Research paper

Decreased infectivity following BNT162b2 vaccination: A prospective cohort study in Israel

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ABSTRACT

Background: BNT162b2 was shown to be 92% effective in preventing COVID-19. Prioritizing vaccine rollout, and achievement of herd immunity depend on SARS-CoV-2 transmission reduction. The vaccine's effect on infectivity is thus a critical priority.

Methods: Among all 9650 HCW of a large tertiary medical center in Israel, we calculated the prevalence of positive SARS-CoV-2 qRT-PCR cases with asymptomatic presentation, tested following known or presumed exposure and the infectious subset (N-gene-Ct-value<30) of these. Additionally, infection incidence rates were calculated for symptomatic cases and infectious (Ct<30) cases. Vaccine effectiveness within three months of vaccine rollout was measured as one minus the relative risk or rate ratio, respectively. To further assess infectiousness, we compared the mean Ct-value and the proportion of infections with a positive SARS-CoV-2 antigen test of vaccinated vs. unvaccinated. The correlation between IgG levels within the week before detection and Ct level was assessed.

Findings: Reduced prevalence among fully vaccinated HCW was observed for (i) infections detected due to exposure, with asymptomatic presentation (VE(i)=65.1%, 95%CI 45-79%), (ii) the presumed infectious (Ct<30) subset of these (VE(ii)=69.6%, 95%CI 43-84%) (iii) never-symptomatic infections (VE(iii)=72.3%, 95%CI 48-86%), and (iv) the presumed infectious (Ct<30) subset (VE(iv)=83.0%, 95%CI 51-94%).

Incidence of (v) symptomatic and (vi) symptomatic-infectious cases was significantly lower among fully vaccinated vs. unvaccinated individuals (VE(v)= 89.7%, 95%CI 84-94%, VE(vi)=88.1%, 95%CI 80-95%).

The mean Ct-value was significantly higher in vaccinated vs. unvaccinated (27.3±1.2 vs. 22.2±1.0, p<0.001) and the proportion of positive SARS-CoV-2 antigen tests was also significantly lower among vaccinated vs. unvaccinated PCR-positive HCW (80% vs. 31%, p<0.001). Lower infectivity was correlated with higher IgG concentrations (R=0.36, p=0.01).

Interpretation: These results suggest that BNT162b2 is moderately to highly effective in reducing infectivity, via preventing infection and through reducing viral shedding.

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Research in Context

Evidence before this study

We searched PubMed, MedRxiv, and Preprints with the *Lancet* up to March 28, 2021, with search terms "BNT162b2" and "effectiveness" with or without the terms: "infectivity"/"infectiousness"/"transmission". We identified 2 studies describing the efficacy in preventing symptomatic disease in clinical trials, 3 published studies that assessed effectiveness of the vaccine in reducing COVID-19 symptomatic disease, hospitalizations or severe disease. While many preprints report the effectiveness of the vaccine in reducing these outcomes only 3 may suggest reduced infectivity.

Added value of this study

Prioritizing vaccine rollout, and achievement of herd immunity depend on reduced SARS-CoV-2 viral circulation. The vaccine's effect on infectivity is thus a critical priority. Here, we assess the vaccine effectiveness in reducing infectiousness via two routes: through preventing infection, and through reducing viral shedding, in those who become infected despite vaccination. This is the first study, to the best of our knowledge to estimate the prevalence of infection among exposed individuals, providing an estimate of the vaccine impact on susceptibility to infection, independent of its impact on symptoms. This effect, along with reduced shedding, is a key determinant of the vaccine's ability to reduce transmission. We show that BNT162b2 was 65% effective in preventing infections following exposures, and 83% effective in preventing never-symptomatic, infectious (N-gene Ct value<30) infections, and that viral load, was significantly lower in vaccinated vs. unvaccinated infected HCW.

Implications of all the available evidence

These results imply that while BNT162b2 is moderately to highly effective in reducing infectivity, vaccinated HCW treating vulnerable populations should still be tested following major exposure and continue using PPE, for protection of their patients.

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in December 2019 in Wuhan, China and rapidly spread globally. On March 11, 2020, coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization (WHO) [1]. Within one year of its emergence, over 100 million cases were detected and over 2 million deaths occurred. In the absence of effective preventive measures, current mitigation strategies include lockdowns, isolation, masks and social distancing. Thus, the urgent need for vaccines prompted an international response with more than 120 candidate SARS-CoV-2 vaccines in development within several months. Two lipid nanoparticle-encapsulated messenger RNA (mRNA) vaccines received emergency use authorization (EUA) by the US Food and Drug Administration (FDA) by December 2020 [2,3]. The BNT162b2 COVID-19 vaccine was shown to be highly efficacious (95%) in preventing clinical COVID-19 infection [4] and highly effective following the first and second doses [5,6]. On December 19, Israel launched BNT162b2 rollout which coincided with a third surge of COVID-19 infections, which continued throughout the study period, peaking to over 10,000 new daily detected cases by mid-January, and with a

persistent average of over 6000 new daily detected cases since the end of January.

Between December 19, 2020 and March 14, 2021, 7794 of 9347 (83%) eligible HCW of the Sheba Medical Center received the first dose of BNT162b2, and 7324 (78%) received two doses (Fig. 1).

Here, we assess the effectiveness of the vaccine in reducing infectiousness via two routes: through preventing infection, and through reducing viral shedding – for which we use Ct value as a proxy in those who become infected despite vaccination. Importantly, our main analysis estimates the prevalence of infection among exposed individuals ascertained independent of whether they had symptoms, providing an estimate of the vaccine impact on susceptibility to infection, independent of its impact on symptoms [7]. This effect, along with reduced shedding, is a key determinant of the vaccine's ability to reduce transmission. The estimates are performed in a large cohort of HCW comparing fully vaccinated to partially and to unvaccinated HCW. We also show that in this cohort, effectiveness for symptomatic COVID-19 disease is comparable to that found in prior studies.

Methods

Study design, period, setting and population

We conducted a cohort study to determine BNT162b2 vaccine effectiveness in reducing infectivity. We reasoned that a vaccinated individual who does not become infected cannot transmit, and that moreover those vaccinated individuals who become infected may be less infectious if their viral load is lowered by vaccination. We thus defined reduced infectivity as reductions in the probability of infection upon exposure (among individuals tested due to the exposure, regardless of symptoms), combined with reduction in viral load among those infected. Ct values represent the number of PCR cycles needed to detect SARS-CoV-2 positivity. Fewer cycles indicate higher numbers of viral RNA copies present in the sample. We thus used N-gene Ct-value as a semiquantitative measure of viral load. Ct-value of 30 was used here as the cutoff, since several studies have shown no viable virus detected using Ct cut-offs ranging from Ct>24 to Ct<35 [8−14]. Another measure for infectivity used was a positive SARS-CoV-2-antigen rapid detection test (Ag-RDT), which has been correlated both with lower Ct-values and with viable virus detection [15−18]. We estimated these separately and in a combined measure of effectiveness against infection with high viral load, given exposure.

The study took place at the Sheba Medical Center, the largest tertiary medical center in Israel, with 1400 acute care beds and 200 rehabilitation beds, from December 19, 2020, when vaccine rollout began, until March 14, 2021. All HCW were allowed and encouraged to receive the vaccine, without any prioritization, except that initially those with previous documented SARS-CoV-2 infection were not eligible. During this period, a third surge of COVID-19 took place in Israel, peaking on January 14, 2021, with 8,424 daily detected cases (7- day moving average).

SARS-CoV-2 testing strategy and data collection

Real-Time quantitative polymerase chain reaction (RT-qPCR, hereafter PCR) for SARS-CoV-2 is readily available to all HCW who have had a possible or confirmed exposure to a SARS-CoV-2-infected person and/or have any COVID-19-associated symptom, including low grade fever, new cough, rhinorrhea, sore throat, myalgia, anosmia, ageusia or unexplained severe fatigue. Any exposure to a COVID-19 detected individual, whether at work, at home or in the community is reported to the Infection Prevention & Control Unit, and an epidemiologic investigation is immediately initiated. Any exposed HCW, whether high-risk exposure, requiring isolation, or non-significant exposure, allowing the HCW to attend, is required to
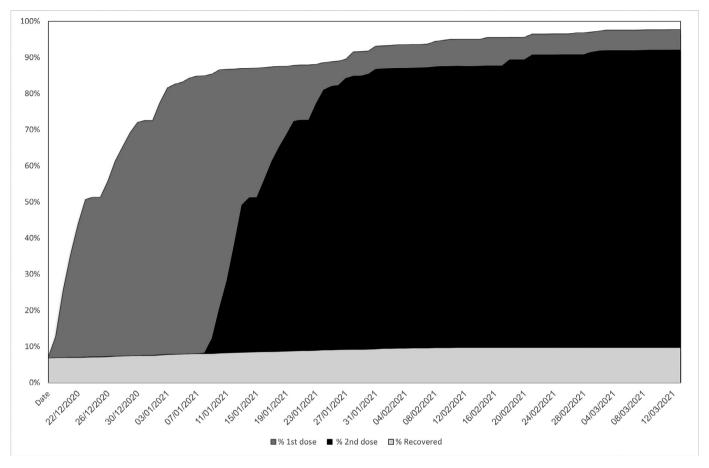
Fig. 1. Cumulative percentage of vaccination coverage of the Sheba Medical Center HCW cohort. Light grey denotes recovered patients, not eligible to receive the vaccine. Dark grey denotes administration of 1st dose. Black denotes administration of 2nd dose.

undergo a SARS-CoV-2 PCR. An antigen rapid detection test (Ag-RDT) is required when an exposed HCW is allowed to remain at work, mostly after a non-significant exposure. In addition, every HCW is required to report a daily health status upon arrival to the hospital, and if any symptom is reported, a PCR test is required. If only mild symptoms are reported, HCW are allowed to attend work, but an Ag-RDT is required in addition to the PCR, before starting the workday [15]. Only commercial FDA and/or CE approved diagnostic platforms are in use at Sheba's Clinical Microbiology Laboratory. For qRT-PCR Allplex™ 2019-nCoV (Seegene Inc., S. Korea), was used for all samples from the personnel clinic. In rare occasions of technical failure, we used either NeuMoDx™ SARS-COV-2 assay (NeuMoDx, MI, USA) or Xpert Xpress SARS-CoV-2 assay (Cepheid, CA, USA). Lateral-flow, Ag-RDT for SAR-CoV-2 were used according to suppliers' availability of the following kits: NowCheck, (BIONOTE, S. Korea), SD Biosensor, (S. Korea), Panbio™, (Abbott, IL, USA); Veritor™, (BD, NJ, USA). All HCW were encouraged to test for SARS-CoV-2 IgG antibody levels before their first vaccine dose and over 2000 HCW were recruited to a prospective longitudinal study assessing vaccine-induced antibody responses [19]. Additionally, COVID-19-exposed HCW were encouraged to test for SARS-CoV-2 IgG. Anti-RBD (access SARS-CoV-2 RBD IgG assay (Beckman-Coulter, CA, USA)) was used, according to manufacturer's instructions [20]. We associated IgG quantifications with infection episodes if they were taken within 5 days before the first positive PCR.

Epidemiologic investigations included electronic questionnaires and direct additional questioning when necessary. The epidemiologic investigation database includes all the data collected from exposed and positive HCW, including demographic data, symptoms, and origin and risk of potential exposures.

Vaccination stages and outcomes

On each day, we considered individuals to have a status of being either Unvaccinated, in the Early Vaccine stage (defined as 4 to 10 days post the first dose), those Partially Vaccinated (11 days post first dose to 10 days post second dose), or Fully Vaccinated (11 days or more post second dose). Since the first 3 days following the first dose have been shown to have a seemingly protective effect, attributed to a deferral effect bias [21], we counted the early vaccine stage starting from day 4 post the first dose.

Our primary analysis focused on the vaccine's effectiveness against infection and presumed infectivity, key determinants of potential for interrupting transmission. For individuals in each vaccination stage, we assessed the following outcomes: (i) infection detected among individuals tested because of reported exposure, limited to those not symptomatic at the time of first testing; (ii) "infectious" infection detected among individuals tested because of reported exposure and not symptomatic at the time (those with N-gene Ct value<30 on their first positive test) [12], a subset of group (i); (iii) infection detected among individuals tested because of reported exposure that never became symptomatic (true asymptomatics, also a subset of (i)), and (iv) the infectious (Ct<30) cases amongst these. These were assessed as proportions reflecting the prevalence of infection conditional on exposure [7,22], where

Table 1
Demographic characteristics of HCW at their exposure events.

		Unvaccinated	Early vaccinated	Partially vaccinated	Fully Vaccinated
Exposure events		1441	490	1442	1300
Gender	Male	284 (19%)	131 (27%)	387 (27%)	365 (28%)
Age	18-45	1080 (75%)	315 (64%)	881 (61%)	785 (60%)
	46-65	331 (23%)	162 (33%)	504 (35%)	464 (36%)
	>65	15 (1%)	11 (2%)	49 (3%)	47 (4%)
HCW occupation	Physician	197 (14%)	100 (20%)	307 (21%)	312 (24%)
	Nurse	726 (50%)	205 (42%)	656 (45%)	585 (45%)
	Administrator	244 (17%)	89 (18%)	251 (17%)	214 (16%)
	Allied health professions	268 (19%)	94 (19%)	222 (15%)	187 (14%)

Early vaccinated=days 4-10 following first dose. Partially vaccinated=from day 11 following first dose up to day 10 following the second dose. Fully vaccinated= from day 11 after second dose.
*233 events were excluded since they were detected in the immediate post-first dose period (days 1-4).

exposure events were defined as described below. The index date was defined as the day of first test following exposure.

For comparison with other studies, we also assessed the following outcomes for individuals in each vaccination stage: (v) incidence of symptomatic, PCR-positive COVID-19; symptomatic COVID-19 cases were defined as any positive PCR case who reported one or more symptoms regardless of the indication for testing. (vi) incidence of infectious (Ct<30 on their first positive test) symptomatic COVID-19; (vii) incidence of all SARS-CoV-2 laboratory confirmed infections (positive PCR), regardless of the indication for testing. The index date for these outcomes was defined as the day of first positive RT-PCR.

To further assess infectivity, we used two test results as proxies for infectivity; First, N-gene Ct-value<30, which was reported to be the cut-off at which the probability of culturing virus declines dramatically [8−14], and a positive Ag-RDT result which was shown to be correlated with SARS-CoV-2 culture positivity [15−18]. The mean N-gene Ct values and the proportion of positive Ag-RDT were compared between individuals in each vaccination stage.

Where available, we also assessed the correlation between SARS-CoV-2 anti-RBD IgG concentration and N-gene Ct-value.

Statistical analysis

For outcomes (i-iv), HCW who were tested following suspected or known exposure, the prevalence of SARS-CoV-2 laboratory confirmed cases among exposure events was calculated, as appropriate for a vaccine effectiveness measure conditioned on exposure [7,22]. An exposure event was defined by a PCR test performed (regardless of the result), and a new event could be defined only after a period of 10 days following the first PCR, since repeated testing was instructed for up to 10 days following exposure. The exposure event was assigned to the person's vaccination status (unvaccinated to fully vaccinated) on the day on which the event began (first test performed). The risk ratio of having at least one positive PCR among events occurring in vaccinated periods vs. those in the unvaccinated period was calculated using a logistic mixed model with random effect of a person, with separate outcomes for each exposure event.

To estimate incidence rates of outcomes v-vii, we calculated the number of person days spent in each of the vaccination periods, and separately "adjusted" person-days, proportional to the daily 7-day moving average of national detected cases to account for intensity of exposure at different time periods. All persons were followed until the first positive PCR test or up to 84 days. For each period, we summarized the number of detected cases. The rate ratio of incidence estimation was obtained by Poisson regression of number of cases with the logarithm of adjusted person-days as the offset.

Vaccine effectiveness (VE) was calculated as 1-RR, whether this was the risk ratio (outcomes i-iv) or the incidence rate ratio (outcomes v-vii), 95% confidence intervals (CI) were reported.

Means of Ct values were compared using two-sample t tests and mean difference with 95%CI were calculated. The positive percent agreement (PPA) between Ag-RDT and PCR was calculated as the proportion of positive Ag-RDT among positive PCR tests.

All calculations were done using SAS 9.4 software.

Results

A total of 9911 HCW were employed at the Sheba Medical Center (SMC) during the study period. Prior to vaccine rollout or entry to the study, 564 HCW were infected by SARS-CoV-2, thus 9347 HCW were eligible to receive BNT162b2 vaccine and included in the cohort (Fig. 2).

A total of 3578 HCW, with 4906 defined events, received a total of 26651 RT-PCR tests for SARS-CoV-2 during the study period. The immediate post-first dose period (days 1−4) was excluded and thus 233 exposure events including nine positive cases occurring during this period were omitted (Fig. 2). Among those exposed, 295 individuals (8.2%) had a positive result. N-gene Ct value was available for 224 (75.9%) cases. The different demographic characteristics of the tested HCW is described in Table 1 and the characteristics of the infected HCW of the different groups is described in Supplementary Table 1.

The prevalence of laboratory-confirmed infections asymptomatic at the time of presentation, among unvaccinated HCW tested due to exposure was 5.2% vs. 1.8% among fully vaccinated HCW (VE 65%, 95%CI 45-79%). Vaccine effectiveness in preventing presumably infectious (Ct<30) cases amongst these was 70% (95%CI 43-84%). The prevalence of never-symptomatic SARS-CoV-2 infections, among all exposure events (whether initially asymptomatic or not) was 3.3% among vaccinated vs. 0.9% in fully vaccinated (VE=72%, 95%CI 48-86%). The vaccine effectiveness in reducing infectious (Ct<30) totally asymptomatic infections was 83.0%, 95%CI 51-94% (Table 2a).

While the incidence rate of symptomatic disease (whether tested due to exposure, or due to symptoms) among unvaccinated HCW was 5.8/10,000 person days, this was significantly lower among the partially and fully vaccinated population, (1.7 and 0.6/10,000 person days, respectively) (adjusted VE= 79%, 95%CI=69-87% and 90%, 95%CI=84-94%, respectively). Vaccine effectiveness in preventing infectious (Ct<30), symptomatic disease among fully vaccinated HCW was 88%, 95%CI 80-95% (Table 2b).

To further assess the effect on infectiousness, we compared the mean and median N-gene Ct value among the different groups: Mean Ct= 22.2±1.0 vs. 27.3±2.2 (mean difference 5.09, 95%CI 2.8-7.4, p<0.001), and median Ct=23.3 vs. 25.8 (p<0.001) for unvaccinated vs. fully vaccinated, infected persons.

Comparing symptomatic and asymptomatic infections, the mean Ct value was lower for each group, but did not reach statistical significance for the separate groups. Overall, the mean Ct was significantly lower in asymptomatic than symptomatic cases (mean Ct 21.7 vs.
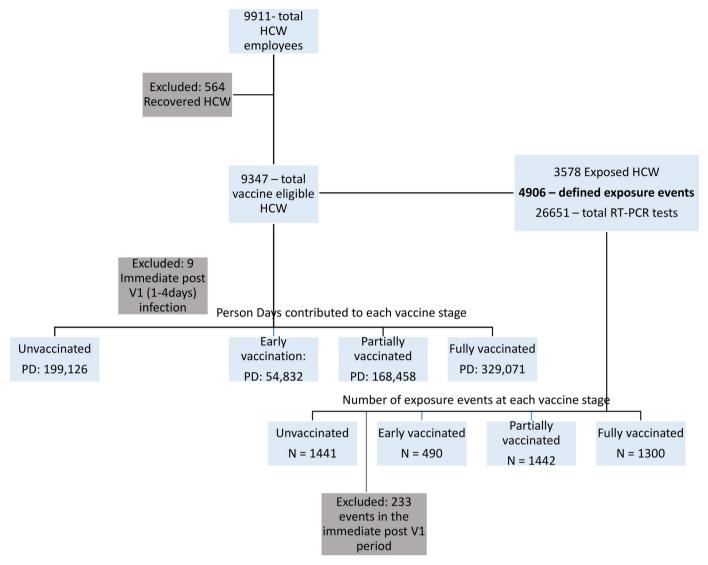
Fig. 2. Flowchart of study population. PD=person days. Early vaccinated=days 4-10 post first dose of BNT162b2, Partially vaccinated=day 11 post first dose until 10 days post 2nd dose. Status at end point where endpoint is either end of study or date of laboratory detected SARS-CoV-2.

25.8, mean difference 4.1, 95%CI 2.5-5.7, p<0.001), and median Ct 20.9 vs. 24.6 for symptomatic vs. asymptomatic (p<0.001) (Fig. 3).

As another measure of infectivity, we assessed Ag-RDT positive cases. Ag-RDT was performed in 123 of 295 PCR-positive cases. In the fully vaccinated SARS-CoV-2 PCR positive group, it was detected only in 6 out of 19 (32%) tests, vs. 28 out of 35 (80%) of the unvaccinated cases (RR 0.39, 95%CI 0.20-0.78, p<0.001) (Supplementary Table 1).

The positive percent agreement (PPA) between Ag-RDT and PCR among cases where Ct value was lower than 30, was significantly higher among unvaccinated than among vaccinated cases; 27/32, 84% vs. 6/13, 46% (RR 1.83, 95%CI 1.0-3.4, p= 0.05).

Last, we found a significant correlation between IgG levels from within the 5 days prior to detection and Ct values among vaccinated HCW (R=0.37, p=0.01) (Fig. 4).

Discussion

Rollout of vaccination among a large cohort of health care workers with ready access to PCR and antigen testing, combined with a requirement to report and get tested following known or suspected exposure to a SARS-CoV-2 positive person, offered us an opportunity to estimate the effect of the BNT162b2 vaccine on infection following exposure, and on infectivity. These two outcomes are of particular interest for understanding the ability of the vaccine to break the transmission chain of SARS-CoV-2, and present an important complementary outcome to the symptomatic infection outcome assessed in randomized trials [4,23,24] and to the "all documented infections" assessed in other observational studies [5,6,25−28]. The estimates provided here measure the vaccine's ability to reduce transmission, combining its effects in reducing susceptibility to infection (which thus prevents onward transmission) and on reducing a correlate of viral shedding among infected and thus of infectivity [8−14] of those who do become infected. By testing those who had been exposed, we estimated that full vaccination reduced susceptibility to infection by 65% (45-79%), and by comparing the Ct values we show significant reduction in presumed viral shedding, with a mean Ct value increased by 5.09 in fully vaccinated vs. unvaccinated HCW. A combined approach showed that among exposed individuals, the risk of infection with a Ct value <30 (our definition of infectious) was reduced by 70% (43-84%). This provides clear evidence of at least a 70% reduction in likely transmission. Compared to prior published data, these are the first

Table 2a
Vaccine effectiveness in reducing infections conditional on exposure as the indication of testing.

	Unvaccinated	Early V1	Partially vaccinated (V1)	Fully vaccinated (V2)
i) Prevalence of infections detected due to exposure (asymptomatic presentation)				
Number of cases	75	18	34	23
Number of exposure events	1441	490	1442	1300
Prevalence	5.2%	3.7%	2.4%	1.8%
Risk Ratio	REF	0.71	0.45	0.34
Vaccine effectiveness	REF	28% (-18-+57%)	55% (32-70%)	65% (45-79%)
ii) Prevalence of infective (Ct<30) infections detected due to exposure (asymptomatic presentation)				
Number of cases	44	8	18	12
Number of events*	1394	476	1432	1300
Prevalence	3.1%	1.7%	1.2%	0.9%
Risk Ratio	REF	0.55	0.41	0.30
Vaccine effectiveness	REF	45% (-18-+74%)	59% (28-76%)	70% (43-84%)
iii) Prevalence of never-symptomatic infections detected due to exposure				
Number of cases	48	12	21	12
Number of events	1441	490	1442	1300
Prevalence	3.3%	2.4%	1.5%	0.9%
Risk Ratio	REF	0.74	0.44	0.28
Vaccine effectiveness	REF	27% (-38-+61%)	56% (27-74%)	72% (48-86%)
iv) Prevalence of infectious (Ct<30) never-symptomatic infections detected due to exposure				
Number of cases	25	5	8	4
Number of events*	1394	476	1432	1300
Prevalence	1.8%	1.0%	0.6%	0.3%
Risk Ratio	REF	0.58	0.31	0.17
Vaccine effectiveness	REF	42% (-52-+78%)	69% (31-86%)	83% (51-94%)

REF- Reference group.
Mixed effects logistic regression model was used, the random effect being a person, and the fixed effect − a period.
Cases included are only those that were tested due to a known exposure event.
An exposure event was defined by a PCR test performed, where a new event could be defined only after a period of 10 days following the first PCR. Each case could have more than one exposure event.
* Only events where a Ct value was available are included.

Table 2b
Vaccine effectiveness in infection incidence rate reduction (symptomatic disease, infective symptomatic disease and all laboratory detected infections).

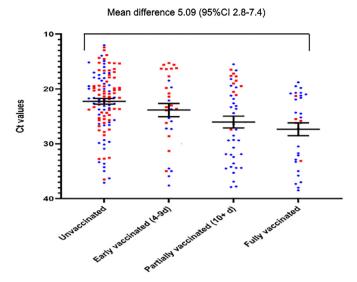| Indication for testing	Unvaccinated	Early V1	Partially vaccinated (V1)	Fully vaccinated (V2)
v) All Symptomatic cases				
Number of cases	115	30	29	19
Number of person days	199126	54832	168458	329071
Rate/10,000 pd	5.8	5.5	1.7	0.6
Vaccine effectiveness (1-RR)	Ref	5% (-41-37%)	70% (55-80%)	90% (84-94%)
Adjusted* VE	Ref	21% (-32-+41%)	80% (69-87%)	90% (84-94%)
vi) Infective symptomatic cases (N-gene Ct value<30)				
Number of cases	78	18	20	15
Number of exposure days	199126	54832	168458	329071
Rate/10,000 pd	3.92	3.28	1.19	0.46
Vaccine effectiveness VE=1-RR	REF	16% (-40-+50%)	70% (50-81%)	88% (80-94%)
VE adjusted by daily exposure	REF	23% (-31-+53%)	80% (66-87%)	88% (80-95%)
vii) All RT-PCR pos cases (among the full cohort)				
Number of cases	163	42	50	31
Number of person days	199126	54832	168458	329071
Rate/10,000 pd	8.19	7.77	2.98	0.94
Vaccine effectiveness (VE= 1-RR)	REF	6.4% (-31-+33%)	64% (50-74%)	89% (83-92%)
VE adjusted by daily exposure	REF	13% (-23-+38%)	75% (66-82%)	88% (83-92%)

REF- Reference group.
pd – person days.
Poisson regression model was used.
Adjustment was for the intensity of exposure at different time periods, by using the daily 7-day moving average of national detected cases.

to our knowledge to assess reductions in infection in a group not selected by their symptoms, and thus to obtain a "clean" estimate of reduction in susceptibility to infection, of crucial importance for herd immunity. We also replicated earlier findings in our cohort [5] and others [6] of high effectiveness in preventing symptomatic and all documented infections. We demonstrate that low viral loads were correlated with higher anti-SARS-CoV-2 IgG titers in vaccinees and with asymptomatic infection, buttressing the causal interpretation of these observational findings. Moreover, we were conservative in defining the infection day as the day of first positive PCR and not the day of exposure, which was available only for some SARS-CoV-2 negative exposed cases.
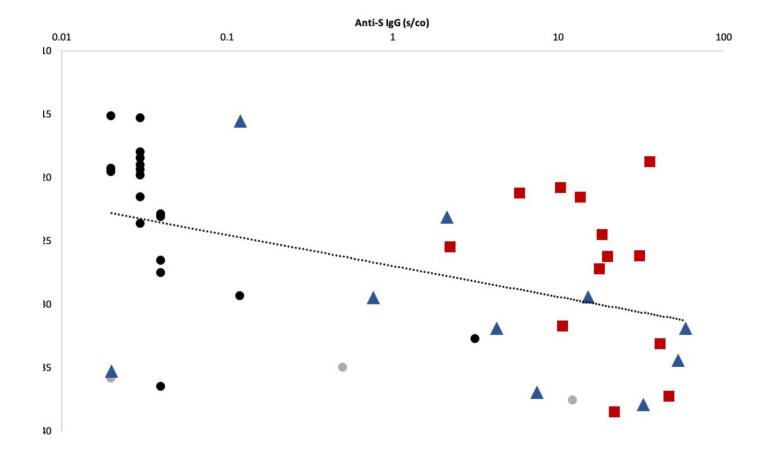
Fig. 3. Ct value distribution of SARS-CoV-2 RT-PCR positive patients among the 4 groups: 1. Unvaccinated, 2. Early vaccinated: from 4 days up to 10 days post 1st dose, 3. Partially vaccinated = from 11 days post 1st dose up to 10 days post 2nd dose, 4. Fully vaccinated =11 days or more post 2nd dose. Mean and SEM noted. Blue circles denote asymptomatic patients tested following exposure and Red squares denote patients tested due to symptoms.

Among those who do become infected despite vaccination, the vaccine's impact on their ability to transmit viable virus following immunization is of critical importance, especially among those who frequently encounter vulnerable populations as HCW, caretakers in long-term-care-facilities, etc. As viral cultures are laborious, two surrogates for infectivity are in frequent use in clinical and academic settings: Ct values - inversely correlated with log viral load, and antigen tests, targeting viral proteins, and repeatedly proved to better correlate with cultivable virus than PCR [8,12−14,17,18,25] . We found an increase in Ct values (i.e. lower viral loads), in parallel to lower proportions of positive antigen test as time elapsed from the first week following vaccination. Interestingly, a significant mismatch between positive PCR and antigen results, for tests with Ct<30, was noted in the fully vaccinated group (PPA of 50%) but not in the unvaccinated, with PPA of 84%, which is similar to previous reports of PPA between these tests by us and others [15,16]. This also suggests that these individuals may have been shedding untranslated or poorly translated viral RNA. This cumulatively suggests less effective viral replication and/or shedding in the nasopharynx of both symptomatic and asymptomatic laboratory-confirmed SARS-CoV-2 vaccinees, which together with reduced probability of infection lead to reduced transmission from infected individuals.

As antibodies play a central role in viral elimination, our finding of correlation between higher concentrations of anti-SARS-CoV-2 antibodies and lower viral loads (higher Ct values), supports a causal rela-

Fig. 4. Correlation between IgG levels and N-gene Ct-values−Black circles denote unvaccinated infected people, Grey circles, denote people infected within days 4-9 following the 1st dose, Blue triangles denote partially vaccinated people, i.e. after at least 11 days from 1st dose, and up to 10 days after the 2nd dose, and Red squares denote people infected after being fully vaccinated (>10 days from 2nd dose).

Supplementary Table 1
Demographic and clinical characteristics of infected HCW.

		Unvaccinated	Early vaccinated	Partially vaccinated	Fully Vaccinated
RT-PCR positive N		163	42	50	31
Ag-RDT tested N (% pos)		35 (80%)	11 (45%)	15 (33%)	19 (31%)
Gender	Male	34 (21%)	18 (43%)	11 (22%)	10 (32%)
Age	18-45	116 (73%)	28 (67%)	26 (52%)	20 (65%)
	46-65	42 (26%)	14 (33%)	19 (38%)	11 (35%)
	>65	1 (1%)	0 (0%)	5 (10%)	0 (0%)
HCW profession	Physician	17 (11%)	8 (19%)	7 (14%)	3 (11%)
	Nurse	81 (51%)	15 (36%)	25 (50%)	17 (55%)
	Administrator	39 (24%)	12 (29%)	15 (30%)	8 (26%)
	Allied health professions	23 (14%)	7 (17%)	3 (6%)	3 (9%)
Severity	Asymptomatic	45 (27%)	12 (29%)	22 (44%)	12 (39%)
	Mild Disease	117 (72%)	30 (71%)	28 (56%)	19 (61%)
	Severe Dis.	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Test indication					
	Symptoms	88 (54%)	24 (57%)	16 (32%)	8 (26%)
	Exposure	75 (46%)	18 (43%)	34 (68%)	23 (74%)

Early vaccinated=days 4-10 following first dose. Partially vaccinated=from day 11 following first dose up to day 10 following the second dose. Fully vaccinated= from day 11 after second dose.

tionship between vaccination and lower infectivity among positive vaccinees.

Our study is unique is several aspects, first, while it is an observational study, it reports on a full cohort of HCW of a single center with thorough, exhaustive follow up of infected individuals, with epidemiologic investigation data and a single policy of extensive testing upon exposure and/or symptoms. Furthermore, the laboratory detailed data, including Ct values for nearly all cases, Ag-RDT and serology available for many individuals shed light on infectivity of cases and enabled an initial assessment of vaccine effectiveness on viral transmission among asymptomatic infected individuals.

Our study has several limitations: being a single center study of HCW, where the majority of the population are younger females, may limit generalizability. Second, results of Ag-RDT and IgG were available only for a subset of the positive cases. Yet, despite the low numbers the results available showed significant reductions in Ag-RDT positivity among breakthrough cases, and significant correlations between IgG and Ct values in those for whom both were available. Additionally, as any observational study, we may have residual confounding. While our cohort was heavily tested for any minor exposures, yet, exposures could have been missed and missed exposures could vary among populations, thus potentially introducing confounding. Furthermore, the small positive point estimate (albeit with a confidence interval including zero) in the 4-10 days post vaccine, despite eliminating the first 3 days from the analysis, which was not detected in the randomized trial [4] or in one observational study in Israel [6], could suggest such residual confounding. While residual confounding cannot be ruled out, we note that our cohort differed from both the randomized trial and the effectiveness study in that our cohort was heavily tested (over a third of the cohort tested during the two-month study period, many of them several times) including in the absence of symptoms due to possible exposures, a system that might detect subtler and earlier effects of the vaccine.

In conclusion, we present a holistic set of data regarding vaccine effectiveness in a large cohort of HCWs, vaccinated in parallel to a massive national wave of COVID-19. Accessibility to various modalities of laboratory assays testing viral RNA, protein and host response, accompanied by rigorous active and passive surveillance, allowed for a unique opportunity to study symptomatic and asymptomatic SARS-CoV-2 infections and infectivity. The results support an early, significant rate-reduction in laboratory confirmed SARS-CoV-2 infections and COVID-19, as well as decreased infectivity, manifested by reduced prevalence of infection in those tested following exposure, and also by higher Ct value and negative antigen tests in vaccinees who did become infected.

Yet, these data suggest that HCW who are treating vulnerable population, should not yet take off masks even when others do, and should be retested upon exposure even if vaccinated, pending greater clarity on the infectiousness of vaccinated individuals. Larger and longer studies are needed to assess the duration of vaccine's effect on morbidity and the kinetics of infectivity.

Authors' Contribution

GRY conceptualization, investigation, supervision, methodology, validation, drafting the original manuscript, reviewing and editing. SA conceptualization, investigation, methodology, writing and reviewing the manuscript. MB data curation, visualisation, reviewing and editing the final version of the manuscript. ML methodology, writing reviewing and editing the mansucript. EL conceptualization, reviewing and editing the final version of the manuscript. RK methodology, reviewing and editing the final version of the manuscript. YL investigation, data curation, reviewing and editing the final version of the manuscript. CC data curation, reviewing and editing the final version of the manuscript. RD data curation, review of final version. AZ, CR, IG - formal analysis, data management, validation, reviewing and editing the final version of the manuscript. IN, AH formal analysis, reviewing and editing the final version of the manuscript. GR, AA reviewing and editing the final version of the manuscript. YK conceptualization, resources, reviewing and editing the final version of the manuscript.

Declaration of Competing Interests

Data Availability Statement

The data collected for the study, including deidentified participant data will be available upon request, after publication to other investigators after approval of a proposal with a signed data access agreement.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.lanepe.2021.100150.

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