giovane, più frequentemente paucisintomatici o asintomatici.

**Tabella 1. Tassi Standardizzati*** *(per 100 mila abitanti)* **di Incidenza di Covid-19 segnalati dalle Regioni e Province Autonome al Sistema di Sorveglianza Integrato, anno 2020 e nel periodo 1 gennaio - 30 aprile 2021, per classi di età**

| Classe di età | Gennaio-Aprile 2021 | | | | Anno 2020 | | | |
|---|---|---|---|---|---|---|---|---|
| | casi | tasso standardizzato | limite inferiore | limite superiore | casi | tasso standardizzato | limite inferiore | limite superiore |
| 0-49 | 1.069.775 | 3.311,5 | 3.305,2 | 3.317,8 | 1.113.355 | 3.446,1 | 3.439,7 | 3.452,5 |
| 50-64 | 427.188 | 3.184,6 | 3.175,0 | 3.194,2 | 522.188 | 3.890,5 | 3.879,9 | 3.901,0 |
| 65-79 | 235.905 | 2.496,4 | 2.486,3 | 2.506,5 | 282.176 | 2.991,5 | 2.980,5 | 3.002,6 |
| 80+ | 116.830 | 2.600,5 | 2.585,4 | 2.615,5 | 215.908 | 4.729,3 | 4.709,2 | 4.749,5 |

** Popolazione Standard di riferimento Italia Censimento 2011.*
*Fonte: ISS, Sistema di sorveglianza integrata Covid-19.*

## L'andamento dei decessi della Sorveglianza Nazionale integrata Covid-19

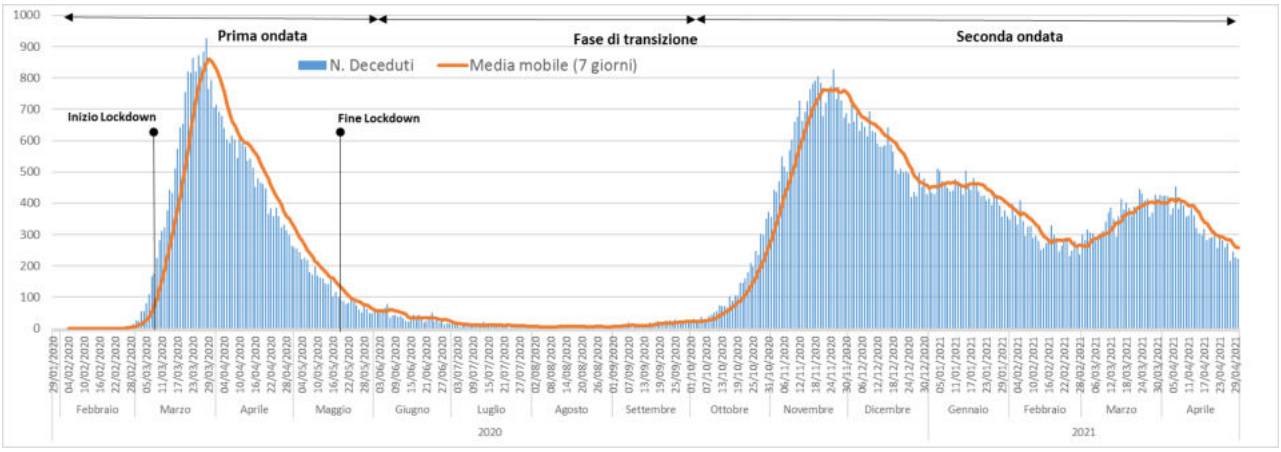
Dall'inizio dell'epidemia sono stati registrati nel Sistema di Sorveglianza Nazionale integrata Covid-19 dell'ISS 120.628 decessi con data di morte entro il 30 aprile 2020.

Si può notale una tendenza simile tra l'andamento dei nuovi casi (Figura 1) e quello dei decessi di persone positive al Covid-19 (Figura 2): per i decessi, le alterne fasi di crescita e diminuzione risultano traslate di alcune settimane rispetto ai picchi dei casi. Occorre considerare che i decessi sono riportati per data di morte, mentre i casi fanno riferimento alla data dell'effettuazione del tampone. Dal momento della positività del tampone al momento del decesso decorrono in media due settimane. Pertanto, i decessi Covid-19 sono da riferirsi più propriamente a diagnosi effettuate nelle settimane precedenti. Ciò spiega il fatto che la curva dei decessi Covid-19 non sia sincrona a quella delle diagnosi.

La curva dei decessi, analogamente a quella dei casi, mostra una seconda fase di crescita a partire da settembre 2020. Pur essendo il numero dei casi con diagnosi confermata con Covid-19 più elevato nella seconda ondata, il numero assoluto di decessi si mantiene leggermente più basso rispetto alla prima. Questo dipende principalmente dal fatto che nella seconda ondata è stato diagnosticato una maggior numero di casi asintomatici e relativamente giovani con un minor rischio di decesso. L'esperienza dei servizi nell'affrontare l'emergenza e le migliorate conoscenze in merito a possibili trattamenti terapeutici possono avere ulteriormente contribuito alla diminuzione della letalità tra i casi diagnosticati con Covid-19 nella seconda ondata.

Il numero più alto di decessi giornalieri si registra il 28 marzo del 2020 con un totale di 928 decessi, mentre se si considera solo la seconda ondata epidemica il 19 novembre (805 decessi). Dal 1° gennaio 2021 al 30 aprile sono stati riportati alla Sorveglianza 42.957decessi. Se si considerano i soli mesi di marzo e aprile 2021 rispetto al 2020 i decessi riportati sono 21.004 rispetto ai 30.064 dei rispettivi mesi nel 2020. Complessivamente dall'inizio dell'epidemia il numero di decessi è avvenuto prevalentemente tra gli uomini (56,7%).

**Figura 2. Andamento giornaliero dei decessi segnalati al Sistema di Sorveglianza Integrata Covid-19, periodo febbraio 2020-aprile 2021**




*Fonte: Iss, Sistema di sorveglianza integrata Covid-19*

In entrambi i generi la quota maggiore di decessi per Covid-19 si osserva, nei primi quattro mesi del 2021, per la classe di età 80 anni e più: 50 per cento decessi Covid-19 nel caso degli gli uomini e ben il 69% per le donne (Tabella 2).

**Tabella 2. Distribuzione percentuale dei decessi Covid-19 segnalati al Sistema di Sorveglianza gennaio-aprile 2021, e della popolazione al 1° gennaio 2020 e 2021 per genere e classi di età - Italia**

| Classe di età | Decessi Covid-19 | | | Popolazione 1° gennaio 2020 | | Popolazione 1° gennaio 2021 | |
|---|---|---|---|---|---|---|---|
| | Maschi | Femmine | Totale | Maschi | Femmine | Maschi | Femmine |
| 0-49 | 0,8 | 1,4 | 1,1 | 56,9 | 52,2 | 56,2 | 51,6 |
| 50-64 | 5,2 | 9,8 | 7,8 | 22,4 | 22,3 | 22,7 | 22,6 |
| 65-79 | 24,7 | 38,6 | 32,6 | 13,9 | 15,3 | 14,0 | 15,4 |
| 80+ | 69,3 | 50,2 | 58,5 | 5,7 | 9,0 | 5,9 | 9,2 |
| totale | 100,0 | 100,0 | 100,0 | 100,0 | 100,0 | 100,0 | 100,0 |

*Fonte: Iss, Sistema di sorveglianza integrata Covid-19*

Questa differenza di genere è in parte spiegata dalla maggiore numerosità della popolazione femminile ultraottantenne (9% della popolazione femminile al 1° gennaio 2020 aveva 80 anni ed oltre rispetto al 6% della popolazione maschile). Resta invariata la percentuale di decessi nella popolazione di età inferiore ai 50 anni che si attesta intorno all'1,1% complessivo. La percentuale dei decessi nella classe di età 65-79 aumenta di due punti percentuali (era di 30,3 considerando l'intero 2020)

## Impatto della vaccinazione anti COVID-19

Alla data del sette giugno 2021 in Italia sono state somministrate 38.178.684 dosi di vaccino anti Covid-19 per la prevenzione dell'infezione da SARS-CoV-2, con un totale di 13.028.350 persone che hanno ricevuto due dosi di vaccino (24,01 % della popolazione over 12). L'82,2% della popolazione over 80 risulta aver completato la vaccinazione.

È stata effettuata una prima valutazione dell'impatto delle vaccinazioni Covid-19 sulle infezioni da SARS-CoV-2 nonché sui successivi ricoveri e decessi, utilizzando due fonti di dati (periodo di

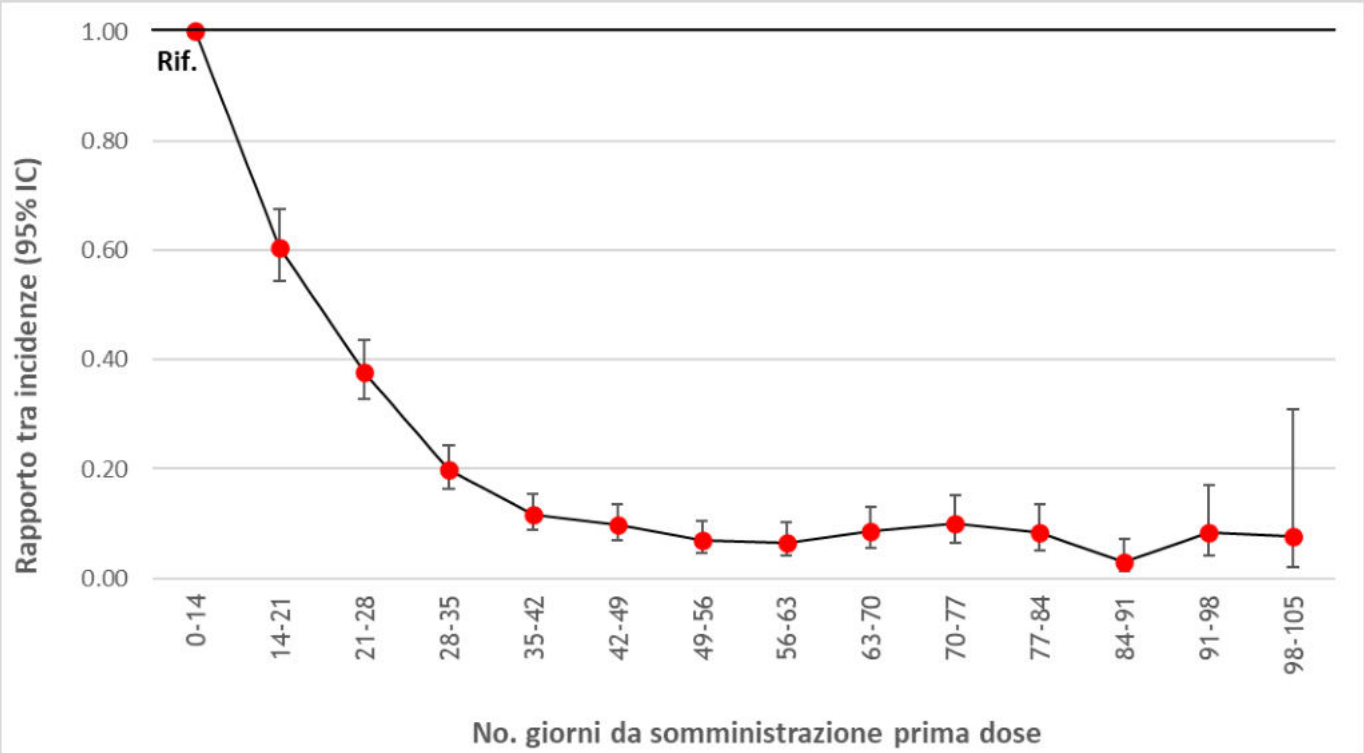
riferimento 27.12.2020 - 30.05.2021): l'anagrafe nazionale vaccini e la sorveglianza integrata Covid-19 dell'ISS (fonte: https://www.epicentro.iss.it/vaccini/covid-19-report-valutazione-vaccinazione/).

L'analisi congiunta dei due "database" ha permesso, quindi, una verifica dell'"efficacia di popolazione", cioè dell'efficacia dei vaccini nella pratica clinica. I vaccini somministrati fino al momento della valutazione erano quattro: 1) Pfizer-BioNtech (prima somministrazione: 27/12/2020), 2) Moderna (prima somministrazione: 14/01/2021), 3) AstraZeneca (prima somministrazione: 01/02/2021) e 4) Johnson&Johnson (prima somministrazione: 22/04/2021).

Si è osservata una buona aderenza della popolazione al piano vaccinale: il 95% dei vaccinati ha seguito la schedula vaccinale per la seconda dose, e a partire dal 15-mo giorno di somministrazione della prima dose, è stata osservata una riduzione progressiva del rischio di infezioni da SARS-CoV-2, di ricovero e di decesso. Dopo sette settimane si è stimata una riduzione di circa l'80% per rischio di infezione, il 90% per il rischio di ricovero e il 95% per il rischio di decesso.

In particolare, per la valutazione dell'impatto dei vaccini sulla mortalità, sono stati selezionati i 7.351.046 individui vaccinati entro il 4 aprile 2021 e per i quali non era stata effettuata una diagnosi precedente di SARS-CoV-2. Sui pazienti selezionati è stata calcolata l'incidenza dei decessi entro 30 giorni dalla diagnosi di Covid-19 a intervalli settimanali dalla somministrazione della prima dose. Nella Figura 3 è mostrato il Rischio Relativo (RR) di decesso per settimana. Gli RR di decesso sono stati stimati in base a un modello statistico (modello di Poisson) che teneva conto oltre che della settimana (tempo trascorso dalla prima dose), anche della regione, dell'età, del genere, della categoria prioritaria di vaccinazione (ad es. operatori sanitari), del tipo di vaccino, della settimana di calendario in cui è avvenuta la vaccinazione e dell'incidenza settimanale a livello regionale. Dalla Figura 3 è possibile vedere come il rischio di decesso, rispetto alle prime due settimane, sia diminuito all'aumentare del tempo trascorso dalla somministrazione della prima dose, arrivando a una riduzione del rischio di morire di circa il 95% a partire dalla settima settimana.

**Figura 3. Stime aggiustate del rapporto tra le incidenze (IRR) di diagnosi e successivo decesso a diversi intervalli di tempo dalla somministrazione della prima dose rispetto al periodo di riferimento (0-14 giorni dalla prima dose); tutti i vaccinati con qualsiasi vaccino**



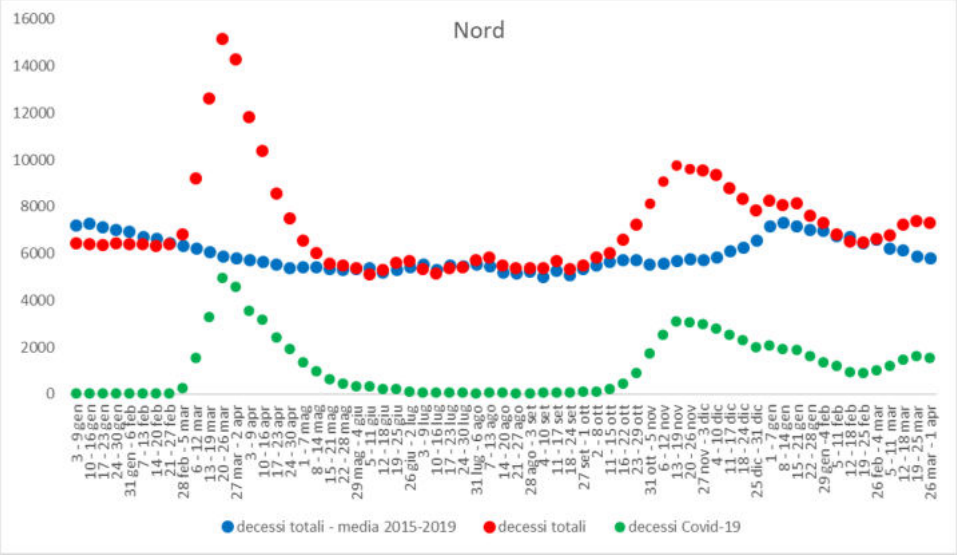

*Fonte: anagrafe nazionale vaccini, contenente le informazioni relative alle vaccinazioni anti COVID-191 eseguite e dei casi di infezione da SARS-CoV-2 notificati alla sorveglianza nazionale integrata COVID-19.*

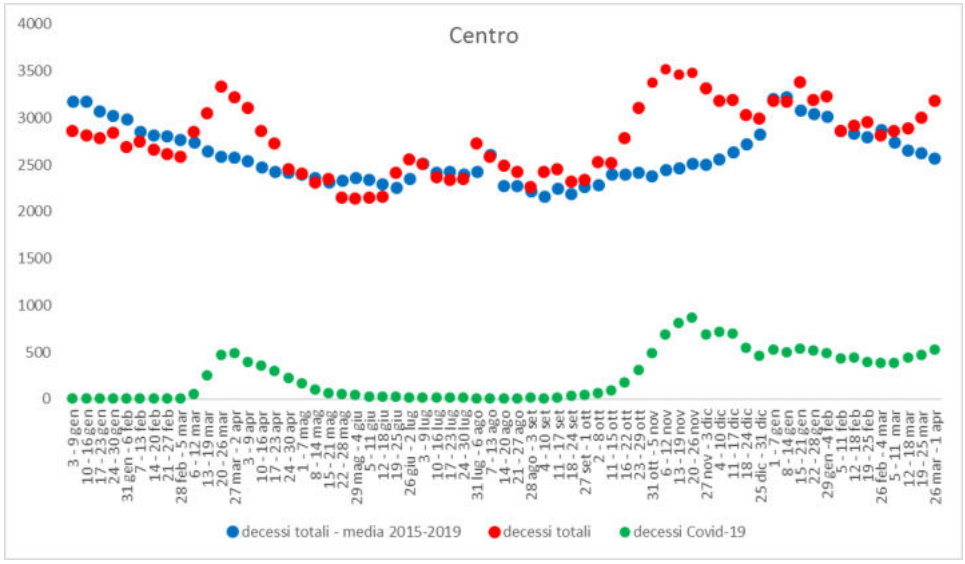
## L’impatto dell’epidemia COVID-19 sulla mortalità generale della popolazione

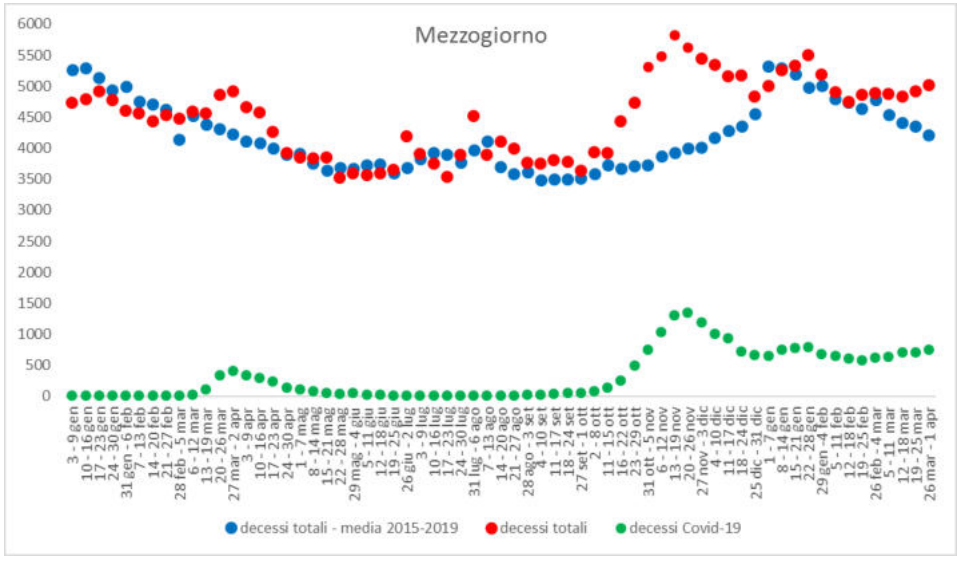
Uno degli approcci più efficaci per misurare l’impatto dell’epidemia di Covid-19 sulla mortalità è quello di conteggiare l’eccesso di decessi per il complesso delle cause, vale a dire quanti morti in più (per tutte le cause) ci sono stati nel Paese rispetto agli anni precedenti. L’eccesso di mortalità può fornire un'indicazione dell'impatto complessivo dell’epidemia, non solo tenendo conto dei decessi attribuiti direttamente a Covid-19, ma anche di quelli che possono essere sottostimati o indirettamente collegati, come le morti causate da un trattamento ritardato o mancato a causa di un sistema sanitario sovraccarico.

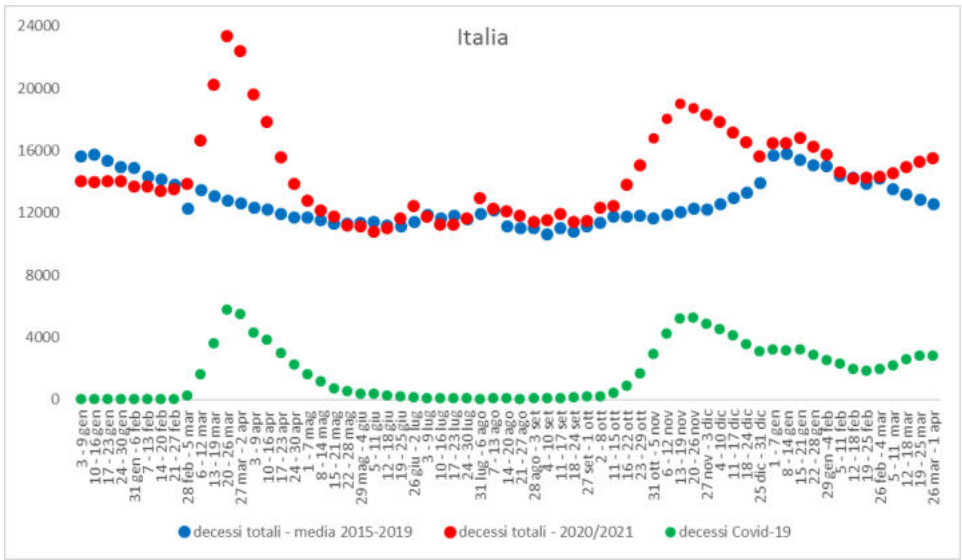
Come già nei precedenti Rapporti congiunti Istat-Iss l’eccesso di mortalità è stato stimato confrontando, a parità di periodo, i dati del 2020 e del 2021 con la media dei decessi del quinquennio 2015-2019. In tal modo si assume implicitamente che la diffusione dell’epidemia produca un aumento di morti anche non direttamente riferibile al numero di casi positivi deceduti. D’altra parte, il dato dei morti riportati alla Sorveglianza Nazionale integrata Covid-19 fornisce solo una misura parziale di questi effetti, essendo riferito ai soli casi di deceduti dopo una diagnosi microbiologica di positività al virus. Si tratta, pertanto, di un indicatore influenzato non solo dalle modalità di classificazione delle cause di morte, ma anche dalla presenza di un test di positività al virus. A partire da marzo 2020, l’andamento dei decessi totali rispecchia in tutte le ripartizioni quello dei decessi Covid-19 (Figura 4).

**Figura 4. Andamento settimanale dei decessi totali e dei decessi covid-19, per ripartizione geografica. Anni 2020 e 2021 e media del periodo 2015-2019.**






*Fonte: Istat. Base dati integrata mortalità giornaliera comunale, Iss registro sorveglianza Covid-19.*

Nell'anno 2020 il totale dei decessi per il complesso delle cause è stato il più alto mai registrato nel nostro Paese dal secondo dopoguerra: 746.146 decessi, 100.526 decessi in più rispetto alla media 2015-2019 (15,6% di eccesso). In tale valutazione occorre tener conto che nei mesi di gennaio e febbraio 2020 i decessi per il complesso delle cause sono stati inferiori di circa 7.600 unità a quelli della media dello stesso bimestre del 2015-2019 e che i primi decessi di persone positive al Covid-19 risalgono all'ultima settimana di febbraio. Pertanto, volendo stimare l'impatto dell'epidemia Covid-19 sulla mortalità totale, è più appropriato considerare l'eccesso di mortalità verificatosi tra marzo e dicembre 2020. In questo periodo si sono osservati 108.178 decessi in più rispetto alla media dello stesso periodo degli anni 2015-2019 (21% di eccesso).

## L'eccesso di mortalità del 2020 si conferma anche a parità di struttura per età

La recente disponibilità dei dati sulla consistenza e la struttura della popolazione residente per genere, età e luogo di residenza al primo gennaio 2021[5], consente di condurre le analisi considerando le variazione anche in termini di tassi standardizzati di mortalità[6]; si tratta di misure che, a differenza dei livelli assoluti dei decessi, permettono di effettuare dei confronti fra periodi (nel nostro caso 2015-2019 *vs* 2020 ) o, a parità di periodo, fra diversi domini territoriali (altri Paesi piuttosto che ripartizioni geografiche, regioni, province, ecc..) depurati dall'effetto delle differenze nella composizione per età delle popolazioni considerate.

I rapporti dei tassi standardizzati di mortalità (SRR) permettono di confrontare la mortalità generale dell'anno 2020 con il tasso standardizzato medio del periodo 2015-2019; essi vengono affiancati dal limite inferiore (SRR INF) e superiore (SRR SUP) degli intervalli di confidenza che indicano la precisione della stima effettuata e la significatività statistica della differenza (Tabella 3).

A livello nazionale è stato registrato un aumento del 9% del tasso di mortalità standardizzato riferito all'anno 2020 rispetto a quello medio del periodo 2015-2019; per effetto del forte aumento del rischio di mortalità, la sopravvivenza media nel corso del 2020 appare in decisa contrazione.

La speranza di vita alla nascita, senza distinzione di genere, scende a 82 anni, ben 1,2 anni sotto il livello del 2019. Per osservare un valore analogo occorre risalire al 2012. Gli uomini sono più penalizzati: la loro speranza di vita alla nascita scende a 79,7 anni, ossia 1,4 anni in meno dell'anno precedente, mentre per le donne si attesta a 84,4 anni, un anno di sopravvivenza in meno. A 65 anni la speranza di vita scende a 19,9 anni (18,2 per gli uomini, 21,6 per le donne). La variazione annuale è sostanzialmente uguale a quella riscontrata nella speranza di vita alla nascita ma ha un impatto relativo più importante, stante l'esiguità della vita media residua sul quale un individuo può contare al 65° compleanno[7].

Le regioni che nel 2020 hanno riportano aumenti significativamente più alti del tasso standardizzato di mortalità sono il Piemonte, la valle D'Aosta, la Lombardia e la Provincia autonoma di Trento. Un caso in controtendenza è invece quello del Lazio unica Regione a riportare un tasso di mortalità nel 2020 leggermente inferiore al quinquennio precedente (Tabella 3).

[5] Demo.istat.it e indicatori demografici

[6] Cfr. nota metodologica e glossario

[7] https://www.istat.it/it/files//2021/05/REPORT_INDICATORI-DEMOGRAFICI-2020.pdf

**Tabella 3. Casi, decessi e tassi di incidenza standardizzata* *(per 100 mila abitanti)* di Covid-19 segnalati dalle Regioni e Province Autonome al Sistema di Sorveglianza Integrato, tasso standardizzato di mortalità covid-19 e di mortalità generale, Rapporti dei Tassi Standardizzati di Mortalità (2020vs1519); Intervalli di Confidenza al 95%**

| Regione\ripartizione | casi 2020 | tasso di incidenza standardizzato | decessi covid 2020 | tasso standardizzato decessi covid | decessi totali 2020 | tasso standardizzato decessi totali | SRR | SRR_INF | SRR_SUP |
|---|---|---|---|---|---|---|---|---|---|
| Piemonte | 198.881 | 4.503,9 | 8.037 | 139,8 | 66.054 | 1.136,8 | 1,17 | 1,16 | 1,18 |
| Valle d'Aosta | 7.269 | 5.666,8 | 383 | 247,3 | 1.849 | 1.196,4 | 1,19 | 1,11 | 1,28 |
| Lombardia | 467.126 | 4.594,3 | 25.157 | 217,4 | 136.249 | 1.155,6 | 1,28 | 1,27 | 1,29 |
| Pa Bolzano | 29.789 | 5.565,8 | 797 | 141,0 | 5.458 | 970,8 | 1,13 | 1,09 | 1,18 |
| Pa Trento | 26.278 | 4.725,1 | 942 | 145,2 | 6.626 | 1.010,5 | 1,22 | 1,17 | 1,26 |
| Veneto | 262.273 | 5.315,1 | 7.202 | 121,0 | 57.836 | 977,3 | 1,09 | 1,08 | 1,11 |
| Friuli-Venezia Giulia | 53.657 | 4.399,3 | 1.812 | 105,4 | 16.617 | 983,9 | 1,07 | 1,04 | 1,09 |
| Liguria | 59.818 | 3.875,0 | 2.916 | 124,2 | 25.827 | 1.077,1 | 1,13 | 1,11 | 1,15 |
| Emilia-Romagna | 172.205 | 3.812,2 | 7.829 | 134,6 | 59.665 | 1.010,7 | 1,12 | 1,11 | 1,14 |
| Toscana | 118.697 | 3.207,9 | 3.615 | 71,4 | 48.135 | 938,9 | 1,04 | 1,02 | 1,05 |
| Umbria | 28.606 | 3.326,5 | 617 | 51,7 | 11.131 | 896,5 | 1,01 | 0,98 | 1,04 |
| Marche | 41.512 | 2.706,5 | 1.635 | 80,8 | 20.123 | 956,9 | 1,08 | 1,06 | 1,10 |
| Lazio | 176.131 | 3.058,5 | 3.887 | 60,6 | 62.161 | 946,9 | 0,98 | 0,97 | 0,99 |
| Abruzzo | 36.431 | 2.805,0 | 1.305 | 80,1 | 16.296 | 979,0 | 1,02 | 1,00 | 1,04 |
| Molise | 7.108 | 2.353,1 | 203 | 50,0 | 4.127 | 1.001,0 | 1,02 | 0,97 | 1,07 |
| Campania | 181.869 | 3.171,5 | 3.525 | 66,6 | 59.425 | 1.126,5 | 1,01 | 1,00 | 1,02 |
| Puglia | 95.080 | 2.391,6 | 2.666 | 61,2 | 44.650 | 1.006,8 | 1,05 | 1,04 | 1,07 |
| Basilicata | 11.223 | 2.017,0 | 270 | 41,5 | 6.839 | 992,6 | 1,01 | 0,97 | 1,04 |
| Calabria | 25.823 | 1.366,8 | 503 | 24,2 | 21.331 | 1.000,5 | 0,99 | 0,97 | 1,01 |
| Sicilia | 101.546 | 2.082,9 | 2.882 | 55,8 | 56.753 | 1.086,9 | 1,01 | 1,00 | 1,02 |
| Sardegna | 32.305 | 2.005,9 | 908 | 46,7 | 18.994 | 967,4 | 1,05 | 1,03 | 1,07 |
| *Nord* | 1.277.296 | 4.554,8 | 55.075 | 160,2 | 376.181 | 1.078,6 | 1,18 | 1,17 | 1,19 |
| *Centro* | 364.946 | 3.081,0 | 9.754 | 66,5 | 141.550 | 942,8 | 1,02 | 1,01 | 1,02 |
| *Mezzogiorno* | 491.385 | 2.427,4 | 12.262 | 57,3 | 228.415 | 1.049,5 | 1,02 | 1,01 | 1,03 |
| **Italia** | 2.133.627 | 3.544,5 | 77.091 | 109,3 | 746.146 | 1.042,6 | 1,09 | 1,09 | 1,10 |

** Popolazione Standard di riferimento Italia Censimento 2011.*
*Fonte: Istat. Base dati integrata mortalità giornaliera comunale, Iss registro sorveglianza Covid-19.*

Come è stato più volte evidenziato, il Nord è stata la ripartizione più interessata alla diffusione della Pandemia: considerando tutto il 2020 il 60% dei casi e il 71% dei decessi si è concentrato in questa area geografica. Inoltre, la Regione Lombardia è stata quella che durante tutto l'anno ha riportato il maggior numeri di casi e conseguentemente di decessi Covid-19. Questo fenomeno ha determinato un alto valore del tasso standardizzato di mortalità generale, anche se considerando questo indicatore la regione con il più alto tasso di mortalità è stata la Valle D'Aosta. In generale il Centro ed il Mezzogiorno registrano tassi di poco superiori agli anni precedenti.

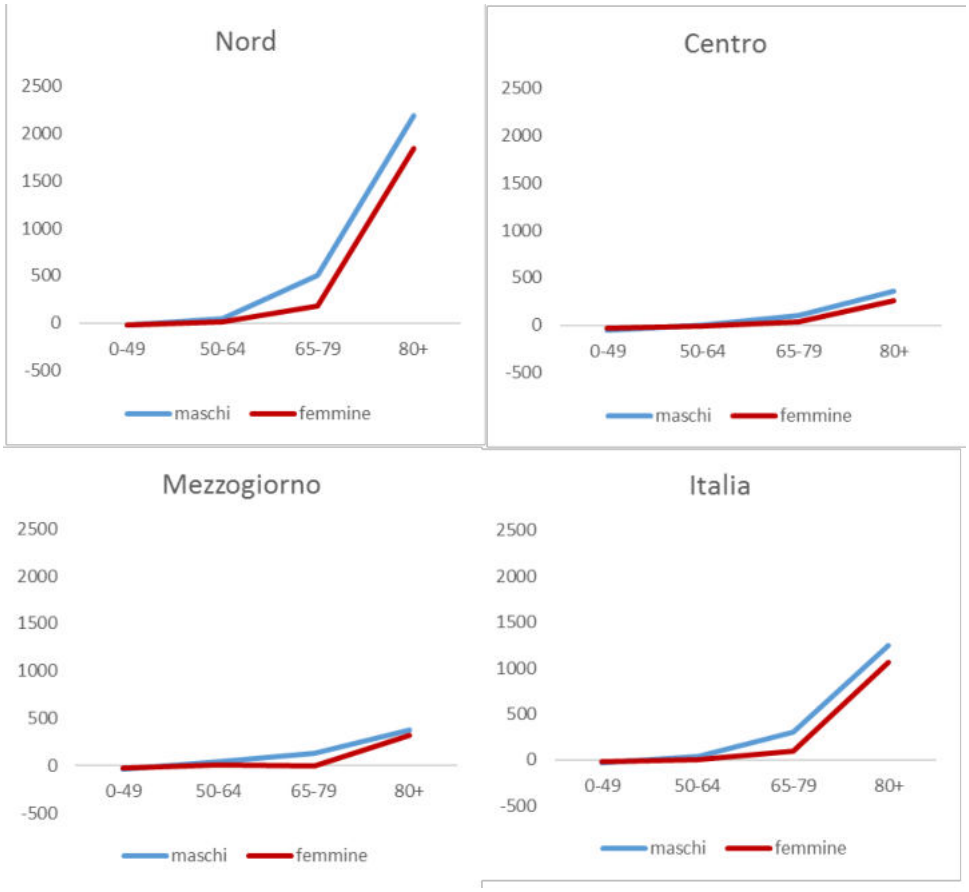
Analizzando i rapporti dei tassi standardizzati a livello provinciale (Allegato A) Bergamo si conferma essere la provincia con la più alta mortalità generale rispetto agli anni precedenti (SRR=1,55), seguita da Cremona (SRR=1,53), Lodi (SRR= 1,47) e Piacenza (SRR= 1,41). Nel centro la Provincia con il più alto tasso di mortalità rispetto al periodo di riferimento 2015-2019 è stata Pesaro Urbino (SRR=1,26), mentre al Mezzogiorno la più colpita è stata Foggia (SRR= 1,16). In linea con i valori regionali Roma ha avuto nel 2020 un tasso di mortalità generale significativamente inferiore al 2015-2019 (SRR=0,97).

Guardando alle classi di età, il contributo più rilevante all'eccesso dei decessi dell'anno 2020, rispetto alla media degli anni 2015-2019, è dovuto all'incremento delle morti della popolazione con 80 anni e più che spiega il 76,3% dell'eccesso di mortalità complessivo; in totale sono decedute 486.255 persone di 80 anni e oltre (76.708 in più rispetto al quinquennio precedente). L'incremento della mortalità nella classe di età 65-79 anni spiega un altro 20% dell'eccesso di decessi; in termini assoluti

l'incremento per questa classe di età, rispetto al dato medio degli anni 2015-2019, è di oltre 20 mila decessi (per un totale di 184.708 morti nel 2020).

Le specificità dell'impatto della pandemia sulla mortalità complessiva per genere, classi di età e territorio si ritrovano anche quando l'analisi è condotta sulla base delle variazioni dei tassi specifici di mortalità (Figura 5).

**Figura 5. Variazione dei tassi specifici di mortalità** *(per 100 mila abitanti)* **per genere, classe di età e ripartizione. Media del periodo 2015-2019 e anno 2020.**




*Fonte: Istat. Base dati integrata mortalità giornaliera comunale.*

Considerando l'intero anno 2020, le differenze maggiori dei tassi di mortalità rispetto alla media del periodo 2015-2019 si hanno nei maschi e nelle classi di età più elevate. Si distingue nettamente il caso del Nord in cui si concentra prevalentemente l'eccesso di mortalità sia per gli uomini che per le donne con 50 anni e più. Al contrario nel corso del 2020 la mortalità nelle età inferiori a cinquanta anni è sempre inferiore a quella della media del periodo 2015-2019, in tutte le ripartizioni.

# L'impatto dell'epidemia COVID-19 sulla mortalità generale di gennaio-aprile 2021

L'andamento dei decessi per il complesso delle cause nei mesi di gennaio-aprile 2021 risente da un lato del contesto epidemiologico, dall'altro degli effetti delle misure di contenimento della diffusione dell'epidemia e della campagna vaccinale (Tabella 4).

**Tabella 4. Decessi per il complesso delle cause e decessi covid-19 per mese e regione. Anni 2021 e variazione percentuale rispetto al dato medio dello stesso mese del periodo 2015-2019 e dell'anno 2020**

| Regione\ripartizione | gennaio | | | | febbraio* | | | |
|---|---|---|---|---|---|---|---|---|
| | decessi 2021 | v% 1519 | v% 2020 | decessi covid | decessi 2021 | v% 1519 | v% 2020 | decessi covid |
| Piemonte | 5.750 | 1,5 | 20,1 | 807 | 4.482 | -6,2 | 1,7 | 582 |
| Valle d'Aosta | 148 | -5,2 | 17,5 | 28 | 127 | -2,2 | -0,4 | 9 |
| Lombardia | 10.812 | 2,3 | 14,0 | 1.791 | 8.593 | -2,7 | -0,6 | 1.172 |
| Pa Bolzano | 493 | 6,8 | 14,1 | 170 | 519 | 31,2 | 22,7 | 159 |
| Pa Trento | 702 | 32,0 | 50,3 | 165 | 483 | 6,6 | 9,2 | 58 |
| Veneto | 6.633 | 29,5 | 37,5 | 2.173 | 4.386 | -1,6 | 4,4 | 591 |
| Friuli-Venezia Giulia | 2.154 | 38,5 | 42,1 | 763 | 1.473 | 8,0 | 17,4 | 354 |
| Liguria | 2.401 | 4,3 | 24,5 | 394 | 1.927 | -1,2 | 12,1 | 250 |
| Emilia-Romagna | 6.068 | 15,5 | 28,6 | 1.699 | 4.726 | 6,5 | 11,2 | 974 |
| Toscana | 4.467 | -2,9 | 7,7 | 545 | 3.802 | -2,3 | 6,2 | 438 |
| Umbria | 1.138 | 2,5 | 15,5 | 164 | 1.091 | 19,5 | 28,8 | 271 |
| Marche | 2.062 | 13,4 | 24,4 | 442 | 1.709 | 10,2 | 17,4 | 291 |
| Lazio | 6.638 | 5,4 | 16,4 | 1.117 | 5.133 | 0,2 | 8,0 | 706 |
| Abruzzo | 1.672 | 2,1 | 12,8 | 251 | 1.401 | 3,1 | 5,4 | 264 |
| Molise | 454 | 4,8 | 25,1 | 75 | 376 | 12,2 | 26,4 | 82 |
| Campania | 5.778 | -5,4 | 1,4 | 629 | 5.077 | 2,1 | 6,4 | 552 |
| Puglia | 4.659 | 9,1 | 16,0 | 780 | 4.000 | 14,2 | 17,5 | 656 |
| Basilicata | 676 | 1,9 | 18,2 | 55 | 563 | -3,2 | -4,4 | 39 |
| Calabria | 2.067 | -7,7 | 1,2 | 115 | 1.802 | -3,0 | 6,3 | 99 |
| Sicilia | 6.174 | 6,7 | 14,6 | 1.100 | 4.741 | -5,5 | 5,6 | 619 |
| Sardegna | 1.902 | 9,7 | 13,0 | 254 | 1.502 | -1,0 | 3,0 | 112 |
| *Nord* | *35.161* | *11,2* | *24,3* | *7.990* | *26.716* | *-0,3* | *4,9* | *4.149* |
| *Centro* | *14.305* | *3,4* | *14,5* | *2.268* | *11.735* | *2,2* | *10,3* | *1.706* |
| *Mezzogiorno* | *23.382* | *2,2* | *10,1* | *3.259* | *19.462* | *1,7* | *7,9* | *2.423* |
| **Italia** | **72.848** | **6,6** | **17,5** | **13.517** | **57.913** | **0,9** | **7,0** | **8.278** |

*La variazione rispetto al 2020 è stata effettuata considerando i decessi per febbraio a 28 giorni

Nei mesi di gennaio e febbraio si assiste ad una progressiva riduzione dell'eccesso di mortalità misurato rispetto alla media dei mesi corrispondenti del periodo 2015-2019, mentre i decessi del primo bimestre del 2021 sono comunque superiori allo stesso periodo del 2020, quest'ultimo come più volte documentato è stato infatti caratterizzato da livelli particolarmente bassi della mortalità totale.

A marzo 2021 si interrompe il calo dei decessi totali che era in atto dal picco della seconda ondata epidemica di novembre 2020, con la curva che inverte la tendenza rispetto al primo bimestre del 2021 (cfr. Figura 4). La causa non può essere ricercata nel fatto che febbraio abbia meno giorni

rispetto a marzo in quanto i decessi medi giornalieri passano da quasi 2 mila a oltre 2 mila 100 e crescono di pari passo con l'aumento dei decessi Covid-19 (Tabella 4).

**Tabella 4 (segue). Decessi per il complesso delle cause e decessi covid-19 per mese e regione. Anni 2021 e variazione percentuale rispetto al dato medio dello stesso mese del periodo 2015-2019 e dell'anno 2020**

| Regione\ripartizione | marzo | | | | aprile | | | |
|---|---|---|---|---|---|---|---|---|
| | decessi 2021 | v% 1519 | v% 2020 | decessi covid | decessi 2021 | v% 1519 | v% 2020 | decessi covid |
| Piemonte | 5.648 | 19,2 | -22,4 | 868 | 6.222 | 48,1 | -16,7 | 632 |
| Valle d'Aosta | 133 | -0,9 | -35,7 | 7 | 160 | 34,2 | -22,0 | 32 |
| Lombardia | 10.786 | 22,9 | -58,0 | 2.460 | 9.686 | 22,6 | -44,0 | 1.900 |
| Pa Bolzano | 447 | 11,2 | -32,9 | 76 | 371 | 3,7 | -34,0 | 23 |
| Pa Trento | 521 | 10,7 | -30,8 | 82 | 474 | 14,5 | -39,2 | 56 |
| Veneto | 4.841 | 8,6 | -11,0 | 691 | 4.469 | 12,6 | -14,0 | 640 |
| Friuli-Venezia Giulia | 1.764 | 30,4 | 15,4 | 389 | 1.451 | 22,0 | 0,5 | 307 |
| Liguria | 1.935 | -1,8 | -36,6 | 233 | 1.982 | 12,6 | -31,1 | 229 |
| Emilia-Romagna | 5.369 | 17,2 | -31,0 | 1.361 | 4.629 | 15,3 | -25,0 | 860 |
| Toscana | 4.502 | 12,6 | -0,9 | 722 | 4.289 | 20,9 | 1,6 | 860 |
| Umbria | 1.105 | 14,8 | 5,8 | 195 | 970 | 13,5 | 11,6 | 94 |
| Marche | 1.984 | 22,5 | -15,1 | 373 | 1.712 | 21,1 | -11,3 | 261 |
| Lazio | 5.518 | 5,2 | 0,9 | 673 | 5.594 | 17,2 | 11,5 | 885 |
| Abruzzo | 1.584 | 15,4 | 0,6 | 398 | 1.399 | 14,0 | -2,9 | 203 |
| Molise | 457 | 26,6 | 20,9 | 106 | 367 | 15,7 | 11,9 | 43 |
| Campania | 5.900 | 17,4 | 14,1 | 1.019 | 5.529 | 23,1 | 19,5 | 756 |
| Puglia | 4.596 | 27,7 | 12,6 | 860 | 4.506 | 40,0 | 19,1 | 1.084 |
| Basilicata | 628 | 4,9 | 8,8 | 63 | 586 | 10,0 | -0,8 | 62 |
| Calabria | 2.054 | 7,7 | 3,0 | 136 | 1.946 | 14,9 | 5,8 | 183 |
| Sicilia | 4.932 | -4,2 | -5,3 | 365 | 4.851 | 9,7 | 4,8 | 522 |
| Sardegna | 1.506 | -2,3 | -13,1 | 58 | 1.436 | 3,7 | -7,5 | 121 |
| *Nord* | *31.444* | *16,9* | *-40,0* | *6.167* | *29.444* | *23,1* | *-29,9* | *4.679* |
| *Centro* | *13.109* | *10,8* | *-2,1* | *1.963* | *12.565* | *18,7* | *4,4* | *2.100* |
| *Mezzogiorno* | *21.657* | *10,8* | *4,5* | *3.005* | *20.620* | *19,3* | *9,8* | *2.974* |
| **Italia** | **66.210** | **13,6** | **-23,5** | **11.135** | **62.629** | **20,9** | **-14,0** | **9.753** |

*Fonte: Istat. Base dati integrata mortalità giornaliera comunale.*

Come è noto, marzo 2020 è stato il primo mese in cui si sono visti gli effetti della pandemia sulla mortalità totale e nei mesi di marzo e aprile 2020 si è registrato il primo picco dei decessi. Considerando marzo e aprile 2021 si evidenzia a livello nazionale un nuovo incremento dell'eccesso di mortalità rispetto alla media degli stessi mesi del periodo 2015-2019, ma un netto calo rispetto al 2020. Questo andamento presenta forte specificità territoriali; spetta al Nord l'eccesso di decessi più consistente rispetto al 2015-2019, mentre il confronto con il 2020, essendo stato il Nord il più colpito dall'eccesso di mortalità della prima fase dell'epidemia, evidenzi un calo importante (-40% e -30%, in Lombardia -58% e -44%). Di contro il Centro ma soprattutto il Mezzogiorno hanno un eccesso di decessi rispetto al 2020 (l'incremento maggiore si osserva in Molise a marzo +30, e in Campania ad aprile +19.5).

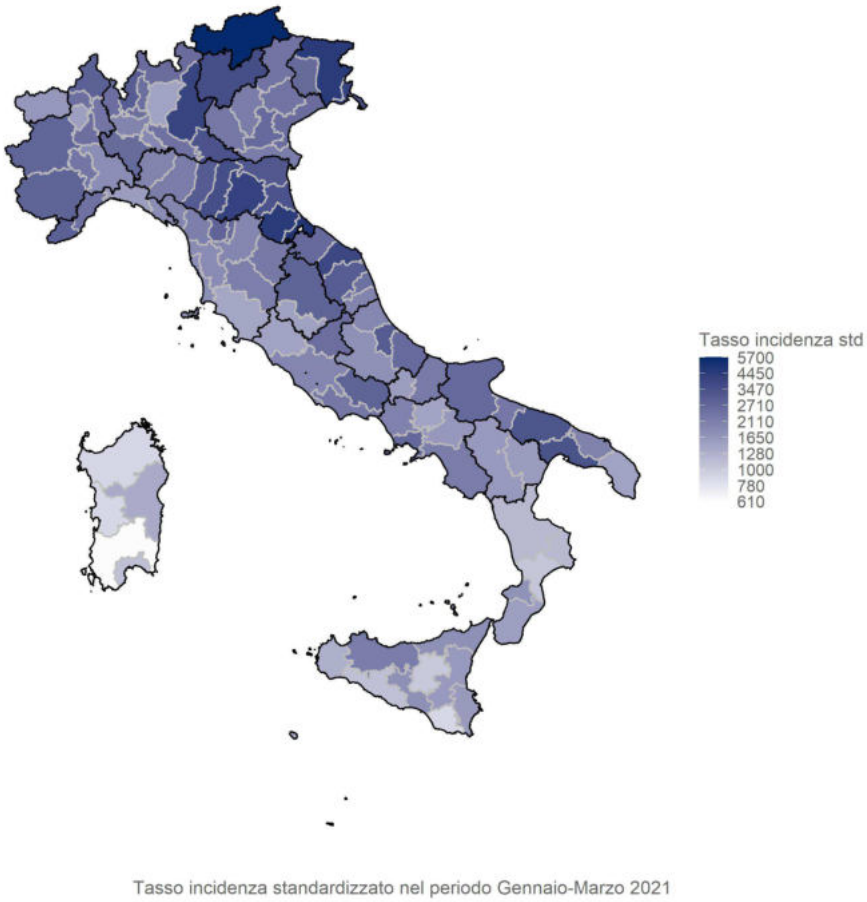
Considerando per analogia ai precedenti Rapporti il dettaglio provinciale, le Figure 6-8 consentono di apprezzare la distribuzione territoriale dei tassi di incidenza dei casi confermati di Covid-19 (per 100.000 abitanti) e l'eccesso di mortalità totale, nel periodo gennaio-marzo 2021, sia rispetto al quinquennio precedente che al 2020.

La rappresentazione delle mappe di diffusione a livello Provinciale mostra come in questi primi 3 mesi dell'anno 2021 le Province con il maggior tasso di incidenza dei nuovi casi di Covid-19 siano quelle del versante Nord-orientale: Bologna, Gorizia, Forlì-Cesena, Udine, Rimini, Bolzano/Bozen. Molto bassa appare l'incidenza in alcune province della Sardegna (Sud Sardegna, Oristano, Sassari), in alcune Province della Calabria (Catanzaro, Cosenza, Crotone) e della Sicilia (Ragusa, Enna Agrigento).

Osservando la distribuzione delle variazioni percentuali dei decessi rispetto ai due periodi di riferimento (gennaio-febbraio 2015-2019 e gennaio-febbraio 2020) si osservano valori alti nella Provincia di Udine (variazione del 42,7% e del 45,3% rispettivamente), Forlì-Cesena (29,8% e 25,9%).

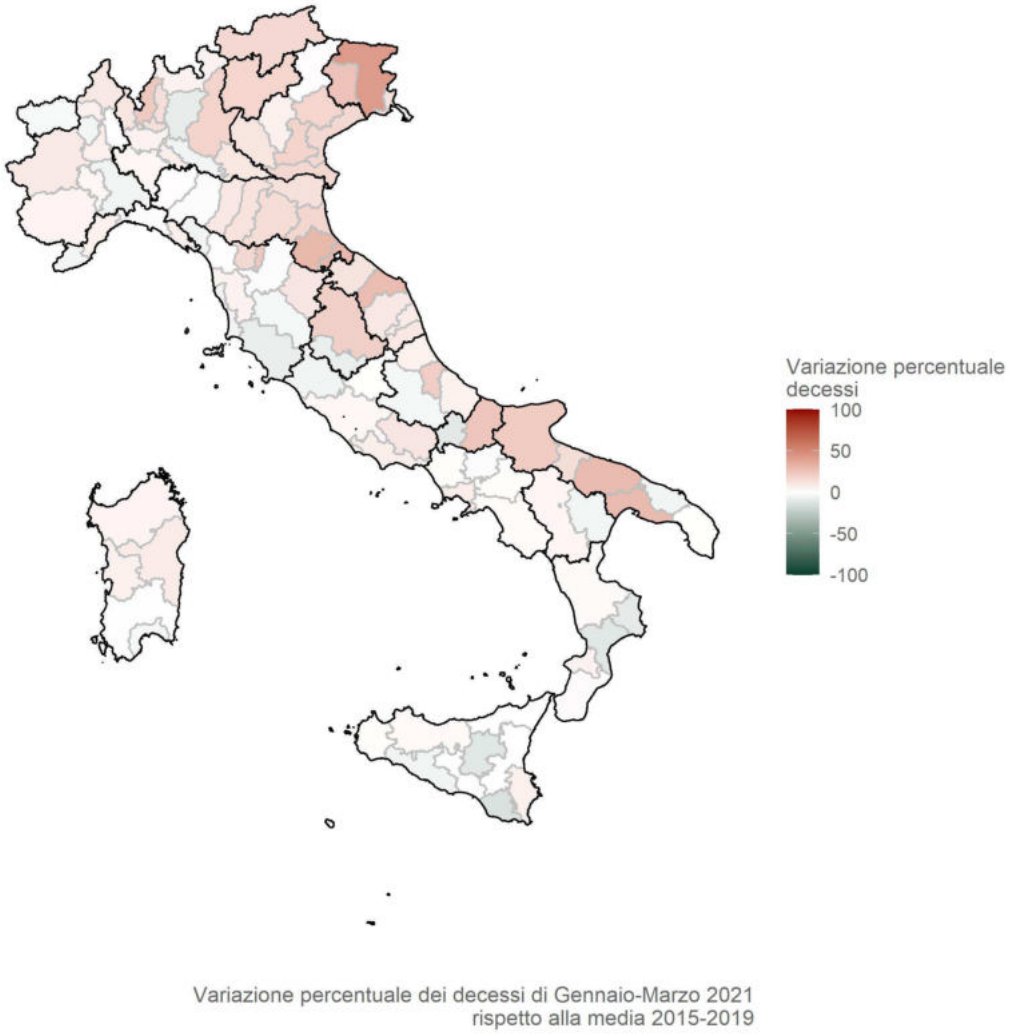
Riportano delle alte variazioni percentuali con segno negativo rispetto al 2020 proprio le città che erano state maggiormente colpite durante la prima ondata del 2020 (Bergamo -84,0%; Cremona -78,1%; Lodi – 77,7%; Piacenza -76,8%).

**Figura 6. Tassi di incidenza cumulata** *(per 100.000 abitanti)* **di casi Covid-19 diagnosticati in Italia, periodo gennaio-marzo 2021**



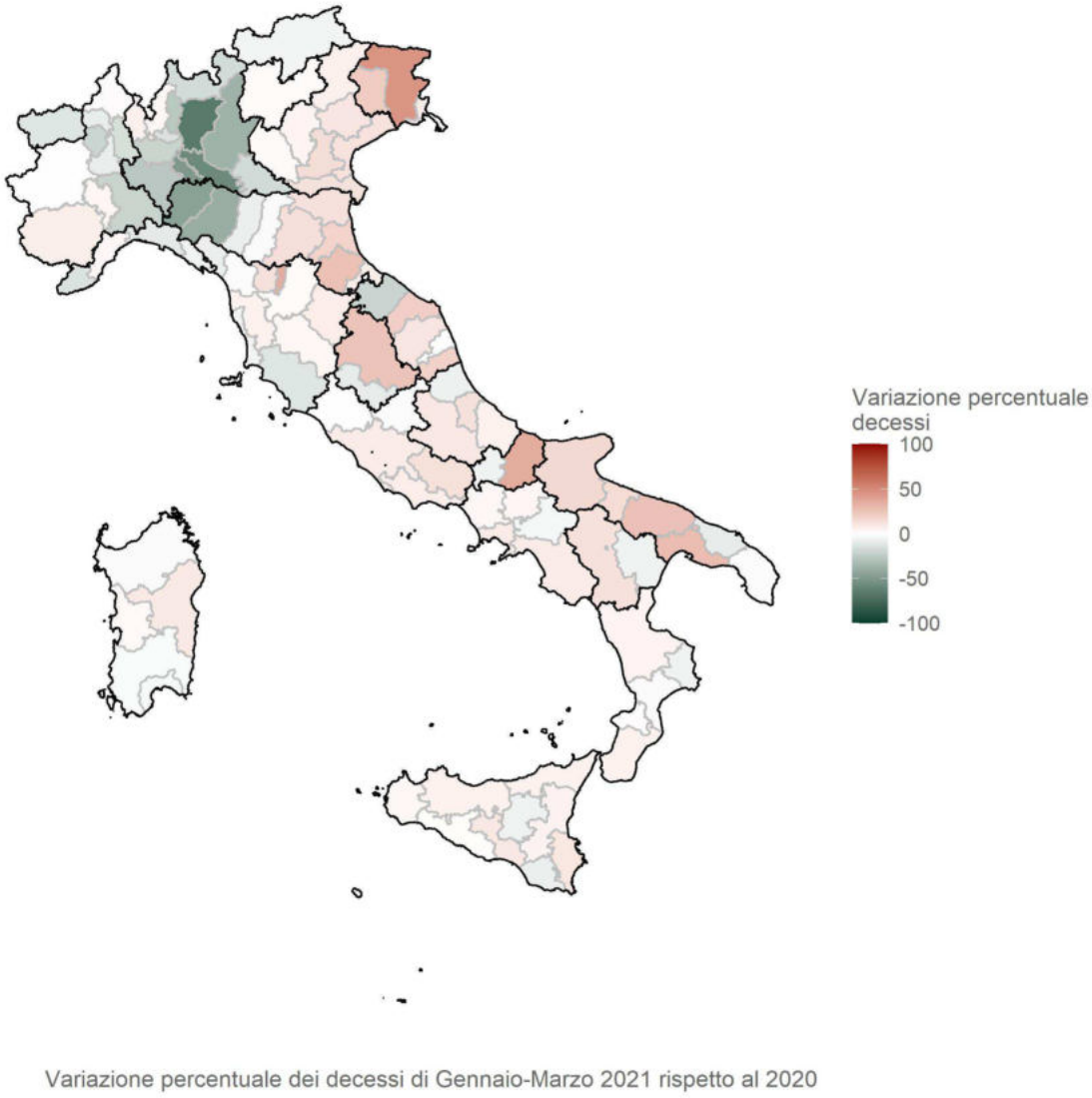

*Fonte: Iss sorveglianza integrata Covid-19.*

**Figura 7. Eccesso di mortalità totale nel periodo gennaio-marzo 2021 rispetto alla media dei decessi 2015-2019** *(valori percentuali)*




*Fonte: Istat. Base dati integrata mortalità giornaliera comunale.*

**Figura 8. Eccesso di mortalità totale nel periodo gennaio-marzo 2021 rispetto alla media dei decessi 2020** *(valori percentuali)*




*Fonte: Istat. Base dati integrata mortalità giornaliera comunale.*

Quanto al dettaglio per età si conferma, anche nei primi mesi del 2021, il drammatico impatto dell'epidemia Covid-19 sulla popolazione di età più avanzata (Tabella 5). Mentre, come era già avvenuto nel 2020, i decessi di persone con età inferiori a 50 anni sono sempre inferiori alla media dei mesi corrispondenti del periodo 2015-2019; nel mese di gennaio l'eccesso di decessi del 2021 rispetto al 2015-2019 è dovuto per i tre quarti all'incremento di morti con 80 anni o più.

Da marzo 2021, si cominciano ad osservare gli effetti positivi della campagna vaccinale che ha prioritariamente puntato a proteggere la popolazione più fragile. Se da un lato l'eccesso di decessi di marzo 2021, rispetto al dato medio dello stesso mese del periodo 2015-2019, continua ad essere attribuibile per quasi il 90% ai morti di 65 anni e più, d'altro canto rispetto al picco di decessi di marzo 2020 il calo più importante si deve soprattutto alla classe 80+; il crollo dei decessi di questa classe di età rispetto a marzo 2021 spiega il 70% della diminuzione dei decessi totali osservata tra marzo 2021 e marzo 2020 ; un altro 26% è dovuto alla minore mortalità della classe 65-79 anni.

**Tabella 5. Variazione dei decessi per il complesso delle cause, per genere, classe di età e ripartizione. Primo trimestre del 2021 vs 2015-2019. Valori assoluti e variazioni percentuali.**

| Classi di età | media 2015/2019 | 2020 | 2021 | % decessi 2021 | differenza 2021, 2015-2019 | % contributo della differenza | differenza 2021, 2020 | % contributo della differenza |
|---|---|---|---|---|---|---|---|---|
| | | | | gennaio | | | | |
| 0-49 | 1.804 | 1.592 | 1.588 | 2,2 | -216 | -4,8 | -4 | 0,0 |
| 50-64 | 5.061 | 4.774 | 5.435 | 7,5 | 374 | 8,3 | 661 | 6,1 |
| 65-79 | 16.818 | 14.849 | 17.764 | 24,4 | 946 | 20,9 | 2.915 | 26,9 |
| 80+ | 44.642 | 40.804 | 48.061 | 66,0 | 3.419 | 75,6 | 7.257 | 67,0 |
| Totale | 68.324 | 62.019 | 72.848 | | 4.524 | | 10.829 | |
| | | | | febbraio* | | | | |
| 0-49 | 1.558 | 1.452 | 1.293 | 2,2 | -265 | -53,4 | -109 | -2,9 |
| 50-64 | 4.392 | 4.311 | 4.653 | 8,0 | 261 | 52,5 | 491 | 13,0 |
| 65-79 | 14.324 | 13.574 | 14.504 | 25,0 | 180 | 36,2 | 1.398 | 37,0 |
| 80+ | 37.142 | 36.733 | 37.463 | 64,7 | 321 | 64,7 | 1.997 | 52,9 |
| Totale | 57.416 | 56.070 | 57.913 | | 497 | | 3.776 | |
| | | | | marzo | | | | |
| 0-49 | 1.650 | 1.646 | 1.472 | 2,2 | -178 | -2,2 | -174 | 0,9 |
| 50-64 | 4.484 | 5.958 | 5.319 | 8,0 | 835 | 10,5 | -639 | 3,1 |
| 65-79 | 14.742 | 22.695 | 17.427 | 26,3 | 2.685 | 33,8 | -5.268 | 26,0 |
| 80+ | 37.391 | 56.202 | 41.992 | 63,4 | 4.601 | 57,9 | -14.210 | 70,0 |
| Totale | 58.267 | 86.501 | 66.210 | | 7.943 | | -20.291 | |

**La variazione rispetto al 2020 è stata effettuata considerando i decessi per febbraio a 28 giorni.*
*Fonte: Istat. Base dati integrata mortalità giornaliera comunale.*

## Il contributo dei decessi Covid-19 alla mortalità totale nel periodo gennaio aprile 2021 in Italia

Dall'inizio dell'anno 2021 e fino al 30 aprile il contributo dei decessi Covid-19 alla mortalità per il complesso delle cause è stato, a livello nazionale, del 16%, con differenze fra le varie ripartizioni geografiche che vanno dal 19% del Nord, al14% del Centro e al 16% del Mezzogiorno.

Rispetto all'intero anno 2020 l'impatto della mortalità per Covid-19 sulla mortalità generale è aumentato soprattutto nelle regioni del Centro e del Mezzogiorno: questo fenomeno è ascrivibile a vari fattori. In primis è aumentata la capacità di rilevazione dei decessi Covid-19 da parte delle Regioni e conseguentemente del Sistema di sorveglianza, inoltre lo scenario di diffusione del virus è notevolmente mutato interessando le regioni del Centro e del Mezzogiorno le quali avevano registrato una scarsa presenza del virus nella prima parte del 2020.

Questo dato è particolarmente evidente se si mettono a confronto i mesi di marzo e aprile 2021 con quelli del 2020: soprattutto ad aprile il contributo dei decessi Covid-19 alla mortalità sembra omogeneo tra le varie ripartizioni mentre nei rispettivi mesi del 2020 il Nord contribuiva in maniera prevalente al valore medio nazionale.

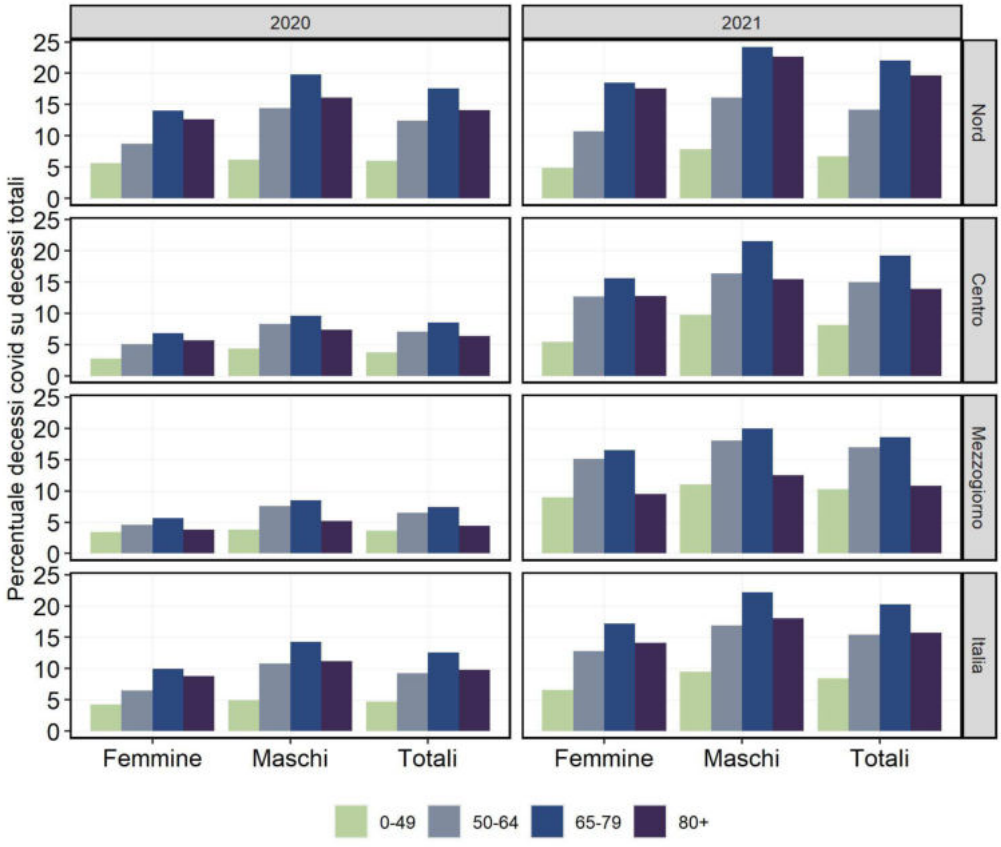
**Tabella 6. Decessi Covid-19 per cento decessi totali per periodo e ripartizione geografica, periodo gennaio -aprile 2021 e anno 2020 e marzo e aprile 2020**

| Ripartizione | Anno 2020 | Gennaio 2021 | Febbraio 2021 | Marzo 2020 | Marzo 2021 | Aprile 2020 | Aprile 2021 |
|---|---|---|---|---|---|---|---|
| Nord | 14,5 | 22,7 | 15,5 | 25,5 | 19,6 | 29,0 | 15,9 |
| Centro | 6,8 | 15,9 | 14,5 | 8,5 | 15,0 | 11,5 | 16,7 |
| Mezzogiorno | 5,2 | 13,9 | 12,5 | 3,7 | 13,9 | 5,8 | 14,4 |
| Italia | 10,2 | 18,6 | 14,3 | 17,7 | 16,8 | 20,2 | 15,6 |

*Fonte: Istat. Base dati integrata mortalità giornaliera comunale, Iss registro sorveglianza Covid-19.*

Per il 2021 la stima del contributo dei decessi Covid-19 per fasce di età è possibile solo per il periodo gennaio-marzo 2021, l'analisi dei contributi evidenzia come il contributo dei decessi Covid-19 alla spiegazione della mortalità generale sia più marcato nel genere maschile, questo dato è atteso infatti è ormai noto che le conseguenze di questo virus siano state più marcate negli uomini.
Il confronto con l'intero anno 2020 mostra in tutte le età un maggior contributo dei decessi Covid-19 alla mortalità generale, ma non un conseguente aumento dell'eccesso di mortalità rispetto all'anno 2020: una possibile spiegazione del fenomeno potrebbe essere dovuta al fatto che è aumentata la capacità di rilevazione dei decessi per Covid-19 ed inoltre che la mortalità per Covid-19 potrebbe aver sostituito in alcune fasce di età la mortalità per altre cause di decesso.

**Figura 9. Contributo percentuale per classi di età dei decessi Covid-19 alla mortalità totale, periodo gennaio-marzo 2021 e anno 2020**



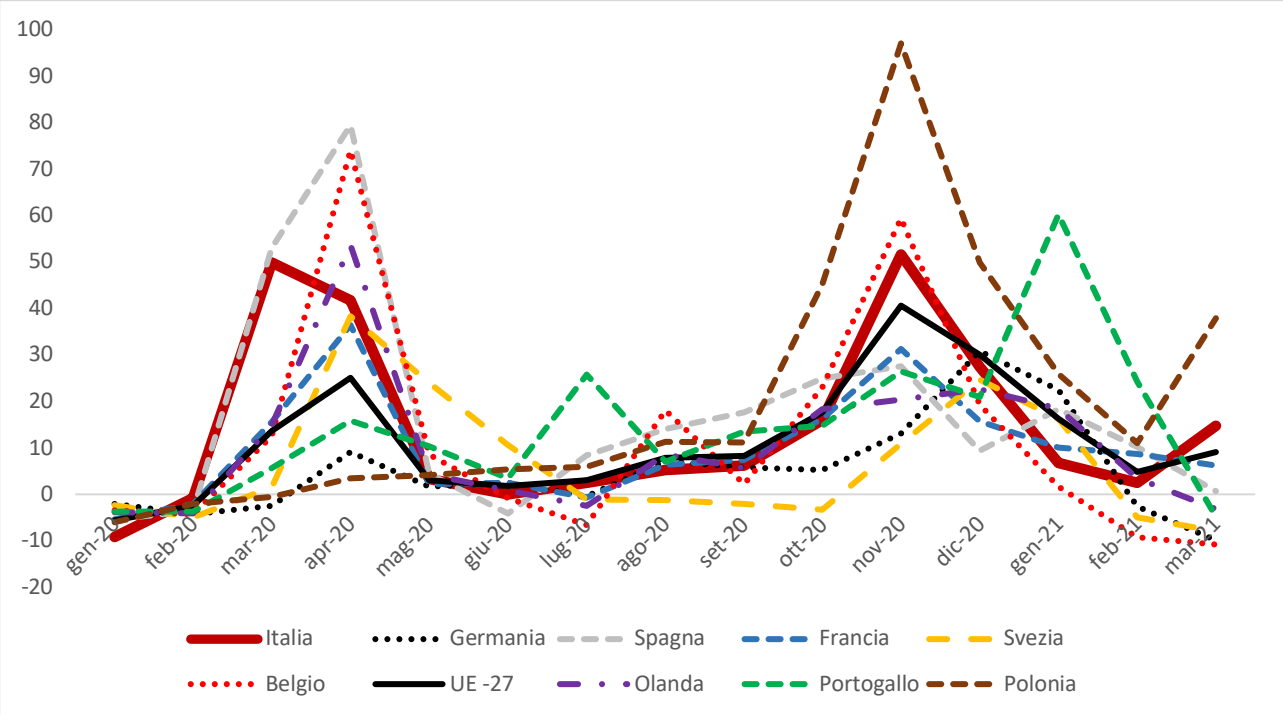

*Fonte: Istat. Base dati integrata mortalità giornaliera comunale, Iss registro sorveglianza Covid-19.*

## L'impatto dell'epidemia Covid- 19 sulla mortalità totale in Europa

Con il diffondersi della pandemia Covid-19 Eurostat ha avviato presso i Paesi europei una nuova raccolta di informazioni sui decessi per monitorare tempestivamente l'andamento settimanale dell'eccesso di mortalità totale. L'approccio è simile a quello adottato nel presente report, la differenza risiede nella scelta del periodo di riferimento rispetto al quale considerare la variazione dei decessi per il complesso delle cause del 2020: il quinquennio 2015-2019 nel presente report, il quadriennio 2016-2019 nella base dati di mortalità totale settimanale resa disponibile da Eurostat, aggiornata al 9 giugno 2021[8].

I dati Eurostat consentono di confrontare l'impatto dell'epidemia di Covid-19 sulla mortalità nei diversi Paesi. Nella figura 10 si considera l'andamento dell'eccesso di decessi osservato in Italia con quello di altri paesi più la media UE (il cui dato è stato ricalcolato aggiungendo le nuove stime italiane presentate in questo lavoro).

**Figura 10. Decessi mensili nel periodo Anno 2020 e gennaio-marzo 2021 per l'Italia ed alcuni Stati Europei - incremento percentuale rispetto alla media 2016-2019**




*Fonte: Eurostat. Base dati mortalità settimanale (aggiornata al 09/06/2021), il dato di marzo 2021 dell'UE è stato calcolato come media ponderata dei decessi dei paesi che hanno reso disponibile il loro dato e con i pesi relativi alla % delle popolazioni dei paesi EU27.*

Per tutti i Paesi considerati, e per la media UE, i decessi dei mesi di gennaio e febbraio 2020 risultavano inferiori alla media dei quattro anni precedenti. L'Italia e la Spagna hanno condiviso per prime il drammatico incremento dei decessi già a partire dal mese di marzo 2020, ma mentre in Italia la tendenza all'aumento si arresta dal mese di aprile 2020, per la Spagna l'incremento procede ancora per alcune settimane fino a far registrare ad aprile 2020 l'aumento più consistente della prima ondata epidemica (80% dei decessi in più). Nello stesso mese l'incremento dei decessi ancora sostenuto nel nostro Paese (+42% rispetto alla media dei decessi di aprile del periodo 2016-2019) è superato da quello del Belgio (+74%) e dell'Olanda (+56,3%), mentre la Francia e l'Olanda si collocano subito a ridosso (+38% circa). La Germania presenta invece durante la prima ondata un aumento dei decessi inferiore al 10%.

[8] https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Excess_mortality_-_statistics#Excess_mortality_in_Europe_between_January_and_November_2020

A partire da luglio 2020 i decessi iniziano di nuovo ad aumentare, soprattutto in Spagna. Negli altri paesi, inclusa l'Italia, il ritmo di incremento è generalmente più lento fino al mese di ottobre quando si verifica una nuova fase di rapida crescita dei decessi rispetto alla media del 2016-2019. A novembre 2020 molti Paesi, tra cui l'Italia, sperimentano un nuovo picco dei decessi. L'incremento maggiore si registra in Polonia (+97%) e in Belgio (+59%) e in Italia (+52%). In Germania, dove l'incremento autunnale dei decessi era apparso posticipato di un mese rispetto agli altri Paesi, l'eccesso di mortalità è continuato a crescere fino a dicembre, al contrario degli altri paesi in cui è stata osservata una riduzione dell'eccesso di mortalità nell'ultimo mese dell'anno. A gennaio 2021 l'incremento dei decessi in Germania è il terzo più alto (+22%) dopo il Portogallo (+25%) e la Polonia (+60%).

Questi confronti, seppur importanti, hanno in sé dei forti limiti in quanto non tengono conto della diversa struttura per età delle popolazioni e della completezza dei dati forniti da ciascun paese. Infatti il totale dei decessi mensili potrebbe subire delle variazioni in base agli aggiornamenti fatti mensilmente da ogni Paese.

Come già evidenziato nel precedente rapporto, la correlazione tra la percentuale di popolazione di 80 anni e più sul totale della popolazione e l'entità dell'eccesso di decessi è massima proprio per l'Italia, che presenta la quota più alta di popolazione più esposta a rischio in Europa, e un elevato eccesso di decessi. L'effetto della diversa proporzione di popolazione anziana, tuttavia, non sembra sufficiente a dar conto delle differenze nell'eccesso di mortalità quando si confrontano i dati di paesi, quali ad esempio la Germania, dove a fronte di una proporzione di persone di 80 anni e più leggermente inferiore rispetto all'Italia, si è osservato un incremento dei decessi totali decisamente più contenuto. Nella spiegazione dell'eccesso di mortalità le differenze osservate possono essere dovute, infatti, a molteplici fattori: dalla rapidità di diffusione della prima ondata in alcuni Paesi, alla velocità di diffusione e alle misure di contenimento e mitigazione intraprese.

Resta tuttavia importante anche la struttura per età delle popolazioni, con i Paesi più "anziani" tendenzialmente più penalizzati. E' quanto emerge da uno studio recente pubblicato sulla rivista British Medical Journal[9] che ha valutato l'eccesso di mortalità associato con COVID-19 in 29 paesi a sviluppo avanzato. Lo studio ha confrontato la mortalità osservata nel 2020 con quella attesa in base ai decessi registrati nel quadriennio 2016-2019. Dallo studio è emerso come l'eccesso di mortalità grezzo registrato in Italia nel 2020 sia stato tra i più elevati (circa 170 X 100.000 tra gli uomini e 130 X 100.000 tra le donne), inferiore solamente a quello osservato in Lituania, Polonia, Spagna e Ungheria. Nel momento in cui però l'eccesso di mortalità è stato calcolato standardizzando per età, usando la popolazione Europea standard del 2103 come riferimento, è stato evidenziato come l'eccesso di mortalità registrato in Italia nel 2020 sia stato inferiore, in particolar modo tra le donne. Tenendo quindi conto della diversa struttura per età della popolazione italiana, l'eccesso di mortalità nel nostro Paese è risultato inferiore a quello registrato in altri paesi Europei, tra i quali Spagna, Belgio e Regno Unito, e negli Stati Uniti.

[9] the bmj | BMJ 2021;373:n1137 | doi: 10.1136/bmj.n1137 1 RESEARCH Excess deaths associated with covid-19 pandemic in 2020: age and sex disaggregated time series analysis in 29 high income countries https://www.bmj.com/content/bmj/373/bmj.n1137.full.pdf

# Nota metodologica

## La nuova base dati di mortalità giornaliera della popolazione residente

L'Istat elabora e diffonde informazioni utili alla comprensione dell'impatto dell'emergenza sanitaria da COVID-19 sulla mortalità totale della popolazione residente. Le tempistiche richieste per il completamento dell'acquisizione e per il trattamento dei dati sui decessi richiedono usualmente un periodo di circa 10 mesi per assicurare il consolidamento della base dati dei decessi della popolazione residente; il piano di diffusione prevede che ad ottobre dell'anno t vengono diffusi i dati validati dell'anno t-1.

In virtù della situazione emergenziale, l'Istat si è impegnato a garantire una diffusione anticipatoria di dati provvisori con una tempistica molto serrata, circa 45 giorni di ritardo data per la fase di acquisizione e circa 15 giorni per il trattamento finalizzato alla validazione e diffusione.

La diffusione anticipatoria di dati tempestivi dei decessi giornalieri comunali - per il complesso delle cause, per genere ed età - è possibile grazie alla collaborazione con il Ministero dell'Interno per l'acquisizione dei dati ANPR (Anagrafe Nazionale della Popolazione Residente) e con il Ministero dell'economia e delle finanze per l'acquisizione del flusso dei deceduti risultanti dall'Anagrafe Tributaria.

Con la diffusione odierna vengono aggiornati, per i mesi di gennaio e febbraio 2021, i decessi della base dati giornaliera per tutti i comuni italiani (7.903 comuni al 31 marzo 2021). I dati per l'anno 2020 sono da considerarsi consolidati ma ancora provvisori; è possibile che subiscano un ultimo aggiornamento in occasione della diffusione del bilancio annuale definitivo riferito all'anno 2020 prevista per dicembre 2021. I dati del 2021 vengono al contrario rivisti ad ogni aggiornamento.

La serie storica disponibile parte dal 2011, ma il periodo 2015-2019 è quello che viene assunto come riferimento per la valutazione dell'eccesso di mortalità per gli anni 2020 e 2021. Sebbene sia senz'altro possibile assumere come riferimento delle stime del numero "atteso" di decessi dell'anno 2020 e 2021 altri valori derivati da opportune metodologie statistiche, la media dei decessi del quinquennio 2015-2019 resta un buon riferimento per una prima valutazione di massima dell'eccesso di mortalità totale indotto dall'epidemia di Covid-19. Un approccio analogo è riscontrabile in numerosi lavori scientifici sia nazionali che internazionali.

Il numero di decessi dipende dall'ammontare degli esposti a rischio (la popolazione) ma in maggior ragione dall'intensità della mortalità che può essere misurata attraverso i tassi di mortalità specifici per età. Queste misure sono comparabili nel tempo e nello spazio e il loro andamento nel nostro Paese evidenzia che ogni anno che passa i tassi di mortalità specifici diminuiscono. Questa diminuzione è dovuta alla riduzione dell'intensità della mortalità (che ha come conseguenza l'aumento della speranza di vita e l'invecchiamento della popolazione). La diminuzione dell'intensità della mortalità va a compensare in parte il numero di decessi in più che ci si potrebbe aspettare "a parità di intensità della mortalità" avendo una popolazione esposta al rischio più numerosa rispetto a quella dell'anno precedente. In altri termini non è ragionevole attendersi necessariamente più decessi da una popolazione che invecchia, o comunque non è corretto attendersi un aumento dei decessi proporzionale alla crescita degli esposti al rischio in un contesto di mortalità in diminuzione. Possiamo tuttavia affermare che in una popolazione che invecchia aumentano nelle età avanzate della vita anche gli individui "fragili", non in buona salute, affetti da co-morbosità dovute alla simultanea presenza di patologie croniche gravi. Questi individui sono più esposti alle variazioni congiunturali climatiche ed epidemiologiche che generano un eccesso di mortalità, come inverni più freddi oppure estati più calde, o come stagioni influenzali più letali o una pandemia.

Per gli anni 2011-2019, è possibile che siano presenti differenze con i dati mensili dei decessi comunali già diffusi con le statistiche relative al Bilancio annuale della popolazione residente. Per esigenze di comparabilità nel tempo dei dati provvisori relativi ai decessi del 2020 si è adottata la stessa metodologia anche per elaborare il totale giornaliero dei decessi per il periodo 2011-2019. Sulla base di tale metodologia, si assume come riferimento temporale per la costruzione della base dati giornaliera dei decessi, la data di evento e non la data di cancellazione anagrafica (usata nel bilancio demografico), e si ricorre all'integrazione dei dati anagrafici con quelli provenienti dall'Anagrafe Tributaria per il recupero di eventi sfuggiti alla rilevazione di fonte anagrafica perché registrati dopo la chiusura dell'acquisizione dei dati dai comuni da parte di Istat. I dati sui decessi mensili 2011-2019 diffusi attraverso questo sistema integrato, dunque, possono essere correttamente utilizzati come termine di confronto con il dato provvisorio del 2020. In nessun caso sono da considerarsi come rettifiche dei dati del bilancio demografico già diffusi da Istat per gli stessi anni.

Ad ogni successivo aggiornamento dei dati riferiti al 2021 la base dati viene rivista per tener conto del consolidamento progressivo dei flussi, questi aggiornamenti hanno un impatto soprattutto sul mese più recente. A livello locale si possono trovare situazioni molto eterogenee e in alcuni casi i dati dei decessi dei mesi più recenti possono risultare affetti da una sotto-copertura di entità anche ben superiore al livello medio nazionale, a causa del ritardo nella registrazione dei decessi in anagrafe.

L'Istat, utilizzando queste informazioni, ha studiato delle soluzioni organizzative e metodologiche che consentano di produrre stime ancora più tempestive almeno a livello regionale (meno di un mese di ritardo data). In occasione dell'ultima diffusione dei dati del 29 aprile scorso è stata rilasciata a livello regionale una stima dei decessi del mese di marzo 2021, per il quale ancora non si disponeva di una base dati sufficientemente consolidata. Tale stima è stata ottenuta applicando, ai dati disponibili a 15 giorni di ritardo, dei coefficienti di correzione della sottocopertura elaborati sulla base dell'entità media nei mesi giugno-novembre 2020 della sottocopertura dei decessi di ciascun comune a 15 giorni di ritardo data.

Con quest'ultimo aggiornamento è possibile fare una valutazione della bontà delle stime elaborate per il mese di marzo 2021. La stima a livello nazionale è uguale rispetto al dato provvisorio. A livello regionale solo il Piemonte, Lombardia e Lazio presentano un dato osservato esterno all'intervallo di confidenza al 90% (Tab.1). Ciò può essere spiegato dal fatto che in queste regioni la sottocopertura dei decessi è maggiore e con gli aggiornamenti futuri il dato tenderà ad aumentare in maniera maggiore rispetto alla media nazionale.

**Tab. 1 – Base dati a 45 giorni di ritardo data (dato stimato diffuso il 29 aprile 2021) e stima dei decessi per il mese di marzo 2021, per regione, ripartizione e intervallo di confidenza al 90 %**

| Regioni | Base dati a 15 giorni di ritardo data | Stima | Intervallo di confidenza al 90% | |
|---|---|---|---|---|
| | | | Estremo inferiore | Estremo superiore |
| Piemonte | 5.648 | 6.484 | 6.345 | 7.313 |
| Valle d'Aosta | 133 | 133 | 131 | 174 |
| Lombardia | 10.786 | 10.909 | 10.790 | 11.997 |
| Pa Bolzano | 447 | 448 | 446 | 508 |
| Pa Trento | 521 | 523 | 519 | 628 |
| Veneto | 4.841 | 4.799 | 4.767 | 5.144 |
| Friuli-Venezia Giulia | 1.764 | 1.725 | 1.712 | 1.885 |
| Liguria | 1.935 | 1.905 | 1.887 | 2.039 |
| Emilia-Romagna | 5.369 | 5.339 | 5.311 | 5.554 |
| Toscana | 4.502 | 4.500 | 4.476 | 4.678 |
| Umbria | 1.105 | 1.101 | 1.090 | 1.169 |
| Marche | 1.984 | 1.993 | 1.972 | 2.159 |
| Lazio | 5.518 | 5.000 | 4.831 | 5.486 |
| Abruzzo | 1.584 | 1.592 | 1.539 | 1.853 |
| Molise | 457 | 458 | 448 | 556 |
| Campania | 5.900 | 5.820 | 5.728 | 6.241 |
| Puglia | 4.596 | 4.534 | 4.478 | 4.743 |
| Basilicata | 628 | 613 | 606 | 698 |
| Calabria | 2.054 | 2.008 | 1.983 | 2.286 |
| Sicilia | 4.932 | 4.868 | 4.792 | 5.160 |
| Sardegna | 1.506 | 1.456 | 1.435 | 1.697 |
| *Nord* | *31.444* | *32.265* | *31.908* | *35.242* |
| *Centro* | *13.109* | *12.594* | *12.369* | *13.492* |
| *Sud* | *21.657* | *21.349* | *21.009* | *23.234* |
| **ITALIA** | **66.210** | **66.208** | **65.286** | **71.968** |

*Fonte: Istat. Base dati integrata mortalità giornaliera comunale.*

## I dati sui casi e sui decessi del Sistema di sorveglianza Integrato Covid-19

Con l'ordinanza del n. 640 del 27 febbraio 2020, l'Istituto Superiore di Sanità (ISS), dal 28 febbraio, coordina un Sistema di sorveglianza che integra a livello individuale i dati microbiologici ed epidemiologici forniti dalle Regioni e Provincie Autonome (PA) e dal Laboratorio nazionale di riferimento per SARS-CoV-2 dell'ISS. I dati vengono raccolti attraverso una piattaforma web dedicata e riguardano tutti i casi di COVID-19 diagnosticati dai laboratori di riferimento regionali. I dati vengono aggiornati giornalmente da ciascuna Regione anche se alcune informazioni possono richiedere qualche giorno per il loro inserimento. Per questo motivo, potrebbe non esserci una completa concordanza con quanto riportato attraverso il flusso informativo della Protezione Civile e del Ministero della Salute che riportano dati aggregati. La sorveglianza raccoglie dati individuali dei soggetti positivi al Covid-19 e in particolare le informazioni anagrafiche, i dati sul domicilio e sulla residenza, alcune informazioni di laboratorio, informazioni sul ricovero e sullo stato clinico (indicatore sintetico di gravità della sintomatologia), la presenza di alcuni fattori di rischio (patologie croniche di base), e l'esito finale (guarito o deceduto).

Per descrivere l'andamento e le caratteristiche dell'epidemia da Covid-19, è stata predisposta una dashboard online sia in lingua italiana che in inglese che fornisce un aggiornamento dell'epidemia in Italia sia negli ultimi 30 giorni che dall'inizio dell'epidemia. La dashboard è aggiornata quotidianamente ed è disponibile al seguente indirizzo: https://www.epicentro.iss.it/coronavirus/sars-cov-2-dashboard.

# GLOSSARIO

**Anagrafe della popolazione:** il sistema continuo di registrazione della popolazione residente. Viene continuamente aggiornata tramite iscrizioni per nascita da genitori residenti nel Comune, cancellazioni per morte di residenti e iscrizioni/cancellazioni per trasferimento di residenza da/per altro Comune o da/per l'Estero.

**ANPR:** Anagrafe Nazionale della Popolazione Residente (ANPR). È la banca dati nazionale nella quale confluiscono progressivamente tutte le anagrafi comunali.
È stata istituita presso il Ministero dell'Interno ai sensi dell'articolo 62 del Dlgs n. 82/2005 (Codice dell'Amministrazione Digitale).

**Caso positivo Covid-19:** per Covid-19 (sintesi dei termini CO-rona VI-rus D-isease e dell'anno d'identificazione, 2019) l'Organizzazione Mondiale della Sanità (OMS) intende la malattia respiratoria causata dal nuovo coronavirus SARS-Cov-2. La definizione di caso confermato positivo Covid-19 secondo la Sorveglianza Integrata Covid-19 è basata su una definizione di caso definita attraverso circolari ministeriali tenendo conto delle evidenze scientifiche e delle indicazioni degli organismi internazionali quali OMS e ECDC. L'attuale definizione è di tipo microbiologico: risultato positivo con test di conferma effettuato dal/i laboratorio/i di riferimento Regionale/i effettuato su tampone naso-faringeo. (https://www.fnopi.it/wp-content/uploads/2020/03/Circolare_9_marzo_2020.pdf)

**Causa di morte:** si intende la causa "iniziale" di morte, ovvero la condizione morbosa direttamente responsabile del decesso. È definita e individuata tra tutte le malattie certificate dal medico sulla scheda di morte, in base a stringenti regole dettate dall'Organizzazione Mondiale della Sanità (riportate nella Classificazione Internazionale delle Malattie Icd-10) ed è l'indicatore più utilizzato e consolidato per le statistiche ufficiali e i confronti a livello nazionale e internazionale.

**Classificazione internazionale delle malattie (Icd):** International Classification of Diseases and Related Health Problems, è il sistema di classificazione delle malattie, stilato dall'Organizzazione Mondiale della Sanità. Con questo standard internazionale vengono classificate le informazioni sanitarie della rilevazione Istat sui decessi e le cause di morte. (https://icd.who.int/browse10/2019/en#/)

**Co-morbidità:** si intende la pre-esistenza di condizioni croniche al momento della diagnosi; queste includono: patologie cardiovascolari, patologie respiratorie, diabete, deficit immunitari, patologie metaboliche, patologie oncologiche, obesità, patologie renali o altre patologie croniche.

**Copertura (Tasso di) dei comuni:** rapporto tra il numero dei comuni considerati e il numero di tutti i comuni italiani.

**Copertura (Tasso di) della popolazione:** rapporto tra la somma della popolazione residente nei comuni considerati e la popolazione residente totale.

**Decesso Covid-19:** l'Organizzazione Mondiale della Sanità definisce un decesso da COVID-19 come segue: un decesso COVID-19 è definito per scopi di sorveglianza come una morte risultante da un quadro clinico patologico con un caso probabile o confermato (microbiologicamente) di Covid-19, a meno che ci sia una chiara causa alternativa di morte non riconducibile alla malattia associata a COVID disease (per esempio un trauma).
https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200411-sitrep-82-Covid-19.pdf?sfvrsn=74a5d15_2

**Cancellazione dall'anagrafe per decesso:** la rilevazione sui cancellati dall'anagrafe per decesso raccoglie le principali caratteristiche individuali dei deceduti con le quali successivamente derivare le principali misure di sopravvivenza della popolazione residente. Le informazioni riguardanti le persone decedute sono quelle in possesso dell'Anagrafe del comune.

**Eccesso di mortalità:** differenza tra i decessi totali nel periodo 20/2/2020-31/12/2020 e la media dei decessi totali del quinquennio 2015-2019 nello stesso periodo.

**Età mediana:** età che divide una popolazione in due gruppi numericamente uguali; l'uno avente la popolazione di età inferiore a quella individuata, l'altro superiore.

**Effetto harvesting:** Si tratta dell'aumento della mortalità generale a seguito di fattori ambientali o climatici particolarmente sfavorevoli (ad esempio inquinamento, caldo eccessivo) o a condizioni epidemiologiche (come in caso di epidemie) dovuto ai decessi in prevalenza di persone con condizioni di salute molto compromesse; si verificherebbe in questo caso un'anticipazione di decessi che sarebbero comunque avvenuti nel breve periodo (questo fenomeno è noto col nome di harvesting, cioè "mietitura"), mentre successivamente si dovrebbe assistere a una diminuzione della mortalità.

**Incidenza:** rapporto tra numero di casi di una malattia sulla popolazione a rischio in un certo periodo di tempo. Se il periodo di tempo è uguale per tutta la popolazione l'incidenza viene definita cumulativa.

**Letalità:** rapporto tra il numero di morti e il numero di malati con una determinata malattia, relativamente a una data popolazione e a un dato intervallo.

**Popolazione residente:** è costituita dalle persone, di cittadinanza italiana e straniera, aventi dimora abituale nel territorio nazionale anche se temporaneamente assenti. Ogni persona avente dimora abituale in Italia deve iscriversi, per obbligo di legge, nell'anagrafe del comune nel quale ha stabilito la sua dimora abituale. In seguito ad ogni Censimento della popolazione viene determinata la popolazione legale. A tale popolazione si somma il movimento anagrafico dei periodi successivi e si calcola così la popolazione residente in ciascun comune al 31 di dicembre di ogni anno.

**Tampone positivo:** con tale termine si intende il risultato positivo ad un test diagnostico di riferimento su un saggio di real-time RT-PCR che consiste sostanzialmente in un'amplificazione del genoma. Nel caso del SARS-Cov-2 il prelievo del materiale biologico (campione) viene effettuato attraverso un aspirato rino-faringeo o a un tampone naso-faringeo o oro-faringeo. L'analisi dei tamponi viene effettuata in tutti i laboratori di riferimento regionali e presso i principali ospedali individuati dalle Regioni.

**Tasso standardizzato di mortalità:** aggiustamento del tasso di mortalità che permette di confrontare popolazioni che hanno distribuzione per età tra loro diverse. Il metodo di standardizzazione diretto per età è quello più utilizzato e consiste nel sommare i tassi che sono calcolati per ogni specifico gruppo di età su una popolazione di struttura standard.

**Rapporto dei tassi standardizzati:** è calcolato come rapporto tra due tassi standardizzati (tasso standardizzato dell'anno 2020 e il tasso di riferimento del periodo 2015-2019) esprime l'eccesso di mortalità rispetto al valore di riferimento (RR=1). Gli SRR sono riportati con i corrispondenti intervalli di confidenza al 95% (IC 95%), che esprimono la precisione della stima effettuata.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Cabina di Regia ai sensi del DM Salute 30 aprile 2020

# Monitoraggio Fase 2
# Report settimanale

## Report 56
## Sintesi nazionale

**Monitoraggio Fase 2 (DM Salute 30 aprile 2020)**
**Dati relativi alla settimana 31/5/2021-6/6/2021**
**(aggiornati al 9/6/2021)**

**Aggiornamento 09 giugno 2021 - Periodo di riferimento: 31/5/2021-6/6/2021**

## *Headline della settimana:*

*L'incidenza, sia sull'intero territorio nazionale che in tutte le regioni/PPAA, continua a diminuire ed è in tutte le Regioni/PPAA sotto il 50 per 100.000 abitanti ogni 7 giorni. L'effettuazione di attività di tracciamento sistematico possono consentire una gestione basata sul contenimento ovvero sull'identificazione dei casi e sul tracciamento dei loro contatti.*

*La pressione sui servizi ospedalieri si conferma al di sotto della soglia critica in tutte le Regioni/PA e la stima dell'indice di trasmissibilità Rt medio calcolato sui casi sintomatici è stabilmente al di sotto della soglia epidemica.*

*La circolazione di varianti che possono avere una maggiore trasmissibilità e/o eludere parzialmente la risposta immunitaria, che ha portato ad un inatteso aumento dei casi in paesi europei con alta copertura vaccinale, richiede un capillare tracciamento e sequenziamento dei casi.*

*Il raggiungimento di una elevata copertura vaccinale ed il completamento dei cicli di vaccinazione rappresenta uno strumento indispensabile ai fini della prevenzione di ulteriori recrudescenze di episodi pandemici.*

**Punti chiave:**

- Si riporta una analisi dei dati relativi al periodo 31 maggio – 6 giugno 2021. Per i tempi che intercorrono tra l'esposizione al patogeno e lo sviluppo di sintomi e tra questi e la diagnosi e successiva notifica, verosimilmente molti dei casi notificati in questa settimana hanno contratto l'infezione nella seconda metà di maggio.

- **Continua il calo nell'incidenza settimanale** (26 per 100.000 abitanti (31/05/2021-06/06/2021) vs 36 per 100.000 abitanti (24/05/2021-30/05/2021) dati flusso ISS). L'incidenza scende in tutte le regioni/PPAA ed è sotto il valore di 50 per 100.000 abitanti ogni 7 giorni in tutto il territorio. La campagna vaccinale progredisce velocemente e l'incidenza è a un livello che permetterebbe il contenimento dei nuovi casi.

- Nel periodo 19 maggio – 1 giugno 2021, l'Rt medio calcolato sui casi sintomatici è stato pari a **0,68 (range 0,67– 0,69), stabile rispetto alla settimana precedente, e sotto l'uno anche nel limite superiore.** Per dettagli sulle modalità di calcolo ed interpretazione dell'Rt riportato si rimanda all'approfondimento disponibile sul sito dell'Istituto Superiore di Sanità (https://www.iss.it/primo-piano/-/asset_publisher/o4oGR9qmvUz9/content/id/5477037).

- **Tutte le Regioni/PPAA sono classificate a rischio basso secondo il DM del 30 Aprile 2020 tranne una, Sardegna, a rischio moderato**. Tutte le Regioni/PPAA hanno un Rt medio inferiore a 1 nel limite inferiore del range, e quindi una trasmissibilità compatibile con uno scenario di tipo uno.

- **Nessuna Regione/PPAA supera la soglia critica di occupazione dei posti letto in terapia intensiva o area medica**. Il tasso di occupazione in terapia intensiva è 8%, sotto la soglia critica, con una diminuzione nel numero di persone ricoverate che passa da 1.033 (31/05/2021) a 688 (08/06/2021). Il tasso di occupazione in aree mediche a livello nazionale scende ulteriormente (8%). Il numero di persone ricoverate in queste aree passa da 6.482 (31/05/2021) a 4.685 (08/06/2021).

- Due Regioni, Puglia e Sardegna, riportano una allerta di resilienza, nessuna riporta molteplici allerte.

- **Si osserva una ulteriore diminuzione nel numero di nuovi casi non associati a catene di trasmissione** (4.992 vs 7.424 la settimana precedente). La percentuale dei casi rilevati attraverso l'attività di tracciamento dei contatti è stabile (40,3% vs 40,1% la scorsa settimana). Stabile anche la percentuale dei casi rilevati attraverso la comparsa dei sintomi (38,6 vs 38,6%). Infine, il 21,0% è stato diagnosticato attraverso attività di screening.

# Sommario

# 1. Valutazione del rischio

## Valutazione del rischio - Valutazione di probabilità di diffusione

### Algoritmo di valutazione di probabilità e indicatori rilevanti per fase di riferimento

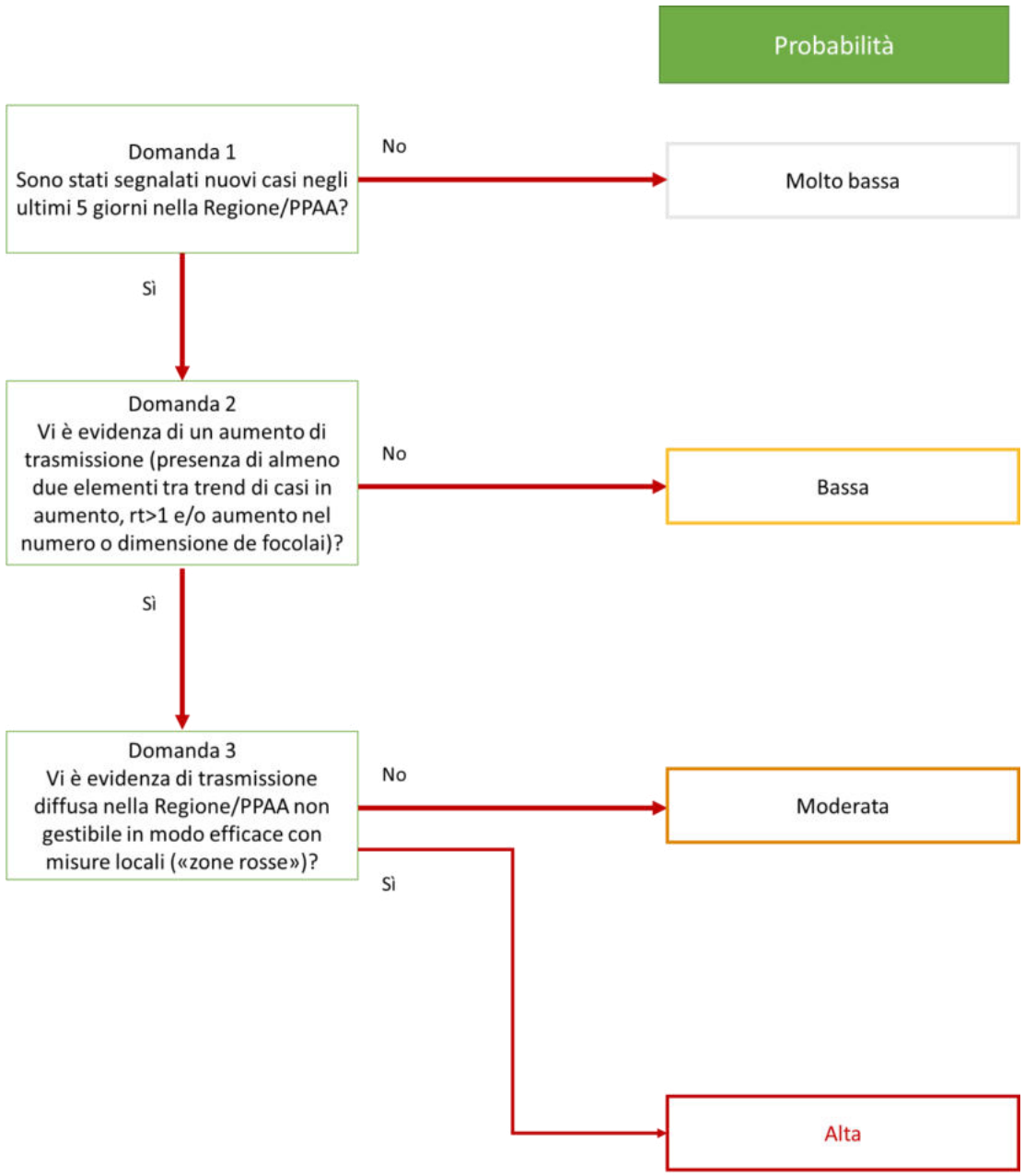


*Tabella 1 - Valutazione della probabilità di diffusione d'accordo all'algoritmo di valutazione del DM Salute 30 aprile 2020, dati al 9 giugno 2021 relativi alla settimana 31/5/2021-6/6/2021*

| Regione.PA | Completezza dei dati sopra-soglia (appendice-tabella 2)? | Domanda 1 | Domanda 2 | | | | Domanda 3 | Valutazione della probabilità |
|---|---|---|---|---|---|---|---|---|
| | | Nuovi casi segnalati negli ultimi 5 giorni? | Trend di casi (Ind3.1) | Trend di casi (Ind3.4) | Rt puntuale sopra uno? | Trend focolai | Dichiarata trasmissione non gestibile in modo efficace con misure locali (zone rosse)?* | |
| **Abruzzo** | Sì | **Sì** | ↓ | ↓ | No | ↓ | No | Bassa |
| **Basilicata** | Sì | **Sì** | ↓ | ↓ | **Sì** | ↓ | No | Bassa |
| **Calabria** | Sì | **Sì** | ↓ | ↓ | No | ↓ | No | Bassa |
| **Campania** | Sì | **Sì** | ↓ | ↓ | No | ↓ | No | Bassa |
| **Emilia-Romagna** | Sì | **Sì** | ↓ | ↓ | No | ↓ | No | Bassa |
| **FVG** | Sì | **Sì** | ↓ | ↓ | No | ↓ | No | Bassa |
| **Lazio** | Sì | **Sì** | ↓ | ↓ | No | ↓ | No | Bassa |
| **Liguria** | Sì | **Sì** | ↓ | ↓ | No | ↓ | No | Bassa |
| **Lombardia** | Sì | **Sì** | ↓ | ↓ | No | ↓ | No | Bassa |
| **Marche** | Sì | **Sì** | ↓ | ↓ | No | ↓ | No | Bassa |
| **Molise** | Sì | **Sì** | ↓ | ↓ | No | 0 | No | Bassa |
| **Piemonte** | Sì | **Sì** | ↓ | ↓ | No | ↓ | No | Bassa |
| **PA Bolzano/Bozen** | Sì | **Sì** | ↓ | ↓ | No | ↓ | No | Bassa |
| **PA Trento** | Sì | **Sì** | ↓ | ↓ | No | ↓ | No | Bassa |
| **Puglia** | Sì | **Sì** | ↓ | ↓ | No | ↓ | No | Bassa |
| **Sardegna** | Sì | **Sì** | ↑ | ↑ | No | ↓ | No | **Moderata** |
| **Sicilia** | Sì | **Sì** | ↓ | ↓ | No | ↓ | No | Bassa |
| **Toscana** | Sì | **Sì** | ↓ | ↓ | No | ↓ | No | Bassa |
| **Umbria** | Sì | **Sì** | ↓ | ↓ | No | ↓ | No | Bassa |
| **V.d'Aosta/V.d'Aoste** | Sì | **Sì** | ↓ | ↓ | No | ↑ | No | Bassa |
| **Veneto** | Sì | **Sì** | ↓ | ↓ | No | ↓ | No | Bassa |

** elemento considerato come allerta di resilienza ai sensi dell'articolo 30 comma 1 del DL n. 149 del 9 novembre 2020*

## Algoritmo di valutazione di impatto e indicatori rilevanti per fase di riferimento

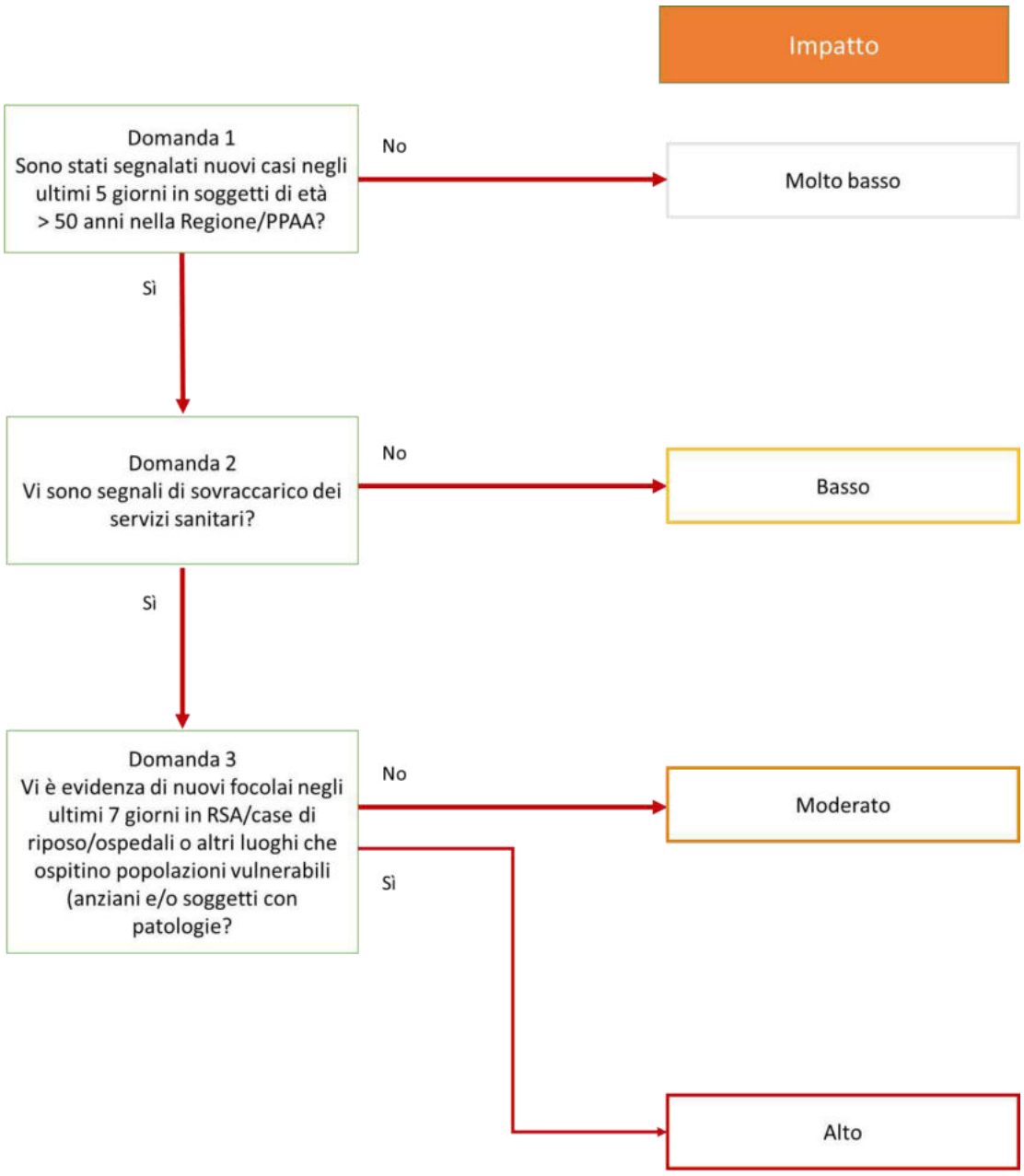


*Tabella 2 – Valutazione di impatto d'accordo all'algoritmo di valutazione del DM Salute 30 aprile, dati al 9 giugno 2021 relativi alla settimana 31/5/2021-6/6/2021*

| Regione.PA | Domanda 1 | Domanda 2 (dati più recenti disponibili*) | | Domanda 3 | Valutazione di impatto |
|---|---|---|---|---|---|
| | Nuovi casi segnalati negli ultimi 5 giorni in soggetti di età >50 anni? | Sovraccarico in Terapia Intensiva (Ind3.8 sopra 30%)? | Sovraccarico in aree mediche (Ind3.9 sopra 40%)? | Evidenza di nuovi focolai negli ultimi 7 giorni in RSA/case di riposo/ospedali o altri luoghi che ospitino popolazioni vulnerabili (anziani e/o soggetti con patologie)? | |
| **Abruzzo** | **Sì** | No | No | - | Bassa |
| **Basilicata** | **Sì** | No | No | - | Bassa |
| **Calabria** | **Sì** | No | No | - | Bassa |
| **Campania** | **Sì** | No | No | - | Bassa |
| **Emilia-Romagna** | **Sì** | No | No | - | Bassa |
| **FVG** | **Sì** | No | No | - | Bassa |
| **Lazio** | **Sì** | No | No | - | Bassa |
| **Liguria** | **Sì** | No | No | - | Bassa |
| **Lombardia** | **Sì** | No | No | - | Bassa |
| **Marche** | **Sì** | No | No | - | Bassa |
| **Molise** | **Sì** | No | No | - | Bassa |
| **Piemonte** | **Sì** | No | No | - | Bassa |
| **PA Bolzano/Bozen** | **Sì** | No | No | - | Bassa |
| **PA Trento** | **Sì** | No | No | - | Bassa |
| **Puglia** | **Sì** | No | No | - | Bassa |
| **Sardegna** | **Sì** | No | No | - | Bassa |
| **Sicilia** | **Sì** | No | No | - | Bassa |
| **Toscana** | **Sì** | No | No | - | Bassa |
| **Umbria** | **Sì** | No | No | - | Bassa |
| **V.d'Aosta/V.d'Aoste** | **Sì** | No | No | - | Bassa |
| **Veneto** | **Sì** | No | No | - | Bassa |

**aggiornato al 08/06/2021*

## Valutazione del rischio - Classificazione complessiva di rischio

### Matrice di attribuzione del rischio in base agli algoritmi di valutazione di probabilità ed impatto

| Probabilità / Impatto | Molto Bassa | Bassa | Moderata | Alta |
|---|---|---|---|---|
| Molto Basso | Rischio Molto basso | Rischio Basso | Rischio Basso | Rischio Moderato |
| Basso | Rischio Basso | Rischio Basso | Rischio Moderato | Rischio Moderato |
| Moderato | Rischio Basso | Rischio Moderato | Rischio Moderato | Rischio Alto |
| Alto | Rischio Moderato | Rischio Moderato | Rischio Alto | Rischio Molto Alto |

\+ Resilienza territoriale = Classificazione del rischio complessiva

Note: Come segnalato nel DM Salute 30 aprile 2020:" Qualora *gli indicatori non opzionali di processo sulla capacità di accertamento diagnostico, indagine e di gestione* [Tabella 3] *dei contatti non siano valutabili o diano molteplici segnali di allerta, il rischio così calcolato dovrà essere rivalutato al livello di rischio immediatamente superiore."*

NB Poiché ai sensi del documento "Prevenzione e risposta a COVID-19: evoluzione della strategia e pianificazione nella fase di transizione per il periodo autunno-invernale" e della legislazione corrente, le misure di risposta non differiscono per la classificazione di rischio "bassa" e "molto bassa" e per la classificazione di rischio "alta" e "molto alta", tale distinzione non viene riportata in questa relazione.

*Tabella 3 – Valutazione complessiva di rischio d'accordo alla matrice di rischio del DM Salute 30 aprile e sulla probabilità di raggiungere le soglie critiche di occupazione dei PL in area medica e terapia intensiva nei prossimi 30 giorni, dati al 9 giugno 2021 relativi alla settimana 31/5/2021-6/6/2021*

| Regione.PA | Valutazione della probabilità | Valutazione di impatto | Molteplici allerte di resilienza? (Appendice tabella 3) | Probabilità di una escalation nei prossimi 30 giorni (proiezioni al giorno 09/07/2021 della probabilità di superare le soglie di occupazione dei PL) | | Classificazione complessiva del rischio |
|---|---|---|---|---|---|---|
| | | | | % probabilità raggiungere occupazione TI 30% | % probabilità raggiungere occupazione aree mediche 40% | |
| **Abruzzo** | Bassa | Bassa | No | <5% | <5% | Bassa |
| **Basilicata** | Bassa | Bassa | No | <5% | <5% | Bassa |
| **Calabria** | Bassa | Bassa | No | <5% | <5% | Bassa |
| **Campania** | Bassa | Bassa | No | <5% | <5% | Bassa |
| **Emilia-Romagna** | Bassa | Bassa | No | <5% | <5% | Bassa |
| **FVG** | Bassa | Bassa | No | <5% | <5% | Bassa |
| **Lazio** | Bassa | Bassa | No | <5% | <5% | Bassa |
| **Liguria** | Bassa | Bassa | No | <5% | <5% | Bassa |
| **Lombardia** | Bassa | Bassa | No | <5% | <5% | Bassa |
| **Marche** | Bassa | Bassa | No | <5% | <5% | Bassa |
| **Molise** | Bassa | Bassa | No | <5% | <5% | Bassa |
| **Piemonte** | Bassa | Bassa | No | <5% | <5% | Bassa |
| **PA Bolzano/Bozen** | Bassa | Bassa | No | <5% | <5% | Bassa |
| **PA Trento** | Bassa | Bassa | No | <5% | <5% | Bassa |
| **Puglia** | Bassa | Bassa | No | <5% | <5% | Bassa |
| **Sardegna** | **Moderata** | Bassa | No | <5% | <5% | **Moderata** |
| **Sicilia** | Bassa | Bassa | No | <5% | <5% | Bassa |
| **Toscana** | Bassa | Bassa | No | <5% | <5% | Bassa |
| **Umbria** | Bassa | Bassa | No | <5% | <5% | Bassa |
| **V.d'Aosta/V.d'Aoste** | Bassa | Bassa | No | <5% | <5% | Bassa |
| **Veneto** | Bassa | Bassa | No | <5% | <5% | Bassa |

# 2. Appendice- Indicatori per la valutazione del rischio

*Appendice - Tabella 1 – Quadro sintetico con i principali indicatori del monitoraggio e compatibilità con gli Rt puntuali con gli scenari ai sensi del documento "Prevenzione e risposta a COVID-19: evoluzione della strategia e pianificazione nella fase di transizione per il periodo autunno-invernale", dati al 9 giugno 2021 relativi alla settimana 31/5/2021-6/6/2021*

| Regione.PA | Nuovi casi segnalati nella settimana | Trend settimanale COVID-19 | | Stima di Rt-puntuale (calcolato al 26/05/2021) | Dichiarata trasmissione non gestibile in modo efficace con misure locali (zone rosse) | Valutazione della probabilità | Valutazione di impatto | Allerte relative alla resilienza dei servizi sanitari territoriali | Compatibilità Rt sintomi puntuale con gli scenari di trasmissione* | Classificazione complessiva di rischio | Classificazione Alta e/o equiparata ad Alta per 3 o più settimane consecutive |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Casi (Fonte ISS) | Focolai | | | | | | | | |
| Abruzzo | 244 | ↓ | ↓ | 0.66 (CI: 0.58-0.76) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| Basilicata | 171 | ↓ | ↓ | 1.21 (CI: 0.82-1.68) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| Calabria | 696 | ↓ | ↓ | 0.69 (CI: 0.59-0.8) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| Campania | 1968 | ↓ | ↓ | 0.62 (CI: 0.58-0.66) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| Emilia-Romagna | 1017 | ↓ | ↓ | 0.64 (CI: 0.6-0.68) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| FVG | 144 | ↓ | ↓ | 0.67 (CI: 0.55-0.81) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| Lazio | 1336 | ↓ | ↓ | 0.62 (CI: 0.59-0.66) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| Liguria | 179 | ↓ | ↓ | 0.64 (CI: 0.56-0.72) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| Lombardia | 2545 | ↓ | ↓ | 0.65 (CI: 0.63-0.68) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| Marche | 429 | ↓ | ↓ | 0.84 (CI: 0.71-1) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| Molise | 23 | ↓ | 0 | 0.86 (CI: 0.19-1.8) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| Piemonte | 1189 | ↓ | ↓ | 0.71 (CI: 0.65-0.77) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| PA Bolzano/Bozen | 169 | ↓ | ↓ | 0.73 (CI: 0.62-0.84) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| PA Trento | 147 | ↓ | ↓ | 0.9 (CI: 0.76-1.06) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| Puglia | 912 | ↓ | ↓ | 0.72 (CI: 0.68-0.76) | No | Bassa | Bassa | 1 allerta segnalata. Ind 2.6 sotto soglia | 1 | Bassa | No |
| Sardegna | 210 | ↑ | ↓ | 0.91 (CI: 0.75-1.06) | No | **Moderata** | Bassa | 1 allerta segnalata. Ind 2.1 in aumento | 1 | **Moderata** | No |

| Regione.PA | Nuovi casi segnalati nella settimana | Trend settimanale COVID-19 | | Stima di Rt-puntuale (calcolato al 26/05/2021) | Dichiarata trasmissione non gestibile in modo efficace con misure locali (zone rosse) | Valutazione della probabilità | Valutazione di impatto | Allerte relative alla resilienza dei servizi sanitari territoriali | Compatibilità Rt sintomi puntuale con gli scenari di trasmissione* | Classificazione complessiva di rischio | Classificazione Alta e/o equiparata ad Alta per 3 o più settimane consecutive |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Casi (Fonte ISS) | Focolai | | | | | | | | |
| Sicilia | 1785 | ↓ | ↓ | 0.8 (CI: 0.76-0.86) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| Toscana | 1061 | ↓ | ↓ | 0.69 (CI: 0.66-0.73) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| Umbria | 156 | ↓ | ↓ | 0.77 (CI: 0.67-0.89) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| V.d'Aosta/V.d'Aoste | 36 | ↓ | ↑ | 0.78 (CI: 0.63-0.95) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| Veneto | 746 | ↓ | ↓ | 0.68 (CI: 0.63-0.73) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |

PA: Provincia Autonoma; gg: giorni

* ai sensi del documento "Prevenzione e risposta a COVID-19: evoluzione della strategia e pianificazione nella fase di transizione per il periodo autunno-invernale

## Dimensione 1 - completezza dei dati

### Indicatori di processo sulla capacità di monitoraggio:

| Settore | N | Indicatore | Soglia | Allerta | Allerta |
|---|---|---|---|---|---|
| **Capacità di monitoraggio (indicatori di qualità dei sistemi di sorveglianza con raccolta dati a livello nazionale)** | 1.1 | Numero di casi sintomatici notificati per mese in cui è indicata la data inizio sintomi / totale di casi sintomatici notificati al sistema di sorveglianza nello stesso periodo | Almeno il 60% con trend in miglioramento<br>Un valore di almeno 50% con trend in miglioramento sarà considerato accettabile nelle prime 3 settimane dal 4 maggio 2020 | <60% | Sorveglianza integrata nazionale |
| | 1.2 | Numero di casi notificati per mese con storia di ricovero in ospedale (in reparti diversi dalla TI) in cui è indicata la data di ricovero/totale di casi con storia di ricovero in ospedale (in reparti diversi dalla TI) notificati al sistema di sorveglianza nello stesso periodo | | | |
| | 1.3 | Numero di casi notificati per mese con storia di trasferimento/ricovero in reparto di terapia intensiva (TI) in cui è indicata la data di trasferimento o ricovero in TI/totale di casi con storia di trasferimento/ricovero in terapia intensiva notificati al sistema di sorveglianza nello stesso periodo | | | |
| | 1.4 | Numero di casi notificati per mese in cui è riportato il comune di domicilio o residenza/totale di casi notificati al sistema di sorveglianza nello stesso periodo | | | |

*Appendice - Tabella 2 – Indicatori di processo sulla capacità di monitoraggio, monitoraggio per Regione, dati al 9 giugno 2021 relativi alla settimana 31/5/2021-6/6/2021*

| Regione.PA | Ind1.1 settimana precedente (%) | Ind1.1 settimana di riferimento (%) | Variazione | Ind1.2 (%) | Ind1.3 (%) | Ind1.4 (%) |
|---|---|---|---|---|---|---|
| **Abruzzo** | 97.4 | 98.4 | Stabilmente sopra-soglia | 100.0 | 100 | 99.8 |
| **Basilicata** | 99.1 | 98.5 | Stabilmente sopra-soglia | 100.0 | 100 | 100.0 |
| **Calabria** | 89.4 | 87.1 | Stabilmente sopra-soglia | 100.0 | 100 | 99.8 |
| **Campania** | 99.9 | 99.9 | Stabilmente sopra-soglia | 100.0 | 100 | 99.9 |
| **Emilia-Romagna** | 100.0 | 100.0 | Stabilmente sopra-soglia | 100.0 | 100 | 99.8 |
| **FVG** | 99.4 | 99.5 | Stabilmente sopra-soglia | 100.0 | 100 | 99.5 |
| **Lazio** | 94.7 | 95.1 | Stabilmente sopra-soglia | 100.0 | 100 | 94.4 |
| **Liguria** | 93.7 | 95.0 | Stabilmente sopra-soglia | 100.0 | 100 | 97.0 |
| **Lombardia** | 84.4 | 83.3 | Stabilmente sopra-soglia | 99.9 | 100 | 97.8 |
| **Marche** | 100.0 | 100.0 | Stabilmente sopra-soglia | 100.0 | 100 | 100.0 |
| **Molise** | 86.7 | 75.0 | Stabilmente sopra-soglia | 100.0 | NC* | 100.0 |
| **Piemonte** | 78.2 | 78.4 | Stabilmente sopra-soglia | 100.0 | 100 | 98.6 |
| **PA Bolzano/Bozen** | 98.3 | 98.8 | Stabilmente sopra-soglia | 100.0 | 100 | 99.2 |
| **PA Trento** | 98.9 | 99.7 | Stabilmente sopra-soglia | 100.0 | 100 | 94.7 |
| **Puglia** | 97.6 | 97.6 | Stabilmente sopra-soglia | 100.0 | 100 | 99.9 |
| **Sardegna** | 97.9 | 97.7 | Stabilmente sopra-soglia | 100.0 | 100 | 100.0 |
| **Sicilia** | 96.4 | 98.9 | Stabilmente sopra-soglia | 100.0 | 100 | 100.0 |
| **Toscana** | 98.8 | 99.0 | Stabilmente sopra-soglia | 100.0 | 100 | 98.6 |
| **Umbria** | 96.8 | 97.4 | Stabilmente sopra-soglia | 100.0 | 100 | 99.1 |
| **V.d'Aosta/V.d'Aoste** | 98.8 | 99.7 | Stabilmente sopra-soglia | 100.0 | 100 | 100.0 |
| **Veneto** | 97.1 | 98.3 | Stabilmente sopra-soglia | 100.0 | 100 | 100.0 |

*NC: Non calcolabile in quanto non ci sono casi attualmente ricoverati in terapia intensiva

## Dimensione 2 - la classificazione della trasmissione ed impatto

# Indicatori di risultato relativi a stabilità di trasmissione

| Settore | N | Indicatore | Soglia | Allerta | Fonte dati |
|---|---|---|---|---|---|
| **Stabilità di trasmissione** | 3.1 | Numero di casi riportati alla protezione civile negli ultimi 14 giorni | Numero di casi con trend settimanale in diminuzione o stabile | Casi in aumento negli ultimi 5gg (% di aumento settimanale con soglie standard da utilizzare come "cruscotto informativo") | Ministero della salute |
| | 3.2 | Rt calcolato sulla base della sorveglianza integrata ISS (si utilizzeranno due indicatori, basati su data inizio sintomi e data di ospedalizzazione) | Rt regionale calcolabile e ≤1 in tutte le Regioni/PPAA in fase 2 A | Rt>1 o non calcolabile | Database ISS elaborato da FBK |
| | 3.4 | Numero di casi per data diagnosi e per data inizio sintomi riportati alla sorveglianza integrata COVID- 19 per giorno | Trend settimanale in diminuzione o stabile | Casi in aumento nell'ultima settimana (% di aumento settimanale con soglie standard da utilizzare come "cruscotto informativo") | ISS - Sistema di Sorveglianza integrata COVID-19 |
| | 3.5 | Numero di nuovi focolai di trasmissione (2 o più casi epidemiologicamente collegati tra loro o un aumento inatteso nel numero di casi in un tempo e luogo definito) | Mancato aumento nel numero di focolai di trasmissione attivi nella Regione<br><br>Assenza di focolai di trasmissione sul territorio regionale per cui non sia stata rapidamente realizzata una valutazione del rischio e valutata l'opportunità di istituire una "zona rossa" sub-regionale | Evidenza di nuovi focolai negli ultimi 7 giorni in particolare se in RSA/case di riposo/ospedali o altri luoghi che ospitino popolazioni vulnerabili. La presenza nuovi focolai nella Regione richiede una valutazione del rischio ad hoc che definisca qualora nella regione vi sia una trasmissione sostenuta e diffusa tale da richiedere il ritorno alla fase 1 | ISS - Monitoraggio dei focolai e delle zone rosse con schede di indagine |
| | 3.6 | Numero di nuovi casi di infezione confermata da SARS-CoV-2 per Regione non associati a catene di trasmissione note | Nel caso vi siano nuovi focolai dichiarati, l'indicatore può monitorare la qualità del contact-tracing, nel caso non vi siano focolai di trasmissione la presenza di casi non collegati a catene di trasmissione potrebbe essere compatibile con uno scenario di bassa trasmissione in cui si osservano solo casi sporadici (considerando una quota di circolazione non visibile in soggetti pauci- sintomatici) | In presenza di focolai, la presenza di nuovi casi di infezione non tracciati a catene note di contagio richiede una valutazione del rischio *ad hoc* che definisca qualora nella regione vi sia una trasmissione sostenuta e diffusa tale da richiedere il ritorno alla fase 1 | Valutazione periodica settimanale |
| **Servizi sanitari e assistenziali non sovraccarichi** | 3.8 | Tasso di occupazione dei posti letto totali di Terapia Intensiva (codice 49) per pazienti COVID-19 | ≤ 30% | >30% | Piattaforma rilevazione giornaliera posti letto MdS. |
| | 3.9 | Tasso di occupazione dei posti letto totali di Area Medica per pazienti COVID-19 | ≤ 40% | > 40% | |

## *Nota Metodologica*

***NB Classificazioni non valutabili nella attuale situazione sono da considerarsi equiparabili a classificazioni di rischio alto/molto alto***

**Stima di Rt:** La renewal equation che è alla base del metodo per il calcolo di Rt considera "il numero di nuovi casi locali con inizio sintomi al giorno t" (x) trasmessi dai "casi con inizio sintomi nei giorni precedenti" (y). Quando abbiamo dei casi importati, questi vengono contati insieme a tutti gli altri casi in y, in quanto potenziali "infettori" di nuovi casi locali, ma non in x, in quanto infezioni che sono state trasmesse altrove. Dal punto di vista computazionale è sufficiente, per le regioni, continuare ad utilizzare gli script basati sul software EpiEstim, avendo cura di inserire nella terza colonna del file di input il numero corretto di casi giornalieri che sono stati importati da un'altra regione o dall'estero.

**Valutazione del Rischio:** nel caso in cui venga riscontrato un aumento in entrambi i flussi di sorveglianza ma questo sia attribuibile esclusivamente a casi importati e immediatamente isolati al loro arrivo sul territorio regionale, questo non porta automaticamente ad un aumento nel livello di rischio.

**Dati sui focolai:** appurato ormai il consolidamento del dato sui focolai riportati da ciascuna Regione/PA, il trend nel numero di focolai per settimana è utilizzato dal report numero 12 nella valutazione del rischio in linea con quanto riportato alla Figura 1 del DM Salute del 30 aprile 2020.

**Casi importati:** La completezza del dato sulla provenienza dei casi (autoctoni, importati da altra Regione, importati da Stato estero) è considerata sufficiente e ne è quindi tenuto conto nel calcolo dell'Rt e nella valutazione del rischio (interpretazione dell'indicatore 3.4).

**Scenario settimanale di riferimento:** viene introdotta la analisi dello scenario settimanale sulla base del dato Rt sintomi (puntuale) in base a quanto definito nel documento Prevenzione e risposta a Covid-19: evoluzione della strategia e pianificazione nella fase di transizione per il periodo autunno-invernale :

- **Compatibile con Scenario 1:** Rt regionali sopra soglia per periodi limitati (inferiore a 1 mese)
- **Compatibile con Scenario 2:** Rt regionali significativamente compresi tra Rt=1 e Rt=1,25
- **Compatibile con Scenario 3:** Rt regionali significativamente compresi tra Rt=1,25 e Rt=1,5
- **Compatibile con Scenario 4:** Rt regionali significativamente maggiori di 1,5

**Probabilità di raggiungere soglie di occupazione posti letto:** Viene introdotto il dato **stimato a 1 mese** in base all'Rt di ospedalizzazione sulla probabilità di raggiungere le soglie previste negli indicatori 3.8 e 3.9 relative al tasso di occupazione dei posti letto in terapia intensiva ed area medica **qualora si mantengano le condizioni osservate nella settimana di monitoraggio corrente**. Viene fornito il dato categorizzato come segue: <5%, 5-50%, > 50%. Sono integrate nelle stime di proiezione i posti letto attivabili nel periodo compatibile con la stima stessa.

**Occupazione posti letto:** si riporta in questa relazione il dato più recente trasmesso dalle Regioni/PA alla DG Programmazione del Ministero della Salute. Il tasso di occupazione è calcolato dal mese di maggio tenendo conto dei soli posti letto attivi al momento della rilevazione.

*Appendice - Tabella 3 – Indicatori di risultato relativi a stabilità di trasmissione, dati al 9 giugno 2021 relativi alla settimana 31/5/2021-6/6/2021*

| Regione.PA | Ind3.1 | Trend 3.1 (% variazione settimanale) | Trend 3.4 (% variazione settimanale) | Ind3.2 (Rt puntuale) | Ind3.5 | Ind3.6 | Ind3.8* | Ind3.9* |
|---|---|---|---|---|---|---|---|---|
| Abruzzo | 588 | -25.0 | -20.8 | 0.66 (CI: 0.58-0.76) | 51 | 62 | 3% | 6% |
| Basilicata | 478 | -38.0 | -40.6 | **1.21 (CI: 0.82-1.68)** | 6 | 0 | 0% | 10% |
| Calabria | 1777 | -21.2 | -24.9 | 0.69 (CI: 0.59-0.8) | 16 | 78 | 8% | 20% |
| Campania | 5147 | -29.6 | -33.2 | 0.62 (CI: 0.58-0.66) | 220 | 466 | 7% | 13% |
| Emilia-Romagna | 2747 | -30.4 | -26.6 | 0.64 (CI: 0.6-0.68) | 18 | 407 | 9% | 6% |
| FVG | 409 | -22.2 | -33.2# | 0.67 (CI: 0.55-0.81) | 20 | 42 | 2% | 2% |
| Lazio | 3653 | -30.9 | -35.0 | 0.62 (CI: 0.59-0.66) | 153 | 64 | 11% | 10% |
| Liguria | 637 | -48.7 | -48.2 | 0.64 (CI: 0.56-0.72) | 24 | 51 | 10% | 4% |
| Lombardia | 6499 | -33.3 | -31.7 | 0.65 (CI: 0.63-0.68) | 336 | 1495 | 10% | 11% |
| Marche | 1176 | -29.1 | -33.5 | 0.84 (CI: 0.71-1) | 51 | 40 | 7% | 7% |
| Molise | 57 | -41.7 | -29.4 | 0.86 (CI: 0.19-1.8) | 2 | 0 | 0% | 3% |
| Piemonte | 2942 | -25.8 | -30.3 | 0.71 (CI: 0.65-0.77) | 179 | 208 | 9% | 7% |
| PA Bolzano/Bozen | 472 | -41.6 | -37.5 | 0.73 (CI: 0.62-0.84) | 9 | 109 | 1% | 3% |
| PA Trento | 390 | -36.8 | -37.2 | 0.9 (CI: 0.76-1.06) | 5 | 114 | 7% | 4% |
| Puglia | 2624 | -27.3 | -37.0 | 0.72 (CI: 0.68-0.76) | 40 | 547 | 5% | 10% |
| Sardegna | 448 | **9.3** | **10.3** | 0.91 (CI: 0.75-1.06) | 57 | 43 | 3% | 6% |
| Sicilia | 4632 | -25.8 | -25.5 | 0.8 (CI: 0.76-0.86) | 303 | 667 | 6% | 11% |
| Toscana | 2935 | -37.0 | -35.7 | 0.69 (CI: 0.66-0.73) | 232 | 478 | 18% | 6% |
| Umbria | 429 | -44.6 | -44.8 | 0.77 (CI: 0.67-0.89) | 25 | 53 | 5% | 7% |
| V.d'Aosta/V.d'Aoste | 127 | -48.8 | -57.6# | 0.78 (CI: 0.63-0.95) | 5 | 25 | 0% | 3% |
| Veneto | 2078 | -45.3 | -39.2 | 0.68 (CI: 0.63-0.73) | 133 | 43 | 4% | 3% |

* dato aggiornato al giorno 08/06/2021

\# Regioni/PPAA dove è stato rilevato un forte ritardo di notifica dei casi nel flusso ISS che potrebbe rendere la valutazione di questi indicatori meno affidabile.

## Dimensione 3 - Resilienza dei servizi sanitari preposti nel caso di una recrudescenza dell'epidemia da COVID-19

# Indicatori di processo sulla capacità di accertamento diagnostico, indagine e di gestione dei contatti

| Settore | N | Indicatore | Soglia | Allerta | Fonte dati |
|---|---|---|---|---|---|
| **Abilità di testare tempestivamente tutti i casi Sospetti** | 2.1 | % di tamponi positivi escludendo per quanto possibile tutte le attività di screening e il "re-testing" degli stessi soggetti, complessivamente e per macro-setting (territoriale, PS/Ospedale, altro) per mese.*<br><br>*Il calcolo di questo indicatore, senza modificarne la definizione, sarà oggetto di rivalutazione in collaborazione con le Regioni/PA alla luce delle modifiche previste nella definizione internazionale di caso per gli aspetti legati all'accertamento diagnostico dei casi COVID-19 | Trend in diminuzione in setting ospedalieri/ PS<br><br>Valore predittivo positivo (VPP) dei test stabile o in diminuzione | Trend in aumento in setting ospedalieri/ PS<br><br>VPP in aumento | Valutazione periodica settimanale |
| | 2.2 | Tempo tra data inizio sintomi e data di diagnosi | Mediana settimanale ≤ 5gg | Mediana settimanale > 5gg | ISS - Sistema di Sorveglianza integrata COVID-19 |
| | 2.3 (opzionale) | Tempo tra data inizio sintomi e data di isolamento | Mediana settimanale ≤ 3gg | Mediana settimanale > 3gg | ISS - Sistema di Sorveglianza integrata COVID-19 con integrazione di questa variabile |
| **Possibilità di garantire adeguate risorse per contact-tracing, isolamento e quarantena** | 2.4 | Numero, tipologia di figure professionali e tempo/persona dedicate in ciascun servizio territoriale al contact-tracing | Numero e tipologia di figure professionali dedicate a ciascuna attività a livello locale progressivamente allineato con gli standard raccomandati a livello europeo | Numero e tipologia di figure professionali dedicate a livello locale riportato come non adeguato in base agli standard raccomandati a livello europeo | Relazione periodica (mensile) |
| | 2.5 | Numero, tipologia di figure professionali e tempo/persona dedicate in ciascun servizio territoriale alle attività di prelievo/invio ai laboratori di riferimento e monitoraggio dei contatti stretti e dei casi posti rispettivamente in quarantena e isolamento | | | |
| | 2.6 | Numero di casi confermati di infezione nella regione per cui sia stata effettuata una regolare indagine epidemiologica con ricerca dei contatti stretti/totale di nuovi casi di infezione confermati | Trend in miglioramento con target finale 100% | | |

*Appendice - Tabella 4 – Indicatori di processo sulla capacità di accertamento diagnostico, indagine e di gestione dei contatti e valutazione della resilienza dei servizi sanitari territoriali*

| Regione.PA | Ind2.1* (precedente) | Ind2.1 (settimana di riferimento) | Ind2.2 (mediana giorni tra inizio sintomi e diagnosi**) | Ind2.3 (mediana) | Ind2.4 | Ind2.5 | Totale risorse umane | Ind2.6 | Resilienza dei servizi sanitari territoriali |
|---|---|---|---|---|---|---|---|---|---|
| **Abruzzo** | 2.4% | 2.1% | 3 | 1 | 0.7 per 10000 | 0.8 per 10000 | 1.5 per 10000 | 100% | 0 allerte segnalate |
| **Basilicata** | 4.8% | 4.2% | 3 | 0 | 1.6 per 10000 | 5.2 per 10000 | 6.7 per 10000 | 99.6% | 0 allerte segnalate |
| **Calabria** | 5.2% | 4.6% | 3 | 1 | 0.9 per 10000 | 0.6 per 10000 | 1.4 per 10000 | 90.2% | 0 allerte segnalate |
| **Campania** | 5.1% | 4.8% | 1 | 2 | 0.8 per 10000 | 1.5 per 10000 | 2.3 per 10000 | 98.2% | 0 allerte segnalate |
| **Emilia-Romagna** | 3.1% | 3.1% | 2 | Non calcolabile | 1.2 per 10000 | 1.4 per 10000 | 2.7 per 10000 | 98.2% | 0 allerte segnalate |
| **FVG** | 1.6% | 1.3% | 2.5 | 1 | 0.7 per 10000 | 1 per 10000 | 1.8 per 10000 | 98.4% | 0 allerte segnalate |
| **Lazio** | 6.1% | 4.5% | 3 | 2 | 0.9 per 10000 | 1 per 10000 | 1.9 per 10000 | 96.8% | 0 allerte segnalate |
| **Liguria** | 1.9% | 1.2% | 3 | 1 | 0.7 per 10000 | 0.8 per 10000 | 1.5 per 10000 | 96.2% | 0 allerte segnalate |
| **Lombardia** | 2.1% | 1.7% | 2 | Non calcolabile | 0.6 per 10000 | 0.8 per 10000 | 1.4 per 10000 | 95.9% | 0 allerte segnalate |
| **Marche** | 3.2% | 2.7% | 0 | 0 | 0.6 per 10000 | 1.4 per 10000 | 2 per 10000 | 100% | 0 allerte segnalate |
| **Molise** | 1.4% | 1% | -3 | -3 | 1.1 per 10000 | 2.6 per 10000 | 3.7 per 10000 | 100% | 0 allerte segnalate |
| **Piemonte** | 2.3% | 1.9% | 4 | 1 | 1.5 per 10000 | 2.1 per 10000 | 3.6 per 10000 | 98.1% | 0 allerte segnalate |
| **PA Bolzano/Bozen** | 16.1% | 11.7% | 2 | 2.5 | 1.9 per 10000 | 3.2 per 10000 | 5.1 per 10000 | 100% | 0 allerte segnalate |
| **PA Trento** | 5.9% | 5.5% | 3 | 3 | 1.1 per 10000 | 1.6 per 10000 | 2.7 per 10000 | 100% | 0 allerte segnalate |

| Regione.PA | Ind2.1* (precedente) | Ind2.1 (settimana di riferimento) | Ind2.2 (mediana giorni tra inizio sintomi e diagnosi**) | Ind2.3 (mediana) | Ind2.4 | Ind2.5 | Totale risorse umane | Ind2.6 | Resilienza dei servizi sanitari territoriali |
|---|---|---|---|---|---|---|---|---|---|
| **Puglia** | 6.1% | 4.6% | 2 | 2 | 0.6 per 10000 | 0.8 per 10000 | 1.4 per 10000 | **61.3%** | 1 allerta segnalata. Ind 2.6 sotto soglia |
| **Sardegna** | 1.7% | **1.9%** | 3 | 2 | 0.4 per 10000 | 1.6 per 10000 | 2 per 10000 | 95.6% | 1 allerta segnalata. Ind 2.1 in aumento |
| **Sicilia** | 6.5% | 5.7% | 2 | 1 | 1.5 per 10000 | 3.6 per 10000 | 5 per 10000 | 99.3% | 0 allerte segnalate |
| **Toscana** | 5.8% | 4.7% | 0 | 2 | 1.6 per 10000 | 1.7 per 10000 | 3.3 per 10000 | 100% | 0 allerte segnalate |
| **Umbria** | 4.1% | 3% | 2 | 1 | 0.9 per 10000 | 3 per 10000 | 4 per 10000 | 100% | 0 allerte segnalate |
| **V.d'Aosta/V.d'Aoste** | 8.4% | 4.8% | 2 | 1 | 1.7 per 10000 | 2.1 per 10000 | 3.8 per 10000 | 99.7% | 0 allerte segnalate |
| **Veneto** | 1.7% | 1.3% | 1 | 0 | 1 per 10000 | 1.8 per 10000 | 2.9 per 10000 | 98.9% | 0 allerte segnalate |

* le diverse politiche di offerta di "testing" e l'uso di test alternativi al test molecolare nelle Regioni/PPAA non rendono questo indicatore confrontabile tra le stesse.
** in presenza di numerosi casi che vengono diagnosticati prima dell'inizio dei sintomi (asintomatici alla diagnosi) è possibile il riscontro di tempi mediani molto brevi o, in casi estremi, negativi. Si ricorda che tutti i dati degli indicatori di monitoraggio sono validati con i referenti delle rispettive Regioni/PA prima della finalizzazione delle relazioni settimanali.

## *Indicatori decisionali come da Decreto Legge del 18 maggio 2021 n.65 articolo 13*

### *Aggiornamento del 10/06/2021*

| Regione | Incidenza a 7 gg/100.000 pop - Periodo di riferimento 14-20 maggio 2021 | Incidenza a 7 gg/100.000 pop - Periodo di riferimento 21-27 maggio 2021 | Incidenza a 7 gg/100.000 pop - Periodo di riferimento 28 maggio-3 giugno 2021 | Incidenza a 7 gg/100.000 pop - Periodo di riferimento 4-10 giugno 2021 | % OCCUPAZIONE PL AREA MEDICA DA PAZIENTI COVID al 08/06/2021 | % OCCUPAZIONE PL TERAPIA INTENSIVA DA PAZIENTI COVID al 08/06/2021 |
|---|---|---|---|---|---|---|
| **Abruzzo** | 42 | 35 | 22 | 19 | 6% | 3% |
| **Basilicata** | 100 | 62 | 35 | 39 | 10% | 0% |
| **Calabria** | 71 | 61 | 43 | 36 | 20% | 8% |
| **Campania** | 95 | 66 | 43 | 31 | 13% | 7% |
| **Emilia Romagna** | 67 | 45 | 30 | 22 | 6% | 9% |
| **Friuli Venezia Giulia** | 24 | 17 | 17 | 19 | 2% | 2% |
| **Lazio** | 64 | 46 | 30 | 23 | 10% | 11% |
| **Liguria** | 43 | 28 | 22 | 10 | 4% | 10% |
| **Lombardia** | 63 | 46 | 31 | 23 | 11% | 10% |
| **Marche** | 75 | 55 | 34 | 28 | 7% | 7% |
| **Molise** | 20 | 12 | 9 | 9 | 3% | 0% |
| **PA di Bolzano** | 76 | 59 | 41 | 31 | 3% | 1% |
| **PA di Trento** | 61 | 45 | 35 | 25 | 4% | 7% |
| **Piemonte** | 71 | 49 | 33 | 23 | 7% | 9% |
| **Puglia** | 75 | 50 | 31 | 25 | 10% | 5% |
| **Sardegna** | 25 | 13 | 14 | 12 | 6% | 3% |
| **Sicilia** | 68 | 53 | 47 | 40 | 11% | 6% |
| **Toscana** | 84 | 59 | 39 | 28 | 6% | 18% |
| **Umbria** | 42 | 28 | 25 | 21 | 7% | 5% |
| **Valle d'Aosta** | 107 | 79 | 56 | 31 | 3% | 0% |
| **Veneto** | 45 | 30 | 19 | 15 | 3% | 4% |
| **ITALIA** | ***66*** | ***47*** | ***32*** | ***25*** | ***8%*** | ***8%*** |

***Fonte dati: Ministero della Salute / Protezione Civile***

11 giugno 2021

# Epidemia COVID-19

# Monitoraggio del rischio

*Silvio Brusaferro*
*Istituto Superiore di Sanità*



1

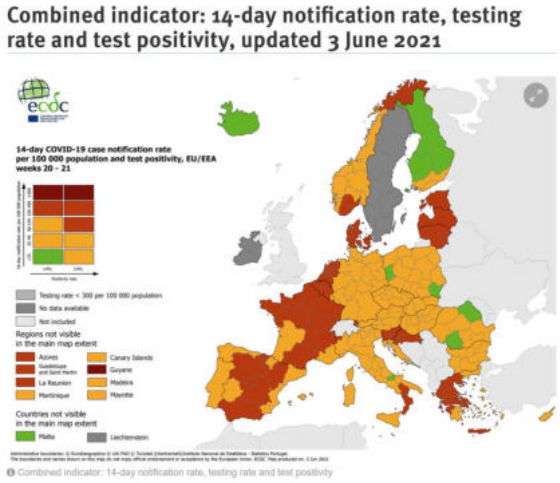
## Situazione epidemiologica in Europa



2

## Casi notificati al Centro Europeo per la Prevenzione ed il Controllo delle Malattie (ECDC)

**La situazione italiana riflette l'epidemiologia di altri paesi UE/SEE**

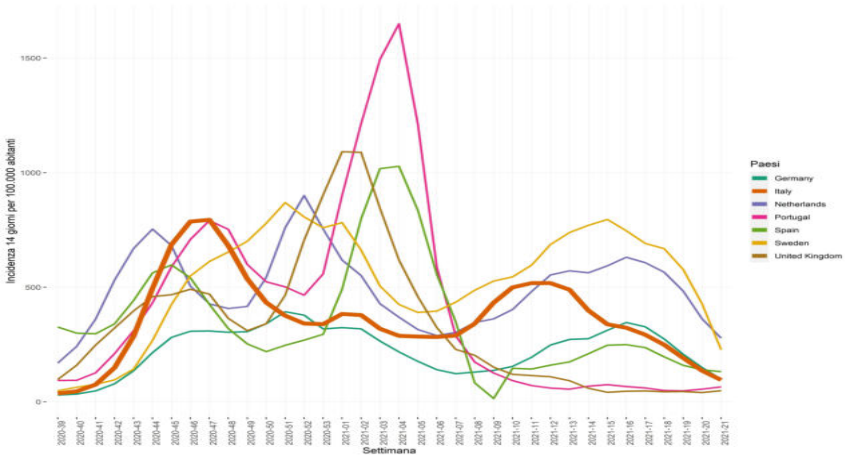



https://www.ecdc.europa.eu/en/covid-19/situation-updates/weekly-maps-coordinated-restriction-free-movement



3

## Andamento incidenza (14 gg) in alcuni paesi europei (ECDC)






**Data di ultimo aggiornamento**: 7 giugno 2021

4

# Situazione epidemiologica in Italia



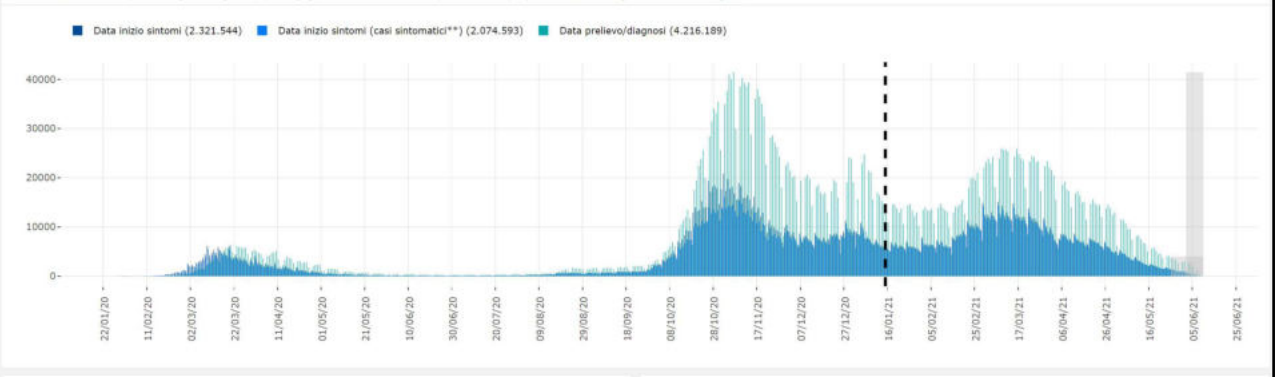
5

## Casi notificati al sistema di Sorveglianza integrata COVID-19 in Italia

| 4.218.979 | 135.212 | 46 anni | 48,9% \| 51,1% | 125.058 (3%) | 3.744.473 |
|---|---|---|---|---|---|
| Casi*** | Casi tra gli operatori sanitari* | Età mediana dei casi | Maschi (%) \| Femmine (%) | Deceduti (CFR) | Guariti |

**Curva epidemica dei casi di COVID-19 segnalati in Italia per data di prelievo o diagnosi (verde) e per data di inizio dei sintomi (blu)**

Nota: il numero dei casi riportato negli ultimi giorni (riquadri grigi) deve essere considerato provvisorio sia per possibili ritardi di segnalazione che di diagnosi.






**Data di ultimo aggiornamento**: 9 giugno 2021

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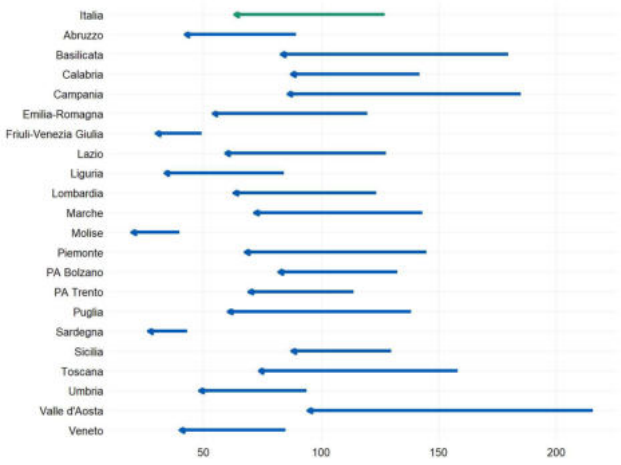
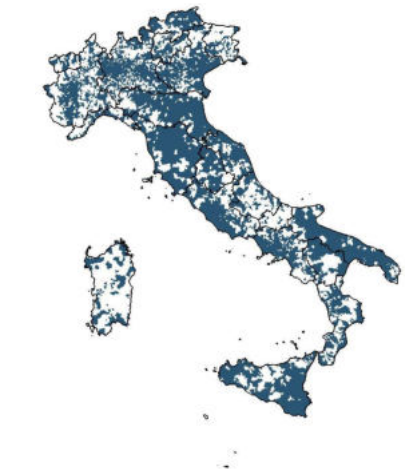
## Casi in diminuzione in tutte le Regioni/PPAA e nuovi casi presenti su tutto il territorio nazionale negli ultimi 14 giorni




*CONFRONTO TRA IL **NUMERO CASI DI COVID-19 (PER 100.000 AB)** DIAGNOSTICATI IN ITALIA PER REGIONE NEL PERIODO 24/5-6/6/2021 E 10/5-23/5/2021*



CASI DI COVID-19 DIAGNOSTICATI IN ITALIA PER COMUNE DI DOMICILIO/RESIDENZA (COMUNI CON ALMENO UN CASO)



**Data di ultimo aggiornamento:** 9 giugno 2021

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## N. assoluto e incidenza casi diagnosticati tra 31/5-6/6 per Regione/PA (FONTE ISS), tra 4-10/6, tamponi e % positività (FONTE MINISTERO DELLA SALUTE)

| Regione/ PA | N. Casi 31/ 5-6/ 6 | Incidenza 7gg (per 100.000 ab) 31/ 5-6/ 6 | N. Casi tra il 4/ 6-10/ 6 | Incidenza 7gg (per 100.000 ab) 4/ 6-10/ 6 | Tamponi 7gg 4/ 6-10/ 6 | Tamponi 7gg/ 100 000 pop 4/ 6-10/ 6 | Percentuale positività 4/ 6-10/ 6 |
|---|---|---|---|---|---|---|---|
| | (Fonte ISS) | | (Fonte MINISTERO DELLA SALUTE) | | (Fonte MINISTERO DELLA SALUTE) | | |
| Abruzzo | 244 | 18,98 | 248 | 19 | 27.630 | 2.150 | 0,9 |
| Basilicata | 171 | 31,23 | 216 | 39 | 5.514 | 1.007 | 3,9 |
| Calabria | 696 | 37,07 | 682 | 36 | 16.231 | 864 | 4,2 |
| Campania | 1.968 | 34,65 | 1.756 | 31 | 87.305 | 1.537 | 2 |
| Emilia-Romagna | 1.017 | 22,88 | 956 | 22 | 120.209 | 2.704 | 0,8 |
| Friuli-Venezia Giulia | 144 | 12,01 | 233 | 19 | 35.180 | 2.935 | 0,7 |
| Lazio | 1.336 | 23,35 | 1.322 | 23 | 148.602 | 2.598 | 0,9 |
| Liguria | 179 | 11,86 | 155 | 10 | 30.617 | 2.028 | 0,5 |
| Lombardia | 2.545 | 25,53 | 2.319 | 23 | 228.406 | 2.292 | 1 |
| Marche | 429 | 28,57 | 425 | 28 | 17.799 | 1.185 | 2,4 |
| Molise | 23 | 7,76 | 26 | 9 | 2.911 | 982 | 0,9 |
| Piemonte | 1.189 | 27,82 | 979 | 23 | 110.102 | 2.577 | 0,9 |
| PA Bolzano | 169 | 31,66 | 166 | 31 | 27.461 | 5.145 | 0,6 |
| PA Trento | 147 | 26,99 | 135 | 25 | 11.779 | 2.162 | 1,1 |
| Puglia | 912 | 23,22 | 994 | 25 | 45.415 | 1.157 | 2,2 |
| Sardegna | 210 | 13,14 | 188 | 12 | 18.662 | 1.168 | 1 |
| Sicilia | 1.785 | 36,87 | 1.943 | 40 | 97.358 | 2.011 | 2 |
| Toscana | 1.061 | 28,92 | 1.031 | 28 | 104.140 | 2.839 | 1 |
| Umbria | 156 | 18,03 | 180 | 21 | 31.395 | 3.629 | 0,6 |
| Valle d'Aosta | 36 | 29,06 | 38 | 31 | 2.688 | 2.170 | 1,4 |
| Veneto | 746 | 15,37 | 713 | 15 | 169.682 | 3.497 | 0,4 |
| **ITALIA** | **15.163** | **25,59** | **14.705** | **25** | **1.339.086** | **2.260** | **1,1** |

Popolazione: ISTAT al 1/1/2021



**Data di ultimo aggiornamento**: 10 giugno 2021

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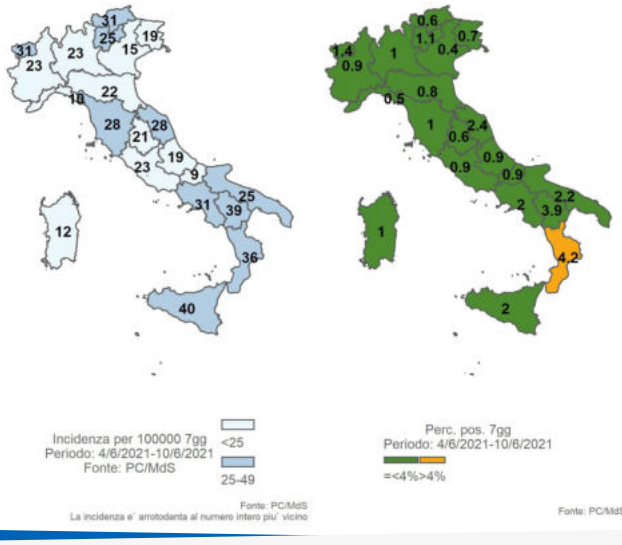
## Incidenza per 100000 e percentuale positività 7gg nel periodo: 4/6/2021-10/6/2021- Fonte: Mds/PC



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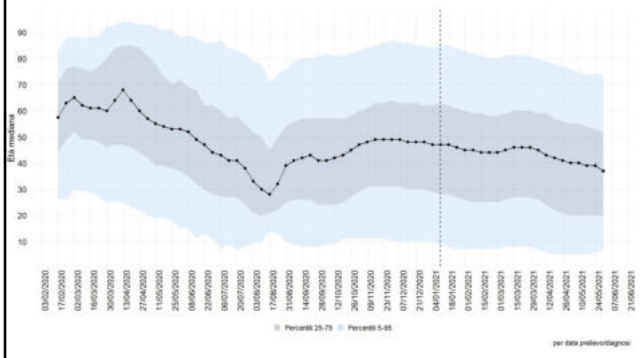
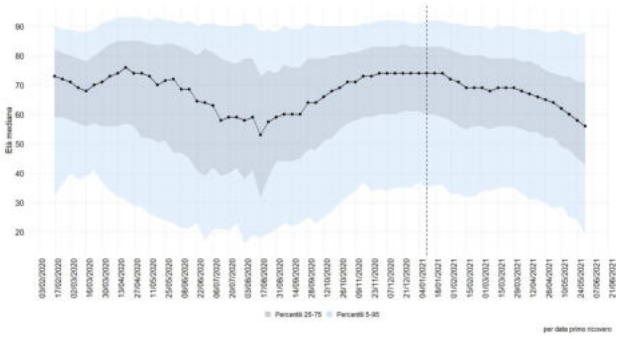
## Caratteristiche della popolazione affetta

**Età mediana alla diagnosi in lieve diminuzione**
**(37 anni ultima settimana - 39 anni settimana precedente)**

**Età mediana al primo ricovero in diminuzione**
**(56 anni ultima settimana - 58 anni settimana precedente)**




ETÀ MEDIANA DEI CASI DI COVID-19 DIAGNOSTICATI IN ITALIA PER SETTIMANA DI DIAGNOSI

ETÀ MEDIANA DEI CASI DI COVID-19 AL PRIMO RICOVERO IN ITALIA PER SETTIMANA DI DIAGNOSI



**Data di ultimo aggiornamento**: 9 giugno 2021

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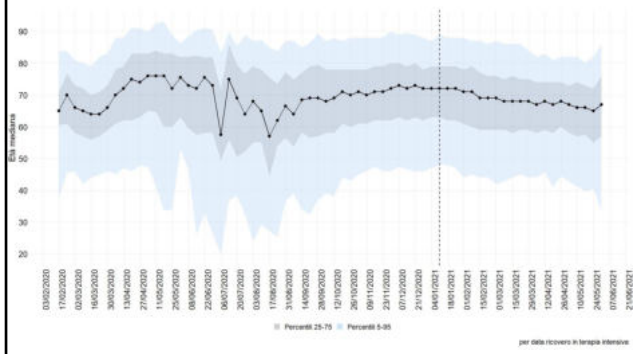
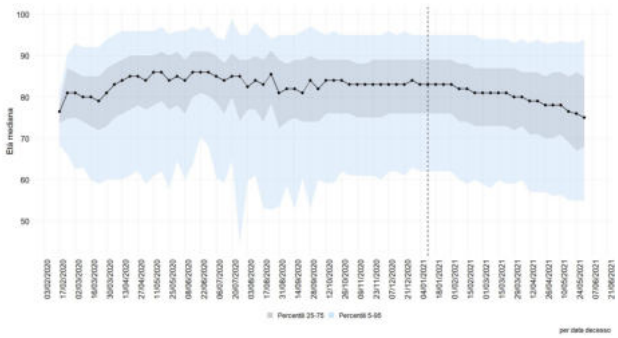
# Caratteristiche della popolazione affetta

**Età mediana all'ingresso in terapia intensiva**
**(67 anni ultima settimana - 65 anni settimana precedente)**



ETÀ MEDIANA DEI CASI DI COVID-19 ALL'INGRESSO IN TERAPIA INTENSIVA IN ITALIA PER SETTIMANA DI DIAGNOSI

**Età mediana al decesso in diminuzione**
**(75 anni ultima settimana - 76 anni settimana precedente)**

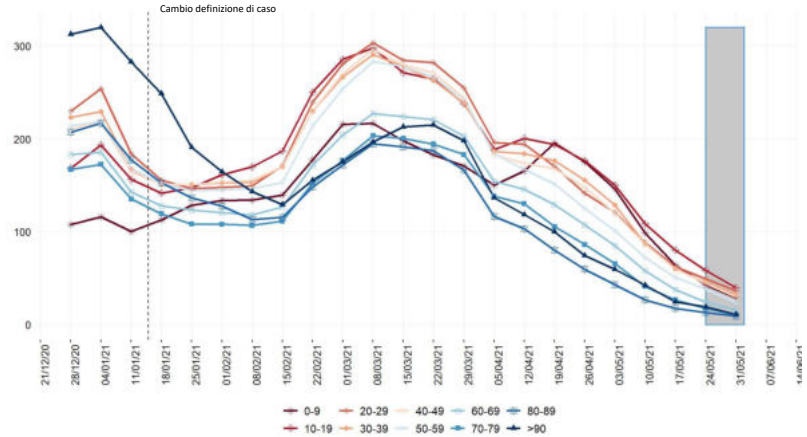


ETÀ MEDIANA DEI CASI DI COVID-19 AL DECESSO IN ITALIA PER SETTIMANA DI DIAGNOSI



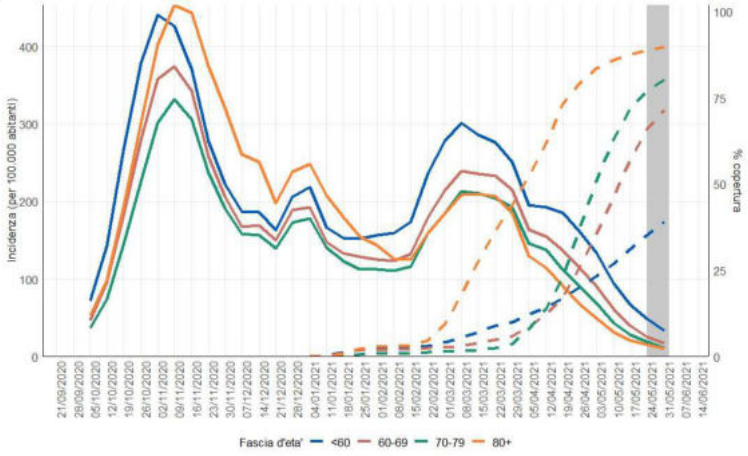
# Tasso d'incidenza per fascia d'età a livello nazionale
## (dall'inizio del 2021)

**Incidenza in diminuzione nell'ultimo periodo in tutte le fasce d'età**



## Tasso d'incidenza nazionale <60 anni vs 60-69 anni vs 70-79 anni vs >=80 anni

**Trend in calo per gli <60 anni, 60-69 anni, 70-79 anni e >=80 anni**




www.iss.it/presidenza

**Data di ultimo aggiornamento**: 9 giugno 2021

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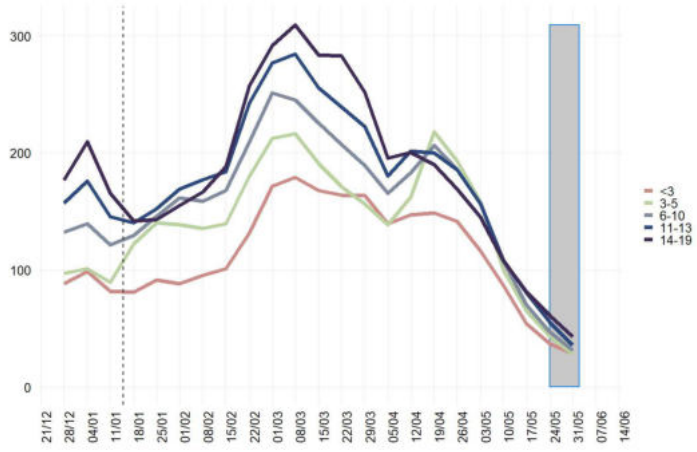
## Tasso d'incidenza nazionale per fascia d'età popolazione in eta' scolare (dall'inizio del 2021)

**Situazione di nuovo in netto miglioramento nella popolazione di età 0-18 anni**




www.iss.it/presidenza

**Data di ultimo aggiornamento**: 9 giugno 2021

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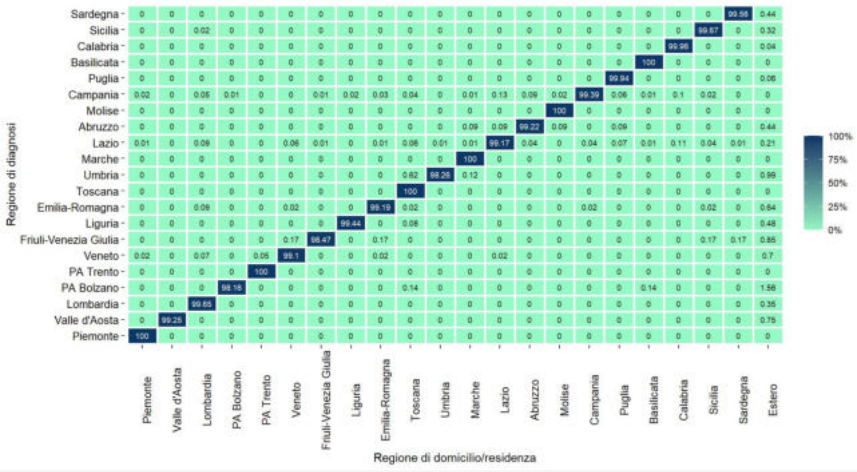
## Proporzione di casi di COVID-19 (per 100.000 Ab) provenienti da altra regione/PA o stato estero sul totale dei casi diagnosticati da ciascuna Regione/PA negli ultimi 14gg

**Ancora limitata la proporzione dei casi con esposizione fuori dall' Italia o fuori Regione/PA.**

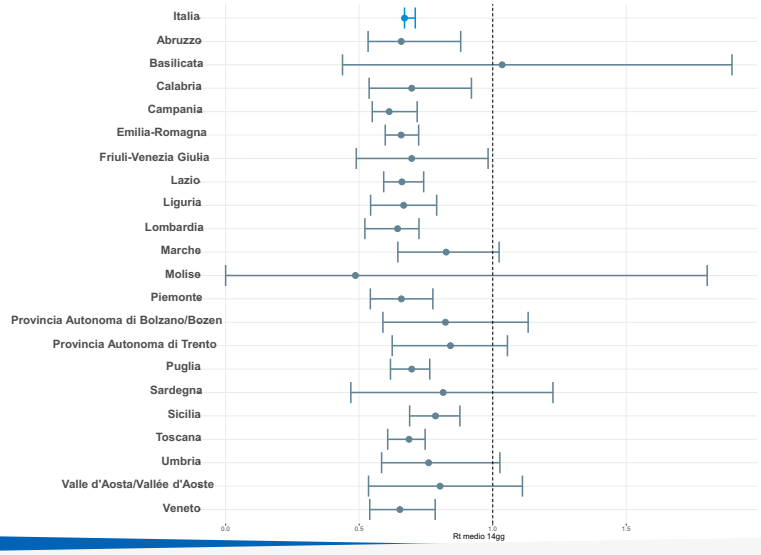





**Data di ultimo aggiornamento**: 9 giugno 2021

15

## STIMA DELL'RT MEDIO14gg PER REGIONE/PA BASATO SU INIZIO SINTOMI FINO TRA IL 19 MAGGIO E IL 1' GIUGNO 2021, CALCOLATO IL 9/06/2021






**Data di ultimo aggiornamento**: 9 giugno 2021

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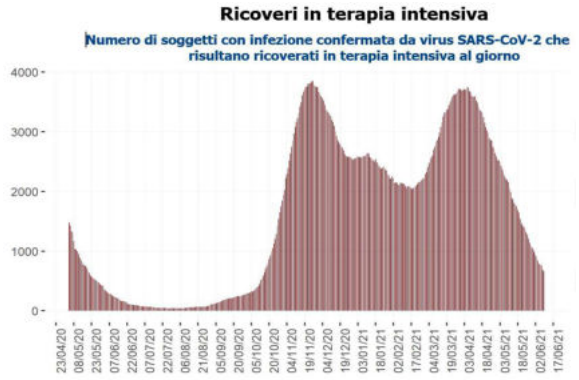
# Ricoveri

**Ricoveri in area medica e in terapia intensiva in diminuzione da molte settimane**


**Occupazione posti letto in area medica**
**8% ultima settimana – 11% settimana precedente**




**Occupazione posti letto in terapia intensiva**
**8% ultima settimana – 12% settimana precedente**



**Data di ultimo aggiornamento**:8 giugno 2021

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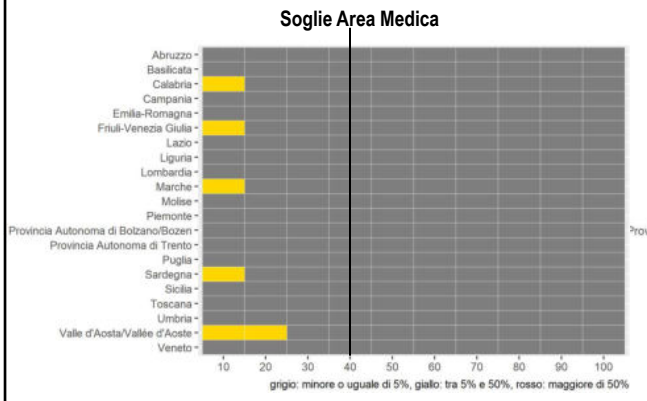
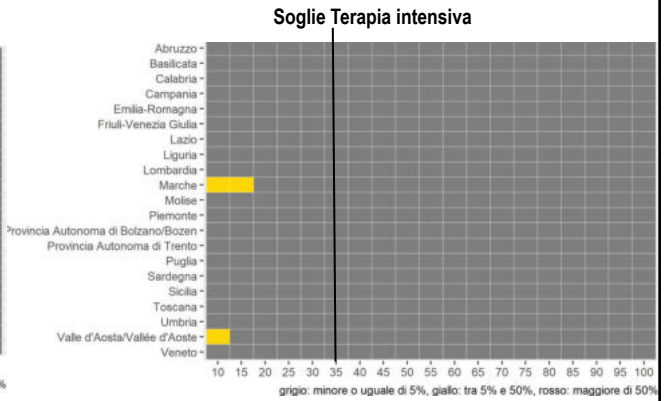
# Proiezioni dell'occupazione dei posti letto a 30 giorni

**% di probabilità di superamento delle soglie critiche di occupazione in area medica e terapia intensiva al 09/07/2021 se si mantiene invariata la trasmissibilità (tenendo conto dei PL attivabili nel periodo della stima)**






**Data di ultimo aggiornamento**: 9 giugno 2021

18

# Vaccinazioni somministrate al 9/06/2021 e loro impatto

https://github.com/italia/covid19-opendata-vaccini



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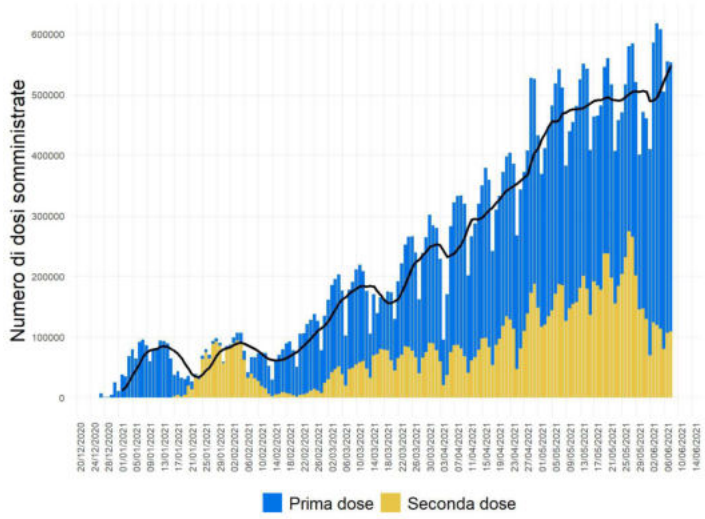
## Numero di prime e seconde dosi di vaccino somministrate giornalmente dal 27/12/2020 al 09/06/2021






**Data di ultimo aggiornamento**: 9 giugno 2021

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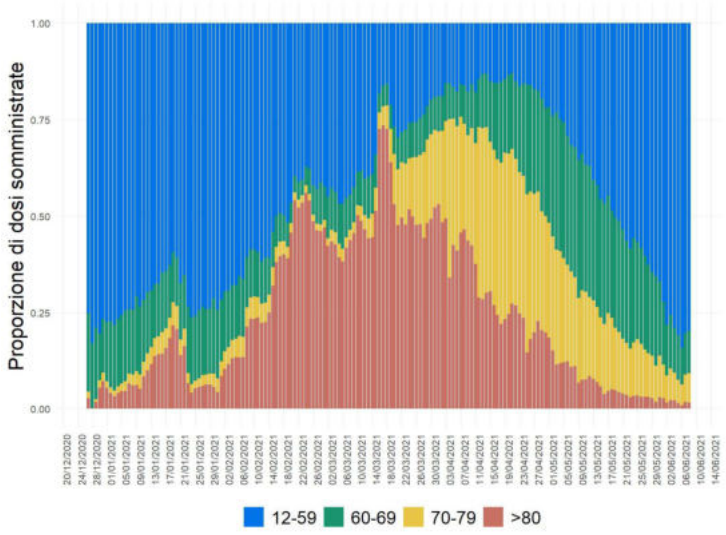
# Numero cumulativo di dosi somministrate per classe d'età

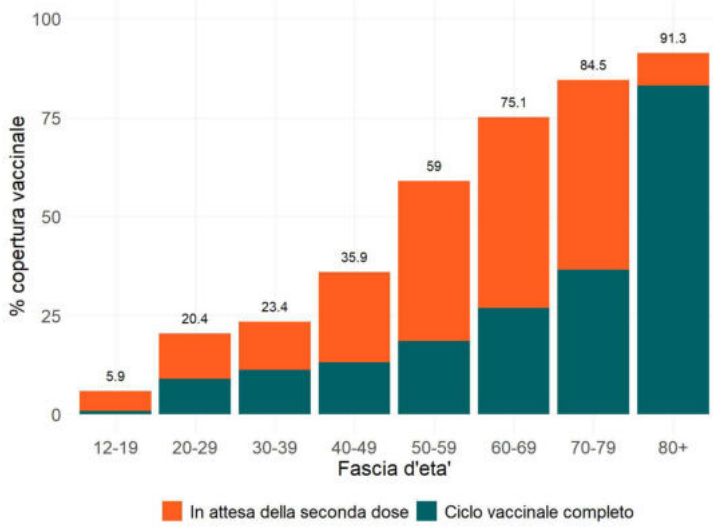





**Data di ultimo aggiornamento**: 9 giugno 2021

21

# Percentuale copertura vaccinale






**Data di ultimo aggiornamento**: 9 giugno 2021

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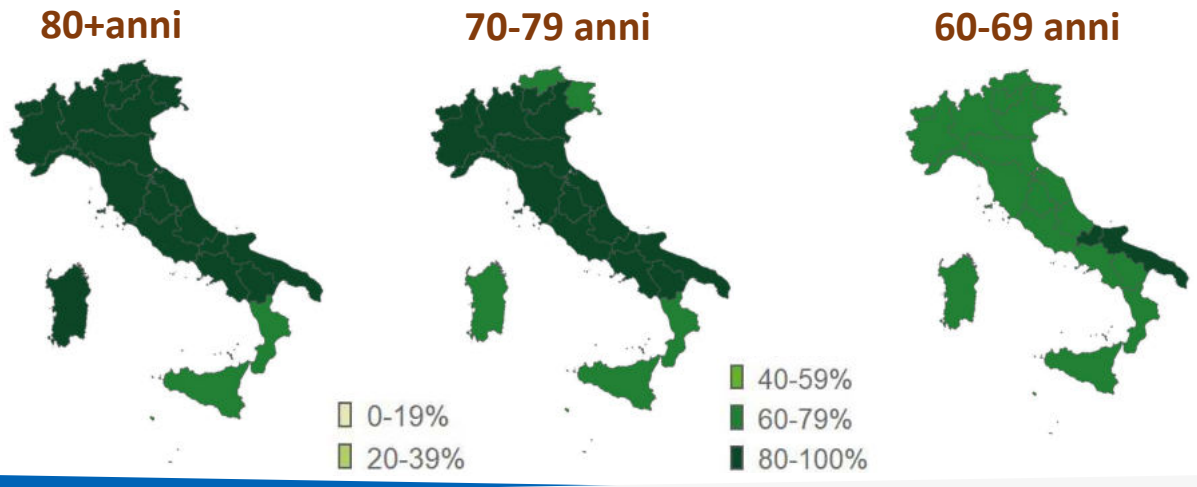
## Percentuale di soggetti che hanno ricevuto almeno una dose di vaccino per Regione/PA

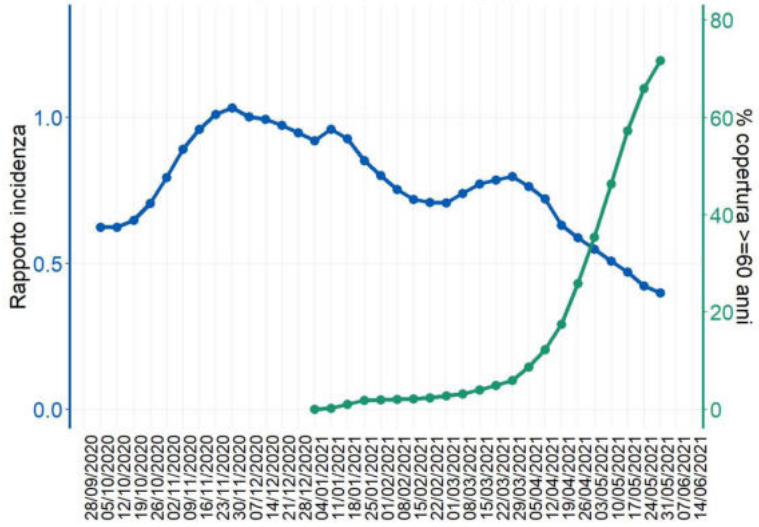



www.iss.it/presidenza

**Data di ultimo aggiornamento**: 9 giugno 2021

23

## Rapporto tra l'incidenza settimanale nei soggetti ≥60 anni vs <60 anni SINTOMATICI e la copertura vaccinale nei soggetti ≥60 anni (15gg dopo prima dose)




www.iss.it/presidenza

**Data di ultimo aggiornamento**: 9 giugno 2021

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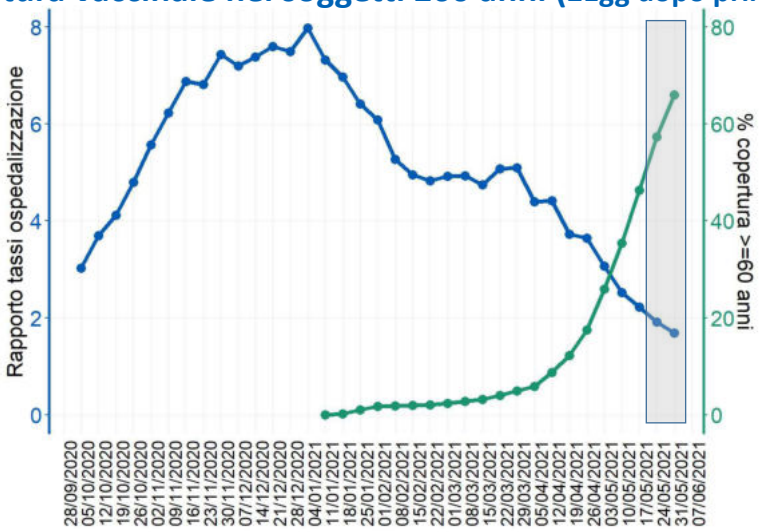
## Rapporto tra il tasso di ospedalizzazione settimanale nei soggetti ≥60 anni vs <60 anni e la copertura vaccinale nei soggetti ≥60 anni (21gg dopo prima dose)






**Data di ultimo aggiornamento**: 9 giugno 2021

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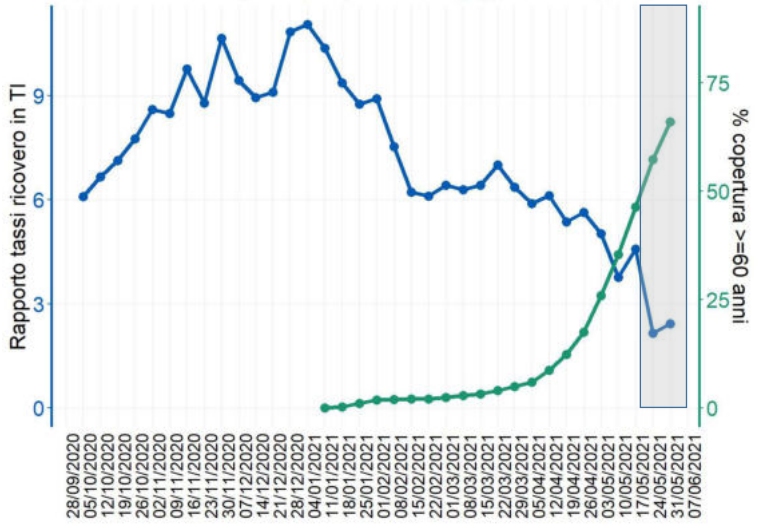
## Rapporto tra il tasso di ricovero in terapia intensiva settimanale nei soggetti ≥60 anni vs <60 anni e la copertura vaccinale nei soggetti ≥60 anni (21gg dopo prima dose)






**Data di ultimo aggiornamento**: 9 giugno 2021

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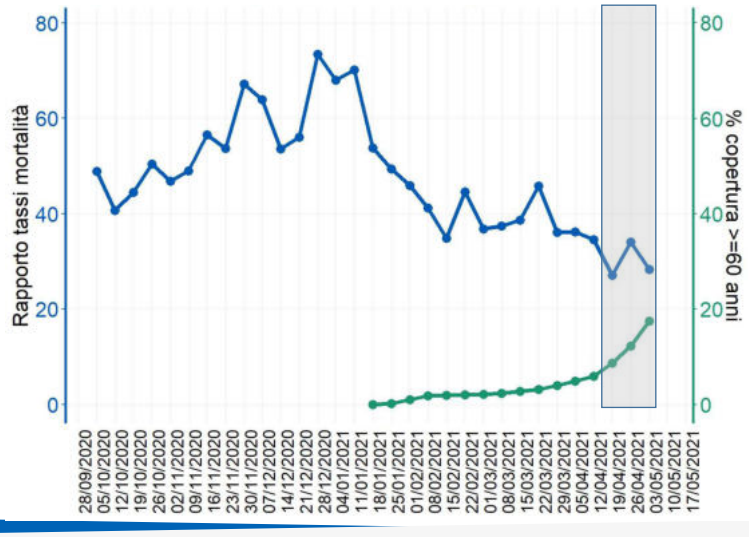
## Rapporto tra il tasso di mortalità settimanale nei soggetti ≥60 anni vs <60 anni e la copertura vaccinale nei soggetti ≥60 anni (28gg dopo prima dose)






**Data di ultimo aggiornamento**: 9 giugno 2021

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## Impatto dell'epidemia covid-19 sulla mortalità totale della popolazione residente.
## Anno 2020 e gennaio-aprile 2021

https://www.istat.it/it/files//2021/06/Report_ISS_Istat_2021_10_giugno.pdf



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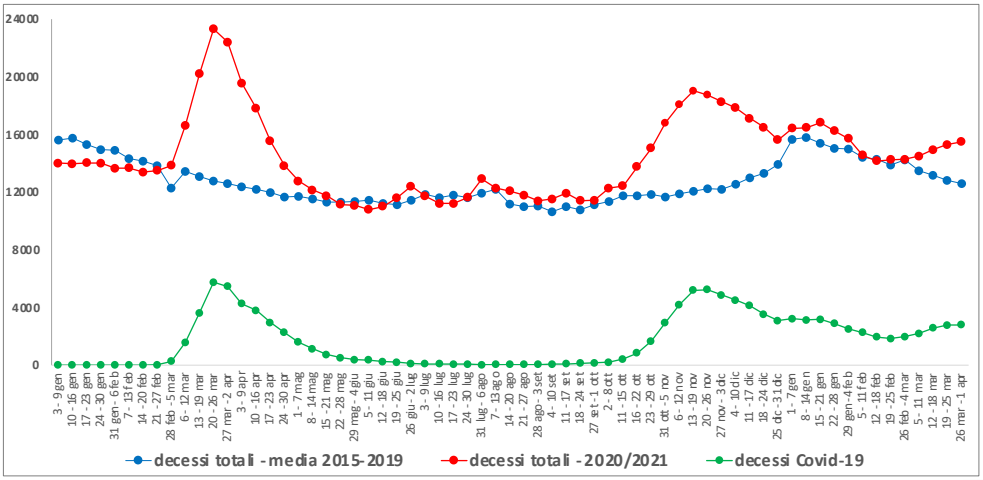
https://www.istat.it/it/files//2021/06/Report_ISS_Istat_2021_10_giugno.pdf

## Andamento settimanale dei decessi totali e dei decessi Covid-19 in Italia. Anni 2020 e 2021 e media del periodo 2015-2019



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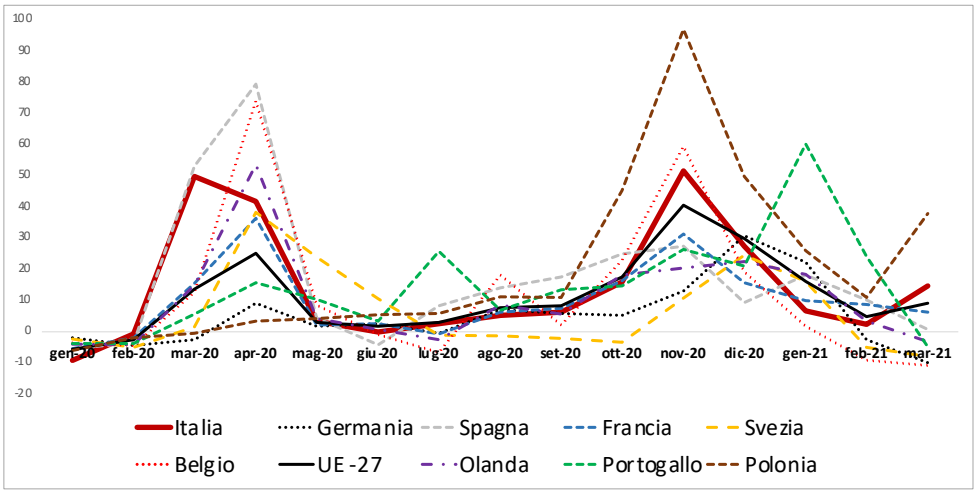
https://www.istat.it/it/files//2021/06/Report_ISS_Istat_2021_10_giugno.pdf

## Decessi mensili nel periodo Anno 2020 e gennaio-marzo 2021 per l'Italia ed alcuni Stati Europei - incremento percentuale rispetto alla media 2016-2019 (FONTE: Eurostat)



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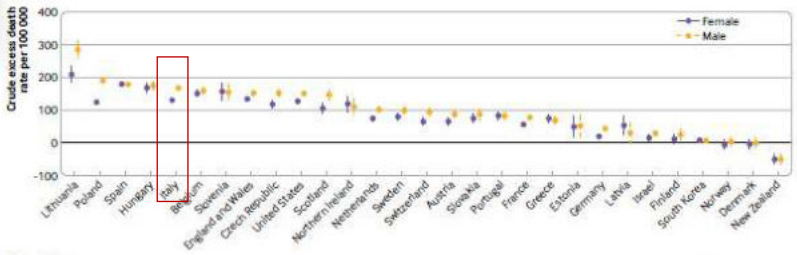
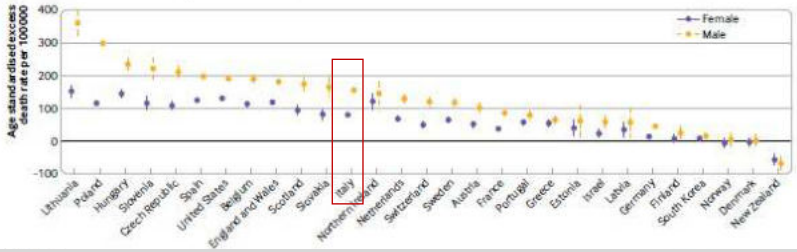
Excess deaths associated with covid-19 pandemic in 2020: age and sex disaggregated time series analysis in 29 high income countries BMJ

Nazrul Islam,[1,2] Vladimir M Shkolnikov,[3,4] Rolando J Acosta,[5] Ilya Klimkin,[4] Ichiro Kawachi,[6] Rafael A Irizarry,[1,7] Gianfranco Alicandro,[8] Kamlesh Khunti,[9,10] Tom Yates,[9,11] Dmitri A Jdanov,[3,4] Martin White,[2] Sarah Lewington,[1,12] Ben Lacey[1]

Eccesso di mortalità grezzo




Eccesso di mortalità aggiustato




Crude and age standardised excess death rates in 29 high income countries in 2020, by sex. Excess death rate (per 100 000) in 2020 was calculated as difference in observed deaths and expected deaths predicted using over-dispersed Poisson model that accounts for temporal trends and seasonal and natural variability.



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## Variante prevalente nel nostro paese: Variante Alfa

| Etichetta OMS | lineage Pangolino | clade/lineage GISAID | Nextstrain clade | Primi campioni documentati | Data di designazione |
|---|---|---|---|---|---|
| **Alpha** | B.1.1.7 | GRY (ex GR/501Y.V1) | 20I/S:501Y.V1 | Regno Unito settembre-2020 | 18-dicembre-2020 |


- **Diffusa su tutto il territorio nazionale** (21.288 casi di infezione va Virus SARS-CoV-2 variante alfa segnalati dal 28 dicembre 2020 al 6 giugno 2021 sono stati segnalati al Sistema di Sorveglianza Integrata COVID-19 – il 74,89% di tutti i casi genotipizzati)
- **Prevalenza nazionale** al 18 maggio 2021 dell'88,1% (range regionale: 40 - 100%).
- Aumentata **trasmissibilità**
- **Efficacia vaccinale mantenuta**



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## Altre varianti presenti nel nostro paese (classificazione OMS)

**VOC**

| Etichetta OMS | lineage Pango | clade/lineage GISAID | Nextstrain clade | Primi campioni documentati | Data di designazione |
|---|---|---|---|---|---|
| **Beta** | B.1.351 | GH/501Y.V2 | 20H/S:501Y.V2 | Sud Africa, maggio-2020 | 18-dicembre-2020 |
| **Gamma** | P.1 | GR/501Y.V3 | 20J/S:501Y.V3 | Brazile, novembre-2020 | 11- gennaio-2021 |
| **Delta** | B.1.617.2 | G/452R.V3 | 21A/S:478K | India, ottobre-2020 | VOI: 4-aprile -2021<br>VOC: 11-maggio -2021 |

**VOI**

| Etichetta OMS | lineage Pango | clade/lineage GISAID | Nextstrain clade | Primi campioni documentati | Data di designazione |
|---|---|---|---|---|---|
| **Zeta** | P.2 | GR | 20B/S.484K | Brazile, aprile-2020 | 17-marzo-2021 |
| **Eta** | B.1.525 | G/484K.V3 | 20A/S484K | Paesi multipli, dicembre-2020 | 17-marzo-2021 |
| **Kappa** | B.1.617.1 | G/452R.V3 | 21A/S:154K | India, ottobre-2020 | 4-aprile-2021 |



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## Altre varianti presenti nel nostro paese: frequenza di genotipizzazione

Italia, 28 dicembre 2020 – 6 giugno 2021 (Fonte - Sistema di Sorveglianza Integrata COVID-19)

| Etichetta OMS | Lignaggio | Numero di casi | % |
|---|---|---|---|
| Alpha | B.1.1.7 | 21.288 | 74,89 |
| **Beta** | **B.1.351** | **215** | **0,76** |
| **Gamma** | **P.1** | **1.780** | **6,26** |
| **Zeta** | **P.2** | **9** | **0,03** |
| **Eta** | **B.1.525** | **338** | **1,19** |
| **ND[a]** | **B.1.1.7 + E484K** | **11** | **0,04** |
| **Kappa/Delta** | **B.1.617.1/2[b]** | **91[c]** | **0,32** |
| **ND[a]** | **Altro lignaggio /non indicato[d]** | **4.694** | **16,51** |
| **Totale** | | **28.426** | **100** |



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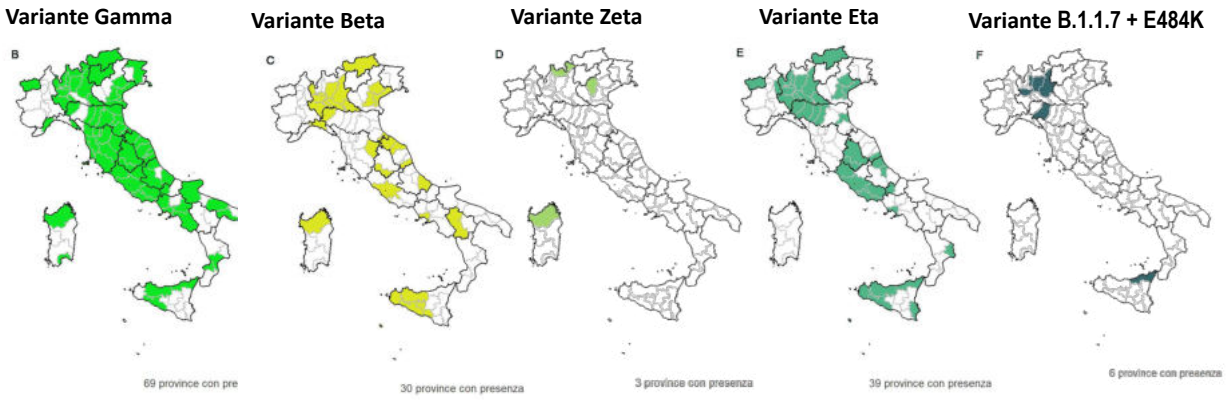
## Altre varianti presenti nel nostro paese: diffusione

Italia, 28 dicembre 2020 – 6 giugno 2021 (Fonte - Sistema di Sorveglianza Integrata COVID-19)



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## Altre varianti presenti nel nostro paese: diffusione

Italia, 28 dicembre 2020 – 6 giugno 2021 (Fonte - Sistema di Sorveglianza Integrata COVID-19)

**Variante Kappa/Delta**


- **Presente in alcune provincie italiane** (91 casi di infezione segnalati dal 28 dicembre 2020 al 6 giugno 2021 sono stati segnalati al Sistema di Sorveglianza Integrata COVID-19 – il 0,32% di tutti i casi genotipizzati)
- **Prevalenza nazionale** al 18 maggio 2021 varianti kappa (lignaggio B.1.617.1) e delta (lignaggio B.1.617.2): 1% (range regionale: 0 – 3,4%). Di 18 casi ascrivibili al lignaggio B.1.617 (che comprende le varianti kappa e delta), 16 sono risultati appartenenti al sotto-lignaggio B.1.617.2 (variante delta).
- Documentato dall'OMS un impatto sostanziale nell'efficacia di alcuni cicli vaccinali non completi in caso di infezione con variante delta, che sebbene rara in Italia è pertanto al momento oggetto di un attento monitoraggio.



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# Valutazione del rischio

Processo strutturato volto a quantificare la probabilità che un agente patogeno o una minaccia sconosciuta abbiano un effetto negativo su individui o sulla popolazione




# Analisi del rischio e scenario per Regione/PA

31maggio – 6 giugno2021 (9 giugno 2021),
analisi dell'occupazione dei PL attivi aggiornata al 8 giugno 2021

**Fonte: Cabina di Regia**

*Tabella 1 - Valutazione della probabilità di diffusione d'accordo all'algoritmo di valutazione del DM Salute 30 aprile 2020, dati al 1 giugno 2021 relativi alla settimana 24/5/2021-30/5/2021*

| Regione.PA | Completezza dei dati sopra-soglia (appendice-tabella 2)? | Domanda 1 | Domanda 2 | | | | Domanda 3 | Valutazione della probabilità |
|---|---|---|---|---|---|---|---|---|
| | | Nuovi casi segnalati negli ultimi 5 giorni? | Trend di casi (Ind3.1) | Trend di casi (Ind3.4) | Rt puntuale sopra uno? | Trend focolai | Dichiarata trasmissione non gestibile in modo efficace con misure locali (zone rosse)?* | |
| Abruzzo | Si | Si | ↓ | ↓ | No | ↓ | No | Bassa |
| Basilicata | Si | Si | ↓ | ↓ | No | ↓ | No | Bassa |
| Calabria | Si | Si | ↓ | ↓ | No | ↓ | No | Bassa |
| Campania | Si | Si | ↓ | ↓ | No | ↓ | No | Bassa |
| Emilia-Romagna | Si | Si | ↓ | ↓ | No | ↓ | No | Bassa |
| FVG | Si | Si | ↓ | ↓ | No | ↓ | No | Bassa |
| Lazio | Si | Si | ↓ | ↓ | No | ↓ | No | Bassa |
| Liguria | Si | Si | ↓ | ↓ | No | ↓ | No | Bassa |
| Lombardia | Si | Si | ↓ | ↓ | No | ↓ | No | Bassa |
| Marche | Si | Si | ↓ | ↓ | No | ↓ | No | Bassa |
| Molise | Si | Si | = | ↓ | No | = | No | Bassa |
| Piemonte | Si | Si | ↓ | ↓ | No | ↓ | No | Bassa |
| PA Bolzano/Bozen | Si | Si | ↓ | ↓ | No | ↑ | No | Bassa |
| PA Trento | Si | Si | ↓ | ↓ | No | ↓ | No | Bassa |
| Puglia | Si | Si | ↓ | ↓ | No | ↓ | No | Bassa |
| Sardegna | Si | Si | ↓ | ↓ | No | ↓ | No | Bassa |
| Sicilia | Si | Si | ↓ | ↓ | No | ↓ | No | Bassa |
| Toscana | Si | Si | ↓ | ↓ | No | ↓ | No | Bassa |
| Umbria | Si | Si | ↓ | ↓ | No | ↓ | No | Bassa |
| V.d'Aosta/V.d'Aoste | Si | Si | ↓ | ↓ | No | ↓ | No | Bassa |
| Veneto | Si | Si | ↓ | ↓ | No | ↓ | No | Bassa |

* elemento considerato come allerta di resilienza ai sensi dell'articolo 30 comma 1 del DL n. 149 del 9 novembre 2020



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*Tabella 2 – Valutazione di impatto d'accordo all'algoritmo di valutazione del DM Salute 30 aprile, dati al 1 giugno 2021 relativi alla settimana 24/5/2021-30/5/2021*

| Regione.PA | Domanda 1 | Domanda 2 (dati più recenti disponibili*) | | Domanda 3 | Valutazione di impatto |
|---|---|---|---|---|---|
| | Nuovi casi segnalati negli ultimi 5 giorni in soggetti di età >50 anni? | Sovraccarico in Terapia Intensiva (Ind3.8 sopra 30%)? | Sovraccarico in aree mediche (Ind3.9 sopra 40%)? | Evidenza di nuovi focolai negli ultimi 7 giorni in RSA/case di riposo/ospedali o altri luoghi che ospitino popolazioni vulnerabili (anziani e/o soggetti con patologie)? | |
| Abruzzo | Si | No | No | - | Bassa |
| Basilicata | Si | No | No | - | Bassa |
| Calabria | Si | No | No | - | Bassa |
| Campania | Si | No | No | - | Bassa |
| Emilia-Romagna | Si | No | No | - | Bassa |
| FVG | Si | No | No | - | Bassa |
| Lazio | Si | No | No | - | Bassa |
| Liguria | Si | No | No | - | Bassa |
| Lombardia | Si | No | No | - | Bassa |
| Marche | Si | No | No | - | Bassa |
| Molise | Si | No | No | - | Bassa |
| Piemonte | Si | No | No | - | Bassa |
| PA Bolzano/Bozen | Si | No | No | - | Bassa |
| PA Trento | Si | No | No | - | Bassa |
| Puglia | Si | No | No | - | Bassa |
| Sardegna | Si | No | No | - | Bassa |
| Sicilia | Si | No | No | - | Bassa |
| Toscana | Si | No | No | - | Bassa |
| Umbria | Si | No | No | - | Bassa |
| V.d'Aosta/V.d'Aoste | Si | No | No | - | Bassa |
| Veneto | Si | No | No | - | Bassa |

*aggiornato al 31/05/2021



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*Tabella 3 – Valutazione complessiva di rischio d'accordo alla matrice di rischio del DM Salute 30 aprile e sulla probabilità di raggiungere le soglie critiche di occupazione dei PL in area medica e terapia intensiva nei prossimi 30 giorni, dati al 1 giugno 2021 relativi alla settimana 24/5/2021-30/5/2021*

| Regione.PA | Valutazione della probabilità | Valutazione di impatto | Molteplici allerte di resilienza? (Appendice tabella 3) | Probabilità di una escalation nei prossimi 30 giorni (proiezioni al giorno 01 /07/2021 della probabilità di superare le soglie di occupazione dei PL) | | Classificazione complessiva del rischio |
|---|---|---|---|---|---|---|
| | | | | % probabilità raggiungere occupazione TI 30% | % probabilità raggiungere occupazione aree mediche 40% | |
| Abruzzo | Bassa | Bassa | No | <5% | <5% | Bassa |
| Basilicata | Bassa | Bassa | No | <5% | <5% | Bassa |
| Calabria | Bassa | Bassa | No | <5% | <5% | Bassa |
| Campania | Bassa | Bassa | No | <5% | <5% | Bassa |
| Emilia-Romagna | Bassa | Bassa | No | <5% | <5% | Bassa |
| FVG | Bassa | Bassa | No | <5% | <5% | Bassa |
| Lazio | Bassa | Bassa | No | <5% | <5% | Bassa |
| Liguria | Bassa | Bassa | No | <5% | <5% | Bassa |
| Lombardia | Bassa | Bassa | No | <5% | <5% | Bassa |
| Marche | Bassa | Bassa | No | da 5 a 50% | da 5 a 50% | Bassa |
| Molise | Bassa | Bassa | No | <5% | <5% | Bassa |
| Piemonte | Bassa | Bassa | No | <5% | <5% | Bassa |
| PA Bolzano/Bozen | Bassa | Bassa | No | <5% | <5% | Bassa |
| PA Trento | Bassa | Bassa | No | da 5 a 50% | <5% | Bassa |
| Puglia | Bassa | Bassa | No | <5% | <5% | Bassa |
| Sardegna | Bassa | Bassa | No | <5% | <5% | Bassa |
| Sicilia | Bassa | Bassa | No | <5% | <5% | Bassa |
| Toscana | Bassa | Bassa | No | <5% | <5% | Bassa |
| Umbria | Bassa | Bassa | No | <5% | <5% | Bassa |
| V.d'Aosta/V.d'Aoste | Bassa | Bassa | No | <5% | <5% | Bassa |
| Veneto | Bassa | Bassa | No | <5% | <5% | Bassa |



*Appendice - Tabella 1 – Quadro sintetico con i principali indicatori del monitoraggio e compatibilità con gli Rt puntuali con gli scenari ai sensi del documento "Prevenzione e risposta a COVID-19: evoluzione della strategia e pianificazione nella fase di transizione per il periodo autunno-invernale", dati al 1 giugno 2021 relativi alla settimana 24/5/2021-30/5/2021*

| Regione.PA | Nuovi casi segnalati nella settimana | Trend settimanale COVID-19 | | Stima di Rt-puntuale (calcolato al 18/05/2021) | Dichiarata trasmissione non gestibile in modo efficace con misure locali (zone rosse) | Valutazione della probabilità | Valutazione di impatto | Allerte relative alla resilienza dei servizi sanitari territoriali | Compatibilità Rt sintomi puntuale con gli scenari di trasmissione* | Classificazione complessiva di rischio | Classificazione Alta e/o equiparata ad Alta per 3 o più settimane consecutive |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Casi (Fonte ISS) | Focolai | | | | | | | | |
| Abruzzo | 292 | -29.7 | -89 | 0.64 (CI: 0.58-0.72) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| Basilicata | 280 | -21.7 | -7 | 0.64 (CI: 0.44-0.87) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| Calabria | 879 | -22.2 | -10 | 0.78 (CI: 0.7-0.88) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| Campania | 2707 | -32.6 | -332 | 0.57 (CI: 0.55-0.6) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| Emilia-Romagna | 1228 | -44.8 | -328 | 0.69 (CI: 0.65-0.73) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| FVG | 206 | -9.3 | -71 | 0.59 (CI: 0.5-0.68) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| Lazio | 2027 | -32.8 | -3 | 0.65 (CI: 0.62-0.67) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| Liguria | 320 | -20.0 | -99 | 0.68 (CI: 0.61-0.75) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| Lombardia | 3733 | -27.0 | -1187 | 0.68 (CI: 0.65-0.7) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| Marche | 629 | -26.7 | -39 | 0.8 (CI: 0.69-0.92) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| Molise | 35 | -8.1 | 0 | 0.45 (CI: 0.15-1.03) | No | Bassa | Bassa | 1 allerta segnalata. Ind 2.1 in aumento. | 1 | Bassa | No |
| Piemonte | 1672 | -31.8 | -317 | 0.64 (CI: 0.61-0.68) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| PA Bolzano/Bozen | 243 | -26.6 | 6 | 0.99 (CI: 0.87-1.12) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| PA Trento | 229 | -13.5 | -13 | 0.93 (CI: 0.8-1.06) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| Puglia | 1361 | -34.2 | -6 | 0.67 (CI: 0.64-0.71) | No | Bassa | Bassa | 1 allerta segnalata. Ind 2.6 in diminuzione e sotto il 90% | 1 | Bassa | No |
| Sardegna | 197 | -24.5 | -84 | 0.55 (CI: 0.46-0.65) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| Sicilia | 2312 | -13.1 | -296 | 0.7 (CI: 0.67-0.75) | No | Bassa | Bassa | 1 allerta segnalata. Ind 2.1 in aumento. | 1 | Bassa | No |
| Toscana | 1594 | -30.4 | -199 | 0.74 (CI: 0.7-0.77) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| Umbria | 260 | -9.0 | -71 | 0.66 (CI: 0.58-0.74) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |
| V.d'Aosta/V.d'Aoste | 84 | -24.1 | -8 | 0.8 (CI: 0.65-0.96) | No | Bassa | Bassa | 1 allerta segnalata. Ind 2.1 in aumento. | 1 | Bassa | No |
| Veneto | 1196 | -29.4 | -681 | 0.64 (CI: 0.61-0.68) | No | Bassa | Bassa | 0 allerte segnalate | 1 | Bassa | No |

PA: Provincia Autonoma; gg: giorni
* ai sensi del documento "Prevenzione e risposta a COVID-19: evoluzione della strategia e pianificazione nella fase di transizione per il periodo autunno-invernale

## **Indicatori decisionali** come da Decreto Legge del 18 maggio 2021 n.65 articolo 13 - **Aggiornamento del 10/06/2021**

| Regione | Incidenza a 7 gg/100.000 pop - Periodo di riferimento 14-20 maggio 2021 | Incidenza a 7 gg/100.000 pop - Periodo di riferimento 21-27 maggio 2021 | Incidenza a 7 gg/100.000 pop - Periodo di riferimento 28 maggio-3 giugno 2021 | Incidenza a 7 gg/100.000 pop - Periodo di riferimento 4-10 giugno 2021 | % OCCUPAZIONE PL AREA MEDICA DA PAZIENTI COVID al 08/06/2021 | % OCCUPAZIONE PL TERAPIA INTENSIVA DA PAZIENTI COVID al 08/06/2021 |
|---|---|---|---|---|---|---|
| Abruzzo | 42 | 35 | 22 | 19 | 6% | 3% |
| Basilicata | 100 | 62 | 35 | 39 | 10% | 0% |
| Calabria | 71 | 61 | 43 | 36 | 20% | 8% |
| Campania | 95 | 66 | 43 | 31 | 13% | 7% |
| Emilia Romagna | 67 | 45 | 30 | 22 | 6% | 9% |
| Friuli Venezia Giulia | 24 | 17 | 17 | 19 | 2% | 2% |
| Lazio | 64 | 46 | 30 | 23 | 10% | 11% |
| Liguria | 43 | 28 | 22 | 10 | 4% | 10% |
| Lombardia | 63 | 46 | 31 | 23 | 11% | 10% |
| Marche | 75 | 55 | 34 | 28 | 7% | 7% |
| Molise | 20 | 12 | 9 | 9 | 3% | 0% |
| PA di Bolzano | 76 | 59 | 41 | 31 | 3% | 1% |
| PA di Trento | 61 | 45 | 35 | 25 | 4% | 7% |
| Piemonte | 71 | 49 | 33 | 23 | 7% | 9% |
| Puglia | 75 | 50 | 31 | 25 | 10% | 5% |
| Sardegna | 25 | 13 | 14 | 12 | 6% | 3% |
| Sicilia | 68 | 53 | 47 | 40 | 11% | 6% |
| Toscana | 84 | 59 | 39 | 28 | 6% | 18% |
| Umbria | 42 | 28 | 25 | 21 | 7% | 5% |
| Valle d'Aosta | 107 | 79 | 56 | 31 | 3% | 0% |
| Veneto | 45 | 30 | 19 | 15 | 3% | 4% |
| ITALIA | ***66*** | ***47*** | ***32*** | ***25*** | ***8%*** | ***8%*** |

*Fonte dati: Ministero della Salute / Protezione Civile*



Fonte dati: Ministero della Salute / Protezione Civile



## Headline della Cabina di Regia (11 giugno 2021)

*L'incidenza, sia sull'intero territorio nazionale che in tutte le regioni/PPAA, continua a diminuire ed è in tutte le Regioni/PPAA sotto il 50 per 100.000 abitanti ogni 7 giorni. L'effettuazione di attività di tracciamento sistematico possono consentire una gestione basata sul contenimento ovvero sull'identificazione dei casi e sul tracciamento dei loro contatti.*

*La pressione sui servizi ospedalieri si conferma al di sotto della soglia critica in tutte le Regioni/PA e la stima dell'indice di trasmissibilità Rt medio calcolato sui casi sintomatici è stabilmente al di sotto della soglia epidemica.*

# Headline della Cabina di Regia (11 giugno 2021)

*La circolazione di varianti che possono avere una maggiore trasmissibilità e/o eludere parzialmente la risposta immunitaria, che ha portato ad un inatteso aumento dei casi in paesi europei con alta copertura vaccinale, richiede un capillare tracciamento e sequenziamento dei casi.*

*Il raggiungimento di una elevata copertura vaccinale ed il completamento dei cicli di vaccinazione rappresenta uno strumento indispensabile ai fini della prevenzione di ulteriori recrudescenze di episodi pandemici.*

# Heterologous prime-boost COVID-19 vaccination: initial reactogenicity data

There is significant international interest in heterologous prime-boost COVID-19 vaccination to mitigate against supply shocks or shortages that might otherwise reduce the speed of vaccine roll-out. Additionally, in light of changing recommendations regarding use of the ChAdOx1 nCoV-19 (ChAd) COVID-19 vaccine (Vaxzevria, AstraZeneca), several countries are now advising that individuals previously primed with this vaccine should now receive an alternative vaccine as their second dose, most commonly mRNA vaccines such as the BNT162b2 (BNT) COVID-19 vaccine (Comirnaty, Pfizer–BioNTech), administered in a heterologous prime-boost schedule.[1–3] To date there are no data on the immunogenicity, reactogenicity, or safety of such schedules. Com-COV (ISRCTN 69254139) is a UK multicentre, participant-masked, randomised heterologous prime-boost COVID-19 vaccination study comparing all four prime-boost permutations of the ChAd and BNT vaccines both at 28-day and 84-day prime-boost intervals. Participants are 50 years and older with no or mild-to-moderate, well controlled comorbidity and were recruited across eight sites. The protocol is available online.

Following consultation with the study trial steering committee, here we present the initial reactogenicity and safety data, ahead of the primary immunological outcome, which is projected to be available in June, 2021. Reactogenicity data presented here consist of self-reported solicited local and systemic symptoms collected in the 7 days after both prime and boost vaccination in participants randomised to receive vaccines at 28-day intervals. Haematology and biochemistry safety monitoring blood results are also reported from the immunology cohort (100 participants with additional visits), at baseline (before the prime dose), at day 28 (before the boost dose) and 7 days post-boost, graded according to a modified US Food and Drug Administration toxicity scale (appendix). All analyses are descriptive, as the study was not powered for reactogenicity, with endpoints reported as frequencies and percentages, together with absolute differences between heterologous and homologous vaccine schedules and corresponding 95% CIs.

Recruitment commenced on Feb 11, 2021, and was completed on Feb 26, 2021, with 830 participants enrolled and randomised from 978 screened (the CONSORT flow diagram is available in the appendix). 463 participants were randomly assigned to the four groups with a 28-day prime-boost interval, and 367 participants randomised to groups with an 84-day prime-boost interval. All 463 participants in the 28-day prime-boost interval group received their prime vaccine, and 461 participants received their boost vaccine. Among the 463 participants, the median age was 57 years (range 50–69), 212 (46%) participants were female, and 117 (25%) from ethnic minorities, with baseline characteristics well balanced across study groups. In groups with homologous vaccine schedules, systemic reactogenicity was greater after the prime dose in the ChAd group, and after the boost dose in the BNT group (figure).

Both heterologous vaccine schedules induced greater systemic reactogenicity following the boost dose than their homologous counterparts, with feverishness reported by 37 (34%) of 110 recipients of ChAd for prime and BNT for boost compared with 11 (10%) of 112 recipients of ChAd for both prime and boost (difference 24%, 95% CI 13–35%). Feverishness was reported by 47 (41%) of 114 recipients of BNT for prime and ChAd for boost, compared with 24 (21%) of 112 recipients of BNT for both prime and boost (difference 21%, 95% CI 8–33%). Similar increases were observed for chills, fatigue, headache, joint pain, malaise, and muscle ache (figure; appendix). There were no hospitalisations due to solicited symptoms, and most of this increase in reactogenicity was observed in the 48 h after immunisation (appendix).

Participants were advised that paracetamol might reduce vaccine side-effects but were not actively counselled to medicate prophylactically. Paracetamol use in the 48 h post-boost vaccine was reported by 40 (36%) of 112 recipients of ChAd for both prime and boost, 63 (57%) of 110 recipients of ChAd for prime and BNT for boost, 48 (41%) of 117 recipients of BNT for both prime and boost, and 68 (60%) of 114 recipients of BNT for prime and ChAd for boost, thereby mirroring the reactogenicity pattern.

Haematology and biochemistry profiles were similar between heterologous and homologous vaccine schedules, with all laboratory adverse events of grade 2 severity or less in the heterologous vaccine schedule, and no thrombocytopenia in any group at day 7 post-boost (appendix).

In this interim safety analysis, we found an increase in systemic reactogenicity after the boost dose reported by participants in heterologous vaccine schedules in comparison to homologous vaccine schedules, and this was accompanied by increased paracetamol usage. Of note, these data were obtained in participants aged 50 years and older, and reactogenicity might be higher in younger age groups[4,5] for whom a mixed vaccination schedule is being advocated in Germany, France, Sweden, Norway, and Denmark among those who have received a ChAd prime dose, in light of concerns regarding thrombotic thrombocytopenia after the first dose of ChAd.[6]

Pending availability of a more complete safety dataset and immunogenicity results for heterologous

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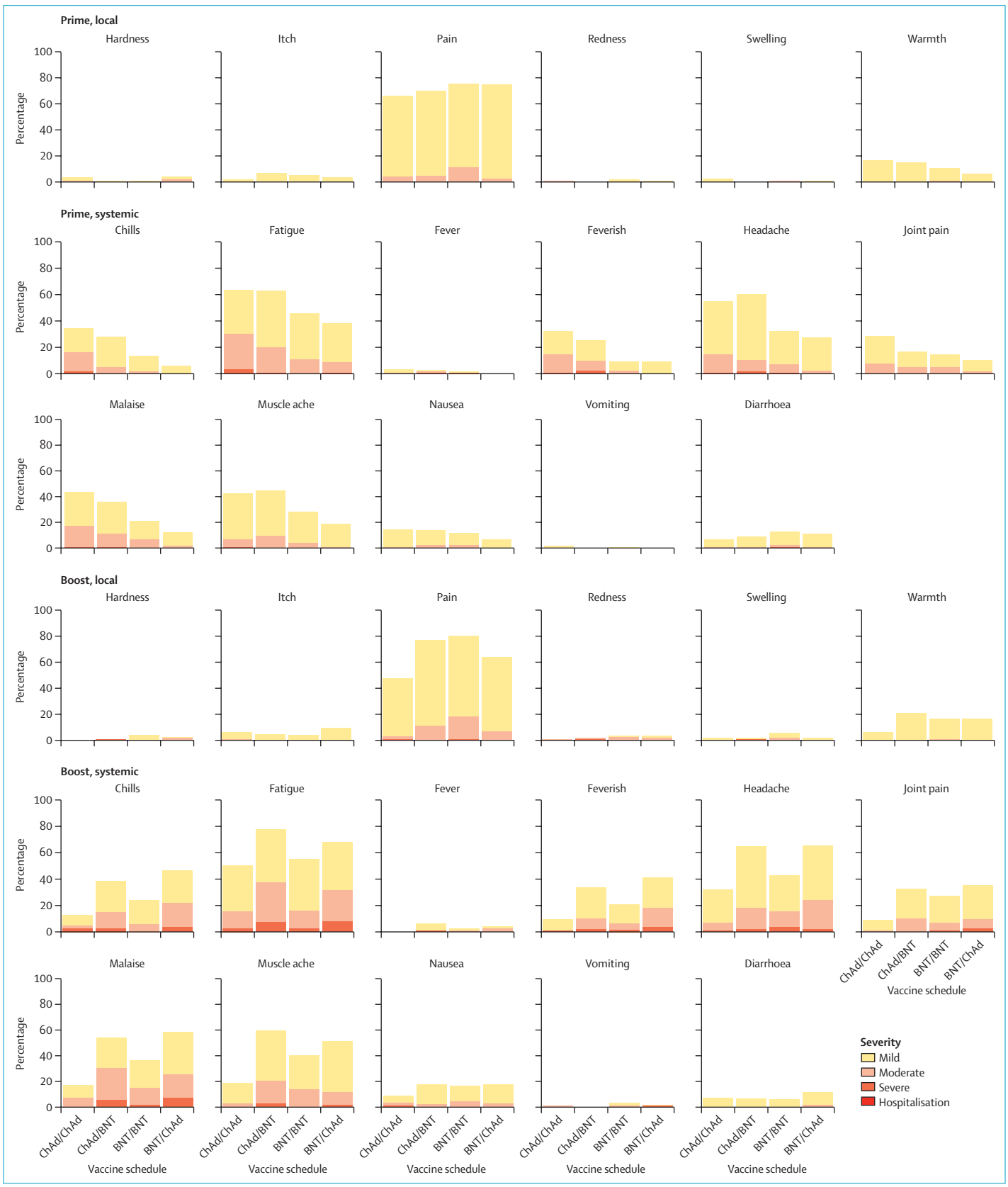



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prime-boost schedules (to be reported shortly), these data suggest that the two heterologous vaccine schedules in this trial might have some short-term disadvantages. Routine prophylactic use of paracetamol after immunisation could help mitigate these[7] and is being studied in Com-COV participants receiving prime and boost vaccines at 12-week intervals. Regardless, it is reassuring that all reactogenicity symptoms were short lived, and there were no concerns from the limited haematology and biochemistry data available. Further studies evaluating heterologous prime-boost schedules, incorporating vaccines manufactured by Moderna and Novavax, are ongoing, and are crucial to informing the appropriateness of mixed COVID-19 vaccine schedules.

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***Figure*: Severity of solicited local and systemic reactions in days 0–7 after vaccination with ChAdOx1 nCoV-19 (ChAd) or BNT162b2 (BNT), by prime and boost vaccination and by vaccination group, as self-reported in participant electronic diaries**
ChAd/ChAd denotes a ChAd vaccine for prime and boost doses. ChAd/BNT denotes a ChAd vaccine for prime dose and a BNT vaccine for boost dose. BNT/BNT denotes a BNT vaccine for prime and boost doses. BNT/ChAd denotes a BNT for prime dose and a ChAd vaccine for boost dose.
The severity presented is the participant's highest severity across 7 days after vaccination for each solicited adverse event. Fever was categorised as mild (38·0°C to <38·5°C), moderate (38·5°C to <39°C), or severe (≥39·0°C). Feverish was a self-reported feeling of feverishness. For systemic symptoms, grading was classified as mild (easily tolerated with no limitation on normal activity), moderate (some limitation of daily activity), and severe (unable to perform normal daily activity).

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## An acute-on-chronic health crisis in Gaza

The Palestinian Gaza Strip is a 365 km² piece of land on the eastern coast of the Mediterranean, inhabited by more than 2 million Palestinians. This open-air enclave has been under siege for the past 14 years, which has left the health system jeopardised by limited resources, failing equipment, and many essential drugs in dangerously low supply. This grim situation was worsened by the arrival of the COVID-19 pandemic, threatening health services with collapse. Beginning on May 9, 2021, the Israeli Government and Hamas launched a military offensive against one another, the severity of which for the Gaza Strip is believed to be the worst since 2014.[1]

The background to this situation is important. There has been increasing tension in Israeli-occupied Palestinian East Jerusalem, with Palestinian families living in the Sheikh Jarrah neighbourhood fighting a legal struggle against their eviction.[2] Tensions grew further at the beginning of the Muslim holy month of Ramadan, with Israel blocking Palestinian gatherings, and with Palestinian worshippers calling for the removal of Israeli police from the al-Aqsa mosque, one of the three holiest sites of Islam where Palestinians pray during Ramadan. In the early morning of May 10, 2021, Israeli forces entered the al-Aqsa mosque while people were praying, with Palestinians injured by rubber bullets and tear gas.[3,4]

In the Gaza Strip, Hamas responded by firing rockets into Israel. Israel responded with strikes by fighter jets and attack helicopters on military targets, which also, and inevitably, included densely populated civilian areas. As of May 18, 2021, Israeli attacks are ongoing, and the Palestinian Ministry of Health has reported at least 212 Palestinians killed, including 36 women and 61 children, and about 1500 Palestinians wounded.[5,6] Hamas rockets have killed ten Israelis, including two children, and wounded at least 300 Israelis.[6] Hospital emergency departments in Gaza are unable to cope with critical medical conditions, including severe hypovolemic shock, penetrating head, chest, and abdominal injuries, burns, blast injures, and severe lacerated and fragmented lower limbs. The continuous attacks on dense Gaza urban settings have not only led to the deaths and injuries of civilians but have also left hundreds of people homeless.

We call upon world leaders to intervene for an immediate de-escalation of attacks by both the Israeli Government and Hamas and to end the violence, protect civilians from political violence in the Gaza Strip and the West Bank, and protect civilians in Israel. We also call for renewed international action to deliver justice, freedom, and self-determination for Palestinians.

We declare no competing interests.

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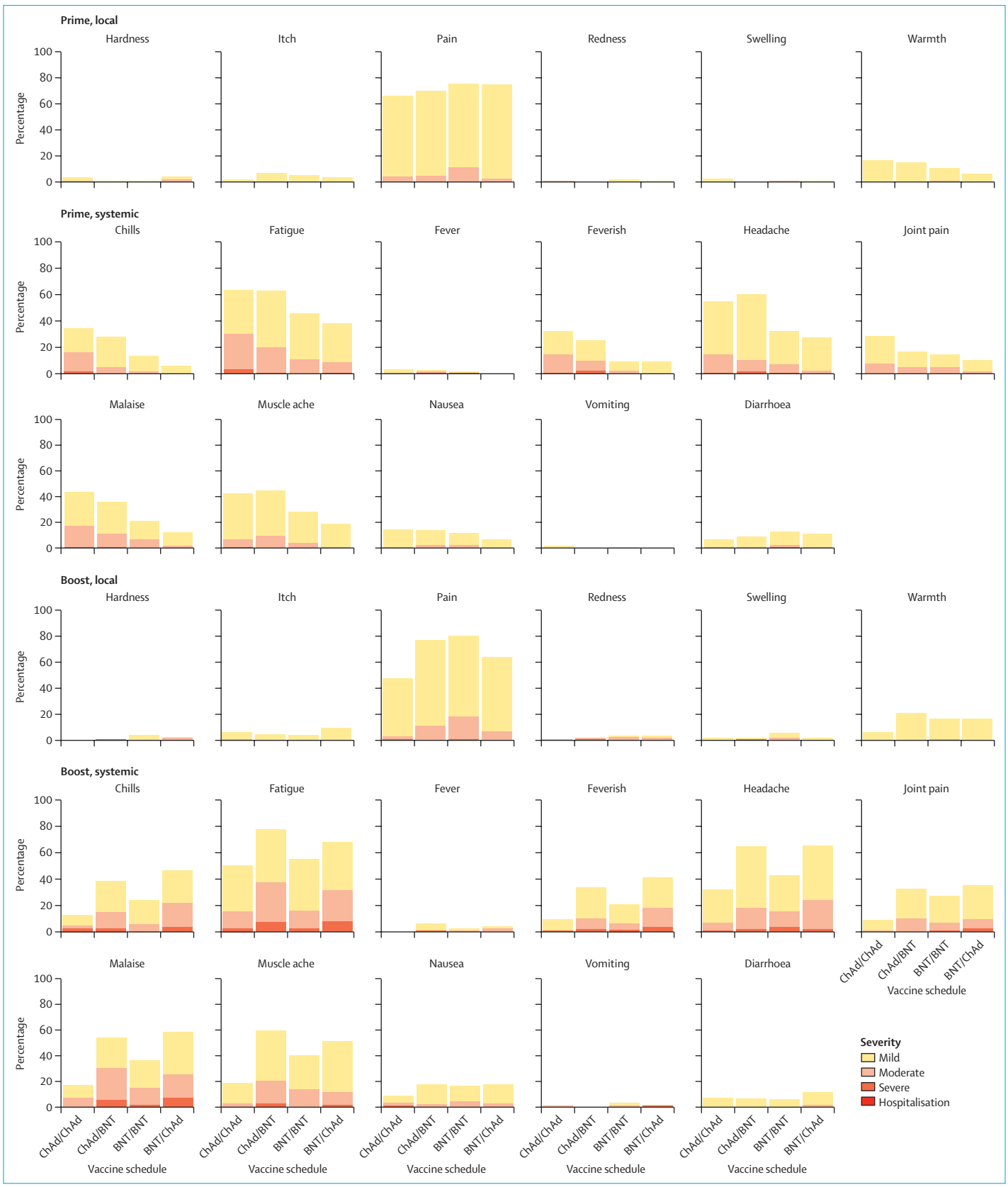
Prime, local
Hardness
Itch
Pain
Redness
Swelling
Warmth
Prime, systemic
Chills
Fatigue
Fever
Feverish
Headache
Joint pain
Malaise
Muscle ache
Nausea
Vomiting
Diarrhoea
Boost, local
Hardness
Itch
Pain
Redness
Swelling
Warmth
Boost, systemic
Chills
Fatigue
Fever
Feverish
Headache
Joint pain
Malaise
Muscle ache
Nausea
Vomiting
Diarrhoea
Percentage
0
20
40
60
80
100
ChAd/ChAd
ChAd/BNT
BNT/BNT
BNT/ChAd
Vaccine schedule
Severity
Mild
Moderate
Severe
Hospitalisation

(100 participants with additional visits), at baseline (before the prime dose), at day 28 (before the boost dose) and 7 days post-boost, graded according to a modified US Food and Drug Administration toxicity scale (appendix). All analyses are descriptive, as the study was not powered for reactogenicity, with endpoints reported as frequencies and percentages, together with absolute differences between heterologous and homologous vaccine schedules and corresponding 95% CIs.

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Haematology and biochemistry profiles were similar between heterologous and homologous vaccine schedules, with all laboratory adverse events of grade 2 severity or less in the heterologous vaccine schedule, and no thrombocytopenia in any group at day 7 post-boost (appendix).

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Pending availability of a more complete safety dataset and immunogenicity results for heterologous prime-boost schedules (to be reported shortly), these data suggest that the two heterologous vaccine schedules in this trial might have some short-term disadvantages. Routine prophylactic use of paracetamol after immunisation could help mitigate these[7] and is being studied in Com-COV participants receiving prime and boost vaccines at 12-week intervals. Regardless, it is reassuring that all reactogenicity symptoms were short lived, and there were no concerns from the limited haematology and biochemistry data available. Further studies evaluating heterologous prime-boost schedules, incorporating vaccines manufactured by Moderna and Novavax, are ongoing, and are crucial to informing the appropriateness of mixed COVID-19 vaccine schedules.

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See **Online** for appendix

***Figure*: Severity of solicited local and systemic reactions in days 0–7 after vaccination with ChAdOx1 nCoV-19 (ChAd) or BNT162b2 (BNT), by prime and boost vaccination and by vaccination group, as self-reported in participant electronic diaries**

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For more on **vaccine doses administered** see https://ourworldindata.org/covid-vaccinations

See **Online** for appendix

For more on **COVAX** see https://www.who.int/initiatives/act-accelerator/about

## A global compact to counter vaccine nationalism

Vaccine nationalism threatens to turn the triumph of science to give the world vaccines against COVID-19 into tragedy. The success of several initiatives, many funded by taxpayers, to rapidly develop and test several safe and effective vaccines has been nothing short of spectacular. The social promise of SARS-CoV-2 vaccines was to reduce the underlying inequalities by race, ethnicity, and geography that COVID-19 has both made visible and amplified.[1] Yet, most of the billion vaccine doses administered have been in high-income countries (HICs), with most low-income and middle-income countries (LMICs) left behind (appendix). WHO and Gavi, the Vaccine Alliance have created COVAX to finance SARS-Cov-2 vaccines for LMICs, yet supply of vaccines is still short and coming from only a few companies. India's mostly uncontrolled second viral wave threatens exports of vaccines promised to many countries. The US Government suspending its objections to COVID-19 vaccine patents could help. However, the priority is to produce sufficient quantities on an urgent basis to provide global coverage.

Aspirations to return to some sense of normality might well remain wishful thinking until most adults globally are vaccinated. How do we do that? We propose an integrated three-pillar global vaccine compact to expand vaccine supply and counter vaccine nationalism.

Global vaccine production capacity in non-pandemic times is too small and too concentrated in a handful of pharmaceutical companies.[2] The first pillar of our proposed compact would be for countries to adopt the idea of a fully immunised adult, and launch national adult vaccination programmes. Using the US Disease Control Priorities Cost Model,[3] we estimate that the total cost of routine annual influenza vaccination, 5-yearly pneumococcal vaccines, HPV vaccines for adolescent girls, and tetanus for expectant mothers (including HICs) could be US$34 billion annually. National governments would need to pay for adult programmes, aided by an expanded mandate for Gavi. Per year, an average of about 1·1 vaccines for 5 billion adults might save one million lives from the targeted diseases. Existing live attenuated vaccines have shown action against multiple pathogens, although COVID-19 trials remain to be done.[4] These vaccines might prove to be valuable additions to adult vaccination schedules in some circumstances. Analogously, preliminary data in preprint suggest that annual influenza vaccination reduces the risk of influenza pandemics and perhaps even COVID-19 infection.[5] Should SARS-CoV-2 vaccination need to be seasonal, adult vaccination programmes establish a delivery platform. Moreover, the world might well be entering the era where major zoonotic diseases are not events that happen once a century but once a decade. Thanks to the Bill & Melinda Gates Foundation and others, the world has endorsed universal access to life-saving vaccines for each of the 125 million children born annually. Adult and child vaccination programmes provide a cost-effective platform to prepare for future pandemics. A far larger market enables dispersed production, incentivises more companies to enter the market, and spurs innovation in vaccine design and delivery.

Next, uninterrupted supply of life-saving vaccines cannot be left only to market forces, or worse—insular political decisions. The second pillar we propose is a global vaccine manufacturing compact housed in less populous countries with good scientific and training infrastructure, a respect for legal contracts, and a reputation for fair play. Canada, Norway, Singapore, and Switzerland are possibilities, as might be several others—some of which are in Africa. The manufacturing compact would produce vaccines in the billions, far in excess of domestic demand. The compact would negotiate licences with vaccine producers but have as its core business model the sale of vaccines very near cost price. An independent governance model using professional business or civil service could counter political interference or cronyism. The facilities can learn from the successful Serum Institute of India, which helps vaccinate many of the world's children at low cost, and from Brazil's Fiocruz public partnership.[6] We estimate such a manufacturing pillar would cost about $4 billion to start (with variable running costs that can be priced into sales). It can proceed quickly. The UK was

# Reactogenicity and immunogenicity of BNT162b2 in subjects having received a first dose of ChAdOx1S: initial results of a randomised, adaptive, phase 2 trial (CombiVacS)

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## ABSTRACT

### Background

There are no immunological data on SARS-CoV-2 heterologous vaccinations schedules in humans. We assessed the immunogenicity and reactogenicity of BNT162b2 (Comirnaty, BioNTech) administered as second dose in participants primed with ChAdOx1-S (Vaxzevria, Astra Zeneca).

### Methods

We did a phase 2, open-label, adaptive, randomised, controlled clinical trial on adults under 60 years old, vaccinated with a single dose of ChAdOx1-S between 8 and 12 weeks before screening, and no history of SARS-CoV-2 infection (EudraCT No. 2021-001978-37 and NCT04860739). Participants were randomly assigned (2:1) to receive BNT162b2 (0.3 mL, single intramuscular injection) or observation. The primary outcomes were 7-day reactogenicity and 14-day anti-spike IgG response, measured by immunoassays covering SARS-CoV-2 trimeric spike protein and receptor binding domain (RBD). Antibodies functionality and cellular immune response were assessed using a pseudovirus neutralization assay and IFN-gamma immunoassay, respectively.

### Findings

Between April 24 and April 30, 2021, 676 individuals were randomized (n=450 intervention group, n=226 control group) at 5 sites in Spain, and 663 (441 and 222, respectively) completed the study up to day 14 (mean age 44 [SD 9], 56·5% female). In the intervention group, geometric mean titres (GMT) of IgG-RBD increased from 71·46 BAU/mL (95% CI 59·84-85·33) at baseline to 7756·68 (7371·53; 8161·96) at day 14 ($p < 0·0001$). IgG against trimeric spike-protein increased from 98·4 [85.69–112.99] to 3684·87 [3429·87–3958·83]). 100% participants exhibited neutralizing antibodies 14 days after BNT162b2 administration, in comparison to 34.1% at enrolment. A 4-fold increase in cellular immune response was also observed. Reactions were predominantly mild (68·3%) or moderate (29·9%), and consisted more frequently on injection site pain (88·2%), induration (35·5%), headache (44·4%) and myalgia (43·3%). No serious adverse events were reported.

### Interpretation

BNT162b2 given as a second dose in individuals prime vaccinated with ChAdOx1-S induced a robust immune response with an acceptable and manageable reactogenicity profile.

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## RESEARCH IN CONTEXT

### Evidence before this study

Heterologous regimes in Covid-19 has been proposed as an option to best elicit combined antibody and cellular responses resulting in stronger, broader and/or longer-lasting immunity. However, no clinical evidences exist so far.

### Added value of this study

This is the first study evaluating the immune and cellular response to a heterologous vaccination strategy against SARS-Cov-2. Administration of a dose of BNT162b2 vaccine after a first dose of ChAdOx1S provides a strong immune humoral and cellular response.

### Implications of all the available evidence

This study confirms preclinical studies and suggestions anticipating that heterologous vaccination regimen could provide elicit potent combined antibody and cellular responses and pave the way for mix-and-match COVID-19 vaccines development and warrant future studies evaluating this strategy.

## INTRODUCTION

The dramatic impact of COVID-19 on healthcare systems and economies over the world has driven an unprecedented research effort globally to find curative and/or prophylactic therapies. As a result, thousands of COVID-19-related clinical trials have been registered and hundreds of vaccine candidates started testing in record time.[1] Indeed, active immunization has become the cornerstone of global healthcare policies against COVID-19. To date, four vaccines have been granted a conditional marketing authorization by the European Commission: mRNA vaccine BNT162b2 (Comirnaty, BioNTech), mRNA vaccine CX-024414 (Moderna), adenovirus vaccine ChAdOx1-S (Vaxzevria, AstraZeneca) and adenovirus vaccine Ad26.Cov2.S (Janssen-Cilag International NV). Both mRNA vaccines and ChAdOx1-S are used based on homologous regimes.[2] As an alternative, the possibility of sequentially administering different SARS-CoV-2 vaccines, known as heterologous schedules, could be an opportunity to make vaccination programs more flexible and reliable in the face of supply fluctuations. In addition, these schemes are also being studied to identify the best option for the administration of third or successive booster doses.

The decisive factor in generating interest in this type of schedules was the appearance of rare but severe thrombotic with thrombocytopenia events in subject vaccinated with ChAdOx1-S. As these uncommon side effects were more frequent in young people, health authorities of several European countries[3] and Canada, among others, modified their national strategies reserving ChAdOx1-S vaccine for older groups of subjects. Consequently, some countries including Sweden, France, Germany, Norway and Denmark advised for administering a second dose with BNT162b2 vaccine in people primed with ChAdOx1-S, even without supporting data regarding reactogenicity or immunogenicity of this schedule. Obviously, heterologous approaches were not novel as they have been previously used in multiple HIV vaccines under development,[2] in the recently authorized Ebola vaccine[4,5] and it is also one of the current strategies to obtain a universal influenza vaccine.[6,7]

Regarding SARS-CoV-2, Spencer et al had recently evidenced immunological advantages using heterologous vaccination regimens in animal models (21) which concurs with the clinical efficacy showed by the heterologous vaccine Gam-COVID-Vac (Sputnik V, Gamaleya National Research Centre for Epidemiology and Microbiology [NRCEM]).[8] Regarding safety, Shaw et al published initial

data from the Com-Cov trial evidencing limited and short-lived reactogenicity when heterologous schedules were used in humans.[3] Unfortunately, no evidence of immunogenicity outcomes in humans with heterologous vaccination strategies are available to date. To answer this fundamental question, we designed a phase 2 randomised controlled trial to evaluate immunogenicity and reactogenicity of second dose of a mRNA COVID19 vaccine BNT162b2 in subjects prime vaccinated with ChAdOx1-S. Here, we present reactogenicity and immunogenicity at 14-day cut-off.

## METHODS

### Trial design and participants

The study CombiVacS is a phase 2, non-blinded, adaptive, randomized, controlled, multicentre, clinical trial design being done at five centres in Spain (University Hospital de Cruces, Vizcaya; University Hospital Vall d´Hebron, Barcelona; University Hospital Clinic de Barcelona, Barcelona; University Hospital Clínico San Carlos, Madrid; and University Hospital La Paz, Madrid).

An adaptive design was decided to allow flexibility if primary analysis at 14 days confirmed the starting hypothesis, namely immunogenicity after BNT162b2 dose is superior to no vaccination in ChAdOx1-S-primed patients. Participants were healthy, or clinically stable, adults (aged ≥18 and ≤60) who had received a prime ChAdOx1-S vaccination between 8 and 12 weeks before the screening visit. Patients with documented COVID19 or vaccinated with any other vaccine since the prime dose were excluded. A SARS-CoV-2 RT-PCR test was performed at the randomization visit, and blood samples were collected to determine baseline SARS-CoV-2 serological status. Additional key exclusion criteria were the presence of clinically significant acute illness or temperature ≥ 38ºC within 24 hours prior to the planned dose of study vaccine, clinical manifestations compatible with COVID-19 and any condition contraindicating or discouraging BNT162b2 administration, including pregnancy. Full details of the eligibility criteria are described in the trial protocol provided in the appendix 1.

All the participants provided written informed consent before enrolment. The trial complies with the principles of the Declaration of Helsinki and Good Clinical Practice. This study was approved by the Spanish Agency of Medicines and Healthcare Products (AEMPS) and by the Ethics Committee at University Hospital La Paz.

**Randomisation and masking**

Participants were randomly assigned (2:1) to receive one intramuscular injection of BNT162b2 (interventional group) or maintain observation (control group). Subjects assigned to the interventional group were vaccinated by healthcare personnel who were aware of trial-group assignments but were not otherwise involved with other trial procedures or data collection. If the main immunogenicity objective is met, and always under the perspective of acceptable reactogenicity, participants included in the control group would be offered to receive BNT162b2 as a second dose at day 28. Alternatively, ChAdOx1-S may be used as a second dose in the control group if requested by the participant or established by local health authorities. The randomization list was centrally generated with the SAS software for Windows (version 9.4; SAS Institute Inc., Cary, NC, USA); systematic randomisation stratified by study site, gender and age (18-49 years, and 50-59 years) was used to achieve balanced randomization in the two treatment groups. The randomization list was imported into the secure Research Electronic Data Capture platform (REDCap version 8.7.4; Vanderbilt University, Nashville, TN, USA) used for the study electronic case report form (eCRF).

**Procedures**

The BNT162b2 vaccine used in this trial is available in Europe after a conditional marketing authorization was granted by the European Medicines Agency (EMA) in December 2020. BNT162b2 was administered at the approved dose of 0.3 mL as a single intramuscular injection. All participants were RT-PCR tested for SARS-CoV-2 infection, clinically assessed and had blood samples drawn for safety as well as immunology at day 0 (randomisation, BNT162b2 dose administration). Follow-up visits on days 7 and 14 were scheduled to measure vital signs, review any adverse events, update medical and medication records and collect blood samples. Participants will also be followed-up at days 28, 90 (month 3), 180 (month 6) and 360 (month 12). Participants in the interventional group were observed on site for at least 15 minutes after BNT162b2 vaccination for safety monitoring. Any adverse events occurred up to the end of the observation period were recorded. Participants in both groups were asked to record any adverse events using an electronic diary throughout the follow-up period. Participant uploaded events were

accessible online through the electronic diary, which emailed an automatic alert to the investigator when the adverse event was reported as severe by the participant. In all these cases, the investigator contacted the participant to assess seriousness. At the present cut-off, participants were inquired about both solicited and unsolicited adverse events up to day 7 as well as unsolicited adverse events up to day 14. Intensity of adverse events was graded according to a 4-grade scale: grade 1 (mild), grade 2 (moderate), grade 3 (severe), and grade 4 (life-threatening). Causality of unsolicited adverse events was defined as related or not related to study treatment based on reasonable possibility, temporal relationship and alternate aetiology criteria, and was assessed in reported unsolicited adverse events. Full description of safety definitions and a list of solicited adverse events are provided in the trial protocol supplied as appendix 1.

Antigen-specific humoral immune response was analysed using two commercial immunoassays and one pseudovirus neutralization assay. The Elecsys® Anti-SARS-CoV-2 S assay (Roche Diagnostics GmbH, Mannheim, Germany) is an electrochemiluminescence immunoassay (ECLIA) detecting IgG antibodies to the SARS-CoV-2 spike protein receptor binding domain (RBD) on the cobas e411 module.[9] According to the manufacturer, the measuring range spanned from 0.4 U/mL to 250 U/ml (up to 2,500 U/ml with on-board 1:10 dilution and up on 12,500 with on-board 1:50 dilution). Values higher than 0.8 BAU/mL were considered positive. Correlation between U/ml and BAU (International OMS standard) is U=0.972 BAU. The LIAISON® SARS-CoV-2 TrimericS IgG assay (DiaSorin Inc., Stillwater, USA) is a chemiluminescence immunoassay (CLIA), detecting IgG antibodies anti-trimeric spike glycoprotein of SARS-CoV-2 in human serum or plasma samples on the LIAISON® XL.[10] Measuring range spanned from 4·81 BAU/mL to 2,080·00 BAU/mL. According to the manufacturer, values > 2,080·00 BAU/mL were diluted 1:20 and values higher than 33·8 BAU/mL were considered positive. To measure neutralizing antibodies titres, dilutions of participants' plasma samples were pre-incubated with pseudoviruses generated by co-transfection of pNL4-3ΔenvRen and an expression vector for the viral spike (pcDNA3.1-S-CoV2Δ19-G614) and added at a concentration of 10ng p24Gag/well to Vero E6 cells in 96-well plates. At 48 hours post-infection, viral infectivity was assessed by measuring luciferase activity (Renilla Luciferase Assay, Promega) using a 96-well plate luminometer "LB 960 Centro XS³" (Berthold). The titre of

neutralizing antibodies was calculated as 50% inhibitory dose (neutralizing titre 50, NT50), expressed as reciprocal of four-fold serial dilution of heat-inactivated sera (range 1:32 – 131·072) resulting in a 50% reduction of pseudovirus infection compared to control without serum. Samples below the detection threshold (1:32 serum dilution) were given 1:16 value. Positive and negative controls were included in the assay and non-specific neutralization was assessed using a non-related pseudovirus expressing the Vesicular Stomatitis Virus envelope. Cellular immune response was measured by quantification of IFN-gamma present in plasma upon overnight stimulation of whole blood with pools of SARS-CoV-2 peptides (S; 2 µg/ml) or DMSO control in whole blood culture. This methodological approach requires only 1 ml of blood, which facilitates longitudinal tests in a large cohort of individuals, allowing the rapid quantification of SARS-CoV-2-specific T cells in vaccine recipients.[11,12] Cytokines were quantified using Ella (ProteinSimple, San Jose, California). Neutralizing antibodies were planned to be analyzed in 200 participants randomly selected from the full sample included, while cellular immune response was analysed in participants from two study sites (University Hospital Clínico San Carlos, and University Hospital La Paz). Full details on the pseudovirus neutralising assay and cellular immunity quantification are provided in the appendix 1 (pp 14).

**Outcomes**

The primary outcomes were reactogenicity and immunological response to vaccination as per antibodies against SARS-CoV-2 spike protein titres measured by immunoassay 14 days after the BNT162b2 dose. A secondary immunogenicity outcome measure was neutralizing antibodies titres measured by virus neutralization assay at day 14. 1-year safety was also planned to be assessed. Two exploratory outcomes were included: a) the relationship between neutralizing antibodies and antibodies against SARS-CoV-2 spike protein measured by immunoassay, and b) cellular response to vaccination defined as inflammatory IFN-gamma cytokine production against SARS-CoV-2 spike peptide pools at day 14. Another secondary and exploratory immunogenicity and efficacy outcomes – planned at 28, 90, 180 or 360 days – are not applicable to the present analysis but are also detailed in the protocol provided in the appendix 1.

**Statistical Analysis**

The immunogenicity analysis population included all the participants who were randomized, completed all visits and for whom serological samples were available both on day 14 and at the baseline visit. Data was presented as geometric mean and 95% confidence interval (95% CI) or, for categorical variables, number and percentage, unless otherwise stated. Antibodies titres against SARS-CoV2 spike protein at 14 days was the response variable and treatment effect was evaluated comparing those titres between interventional versus control group. Additional post-treatment ANCOVA adjusting for pre-treatment was performed, with baseline immunity value, age, and sex as co-variable. The primary and secondary laboratory objectives were described using geometric means and difference at each time, basal, 7 (only for serologic determinations) and 14 days, was evaluated with ratio of geometric means. Additionally, reverse cumulative distribution curve was plotted. A subgroup analysis by sex, and age groups was performed at each time, baseline and 14 days, for the primary and secondary endpoints. Laboratory parameter with value below detection limit were replaced by a value equal to the lowest limit divided by 2. All analyses were carried out using the statistical software SAS, version 9.4 of the SAS system for Windows (SAS Institute Inc., Cary, NC, USA). All analyses were carried out using the statistical software SAS, version 9.4 of the SAS system for Windows (SAS Institute Inc., Cary, NC, USA). The reactogenicity analysis population included all the participants who had received at least one dose of BNT162b2 in the interventional group regardless the availability of data for primary endpoint analysis. Reactogenicity analyses were presented as numbers and percentages of participants who had suffered local and systemic adverse events during 7 consecutive days after each vaccination. Sample size calculation for a log-transformed outcome measure[13] was performed to assess the humoral immune response against SARS-CoV-2 14 days after dose of BNT162b2 in subjects that received a prior single dose of ChAdOx1-S, as compared with no dosing. A sample size of 600 participants (400 in the interventional group) was required to identify a 35% of increase in antibodies titres in subjects receiving the dose of BNT162b2, G(Y1), in relation with those not receiving it, G(Y2) at 14 days, assuming a coefficient of variation equal to 1.2 or 1.0 and similar between arms, at least 80% power and a one-sided 1% significance level (H1: G(Y1)/G(Y2) >1). A low value alpha, 0·01, was used for the one-sided hypothesis to avoid a type I error, especially when the evaluation will be replicated at

other specific times. The sample size was increased by 15% due to possible no-participation. This study is registered at EudraCT (No. 2021-001978-37) and ClinicalTrials.gov (NCT04860739).

**Role of the funding source**

The funder – Institute of Health Carlos III, or ISCIII – designed the trial in cooperation with the Spanish Clinical Trials Platform (SCReN), a public network of clinical trials unit at the Spanish National Health System funded by the ISCIII through PTC20/00018 and PT17/0017 Trial coordination, patient recruitment and data analysis has been performed by SCReN. All immunological procedures were performed at ISCIII. All authors review and approve the original draft. All authors had full access to the full data in the study and accept responsibility to submit for publication.

**RESULTS**

Between April 24 and April 30, 2021, 676 patients were enrolled into the study and randomly assigned to receive BNT162b2 vaccine (n=450) or no vaccine (n=226) but 2 and 1 individuals withdrew consent before vaccination and were discontinued in experimental and control group, respectively. A total of 663 participants were included in the immunogenicity analyses, after 7 participants from the vaccine group and 3 from the control group were excluded (figure 1). 448 participants who received the second dose were included in the reactogenicity population, including 1 from the control group who was erroneously vaccinated. One individual was excluded due to lost to follow-up after receiving the BNT162b2 dose.

Demographics and baseline characteristics (table 1) were balanced between the two study groups, 382 (56·5%) participants were female, 437 (64·6%) participants were within 18-49 age group and the mean age was 43·98 (SD 8·85). Time elapsed since ChAdOx1-S administration was between 8 and 9 weeks for 411 participants (60·8%) and between 10 and 12 weeks for 263 participants (38·9%).

In the interventional group, geometric mean titres (GMT) of IgG specific to the SARS-CoV-2 RBD at day 14 were significantly ($p<0·0001$) higher in the interventional group (7756·68 BAU/mL, 95% CI 7371·53;8161·96) vs. the control group (99·84 BAU/mL, 95% CI 76·93;129·59). Immunogenic response in the interventional group was observed as soon as day 7 (4353·51 BAU/mL, 95% CI

3851·58-4920·85 [interventional group] vs. 90·05 BAU/mL, 95% CI 69·16-117·27 [control group]; p < 0·0001) (figure 2a; appendix 1 pp 2). When antibodies against SARS-CoV-2 spike protein were measured by a CLIA technique covering the trimeric spike protein, 14-day immunogenic response in the interventional group was also confirmed as statistically significant (3684·87 BAU/mL, 95% CI 3429·87-3958·83 [interventional group] vs. 101·2 BAU/mL, 95% CI 82·45-124·22 [control group]; p < 0·0001), which meant a 37-fold increase from baseline. Likewise, titres of antibodies at day 7 were significantly higher in the interventional group (2246·25 BAU/mL, 95% CI 2010.4-2509.78 [interventional group] vs. 102·25 BAU/mL, 95% CI 83·52-125·18 [control group]; p < 0·0001) (figure 2b; appendix 1 pp 2). Reverse cumulative distribution curves for RBD- and trimeric- S protein antibodies are shown in appendix 1 (pp 3-4). Titres of antibodies measured by both techniques showed strong positive correlation ($R^2$=0·85; p<0·001) (appendix 1 pp 5). Subgroup analysis evidenced that immunological response was numerically lower in males but no differences were evidenced by age subgroups (Appendix 1 pp 6-7).

The functional capability of the antibodies induced in the interventional group were analysed in 198 participants randomly selected (129 from the interventional group and 69 from the control group). In the interventional group, 74·4% participants showed no or very low neutralizing activity at day 0, whereas 100% exhibited neutralizing antibodies at day 14, showing high (NT50 >1:300/<1:1000) or very high (NT50 >1:1000) activity in 99·7% of them (appendix 1 pp 8). At day 14, GMT of neutralizing antibodies increased 45-fold from 41·84 (95% CI 31·28-55·96) to 1905·69 (95%CI1625·65; 2233·98) in the interventional group, compared to 41·81 (95% CI 27·18;64·32) present at day 14 in the control group (p<0·0001). GMT of neutralizing antibodies in controls was not significantly different from baseline (GMT 50·84, 95%CI 33.56-76.99) (figure 3a; appendix 1 pp 9). Reverse cumulative distribution curves for neutralizing antibodies are shown in appendix 1 (pp 10). Neutralizing antibody responses had a strong positive correlation with RBD antibody titres ($R^2$=0·82; p<0·001) (figure 3b).

Dynamic changes of functional spike-specific T cell response were analysed in 151 participants (n=99 [interventional group] and n=52 [control group]). Results revealed substantial levels of IFN-gamma production at day 0 (geometric mean 129·63 pg/mL, 95% CI 103·51-162·35 [interventional

group]; and 151·63 pg/mL, 95% CI 114·09-201·53 [control group]), consistent with a prior immunization with a single dose of ChAdOx1-S. On day 14, the production of IFN-gamma had significantly increased in the interventional group (geometric mean 521·22 pg/mL, 95% CI 422·44;643·09; p<0·0001) in comparison with the control group (122·67 pg/mL, 95% CI 88·55;169·95; p<0·0001) that remain unchanged. Reverse cumulative distribution curves for immunological response are shown in appendix 1 (pp 11).

Reactogenicity analysis was based on solicited adverse events in 448 individuals from the intervention group evidencing headache (194; 44·4%), myalgia (194; 43·3%) and malaise (187; 43·3%) as the most commonly reported systemic reactions. Other systemic adverse reactions, including fever (2·5%) were less common and shown in appendix 1 (pp 12). As expected, injection site pain (395; 88·2%), induration (159; 35·5%) and erythema (139; 31%) were the most commonly reported local reactions. Other local adverse reactions were less common and shown in appendix 1 (pp 12). In general, local and systemic reactions were most frequently reported by female participants. No differences in frequency were observed by age groups (appendix 1 pp 13). Solicited adverse events in the 7 days following vaccination in the interventional group were predominantly mild (68·3%) and moderate (29·9%), and self-limited. Importantly, only 1.75% of the adverse events were self-reported as severe. Within this category, the most frequent symptoms were malaise (22·5%), myalgia (19·3%) and headache (16·1%). All these subjects were contacted and subsequently evaluated by investigators, who did not report any serious adverse events. The severity of solicited local and systemic reactions was highest on day 2 after vaccination (figure 5).

## DISCUSSION

This is the first report evidencing that a SARS-CoV-2 heterologous vaccination schedule induces a strong immune response in humans and is associated to an acceptable and manageable reactogenicity profile. Our approach is based on BNT162b2 given as a second dose 8-12 weeks after a first dose of ChAdOx1-S and the potent immune response was confirmed using four different tests.

Although our conclusions should be restricted to this scenario keeping in mind the absence of a homologous vaccination arm, comparison with previously reported immunogenicity data may help to

put in context the results of the study. This indirect comparison suggests that the intensity of the immune response with the heterologous vaccination schedule used in this study is higher than those previously reported by other authors using homologous schedules. According to previous data coming from the Oxford COVID Vaccine Trial Group, after a second dose of ChAdOx1-S humoral response is associated with a 10-fold increase of anti SARS-CoV-2 spike protein IgG standardised ELISA titres.[14,15] On the other hand, in phase I/II BNT162b2 trials[16] RBD-binding antibodies also increased 10-fold after the second dose of BNT162b2 vaccine in comparison with first dose (from 1,536 U/ml to 16,166 U/ml) whereas neutralizing antibody titres raised from 29 to 437 (15-fold). In phase I/II CX-024414 trials,[17] in the 100 μg group, antibodies against the RBD raised 6-fold two weeks after the second vaccine dose (from 93,281 to 558,905). In our study heterologous second vaccination with BNT162b2 induced a 108/37-fold increase in IgG against RBD and trimeric spike protein, respectively. Although these effects could come from the different techniques to measure SARS-CoV-2 IgG employed in these studies, the strong positive correlation observed between the two IgG CLIA/ECLIA methods and the pseudovirus neutralization assay employed in the present work ensure the robustness of the measures and suggest a potential advantage of the heterologous over the homologous vaccination strategies. In this regard, it is very important to note that in our study immunogenicity response explored by spike protein-binding antibodies titres was in a similar incremental ratio between baseline and day 14 (37- and 108-fold) to the immunological response evidenced by neutralizing antibodies titres (40-fold). The proportionality between the increase in anti-RBD, anti-trimericS and neutralizing antibodies from our study agrees with the published data for BNT162b2[16] but are quite different to that reported in the public assessment report of ChAdOx1-S wherein the bright increase in anti-spike titres after a homologous boost was associated with a very modest increase in neutralizing antibodies titres.[18] Therefore, the sequential use of ChAdOx1-S and BNT162b2 may be the explanation to our findings. Besides, the time elapsed between the first and second dose probably have played a relevant role, since our participants received the second dose of vaccine a minimum of 50 days after the first dose. In this regard, two studies[14,15] and a pooled analysis of four randomised trials from the Oxford COVID Vaccine Trial Group[19] evidenced that the longer interval before the ChAdOx1-S second

dose administration, the higher SARS-CoV-2 IgG spike specific response. This effect was more evident in individuals younger than 55 years old using ChAdOx1-S but also described in people aged over 80 years vaccinated under an extended interval between two doses of BNT162b2.[20] Consequently, our study design could have maximized the effect of the interval between the two doses.

We also found that neutralizing activity as determined using a pseudovirus assay was strongly increased after BNT162b2 immunization. In fact, deployment a neutralizing capacity after our heterologous regimen was not due to a minority of subjects as 14 days after intervention NT50 was above 1.000 in 75·2% of subjects and overall 97·7% of all subjects increased NT50 value above 1:300. Because our study did not include an arm immunized with a second ChAdOx1-S dose it is not possible to compare both strategies. However, neutralization assays using pseudoviruses are quite similar across our study and ChAdOx1-S trials,[14,15,19] allowing some comparisons. In this regard, in ChAdOx1-S trials neutralization titres 28 days after vaccination with first dose were between 40 and 162 (expressed as median), and increased 3- to 6-fold (NT50 between 237 and 451) after a second dose of ChAdOx1-S. In our study, patients were included between 8 and 12 weeks after first ChAdOx1-S dose and basal levels were in the 40-50 (expressed as geometric mean) range in both control and intervention groups, which is very similar to basal data 56 days after priming with ChAdOx1-S.[12] After BNT162b2 immunization NT50 raised to 1,950 (45-fold increase) confirming a strong immunogenicity and the induction of strong humoral responses and neutralization titres with the heterologous vaccination regimen proposed. Of note, a recent study has reported that neutralization level is highly predictive of immune protection and suggest that neutralization titre will be an important predictor of vaccine efficacy in the future as new vaccines emerge.[21]

In addition, our results indicate that the use of BNT162b2 as a second dose in a heterologous scheme increases the cellular immunity responses obtained after the initial dose of ChAdOx1-S. This enhancer effect is very interesting since second doses of ChAdOx1-S in homologous schedules have failed to demonstrate an improvement in the cellular response obtained after an initial dose,[14,15,22] suggesting that cellular response is maintained during time irrespective of vaccination interval, age

and gender following a two-dose homologous vaccination strategy with ChAdOx1. On the contrary, the enhancer effect of the second dose on the cellular immune response has been described in the limited data available with homologous mRNA vaccine schedules.[23–25]

Regarding reactogenicity, solicited adverse events profile in CombiVacS is similar to those showed after homologous vaccination with ChAdOx1-S[14] or BNT162b2;[26] and those recently communicated in a cohort of healthcare workers in Germany.[27] However, our findings differ from those reported by Shaw and the Com-COV Study Group.[3] Shaw and colleagues[3] describes an increase in systemic reactogenicity after the boost dose reported by participants in heterologous vaccine schedules in comparison to homologous vaccine schedules, particularly in a self-reported feeling of feverishness. In contrast, although participants in our study were younger (mean 44 years old), results showed a lower frequency of reactogenicity events, which was unexpected and may be explained, at least in part, by different administration interval between both studies (28 day in Shaw and colleagues vs. 8-12 weeks in ours). Notwithstanding this, comparisons must be cautious due to differences between both studies. Apart from this limitation, the lack of an active control arm does not allow us direct comparisons with reactogenicity elicited by homologous ChAdOx1-S/ ChAdOx1-S vaccination.

Finally, in figures 2a, 2b and 3a the presence of individuals with elevated antibody titres at the time of randomization is evident. In the event that we can rule out individual variability as a cause of these titres, we would have to hypothesize the participation of individuals who had been inadvertently infected at some time prior to the start of the trial. In that case, the titres obtained in these individuals would depend directly on a heterologous combination of antigens as they have been exposed to wild-type SARS-CoV-2 and ChAdOx1-S, which would confirm our findings. However, this is a hypothesis to be assayed in the population of our study.

In summary, our study confirms a robust humoral and cellular inmmune response after a second dose of BNT162b2 in individuals previously primed with ChAdOx1-S between 8 and 12 weeks before. Future studies comparing homologous versus heterologous vaccination schedules will help to confirm and better understand the humoral and cellular immune responses observed in this clinical trial.

## Contributors

Trial conceptualization was performed by CB, AMB, AJC, JA and JF. AJC, IF and AA developed the study methodology. AMB, MPO, LC, MJB, JGC, MC, AP, MGP, EAA, MAN, FDF, AA, NIA, LBM, CP and JO were study investigators. MTGM, DL and AGC contributed to ensure data accuracy. AMB, AJC, MPO, DL, AGC, JO, JA and JF were responsible for statistical analysis. CB, AMB, MPO, LC, MC, MJB, AP, JO, JA and JF contributed to study supervision. CB was responsible for funding acquisition. CB, AMB, AJC, MPO, JO, JA and JF contributed to write the original draft and all authors contributed to the manuscript review and editing.

## Declaration of interests

CB is the Deputy General Manager of the ISCIII. JRA has received fees from Janssen, outside of the submitted work. AMB is principal investigator of clinical trials sponsored by GSK, Daiichi-Sankyo, Janssen and Farmalider, outside of the submitted work. The other authors declare no competing interests

## Data sharing

The study protocol and the statistical analysis plan are provided in the appendix 1 (pp16 et seq.). Individual participant data will be made available when the trial is complete, upon requests directed to the corresponding authors; after approval of a proposal, data can be shared through a secure online platform.

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**Table 1. Baseline characteristics of the randomized population**

| | Interventional group (n=450) | Control group (n= 226) | Overall (n=676) |
|---|---|---|---|
| **Sex** | | | |
| Male | 193 (42·9%) | 101 (44·7%) | 294 (43·5%) |
| Female | 257 (57·1%) | 125 (55·3%) | 382 (56·5%) |
| **Age (years)** | 43·93 (8·88) | 44·10 (8·82) | 43·98 (8·85) |
| **Age group** | | | |
| **18-49 years** | 293 (65·1%) | 144 (63·7%) | 437 (64·6%) |
| Male | 123 (27·3%) | 65 (28·8%) | 188 (27·8%) |
| Female | 170 (37·8%) | 79 (34·9%) | 249 (36·8%) |
| **50-59 years** | 157 (34·9%) | 82 (36·3%) | 239 (35·3%) |
| Male | 70 (15·5%) | 36 (15·9%) | 106 (15·7%) |
| Female | 87 (19·3%) | 46 (20·3%) | 133 (19·7%) |
| **Time since prime ChAdOx1-S vaccination*** | | | |
| 8-9 weeks | 273 (60·7%) | 138 (61·1%) | 411 (60·8%) |
| 10-12 weeks | 176 (39·1%) | 87 (38·5%) | 263 (38·9%) |

Data are n (%) and mean (SD). *Two patients excluded: (1) 7 weeks elapsed since ChAdOx1-S vaccine, and (2) dropout on day 0.

**Figure 1. Trial profile**

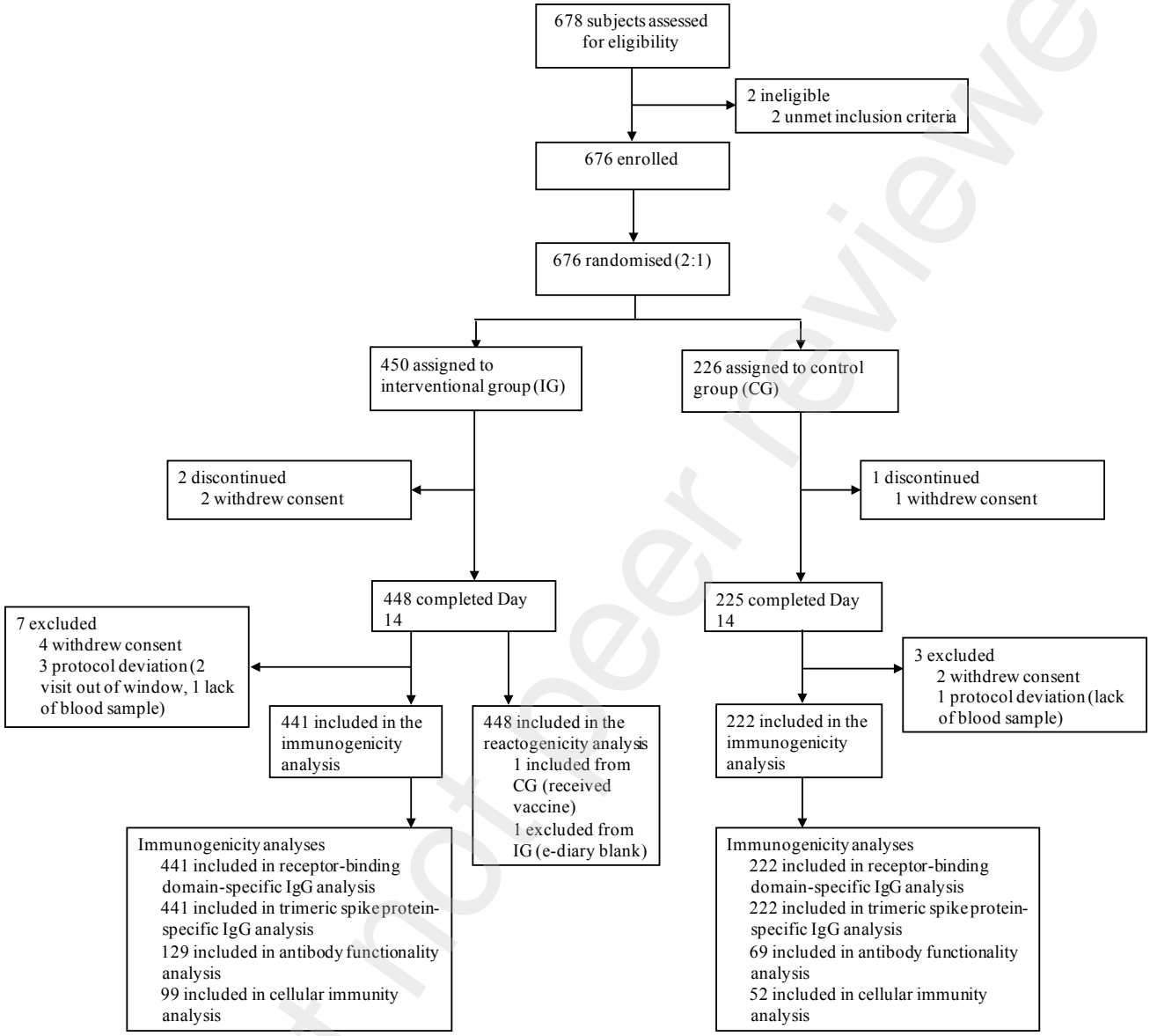
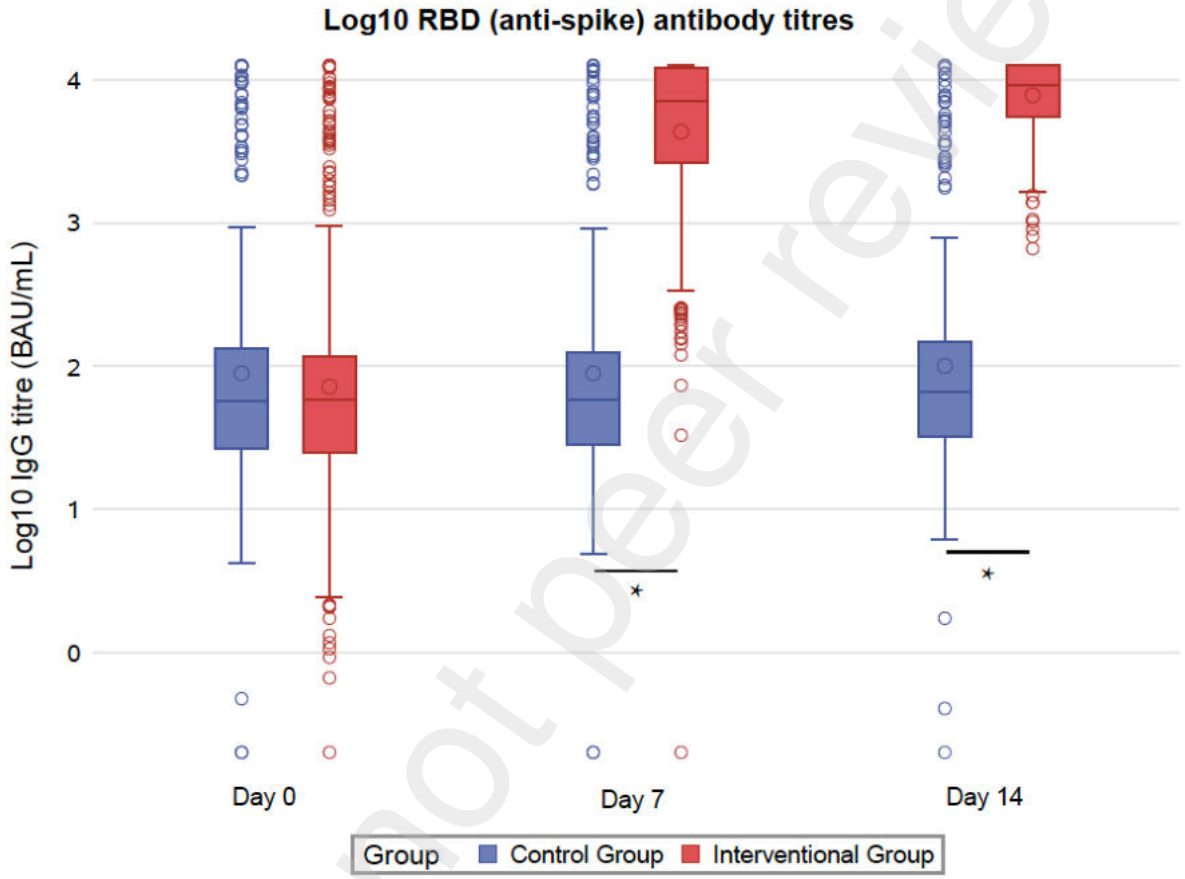


**Figure 2. a) RBD (anti-spike) antibody titres, and b) Trimeric S protein antibody titres, measured in both interventional (red) and control (blue) groups on days 0, 7 and 14**

* p<0·0001

2a)



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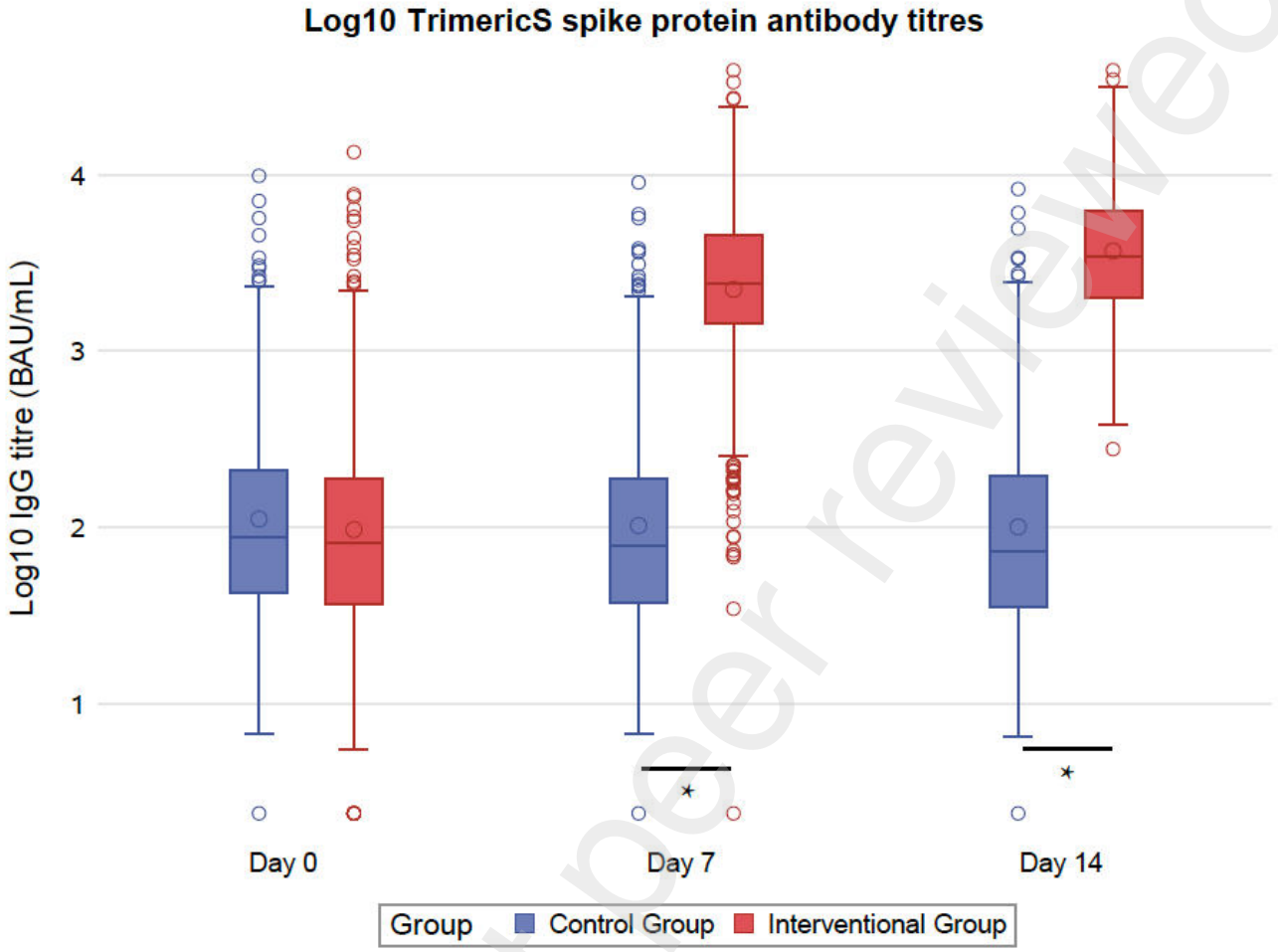
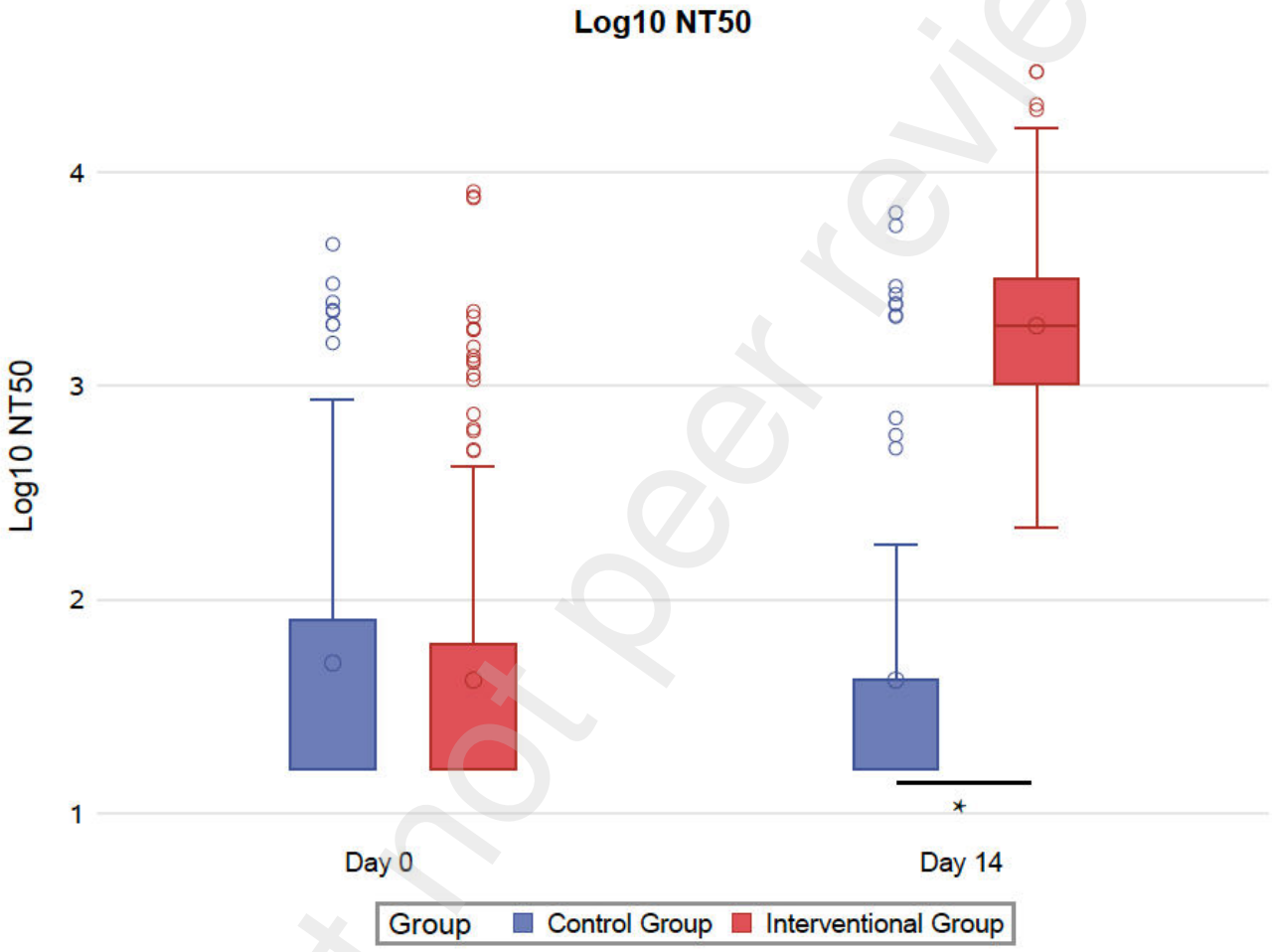


**Figure 3. a) Neutralizing antibodies measured in both interventional (red) and control (blue) groups on days 0 and 14. b) Correlation between Focus Reduction Neutralization Test 50 (FRNT50) and RBD (anti-spike) antibody titres**

* p<0·0001

3a)



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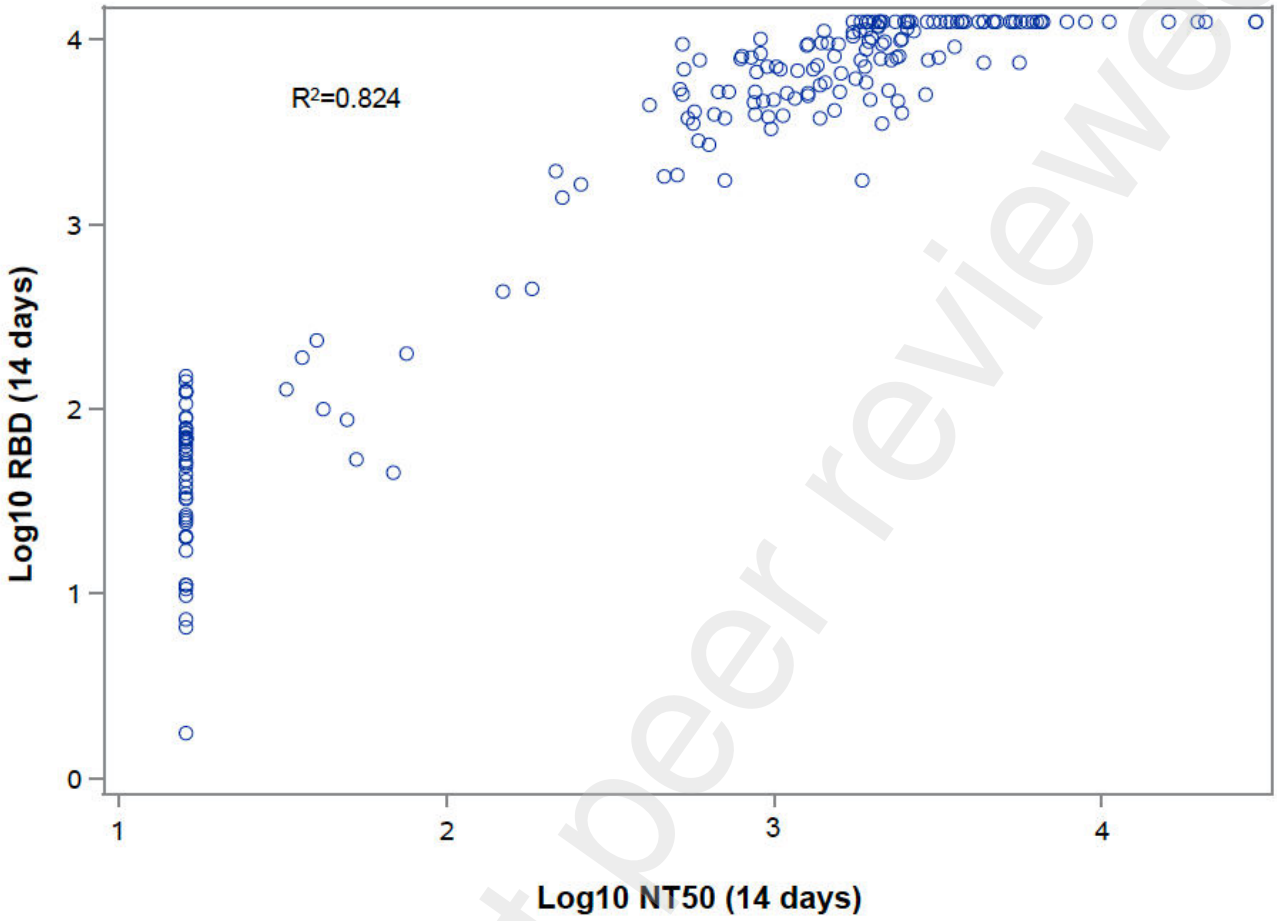


**Figure 4. IFN-gamma concentrations measured in both interventional (red) and control (blue) groups on days 0 and 14**

* p<0·0001

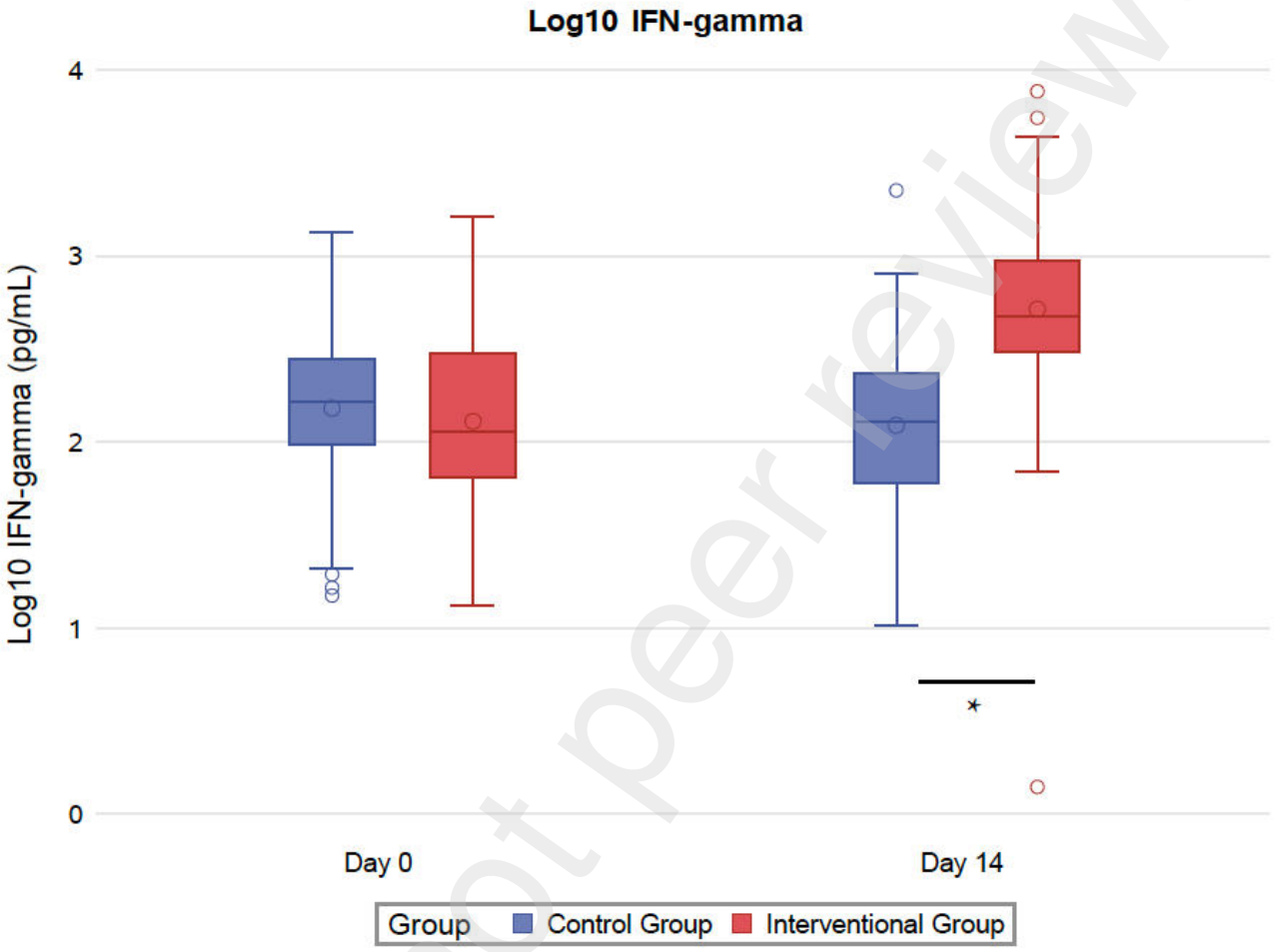
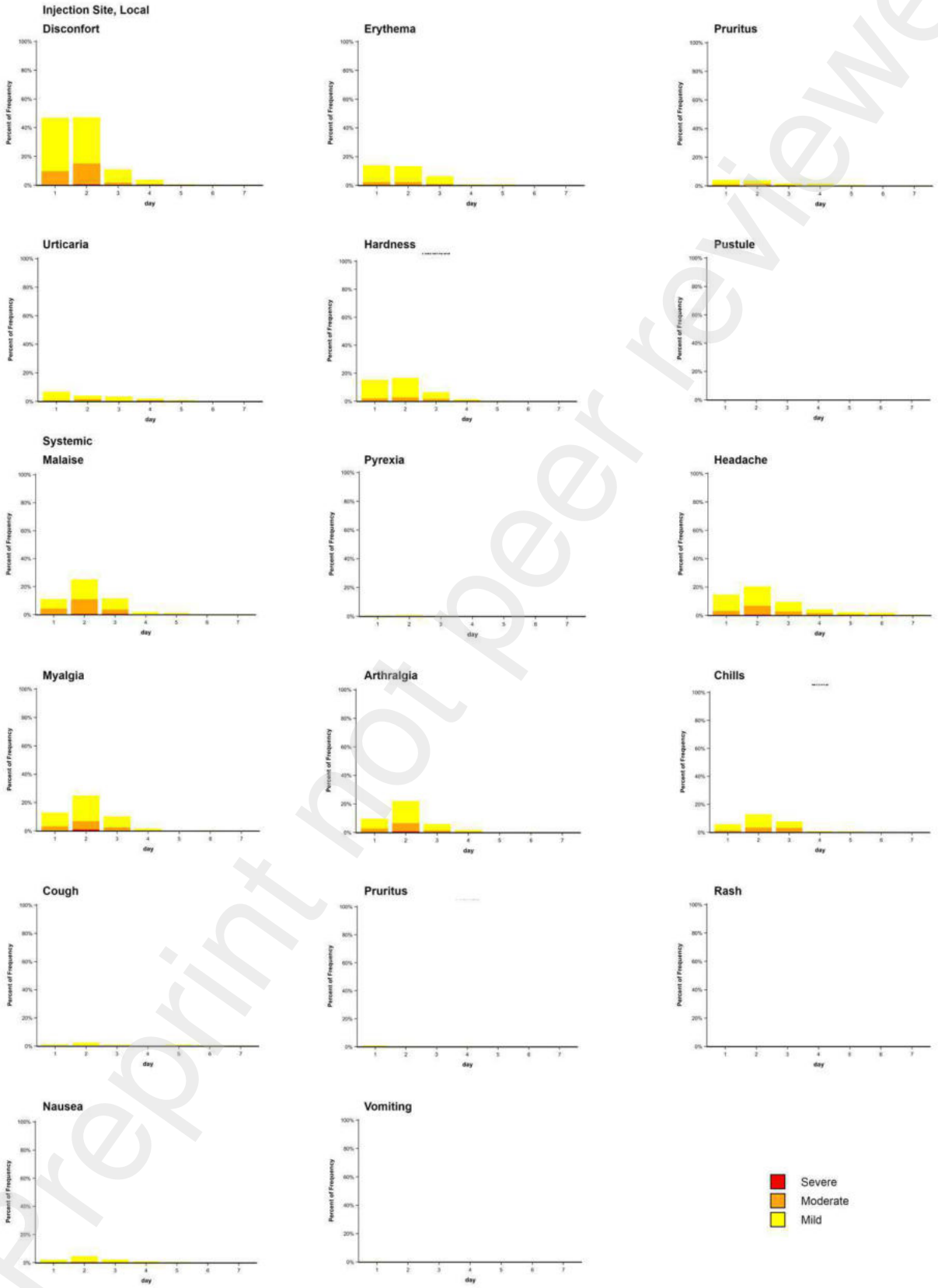
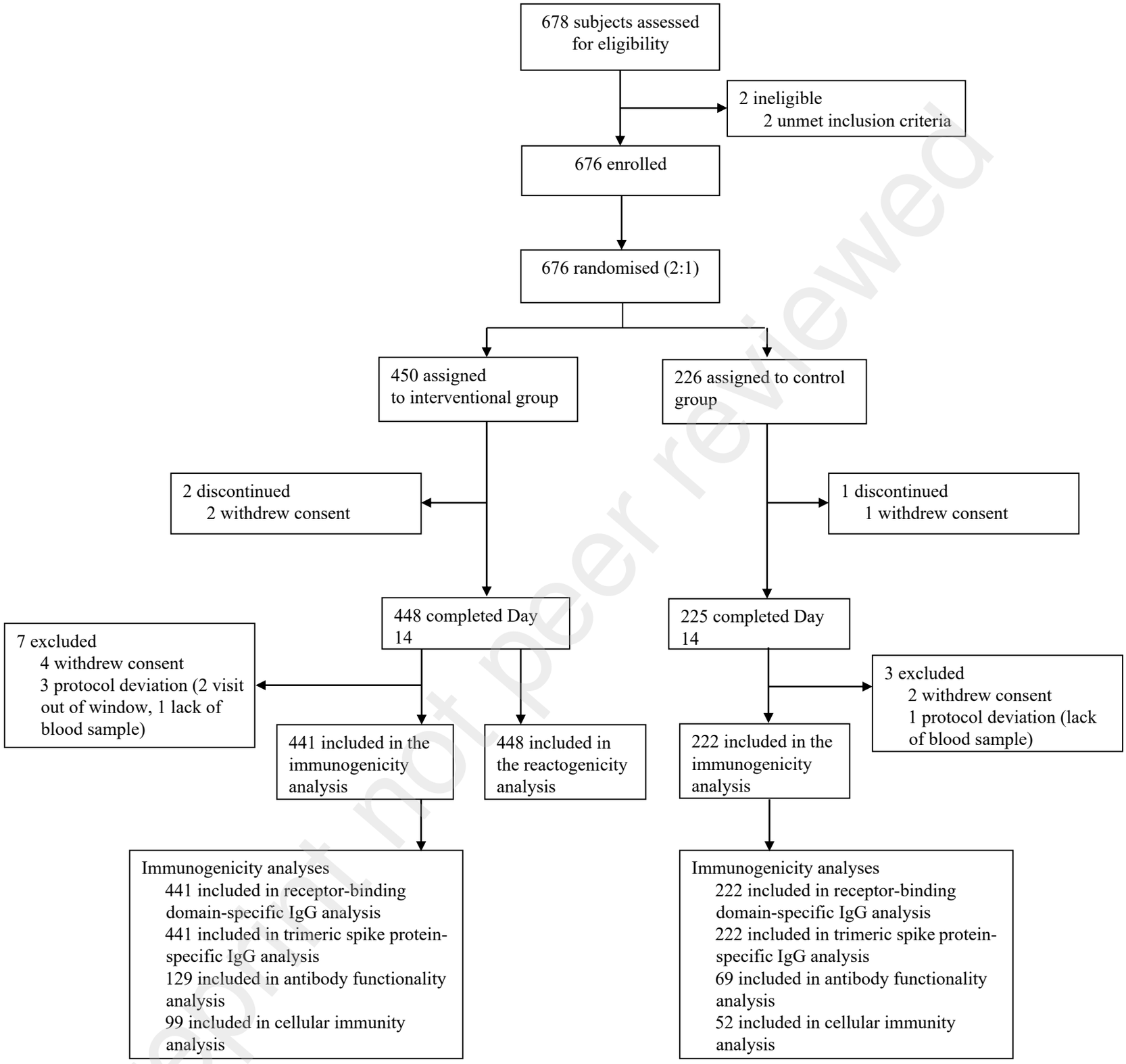
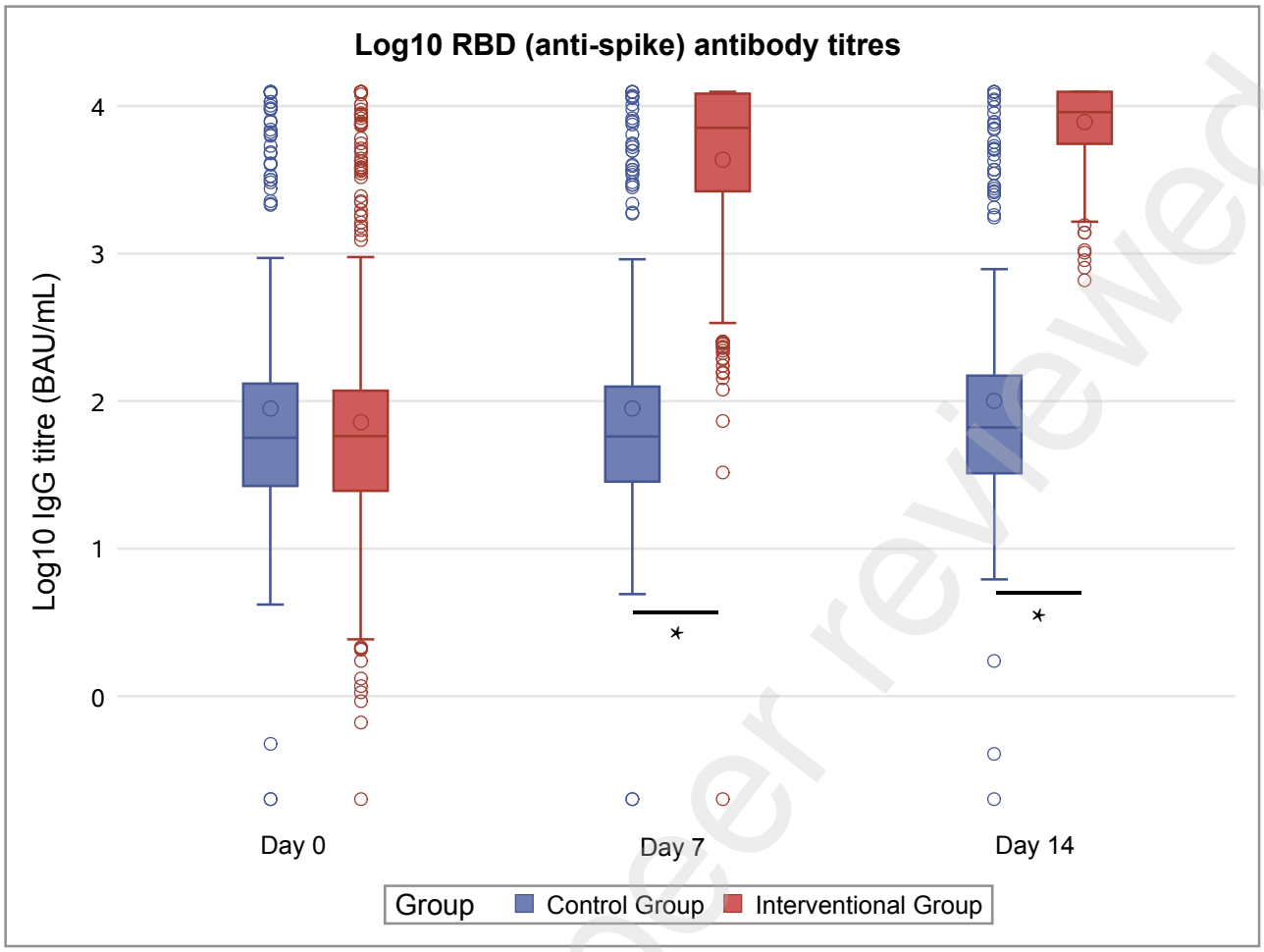
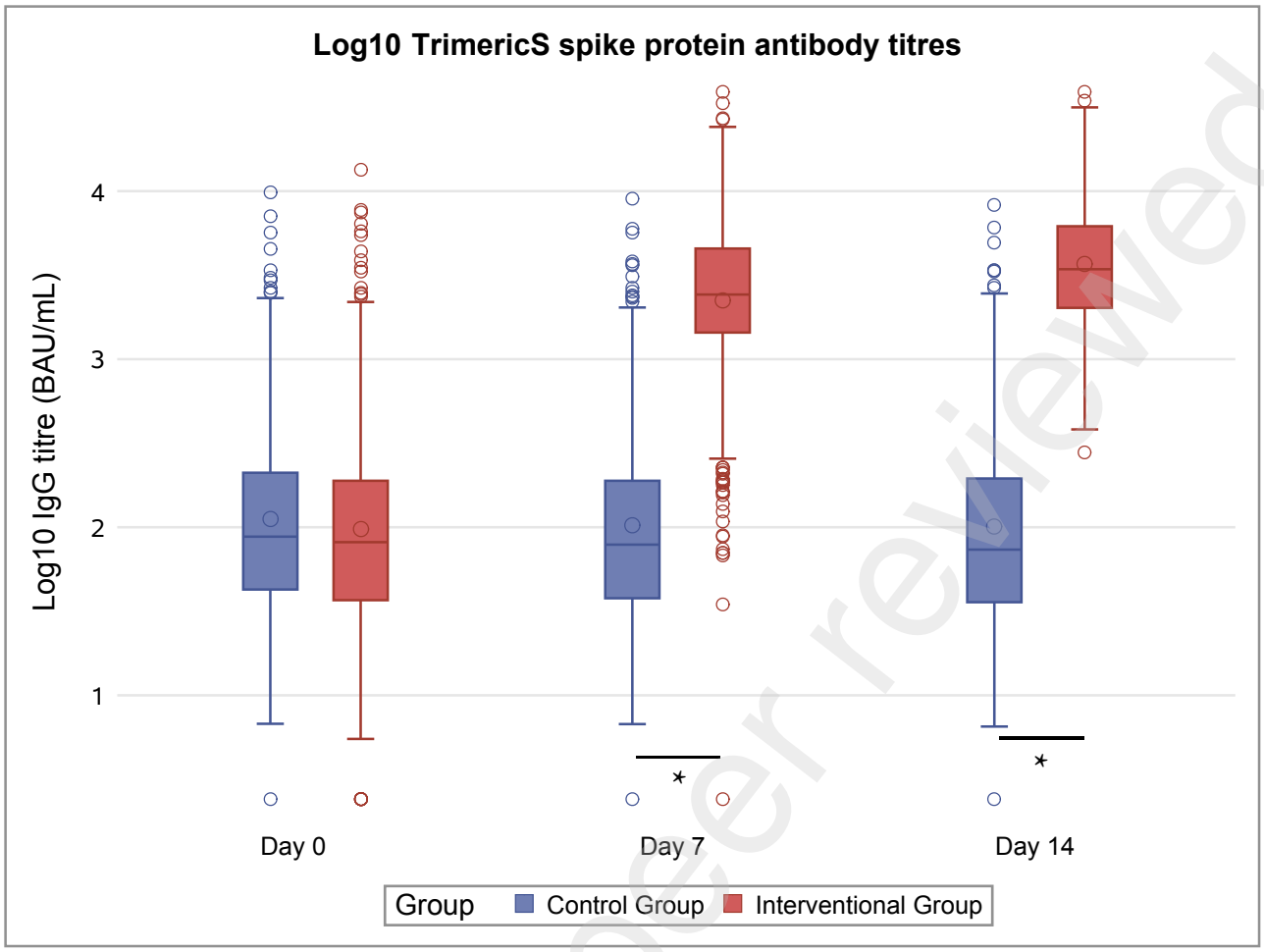


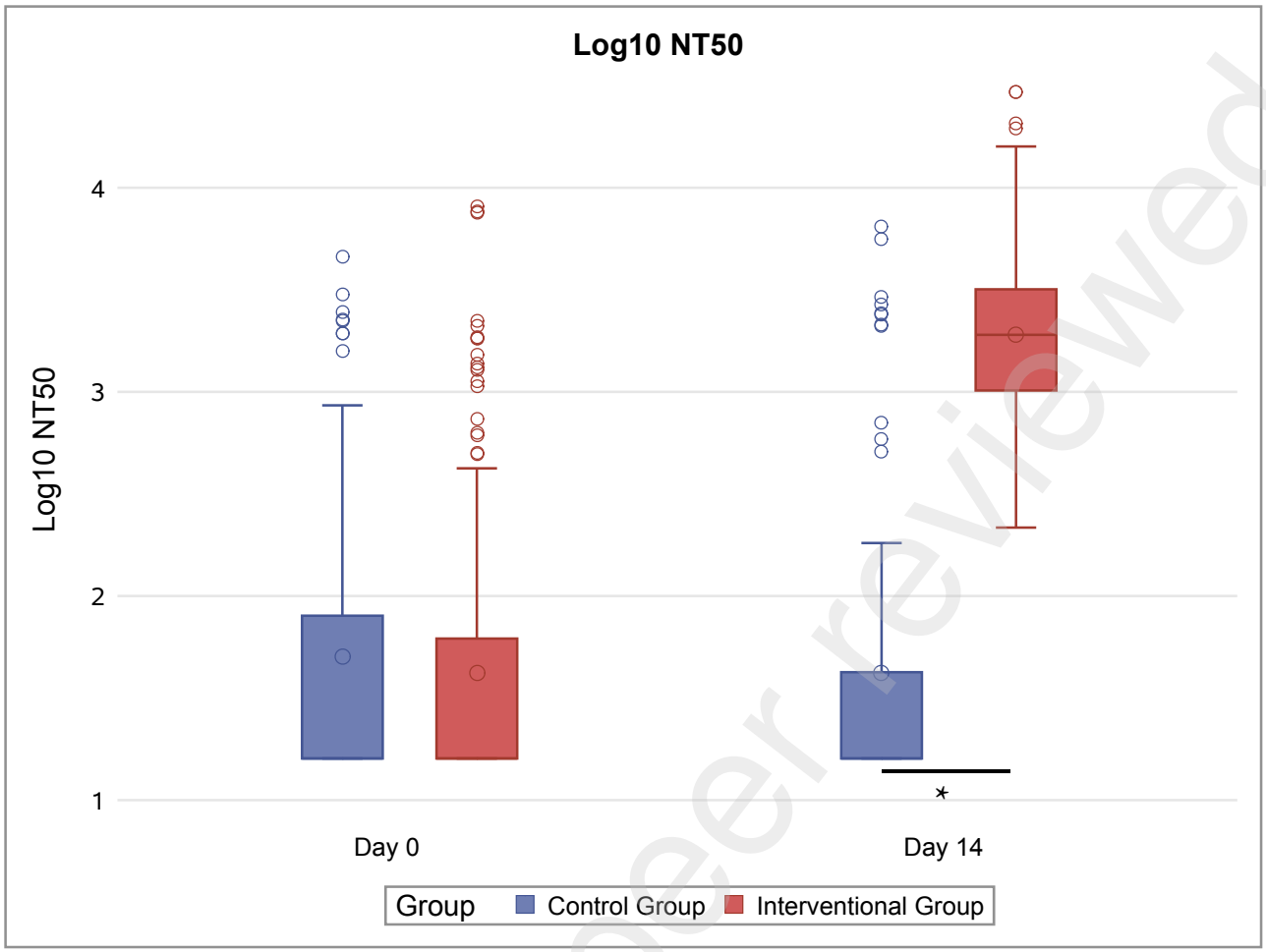
**Figure 5. Solicited local and systemic adverse reactions in first 7 days after vaccination as recorded in participant symptom electronic diaries**

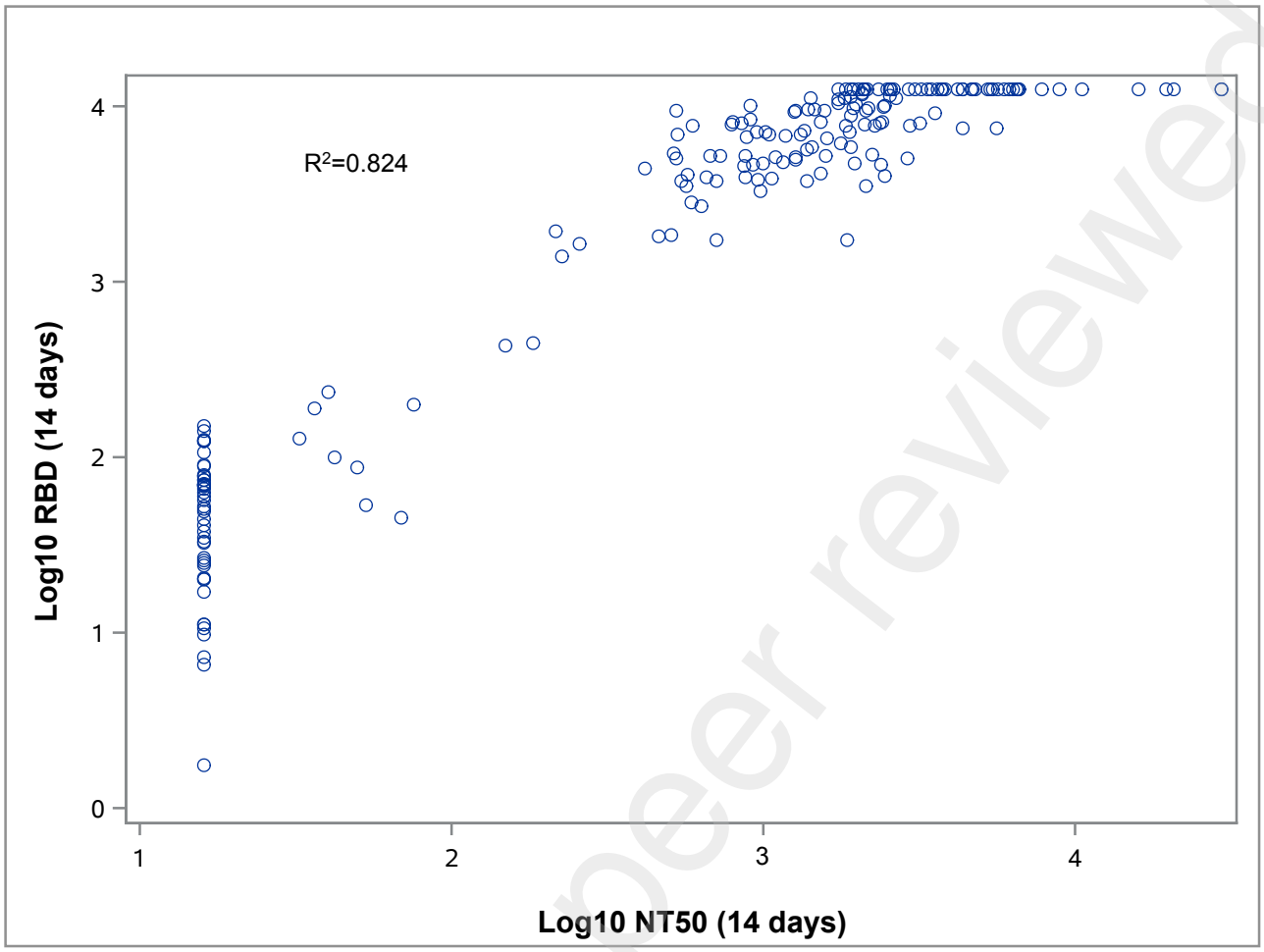


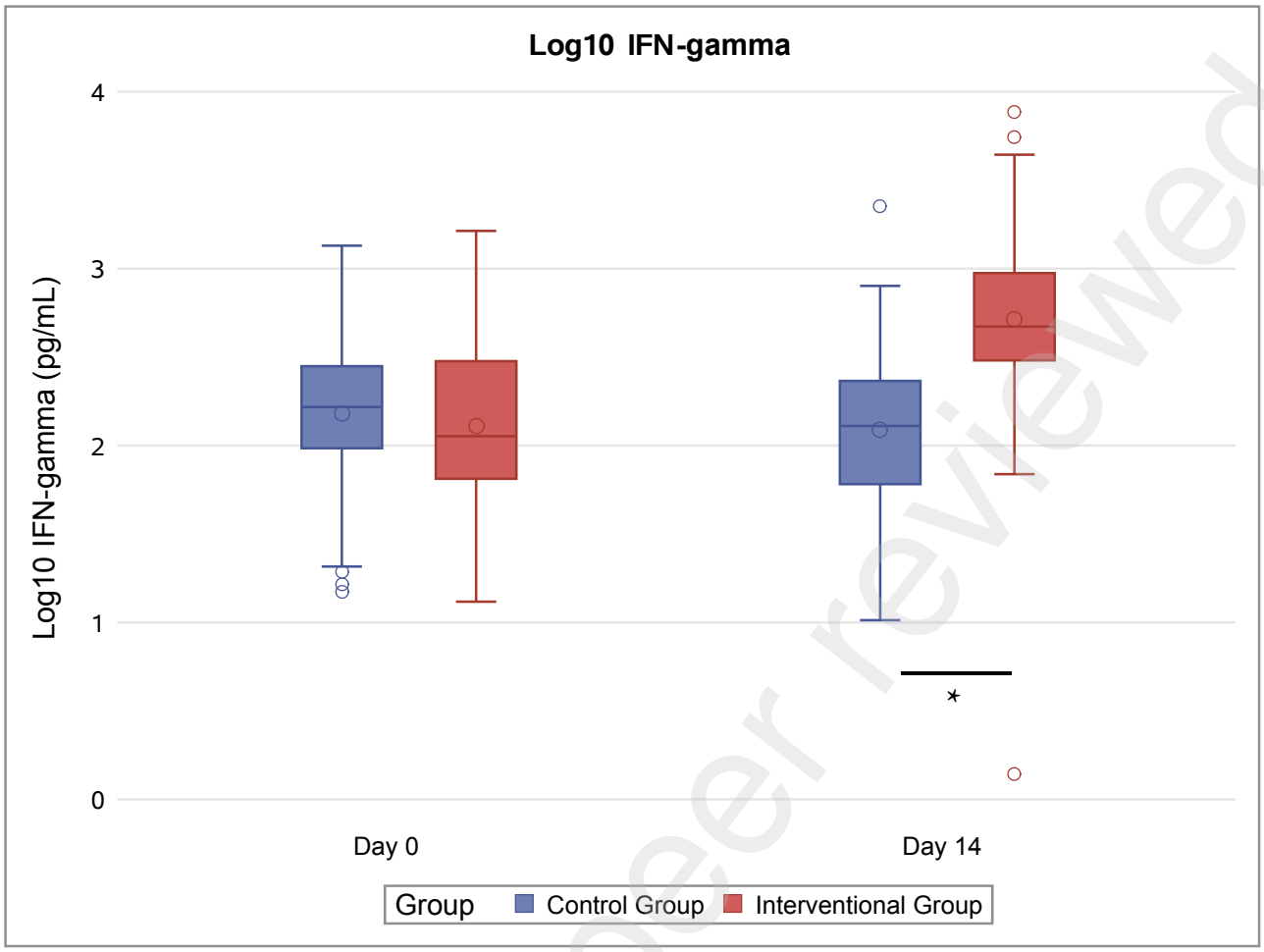


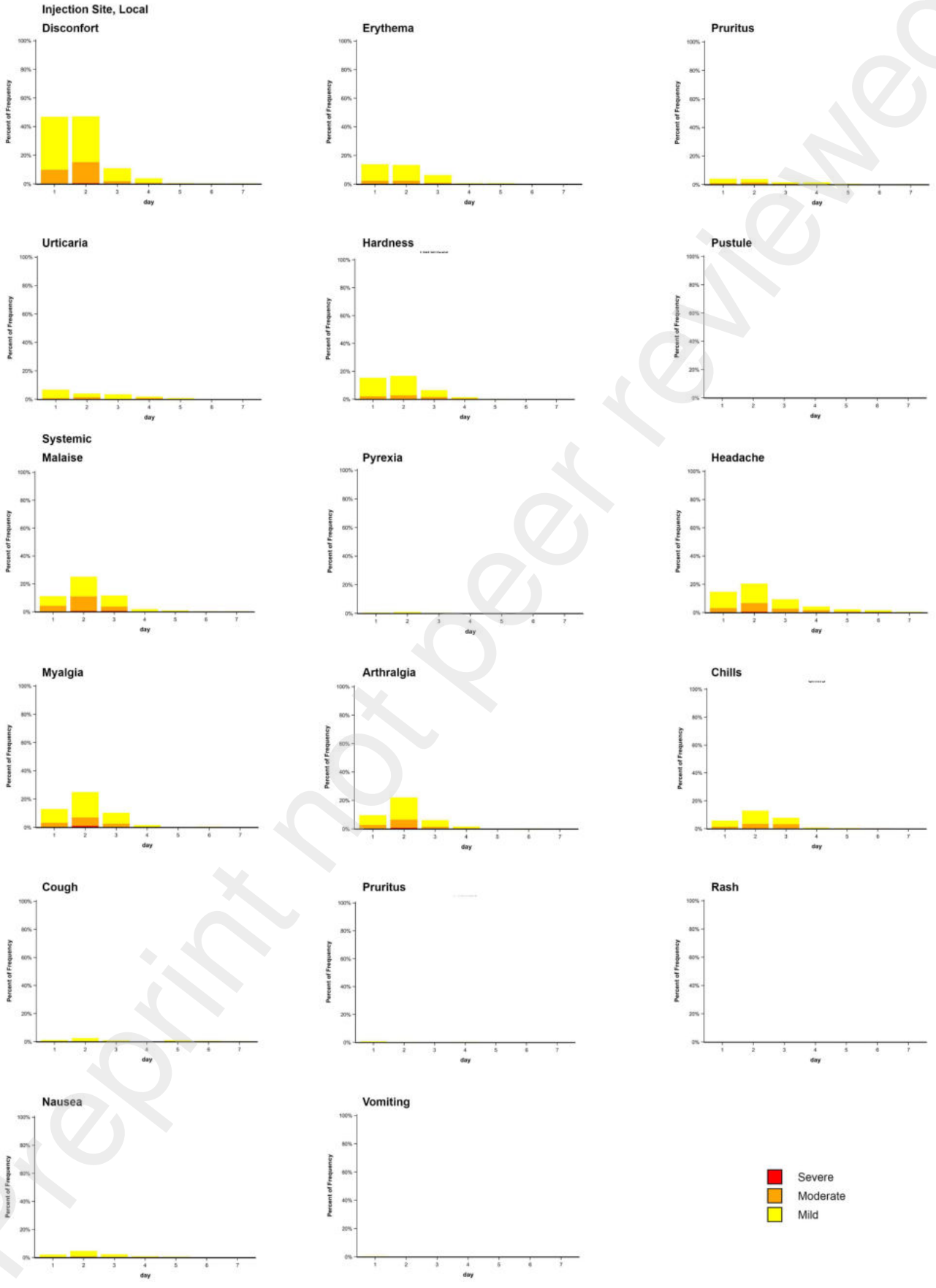












# Heterologous ChAdOx1 nCoV-19 and BNT162b2 prime-boost vaccination elicits potent neutralizing antibody responses and T cell reactivity

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**Abstract:**

**Background**

Heterologous prime-boost schedules with vector- and mRNA-based COVID-19 vaccines are already administered, but immunological responses and elicited protection have not been reported.

**Methods**

We here analyzed a cohort of 26 individuals aged 25-46 (median 30.5) years that received a ChAdOx1 nCoV-19 prime followed by a BNT162b2 boost after an 8-week interval for reactogenicity, antibody responses and T cell reactivity.

**Results**

Self-reported solicited symptoms after ChAdOx1 nCoV-19 prime were in line with previous reports and less severe after the BNT162b2 boost. Antibody titers increased significantly over time resulting in strong neutralization titers 2 weeks after the BNT162b2 boost. Neutralizing activity against the prevalent strain B.1.1.7 was 3.9-fold higher than in individuals receiving homologous BNT162b2 vaccination, only 2-fold reduced for variant of concern B.1.351, and similar for variant B.1.617. In addition, $CD4^+$ and $CD8^+$ T cells reacted to SARS-CoV-2 spike peptide stimulus 2 weeks after the full vaccination.

**Conclusions**

The heterologous ChAdOx1 nCoV-19 / BNT162b2 prime-boost vaccination regimen is not associated with serious adverse events and results in a potent humoral immune response and elicits T cell reactivity. Variants of concern B.1.1.7, B.1.351 and B.1.617 are potently neutralized by sera of all participants. These results suggest that this heterologous vaccination regimen is at least as immunogenic and protective as homologous vaccinations.

## Introduction:

The first cases of the coronavirus disease 2019 (COVID-19) were reported to the World Health Organization on December 31st 2019[1], and within 93 days the causative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had infected over 1 million people worldwide [2]. Only 250 days later, the first person received a COVID-19 vaccine outside a clinical trial, and vaccinations are now considered a key strategy for ending the pandemic[3]. Approved vaccines include the adenovirus-based ChAdOx1 nCoV-19 (Vaxzevria, AstraZeneca) and mRNA-based BNT162b2 (Comirnaty, BioNTech/Pfizer), which induce humoral and cellular immunological responses [4–7], showed high efficacy in clinical trials [8,9] and a high degree of protection from COVID-19 in real-world settings[10,11]. However, the occurrence of rare thrombotic events after ChAdOx1 nCoV-19 vaccinations, especially in individuals younger than 60 years, associated with the generation of auto-platelet factor 4 antibodies halted the administration of the second dose of ChAdOx1 nCoV-19 for this group [12–14]. As a consequence, several public health agencies now recommend that boost vaccination for these individuals is carried out in a heterologous regimen with an mRNA vaccine [15]. Recent studies indicate that such a heterologous schedule is associated with more severe [16] or similar [17] solicited symptoms, and preclinical data suggests immunogenicity to be similar to or higher than in animals receiving homologous mRNA-based prime-boost vaccination[18]. However, evidence for immunogenicity of such a regimen in humans and for optimal timing between prime and boost is lacking. In addition, it is currently unclear to which degree a heterologous vaccination regimen confers protection against the variants of concern[19].

Here, we studied a cohort of 26 individuals (16 female, 10 male; median age 30.5, range 25-46) (Table I) who received ChAdOx1 nCoV-19 prime and, due to changing recommendations in Germany, [15] a BNT162b2 boost vaccination with a 56 day interval and evaluated solicited adverse reactions, humoral and cellular immune responses.

**Table I: Study participants**

| | **Total** | **m** | **f** |
|---|---|---|---|
| Participants | 26 | 10 | 16 |
| Age median | 30.5 (25-46) | 32 (26-44) | 30.5 (25-46) |
| Prior SARS-CoV-2 infection | 1 | 0 | 1 |
| Platelet factor 4 autoantibodies (determined in [20]) | 0 | 0 | 0 |

## Materials and Methods:

### Collection of serum and PBMC samples

Blood samples from individuals were obtained after recruitment of participants and written informed consent as approved by the ethics committee of Ulm university (99/21). Participants received a heterologous vaccination regimen because after their ChAdOx1 nCoV-19 prime vaccination, the German Standing Committee on Vaccination (STIKO) had changed the recommendation for individuals < 60 years of age to receive an mRNA vaccine as boost vaccination to avoid risk of thrombotic complications [12,15]. At days -2/0 before vaccination, days 15-16, 30-37, 53-57 after ChAdOx1 nCoV-19 vaccination, and days 6-11 and 14-19 after heterologous BNT162b2 boost (days 64-65 and 72-73 after ChAdOx1 nCoV-19, respectively), blood was drawn into S-Monovette® Serum Gel (Sarstedt) or S-Monovette® K3 EDTA tubes. Sera from individuals vaccinated twice with BNT162b2 were obtained 13-15 days after the second dose under approval by the ethics committee of Ulm university (31/21); these sera were previously described and re-analyzed for this study[21]. Serum Gel collection tubes were centrifuged at 1,500 × g at 20°C for 15 min, aliquoted stored at -20°C until further use. Peripheral blood mononuclear cells (PBMCs) were obtained from EDTA tubes using density gradient centrifugation by Pancoll human (Pan Biotech, Germany), and erythrocytes removed by ACK lysis buffer (Lonza, Walkersville, MD, U.S.A). Mononuclear cells were counted for viability using a Countess II Automated Cell Counter (Thermo Fisher) with trypan blue stain and were cryopreserved in aliquots of up to $1x10^7$ cells in 10% DMSO in heat-inactivated FCS.

### Vaccine reactogenicity

Solicited adverse reactions (SAR) were self-reported by the participants via questionnaire following prime and boost vaccination. Participants were asked to list symptoms, their duration (< 1 h, few hours, one day or more than one day) and severity (mild (grade 1), moderate (grade 2), severe (grade 3). Grading criteria were adapted from the US Department of Health and Human Services CTCEA (Common Terminology Criteria for Adverse Events, v4.03) [22], with grade 1-2 being considered for some symptoms, grade 1-3 for most. For calculation of cumulative SAR (cSAR) scores, the grades of all symptoms listed were summed up, with an additional score point added for symptoms experienced for more than one day (0-4).

### Determination of antibody titers

IgG and IgA levels in serum were determined by anti-SARS-CoV-2 assay (Euroimmun), an ELISA which detects antibodies against the SARS-CoV-2 S1 spike domain. The assay was performed according to the manufacturer's instructions. Briefly, serum samples were diluted 10-fold in sample buffer and pipetted

into rSARS-CoV-2 spike precoated strips of eight single wells of a 96-well microtiter. After incubation for 60 min at 37°C, wells were washed three times, peroxidase-labeled anti-IgG or anti-IgA added and incubated. After 30 min, three additional washing steps were performed before substrate was added and incubated for 15-30 min in the dark. Thereafter, stop solution was added, and optical density (OD) values measured on a POLARstar Omega plate reader (BMG LABTECH, Ortenberg, Germany) at 450 nm corrected for 620 nm. Finally, OD ratios were calculated based on the sample and calibrator OD values, where a ratio <0.8 was considered to be negative and >1.1 to be positive. To quantify antibody responses, IgG and IgM were measured as units per ml (U/ml) that correlates with the WHO standard unit for the SARS-CoV-2 binding antibody units per ml (BAU/ml). To this end, serum was analyzed using the commercial electrochemiluminescence Elecsys Anti-SARS-CoV-2 S immunoassay (Roche, Mannheim, Germany) by a cobas® e801 immunoassay analyzer according to the manufacturer's instructions (Roche).

**Surrogate SARS-CoV-2 neutralization test**

Prevention of SARS-CoV-2 spike RBD interaction with ACE2 by sera was evaluated by SARS-CoV-2 Surrogate Virus Neutralization Test Kit (GenScript) according to the manufacturer's instructions. To this end, sera were incubated with a peroxidase-conjugated RBD fragment and the mixture added to a human ACE-2 coated plate, and unbound RBD washed away. Thereafter, substrate was added and the reaction stopped by stopping reagent. ODs at 450 nm were measured at a microplate reader. The inhibition score compared to the negative control was calculated as percentages. Scores <20% were considered negative and scores >20% positive.

**Cell culture**

Vero E6 (African green monkey, female, kidney; CRL-1586, ATCC, RRID:CVCL_0574) cells were grown in Dulbecco's modified Eagle's medium (DMEM, Gibco) which was supplemented with 2.5% heat-inactivated fetal calf serum (FCS), 100 units/ml penicillin, 100 µg/ml streptomycin, 2 mM L-glutamine, 1 mM sodium pyruvate, and 1x non-essential amino acids. HEK293T (human, female, kidney; ACC-635, DSMZ, RRID: CVCL_0063) cells were grown in DMEM with supplementation of 10% FCS, 100 units/ml penicillin, 100 µg/ml streptomycin, 2 mM L-glutamine. All cells were grown at 37°C in a 5% $CO_2$ humidified incubator.

**Preparation of pseudotyped particles**

Expression plasmids for vesicular stomatitis virus (VSV, serotype Indiana) glycoprotein (VSV-G) and SARS-2-S variants B.1.1.7, B.1.351 and B.1.617 (codon-optimized; with a C-terminal truncation of 18 amino acid residues) have been described elsewhere [19,21]. Transfection of cells was carried out by Transit LT-1 (Mirus). Rhabdoviral pseudotype particles were prepared as previously described [23]. A replication-

deficient VSV vector in which the genetic information for VSV-G was replaced by genes encoding two reporter proteins, enhanced green fluorescent protein and firefly luciferase (FLuc), VSV∗ΔG-FLuc [24] (kindly provided by Gert Zimmer, Institute of Virology and Immunology, Mittelhäusern, Switzerland) (Berger Rentsch and Zimmer, 2011) was used for pseudotyping. One day after transfection of HEK293T cells to express the viral glycoprotein, they were inoculated with VSV∗ΔG-FLuc and incubated for 1-2 h at 37°C. Then the inoculum was removed, cells were washed with PBS and fresh medium added. After 16-18 h, the supernatant was collected and centrifuged (2,000 × g, 10 min, room temperature) to clear cellular debris. Cell culture medium containing anti-VSV-G antibody (I1-hybridoma cells; ATCC no. CRL-2700) was then added to block residual VSV-G-containing particles. Samples were then aliquoted and stored at -80°C.

**Pseudovirus neutralisation assay**

For pseudovirus neutralisation experiments, VeroE6 were seeded in 96-well plates one day prior (6,000 cells/well). Heat-inactivated (56°C, 30 min) sera were serially titrated in PBS, pseudovirus stocks added (1:1, v/v) and the mixtures incubated for 30 min at 37°C before being added to cells. After an incubation period of 16-18 h, transduction efficiency was analyzed. For this, the supernatant was removed, and cells were lysed by incubation with Cell Culture Lysis Reagent (Promega) at room temperature. Lysates were then transferred into white 96-well plates and FLuc activity was measured using a commercially available substrate (Luciferase Assay System, Promega) and a plate luminometer (Orion II Microplate Luminometer, Berthold). For analysis of raw values (RLU/s), background signal of an uninfected plate was subtracted and values normalized to pseudovirus treated with PBS only. Results are given as serum dilution resulting in 50% virus neutralization (NT50) on cells, calculated by nonlinear regression ([Inhibitor] vs. normalized response -- Variable slope) in GraphPad Prism Version 9.1.1.

**Determination of $CD4^+$ and $CD8^+$ T SARS-CoV-2 spike -specific cell responses by intracellular cytokine staining (ICS)**

Cryopreserved PBMCs of study participants were thawed and rested overnight at 37°C with 1 µl/ml of DNAse (DNase I recombinant, RNase-free (10,000 U) Roche), in RPMI medium supplemented to contain a final concentration of 10% FCS (Corning Life Sciences/Media Tech Inc, Manassas, VA), 10 mM HEPES, 1x MEM nonessential amino acids (Corning Life Sciences/Media Tech Inc, Manassas, VA), 1 mM Sodium Pyruvate (Lonza, Walkersville, MD, U.S.A), 1mM Penicillin/Streptomycin (Pan Biotech, Germany) and 1x 2-Mercaptoethanol (GIBCO, Invitrogen, Carlsbad, CA, U.S.A). Stimulation of PBMCs for detection of cytokine production by T cells was adapted from Kasturi *et al.*, 2020 [25]. Briefly, $1x10^6$ PBMCs were cultured in 200 µl final volume in 96-well U bottom plate in the presence of anti-CD28 (1 µg/ml) and anti-CD49d (1 µg/ml) [Biolegend] under the following conditions: a) negative control with DMSO, b) SARS-CoV-2 spike peptide pool (1-315 peptides from Wuhan SARS-CoV-2 spike, JPT Germany) at a final concentration of 2 µg/ml, c) PMA/Ionomycin. Cells were cultured for 2 hours before adding Brefeldin A at 10 µg/ml (Sigma-Aldrich, St Louis, MO) for an additional 5 hours. Cells were then washed with PBS, and stained for dead cells (Live/ Dead Fixable; Aqua from Thermo Fisher) in PBS at room temperature for

10 minutes. Without washing, cells were incubated with surface antibody cocktail (prepared in 1:1 of FACS buffer and brilliant staining buffer) for 30 minutes at room temperature with BV510-anti-human CD14 (clone M5E2), BV510-anti-human CD19 (clone HIB19), AF700 anti-human CD3 (clone OKT3), BV605 CD4 (clone OKT4), PerCP-Cy5.5 CD8 (clone RPA-T8) from Biolegend. Next, cells were fixed using Cytofix/Cytoperm buffer (BD Biosciences, CA) for 20 minutes at room temperature, and then kept in FACS buffer at 4°C overnight. 1x Perm/Wash (BD Biosciences, CA) was used for cells permeabilization for 10 minutes at room temperature and followed by intracellular staining for 30 minutes at room temperature with AF647 anti-human IFNγ (clone 4S.B3) and AF488 anti- human IL-2 (clone MQ1-17H12) from Biolegend, and PE/Cy7 anti- human TNFα (clone Mab11) from Thermo Fisher Scientific. Up to 100,000 live $CD3^+$ T cells were acquired on a LSRFortessa flow cytometer (BD Biosciences), equipped with FACS Diva software. Analysis of the acquired data was performed using FlowJo software (version 10.7.1). The background from each participant was removed by subtracting the % of $spike^+$ cells to the % of $DMSO^+$ cells. An arbitrary value below 0.01% of $CD4^+/CD8^+$ T cells was considered negative.

**Statistical analysis**

The SARS-CoV-2 convalescent individual was excluded in all statistical analyses. Non-parametric Spearman rank correlation was used to check for possible associations at single blood sample measurements. A paired t-test was used to compare the adverse event scores calculated for each participant after both vaccinations. For this, the individual mean differences were checked for normal distribution by means of QQ-plots and histograms. A comparison of participants receiving heterologous vaccination with controls who received homologous BNT162b2 vaccinations after the last blood sample measurements was done by the Mann-Whitney-U test because of skewed distributions for neutralization scores as well as IgM/IgG measurements. Longitudinal antibody measurements were analyzed by means of a mixed linear regression model including a random intercept in order to account for the repeated measures structure of the underlying data. The mixed linear model approach enabled to simultaneously account for possible confounding due to participants' sex and for the presence of missing data [26]. Therefore, no formal imputation of missing interim values was required. A two-sided alpha error of 5% was applied to analyses. Analysis of repetitive measurements of sera provided by a cohort of 26 participants can be considered statistically valid. All analyses were done by GraphPad Prism version 9.1.1 for Windows, GraphPad Software, San Diego, California USA, www.graphpad.com, R (version 4.0.1) and SAS (version 9.4).

**Results:**

Reactogenicity following prime and boost vaccination was evaluated by all study participants by self-reporting of solicited local and systemic symptoms according to a standardized questionnaire. Symptom severity (mild, moderate, severe) and duration (<1 h, few h, ~1 day, > 1 day) is reported for each individual participant (Figure S1A) and percentage of participants (Figure 1A,B).

Both, prime and boost vaccination, induced mild to moderate solicited adverse reactions in most participants with 88.4% (23/26) reporting at least one mild or moderate symptom following prime; 23/26 (88.4%) and 21/26 (80.8%) reporting at least one mild or moderate symptom following boost vaccination (Figure 1A,B). Most common symptoms after prime vaccination with ChAdOx1 nCoV-19 were pain at the injection site (92.3%), fatigue (80.8%), headache (73.1%), chills (61.5%), myalgia (61.5%) and fever (61.5%). Following boost vaccination with BNT162b2, most participants again reported pain at the injection site (84.6%) and fatigue (84.6%), but chills (19.2%), myalgia (38.5) and fever (19.2%) were less common. 23% of participants (6/26) reported at least one severe symptom following prime, 15.4% (4/26) after boost. Fatigue (7.7%) and headache (15.4% for prime, 3.8% for boost) were amongst symptoms reported as severe for both doses, while myalgia was reported as severe by 11.5% of participants following prime, but none after boost.

Comparing cumulative solicited adverse reaction (cSAR) scores, reactogenicity following prime with ChAdOx1 nCoV-19 was significantly ($p = 0.005$) higher than following boost with BNT162b2 (cSAR score median 11 and 6 respectively, Figure 1C). Individually, most participants (19/26, 73.07%) had milder reaction to boost compared to prime. 6/26 (23.07%) of participants described more severe reactions to boost vaccination (Figure S1B). A trend towards higher cSAR scores reported by female participants was seen for both boost and prime vaccinations (Figure 1D,E). No correlation was observed between participant age and reactogenicity (Figure S1C,D). Reactogenicity towards prime and boost vaccination was weakly but significantly correlated (Figure 1F, $p = 0.039$).

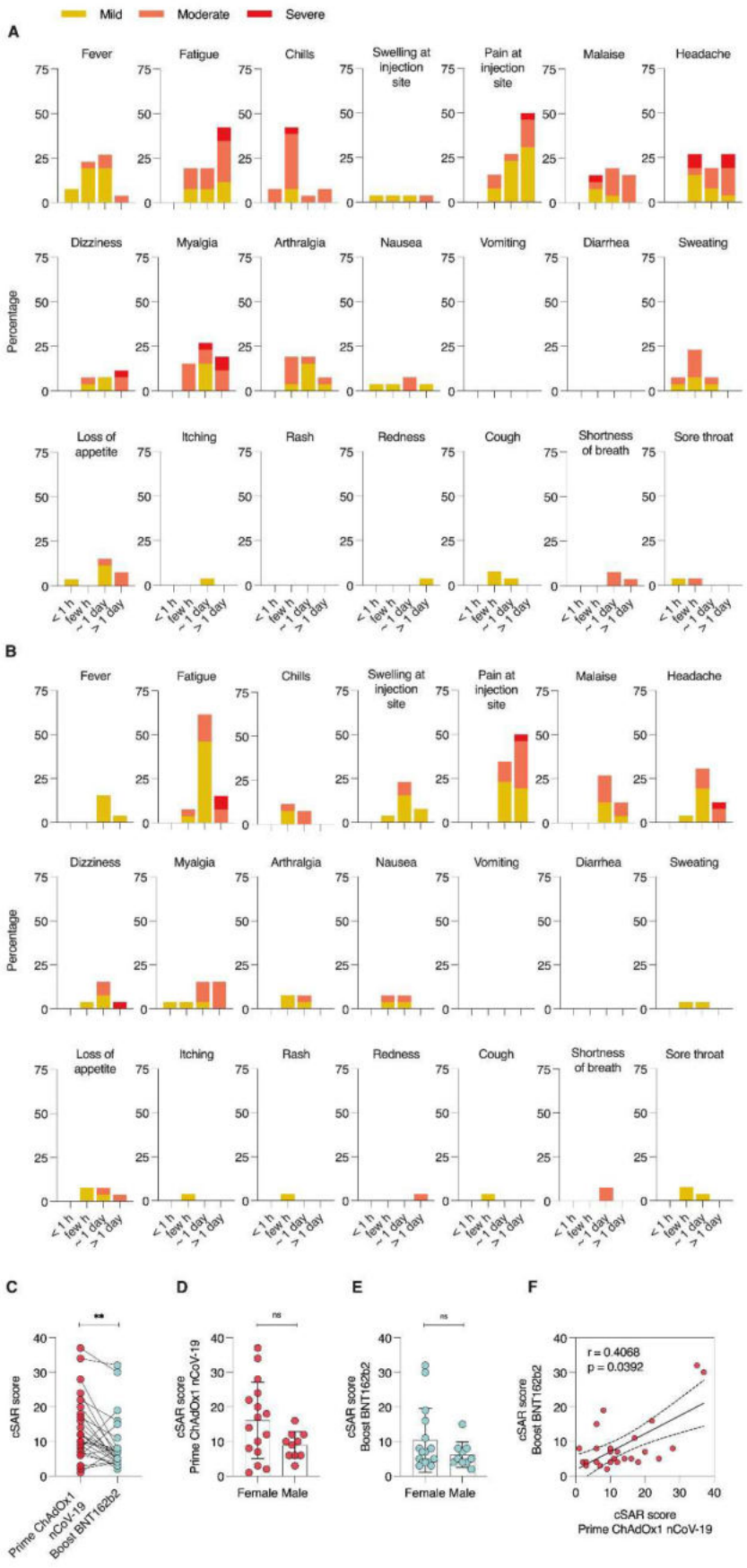

**Fig. 1. Solicited adverse reactions following ChAdOx1 nCoV-19 prime and BNT162b2 boost vaccination.** Percentages of participants with individual symptoms following prime (A) or boost (B) vaccination. Severity is graded on a scale of 1-2 (for some symptoms) or 1-3 (for most), according to Common Terminology Criteria for Adverse Events (US Department of of Health and Human Services, Version 4.03) [22]. (C) Cumulative solicited adverse reaction (cSAR) scores of all participants following prime and boost vaccination. For calculation of cSAR scores, symptom gradings are summed and an additional score point is added for symptoms lasting more than 24 h. Analysis of cSAR scores by (D, E) participant gender, and (F) comparison between cSAR scores following prime and boost vaccination. The SARS-CoV-2 convalescent individual was excluded in all statistical analyses. Paired t-test; ns not significant; ** $p < 0.01$

We collected sera from participants 2 days (-2) or on the same day (0) before vaccination, and at days 15 – 16, 30 – 37, and 53 – 57 after ChAdOx1 nCoV-19 prime, and days 6 - 11 and 14 – 19 after BNT162b2 boost (64 – 65 or 72 – 73 after prime, respectively) to determine antibody responses (Figure 2). Already 15-16 days after prime, 19/25 (76%) participants showed detectable anti-SARS-CoV-2-spike-IgG levels and 17/25 (65%) detectable IgA levels (Figure 2A,B). IgG levels peaked after 30 - 37 days and were detectable in 24/25 (96%) participants. Until days 53 – 57, IgG levels slightly decreased, consistent with previous results after single ChAdOx1 nCoV-19 dose [4,5]. IgA values were highest already at days 15-16 and became undetectable in 24 (92%) participants at days 53 - 57. Notably, only 6 - 11 days after the BNT162b2 boost, IgG was detectable in all (100%) and IgA in 23 (92%) of 25 participants. Until day 14-19 after boost (72-73 post ChAdOx1 nCoV-19), IgG and IgA were detectable in all participants. This corresponds to an at least 3.7-fold increase in median IgG levels from pre-boost to 2 weeks post-boost. We next quantified cumulative anti-SARS-CoV-2-spike-IgM and IgG concentrations and detected median antibody levels of 3.39 (range 0-2,126) units per ml (U/ml) 15-16 days after prime vaccination in 22/25 (88%) participants (Figure 2C). From days 30 – 37 on, IgM and IgG were detected in all participants and medians continuously increased to 28 (1.86-1,436) and 63.9 (4.27-1,005) U/ml after days 30 - 37 or 53 - 57, respectively. After BNT162b2 boost, titers increased 134-fold to 8,614 (126 – 24,831) at days 6 – 11 and 135-fold to 8,815 (1,206 – 19,046) 14 - 19 days after the second dose. Strikingly, the resulting titers were 8.1-fold higher than those determined for sera obtained after 13-15 days of a homologous BNT162b2 boost (individuals with median age 41 (25-55); median titers 1,086; range 498-3,660). Cumulative IgM/G titers correlated with IgG titers at each timepoint analysed post prime (Figure S2, Table S1).

Sera were also evaluated for their potential to inhibit SARS-CoV-2-spike-receptor binding domain/ACE2 interaction using a surrogate virus neutralisation test (sVNT) (Figure 2D). 15-16 days after ChAdOx1 nCoV-19 administration 13/25 (52%) participant sera showed ACE2 neutralizing activity, correlating significantly with IgG and IgM/G titers (Figure S2, Table S1). Median neutralization activity of the positive sera was 46% (range 32-97%). Until days 53-57, the number of participants with neutralizing sera increased to 19/26 (73%) and the median ACE2 neutralization to 62% (range 32-95%), again in correlation with IgG and IgM/G values (Figure S2, Table S1). After BNT162b2 boost, all participants showed potent neutralization with a median of 97% (range 32-98%) after 6-11, and 98% (range 89-98%) after 14-16 days suggesting a strong and functional antibody response after heterologous vaccination in all participants.

The potency of neutralizing activity was further quantified using vesicular stomatitis virus (VSV)-based pseudoviruses carrying the SARS-CoV-2 spike protein of the most prevalent SARS-CoV-2 B.1.1.7 variant. This system faithfully recapitulates SARS-CoV-2 entry into cells and its inhibition[21,27,28]. 15-16 days after ChAdOx1 nCoV-19 prime, neutralizing titers ranging from 36-906 were detectable in 8/25 (32%) participants (Figure 2E). The number of participants with detectable neutralization increased to maximum in 12/25 (48%) individuals at days 30-37 with a median neutralization titer of 74 (range 20-

552) in responders, which slightly decreased until days 53-58. Two weeks after the BNT162b2 boost, neutralizing titers were detected in all participants with a median titer of 2,744 (range 209-8,985). Of note, while for some individuals the titers further increased from week 1 to week 2 after BNT162b2 boost, other individuals plateaued at titers > 1,000 (Figure S3). At all time points, neutralizing activity correlated with IgG or IgM/G titers (Figure S2, Table S1). Remarkably, the median titer of these individuals was 3.9-fold higher than the median titer of 14 individuals vaccinated with BNT162b2 in a homologous regimen (709; range 305-1,806) suggesting a stronger humoral protection after a heterologous vaccination. Of note, a SARS-CoV-2 convalescent individual (triangle symbol) showed a strong response after the first dose in all assays, high IgG, IgA or IgM/G values, most effective ACE2- neutralization and a high neutralization titer of 906 15 – 16 days after prime that decreased over the days to 201 at day 53-57 (Figure 2A-E).

Additionally, we evaluated the neutralizing activities of sera obtained 2 weeks post full vaccination against the variants of concern (VOCs) B.1.351 and B.1.617. Pseudovirus entry driven by B.1.351 spike was neutralized with 2-fold lower potency ($p < 0.05$) compared to B.1.1.7 spike. However, it was still entirely blocked at higher doses with a median titer of 1,297 (range 252 - 6,523). Neutralization of the B.1.617 spike was not reduced compared to B.1.1.7 spike (median titer of 1,309; range 150 – 13,252) (Figure 2F). Sera of individuals vaccinated with homologous BNT162b2 showed lower neutralizing titers against all spike variants tested (Figure 2F), suggesting stronger humoral protection after a heterologous vaccination also against VOCs.

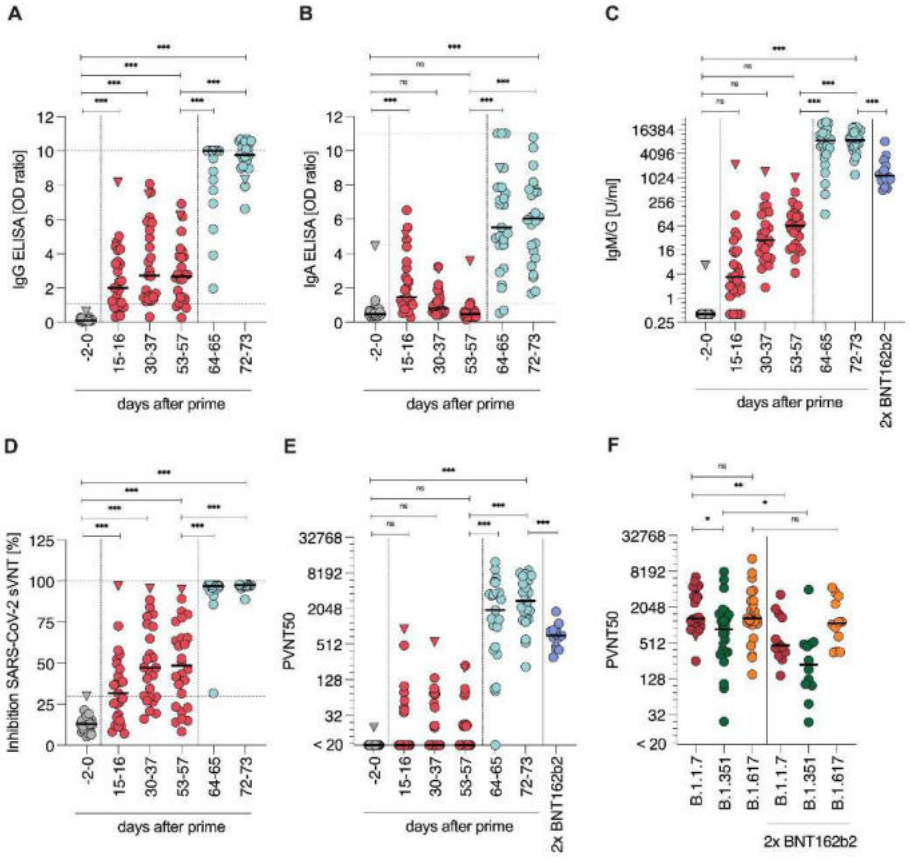


**Fig. 2. Humoral response.** Quantification of anti-SARS-CoV-2 S1 spike domain (A) IgG and (B) IgA titers. (C) Quantification of anti-SARS-CoV-2 spike IgG and IgM responses as units per ml (U/ml) by immunoassay. (D)

SARS-CoV-2 surrogate virus ACE2 neutralization test. (E) VSV-based B.1.1.7 SARS-CoV-2 spike pseudovirus neutralization assay. (F) VSV-based B.1.1.7, B.1.351 and B.1.617-SARS-CoV-2 spike pseudovirus neutralization assay. Titers expressed as serum dilution resulting in 50% pseudovirus neutralization (PVNT50). Triangle indicates SARS-CoV-2 convalescent individual, who was excluded from all statistical analyses. Grey symbols indicate datapoints pre-vaccination, red datapoints indicate datapoints after prime and light-blue after boost vaccination. Dark-blue indicates samples of participants with homologous BNT162b2 prime-boost regimen. Dashed horizontal lines indicate upper and lower limit of detection/cutoff, respectively. Dashed vertical lines indicate prime and boost vaccination. Longitudinal antibody measurements were analyzed by means of a mixed linear regression model. Mann-Whitney-U test compares ChAdOx1 nCoV-19 and BNT162b2 titers *** $p < 0.0001$, ** $p < 0.001$, * $p < 0.05$, ns not significant

To evaluate cellular immunity, we isolated peripheral blood mononuclear cells from blood samples provided by 19/26 participants on days 14-19 post BNT162b2 boost (72-73 days post prime), considered as full vaccination according to the vaccination schedule. Cells were exposed to a SARS-CoV-2 spike-spanning peptide-pool and analyzed for intracellular cytokines TNFα, IFNγ, and IL2 to determine spike-specific $CD4^+$ and $CD8^+$ T cell responses (Figure 3, S4). Upon antigen stimulation, $CD4^+$ T cells secreting IFNγ (median 0.055, range 0.018-0.168), IL2 (median 0.055, range 0-0.134) or TNFα (median 0.057; range 0.01 – 0.193) were detected in all participants suggesting they developed a robust spike-specific T helper 1 (TH1) $CD4^+$ T cell response. In addition, in 89% (17/19) of participants a substantial population of spike-specific $CD8^+$ T cells, with a predominant $IFN\gamma^+$ (median 0.092, range 0-0.665) and $TNF\alpha^+$ (median 0.055, range 0 – 0.375) phenotype was detected. We observed lower levels of $CD8^+$ $IL2^+$ (median 0.01, range 0-0.052) T cells which is in agreement with responses after homologous BNT162b2 vaccination [6]. Interestingly, unstimulated $CD8^+$ T cells of the convalescent individual were already reactive before SARS-CoV-2 spike peptide stimulation. Overall, these findings show a robust humoral and cellular immune response after heterologous vaccination.

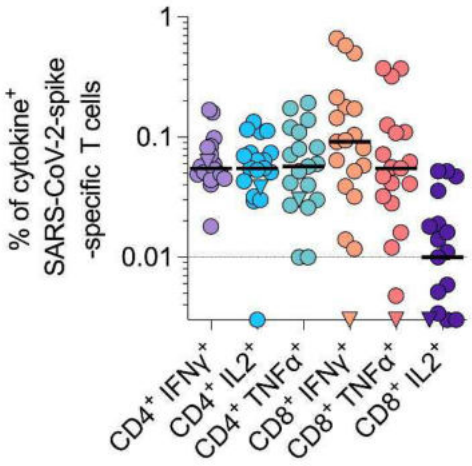


**Fig. 3. SARS-CoV-2 spike-specific $CD4^+$ and $CD8^+$ T cell responses.** PBMCs of study participants were stimulated with a SARS-CoV-2 spike peptide-pool and cytokine secretion determined by flow cytometry. $Cytokine^+$ T cells were background corrected for unstimulated cells and values lower than 0.01% were considered negative. Triangle symbol indicates SARS-CoV-2 convalescent individual, where cytokine release was already high in absence of stimulation.

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## Discussion

Based on the regulatory approvals for ChAdOx1 nCoV-19 and mRNA vaccines, the interval between prime and boost vaccinations ranges between 4 -12 weeks [29–31]. For ChAdOx1 nCoV-19, a 12 week interval has been shown to result in stronger immune responses [32], most likely because the immunity against the vector wanes. Accordingly, e.g. in Germany heterologous vaccinations are currently typically performed after 12 weeks. Existing vector immunity, however, is irrelevant in the context of a mRNA boost vaccination, on which basis our cohort received the boost after 8 weeks. This heterologous ChAdOx1 nCoV-19/BNT162b2 vaccination elicited strong IgM/G and IgA responses, neutralizing activities and T cell responses in all previously uninfected participants, while solicited adverse reactions to vaccination were as expected for a prime ChAdOx1 nCoV-19 vaccination and reduced following heterologous BNT162b2 boost.

A previous study showed that a heterologous vaccination schedule with 4-week interval results in stronger reactogenicity after boost [16], whereas a preprinted study with a 12-week interval did not confirm this effect [17]. We did not directly compare different vaccination schemes. Thus, we cannot draw definitive conclusions on differences, which might also depend on cohort age [5]. With an 8-week interval, we observed an overall milder reactogenicity following heterologous boost with BNT162b2 than after initial prime vaccination with ChAdOx1 nCoV-19 and no serious adverse events, arguing for the safety of this regimen in young adults.

Our immunological data suggest that a heterologous vector-based/mRNA prime-boost schedule is highly effective in preventing COVID-19, as neutralizing antibody levels correlate with immune protection from symptomatic SARS-CoV-2 infection [33] and $CD8^+$ T cell responses have been associated with a mild disease course [34,35]. Endpoint antibody titers determined 2 weeks post boost were significantly higher than those detected upon homologous BNT162b2 vaccinations (Figure 2 C,E). This is in line with findings in preclinical models [18], but might also be influenced by cohort age. Factors contributing to this high degree of immunogenicity might be the circumvention of vector immunity. The BNT162b2 encoded spike sequence contains a two-proline mutation not present in ChAdOx1 nCoV-19, which fix spike in a pre-fusion confirmation [9]. It is tempting to speculate that altered spike confirmations may be beneficial for effective neutralizing responses.

Neutralizing activity towards VOC B.1.351, previously reported to show partial evasion of vaccination-induced antibodies [21,36,37], was only slightly decreased following heterologous vaccination. Neutralization of emerging VOC B.1.617 was not reduced compared to B.1.1.7. Whether these immunological findings translate into effective general protection from VOCs in real-life setting remains to be determined. However, the substantial neutralization capacity against two highly transmissible virus variants is encouraging.

Secretory IgA responses at the mucosal site of SARS-CoV-2 entry are of particular interest with regard to prevention of virus transmission and (re-)infection [38]. We detected a general increase in serum IgA levels with strong variation between participants, suggesting mucosal protection shortly after vaccination. However, IgA levels decreased over time after prime vaccination, and future studies, especially assessing IgA and secretory IgA levels and persistence at mucosal entry sites after boost are warranted.

In all participants SARS-CoV-2 specific $CD8^+$ or $CD4^+$ T cells were detected 2 weeks after full vaccination. These effects were similar to those reported after a single ChAdOx1 nCoV-19 dose and after homologous BNT162b2 vaccination [4,6]. This suggests that T cell responses are similarly effective after heterologous vaccination.

In line with previous results, in an individual participant who was previously tested SARS-CoV-2 positive, a single prime vaccination dose already elicited strong antibody responses [39,40]. In this case, the observed neutralizing titers 2 weeks after prime were as high as the median titer of those receiving the homologous BNT162b2 vaccination, However, titers (IgM/G) further increased 8-fold after boost, suggesting that prime-boost might provide more potent and longer lasting protection.

In conclusion, heterologous vaccination schedule of ChAdOx1 nCov-19 prime, followed by BNT162b2 boost after 8 weeks for participants with a median age of 30 years was safe and effective. This provides flexibility for future vaccination strategies and will be useful for vaccine schedules during shortages. Whether heterologous vaccination is superior to homologous regimens and should be considered as a strategy to elicit particularly strong immune responses e.g. against VOCs or for highly exposed individuals remains to be determined. Similarly, whether other vector- or mRNA-based vaccine combinations or those based on other technologies are similarly effective needs to be addressed in future studies.

Limitations

The study cohort of 26 participants is not large, but the repetitive measurements suffice for a comprehensive analysis of serological responses. With a median age of 30.5 (range 25 - 46) years, the results do not provide information on the elderly. However, our study offers insight into how the younger age group reacts to a heterologous vaccination regimen. This is of high significance, because individuals younger than 60 have regularly been primed with ChAdOx1 nCov-19 and are now offered heterologous boost vaccination. Our study group received the second vaccination after 8 weeks, which is within the range of recommendation of 4-12 weeks.

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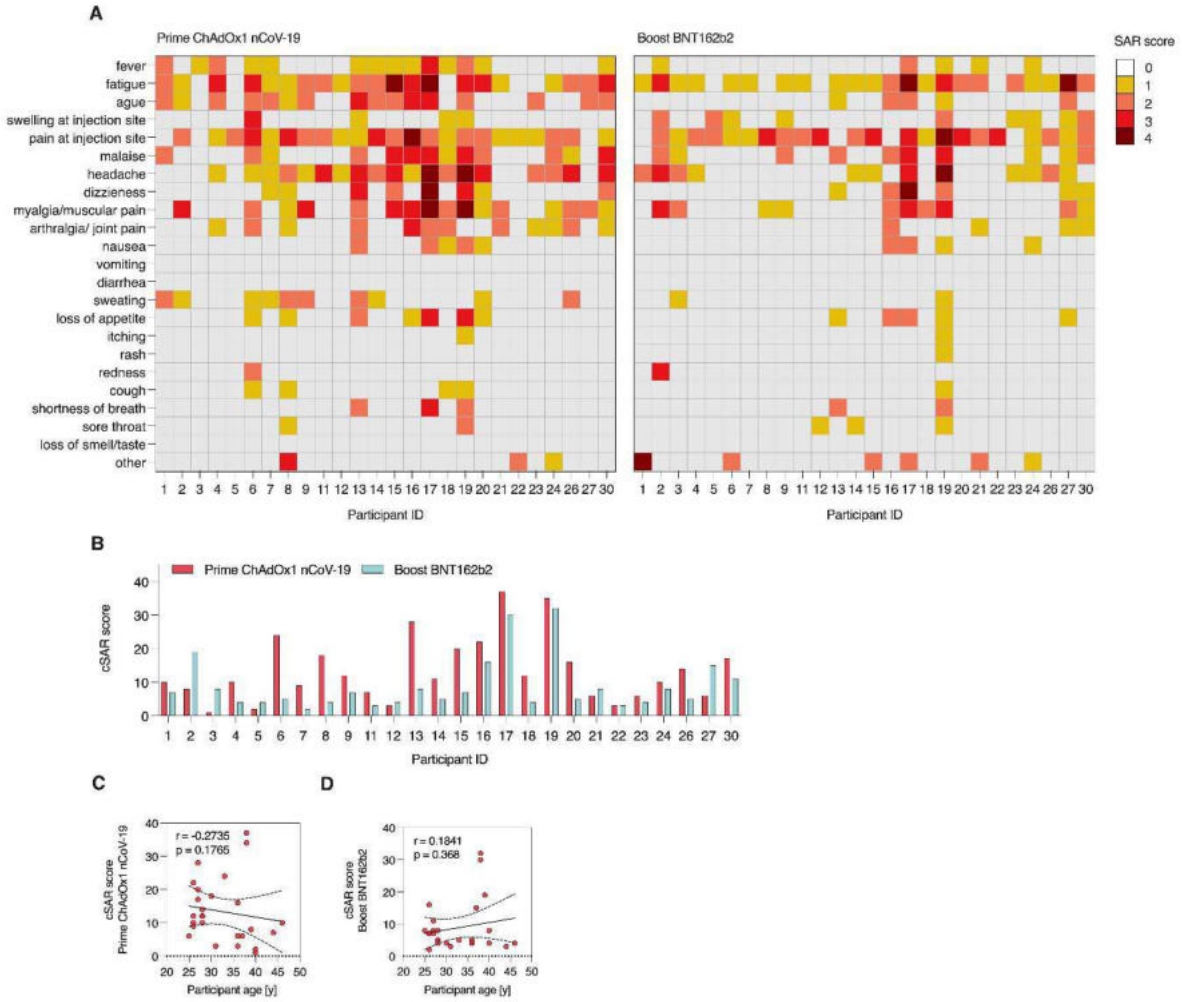


**Figure S1: Extended analysis of solicited adverse reactions following ChAdOx1 nCoV-19 prime and BNT162b2 boost vaccination.** (A) Heatmap showing SAR scores per participant and symptom used for calculation of cSAR scores. Severity is graded on a scale of 1-2 (for some symptoms) or 1-3 (for most), according to Common Terminology Criteria for Adverse Events (US Department of Health and Human Services, Version 4). For calculation of cSAR score (A, B), symptom gradings are summed and an additional score point is added for symptoms lasting more than 24 h (final scores 1-4 per symptom). Correlation analysis for cSAR scores with participant age for prime (C) and boost (D) vaccination.

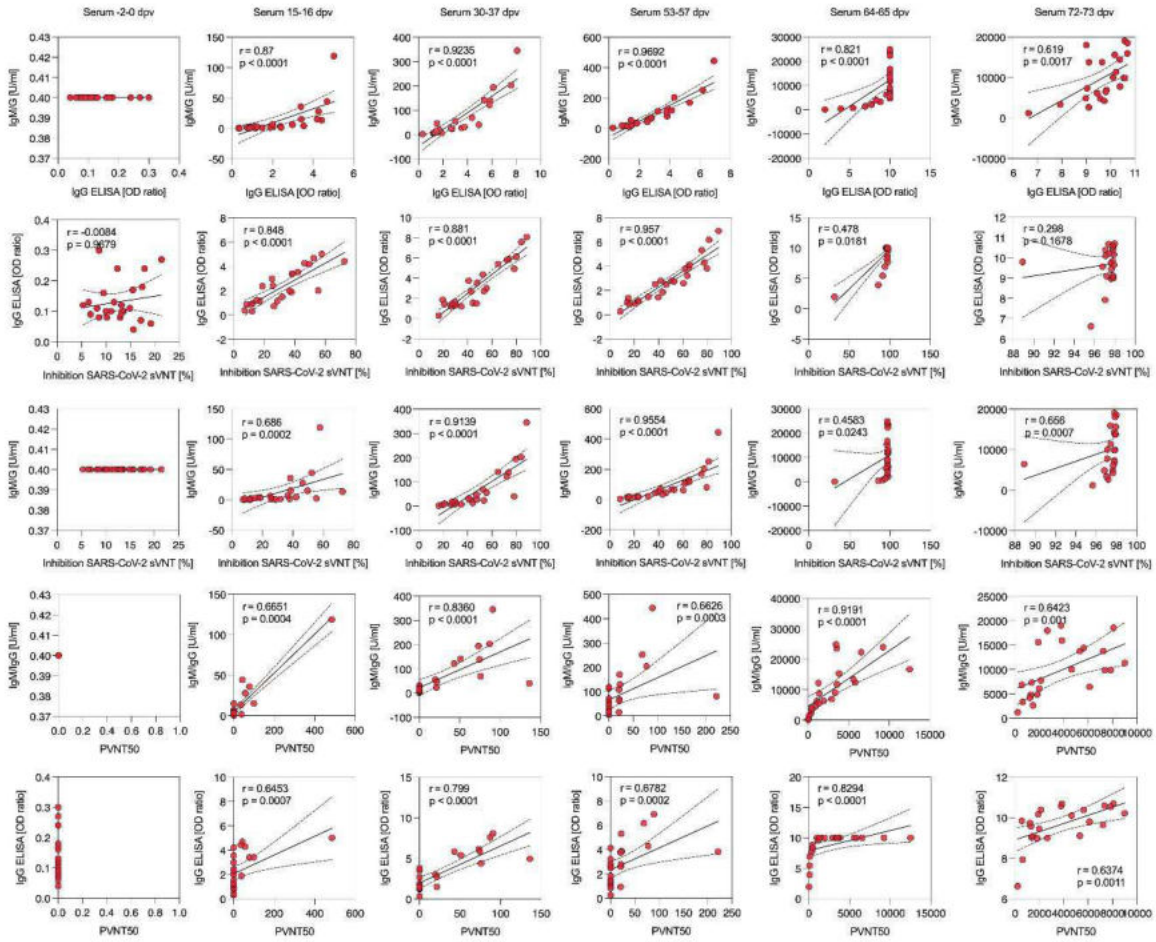


**Figure S2. Correlation analysis of humoral response metrics.** Data on humoral response (IgG, IgA, IgM/G, PVNT50, Inhibition SARS-CoV-2-sVNT) were analysed for correlation for each timepoint. Spearman correlation, two-tailed p values, dashed lines indicate 95% confidence interval. The SARS-CoV-2 convalescent individual was excluded from the analysis.

561 **Table S1. Summary of correlation analysis of humoral response metrics.** Spearman r values of Figure S2.

562

563

| | -2 - 0 | 15 – 16 | 30 - 37 | 53 - 57 | 64 - 65 | 72 - 73 |
|---|---|---|---|---|---|---|
| IgG:IgM/G | / | 0.87 | 0.9235 | 0.9692 | 0.821 | 0.619 |
| sVNT:IgG | -0.0084 | 0.848 | 0.881 | 0.957 | 0.478 | 0.296 |
| sVNT:IgM/G | / | 0.686 | 0.9139 | 0.9554 | 0.4583 | 0.656 |
| PVNT50:IgM/G | / | 0.6651 | 0.836 | 0.6626 | 0.9191 | 0.6423 |
| PVNT50:IgG | / | 0.6453 | 0.799 | 0.6782 | 0.8294 | 0.6374 |

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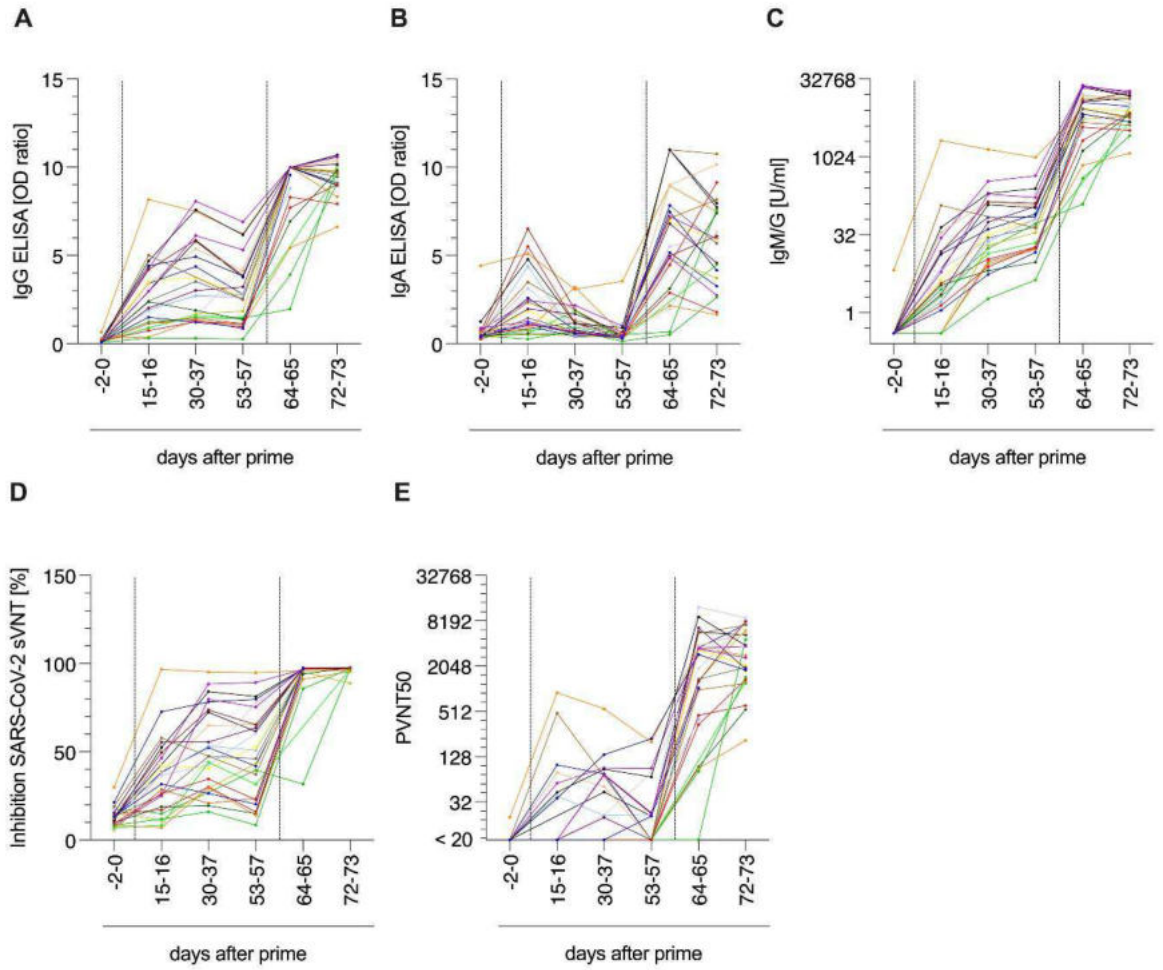


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566 **Figure S3. Time course of humoral responses.** Time course of anti-SARS-CoV-2 S1 spike domain (A) IgG and (B) IgA
567 titers. (C) Time course of anti-SARS-CoV-2 spike IgG and IgM responses as units per ml (U/ml) by immunoassay. (D)
568 Time course of SARS-CoV-2 surrogate virus ACE2-RBD interaction neutralization as assessed by surrogate virus
569 neutralisation test (sVNT). (E) VSV-based B.1.1.7 SARS-CoV-2 spike pseudovirus neutralization assay. Titers
570 expressed as serum dilution resulting in 50% pseudovirus neutralization (PVNT50).

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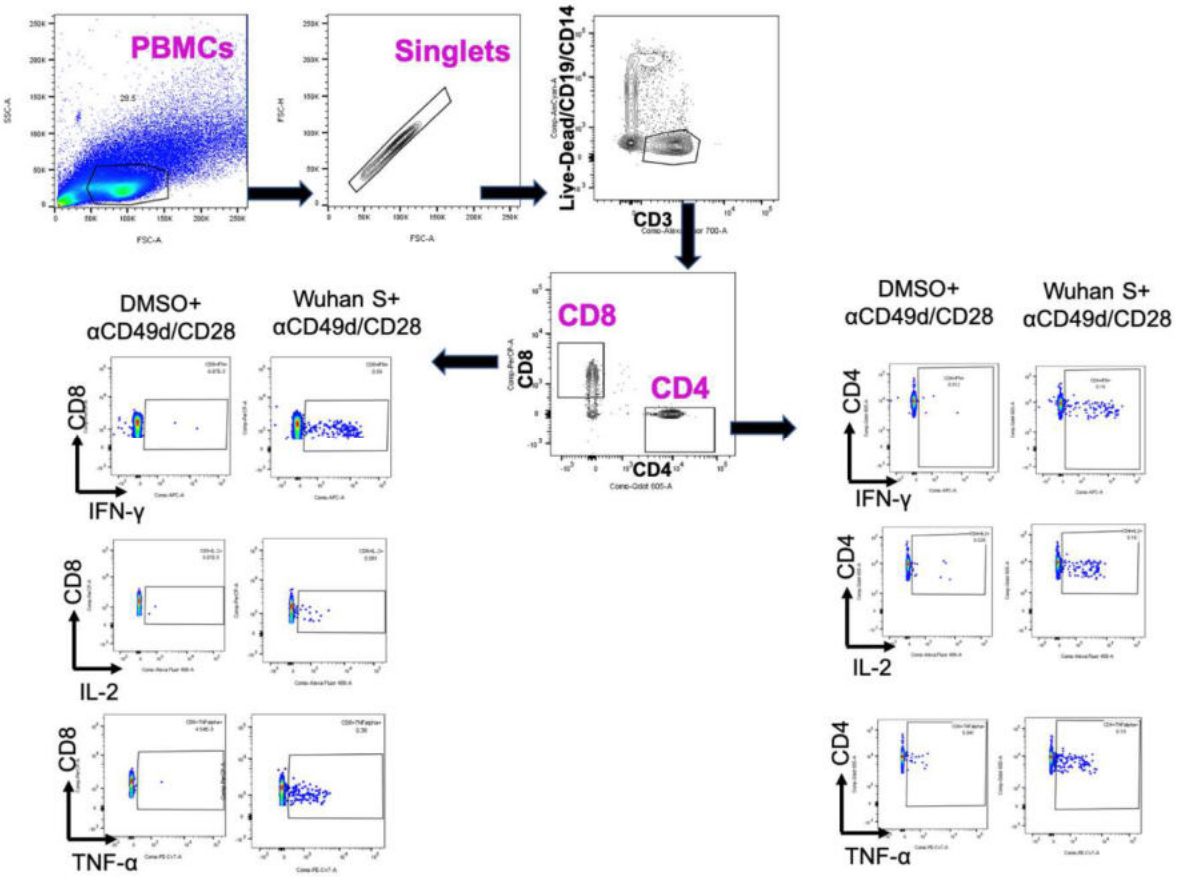


**Figure S4.** Gating strategy for analysis of T cell reactivity. SARS-CoV-2 spike peptide stimulated and unstimulated (DMSO) PBMCs were initially gated on the basis of light scatter (SSC-A versus FSC-A) and for singlets (FSC-H versus FSC-A). Dead cells, monocytes, and B cells were excluded using a dump channel and by gating on $CD3^+$ T cells. Total $CD8^+$ and $CD4^+$ cells were then selected, and individual cytokine gating was performed.

# Safety, reactogenicity, and immunogenicity of homologous and heterologous prime-boost immunisation with ChAdOx1-nCoV19 and BNT162b2: a prospective cohort study

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# Abstract

**Objective:** to assess reactogenicity and immunogenicity of heterologous prime-boost immunisations of ChAdOx1-nCoV19 (Vaxzevria, ChAdOx) followed by BNT162b2 (Comirnaty, BNT) compared to homologous BNT/BNT immunisation.

**Design:** prospective, observational cohort study.

**Setting:** unicenter study in a cohort of health care workers at a tertiary care center in Berlin, Germany.

**Participants:** 340 health care workers immunised between 27 December 2020 and 21 May 2021 at Charité - Universitätsmedizin Berlin, Germany

**Main outcome measures:** the main outcomes were reactogenicity assessed on days one, three, five and seven post prime and boost vaccination, and immunogenicity measured by serum SARS-CoV-2 full spike-, spike S1-, and spike RBD-IgG, virus neutralisation capacity, anti-S1-IgG avidity, and T cell reactivity measured by Interferon gamma release assay at 3-4 weeks post prime and boost immunisation.

**Results:** Heterologous ChAdOx/BNT booster vaccination was overall well-tolerated and reactogenicity was largely comparable to homologous BNT/BNT vaccination. Systemic reactions were most frequent after prime immunisation with ChAdOx (86%, 95CI: 79-91), and less frequent after homologous BNT/BNT (65%, 95CI: 56-72), or heterologous ChAdOx/BNT booster vaccination (48%, 95CI: 36-59). Serum antibody responses and T cell reactivity were strongly increased after both homologous and heterologous boost, and immunogenicity was overall robust, and comparable between both regimens in this cohort, with slightly increased S1-IgG avidity and T cell responses following heterologous booster immunisation.

**Conclusions:** Evidence of rare thrombotic events associated with ChAdOx has led to recommendation of a heterologous booster with mRNA vaccines for certain age groups in several European countries, despite a lack of robust safety and immunogenicity data for this vaccine regimen. This interim analysis provides evidence that the currently recommended heterologous ChAdOx/BNT immunisation regimen with 10-12 week vaccine intervals is well tolerated and slightly more immunogenic compared to homologous BNT/BNT vaccination with three week vaccine intervals. Heterologous prime-boost immunisation for COVID-19 may be generally applicable to optimise logistics and improve immunogenicity and to mitigate potential intermittent supply shortages for individual vaccines.

# Introduction

In light of intermittent supply shortages of individual vaccines and evidence of rare, but severe adverse events following vaccination with vector-based vaccines such as ChAdOx1-nCoV19 COVID-19 vaccine (Vaxzevria, AstraZeneca, ChAdOx) [1–4], heterologous prime-boost regimens for COVID-19 vaccines have gained significant interest [5]. Heterologous booster vaccination with an mRNA vaccine following initial immunisation with ChAdOx is now recommended in specific age groups in several countries, including Germany [6], despite limited or absent data on reactogenicity, safety and immunogenicity of this prime-boost regimen in humans.

On January 29, 2021, the German standing committee on vaccination (STIKO) recommended that ChAdOx should only be administered to persons between 18-64 years of age. Consequently, mainly younger persons, including healthcare workers, received ChAdOx while mRNA vaccines (BNT162b2 (BNT) and Moderna mRNA-1273) were prioritized for use in the elderly. In response to reports about rare blood clotting events, including cerebral venous sinus thrombosis associated with ChAdOx vaccination, especially in younger women [2–4], several European countries restricted their recommendations for ChAdOx vaccination to individuals above a certain age limit (e.g. above 60 years in Germany, and 55 years in France) [7]. Heterologous boost immunisation with an mRNA vaccine (BNT or mRNA-1273) was recommended for persons who had already received a first immunisation with ChAdOx, but who are younger than the revised age limit for ChAdOx [7]. In Phase 2/3 trials, both BNT and ChAdOx demonstrated significant reactogenicity, most commonly pain at the injection site, fatigue, headache, chills, and fever, with only a minor fraction of study participants reporting severe reactions [8,9]. A recent interim analysis of reactogenicity data in the Com-COV trial, investigating various heterologous prime-boost regimens of licensed COVID-19 vaccines, reported no serious side effects, but clearly increased reactogenicity following heterologous boost with BNT 28 days after initial vaccination with ChAdOx [10]. In this interim analysis, up to 80% of persons receiving a heterologous prime-boost with ChAdOx/BNT reported fatigue and other systemic reactions, an up to 40-fold increase compared to the respective homologous boost vaccinations [10]. Both BNT and AZ have been shown to elicit robust immune responses with a significant increase following homologous boost vaccination in clinical trials and real world studies [8,9,11–13]. Heterologous prime-boost immunisation has been shown to elicit increased immunogenicity for other vaccines [5,14,15], and early animal experiments suggest increased immunogenicity of boost vaccination with an mRNA vaccine following initial immunization with adeno-vector based COVID-19 vaccines [16]. However, data on immunogenicity of heterologous prime-boost vaccination for COVID-19 in humans is still lacking.

Heterologous ChAdOx/mRNA vaccination has already commenced across Europe, despite a lack of robust immunogenicity and safety data for this combination. No data on immunogenicity and reactogenicity of heterologous versus homologous BNT/ChAdOx vaccination at 10-12 week intervals, as recommended in many countries, is available to date. Here, we report reactogenicity and immunogenicity data of homologous BNT/BNT and heterologous ChAdOx/BNT prime-boost immunisations in a prospective observational cohort study of 340 healthcare workers in Berlin, Germany. We found comparable reactogenicity and robust immunogenicity of homologous and heterologous vaccine regimens.

# Methods

Methodology and study design and assessment of immunogenicity have also been described in detail previously [17].

### Study design

Health care workers receiving routine COVID-19 vaccination were enrolled in the EICOV and COVIM prospective, observational cohort studies conducted at Charité - Universitätsmedizin Berlin, Germany, after written informed consent was obtained. EICOV was approved by the ethics committee (IRB) of Charité - Universitätsmedizin Berlin (EA4/245/20) and COVIM (EudraCT-No. 2021-001512-28) was approved by the Federal Institute for Vaccines and Biomedicines (Paul Ehrlich Institute) and by the Ethics committee of the state of Berlin. Both studies were carried out in accordance with the guidelines of Good Clinical Practice (ICH 1996) and the Declaration of Helsinki.

Study participants either received two doses of BNT three weeks apart or an initial dose of ChAdOx followed by a heterologous boost with BNT 10-12 weeks later, in accordance with the recommendations of the German standing committee on vaccination (STIKO). Baseline data on demographics were collected by questionnaire (eCRF) at enrollment. Blood samples for detection of SARS-CoV-2 specific antibodies and T cell response were collected immediately prior to the first vaccination, and three to four weeks after the first and the second vaccination.

### Assessment of reactogenicity and safety

Participants were asked to fill out electronic questionnaires on reactogenicity, adverse events, medication, and medical visits on days 1, 3, 5, and 7 after the first and second vaccination. In addition, the use of antipyretic medication (NSAID, acetaminophen) before and after vaccination was recorded. We assessed local and systemic reactions to the different vaccines using a modified Food and Drug administration (FDA) toxicity scale [18]. Following the initial assessments, all participants were asked to self-report any systemic symptoms and intake of pain medication through an electronic questionnaire every two weeks. Here, we report on the results of questionnaires collected the first seven days following first and second vaccination.

### Assessment of immunogenicity

Participants with PCR-confirmed infection or detectable anti-nucleocapsid protein (NP) IgG at any time point in the study were excluded from further analysis. A subset of all study participants was selected for immunogenicity analysis based on multivariate matching for sex and age between vaccine groups. Presence of SARS-CoV-2 specific antibodies was investigated using a microarray-based immunoassay including spike (full spike,S1, RBD) and nucleocapsid (N) as antigens in order to discriminate between vaccine-induced antibody response and convalescent SARS-CoV-2 infection (SeraSpot®Anti-SARS-CoV-2 IgG, Seramun Diagnostica GmbH, Heidesee, Germany, [17]). Functional neutralization capacity was investigated using a surrogate SARS-CoV-2 neutralization test (sVNT, cPass, medac GmbH, Wedel, Germany), following the manufacturer's instructions [17,19]. Maturation of IgG avidity was characterized by a modified anti-SARS-CoV-2 S1 IgG ELISA (anti-SARS-CoV-2 S1 IgG ELISA Kit; Euroimmun Medizinische Labordiagnostika AG, Lübeck, Germany) [17] in 30 randomly selected samples each from the homologous and heterologous boost cohorts who were seroreactive three weeks after prime vaccination. SARS-CoV-2 spike specific T cell

responses were measured by an interferon-γ release assay (IGRA; Euroimmun [17]) of S1 peptide stimulated T cells in heparinized whole blood. IFN-γ was measured by ELISA and an arbitrary unit was displayed subtracting the blank optical density (OD) 450/620nm from S1-peptide-pool stimulated samples.

**Statistics**

Data are presented as median and interquartile range, unless stated otherwise. Statistical analysis was performed using GraphPad PRISM statistics version 27.0 (IBM Deutschland, Ehningen, Germany). Group comparisons were performed in a univariate analysis using Fisher's exact test or nonparametric Kruskal-Wallis test with Dunn's multiple comparisons test. All 95% confidence intervals were calculated according to the Wilson and Brown method [20]. P-values <0.05 were considered statistically significant.

# Results

From December 27, 2020, to March 30, 2021, a total of 340 healthcare workers were enrolled at Charité - Universitätsmedizin Berlin, Germany. Twenty-six participants had either a positive PCR result for SARS-CoV-2 during the study or a detectable anti-spike IgG or anti-N IgG antibody response at baseline or follow up (N), and were therefore excluded from further analysis. Eight participants opted for a homologous ChAdOx/ChAdOx booster immunisation and were only included for reactogenicity analysis of prime immunisation. Baseline characteristics of the study population, an overview of the vaccine groups and respective study sub-cohorts for reactogenicity and immunogenicity analyses are given in **Table 1**.

| **Vaccine group** | **BNT/BNT[1] homologous boost** | | **ChAdOx[2]/BNT heterologous boost** | |
|---|---|---|---|---|
| Prime to boost interval , median days (IQR) | 21 (21-21) | | 71 ( 70-73) | |
| Prime and boost vaccination | 1st BNT, n=179 | 1st BNT / 2nd BNT n=189 | 1st ChAdOx n=151 | 1st ChAdOx / 2nd BNT n=110 |
| **Reactogenicity data, n** | 178 | 159 | 148 | 99 |
| Age, median years (IQR) | 34 (29-44) | 34 ( 29-43) | 35 (28-47) | 37 (29-51) |
| Female, n (%) | 98 (55.0%) | 87 (54.7%) | 101 (68.2%) | 77 (77.8%) |
| **Serology data measured, n** | 94 | 101 | 57 | 61 |
| Δvaccination to sampling, median days (IQR) | 21 (21-21) | 28 (27-30.5) | 26 (22-28) | 21 (I21-21) |
| Age, median years (IQR) | 35 (30.75-48) | 35 (30.5-47.5) | 38 (31-52.5) | 38 (30.5-51.5) |
| Female, n (%) | 66 (70.2%) | 73 (72.3%) | 46 (80.7%) | 47 (77.1%) |

**Table 1**: **Baseline characteristics and schedule of BNT/BNT homologous prime and boost and ChAdOx/BNT heterologous prime and boost study participants.**
[1]BNT: BNT162b2 mRNA COVID-19 vaccine, [2]ChAdOx: ChAdOx1-nCoV19 COVID-19 vaccine, IQR: interquartile range

## Reactogenicity

All vaccinations were associated with a relatively high frequency of local reactions, most commonly pain and tenderness. Local reactions were usually mild or moderate (**Fig. 1A, B, Table S1**). No major differences were observed in the frequency or severity of local reactions after either of the prime or boost immunisations, with the exception of a slightly higher frequency of local reactions after heterologous ChAdOx/BNT booster vaccination in comparison to homologous BNT/BNT booster vaccination (**Fig. 1A, B, Table S1**). In contrast, notable differences were reported for systemic reactions. These were most frequently reported following prime immunisation with ChAdOx (86.49%, 95%CI: 80.05-91.08), and after homologous BNT/BNT booster immunisation (64.78%, 95%CI: 57.09-71.78), whereas only 51.52% (95%CI: 41.80-61.12) of participants after the heterologous BNT booster (ChAdOx/BNT) vaccination, and 38.76% (95%CI: 31.92-46.09) of participants after the first immunisation with BNT reported systemic reactions (**Fig. 1C**). Severe systemic symptoms, including fatigue, myalgia, headache, feverishness or chills, and fever >38°C, were reported more frequently following ChAdOx prime immunisation and homologous BNT/BNT booster immunisation compared to heterologous ChAdOx/BNT booster vaccination (**Fig. 1D, Table S1**).

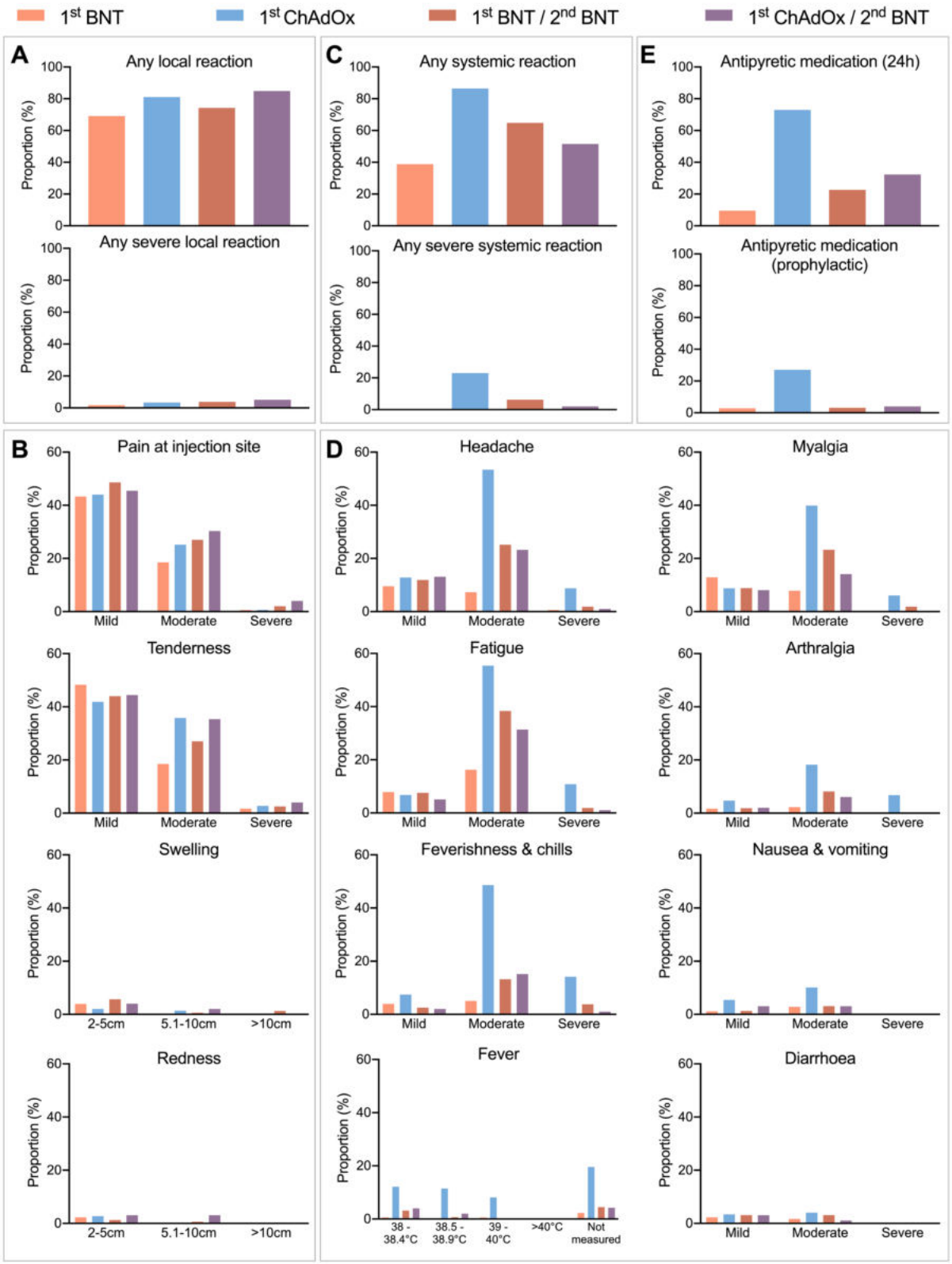


**Fig. 1. Local and systemic reactogenicity of BNT or ChAdOx prime immunisations and homologous or heterologous boosting until day seven after vaccination.** (**A, B**) Proportion of participants reporting any local reaction (A), and indicated local reactions grouped by severity (B). (**C, D**) Proportion of participants reporting any systemic reaction (C), and indicated systemic symptoms grouped by severity (D). (**E**) Proportion of participants reporting intake of antipyretic medication within 24 hours after vaccination (top) and prophylactic intake of antipyretic medication (bottom). BNT: BNT162b2 / Comirnaty, ChAdOx: ChAdOx1-nCoV19 / Vaxzevria. Definition of severity according to modified Food and Drug administration (FDA) criteria [18]: mild: does not interfere with daily activities, moderate: interferes with daily activities, severe: daily activities no longer feasible.

No potentially life-threatening reactions were reported after any of the vaccine regimens in this study. Intake of antipyretic medication was reported most frequently in conjunction with the first ChAdOx immunisation (**Fig. 1E**). Within 24 hours after the first vaccination with ChAdOx, 72.97% (95%CI: 65.30-79.48) of participants reported antipyretic medication, which was markedly lower following heterologous ChAdOx/BNT boost (32.32%, 95%CI: 23.92-42.05), homologous BNT/BNT boost (22.64%, 95%CI: 16.83-29.75), and after prime immunisation with BNT (9.55%, 95%CI: 6.05-14.76) (**Fig. 1E**). The proportion of participants who reported prophylactic antipyretic medication was highest in the ChAdOx prime immunisation group (27.03%, 95%CI: 20.52-34.70), and distinctly lower in all other groups (1.BNT: 2.81% (95%CI: 1.21-6.41), 1.ChAdOx/2.BNT: 4.04% (95%CI: 1.58-9.93), 1.BNT/2.BNT: 3.14% (95%CI: 1.35-7.15). Thus, prophylactic intake of antipyretics cannot explain differences in adverse reactions between ChAdOx/BNT boost vaccination compared to ChAdOx prime vaccination.

The majority of vaccine reactions were reported on day one and three after vaccination and receded by day seven (**Fig. 2**).

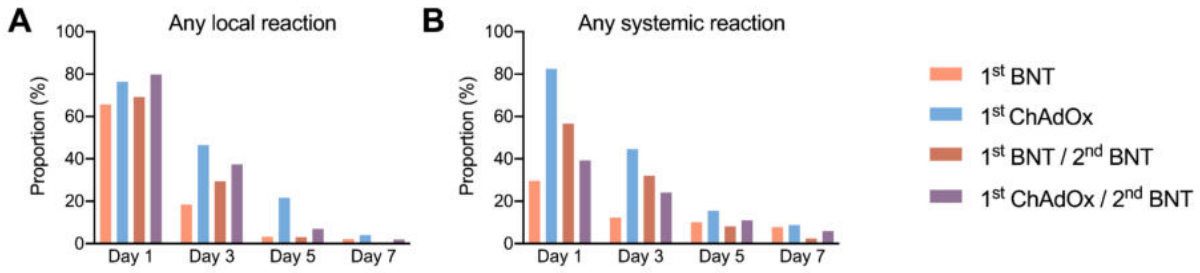


**Figure 2: Reactogenicity of BNT or ChAdOx prime immunisation and homologous or heterologous booster vaccination reported until day seven after vaccination.** (**A**) Local reactions (any severity) reported by day, over the course of seven days. (**B**) Systemic reactions (any severity) reported by day, over the course of seven days.

## Immunogenicity

Three weeks after prime immunisation with BNT, 63/94 (67.02%, 95%CI: 57.01-75.69) participants were reactive for anti-SARS-CoV-2-S1 (S1) IgG compared to only 16/57 (28.07%, 95%CI:18.08-40.43, p<0.0001) participants after ChAdOx prime immunisation (**Fig. 3A**). The proportion of S1 reactivity increased to 100/101 (99.01%, 95%CI: 94.60-99.95) three weeks after homologous BNT/BNT boost immunisation, and to 61/61 (100.00%, 95%CI:94.08-100.00) three weeks after heterologous ChAdOx/BNT boost immunisation (**Fig. 3A**). Compared to BNT immunised participants, ChAdOx immunised participants had significantly lower anti-S1 IgG levels three weeks after prime immunisation (median 2.08 S/Co, IQR:1.45-3.04 vs 0.52 S/Co, IQR: 0.28-1.00, p=0.02, **Fig. 3A**). Levels of anti-RBD IgG (median 1.28 S/Co, IQR: 0.57-2.16 vs 2.84 S/Co, IQR: 2.02-4.06, p=0.14) and anti-full spike IgG (median 1.23 S/Co, IQR: 0.61-1.73 vs 2.08 S/Co, IQR: 1.45-3.04, p=0.62) were slightly lower, but not significantly reduced when correcting for multiple testing following prime immunisation with ChAdOx compared to BNT (**Fig. 3B, Fig. S1**). Three weeks after boost immunisation, antibody responses in homologous BNT/BNT immunised participants was comparable to heterologous ChAdOx/BNT immunised participants (anti-S1 IgG median: 4.52 S/Co, IQR:3.92-5.10 vs 5.37 S/Co, IQR: 4.82-5.86, p=0.31) (**Fig. 3A,B, Fig. S1**).

In addition to antibody levels, we measured serum antibody avidity. High avidity serum antibodies, defined as an antibody avidity index >60%, were not detected after prime immunisation with either BNT or ChAdOx (**Fig. 3C**). Three weeks after boost immunisation 27/30 (90.00%, 95%CI: 74.38-96.54) participants in the homologous BNT/BNT group and 30/30 (100.00, 95%CI: 94.08-100.00) in the heterologous ChAdOx/BNT immunised group exhibited high anti-S1 IgG avidity indices (**Fig. 3C**). Hence, maturation of IgG avidity following boost vaccination was observed with both regimens. The median relative avidity index was slightly higher after heterologous ChAdOx/BNT boost (93.50%, IQR: 91.10-95.41) compared to homologous BNT/BNT boost (73.86%, 95%CI: 62.99-81.55, p=0.04, **Fig. 3C**), which may also be due to the longer dosing interval in the heterologous boost group.

Neutralising antibodies were detected in 89/94 (94.68%, 95%CI: 88.15-97.01) participants receiving BNT and in 48/57 (84.21%, 95%CI:72.64-91.46) participants receiving ChAdOx prime vaccination (**Fig. 3D**). At week three after boost immunisation with BNT, neutralising antibody response rate had increased in both cohorts to 100/101 (99.01%, 95%CI: 94.60-99.95) after BNT/BNT boost and 61/61 (100.00%, 95%CI: 94.08-100.00) after heterologous ChAdOx/BNT boost (**Fig. 3D**). Surrogate virus neutralisation test (sVNT) titers were comparable after homologous and heterologous prime-boost immunisation (**Fig. 3D**).

Serological responses are most widely used to assess immunogenicity of vaccination, but T cell responses are another important marker of anti-SARS-CoV-2 immunity. The spike S1-specific T cell response was measured in 47 ChAdOx prime immunised, 60 ChAZOx/BNT boost immunised and 66 BNT/BNT boost immunised subjects by IFN-γ release (IGRA). Three weeks after ChAdOx prime immunisation, participants showed robust T cell responses (**Fig. 3E**). Notably, T cell reactivity was significantly higher after heterologous ChAdOx/BNT boost immunisation compared to homologous BNT/BNT boosting (1.67 AU, IQR: 1.29-2.45, vs. 2.25 AU, IQR: 1.57-2.73, p=0.0255) (**Fig. 3E**).

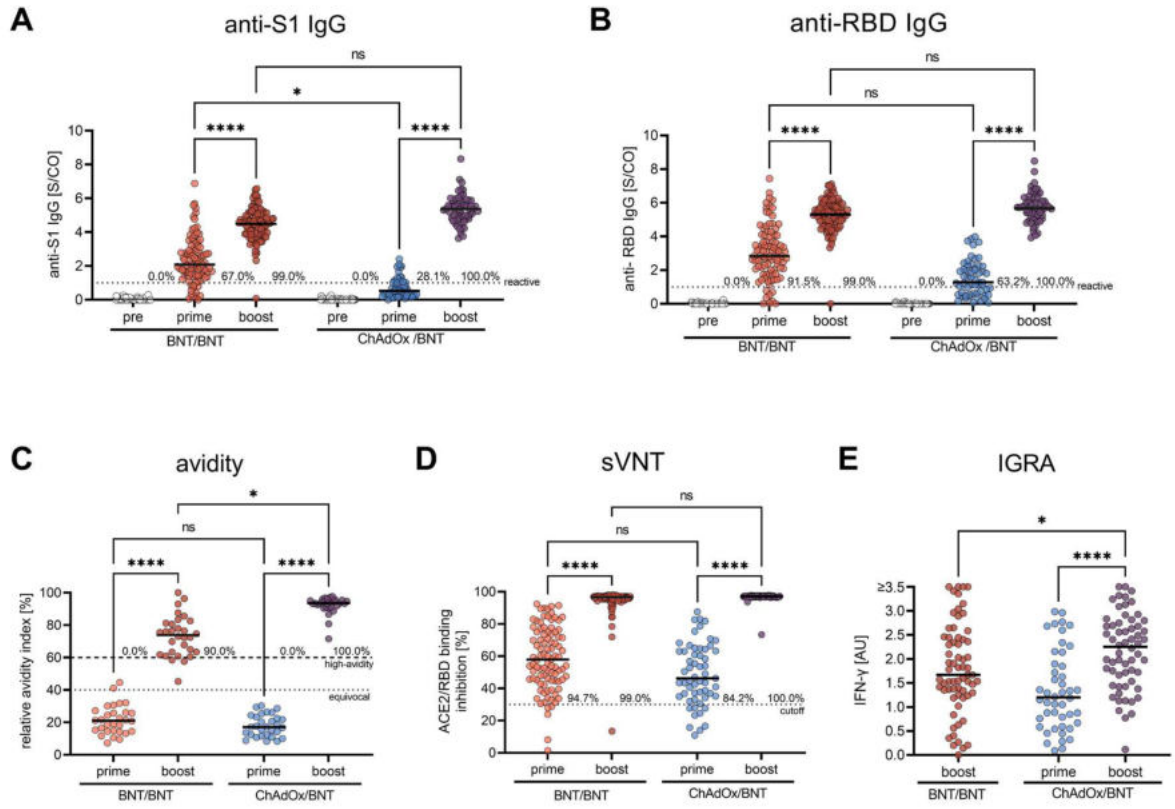


**Fig. 3. SARS-CoV-2 specific antibody- and T cell response after BNT or ChAdOx prime immunisations and homologous or heterologous booster vaccination.** (**A**) Anti-S1 IgG and (**B**) anti-RBD IgG measured by SeraSpot Anti-SARS-CoV-2 IgG assay, (**C**) anti-S1 IgG avidity, and (**D**) neutralizing capacity measured by sVNT in serum of subjects who had received prime immunisation with BNT or ChAdOx, and homologous BNT/BNT or heterologous ChAdOx/BNT boost. (**E**) T cell reactivity in whole blood samples measured by IGRA. BNT: BNT162b2 / Comirnaty, ChAdOx: ChAdOx1-nCoV19 / Vaxzevria. IgG: Immunoglobulin G, S/CO: signal-to-cutoff ratio, sVNT: surrogate virus neutralization assay, ACE2: angiotensin-converting enzyme 2, RBD: SARS-CoV-2 receptor-binding domain, S1: SARS-CoV-2 Spike protein S1 domain, AU: arbitrary unit. Sampling time points: pre: pre-immune sample prior to first immunisation, prime: three weeks after first vaccination, boost: three to four weeks after boost vaccination. Dotted lines indicate the manufacturer's pre-specified threshold, for anti-RBD IgG >1 S/Co, for sVNT >30% and for avidity 40-60%: borderline avidity, >60%; high avidity. Lines indicate the median. * = p<0.05; ** = p<0.01; **** = p<0.000; ns: not significant.

# Discussion

This observational cohort study involving 340 health care workers provides real-world data on reactogenicity and immunogenicity of homologous BNT/BNT immunisation compared to heterologous ChAdOx/BNT vaccination against COVID-19. Overall, both regimens were well-tolerated. We observed no major difference in reactogenicity between both prime-boost regimens. Overall, local reactions were frequently observed for all vaccines. Systemic reactions, including severe reactions, were most frequent following prime immunisation with ChAdOx, whereas reactogenicity of BNT/BNT and ChAdOx/BNT was comparable, with slightly decreased systemic reactions of the heterologous booster. We observed robust immunogenicity of both homologous and heterologous prime-boost regimens. Increased S1-reactive T cell responses as measured by IGRA, were increased three weeks after heterologous ChAdOx/BNT boost compared to BNT/BNT boost vaccination. Thus, heterologous ChAdOx/BNT immunisation with a vaccine interval of 10-12 weeks is well tolerated and highly immunogenic, comparable to homologous BNT/BNT vaccination.

### Strengths and limitations of this study

This is the first report of immunogenicity of heterologous ChAdOx/BNT compared to homologous BNT/BNT prime-boost vaccination. This is also the first report of real-world reactogenicity of ChAdOx/BNT vaccination with a 10-12 week vaccine interval, compared to BNT/BNT vaccination with a 3-week vaccine interval. Another strength is the longitudinal follow-up of up to 15 weeks after first immunisation. Data of this nature is urgently needed due to ongoing heterologous vaccinations in several countries.

Our study also has several potential limitations, as it is not a randomized controlled trial. Due to the current recommendations for heterologous ChAdOx/mRNA vaccination in persons <60 years of age, we were not able to recruit a matched cohort of homologous ChAdOx/ChAdOx vaccinated health care workers, since most of the study participants opted for the recommended heterologous booster. Hence, we cannot determine the exact effect of the heterologous BNT booster vaccine compared to ChAdOx homologous boosting alone. This is an interim analysis as the study is still recruiting and a comparison with homologous ChAdOx/ChAdOx vaccination may be possible with the next analysis. Here, we compared reactogenicity and immunogenicity of homologous BNT/BNT and heterologous ChAdOx/BNT vaccination. In addition to the different combinations of prime and boost vaccines, the interval between first and second vaccine was significantly different in the homologous (21 days) and heterologous vaccination group (71 days) (**Table 1**). Thus, it is unclear to which extent the observed differences may also be attributable to the extended vaccine interval in the heterologous vaccination group. The observed increased anti-S1 IgG avidity, for instance, is likely to be caused by the extended vaccination interval, since antibody affinity maturation increases over time.

### Comparison to other studies

We observed comparable reactogenicity of homologous BNT/BNT vaccination and heterologous ChAdOx/BNT vaccination, both of which were well-tolerated in our cohort with a 10-12 week dosing interval. This is in contrast with interim results of the Com-COV trial, which reported increased systemic vaccine reactions following heterologous ChAdOx/BNT vaccination, compared to homologous ChAdOx/ChAdOx and BNT/BNT regimens in a

comparable sample size [10]. There are several differences in the study design (RCT vs. observational study), study population demographics, and vaccine interval that may explain this discrepancy. The median age in Com-CoV was 57 years (46% females), and 34 years (29-45 years, 60.18% females) in the present study (**Table 1**). The interval between first and second vaccination with either BNT or ChAdOx was 28 days in the Com-COV study, compared to 71 days reported here. We hypothesize that extending the vaccine interval to 10-12 weeks may limit the reactogenicity of heterologous ChAdOx/BNT vaccination.

Phase 1/2 studies have previously reported robust immunogenicity of homologous BNT and ChAdOx immunisations [21,22]. In contrast, immunogenicity of heterologous ChAdOx/BNT immunisation has not been previously reported. Our data indicate that both homologous and heterologous regimens induced high titers of high-affinity antibody responses and high T cell reactivity in healthy individuals. Whereas a slightly higher humoral response was noted after prime immunization with BNT compared to ChAdOx, we found no significant difference in antibody levels, or -neutralisation capacity at three weeks post homologous or heterologous booster vaccination, indicating that BNT booster immunisation induces strong humoral immune responses, even following weaker initial responses after ChAdOx prime immunisation. This is in line with previous studies reporting increased antibody responses in COVID-19 convalescents following a single dose of BNT, compared to seronegative persons receiving two doses of BNT [23]. Both vaccine regimens induced robust T cell responses, but, we observed slightly increased T cell reactivity after heterologous ChAdOx/BNT immunisation compared to the homologous BNT/BNT regimen, indicating that heterologous vaccination may increase immunogenicity.

## Policy implications

Heterologous prime-boost vaccination is currently recommended for individuals with ChAdOx prime immunisation in several countries, following reports of rare but serious adverse events associated with ChAdOx, particularly in younger women [7]. A heterologous boost with an mRNA vaccine (BNT or mRNA1273) with a vaccine interval of 12 weeks is currently recommended in Germany for persons under the age of 60 who have previously received one dose of ChAdOx [6]. Our study provides real-world evidence for the safety and immunogenicity of this vaccine regimen. Heterologous vaccination schedules might also alleviate logistical challenges and mitigate intermittent supply shortages of individual vaccines. In light of increasing occurrence of new virus variants carrying immune escape mutations, it will be important to determine whether heterologous vaccination regimens might enhance protection against infection and severe COVID-19. Further controlled studies are required to answer this question.

## Conclusions

In summary, this study provides evidence that heterologous ChAdOx/BNT immunisation with 10-12 week intervals, currently recommended in several countries, is well tolerated and equally immunogenic as homologous BNT/BNT vaccination, with evidence of enhanced T cell responses. Our data support further studies into the applicability of heterologous prime-boost vaccination strategies for COVID-19.

## Acknowledgements

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## Conflict of interest

VMC is named together with Euroimmun GmbH on a patent application filed recently regarding the diagnosis of SARS-CoV-2 by antibody testing.

# Supplementary Material

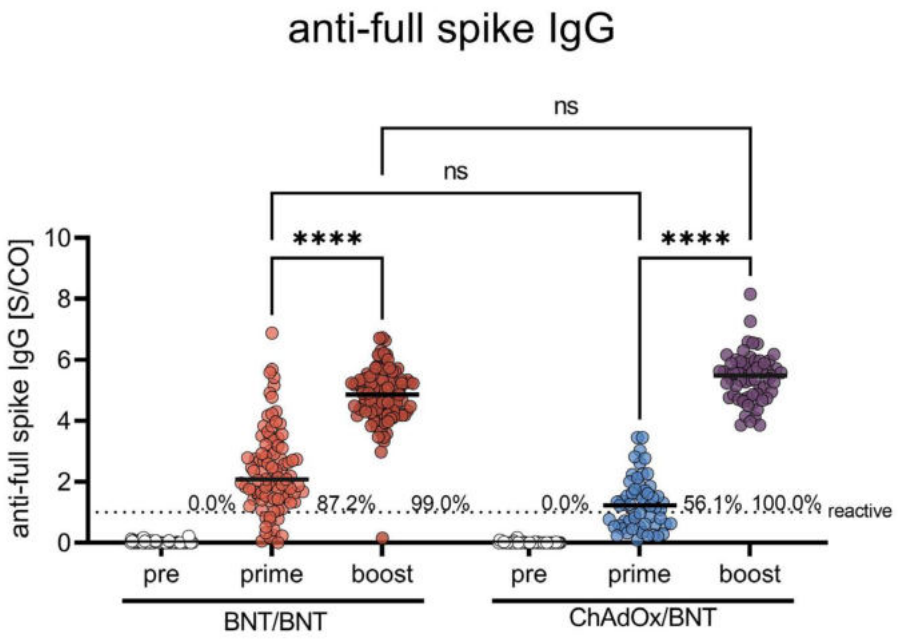


**Figure S1: Serum anti-full spike IgG response after BNT or ChAdOx prime immunisations and homologous or heterologous booster vaccination.**
Anti-full spike- IgG in serum measured by SeraSpot Anti-SARS-CoV-2 IgG assay. BNT: BNT162b2 / Comirnaty; ChAdOx: ChAdOx1-nCoV19 / Vaxzevria; IgG: Immunoglobulin G; S/CO: signal-to-cutoff ratio. Sampling time points: pre: pre-immune sample prior to first immunisation; prime: three weeks after first vaccination; boost: three to four weeks after boost vaccination. The dotted line indicates the manufacturer's pre-specified threshold (>1 S/Co). Lines indicate the median. **** = p<0.0001; ns: not significant.

| Local reaction | 1st BNT | 1st BNT / 2nd BNT | 1st ChAdOx | 1st ChAdOx / 2nd BNT |
|---|---|---|---|---|
| Local reaction (any severity) | 69,10 (61,97 - 75,43) | 74,21 (66,9 - 80,39) | 81,08 (74,02 - 86,57) | 84,85 (76,5 - 90,6) |
| Local reaction (only severe) | 1.68 (0.45 - 4.83) | 3.77 (1.74 - 7.99) | 3.38 (1.45 - 7.66) | 5.05 (2.18 - 11.28) |
| Pain at injection site (any severity) | 62.36 (55.05 - 69.15) | 69.81 (62.28 - 76.41) | 77.70 (70.34 - 83.66) | 79.80 (70.85 - 86.52) |
| Tenderness (any severity) | 68.54 (61.39 - 74.91) | 73.58 (66.23 - 79.82) | 80.41 (73.28 - 86.00) | 83.84 (75.35 - 89.80) |
| Swelling (any severity) | 3.93 (1.92 - 7.89) | 7.55 (4.37 - 12.73) | 3.38 (1.45 - 7.66) | 6.06 (2.81 - 12.60) |
| Redness (any severity) | 2.25 (0.88 - 5.63) | 1.89 (0.51 - 5.40) | 2.70 (1.06 - 6.74) | 6.06 (2.81 - 12.60) |
| **Systemic reaction** | | | | |
| Systemic reaction (any severity) | 38.76 (31.92 - 46.09) | 64.78 (57.09 - 71.78) | 86.49 (80.05 - 91.08) | 51.52 (41.80 - 61.12) |
| Systemic reaction (only severe) | 0.56 (0.03 - 3.11) | 6.29 (3.45 - 11.19) | 22.97 (16.93 - 30.38) | 2.02 (0.36 - 7.07) |
| Headache (any severity) | 17.42 (12.55 - 23.66) | 38.99 (31.76 - 46.75) | 75.00 (67.45 - 81.28) | 37.37 (28.48 - 47.21) |
| Fatigue (any severity) | 24.16 (18.46 - 30.95) | 47.80 (40.18 - 55.52) | 72.97 (65.30 - 79.48) | 37.37 (28.48 - 47.21) |
| Feverishness & chills (any severity) | 8.99 (5.61 - 14.1) | 19.50 (14.09 - 26.34) | 70.27 (62.47 - 77.05) | 18.18 (11.82 - 26.92) |
| Myalgia (any severity) | 20.79 (15.47 - 27.33) | 33.96 (27.06 - 41.62) | 54.73 (46.69 - 62.53) | 22.22 (15.16 - 31.36) |
| Arthralgia (any severity) | 3.93 (1.92 - 7.89) | 10.06 (6.29 - 15.72) | 29.73 (22.95 - 37.53) | 8.08 (4.15 - 15.14) |
| Nausea & vomiting (any severity) | 3.93 (1.92 - 7.89) | 4.40 (2.15 - 8.81) | 15.54 (10.58 - 22.24) | 6.06 (2.81 - 12.60) |
| Diarrhoea (any severity) | 3.93 (1.92 - 7.89) | 6.29 (3.45 - 11.19) | 7.43 (4.20 - 12.82) | 4.04 (1.58 - 9.93) |
| **Antipyretic medication** | | | | |
| Intake within first 24 hours | 9.55 (6.05 - 14.76) | 22.64 (16.83 - 29.75) | 72.97 (65.30 - 79.48) | 32.32 (23.92 - 42.05) |
| Prophylactic intake | 2.81 (1.21 - 6.41) | 3.14 (1.35 - 7.15) | 27.03 (20.52 - 34.70) | 4.04 (1.58 - 9.93) |

**Table S1: Local and systemic reactogenicity of BNT or ChAdOx prime immunisations and homologous or heterologous boosting until day 7 after vaccination.**
Proportion of participants reporting local and systemic reactions and intake of antipyretic medication per group (95% CI). 95% confidence intervals were calculated according to the Wilson and Brown method.

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# Humoral and cellular immune response against SARS-CoV-2 variants following heterologous and homologous ChAdOx1 nCoV-19/BNT162b2 vaccination.

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**Brief Communication**

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# Abstract

Cerebral venous thrombosis was reported as a rare but serious adverse event in young and middle-aged vaccinees following immunization with AstraZeneca's ChAdOx1-nCov-19 vaccine. As a consequence, several European governments recommended using this vaccine only in individuals older than 60 years leaving millions of ChAd primed individuals with the decision to either receive a second shot of ChAd or a heterologous boost with mRNA-based vaccines. However, such combinations have not been tested so far. We used Hannover Medical School's COVID-19 Contact (CoCo) Study cohort of health care professionals (HCP) to monitor ChAd primed immune responses before and three weeks after booster with ChAd or BioNTech/Pfizer's BNT162b2. Whilst both vaccines boosted prime-induced immunity, BNT induced significantly higher frequencies of Spike-specific CD4 and CD8 T cells and, in particular, high titers of neutralizing antibodies against the B.1.1.7, B.1.351 and the P.1 variants of concern of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2).


# Main Text

Tremendous worldwide efforts since the outbreak of the pandemic resulted in effective vaccines against SARS-CoV-2. The first European Medicines Agency (EMA) approved vaccine reaching market was the lipid nanoparticle-formulated mRNA vaccine BNT162b2 (Comirnaty; BNT) developed by BioNTech/Pfizer. BNT, encoding for the full length of SARS-CoV-2 structural surface glycoprotein (spike; S protein), was proven safe and 95% effective in preventing coronavirus disease 2019 (COVID-19) [1]. Oxford University in collaboration with AstraZeneca developed ChAdOx1-nCov-19 (Vaxzevria, ChAd), a replication-deficient chimpanzee adenovirus-vectored vaccine encoding also the full-length of SARS-CoV-2 S protein. In the initial clinical trials, ChAd had an acceptable safety profile, albeit somewhat lower efficacy of 70.4% against symptomatic COVID-19 [2]. These data, together with the efficacy of other vaccines including those from Moderna [3] and Johnson&Johnson [4], raised hopes for expeditious ending of the SARS-CoV-2 pandemic.

However, in the first half of March 2021, vaccinations with ChAd were abruptly halted due to increasing numbers of moderate-to-severe thrombocytopenia and unusual thrombosis cases, particularly cerebral venous thrombosis and splanchnic-vein thrombosis among vaccinees [5]. This new syndrome, termed vaccine-induced thrombotic thrombocytopenia (VITT) [6], developed within 28 days after vaccination and was confirmed by a large population study in Denmark and Norway [7]. Although exact mechanisms are still unclear, VITT appears to be induced by antibodies directed against platelet factor 4 that lead to platelet activation [8]. Despite concerns, European Medicine Agency (EMA) concluded that ChAd vaccination benefits outweigh the potential risks for an individual (https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-benefits-risks-context, accessed May 31st, 2021) and ChAd remains a valuable asset against COVID-19. However, many countries offered to vaccinees, who received the first ChAd dose, to choose between ChAd or mRNA-based vaccines as a

second (boost) dose, despite lack of data showing safety, reactogenicity or immunogenicity of such heterologous prime-boost schedules [9].

Furthermore, mutations in SARS-CoV-2 caused the emergence of rapidly expanding variants, especially B.1.1.7 (British), P.1 (formerly named B.1.1.28.1; Brazilian), and B.1.351 (South African) variants [10], which raised concerns on the feasibility of containing the pandemic through vaccination. Antibodies induced by BNT and ChAd vaccines efficiently neutralize the B.1.1.7 variant, while the neutralization P.1 and B.1.351 variants seems to be reduced [11–13]. Moreover, BNT vaccination has been shown to be about 13% and 28% less protective against development of symptomatic COVID-19 for variants B.1.1.7 and B.1.351, respectively [14]. Similarly, it has been reported that protection from symptomatic COVID-19 following ChAd vaccination is slightly reduced for B.1.1.7 variant [15], while no protection against mild-to-moderate COVID-19 caused by B.1.351 variant was observed [16]. It remains to be determined whether heterologous prime-boost regimens could induce equal or even stronger immune responses against the novel viral variants as compared to the homologous prime-boost regiments.

To analyze the efficacy of the heterologous prime-boost vaccination schedule, we used our CoCo cohort of HCP[17,18] and monitored response to homologous and heterologous prime-boost COVID-19 vaccine treatment schedules. Vaccinees who received one dose of ChAd were, according to the current vaccination strategy in Germany, offered to choose between ChAd and BNT vaccines for a second dose. To determine immunogenicity of the homologous and heterologous immune regimens, we studied n=129 ChAd-primed vaccinees without previous SARS-CoV-2 infection, of which n=32 chose homologous and n=55 heterologous boosting. For comparison, we included a group of BNT/BNT vaccinated HCP. The vaccination and blood collection schedule is depicted in Fig. 1A with additional information (age, sex) in Extended Data Fig. 1A-C. A retrospective analysis revealed that anti-SARS-CoV-2 S IgG (anti-S IgG) and IgA had declined by 43% and 65%, respectively, from mean 30 days after ChAd prime to shortly before boosting, similar to declines in BNT/BNT vaccinated individuals (Extended Data Tab. 1A, B). Importantly, we found comparable levels of anti-S IgG and IgA antibodies against the S-protein in the ChAd/ChAd and the ChAd/BNT groups before booster indicating that both groups responded equally well after priming with ChAd.

Following the booster immunization, increased anti-S IgG and IgA responses were found in both groups. Heterologous ChAd/BNT vaccination led to a highly significant 11.5-fold increase for anti-S IgG as compared to a 2.9-fold increase after homologous ChAd vaccination (Fig. 1B, Extended Data Tab. 1C). We observed similar changes for anti-S IgA (Fig. 1B) indicating better humoral immune responses after heterologous prime/boost immunization. Anti-S IgG and IgA concentration after ChAd/BNT vaccination were within the range of fully BNT/BNT vaccinated individuals (Extended Data Tab. 1B and Extended Data Fig. 2A-B).

To test for neutralizing activity of antibodies induced by infection or vaccination, we recently developed an ELISA-based surrogate virus neutralization test (sVNT)[19]. In this assay, the soluble receptor for SARS-CoV-2, ACE2, is bound to 96-well-plates to which a purified tagged receptor binding domain (RBD) of the

S-protein from the Wuhan strain (hCoV-19/Wuhan/Hu-1/2019) can bind once added to the assay. Binding is further revealed by an anti-tag peroxidase-labelled antibody and colorimetric quantification. Pre-incubation of the S-protein with serum or plasma of convalescent patients or vaccinees prevents subsequent binding to ACE2 to various degrees, depending on the amount of neutralizing antibodies present. Since we were interested to not only determine the neutralizing capacity of vaccination-induced antibodies against the Wuhan strain but also against some of the recently emerged variants of concern (VoC), we adapted the sVNT also to S proteins of the B.1.1.7, P.1, and B.1.351 variants. To validate these new assays, we applied sera from vaccinees that had been recently tested for their neutralizing capacity applying vesicular stomatitis virus (VSV)-based pseudotyped virus neutralization assays (pVNT)[12]. Comparing results obtained using pVNT with those of the newly developed sVNTs, we observed a high degree of correlation between both assays with R square values ranging between 0.50 and 0.69 (Extended Data Fig. 3). These findings demonstrate that the sVNT is suited to quantitatively assess the neutralization capacity of vaccination-induced antibodies not only against the Wuhan but also against the B.1.1.7, P.1, and B.1.351 variants of SARS-CoV-2.

Applying sVNT assays, we found that 81/88 participants possessed neutralizing antibodies against the Wuhan strain in pre-boost plasma. In contrast, neutralizing antibodies against the B.1.1.7 (17/88), P.1 (12/88), and B.1.351 (5/88) variants were less frequent (Fig. 1C; Extended Data Fig. 4). At 2-3 weeks after the booster immunization, frequencies and titers of neutralizing antibodies against the Wuhan strain increased in the ChAd/ChAd and the ChAd/BNT group with titers reaching higher values in the latter group (Fig. 1C; Extended Data Fig. 4). Differences between the ChAd and the BNT booster vaccination became even more evident when analyzing the neutralization capacity of antibodies induced against the VoC. In the ChAd/ChAd group booster immunization increased neutralization of the B.1.1.7 variant in some individuals but showed no effect against variants P.1 and B.1.351 (Fig. 1C; Extended Data Fig. 4). In contrast, booster immunization with BNT induced neutralizing antibodies at high frequencies against all analyzed VoC. In the ChAd/BNT group, all participants had neutralizing antibodies against the B.1.1.7 and P.1 variant and all but two participants possessed neutralizing antibodies against the B.1.351 variant (Fig. 1C; Extended Data Fig. 4). In the ChAd/BNT group the post boost neutralization capacity was highest against the Wuhan strain followed by the B.1.1.7 variant and less efficient against the P.1 and B.1.351 variant (Fig. 1C; Extended Data Fig. 4). Altogether, these data indicate that the booster immunization led to an increase of neutralizing antibodies in both vaccination groups and that the heterologous BNT booster vaccination efficiently induced neutralizing antibodies against all tested VoC.

We next determined the frequency and phenotype of B cells carrying membrane bound immunoglobulins specific for the S protein. PBMC were stained with 15 mAb, a viability dye, and an S-protein fused to a neo-green fluorescent protein (S-neoGreen; Extended Data Tab. 2) and analyzed by spectral flow cytometry (Ext. Data Fig. 5). Up to 0.2% of blood B cells in samples taken before booster vaccination were specific for the S-protein, with no significant difference between the ChAd/ChAd and the ChAd/BNT group (Fig. 1D open circles). In the ChAd/ChAd group, blood samples taken 2 to 3 weeks after the booster immunization did not reveal differences regarding frequencies of S-specific B cells compared to the pre-

boost samples (Fig. 1D, filled dots). In contrast, S-specific B cells were strongly increased in the ChAd/BNT group following booster vaccination (Fig. 1D, filled dots). Furthermore, analysis of the IgM/IgD phenotype of the S-specific B cells revealed an increase in recently isotype switched B cells ($IgD^-IgM^-$) after booster immunization in both groups with higher frequencies in the BNT boosted group (Fig. 1E). The increased frequencies of isotype switched S-specific B cells after booster immunization went along with increased amounts of S-specific antibodies as well as increased neutralization capacities observed in both groups. Finally, the significantly increased overall frequency of S-specific B cells after BNT booster was paralleled by profound neutralization capacities against the VoC.

In addition to B cell-mediated immune responses, we also analyzed frequencies and phenotypes of S-specific T cells. To that end, density gradient-purified PBMCs were stimulated over night with DMSO alone or with pools of overlapping peptides dissolved in DMSO either covering the entire S-protein or the membrane (M), nucleocapsid (N), and the envelope (E) proteins. Cells were then stained with antibodies against cell surface molecules, fixed, permeabilized and then stained with antibodies against intracellular interferon (IFN)-g and tumor necrosis factor (TNF)-a. Frequencies of (IFN)-g and (TNF)-a were determined by flow cytometry (Fig. 2A).

The frequencies of S-specific CD4 T cells in blood samples collected before booster vaccination were significantly higher for both vaccination groups as compared to the MNE (control) peptides or DMSO alone (Fig. 2B, Extended Data Fig. 6). No significant differences were found between the ChAd/ChAd and the ChAd/BNT group (Fig. 2B, open circles). After boosting, the frequencies for S-specific CD4 T cells increased in both groups and were significantly higher in the ChAd/BNT group (Fig. 2B, filled dots). The same effect was observed for S-specific CD8 T cells. These cells were present at comparable frequencies in both groups prior boosting and increased in frequencies after boosting. Again, boosting with BNT induced higher frequencies than boosting with ChAd (Fig. 2C, filled dots). Regarding the distribution of S-specific CD8 T cells producing IFN-g or TNF-a, application of both booster vaccines led to an increase in the proportion of cells producing both cytokines simultaneously (Fig. 2D). Significant increase in S-specific IFN-g release in the ChAd/BNT but not in the ChAd/ChAd group was confirmed independently (Fig. 2E).

Due to the abrupt recommendation of several European governments to discontinue the use of ChAd in the young- and middle-aged population, a unique situation was created in which heterologous prime-boost vaccination regimens were applied despite the lack of any information available regarding immunogenicity and safety aspects. Applying a broad array of tests, this study qualitatively and quantitatively assessed B- and T-cell mediated immune responses. It provides first insights into the immunogenic outcome of homologous and heterologous vaccination protocols with two vaccines – BNT and ChAd. Head-to-head comparison of ChAd-prime vaccinees who received either a ChAd or BNT booster immunization revealed that both regiments elicited additional immunity. Although this setup did not allow for randomization of the participants, our study unequivocally revealed that the group boosted with BNT showed stronger immune responses than the group boosted with ChAd. CD4 and CD8 T cell responses directed against S-protein epitopes were higher in frequencies and cells produced more IFN-g upon re-

stimulation. Likewise, the group boosted with BNT developed higher titers of anti-S-protein antibodies of both the IgG and IgA subclasses. It should be noted that these antibodies were highly efficient in neutralizing all three VoC tested in the present study. It had been reported before that vaccinees immunized with BNT/BNT also develop neutralizing antibodies against the VoC [20]. Based on the data of n=46 participants of the CoCo Study cohort that were also immunized with BNT/BNT, we could confirm these findings in the present study. Our data also indicate that BNT/BNT and ChAd/BNT vaccinated individuals develop neutralizing antibodies to similar degrees two to three weeks after booster vaccination. Likewise, immune responses of the ChAd/ChAd group were in the range of earlier reported results [11–13,21]. Although it would have been interesting to also characterize immune responses in a cohort of people immunized with BNT/ChAd, such individuals had not been available to us.

Extended studies, ideally including clinical endpoints, are needed to further characterize immune responses not only in heterologous immunized cohorts. It would be of particular importance to address for how long protective immune responses are maintained, first of all in people that are at elevated risk for developing severe COVID-19 but also in individuals that are known for mounting impaired immune responses.

# Declarations


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### Contributions

Study design: G.M.N.B and R.F.

Data collection: J.B.-M., S.I.H., A.C., I.O., M.V.S., G.M.R., A.D.-J., A.H., C.R., M.F., C. S.-F., I.R., S.W., A.B., J.M., J.R., A.J., G.S., G.B., J.M., M.H., S.P., T.K.

Data analysis: J.B.-M., S.I.H., A.C., I.O., M.H., B.B, M.V.S.

Data interpretation: B.B., R.F., G.M.N.B.

Writing: B.B., G.M.N.B., R.F. with comments from all authors.

### Competing Interests statement

The authors declare no competing interests.

### Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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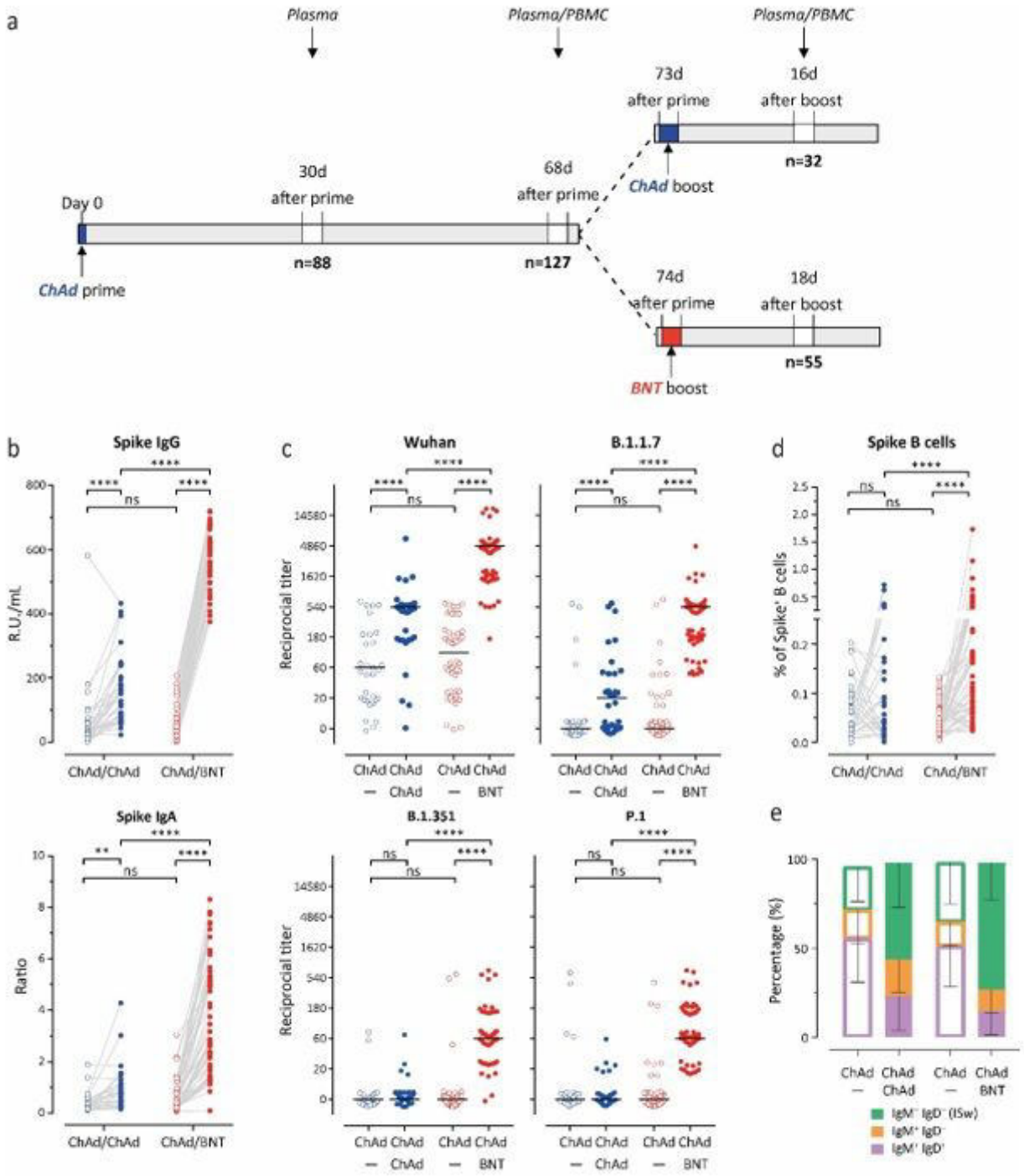
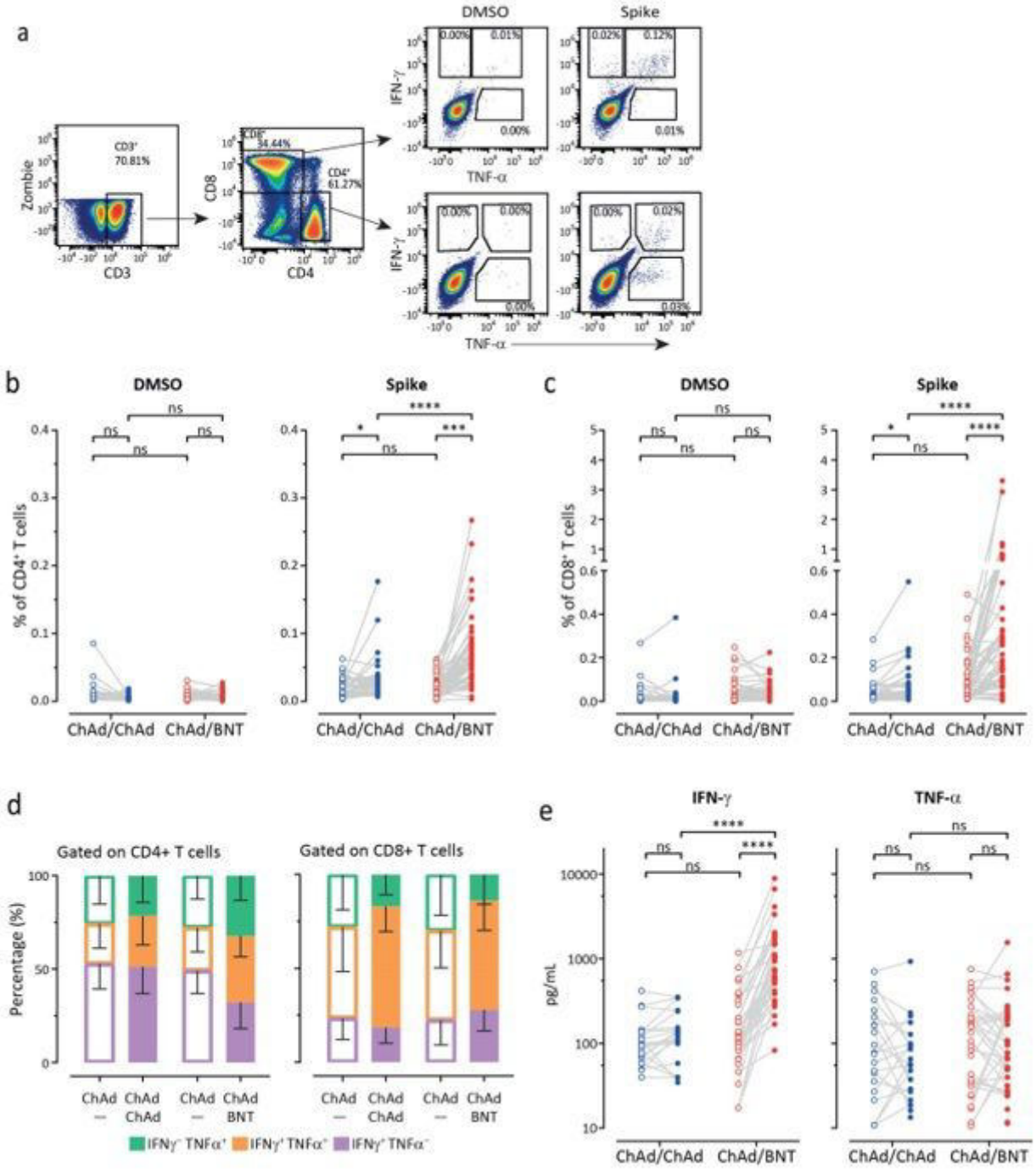
# Figures




## Figure 1

Stronger humoral immune response against all SARS-CoV-2 variants following heterologous ChAdOx1 nCoV-19 (ChAd) / BNT162b2 (BNT) than homologous ChAd / ChAd vaccination. a. Participant recruitment scheme. b. Spike (S)-specific IgG and IgA levels in plasma after prime (open circles) and after boost (closed circles) from homologous ChAd/ChAd (blue symbols) and heterolgous ChAd/BNT (red symbols) vaccinees. c. Reciprocal titers of neutralizing antibodies against Wuhan, B.1.1.7 (British), P.1 (B.1.1.28.1; Brazilian), and B.1.351 (South African) SARS-CoV-2-S variants measured using surrogate virus neutralization test (sVNT). d. Percentage of Spike-specific from total B cells in the whole blood

measured using flow cytometry. e. Spike-B cells show isotype-switched (IgM-IgD-) phenotype following second immunization. Statistics: b. and d. **** p<0.001 Paired t test (within groups) or 2-way ANOVA followed by Sidak's multiple comparison test (between groups); c. **** p<0.001 Chi-square test for trend.




## Figure 2

Heterologous ChAd / BNT vaccination induces stronger anti-SARS-CoV2 S T cell response than homologous ChAd / ChAd vaccination. a. Gating strategy used for detection of cytokine producing CD4+ and CD8+ T cells after ex vivo re-stimulation with DMSO or the pool of spike-specific peptides for 16hr. b. – c. Boost vaccination increased total percentage of cytokine-secreting CD4+ (b) and CD8+ (c) T cells. We

calculated the total number of cytokine secreting cells as sum of IFN-g+TNF-a-, IFN-g+TNF-a+, IFN-g-TNF-a+ cells in the gates indicated in a. d. Increased percentage of double-cytokine secreting CD4+ and CD8+ T cells after the second vaccine dose. e. IFN-g and TNF-a concentration in full blood supernatants after stimulation with SARS-CoV-2 S1 domain for 20-24 h measured by LEGENDplex™ (Biolegend). Statistics: b., c., and e. **** $p<0.001$ Paired t test (within groups) or 2-way ANOVA followed by Sidak's multiple comparison test (between groups).

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Onlinemethods010621NMEDPI113581.docx
- Extendeddata010621NMEDPI113581.docx
- flatBehrensepc.pdf
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RISK ASSESSMENT

# Assessing SARS-CoV-2 circulation, variants of concern, non-pharmaceutical interventions and vaccine rollout in the EU/EEA, 15th update

10 June 2021


## Summary

Although SARS-CoV-2 transmission remains widespread in large parts of the EU/EEA, most countries report declining trends in 14-day COVID-19 notification rates, hospital and intensive care unit (ICU) occupancy, and mortality. Many countries have initiated partial lifting of different non-pharmaceutical interventions (NPIs) that aim to reduce the degree of citizens physical contact and mobility. Since January 2021, EU/EEA countries have reported an increase in the number and proportion of SARS-CoV-2 cases of variants of concern (VOC) associated with increasing transmissibility and/or severity, with Alpha (B.1.1.7) the current dominant variant across the EU/EEA. Estimates across the region show that a large proportion of the population across Europe still remains susceptible to SARS-CoV-2 and that population immunity is far from being reached. As of 3 June, the median cumulative vaccine uptake in the EU/EEA adult population (aged 18 years and older) had reached 46.2% for at least one vaccine dose and 22.3% for the full vaccination course. The highest level of vaccine uptake was observed among the elderly aged over 80, in which the uptake reached 80.5% for at least one dose and 66.3% for full vaccination coverage. For healthcare workers, the median level of at least one dose uptake was 87% and the median uptake for the full vaccination course was 65.2%. Increased vaccine supply has allowed countries to expand eligibility for vaccination to younger age groups.


## Risk assessed in this update

The assessment of the risk posed by the current SARS-CoV-2 pandemic is stratified by four population groups (the vaccinated and unvaccinated general population and the vaccinated and unvaccinated vulnerable population). The assessment is based on the following elements: i) the vaccinated group has a lower probability of infection and ii) a lower impact of such infection than the unvaccinated, while iii) the vulnerable population suffers a higher impact of such infection when compared with the general population. Specific separate assessments were not performed for partially vaccinated and previously infected individuals in this risk assessment, although it is known that some protection is conferred to such persons. Due to differences in the epidemiological situation, vaccination strategies and NPIs implemented, EU/EEA countries are experiencing different levels of risk posed by SARS-CoV-2 to the general population and to vulnerable groups and, thus, require different targeted interventions. ECDC classifies the epidemiological situation in EU/EEA countries into four categories based on the level of concern (low, moderate, high, very high). In most countries, the contribution of the intensity indicators to the overall score has been higher than that of the severity indicators in recent weeks. As such, the overall classification shown below provides a conservative estimate of transmission intensity.


Suggested citation: European Centre for Disease Prevention and Control. Assessing SARS-CoV-2 circulation, variants of concern, non-pharmaceutical interventions and vaccine rollout in the EU/EEA, 15th update – 10 June 2021. ECDC: Stockholm; 2021.

In countries with an epidemiological situation classified as low concern, widespread transmission is falling with consequent low case notification rates. Due to the large proportion of the vulnerable population vaccinated with at least one dose, very low notification rates are recorded among the elderly. In these countries, the risk posed by the SARS-CoV-2 pandemic is assessed as low for the general population (both vaccinated and unvaccinated) and the vaccinated vulnerable population; for the unvaccinated vulnerable population there is a moderate-to-high risk.

Countries classified as moderate concern continue experiencing widespread SARS-CoV-2 transmission associated with a dominating highly transmissible variant. The highest notification rates are observed in the general population and, although a high proportion of the vulnerable population has been vaccinated with at least one dose, the probability of infection is higher than in the previous group of countries. A large part of the population is still susceptible to the infection. In these countries, the risk posed by the SARS-CoV-2 pandemic ranges from low for the vaccinated general population to high-to-very high for the unvaccinated vulnerable population.

Countries classified as high concern experience widespread SARS-CoV-2 transmission not only in the general population, but also among vulnerable individuals. The NPIs in place appear to be having a limited effect, either because adherence to the measures may not be optimal or the measures in place may not be sufficient to reduce or control exposure. Vaccination uptake in the general population and, particularly, in the vulnerable population appears to be still low. In these countries, the risk posed by the SARS-CoV-2 pandemic ranges from low-to-moderate for the vaccinated general population to very high for the unvaccinated vulnerable population.

The current assessment represents a decrease in the risk levels compared with the 14th update of the ECDC COVID-19 risk assessment published in February 2021 [1]. Still, in any of the country scenarios, should mass gathering events such as the UEFA European Football Championship take place in the absence of sufficient mitigation measures, the risk of local and pan-European transmission risk of COVID-19, including the spread of variants of concern, would increase.

There is a continuous risk of the emergence and spread of variants of concern (VOCs) that are potentially more transmissible or cause serious disease or escape natural or vaccinated immunity. The VOC B.1.617.2 (Delta) associated with increased transmissibility and a slight to moderate reduction in vaccine effectiveness after one vaccine dose is rising in some EU/EEA countries. Modelling suggests that a significant increase in COVID-19-related cases in the EU/EEA remains possible when NPIs are rapidly relaxed or vaccination rollout delayed.

# Options for response

One of the main public health goals in the current phase of the pandemic is to reduce severe COVID-19 disease and mortality by ensuring full vaccination for risk groups, including the elderly and those with underlying medical conditions. COVID-19 vaccination campaigns should remain a priority for all countries and vaccine rollout should continue, and possibly be accelerated whilst tailored to ensure access for vulnerable, hard-to-reach and hesitant populations.

Countries with a favourable epidemiological situation and progress toward high vaccine uptake in priority groups may consider adjusting and phasing out their NPIs, following a careful assessment of their local situation. A comprehensive testing strategy to enable the timely detection of cases and a robust system for contact tracing should remain a priority for all public health authorities.

The emergence and spread of VOCs, that are potentially more transmissible or cause more severe disease or escape natural or vaccine-induced immunity, requires strong surveillance measures and enhanced measures to stop, delay or reduce the spread of these VOCs. To be able to confirm infection with a specific variant, timely sequencing of the whole SARS-CoV-2 genome, or at least the whole or partial S-gene for current variants is required.

The risk of introduction of new variants in the EU is closely related to the pandemic evolution, within, as well as outside, of the EU. Efforts to ensure more equitable access to vaccination globally can mitigate the risk of the emergence of new variants.

Introduction of SARS-CoV-2 by travel-related cases, including of new virus variants, can play a role in triggering increased community transmission of COVID-19, particularly when levels of transmission in the receiving locality are low. As such, carefully and rigorously implemented travel measures can have an impact on the introduction and further transmission of new variants of virus, or on re-introduction of any form of virus, if local levels of transmission are low. Travel measures, including the requirement to provide proof of a negative test before travel or on arrival and quarantine for incoming individuals can be tailored according to considerations of vaccination status and VOC circulation and should be coordinated internationally.

Although increasing vaccination coverage will mitigate the effect of replacement with more transmissible variants, decisions to ease measures need to be highly sensitive to the local context and include considerations about the current viral circulation, the prevalence of VOCs and the vaccination status. Modelling analysis shows that a significant increase in COVID-19-related cases in the EU/EEA remains possible if NPIs are relaxed too rapidly.

For events with the potential to give rise to mass gatherings, such as the UEFA Euro 2020, monitoring of the epidemiological situation and implementation of preventive and mitigation measures should be done with a coordinated intersectoral approach.

Risk communication strategies need to highlight the fact that the pandemic is not over yet. People should be well informed about the need to respect NPIs that remain in place and reminded of the importance of full vaccination coverage as an effective measure to protect against infection and severe disease in priority groups and control the future transmission of the virus.

# Event background

As of 4 June 2021, more than 171 000 000 COVID-19 cases and 3 500 000 deaths have been reported worldwide. Currently, the countries with the highest case notification rates are the Maldives, Seychelles, Bahrain, Uruguay and Argentina, with the Americas and south-east Asia experiencing the highest case notification rates worldwide [2]. By 3 June, 5.7% of the global population had been fully vaccinated, although vaccination coverage varied by region, with the highest rates of full vaccination coverage in North America (26.4%) and Europe (17.8%), and lower rates in South America (9.4%), Asia (2.3%) and Africa (0.7%) [3].

The timeline of the major events in the COVID-19 pandemic can be found on ECDC's website: https://www.ecdc.europa.eu/en/covid-19/timeline-ecdc-response.

The latest available data on the number of cases and the number of deaths globally is published daily on ECDC's website: https://www.ecdc.europa.eu/en/covid-19/situation-updates.

EU/EEA countries have reported more than 32 000 000 cases and 725 000 deaths (representing 19% of all cases and 4.9% of all deaths reported worldwide) due to COVID-19. Detailed epidemiological information on laboratory-confirmed cases reported to The European Surveillance System (TESSy) is published in ECDC's weekly COVID-19 surveillance report and the overview of the epidemiological situation in relation to the COVID-19 pandemic by country is also published in ECDC's weekly COVID-19 country overview [4].

## Trends in reported cases, testing, hospitalisation, and mortality

By the end of week 21, 2021 (23 May 2021), the 14-day case notification rate for the EU/EEA was 111 per 100 000 population (country range: 10-312). This reflects a decrease of 75% when compared with the case notification rate of 459 at the peak of the last wave of infection in the EU/EEA in week 13, 2021 (ending 4 April 2021). The overall notification rate is at its lowest since Oct 2020 with high testing rates (>4 000 tests per week per 100 000). Decreases in case notification rates have been seen in almost all EU/EEA countries in recent weeks. Testing rates in the EU/EEA increased by 26% between weeks 13 and 20, 2021, from 3 778 to 4 762 per 100 000 population [4].

Rates of hospital and/or ICU admissions and/or occupancy have similarly decreased in 26 out of 27 EU/EEA countries with available data since week 13, 2021, with a median decrease of 73% in hospital admissions. Death notification rates have decreased by 65% from the last peak of 80 per million population during week 15 (ending 18 April 2021) to 28 per million population (country range: 0-71) in week 21, 2021.

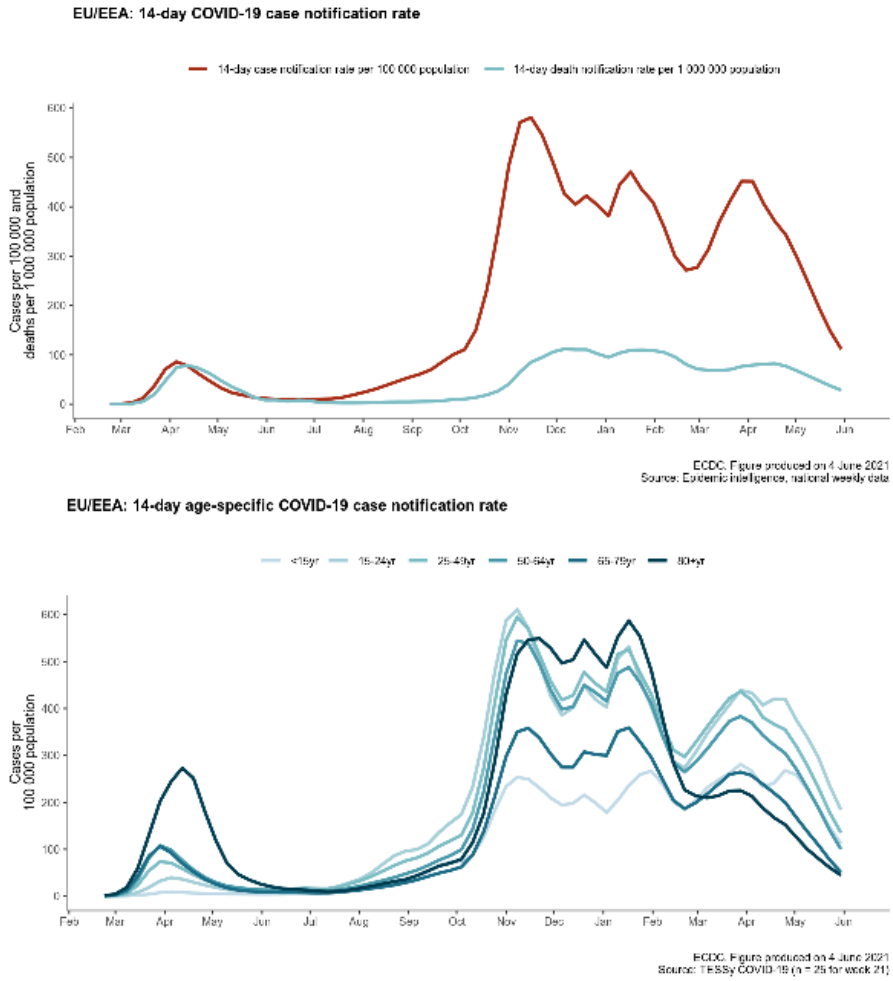
Pooled excess mortality data from EuroMOMO [5] indicate that no excess deaths have been observed among persons aged 85 years and over since week seven to eight, 2021. In contrast, excess deaths were reported during the last wave of infections in Europe (increase starting around week nine and peaking during week 13-14) among 45-64 year olds, 65-74 year olds and to a lesser extent 75-84 year olds.

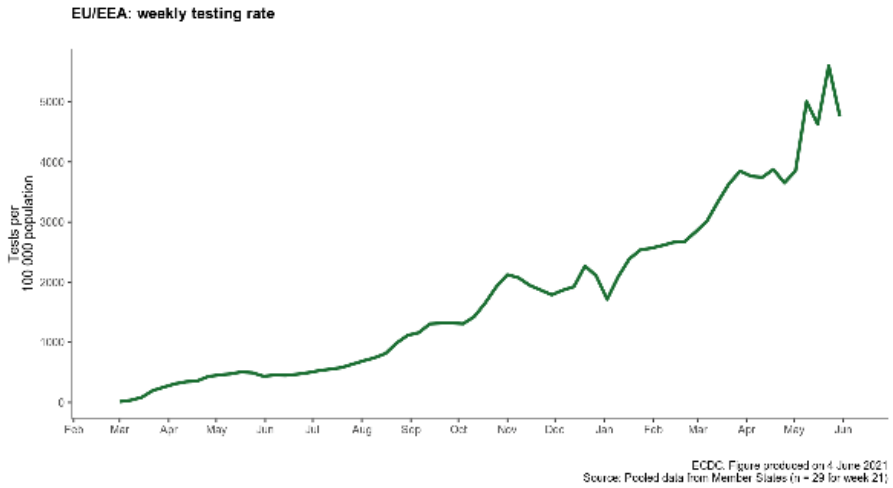
Notification rates among persons aged 80 years and over decreased from 587 per 100 000 during the previous peak in January 2021 (week 2) to 248 in week 13 and 48 per 100 000 in week 21 (total decrease of 92%). Notification rates among persons aged 25-49 years were 593 per 100 000 in week two, 442 in week 13 and 129 per 100 000 in week 20 (total decrease of 78%) [4].

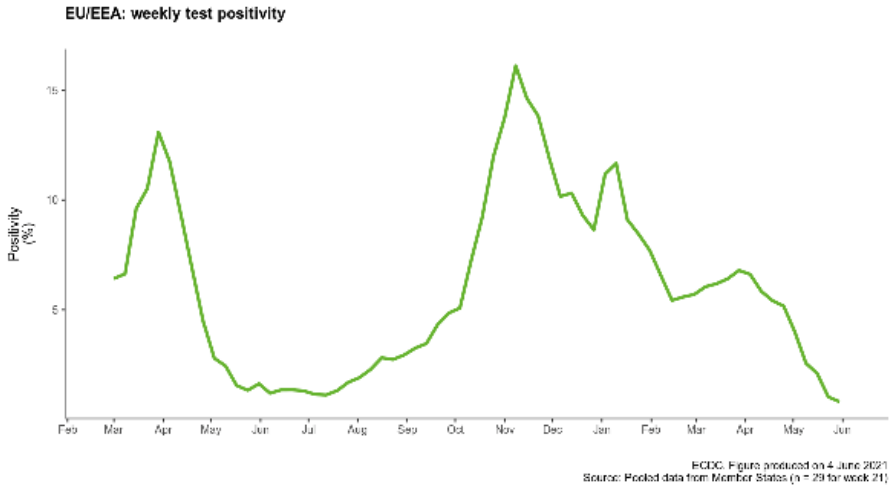
Since week nine, 2021, notification rates among the elderly have been the lowest among all age-groups. It is the first time that this has been observed since the start of the pandemic, and a drastic change from January 2021, when rates were highest among the elderly. The ratio of notification rates among persons aged 80 years to that among 25-49 year-olds decreased from 1.06 in week 3, 2021 to 0.56 in week 13 and 0.48 in week 21.

Despite the decreasing trends, as of week 20, 2021, case notification rates, mortality rates and hospitalisation and ICU admission/occupancy rates remain above the levels detected during the summer of 2020 in almost all EU/EEA countries (Figure 1).

**Figure 1. Pooled overall case and death notification rates, age-specific case notification rates, testing rates and test positivity, EU/EEA, March 2020 to May 2021.**






# SARS-CoV-2 variants of concern

The current list of variants of concern (VOCs) maintained by ECDC currently includes B.1.1.7 (referred to by the new World Health Organization (WHO) labelling for communicating with the public about variants as Alpha), B.1.1.7+E484K, B.1.351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta). Additional information on the characteristics of such VOCs is provided in Annex 1. For the purposes of this document, the variants will be referred to by their Pango lineage name.

The VOC B.1.1.7, first reported by the United Kingdom (UK), has been reported by 138 countries globally in GISAID EpiCoV and it is the predominant variant in the EU/EEA [1]. The UK reported a recent decline in the prevalence of the variant and a corresponding rapid increase of the VOC B.1.617.2 [6], which suggests that replacement of B.1.1.7 by B.1.617.2 could also be observed in the EU/EEA in the coming months.

The VOC B.1.1.7+E484K, first reported in the UK, has a B.1.1.7 genetic background that carries the additional change E484K in the spike protein. This substitution has been associated with reduction in neutralising activity by antibodies and it is also found in VOCs B.1.351 and P.1. The VOC B.1.1.7+E484K has been reported by 32 countries so far in GISAID EpiCoV. Outbreaks involving the B.1.1.7+E484K have been reported in the EU/EEA region, but no significant increase in prevalence has been observed so far.

The VOC B.1.351, first identified in South Africa, has been registered by 91 countries globally in GISAID EpiCoV. Community transmission and outbreaks related to this variant have been reported in the EU/EAA region, but no significant overall increase in prevalence has been observed so far. It is defined by multiple spike protein changes present in all viruses in the cluster (amino acid change D80A, D215G, E484K, N501Y and A701V), and more recently collected viruses have additional changes (amino acid change L18F, R246I, K417N, and deletion 242-244). Three of the changes (amino acid change K417N, E484K, and N501Y) are located within the receptor-binding domain [1].

The VOC P.1, first reported by Japan in returning travellers from Brazil, and then later in Brazil, has been reported by 54 countries globally in GISAID EpiCoV. Community transmission and outbreaks related to this variant have been reported in the EU/EAA region, but no significant increase in prevalence has been observed so far. The variant is characterised by 11 amino acid changes in the spike protein compared to its ancestral lineage B.1.1.28, three of which are located in the receptor-binding domain. [1].

The VOC B.1.617.2, first detected in India in December 2020 has been reported by 58 countries globally in GISAID EpiCoV. B.1.617.2 is defined by multiple spike protein changes as well as by mutations in other genomic regions [1]. Recent data reports from the UK public health authorities have shown that this variant is associated with transmissibility at least as high as B.1.1.7, and with a slight to moderate reduction in vaccine effectiveness, especially after only one vaccine dose. Assessment of these data led to an upgrade in the classification of this variant by ECDC on 24 May 2021, from variant of interest (VOI) to VOC [7].

According to data reported as of 23 May 2021, the situation regarding VOIs and VOCs in EU/EEA countries remained stable, with B.1.1.7 being the dominant variant in the EU/EEA. However, only 12 EU/EEA countries were reporting sequences at the recommended level of at least 500 sequences per week or 10% of SARS-CoV-2-positive cases (Belgium, Denmark, Estonia, France, Germany, Hungary, Iceland, Ireland, Luxembourg, Malta, Norway and Poland)[1]. Among the 12 EU/EEA countries with the recommended level of sequence reporting in the period from 10 May to 23 May 2021, 10 had a valid denominator. The median (range) of the VOC reported in all samples sequenced in the period in these 10 countries was 91.6% (70.2–97.1%) for B.1.1.7, 0.5% (0.0–7.2%) for B.1.351, 0.3% (0.0–5.3%) for B.1.617, 0.2% (0.0–10.1%) for P.1 and 0.0% (0.0–1.6%) for B.1.1.7+E484K.

None of the variants of interest (VOIs) were detected with a proportion of greater than 1%: median (range) were 0.0% (0.0–3.1%) for B.1.525, 0.0% (0.0–0.1%) for B.1.620 and 0.0% (0.0–0.0%) for B.1.621. A list of current VOCs and VOIs for the EU/EEA is published on ECDC's website.

# Prevalence of SARS-CoV-2 antibodies in Europe

ECDC, in collaboration with WHO EURO, is monitoring the results of the seroprevalence studies performed in the WHO-EURO region. Up to end of 2020, the overall prevalence of SARS-CoV-2 antibodies relating to natural infection in the region still remained at low levels (<15%) [10,11], with large variations between and within countries. Some higher regional estimates (up to 52%) [8,9] of SARS-CoV-2 antibodies were measured in areas with extensive local community transmission. It is likely that a large proportion of the population across Europe still remains susceptible to SARS-CoV-2 infection and that population immunity is far from being reached. Ongoing monitoring of the natural and vaccine-induced immunity in the region remains important, in order to provide a better understanding of the epidemiological situation and help guide the effective implementation of control measures.

# Non-pharmaceutical interventions

ECDC collects information on non-pharmaceutical interventions (NPIs) implemented in EU/EEA countries in response to the COVID-19 pandemic. After intensive measures implemented throughout the course of the pandemic and continuing through spring 2021, most EU countries are in the process of relaxing NPI's to a greater or lesser extent.

Detailed up-to-date information on the public health measures implemented at national level are available in the Weekly COVID-19 country overview. In addition, a repository with all current and past NPIs for each EU/EEA country is made publicly available by ECDC and the Joint Research Centre (JRC) at https://covid-statistics.jrc.ec.europa.eu/RMeasures.

# Vaccination

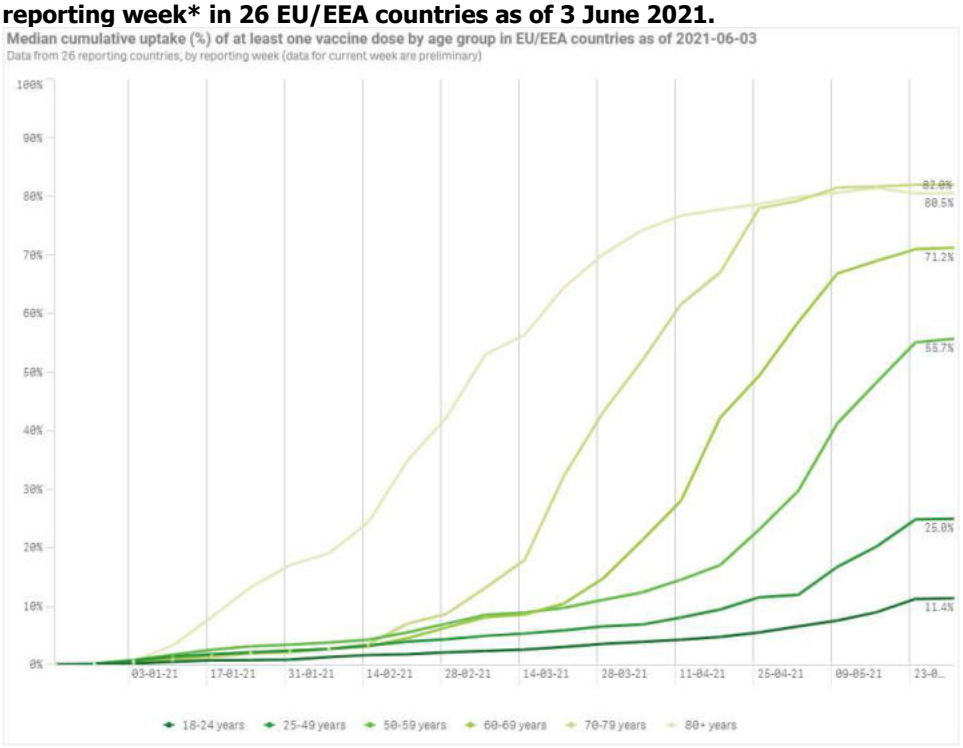
Currently, four COVID-19 vaccines have received conditional marketing authorisation in the EU [12], following evaluation by the European Medicine Agency (EMA), and are part of the EU Coronavirus Vaccines Strategy Portfolio: Comirnaty (BNT162b2) developed by BioNTech/Pfizer, COVID-19 Vaccine Moderna (mRNA-1273), Vaxzevria (AZD1222) previously COVID-19 Vaccine AstraZeneca, and COVID-19 Vaccine Janssen (Ad26.COV 2.5). In addition, vaccines that have not been authorised at the EU level (Sputnik V, Beijing CNBG) are currently being used in one Member State under national licensing arrangements [13]. In most EU/EEA countries, the vaccination rollout started at the end of December 2020, when the first batches of Comirnaty were distributed. Because of limited vaccine supply, prioritisation strategies initially focused on groups with higher risk of exposure to the virus or higher risk of severe disease or death (e.g. healthcare workers and the elderly, including those living in long-term care facilities (LCTFs)). The main objectives for the rollout of vaccination in countries were to reduce the number of deaths, to protect the healthcare workforce, and to reduce the pressure on healthcare systems by reducing the number of individuals being hospitalised and in need of intensive care. The escalation of vaccine supplies has subsequently allowed countries to expand eligibility for vaccination to younger age groups.

[1] Based on data reported to the GISAID EpiCoV database by 25 May 2021, or to TESSy by 23 May 2021 (data referring to the period 3 May to 16 May 2021).

As of 3 June, the median cumulative vaccine uptake in the EU/EEA adult population (aged 18 years and older) reached 46.2% for at least one vaccine dose (range: 14.1-65.8%) and 22.3% for the full vaccination course (range: 10.1-49.7%). The highest level of vaccine uptake was observed among the elderly aged 80+ in which the uptake reached 80.5% for at least one dose (range: 13.8-100%) and 66.3% for full vaccination (range: 9-99.6%) (26 reporting EU/EEA countries). For healthcare workers, the median level of at least one dose uptake was 87% (range: 21.3-100%) and the median uptake for the full vaccination course was 65.2% (range: 19.7-100%) (16 reporting EU/EEA countries).

More information, with country specific data, can be found in ECDC's vaccine tracker [13] and the related weekly vaccine rollout overview [14].

**Figure 2. Median cumulative uptake (%) of at least one dose of COVID-19 vaccine, by age group and reporting week* in 26 EU/EEA countries as of 3 June 2021.**




## Mass gathering: UEFA EURO 2020

The UEFA European Football Championship (UEFA EURO 2020), which was postponed in March 2020 due to the COVID-19 pandemic, will take place between 11 June and 11 July 2021. Eleven countries will host the games, of which seven are EU Member States: Denmark, Germany, Hungary, Italy, the Netherlands, Romania, and Spain. Other countries hosting games are Azerbaijan, Russia and the United Kingdom. Twenty-four teams will be playing the matches during this period, watched by an estimated 460 000 spectators.

# Disease background

For additional information on the latest scientific evidence relating to COVID-19, SARS-CoV-2, virus transmission, diagnostic testing, infection, clinical characteristics, risk factors and risk groups, immunity, treatment and vaccines please visit ECDC's website: https://www.ecdc.europa.eu/en/covid-19/latest-evidence.

## Effectiveness of vaccination

Evidence from real-world use of COVID-19 vaccines authorised in Europe has confirmed the clinical trial findings and demonstrated high vaccine effectiveness against PCR-confirmed SARS-CoV-2 infection and symptomatic disease [15]. There are also an increasing number of real-world studies, especially coming from Israel, US and the UK, showing high vaccine effectiveness against severe disease, hospitalisation and death. In a large observational study from Israel, vaccine effectiveness was 87% (95% CI 55-100%) against hospitalisation and 92% (95% CI 75-100%) against severe disease after two doses of Comirnaty vaccine [16]. A retrospective cohort study (preprint) in the US found mRNA vaccines (Comirnaty and COVID-19 vaccine Moderna) were 96% (95% CI 95-99) effective at preventing hospitalisation and 98.7% (95%CI 91.0-99.8) effective at preventing deaths when the individuals were fully vaccinated [17].

A test negative case-control study from the UK found that one dose of either Comirnaty or Vaxzevria provided 60-70% protection against symptomatic COVID-19 and about 80% effectiveness at preventing admissions to hospital [18]. In addition, evidence is beginning to emerge on the impact of vaccination on risk of transmission [19]. A large register-based study on prevention of SARS-CoV-2 transmission in households of vaccinated healthcare workers from Scotland suggests that vaccination of a household member reduces the risk of infection in susceptible household members by at least 30% [20]. A recent study examining the impact of vaccination on household transmission in England found that the likelihood of household transmission is 40−50% lower for households where the index cases were vaccinated 21 days or more prior to testing positive (93% of the vaccinated index cases had received only one dose of vaccine), compared to no vaccination[21]. The effects are similar for Comirnaty and Vaxzevria vaccines. There is evidence that vaccination significantly reduces viral load [22] when infection happens in vaccinated individuals and this could translate into reduced transmission, although vaccine effectiveness does vary by vaccine product and target group.

# Impact of SARS-CoV-2 variants of concern on COVID-19 vaccine efficacy

In studies that have addressed the VOCs, there is limited preliminary evidence of reduced vaccine efficacy, in particular for B.1.351 and possibly also for P.1 and B.1.617.2 [17-22]. Data are emerging which indicate that vaccine efficacy is maintained for B.1.1.7 [19,23,24]. Infections with VOCs have been reported in fully vaccinated individuals, although the frequency of this and the severity of illness following infection is not yet well understood [19]. Assessment of the emerging variants' potential to escape the immunity induced by the currently available vaccines is ongoing. More information on this will be needed as new variants emerge in the future.

# Vaccine effectiveness and number of doses

## One dose vs two dose schedule

Effectiveness studies of a single dose of Comirnaty, COVID-19 Vaccine Moderna or Vaxzevria vaccines have shown that a single dose is immunogenic in previously *naïve* vaccine recipients, reduces risk of infection and can reduce risk of severe disease (including hospitalisation) [14,25-28]. However, the follow-up period after one dose is limited in most studies, so the duration of immunity after one dose is not known. The two-dose strategy proposed for many vaccines aims to ensure that potential weak antibody responses generated via a single dose – particularly, but not exclusively in the elderly – are adequately boosted to maximise protection as shown in efficacy clinical trials [29-31].

In addition, the effect that current and emerging VOCs may have on vaccine efficacy and effectiveness and vaccine dosing schedules is emerging. A recent preprint study from the UK on the effectiveness of Comirnaty and Vaxzevria vaccines against symptomatic COVID-19 cases identified as infected with the B.1.617.2 VOC showed that effectiveness was lower after one dose of vaccine with B.1.617.2 cases (33.5%, 95%CI 20.6-44.3) compared to B.1.1.7 cases (51.1%, 95%CI 47.3-54.7) with similar results for both vaccines, however after two doses of either vaccine there were only small non-significant reductions in vaccine effectiveness. These results would support maximising vaccine uptake with two doses among vulnerable groups [28].

In response to the rising cases of the B.1.617.2 VOC, following advice from the UK Joint Committee on Vaccination and Immunisation (JCVI), on 14 May 2021 the UK government reduced the timing for administering the second dose of COVID-19 vaccines from 12 to eight weeks for the priority groups [37] to ensure adequate protection.

## One dose following previous SARS-CoV-2 infection (for vaccines given in a two-dose schedule)

In order to achieve rapid vaccination rollout, and taking into account the limited doses available, some EU/EEA countries have put in place policies to vaccinate as many people in the groups at high risk of severe COVID-19 as possible. This includes recommending only one dose of vaccine (in a two-dose schedule) to those individuals who have previously been infected with SARS-CoV-2. There is emerging evidence that for those individuals who have been previously infected with SARS-CoV-2, a single dose of Comirnaty and COVID-19 Vaccine Moderna appears to generate similar antibody, B cell and T cell responses to those found in non-infected individuals who have received two vaccine doses [33-36]. There is also emerging evidence of higher antibody levels after one dose of the Vaxzevria vaccine in previously infected individuals compared to one dose in non-previously infected individuals, and a single dose in previously infected individuals appears to generate similar antibody responses to those found in non-infected individuals who received two doses of vaccine [36-38]. However, follow-up periods for vaccinated individuals completing the full two-dose regimen are not yet sufficiently long enough to be able to draw conclusions on the duration of protection against infection beyond six months. Whilst studies of single-dose regimens for previously infected individuals are promising in the short term, evidence on the duration of protective immunity for such individuals is even sparser.

Based on the available clinical trial data, the current EMA product information for the vaccines authorised in EU/EEA countries is that the Comirnaty, COVID-19 Vaccine Moderna and Vaxzevria vaccines should be provided in a two-dose schedule and the COVID-19 Vaccine Janssen in a one-dose schedule to ensure adequate, long-term protection. The World Health Organization's (WHO) Strategic Advisory Group of Experts on Immunization (SAGE) currently recommends a two-dose schedule for individuals with Comirnaty, COVID-19 Vaccine Moderna and Vaxzevria, and the one-dose schedule for COVID-19 Vaccine Janssen, irrespective of prior infection.

### Heterologous COVID-19 vaccine schedule

Heterologous combination of vaccine doses (mix and match), where different COVID-19 vaccines are used for the first and the second dose in a COVID-19 vaccination regime, is already in use in a number EU/EEA countries [44]. After the safety signals from thrombosis with thrombocytopenia syndrome (TTS) following vaccination with Vaxzevria, some countries have started recommending a second dose of an mRNA vaccine (Comirnaty or COVID-19 Vaccine Moderna) to individuals who received a first dose of Vaxzevria [44].

There is some evidence on the immunogenicity, safety and efficacy of heterologous schedules from clinical trials, and also several ongoing studies. A good immune response could be expected from combining different COVID-19 vaccines, as all licensed vaccines induce an immune response against the SARS-CoV-2 spike protein, and it is expected that mixing vaccines could potentially boost immune responses in the process [45].

The Com-Cov study is an ongoing trial in the UK, which started in February 2021. Combinations of Vaxzevria and Comirnaty are tested in four or 12 weeks intervals, and from April, the trial also included the COVID-19 Vaccine Moderna and NVX-CoV2373 by Novavax. A preliminary analysis of reactogenicity indicates an observed slight increase in side effects with a heterologous schedule, such as fever, headache and malaise, albeit mild [46]. Preliminary results reported from the Spanish CombivacS study, show that a combination of Vaxzevria and Comirnaty is well tolerated and induces a sevenfold increase in neutralizing antibodies after a second dose of Comirnaty, which is more than double the effect seen in other studies using a second dose of Vaxzevria, notwithstanding differences in assays. The observed side effects in this study were mild and reported to a similar extent as for homologous vaccination schedules [47].

In addition to the studies and results described above, several EU/EEA countries have either already started or are planning to start various types of studies investigating immunogenicity and safety of different combinations of COVID-19 vaccines. The results from these studies will also be important for potential booster doses in the future, as a mixing of vaccines also increases flexibility in the vaccine rollout.

### Reinfection with SARS-CoV-2

Reinfection with SARS-CoV-2 is possible, but appears to be rare [48]. SARS-CoV-2 VOCs have demonstrated increased transmissibility in humans. Seroconversion to previously circulating SARS-CoV-2 strains may generate neutralising antibodies that protect against reinfection by a homologous virus, but the neutralising capacity of these antibodies is reduced against VOCs, particularly those carrying the E484K mutation [48].

# ECDC risk assessment for the EU/EEA

This assessment is based on information available to ECDC at the time of publication and, unless otherwise stated, the assessment of risk refers to the risk that existed at the time of writing. It follows the ECDC rapid risk assessment methodology, with the overall risk determined by a combination of the probability of an event occurring and its consequences (impact) for individuals or the population [49].

# Risk assessment question

## Based on current vaccination coverage and circulating variants in the EU/EEA, what risk does SARS-CoV-2 pose to the general population and vulnerable individuals?

In recent weeks, a similar picture has been observed in most EU/EEA countries. Rates of notifications, hospitalisations, ICU admissions/occupancy and death have been decreasing [4]. At the same time, the vaccination uptake has been steadily increasing, with over 40% of the EU/EEA population vaccinated with at least one dose of the vaccine and almost 20% fully vaccinated [13]. In most countries, vulnerable populations (individuals with risk factors for severe COVID-19 disease), such as the elderly [50] have been prioritised for vaccination and the median uptake of at least one dose reached 80% in this population group among reporting countries [13]; this has occurred alongside decreasing notification rates in the elderly and an absence of excess mortality in those aged over 85 years since the end of February 2021 [4,5].

Even though vaccine effectiveness varies to a certain degree by vaccine product and target group, a single dose of Comirnaty, COVID-19 Vaccine Moderna or Vaxzevria has been shown to be immunogenic in non-previously infected individuals, reducing the risk of infection, the risk of severe disease (including hospitalisation) and the risk of transmission [14,16,25-28]. The variant of concern B.1.1.7 dominates circulation throughout the EU/EEA. It is associated with increased transmissibility, severity and mortality, but proved not to be associated with immune escape, and effectiveness against infection after two doses of the vaccine remains high [19,23,24]. Finally, large proportions of the EU/EEA population remain susceptible to SARS-CoV-2 [10,11].

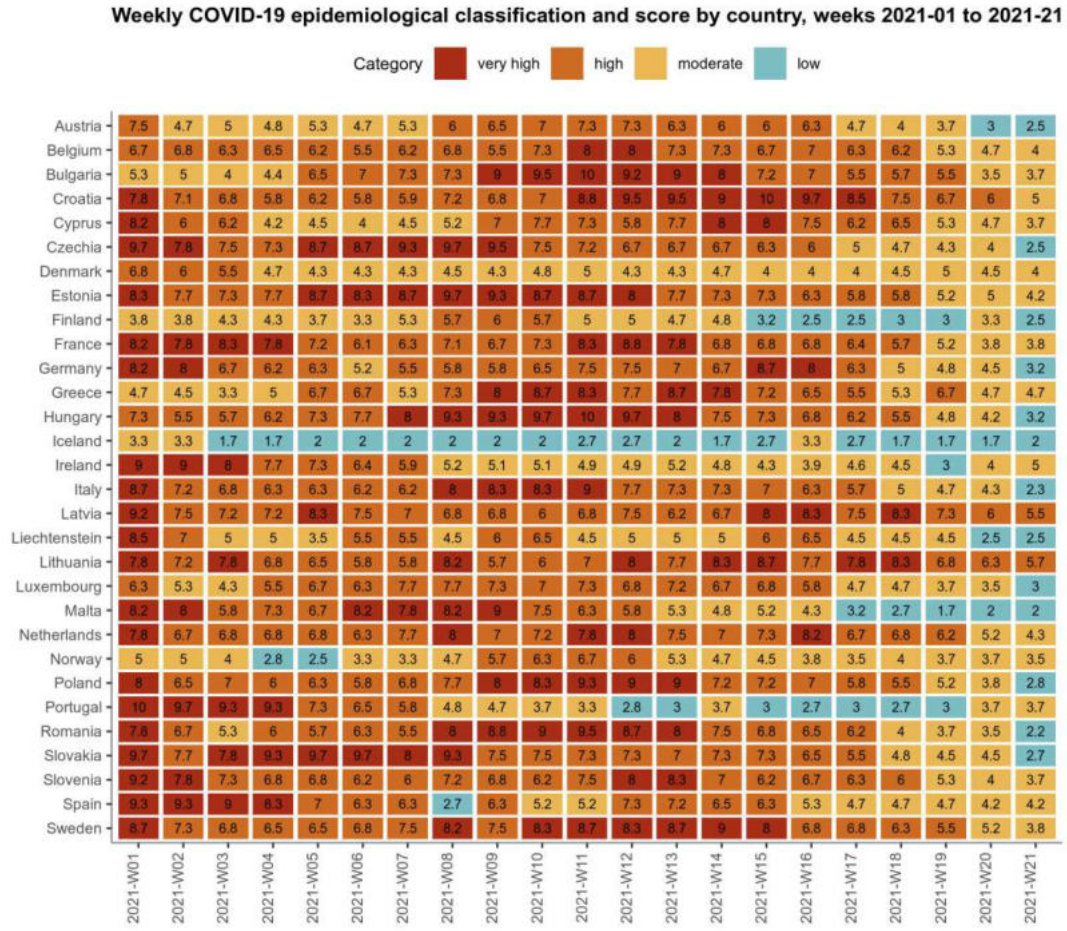
However, due to differences in the epidemiological situation, vaccination strategies and implemented NPIs, EU/EEA countries are experiencing different levels of risk and require different targeted interventions.

ECDC classifies the epidemiological situation in EU/EEA countries into four categories based on the level of concern (low, moderate, high, very high). These are derived from a combination of the absolute value and trend of five weekly COVID-19 indicators (intensity indicators: test positivity and total case notification rates; and severity indicators: hospital or ICU admissions or occupancy, death rates, case rates among people aged 65 years and above; methods outlined in Annex). In most countries, the contribution of the intensity indicators to the overall score has been higher than that of the severity indicators in recent weeks. As such, the overall classification shown below provides a conservative estimate of transmission intensity.

In week 21, 2021, there was no country where the epidemiological situation was classified as very high concern (Figure 3). The distribution across the three remaining categories is as follows:

- Low concern: Austria, Czechia, Finland, Germany, Hungary, Iceland, Italy, Liechtenstein, Luxembourg, Malta, Poland, Romania and Slovakia;
- Moderate concern: Belgium, Bulgaria, Croatia, Cyprus, Denmark, Estonia, France, Greece, Ireland, the Netherlands, Norway, Portugal, Slovenia, Spain and Sweden;
- High concern: Latvia and Lithuania.

**Figure 3. Weekly COVID-19 epidemiological classification and score by country in EU/EEA, by week, 2021**



The current assessment of the risk posed by the current SARS-CoV-2 pandemic is stratified by four population groups (vaccinated and unvaccinated general population, and vaccinated and unvaccinated vulnerable population), it is based on the different epidemiological situations experienced in the EU/EEA countries, and on the following elements i) the vaccinated group has a lower probability of infection and ii) a lower impact of such infection than the unvaccinated, while iii) the vulnerable population suffers of a higher impact of such infection when compared with the general population.

## Countries in which the epidemiological situation is classified as low concern

In these countries, widespread transmission is falling with consequent low case notification rates. Due to the large proportion of the vulnerable population vaccinated with at least one dose, very low notification rates are recorded among the elderly. Based on this, the probability of infection ranges from very low in the vaccinated general population to moderate in the unvaccinated (both general population and vulnerable groups). The impact of the disease ranges from low in the vaccinated general population to very high in the unvaccinated vulnerable population.

General population

- Fully vaccinated: probability of infection VERY LOW + impact of infection LOW ➔ **LOW RISK**
- Unvaccinated: probability of infection MODERATE + impact of infection LOW ➔ **LOW RISK**

Vulnerable populations

- Fully vaccinated: probability of infection LOW + impact of infection MODERATE ➔ **LOW RISK**
- Unvaccinated: probability of infection MODERATE + impact of infection VERY HIGH ➔ **MODERATE-to-HIGH RISK**

## Countries classified as moderate concern

These countries continue observing widespread SARS-CoV-2 transmission with the highest notification rates in the general population and, although a high proportion of the vulnerable population has been vaccinated with at least one dose, the probability of infection is higher than in the previous group of countries. These countries still experience widespread transmission associated with a dominating highly transmissible variant and a large part of the population is still susceptible to the infection. Based on this, the probability of infection ranges from low in the vaccinated general population to high in the unvaccinated (both general population and vulnerable groups). As long as NPIs are maintained to avoid worsening of the epidemiological situation, the impact of the disease ranges from low in the general population (both vaccinated and unvaccinated) to very high in the unvaccinated vulnerable population.

General population

- Fully vaccinated: probability of infection LOW + impact of infection LOW ➔ **LOW RISK**
- Unvaccinated: probability of infection HIGH + impact of infection LOW ➔ **LOW-to-MODERATE RISK**

Vulnerable populations

- Fully vaccinated: probability of infection MODERATE + impact of infection MODERATE ➔ **LOW-to-MODERATE RISK**
- Unvaccinated: probability of infection HIGH + impact of infection VERY HIGH ➔ **HIGH-to-VERY HIGH RISK**

## Countries classified as high concern

These countries experience widespread SARS-CoV-2 transmission not only in the general population, but also in vulnerable individuals. The NPIs in place appear to be having a limited effect, either because adherence to the measures may not be optimal or the measures in place may not be sufficient to reduce or control exposure. Vaccination uptake in the general population and, particularly, in the vulnerable population appears to be still low. Based on this, the probability of infection ranges from moderate in the vaccinated general population to very high in the unvaccinated (both general population and vulnerable groups). In these settings, due to the pressure to the health system posed by high notification, hospitalisation and death rates, the impact of the disease is higher compared to the previous country groups resulting in moderate impact in the general population (both vaccinated and unvaccinated) and in the vaccinated vulnerable population, and very high in the unvaccinated vulnerable population.

General population

- Fully vaccinated general population: probability of infection MODERATE + impact of infection MODERATE ➔ **LOW-to-MODERATE RISK**
- Unvaccinated general population: probability of infection VERY HIGH + impact of infection MODERATE ➔ **HIGH RISK**

Vulnerable populations

- Fully vaccinated vulnerable population: probability of infection HIGH + impact of infection MODERATE ➔ **MODERATE RISK**

- Unvaccinated vulnerable population: probability of infection VERY HIGH + impact of infection VERY HIGH ➔ **VERY HIGH RISK**

The current assessment represents a decrease in most risk levels compared to the 14th update of the ECDC COVID-19 risk assessment published in February 2021 [1]. This assessment considers the current variant circulation, rollout of vaccination and NPIs in place. Scenarios considering variant replacement and reduced vaccine effectiveness are discussed in the following section based on modelling forecasts. Close monitoring of the evolving epidemiological situation, paying particular attention to the circulation of new variants (e.g. VOC B.1.617.2) associated with reduced vaccine effectiveness and/or increased transmissibility and severity, or to increasing transmission and death rates due to the relaxation of the current NPIs, is key to avoid a rapid increase in the risk level in the coming weeks. In any of the country scenarios, should mass gathering events such as the UEFA Euro 2020 take place in the absence of sufficient mitigation measures, the risk of local and pan-European transmission risk of COVID-19, including the spread of variants of concern, would increase.

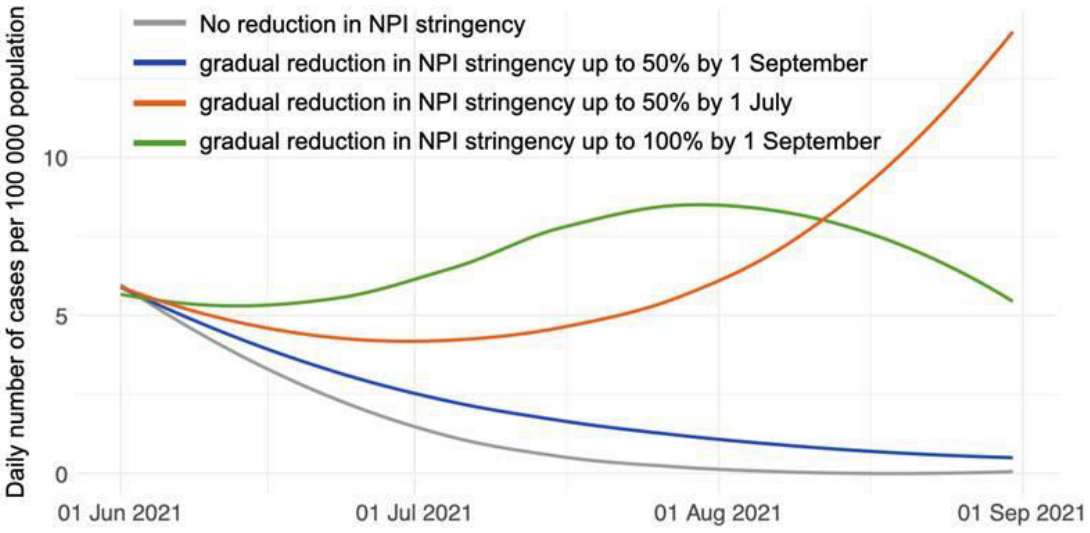
# Modelling forecasts

Case notification rates in the EU/EEA have been falling consistently since April 2021 and many countries are now implementing or considering the partial lifting of the NPIs that aim to reduce the degree of physical contact between citizens. If the level of immunity in the population were constant, the lifting of such measures would result in increased levels of viral transmission. However, vaccination rollout continues and case notification rates will depend on the interaction between increasing immunity and the likely increasing contact between people as measures are eased. We simulate the projected number of cases per 100 000 members of the population, assuming that the rollout of the vaccination programme continues at its current rates and allowing for decreasing rates of uptake in older people and increased rates in younger people. We project changes in contact reduction based on the trend in the ECDC-JRC Response Measures Database of the past three months. We project the proportion of a new variant based on the assumed transmission advantage and assuming the same generation interval as the wildtype. The current viral transmission trend is based on reported cases across all EU/EEA Member States, and the forecasted transmission is assumed to be affected by changes in contact reductions, changed transmissibility of the projected mix of variants, and the effects of vaccination. This vaccine effect is reduced proportional to the assumed vaccine escape. Specifically, we forecast vaccination uptake by 10-year age groups, using the data presented in the ECDC Vaccination Tracker and extrapolating continued rollout at the current speed [13]. Figure 4 presents four scenarios:

- Continuation of the NPIs in place today (grey);
- A 50% reduction in the stringency of NPIs by 1 July 2021 (orange);
- A 50% reduction in the stringency of NPIs by 1 September 2021 (blue);
- A 100% lifting of NPIs by 1 September 2021 (green).

Where measures are lifted, the change begins from 1 June 2021 and continues gradually. Where the target date for reduction in NPIs is July, we assume unchanged contact reductions after that date.

**Figure 4. Estimation of possible changes in daily COVID-19 incidence in the EU/EEA according to four NPI relaxation scenarios24 May – –31 August 2021.**



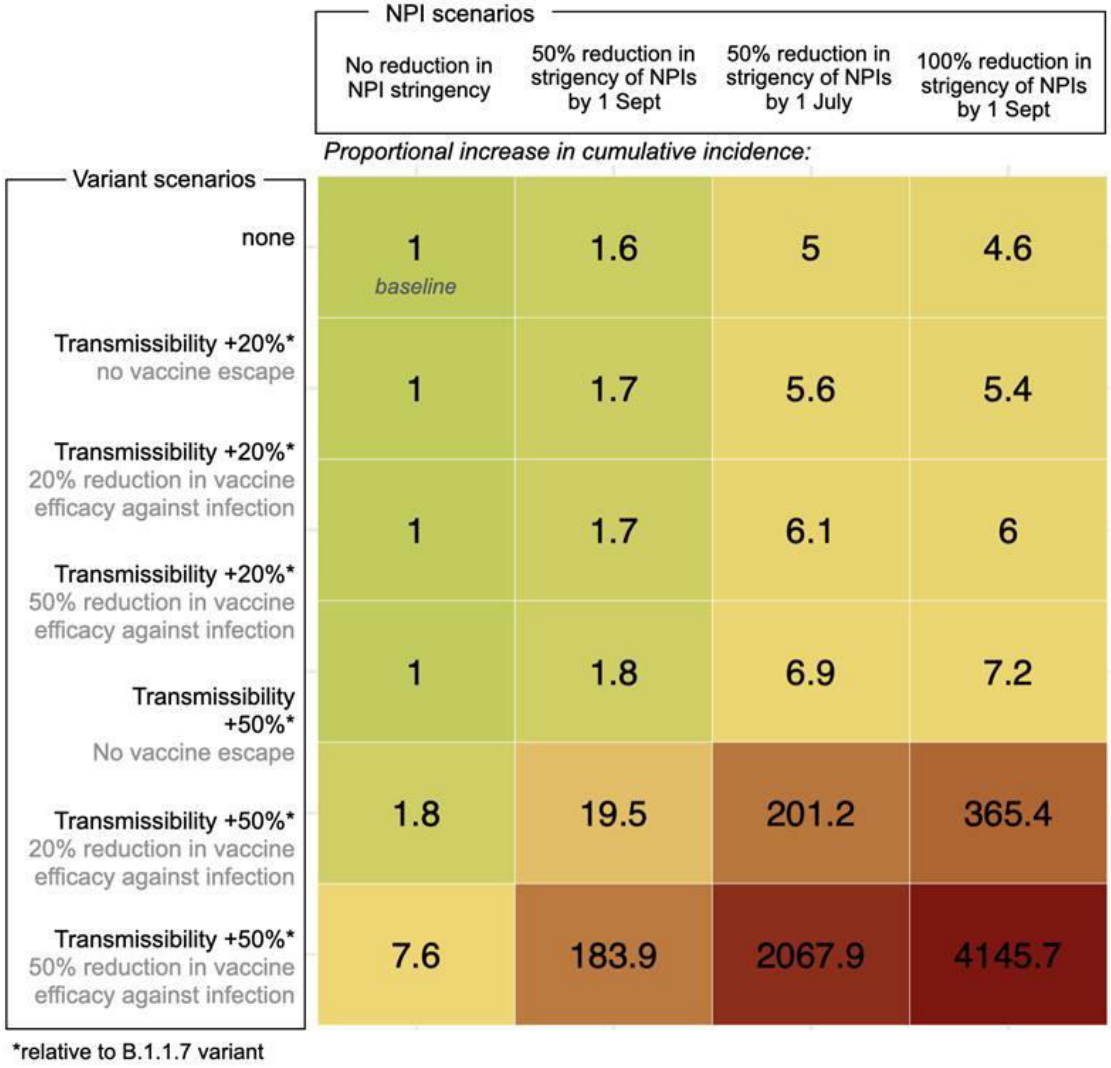

*Note: no change in contact reduction (grey) or, alternatively, that current NPIs are gradually reduced up to 50% (green) by 1 July 2021 or 50% (blue) or 100% (orange) by 1 September 2021. We assume that age-prioritised vaccine rollout continues at current rates and that there is no replacement with a new variant. Note that although it appears that case numbers would fall to very low levels if vaccination rates and NPIs are maintained, this does not equate to an elimination scenario.*

A slow reduction in the stringency of measures, resulting in a 50% lightening of current measures by 1 September 2021 may result in a continuing fall in case notification rates. However, reaching the same lifting of measures by 1 July 2021 would cause an increase of up to 40% in case notification rates by the end of July when increased vaccination coverage would bring transmission back to manageable levels. Lifting NPIs completely by 1 September 2021 would mean that case notification rates would continue to increase, even as the vaccination rollout proceeds. That is, the increased transmission due to people interacting would be too great a hurdle for the vaccination programmes to overcome.

The dynamics of SARS-CoV-2 transmission may also be affected by the emergence of new variants of concern. We additionally simulate a new variant, which replaces the current circulating strains. If the new variant is 20% more transmissible than the current mix of strains, replacement occurs over a period of 180 days; if it is 50% more transmissible, replacement takes 74 days. To explore the potential impact of a novel variant, we also simulate vaccine escape i.e. the reduced effectiveness of vaccines to prevent infection with SARS-CoV-2.

Figure 5 presents the cumulative number of cases that are predicted per 100 000 members of the EU/EEA population between 1 July 2021 and 31 August 2021 for different assumptions of transmissibility and vaccine escape potential of a new variant.

**Figure 5. Proportional increase in the cumulative incidence of COVID-19 in six hypothetical scenarios of strain replacement with variants in EU/EEA between 1 June and 31 August 2021.**




*Note: The baseline is no variant replacement and no change of NPI stringency (top left).*

The impact on case numbers of an emerging variant with 20% increased transmissibility is less than the impact of lifting NPIs by 50%-100% over the summer months. However, clearly, there is an increased risk of lifting NPIs in the presence of a more transmissible variant. If vaccines have a reduced effectiveness at preventing infection against such variants, the population remains susceptible, and numbers could increase rapidly. A variant with an increased transmissibility of 20% and a 50% reduction in vaccine effectiveness gives an estimated increase of 5% in the case numbers between 1 June and 31 August 2021, however this impact would be compounded over time and would lead to rapidly increasing case rates into the autumn.

# Options for response

Viral circulation in the EU/EEA has been decreasing in the majority of countries. However, sero-epidemiology studies as mentioned above, are showing overall prevalence of SARS-CoV-2 antibodies relating to natural infection at <15% in the European region at the end of 2020. In addition, the cumulative vaccination uptake, especially for full vaccination in the EU/EEA is still low but increasing in the adult population aged 18 years and older. Vaccine uptake is higher in specific groups of the population targeted in the initial phases of the COVID-19 vaccine rollout, such as people aged 80 years and older, which is anticipated to have an effect on the COVID-19-related hospitalisations and deaths. Although increasing vaccination coverage will also mitigate the effect of replacement with more transmissible variants, decisions to ease measures need to be highly sensitive to the local context and include considerations about the current viral circulation, the prevalence of VOCs, setting, and the vaccination status. Modelling analysis shows that a significant increase in COVID-19-related cases in the EU/EEA remains possible if NPIs are relaxed too rapidly. Optimal use of vaccines remains the cornerstone of the public health response, supplemented by continued early case detection with associated contact tracing (test and trace approaches), strong surveillance and characterisation of circulating viruses by sequencing. Finally, considerations for travel-related measures and effective risk communication are provided.

## Vaccination

With increased vaccine availability, the key priority remains to accelerate the vaccine rollout to ensure that all eligible individuals receive a full course vaccination. The main focus should be on further increasing vaccination coverage, with a rapid and effective deployment of vaccines, in order to reduce the number of susceptible individuals, the number of hospitalisations and deaths and the viral circulation in the community. This should be done by pursuing clear vaccination goals following suitable and coherent strategies as established by all EU/EEA countries and indicated in the recent ECDC report on 'Objectives of vaccination strategies against COVID-19' [51].

Achieving high antibody levels via a full vaccination course confers the additional benefit of sustained protection and sufficiently high levels to confer protection even against emerging SARS-CoV-2 variants which have demonstrated increased immune escape potential. In the absence of more definitive data, and in the context of current and emerging VOCs with immune escape potential, any national changes to the recommended schedule should weigh uncertainties in the long-term immunity against the need to rapidly immunise the population, taking into account the national epidemiological situation.

While countries keep working on reaching national goals as well as those set up by the European Commission in January (vaccinating at least 80% of people over the age of 80 years, and 80% of health and social care professionals by March 2021, as well as a minimum of 70% of the adult population by the summer) [52], the ultimate goal is to reopen society entirely and vaccination has a major role to play in reaching this.

As vaccination coverage of adult groups gradually increases and countries start expanding coverage, it will be especially important to monitor vaccine uptake and acceptance across the population and to have strategies in place to reach out to those individuals, groups and/or communities that are hesitant or sceptical. It is also essential to reach those that find it difficult to access vaccination sites, such as vulnerable or hard-to-reach individuals, for example by utilising mobile vaccination sites and teams [53]. Strategies will require constant adaptation to unexpected changes in the epidemiology of the disease as well as any suspected adverse events following immunisation that may affect trust in the vaccination programme. In addition, the acceleration of the vaccination campaign is one important way to protect against emerging more transmissible variants [54]. The risk of introduction of new variants in the EU/EEA is closely related to the pandemic evolution outside the EU/EEA. Efforts to enhance more equitable access to vaccination globally can mitigate the risk of emergence of new variants.

## Surveillance and monitoring

Although the effectiveness of COVID-19 vaccines authorised in the EU is generally very high, no vaccine is 100% effective. Infections amongst vaccinated persons (i.e. 'breakthrough infections') are therefore expected and more will be seen as vaccination uptake increases. These may include severe and fatal cases among vaccinated persons, particularly the elderly and those with pre-existing conditions. There is limited preliminary evidence for known circulating variants having immune escape capacity and reduced vaccine susceptibility, particularly the variant B.1.351 [55]. However, the potential remains for the emergence of new variants, which evade the protection conferred by current vaccines. Continued comprehensive surveillance of COVID-19 cases, including severity, vaccination history and ideally linked to sequencing results where available, is therefore essential, in order to rapidly detect the emergence of novel variants, their spread, as well as the public health impact.

Currently, in the EU/EEA, long-term care facilities (LTCFs) are the closed settings with the highest vaccine coverage, and are also home to those with highest risk of severe COVID-19 outcomes. To date, reports of COVID-19 outbreaks of breakthrough infections in LTCFs with high vaccination coverage have mostly had mild or asymptomatic cases [55]. Still, vigilance is required at national level, to ensure early communication of such outbreaks, most especially those with unexpectedly high proportions of severe, hospitalised or fatal cases, including prompt typing of samples.

Identification of new variants which are able to evade a vaccine efficiently would warrant an International Health Regulation (IHR) and EWRS notification, whilst operational discussion of ongoing investigations of any notable LTCF outbreak is well-suited to discussion within the secure ECDC platform 'Epidemic Intelligence Information System' for healthcare-associated infections and antimicrobial resistance (EPIS AMR-HAI), or the recently launched ECDC platform 'EpiPulse'. In support of this, on 6 May 2021, ECDC published the protocol 'Data collection on COVID-19 outbreaks with a completed vaccination programme: LTCFs' and an associated data collection tool [56]. Its main aim is to collect information on the severity of breakthrough COVID-19 infections in outbreaks, by SARS-CoV-2 variant and vaccine product. This activity is not intended to capture all outbreaks, generate comparative statistics, or obtain a (sub-)nationally representative sample.

# Testing and sequencing capacity

## Testing strategies

Timely testing of people with symptoms, through improving access to testing and encouraging people to seek testing as soon as possible after symptom onset, remains important to enable rapid initiation of contact tracing. Depending on available resources, testing strategies could include additional objectives, such as outbreak analyses, phylodynamic analyses and other research studies. Several EU/EEA countries have introduced the use of rapid antigen detection tests (RADTs) for screening asymptomatic persons at the workplace, school or other settings. The use of RADTs and/or self-RADTs in occupational settings can complement, but not replace, public health measures and existing NPIs aimed at preventing the introduction and spread of SARS-CoV-2. ECDC has published a technical report outlining the considerations on the use of rapid antigen detection (including self-) tests for SARS-CoV-2 in occupational settings [57].

Self-tests using RADTs can offer advantages when used to complement professionally administered RADTs or RT-PCR tests. They can improve the accessibility to testing. They allow individuals to obtain the result quickly, which could support the early detection and subsequent isolation of infectious cases and hence reduce further community transmission [58]. However, shifting the responsibility of reporting test results from health professionals and laboratories to individuals could lead to underreporting, and make response measures such as contract tracing and quarantine of contacts and monitoring of disease trends over time even more challenging.

A current priority is the assessment of the circulation of known VOCs in the community. To be able to confirm infection with a specific variant, sequencing of the whole SARS-CoV-2 genome, or at least the whole or partial S-gene for the current variants, is required. For Sanger sequencing or next generation sequencing (NGS), amplicon-based sequencing of selected parts of the viral genome are alternative methods for the identification of variants. ECDC has published a document that presents the available methods (screening and sequencing) for detection and identification of circulating SARS-CoV-2 VOCs B.1.1.7, B.1.351 and P.1 [59]. Methods for detection and differentiation of B.1.617 variants are available in the ECDC threat assessment brief published on 11 May 2021 [7].

Diagnostic laboratories should remain vigilant to detect any mismatches of specific RT-PCR assay primers and probes in comparison to circulating virus genomes. It should be noted that the majority of primer/probe binding sites of commercial assays are not publicly known. For in-house or commercial RT-PCR assays for which the primer/probe sequences are available, validation can be done via the ECDC PrimerScan [60] or similar tools that identify mismatches. For commercial assays where the primer/probe sequences are unknown, a validation procedure for the capacity of the molecular assays to detect variants is needed. For laboratories using S-gene target failure to identify variants, it is important to note that S-gene target failure is expected to occur for B.1.1.7among currently circulating VOCs, but as this target failure is not exclusive to B.1.1.7, sequencing is recommended at least for a subset of samples, especially in a low prevalence setting. For laboratories using the ARCTIC protocol for sequencing of SARS-CoV-2 it is important to use the latest version of the primers (https://artic.network/ncov-2019) as mismatches may occur with variant viruses. While RADTs are useful tools for the prompt identification of infectious cases, there are limited data from clinical validation studies in light of the new emerging variants [61]. RADTs detect specific proteins of the virus. Some mutations could alter the structure of these proteins, allowing them to escape detection. Many RADTs however target the nucleocapsid protein (N gene) that is more stable and less likely to mutate than the S gene. Laboratories should always remain vigilant to identify reductions in RADTs sensitivity.

In general, laboratories should have a quality assurance system in place and are encouraged to participate in external quality assessment (EQA) schemes or perform result comparison between laboratories, for a subset of samples. ECDC is planning a molecular EQA for national COVID-19 reference laboratories in June 2021. Please contact PHE.Support.Microbiology@ecdc.europa.eu for more information.

Community-level screening can be performed by sequencing SARS-CoV-2 from wastewater and the presence of signature mutations can be used to assess the presence of variants, although this technique is still under development [62]. The European Commission has published a Recommendation to support EU/EEA countries in establishing wastewater surveillance systems across the EU [63].

### Genomic surveillance and antigenic characterisation of SARS-CoV-2 variants

Early detection, genetic and antigenic characterisation of SARS-CoV-2 variants should be strengthened in all EU/EEA countries.

As part of targeted genomic surveillance, ECDC recommends increased sequencing of travel-related cases according to ECDC's guidance for genomic SARS-CoV-2 monitoring [64]. In order to detect the importation into countries and to slow down the spread of variants of concern in areas or countries where they are not yet present or only circulating at very low levels, ECDC recommends comprehensive sequencing of all SARS-CoV-2 positive cases with travel history to areas/countries where those variants are circulating. This is particularly relevant for, but not limited to, those coming from areas where variants of concern are endemic.

COVID-19-vaccinated individuals need to be closely monitored for breakthrough infections and virus isolates from these cases should be comprehensively sequenced and reported, irrespective of the variant identified [64]. Reports of suspected cases of SARS-CoV-2 reinfection also need to be investigated and sequence analysis of virus isolates from all these cases should be initiated. Mechanisms for antigenic characterisation to confirm or exclude vaccine escape mutants need to be established to support any need for reassessment of vaccine composition and strategy.

Furthermore, a representative sample of clusters or outbreaks associated with a specific setting/behaviour/age group with a minimum of five specimens (to be able to assess whether the event is dominated by a certain variant of concern) should be sequenced [64]. Other examples of situations that require sequencing, including to monitor variants of concern, can be cases with an unusual clinical presentation, such as severe infections and deaths in younger age groups with no underlying diseases, prolonged infections, a general change in the clinical presentation and cases where zoonotic transmission has been raised as a possibility and cannot be ruled out. This may indicate a change in pathogen virulence or inter-species transmission which should be monitored.

In addition to targeted genomic surveillance, a current priority should be to assess the level of circulation of known variants of concern in the community. Therefore, representative sequencing should be performed in order to generate data that reflect the overall variant situation in the country [64]. Specimens for genome analysis should be selected as being representative of SARS-CoV-2 cases in the country. Sample collection should be made using methods that ensure the unbiased selection of cases for sequencing. It is important to ensure that sequencing is performed on a sufficient number of cases every week (representative in terms of time), at every level of healthcare systems (representative in terms of clinical spectrum), and in all regions or other administrative areas of a country (representative in terms of geography). This should ensure representativeness in terms of age, gender, and disease severity of cases.

ECDC offers the possibility for antigenic characterisation of SARS-CoV-2 isolates, to support the detection of variant viruses that may escape natural immunity and/or vaccines. This is done through antigenic characterisation of SARS-CoV-2 isolates and by supporting the scaling up of sequencing capacity in EU/EEA countries. Please contact PHE.Support.Microbiology@ecdc.europa.eu for more information.

## Non-pharmaceutical interventions

### Maintaining and gradual relaxation of non-pharmaceutical interventions

Non-pharmaceutical interventions to reduce transmission in the general population are fundamental elements of the public health approach to controlling COVID-19. Therefore these measures should continue to be implemented and maintained in accordance with the local epidemiological situation, the vaccination coverage in the general population, and the prevalence of VOCs, taking into account that in a situation of increased community transmission, more measures or stricter compliance will be needed.

Due to the low risk of fully vaccinated individuals being infected and suffering from severe COVID-19, some NPIs, such as physical distancing and face mask wearing can be relaxed when fully vaccinated individuals meet other fully vaccinated individuals, as well as when an unvaccinated individual or unvaccinated individuals from the same household or social bubble meet fully vaccinated individuals, if there are no risk factors for severe disease or lower vaccine effectiveness in anyone present (e.g. older age, immunosuppression, other underlying conditions) [19]. However, in the current epidemiological context in the EU/EEA, in public spaces and in large gatherings, including during travel, NPIs should be maintained irrespective of the vaccination status of the individuals.

Where the epidemiological situation allows, countries may consider gradually lifting and adapting their NPIs, e.g. by opening (or keeping open) in-person educational and vocational activities both for children and adults, opening non-essential business, increasing the allowed size of social gatherings and cultural events.

This should be done with adherence to personal measures such as physical distancing, hand hygiene, use of face masks where recommended, and optimal ventilation of closed spaces. If gatherings and events are allowed, the limits on number of participants should still aim to avoid crowding, and gatherings outdoors are preferred when possible. Continuous, intense surveillance, identification of cases, contact tracing and quarantine of contacts remain key for monitoring the epidemiological situation and preventing a further surge of cases while measures are lifted or adapted. Countries' efforts should focus on the vaccination rollout, whilst individuals should continue to apply personal measures such as hand and respiratory hygiene, wearing a face mask when recommended and staying home when ill.

Countries and/or areas where the epidemiological situation remains concerning should maintain their NPIs and introduce additional targeted measures where required. Efforts should focus on the vaccination rollout, enhancing adherence to the current measures, protecting vulnerable populations such as LTCF residents, and ensuring healthcare capacity. Additionally, these countries/areas should consider maintaining physical distancing between individuals as much as possible, maintaining limits on the size of public gatherings, especially those indoors, as well as recommending only limited size private gatherings, promoting hand hygiene and respiratory etiquette, providing advice on use of face masks where necessary, continuing with contact tracing, quarantine of contacts and isolation of cases as well as limiting transmission in workplaces by encouraging teleworking whenever possible. Individuals in these countries should continue application of recommended NPIs at a personal level. For people vulnerable to severe COVID-19 who are not fully vaccinated, such as the elderly or those with underlying medical conditions, the use of medical face masks is also recommended as a means of personal protection in the above-mentioned settings, and these individuals should follow recommendations on continued physical distancing until fully vaccinated.

For analysis and available evidence on NPIs used to respond to the COVID-19 pandemic, please refer to ECDC's technical document 'Guidelines for the implementation of NPIs against COVID-19' [65]. For analysis and available evidence on the impact of vaccination on NPIs, please refer to ECDC's 'Interim guidance on the benefits of full vaccination against COVID-19 for transmission and implications for non-pharmaceutical interventions' [19].

## Contact tracing

Contact tracing remains a key tool to break transmission chains. For countries with high transmission, contact tracing will complement other measures and contribute to reducing transmission. For countries with lower levels of transmission, contact tracing is a key tool in outbreak management and controlling transmission. Contact tracing in the context of cases suspected to be infected with a VOC can help prevent the establishment of the VOC in the country. Countries should follow the latest ECDC contact tracing guidance [66].

Contact tracing can also be used to investigate the source of infection of a newly identified case – so-called backward contact tracing. This can allow for the identification of further cases around that source of infection, and subsequent contact tracing around those additional cases. This is further outlined in the ECDC contact tracing guidance.

For contact tracing to be effective, timeliness is key. This includes testing cases as soon as possible after symptom onset – which requires a high level of public awareness and easy access to testing. Test turnaround time should be minimised, and contacts traced as soon as possible after a positive result. Symptomatic people awaiting the result of their test can be encouraged to encourage their close contacts to adhere to physical distancing until the result is known.

For cases suspected to be infected with a VOC, for example through laboratory pre-screening [59] or an epidemiological link, enhanced contact tracing measures can be considered, as outlined in the ECDC publication 'Risk related to the spread of new SARS-CoV-2 variants of concern in the EU/EEA – first update '[67].

Fully vaccinated contacts who have been exposed to a confirmed COVID-19 case should continue to be managed according to existing ECDC guidance [66]. Health authorities should undertake risk assessment on a case-by-case basis, where possible, and may subsequently classify some fully vaccinated contacts as low-risk contacts. Factors that need to be taken into consideration in such assessments include, for example, the local epidemiological situation in terms of circulating variants, the type of vaccine received, and the age of the fully vaccinated contact (as older people may not mount as effective an immune response). The risk of onward transmission to vulnerable people by the contact should also be considered for individuals who work or reside in an institutionalised setting (e.g. LCTFs) [19].

ECDC and WHO encourage countries to monitor the effectiveness of their contact tracing operations to identify where coverage or timeliness needs to be increased [68]. To learn more about the transmissibility and characteristics of the VOCs, countries are encouraged to collect and analyse data from contact tracing of these cases and to share findings with ECDC, WHO and other EU/EEA countries.

Countries using mobile apps for contact tracing are also encouraged to monitor their effectiveness using the joint WHO-ECDC indicator framework which will shortly be published. On 27 May 2021, the European Commission published the Implementing Decision 2021/858 outlining the function of the digital Passenger Locator Form (dPLF) in the EU/EEA [69].

# Travel measures

In general, travel measures are unlikely to have any long-term major impact on the timing or intensity of local epidemics in comparison to rigorous local implementation of NPIs. However, travel measures can be considered when levels of transmission have been reduced to very low levels in the receiving locality or for those coming from areas which continue to have an epidemiological situation of high or serious concern level, irrespective of the conveyance and the extent of community transmission at the destination. Such measures are particularly important if there is clear evidence of circulation of new virus variants, or if the evidence that exists does not allow an accurate assessment (for example, due to insufficient sequencing capacity) of the extent to which new virus variants are circulating in the place of origin. Any measures implemented on internal or external EU borders need to be non-discriminatory in terms of nationality, place of residence and occupation and will need to consider the epidemiological situation in the countries of departure and arrival.

Measures that are being considered for incoming travellers include:

- Request of proof of negative pre-departure test or test upon arrival, and quarantine for 5-7 days with a test before release;
- Quarantining of travellers for 14 days without test, in case testing capacity is not sufficient;
- Enhanced contact tracing upon identification of a positive case related to travel, as described above.

Requirements for testing and quarantine of travellers (if implemented) can be waived or modified for fully vaccinated individuals as long as there is no or very low level circulation of immune escape variants in the community in the country of origin [19].

During travel, NPIs should be maintained regardless of the vaccination status of the traveller. Fully vaccinated travellers should also respect any NPIs for fully vaccinated people in the country of destination. Documents informing about the safety measures on various travel conveyances have been developed: air travel [70], cruises [71], and rail [72].

ECDC has published a guidance for COVID-19 quarantine and testing of travellers [73], also highlighting the considerations around the use of RADTs for travelling. RADTs can be useful for detection of infectious cases in the first five days from disease onset, they have, however, reduced sensitivity for detecting asymptomatic cases [57].

It is important to underline that whilst RADTs and regular RT-PCR will detect a SARS-CoV-2 infection, they will not distinguish SARS-CoV-2 variants (including VOCs). Specialised RT-PCR tests or sequencing are able to discriminate the presence of known variants and can be used, if available. RADTs can help to reduce further transmission of SARS-CoV-2 or SARS-CoV-2 VOCs through early detection of highly infectious cases, enabling immediate isolation and the rapid commencement of contact tracing. The UK has evaluated five RADTs (targeting the nucleocapsid protein) and they all detected cases that later on were identified as carrying the variant B.1.1.7, but validation studies for the rest of the VOCs are still lacking [74]. Further validation of RADTs is needed to ensure that they also detect future/emerging variants without reduction in their sensitivity.

An EU digital COVID certificate is planned to be introduced as proof that a person has been vaccinated against COVID-19, has recovered from COVID-19 or has a negative test result with the aim to facilitate safe and free movement during the COVID-19 pandemic. The EU digital COVID certificate can be available in both digital and paper formats and will be in use by 1 July 2021. When travelling, every EU citizen or third-country national legally staying or residing in the EU, who holds an EU digital COVID certificate, should be exempt from free movement restrictions in the same way as citizens of the visited EU country [75,76].

In addition, in the updated recommendation on restrictions to travel from third countries, the Council introduced the 'emergency brake mechanism', where EU/EEA countries can adopt an ad hoc restriction on travel to the EU from countries or regions where the epidemiological situation or the circulation of a VOC is of concern [77].

# Mass gathering events

For mass gathering events, such as the UEFA Euro 2020, monitoring of the epidemiological situation and implementation of preventive and mitigation measures should be done with a coordinated intersectoral approach.

EU/EEA travellers to UEFA matches abroad will have to comply with border entry restrictions, including COVID-19 restrictions, and requirements that will be in force at the time of the games in the host country. Access to stadiums could be conditional upon proof of negative COVID-19 test and/or vaccination and/or proof of COVID-19 diagnosis within certain time-periods. Before travelling, travellers should be strongly advised to check the latest COVID-19 restrictions on the official websites of the host country.

For host countries, surveillance, identification of cases, contact tracing and quarantine of contacts remain key cornerstones for monitoring the epidemiological situation and preventing a surge of cases after the event.

Health promotion and risk communication messaging alongside non-pharmaceutical interventions such as physical distancing and measures to avoid crowding as well as environmental, respiratory and hand hygiene should be strictly practiced at all times, both outside and inside sporting venues. Testing strategies for COVID-19 should be established at or near the venues depending on the agreed national policy for access.

If the policy in the hosting country is to allow approximately >50% capacity in the stadiums, then the use of face masks by the attendees should be strongly considered even if the stadium is an open space venue. EU/EEA travellers with significant underlying conditions should be discouraged from attending. In addition, any person with COVID-19 compatible symptoms should not attend match or post-match events, irrespective of their vaccination status.

ECDC enhanced Epidemic Intelligence activities on the Euro 2020 event will take place between 4 June and 16 July 2021 and reports provided in the weekly Communicable Disease Threats Report (CDTR).

# Risk communication

With the combination of increasing but still sub-optimal COVID-19 vaccination rates, decreased but still widespread transmission of the virus (including community transmission of several VOCs), and a general, EU-wide relaxation in NPIs, the environment for risk communication activities has become challenging. There is the possibility of an upsurge in the number of infections, and potentially, therefore, for the need to a return to more restrictive NPIs. This would be unpopular both with the general public, who may be struggling with the continuation of NPIs and are anticipating their relaxation, and with the business community, which is looking forward to an irrevocable return to more predictable economic conditions [78].

Within this context, it is important for people to understand that the pandemic is not yet over, and that everything we have collectively achieved in bringing down infection rates must not now be wasted by letting down our guard prematurely. It is important for people to be mindful of the risk posed by certain activities, in particular in relation to the '3 Cs' [79]. Crowded places, close-contact settings, and confined/enclosed spaces. Two key areas may need particular consideration:

- **Public spaces and large gatherings:** The public needs to be informed about, and to accept the safety measures that will be put in place for large sports, music and cultural events that are expected to be held over the summer. Minimising the risk of infection at these events is essential if an upsurge in infections is to be avoided [80].
- **Travel:** In order to minimise the potential spread of infection (and especially of VOCs) across the EU, people may want to consider whether their journey is really necessary – even if it is legally permitted. If they do decide to travel, it is essential that they consider how they can undertake their journey as safely as possible. Further, there is currently a range of different travel restrictions between different EU countries, and citizens will need clear and easy to access to information regarding requirements and measures in place at their destination. In addition, people relying on a negative COVID-19 test result need to understand that this only reflects infection status at the time the test was taken. Subsequent exposure to the virus remains a risk that could render the snapshot test result outdated.

Communication around vaccination needs to strike a balance between the encouraging news on effectiveness of vaccination with caution regarding current unknowns and the related need to remain vigilant. Evidence from real-life usage of COVID-19 vaccines is confirming high effectiveness against symptomatic and severe disease, as well as against PCR-confirmed infection [19], and data also point to correlation between increasing vaccination uptake in all age groups and decreasing mortality in specific age groups [81]. This good news needs to be promoted but balanced with the uncertainties regarding the impact of the vaccines on transmission, duration of protection, and possible protection against emerging SARS-CoV-2 variants [19]. In addition, the vaccine rollout and the epidemiological situation varies across countries. Therefore, people who are fully vaccinated need to be mindful that there is still a potential risk that they could transmit the virus to people who have not yet been or who cannot be vaccinated. Until a high proportion of the population is fully protected, other public health measures will need to remain in place.

As vaccination progresses in the EU/EEA towards the wider population, and as vaccine supply begins to outstrip demand, countries may face challenges in achieving high immunisation rates. This can be related to issues of vaccine acceptance, barriers to access, and perception of low risk from disease in some people. To optimise vaccination uptake, communication and community engagement efforts need to be enhanced, in order to build local vaccine acceptability and confidence, and overcome cultural, socioeconomic, and political barriers that lead to mistrust and hinder uptake [82]. Strategies can include:

- Reminding people of the importance of getting vaccinated to protect themselves and protect others: 'Nobody is safe until everybody is safe' [83];
- Encouraging people to support family and friends who are uncertain about vaccinating, or who face difficulties in accessing services [84];
- Monitoring acceptance and potential barriers through behavioural insights research [85], thereby informing communication strategies;

- Making vaccines available in safe, familiar, and convenient settings in order to facilitate uptake [86];
- Applying strategies to foster demand, including persuasive communication and 'nudge' or default option approaches that seek to encourage behaviour adoption, overcome barriers, and maintenance of behaviour change [87];
- Addressing misinformation circulating that can impact vaccine uptake [88];
- Reminding people of the importance of receiving the full vaccination course (for 2-dose recommendations) to ensure adequate long-term protection.

As vaccine roll out progresses, pharmacovigilance structures will continue to monitor any potential adverse events following immunisation. Early communication about possible side effects, as well as rapid investigation of any safety signals and transparent communication of results will be key to ensure continued community trust in the vaccination programme [89].

# Knowledge gaps

Much of the evidence presented here regarding the SARS-CoV-2 variants is based on unpublished data, which has not been peer-reviewed yet and is evolving daily. Therefore, there are still many knowledge gaps and major uncertainties regarding the interpretation of the data and conclusions.

Major knowledge gaps on virus variants that should be addressed urgently by public health authorities and scientists include the following:

- Incidence of variants in EU/EEA populations and elsewhere, where sufficient sequencing is not available;
- Clinical presentation (e.g. infection severity) and epidemiological profile (affected population groups);
- Competitive advantage of different variants, and consequences of co-circulation;
- Unknown genetic markers related to receptor binding, infectivity, severity, etc.;
- Antigenic characteristics of variant viruses;
- Incidence of re-infections or breakthrough infections following vaccination;
- Transmissibility between humans;
- Binding properties to human receptors, including ACE2 receptors;
- Cross-protection, susceptibility and immunity of the population;
- Impact on effectiveness and safety of available COVID-19 vaccines and candidates in development;
- Duration of protection for a single dose of COVID-19 vaccines (in a two-dose schedule) and the potential for waning immunity;
- Impact on possible treatment options (e.g. convalescent sera and antibodies);
- Possible animal reservoir (species) being a risk for adaptive mutations and an ongoing source of infection for humans (e.g. mink).

# Limitations

This assessment is undertaken based on information known to ECDC at the time of publication and has several key limitations, reason why it should be interpreted with caution taking into account the national and sub-national contexts.

The epidemiological data used in this assessment are dependent on availability from EU/EEA countries through surveillance reporting or publicly available websites. The data not only reflect the epidemiological situation but are also dependent on local testing strategies and local surveillance systems.

It is important to consider the time lag between infection, symptoms, diagnosis, case notification, death, and death notification, as well as the time lag for reporting to the EU level. Assessing the impact of response measures is complex due to the implementation of different components of NPIs and the pace of implementation for vaccination programmes.

The natural evolution of the virus (including the spread of mutated versions of the virus), compliance with measures, cultural, societal, environmental, and economic factors will all continue to play a role in the dynamics of disease transmission. There is still limited knowledge and uncertainty around VOCs. The assessment of the future trend of disease transmission is limited by the lack of knowledge from previous outbreaks.

# Source and date of request

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All experts have submitted declarations of interest, and a review of these declarations did not reveal any conflict of interest.

# Disclaimer

ECDC issues this risk assessment document based on an internal decision and in accordance with Article 10 of Decision No 1082/13/EC and Article 7(1) of Regulation (EC) No 851/2004 establishing a European centre for disease prevention and control (ECDC). In the framework of ECDC's mandate, the specific purpose of an ECDC risk assessment is to present different options on a certain matter. The responsibility on the choice of which option to pursue and which actions to take, including the adoption of mandatory rules or guidelines, lies exclusively with the EU/EEA Member States. In its activities, ECDC strives to ensure its independence, high scientific quality, transparency and efficiency.

This report was written with the coordination and assistance of an Internal Response Team at the European Centre for Disease Prevention and Control. All data published in this risk assessment are correct to the best of our knowledge at the time of publication. Maps and figures published do not represent a statement on the part of ECDC or its partners on the legal or border status of the countries and territories shown.

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# Annex 1

## Variants of concern

ECDC regularly assesses new evidence on variants detected through epidemic intelligence, rules-based genomic variant screening, or other scientific sources. Currently, five variants designated as VOCs by ECDC are under surveillance in the EU/EEA and around the world: B.1.1.7 (Alpha), B.1.1.7+E484K, B.1.351 (Beta), P.1 (Gamma) and B.1.617.2 (Delta). Another seven SARS-CoV-2 variants are considered variants of interest (VOI) by ECDC and additional variants are being monitoring [90].

### B.1.1.7 (Alpha)

#### *Transmissibility*

Several studies provide evidence of increased transmissibility of B.1.1.7 [90-93], based on contact tracing data from the UK. Attack rates are around 10-55% higher across most age groups when the case is infected with the B.1.1.7 variant compared to earlier circulating variants in the UK [94].

#### *Severity*

Based on studies in the UK and Denmark, B.1.1.7 is associated with increased severity and mortality. The hazard of death associated with B.1.1.7 is 61% (95%CI 42-82%) higher than with pre-existing variants [95] and infection with lineage B.1.1.7 is associated with an increased risk of hospitalisation compared to other lineages (adjusted odd ratio (OR) 1.64 (95%CI 1.32-2.04)) [96].

#### *Immunity, reinfection and vaccination*

Sera from subjects immunised using the Vaxzevria vaccine showed reduced neutralisation activity against the B.1.1.7 VOC compared with a non-B.1.1.7 lineage *in vitro*, but the vaccine showed efficacy against the B.1.1.7 VOC. Clinical vaccine efficacy against symptomatic infection was 70.4% (95% CI 43.6–84.5) for B.1.1.7 and 81.5% (95%CI 67.9–89.4) for non-B.1.1.7 lineages [97]. For the Comirnaty vaccine the estimated effectiveness against infection with the B.1.1.7 VOC was 89.5% (95%CI 85.9-92.3) at 14 or more days after the second dose [27] compared to a vaccine effectiveness at seven days or longer after the second dose of 95.3% against any SARS-CoV-2 infection [15].

A study in the UK evaluated longitudinal symptom and test reports spanning a three-month period (28 September-27 December 2020) from 36 920 users of the COVID Symptom Study app which had previously tested positive for COVID-19. Although they observed cases of reinfections (0.7% [95%CI 0.6-0.8]), they did not find evidence for the reinfection rate being higher for the B.1.1.7 variant compared to other pre-existing variants [98].

### B.1.1.7+E484K

The data about the transmissibility, severity and immunity of this variant are still very limited.

However, the E484K mutation of the spike protein has been associated with a reduction in neutralisation activity by convalescent and vaccinee sera in multiple studies. For instance, this mutation was shown to reduce the antibody neutralization compared to a wild type variant when introduced in the USA-WA1/2020 background [99]. Another study evaluated the neutralizing activity against SARS-CoV-2 variants of the serum of healthcare workers vaccinated with CoronaVac. They found that the neutralization efficiency was significantly decreased for viruses with the B.1.351, P.1 or B.1.526 genetic backgrounds (which all carry the E484K spike protein change) compared to B.1.1.7 and B.1.429 (which do not carry the change) [100].

### B.1.351 (Beta)

#### *Immunity, reinfection, vaccination*

A study from Qatar showed that the effectiveness of Comirnaty against any documented infection with the B.1.351 variant was 75.0% (95% CI 70.5-78.9) at 14 or more days after the second dose [101].

Another study investigated the efficacy of Vaxzevria in South Africa with a multi-centre, double-blind, randomised controlled trial [23]. A two-dose regimen of this vaccine did not show protection against mild-to-moderate COVID-19 caused by the B.1.351 variant. In a secondary-outcome analysis, efficacy against B.1.351 was not evident (vaccine efficacy, 10.4%; 95% CI, −76.8 to 54.8). No cases of hospitalisation for severe Covid-19 were observed in the study, hence, the trial findings are inconclusive with respect to whether Vaxzevria protects against severe Covid-19 caused by infection with the B.1.351 variant.

### P.1 (Gamma)

#### *Transmissibility*

In a recent study the epidemiological characteristics of P.1 and of other lineages endemic in Manaus, Brazil were modelled using a two-category (P.1, non-P.1) Bayesian model. P.1 was estimated to be 1.7 to 2.4-fold more transmissible than other locally circulating variants [102].

### *Immunity, reinfection, vaccination*

A study published in Science on May 2021 estimated, with a modelling approach, the protection against reinfection by P.1 or non-P.1 variants. P.1 can evade 21 to 46% of protective immunity elicited by a previous infection (with a non-P.1 variant) compared to other variants [102].

Another study evaluated the levels of P.1 neutralization following natural infection and vaccination with CoronaVac, an inactivated COVID-19 vaccine developed by the Chinese company Sinovac Biotech. The vaccine has been approved in several countries, amongst them China, Brazil, Turkey, Mexico, Thailand and others, but has not been authorised for use in the EU. Plasma from COVID-19 convalescent donors had 6-fold less neutralizing activity against P.1 compared to the B-lineage. Moreover, five months after booster immunization with CoronaVac, plasma from vaccinated individuals failed to efficiently neutralize the P.1 variant. This suggests that P.1 may escape from neutralizing antibodies derived from previously circulating variants of SARS-CoV-2 [26].

## B.1.617.2 (Delta)

### *Transmissibility*

Compared to B.1.1.7, B.1.617.2 is highly likely to be more transmissible based-on epidemiological and in-vitro data. A comparison of secondary attack rates (including in households) of B.1.1.7 and B.1.617.2 showed that B.1.617.2 has higher rates of secondary attack compared to B.1.1.7. However, these data were not yet corrected for vaccination status [6].

### *Severity*

Analyses of data from England and Scotland showed an increased risk of hospitalisation among cases of B.1.617.2. However, the magnitude of the change in risk and link to vaccination are not yet clear and confirmatory analyses are needed [103,104].

### *Immunity, reinfection, vaccination*

In a recent pre-print [28] the effectiveness of Vaxzevria and Comirnaty was compared for the VOCs B.1.1.7 and B.1.617.2. With one dose, vaccine effectiveness dropped from 51.1% for B.1.1.7 (95%CI 47.3-54.7) to 33.5% for B.1.617 (95%CI 20.6-44.3), with the two vaccines showing similar results. With two doses of Vaxzevria, the effectiveness went down from 66.1% (95%CI 54.0-75.0) for B.1.1.7 to 59.8% (95%CI 28.9-77.3) for B.1.617.2. Finally, with two doses of Comirnaty the effectiveness went down from 93.4% (95%CI 90.4-95.5) for B.1.1.7 to 87.9% (95%CI 78.2-93.2) for B.1.617.2. The authors also compared these results with those from another study [27] which investigated effectiveness of the Comirnaty vaccine against the B.1.1.7 and B.1.351 variants. They concluded that the effectiveness against B.1.617.2 of the Comirnaty vaccine after a full course lies between the ones observed for B.1.1.7 and B.1.351. At the moment data are insufficient to assess vaccine effectiveness against severe disease.

# Annex 2

## Methods for classification of the epidemiological situation in EU/EEA countries

**First, the current weekly value** is used to assign a score (1-4) to each of five indicators. The thresholds used for indicators 1, 2, 4 and 5 are informed by those published in WHO guidance https://www.who.int/publications/i/item/considerations-in-adjusting-public-health-and-social-measures-in-the-context-of-covid-19-interim-guidance, corresponding to different levels of community transmission. The WHO thresholds have been modified so they work with 14-day rates and further adapted (test positivity thresholds have been lowered) where appropriate to the observed epidemiological situation in the EU/EEA since week 40, 2020. Indicator 3 is a combined hospital/ICU indicator, which utilises available data for each country in following order of priority: hospital admission > ICU admission > hospital occupancy > ICU occupancy. Thresholds for these were determined separately for admissions and current occupancy through internal expert agreement at ECDC.

| Indicator | | Domain | 1 | 2 | 3 | 4 | Source |
|---|---|---|---|---|---|---|---|
| 1. 14-day case notification rates per 100k among people aged 65+ years | | Severity | <20 | 20 - <50 | 50 - <150 | ≥150 | TESSy |
| 2. 14-day COVID-19 death rate per million | | Severity | <20 | 20 - <40 | 40 - <100 | ≥100 | EI |
| 3. COVID-19 hospital/ICU indicator, current value as a proportion of the peak value in the country to date (%) | Weekly admissions rate per 100k | Severity | <10 | 10 - <25 | 25 - <50 | ≥50 | TESSy or public online sources |
| | Current occupancy (mean weekly occupancy per 100k) | | <25 | 25 - <50 | 50 - <75 | ≥75 | Public online sources |
| 4. 14-day COVID-19 case notification rate per 100k (all ages) | | Intensity | <40 | 40 - 100 | 100 - 300 | ≥300 | EI* |
| 5. Test positivity (%) from all national reported tests and cases | | Intensity | <2 | 2 - <4 | 4 - <10 | ≥10 | TESSy and EI |

** TESSy data were used for case rates in France due to a change in the surveillance system which led to negative case values being reported by EI.*

**Second**, the above scores are **adjusted based on the current trend** of each indicator, with -0.5, 0 or 1 added to each score for decreasing, stable or increasing trends, respectively. As a result, each indicator is can have a possible score of between 0.5 and 5.

The following definitions of trends have been in use for many months in ECDC's weekly country overview report:

- 14-day (two-week) notification rates for cases (all ages and age-specific) per 100 000 and deaths per 1 000 000 population. Trend for week W compares rate on week W with that in week W-1. Countries with low rates (cases: <10, deaths: <2) or which do not meet the criteria below are classified as stable trend. Increasing/decreasing trend: relative rate change (cases: >10%, deaths: >10%) OR absolute rate change (cases: >10, deaths: >5).
- Test positivity (%) = number of confirmed cases/number of tests done per week. Trend for week W compares positivity on week W with that in week W-1. Stable: relative change =<10% or absolute change =<1 percentage points. Increase/decrease: relative positivity change >10% and absolute positivity change >1 percentage points.
- Hospital or ICU admission rate: Trend for week W compares the admission rate per 100 000 population on week W with that in week W-1. Countries with low rates (<10% of the maximum weekly rate during the pandemic) or which do not meet the criteria below are classified as stable trend. Increasing/decreasing trend: relative rate change >10%
- Hospital or ICU occupancy. Trend for day D compares the mean daily occupancy rate per 100 000 population for all days in week W with that in week W-1. Countries with low occupancy (<10% of the maximum 7-day rate during the pandemic) or which do not meet the criteria below are classified as stable trend. Increasing/decreasing trend: relative rate change >10%.

**Thirdly**, a score for each domain (severity and intensity) is obtained from the mean of the trend-adjusted scores for each contributing indicator. The score for 14-day case notification rates is double-weighted (in both the numerator and denominator) within the intensity domain to make up for the fact that there are only two intensity indicators (compared to three severity indicators) and to give it greater weight than test positivity, which is becoming less reliable due the widespread use of antigen tests.

If data are missing for a given indicator it is not included in the calculation of the mean domain score. This results in a possible mean domain score of between 0.5 and 5.

**Finally,** the scores for each domain are considered to have equal weighting so are summed to give a final score per country per week of between 1 and 10. This range is divided into quartiles which correspond to the four categories:

1. Low: 1 to <3.25,
2. Moderate: 3.25 to <5.5,
3. High: 5.5 to <7.75
4. Very high: 7.75 to 10.

A **worked example** is shown below

| Domain | Indicator | Weekly value | Score (value) | Trend adjustment | Weight | Final score | Domain score | Total score | Category |
|---|---|---|---|---|---|---|---|---|---|
| **Severity** | Cases 65+yr | 70 | 3 | -0.5 | 1 | 2.5 | 1.8 | 3.8 | Moderate |
| | Hosp/ICU | 12 | 2 | -0.5 | 1 | 1.5 | | | |
| | Death rate | 30 | 2 | -0.5 | 1 | 1.5 | | | |
| **Intensity** | Case rate | 118 | 3 | -1 | 2 | 5 | 2 | | |
| | Positivity | 0.3 | 1 | 0 | 1 | 1 | | | |

23 April 2021 Corr[1]
EMA/234525/2021
European Medicines Agency

# Annex to Vaxzevria Art.5.3 - Visual risk contextualisation

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# 1. Introduction

To support national authorities making decisions on how to best use the vaccine in their territories, EMA's human medicines committee (CHMP) has further analysed available data to put the risks of very rare blood clots (thrombosis with thrombocytopenia syndrome, TTS) in the context of the benefits for different age groups and different rates of infection.

The analysis will inform national decisions on the roll out of the vaccine, taking into account the pandemic situation as it evolves and other factors, such as vaccine availability. The analysis could change as new data become available.

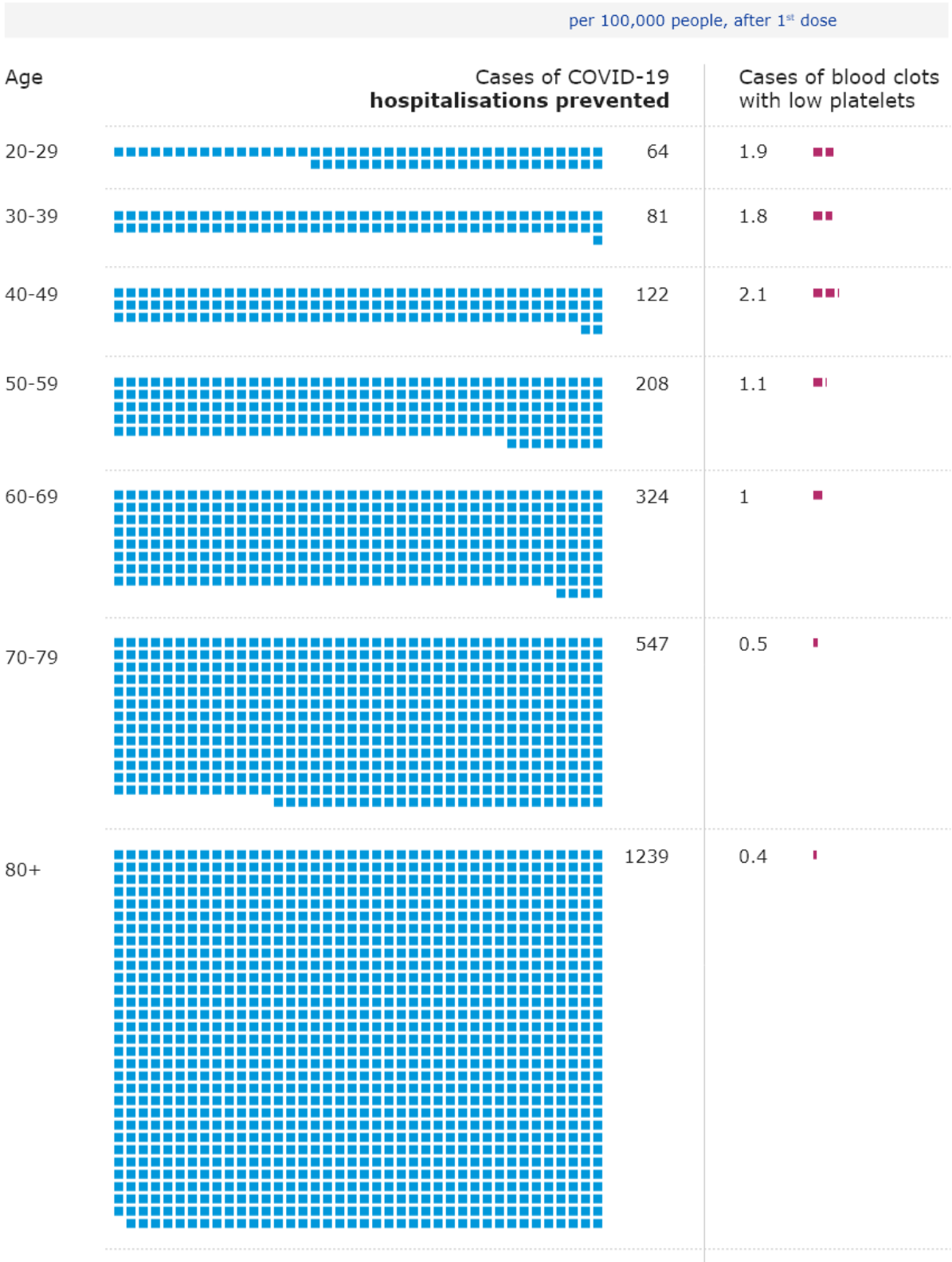
The Committee analysed the benefits and the risk of unusual blood clots with low platelets in different age groups in the context of the monthly[1] infection rate: low (55 per 100,000 people), medium (401 per 100,000 people) and high (886 per 100,000 people).

The analysis looked at prevention of hospitalisations, ICU admissions and deaths due to COVID-19, considering an 80% vaccine effectiveness over a period of four months. The details of the full analysis and methodology are available in the assessment report which will be published shortly.

[1] Correction on page 2 to state that the infection rates were monthly and not daily rates

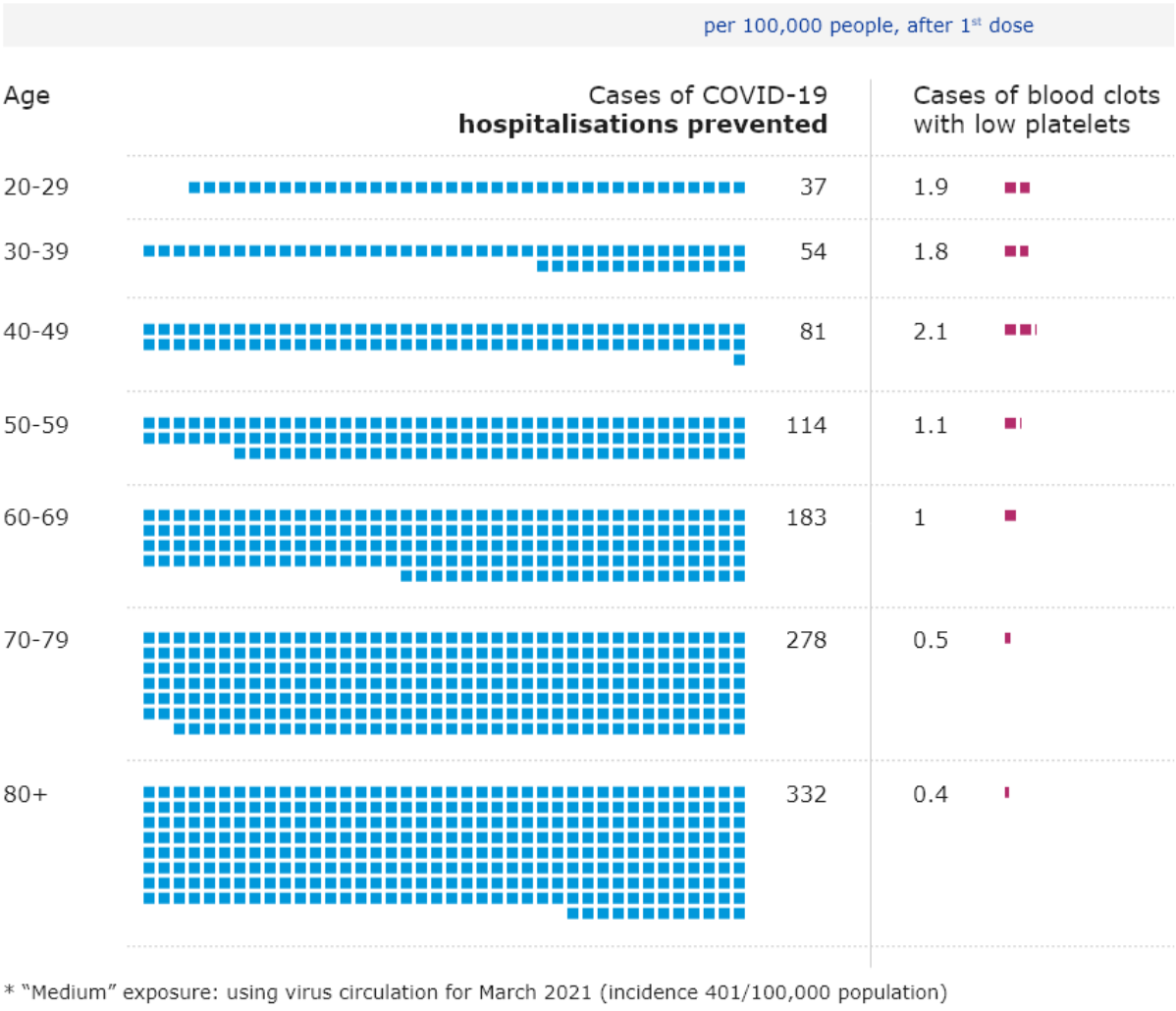
## 2. COVID-19 hospitalisations prevented with Vaxzevria compared with unusual blood clots with low platelets

### High infection rate*



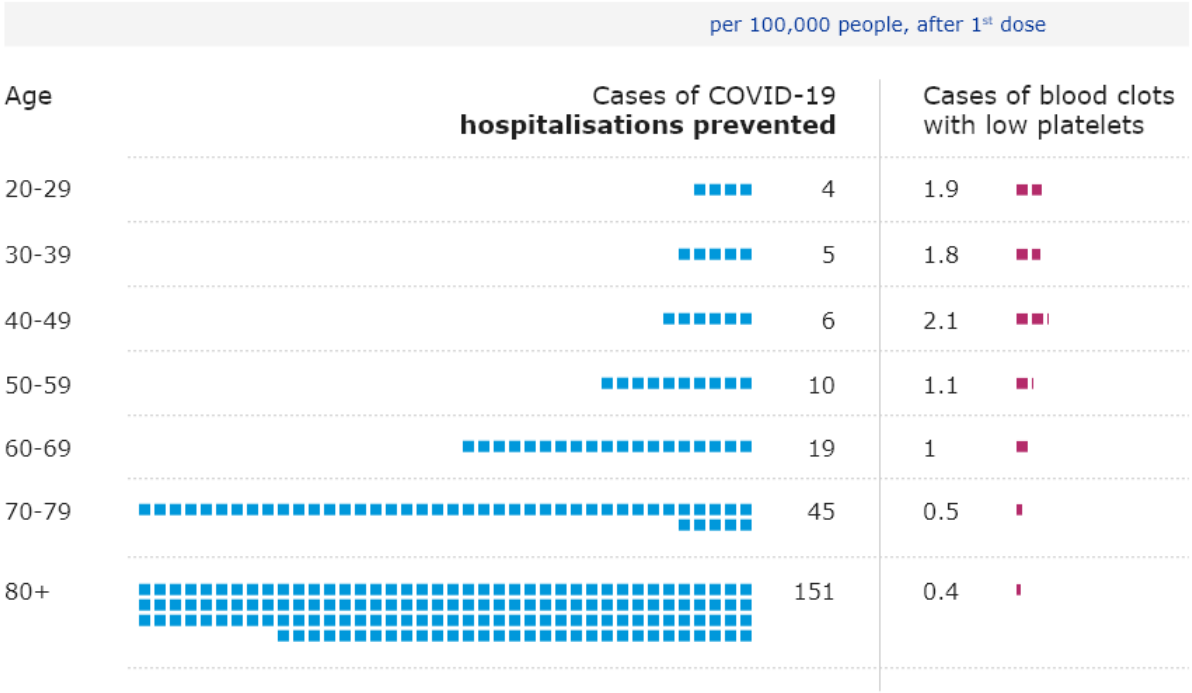

* "High" exposure: using virus circulation for January 2021 (incidence 886/100,000 population)

## Medium infection rate*




* "Medium" exposure: using virus circulation for March 2021 (incidence 401/100,000 population)

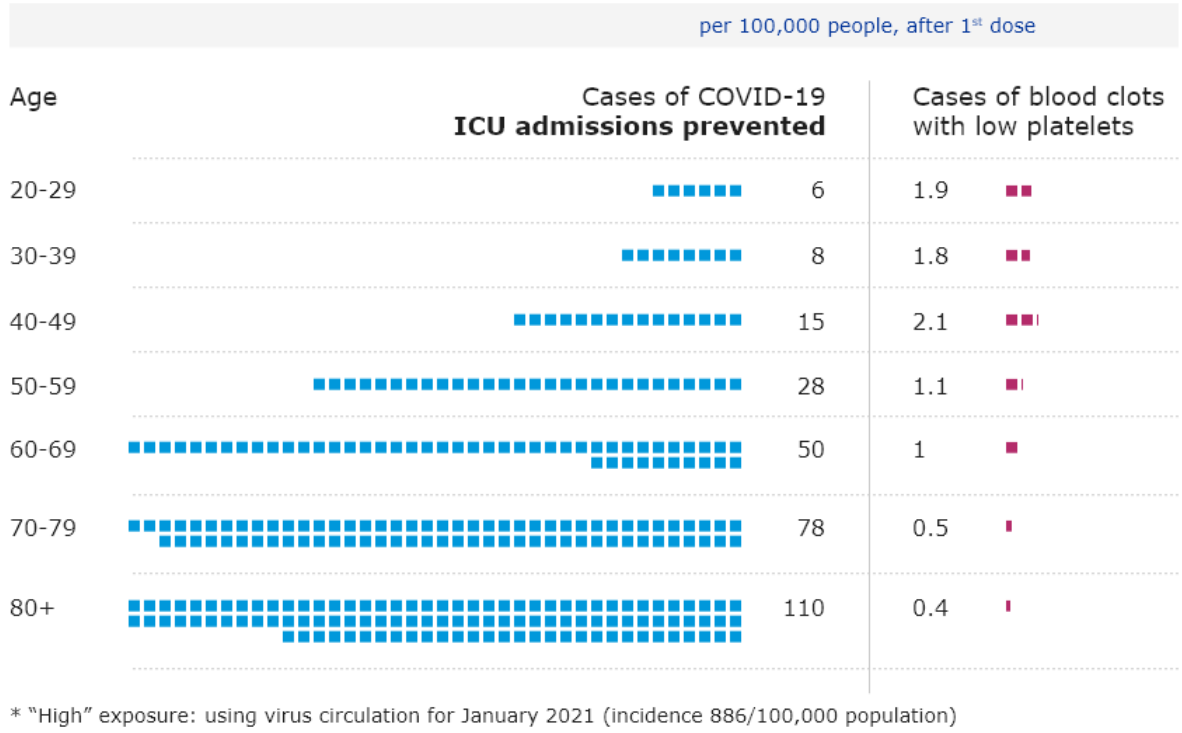
## Low infection rate*




* "Low" exposure: using virus circulation for September 2020 (incidence: 55/100,000 population)

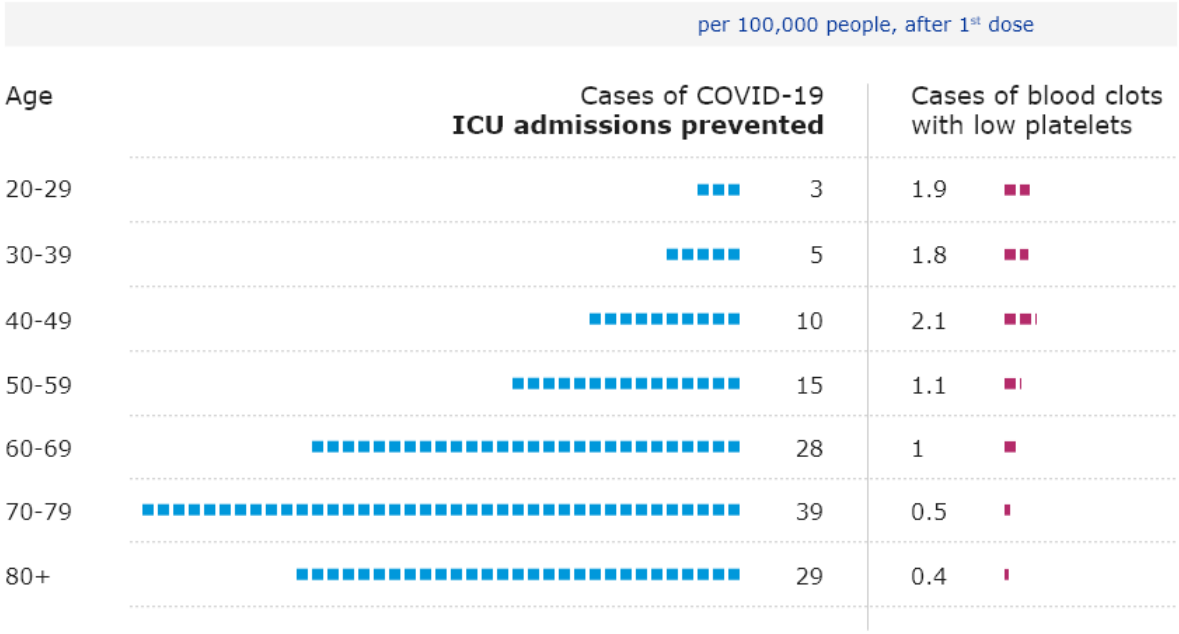
# 3. COVID-19 ICU admissions prevented with Vaxzevria compared with unusual blood clots with low platelets

## High infection rate*



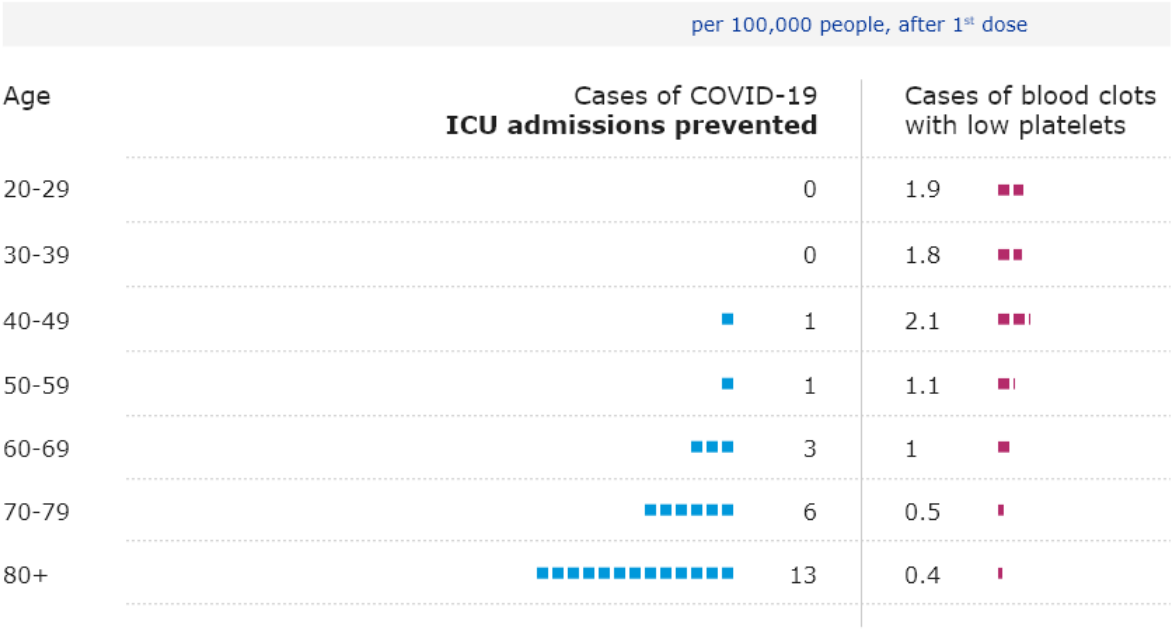

* "High" exposure: using virus circulation for January 2021 (incidence 886/100,000 population)

## Medium infection rate*




* "Medium" exposure: using virus circulation for March 2021 (incidence 401/100,000 population)

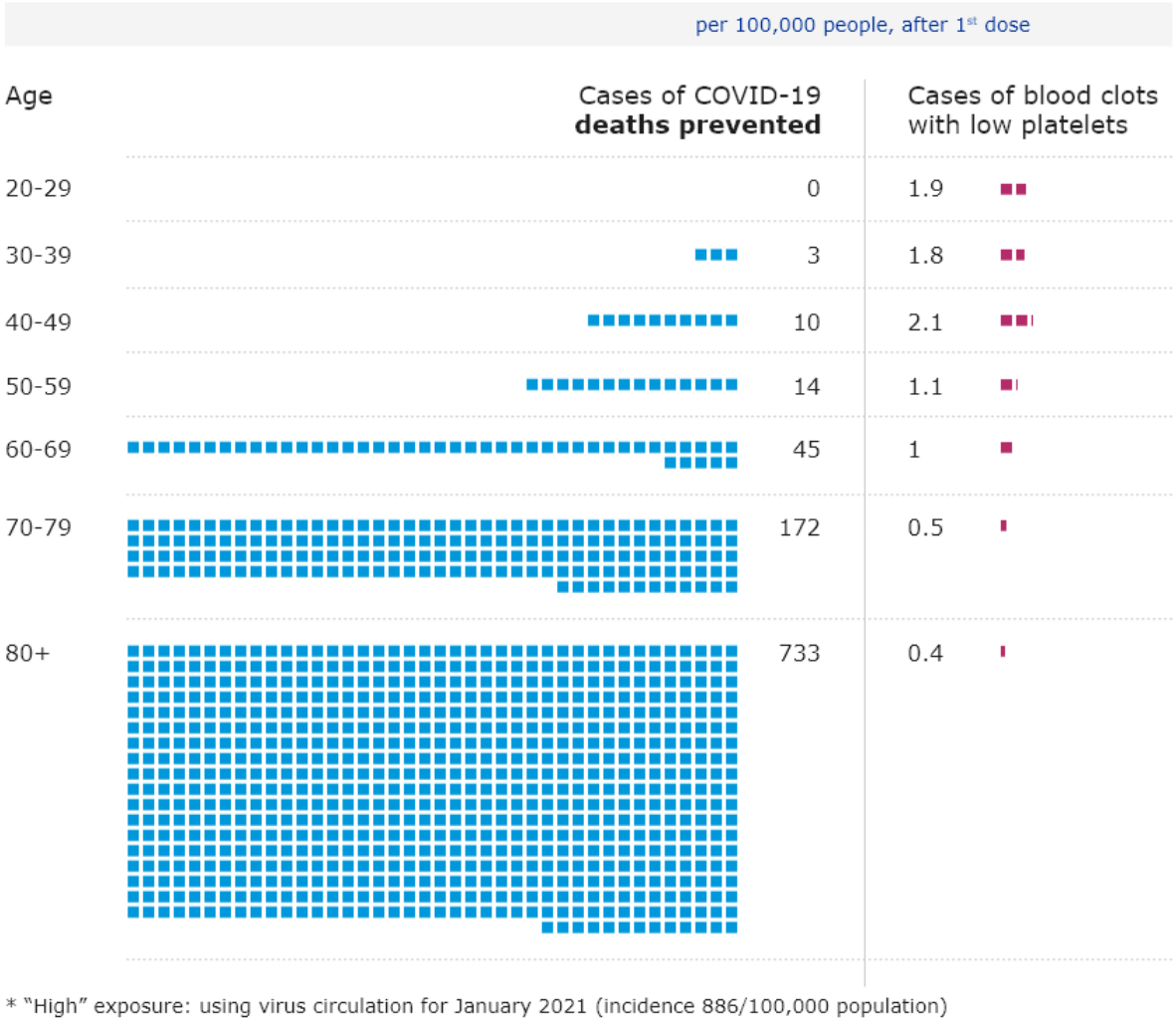
## Low infection rate*




* "Low" exposure: using virus circulation for September 2020 (incidence: 55/100,000 population)

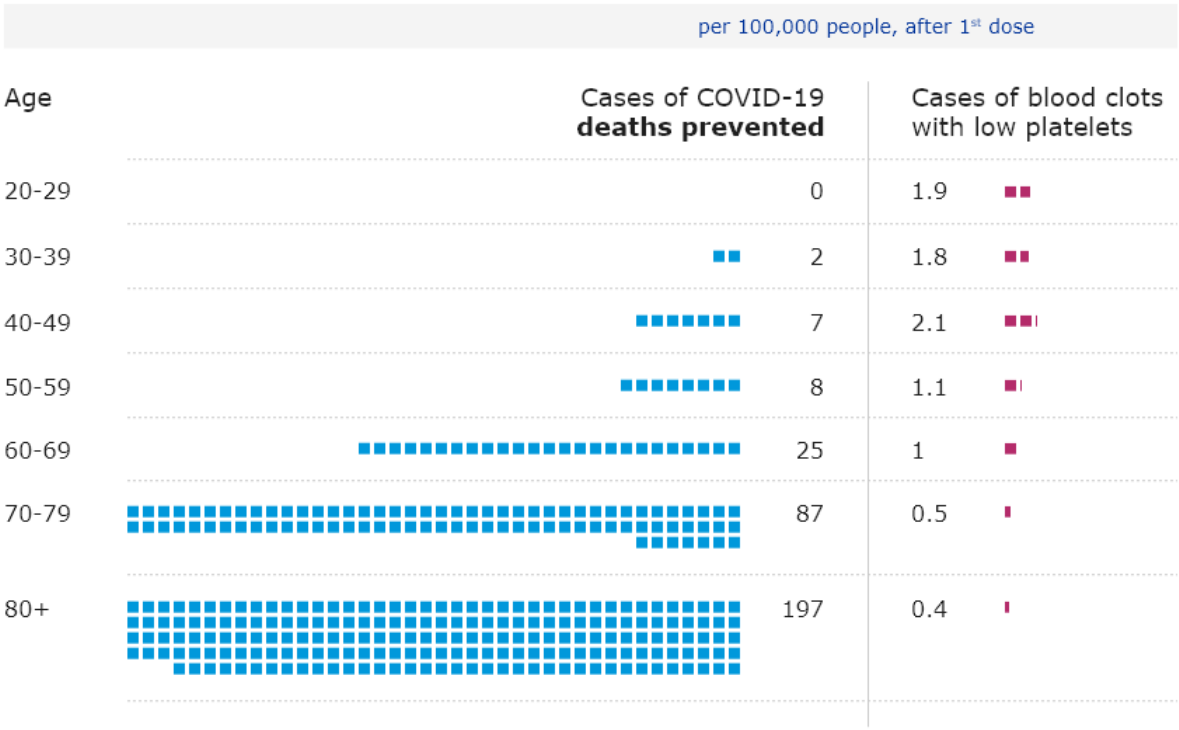
# 4. COVID-19 deaths prevented with Vaxzevria compared with unusual blood clots with low platelets

## High infection rate*



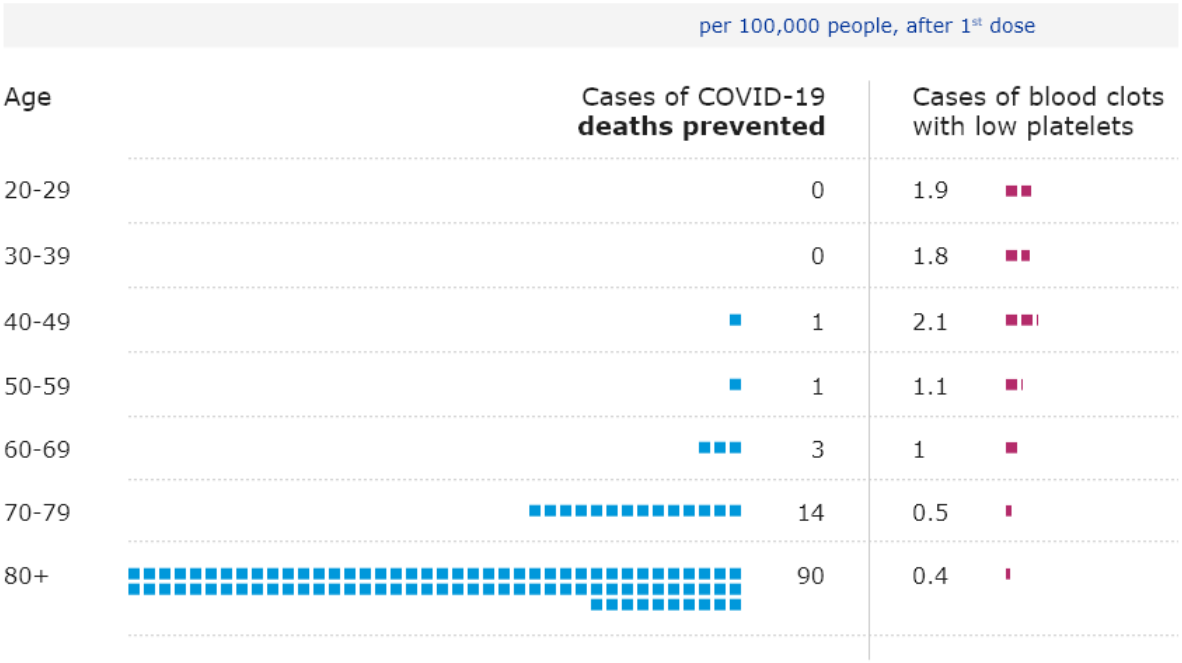

* "High" exposure: using virus circulation for January 2021 (incidence 886/100,000 population)

## Medium infection rate*




* "Medium" exposure: using virus circulation for March 2021 (incidence 401/100,000 population)

## Low infection rate*




* "Low" exposure: using virus circulation for September 2020 (incidence: 55/100,000 population)

# 5. Acknowledgements

These visuals are based on similar ones produced by the Winton Centre for Risk and Evidence Communication. Additional risk-communication experts and healthcare professional representatives were consulted during the preparation of these visuals:

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# Using Italian data to illustrate the potential harms and benefits of the AstraZeneca vaccine.

After request from a science reporter in Italy, we have produced a similar graphic for Italy to those we have produced with UK data to illustrate the potential benefits and harms of the AstraZeneca COVID-19 vaccine.

There are two elements to the graphic and the methodology is broadly based on the methodology used in the assessment of the UK harm / benefits.

**Potential harms**: This was taken directly from the European Medicines Agency Assessment from 23 April 2021 and represent exact rates for each age bracket (i.e. no modelling as we did for the UK data).

**Potential benefits**: This was calculated in the following way:

- All cases aged ≥ 20 years tested positive for SARS-CoV-2 infection between 21 October 2020 and 20 November 2020 (symptomatic or asymptomatic) in Italy were collected. These are the cases notified to the COVID-19 Italian Surveillance System (information extracted on 21 April 2021). Hospitalisations and admissions to ICU were counted if occurred within 28 days since the date of testing positive.
- A constant (not age dependent) underreporting rate of 25% was assumed. This is in line with previous Italian estimates. This is because, unlike with the UK Office of National Statistics' Infection Survey, in Italy there is no randomised population testing to give a more direct assessment of the number of cases of COVID-19 (including asymptomatic cases).
- The direct positive case to ICU percentages were used for each age group to determine risk of entering ICU.
- A vaccine efficacy of 80% at reducing ICU admissions was used.
- A high rate of 200 new infections per 100,000 per day was used; a medium rate of 100 new infections per 100,000 per day was used; a low rate of 20 new infections per 100,000 per day was used.
- Benefits were calculated over 16 weeks.