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Systematic Review

Does COVID-19 Vaccination Protect Contact Persons? A Systematic Review

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Abstract: The protective effect of COVID-19 vaccination for contact persons is controversial. Therefore, the aim of this review was to determine whether COVID-19 vaccination provides significant protection for them. A PubMed search was carried out using the terms "unvaccinated vaccinated covid" in combination with "viral load" and "transmission". Studies were included if they reported original comparative data on the SARS-CoV-2 viral load, duration of SARS-CoV-2 detection, or SARS-CoV-2 transmission rates. A total of 332 articles were identified, of which 68 were included and analyzed. The differences in the viral load were equivocal in 57% of the 35 studies, significantly lower in the vaccinated in 11 studies and in the unvaccinated in 3 studies. The infectious virus levels were significantly lower in the vaccinated in two out of six studies. Virus clearance was significantly faster in vaccinated subjects in two of eight studies (detection of viral RNA) and two of four studies (detection of infectious virus). The secondary attack rates were significantly lower in vaccinated index cases in 6 of 15 studies. The vaccination status of contacts was described in two of the six studies and was 31.8% and 39.9% lower in households with an unvaccinated index case. The inconsistent and variable differences in the viral load, viral clearance and secondary attack rates between vaccinated and unvaccinated individuals, especially during the omicron predominance, suggests that COVID-19 vaccination is unlikely to prevent a relevant proportion of transmissions to contact persons, taking into account the relevance of the immunological status of the contact population (vaccination rates and previous infection).

Keywords: COVID-19 vaccination; viral load; viral clearance; transmission; previous infection

Citation: Kampf, G. Does COVID-19 Vaccination Protect Contact Persons? A Systematic Review. *Hygiene* **2024**, *4*, 23–48. https://doi.org/10.3390/hygiene4010003

Academic Editor: Maria Chironna

Received: 14 September 2023
Revised: 14 November 2023
Accepted: 21 December 2023
Published: 9 January 2024

1. Introduction

The primary goal of COVID-19 vaccination is to protect the vaccinated individual [1]. Self-protection is well established. Vaccination reduces the risk of symptomatic [2], severe [3] and fatal COVID-19 [3], although protection against SARS-CoV-2 infection declines from 83% at one month to only 22% at five months [4] and even faster for the omicron variant [5]. The personal motivation for COVID-19 vaccination was partly the expected self-protective effect. A substantial proportion of priority occupational groups, however, wanted to receive the COVID-19 vaccination mainly to protect their family members (76.2%) or colleagues (72.3%), and less often to protect themselves (49.1%) [6]. Official campaigns in some countries repeatedly claimed that the COVID-19 vaccination of index cases also protects contact persons [7,8].

However, the protective effect of the vaccination of individuals on the risk of contact persons acquiring COVID-19 is controversial. Several outbreaks have shown that vaccinated healthcare workers, for example, can still transmit SARS-CoV-2 to colleagues, patients or residents in nursing homes [9–11]. The WHO stated in 2021 that vaccines provide some protection against transmission [12]. However, it is currently not clear whether vaccinated individuals provide clinically relevant protection against infection to their contacts.

The aim of this review was therefore to find out whether full vaccination of individuals against COVID-19 provides clinically relevant protection for their contact persons, for

example, by reducing the level of the viral load (RNA and infectious virus) in the event of infection (breakthrough infection), by shortening the duration of virus detection in respiratory tract specimens, or by preventing transmission from fully vaccinated individuals to close contacts, referred to as secondary attack rates.

2. Materials and Methods

2.1. Search Results

A literature search was conducted on PubMed using two combinations of terms: "unvaccinated vaccinated viral load covid" (30 November 2022) and "unvaccinated vaccinated transmission covid" (8 December 2022). The search protocol was developed for a previous search on a similar topic. Different combinations of search terms were initially evaluated, leading to the selection of the search terms used for this review. No changes were made during the review. The PRISMA statement standards were followed to conduct the systematic review.

2.2. Inclusion and Exclusion Criteria

Studies were included if they reported original comparative data on the SARS-CoV-2 viral load (cycle threshold values [Ct values], RNA copies per ml, infectious virus assessed by viral infectivity assays in cell culture) in both vaccinated and unvaccinated individuals, including those with a history of COVID-19 infection, if they reported the duration of SARS-CoV-2 detection (RNA, infectious virus) in both groups of vaccinated and unvaccinated individuals, including those with a history of infection, or if they reported the comparative secondary attack rates in vaccinated and unvaccinated individuals, including those with a history of previous infection. Fully vaccinated was defined as having received all the doses of the vaccine regime intended by the manufacturers at the time of vaccine approval. This means two doses of Comirnaty (BioNTech/Pfizer), Spikevax (Moderna), AZD1222 (AstraZeneca), CoronaVac/SinoVac (Sinovac Biotech), Sputnik V (Biocad), or CoviVac (Nanolek) or one dose of Jcovden (Janssen). For transmission studies, information on the COVID-19 vaccination status of contacts was included whenever possible. Studies were excluded if they did not meet the inclusion criteria, did not report original comparative human viral load or transmission data, were subsequently updated, were not in English, were based on modeling studies only, or were classified as reviews.

2.3. Data Extraction

The data were summarized in tables using a pre-specified data extraction table. The following data were extracted from the studies on the level of the viral load and on the duration of viral detection: viral load, including sample size, variant of SARS-CoV-2, study population, sampling period, country, number of vaccine doses administered, types of vaccine products, type of gene (PCR test), the duration of SARS-CoV-2 detection (if it was the endpoint) and the *p*-value. These data were extracted from the studies on the secondary attack rates: variant of SARS-CoV-2, study population, sampling period, country, vaccination status of index cases and sample size, vaccination status of contacts and sample size, type of contact, types of vaccine products, secondary attack rates per group, proportion of fully vaccinated contacts per group and *p*-value. Whenever possible, data on study participants with a previous COVID-19 infection were also extracted. The data in the tables were stratified according to the predominant SARS-CoV-2 variant at the time and place of the studies. When necessary, supplements were reviewed to identify more specific data, e.g., when relevant data such as the case numbers per vaccination group [13] or the types of vaccines were not described in the manuscript itself [14,15]. The search protocol was not registered.

2.4. Assessment of Study Quality

The risk of bias in each study was assessed using the Newcastle–Ottawa scale for cohort studies and the modified Newcastle–Ottawa scale for cross-sectional studies. The scales were adapted to the corresponding research questions and the type of study.

For cohort studies on the viral load and duration of detection, the following details were assessed: representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure (confirmation of vaccination or prior infection, respectively), comparability of cohorts based on design or analysis, assessment of outcome (always viral load), and adequacy of follow-up of cohorts. For cross-sectional studies on the viral load and duration of detection, the following details were assessed: representativeness of the sample, sample size, ascertainment of exposure (confirmation of vaccination), comparability of groups based on design or analysis, focusing on the time since symptom onset and additional relevant clinical parameters such as age, sex or comorbidities, assessment of outcome (measurement of viral load, test protocol) and a statistical test.

For cohort studies on the transmission and secondary attack rates, the following details were evaluated: representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure (complete vaccination of index case or prior infection, respectively), demonstration that the outcome of interest was not present at the start of the study (no detection of SARS-CoV-2 among any contact person), comparability of cohorts on the basis of the design or analysis (contact persons: vaccination status of contacts, duration and frequency of contacts, frequency of COVID tests; proportion of recovered contact persons; physical distancing behavior at home; hand hygiene behavior at home) and assessment of outcome (SARS-CoV-2 detection in contact persons). For cross-sectional studies on the transmission and secondary attack rates, the following details were evaluated: representativeness of the sample, sample size, ascertainment of exposure (complete vaccination of index case), comparability of cohorts on the basis of the design or analysis (vaccination status of contacts; other parameter may be duration and frequency of contacts, frequency of COVID tests; proportion of recovered contact persons; physical distancing behavior at home; hand hygiene behavior at home), assessment of outcome (confirmed COVID-19 case among contacts) and statistical test. Further details are provided in the four tables in the Supplementary Materials.

3. Results

3.1. Search Results

A total of 332 articles were found. Twenty-nine of them were removed as duplicate records so that 303 articles remained. A total of 200 articles were excluded because no comparative data on the viral load or transmission in the distinctive groups of vaccinated and unvaccinated individuals were found. Thirteen articles were reviews and so were excluded. Eleven articles were later updated and excluded. Seven articles described transmission based only on modeling efforts and so were excluded. Finally, four articles were in the Chinese language and so were excluded. Sixty-eight studies remained and were analyzed (Figure 1). Those were all observational studies; notably, no randomized controlled trials were identified in the search. Some studies might have appeared to meet the inclusion criteria but were excluded because the authors did not describe comparative data between vaccinated and unvaccinated subjects [16] or compared two heterogenous groups (vaccinated or boosted versus unvaccinated or unboosted parents) [17].

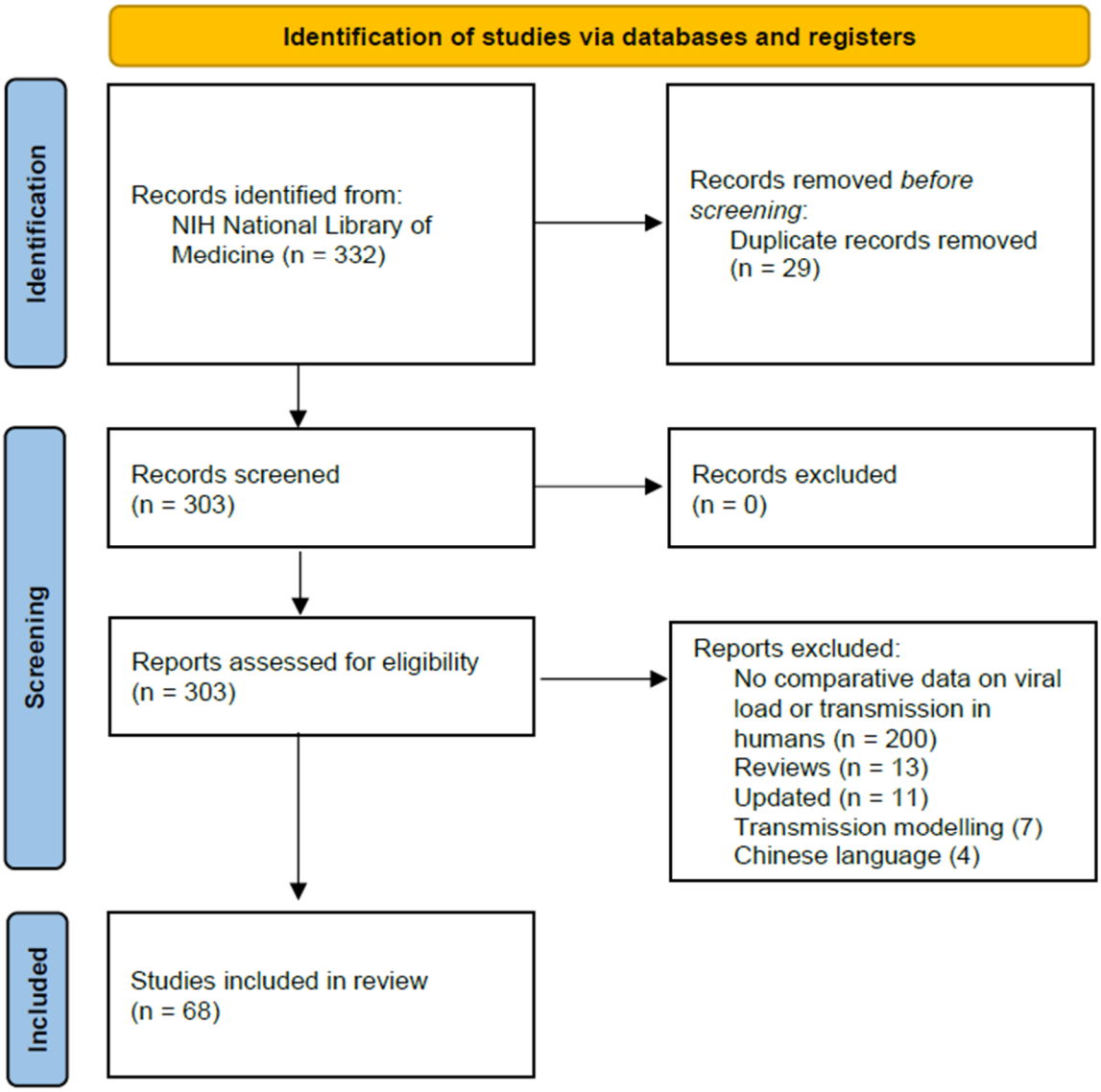

Figure 1. Flow diagram of the study selection, exclusion and inclusion within the systematic review (PRISMA).

3.2. Level of Viral Load

The level of the viral load was described in 18 cohort studies and 22 cross-sectional studies of mostly moderate quality. The evaluations of the study quality can be found in the Supplementary Materials in Tables S1 and S2.

3.2.1. Ct Values According to Vaccination Status

In 30 studies, the comparative viral load was described with Ct values (Table 1). In the data sets of 20 studies, a lower viral load (higher Ct value; median or mean) was found among the vaccinated, with 10 of them reporting the difference as statistically significant, 10 of them being not significant and 3 of them without a *p*-value. In the data sets of 15 studies, a lower viral load was found among the unvaccinated, with three of those differences being significant, eleven of them being not significant and two of them without reporting results on statistical significance testing. Two studies described the same viral load in vaccinated and unvaccinated individuals.

Table 1. Ct values from respiratory tract samples of COVID-19 cases according to their vaccination status and the SARS-CoV-2 variant (different data sets may be derived from the same study).

SARS-CoV-2 Variant	Type of Gene	Sampling Period (Country)	Type of Population	Ct Values According to Number of Applied Vaccine Doses (Number of Samples)				*p*-Value	Source
				None	1 Dose	2 Doses	3 Doses		
Ancestral variant	E gene	4/20–9/20 (Switzerland)	Any individual with symptoms	13.9–26.6 * (118)	-	-	-	-	[18]
Mainly beta	N, ORF1ab and S gene	2/20–7/21 (Qatar)	General population	24.0 [95% CI: 23.8–24.2] ** (4035)	-	25.0 [95% CI: 24.8–25.2] ** (4035 #)	-	<0.001	[19]
Mainly beta	N, ORF1ab and S gene	2/20–7/21 (Qatar)	General population	26.8 [95% CI: 25.9–27.6] ** (265)	-	30.3 [95% CI: 29.6–31.0] ** (265 ##)	-	<0.001	[19]
Alpha	N gene	1/21–9/21 (USA)	Patients	Approx. 20.9 *** (470)	-	Approx. 21.0 *** (94)	-	n.s.	[20]
Alpha	ORF1ab gene	9/20–1/21 (Israel)	Healthcare workers	26.7 [IQR: approx. 23–31] *** (40)		32.0 [IQR: approx. 28–33.5] *** (20)		0.008	[21]
Alpha B.1.1.7	N, ORF1ab and S gene	12/10–5/21 (UK)	General population	28.7 [IQR: 20.4–32.9] *** (10,853)	31.6 (IQR: 26.6–33.7] *** (577)	33.3 [IQR: 31.6–34.0] *** (56)	-	-	[22]
Alpha B.1.1.7	Various genes ###	12/20–3/21 (UK)	Nursing home residents	26.6 [95% CI: 26.0–27.1] ** (552)	25.9 [95% CI: 25.2–26.6] ** (411; 0–27 days after vaccination with dose 1)	-	-	0.158	[23]
Alpha B.1.1.7	Various genes ###	12/20–3/21 (UK)	Nursing home residents	26.6 [95% CI: 26.0–27.1] ** (552)	31.3 [95% CI: 29.6–33.0] ** (107; ≥28 days after vaccination with dose 1)	-	-	<0.0001	[23]
Mainly alpha	N, ORF1ab and S gene	1/21–4/21 (Greece)	Healthcare workers	18.5 [IQR: 13.5–24.0] *** (31)	-	18.5 [IQR: 16.0–26.0] *** (24)	-	0.70	[24]
Mainly alpha	N gene	12/20–3/21 (Israel)	Healthcare workers	22.2 [SD: 1.0] *** (163)		27.3 [SD: 2.2] *** (31)		<0.001	[25]
Delta	E gene	6/21–12/21 (Switzerland)	Any individual with symptoms	13.8–26.3 * (127)	-	16.3–26.1 * (104)	-	0.0002	[18]
Delta	N gene	6/21–8/21 (USA)	General population	23.4 [IQR: approx. 19.0–28.5] *** (198)	-	23.1 [IQR: approx. 17.0–27.0] *** (171)	-	0.54	[26]
Delta	N gene	6/21–8/21 (USA)	General population (HYT cohort)	25.4 [IQR: approx. 23.0–28.0] *** (375)	-	25.5 [IQR: approx. 23.0–29.0] *** (125)	-	0.80	[26]
Delta	N gene	1/21–9/21 (USA)	Patients	Approx. 21 *** (134)		20.5 *** (117)		n.s.	[20]
Delta	RdRp gene	6/21–9/21 (Israel)	Patients	27.7 [SD: 5.0] ** (3100)		26.9 [SD: 5.0] ** (12,934)	29.1 [SD: 4.7] ** (519)	<0.05 (0 versus 2 doses) <0.001 (0 versus 3 doses)	[27]
Delta	N gene	6/21–9/21 (Israel)	Patients	25.1 [SD: 5.0] ** (3100)		25.4 [SD: 5.0] ** (12,934)	27.5 [SD: 4.7] ** (519)	<0.05 (0 versus 2) <0.001 (0 versus 3)	[27]

Table 1. *Cont.*

SARS-CoV-2 Variant	Type of Gene	Sampling Period (Country)	Type of Population	Ct Values According to Number of Applied Vaccine Doses (Number of Samples)				*p*-Value	Source
				None	1 Dose	2 Doses	3 Doses		
Delta	E gene	6/21–9/21 (Israel)	Patients	22.7 [SD: 4.9] ** (3100)		22.9 [SD: 4.9] ** (12,934)	25.2 [SD: 4.6] ** (519)	n.s. (0 versus 2) <0.001 (0 versus 3)	[27]
Delta B.1.617.2 (early period)	N, ORF1ab and S gene	12/10–5/21 (UK)	General population	21.5 [IQR: 16.4–31.7] *** (75)	30.1 [IQR: 18.6–31.7] *** (110)	32.2 [IQR: 26.0–34.0] *** (104)	-	-	[22]
Delta B.1.617.2 (late period)	N, ORF1ab and S gene	12/10–5/21 (UK)	General population	25.7 [IQR: 19.1–30.8] *** (326)	24.7 [IQR: 18.8–31.3] *** (705)	25.3 [IQR: 19.1–31.3] *** (1593)	-	-	[22]
Delta	N and S gene	4/21–6/21 (Singapore)	Patients	18.8 [IQR: 14.9–22.7] *** (130)	-	19.2 [IQR: 15.2–22.2] *** (71)	-	0.929	[28]
Delta	N gene	11/21–12/21 (USA)	Patients	Approx. 18.5 [IQR: approx. 15.0–21.5] *** (400)	-	Approx. 17 [IQR: approx. 15.0–21.0] *** (230)	-	n.s.	[29]
Mainly delta	N and S gene	3/20–11/21 (Republic of Korea)	Healthcare worker, inpatients, caregivers	20 [IQR: 15.0–29.0] *** (109)	-	19 [IQR: 16.0–24.0] *** (45)	-	0.64	[30]
Mainly delta (May 2021)	ORF1ab gene N gene	5/21–7/21 (USA)	General population	22.8 [IQR: approx. 18.0–31.0] *** (-) 24.0 [IQR: approx. 18.0–33.0] *** (-)	36.6 [IQR: approx. 28.0–37.0] *** (-) 36.0 [IQR: approx. 33.0–37.0] *** (-)	27.7 [IQR: approx. 23.0–37.0] *** (-) 30.6 [IQR: approx. 23.0–36.0] *** (-)	- -	- -	[31]
Mainly delta (July 2021)	ORF1ab gene N gene	5/21–7/21 (USA)	General population	18.8 [IQR: approx. 16.0–24.0] *** (-) 19.3 [IQR: approx. 16.0–25.0] *** (-)	17.8 [IQR: approx. 16.0–23.0] *** (-) 18.6 [IQR: approx. 14.0–29.0] *** (-)	19.0 [IQR: approx. 15.0–26.0] *** (-) 19.5 [IQR: approx. 16.0–23.0] *** (-)	- -	- -	[31]
Mainly delta	N and O genes	7/21–9/21 (India)	Patients	24 [IQR: 20.5–28.6] *** (14)	19 [IQR: 17.0–23.0] *** (31)	21 [IQR: 16.0–24.0] *** (50)	-	-	[32]
Delta	N and S gene	7/21–11/21 (Republic of Korea)	Healthcare worker, inpatients, caregivers	25 [IQR: 18.0–32.0] *** (28)	-	19 [IQR: 16.0–26.0] *** (44)	-	0.04	[30]
Delta	Not described	2/20–9/21 (Singapore)	Hemodialysis patients	19.0 [SD: 3.0] ** (10)	-	17.0 [SD: 3.5] ** (24)	-	0.37	[33]
Delta	ORF1ab gene	2021 (China)	Patients	Approx. 28 [SD: approx. 7.5] ** (14)	-	Approx. 26 [SD: approx. 6.5] ** (6)	-	0.528	[34]
Delta	N gene	2021 (China)	Patients	Approx. 27 [SD: approx. 7.5] ** (14)	-	Approx. 25 [SD: approx. 7.5] ** (6)	-	0.427	[34]
Delta	N gene	11/21 (Germany)	Patients	23.2 [SD: 6.0] ** (107)	-	27.5 [SD: 6.1] ** (127)	-	0.012	[35]
Delta	ORF1a region	11/21 (Germany)	Patients	22.9 [SD: 6.1] ** (107)	-	27.0 [SD: 6.0] ** (127)	-	0.019	[35]
Delta	N1 gene	11/21 (Germany)	Patients	24.4 [SD: 6.7] ** (107)	-	23.8 [SD: 5.8] ** (127)	-	0.80	[35]
Delta	N2 gene	11/21 (Germany)	Patients	26.1 [SD: 5.8] ** (107)	-	25.5 [SD: 5.0] ** (127)	-	0.42	[35]
Delta	E gene	11/21 (Germany)	Patients	24.6 [SD: 6.0] ** (107)	-	23.8 [SD: 4.9] ** (127)	-	0.37	[35]

Table 1. *Cont.*

SARS-CoV-2 Variant	Type of Gene	Sampling Period (Country)	Type of Population	Ct Values According to Number of Applied Vaccine Doses (Number of Samples)				*p*-Value	Source
				None	1 Dose	2 Doses	3 Doses		
Delta	N gene	6/21–7/21 (UK)	General population	23.1 [95% CI: 20.3–25.8] **** (28)	27.4 [95% CI: 24.8–30.0] **** (76)	27.6 [95% CI: 25.5–29.7] **** (145)	-	0.01 (2 versus 0) 0.04 (1 versus 0)	[36]
Delta	S gene	6/21–8/21 (USA)	General population and patients	19.0 [SD: 3.0] ** (59)	-	20.0 [SD: 3.5] ** (28)	-	n.s.	[37]
Delta	N gene	6/21–12/21 (USA)	General population	22.9 [95% CI: 22.8–23.0] ** (11,084)	-	22.1 [95% CI: 22.0–23.2] ** (9347)	-	<0.0001	[38]
Delta	Not described	7/21–8/21 (USA)	Patients	Approx. 23 *** (25) ####	-	Approx. 24 *** (47)	-	n.s.	[39]
Delta	RdRp/ORF1ab gene	9/21–10/21 (Republic of Korea)	Healthcare workers (61), inpatients (18), caregivers (15) in an outbreak situation	19.9 [SD: 5.4] ** (24)	-	20.9 [SD: 6.3] ** (70)	-	0.52	[10]
Mainly delta	N gene	5/21–7/21 (Kuwait)	General population	19.7 [range: approx. 13.0–33.0] *** (91)	-	19.6 [range: approx. 10.0–33.0] *** (59)	-	0.42	[40]
Mainly delta	N genes	12/20–9/21 (USA)	General population	23.1 [IQR: 19.4–29.0] *** (160)	-	25.8 [IQR: 20.6–31.2] *** (112)	-	0.02	[41]
Mainly delta	Not described	7/21 (USA)	General population	21.5 [IQR: approx. 19.0–26.0] *** (84) #####		22.8 [IQR: approx. 18.0–27.0] *** (127)		n.s.	[42]
Omicron	N gene	11/21–12/21 (USA)	Patients	Approx. 18.4 [IQR: approx.16.0–22.0] *** (166)	-	Approx. 17 [IQR: approx. 15.0–19.0] *** (229)	-	n.s.	[29]
Omicron BA.1	E gene	12/21–2/22 (Switzerland)	Any individual with symptoms	16.6–26.7 * (33)	-	14.6–26.7 * (121) *****		n.s.	[18]
Mainly omicron	RdRp gene	1/22 (Bosnia and Herzegovina)	Healthcare workers (141)	Approx. 32.0 [IQR: approx. 28.0–34.0] *** (44)	-	Approx. 30.5 [IQR: approx. 27.5–33.0] (26)	-	n.s.	[43]
Mainly omicron	E gene	1/22 (Bosnia and Herzegovina)	Healthcare workers (141)	Approx. 27.5 [IQR: approx. 22.0–29.0] *** (44)	-	Approx. 24.0 [IQR: approx. 22.0–27.0] (26)	-	n.s.	[43]
Mainly omicron	N gene	1/22 (Bosnia and Herzegovina)	Healthcare workers (141)	Approx. 28.0 [IQR: approx. 26.0–32.0] *** (44)	-	Approx. 27.0 [IQR: approx. 25.5–30.5] (26)	-	n.s.	[43]
Multiple variants	ORF1ab gene	12/20–3/21 (Italy)	General population	19.4 [IQR: 18.0–28.7] *** (31)	-	21.2 [IQR: 17.5–31.3] *** (54)	-	0.20	[44]
Multiple variants	N gene	2/21–6/21 (USA)	General population and patients	23.1 ** (1061)	-	23.1 ** (121)		0.99	[45]
Multiple variants	Not described	12/20–8/21 (Germany)	General population, index cases	25.7 [SD: 6.6] ** (287)	-	29.5 [SD: 7.5] ** (300)	-	<0.001	[46]

Table 1. *Cont.*

SARS-CoV-2 Variant	Type of Gene	Sampling Period (Country)	Type of Population	Ct Values According to Number of Applied Vaccine Doses (Number of Samples)				*p*-Value	Source
				None	1 Dose	2 Doses	3 Doses		
Multiple variants	Not described	12/20–8/21 (Germany)	General population, contact persons of index cases	25.6 [SD: 6.5] ** (270)	-	26.2 [SD: 7.3] ** (56)	-	0.599	[46]
Multiple variants	Not described	11/20–8/21 (USA)	Participants of the occupational health program of the National Basketball Association, infected upon inclusion	20.7 [95% CI: 19.8–20.2] ** (136)	-	20.5 [95% CI: 19.0–21.0] ** (37)	-	n.s.	[47]

* range; ** mean with 95% confidence interval (95% CI) or standard deviation (SD); *** median with interquartile range (IQR); **** comparison between unvaccinated, partly vaccinated and fully vaccinated; ***** with 30 boosted subjects; # vaccinated with BNT162b2; ## vaccinated with mRNA 1273; ### data from 13 laboratories using 6 different validated assays; #### includes unvaccinated and not fully vaccinated; ##### includes unvaccinated, not fully vaccinated and whose vaccination status was unknown; patients were defined as those who are treated in hospitals (inpatients) or asked for medical treatment (outpatients); n.s. = not significant.

With the ancestral strain, the Ct values in individuals infected with SARS-CoV-2 ranged between 13.9 and 26.6 [18]. Comparisons between vaccinated and unvaccinated individuals were not possible due to the lack of vaccines during the period of dominance of the ancestral strain. During the dominance of the beta variant, one study with two different vaccination protocols showed a significantly higher viral load (lower Ct value; median or mean) among the unvaccinated individuals [19].

During the alpha wave, five of six studies demonstrated a higher viral load among the unvaccinated subjects, with a significant difference in two of the studies [21,25], whereas in two other studies, no significant difference was found [20,22]. Among nursing home residents, a significantly lower viral load among the vaccinated individuals was found only when the vaccination completion was at least 28 days ago [23]. The viral load among vaccinated and unvaccinated healthcare workers was the same, with a median of 18.5 (interquartile range, IQR 13.5–24.0 and 16.0–26.0 for unvaccinated or vaccinated, respectively) in one study [24]. In an additional study without a description of the mean or median Ct values, the evaluation of 85 unvaccinated and 165 vaccinated cases during an outbreak in a nursing home with the alpha variant of SARS-CoV-2 revealed a lower mean Ct value among the vaccinated residents (3.04 cycles lower), but the difference was not significant ($p = 0.38$) [48].

Data obtained during the delta wave revealed an inconsistent picture. Overall, the data sets in 13 studies described a lower viral load among the vaccinated compared to the unvaccinated. The difference was significant in five studies [18,27,35,36,41], not significant in seven studies [10,26–28,37,39,42] and without reporting results of a statistical evaluation in two studies [22,31]. On the other hand, the data sets in 12 studies described a higher viral load among the vaccinated compared to the unvaccinated. The difference was significant in three studies [27,30,38], not significant in eight studies [20,26,29,30,33–35,40] and without reporting results of a statistical evaluation in two studies [22,32]. Among the boosted population (having received one dose of booster after the completion of the original course of vaccination), the effect of a lower viral load is insignificant within 61 to 120 days [49].

In three studies during the omicron period, no significant difference in the viral load was found between vaccinated and unvaccinated individuals [18,29,43]. Four data sets from three studies examined the viral load during various pandemic periods, resulting in data with multiple variants. In one data set, the viral load was significantly higher in unvaccinated subjects [46], whereas in the other data sets, no significant difference was found [44–46].

3.2.2. Viral RNA Copies According to Vaccination Status

Across all the variants, nine studies described the viral load by calculating the number of viral RNA copies per ml (Table 2). In nine data sets from seven studies, a lower viral load was found among the vaccinated, with seven of those differences being significant and two of them being not significant. In the data sets of three studies, a lower viral load was found among the unvaccinated, with all of them being not significant.

During the delta predominance, a lower viral load was found among the vaccinated in three studies [14,50,51], which was in one study not associated with a specific vaccine [14]. The effect, however, was waning within five months [51], although it could be restored by a booster dose [51]. During the omicron predominance, almost all the data sets from two studies showed a similar viral load for unvaccinated, fully vaccinated and boosted [18,51], with the exception of those who received the second dose 14 to 149 days before their infection (mean difference [95%-CI]: −1 [–1.7 to −0.3]), as based on a regression model. In investigations with multiple SARS-CoV-2 variants, the number of RNA copies from vaccinated individuals was lower in two studies [52,53], higher in one study [47], and equal to the viral load in vaccinated individuals in one study [45], with one of those differences showing a lower viral load in vaccinated individuals being statistically significant [53].

Table 2. Log_{10} viral copies per ml from respiratory tract samples of COVID-19 cases according to the vaccination status and the SARS-CoV-2 variant.

SARS-CoV-2 Variant	Type of Gene	Sampling Period (Country)	Type of Population	Log_{10} Viral Copies per mL According to the Number of Vaccination Doses (Number of Samples)				*p*-Value	Source
				None	1 Dose	2 Doses	3 Doses		
Delta	E gene	6/21–12/21 (Switzerland)	Any individual with symptoms	Approx. 8.5 [SD: 0.8] * (127)	-	Approx. 8.2 [SD: 1.0] * (104)	-	0.0002	[18]
Delta	N gene	12/20–4/22 (USA)	Healthcare workers, essential frontline workers, uninfected upon inclusion	4.1 * (78)	-	3.0 * (27) # 4.2 * (165) ##	3.2 * (18)	"significant" n.s. n.s.	[51]
Delta	N gene	10/20–8/21 (USA)	General population	7.4 [IQR: 3.3–10.8] ** (36)	-	4.7 [IQR: approx. 1.0–10.6] * (56)	-	<0.0001	[14]
Mainly delta	N gene	7/21–9/21 (France)	Patients	7.1 [IQR: 5.7–7.9] ** (2619)	7.0 ** [IQR: 5.6–7.8] ** (636)	6.6 [IQR: 5.5–7.6] ** (520)	-	<0.0001 for delta variant (0 versus 2)	[50]
Mainly delta	N genes	12/20–9/21 (USA)	General population	1.1 [95% CI: approx. 0.7–1.6] * (160)	-	0.3 * [95% CI: approx. 0.3–0.8] * (112)	-	0.02	[41]
Omicron	N gene	12/20–4/22 (USA)	Healthcare workers, essential frontline workers, uninfected upon inclusion	3.5 * (109)	-	2.8 * (42) # 3.3 * (209) ##	3.1 * (383)	"significant" n.s. n.s.	[51]
Omicron BA.1	E gene	12/21–2/22 (Switzerland)	General population	Approx. 7.6 [SD: approx. 0.8] * (33)	-	Approx. 7.8 [SD: approx. 0.8] * (91)	Approx. 7.7 [SD: approx. 0.7] * (30)	n.s.	[18]
Multiple variants	ORF1ab, N and S gene	12/20–4/21 USA)	General population	3.8 [SD: 1.7] * (155)	2.3 [SD: 1.7] * (16) ***	-	-	"significant"	[53]
Multiple variants	N gene	2/21–6/21 (USA)	General population and patients	6.6 * (1061)	-	6.6 * (121)	-	0.99	[45]

Table 2. *Cont.*

SARS-CoV-2 Variant	Type of Gene	Sampling Period (Country)	Type of Population	Log_{10} Viral Copies per mL According to the Number of Vaccination Doses (Number of Samples)				*p*-Value	Source
				None	1 Dose	2 Doses	3 Doses		
Multiple variants	Not described	11/20–8/21 (USA)	Participants of the occupational health program of the National Basketball Association, infected upon inclusion	8.0 [95% CI: 8.2–11.5] * (136)	-	8.1 [95% CI: 7.9–11.5] * (37)	-	n.s.	[47]
Multiple variants	N gene	9/20–9/21 (USA)	General population, infected non-hospitalized	7.5 [IQR: 0.004–108.0] ** (52)	-	1.0 [IQR: 0.2–32.0] ** (32)	-	0.39	[52]
Multiple variants	E gene	9/20–9/21 (USA)	General population, infected non-hospitalized	1.2 [IQR: 0.005–27.4] ** (52)	-	0.6 [IQR: 0.07–23.3] ** (32)	-	0.88	[52]

* mean with 95% confidence interval (95% CI) or standard deviation (SD); ** median with interquartile range (IQR); *** at least 1 dose; # received 2nd dose 14–149 days before infection; ## received 2nd dose $\geq$ 150 days before infection; patients were defined as those who are treated in hospitals (inpatients) or asked for medical treatment (outpatients); n.s. = not significant.

3.2.3. Infectious Virus According to Vaccination Status

Five studies measured the load of infectious SARS-CoV-2 in the vaccinated and unvaccinated populations (Table 3). In seven data sets of four studies, a lower load of infectious virus was found among the vaccinated or boosted. Five of those differences described in three studies were significant [18,37,51] and two were not significant [51,52]. In the data sets of two studies, a lower load of infectious virus was found among the unvaccinated compared to those who received two doses, without reaching statistical significance [18,38].

3.3. Duration of Viral Detection

The duration of viral detection was described in nine cohort studies of mostly moderate quality. The evaluations of the study quality can be found in the Supplementary Materials in Table S1.

3.3.1. Detection of SARS-CoV-2 Genes

In three studies during the delta predominance, vaccinated COVID-19 cases had a shorter duration of RNA detection compared to unvaccinated or partly vaccinated control cases (Table 4) [15,30,33]. The difference, however, was significant in only one study [33]. Five studies described the duration of RNA detection with various SARS-CoV-2 variants. Here, all the data sets indicated a shorter RNA detection duration in the partly vaccinated [53] and fully vaccinated [47,52,54,55], with the difference being significant in two of the four studies [47,54].

3.3.2. Detection of Infectious SARS-CoV-2

Four studies described the duration of detection of infectious SARS-CoV-2 in vaccinated and unvaccinated subjects (Table 5). Two studies with the delta variant found a shorter duration of detection in fully vaccinated subjects compared to the group of unvaccinated and partly vaccinated subjects (median: 5 versus 11 days [15]; median: 1.8 versus 4.4 days [30]). The difference, however, was significant in only one study [15]. Two other studies described the persistence of infectious virus with various viral variants. A shorter duration of detection was found in fully vaccinated compared to the unvaccinated subjects (median: 5 versus 7 days [52]; mean: 0.8 versus 2.8 days [56]). The difference was significant in one study [56].

3.4. Transmission from COVID-19 Cases

The secondary attack rates from both unvaccinated and vaccinated index cases were described in nine cohort studies and seven cross-sectional studies. They were mostly of moderate quality. The results of the study quality evaluations are described in Tables S3 and S4 in the Supplementary Materials.

Without any vaccination, the secondary attack rate in households was described to be as high as 64.3% [57]. In both of the included studies that were conducted during the alpha variant predominance (Table 6), the secondary attack rates were significantly lower when the index case was vaccinated compared to unvaccinated index cases (19% versus 42% [58]; 22.2% versus 66.7% [48]). The contact persons were all unvaccinated in one of the two studies [48].

An additional study was found during the alpha variant dominance without a complete description of the case numbers [17]. A transmission analysis revealed that among 127 households, no household with secondary cases was found in three households with the primary case being fully vaccinated, one household with secondary cases was found in five households with the primary case being partially vaccinated and nine households with secondary cases were found in 11 households with the primary case being unvaccinated [59]. In households with children, the vaccination status of the parents was associated with a lower COVID-19 case number (mainly alpha variant) among the unvaccinated children (risk reduction when one parent is vaccinated: −26.0%; risk reduction when both parents are vaccinated: −71.7%) [17]. In addition, in households of healthcare workers, less secondary cases were found among unvaccinated household members when the index case was vaccinated [60].

Table 3. Log_{10} infectious virus titer per ml from respiratory tract samples of COVID-19 cases according to the vaccination status and the SARS-CoV-2 variant.

SARS-CoV-2 Variant	Sampling Period (Country)	Type of Population	Log_{10} Infectious Virus Titer per ml According to Vaccination Status (Number of Samples)				*p*-Value	Source
			None	1 Dose	2 Doses	3 Doses		
Delta	6/21–12/21 (Switzerland)	Any individual with symptoms	Approx. 2.5 [SD: 1.2] * (127)	-	Approx. 1.7 [SD: 1.3] * (104)	-	<0.0001	[18]
Delta	6/21–8/21 (USA)	Patients	Approx. 2.9 [SD: approx. 1.0] * (59)	-	Approx. 2.4 [SD: approx. 1.0] * (28)	-	<0.05	[37]
Delta	12/20–4/22 (USA)	Healthcare workers, essential frontline workers, uninfected upon inclusion	4.8 * (36)	-	3.8 * (9) [#] 4.1 * (61) [##]	3.1 * (10)	n.s. "significant" "significant"	[51]
Delta	6/21–12/21 (USA)	General population	Approx. 2.3 ** (24)	-	Approx. 2.4 ** (23)	-	n.s.	[38]
Omicron BA.1	12/21–2/22 (Switzerland)	Any individual with symptoms	Approx. 1.6 [SD: 1.2] ** (33)	-	Approx. 1.7 [SD: 1.2] ** (91)	Approx. 0.9 [SD: 0.9] ** (30)	0.038	[18]
Multiple variants	9/20–10/21 (USA)	General population, infected non-hospitalized	3.9 [IQR: 0.0–5.4] ** (52)	-	3.2 [IQR: 0.0–6.1] ** (32)	-	0.60	[52]

* mean with standard deviation (SD); ** median with interquartile range (IQR); [#] received 2nd dose 14–149 days before infection; [##] received 2nd dose ≥ 150 days before infection; patients were defined as those who are treated in hospitals (inpatients) or asked for medical treatment (outpatients); n.s. = not significant.

Table 4. Duration of SARS-CoV-2 gene detection from respiratory tract samples of COVID-19 cases according to the vaccination status and the SARS-CoV-2 variant.

SARS-CoV-2 Variant	Type of Gene	Sampling Period (Country)	Type of Population	Duration of SARS-CoV-2 Detection (Days) According to Vaccination Status (Number of Samples)				*p*-Value	Source
				None	1 Dose	2 Doses	Prior Infection		
Delta	Not described	2/20–9/21 (Singapore)	Hemodialysis patients	32 [IQR: 30.0–34.0] * [#] (10)	-	24 [IQR: 21.0–26.0] * [#] (24)	-	<0.01	[33]
Delta	N and S gene	9/21–1/22 (Republic of Korea)	Patients, infected upon inclusion	-	>26 [95% CI: 18–NA] * (30) **	15 [95% CI: 12–NA] * (19)	-	0.15	[15]
Delta	N and S gene	3/20–11/21 (Republic of Korea)	Patients	≥10 (28)	≥10 (11)	≥ 10 (6)	-	n.s.	[30]
Multiple variants	ORF1ab, N and S gene	12/20–4/21 USA)	Healthcare workers, essential frontline workers, uninfected upon inclusion	8.9 [SD: 10.2] *** (155)	2.7 [SD: 3.0] *** (16) ****	-	-	significant	[53]

Table 4. *Cont.*

SARS-CoV-2 Variant	Type of Gene	Sampling Period (Country)	Type of Population	Duration of SARS-CoV-2 Detection (Days) According to Vaccination Status (Number of Samples)				*p*-Value	Source
				None	1 Dose	2 Doses	Prior Infection		
Multiple variants	Not described	11/20–8/21 (USA)	Participants of the occupational health program of the National Basketball Association	7.5 [95% CI: 6.8–8.2] *** (136)	-	5.5 [95% CI: 4.6–6.5] *** (37)	-	significant	[47]
Multiple variants	N and E genes	9/20–10/21 (USA)	General population, infected non-hospitalized	9.0 [IQR: 7.0–12.0] * (52)	-	8.0 [IQR: 4.5–12.0] * (32)	-	0.52	[52]
Multiple variants	ORF1ab and N gene	5/20–3/22 (Nicaragua)	General population	28.2 [IQR: 16.5–43.1] *	-	12.9 [IQR: 7.6–19.8] *		significant	[54]
Multiple variants	ORF1ab and N gene	1/20–1/22 (China)	Hospitalized patients	19.0 [IQR: 12.0–24.5] * (171) ***** Approx. 16 * ******	-	17.0 [IQR: 12.3–19.5] * (165) ***** Approx. 16 * ******	-	0.038 -	[55]

* median with interquartile range (IQR) or 95% confidence interval (95% CI); ** partly vaccinated and unvaccinated; *** mean with standard deviation (SD) or 95% confidence interval (95% CI); **** at least 1 dose; ***** moderate COVID-19; ****** mild COVID-19; # two negative swabs at least 24 h apart; patients were defined as those who are treated in hospitals (inpatients) or asked for medical treatment (outpatients); n.s. = not significant.

Table 5. Duration of detection of infectious SARS-CoV-2 from respiratory tract samples of COVID-19 cases according to the vaccination status.

SARS-CoV-2 Variant	Sampling Period (Country)	Type of Population	Duration of SARS-CoV-2 Detection (Days) According to Vaccination Status (Number of Samples)			*p*-Value	Source
			None	1 Dose	2 Doses		
Delta	9/21–1/22 (Republic of Korea)	Patients, infected upon inclusion	-	11 [95% CI: 9.0–15.0] * (30) **	5 [95% CI: 4.0–NA] * (19)	0.0013	[15]
Delta	3/20–11/21 (Republic of Korea)	Inpatients	-	4.4 [95% CI: 2.0–7.0] * (39) **	1.8 [95% CI: 1.0–NA] * (6)	0.42	[30]
Multiple variants	9/20–10/21 (USA)	General population, infected non-hospitalized	7.0 [IQR: 0.0–8.0] * (52)	-	5.0 [IQR: 0.0–7.0] * (32)	0.12	[52]
Multiple variants	12/20–3/21 (USA)	Students and university staff who tested positive	2.8 *** (70)	-	0.8 *** (12)	< 0.01	[56]

* median; ** partly vaccinated and unvaccinated; *** mean.

Table 6. Secondary attack rates with 95% confidence intervals (95% CI) or standard deviation (SD) from COVID-19 cases with different vaccination statuses infected with different SARS-CoV-2 variants.

SARS-CoV-2 Variant	Study Period (Country)	Vaccination Status Index Cases (n)	Type of Contact	Secondary Attack Rate per Group	Proportion of Fully Vaccinated Contacts (Group)	*p*-Value	Source
Mainly alpha	12/20–4/21 (Israel)	Unvaccinated (200) Fully vaccinated (15)	Household contacts of healthcare workers	42.0% *** [95% CI: 38%–46%] 19.0% *** [95% CI: 9%–34%]	-	significant	[58]
Mainly alpha	1/21–3/21 (Germany)	Unvaccinated (11) Fully vaccinated (5)	Household contacts	66.7% 22.2%	0% ** (all contacts) 0% ** (all contacts)	0.046	[48]
Alpha and delta	1/21–8/21 (UK)	Unvaccinated (218,946) Partially vaccinated (91,394) Fully vaccinated (63,775)	"Close contacts" of infected adult patients	46.4% 28.0% 26.8%	27.8% (all contacts with PCR tests)	- *	[13]
Delta	9/20–9/21 (UK)	Unvaccinated (63) Partially vaccinated (25) Fully vaccinated (50)	Mainly household contacts	23.0% 37.1% 24.6%	63.0% (contacts of unvaccinated index cases) 54.3% (contacts of partially vaccinated index cases) 62.3% (contacts of fully vaccinated index cases)	n.s. #	[61]
Delta	2/21–5/21 (The Netherlands)	Unvaccinated (110,872) Partially vaccinated (2088) Fully vaccinated (622)	Household contacts	30.8% 28.9% 11.2%	2.1% (all contacts)	-	[62]
Delta	6/21–10/21 (Denmark)	Unvaccinated (16,431) Fully vaccinated (8262)	Household contacts	22.3% 20.1%	Correlation coefficient of 0.72 of the vaccination status between primary cases and contacts among individuals of ≥13 years of age	-	[63]
Delta	6/21–7/21 (USA)	Unvaccinated (61) Fully and partially vaccinated (22)	Household contacts	57.8% 16.7%	35.7% (contacts of unvaccinated index cases) 75.0% (contacts of fully vaccinated index cases)	<0.01	[64]
Delta	6/21–10/21 (Denmark)	Unvaccinated (8611) Fully vaccinated, no previous infection (8765) Boosted (528) Unvaccinated, previous infection (145) Fully vaccinated, previous infection (58)	Household contacts	21.5% 20.2% 18.0% 7.5% 7.5%	48.7% (all contacts, delta and omicron)	-	[65]
Delta	3/20–11/21 (Republic of Korea)	Unvaccinated (100) Partially vaccinated (10) Fully vaccinated (43)	Healthcare setting	27.0% 20.0% 7.0%	-	0.03	[30]

Table 6. *Cont.*

SARS-CoV-2 Variant	Study Period (Country)	Vaccination Status Index Cases (n)	Type of Contact	Secondary Attack Rate per Group	Proportion of Fully Vaccinated Contacts (Group)	*p*-Value	Source
Delta	8/21–9/21 (The Netherlands)	Unvaccinated (2641) Partially vaccinated (540) Fully vaccinated (1740)	Household contacts	17.7% 7.9% 12.4%	35.3% (contacts of unvaccinated index cases) 67.3% (contacts of partially vaccinated index cases) 79.6% (contacts of fully vaccinated index cases)	-	[66]
Delta	9/21–1/22 (Republic of Korea)	Partially or unvaccinated (30) Fully vaccinated (19)	"Close contacts"	14.1% 3.7%	-	0.001	[15]
Omicron	11/21–12/21 (Denmark)	Unvaccinated (1166) Fully vaccinated, no previous infection (6934) Boosted (468) Unvaccinated, previous infection (128) Fully vaccinated, previous infection (414)	Household contacts	30.8% 29.5% 31.8% 15.0% 16.0%	48.7% (all contacts, delta and omicron)	-	[65]
Omicron	11/21–2/22 (USA)	Unvaccinated (36) Fully vaccinated (12) **** Boosted (57)	Household contacts	63.9% 43.6% 42.7%	35.1% (all contacts); an additional 26.0% were boosted.	-	[67]
Omicron	12/21–1/22 (Germany)	Unvaccinated (202) Fully vaccinated (202) Boosted (204)	"Close contacts"	47.9% 49.5% 34.8%	-	-	[68]
Multiple variants	9/20–1/22 (USA)	Unvaccinated (21) Fully vaccinated (21)	Household contacts	45.0% [95% CI: 29.0%–62.0%] 41.4% [95% CI: 25.0%–59.0%]	20.0% (contacts of unvaccinated index cases) 85.3% (contacts of fully vaccinated index cases)	0.60	[69]
Multiple variants	4/21–9/21 (Thailand)	Unvaccinated (177) Fully vaccinated (231)	Household contacts	46.8% 50.8%	3.1% (contacts of unvaccinated index cases) 14.7% (contacts of fully vaccinated index cases)	0.177	[70]
Multiple variants	12/20–8/21 (Germany)	Unvaccinated (357) Fully vaccinated (357)	"close contacts"	37.8% 10.1%	Significantly more secondary cases among unvaccinated contacts ($p < 0.001$)	<0.001	[46]

* significantly lower transmission rate ratios (multivariable model) for partly and fully vaccinated index cases; ** vaccine was prioritized in January 2021 for selected population groups only; *** mean number of infected contacts per index case; **** vaccinated < 5 months before index date; # based on vaccine effectiveness estimate for secondary attack rates; n.s. = not significant.

Significantly lower secondary attack rates were also found during the period when both the alpha and delta variants were present for both the fully and partly vaccinated index cases [13].

During the delta variant predominance, eight studies were carried out (Table 6). The secondary attack rates were lower from fully vaccinated index cases in all of those studies, with three of them being statistically significant [15,30,64] and four of them without a statistical evaluation [62,63,65,66]. In one study, the secondary attack rate was higher from fully vaccinated index cases but the difference was not significant or not statistically evaluated [61].

An additional transmission analysis was performed during the delta wave between index cases and contacts in households. The proportion of COVID-19 cases among contacts was not significantly different between vaccinated and unvaccinated index cases [71]. In households with children, the vaccination status of the parents was associated with a lower COVID-19 case number (mainly delta variant) among the unvaccinated children (risk reduction when one parent is vaccinated: −20.8%; risk reduction when both parents are vaccinated: −58.1%) [17]. One additional study did not describe the secondary attack rates but a significantly higher mean number of infected contacts per unvaccinated index case [72].

When the omicron variant became predominant in the second half of 2021, three studies were carried out (Table 6), with a lower secondary attack rate from fully vaccinated individuals compared to the unvaccinated in two studies (29.5% versus 30.8% [65]; 43.6% versus 63.9% [67]) and a higher secondary attack rate in one study (49.5% versus 47.9% [68]). Boosted index cases revealed a lower secondary attack rate compared to fully vaccinated index cases in two studies (42.7% versus 43.6% [67]; 34.8% versus 49.5% [68]) and a higher secondary attack rate in one study (31.8% versus 29.5% [65]).

Three more studies with multiple SARS-CoV-2 variants described a lower secondary attack rate from vaccinated index cases compared to the unvaccinated in two studies (41.4% versus 45.0% [69]; 10.1% versus 37.8% [46]) and a higher rate in the other study (50.8% versus 46.8% [70]; Table 6). A significant difference, however, was described only in one study [46].

Several transmission studies did not report the vaccination status or the history of any past SARS-CoV-2 infection of the contact persons. In five studies, however, the majority of contact persons of fully vaccinated index cases were also fully vaccinated, whereas the vaccination rate in households from unvaccinated index cases was much lower [63,64,66,69,72]. In one study, however, the proportion of vaccinated households' contacts was similar for vaccinated and unvaccinated index cases [61].

3.5. Previous COVID-19 Infection

Three studies have addressed the level of the viral load in reinfections compared to unvaccinated and fully vaccinated COVID-19 cases (Table 7). Patients with a COVID-19 reinfection mostly had a lower viral load, as indicated by the higher Ct values compared to unvaccinated cases with a primary infection (29.8 versus 28.0, $p = 0.0004$ [54]; 29.9 versus 23.6, $p < 0.001$, [19]; 32.8 versus 28.7, no p-value [22]), although another study demonstrated a higher viral load for the same comparison (22.3 versus 25.7, no p-value, [22]). The comparison of the viral load in reinfections and fully vaccinated but previously uninfected revealed a lower viral load in reinfections in two data sets [19] and a higher viral load in three data sets (Table 7) [22].

Another study described the viral load in healthcare workers, with 46 of them being neither vaccinated nor previously infected, 45 being unvaccinated but previously infected, 26 being fully vaccinated without a previous infection and 26 being fully vaccinated and previously infected. There was no significant difference between all four groups regarding the Ct values of various genes [43].

Table 7. Ct values from respiratory tract samples of unvaccinated COVID-19 cases having a reinfection compared unvaccinated COVID-19 cases (primary infection) and to fully vaccinated COVID-19 cases with a breakthrough infection.

SARS-CoV-2 Variant	Number of Samples (Reinfection in Unvaccinated)	Type of Control	Number of Samples from Control	Type of Gene	Ct Values (Reinfection in Unvaccinated)	Ct Values (Control Group)	*p*-Value	Source
Mainly beta	1686	Primary infection in unvaccinated	1686	N, ORF1ab and S gene	29.9 * [IQR: 22.3–33.5]	23.6 * [IQR: 18.5–29.9]	<0.001	[19]
Mainly beta	761	BNT162b2 breakthrough infections	761	N, ORF1ab and S gene	29.5 * [IQR: 22.0–33.4]	26.4 * [IQR: 20.2–31.9]	<0.001	[19]
Mainly beta	85	mRNA-1273 breakthrough infections	85	N, ORF1ab and S gene	33.0 * [IQR: 29.4–34.4]	31.6 * [IQR: 24.1–34.2]	<0.001	[19]
Alpha B.1.1.7	68	Primary infection in unvaccinated	10,853	N, ORF1ab and S gene	32.8 * [IQR: 30.9–34.2]	28.7 * [IQR: 20.4–32.9]	-	[22]
Alpha B.1.1.7	68	BNT162b2 and ChAdOx1 breakthrough infections	56	N, ORF1ab and S gene	32.8 * [IQR: 30.9–34.2]	33.3 * [IQR: 31.6–34.0]	-	[22]
Delta B.1.617.2 (early period)	5	Primary infection in unvaccinated	75	N, ORF1ab and S gene	30.8 * [IQR: 29.5–34.3]	21.5 * [IQR: 16.4–31.7]	-	[22]
Delta B.1.617.2 (early period)	5	BNT162b2 and ChAdOx1 breakthrough infections	104	N, ORF1ab and S gene	30.8 * [IQR: 29.5–34.3]	32.2 * [IQR: 26.0–34.0]	-	[22]
Delta B.1.617.2 (late period)	20	Primary infection in unvaccinated	326	N, ORF1ab and S gene	22.3 * [IQR: 16.5–30.3]	25.7 * [IQR: 19.1–30.8]	-	[22]
Delta B.1.617.2 (late period)	20	BNT162b2 and ChAdOx1 breakthrough infections	1593	N, ORF1ab and S gene	22.3 * [IQR: 16.5–30.3]	25.3 * [IQR: 19.1–31.3]	-	[22]
Multiple variants	443 **	Primary infection in mostly unvaccinated	302 ***	ORF1ab and N gene	29.8 ****	28.0 ****	0.0004	[54]

* median with interquartile ranges (IQR); ** 49 subjects (11.1%) were fully vaccinated *** 4 subjects (1.3%) were fully vaccinated; **** mean.

4. Discussion

Some scientists and politicians repeatedly spoke out in favor of COVID-19 vaccination in order to protect contact persons. Protection of contact persons became the main motivation for vaccination in some population groups [6]. A lower risk of transmission from vaccinated subjects may be explained by a lower viral load, a shorter viral persistence or a reduced transmission in a defined setting such as a household.

The viral load substantially contributed to human-to-human transmission, with a higher viral load posing a greater risk of onward transmission [73]. For example, a significantly higher viral load (lower Ct values) was described in index cases from households with a secondary transmission (N gene: 23.1; ORF1ab gene: 23.2) compared index cases from households without a secondary transmission (N gene: 27.1; ORF1ab gene: 29.1) [74]. But the vaccination status does obviously not have a consistent and relevant impact on the viral load of individuals infected with SARS-CoV-2. In 2021, during the beta and alpha variant dominance, three of seven studies showed a statistically significantly lower viral load among the vaccinated as demonstrated by higher Ct values. Data obtained during the delta and omicron waves, however, found a significantly lower viral load in the vaccinated in the data sets of five studies and a significantly higher viral load in the vaccinated in the data sets of three studies with regard to the Ct values. These findings were confirmed by the results from more than 460,000 individuals, showing that the effect of a recent vaccination on the viral load of the omicron variant is rapidly waning and thereby raising doubts about the effect of vaccination on viral transmissibility [75]. This is why an expected lower viral load as a single parameter does not seem to reduce the risk of transmission to a great extent.

A major limitation regarding the interpretation of Ct values is that the values obtained from the same samples can vary substantially depending on the investigated gene. For example, significantly lower Ct values were detected in samples from vaccinated individuals when the RdRp gene or the N gene were tested, whereas no significant difference was found when the E gene was tested [27]. Similar results were obtained by Bollinger et al. [35]. Caution has been advised when interpreting single Ct values as a proxy for infectivity, especially in intermittently positive test results and in different stages of infection with a variable decline of viral RNA [76]. In the current review, however, the Ct values are not analyzed as single results per person to determine the person's current individual infectivity. It is likely that additional factors contribute to transmission, such as physical distance or duration of contact [77,78]. An analysis of 602 PCR test samples was performed from COVID-19 cases among students. Contact tracing information was available for 195 index cases, with 101 of them being non-spreaders and 94 of them being spreaders. The mean Ct values of the spreaders and the non-spreaders were nearly identical, suggesting that the Ct values do not predict the transmissibility of SARS-CoV-2 [79].

Viral clearance, including the detection of infectious virus, has been described to be faster in the vaccinated population so that their expectable duration as a possible source for transmission is mostly shorter. Viral shedding, however, is continuously decreasing with time over the course of infection [80]. This is why the overall relevance of a somewhat faster clearance of viral RNA or infectious SARS-CoV-2 to the transmissibility of SARS-CoV-2 is not clear.

An analysis of the secondary attack rates provided some evidence that in household settings, vaccination of the index cases was associated with fewer secondary cases in their household contacts compared to no vaccination of the index cases. The difference was significant in 6 of the 16 studies. But with a lack of data obtained from RCTs, the causality of the observed findings remains uncertain. One possibility is that the vaccination of the index cases has caused the lower attack rate among contact persons. But it may as well be the vaccination status of the contact persons that has caused lower secondary attacks rates among household members of vaccinated index cases, i.e., vaccination coverage of the contact persons confounding the results of lower secondary attack rates when the index was vaccinated.

Two of the six studies with a significant difference were performed during the alpha wave, when COVID-19 vaccination was not broadly available yet [48,58], while three of the studies were conducted during the delta wave, with small sample sizes of 153 [30], 83 [64] or 49 index cases [15]. The proportions of fully vaccinated contact persons are, however, not described in any of the three studies. One study with a significant difference included data from multiple SARS-CoV-2 variants. It was based on 714 index cases. The authors provided a possible explanation for their finding because they found significantly more secondary cases among unvaccinated contacts ($p < 0.001$) [46]. Although the authors focused in all studies on the vaccination status of the index cases, they did not always adequately take into account the vaccination status of the contact persons.

In five of the 16 studies, the vaccination coverage of the contact persons was described according to the vaccination status of the index cases. Four of the studies indicated that contact persons were more often vaccinated when the index case was also vaccinated. The differences in vaccination rates varied between 11.6% [70], 39.3% [64], 44.3% [66] and 65.3% [69]. Population-based data from Denmark also described a correlation coefficient of 0.72 for the vaccination status between primary cases and contacts among individuals of $\geq$ 13 years of age [63]. It is therefore plausible to assume that the vaccination status of the contact persons may be a more suitable factor to explain the observation of lower secondary attack rates in contacts to vaccinated index persons. This assumption is supported by a finding from South Korea. A population-based study during the omicron predominance indicated that fully vaccinated and boosted contacts have a lower incidence ratio compared to unvaccinated contacts [81]. This assumption is supported by the finding that those who encouraged their families and friends to get vaccinated are more likely to accept a COVID-19 vaccination [82]. The presence of symptoms may also be relevant for a secondary transmission from index cases, as symptomatic infections have been described to increase transmissibility from the index cases [83]. Finally, the behavior may be different between households of vaccinated and unvaccinated index cases. It has been described that those who are willing to get vaccinated have a higher adherence to physical distancing guidelines compared to the unvaccinated [84]. In addition, mitigation behaviors such as masking, physical distancing and hand hygiene are significantly more performed by the vaccinated [85]. Keeping more physical distance may also have a relevant impact on the incidence of secondary cases [77]. It is therefore highly questionable if the partly observed lower secondary attack rates in contact populations of vaccinated index cases, which are based entirely on observational studies, are best explained by the vaccination status of the index cases, as there remain other and more plausible factors to explain the observed differences.

This interpretation is strongly supported by recent data on secondary transmission rates obtained during four COVID-19 waves among 50,973 index cases and 111,674 contacts. The authors considered the immune status of the index cases and their contacts and categorized the results accordingly. Vaccination of index cases reduced their infectiousness by 1.3% to 6.5% depending on the variant of SARS-CoV-2 and the timing of vaccination. A previous infection of index cases yielded a stronger reduction in their infectiousness (4.3% to 11.3%). Recent vaccination of the contact persons reduced their susceptibility to being infected significantly by 9.5% (delta variant) and 12.9% (alpha variant), whereas it increased susceptibility to be infected during the omicron wave significantly by 6.9%. Vaccination at least six months ago increased the susceptibility to being infected strongly during the omicron wave significantly by 13.3%. A previous infection provided consistently a stronger reduction in susceptibility to being infected compared to vaccination [86]. This is why the knowledge of the immune status of the contact persons is indispensable for the analysis of secondary transmission rates in the studies described above.

Another aspect with relevance to transmission may be a previous COVID-19 infection of the index case resulting in natural immunity. A previous COVID-19 infection reduced the duration of viral RNA detection from 26.4 to 13.7 days [55], a magnitude of reduction not observed among the fully vaccinated (Table 4). Household transmission studies

described a lower secondary attack rate from unvaccinated index cases with a previous infection compared to unvaccinated index cases without a previous infection (delta variant: 7.5% versus 21.5% [65]; omicron variant: 15.0% versus 30.8% [65]; omicron 40.9% versus 63.9% [67]). Importantly, the secondary attack rates from vaccinated index cases without a previous infection were consistently higher than those from unvaccinated index cases with a previous infection (delta variant: 20.2% versus 7.5% [65]; omicron variant: 29.5% versus 15.0% [65]; omicron 43.6% versus 40.9% [67]). Natural immunity has been described to be at least as effective as vaccination [87]. One of the reasons may be that natural immunity results in local tissue immunity (nose, mouth, saliva, lungs) as a first-line defense against SARS-CoV-2, which is not generated by intramuscular injection [87].

Only some of the included studies considered the time since vaccination as a factor to account for the waning of vaccine effectiveness over time with respect to our main outcomes [13,22,30,61]. In those, this information was incorporated in multivariate models or included in the stratified reporting of data. A decline in the effect of vaccination on the viral burden was shown in one study [22], while another study showed no effect of the time since vaccination on the viral burden [30]. Vaccine effectiveness against transmission was found to decline substantially after 12 weeks since the second dose of BNT162b2 or ChAdOx1 [13], while another study indicated that the protective effect of the full vaccination of the contacts with BNT162b2 or ChAdOx1 declined in a likewise manner within two to three months [61].

The phase 3 COVID-19 vaccine trials were carried out in 2020 and found a significant reduction in symptomatic COVID-19 cases among the vaccinated [88–91]. This may have led to the assumption that transmission of SARS-CoV-2 can be slowed down or prevented by the increasingly vaccinated population, as was then soon perpetrated in official campaigns in numerous countries during 2021. In one of the trials, however, it was already described that the proportion of asymptomatic COVID-19 was the same among the vaccinated (1.0%) and the unvaccinated (1.0%), suggesting that the proportion of asymptomatic viral carriers may not be affected by vaccination status [88]. The epidemiology of COVID-19 has changed in the meantime and the epidemiological relevance of the vaccinated population as a possible source of transmission is increasingly recognized [92]. Only a few countries provided epidemiological data on the COVID-19 incidence per 100,000 unvaccinated, vaccinated or boosted. The UK is one of them. The case rates were published in the weekly COVID-19 vaccine report until week 13 in 2022 [93]. It describes the unadjusted case rates among persons vaccinated with at least 3 doses per 100,000 and among unvaccinated persons also per 100,000 (between week 9 and week 12 2022, omicron period). The proportion of confirmed cases in each of the two groups indicates their epidemiological relevance as possible sources of transmission. Among the boosted population in the UK, the COVID-19 case rates per 100,000 were much higher compared to the unvaccinated (all age groups of $\geq$ 18 years) [93]. For example, in citizens of 30 to 39 years, 4325 cases per 100,000 were found among the boosted and 1086 among the unvaccinated [93]. Based on the UK data, the possible sources for COVID-19 transmission are overall more likely among the boosted compared to the unvaccinated population.

A limitation of this review may be that studies were only identified and extracted from PubMed. The inclusion of other sources may have added more relevant information on the topic, which may have resulted in an even broader compilation of evidence and a possible different overall result.

A further limitation of this work is that no randomized controlled trials on this topic were found. This is why the causality of the observed findings remains undetermined. Linked to this, it has to be considered that only a portion of the included studies controlled for potential confounders for differences in the Ct values such as age and sex [22] or the time between onset of illness and specimen collection [51] and potential confounders as the type of exposure and characteristics of contacts of an index person [13]. In most of the included studies, however, the outcomes were reported and compared as unadjusted estimates of the respective values of the viral load or secondary transmission.

5. Conclusions

At the beginning of the COVID-19 pandemic, it seemed possible and plausible to assume that COVID-19 vaccination has partially slowed down transmission by reducing the number of symptomatic cases. But considering the differences in the viral load, viral clearance and secondary attack rates between vaccinated and unvaccinated, and considering the limitations regarding the interpretation of the studies, it can be assumed that COVID-19 vaccination is unlikely to prevent a relevant proportion of transmissions to contact persons when taking into account the relevance of the immunological status of the contact population (rates of vaccination and previous infection) and the previously described higher adherence level to physical distancing, masking and hand hygiene guidelines in the vaccinated population.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/hygiene4010003/s1: Table S1: Summary of quality assessment based on the Newcastle-Ottawa quality assessment scale for cohort studies on viral load and duration of detection; Table S2: Summary of quality assessment based on the Newcastle-Ottawa quality assessment scale for cross-sectional studies on viral load and duration of detection; Table S3: Summary of quality assessment based on the Newcastle-Ottawa quality assessment scale for cohort studies on transmission and secondary attack rates; Table S4: Summary of quality assessment based on the Newcastle-Ottawa quality assessment scale for cross-sectional studies on transmission and secondary attack rates.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: The author is very grateful for the significant support provided by Andreas Hoffmann, who double-checked many of the extracted data and provided relevant aspects regarding the interpretation of the results.

Conflicts of Interest: The author has received an honorarium from Schülke & Mayr, Germany, outside the submitted work.

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