IMPACT DE LA STRATÉGIE DE VACCINATION SUR LES MESURES EN PLACE POUR LES TESTS ET LA QUARANTAINE – 3ième MISE À JOUR.

Réunion du RAG 18/05/2021 – validé en RMG 20/05

Attention : décisions prises (avec changements par rapport à l'avis des experts comme présenté ici) en CODECO 04/06/2021 et en CIM 16/06/2021

À la fin du mois de décembre, un premier avis avait été émis concernant d'**éventuelles modifications des procédures actuellement en place pour la quarantaine et les tests des personnes vaccinées**. Ce premier conseil a ensuite été actualisé en février et en avril. En raison d'un taux de vaccination initial faible et de données insuffisantes sur l'effet sur la transmission, seules des modifications très limitées des lignes directrices actuelles avaient été recommandées. Dans ses avis précédents, le RAG a déjà mentionné d'éventuels problèmes d'équité tant que tout le monde n'a pas eu accès à la vaccination et tant qu'il n'y a pas de libre choix du type de vaccin. Actuellement, un groupe d'experts du GEMS, complété par des experts en droit, en éthique et en sociologie, se penche sur ces questions éthiques et sociales. Le RAG se focalise dans cet avis uniquement sur la base scientifique, la couverture vaccinale et la situation épidémiologique présente et propose que les recommandations soient intégrés dans le débat plus large sur le traitement différent des personnes vaccinées et non-vaccinées.

1. Recommandations :

- **Les premiers résultats obtenus dans d'autres pays confirment que la vaccination joue un rôle clé dans le retour à une vie normale. Il est donc extrêmement important de motiver la population à se faire vacciner. Une information correcte et une communication ciblée sont indispensables à cet égard, en soulignant à la fois les avantages pour l'individu (protection contre les maladies graves) et pour la société (protection du système de santé, réduction de la circulation du virus).**
- Toutefois, étant donné la disponibilité limitée des vaccins, le déploiement de la vaccination est progressif. La couverture vaccinale a récemment fortement augmenté, mais la vaccination complète des groupes à risque n'a pas encore été atteint. Dans ces circonstances, les interventions non pharmaceutiques (telles que le port du masque, les tests et la quarantaine) restent particulièrement importantes. Le rythme auquel un assouplissement des règles pour l'ensemble de la population peut avoir lieu fait l'objet de décisions politiques, aidé par les avis scientifiques.
- Les différents aspects influençant cet avis, à savoir la situation épidémiologique en Belgique (en particulier les hospitalisations), la couverture vaccinale, la circulation des variants de préoccupation (VOC), et les connaissances scientifiques liées à la vaccination (en particulier concernant le risque de transmission après vaccination) seront suivis de près. Une mise à jour de cet avis est donc prévue dans un délai d'un mois.
- Pour des raisons pratiques (vérifiabilité) et compte tenu de l'effet incomplet de la vaccination sur la transmission, les mesures préventives générales telles que la distance physique et le port du masque dans les lieux publics continuent de s'appliquer aux personnes déjà vaccinées.

- Dans les recommandations formulées dans le présent document, le terme "vacciné" signifie que les personnes ont été entièrement vaccinées, c'est-à-dire qu'elles ont reçu un vaccin complet :
    - pour Comirnaty® (Pfizer-BioNTech) : ≥7 jours après la deuxième dose.
    - pour le vaccin COVID-19 Moderna : ≥14 jours après la deuxième dose
    - pour Vaxzevria® (AstraZeneca-Oxford) : ≥15 jours après la deuxième dose.
    - pour le vaccin COVID-19 Janssen: ≥14 jours après la première dose

  Pour les personnes qui ont été partiellement vaccinées, les mêmes règles que pour les personnes qui n'ont pas encore été vaccinées s'appliquent.

- La protection offerte par les vaccins est élevée, mais n'est pas à 100 %. Les **personnes vaccinées qui présentent des symptômes possibles de COVID-19 doivent donc contacter un médecin pour subir un test, tout comme les personnes non vaccinées**. Il est rappelé que l'autotest ne peut PAS être utilisé chez les personnes symptomatiques (vaccinées ou non).
- Les personnes qui sont infectées par le SARS-CoV-2 alors qu'elles ont été vaccinées doivent être isolées, tout comme les personnes non vaccinées, même si elles ne présentent aucun symptôme. Certains éléments indiquent que ces personnes sont généralement moins infectieuses, mais la contagiosité ne peut certainement pas être exclue. Cela s'applique également aux résidents de MRS où un taux de vaccination élevé a été atteint.

- Il y a de plus en plus de données montrant que la vaccination a également un effet sur la transmission. Cependant, la protection est partielle et peut dépendre du type de vaccin, de l'âge et des maladies pré-existantes de la personne vaccinée ainsi que des variants du virus en circulation. Une vigilance accrue est alors encore nécessaire après contact à haut risque, même pour les personnes vaccinées. **Les personnes avec une vaccination complète peuvent être exemptées de quarantaine à condition de se soumettre à 2 tests : le plus tôt possible après l'identification et 7 jours après le dernier contact à haut risque**[1]. La stratégie de test est donc la même que pour les contacts à haut risque non vaccinés.
    - Les personnes entièrement vaccinées qui refusent de se faire tester doivent respecter une quarantaine de 10 jours après le dernier contact à risque.
    - Si un cluster d'infections est détecté dans une collectivité résidentielle, même les personnes entièrement vaccinées doivent respecter la quarantaine.
    - Il est possible que les vaccins soient moins efficaces chez les personnes souffrant d'une immunodépression sévère (par exemple en cas de cancer hématologique ou de transplantation d'organe solide). Le risque qu'elles soient infectées après un contact à haut risque et transmettent le virus est alors plus élevé. Dans ces cas et en concertation avec le médecin-spécialiste traitant, une mise en quarantaine doit être envisagée, même s'ils ont été entièrement vaccinés.
- L'exception à la quarantaine, à condition de deux tests J1 et J7, s'applique également aux voyageurs vaccinés qui rentrent d'une zone rouge et qui sont soumis à une quarantaine, sauf s'ils rentrent d'une zone avec circulation intense de VOC/VOI avec possible immune escape.

[1] Si le cas index ne peut ou ne veut pas s'isoler, le deuxième test sera alors effectué 7 jours après la fin de l'isolement (c.à.d 17 jours après le début de symptômes du cas index).

- Le dépistage préventif a une probabilité pré-test plus faible que les autres indications. Chez les personnes vaccinées, le risque a priori d'infection est encore plus faible, de sorte que le dépistage préventif ne doit être effectué que si le risque en cas d'infection non détectée est particulièrement élevé. C'est par exemple le cas avant une transplantation (risque pour le récepteur) ou lors d'une admission à l'hôpital (risque pour les autres patients non vaccinés). Les décisions relatives au dépistage préventif dans les centres de soins résidentiels doivent toujours tenir compte de la couverture vaccinale du personnel et des résidents (et de la prévalence).
- Dans les centres de soins résidentiels ou autres collectivités résidentielles qui ont atteint une couverture vaccinale élevée, le risque d'une épidémie parmi les résidents est plus limité que dans la population générale. Cependant, les centres de soins résidentiels ne sont pas des îlots isolés de la société: il existe toujours une interaction par le biais des visiteurs et du personnel. Certaines mesures, telles que le port du masque par le personnel, devraient donc continuer à s'appliquer.

- **Les recommandations sont résumées dans le tableau de la page suivante.**

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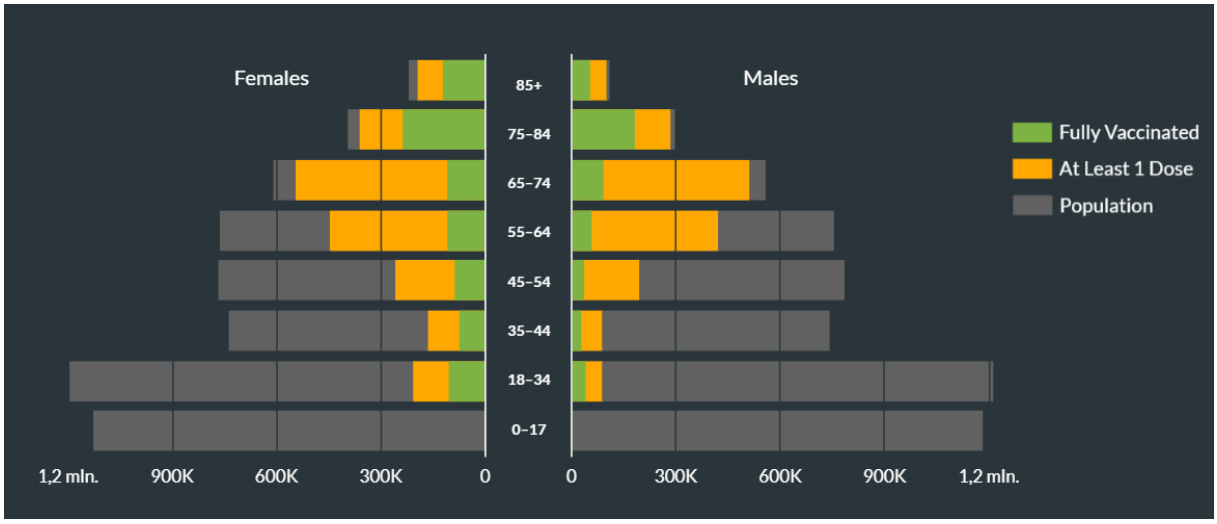
2. Aperçu des impacts possibles et des recommandations

Sujet	Principaux points de la procédure actuelle (lien)	Recommandation pour les personnes vaccinées
Cas possibles de COVID-19	Chaque cas possible est testé. Test antigène possible si les symptômes sont ≤5 jours.	Mêmes indications pour les tests **Préférence forte pour un test PCR** Si positif : déclaration + séquençage
Isolement des personnes concernées	10 jours dont au moins 3 jours sans fièvre Règles spéciales dans les hôpitaux, les personnes immunodéprimées, les maladies graves.	Aucun changement.
Recherche des contacts		
Cas index	Identifier les HRCs à partir de 2d avant l'apparition des symptômes et les mettre en quarantaine	Aucun changement.
Contact à haut risque (HRC)	Test et quarantaine de 7 à 10 jours Travail exceptionnellement autorisé pour les soignants si nécessaire	Pas de quarantaine à condition de se soumettre à un test après identification et un deuxième test 7 jours après le dernier contact à haut risque. Considérer de maintenir la quarantaine pour les personnes avec une immunodépression sévère (p.ex. cancer hématologique, post-transplants), en concertation avec médecin.
Contact à faible risque (LRC)	Vigilance accrue. Test J5 (*recommandé, mais pas encore implémenté)*.	Classer comme : « pas de contact à risque »
Cluster	Hors hôpital : tests plus poussés des contacts à faible risque avec des tests antigéniques- Hôpital: tests poussés du personnel/des résidents avec la PCR.	Dans les collectivités résidentielles: maintenir la quarantaine pour les HRC vaccinés en cas de cluster.
Voyageurs		
Retour d'une zone rouge	Test négatif obligatoire et mise en quarantaine dans certaines circonstances	Pas de quarantaine sur condition de test J1+J7. Maintenir quarantaine et testing si retour de zone VOC/VOI
Dépistage préventif		
Personnel MRS	Envisager un dépistage régulier par PCR sur un échantillon de salive	Pas de dépistage si couverture vaccinale résidents ≥90% et personnel ≥70%.
Visiteurs MRS	Envisager l'utilisation de tests rapides antingéniques avant les visites	Pas de dépistage si couverture vaccinale résidents ≥90% et personnel ≥70%.
Admission à l'hôpital	Dépistage systématique dans les unités à haute prévalence/risque	Dépistage si risque de transmission à d'autres patients non vaccinés.
Nouveau résident en collectivité (admission à partir du milieu familial)	Dépistage systématique et isolement en chambre en attendant les résultats	Tests systématiques. Aucun isolement dans la chambre n'est nécessaire dans l'attente des résultats, sauf si le taux de vaccination des résidents est <90 % ou <70% pour le personnel.
Autres professions (p.ex enseignants)	Médecin du travail peut décider d'un dépistage systématique	Aucun avantage du dépistage si vacciné sans contact groupes à risque.
Autotests	« Geste de courtoisie », après comportement à risque	Pas de dépistage.
Dépistage du donneur avant la transplantation	Examen systématique	Aucun changement (en raison du risque élevé pour l'accepteur)

3. Situation en Belgique

- Le 18/05/2021, l'incidence cumulée sur 14 jours des nouveaux cas de maladie est de 313/100 000 personnes. La moyenne hebdomadaire des nouvelles admissions en hôpital et de 133 par jour. 610 lits en soins intensives sont occupés par des patients COVID-19.
- 3,9 millions de Belges (33,9 % de la population totale) ont reçu la première dose de vaccin, 1,4 million (11,9 %) ont été complètement vacciné.

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*

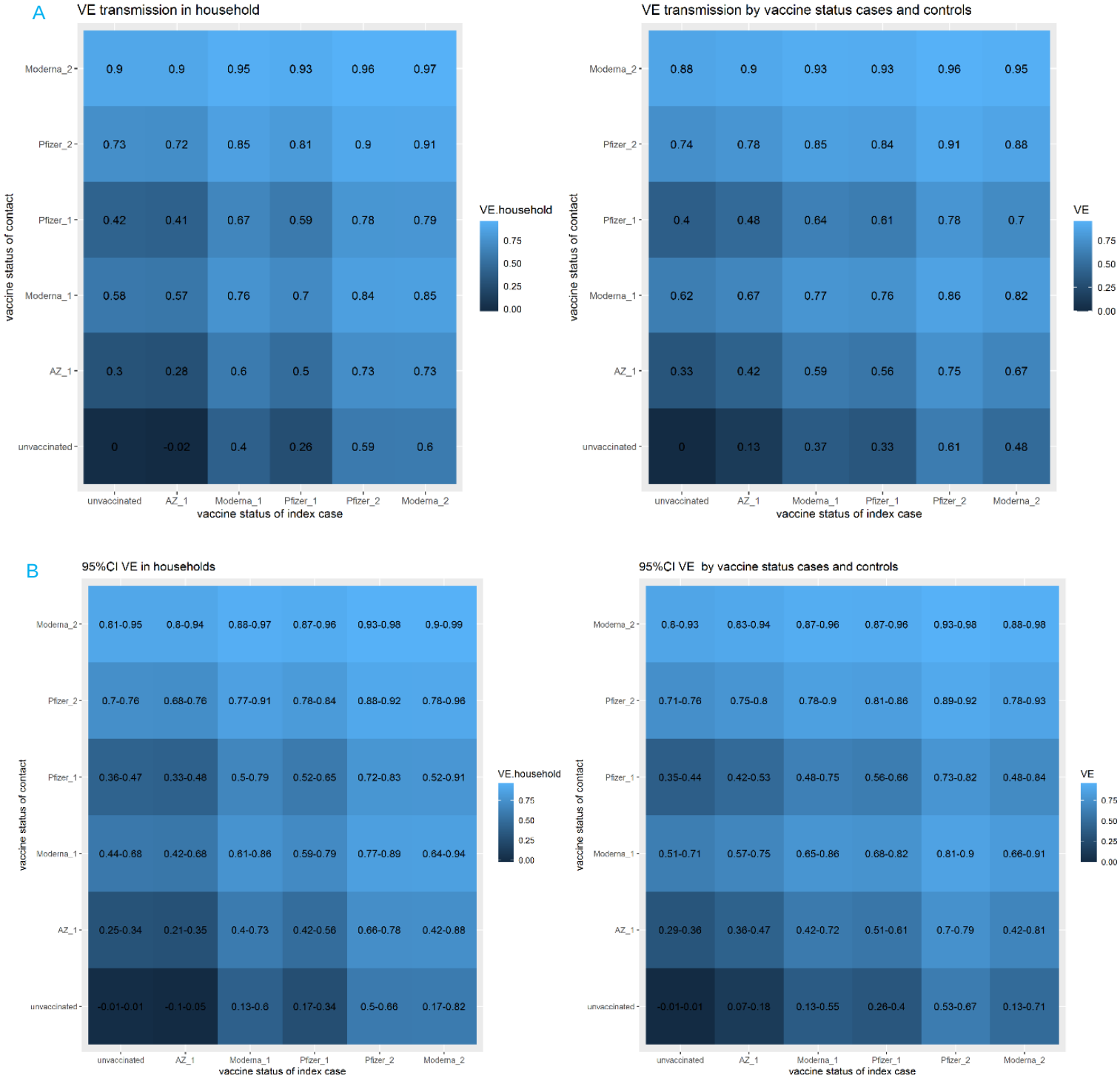


4. Données du suivi de contacts en Belgique

Sur base des résultats du suivi des contacts en Belgique entre le 1/02/2021 et le 04/05/2021, il est possible de déterminer la protection offerte par un vaccin contre l'infection, définie comme une personne ayant un test positif. Comme référence on utilise le 'secondary attack rate' après un contact à haut risque entre des personnes non-vaccinées (~20%). Les chiffres sont présentés dans la figure 2. Principaux résultats :

- On ne dispose pas encore des données sur des personnes complètement vaccinées avec le vaccin Vaxzevria (jusqu'au 04/05, seule la première dose a été administrée). Pour les vaccins ARNm, les données sont disponibles pour plus de 14 000 personnes de contact complètement vaccinées et plus de 3 000 personnes cas-index vaccinées.
- **Le risque d' infection secondaire chez une personne non-vaccinée ayant été en contact avec un cas index vacciné, est la moitié du risque d'infection secondaire après un contact avec un cas index non-vacciné.** Les personnes vaccinées sont donc moins contagieuses.
- **Une personne complètement vaccinée a un risque réduit de d'environ 70 à 80 % d'être infectée, défini comme avoir un test positif, après un contact avec un cas index non-vacciné,** par rapport à une personne non vaccinée. Le risque résiduel après un contact à haut risque serait alors de l'ordre de 4-6% (20-30% de 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. *(Source: Contact tracing database Sciensano)*



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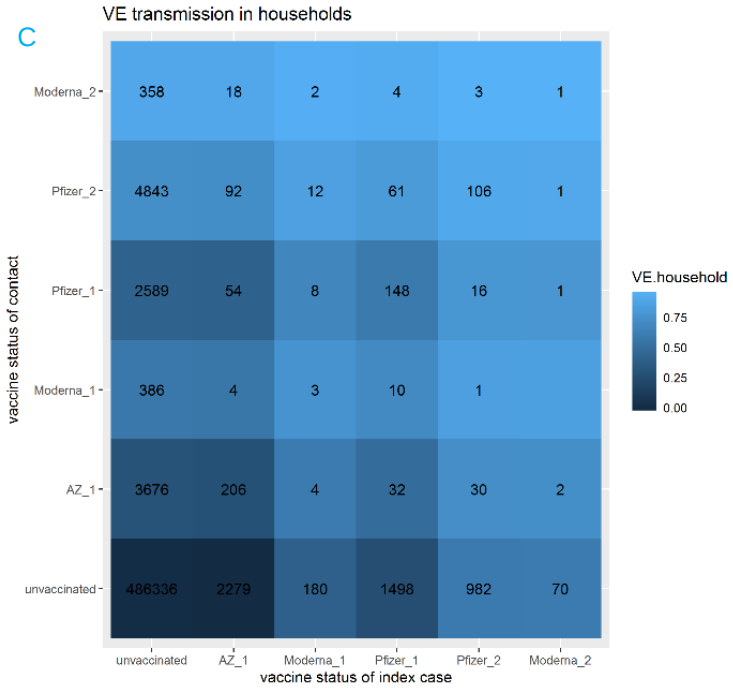
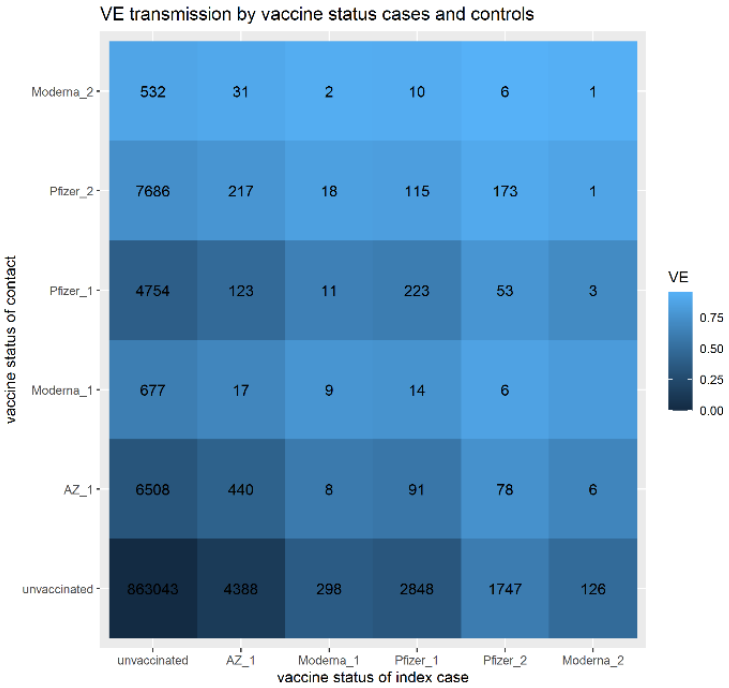




5. Considérations

- Il y a de plus en plus de données montrant l'effet de la vaccination sur la transmission. Un risque de transmission persiste selon le type de vaccin (données disponibles surtout pour Comirnaty), l'âge, les maladies pré-existantes chez la personne vaccinée ainsi que la circulation de variants du virus qui échapperaient à la vaccination.
- Toute modification des procédures existantes nécessite un temps suffisant pour sa mise en œuvre sur le terrain (information des parties prenantes, formation du personnel du centre d'appels, mise en œuvre technique...) et ne doit pas, de préférence, être trop complexe. Ainsi, même s'il existe aujourd'hui sur le marché plusieurs vaccins présentant des caractéristiques différentes, et tenant compte aussi que l'individu n'est pas libre de choisir le type de vaccin, les directives traitent toutes les personnes vaccinées de la même manière (quel que soit le type de vaccin reçu). Cette approche facilite la logistique et la clarté de la communication à la population.
- Au-delà des évidences scientifiques – ou de l'absence de celles-ci- qui sous-tendent leurs avis, les membres du RAG ont déjà exprimé certaines préoccupations :
    - D'un point de vue motivationnel, le fait de lier certains avantages à la vaccination (par exemple l'absence de quarantaine ou une quarantaine réduite) pourrait accroître la volonté de se faire vacciner. D'autre part, la politique suivie jusqu'à présent a toujours été celle de la solidarité et de la limitation de la transmission en exigeant que les personnes présentant un faible risque personnel de maladie grave (par exemple les jeunes) respectent également les mesures.
    - Attacher actuellement certains avantages à la vaccination pose potentiellement un problème d'équité tant que l'accès aux vaccins n'est pas égal pour tous. De plus, l'intervalle entre la 1ère dose et l'obtention d'une protection vaccinale complète est différent selon le vaccin, de sorte que même les personnes appartenant au même groupe, comme les prestataires de soins de santé en 1ère ligne, ne seront pas complètement vaccinées au même moment.

Le RAG note que ces préoccupations font actuellement l'objet d'un avis pluridisciplinaire préparé par un groupe de travail distinct et sur base duquel une décision politique devra être prise. Par conséquent, le RAG a abordé les questions présentées concernant les exceptions possibles à la quarantaine d'un point de vue scientifique : quelles recommandations sur base des données disponibles, de la couverture vaccinale actuelle et de la situation épidémiologique si tout le monde avait déjà eu l'opportunité de se faire vacciner ?

- Le port du masque et d'autres mesures renforcées de prévention des infections ont également eu un effet bénéfique démontrable sur d'autres maladies respiratoires, comme la grippe, ce qui constitue un argument supplémentaire pour continuer à recommander l'application de ces mesures par les membres du personnel, même dans les MRS où la couverture vaccinale est élevée.

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.**

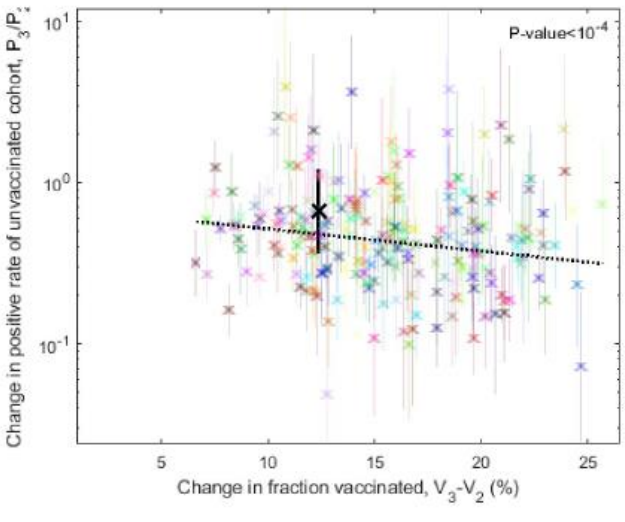
6.2. EFFECT ON TRANSMISSION

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 still contribute 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.*

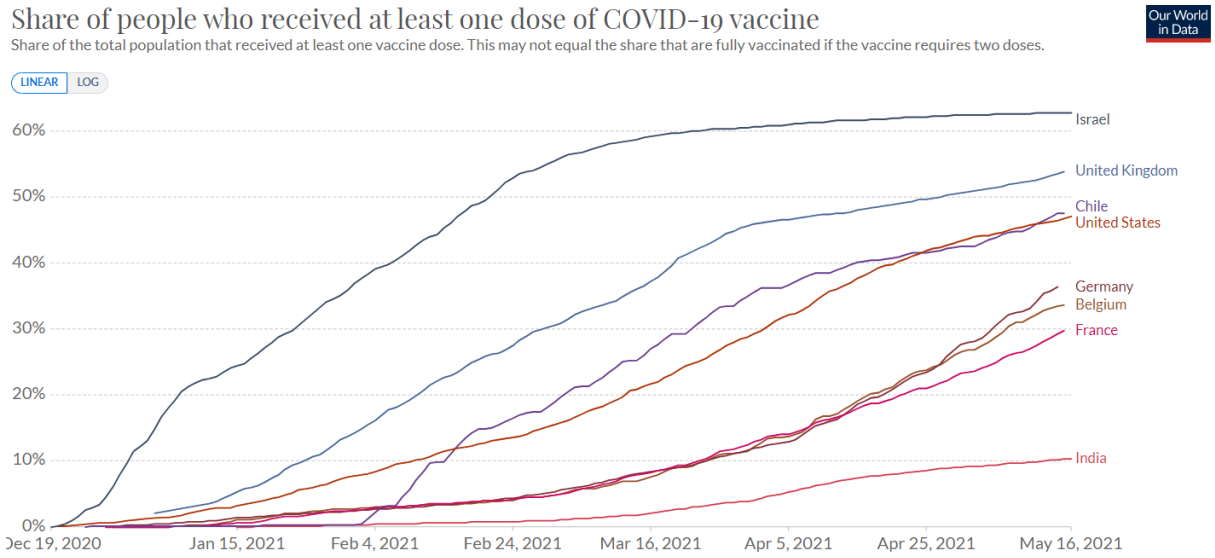
Specific measures are detailed for residents and staff of healthcare structures:

- ***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.

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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%]