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RAPID REVIEW OF THE EVIDENCE ON A COVID-19 BOOSTER DOSE AFTER A PRIMARY VACCINATION SCHEDULE

REPORT FOR THE TASK FORCE VACCINATION

(VERSION WITH SUMMARY IN DUTCH)

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1 VOORWOORD

Op het moment van het schrijven van dit advies is België vergevorderd in haar vaccinatiecampagne. In vergelijking met andere landen halen we een hoge vaccinatiecompliantie. Technologisch hebben we hiervoor hoog werkzame en veilige vaccins kunnen gebruiken die vooral via de vaccinatiecentra aan iedereen van 12 jaar en ouder worden aangeboden.

Volledig gevaccineerde personen zijn in grote mate beschermd tegen ernstige ziekte en overlijden ten gevolge van Sars-CoV-2, inclusief de actueel dominante delta variant. Voornamelijk niet-gevaccineerden hebben nog een risico op ziekenhuisopname en ernstig ziekteverloop. Persisterende inspanningen om ook de resterende vaccinweigeraars alsnog te vaccineren blijven primordiaal om henzelf en hun omgeving te beschermen.

In dit rapport wordt een overzicht gegeven van de actueel beschikbare *evidence* uit verschillende klinische studies: studies over doorbraakinfecties, effect, immunologische respons na primaire vaccinatie, immunologische respons en veiligheid van heterologe vaccinatie en van een extra of boostervaccinatie. We hebben ook een overzicht toegevoegd van de lopende studies in België. Tot slot werd een internationaal overzicht van de uiteenlopende beleidsbeslissingen over een boosterdosis toegevoegd.

Nog steeds lopen er vele klinische studies en blijven de wetenschappelijke inzichten groeien. De exacte duurtijd van de immuniteit na primaire vaccinatie is momenteel een onzekerheid. Een belangrijk probleem is dat we nog steeds niet goed weten hoe we de bescherming tegen Covid-19 kunnen meten (zogenaamd '*correlate of protection*'). De meeste studies beperken zich tot antistofbepalingen, terwijl bijvoorbeeld ook T-cel en B-cel immuniteit belangrijke onderdelen van de bescherming zijn. We kunnen dus momenteel voor immuungecompromitteerde risicopatiënten - waarvan we vermoeden dat ze mogelijks een mindere immuniteit ontwikkelden na de primaire vaccinatie - niet de exacte timing bepalen wanneer een boostervaccinatie dan wel andere maatregelen aangewezen zijn.

Een belangrijk klinisch eindpunt om op te volgen zijn de doorbraakinfecties, Covid-19 infectie en gerelateerde ziekte die ontstaan bij personen na volledig primaire vaccinatie. Meerdere studies, onder meer van Sciensano, toonden voorheen de gunstige effecten van vaccinatie voor de residenten van woonzorgcentra en risicopersonen in het algemeen. De komende maanden verwachten we meer data over eventuele doorbraakinfecties.

Internationaal lopen de beleidsbeslissingen rond een extra/booster vaccinatie sterk uiteen. Sommige landen zoals bijvoorbeeld Israël en het Verenigd Koninkrijk starten pragmatisch, ondanks een hoge vaccinatiewerkzaamheid, versneld met een 3e dosis bij bepaalde groepen. Andere landen zoals Zweden en Denemarken wachten voorlopig meer onafhankelijke *evidence* af.

Dit advies tracht de huidige wetenschappelijke stand van zaken weer te geven om een weloverwogen beleidsbeslissing toe te laten. Daarbij speelt internationaal ook een ethische dimensie. De focus van de vaccinatie verlegt zich meer en meer naar landen met een laag en modaal inkomen via onder meer het Covax-initiatief. Een versnelde ondoelmatige universele toediening van een boosterdosis in landen met een hoog inkomen, zou bijdragen aan een (nog) grotere globale vaccinatie-ongelijkheid. Bovendien vormt een blijvende circulatie van het virus een mogelijke voedingsbodem voor nieuwe varianten.

De Task Force stelt, rekening houdende met de wetenschappelijke onzekerheden, een stapsgewijze aanpak voor met continue verdere evaluatie. Dit advies vergt dan ook een regelmatige update.

2 SAMENVATTING EN BELEIDSAANBEVELINGEN

Inleiding

Infectie met SARS-COV-2 kan asymptomatisch verlopen maar ook leiden tot zeer ernstige Covid-19 ziekte en overlijden. De overdracht van het virus is vooral via de lucht. Vaccins voor de bevolking (vanaf 12 jaar) zijn in een recordtempo ontwikkeld na de start van de pandemie begin 2020. Een toenemend aantal vaccins zijn goedgekeurd en worden nu nog volop uitgerold wereldwijd. Deze preventieve vaccins stimuleren de twee componenten van het immuunsysteem: de humorale immuniteit (d.i. de productie van antilichamen of antistoffen) en de cellulaire immuniteit. Momenteel zijn er 4 basisvaccinaties (of primaire vaccinatieschema's) met een voorwaardelijke marktvergunning van EMA. De basisvaccinatie bestaat uit twee dosissen mRNA vaccin van Pfizer-BioNTech of van Moderna, twee dosissen adenovector vaccin van Astra-Zeneca of een enkele dosis adenovector vaccin van Janssen/Johnson&Johnson.

Welke doeltreffendheid heeft een basisvaccinatie en wat zijn doorbraakinfecties?

In de grootschalige gerandomiseerde studies reduceerde elk van de beschikbare vaccins de kans op infectie (en gepaard gaande het risico op transmissie) met meer dan 50%, het minimum criterium voor markttoelating. Bovendien reduceren de vaccins nog sterker de infecties met ernstige ziekte en overlijden (met ongeveer 90%). Gerandomiseerde onderlinge vergelijkingen van de klinische werkzaamheid van de vaccins ontbreken vooralsnog. De hoeveelheid opgewekte virus neutraliserende antistoffen tegen de circulerende varianten zijn wel hoger na mRNA vaccins dan na adenovector vaccins. Alle vaccins geven frequent tijdelijke milde nevenwerkingen. Dit is ook zo indien (off-label) van vaccin veranderd wordt voor een tweede dosis.

De beschikbare gegevens na toedienen van een extra dosis of boosterdosis (cf. infra) mRNA na basisvaccinatie in studies met risicogroepen tonen geen noemenswaardig verschil in nevenwerkingen na vaccinatie. Ernstige nevenwerkingen bij basisvaccinatie komen zeer zelden voor. Ze verschillen tussen adenovector vaccins (o.a. trombose met lage hoeveelheid bloedplaatjes) en mRNA vaccins (o.a. hartspierontsteking).

Een infectie die nog plaatsvindt na een basisvaccinatie (minimum 1-4 weken na laatste dosis) wordt een doorbraakinfectie genoemd ('*breakthrough infection'*). De gehanteerde definitie van zulke doorbraakinfecties varieert echter in de gepubliceerde studies, wat vergelijking bemoeilijkt.

Welke variabelen kunnen een effect hebben op de vaccinatie doeltreffendheid?

1. **De vaccinatie:** de gebruikte vaccins, de toedieningsweg, de dosis, het bewaringsproces, het toedieningsschema en de tijdsperiode na vaccinatie. Een daling van de bescherming over de tijd wordt *'waning'* genoemd.
2. **De persoon:** het immuunsysteem, leeftijd en geslacht, een voorgeschiedenis van Covid-19 met een specifieke variant en ziekte of behandelingen die maken dat het immuunsysteem van de persoon gecompromitteerd is ("immunocompromised")
3. **Het virus:** de specifieke variant en de hoeveelheid virus waaraan de persoon wordt blootgesteld.

Een aantal van die variabelen hebben we in de hand. De hoeveelheid virus waaraan we worden blootgesteld kan verminderd worden door bv. ventilatie, afstand houden en mondmaskers.

Wat is het verschil tussen een boosterdosis en een extra dosis?

Een klassieke boosterdosis bij vaccinatie wordt toegediend minimum zes maand na de laatste dosis van de basisvaccinatie. Wanneer een extra dosis wordt toegediend binnen de zes maand wordt er over een extra dosis gesproken in deze tekst. In deze situatie spreken we dus van een uitbreiding van het basisvaccinatieschema en wordt minder op een echt booster effect gerekend. In dit rapport beschouwen we de studies over een extra dosis en de studies over een booster dosis. Met de term "extra/booster dosis" worden beide concepten bedoeld.

EMA heeft nog geen enkel vaccin goedgekeurd met de indicatie extra dosis of booster dosis, m.a.w. zulke toediening is momenteel nog off-label. FDA heeft een bijkomende dosis voor bepaalde immuungecompromitteerde patiënten goedgekeurd op 12 augustus. Vaccins op basis van nieuwe varianten van het virus zijn in ontwikkeling maar momenteel ook nog niet goedgekeurd.

Mogelijke eindpunten voor doeltreffendheid van een extra/booster dosis mRNA vaccin

Bij de evaluatie van doeltreffendheid dient er telkens een onderscheid te worden gemaakt tussen enerzijds de bescherming tegen infectie en de mogelijkheid tot transmissie (‘*sterile immunity’*) en anderzijds de bescherming tegen ernstige Covid-19 ziekte op individueel vlak. Mogelijk is de optimale vaccinatiestrategie verschillend voor elk van deze doelstellingen. Zo kan een extra/booster dosis met mRNA de hoeveelheid virus-neutraliserende antistoffen verhogen. Wellicht kan dit het aantal doorbraakinfecties en de verdere transmissie doen dalen, tenminste voor varianten die voldoende gevat worden.

Wat betreft individuele bescherming tegen ernstige Covid-19 bij nieuwe varianten is een brede cellulaire immuniteit wellicht belangrijk. Personen die de vaccinatie kregen na het doormaken van een natuurlijke infectie hebben theoretisch een bredere basis als bescherming in vergelijking met gevaccineerde personen die nooit een infectie doormaakten. Er is een zekere vrees dat het immunologische effect van een extra/booster dosis met eenzelfde vaccin in deze laatste groep eerder kwantitatief zal zijn (verhoogde antistoffen) en niet in de breedte (kwalitatief, cel-immuniteit). Doeltreffendheidsstudies na extra/booster dosis mRNA vaccin bij wie Covid-19 doormaakte, ontbreken alsnog om deze theoretische overwegingen te toetsen.

Is er een rol voor het meten van een ‘correlate of protection’ alvorens een extra/booster dosis te geven?

Studies van doorbraakinfecties in groepen met een verschillend basisvaccinatieschema en/of specifieke patiëntkenmerken zijn zeer relevant. In een grootschalig onderzoek in Israël werden lagere antistoffen gevonden bij personen met een doorbraakinfectie na volledige Pfizer basisvaccinatie in vergelijking met personen met hetzelfde schema zonder doorbraakinfectie. Binnen de doorbraakinfectiegroep was de virushoeveelheid ook nog eens hoger wanneer de persoon lagere antistoffen had.

In een andere studie in Israël onderzocht men 152 doorbraakinfecties die gepaard gingen met een ziekenhuisopname. Opmerkelijk was dat 96% van de opgenomen patiënten minstens een co-morbiditeit hadden (o.a. hoge bloeddruk, hartfalen, chronische nier- of longziekte, dementie, kanker). Bij 24 doorbraakinfecties in de VS bij jongere volwassenen werden geen hospitalisaties gezien en had één op drie een co-morbiditeit.

Indien een eenvoudige test uitsluitsel zou kunnen geven over de bescherming van een persoon na vaccinatie en tegen de huidige variant(en) (‘*correlate of protection’*), zou deze test kunnen gebruikt worden om te bepalen aan welke personen best een extra/booster dosis wordt gegeven (test-en-boost).

Sommigen suggereren om hiervoor de antistoffen in het bloed te meten, bv. anti-RBD IgG (antistoffen gericht tegen het receptorbindend domein van het spike-eiwit van het virus), wat goed correleert met de complexe virus neutralisatietest. Het WHO referentiemateriaal voor de kalibratie van de test resultaten is beschikbaar voor de laboratoria en dit moet de standaardisatie bevorderen. Een combinatie van deze test met een meting van de cellulaire immuniteit lijkt volgens sommigen zinvol bv. bij patiënten met specifieke kankerbehandeling of op chronische hemodialyse, maar die cellulaire testen zijn te complex om grootschalig uit te rollen. Met andere woorden, er is vandaag nog geen gevalideerde test en cut-off waarde die op individueel niveau kan bepalen wie ondermaats beschermd is en een extra dosis of booster dosis nodig heeft. De test-en-boost aanpak is daarom wellicht nog niet voor morgen.

Wat weet men over de effectiviteit van de extra/booster mRNA dosis bij risicogroepen?

Met toenemende leeftijd veroudert ook het immuunsysteem en daalt het aantal cellen dat voor een nieuw immuunantwoord kan zorgen na infectie of vaccinatie (‘immunosenescentie’).

Immuungecompromitteerde personen hebben afweerstoornissen die ofwel zijn aangeboren (eerder zeldzaam) of verworven. Dit kan het gevolg zijn van een ziekte (bv. bij bloedkankers en andere kankers, nierfalen, HIV) of een behandeling (bv. anti-CD20, cytotoxische chemotherapie, immunosuppressiva bij transplantatie of inflammatoire ziekten).

Bij de basisvaccinatie werd daarom gekozen voor een relatief hoge dosis per toediening zodat ook bij hoogbejaarden en immuungecompromitteerde personen een afdoende doeltreffendheid kon verwacht worden.

Hoogbejaarden

Studies in woonzorgcentra vinden bij één op drie bewoners duidelijk lagere hoeveelheden antilichamen na vaccinatie in vergelijking met zorgverleners. Bij grootschalig onderzoek naar doorbraakinfecties na basisvaccinatie is het dan ook niet verwonderlijk dat leeftijd als een risicofactor wordt bevestigd. De bescherming tegen infectie vanaf 7 dagen na een Pfizer basisvaccinatie in woonzorgcentra in Denemarken bij 39 040 bewoners was 64%. Bij zorgpersoneel was dit 90%.

Recente observationele gegevens uit Israel tonen 608 (1.8%) positieve RT-PCR testen bij 33 993 personen met een volledige basisvaccinatie (Pfizer mRNA) over een mediane opvolgperiode van 146 dagen. De proportie personen met een positieve test op het aantal geteste personen neemt toe met de tijd na de basisvaccinatie en met de leeftijd. Er zijn nog geen gegevens over de ernst van die infecties. De analyse veronderstelt dat het testbeleid, de testnoden en de testbereidheid bij alle groepen niet wijzigde met de tijd.

Bij hoogbejaarden zijn er momenteel nog geen resultaten van antistoffen na een extra/booster dosis mRNA, maar het onderzoek loopt, onder andere in Belgische woonzorgcentra.

Orgaantransplantatie

De medicatie gegeven tegen afstoting na orgaantransplantatie onderdrukt ook het immuunantwoord op de vaccinatie. Gemiddeld één op twee patiënten ontwikkelt detecteerbare antistoffen, vooral wanneer er nog voldoende T-helper cellen aanwezig zijn bij de start van vaccinatie. Drie op vier transplantpatiënten die Covid-19 doormaakten reageren dan weer wel zeer goed op het basisvaccinatieschema.

Bij drie studies in Frankrijk van in totaal meer dan 500 transplantpatiënten ziet men een sterke stijging in antistoffen na een derde dosis mRNA vaccin een tweetal maand na basisvaccinatie. De stijging is er vooral in geval er reeds detecteerbare antistoffen zijn na de basisvaccinatie. Indien er na basisvaccinatie geen antistoffen gedetecteerd worden, blijft dit zo na een derde dosis in de drie studies voor respectievelijk 55%, 67% en 73% van de gevallen. Het gaat hier om een extra vaccindosis (2 maanden na basisvaccinatie).

Chronische hemodialyse

Een grote studie in de Verenigde Staten bij chronische hemodialyse patiënten toont dat 20% geen detecteerbare hoeveelheid antistoffen heeft na basisvaccinatie (10 op 353, 2,8% na Moderna, 28 op 293, 9.6% na Pfizer en 15 op 18, 83.3% na Johnson&Johnson). Dit blijkt onafhankelijk te zijn van een vroeger doorgemaakte Covid-19 infectie.

Een Franse studie in 75 chronische hemodialyse patiënten toont een stijging van de antistoffen na een derde dosis Pfizer vaccin, gegeven binnen de drie maand na de basisvaccinatie. Bij degenen die geen detecteerbare antilichamen hadden na de basisvaccinatie resulteerde een derde dosis in detecteerbare antistoffen voor 50% van de patiënten. Het gaat ook hier om een extra vaccindosis (3 maanden na basisvaccinatie).

Oncologie en hemato-oncologie

De aanmaak van vaccingeïnduceerde antistoffen bij patiënten met kanker kan verlaagd en vertraagd zijn, afhankelijk van het type maligniteit en de behandeling. Bij sommige kankerbehandelingen zoals immuuntherapie of hormonale therapie wordt een eerder normale aanmaak van antistoffen gezien. Patiënten met een hematologische maligniteit, o.a. bij behandeling met anti-CD20 of na stamceltransplantatie, maken veel minder antistoffen aan na vaccinatie. Ook cytotoxische chemotherapie leidt tot minder antistoffenproductie en minder specifieke T-cellen. De situatie van het immuunsysteem na twee dosissen mRNA vaccin bij chemotherapie patiënten lijkt sterk op deze na één dosis bij gezonde personen. Daarom wordt verwacht dat een derde mRNA dosis nuttig kan zijn bij patiënten op chemotherapie.

Bij 43 patiënten met bepaalde vormen van hematologische maligniteit kon een derde dosis Pfizer/BioNTech vaccin (78 dagen na basisvaccinatie) de antistoffen sterk doen toenemen, maar alleen bij de 25 patiënten die na de basisvaccinatie reeds detecteerbare antilichamen hadden.

Inflammatoire aandoeningen

Drie studies onderzochten patiënten met inflammatoire aandoeningen, bv. chronisch inflammatoir darmlijden, reumatoide arthritis. Deze patiënten gebruiken medicatie die het immuunsysteem deels onderdrukt. Bij 85% tot 88% van de patiënten werden na basisvaccinatie antistoffen gedetecteerd.

Een andere studie identificeerde 16 doorbraakinfecties bij patiënten met inflammatoire aandoeningen. Zeven patiënten kregen basisvaccinatie met Pfizer-BioNTech, vijf met Moderna en vier met Janssen/Johnson & Johnson. Zes patiënten werden gehospitaliseerd, waarvan 3 onder de 65 jaar. Vier stonden op anti-CD20 behandeling en twee op mycofenolaat. Twee patiënten overleden.

Tot heden zijn er geen studies over het toedienen van een extra mRNA dosis in deze populatie.

Conclusie: kan een extra/booster (mRNA-) dosis het verschil maken?

De beschikbare gegevens duiden erop dat bij risicogroepen met een ernstige afweerstoornis het toedienen van een extra dosis mRNA vaccin kan resulteren in een toename van antistoffen. Ook een sterkere cellulaire immuunrespons is gerapporteerd. Deze hoopgevende resultaten laten toe te hopen op een betere bescherming tegen infectie maar dit is nog niet aangetoond.

Volgende kanttekeningen kunnen daarbij gemaakt worden. Indien geen antistoffen detecteerbaar zijn na de basisvaccinatie, is er duidelijk minder effect na een extra dosis mRNA. Personen die een natuurlijke infectie doormaakten hebben meestal al een sterker antwoord op de basisvaccinatie en mogelijks minder voordeel van een extra dosis. Het duidelijk lagere immuunantwoord na adenovector vaccin Johnson&Johnson bij een klein aantal nierdialyse patiënten verdient verder onderzoek.

Beleidsaanbevelingen – advies Task Force

- Met de huidige kennis lijkt een selectief gebruik van een extra/booster mRNA-dosis (zelfs vanaf een paar maand na basisvaccinatie) zinvol in immuun-gecompromitteerde personen:
  - Patiënten met aangeboren afweerstoornissen
  - Patiënten op chronische nierdialyse
  - HIV-patiënten (CD4 T-cellen <200 cellen per mm^3)
  - Patiënten met bloedkanker of andere maligne tumoren die in actieve behandeling zijn/waren de voorbije jaren
  - Stamcel transplant en orgaantransplant patiënten
  - Patiënten met inflammatoire ziekten die behandeld worden met immunosuppressiva
- Voor hoogbejaarden wordt een lagere immuunrespons gezien maar voorlopig zijn er nog geen gepubliceerde resultaten van studies over de toediening van een extra/booster dosis mRNA vaccin. Bejaarden in WZC en bijhorende serviceflats werden eerder gevaccineerd dan bejaarden daarbuiten en zouden daarom ook eerder in aanmerking kunnen komen voor een extra dosis (< zes maanden na basisvaccinatie) of boosterdosis (> zes maanden). Verder kan het collectief verblijf in een voorziening een bijkomend risico op infectie vormen. De Task Force adviseert om de geplande analyses op doorbraakinfecties en de resultaten van klinische studies omtrent extra/booster dosis de komende weken voorlopig af te wachten.
- Een stapsgewijze uitrol van deze extra/booster dosis naar bijkomende risicogroepen is mogelijk maar moet bij elke stap ondersteund worden door gedegen internationaal en nationaal onderzoek en voortschrijdende inzichten op *evidence* gebaseerd.
- Het breed preventief of therapeutisch toedienen van monoclonale antilichamen in risicogroepen staat voor de deur. Het implementeren van een extra/booster dosis is in veel gevallen wellicht een meer praktische en kosteneffectieve preventieve aanpak. Dit dient verder te worden onderzocht samen met een evaluatie voor terugbetaling door het RIZIV.
- De Task Force blijft benadrukken dat, afhankelijk van de variant, het effect van vaccinatie op de transmissie van het virus beperkt is. Dit is zeker zo voor de huidige delta variant. Daarom blijft het belangrijk de hoeveelheid virus waaraan we worden blootgesteld te verminderen met de gekende niet-farmacologische interventies bv. ventilatie, fysiek afstand houden en mondmaskers.
- Bijkomend dient er verder naar gestreefd te worden om de bevolking, zowel volwassenen als jongeren boven 12 jaar, in ons land zoveel als mogelijk de basisvaccinatie toe te dienen.

3 REVIEW OF THE EVIDENCE

Disclaimer

Given the short time interval available for the present rapid review, the authors sometimes literally copied the text and/or tables and/or figures from the original articles. References to the respective publications are provided in the text.

3.1 Background

Infection with SARS-COV-2 can be asymptomatic but also lead to very severe Covid-19 illness and death. Airborne transmission of the virus is the common route of transmission. Vaccines for the population (starting from age 12) have been developed very quickly after the start of the pandemic in early 2020. A growing number of vaccines have been approved (conditional marketing approval) and are being rolled out worldwide. These preventive vaccines stimulate the two components of the immune system: the humoral immunity (i.e. the production of antibodies) and the cellular immunity. The EMA approved base-vaccination schemes include vaccines based on mRNA (2 doses for the vaccines of Pfizer–BioNTech and Moderna) or based on an adenovector (2 doses of Astra-Zeneca or 1 dose of Johnson & Johnson/Janssen).

What is the effectiveness of vaccination and what are breakthrough infections?

In the large scale phase 3 randomized trials, each of the available vaccines reduced the probability of infection (and the associated risk of transmission) with at least 50%, the minimum criterion for marketing authorization. In addition, the vaccines reduce even more the risk of infection with severe disease and death (reduction of about 90%). Randomized direct comparisons of the clinical effectiveness of the vaccines are still missing. The level of neutralizing antibodies against the circulating variants are higher after mRNA vaccines than after adenovector-based vaccines. All vaccines frequently cause transient and mild side-effects. This also the case if a different vaccine is used as a second dose (off-label).

The available data after administration of an extra dose of mRNA vaccine in risk groups do not suggest any major difference in side-effect profile. Serious side-effects caused by vaccination occur very rarely. These differ for adenovector vaccines (e.g. thrombosis with low levels of platelets) and mRNA vaccines (e.g. myocarditis and pericarditis).

An infection after a full base-vaccination scheme (minimum 1-4 weeks after the last dose) is called a breakthrough infection. The definition used however varies between different publications, which hampers comparisons across studies.

Which variables can have an impact on the effectiveness of vaccination?

There are multiple variables that may have a possible effect, and possibly the effect may differ for the protection against infection (“sterile immunity”) and the protection against severe Covid-19.

1. **The vaccine(s) itself**, the route of administration, the dose, the storage conditions, the scheme of administration and the time period after vaccination, given a possible decrease of the protection over time (“waning”)
2. **The person** and the immune system, age and gender, a history of Covid-19 with a specific variant, and diseases or treatments that compromise the immune response (“immunocompromised patients”)
3. **The virus** variant and the quantity of virus the person is exposed to.

A number of the variables we can control. The quantity of virus we are exposed to can be reduced using e.g. ventilation, physical distancing and masks.

Another possibility consists of an adaptation of the vaccination schemes in the short term using an extra/booster dose of a (mRNA) vaccine. EMA did not yet approve any vaccine for such booster vaccination. This mean such use is still considered off-label. Vaccines based on another variant of the virus are in development but not yet approved.

A booster dose is typically administered at least 6 months after the base vaccination. In the published studies of an extra mRNA dose, this dose was sometimes already administered two months after base-vaccination (note: this is called 'extra dose' in the present report). It is more of an extension of a base vaccination scheme without counting on a real booster effect. These results have also been considered in this report.

Possible endpoints of effectiveness of an extra/booster dose of mRNA vaccine

For the evaluation of effectiveness a distinction is to be made between protection against infection and transmission ('*sterile immunity*') and protection against severe Covid-19 disease. It has been suggested that the optimal vaccination strategy might differ for these two aims. An extra/booster dose of mRNA is likely to increase the quantity of virus-neutralizing antibodies and this may decrease breakthrough infections and further transmission, at least of those variants being bound sufficiently.

For the protection against severe Covid-19 caused by the new variants a broad cellular immunity might be important. In theory, those who were vaccinated after a history of a natural infection have a broader base as protection compared with those who never had an infection.

"Finally, timing a boost for optimal responses will depend on whether the objective is to prevent viral acquisition or disease. Given the rapid emergence of variants, in the former, boosting would be needed on a far shorter time scale than the latter. The optimal timing for boosting to prevent serious disease will depend on the stability and further evolution of the memory B cell compartment." https://www.biorxiv.org/content/10.1101/2021.07.29.454333v1

Effectiveness trials after an extra/booster mRNA dose are still missing to confirm or refute these theoretical considerations.

Use of a correlate of protection?

There is growing evidence that a breakthrough infection with a specific variant after vaccination in immunocompromised patients[1], and healthy individuals[2] is associated with absence of the pre-exposure virus-blocking antibody levels (as a first step towards a correlate of protection). Earle et al. described a robust correlation between neutralizing titre and efficacy (ρ= 0.79) and binding antibody titre and efficacy (ρ= 0.93).[3]

The measure of a specific cellular immune response is more complex compared with the assessment of specific antibody levels. But also the minimum level of detection as well as the reported level of antibodies and its specificity (anti-Spike (S), anti-RBD IgG) depend on the assay used. A standardized assay of virus-blocking antibody levels could potentially identify subjects in need of an extra/booster dose. The WHO International Standard (IS) for anti-SARS-CoV-2 antibody allows for assay unit conversion to international units. This facilitates the comparison of datasets and the further research for a correlate of protection. https://www.who.int/publications/m/item/WHO-BS-2020.2403

A single immune response cut-off value by variant which would protect an individual against mild or severe Covid-19 has not yet been determined. Therefore this test-and-boost approach (as in use for hepatitis B in healthcare workers) has been proposed but is still under research for SARS-CoV-2 and not yet ready for routine implementation.

On duration of protection after vaccination

According to Barclay[4]: "It is highly likely that vaccine induced immunity to SARS-CoV-2 infection, and potentially severe disease (but probably to a lesser extent) will wane over time. This is likely to be first detected by vaccine failures in vulnerable cohorts (for example a high rate of infections in people vaccinated over time, including hospitalized cases). It is therefore likely that there will be vaccination campaigns against SARS-CoV-2 for many years to come, but currently we do not know what will be the optimal required frequency for re-vaccination to protect the vulnerable from COVID disease."

Shrotri et al. showed a significant trend of declining Spike (S)-antibody levels for both ChAdOx1 and BNT162b2, with levels reducing by about five-fold for ChAdOx1, and by about two-fold for BNT162b2, between 21–41 days and 70 days or more after the second dose.[5] Results were consistent for sex, age, and clinical vulnerability. For BNT162b2, S-antibody levels reduced from a median of 7 506 U/mL (IQR 4 925–11 950) at 21–41 days, to 3 320 U/mL (1 566–4 433) at 70 or more days. For ChAdOx1, S-antibody levels reduced from a median of 1201 U/mL (IQR 609–1 865) at 0–20 days to 190 U/mL (67–644) at 70 or more days.

Thomas et al. (pre-print) describes a vaccine efficacy (VE) of BNT162b2 against lab confirmed COVID-19 cases of 91% (95% CI 89.0-93.2) through up to 6 months of follow-up, among evaluable participants and irrespective of previous SARS-CoV-2 infection.[6] VE of 86%-100% was seen across countries and in populations with diverse characteristics of age, sex, race/ethnicity, and COVID-19 risk factors in participants without evidence of previous SARS-CoV-2 infection. VE against severe disease was 97% (95% CI 80.3−99.9). In South Africa, where the SARS-CoV-2 variant of concern, B.1.351 (beta), was predominant, 100% (95% CI 53.5, 100.0) VE was observed.

Sampling of germinal centre B cells in 14 individuals who received two doses of BNT162b2 revealed binding of S protein in all participants, demonstrating that SARS-CoV-2 mRNA-based vaccination of humans induces a persistent germinal centre B cell response, which enables the generation of robust humoral immunity.[7] High frequencies of S-binding germinal centre B cells and plasmablasts were sustained in these draining lymph nodes for at least 12 weeks (samples between 3 and up to 15 weeks) after the second dose.

Zou et al. studied the SARS-CoV-2-specific T cell immunity at 6 months following primary infection in 100 donors from a multicentre trial (mostly US) with 45 441 participants.[8] Predominant CD4+ T cell responses with strong interleukin (IL)-2 cytokine expression were present and median T cell responses were 50% higher in donors who had experienced a symptomatic infection, indicating that the severity of primary infection establishes a 'set point' for cellular immunity. T cell responses to spike and nucleoprotein/membrane proteins were correlated with peak antibody levels. Furthermore, higher levels of nucleoprotein-specific T cells were associated with preservation of nucleoprotein-specific antibody level although no such correlation was observed in relation to spike-specific responses. In conclusion, our data are reassuring that functional SARS-CoV-2-specific T cell responses are retained at 6 months following infection.

Barouch et al. describe the duration of protection following Ad26.COV2.S vaccination for COVID-19 with a sub-analysis of their Phase 1/2a trail showing results indicating that humoral and cellular immune responses were maintained until at least 8 months after vaccination.[9] Results of these laboratory experiments should however be confirmed with effectiveness data.

3.2 Literature search

Publications and reports (n=41) known by the experts were collected and included in the endnote file (up to August 8th 2021). Searches were performed for publications on breakthrough infections and a booster vaccination after complete schedule.

Several publications are in the pre-print phase and may not have been fully peer-reviewed. Publications in pre-print status at the time of the search are indicated with 'pre-print'.

3.3 Breakthrough infections

3.3.1 Literature

A search in Pubmed for publications on 'breakthrough infections' with the new Mesh term https://www.ncbi.nlm.nih.gov/mesh/?term=breakthrough+COVID was performed on August 3th 2021. This search resulted in 175 hits; of these 175, 21 publications answering one of the topics below were selected.

A summary of the retrieved publications is presented below. A more extensive description is in the Appendix.

3.3.2 Definition

An internationally agreed definition for 'breakthrough' infections is currently not available. Therefore, the results on breakthrough infections in this review are not comparable but should be used as a guidance. Two important factors that may differ across studies are firstly, the inclusion of symptomatic cases only versus inclusion of both symptomatic and asymptomatic persons, and secondly, the days from full vaccination that are applied e.g. 7 days versus 14 days. An example for a definition in the literature is presented by Schieffelin et al. (see Appendix).[10] The definitions used by Belgium (Sciensano) are: a breakthrough infection is a laboratory confirmed Covid-19 infection (PCR/Rapid Ag) occurring **14 days or more** after full-dose schedule; a confirmed breakthrough

cases is the occurrence of **at least 1 major symptom or at least 2 minor symptoms** consistent with Covid-19 **confirmed by PCR 14 days** or more after full-dose schedule (i.e. the Belgian case definition of confirmed Covid-19 + 14days after full vaccination).

3.3.3 Incidence of breakthrough infections – international data

The incidence for retrieved studies is presented in Table 1. As mentioned above, caution is advised when comparing results as different definitions for breakthrough infections have been used. In these studies, the time since last vaccination to identify breakthrough infections varies between 7 and 21 days (indicated in the table). Study results are strongly related to the 'epidemic phase' at the time of recruiting patients (e.g. the higher incidence in Israel could reflect the ongoing third wave at the time of the study) and how long the follow-up lasted for. It is more likely to have breakthrough infections in those who have been vaccinated the longest, e.g. the elderly and healthcare workers, as the exposure time since vaccination will be the longest and waning may occur. Ideally, future studies should be of a longer duration to allow for a survival analysis to be performed.

Table 1 – Incidence of breakthrough infections from literature*

Country & reference	Population	Number of people (fully) vaccinated	Number of breakthrough infections	Breakthrough infections per 1000
US[11]	All US veterans	258 716	410[1]	1.58 (0.66 per 1000 person-days CI:0.60,0.72)
Israel[12] **(Pre-print)**	Adult population in Israel	33 993	608	0.18
US[13]**	Solid organ transplant recipients	18 215	151[2]	0.83
US MMWR report[14]	Nursing home residents and staff members	7 931 residents and 6 834 staff members =14 765	22[2]	1.49
UK[15]	Staff working in NHS hospitals	13 716	71[3] 9[1]	5.18 (0.8 per 1000 person-days) 0.66 (0.4 per 1000 person-days)
Belgium[16]	Health care workers hospital	3 491	9[2]	2.58
US[17]	Health care workers including first line	2 510	5[2]	1.99
US[18]	Military service members (including health care workers)	1 547 (1 229 outpatients, 318 inpatients)	24[2]	15.51
Israel[2]	Staff at the largest hospital in Israel	1 497	39[4]	26.05
US[19]	Solid organ transplant recipients -symptomatic	912	4[2]	4.39 (0.065 per 1000/person-days (CI 0.024–0.17)
US[20]**	Kidney transplant recipients	380	17[2]	44.74

Details of the studies are presented in the appendix;paper of low quality due to limited information; [1] ≥7 days after second vaccine dose; [2] ≥14 days after second vaccine dose; [3] ≥21 days after second vaccine dose; [4] ≥11 days after second vaccine and no exposure or symptoms reported during the first 6 days.*

The largest study was performed in vaccinated veterans across the US before the delta variant became widespread (Table 2 and Table 3).[11] The factors associated with increased risk of breakthrough infection was age (per 10 year increase the hazard of breakthrough infection increased with 1.11) and anaemia. Again, this should be interpreted with caution as follow-up time was less than 3 months (Table 3). The reason for the association with anaemia was unclear. A similar incidence was recorded for nursing home residents and staff in the US who were tested regularly beginning of 2021.[14] In hospital staff in England, the incidence increase between 7 and 21 days after last vaccination corresponds to the previous studies.[15]

The paper by Israel finds 608 (1.8%) positive RT-PCR cases among 33 993 individuals with a full base vaccination (Pfizer mRNA). The authors shows that the odds for a breakthrough infection was higher for patients vaccinated longer than 146 days ago compared to before 146 days ago.[12] Older patients were more likely to present with a breakthrough infection (odds 3 times higher for 60+ of age).[12] There are no data yet on the severity of these infections. The analysis assumes that the test strategy, the need for testing and the willingness to get tested remained stable over time. Another study identified 16 breakthrough infections in patients with inflammatory conditions. Seven patients received basic vaccination with Pfizer-BioNtech, five with Moderna and four with Janssen/Johnson & Johnson. Six patients were hospitalized, three of whom were under 65 years of age. Four were on anti-CD20 treatment and two on mycophenolate. Two patients died.[21]

Table 2 – Incidence of breakthrough infection by age, race, comorbidities and vaccine[11]

Infection rate per 1000 person-days ≥7 days after second vaccine dose, by sub-groups.

	N	Rate (95% CI)	P-Value
Infection rate, overall	410	0.66 (0.60,0.72)	N/A
By age			
<=40	6	0.41 (0.08,0.73)	comparator
>40 – 60	41	0.54 (0.37,0.70)	0.53
>60 – 70	96	0.60 (0.48,0.72)	0.36
>70	267	0.72 (0.637,0.81)	0.16
By race			
White	314	0.73 (0.65,0.81)	comparator
Black	70	0.49 (0.37,0.60)	0.002
Other/Unknown	26	0.54 (0.33,0.74)	0.13
By sex			
Female	24	0.69 (0.42,0.97)	comparator
Male	386	0.66 (0.59,0.72)	0.81
By comorbidities			
None	22	0.44 (0.25,0.62)	comparator
1–3	257	0.68 (0.59,0.76)	0.05
4 or more	131	0.69 (0.57,0.80)	0.05
By vaccine type			
Pfizer	266	0.69 (0.60,0.77)	comparator
Moderna	144	0.62 (0.52,0.72)	0.32

Table 3 – US veteran study risk factor analysis for breakthrough infection[11]

Factors associated with SARS-CoV-2 infection after vaccination (infection ≥7 days after second vaccine dose; Cox proportional hazards model).

	Hazards ratio (95% CI)	P-value
Age (per 10 years increase)	1.11 (1.01,1.23)	0.04
Race (comparator: White)		
Black	0.65 (0.5,0.85)	0.001
Other/unknown	0.75 (0.5,1.13)	0.17
Body mass index >30 (comparator: <30)	0.91 (0.73,1.12)	0.36
Comorbidities		
Diabetes	1.1 (0.9,1.35)	0.36
Coronary artery disease	0.97 (0.79,1.2)	0.78
Chronic kidney disease	1.11 (0.88,1.39)	0.38
Chronic lung disease (COPD)	0.88 (0.72,1.08)	0.21
Anemia (Hb<13 for men; <12 for women)	1.37 (1.09,1.73)	0.01
Cancer diagnosis	0.86 (0.7,1.05)	0.14
Human immunodeficiency virus infection	0.38 (0.1,1.54)	0.18
Vaccine type (comparator: Pfizer)		
Moderna	0.82 (0.67,1.01)	0.06

The study by Aslam et al. among 912 (symptomatic) **solid organ transplant recipients** (SOTRs), showed a lower incidence rate for vaccinated versus partially or unvaccinated recipients for symptomatic COVID-19 (0.065 versus 0.34 per 1000 person-days with an incidence rate ratio of 0.19 (CI 0.049 −0.503, p < 0.005) which means 5 times less risk).[19] The number of breakthrough infections in the paper on **kidney transplant** patients is higher but numbers are small and information is lacking.[20]

The younger cohort of breakthrough infections in military personnel (study by Pollet et al.), mean age was 37.8 years, included participants with high shedding of live virus and both variant-of-concern (VOC) and non-VOC strains.[18] Most infections (67%) were observed in those without comorbidities. One subject reported receiving immunosuppressant medication (mycophenolate and prednisone) for a renal transplant. No participant was admitted. Similarly, Brosh-Nissimov et al. (Israel) demonstrated that among patients with breakthrough infections (≤7 days after second dose Pfizer) that were admitted to hospital and had a poor outcome, the rate of comorbidities was high.[22]

3.3.4 Incidence of breakthrough infections – national data

3.3.4.1 COVID-19 breakthrough infections in the general population

By linking data from the Vaccinnet+ registry and the COVID-19 laboratory test results database, Sciensano closely monitors breakthrough infections. Breakthrough infections are defined here as new laboratory confirmed COVID-19 infection (by PCR or Rapid Antigen test), occurring in fully immunized persons (fully vaccinated for at least 14 days).

The incidence of COVID-19 breakthrough infections overall is low. By August 8th, 2021, of a total of 6 232 320 fully immunized individuals in Belgium, 0.20% (n= 12 332) had been identified as having a breakthrough infection during follow-up. The median time to infection was 52 days (IQR 32-83) after final vaccine dose. Mean age of persons presenting with a breakthrough infection was 53 (±22) years, 61.7% were female, and 71.2% had been vaccinated with Pfizer/BioNTech. These results most probably reflect the roll-out of the vaccination campaign, as Pfizer/BioNTech has been the most frequently used vaccine, and women are overrepresented in the priority groups targeted within the earlier stages of the vaccination campaign (healthcare workers and elderly). Of the 12 332 persons with a breakthrough infection, 10 186 (82.6%) had retrievable information on symptoms based on contact-tracing data. Of these persons, 52.4% (5 341/10 186) had symptoms compatible with COVID-19 at the time of the contact-tracing call. However, the surveillance system does not inform

whether the asymptomatic cases go on to develop symptoms, nor on the outcome of breakthrough infections in terms of severity.

3.3.4.2 Breakthrough infections among COVID-19 hospitalized cases

Clinical information on hospitalized COVID-19 patients is collected in the COVID-19 Clinical Hospital Surveillance. This surveillance covers approximately 2/3^{rds} of all hospitalized COVID-19 patients in Belgium. Data is obtained with a delay of approximately 1-3 weeks. Linking with Vaccinnet+ data allows to identify the vaccine status of these cases.

From January 1st to August 8th, 2021 there have been 19 723 hospitalized patients registered. Of these, 2.1% (416/19 723) were fully immunized (≥14 days after completing vaccination schedule). Patients with partial vaccination (≥14 days after dose 1 and <14 days after dose 2) accounted for 6.4% of hospitalizations (1 267 / 19 723).

A comparison was made between the 416 fully immunized and the 16 866 non-vaccinated hospitalized COVID-19 patients. No comparison between vaccine brands was made for this analysis as 91% had been vaccinated with Pfizer/BioNTech. Median age of the fully immunized patients (= breakthrough cases) was 82 years, 47.6% were nursing home residents, and 61.3% were females. In contrast, unvaccinated COVID-19 patients had a median age of 64, only 3.8% were nursing home residents, and 47.1% were female. These differences may reflect the vaccination roll-out, with priority groups vaccinated for a longer period of time and thereby becoming overrepresented among the fully immunized patients. On the other hand, advancing age is associated with a weakened immune system and is a major risk factor for poor outcomes among COVID-19 infected patients. Conversely, only three healthcare workers were registered among the fully immunized hospitalized cases. 92.5% of fully-immunized COVID-19 patients had underlying comorbidities versus 75.2% among the non-vaccinated patients, a difference that could result from the older age of the former. Notably, a large proportion of the hospitalized breakthrough cases were identified through systematic screening (50.2%, 209/416) rather than because of COVID-19 compatible symptoms at admission (44.2%, 184/416). Nonetheless, patients identified through systematic screening may still go on to develop severe symptoms and complications during hospitalization.

Of the 416 breakthrough infections, 319 had a completed discharge form, which allows to analyze their clinical outcomes. Among them, 7.5% were transferred to the intensive care unit (ICU) and 17.2% did not survive (all-cause death). Non-vaccinated people were more often transferred to ICU (18.8%), however proportionally less patients died (14.0%). However, the two groups should not be directly compared, as patients with breakthrough infections were of older age and with more comorbidities, which highly increases their risk of death, whilst nursing home residents are less likely to be transferred for intensive care.

3.3.4.3 Limitations and next steps in analysis

These basic descriptive analyses do not take into account the vaccination campaign roll-out (e.g. priority groups; proportion of vaccine brands), the impact of the changing epidemic (e.g. third wave; lower circulation of virus in more recent months; emergence of variants of concern), nor the time since vaccination (e.g. longer exposure risk versus potential waning immunity). Further analyses of these data are ongoing to take into account key confounding variables in order to correctly investigate potential risk factors of developing a breakthrough case, and in particular of a severe outcomes among those hospitalized.

3.3.5 Variants identification

Tremendous progress has been made with the development of vaccines and antibody therapies. These strategies are directed at the viral spike protein, but the emergence of viral variants, particularly with key mutations in the S gene, threatens their continued efficacy and increases concern for severe SARS-CoV-2. Variants of concern (VOCs) are those strains that show evidence of increased transmissibility, more severe disease, reduced neutralization by antibodies elicited by past infection or vaccination, reduced efficacy of treatments, or failures in diagnostic detection. VOCs include: Alpha variant (B.1.1.7 UK), Beta (B.1.351 S. Africa), Gamma (P.1 Brazil), Epsilon (B.1.429 California), Iota (B.1.526 New York) and Delta and Kappa (B.1.617.2 and B.1.617.1 India). Evasion of vaccine-induced immunity could cause asymptomatic infection and promote viral spread or illness. The observations in the studies below (Table 4) indicate a potential risk of illness after successful

vaccination and subsequent infection with variant virus, and they provide support for continued efforts to prevent and diagnose infection and to characterize variants in vaccinated persons.

Table 4 – Overview of studies on variants of concern

Country & reference	Population	Number of people (fully) vaccinated and followed-up	Variants of concern	Symptoms
US[23]	University students and employees New York	417 (BNT162b2 or mRNA-1273)	2 women: E484K in 1 woman and three mutations (T95I, del142–144, and D614G) in both	Patient 1: healthy 51 years, mild symptoms 19 days after vaccine dose 2 Patient 2: healthy 65 year old, mild symptoms 36 days after vaccine dose 2 Immune response effective
US[24]	Wedding party Texas	<100 guests (BNT162b2, mRNA-1273, BBV152)	SARS-CoV-2 Delta variant	Three males and three females ranged from 49 to 69 years old with 2 index cases from India (travel was 10 days after last second dose). All were symptomatic, the index male case died.
US[25]	University of Washington samples	20 samples tested (14 BNT162b2, 5 mRNA-1273)	All 20 samples had a variant: 8 (40%) B.1.1.7, 1 (5%) B.1.351, 2 (10%) B.1.427, 8 (40%) B.1.429, and 1 (5%) P.1	15 out of 18 reported symptoms, and none required hospitalization.
Greece[26]	Healthcare workers at hospital	1 800 (BNT162b2)	21 breakthrough infection fully vaccinated and 3 in partially vaccinated Of those 24: SARS-CoV-2 B.1.1.7 in 23 cases	The majority had symptoms: 19 out of 24 (including partially vaccinated)
French Guiana[27]	44 employees of a gold mine in French Guiana	25 (BNT162b2)	Attack rate was 60% (15/25) among fully vaccinated miners with the Gamma variant P.1	24/44 (55%) employees of a gold mine in French Guiana (87% moderate symptomatic). The SARS-CoV-2 IgG ratio was high for most.

3.4 Effectiveness and immune response after two doses of vaccine

3.4.1 Literature search

Articles were provided by experts and no further search was performed. The literature for the tables' content on immune mediated conditions, oncology and hematology patients is based on the draft review advisory report of the Superior Health Council no 9 650: "Vaccination of immunocompromised or chronically adults: COVID vaccination" (personal communication). An overview and summary review of vaccine efficacy is also available on the Sciensano website in the factsheet: https://covid-19.sciensano.be/sites/default/files/Covid19/COVID-19_fact_sheet_ENG.pdf.

3.4.2 *Effectiveness in general population, healthcare workers and elderly residents*

The large study in England included all symptomatic cases to estimate the effectiveness of vaccination against symptomatic disease caused by the delta variant or the predominant strain (B.1.1.7, or alpha variant) over the period that the delta variant began circulating (Table 5).[28] The vaccine effectiveness in Israel for the Pfizer vaccine was of the same magnitude.[29]

In Denmark the vaccine effectiveness was low at 64% for residents in care (median age of 84 years) whereas the healthcare workers of the long-term-care residents had a vaccine effectiveness of 90%.[30]

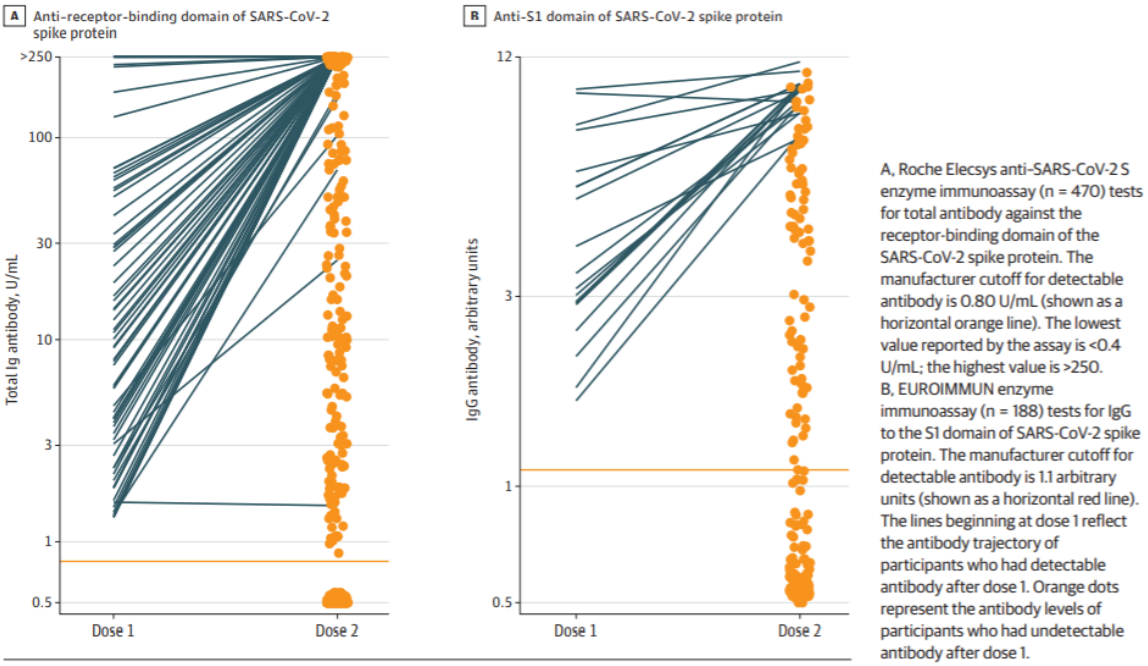
Table 5 – Examples for vaccine effectiveness general population, healthcare workers and elderly residents

Country & reference	Population	SARS-CoV-2 cases unvaccinated groups	SARS-CoV-2 cases vaccinated groups	Vaccine and vaccine effectiveness after 2 doses
UK[28]	Any person living in England	Alpha: 7 313 Delta: 4 043	Alpha: 143 Delta: 340	≥14 days after 2nd dose: BNT162b2 vaccine: 93.7% alpha, 88% delta ChAdOx1 nCoV-19: 74.5% alpha, 67% delta
Israel[29]	Population of Israel ≥16 years (4,714,932 2 doses or 72.1% population)	109 876	6266	≥7 days after 2 dose BNT162b2: 95.3% against SARS-CoV-2 infection
Denmark[30] Pre-print	Healthcare workers n=331 039 (27.8% first dose and 24.4%, n=80 774 received second dose)	5 663 Follow-up of 53 days	10	>7 after second dose BNT162b2 mRNA: 90% (95% CI; 82-95)
Denmark[30] Pre-print	Long-term care facility residents n=39 040 (95.2% first dose and 86.0%, n=33 574 received second dose)	488 Follow-up of 53 days	27	>7 after second dose BNT162b2 mRNA: 64% (95% CI; 14-84)

3.4.3 *Immune response in transplant patients*

The immune response to two doses of vaccine against SARS-CoV-2 has been observed as weak in recipients of solid-organ (kidney, liver, thoracic organs, pancreas) transplants.[31-34] The largest study by Boyarsky et al. demonstrated a seroconversion rate of 54% after the second dose of a mRNA SARS-CoV-2 vaccine in solid organ transplant recipients (n=658).[33] Poor humoral response, presented in Figure 1, was associated with antimetabolite immunosuppression medication ($p<0.001$). The other studies had a lower seroconversion rate below 40%.

Figure 1 – Antibody levels of organ transplant recipients after 2-doses mRNA vaccine[33]



A, Roche Elecsys anti-SARS-CoV-2 S enzyme immunoassay (n = 470) tests for total antibody against the receptor-binding domain of the SARS-CoV-2 spike protein. The manufacturer cutoff for detectable antibody is 0.80 U/mL (shown as a horizontal orange line). The lowest value reported by the assay is <0.4 U/mL; the highest value is >250. B, EUROIMMUN enzyme immunoassay (n = 188) tests for IgG to the S1 domain of SARS-CoV-2 spike protein. The manufacturer cutoff for detectable antibody is 1.1 arbitrary units (shown as a horizontal red line). The lines beginning at dose 1 reflect the antibody trajectory of participants who had detectable antibody after dose 1. Orange dots represent the antibody levels of participants who had undetectable antibody after dose 1.

3.4.4 Immune response in patients with immunesuppressive conditions

Table 6 – Immune-mediated inflammatory diseases (IMID) & immunosuppressive drugs (ISD)

Country & reference & vaccine	Type of patient	Serological response after second dose
UK[35] (review pre-print) BNT162b2 mRNA and ChAdOx1 258 nCoV-19	Inflammatory bowel disease: infliximab (n=865) vedolizumab (n=428)	In both infliximab- and vedolizumab treated patients, antibody levels and seroconversion rates were higher after two doses than after a single dose without prior infection (geometric means infliximab 158U/mL (7.0) vs 6.0U/ mL (5.9), p<0.0001; vedolizumab 562U/mL (11.5) vs 28.8U/ mL (5.4), p= 0.018). After second-vaccine doses**, 85%** (17/20) infliximab-treated patients and **86%** (6/7) vedolizumab-treated patients seroconverted
Israel[36] (pre-print) BNT162b2 mRNA	autoimmune inflammatory rheumatoid diseases (n=156)	**88%** (137/156) seroconversion
Israel[37] BNT162b2 mRNA	Patients with inflammatory rheumatic diseases (n=264)	After the second dose, 227 patients (**86%**) mounted a significant humoral response of neutralising IgG Ab against SARS-CoV-2 virus (mean (SD) 6 764.27 (9 291.61) AU/mL, median 3 058 AU/mL, range 58–40 000

Table 7 – Oncology and Hematology

Country & reference & vaccine	Type of patient	Serological response after second dose
Israel[38] **BNT162b2 mRNA**	Patients with solid tumor cancer (n=102)	92 (**90%**) were seropositive for SARS-CoV 2 antispike IgG antibodies after the second vaccine dose
UK[39] **(pre-print) BNT162b2 mRNA**	Solid tumor cancer patients (n=54) and patients with hematological malignancies (n=39)	Solid tumor cancer patients:18 of 19 (**95%**) seropositive after boost Hematological patients: low number of patients
US[40] **BNT162b2 mRNA, mRNA-1273, AD26.COV2.S (one dose)**	200 patients with cancer (n=66 hematologic: n=134 solid tumor)	Overall seroconversion rate **94%:** solid tumors 98%, hematological malignancies 85% with immunosuppressive therapies such as anti-CD20 therapies **70%** (n=23) and stem cell transplantation **73%** (n=26; 3 allo, 23 auto), immune checkpoint inhibitor therapy 97% or hormonal therapies 100%. Active cancer 96% and non-active cancer therapy 93% Lower IgG titres with the adenoviral than mRNA-based vaccines.
Italy[41] **BNT162b2 mRNA**	Multiple myeloma n=42 Myelo-proliferative malignancies n=50	Seroprotection rate **78.6%** in MM and **88%** in MPM patients (cut-off of 15 AU/mL)
Istael[42] **BNT162b2 mRNA**	Chronic lymphotic leukemia n=167	**39.5%** seropositivity: 79.2% in patient in remission after treatment, 55.2% in treatment naïve patients, 16% in patients under treatment. **0%** of the patients, treated past 12 months with **anti-CD20 antibodies** (n=22)
US[43] **BNT162b2 mRNA, mRNA-1273**	Chronic lymphocytoic leukemia (n=44)	Antibodies detected: 6/26 (**23%)** treated patients, 17/18 (94%) never treated
US[44] **BNT162b2 mRNA, mRNA-1273**	Multiple myeloma (n=320)	Antibodies in 84**.2%** (219/260), 41 (15.8%) values below the level of detection
Lithuania[45] **BNT162b2 mRNA**	National cohort: hematological malignancies (n=857)	Neutralizing antibodies 3 times lower compared to health care workers (6 961 Au/ml versus 21 395). Very low response with concomitant treatment (anti-CD20, bruton tyrosine kinase, venetoclax, ruxolitinib)
US[46] **BNT162b2 mRNA**	Solid tumor patients (n=52) on active cytotoxic anti-cancer therapy	Neutralizing antibodies in **80%**

3.4.5 *Patients receiving dialysis*

Table 8 – Patients receiving dialysis

Country & reference & vaccine	Type of patient	Serological response after second dose
US[47] (pre-print) BNT162b2 mRNA, mRNA-1273, AD26.COV2.S (one dose)	Patients Receiving Dialysis n=610	Seroconversion **80%** (20% still no antibodies despite including patients with prior infection)
Austria[48] (pre-print) BNT162b2 mRNA	Hemodialysis patients n=81	Overall response: **64%**. 11% antibody titre > 200 U/ml (good response). 53% antibody titre lower than 200 U/ml (below maximum), 27% titre lower than 29 U/ml (likely no neutralization) 9% no detectable antibodies

3.5 Safety of heterologous Covid-19 vaccine schedules

The use of heterologous Covid-19 vaccine schedules could facilitate mass Covid-19 immunisation. As the recommendations in several countries were changed in March 2021, formulating to stop using the ChAdOx1 vaccine, this has led to vaccine programs combining different vaccine types. In addition, data on the safety and immunogenicity of heterologous vaccine schedules will help inform the use of these schedules in individuals who develop a contraindication to a specific vaccine after their first dose, and for vaccine programmes looking to mitigate vaccine supply chain disruption. Last, it has been suggested that mixed schedules might induce an enhanced or more durable humoral or cellular immune response compared with licensed schedules, and might do so against a greater range of SARS-CoV-2 variants.

Some early results are presented in Table 9; the safety aspects are summarized in the following paragraphs.

Table 9 – Overview of studies with heterologous second dose of vaccine

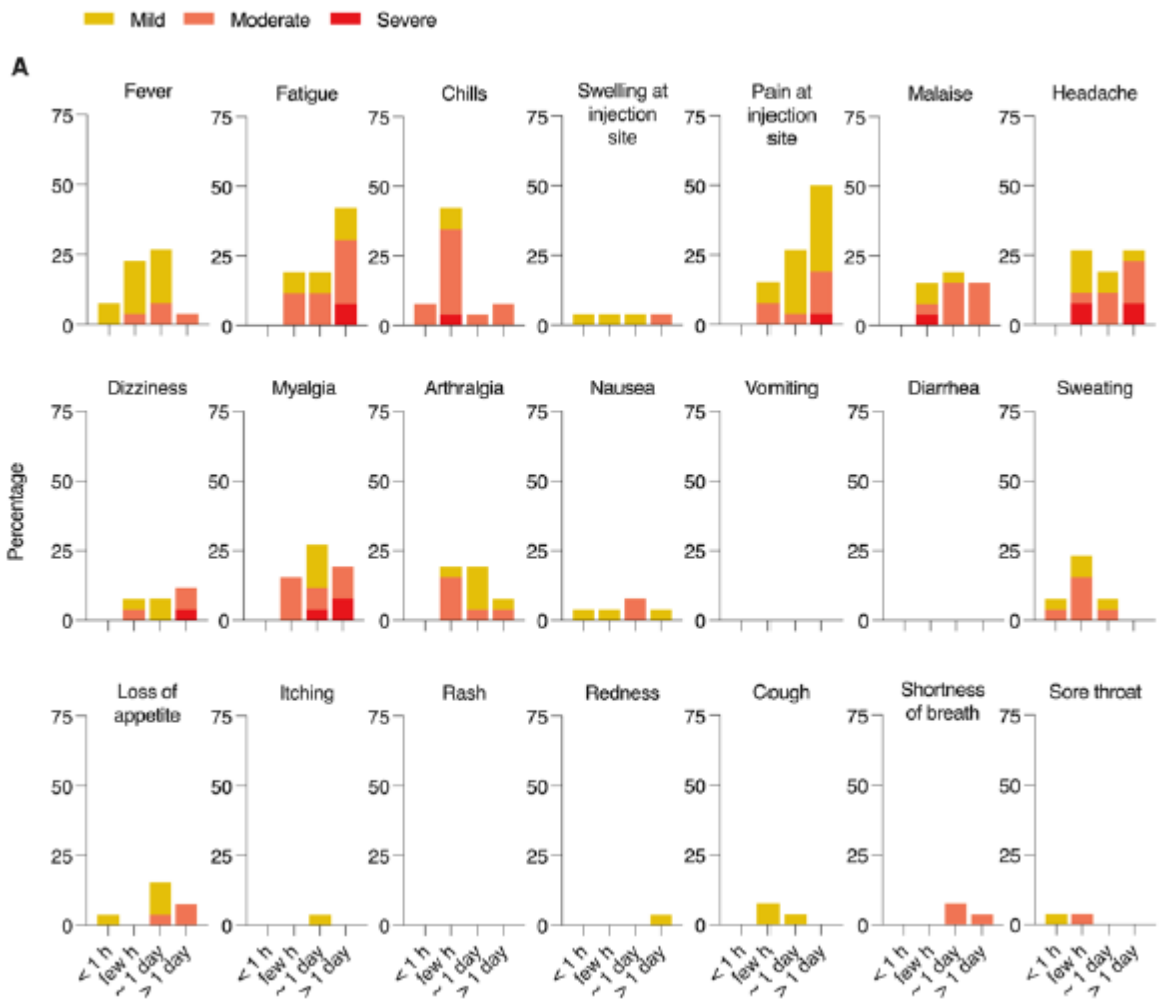
Country & reference	Population	Method / comparison	Measurements	Results
UK (Liu et al.[49])	Adults ≥ 50 years n=463 (including well controlled comorbidities) randomized: • ChAd/ChAd, • ChAd/BNT • 58 BNT/BNT • BNT/ChAd 28 day interval	Homologous and heterologous combinations of AZ and Pfizer	Comparison of the geometric mean titre of Spike specific IgG ELISA at 1 month post boost	Mean titre in ELU/ml: Pfizer homologous: 14 080; AZ homologous: 1 392 Pfizer + AZ hetero: 7 133; AZ+ Pfizer hetero: 12 906
Denmark (Gram et al.[50]; pre-print)	Nationwide population study n=5 542 079 • ChAd/mRNA : n=136 551	Unvaccinated, one dose of AZ, heterologous combinations of AZ and Pfizer or Moderna	Incidence of (symptomatic) SARS-CoV-2, hospitalisations and death	Vaccine efficacy: ChAd/mRNA: 88%(14 days after 2nd dose)
Germany (Schmidt et al.[51])	N=216 healthy adults Homologous ChAd n=55, mRNA n=64	Homologous and heterologous combinations of	Neutralizing antibodies and cellular immunity	Neutralizing antibodies, and CD4 T-cells significantly more pronounced than after homologous vector boost, and higher or comparable in

Country & reference	Population	Method / comparison	Measurements	Results
	Heterologous n=97 ChAd/mRNA	AZ and mRNA vaccine		magnitude to the homologous mRNA regimens. Moreover also spike-specific CD8 T-cell levels after heterologous vaccination were significantly higher than after both homologous regimens.
Germany (Gros et al.[52])	26 individuals aged 25-46 years: Heterologous ChAd/BNT	Heterologous BNT boost after ChAd with 8-week interval	Humoral and cellular immune responses towards different SARS-CoV-2 variants	Strong neutralization titres two weeks after the BNT162b2 boost The heterologous regimen induces slightly higher neutralizing antibodies against alpha, gamma and kappa VOC (delta not tested)
Germany (Tenbush et al. [53])	N=1 085 adults Homologous ChAd n=66, BNT n=537 Heterologous n=482 ChaAd/BNT	Homologous and heterologous combinations of AZ and mRNA vaccine	Humoral and cellular immune responses	ChAd/BNT higher surrogate neutralisation activity than homologous ChAdOx1 or homologous BNT162b2 vaccination.
Spain (Borobia et al. [54])	N= 676 adults (18–60 years) Heterologous n=450 ChAd/BNT Homologous n=226 ChAd/ChAd	Second dose (ChAd or BNT) 8-12 weeks after ChAd	Humoral and cellular immune responses, 7-day reactogenicity	Administration of a dose of BNT162b2 vaccine after a first dose of ChAdOx1-S provides a strong immune humoral and cellular response.

In a **small German study**, which included a cohort of 26 individuals aged 25-46 (median 30.5) years who received a ChAdOx1 nCoV-19 prime followed by a BNT162b2 boost after an 8-week interval, reactogenicity following prime and second vaccination was evaluated by all study participants by self-reporting of solicited local and systemic symptoms according to a standardized questionnaire.[52] Both, prime and second 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 second vaccination (Figure 2, Figure 3). 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 a second 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 second vaccination. 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 vaccination. Comparing cumulative solicited adverse reaction (cSAR) scores, **reactogenicity following prime with ChAdOx1 nCoV-19 was significantly (p = 0.008) higher than following second vaccination with BNT162b2** (cSAR score median 11 and 6 respectively, Figure 4C). Individually, most participants (19/26, 73.07%) had **milder reaction to second vaccination** compared to prime. 6/26 (23.07%) of participants described more severe reactions to second vaccination (Figure 4B). A trend towards higher cSAR scores reported by female participants was seen for both second and prime

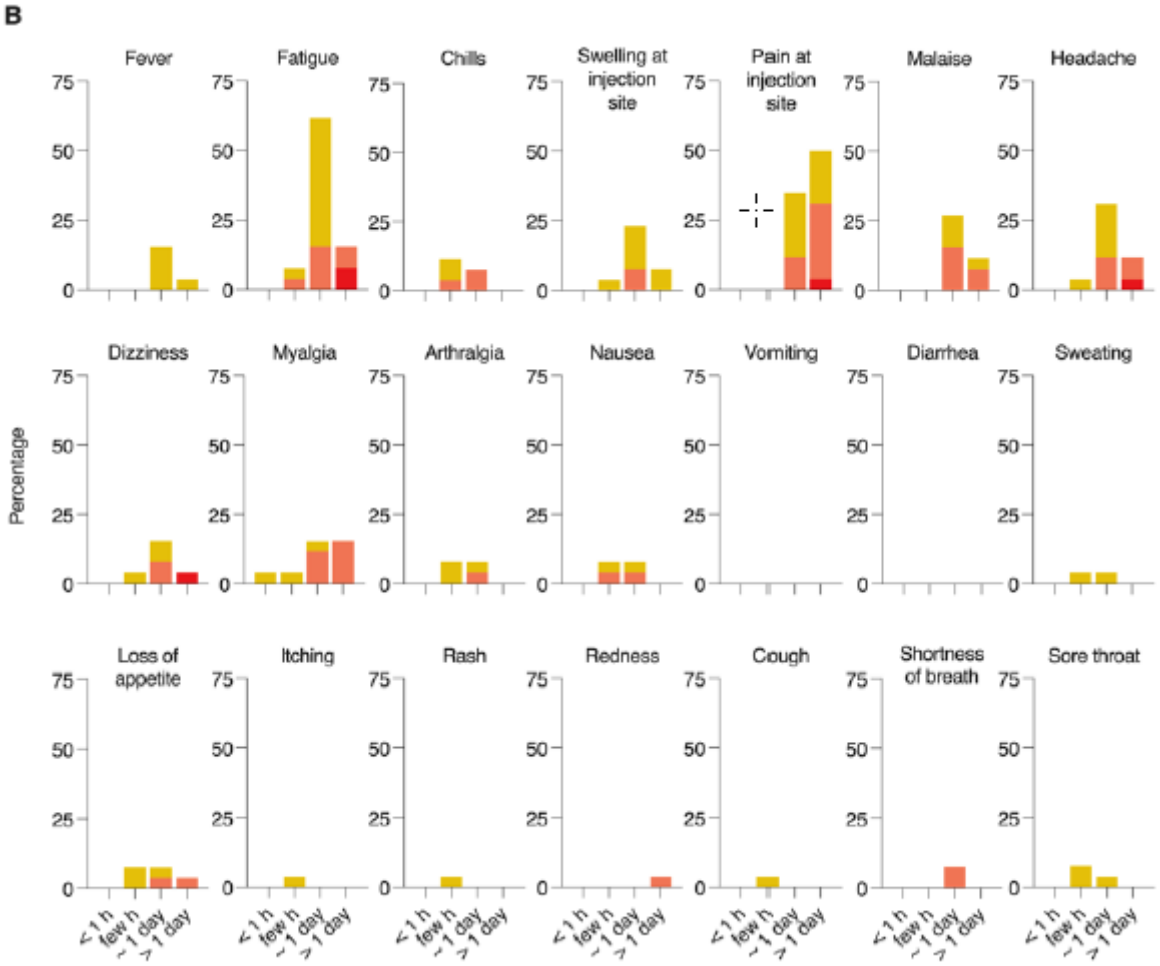
vaccinations (Figure 4 D,E). No correlation was observed between reactogenicity and age (Figure 4 C,D). Individual reactogenicity towards prime and second vaccination showed a weak but significant correlation (Figure 4 F, p = 0.039).

Figure 2 – Solicited adverse reactions following ChAdOx1 nCoV-19 prime vaccination



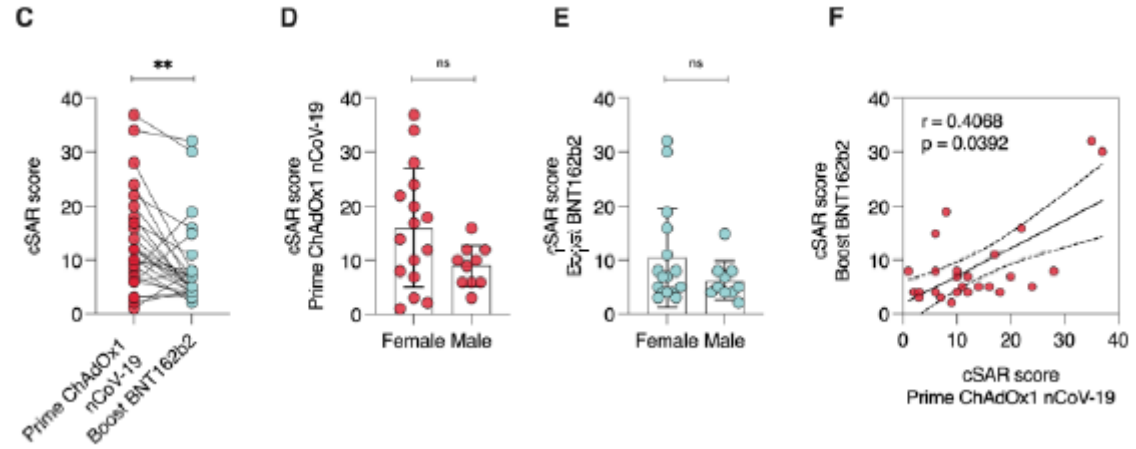
Percentages of participants with individual symptoms following prime (A) or boost (B) vaccination; severity is graded on a scale of 1-2 (for some symptoms) or 1-3 (for most), according to Common Terminology Criteria for Adverse Events (US Department of Health and Human Services, Version 4.03).

Figure 3 – Solicited adverse reactions following 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 Health and Human Services, Version 4.03).

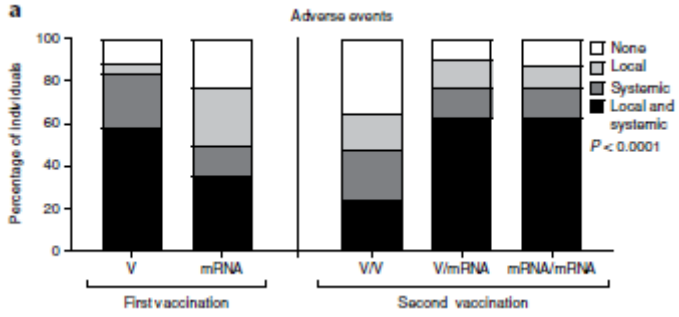
Figure 4 – Cumulative solicited adverse reaction (cSAR) scores of all participants following prime and boost vaccination



*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*

In a larger German study, 216 immunocompetent individuals were assigned to one of three vaccination regimens: homologous AstraZeneca (ChAdOx1) vaccination (V/V, n = 55), homologous mRNA vaccination (mRNA/mRNA, n = 64) and heterologous ChAdOx1/mRNA vaccination (V/mRNA, n = 97).[51] Three individuals were excluded from further analysis due to IgG positivity in a SARS-CoV-2 nucleocapsid ELISA. Adverse events within the first week after the priming and second doses were self-reported based on a standardized questionnaire (Figure 5). Local reactions, such as pain at the injection site and swelling, were similar after priming with the vector and mRNA vaccines. However, participants reported significantly more systemic adverse events, including fever, chills, gastrointestinal events, headache, fatigue, myalgia or arthralgia, after the vector vaccine; participants also reported more frequent use of antipyretic drugs. When comparing reactogenicity after secondary vaccination, both local and systemic events were markedly less frequent in vector-primed individuals after the second vector vaccine. Second vaccination with an mRNA vaccine was less well tolerated in both vector- and mRNA-primed individuals, and the spectrum of local and systemic adverse events was very similar for both groups. Thus, **heterologous boosting** was **well tolerated and comparable to homologous mRNA second vaccination**.

Figure 5 – Reactogenicity within the first week after primary and secondary vaccination with homologous and heterologous regimens



First vaccination: V: vector (n = 150) and mRNA vaccine (mRNA, n = 48); second vaccination with homologous (V/V, n = 54; mRNA/mRNA, n = 48) and heterologous (V/mRNA, n = 95) vaccine regimens

In a participant-blinded, randomized, non-inferiority trial performed in the UK, 463 adult participants with no or well controlled comorbidities and no previous SARS-CoV-2 infection by laboratory confirmation (mean age: 57.8 years (SD 4.7)) were randomly assigned to receive ChAd/ChAd (AstraZeneca; n=90), ChAd/BNT (AstraZeneca/ Pfizer–BioNTech; n=90), BNT/BNT (n=93), or BNT/ChAd (n=90), with a 28-day prime-second dose interval. Safety analyses were done among participants receiving at least one dose of a study vaccine.[49] An **increase in systemic reactogenicity** after second vaccination in participants receiving **heterologous schedules** compared with homologous schedules with the same prime vaccine was observed. Overall, there were 316 adverse events in 178 participants up to 28 days after second immunization. No significant difference was observed between the vaccine schedules in the proportion of participants with at least one adverse event (p=0·89). Among all participants up to June 6th, 2021 (date of data lock), there were seven adverse events of special interest, of which four were Covid-19 diagnoses. Three of the cases of COVID-19 diagnosis were within 7 days of prime immunisation; one was 54 days after prime immunisation, and the individual had not received their planned 28-day second vaccination due to travel. The non-COVID-19 adverse events of special interest were not considered to be related to immunisation. **Four serious adverse events** occurred across all groups, none of which were considered to be related to immunisation.

In a Spanish phase 2, open-label, randomised, controlled trial in adults (aged 18–60 years), vaccinated with a single dose of ChAdOx1-S 8 to 12 weeks before screening, and no history of SARS-CoV-2 infection, 676 participants were randomly assigned (2:1) to receive either BNT162b2 (0·3 mL) (intervention group, n=450) or continue observation (control group, n=226).[54] Seven day reactogenicity analysis was based on solicited adverse events in 448 individuals from the intervention group. The following systemic adverse reactions were reported: headache (n=199 [44%]), myalgia (n=194 [43%]), and malaise (n=187 [42%]), and fever (n=11 [2%]). Injection site pain (n=395 [88%]), induration (n=159 [35%]), and erythema (n=139 [31%]) were the most commonly reported local reactions. Of 1 771 solicited adverse events reported in the 7 days after vaccination in the

intervention group, most were mild (n=1 210 [68%]) or moderate (n=530 [30%]), and self-limited. In 31 participants, the most frequent severe adverse events were malaise (n=7 [23%]), myalgia (n=6 [19%]), and headache (n=5 [16%]).

The Danish study (pre-print), which included 136 551 individuals who were vaccinated with the AstraZeneca Covid-19 vaccine (ChAdOx1) as the first dose and who received an mRNA vaccine as the second dose, does not provide information on safety aspects.[50]

Similarly, the German study on more than 480 individuals who were primed with AstraZeneca Covid-19 vaccine (ChAdOx1) and who received an mRNA Covid-19 vaccine as second dose (BioNTech-Pfizer) only report on effectiveness and not on safety aspects.[53]

3.6 Effectiveness and safety after three doses of Covid-19 vaccine

As currently no clinical effectiveness data are available, only immune response data are presented in the following paragraphs.

3.6.1 Literature search

On 4 August, 2021, two searches were performed in Pubmed (((covid-19[Title/Abstract] OR SARS-CoV-2[Title/Abstract]) AND (vaccine[Title/Abstract])) AND (boost[Title/Abstract]) – filter: last year; ((((covid-19[Title/Abstract] OR SARS-CoV-2[Title/Abstract]) AND (vaccine[Title/Abstract])))) AND (three AND doses) – filter: last year), which resulted in 116 and 80 hits, respectively. Screening of titles and abstracts resulted in two full text documents which were included in the literature review. [32, 55]

In addition, a search for pre-publications (https://www.medrxiv.org/; "COVID-19 AND vaccine AND boost" - filter: between 01 May, 2021 and 04 Aug, 2021) yielded 245 hits. After screening of titles and abstracts, two full text documents were identified, which were included in the literature review. [56, 57] Publications in pre-print status at the time of the search are indicated with 'pre-print'.

Three more publications were identified by the experts.[1, 58, 59]

A narrative review of the retrieved publications is presented below.

3.6.2 Healthy adults

Interim results are available from a double-blind, randomized, placebo-controlled phase 2 clinical trial in China in which 540 healthy adults (aged 18-59 years) received a third dose of the CoronaVac vaccine (pre-print; Box 1).[56]

3.6.2.1 Immune response

The primary outcome was **geometric mean titres** (GMTs) of neutralizing antibody to live SARS-CoV-2.

In the 3 µg group, neutralizing antibody titres induced by the first two doses declined after 6-8 months to below the seropositive cut-off (Schedule 2: GMT= 4.1 [95%CI 3.3-5.2]; schedule 4: GMT= 6.7 [95%CI 5.2-8.6] for). When a third dose was given 6-8 months after a second dose, GMTs assessed 14 days later increased to 137.9 [95%CI 99.9-190.4] for schedule 2, and 143.1 [95%CI 110.8-184.7] for schedule 4, approximately **3-fold above** Schedule 1 and Schedule 3 GMTs after third doses.

In the 6 µg group, similar patterns were observed.

Box 1 – Pan et al., 2021[56] (pre-print)

- **Country:** China
- **Design:** double-blind, randomized, placebo-controlled phase 2 clinical trial (interim results)
- **Subjects:** 540 healthy adults, aged 18-59 years
- **Vaccine:** CoronaVac (Dose 1, 2 & 3)
- **Schedule(s):**
  - Schedule 1: days 0, 14, 42; 3 subgroups: medium dose* (n=60), high dose (n=60) and placebo (n=30) – third dose: n=139
  - Schedule 2: days 0, 14, 194; 3 subgroups: medium dose* (n=60), high dose (n=60) and placebo (n=30) – third dose: n=141
  - Schedule 3: days 0, 28, 56; 3 subgroups: medium dose* (n=60), high dose (n=60) and placebo (n=30) – third dose: n=130
  - Schedule 4: days 0, 28, 208; 3 subgroups: medium dose* (n=60), high dose (n=60) and placebo (n=30) – third dose: n=130
- **Follow-up:**
  - Schedule 1 & 3: six months after third dose
  - Schedule 2 & 4: six months after second dose

**Medium dose: 3 µg per 0.5 mL of aluminium hydroxide diluent per dose; high dose: 6 µg per 0.5 mL of aluminium hydroxide diluent per dose*

3.6.2.2 Safety

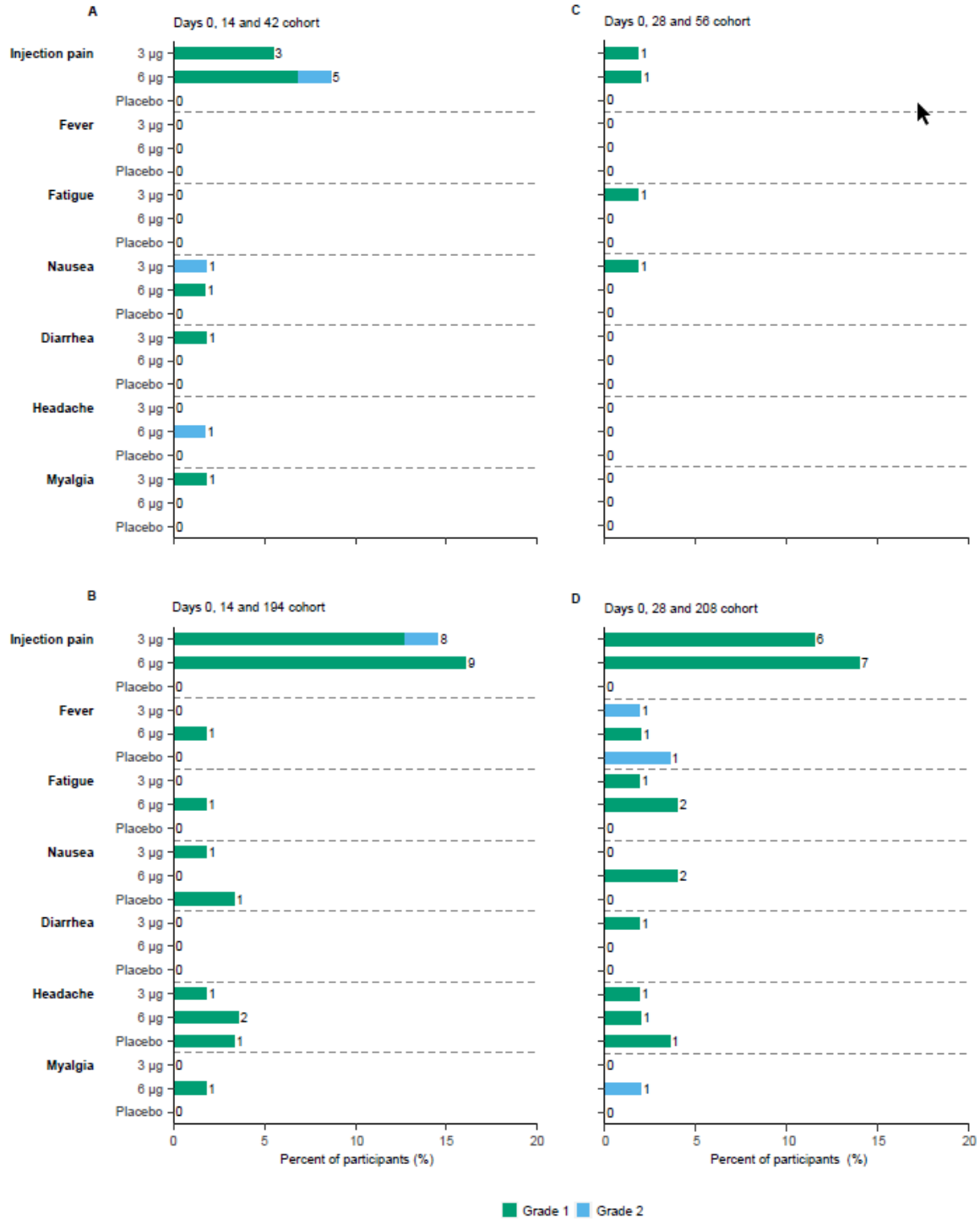
Participants were required to record injection-site adverse events (e.g., pain, redness, swelling), or systemic adverse events (e.g., allergic reaction, cough, fever) on diary cards within 7 days after the third dose. From days 8-28 after the third dose, unsolicited adverse reactions were collected by spontaneous reporting from participants. Serious adverse events were collected until 6 months after the second dose for schedule 2 and 4 groups, and until 6 months after three doses for schedule 1 and 3 groups.

The severity of solicited **local and systemic adverse reactions** reported within 28 days after the third dose were grade 1 to grade 2[a] in all vaccination cohorts (Figure 6). The most common reported reaction was injection-site pain. Incidences of adverse reactions after the third dose were 7.91% and 3.08% for schedule 1 and schedule 3; in the 3 µg group, the overall incidence of adverse reactions with 28 days after the third dose was ten (18.18%) of 55 participants in schedule 2 and ten (19.23%) of 52 in schedule 4, which was similar with the highest incidence of adverse reactions for schedule 1 (18.33%) after the first dose) and schedule 3 (18.33% after the first dose). Most adverse reactions were grade 1 in severity. There were no significant differences among the 3 µg, 6 µg, and placebo groups in any of the schedules.

A total of fourteen **serious adverse** events among nine participants were reported from the beginning of vaccination to 6 months after the second dose for schedule 2 and 4, and to 6 months after the third dose for schedule 1 and 3. None of the serious adverse events were considered by the investigators to be related with vaccination. The authors do not specify after which dose the serious adverse events occurred.

[a] Grading according to China National Medical Products Administration guideline.

Figure 6 – Incidence of selected adverse reactions within 28 days after the third dose[56]



3.6.3 Lymphoid malignancies

In France (Nice), a prospective case series was analysed on 45 patients with lymphoid malignancies, who were given a third dose of Pfizer–BioNTech (pre-print; Box 2).[57]

3.6.3.1 Immune response

Among the 43 assessable patients, 18 (n=9 CLL, n=8 NHL, n=1 MM; 41.8%) patients had **no anti-S Abs before dose 3** was administered; they all remained negative after dose 3. Fourteen of these 18 patients had already received an anti-CD20 Mab treatment, nine of them within the 12 months

preceding the vaccine. One seronegative patient with MM was under active treatment for HIV infection.

Among the 25 patients with **positive anti-S titres before dose 3**, all patients remained positive and 23 of them increased their anti-S titre after dose 3. Their median anti-S titre increased from 87.1 U/mL [range: 1.2-693] to 3386 U/mL [range: 6.6-20312] ($p < 0.001$).

Patients with CLL and/or with previous anti-CD20 therapy treated within 12 months of administration of dose 3 had no significant increase of the humoral response. Among 22 available patients (CLL n=10, NHL n=12), dose 3 significantly increased the median IFN-gamma secretion. On eight (36.4%) patients who were double-negative for both immune and cellular response, five (22.7%) patients remained double-negative after dose 3.

Box 2 – Re et al., 2021[57] (pre-print)

- **Country:** France (Nice)
- **Design:** case series
- **Subjects:** 45 adult patients (median age of 43 patients included in analysis: 77 years [range: 37-92]
  - Chronic lymphocytic leukemia (CLL): n=15
  - Indolent and aggressive B cell non-Hodgkin lymphoma (NHL): n=14
  - Multiple myeloma (MM): n=16
- **Vaccine:** Pfizer–BioNTech (BNT162b2; Dose 1, 2 & 3)
- **Schedule(s):** dose 3 given 78 days [range: 47-114] after dose 2* of the same vaccine
- **Follow-up:** not reported

**Not specified when dose 2 was given*

3.6.3.2 Safety

Among the 43 patients no novel adverse events were observed after the third dose.[57]

3.6.4 Hemodialysis

Another French study assessed the efficacy and safety of a third dose of vaccine BNT162b2 (Pfizer–BioNTech) in **maintenance hemodialysis** (MHD) patients (**Box 3**).[1] The third dose was administered to 56/66 (84.8%) of MHD patients with suboptimal anti-RBD IgG response and also to 19/40 (47.5%) MHD patients with optimal IgG response. The following patients were excluded from the third dose: diagnosis of COVID-19 within the last 3 months, organ transplantation within the last 3 months, Rituximab injection within the last 3 months, ongoing flare of vasculitis, acute sepsis, major surgery within the last 2 weeks.

Box 3 – Espi et al., 2021[1] (pre-print)

- **Country:** France (Lyon)
- **Design:** case series
- **Subjects:** 75 patients in maintenance hemodialysis (MHD; 56 with suboptimal anti-RBD IgG response and 19 with optimal IgG response after two doses; mean age: 65.8± 14.4 years)
- **Vaccine:** Pfizer–BioNTech (BNT162b2; Dose 1, 2 & 3)
- **Schedule(s):** third dose 'within 3 months after the second vaccine injection'
- **Follow-up:** immune response assessed 10 to 14 days after the 3rd vaccine injection; data on adverse events collected within 7 days after 3rd vaccine

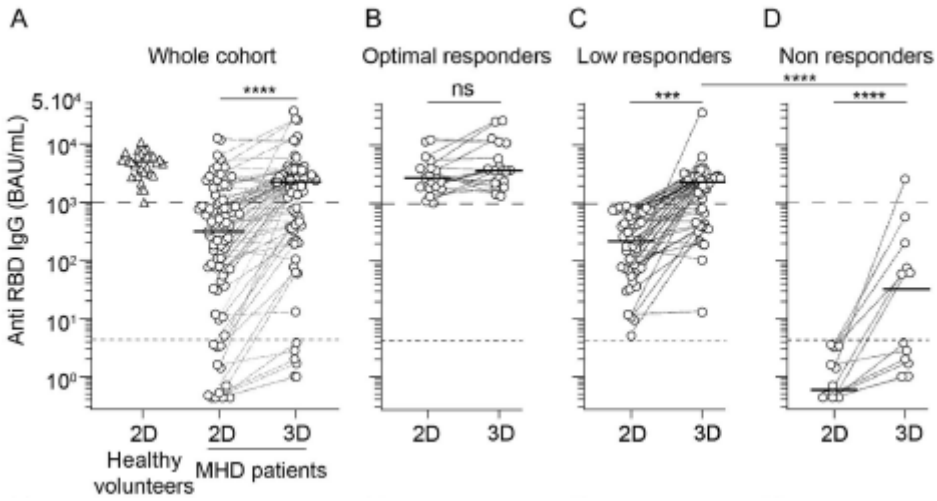
3.6.4.1 Immune response

When the whole cohort of MHD patients (n=75) was considered, a significant increase in the median titre of anti-RBD IgG was observed after the third dose of the vaccine (309.8 [36.5 –996.3] vs. 2 212 [394.9 – 3247]; p<0.0001) binding arbitrary units (BAU)/mL after the second and third dose, respectively. However, this **global positive result hides major inter-individual heterogeneity**.

The 19 MHD patients with **optimal humoral response** after the second dose of vaccine, all maintained high levels of anti-RBD IgG after the third dose but **without significant increase of their titre** (2724 [1812 – 4018] vs 3620 [2212 – 10907] BAU/mL after the second and third dose, respectively; p=0.087;Figure 7).

The remaining 56 MHD patients with **suboptimal humoral response** after the second dose were divided into two categories: i) those with anti-RBD IgG titre below the threshold of positivity of the assay (dotted line Figure 7A): non responders (n=12), and ii) those with low but detectable levels of anti-RBD IgG: low responders (n=44). In contrast with MHD patients with optimal humoral response after the second dose, both of the suboptimal humoral response subgroups experienced a significant increase of anti-RBD IgG after the third dose: 217.8 [71.2 – 617.9] vs 2281 [441.4 – 2855] BAU/mL (Figure 7C; p<0.0001) for low responders and 0.61 [0.43 – 2.8] vs 31.5 [1.76 – 171.8] BAU/mL (Figure 7D; p=0.0005) for non-responders. However, 29/44 (66%) of low responders but only 1/12 (8%) of non-responders reached optimal titre of anti-RBD IgG (Figure 7C-D; p= 0.0006). In fact, half of non-responders after the second dose of vaccine remained without detectable anti-RBD IgG after dose three (6/12, 50%; Figure 4D), while the rest (5/12, 42%; Figure 7D) did develop anti-RBD IgG but at suboptimal titres.

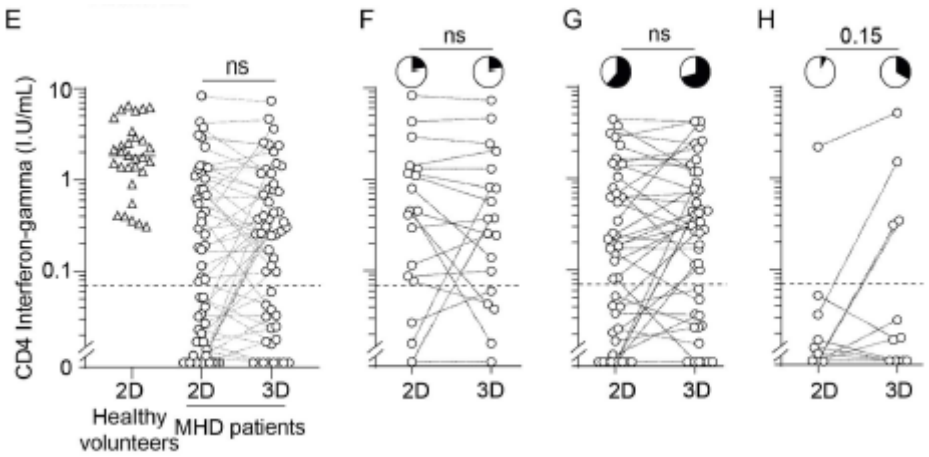
Figure 7 – Evolution of humoral response between the second and third vaccine dose in MHD patients



Immune effectors directed against the spike protein of SARS-Cov-2 were quantified in 30 healthy volunteers (open triangles) after second vaccine dose and in 75 MHD patients (open circles) after the second and third dose; A-D/ Anti RBD-IgG titres expressed in binding arbitrary units (BAU/mL). Upper dashed line represents the lowest value observed in healthy volunteers after the standard (2 doses) scheme of vaccination and define the threshold for optimal response. MHD patients with sub-optimal response after the second dose of vaccine were further divided into non-responders and low responders, depending whether anti RBD-IgG titre was respectively below or above the threshold of positivity (dotted line) of the assay (Figure 7A). Evolution of anti RBD-IgG titres between the second and third dose of vaccine were compared in optimal responders (n=19, Figure 7B), low responders (n=44, Figure 7C) and non-responders (n=12, Figure 7D). Wilcoxon test.

The **T cell responses** of MHD patients after the second dose was **much more heterogeneous** than that of healthy volunteers (Figure 8). The third dose of vaccine did not result in a significant increase in spike-specific CD4+ T cells in the circulation of MHD patients, neither when the amount of IFN gamma (0.101 [0.016 - 0.856] vs. 0.269 [0.030 – 0.825] I.U/mL; p=0.817) nor when the proportion of MHD patients with detectable spike-specific CD4+ T cells (57% vs. 64%; p=0.50) were considered (Figure 8E).

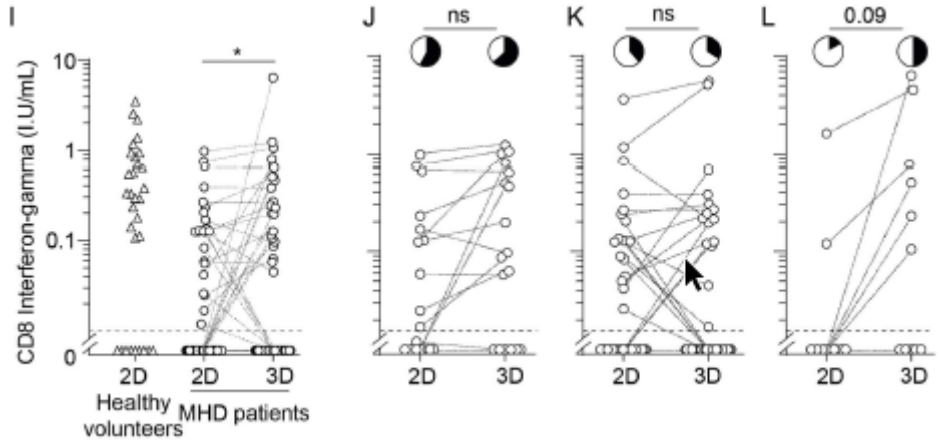
Figure 8 – Evolution of cellular response (CD4+ T cells) between the second and third vaccine dose in MHD patients



E: Secretion of interferon gamma by circulating spike-specific CD4+ T cells; F-H: The proportion of MHD patients with spike-specific CD4+ T cells were compared between the second and third dose of vaccine for optimal- (F), low- (G), and non-responders (H); ns: non-significant.

In contrast with CD4+ T cell response, the third dose of vaccine induced a significant increase in the production of IFN gamma by spike-specific CD8+ T cells of MHD patients: 0 [0 – 0.093] vs. 0 [0 - 0.206] I.U/mL (p=0.015; Figure 9 I). Interestingly, the stronger effect was observed in the subpopulation of MHD patients with no-response after the second dose of vaccine, the proportion with detectable spike-specific CD8+ T cells increases from 17% to 50% between the second and third dose (p=0.09; Figure 9 J-L)

Figure 9 – Evolution of cellular response (CD8+ T cells) between the second and third vaccine dose in MHD patients

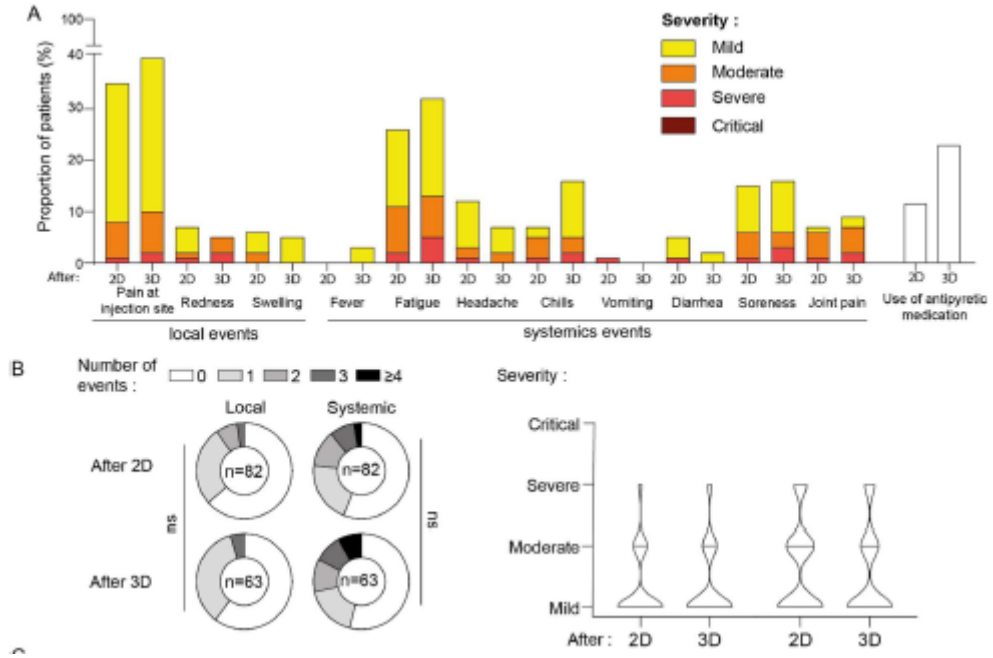


*I: Secretion of interferon gamma by circulating spike-specific CD8+ T cells; F-H: The proportion of MHD patients with spike-specific CD8+ T cells were compared between the second and third dose of vaccine for optimal- (F), low- (G), and non-responders (H); ns: non-significant; ****, p<0.0001.*

3.6.4.2 Safety

Local and systemic adverse events and use of anti-pyretic medications within 7 days after the third dose were collected retrospectively, based on a self-assessment questionnaire; tolerability data were available for 63/75 (84%) after the third dose. No patients developed critical side effects requiring hospitalization. Forty-six percent (29/63) reported systemic side effects, including fatigue (32%), chills (16%) and soreness (16%). Forty percent (25/63) developed local side effects, the most frequently reported being pain at the injection site (40%). In almost all cases (74/83, 89%) the intensity of the symptoms was mild or moderate.

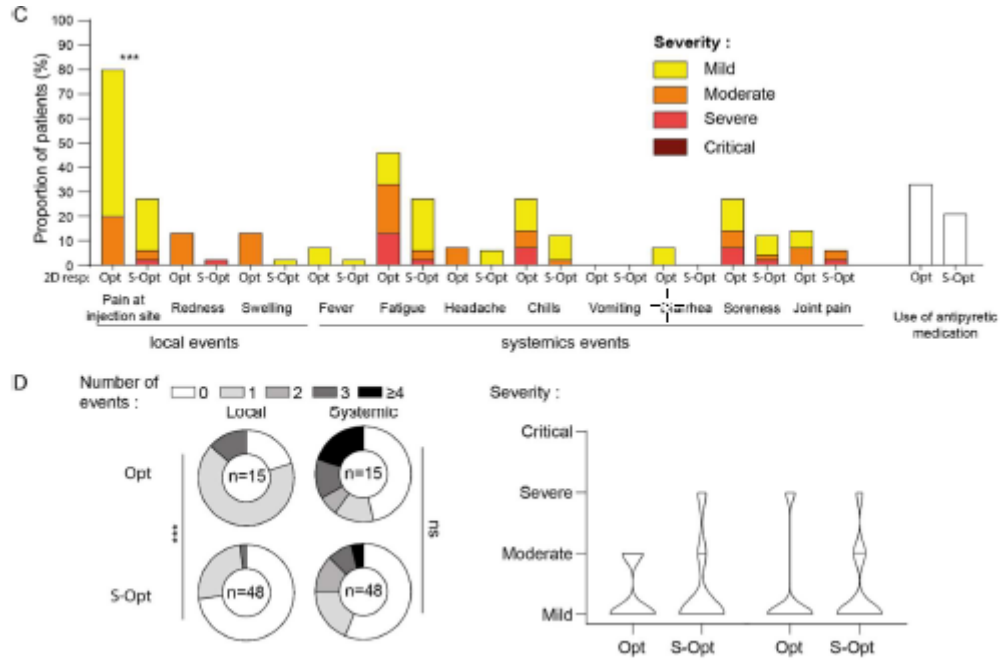
Figure 10 – Reactogenicity to the 3rd dose of mRNA vaccine in MHD patients after second and third dose of vaccine[1]



2D: second dose; 3D: third dose; pain at the injection site was assessed according to the following scale: mild, does not interfere with activity; moderate, interferes with activity; severe, prevents daily activity; and critical, emergency department visit or hospitalization. Redness and swelling were measured according to the following scale: mild, 2.0 to 5.0 cm in diameter; moderate, >5.0 to 10.0 cm in diameter; severe, >10.0 cm in diameter; and critical, necrosis or exfoliative dermatitis (for redness) and necrosis (for swelling). Fever categories were mild, 38.0°C to 38.4°C; moderate > 38.4°C to 38.9°C; severe, >38.9°C to 40° and critical, >40°C. Medication use was not graded. Additional scales were as follows: fatigue, headache, chills, new or worsened muscle pain, new or worsened joint pain (mild: does not interfere with activity; moderate: some interference with activity; or severe: prevents daily activity), vomiting (mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; or severe: requires intravenous hydration), and diarrhea (mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; or severe: 6 or more loose stools in 24 hours); critical for all events indicated an emergency department visit or hospitalization.

For several side effects, the frequency was higher after the third dose (Figure 11), but the differences were not statistically significant (*Note: due to the small sample size?*). The authors further note that when the profile of tolerance was compared between MHD patients according to the intensity of the humoral response after the second dose of the vaccine, a significant trend for more side effects was observed in patients with an optimal response (who did not improve significantly their immune response against the spike protein of SARS-Cov-2 after this additional injection; Figure 11).

Figure 11 – Reactogenicity to the 3rd dose of mRNA vaccine in MHD patients according to their humoral status after the 2nd injection[1]



*Optimal (Opt; n=19): same titre than healthy volunteers vs. sub-optimal (S-Opt; n=56): lower titre than healthy volunteers; ****: p<0.0001.*

3.6.5 Organ transplant recipients

So far four publications were retrieved on solid organ recipients who received a third dose of a Covid-19 vaccine: two French studies (one in Toulouse, which is described in two publications,[32, 55] and another performed in Strasbourg[59]) and one American study.[58]

3.6.5.1 Immune response

In the **French** study which included **396 patients with solid organ transplants** (Box 4), **t**he prevalence of anti–SARS-CoV-2 antibodies was 1.3 % (95% CI, 0.2 % to 2.4 %; 5 out of 396 patients) before the first injection, 5.1 % (95% CI, 3.0 % to 7.4 %; n = 20) before the second one, 41.4 % (95% CI, 36.5 % to 46.3 %; n = 164) before the third one, and 67.9 % (95% CI, 63.3 % to 72.6 %; n = 269) 4 weeks after the third dose, p<0.0001 (Figure 12).[55] Among the 232 patients who were seronegative before the third dose, 105 (45.25%) turned positive. All patients who were seropositive before the third dose were still seropositive 4 weeks later. Figure 12 illustrates the immunogenicity after three doses BNT162b2 in the first 101 solid organ transplant patients of the same study which were published by Kamar et al., 2021.[32]

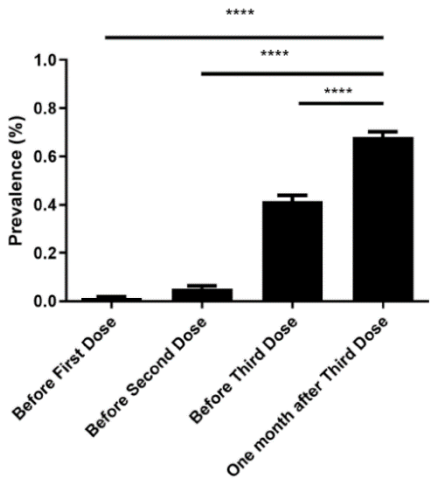
Box 4 – Del Bello et al., 2021*[55] (Kamar et al., 2021[32])**

- **Country:** France (Toulouse)
- **Design:** case series
- **Subjects:** 396 patients with solid organ transplants
- **Vaccine:** Pfizer–BioNTech (BNT162b2; Dose 1, 2 & 3)
- **Schedule(s):** dose 1 and 2 were given one month apart; the third dose was administered 59 (IQR: 47-67) days after the second dose
- **Follow-up:** immune response assessed 4 weeks after the 3rd vaccine injection

**: Publication by Del Bello et al., 2021 currently limited to an abstract and 4 figures; **: publication by Kamar et al., 2021 restricted to first 101 patients discussed in the paper by Del Bello et al.*

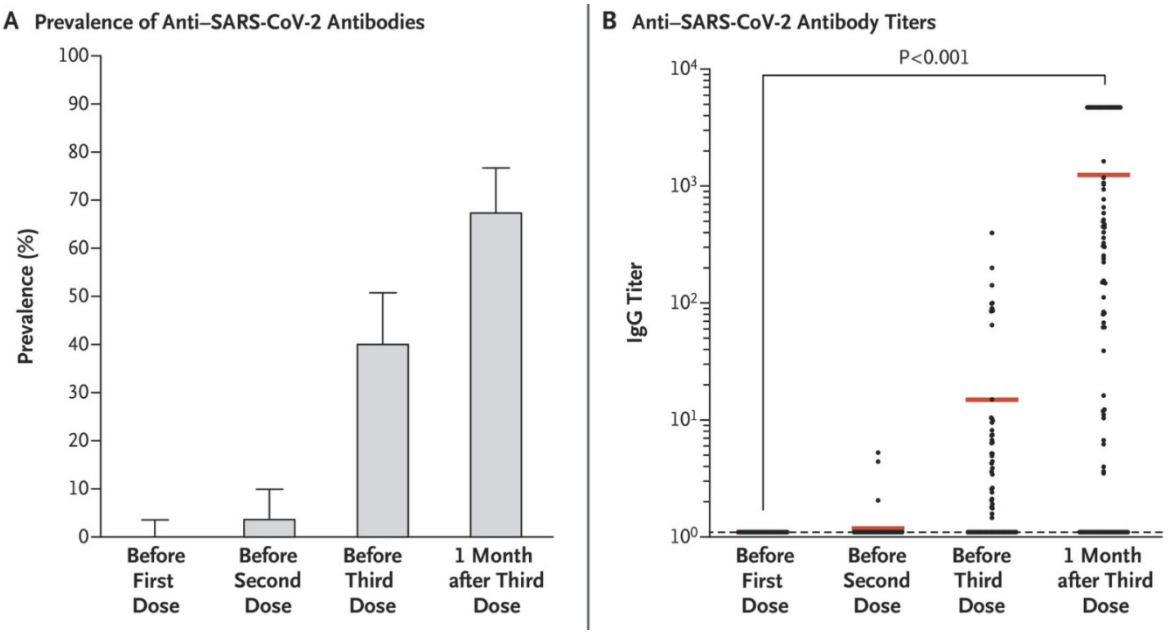
Multivariable analyses indicated that patients receiving mycophenolic acid (OR= 0.28, 95%CI [0.14-0.54], p=0.0002) or belatacept (OR= 0.14, 95%CI [0.43- 0.46], p=0.001), and patients who received at least a triple immunosuppression (OR= 0.42, 95%CI [0.21- 0.86], p=0.02) presented a lower seroconversion rate. After 3 doses, the seroconversion rate remained low in patients given belatacept with [5/16 (31%)] or without [3/9 (33%)] mycophenolic acid.

Figure 12 – Immune response after three doses BNT162b2 in 396 solid organ transplant patients



Note: Results are means ± SEM

Figure 13 – Immunogenicity after three doses BNT162b2 in 101 solid organ transplant patients[32]



Panel A shows the prevalence of anti–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies before and after vaccination in the study population. Panel B shows anti–SARS-CoV-2 antibody titres before and after vaccination in the study population.

In another French study, all kidney transplant patients with a negative history for COVID-19 and SARS-CoV-2 antispike IgG levels less than 50 arbitrary units (AU)/mL on the day of the first vaccine injection and 1 month after the second dose, received a third dose (100 µg) of the Moderna vaccine (mRNA-1273).[59] Ninety-five patients (59.7%) had no antibody response after 2 doses (titres <6.8

AU/mL), and 64 patients (40.3%) showed a response below the positivity limit (titres, 6.8-49.9AU/mL).

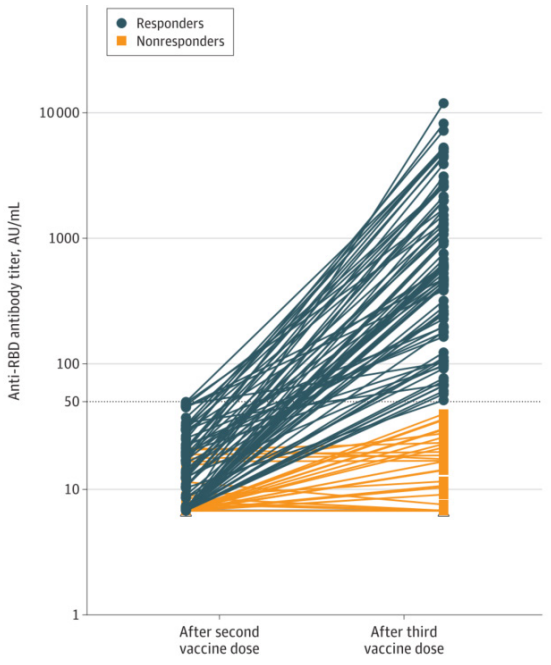
Box 5 – Benotmane et al., 2021[59]

- **Country:** France (Strasbourg)
- **Design:** case series
- **Subjects:** 159 kidney transplant recipients* (median age: 57.6 years [IQR: 49.6-66.1])
- **Vaccine:** Moderna
- **Schedule(s):** the third vaccine dose was given at a median of 51 days [IQR: 48 to 59] after the second dose of their initial vaccine series
- **Follow-up:** immune response assessed at a median of 28 days (IQR, 27-33 days) after the third vaccine injection

**In 84 (52.8%) patients, immunosuppression maintenance therapy comprised Tacrolimus, mycophenolate mofetil/mycophenolic acid and steroids; 75 (47.2%)had 'other regimens'.*

At a median of 28 days (IQR, 27-33 days) after the third vaccine injection, 78 patients (49%) had antibody levels greater than 50 AU/mL (median antibody titres of responders, 586AU/mL; IQR, 197.2-1920.1 AU/mL) (Figure 14). **Patients who had a weak response after the second dose** were **more likely to develop an antibody response** after the third dose compared with those without an antibody response (81.3% vs 27.4%, respectively; mean adjusted difference of antibody titres, 894.89 AU/mL [95% CI, 377.41-1410.37]; p = 0.001). Patients taking tacrolimus, mycophenolate, and steroids were less likely to develop anti–SARS-CoV-2 antibodies than those treated with other regimens (35% vs. 63%, respectively; mean adjusted difference of antibody titres, −697.28AU/mL [95%CI, −1193.00to −201.56]; p = 0.006).

Figure 14 – Immunogenicity after three doses Moderna vaccine in 159 kidney transplant patients[59]



Horizontal dotted line indicates the cutoff for positivity (50 arbitrary units [AU]/mL). Blue lines indicate the antibody titers of kidney transplant recipients who seroconverted after the third dose (titers ≥50 AU/mL); orange lines, the evolution of antibody titers among nonresponders (titers <50 AU/mL). mRNA indicates messenger RNA.

In the **American** study (Box 6) with **30 solid organ recipients**, all patients were tested for antibodies against the spike protein at a median of 9 days (IQR, 2 to 33 days) before they received their third dose of vaccine; 24 patients had negative antibody titres and 6 patients had low-positive antibody titres.[58] Antibody testing was repeated a median of 14 days (IQR, 14 to 17 days) after the third dose of vaccine. Of the 6 patients with low-positive antibody titres before the third dose, all had high-positive antibody titres after the third dose. In contrast, of the 24 patients with negative antibody titres before the third dose, only 6 (25%) had high-positive antibody titres after the third dose. Two (8%) had low-positive antibody titres, and 16 (67%) remained negative.

Box 6 – Werbel et al., 2021[58]

- **Country:** USA (Baltimore)
- **Design:** case series
- **Subjects:** 30 patients* with solid organ transplants (median age: 57 years [IQR: 44 to 62])
- **Vaccine:**
  - Dose 1 & 2: Pfizer–BioNTech – Dose 3: Johnson & Johnson/Janssen (n=7)
  - Dose 1 & 2: Pfizer–BioNTech – Dose 3: Moderna (n=7)
  - Dose 1 & 2: Pfizer–BioNTech – Dose 3: Pfizer–BioNTech (n=3)
  - Dose 1 & 2: Moderna – Dose 3: Johnson & Johnson/Janssen (n=8)
  - Dose 1 & 2: Moderna – Dose 3: Moderna (n=3)
  - Dose 1 & 2: Moderna – Dose 3: Pfizer–BioNTech (n=2)
- **Schedule(s):** the third vaccine dose was given at a median of 67 days [IQR: 54 to 81] after the second dose of their initial vaccine series
- **Follow-up:** immune response assessed at a median of 14 days (IQR,14 to 17 days) after the 3rd vaccine injection

**: In 25 patients, maintenance immunosuppression included tacrolimus or cyclosporine plus mycophenolate; corticosteroids were used for 24 patients, sirolimus for 1, and belatacept for 1.*

3.6.5.2 Safety

Kamar et al. (Box 4) notes that no serious adverse events were reported after the administration of the third dose, and no acute rejection episodes occurred in their study on 101 consecutive **solid organ transplant recipients** who were given three doses of the Pfizer–BioNTech vaccine.[32] The authors come to the same conclusion when there case series is extended to 396 patients.[55]

The other French study which included 159 **kidney transplant** recipients who were offered a third dose of Moderna vaccine (Box 5), only reported that no severe adverse events were observed after the third dose.[59]

In the American study on **solid organ transplant patients** (Box 6), 23 of the 30 included patients completed a questionnaire 7 days after receiving their third dose (Johnson & Johnson/Janssen Vaccine, Pfizer/BioNTech or Moderna; Table 10).[58] The most frequent systemic reaction was mild or moderate fatigue in 14 participants; 1 patient reported severe headache, and 1 patient reported severe myalgia. No patient reported fever, and no anaphylactic reactions or neurologic complications were observed. One heart transplant recipient had biopsy-proven, antibody-mediated rejection 7 days after her third dose of vaccine in the setting of acute volume overload. She did not experience an increase in her titre of antibodies against the spike protein, heart function remained normal, and immunosuppressive intensification was not initiated. Fifteen patients reported mild or moderate local reactions, and 1 reported severe arm pain.

Table 10 – Self-Reported reactions by 23 patients after a third dose of vaccine[58]

Reaction and Severity*	Johnson & Johnson/ Janssen Vaccine Recipients (*n* = 11‡), *n* (%)	mRNA Vaccine† Recipients (*n* = 12‡), *n* (%)
Local symptoms		
Pain		
None	5 (45)	0 (0)
Mild	5 (45)	6 (50)
Moderate	1 (9)	5 (42)
Severe	0 (0)	1 (8)
Redness		
None	9 (82)	8 (67)
Mild	1 (9)	3 (25)
Moderate	1 (9)	1 (8)
Swelling		
None	9 (90)	8 (67)
Mild	0 (0)	2 (17)
Moderate	1 (10)	2 (17)
Systemic symptoms		
Fever (none)	11 (100)	11 (100)
Chills		
None	9 (82)	11 (92)
Mild	1 (9)	0 (0)
Moderate	1 (9)	1 (8)
Headache		
None	6 (55)	6 (50)
Mild	3 (27)	3 (25)
Moderate	2 (18)	2 (17)
Severe	0 (0)	1 (8)
Fatigue		
None	3 (27)	6 (50)
Mild	5 (45)	3 (25)
Moderate	3 (27)	3 (25)
Myalgia		
None	7 (64)	8 (67)
Mild	2 (18)	4 (33)
Moderate	1 (9)	0 (0)
Severe	1 (9)	0 (0)
Diarrhea		
None	10 (91)	10 (83)
Mild	1 (9)	2 (17)

* Symptoms were defined as mild if they did not interfere with daily activities, moderate if they produced some interference with daily activity, and severe if they prevented daily activity.
† Pfizer/BioNTech or Moderna.
‡ Questionnaires were not reported for 4 Johnson & Johnson/Janssen vaccine recipients and 3 mRNA vaccine recipients.

3.6.6 Overview of side effects for the retrieved studies

Table 11 – Overview of reported side effects of a third dose

Country (vaccine) & reference	Population	Systemic adverse events	Local adverse events	Serious adverse events
China (CoronaVac; pre-print)[56]	540 **healthy** adults (4 different schedules; in each schedule: medium, high dose and placebo)	Fever: 3/540 (0.6%); fatigue: 5/540 (0.9%); nausea: 6/540 (1.1%); diarrhea: 2/540 (0.4%); headache: 6/540 (1.1%); myalgia: 3/540 (0.6%)	Injection pain: 40/540 (7.4%)	No exact incidence data for the third dose
US (Johnson & Johnson/Janssen Vaccine, Pfizer/BioNTech or Moderna)[58]	30 patients with **solid organ transplants**; adverse event data available for 23/30 (76.7%)	Fever: 0/23; chills: 3/23 (13.0%); headache: 11/23 (47.8%); fatigue: 14/23 (60.9%); myalgia: 8/23 (34.8%); diarrhea: 3/23 (13.0%)	Pain: 18/23 (78.3%); redness: 6/23 (26.1%); swelling: 6/23 (26.1%)	No anaphylactic reactions; no neurologic complications; 1 case of biopsy-proven, antibody-

Country (vaccine) & reference	Population	Systemic adverse events	Local adverse events	Serious adverse events
				mediated rejection in a heart transplant recipient
France (Pfizer–BioNTech) [32, 55]	396 patients with **solid organ transplants** (publication by Kamar restricted to first 101 patients)	Not reported	Not reported	No serious adverse events; no acute rejection episodes
France (Moderna)[59]	159 **kidney transplant recipients**	Not reported	Not reported	No severe adverse events
France (Pfizer–BioNTech; pre-print) [1]	75 patients in maintenance **hemodialysis** (56 with suboptimal anti-RBD IgG response and 19 with optimal IgG response after two doses); adverse event data available for 63/75 (84%)	Overall: 29/63 (46%); fatigue: 32%, chills: 16%; soreness: 16%	Overall: 25/63 (40%); pain at the injection site: 40%	No critical side effects requiring hospitalization
France (Pfizer–BioNTech; pre-print) [57]	43 **oncological** patients (15 with chronic lymphocytic leukemia, 14 with indolent and aggressive B cell non-Hodgkin lymphoma and 16 with multiple myeloma)	'No novel adverse events'	'No novel adverse events'	'No novel adverse events'

4 INTERNATIONAL OVERVIEW OF RECOMMENDATIONS ON AN EXTRA/BOOSTER VACCINE DOSE

This section provides an overview of the extra dose (< 6 months following primary vaccination) or the booster dose (> 6 months following primary vaccination) policies across selected countries. Special attention is given to start date of the extra/booster dose campaign, the time between completion of the primer vaccination[b] and administration of the extra/booster dose, target population, vaccine used for the extra/booster dose, and rationale for administering an extra/ booster dose. This section will be updated regularly in function of new information that becomes available.

Table 12 – Overview of extra/booster dose policies across selected countries

Country	Start date extra/booster dose campaign	Time between primer completion and extra/booster dose	Target population	Vaccine used
Canada	Booster vaccination not recommended due to lack of evidence			
Denmark	No indication for a third dose			
France	September 2021		TBC	Not specified
Germany	September 2021	6 months after second dose	Immunocompromised Facilities with vulnerable groups Very elderly living at home	mRNA
Israel	August 2021	Min. 5 months after second dose	People aged over 50 and immunocompromised Priority for people in elderly care facilities and geriatric hospitals	Not specified, likely Pfizer-BioNTech
Malta	Mid September 2021		Immunocompromised and immunosuppressed Residents of elderly care facilities	Not specified
Netherlands	No official decision on booster vaccination			
Sweden	No official decision on booster vaccination			
United Kingdom	September 2021		Stage 1: Immunosuppressed Residential care homes for elderly Adults aged over 70 16+ considered clinically extremely vulnerable Frontline health and social care workers	Not specified
United States	Regulatory approval as of 12 August 2021 for additional dose mRNA vaccines (Pfizer-BioNTech and Moderna) in certain immunocompromised individuals			

[b] Second dose for Vaxzevria, Comirnaty, and Spikevax, and first dose for Janssen

4.1 Canada

The National Advisory Committee on Immunization does not recommend booster vaccination in its update of 22 July 2021[c]. It refers to the lack of evidence on the need for booster doses after complete vaccine series and the fact that there is no immunological correlate of protection determined for SARS-COV-2. Therefore, all immunological evidence in support of vaccine efficacy is indirect and cannot directly be used to estimate efficacy.

4.2 Denmark

There are currently no signs for introducing a third dose in Denmark.

4.3 France

The Conseil d'Orientation de la Stratégie Vaccinale in France has published a recommendation on 6 April 2021[d] to systematically administer a third dose to the **severely immunocompromised**, i.e. solid organ transplant recipients, recent bone marrow transplant recipients, dialysis patients, patients with autoimmune diseases on strong immunosuppressive anti-CD20 or anti-metabolite therapy, patients with certain types of lymphoma treated with anti-CD20, and patients with chronic lymphocytic leukaemia. The extra dose is to be administered **4 weeks after the second dose** or as soon as possible in case this time period has already passed. The administered extra dose will be of the **same type of vaccine used for the primer vaccination**: people that have received an mRNA vaccine will receive a third dose of an mRNA vaccine and people that had received two doses of Vaxzevria will receive a third dose of Vaxzevria. For people aged under 55 who have received a heterologous vaccination regimen (first dose Vaxzevria and second dose an mRNA vaccine) will receive a third dose of an mRNA vaccine.

The extra dose will be administered in the centres where these patients are under treatment, as it was the case for the first and second dose. The estimated magnitude of the target population is 230.000 people.

The **rationale** for administering an extra dose is the high risk of severe COVID-19 for severely immunocompromised people, the uncertainty around the vaccine effectiveness in this group, and the recent insights that the antibody immune response elicited after two doses of vaccine is insufficient in severely immunocompromised individuals.

The Conseil d'Orientation de la Stratégie Vaccinale recommends that all severely immunocompromised people are prescribed a **quantitative anti-S serology test** 30 days after the administration of the third dose. It also mentions the need for developing **clinical trial protocols evaluating different approaches** to increase the immune response of this target population and thus their immunity, in particular to investigate the effectiveness of the recombinant protein vaccines that make use of an adjuvant which may elicit a better response in severely immunocompromised people.

On 5 August 2021, president Macron has announced on social media that France will offer a booster dose to seniors and vulnerable people, citing decline in antibodies and concerns on the Delta variant. The administration will start in September 2021. The precise definition of the target population will be discussed in the week of 9 August 2021[e]. The type of vaccine to be used is not yet determined.

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[c] National Advisory Committee on Immunization (2021). Recommendations on the use of COVID-19 vaccines. Last updated 22 July 2021. Consulted on 8 August 2021 via Recommendations on the use of COVID-19 vaccines - Canada.ca

[d] Conseil d'Orientation de la Stratégie Vaccinale. Avis de 6 avril 2021 : Elargissement des priorités d'accès à la vaccination antiCovid-19 - mise à jour du 7 mai 2021. Consulted on 5 August 2021 via https://solidarites-sante.gouv.fr/IMG/pdf/avis_du_cosv_6_avril_2021pdf.pdf

[e] LCI (2021). Vers une troisième dose en France ? Arbitrage attendu "la semaine prochaine". Last updated 4 August 2021. Consulted on 8 August 2021 via https://www.lci.fr/sante/covid-19-vers-une-troisieme-dose-en-france-de-vaccin-contre-le-coronavirus-arbitrage-attendu-la-semaine-prochaine-2193032.html

4.4 Germany

The German Health Ministers Conference decided on 2 August 2021[f] to offer a booster vaccination as of September 2021 in **care facilities, integration assistance facilities and other facilities with vulnerable groups**, usually at least **six months after the completion of the primer vaccination**. People with **immunodeficiency or immunosuppression** as well as **those in need for care and the very elderly living at home** should be offered a booster vaccination by their attending physician.

The booster vaccinations will be conducted with one of the two available **mRNA vaccines**, regardless of the vaccine that was used for the primer vaccination.

The vaccination will be done through the regular health care system channels and with (mobile) teams from the vaccination centres.

In addition, as of September 2021, **all German citizens who have been fully vaccinated with a vector vaccine** (AstraZeneca or J&J) will be offered further vaccination with an mRNA vaccine, administered via vaccination centres, treating physicians or occupational physicians.

The rationale behind the administration of a third dose are the initial study results that indicate a reduced or rapidly waning immune response after a full COVID-19 vaccination for certain groups, in particular immunocompromised patients, very old people and those in need of care.

4.5 Israel

The Israelian Vaccines Operation Committee has on 29 July 2021[g] recommended the administration of a booster dose **minimum 5 months after the second dose to all citizens aged over 50**[h]. People in elderly care facilities and geriatric hospitals should be prioritized.

The Committee refers to the increase in incidence of patients in critical condition among people that are vaccinated, the decrease in neutralizing antibodies, and the decrease in protection against serious illness over time in the context of the Delta variant as **justification for the booster**. It also mentions that no major safety issues were detected in studies that investigated a third dose and the demonstrated rise in antibody levels following the administration of a booster, and stresses the strong association between the level of neutralizing antibodies and disease protection. Based on this, the committee expects a significant reduction in severe morbidity and mortality in people at risk. The negative impact of isolation, fear, and loneliness on the mental health of the elderly is also taken into consideration.

The administration of a third dose has been **subject to debate**. On 5 July 2021, the Israelian Ministry of Health wrote in a press release[i] that there is neither a recommendation nor a resolution to administer a third dose to the Israeli public and that the third dose does not have any medical protocol or approval from the regulators. At that point in time, an additional dose for people with reduced immune system in whom the regular vaccination protocol yielded low reaction was already promoted. The Committee's response is that booster administration often occurs prior to FDA approval of a booster protocol. There were other considerations against administration of a booster dose at this point in time. Biopharma companies are developing variant-adapted vaccines. However, these are expected at the earliest in November and considered too late for addressing the experienced need.

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[f] Gesundheitsministerkonferenz (2021). Beschlüsse Auffrischimfungen. Decision of 2 August 2021. Consulted on 5 August 2021 via https://www.gmkonline.de/Beschluesse.html?uid=219&jahr=2021

[g] Vaccines Operation Committee (2021). Background materials and main points of discussion on the usefulness of vaccines and morbidity in the context of a third vaccine dose. Consulted on 8 August 2021 via https://www.gov.il/BlobFolder/reports/vaccine-efficacy-safety-follow-up-committee/he/files_publications_corona_3rd-info.pdf

[h] Reuters (2021). Israel set to offer COVID vaccine booster shots to under 60 year olds. Published 12 August 2021. Consulted on 13 August 2021 via https://www.reuters.com/world/middle-east/israel-set-offer-covid-vaccine-booster-shots-under-60-year-olds-2021-08-12/

[i] Ministry of Health (2021). No Recommendation or Resolution to Administer a Third Dose in the Meantime. Published on 5 July 2021. Consulted on 8 August 2021 via https://www.gov.il/en/departments/news/05072021-04

The committee countered the need for global equality in terms of covid-19 vaccination by emphasizing the importance of developing evidence on the effectiveness of a booster dose and that Israel is well placed for this given it is the most advanced country with regards to the roll-out of the covid-19 vaccination campaign.

4.6 Malta

The Minister of Health announced on 5 August 2021 during a press conference that a booster dose would be rolled out as of mid-September 2021 for people who are **immunosuppressed or immunocompromised as a results of a medical condition, and for residents of elderly homes**[j]. A decision on extending the booster to the wider population has not yet been taken[k].

4.7 The Netherlands

The Dutch National Institute for Public Health and the Environment (RIVM) **does currently not recommend a third dose for immunocompromised people** in an updated advice d.d. 17 June 2021[l]. It refers to the lack of evidence on the necessity of a booster vaccination for immunocompromised people with the objective to achieve better effectiveness or prolonged duration of protection, as well as the uncertainty around safety and reactogenicity of a third dose. The availability of new data could provoke a change in the recommendation for a booster vaccination for specific patient populations and if vaccines are available.

In another advice, the RIVM states that primer vaccination will be sufficient in almost all cases, apart from severely immunocompromised people. The RIVM is making an inventory of those people for whom a booster vaccination could be beneficial and based on this, the Ministry of Public Health will make a decision on a complementary vaccination for this patient group[m].

4.8 Sweden

The Swedish public health authority (Fohm)[n] is likely to foresee a third dose for a larger proportion of the population in 2022 for which the modalities will depend on, amongst other things, possible new virus variants and the results of various studies on the protective effect of vaccines over time. During the autumn of 2021, **certain risk groups, primarily older residents in elderly care homes, people aged over 80 years and people with severely weakened immune systems**, may be offered a booster vaccination.

Vaccination against covid-19 will in the next few years in Sweden likely be carried out with **mRNA vaccines** and possibly an **adjuvanted protein-based vaccine**.

Sweden foresees **four stages** in its vaccination against covid-19:

- Stage 1: Mass vaccination of the adult population

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j The Malta Independent (2021). Quarantine for fully vaccinated case contacts reduced, booster vaccine jabs to start being given out. Last updated 6 August 2021. Consulted on 8 August 2021 via https://www.independent.com.mt/articles/2021-08-05/local-news/Quarantine-for-fully-vaccinated-case-contacts-reduced-booster-vaccine-jabs-to-start-being-given-out-6736235751

k Reuters (2021). Malta to give vaccine booster to the vulnerable and elderly. Last updated on 5 August 2021. Consulted on 8 August 2021 via https://www.reuters.com/world/europe/malta-give-vaccine-booster-vulnerable-elderly-2021-08-05/

l RIVM (2021). COVID-19-vaccinatie van immuungecompromitteerde patiënten. Last update 17 June 2021. Consulted on 5 August 2021 via https://lci.rivm.nl/handleiding-covid-19-vaccinatie-van-immuungecompromitteerde-patienten

m RIVM (2021). Mensen met afweerstoornis (immuungecomprommiteerden). Last update 3 August 2021. Consulted on 6 August 2021 via https://www.rivm.nl/covid-19-vaccinatie/vragen-achtergronden/immuungecompromitteerden

n Folkhälsomyndigheten (2021). Tredje dos mot covid-19 troligen nästa år. Last updated 3 August 2021. Consulted on 6 August 2021 via https://www.folkhalsomyndigheten.se/nyheter-och-press/nyhetsarkiv/2021/augusti/tredje-dos-mot-covid-19-troligen-nasta-ar/

- Stage 2: Increase vaccination rate in difficult to reach groups and offer booster to people with the highest risk of serious illness
- Stage 3: Booster for a larger part of the population
- Stage 4: Working on a long-term vaccination programme

4.9 United Kingdom

Britain will offer COVID-19 booster vaccines to **people aged over 50 or immunocompromised**. The roll out is planned to start in September 2021. The estimated number of eligible people is 32 million (approximately half of the population).

The booster will be administered through +2.000 pharmacies across the country with a target of 2.5 million doses administered every week. It is considered to combine the COVID-19 booster vaccination with the regular influenza vaccination.

The decision follows the interim advice of the Joint Committee on Vaccination and Immunisation (JCVI) published on 30 June 2021[o] that indicates to offer a booster programme, if required, in 2 stages from September, starting with those most at risk for serious disease.

Stage 1:

- adults aged 16 years and over who are immunosuppressed
- those living in residential care homes for older adults
- all adults aged 70 years or over
- adults aged 16 years and over who are considered clinically extremely vulnerable
- frontline health and social care workers

Stage 2:

- all adults aged 50 years and over
- all adults aged 16 to 49 years who are in an influenza or COVID-19 at-risk group
- adult household contacts of immunosuppressed individuals

The JCVI did not make a recommendation on the need for a booster vaccination but on the prioritisation of the target population for such a booster, mentioning they would closely follow-up on the emerging scientific data and that the final advice on booster vaccination may change substantially. The UK government did not wait until the final advice of the JCVI to decide upon the design of the booster vaccination campaign[p].

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[o] JCVI (2021). interim advice on COVID-19 booster vaccination. Published on 30 June 2021. Consulted on 5 August 2021 via https://www.gov.uk/government/news/jcvi-issues-interim-advice-on-covid-19-booster-vaccination

[p] UK Department of Health and Social Care (2021). Most vulnerable could be offered booster COVID-19 vaccines from September. Published on 30 June 2021. Consulted on 5 August 2021 via https://www.gov.uk/government/news/most-vulnerable-could-be-offered-booster-covid-19-vaccines-from-september

4.10 United States

In a joint statement on vaccine boosters of 8 July 2021[q], CDC and FDA refer to the fact that people who are fully vaccinated are protected from severe disease and death, including from the variants currently circulating in the country such as Delta. Therefore **people who have been fully vaccinated do not need a booster shot at this time**. FDA, CDC, and NIH are engaged in a science-based, rigorous process to consider whether or when a booster might be necessary to be prepared for booster doses if and when the science demonstrates that they are needed. On 12 August 2021, the FDA amended the emergency use authorisations of the Pfizer-BioNTech and Moderna COVID-19 vaccines **to allow for the use of an additional dose in certain immunocompromised individuals** (solid organ transplant recipients or those who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise). The CDC's Advisory Committee on Immunization Practices will meet on 13 August 2021 to discuss further clinical recommendations. The FDA determined that a third vaccine dose may increase protection in this population[r].

ECDC and EMEA also released a joint statement on 4 August 2021[s], referring to the importance of being fully vaccinated for protection against serious COVID-19. As opposed to the joint statement of FDA and CDC, it does not refer to the need for a booster vaccination. The rolling review of heterologous extra/booster vaccination with mRNA vaccines by EMA is ongoing.

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[q] US Department of Health & Human Services (2021). Joint CDC and FDA Statement on Vaccine Boosters. Published on 8 July 2021. Consulted on 8 August 2021 via Joint CDC and FDA Statement on Vaccine Boosters | HHS.gov

[r] FDA (2021). Coronavirus (COVID-19) Update: FDA Authorizes Additional Vaccine Dose for Certain Immunocompromised Individuals. Published on 12 August 2021. Consulted on 13 August 2021 via Coronavirus (COVID-19) Update: FDA Authorizes Additional Vaccine Dose for Certain Immunocompromised Individuals | FDA

[s] ECDC and EMA (2021). ECDC and EMA update on COVID-19. Published on 4 August 2021. Consulted on 8 August 2021 via ECDC and EMA update on COVID-19 (europa.eu)

5 ONGOING CLINICAL TRIALS

5.1 Belgian planned and ongoing studies using central lab testing

The study endpoints are immunogenicity and reactogenicity. The results of the Sciensano studies are expected November-December 2021 for humoral immune response 4 weeks after third dose and early in 2022 for the cellular immune response.

Study code and sites	Subjects/Patients	Primo vaccination and third dose	Other parties involved
PICOV-VACdose3 Three nursing homes	Staff and residents, no covid-19 history (n=200)	Pfizer +I Pfizer boost at week 36/M9	Sciensano, Mensura, ULB, ITG
Tri-Voice UZA, Maria Middelares	Oncology, ongoing treatment with chemotherapy or rituximab, no covid-19 history (n=200)	Pfizer + Pfizer boost at week 26/M6-M7	Sciensano, ULB, ITG
Nephro3 Hop Erasme	Hemodialysis and renal transplant, no covid-19 history (n=200)	Pfizer +I Pfizer boost at week 26/M6-M7	Sciensano, ULB, ITG
ImRes3 CHU Liège	Allogeneic hematopoietic stem cell transplantation, no covid-19 history (allo-HCT) (n=60)	Pfizer + Pfizer boost at week 26/M6-M7	Sciensano, ULB, ITG
Tri-Voice UZA	Oncology, ongoing treatment with chemotherapy or rituximab, no covid-19 history (n=200)	ChAd-Ox1-S (Oxford-AZ) + Pfizer boost at week 26 /M6-M7	Sciensano, ULB, ITG
Nephro_ID3 UZA	Hemodialysis and renal transplant, no covid-19 history (n=150)	Pfizer + Pfizer boost at week 26 (IM, ID, or 2x ID (both arms))	Sciensano, ULB, ITG *(pending budget approval)*
Lung3 Hop Erasme	Lung transplant, no covid-19 history (n=65)	Pfizer + Pfizer boost at week 26	Sciensano, ULB, ITG
IMCOVAS KCE trial UA, UGent, ULB, ITG	Healthy volunteers 18-55y, no covid-19 history (n=560)	Adapted schedules (Pfizer, AZ, Moderna) (no *third dose decided yet)*	KCE, Sciensano, ITG, ULB, UHasselt

5.2 International studies

Country & reference	Study	Population	Vaccines	Evaluations	EudraCT/ Clinicaltrials
UK[60]	Cov-Boost: A randomised, phase II UK multi-centre study to determine reactogenicity and immunogenicity of booster vaccination against ancestral and novel variants of SARS-CoV-2	Adults 30+ years who are 84 days post second dose	7 COVID-19 vaccines and half dose of three vaccines and a meningococcal vaccine	Immune responses and safety	Not found
Austria	A Randomized, Single-Blind, Phase II Study to Evaluate Safety and Efficacy to a Third Vaccination with a mRNA or Vector Vaccine in Patients under Immunosuppressive Therapy and no Humoral Response after Standard mRNA SARS-CoV-2	150 health subjects, 75 >60y (3 arms)	mRNA SARS-CoV-2 (Biontech/Pfizer or Moderna) and vector SARS-CoV-2 vaccine (AstraZeneca)	SARS-CoV-2 antibody seroconversion rate by week 4 after vaccination boost	2021-002693-10
Austria	A Randomized, Parallel Group, Single-Blind, Phase 2 Study to Evaluate the immune response of two classes of SARS-CoV-2 Vaccines (COVID-19) employed as Second Boost in Patients under current Rituximab Therapy and no humoral response after standard mRNA vaccination	60 patients overall	mRNA SARS-CoV-2 (Biontech/Pfizer or Moderna) and vector SARS-CoV-2 vaccine (AstraZeneca)	Difference in SARS-CoV-2 antibody seroconversion rate by week 4 after vaccination boost at baseline between 3rd mRNA SARS-CoV-2 (Biontech/Pfizer or Moderna) and vector SARS-CoV-2 vaccine (AstraZeneca).	2021-002348-57
US	A Phase II, open-label, rollover trial to evaluate the safety and immunogenicity of one or two boosting doses of Comirnaty™ or one dose of BNT162b2s01 in BNT162-01 trial subjects, or two boosting doses of Comirnaty™ in	549 participants	Pfizer Comirnaty™ or BNT162b2s01	Safety and immune response	NCT04949490

Country & reference	Study	Population	Vaccines	Evaluations	EudraCT/ Clinicaltrials
	BNT162-04 trial subjects				
Argentina, Brazil, Germany, South Africa, Turkey, United States	A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals	43 998 healthy volunteers	BNT162b2 at 30 µg and 30 µg BNT162b2SA and third, lower, dose of BNT162b2 at 5 or 10 µg.	Efficacy	NCT04368728
Germany	Immunogenicity of COVID-19 vaccines in medical staff and special risk populations	>1000 healthy volunteers	Pfizer/BioNTech at 30 µg, Janssen (dose not specified), Moderna at 100 µg and Astra-Zene-ca	Immune response	2021-001512-28

The seven COVID-19 vaccines given as a third dose in the UK trial Cov-Boost are ChadOx1 nCoV-19 (AstraZeneca), BNT162b2 (Pfizer BioNTech), mRNA-1273 (Moderna), NVX-CoV2373 (Novavax), VLA2001 (Valneva), CVnCoV (Curevac), Ad26.COV2.S (Janssen) and the Meningococcal ACWY vaccine. The Novavax, Valneva and Pfizer/BioNTech COVID-19 vaccines as a half dose will be included as well.

6 APPENDIX

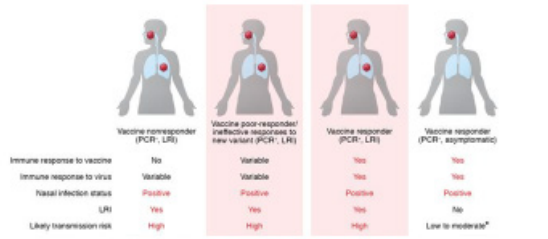
Appendix 1.1. Literature

Appendix 1.1.1. Breakthrough infections

1.1.1.1. Definition publication

The definition by Schieffelin et al. proposes that a breakthrough infection after COVID-19 vaccination is a combination of a “lower respiratory tract infection” and a “positive PCR test for SARS-COV-2”.[10] This is a very stringent definition excluding persons who are asymptomatic or have symptoms limited to an upper respiratory tract infection. The authors state that it is important to understand that these individuals may still be able to transmit virus. They also suggest that those individuals who do not mount an effective immune response to vaccination do not represent cases of breakthrough infection.

Figure 1: What should define a SARS-CoV-2 “breakthrough” infection?



J Clin Invest DOI: 10.1172/JCI151186

1.1.1.2. Incidence publications

Butt [11] US veterans: this is the largest study with 258,716 fully vaccinated persons of which 410 persons had a breakthrough infection together with 14,465 controls. Included were all Veterans who received two doses of the Pfizer-BNT-162b2 or Moderna-mRNA-1273 vaccine between December 15, 2020 and March 31, 2021. Excluded were those with a positive SARS-CoV-2 PCR on a nasopharyngeal swab within 14 days of receiving the first vaccine dose. From the remaining persons, those who had at least one SARS-CoV-2 PCR test performed on a nasopharyngeal swab ≥7 days after the second dose vaccine dose were retained. No information on symptoms is reported. Cases were those with confirmed SARS-CoV-2 infection and controls were those who remained uninfected with at least one confirmed negative test for SARS-CoV-2 ≥ 7 days after their second vaccine dose. The follow-up time is not reported but was short as publication was 2 months after last vaccination period.

Teran[14] MMWR US nursing homes and staff: A confirmed case of SARS-CoV-2 infection was defined as a positive SARS-CoV-2 NAAT or antigen test result from a respiratory specimen collected from a resident or staff member during the investigation period (start vaccination (Moderna or Pfizer) in December 2020–March 2021). Staff members at all Chicago-based SNFs were tested at least twice weekly (until February 4, 2021), then weekly (during February 4–March 18, 2021), then biweekly (from March 18, 2021 through the end of investigation period). In response to a facility outbreak (i.e., a resident or staff member with a case within the past 14 days), all staff members and residents (excluding those who received a positive SARS-CoV-2 test <90 days previously) are required to receive testing at least every 3–7 days until no new cases occur for at least 14 days. At the time a breakthrough infection was identified, frequency of resident testing at the 15 SNFs ranged from monthly to twice per week; frequency of staff member testing ranged from weekly to twice weekly.¶ First round vaccination clinics occurred during December 28, 202 Among 627 persons with SARS-CoV-2 infection (cases) across 75 SNFs since vaccination clinics began, 447 (71%) occurred in unvaccinated persons, 145 (23%) in partially vaccinated persons, 13 (2%) in vaccinated but not immune persons, and 22 (4%) in fully vaccinated persons. The 22 SARS-CoV-2 infections in fully vaccinated persons were identified among 12 residents and 10 staff members across 15 facilities ≥14 days after receiving their second vaccine dose (i.e., breakthrough infections in fully vaccinated

persons). Nearly two thirds (14 of 22; 64%) of persons with breakthrough infections were asymptomatic; two residents were hospitalized because of COVID-19, and one died.

Hall[15] hospital staff UK: 23324 participants from 104 sites (all in England) met the inclusion criteria for this analysis and were enrolled. Included participants had a median age of 46·1 years (IQR 36·0–54·1) and 19692 (84%) were female; 8203 (35%) were assigned to the positive cohort (antibody positive or history of infection (PCR+) at the start of the analysis period, and 15121 (65%) assigned to the negative cohort. Total follow-up time was 2 calendar months (Dec 7, 2020, to Feb 5, 2021) and 1 106905 person-days (396318 vaccinated and 710587 unvaccinated). Vaccine coverage was 89% on Feb 5, 2021, 94% of whom had BNT162b2 vaccine. Significantly lower coverage was associated with previous infection, gender, age, ethnicity, job role, and Index of Multiple Deprivation score. During follow-up, there were 977 new infections in the unvaccinated cohort, an incidence density of 14 infections per 10000 person-days; the vaccinated cohort had 71 new infections 21 days or more after their first dose (incidence density of eight infections per 10000 person-days) and nine infections 7 days after the second dose (incidence density four infections per 10000 person-days). In the unvaccinated cohort, 543 (56%) participants had typical COVID-19 symptoms and 140 (14%) were asymptomatic on or 14 days before their PCR positive test date, compared with 29 (36%) with typical COVID-19 symptoms and 15 (19%) asymptomatic in the vaccinated cohort. A single dose of BNT162b2 vaccine showed vaccine effectiveness of 70% (95% CI 55–85) 21 days after first dose and 85% (74–96) 7 days after two doses in the study population.

Geysels[16] HCWs University Hospital Antwerp (ZNA) Belgium: 3 different vaccines were used: BNT162b2 (Comirnaty, BioNTech/Pfizer, Mainz, Germany), mRNA-1273 (COVID-19 Vaccine Moderna, Moderna, Cambridge, MA) and AZD1222 (Vaxzevria, Astra Zeneca, Cambridge, UK). Vaccination of HCWs in ZNA started on January 18, 2021. The impact of vaccinations on the positive test ratio was evaluated from March 1 through April 30, 2021, a period with continuing and substantial viral circulation in the Belgian population. Tests were performed for contact tracing or COVID-like symptoms. Among 3,491 fully vaccinated ZNA healthcare workers (HCWs), 9 (0.3%) tested positive for SARS-CoV-2 (5 Comirnaty vaccine and 4 Moderna vaccine) 14 days after the second dose. After excluding 1 case, following CDC guidelines on persistent shedding, 22 (1.0%) of 2,215 unvaccinated HCWs (n = 584) or partially vaccinated HCWs (n = 1,631) tested positive. Partially vaccinated was defined as having received only 1 dose or the second dose.

Thompson[17] HCW and frontline personnel US: a prospective cohort study involving 3975 health care personnel, first responders, and other essential and frontline workers. 2686 (2510 included in analysis incidence) of those participants (84%) had received both recommended doses with two-dose messenger RNA (mRNA) vaccines BNT162b2 (Pfizer–BioNTech) and mRNA-1273 (Moderna). From December 14, 2020, to April 10, 2021, the participants completed weekly SARS-CoV-2 testing by providing mid-turbinate nasal swabs for qualitative and quantitative reverse-transcriptase–polymerase-chain-reaction (RT-PCR) analysis. The formula for calculating vaccine effectiveness was 100%×(1−hazard ratio for SARS-CoV-2 infection in vaccinated vs. unvaccinated participants), with adjustments for the propensity to be vaccinated, study site, occupation, and local viral circulation. SARS-CoV-2 was detected in 204 participants (5%), of whom 5 were fully vaccinated (≥14 days after dose 2), 11 partially vaccinated (≥14 days after dose 1 and <14 days after dose 2), and 156 unvaccinated; the 32 participants with indeterminate vaccination status (<14 days after dose 1) were excluded. Adjusted vaccine effectiveness was 91% (95% confidence interval [CI], 76 to 97) with full vaccination and 81% (95% CI, 64 to 90) with partial vaccination. Among participants with SARS-CoV-2 infection, the mean viral RNA load was 40% lower (95% CI, 16 to 57) in partially or fully vaccinated participants than in unvaccinated participants. In addition, the risk of febrile symptoms was 58% lower (relative risk, 0.42; 95% CI, 0.18 to 0.98) and the duration of illness was shorter, with 2.3 fewer days spent sick in bed (95% CI, 0.8 to 3.7).

Pollett[18] US military: Military Health System beneficiaries presenting with a positive SARS-CoV-2 test, a COVID-19–like illness, or a high-risk SARS-CoV-2 exposure were eligible for enrolment from March 2020. From March 2020 through 3 May 2021, the EPICC study enrolled 1547 subjects (1229 outpatients, 318 inpatients) with confirmed SARS-CoV-2 infection. A total of 24 infections occurred 14 or more days after the final dose of a SARS-CoV-2 vaccine (22 BNT162b2 vaccine and 2 mRNA-1273), with a median illness onset of 50.5 days (interquartile range [IQR], 31.5–73.5 days; range, 15–95 days) from final vaccination dose. Most cases were active-duty military service members (19/24, 79%). Fifteen of 24 (63%) were healthcare workers, and 13 of 23 (57%) reported close

contact with a COVID-19 case in the last month. One subject reported receiving immunosuppressant medication (mycophenolate and prednisone) for a renal transplant.

Bergwerk[2] staff at the hospital, Israel: From December 19, 2020, to April 28, 2021, a total of 91% of the center personnel received two doses of the BNT162b2 vaccine. At the largest medical center in Israel, we identified breakthrough infections by performing extensive evaluations of health care workers who were symptomatic (including mild symptoms) or had known infection exposure. Data were collected for 14 weeks, from January 20th until April 28thv 2021. A breakthrough infection was defined as the detection of SARS-CoV-2 on RT-PCR assay performed 11 or more days after receipt of a second dose of BNT162b2 if no explicit exposure or symptoms had been reported during the first 6 days. Among 1497 fully vaccinated health care workers for whom RT-PCR data were available, 39 SARS-CoV-2 breakthrough infections were documented. Of the 39 breakthrough case patients, 18 (46%) were nursing staff members, 10 (26%) were administration or maintenance workers, 6 (15%) were allied health professionals, and 5 (13%) were physicians. The average age of the 39 infected workers was 42 years, and the majority were women (64%). The median interval from the second vaccine dose to SARS-CoV-2 detection was 39 days (range, 11 to 102). Only one infected person (3%) had immunosuppression. Of the 39 cases of infection, 27 occurred in workers who were tested solely because of exposure to a person with known SARS-CoV-2 infection. Of all the workers with breakthrough infection, 26 (67%) had mild symptoms at some stage, and none required hospitalization. The remaining 13 workers (33% of all cases) were asymptomatic during the duration of infection; of these workers, 6 were defined as borderline cases, since they had an N gene Ct value of more than 35 on repeat testing.

Aslam[19] solid organ transplants (SOT) US: Clinical data from the transplant registry from 1/1/2021 to 6/2/2021: demographics, details of COVID-19 vaccination, incidence of COVID-19, and related mortality. The incidence of symptomatic COVID-19 per 1000/person days (> 14 days after last vaccination) at risk and incidence rate ratio (IRR) was calculated. Among 2151 SOTRs, 912 were fully vaccinated, and 1239 were controls (1151 unvaccinated, 88 partially vaccinated). Almost 70% of vaccinated subjects received the mRNA-1273 vaccine (others BNT162b2). There were 65 cases of COVID-19 that occurred during the study period – four occurred among fully vaccinated individuals and 61 among controls (including two in partially vaccinated individuals). Incidence rate for COVID-19 was 0.065 (95% CI 0.024–0.17) per 1000 person days in vaccinated versus 0.34 (95% CI 0.26–0.44) per 1000/person days in the control group; IRR was 0.19 (95% CI 0.049 −0.503, $p < 0.005$). There were no COVID-19 related deaths in the four breakthrough infections and two of 61 (3.3%) among controls. An almost 80% reduction in the incidence of symptomatic COVID-19 versus unvaccinated SOTRs during the same time was demonstrated. Based on primary transplanted organ, the study cohort consisted of 376 (17.4%) heart, 205 (9.5%) lung, 603 (28%) liver, and 967 (44.5%) kidney transplant recipients. Almost 70% of vaccinated subjects received the mRNA-1273 vaccine. Vaccinated patients were older than the control group and had a shorter time from transplant.

Qin[13] adult Transplant Recipients US: Risk of Breakthrough SARS-CoV-2 Infections in Adult Transplant Recipients. In this multicenter study, we estimated the breakthrough infection (≤14 days after second dose) rates after SARSCoV-2 mRNA vaccination in SOTRs and compared them to rates reported in the general population. Among a total of 18 215 fully vaccinated SOTRs at 17 transplant centers, there were 151 breakthrough infections (0.83%), 87 with associated hospitalization (0.48%) and 14 with associated death (0.077%). Mortality among SOTRs with breakthrough infection was 14/151 (9.3%). Center-level breakthrough infection rates varied from 0.23% to 2.52%. Of 101 million fully vaccinated adults in the United States through April 30, 2021, CDC reported 10 262 breakthrough infections (0.0102%), 995 with associated hospitalization (0.00099%), and 160 with associated death (0.00016%).Compared to the general population, SOTRs in our study had an 82-fold higher risk of breakthrough infection and 485-fold higher risks of breakthrough infection with associated hospitalization and death. Quality of the paper is low due to the limited information that is provided in the text.

Brosh-Nissimov[22] Israel: This study does not provide information on incidence. It is included in the text as an example of the 'characterisation' of the patient with severe outcome and demonstrated that among hospitalized patients with breakthrough infections (≥7 days after second dose Pfizer) that were admitted to hospital and had a poor outcome, the rate of comorbidities was high. A retrospective multicentre cohort study of 17 hospitals included patients fully vaccinated with Pfizer/BioNTech's BNT162b2 vaccine who developed COVID-19 more than 7 days after the second vaccine dose and

required hospitalization. The risk for poor outcome, defined as a composite of mechanical ventilation or death, was assessed. A total of 152 patients were included, accounting for half of hospitalized fully vaccinated patients in Israel. Poor outcome was noted in 38 patients and mortality rate reached 22% (34/152). Notably, the cohort was characterized by a high rate of comorbidities predisposing to severe COVID-19, including hypertension (108; 71%), diabetes (73; 48%), congestive heart failure (41; 27%), chronic kidney and lung diseases (37; 24% each), dementia (29; 19%) and cancer (36; 24%), and only six (4%) had no comorbidities. Sixty (40%) of the patients were immunocompromised. Higher viral load was associated with a significant risk for poor outcome. Risk also appeared higher in patients receiving anti-CD20 treatment and in patients with low titres of anti-Spike IgG, but these differences did not reach statistical significance.

1.1.1.3. Variants publications

Hacisuleyman[23] US: Beginning in the fall of 2020, all employees and students at the Rockefeller University campus (approximately 1400 persons) were tested at least weekly with a saliva-based PCR test. In a cohort of 417 persons (twice weekly tested between January 21 and March 17, 2021, and weekly testing continued thereafter) who had received the second dose of BNT162b2 (Pfizer–BioNTech) or mRNA-1273 (Moderna) vaccine at least 2 weeks previously, 2 women with vaccine breakthrough infection were identified. Despite evidence of vaccine efficacy in both women, symptoms of coronavirus disease 2019 developed, and they tested positive for SARS-CoV-2 by polymerase-chain-reaction testing. Viral sequencing revealed variants of likely clinical importance, including E484K in 1 woman and three mutations (T95I, del142–144, and D614G) in both. These observations indicate a potential risk of illness after successful vaccination and subsequent infection with variant virus, and they provide support for continued efforts to prevent and diagnose infection and to characterize variants in vaccinated persons

Farinholt[24] (pre-print) US: identification of the delta variant in 6 breakthrough cases April 2021. The transmission event occurred at events surrounding a wedding outside of Houston, TX. Two patients from India, likely transmitted the Delta variant to other guests as they travelled on day 10 after the second vaccination dose. All guests had to be fully vaccinated. Viral sequencing revealed 6 vaccinated patients were infected with the Delta SARS CoV-2 variant. With no histories of vaccine breakthrough, this suggests Delta variant may possess immune evasion in patients that received the Pfizer BNT162b2, Moderna mRNA-1273, and Covaxin BBV152.

Vignier[27] French Guiana: Breakthrough Infections of SARS-CoV-2 Gamma Variant in Fully Vaccinated Gold Miners, French Guiana, 2021. An outbreak of severe acute respiratory syndrome coronavirus 2 caused by the Gamma variant of concern infected 24/44 (55%) employees of a gold mine in French Guiana (87% symptomatic, no severe forms). The attack rate was 60% (15/25) among fully vaccinated miners and 75% (3/4) among unvaccinated miners without a history of infection.

McEwen[25] US: Seattle laboratory samples: Beginning in February 2021, SARS-CoV-2 genome sequencing was requested at UW Medicine hospitals and partners as part of investigations into postvaccine breakthrough infections. Cases were defined as patients who were fully vaccinated against SARS-CoV-2 (>2 weeks post-second dose of Pfizer or Moderna vaccine) who subsequently tested positive by RT-PCR. A total of 20 cases were sequenced in this study between 23 February and 27 April 2021, including 13 females, 6 males, and 1 with unknown sex. Ages ranged from 26 to 65 years (median, 43 years; interquartile range [IQR], 28–58 years) Across 20 vaccine breakthrough cases detected at our institution, all 20 (100%) infections were due to variants of concern (VOCs), 8 (40%) B.1.1.7, 1 (5%) B.1.351, 2 (10%) B.1.427, 8 (40%) B.1.429, and 1 (5%) P.1, and had a median Ct of 20.2 (IQR, 17.1–23.3). When compared with 5174 contemporaneous samples sequenced in our laboratory, VOCs were significantly enriched among breakthrough infections ($P < .05$). Clinical data, including comorbidities and vaccination type and dates (n = 19), were available for a subset of subjects. All patients received mRNA-based vaccines (14 BNT162b2, 5 mRNA-1273); 15 out of 18 reported symptoms, and none required hospitalization. Specimens were collected at an average of 67.7 days after vaccination (range, 39–112 days; SD, 18.1 days).

Ioannou[26] Greece: Prospective cohort of HWCs (more than 80% of HCWs (1800/2,250) have been vaccinated against COVID-19 with the BNT162b2 mRNA vaccine). Recorded PCR tests were taken in the context of outbreak surveillance screening or due to the development of associated symptoms and diagnosed with COVID-19 by nasopharyngeal PCR from 4 January to 14 April. Viral loads were expressed by the cycle threshold (Ct) in PCR. During the study period 55 HCWs were found positive

for SARS-CoV-2, most of whom (44/55) were identified from March 28 to April 14 during an in-hospital COVID-19 outbreak. Of the 55 HCWs, 21 were fully vaccinated (with BNT162b2) and another three had received one dose. Most cases (54/55) were due to variant B.1.1.7. Vaccinated and unvaccinated HCWs did not differ significantly in regards to age, gender, site of acquisition, presence of symptoms at diagnosis and viral load.

Appendix 1.1.2. Publications vaccine effectiveness after 2 doses

Lopez[28] UK all symptomatic cases in England included: a test-negative case–control design was used to estimate the effectiveness of vaccination against symptomatic disease caused by the delta variant or the predominant strain (B.1.1.7, or alpha variant) over the period that the delta variant began circulating. Variants were identified with the use of sequencing and on the basis of the spike (S) gene status. Data on all symptomatic sequenced cases of Covid-19 in England were used to estimate the proportion of cases with either variant according to the patients' vaccination status. With the BNT162b2 vaccine, the effectiveness of two doses was 93.7% (95% CI, 91.6 to 95.3) among persons with the alpha variant and 88.0% (95% CI, 85.3 to 90.1) among those with the delta variant. With the ChAdOx1 nCoV-19 vaccine, the effectiveness of two doses was 74.5% (95% CI, 68.4 to 79.4) among persons with the alpha variant and 67.0% (95% CI, 61.3 to 71.8) among those with the delta variant. Only modest differences in vaccine effectiveness were noted with the delta variant as compared with the alpha variant after the receipt of two vaccine doses.

Haas[29] Israel national surveillance: data from the first 4 months of the nationwide vaccination campaign to ascertain incident cases of laboratory-confirmed SARS-CoV-2 infections and outcomes, as well as vaccine uptake in residents of Israel aged 16 years and older. Vaccine effectiveness against SARS-CoV-2 outcomes (asymptomatic infection, symptomatic infection, and COVID-19-related hospitalisation, severe or critical hospitalisation, and death) was calculated on the basis of incidence rates in fully vaccinated individuals (defined as those for whom 7 days had passed since receiving the second dose of vaccine) compared with rates in unvaccinated individuals (who had not received any doses of the vaccine), with use of a negative binomial regression model adjusted for age group (16–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, and ≥85 years), sex, and calendar week. The proportion of spike gene target failures on PCR test among a nationwide convenience-sample of SARS-CoV-2-positive specimens was used to estimate the prevalence of the B.1.1.7 variant. During the analysis period (Jan 24 to April 3, 2021), there were 232268 SARS-CoV-2 infections, 7694 COVID-19 hospitalisations, 4481 severe or critical COVID-19 hospitalisations, and 1113 COVID-19 deaths in people aged 16 years or older. By April 3, 2021, 4714932 (72·1%) of 6538911 people aged 16 years and older were fully vaccinated with two doses of BNT162b2. Adjusted estimates of vaccine effectiveness at 7 days or longer after the second dose were 95·3% (95% CI 94·9–95·7; incidence rate 91·5 per 100000 person-days in unvaccinated vs 3·1 per 100000 person-days in fully vaccinated individuals) against SARS-CoV-2 infection, 91·5% (90·7–92·2; 40·9 vs 1·8 per 100000 person-days) against asymptomatic SARS-CoV-2 infection, 97·0% (96·7–97·2; 32·5 vs 0·8 per 100000 person-days) against symptomatic COVID-19, 97·2% (96·8–97·5; 4·6 vs 0·3 per 100000 person-days) against COVID-19-related hospitalisation, 97·5% (97·1–97·8; 2·7 vs 0·2 per 100000 person-days) against severe or critical COVID-19-related hospitalisation, and 96·7% (96·0–97·3; 0·6 vs 0·1 per 100000 person-days) against COVID-19-related death. In all age groups, as vaccine coverage increased, the incidence of SARS-CoV-2 outcomes declined. 8006 of 8472 samples tested showed a spike gene target failure, giving an estimated prevalence of the B.1.1.7 variant of 94·5% among SARS-CoV-2 infections. Interpretation Two doses of BNT162b2 are highly effective across all age groups (≥16 years, including older adults aged ≥85 years) in preventing symptomatic and asymptomatic SARS-CoV-2 infections and COVID-19-related hospitalisations, severe disease, and death, including those caused by the B.1.1.7 SARS-CoV-2 variant. There were marked and sustained declines in SARS-CoV-2 incidence corresponding to increasing vaccine coverage. These findings suggest that COVID-19 vaccination can help to control the pandemic.

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Colophon

Title: Rapid review of the evidence on a covid-19 booster dose after a primary vaccination schedule

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At the request of: Task Force Vaccination

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