IMPACT VAN DE VACCINATIESTRATEGIE OP DE GELDENDE MAATREGELEN ROND TESTEN EN QUARANTAINE – 3e UPDATE.

RAG vergadering 18/05/2021 – gevalideerd door RMG 20/05/2021

Opgepast: de uiteindelijke beslissingen (die op sommige punten afwijken van het advies dat hieronder wordt voorgesteld) werden genomen door het overlegcomité op 04/06/2021 en de IMC op 16/06/2021.

Eind december werd een eerste advies afgeleverd in verband met **eventuele wijzigingen aan de huidige geldende procedures met betrekking tot quarantaine en testen van personen die gevaccineerd zijn**. Dat initiële advies werd reeds tweemaal geactualiseerd, in februari en april. Omwille van een initiële lage vaccinatiegraad bij risicogroepen en onvoldoende gegevens rond het effect op transmissie werden oorspronkelijk slechts erg beperkte wijzigingen aan de geldende richtlijnen aangeraden. De RAG maakte in zijn eerdere adviezen reeds gewag van mogelijke problemen rond billijkheid zolang niet iedereen toegang heeft gehad tot vaccinatie en zolang er geen vrije keuze is van het type vaccin. Momenteel buigt een groep experten van de GEMS aangevuld met juridische, ethische en sociologische experten zich over deze meer ethische en maatschappelijke vraagstukken. De RAG concentreert zich in dit advies enkel op de beschikbare wetenschappelijke kennis, huidige vaccinatiegraad en epidemiologische situatie en stelt voor dat de aanbevelingen geïntegreerd worden in het ruimere debat rond de verschillen tussen gevaccineerden en niet-gevaccineerden.

1. Aanbevelingen :

- **De eerste resultaten uit andere landen bevestigen dat vaccinatie een sleutelrol speelt in de terugkeer naar het normale leven. Het is daarom uitermate belangrijk de bevolking te motiveren om zich te laten vaccineren. Correcte informatie en doelgerichte communicatie zijn daarbij onontbeerlijk, waarbij zowel de voordelen voor het individu (bescherming tegen ernstige ziekte) als voor de samenleving (bescherming gezondheidszorgsysteem, vermindering viruscirculatie) benadrukt moeten worden.**
- Gezien de beperkte beschikbaarheid van vaccins gebeurt de uitrol gradueel. De vaccinatiegraad neemt de laatste tijd sterk toe maar volledige vaccinatie in risicogroepen is nog niet afgerond. In die omstandigheden blijven niet-farmaceutische interventies (zoals het dragen van mondmaskers, testen en quarantaine) bijzonder belangrijk. In welk ritme versoepelingen voor de volledige populatie kunnen gebeuren, vormt het onderwerp van politieke beslissingen, rekening houdend met wetenschappelijk advies.
- De verschillende aspecten die een invloed hebben op dit advies, namelijk de epidemiologische situatie in België (in het bijzonder de hospitalisaties), de vaccinatiegraad, circulatie van VOCs, en de wetenschappelijke kennis rond vaccins worden verder nauw opgevolgd. Indien nodig, zal dit advies herzien worden.
- Zowel uit praktische overwegingen (controleerbaarheid) als omwille van het onvolledige effect van vaccinatie op transmissie, blijven de algemene preventieve maatregelen zoals physical distancing en het dragen van mondmaskers in openbare ruimtes ook gelden voor personen die al gevaccineerd zijn.
- Voor de aanbevelingen in dit document betekent “gevaccineerd” dat personen volledig gevaccineerd zijn, dat wil zeggen:
    - voor Comirnaty® (Pfizer-BioNTech): ≥7 dagen na de tweede dosis
    - voor COVID-19 Moderna vaccin (Moderna): ≥14 dagen na de tweede dosis

- voor Vaxzevria® (AstraZeneca-Oxford): ≥15 dagen na de tweede dosis
- voor Janssen COVID-19 vaccine: ≥14 days na de eerste dosis

Voor personen die partieel gevaccineerd zijn, gelden dezelfde regels als voor personen die nog niet gevaccineerd werden.

- De bescherming die de vaccins bieden is hoog, maar geen 100%. **Gevaccineerde personen die mogelijke symptomen vertonen van COVID-19 moeten daarom net als niet-gevaccineerde personen contact nemen met een arts om een test te ondergaan**. Er wordt herhaald dat zelftesten NIET gebruikt kunnen worden bij symptomatische personen (gevaccineerd of ongevaccineerd.)
- Personen die ondanks vaccinatie toch een COVID-19 besmetting oplopen, moeten net als ongevaccineerde personen in isolatie, ook al vertonen ze geen symptomen. Er zijn aanwijzingen dat deze personen over het algemeen minder besmettelijk zijn, maar besmettelijkheid is zeker niet uitgesloten. Dit geldt óók voor bewoners van WZC waar een hoge vaccinatiegraad behaald is bij de medebewoners.
- Er is toenemend bewijs dat vaccinatie ook een effect heeft op transmissie. De bescherming is weliswaar onvolledig en mogelijk afhankelijk van het type vaccin, leeftijd en onderliggende aandoeningen van de gevaccineerde en circulerende virus-varianten, zodat extra waakzaamheid geboden blijft. **Personen die volledig gevaccineerd werden, kunnen vrijgesteld worden van quarantaine op voorwaarde dat ze 2 testen ondergaan: zo snel mogelijk na identificatie en 7 dagen na het laatste risicocontact[1].** De teststrategie is dus dezelfde als bij ongevaccineerde hoog-risico contacten**.**
    - Volledig gevaccineerde personen die weigeren om getest te worden, moeten een quarantaine respecteren van 10 dagen na het laatste hoog-risicocontact.
    - Indien er een cluster van besmettingen vastgesteld wordt in een residentiële collectiviteit, moeten ook volledig gevaccineerde personen de quarantaine respecteren.
    - Bij personen met ernstige immuunsuppressie (bv. owv. hematologische kanker of orgaantransplantatie) zijn de vaccins mogelijk minder werkzaam en is het risico dus groter dat ze na een hoog-risico contact alsnog besmet raken en het virus ook kunnen doorgeven. Bij hen moet daarom overwogen worden, in overleg met de behandelend specialist, om toch een quarantaine in te stellen, ook al werden ze volledig gevaccineerd.
- De **uitzondering op de quarantaine, op voorwaarde van het ondergaan van een test op D1 en D7, geldt eveneens voor gevaccineerde reizigers die terugkomen uit een rode zone**, tenzij ze terugkeren uit een gebied met intense circulatie van VOC/VOI met mogelijke immuun escape.
- Bij preventieve screening is de pre-test probabiliteit lager dan in andere indicaties. Bij gevaccineerde personen is het a priori risico op besmetting nog lager, zodat preventieve screening enkel dient te gebeuren indien het risico in geval van onopgemerkte infectie bijzonder groot is. Dat is bv. het geval pre-transplant (risico voor receptor) of bij ziekenhuisopname (risico voor ongevaccineerde medepatiënten). Bij beslissingen rond preventieve screening in woonzorgcentra moet steeds rekening gehouden worden met de vaccinatiegraad van zowel personeel als bewoners.
- In woon-zorgcentra of andere residentiële collectiviteiten die een hoge vaccinatiegraad hebben bereikt, is het risico op een uitbraak onder de bewoners beperkter dan in de algemene samenleving. WZC zijn echter geen eilanden die geïsoleerd zijn van de bredere samenleving: er is nog interactie via bezoekers en personeelsleden. Bepaalde maatregelen, zoals het dragen van mondneusmaskers door de personeelsleden, moeten dan ook blijven gelden.

[1] bij huishoudcontacten die zich niet kunnen of willen isoleren van de indexpatiënt, zal de tweede test dus pas gebeuren D7 na het einde van de isolatieperiode van de indexpatiënt (dus D17 na start symptomen van de indexpatiënt)

- **De aanbevelingen worden samengevat in de tabel op volgende bladzijde.**

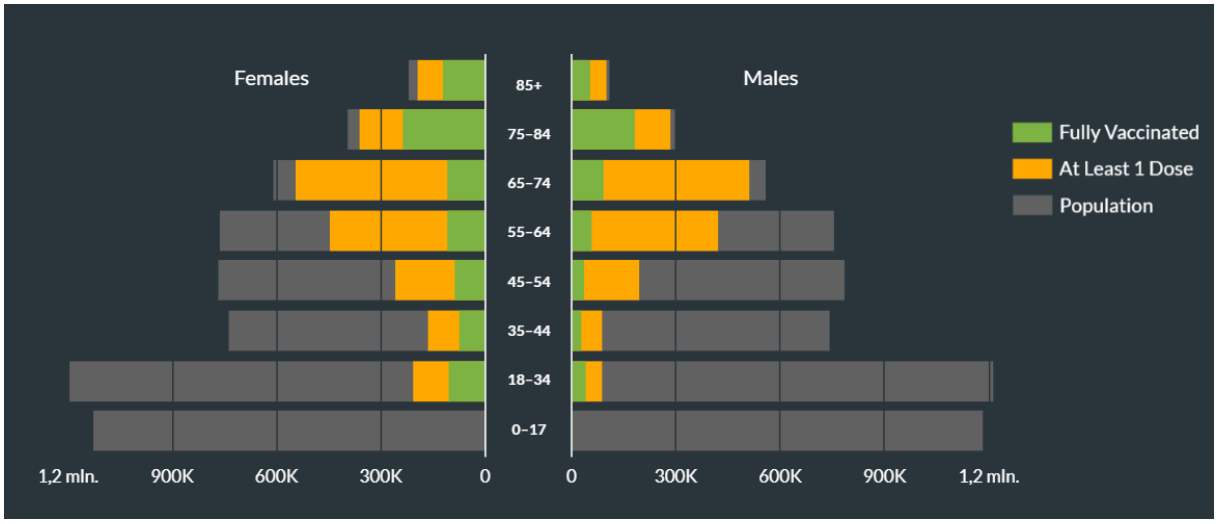
2. Overzicht mogelijke impact en aanbevelingen

Onderwerp	Hoofdpunten huidige procedure (link)	Aanbeveling voor gevaccineerden
Mogelijke gevallen van COVID-19	Elk mogelijk geval wordt getest Antigen-test mogelijk als symptomen ≤5 dagen	Zelfde indicaties voor testen **Sterke voorkeur voor PCR-test** Indien positief: melden + sequencing
Isolatie van bevestigde gevallen	10 dagen waarvan minstens 3d koortsvrij Speciale regels in ziekenhuizen, immunogecompromitteerden, ernstige ziekte.	Geen wijzigingen.
Contact tracing		
Indexgeval	HRC identificeren vanaf 2d vóór symptoombegin → quarantaine	Geen wijzigingen.
Hoogrisicocontact (HRC)	Test en 7-10 dagen quarantaine Werken uitzonderlijk toegestaan voor zorgverleners indien noodzakelijk	Geen quarantaine noodzakelijk op voorwaarde van test zo snel mogelijk na identificatie en op dag 7 na het laatste risicocontact. Overwegen om quarantaine te behouden voor personen met ernstige immuunsuppressie (bv. hematologische kanker, post-transplant), in overleg met behandelend arts.
Laagrisicocontact (LRC)	Verhoogde waakzaamheid. Test dag 5 *(aanbevolen maar nog niet geïmplementeerd)*	Risico-indeling wijzigen naar “geen risico-contact”.
Cluster	Niet-WZC: uitgebreidere testing van laag-risico contacten met antigen-test WZC: uitgebreide testing personeel/bewoners met PCR	In residentiële collectiviteit: quarantaine behouden voor gevaccineerde HRC’en in geval van cluster.
Reizigers		
Reizigers uit rode zones	Quarantaine en test verplicht in bepaalde omstandigheden	Geen quarantaine op voorwaarde van test D1+D7. Quarantaine en testing behouden indien terugkeer uit gebied met VOC/VOI.
Preventieve screening		
Personeel WZC	Overweeg regelmatige screening met PCR op speekselstaal	Geen screening indien vaccinatiegraad bewoners ≥90% en personeel ≥70%
Bezoekers WZC	Overweeg om snelle antigentesten in te zetten vóór bezoek	Geen screening indien vaccinatiegraad bewoners ≥90% en personeel ≥70%
Ziekenhuisopname	Systematische screening bij hoge prevalentie / risicoafdeling	Screening indien risico op overdracht naar ongevaccineerde medepatiënten.
Nieuwe bewoners residentiële collectiviteit (opname vanuit thuis-setting)	Systematische screening & kamerisolatie in afwachting resultaat	Systematische testing. Geen isolatie op kamer noodzakelijk in afwachting van resultaat tenzij vaccinatiegraad bewoners <90% of personeel <70%
Andere beroepen (bv. leerkrachten)	Arbeidsarts kan beslissen tot systematische screening	Geen nut van screening bij gevaccineerde zonder contact risicopopulatie
Zelftesten	Als gebaar van hoffelijkheid naar omgeving, indien bezorgd over risicogedrag zonder geïdentificeerde blootstelling	Geen nut van screening bij gevaccineerde
Pre-transplant screening donor	Systematische screening	Geen wijzigingen (omwille van hoog risico voor acceptor)

3. Situatie in België

- Op 18/05/2021 bedroeg de cumulatieve 14-daagse incidentie van nieuwe gevallen 313/100 000 inwoners en bedroeg het wekelijks gemiddelde 133 nieuwe ziekenhuisopnames per dag. 610 bedden op intensieve zorgen werden ingenomen door COVID-19-patiënten.
- 3,9 miljoen Belgen (33,9% van de totale bevolking) kregen reeds een 1e dosis vaccin toegediend, 1,4 miljoen (11,9%) werd reeds volledig gevaccineerd.

Figuur 1: Cumulatief aantal personen die een eerste en tweede dosis van het COVID-19 vaccin kregen, volgens leeftijdsgroep, status op 18/05/2021 *Bron: Vaccinnet+, interactief dashboard Sciensano*

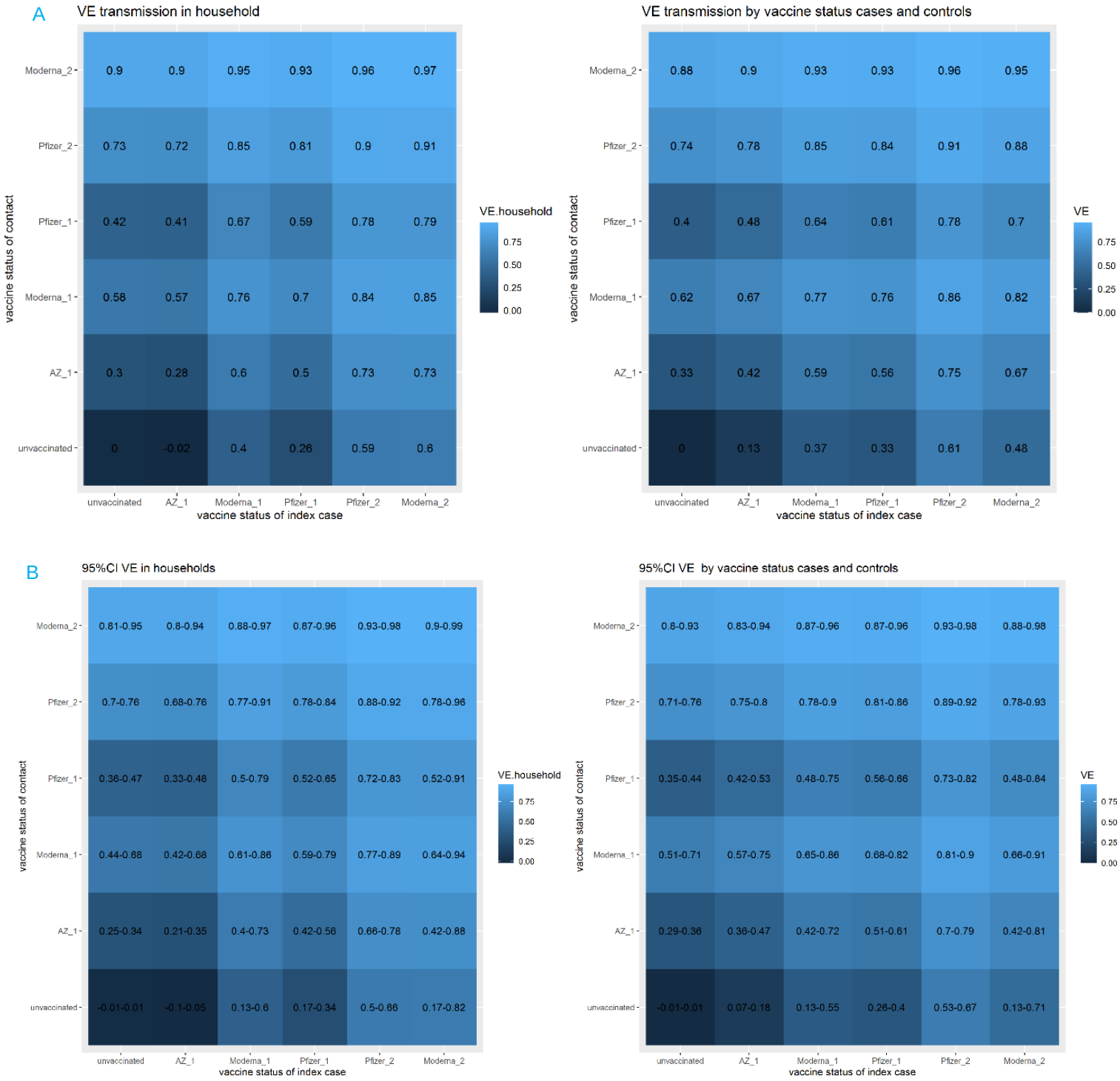


4. Gegevens van contact tracing in België

Op basis van de gegevens van contact-tracing in België tussen 1/02/2021 en 04/05/2021 werd nagegaan hoeveel bescherming een vaccin biedt tegen een positieve test. Als referentie wordt hierbij de secondary attack rate genomen bij hoog-risico contact tussen ongevaccineerde personen (~20%). De gegevens worden weergegeven in Figuur 2. Belangrijkste vaststellingen:

- Er zijn nog geen gegevens beschikbaar over volledig gevaccineerde personen met het Vaxzevria vaccin (tot 04/05 werd enkel de 1e dosis toegediend). Voor de mRNA vaccins waren gegevens beschikbaar van >14,000 volledig gevaccineerde hoog-risicocontacten en >3,000 volledig gevaccineerde indexpersonen.
- **Secundaire besmettingen bij ongevaccineerde contactpersonen van een volledig gevaccineerde persoon met doorbraakinfectie zijn slechts half zo frequent als secundaire besmettingen bij ongevaccineerde indexpersonen**. Gevaccineerde personen zijn dus minder besmettelijk.
- **Volledige vaccinatie doet het risico op een positieve test na hoog-risicocontact met een ongevaccineerde persoon dalen met zo'n 70-80%** in vergelijking met niet-gevaccineerde contactpersonen. Het residuele risico na hoog-risicocontact zal dan rond de 4-6% liggen (20-30% van 20%).

Figure 2: Vaccine effectiveness on the risk of a positive test after high-risk exposure, by vaccination status of cases and index persons, for household contacts (left) and other high-risk contacts (right). A) point-estimates of VE B) 95%-confidence intervals and C) number of people for which information is available.



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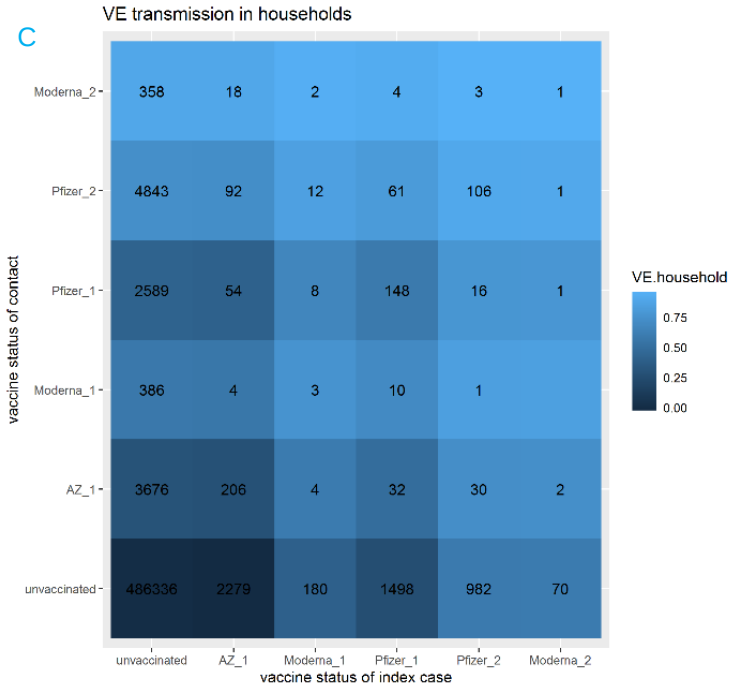
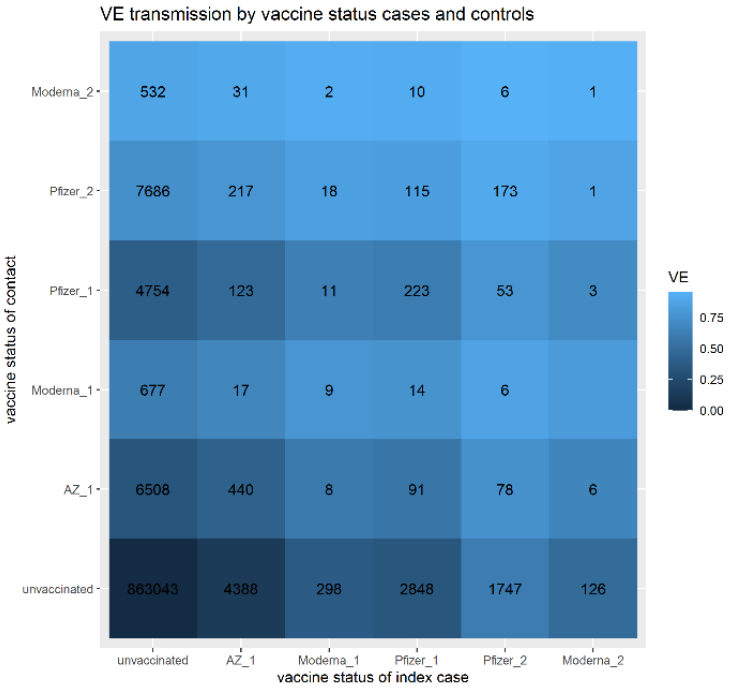




5. Overwegingen

- Er is toenemend bewijs dat vaccinatie ook een effect heeft op transmissie. De bescherming is echter onvolledig en mogelijk afhankelijk van het type vaccin (vooral gegevens beschikbaar voor Comirnaty), leeftijd en onderliggende aandoeningen van de gevaccineerde en circulerende virus-varianten.
- De RAG leden uitten reeds vroeger hun bezorgdheid over mogelijke ongelijke behandeling:
    - Vanuit motivationeel oogpunt zou het verbinden van bepaalde voordelen aan vaccinatie (bv. geen of verkorte quarantaine) de bereidheid tot vaccineren kunnen verhogen. Daar staat tegenover dat tot dusver steeds een beleid gehanteerd is dat gebaseerd is op solidariteit en op het beperken van transmissie: er is steeds geëist dat ook personen met een laag persoonlijk risico op ernstige ziekte (zoals jongeren) de maatregelen respecteren.
    - Het verbinden van bepaalde voordelen aan vaccinatie stelt mogelijk een probleem van billijkheid zolang er geen gelijke toegang tot vaccins is voor iedereen. Bovendien is het interval vanaf de 1e dosis tot volledige vaccinatie verschillend naargelang het vaccin zodat ook personen die behoren tot dezelfde groep, zoals zorgverleners in 1e lijn, niet op hetzelfde moment volledig gevaccineerd zullen zijn.

  De RAG noteert dat deze bezorgdheden momenteel het onderwerp uitmaken van een multidisciplinair advies dat door een aparte werkgroep voorbereid wordt en waarover uiteindelijk een politieke beslissing genomen zal moeten worden. De RAG heeft daarom de voorgelegde vragen rond mogelijke uitzonderingen op quarantaine vanuit een wetenschappelijk invalshoek benaderd: wat zouden we aanbevelen met de huidige kennis, vaccinatiegraad en epidemiologische situatie als iedereen al de kans gekregen had om zich te laten vaccineren?.

    - Het dragen van mondneusmaskers en andere verstrengde maatregelen van infectiepreventie hebben ook een aantoonbaar gunstig effect gehad op andere respiratoire aandoeningen, zoals Influenza, wat een bijkomend argument is om ook in WZC met hoge vaccinatiegraad verder mondmaskers aan te bevelen voor personeelsleden.

6. Update scientific evidence

6.1. VACCINE EFFECTIVENESS (PROTECTION AGAINST SYMPTOMATIC DISEASE)

Clinical trials have reported high efficacy of currently available vaccines (1–3). As opposed to clinical trials, which evaluate vaccines in highly-controlled settings, vaccine effectiveness studies report on vaccine outcomes in real-life settings.

First results of vaccine effectiveness (VE) studies are highly promising, with results mainly available for Comirnaty® (Pfizer-BioNTech) and Vaxzevria® (AstraZeneca-Oxford). In general, a good protection against symptomatic disease (4–11), hospitalization (5,6,11,12) and death (5,6) are found. Furthermore, a majority of these studies show substantial protection after the first dose, which further increases after the second dose (4–8,10).

If VE has been found to decline mildly but significantly with age (10), several studies have now shown that **high effectiveness is still achieved in the elderly** (5,6,12). In a study from Israel, effectiveness of Comirnaty® against symptomatic COVID-19 in individuals of 70 years and older was slightly lower after the first dose but similar after the second dose, when compared to the general population (6). However, the largest VE study published this far, based on population-level surveillance data from Israel, found estimates in individuals of 85 years and older to be very similar to those in younger age groups (13). In an English pre-print focusing on people ≥70 years old, very high effectiveness against symptomatic infection was achieved with both Comirnaty® and Vaxzevria®. In those ≥80 years old with a positive test ≥14 days after the first dose, a substantial reduction was noted in risk for hospitalisation (>37%) and death (51% for Comirnaty®, insufficient data to assess Vaxzevria®) (5). A Scottish pre-print, focusing on VE of the first dose against hospitalisation, found that effectiveness in those ≥80 years old was 81% (95% CI: 65–90) (combined Comirnaty®/Vaxzevria® effect, no separate estimates available). Of note, in this study, peak effectiveness (for all age groups combined) was found at 28-34 days after the first dose (85% (95% CI: 76–91) for Comirnaty® and 94% (95% CI: 73–99) for Vaxzevria®) (12). Interestingly, a Danish pre-print looking at residents (median age 84 years) and staff of long term care facilities found close to no protective effect against laboratory confirmed SARS-CoV-2 14-25 days after the first dose of Comirnaty®, but VE >7 days after the second dose increased to 64% (95% CI: 14–84) in residents and 90% (95% CI: 82–95) in staff. The authors suggest that this may be due to increased testing (and therefore increased detection of asymptomatic cases) (9). However, other studies have found higher VE despite incorporated data from regular testing schemes (4,8), so the exact reason for this difference remains to be elucidated. **In general, direct comparison of the referred articles is hard due to differences in test strategies, dosage schemes, vaccines, outcomes, time points, study populations and epidemic context.**

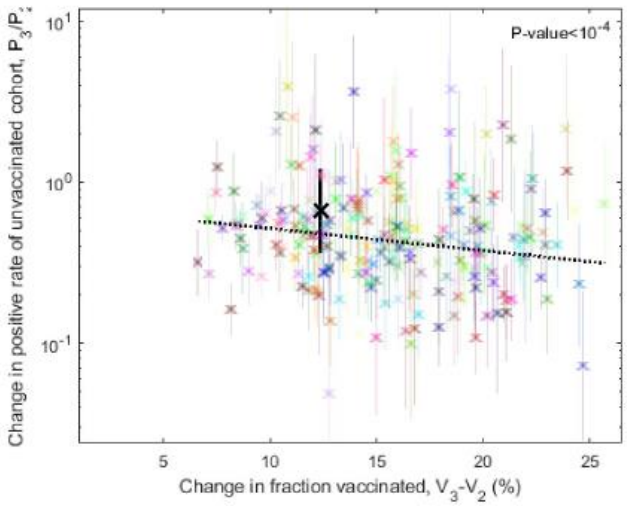
6.2. EFFECT ON TRANSMISSION

Interventions like quarantine and testing seek not to minimize the risk for the individual, but rather aim to protect the community by preventing onwards transmission. Since there is evidence that **truly asymptomatic infections are less contagious than symptomatic disease** (14–17), a vaccine that is effective in preventing symptomatic disease might automatically have some impact on transmission. Additionally, several studies have suggested a lower viral load in infected individuals after the first dose of an mRNA vaccine (18,19). Since viral load seems related to the risk of transmission (20,21), these breakthrough cases might be less transmissible. This has recently been confirmed in a pre-print study from the UK, including 365,447 households from the UK (22). If the index case had received at least one dose of either Vaxzevria or Comirnaty, the risk for household contacts to become infected was approximately halved (aOR 55% [46-67%] for Vaxzevria and 57% [49-65%] for Comirnaty). However, if a vaccinated individual is unaware of his/her asymptomatic infection and no longer complies with non-pharmaceutical interventions, he/she might unknowingly contribute more to the spread of the disease. Studies that assess the risk of transmission and asymptomatic infection are therefore key.

Direct evidence on the risk of transmission from vaccinated individuals is currently only available from one Scottish pre-print study. In the study, based on routinely available national registry data, the risk of infection is assessed in household members (N= 194,362) of healthcare workers (N=144,525). Infection rates are corrected for calendar time, socio-demographic, occupational and comorbidity variants. The main outcome is 'risk of documented COVID-19 infection' in household members of healthcare workers that have received at least one dose of Comirnaty® or Vaxzevria® vs. household members of unvaccinated household members. **The risk of documented COVID-19 infection in household members was 30% lower (hazard ratio: 0.70, 95% CI: 0.63–0.78) ≥14 days after first dose and 50% lower after full vaccination (HR: 0.46, 95% CI 0.3-0.7).** The authors further estimate that a 30% reduction in infection rates amongst household members equals a 60% reduction of transmission through the vaccinated healthcare workers, since the household members are also exposed to other potential sources of infection (11).

Another pre-print study, from Israel, evaluates the risk of infection in (unvaccinated) children <16y old as a function of vaccine coverage in the population (23). They first identify 223 geographically different communities with similar temporal patterns of infection rate prior to vaccination onset. They then capitalize on the different vaccination coverage rates in those regions to evaluate the relative changes in infection rate at fixed time intervals of 3 weeks. The changes in vaccine coverage are compared to changes in infection rates for children 35 days later, to allow time for the potential protective effect of vaccination on the unvaccinated cohort. **The risk of infection in the unvaccinated cohort decreased in proportion to the rate of vaccination in each community**, with an overall strongly significant negative association, although heterogeneity between communities is large (see figure 1).

Figure 1: Correlation between change in infection rates in unvaccinated cohort and change in vaccination coverage rate for 223 communities in Israel *Source: Milman et al.*
For each community, the change in positive rate between consecutive time intervals (*P*3/*P*2) is shown as a function of the change in vaccinated fraction in the corresponding time intervals (*V*3-*V*2). Dash line shows linear fit (P-value<10-4;)



A pre-print study from Spain estimated the indirect protection of unvaccinated residents in long-term care facilities at 81.2% [80.2-82%] after the vaccination campaign with Comirnaty® (24). The indirect protective effect was in identical to direct vaccine effectiveness >28d after the first dose (as a proxy for effectiveness >7d after the second dose). It has to be noted though, that this was in the context of very high vaccination coverage (>99%) amongst all residents, which might be hard to obtain outside this closed setting.

6.3. ASYMPTOMATIC INFECTION (SEE ALSO ANNEX 1)

In order to be able to transmit, people need first to become infected. Therefore, vaccine effectiveness studies that have all infections (including asymptomatic infections) as an outcome, are extremely relevant. Preferably, these studies have a clearly identified testing strategy existing of repeated screening. Annex 1 lists an overview of key studies identified to date.

Two prospective cohort studies (from the US (8) and from the UK (4)) have found **effectiveness against all types of infection (including asymptomatic) of 70-80% after the first dose and 85-90% after the second dose of the Comirnaty® vaccine. Retrospective cohort studies from Israel** (25) **and the US** (26) **show vaccine effectiveness against asymptomatic infection being slightly lower than against symptomatic or any type of infection, but still at very high levels: 86% [69-93%] in the Israeli cohort and 90% [78-96%] in the US.** Similarly, Jones et al report that the test-positivity rate of a weekly screening programme of asymptomatic healthcare staff in the UK dropped from 0.8% in unvaccinated healthcare workers to 0.2% in those having received at least 1 dose of Comirnaty® ≥12 days ago (27) and comparable results have been reported from the US (28). The abovementioned **studies include mainly healthy adults, and effects might not be the same in other groups**. Interesting therefore is the retrospective cohort of Tande et al. using data from screening pre-procedural patients (29). They conclude that the risk of asymptomatic SARS-CoV-2 infection, as compared to unvaccinated individuals, was markedly lower among those >10 days after first dose (RR=0.21; 95% CI: 0.12–0.37) and among those >0 days after second dose (RR=0.20; 95% CI: 0.09-0.44) of either Comirnaty® or Moderna). In contrast, Britton et al. report results from weekly screening of residents of a long-term care facility and find a lower VE of 63% [33-79%] after the first dose of Comirnaty®. Data was insufficient to assess the effect after the second dose (30). These results are in line with data from the VIVALDI study in the UK, reporting on over 10,000 LTCF residents (median age 86 years) who undergo monthly PCR screening. VE was found to be 62% [23-81%] 28-34 days after the first dose of either Comirnaty® (33% of vaccinated) or Vaxzevria® (67%) (31). Interestingly, in a sensitivity analysis excluding unvaccinated individuals from LTCFs where vaccination had been offered, in order to eliminate bias due to possible herd immunity effect, VE increased to 76% [37-91%]. At ≥49 days after the first dose, the point estimate of VE was only a little lower than at 35-48 days, but the confidence intervals were wide and crossing the null (VE 51% [-17 – 80%]). In a comparable population of LTCF residents in Denmark, a similar vaccine effectiveness of 64% [14-84%] was found after full vaccination with the 2 doses of Comirnaty® (9) (pre-print). Notably, the same Danish study found high effectiveness (90% [82-95%]) against infection for staff members that were offered weekly screening. The large vaccine effectiveness study from Israel based on national surveillance data reported vaccine effectiveness of 91.5% [90.7-92.2%] against asymptomatic disease (32). However, during the data collection there was no regular testing of asymptomatic persons in place and 'asymptomatic disease' was only defined as the absence of fever or respiratory symptoms at time of testing.

In the original Moderna COVID-19 vaccine randomized controlled trial (1), a subgroup of asymptomatic participants underwent PCR-testing at the time of administering the second dose. Using these results, another pre-print study estimated that one dose of vaccination reduced the potential for viral transmission with at least 61% (33).

It is possible that effects differ according to vaccine type. Currently, most data is available for mRNA vaccines (Comirnaty® and the COVID-19 Moderna vaccine). Reassuringly though, the abovementioned VIVALDI trial found similar results for both Comirnaty and Vaxzevria (31). For the **Vaxzevria®** vaccine, we can also draw on results of a subgroup of participants of the initial RCT which was tested weekly (regardless of symptoms) with self-administered throat and nose swabs. Overall, no protective effect on asymptomatic infections was noted in this subgroup. However, when limiting the analysis to those who received the two doses with an interval of at least 12 weeks (the current dosing regimen in Belgium), there was **a vaccine efficacy of 47.2% [5.0-70.7%].** Data on overall reduction of infection (i.e. symptomatic + asymptomatic) is not reported separately for this subgroup (34).

5.3 PROTECTION AGAINST VARIANTS OF CONCERN (VOC)

Most studies have been conducted in the absence of circulating VOCs. Concerns have been raised about the efficacy of the vaccines against currently circulating variants of concern, **especially those bearing the E484K-mutation, a mutation improving the ability of the virus to evade the host's immune system.** Both the P1-strain first detected in Brazil and B1.351 first detected in South Africa carry this E484K mutation.

Real life effectiveness data from the UK are reassuring in terms of the effectiveness of both Comirnaty® (Pfizer-BioNTech) and Vaxzevria® (AstraZeneca-Oxford) against the UK variant B.1.1.7 (4,5,12). For the COVID-19 vaccine Moderna®, limited real-life effectiveness data are available. One US preprint found good protection of either Comirnaty® or the COVID-19 vaccine Moderna® (no distinction made between two types of vaccine) against infection during a time at which 69% of the circulating virus belonged to one of the following variants: B.1.1.7, B.1.427, B.1.429 (33). Additionally, a laboratory study suggests no significant reduction of antibody neutralization of COVID-19 vaccine Moderna® elicited sera against the UK variant (34)

A **South African** study, held at a time of high circulation of the **B1.351 variant**, found a very low effectiveness 10.6% (95% CI:-66.4 to 52.2) of two doses of Vaxzevria® against mild to moderate laboratory confirmed COVID-19 (35). It should be noted however that **no data was available on protection against severe disease or death** and that the dosing interval was only 21-35 days, which is substantially lower than the 12 weeks interval used in Belgium. Longer dosing intervals have been shown to yield higher protection. A recent pre-print study from Israel also found a higher than expected proportion of B1.351 breakthrough infections after vaccination with the Comirnaty® vaccine, compared to non-vaccinated individuals (36). The study used a case-control design whereby breakthrough infections were matched to infections in unvaccinated control subjects with similar demographic characteristics (date of PCR, age, sex, ethnic sector, and geographic location). Importantly though, among the 400 case-control pairs (i.e. 800 infections), only 11 infections were caused by the B1.351 variant (8 in fully vaccinated individuals, 1 after the 1st dose and 2 in unvaccinated). The authors therefore note that "there may be higher rates of vaccine breakthrough with B.1.351, but it is possible that (a) vaccine effectiveness coupled with enacted non-pharmaceutical interventions remain sufficient to prevent its spread, and/or (b) B.1.1.7 outcompetes B.1.351, possibly due to its high transmission rate." In addition, several studies suggest a reduction in neutralizing capacity of vaccine elicited antibodies (37–40). Likewise, one real-life effectiveness study from Qatar found that the effectiveness ≥ 14 days after the second dose of Comirnaty® against any documented infection with the South African variant was about 15% lower as compared to the UK variant. However, substantial effectiveness (75%; 95% CI: 70.5-78.9) was still achieved. Moreover, and importantly, **effectiveness against severe infections was high** (100.0%; 95% CI: 73.7–100.0) and in line with that against the UK variant (100.0%; 95% CI: 81.7–100.0) (32).

Little is known concerning the effectiveness of the different vaccines against the **Brazilian variant P1**. Although, according to an ECDC risk assessment, **the presence of the E484K mutation (also present in the South African variant) may indicate a profile similar to the South African variant, some more reassuring preliminary data are coming in.** Two pre-prints of laboratory studies found only moderate reductions (2.6-4.8 fold) of antibody neutralizing capacity of Comirnaty®, COVID-19 vaccine Moderna® or Vaxzevria® elicited sera against the P.1 variant (45,55). In one of these studies, looking at Comirnaty® and Vaxzevria®, the neutralizing capacity was in line with what was found against the UK variant and was substantially higher than that against the South African variant (45). This could indicate that the impact on effectiveness is minor. Caution is however needed when interpreting results of neutralization assays since correlates of protection have not yet been determined and results should be confirmed with real-life effectiveness studies. Limited data are available for the COVID-19 Vaccine Janssen®. According to the phase III J&J clinical trial, efficacy was very similar in Brazil as compared to the US. But at that time 69% of cases were due to Brazilian variant of interest P.2, and not the variant of concern P.1.

Another variant first detected in **India** actually comprises three subtypes: linages B.1.617.1, **B.1.617.2** and B.1.617.3. They have several mutations of interest within the S gene (including L452R, D614G, P681R). Lineage B.1.617.1 and .3 also having a E484Q mutation (similar to E484K in B.1.351 and P1, but substituting with a different amino-acid). There is some laboratory evidence of functional evasion of naturally acquired immunity and of vaccine derived immunity (57,58), but currently not enough to make a definite conclusion.

7. International recommendations

7.1. ECDC

On the 29th of March, the agency published a Technical Report on Risk of SARS-CoV-2 transmission from newly-infected individuals with documented previous infection or vaccination. The key points regarding vaccination are:

> *"The review of evidence on immunity and possibilities for transmission from infected, previously-vaccinated individuals to susceptible contacts found that:*
>
> - *Direct evidence of the impact of vaccination on the risk of transmission is only available from one study, a large register-based household transmission study from Scotland. This study suggests that vaccination of a household member reduces the risk of infection in susceptible household members by at least 30%.*
> - *There is evidence that vaccination significantly reduces viral load and symptomatic/asymptomatic infections in vaccinated individuals, which could translate into reduced transmission, although the vaccine efficacy varies by vaccine product and target group. In light of this fact, the total number of infections is expected to decrease significantly as vaccination coverage increases, provided that there is a match between the vaccine strains and the circulating virus strains. This will lead to decreased transmission overall.*
> - *Follow-up periods for vaccinated persons are not yet sufficiently long enough to draw conclusions on the duration of protection against infection long-term. Antibody titres in vaccinated individuals peak at 3−4 weeks following vaccination.*
> - *Many of the vaccine efficacy studies were carried out before the emergence of SARS-CoV-2 VOCs. In studies that address the variants, there is limited preliminary evidence of reduced vaccine efficacy, in particular for B.1.351 and possibly also for P.1.*
>
> *Follow-up of cohorts with previous SARS-CoV-2 infection and vaccination is needed to better assess the magnitude and duration of protection from reinfection leading to asymptomatic/symptomatic disease, and the effect of protection against further transmission to contacts."*

On the 21st of April, "Interim guidance on the benefits of full vaccination against COVID-19 for transmission and implications for non-pharmaceutical interventions" was published.
On the topic of quarantine and testing of fully vaccinated individuals, it is mentioned that:

- *"When contact tracing,* ***vaccinated contacts who have been exposed to a confirmed case should continue to be managed according to existing ECDC guidance****. However, health authorities may consider undertaking a risk assessment on a case-by-case basis and subsequently classify some fully vaccinated contacts as low-risk contacts. Factors that need to be taken into consideration in such assessments include, for example, the local epidemiological situation in terms of circulating variants, the type of*

vaccine received, and the age of the contact. The risk of onward transmission to vulnerable persons by the contact should also be considered.

- *Requirements for **testing and quarantine of travellers (if implemented) and regular testing at workplaces can be waived** or modified for fully vaccinated individuals as long as there is no or very low level circulation of immune escape variants (in the community in the country of origin, in the case of travellers).”*

7.2. CDC:

CDC updated their Science Brief “Background Rationale and Evidence for Public Health Recommendations for Fully Vaccinated People” on the 2nd of April. Key points are:

- *COVID-19 vaccines currently authorized in the United States are effective against COVID-19, including severe disease.*
- *Preliminary evidence suggests that the currently authorized COVID-19 vaccines may provide some protection against a variety of strains, including B.1.1.7 (originally identified in the United Kingdom). Reduced antibody neutralization and efficacy have been observed for the B.1.351 strain (originally identified in South Africa). However, across studies, antibody neutralizing activity of sera from vaccinated people was still generally higher than that observed for convalescent sera from people who have recovered from COVID-19.*
- *A growing body of evidence suggests that fully vaccinated people are less likely to have asymptomatic infection and potentially less likely to transmit SARS-CoV-2 to others. However, further investigation is ongoing.*
- *Modeling studies suggest that preventive measures such as mask use and social distancing will continue to be important during vaccine implementation. However, there are ways to take a balanced approach by allowing vaccinated people to resume some lower-risk activities.*
- *Taking steps towards relaxing certain measures for vaccinated people may help improve COVID-19 vaccine acceptance and uptake.*
- *The risks of SARS-CoV-2 infection in fully vaccinated people cannot be completely eliminated as long as there is continued community transmission of the virus. Vaccinated people could potentially still get COVID-19 and spread it to others. However, the benefits of relaxing some measures such as testing and self-quarantine requirements for travelers, post-exposure quarantine requirements and reducing social isolation may outweigh the residual risk of fully vaccinated people becoming ill with COVID-19 or transmitting the virus to others.*
- *At this time, there are limited data on vaccine protection in people who are immunocompromised. People with immunocompromising conditions, including those taking immunosuppressive medications, should discuss the need for personal protective measures after vaccination with their healthcare provider.*

Based on these data, CDC suggests that fully vaccinated people can:

- ***Resume activities without wearing masks or physically distancing**, except where required by federal, state, local, tribal, or territorial laws, rules and regulations, including local business and workplace guidance. (newly added 13/05/2021)*
- ***Refrain from quarantine and testing following a known exposure if asymptomatic***
- *Resume travel and refrain from testing before **or after travel** or self-quarantine after travel.*

Specific measures are detailed for residents and staff of healthcare structures:

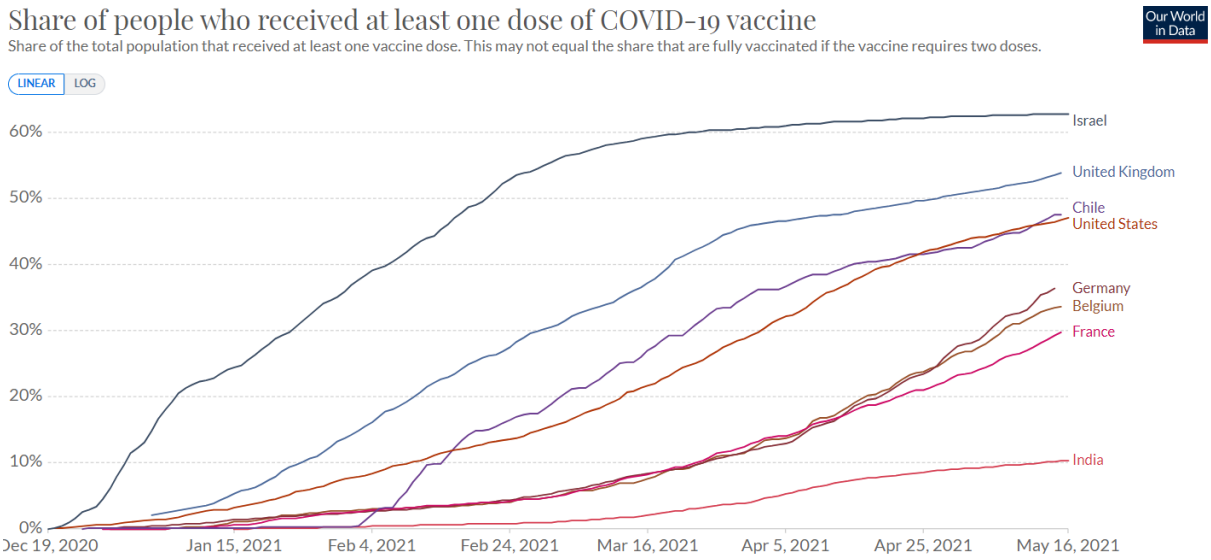
- ***Fully vaccinated healthcare personnel (HCP) with higher-risk exposures who are asymptomatic do not need to be restricted from work for 14 days following their exposure**.*

    - *Work restrictions for the following fully vaccinated HCP populations with higher-risk exposures should still be considered for HCP who have underlying immunocompromising conditions (e.g., organ transplantation, cancer treatment), which might impact level of protection provided by the COVID-19 vaccine. However, data on which immunocompromising conditions might affect response to the COVID-19 vaccine and the magnitude of risk are not available.*
- *HCP who have traveled should continue to follow CDC travel recommendations and requirements, including restriction from work, when recommended for any traveler.*
- *Recommendations for SARS-CoV-2 testing and use of PPE for HCP remain unchanged.*
- ***Fully vaccinated inpatients and residents in healthcare settings should continue to quarantine following prolonged close contact** (within 6 feet for a cumulative total of 15 minutes or more over a 24-hour period) with someone with SARS-CoV-2 infection; outpatients should be cared for using recommended Transmission-Based Precautions. This is due to limited information about vaccine effectiveness in this population, the higher risk of severe disease and death, and challenges with physical distancing in healthcare settings.*

When evaluating the recommendations of the CDC (or other international organizations), it is important to note that:

- Vaccine coverage in the US is significantly higher than in Belgium

  Figure 2: Comparison in vaccine coverage between Belgium and selected other countries 17/05/2021 (*Source: Our World in Data)*



- As of April 13 2021, only mRNA vaccines have been deployed in the US. On April 23 the FDA advised to resume the deployment of the Johnson&Johnson/Janssens-vaccine.

De volgende experten droegen bij aan dit advies:

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8. Annex 1: overview of high-quality studies reporting VE on any SARS-CoV-2 infection (including asymptomatic)

Source	Study type	Population	N	Vaccine	Testing strategy	Outcome
Tande et al.	Retrospective cohort	asymptomatic undergoing pre-procedural screening USA	Total = 39,156 Vaccinated = 2,069 (min. 10d after 1st dose)	mRNA (94% Pfizer)	All pre-procedural	Vacc PCR+ 42/3,006 vs. 1,436/45,327 aRR >10d after D1 = 0.21 [0.12-0.37] aRR >0d after D2 = 0.20 [0.09-0.44]
Thompson et. al	Prospective cohort	HCW (1st line workers) USA	Total = 3,950 Unvaccinated = 989 Infections = 205	mRNA (63% Pfizer)	Weekly self-swab & at onset symptoms	VE ≥14d after D1 = 80% [59-90%] VE ≥14d after D2 = 90% [68-97%] only 10% infections truly asymptomatic
Hall et al (pre-print)	Prospective cohort (SIREN)	HCW UK	Total = 23,324 Unvaccinated = 2,683 Infections = 1,057	mRNA (100% Pfizer)	PCR 1x/2 weeks RDT 2x/week	VE ≥21d after D1= 72% [58-86%] VE ≥7d after D2 = 86% [76-97%]
Britton et al.	Retrospective cohort	Residents of LTCF USA	Total = 463 (50% ≥85y) Unvaccinated = 87 Infections = 97	mRNA (100% Pfizer)	Weekly PCR & at symptoms	VE ≥14d after D1 = 63% [33-79%] insufficient data after D2
Moustsen-Helms et al (pre-print)	Retrospective cohort	Residents and staff of LTCF Denmark	Residents = 39,040 (median age 84y) Infections = 572 Staff = 331,039 Infections = 5,725	mRNA (100% Pfizer)	Weekly screening offered in staff "increased testing" in LTCF (=?)	VE 14-25d after D1 (short window!) residents = 21% [-11-44%] staff = 17% [4-28%] VE >7d after D2 residents = 64% [14-84%] staff = 90% [82-95%]
Shrotri et al (pre-print)	Retrospective cohort	LTCF residents	Total = 10,412 Vaccinated = 1,252 Previous infection= 1,155 (11.1%) Infections = 1,334	33% Pfizer 66% Oxford-AZ	PCR 1x/month + outbreak	VE 28-34d after D1= 53% [0.19-76%] 35-48d after D1= 62% [23-81%]
Voysey et al	RCT (vaccine *efficacy*)	UK – trial particpants	Total = 8,207 Vaccinated = 4,071 Infections = 130	Oxford-AstraZeneca	Weekly self-swab	VE 14d after D2 for asymptomatic infection ONLY overall = 2.0% [-50.7-36.2%] if dosing interval ≥12w = 47.2% [5.0-70.7%]
Angel et al	Retrospective cohort	HCW Israël	Total = 6,710 Vaccinated = 5,517 Infections = 82	mRNA (100% Pfizer)	'Regular screening' PCR	VE 7d after D2 symptomatic = 97% [94-99%] asymptomatic = 86% [69-93%]
Tang et al	Retrospective cohort	HCW USA	Total = 5,217 Vaccinated = 2,776 Infections = 236	mRNA (100% Pfizer)	'Routine screening'	VE 7d after D2 symptomatic = 100% asymptomatic = 90% [78-96%]