COVID-19 Evidence Update

17 February 2021

Symptoms, Vaccination and Infectiousness

Executive Summary

This review covers the available evidence on:

1. *Whether the degree of symptoms experienced by a COVID-19 case correlates to their degree of infectiousness and likelihood of spreading COVID-19 to others including their close contacts*
2. *The likely impact of COVID-19 vaccination on transmission potential in the community (i.e. 'sterilising immunity'), and whether the reduction in illness severity and symptoms is likely to impact on disease transmission risk.*

State of the evidence:

- There are multiple high quality systematic reviews investigating secondary attack rates (SAR) of SARS-CoV-2 and the predictors of infectiousness, including symptom status and severity of disease. Several studies report on specific symptoms (e.g. dry cough, fever) individually, but most studies differentiate cases based on presence/absence of any symptom (asymptomatic, pre-symptomatic, symptomatic – mild/moderate/severe).
- There are systematic reviews which report on viral RNA shedding, viral load and viable virus shedding (capable of transmission). Several of these studies also report on symptom status of cases.
- There are no peer-reviewed studies reporting on the impact of vaccination on transmission. There is one pre-print publication for each of Pfizer and Oxford-AstraZenica vaccines reporting early indications of predictors of infectiousness. Israel has a very high community vaccination rates and provides first real-world evidence of the impact of widespread vaccination.

Overview:

- Systematic reviews [1-5] indicate that secondary attack rates (transmission) are significantly higher:
    - For symptomatic cases than asymptomatic cases (e.g. 18.0% vs 0.7% in households);
    - As severity of COVID-19 increases;
    - Increased age (older adults vs other adults and adults vs children)
    - With household contact, especially spouses, and with prolonged close contact. Risk of transmissions with household and family contacts are magnitudes of risk higher than with other close contacts (e.g. 3 x times higher).
    - In indoor environments (e.g. 18.7 x higher [10]))
- Expectoration (expelling sputum) was associated with 4 times the odds of secondary infection in one study [18].
- Studies [13, 21] of cultivable (infectious or transmissible) virus indicate:
    - Risk of transmission is only present early and for a limited number of days post symptom onset (up to 9 days), duration may be extended with severity of illness and age.
    - However, viral shedding and positive PCR tests may persist.
    - There is a strong relationship between Ct value and ability to recover infectious (transmissible) virus.
- One pre-print study [28] (Oxford-AstraZenica) reports on the substantial impact of the vaccine on reduced PCR positivity in trial participants, indicating the vaccine may impact on transmission by reducing the number of infected people in the population.
- One pre-print study [31] reports on Ct rates of positive qPCR test in real world setting (Pfizer, Israel), pre- and (early) post-population vaccination roll out. Authors estimate vaccination is reducing viral load by 1.6 – 20 times with substantial potential to impact on transmission.

Conclusion: Presence of symptoms and severity correlate with infectiousness/transmission of COVID-19. Early data suggest that vaccination will reduce severity and viral load; indicating potential to reduce transmission.

Suggested citation: Miller C, Dono J, Wesselingh S. (2021) Symptoms, Vaccination and Infectiousness. SAHMRI, Adelaide, South Australia. https://www.sahmri.org/covid19/

1. Symptoms and transmission

Systematic reviews

[1] Madewell, Z. J., et al. (2020). Household Transmission of SARS-CoV-2: A Systematic Review and Meta-analysis. *JAMA network open,* 3(12), e2031756. 10.1001/jamanetworkopen.2020.31756

- Systematic review and meta-analysis of household transmission of SARS-CoV-2 compared with other coronaviruses. Meta-analysis of 54 studies with 77 758 participants. Search up to 19 October 2020.
- The estimated combined overall household and family secondary attack rate was **16.6%**, higher than observed secondary attack rates for SARS-CoV and Middle East respiratory syndrome coronavirus.
- Household secondary attack rates were increased:
    - from **symptomatic index cases (18.0%;** 95% CI, 14.2%-22.1%) than from **asymptomatic index cases (0.7%**; 95% CI, 0%-4.9%), although there were few studies in the latter group
    - to adult contacts (28.3%; 95% CI, 20.2%-37.1%) compared to child contacts (16.8%; 95% CI, 12.3%-21.7%)
    - to spouses (37.8%; 95% CI, 25.8%-50.5%) compared to other family contacts (17.8%; 95% CI, 11.7%-24.8%), and
    - in households with 1 contact (41.5%; 95% CI, 31.7%-51.7%) than in households with 3 or more contacts (22.8%; 95% CI, 13.6%-33.5%). (information was not available on household crowding).
    - One study restricted index cases to children (age <18 years), resulting in a substantially lower secondary attack rate of 0.5%.
- Secondary attack rates for household and family contacts were more than **3 times higher than for close contacts** (**4.8%;** 95% CI, 3.4%-6.5%; P < .001)
- Limitations: Most studies did not describe how co–primary index cases were handled or whether secondary infections could have been acquired from outside the household, both of which can inflate the empirical secondary attack rate.

[2] Koh, W. C., et al. (2020). What do we know about SARS-CoV-2 transmission? A systematic review and meta-analysis of the secondary attack rate and associated risk factors. *PloS one,* 15(10), e0240205. 10.1371/journal.pone.0240205

- Systematic review and meta-analyses of the secondary attack rate (SAR) in household and healthcare settings (35 studies in common with [1])
- Examined whether household transmission differed by symptom status of index case, adult and children, and relationship to index case January to July 2020 search
- 43 studies met the inclusion criteria for household SAR, 18 for healthcare SAR, and 17 for other settings. The **pooled household SAR was 18.1%** (95% CI: 15.7%, 20.6%), with significant heterogeneity across studies ranging from 3.9% to 54.9%.
- The risk of transmission varies by the **symptom status of the index case**. Based on three studies with available data, household SAR of symptomatic index cases were **significantly higher than asymptomatic and pre-symptomatic cases**, with a **relative risk (RR) of 3.23** (95% CI: 1.46, 7.14) (Fig 3 – see below). In all three studies, the household SAR of **symptomatic index cases (20.0%;** 95% CI: 11.4%, 28.6%) was higher than those of **asymptomatic ones (4.7%**; 95% CI: 1.1%, 8.3%) (Fig 4 – see below).
- **Adults** showed higher susceptibility to infection than **children** (RR: 1.71; 95% CI: 1.35, 2.17). **Spouses** of index cases were more likely to be infected compared to other household contacts (RR: 2.39; 95% CI: 1.79, 3.19). In **healthcare settings**, SAR was estimated at 0.7% (95% CI: 0.4%, 1.0%).

Fig 3

Forest plot of household transmission risk by symptom status of index case.

RR is the estimated risk ratio, with 95% confidence intervals (CI). I-squared is the percentage of between-study heterogeneity that is attributable to variability in the true effect, rather than sampling variation.

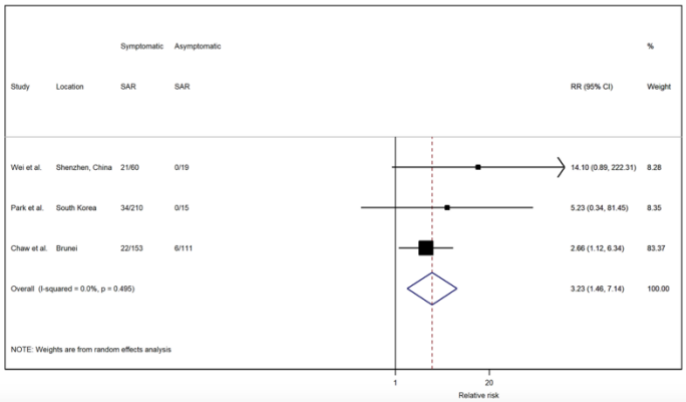
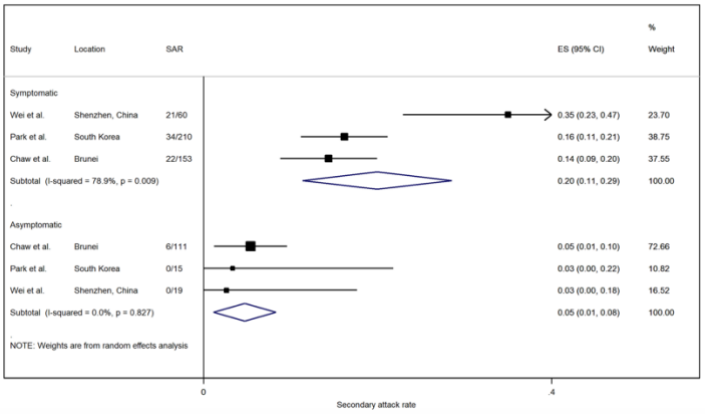


Fig 4

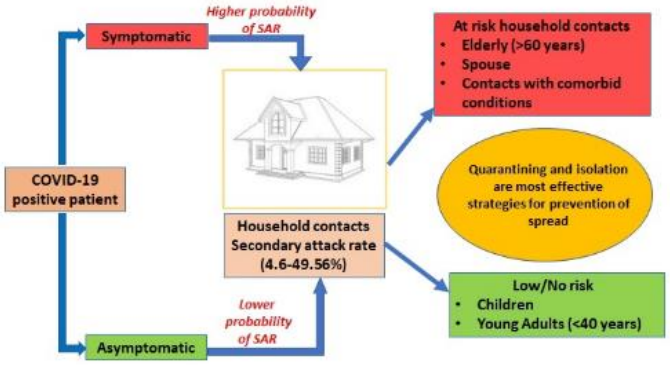
Forest plot of household secondary attack rates (SAR) by symptom status of index case.

ES is the estimated SAR, with 95% confidence intervals (CI). I-squared is the percentage of between-study heterogeneity that is attributable to variability in the true effect, rather than sampling variation.



[3] Shah, K., et al. (2020). Secondary attack rate of COVID-19 in household contacts: a systematic review. *QJM: monthly journal of the Association of Physicians*, 113(12), 841–850. 10.1093/qjmed/hcaa232

- Systematic review of household transmission including 13 eligible studies (7 of which were included in Madewell et al. [1] above)
- **Symptomatic status of the index case** emerged to be a critical factor, with **very low transmission probability during asymptomatic phase**.



Diagrammatical presentation of household transmission of COVID-19

[4] Thompson, et al. (2020). Report 38: SARS-CoV-2 setting-specific transmission rates: a systematic review and meta-analysis. Imperial College London. (self-published)

- Systematic review and meta analysis. Search up to 6 July 2020. 45 studies (26 studies in common with [1])
- Estimates of **SAR for asymptomatic index cases were approximately two thirds of those for symptomatic index (3.5% vs. 12.8%**, p<0.001).
- Households showed the highest transmission rates, with pooled SAR estimate of 21.1% (95% CI: 17.4%-24.8%). Household SAR estimates were significantly higher where the duration of household exposure exceeded 5 days compared with exposure of 5 days or less.
- Attack rates related to familiar and prolonged close contacts, such as social events with family and friends were higher than those related to low-risk casual contacts, such as strangers (SAR of 5.9%, 95% CI: 3.8%-8.1% vs. 1.2%, 95% CI: 0.3%-2.1%).

- The authors found moderate evidence for less transmission both from and to individuals under 20 years of age in the household context, but this difference is less evident when examining all settings.
- There was limited data to allow exploration of transmission patterns in workplaces, schools, and care-homes

Table 1 Summary table of the pooled SAR and R_{obs} for the exposure locations considered in this study. Where values are missing there was not enough data available to estimate a pooled value.

Setting	Pooled SAR	95% Confidence Interval	Pooled R_{obs}	95% Confidence Interval
Households	21.1%	17.4% - 24.8%	0.96	0.67 - 1.32
Social gatherings with family and friends	5.9%	3.8% - 8.1%	0.38	0.18 - 0.64
Travel	5.0%	0.3% - 9.8%	-	-
Healthcare	3.6%	1.0% - 6.9%	1.18	0.65 - 2.04
Workplace	1.9%	0.0% - 3.9%	-	-
Casual close contacts	1.2%	0.3% - 2.1%	-	-

Other Reviews

[5] Cevic M et al. (2020). Severe Acute Respiratory Syndrome Coronavirus 2 (SARS- CoV-2) Transmission Dynamics Should Inform Policy. *Clinical Infectious Diseases.* 10.1093/cid/ciaa1442

- Narrative review, covering a range of factors that influence transmissions dynamics.
- Host Factors: Contact tracing and outbreak investigations suggest that many people with SARS-CoV-2 either do not contribute to onward transmission or have minimal potential to do so, and a large number of secondary cases are often caused by a small number of infected patients. While this may also be due to contact pattern and environmental factors, **host factors strongly influence this variation**; **individual variation in infectiousness is an expected feature of superspreading events**.

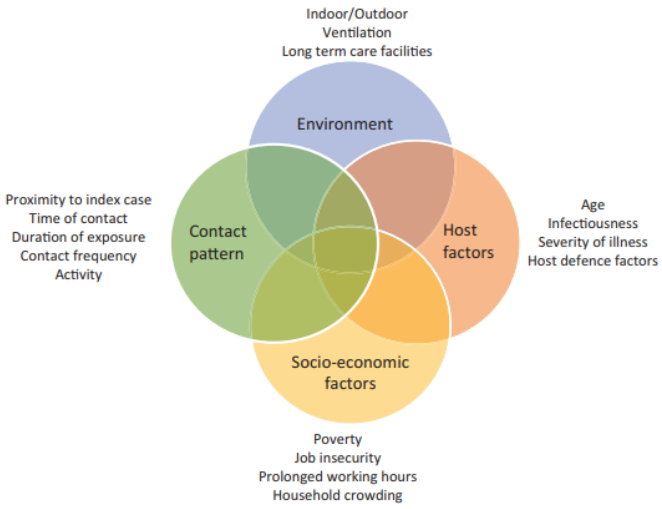


Figure 1. Factors influencing transmission dynamics. Transmission depends on several factors, including contact pattern (duration of contact, gathering, proximity, activity), environment (outdoor, indoor, ventilation), host-related infectivity/susceptibility pattern (ie, viral load in relation to disease course, severity of illness, age), and socioeconomic factors (ie, crowded housing, job insecurity, poverty). Virus infectivity and differences between other viruses and host immune factors are not discussed in this review. (This figure was created by the authors based on available literature about SARS-CoV-2 transmission dynamics.) Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

- In a systematic review of studies published up to 6 June 2020, the authors found that viral load peaks early in the disease course, with the highest viral loads observed from symptom onset to day 5, indicating a high level of infectiousness during this period (Figure 2 – see below).

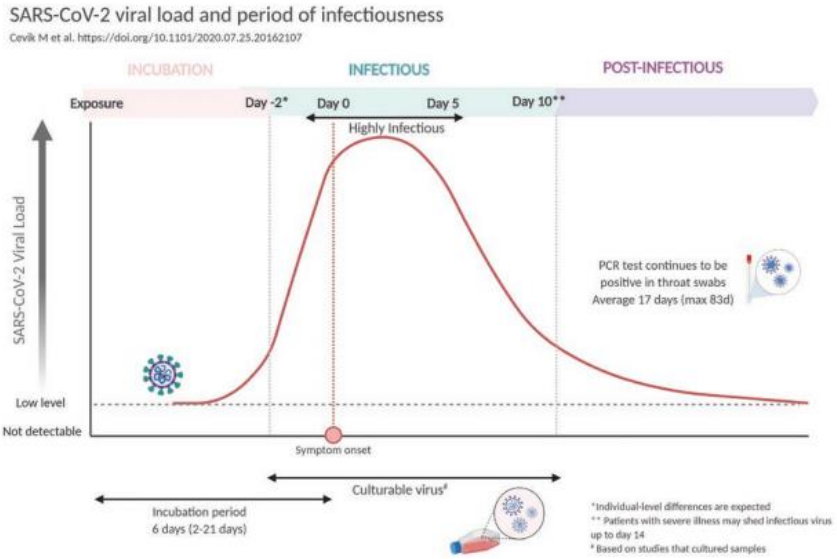


Figure 2. SARS-CoV-2 viral load dynamics and period of infectiousness. Incubation period (time from exposure to symptom onset) of 6 days (2–21 days), peak viral load levels documented from day 0 (symptom onset) to day 5, infectious period starts before symptom onset up to 10 days (this may be extended in patients with severe illness), and RNA shedding continues for a prolonged period of time but culturable virus has been identified up to day 9 of illness. (This figure was created by the authors on Biorender, https://biorender.com based on available literature about SARS-CoV-2 viral load dynamics.) Abbreviations: max, maximum; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

- Transmission events are estimated to occur in a short window, likely a few days prior to and following symptom onset
- A contact tracing study that followed up 2761 contacts of 100 confirmed COVID-19 cases demonstrated that infection risk was higher if the exposure occurred within the first 5 days after symptom onset, with no secondary cases documented after this point. This understanding indicates that **viral dose plays an important role in transmission dynamics**.
- Early viral load peak also explains efficient community SARS-CoV-2 spread in contrast to SARS-CoV-1 and MERS-CoV (where peak viral load is in the second week after symptom onset)
- **Symptoms and severity of illness appear to influence transmission dynamics** as well. People with symptoms appear to have a higher secondary attack rate compared with presymptomatic and asymptomatic index cases (those who develop no symptoms throughout the illness).
- While **asymptomatic patients** can transmit the virus to others, the findings from 9 studies in a systematic review, including studies published up to 3 July 2020, found **secondary attack rates of 0% to 2.8%,** compared with secondary attack rates of 0.7% to 16.2% in symptomatic cases in the same studies, suggesting asymptomatic index cases transmit to fewer secondary cases [6].
- Another systematic review that included studies published up to 10 June 2020 similarly found a reduced risk of transmission for asymptomatic versus symptomatic cases (.35; 95% CI, .10–1.27) and presymptomatic versus symptomatic cases (.63; 95% CI, .18–2.26) [7].
- There are also **differences in attack rates based on symptom severity**. In [8] the secondary attack rate was **3.5% for those with mild symptoms**, **5.7% for those with moderate symptoms**, and **4.5% for those with severe symptoms** (based on the China Centers for Disease Control guidelines).
- In a contact tracing study, contacts of severe cases were more likely to develop severe infections themselves [9].

- Environmental factors
    - Findings from contact-tracing studies in Japan suggest an **18.7-fold higher risk of transmission indoors compared with outdoor environments [10].**
    - **Close contacts with the highest risk of transmission** are typically **friends, household members, and extended family**, with a secondary attack rate that ranges from 4% to 35%
- Clusters and superspreading events
    - Clusters have become a prominent characteristic of SARSCoV-2, which distinguishes it from seasonal influenza. This emphasises that large clusters and superspreading events may be the driver of the majority of infections, just as they were for SARS-CoV-1 in 2002–2003. For instance, during the 2003 SARS-CoV-1 outbreak, over 70% of infections were linked to superspreading events in Hong Kong and Singapore.
    - **Hallmarks for superspreading events** include a **combination of factors**, typically a **highly infectious individual(s)** gathered with other individuals in **enclosed** and **crowded environments**.
    - The **modelling suggests** that **several independent introductions might be needed** before a COVID-19 outbreak eventually takes off, meaning often these large outbreaks occur when multiple infected persons are introduced to the environment, as seen in nursing homes and nightclubs.

[11] Fung, H. F., et al. (2020). The Household Secondary Attack Rate of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): A Rapid Review. *Clinical Infectious Diseases*. 1-8.

- Gathered and analyzed data from 22 published and pre-published studies from 10 countries (20 291 household contacts), through 2 September 2020.
- The overall pooled random-effects estimate of the household SAR was 17.1% (95% confidence interval [CI], 13.7–21.2%). In study-level, random-effects meta-regressions stratified by testing frequency (1 test, 2 tests, >2 tests), SAR estimates were 9.2% (95% CI, 6.7–12.3%), 17.5% (95% CI, 13.9–21.8%), and 21.3% (95% CI, 13.8–31.3%), respectively. Repeated testing yields increased SAR.
- Household SARs tended to be higher among older adult contacts and among **contacts of symptomatic cases**. (See Table 2 below)

Table 2. Household Secondary Attack Rates by Index Case Symptoms

		Household Secondary Attack Rate, % (95% Confidence Interval)		
		By index case symptoms		
Study	Sample Size	Symptomatic	Presymptomatic	Asymptomatic
Chaw et al [19] (Brunei)	264	14.4 (8.8–19.9)	6.1 (.3–11.8)	4.4 (0–10.5)
Park et al [15] (Seoul, South Korea)	225	16.2 (11.6–22.0)	0 (0–28.5)	0 (0–60.2)
Zhang et al [9] (Guangzhou, China)	62	…	16.1 (9.0–27.2)	…

Exact binomial confidence intervals were computed for estimates reported without uncertainty.

[12] Walsh, K. A., et al. (2020). The duration of infectiousness of individuals infected with SARS-CoV-2. *The Journal of Infection,* 81(6), 847–856. 10.1016/j.jinf.2020.10.009

- Rapid review. January to August 2020. 15 relevant studies, including 13 virus culture and 2 contact tracing studies
    - SARS-CoV-2 infection is primarily diagnosed based on detecting the presence of viral RNA by molecular testing, usually by reverse transcription polymerase chain reaction (RT-PCR) in a specimen from an individual's respiratory tract. However, detection of viral RNA does not necessarily mean that a person is infectious, i.e. that they are capable of transmitting the virus to another person.
    - Several factors determine viral transmission risk: these include whether a virus is still replication-competent (or viable); the amount of replicative virus; the presence of symptoms, such as a cough which can spread infectious droplets; the individual's local mucosal immune response to the virus; and the behavioural and environmental factors associated with the infected individual and their contacts.
- Objectives: To summarise the evidence on the duration of infectiousness of individuals in whom SARS-CoV-2 ribonucleic acid is detected. Research question: *What is the duration of infectiousness in those in whom SARS-CoV-2 RNA is detectable?*
- Thirteen of these studies attempted to culture SARS-CoV-2 and 2 studies conducted contact tracing of case contact pairs
- Both contact tracing studies, when close contacts were first exposed greater than 5 days after symptom onset in the index case, found no evidence of laboratory-confirmed onward transmission of SARS-CoV-2. In 1 of the contact tracing studies it was reported that **no onward transmission occurred from the 9 asymptomatic patients** included, despite 91 close contacts being identified for these patients.
- All 15 studies reported results in relation to time since symptom onset.
    - **No studies were found** that reported **duration of infectiousness in asymptomatic individuals** (i.e. patients that never develop symptoms). No information was provided from these studies that could be used to inform the potential duration of infectiousness of asymptomatic patients. Results from serial sampling and attempted virus culture in asymptomatic patients were not reported.
    - COVID-19 patients with mild-to-moderate illness are highly unlikely to be infectious beyond 10 days of symptoms. However, evidence from a limited number of studies indicates that patients with severe-to-critical illness or who are immunocompromised, may shed infectious virus for longer.
- Viral load and duration of infectiousness –
    - The assays used to detect SARS-CoV-2 RNA could be regarded as semi-quantitative, using the cycle threshold (Ct) value as a surrogate marker of the SARS-CoV-2 viral load. Lower Ct values indicate a higher viral load.
    - Of the 6 included studies that examined the relationship between viral load and culture of SARS-CoV-2, all 6 found an inverse correlation.
    - Singanayagam et al. [13] (N = 324 samples) estimated that the **probability of successfully culturing SARS-CoV-2 from samples with a Ct value greater than 35 was 8.3%** (95% CI: 2.8%–18.4%).
    - Basile et al. [14] (N = 234 samples) concluded that **any clinical sample with a Ct value of ≥37 was not indicative of replicative (or potentially transmissible) virus**. Bullard et al. [15] (N = 90 samples) estimated that for every 1 unit increase in Ct value, the odds of culturing SARS-CoV-2 decreased by 32%.
- Three studies presented graphical estimates of the probability of culturing SARS-CoV-2 versus the number of days since symptom onset (Figure 3)
- Estimates of the percentage of samples with replicative SARS-CoV-2 were presented for each of days 7 to 15 post symptom onset, and are reproduced in Table 3. At 10 days post symptom onset, the probability of

a sample with replicative SARS-CoV-2 was 6% (95% CI 0.9–31.2); however, these data carry a high degree of uncertainty, as shown by the wide confidence intervals.

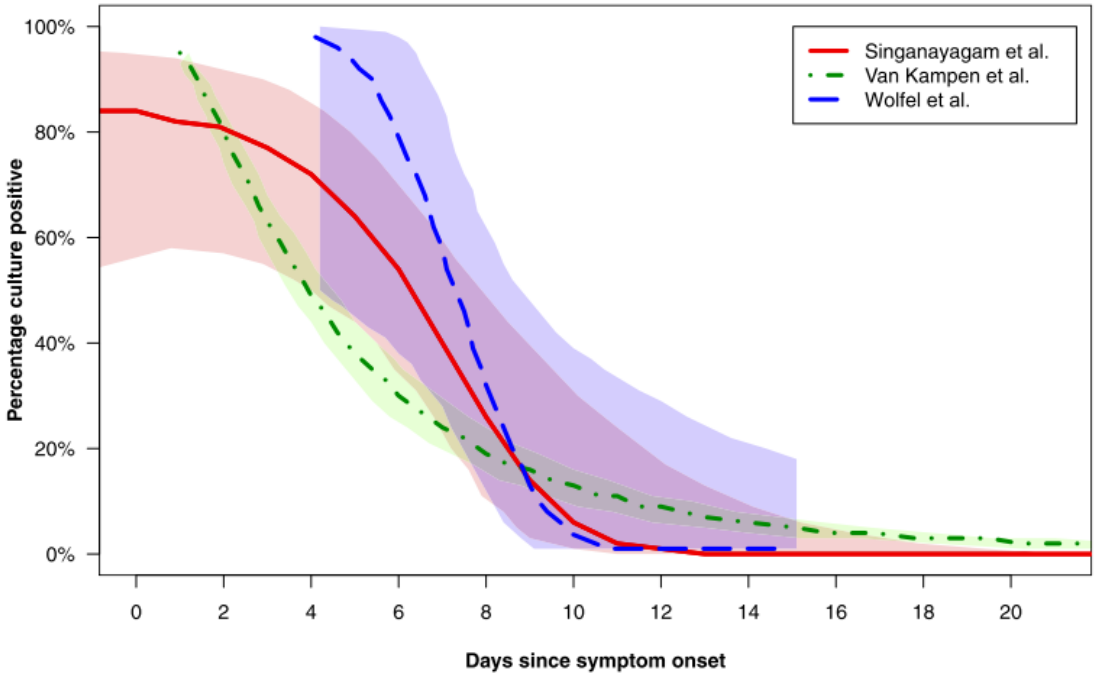


Fig. 3. Probability curves presented in 3 studies (Singanayagam et al., van Kampen et al., Wölfel et al.) which attempted to model the probability of successful virus culture versus duration of days of symptoms.[31–33] *Curves are presented with adaptation from the original presentation in the respective manuscripts in order to provide information for the first 20 days post symptom onset and to permit visual comparison of curves via overlay on a single plot. Lines (solid, dashed or dotted) depict estimated probability of positive virus culture* versus *days post symptom onset, while shaded areas depict 95% confidence intervals around these estimates.*

Table 3
Estimated percentage of samples with infectious SARS-CoV-2 for days 7–15 after symptom onset (adapted from Singanayagam et al.).

Day post symptom onset	Estimated% culture positive (95% CI)		Observed number of samples culture positive	Observed number of samples tested
7	40.1	(22.8 - 60.4)	10	14
8	25.8	(11.0 - 49.4)	9	33
9	13.7	(3.7 - 39.6)	10	34
10	6.0	(0.9 - 31.2)	6	23
11	2.2	(0.2 - 23.9)	1	6
12	0.7	(0.0 - 17.9)	1	3
13	0.2	(0.0 - 13.1)	0	4
14	0.03	(0.0 - 9.4)	0	2
15	0.006	(0.0 - 6.7)	0	2
			Total: 37	Total: 121

- While unpublished, CDC additionally presented a Kaplan-Meier analysis of time to a negative culture SARS-CoV2 following illness onset. This analysis represents an expanded analysis of the results reported by Kujawski et al. [16], including a greater number of patients from the same setting (n = 14 versus n = 12 (9 of whom had samples collected for virus culture)), though the total number of samples tested is not known. CDC reported that the probability of successful SARS-CoV-2 culture fell from 50% at day 4 after illness onset, to 20% at day 8, and approached 0% after day 9.

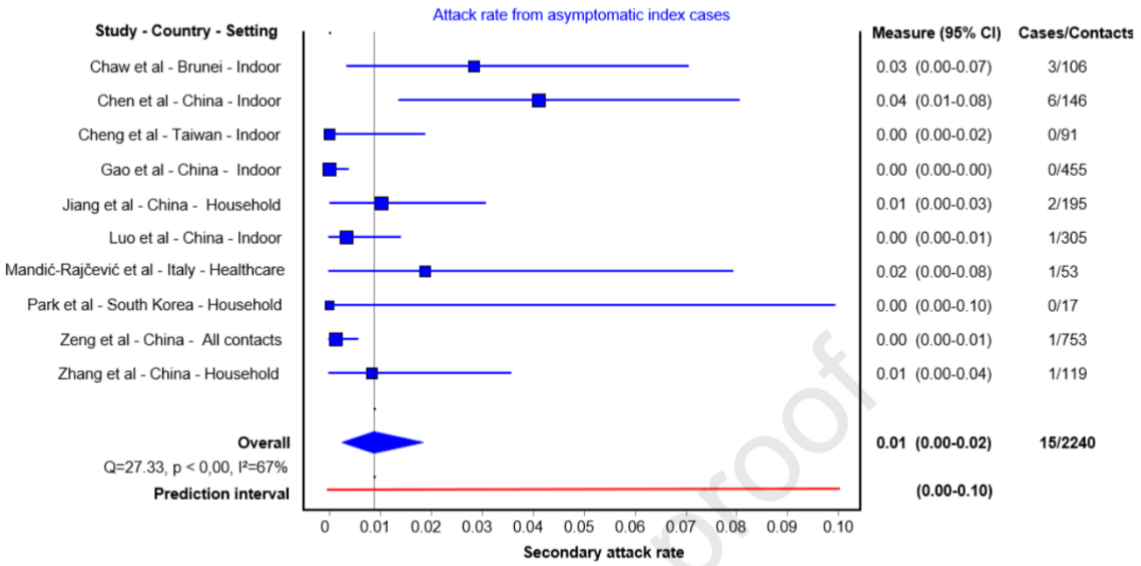
[6] Qiu, X. et al. (2021). Defining the role of asymptomatic and pre-symptomatic SARS-CoV-2 transmission - a living systematic review. Clinical Microbiology and Infection, S1198-743X(21)00038-0. 10.1016/j.cmi.2021.01.011

- "Living review" aims to critically appraise available data about secondary attack rates from people with asymptomatic, pre-symptomatic and symptomatic SARS-CoV-2 infection.
- One of the barriers to understanding the role of asymptomatic transmission is the lack of consistency in case definitions. While symptom severity exists on a spectrum, individuals infected with SARS-CoV-2 can be miscategorized as asymptomatic, when they have milder or atypical symptoms leading to overestimation of the proportion without symptoms. Study thoroughly interrogates definitions of symptomatic.
- 80 studies, living systematic review including of studies published up to 6 June 2020
- Summary secondary attack rate
    - estimates were 1% (95% CI: 0%-2%) with a prediction interval of 0-10% for asymptomatic index cases in 10 studies,
    - 7% (95% CI: 3%-11%) with a prediction interval of 1- 40% for pre-symptomatic cases in 11 studies and
    - 6% (95% CI: 5%-8%) with a prediction interval of 5- 38% for symptomatic index cases in 40 studies.
    - The highest secondary attack rates were found in contacts who lived in the same household as the index case.
    - Other activities associated with transmission were group activities such as sharing meals or playing board games with the index case, regardless of the disease status of the index case.
- Conclusion **Asymptomatic patients** can transmit SARS-CoV-2 to others, but our findings indicate that such individuals are responsible for **fewer secondary infections than people with symptoms.**
- Found that cases with asymptomatic people had a shorter duration of RNA shedding than symptomatic individuals
- In this systematic review, we found that index cases with symptoms had a higher secondary attack rate compared with truly asymptomatic index cases. While there is a need to better understand this difference, it may be due to shorter duration of infectiousness.

354 **Table 1: Transmission from truly asymptomatic index cases**

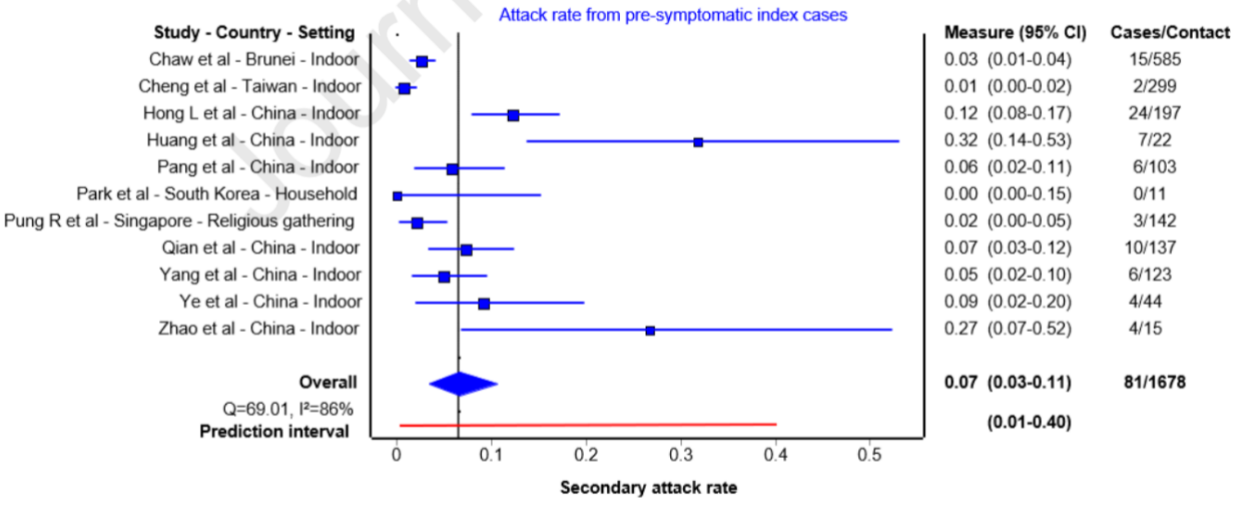
	Index Cases	Environment	Number of contacts	Number of Secondary cases	Asymptomatic SAR (95% CI)	Symptomatic SAR (95% CI)
Chaw et al. * [13]	3	Household Non-household	106	3	2.8% (0.06, 8.0)	14.4% (8.8, 19.9) 0.7% (0.01, 1.3)
Chen Y et al. [29]	30	Household Non-household	146	6	4.1% (1.7, 9.1)	6.3% (5.3, 7.5)
Cheng et al.[26]	9	Non-household	91	0	0% (0.0, 4.1)	Mild 3.76 (1.1-12.8) Severe 3.99 (1.0-15.8)
Gao et al.[25]	1	Household and healthcare	455	0	0% (0.0, 0.08)	
Jiang et al.[22]	3	Household	195	2	1% (0.1, 3.7)	
Luo et al. [28]	8	Household and non-household	305	1	0.33% (0.0, 1.8) OR (0.29 (0.04, 2.2))	Mild 3.3% (OR 0.48 (0.28, 0.82) Mod 5.6% (OR 1.0) Sev 6.2% (OR 1.19 (0.7, 2.1)
Mandić-Rajčević et al.[23]	1	Healthcare	53	1	1.9% (0.0,10.0)	
Park et al.[24]	4	Household	17	0	0% (0.0, 19.5)	16.2 % (11.6,22.0)
Zeng et al. [27]		All contacts	753	1	0.13% (0.0, 0.7)	2.02% (1.8, 2.3)
Zhang et al.[6]	12	Household	119	1	0.8% (0.0, 4.6)	Mild 3.5% (1.5, 8.0) Mod 5.7% (2.5, 12.8) Severe 4.5% (0.8, 21.8)

Figure 2: Secondary attack rates from asymptomatic index cases to their contacts



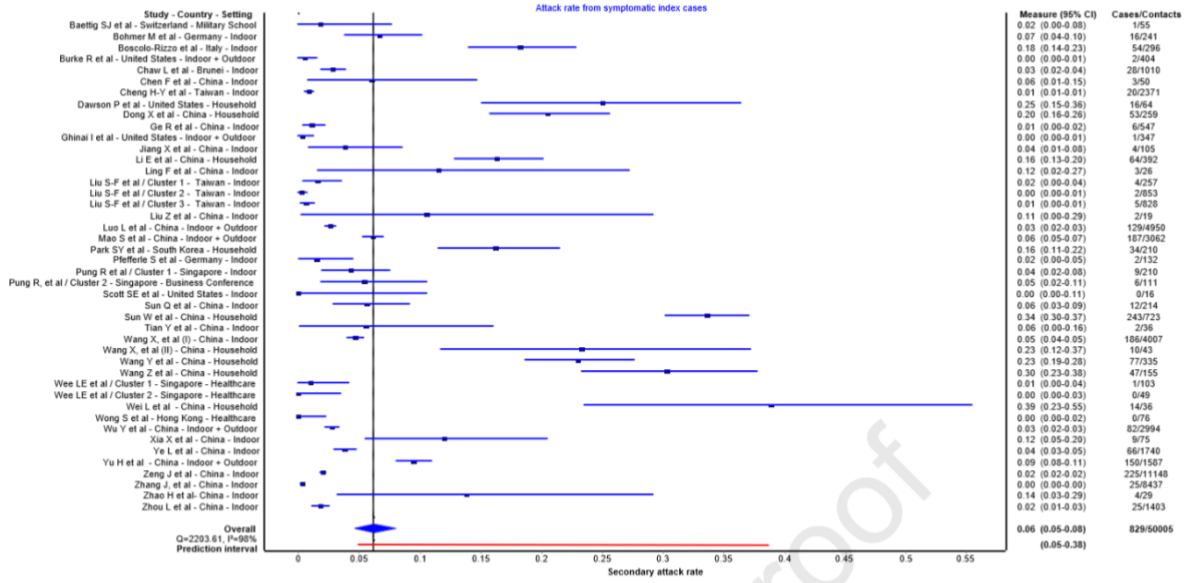
For each study the secondary attack rate is reported with its 95% CI.
A prediction interval at the bottom of the forest is depicted.

Figure 3: Secondary attack rates from pre-symptomatic index cases to their contacts



For each study the secondary attack rate is reported with its 95% CI.
A prediction interval at the bottom of the forest is depicted.

Figure 4: Secondary attack rates from symptomatic index cases to their contacts



For each study the secondary attack rate is reported with its 95% CI.
A prediction interval at the bottom of the forest is depicted.

[17] Byambasuren, O. et al. (2020). Estimating the extent of asymptomatic COVID-19 and its potential for community transmission: systematic review and meta-analysis. *Official Journal of the Association of Medical Microbiology and Infectious Disease Canada*, 5(4), 223-234.

- Although the rate of asymptomatic COVID-19 cases has received considerable attention, we found only 13 studies that provided an adequate sample frame and follow-up to ascertain a valid estimate of the proportion of asymptomatic cases. The combined estimate of the asymptomatic proportion was 17% (95% CI 14% to 20%) but had considerable heterogeneity (I^2 = 84%) and a 95% prediction interval that ranged from 4% to 52%. There was no clear difference in the proportions between aged care and non-aged care studies. Only 5 of the 13 studies provided data on transmission rates from asymptomatic cases. The transmission risk from asymptomatic cases appeared to be lower than that of symptomatic cases, but there was considerable uncertainty in the extent of this (RR 0.58; 95% CI 0.335 to 0.994, p = 0.047).

Primary Studies (selected)

[8] Zhang, W., et al. (2020). Secondary transmission of coronavirus disease from presymptomatic persons, China. *Emerging infectious diseases*, 26(8), 1924.

- Explored the secondary attack rate in different types of **contact with persons presymptomatic** for coronavirus disease (COVID-19).
- Analyzed contact-tracing surveillance data collected during Jan 28–Mar 15, 2020, in Guangzhou, China.
- **Close contacts of asymptomatic index case-patients had the lowest SAR, 0.8%**, but the SAR was **3.5% for those with mild symptoms**, **5.7% for those with moderate symptoms**, and 4**.5% for those with severe symptoms**.*
    - (*Moderate symptoms included fever, respiratory symptoms, and radiographic evidence of pneumonia. Severe symptoms included breathing rate >30/min; oxygen saturation level <93% at rest; oxygen concentration level PaO2/FiO2 <300 mmHg (1 mmHg = 0.133kPa); lung infiltrates >50% within the past 24–48 h; respiratory failure requiring mechanical ventilation; septic shock; or multiple organ dysfunction or failure. All other symptomatic cases were classified as mild.)
- The overall SAR was 3.3% (95% CI 1.9%–5.6%). The SAR among household contacts was 16.1% and was 1.1% for social contacts, and 0 for workplace contacts.
- The probability of infection increased substantially among close contacts who shared living environments or had frequent contact with an index case-patient.
- Authors noted that **persons with asymptomatic infections appeared to be less effective in transmitting the virus**.

Table. Characteristics of and secondary attack rates among 369 close contacts of persons with presymptomatic coronavirus disease 2019, China*

Variable	No. contacts	No. infected	Attack rate, % (95% CI)	Relative risk (95% CI)
Sex				
M	217	5	2.3 (0.1–5.2)	Referent
F	152	7	4.6 (2.2–8.9)	2.1 (0.6–6.6)
Age				
≤17	46	2	4.3 (1.2–14.5)	Referent
18–30	104	3	2.9 (1.0–8.1)	0.7 (0.1–4.1)
31–40	72	1	1.4 (0.2–7.4)	0.4 (0.03–3.5)
41–50	68	1	1.5 (0.3–7.9)	0.4 (0.03–3.7)
51–60	54	3	5.6 (1.9–15.1)	1.3 (0.2–8.1)
≥61	25	2	8.0 (1.4–27.5)	1.9 (0.3–14.5)
Index case-patient status*				
Asymptomatic	119	1	0.8 (0.2–5.6)	Referent
Mild symptoms	141	5	3.5 (1.5–8.0)	4.3 (0.5–37.7)
Moderate symptoms	87	5	5.7 (2.5–12.8)	7.2 (0.8–62.7)
Severe symptoms	22	1	4.5 (0.8–21.8)	5.6 (0.3–93.4)
Contact mode				
Social interaction with friends or relatives	66	1	1.5 (0.3–8.1)	Referent
Lived together	62	10	16.1 (9.0–27.2)	12.5 (1.6–100.8)
Worked together	119	0	0	0
Social interaction with strangers	122	1	0.8 (0.2–4.9)	0.5 (0.03–8.7)
Contact frequency†				
Rare	149	1	0.7 (0.1–3.7)	Referent
Moderate	159	1	0.6 (0.1–3.5)	0.9 (0.1–15.1)
Frequent	61	10	16.4 (9.2–27.6)	29.0 (3.6–232.3)

*Status as of March 30, 2020, based on the person's clinical course assessed by a physician. Moderate symptoms included fever, respiratory symptoms, and radiographic evidence of pneumonia. Severe symptoms included breathing rate ≥30/min; oxygen saturation level ≤93% at rest; oxygen concentration level PaO_2/FiO_2 ≤300 mmHg (1 mmHg = 0.133kPa); lung infiltrates >50% within the past 24–48 h; respiratory failure requiring mechanical ventilation; septic shock; or multiple organ dysfunction or failure. All other symptomatic cases were classified as mild.
†Rare contact was defined as contacted with index cases <2 times during 2 days preceding confirmation of infection. Moderate contact was defined as contacted with index cases 3–5 times during 2 days preceding confirmation of infection. Frequent contact was defined as contacted with index cases ≥5 times during 2 days preceding confirmation of infection.

[18] Luo, L., et al. (2020). Contact Settings and Risk for Transmission in 3410 Close Contacts of Patients With COVID-19 in Guangzhou, China : A Prospective Cohort Study. *Annals of internal medicine*, 173(11), 879–887. 10.7326/M20- 2671

- Prospective cohort study. Close contacts of persons infected with SARS-CoV-2 in Guangzhou, China.
- 3410 close contacts of 391 index cases were traced between 13 January and 6 March 2020. Data on the setting of the exposure, reverse transcriptase polymerase chain reaction testing, and clinical characteristics of index and secondary cases were collected.
- The **secondary attack rate increased with the severity of index cases**, from **0.3%** (CI, 0.0 to 1.0%) **for asymptomatic** to **3.3%** (CI, 1.8% to 4.8%) **for mild**, 5.6% (CI, 4.4% to 6.8%) **for moderate**, and **6.2%** (CI, 3.2% to 9.1%) for **severe or critical cases**. **Index cases with expectoration** were associated with higher risk for secondary infection (13.6% vs. 3.0% for index cases without expectoration; OR, 4.81 [CI, 3.35 to 6.93]).

Table 3. Exposure Settings and Risk for Transmission Among 3410 Close Contacts

Characteristic	Secondary Cases, *n* (% [95% CI])	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*
Age group (*n* = 3410)			
0–17 y (*n* = 357)	14 (3.9 [1.9–5.9])	1.42 (0.77–2.59)	0.78 (0.41–1.50)
18–44 y (*n* = 1784)	50 (2.8 [2.0–3.6])	1.00 (reference)	1.00 (reference)
45–59 y (*n* = 818)	29 (3.6 [2.3–4.8])	1.27 (0.80–2.03)	1.16 (0.70–1.92)
≥60 y (*n* = 451)	34 (7.5 [5.1–10.0])	2.83 (1.81–4.43)	2.34 (1.39–3.97)
Sex (*n* = 3410)			
Male (*n* = 1799)	56 (3.1 [2.3–3.9])	1.00 (reference)	1.00 (reference)
Female (*n* = 1611)	71 (4.4 [3.4–5.4])	1.44 (1.00–2.05)	1.21 (0.82–1.78)
Exposure setting (*n* = 3410)			
Household (*n* = 1015)	105 (10.3 [8.5–12.2])	1.00 (reference)	1.00 (reference)
Public transportation (*n* = 818)	1 (0.1 [0.0–0.4])	0.01 (0.00–0.08)	0.01 (0.00–0.09)
Health care settings (*n* = 679)	7 (1.0 [0.3–1.8])	0.09 (0.04–0.20)	0.13 (0.05–0.32)
Entertainment venues or workplaces (*n* = 875)	11 (1.3 [0.5–2.0])	0.11 (0.06–0.21)	0.12 (0.06–0.22)
Multiple settings (*n* = 23)†	3 (13.0 [0.0–26.8])	1.30 (0.38–4.45)	1.20 (0.32–4.58)
Severity of index cases (*n* = 2610)‡			
Asymptomatic (*n* = 305)	1 (0.3 [0.0–1.0])	0.06 (0.01–0.47)	0.37 (0.04–3.79)
Mild (*n* = 576)	19 (3.3 [1.8–4.8])	0.54 (0.32–0.89)	0.56 (0.33–0.94)
Moderate (*n* = 1469)	82 (5.6 [4.4–6.8])	1.00 (reference)	1.00 (reference)
Severe or critical (*n* = 260)	16 (6.2 [3.2–9.1])	1.14 (0.67–1.94)	1.04 (0.57–1.90)
Symptoms in index cases (*n* = 1813)§			
Fever			
No (*n* = 430)	14 (3.3 [1.6–4.9])	1.00 (reference)	1.00 (reference)
Yes (*n* = 1383)	92 (6.7 [5.3–8.0])	2.90 (1.73–4.86)	1.78 (1.01–3.13)
Dry cough			
No (*n* = 726)	39 (5.4 [3.7–7.0])	1.00 (reference)	1.00 (reference)
Yes (*n* = 1087)	67 (6.2 [4.7–7.6])	1.37 (0.95–1.98)	1.15 (0.76–1.73)
Expectoration			
No (*n* = 1329)	40 (3.0 [2.1–3.9])	1.00 (reference)	1.00 (reference)
Yes (*n* = 484)	66 (13.6 [10.6–16.7])	4.81 (3.35–6.93)	4.39 (2.92–6.61)
Fatigue			
No (*n* = 1366)	76 (5.6 [4.4–6.8])	1.00 (reference)	1.00 (reference)
Yes (*n* = 447)	30 (6.7 [4.4–9.0])	1.15 (0.77–1.72)	0.78 (0.52–1.19)
Myalgia			
No (*n* = 1517)	88 (5.8 [4.6–7.0])	1.00 (reference)	1.00 (reference)
Yes (*n* = 296)	18 (6.1 [3.4–8.8])	1.09 (0.67–1.77)	0.88 (0.52–1.50)

* Adjusted for age, sex, exposure settings, severity of index cases, and symptoms in index cases.
† Includes close contacts with more than 1 exposure setting (household, public transportation, health care setting, workplaces and entertainment venues).
‡ A total of 800 close contacts could not be categorized by severity of index cases owing to lack of data.
§ A total of 1597 close contacts could not be categorized by symptoms in index cases owing to lack of data.

[19] Kuwelker, K., et al. (2020). High attack rates of SARS-CoV-2 infection through household-transmission: a prospective study. *medRxiv preprint.*

- Prospective case-ascertained study was conducted in Bergen, Norway.
- RT-PCR confirmed cases tested at the clinic during the start of the local outbreak (28th February–4th April 2020), and their household members were eligible for the study.
- 112 households (291 participants). Collected demographic and clinical data from index cases and household members. Sera were collected 6-8 weeks after index case symptom onset, to measure **SARS-CoV-2-specific antibodies.**
- Current testing for SARS-CoV-2 relies on amplification of the viral RNA genome from respiratory specimens, which can generally only be detected during acute infection. Whereas serological assays can determine exposure or infection over a longer time period, and are less dependent on the timing of sampling.
- To calculate the attack rate, authors measured SARS-CoV-2-specific IgG in household members using the spike protein ELISA to confirm seroconversion.
- The presence of any COVID-19 symptoms among household contacts significantly increased the likelihood of infection ($p<0.01$), with seroconversion occurring in 56% of symptomatic and 16% of asymptomatic **household members. The risk of household transmission was higher when the index** case had **fever** or **dyspnoea** during acute illness but **not associated with cough**.
- Authors comment that: It may appear **counterintuitive that cough in the index case was not a significant risk** factor for transmission. A likely explanation for this would be that, due to widespread awareness of this transmission route, cough would trigger household-members to use precautions such as distancing and mask use, while a person with other symptoms such as fever and dyspnoea may not be perceived as equally infectious.
- The **risk of transmission was highest from index cases with dyspnoea, fever and high titres of neutralising antibodies, all potential surrogate markers for severity of disease**, illustrating that transmission risk increases with the need for close care.
- The overall **attack rate in households (as measured by seroconversion)** was 45%, with no significant gender difference. Attack rates varied between 25% and 72% among the different age cohorts. The elderly (>60 years old) had a significantly higher attack rate (72%) than adults< 60years old (46%, p=0·045). The attack rate (as measured by seroconversion) in children (43%) was similar to that of adults (46%).

[20] Hu, P., et al. (2020). Retrospective study identifies infection related risk factors in close contacts during COVID-19 epidemic. *International Journal of Infectious Diseases*, 103, 395–401. 10.1016/j.ijid.2020.12.011

- The retrospective cohort study was performed among close contacts of index cases diagnosed with COVID-19 in Guangzhou, China before March 5, 2020. Demographic characteristics, **specific clinical symptoms** and exposure information were extracted. Logistic regression analysis was employed to explore the risk factors.
- The secondary attack rate (SAR) was 4.4% in 1,344 close contacts. The group of household contacts (17.2%) had the highest SAR. The rare-frequency contact ($p < 0.001$) and moderate- frequency contact ($p < 0.001$) were associated with lower risk of infection
- Compared with children, adults had a significantly increased risk of infection ($p = 0.014$). There is a linear positive correlation between age and infection ($p = 0.001$).
- Bivariate analyses showed **increased rate of infection in close contacts** with **increased severity of disease** in index case and **when index case was symptomatic**.
- Multivariate analyses showed that exposure to **index cases with dry cough** increased risk of infection in close contacts, as did increased frequency of contact with index case, and (older) age of close contact.

Table 2
Demographics and clinical characteristics of index and secondary patients with COVID-19.

	Index patients (n = 100)	Patients in close contacts			p-value[a]	p-value[b]
		Total secondary cases (n = 59)	Secondary cases in adults (n = 49)	Secondary cases in children (n = 10)		
Characteristics						
Age, years	48.0 [35.8, 62.0]	43.0 [31.0, 60.5]	54.00 [35.0, 62.0]	6.0 [1.5, 10.8]	0.136[c]	–
Gender					0.273	**0.011**[d]
Male	51 (51.0)	24 (40.7)	16 (32.7)	8 (80.0)		
Female	49 (49.0)	35 (59.3)	33 (67.3)	2 (20.0)		
Occupation					>0.999[d]	>0.999[d]
Health care worker	3 (3.0)	1 (1.7)	1 (2.0)	0 (0.0)		
Other	97 (97.0)	58 (98.3)	48 (98.0)	10 (100.0)		
Clinical severity					0.087[d]	>0.999[d]
Asymptomatic	0 (0.0)	1 (1.7)	1 (2.0)	0 (0.0)		
Mild	27 (27.0)	25 (42.4)	20 (40.8)	5 (50.0)		
Moderate	66 (66.0)	30 (50.8)	25 (51.0)	5 (50.0)		
Severe	7 (7.0)	3 (5.1)	3 (6.1)	0 (0.0)		
Signs and symptoms						
Fever	87 (87.0)	27 (45.8)	23 (46.9)	4 (40.0)	<**0.001**	0.741[d]
Highest temperature	38.0 [37.6, 38.5]	38.0 [37.5, 38.2]	38.0 [37.6, 38.3]	37.8 [37.5, 38.0]	0.181[c]	0.392[c]
Dry cough	46 (46.0)	16 (27.1)	14 (28.6)	2 (20.0)	**0.029**	0.713[d]
Sore throat	20 (20.0)	3 (5.1)	3 (6.1)	0 (0.0)	**0.019**	>0.999[d]
Myalgia	16 (16.0)	2 (3.4)	2 (4.1)	0 (0.0)	**0.030**	>0.999[d]
Any Comorbidity	33 (33.0)	11 (18.6)	11 (22.4)	0 (0.0)	0.077	0.183[d]

Data were displayed by median [Interquartile range] or n (%); Bold indicates statistically significant values.
Adult, age >14 years; Children, age ≤14 years.
[a] Index patients vs. total secondary cases.
[b] Secondary cases in adults vs. secondary cases in children.
[c] Wilcoxon Rank-sum test.
[d] Fisher's exact test.

Table 4
Multivariate analysis of association between potential risk factors and infection.

Characteristic	OR	95% CI	p-value
Age of case in contacts, year			
≤14 (Children)	reference	–	–
>14 (Adults)	**2.54**	**1.26–5.60**	**0.014**
Contact frequency			
Often	reference	–	–
Moderate	**0.01**	**0–0.04**	<**0.001**
Rare	**0.01**	**0–0.05**	<**0.001**
Fever (index cases)			
No	reference	–	–
Yes	2.89	0.83–18.30	0.157
Dry cough (index case)			
No	reference	–	–
Yes	**2.42**	**1.35–4.49**	**0.004**

Bold indicates statistically significant values.
Abbreviations: OR, Odd ratio; CI, Confidence interval.

Viral load, viral shedding and infectiousness

[21] Cevik, M., et al. (2021). SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. *The Lancet. Microbe,* 2(1), e13–e22. 10.1016/S2666-5247(20)30172-5

- Systematic review and meta-analysis
- Aimed to characterise **viral load dynamics**, **duration of viral RNA shedding**, and **viable virus shedding** of severe acute respiratory syndrome coronavirus 2 (**SARS-CoV-2**) in various body fluids, and to compare SARS-CoV-2, SARS-CoV, and Middle East respiratory syndrome coronavirus (**MERS-CoV**) viral dynamics.
- 79 studies (5340 individuals) on SARS-CoV-2, eight studies (1858 individuals) on SARS-CoV, and 11 studies (799 individuals) on MERS-CoV were included.
- Findings suggest that, although patients with SARS-CoV-2 infection might have prolonged RNA shedding of up to 83 days in upper respiratory tract infection, **no live virus was isolated from culture beyond day 9 of symptoms despite persistently high viral RNA loads.**
- This finding is supported by several studies demonstrating an association between viral load and viability of virus, with **no successful culture from samples below a certain viral load threshold**. These findings indicate that, in clinical practice, **repeat testing might not be indicated** to deem patients no longer infectious. Duration of infectiousness and subsequent **isolation timelines could reflect viral load dynamics** and could be counted **from symptom onset for 10 days in non-severe cases**.
- Mean duration of SARS-CoV-2 RNA shedding was:
    - 17·0 days (95% CI 15·5–18·6; 43 studies, 3229 individuals) in upper respiratory tract,
    - 14·6 days (9·3–20·0; seven studies, 260 individuals) in lower respiratory tract,
    - 17·2 days (14·4–20·1; 13 studies, 586 individuals) in stool, and
    - 16·6 days (3·6–29·7; two studies, 108 individuals) in serum samples.
- Maximum shedding duration was 83 days in the upper respiratory tract, 59 days in the lower respiratory tract, 126 days in stools, and 60 days in serum.
- Pooled mean SARS-CoV-2 shedding duration was positively associated with age (slope 0·304 [95% CI 0·115–0·493]; p=0·0016).
- **No study detected live virus beyond day 9 of illness, despite persistently high viral loads, which were inferred from cycle threshold values.** SARS-CoV-2 viral load in the upper respiratory tract appeared to peak in the first week of illness, whereas that of SARS-CoV peaked at days 10–14 and that of MERS-CoV peaked at days 7–10.
- 20 studies evaluated duration of **viral RNA shedding based on disease severity**.
    - 13 of these studies reported longer duration of viral shedding in patients with severe illness than in those with non-severe illness whereas five studies in upper respiratory tract samples and one study in stool samples reported similar shedding durations according to disease severity.
- All but one study that examined the **effect of age on SARS-CoV-2 shedding** identified an association between older age (older than 60 years) and prolonged viral RNA shedding. Three studies identified age as an independent risk factor for delayed viral clearance.
- **Male sex** was also associated with prolonged shedding and the association remained significant even when patients were stratified based on illness severity.
- 12 studies reported viral load dynamics or duration of viral shedding among individuals with **asymptomatic SARS-CoV-2 infection;**
    - Two demonstrated lower viral loads among asymptomatic individuals than among symptomatic individuals, and four found similar initial viral loads. However, Chau et al. [22] reported significantly lower viral load in asymptomatic individuals during the follow-up than in symptomatic individuals.

- **Faster viral clearance was observed in asymptomatic individuals** in five of six studies. The exception, Yongchen et al. [23], found longer shedding duration among asymptomatic cases, but the difference was not significant.
- **Viral loads appear to be similar between asymptomatic and symptomatic individuals infected with SARS-CoV-2**. Nevertheless, **most studies demonstrate faster viral clearance among asymptomatic individuals** than those who are symptomatic.
- This finding is in keeping with viral kinetics observed with other respiratory viruses such as **influenza** and **MERS-CoV**, in which people with asymptomatic infection have a shorter duration of viral shedding than symptomatic individuals.
- However, data on the shedding of infectious virus in asymptomatic individuals are too scarce to quantify their transmission potential in order to inform policy on quarantine duration in the absence of testing.

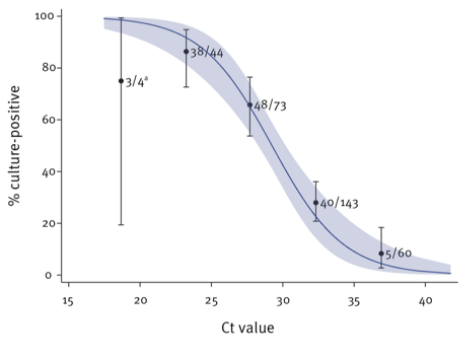
- We identified **11 studies that attempted to isolate live virus**.
  - All eight studies that attempted virus isolation in respiratory samples successfully cultured viable virus within the first week of illness.
  - **No live virus** was isolated from any respiratory samples taken **after day 8 of symptoms** in three studies, or beyond **day 9** in two studies **despite persistently high viral RNA loads**.
  - The success of viral isolation correlated with viral load quantified by RT-PCR. No successful viral culture was obtained from samples with a viral load below 1×10^6 copies per mL in one study, cycle threshold values higher than 24 in another study, or higher than 34 in other studies, with **culture positivity declining with increasing cycle threshold values**.
  - One study reported the duration of viable virus shedding in respiratory samples; time to clearance from symptom onset was 3–12 days in upper respiratory tract samples and 5–13 days in lower respiratory tract samples, and no positive viral culture was obtained after day 4 in upper respiratory tract infection and day 8 in lower respiratory tract infection.
  - Arons et al. [24] **cultured viable virus from the respiratory tract in one of three asymptomatic cases**.
  - **Viral culture was successful in two of three RT-PCR-positive patients** in one study, but the timepoints from symptom onset were not reported.
  - Andersson et al. [25] were unable to culture virus from 27 RT-PCR- positive serum samples.
- Pooled mean SARS-CoV-2 shedding duration was positively associated with age. No study detected live virus beyond day 9 of illness, despite persistently high viral loads. SARS-CoV-2 viral load in the upper respiratory tract appeared to peak in the first week of illness, whereas SARS-CoV and MERS-CoV peaked later. Several studies reported similar viral loads at the start of infection among asymptomatic and symptomatic patients infected with SARS-CoV-2; however, most studies demonstrated faster viral clearance in asymptomatic individuals, as also seen in MERS-CoV, suggesting a shorter infectious period but with similar potential transmissibility at the onset of infection.
- The study shows that despite evidence of prolonged SARS-CoV-2 RNA shedding in respiratory and stool samples, viable virus appears to be short-lived. Therefore, authors concluded RNA detection cannot be used to infer infectiousness.
- Noted study limitations. First, almost all patients in the included studies received a range of treatments, which might have modified the shedding dynamics. Second, our meta-analysis identified substantial study heterogeneity, probably due to differences in study population, follow-up, and management approaches.

[13] Singanayagam, etal (2020). Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020. *Euro surveillance : European communicable disease bulletin*, 25(32), 2001483.

- The aim of this work was to understand how RT-PCR detection relates to cultivable virus, which can be used as a proxy for infectiousness and can inform and support decisions on infection control.
- United Kingdom (late January to early April 2020). 754 URT samples from 425 symptomatic cases that tested positive for SARS-CoV-2 by RT-PCR targeting the RNA-dependent RNA polymerase (RdRp) gene and that had a clear record of the dates of symptom onset and sample collection.
- Relationship between Ct value and virus isolation
    - **We observed a strong relationship between Ct value and ability to recover infectious virus.** The estimated OR of recovering infectious virus decreased by 0.67 for each unit increase in Ct value (95% CI: 0.58–0.77) (see Figure 2 below). Virus propagation was successful from five of 60 samples with Ct>35; all five were from symptomatic cases and none had severe illness. The estimated probability of recovery of virus from samples with Ct>35 was 8.3% (95% CI: 2.8%–18.4%).
- Relationship between 'symptom to test' interval and virus isolation
    - There were 246 samples from 176 symptomatic cases where the date of symptom onset was known, of which 103 (42%) samples from 81 cases were culture- positive. Detection of cultivable virus peaked around the time of symptom onset.
- 13 individuals who were asymptomatic at the time of sampling developed symptoms within 14 days of sampling and were classified as **presymptomatic**, of whom seven were culture-positive. Regression analysis indicates that presymptomatic samples were at least as likely to be culture-positive as samples taken during symptomatic phases.
- Level of SARS-CoV-2 RNA in the URT was greatest around symptom onset, steadily decreased during the first 10 days after illness onset and then plateaued.
- SARS-CoV-2 viral load in the upper respiratory tract peaks around symptom onset and infectious virus persists for 10 days in **mild-to-moderate coronavirus disease** (n = 324 samples analysed).
- RT-PCR cycle threshold **(Ct) values correlate strongly with cultivable virus**. Probability of **culturing virus declines to 8% in samples with Ct > 35 and to 6% 10 days after onset**; it is similar in asymptomatic and symptomatic persons. Asymptomatic persons represent a source of transmissible virus.
- Noted limitations: Recall bias may affect the interpretation of timing of virus detection in relation to symptom onset, particularly in elderly patients and those presenting with atypical symptoms. Duration and cessation of symptoms is also not well recorded. For asymptomatic cases, the time when infection was acquired is not known. A further limitation is that this dataset comprises real-world data and subjects were not sampled systematically.

FIGURE 2

Relationship between RT-PCR Ct value and culture positivity in mixed effects logistic regression analysis, SARS-CoV-2, England, January–May 2020 (n = 324)



Ct: cycle threshold.

[a] Wide confidence intervals due to small sample size.

[26] Kawasuji, H., et al. (2020). Transmissibility of COVID-19 depends on the viral load around onset in adult and symptomatic patients. *PloS one*, 15(12), e0243597. 10.1371/journal.pone.0243597

- Objective: To investigate the relationship between viral load and secondary transmission in novel coronavirus disease 2019 (COVID-19).
- Case-control study. Patients admitted to Toyama University. Hospital index patients who transmitted the disease to at least one other patient were analysed as "cases" (index patients) compared with patients who were **not the cause of secondary transmission** (non-index patients, analysed as "**controls**").
- Viral load at the time of initial sample collection was significantly higher in symptomatic than in asymptomatic patients.
- Viral load at the time of initial sample collection was significantly higher in adults than in children.
- Furthermore, among the adult and the symptomatic patients, the **viral loads in the index patients were significantly higher** than those in the non-index patients. [i.e. in **cases that led to secondary transmission** compared to the controls who did not lead to secondary transmission]
- Among the **asymptomatic carriers, especially children**, it was difficult to determine whether the viral load could impact transmission because **no carrier had a high viral load**.
- Authors conclude it is plausible that high nasopharyngeal viral loads contribute to secondary transmission of COVID-19.
- Noted limitations: study only involved a small number of patients.

[27] Edwards, D. A., et al. (2020). Exhaled aerosol increases with COVID-19 infection, and risk factors of disease symptom severity. *medRxiv preprint*. (Oct 2020)

- Animal (n=8) experimental infection study and healthy human (n=74) observational cohort study.
- Studied respiratory droplet generation and exhalation in human and nonhuman primate subjects with and without COVID-19 infection to explore whether SARS-CoV-2 infection, and other changes in physiological state, translates into observable evolution of **numbers and sizes of exhaled respiratory droplets** in healthy and diseased subjects.
- In the observational cohort study of the exhaled breath particles of 74 healthy human subjects, and in the experimental infection study of eight nonhuman primates infected by aerosol with SARS-CoV-2, the authors observed that **exhaled aerosol particles increase one to three orders of magnitude** with **aging**, **high BMI** (in humans) and **COVID-19 infection** (non-human model).
- Authors observe that these variances appear to be related to changes in airway mucus surface composition and the propensity for mucus surfaces to breakup into small droplets during acts of breathing.
- The authors also observed that 20% of those participating in our human study accounted for 80% of the overall exhaled reflecting a bioaerosol distribution analogous to a **classical 20:80 super spreader** distribution.

2. Indications of impact of vaccines on transmission

AstraZeneca

[28] Voysey, M. et al (2021). Single Dose Administration, And The Influence Of The Timing Of The Booster Dose On Immunogenicity and Efficacy Of ChAdOx1 nCoV-19 (AZD1222) Vaccine. *SSRN preprints*

- Pre-print.
- Building on published main trail findings:
    - [29] Voysey, M., et al (2021). Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *The Lancet,* 397(10269), 99-111.
- Presents data from phase III efficacy trials of ChAdOx1 nCoV-19 in the United Kingdom and Brazil, and phase I/II clinical trials in the UK and South Africa, against symptomatic disease caused by SARS-CoV-2.
- The data cut-off date for analyses - 7 December 2020.
- While transmission studies per se were not included in the analysis, swabs were obtained from volunteers every week in the UK study, regardless of symptoms, to allow assessment of the overall impact of the vaccine on risk of infection and thus a surrogate for potential onward transmission.
- If there was no impact of a vaccine on asymptomatic infection, it would be expected that an efficacious vaccine would simply convert severe cases to mild cases and mild cases to asymptomatic, with overall PCR positivity unchanged. A measure of overall PCR positivity is appropriate to assess whether there is a reduction in the burden of infection.
- Analyses presented here show that a **single standard dose of the vaccine reduced PCR positivity by 67%,** and that, after the **second dose**, the SD/SD schedule **reduced PCR positivity by 49.5% overall**.
- Authors conclude that these data indicate that ChAdOx1 nCoV-19, used in the authorised schedules, **may have a substantial impact on transmission by reducing the number of infected individuals in the population**.

[30] Knoll, M. D., & Wonodi, C. (2021). Oxford-AstraZeneca COVID-19 vaccine efficacy. *Lancet*, 397(10269), 72–74. 10.1016/S0140-6736(20)32623-4

- Commentary in The Lancet
- E**fficacy was lower** (58·9% [1·0 to 82·9]) **against asymptomatic infection** in the LD/SD cohort (and unfortunately only 3·8% [−72·4 to 46·3] in the SD/SD group), although fewer data (69 cases among 6638 participants) were available with this outcome and **more data are needed to confirm**.

Pfizer

[31] Petter E et al., Initial real world evidence for lower viral load of individuals who have been vaccinated by BNT162b2 *GitHub* Feb 7th, 2021 *medRxiv preprint*.

- Pre-print
- Israel has vaccinated substantial parts of the adult population, which enables extracting real world signals.
- The vaccination rollout started on Dec 20th 2020, utilized mainly the BNT162b2 vaccine, and focused on individuals who are 60 years or older.
- At time of writing, more than 75% of the individuals of this age group have been at least 14 days after the first dose, compared to 25% of the individuals between ages 40-60 years old.
- The authors traced the Ct value distribution of 16,297 positive qPCR tests in their lab between Dec 1st to Jan 31st that came from these two age groups. Vaccine status was not available for each test. The

authors' hypothesis was that if vaccines reduce viral load, there should be an observable a difference in the Ct values between these two age groups in late January but not before.

  - Consistent with this hypothesis, until Jan 15th, the authors did not observe any statistically significant differences in the average Ct value between the groups.
  - By contrast, their results in the last two weeks of January show a significant weakening in the average Ct value of 60+ individuals to the 40-60 group.

- To further corroborate these results, the authors also used a series nested linear models to explain the Ct values of the positive tests. This analysis favoured a model that included an interaction between age and the late January time period, consistent with the effect of vaccination. They then used demographic data and the daily vaccination rates to estimate the effect of vaccination on viral load reduction.
  - Their estimate suggests that v**accination reduces the viral load by 1.6x to 20x in individuals who are positive for SARS-CoV-2**.
  - The authors argue that this estimate might improve after more individuals receive the second dose.
- Taken together, the authors conclude that their **findings indicate vaccination** is not only important for individual's protection but **can reduce transmission**.

Nonspecific – commentary

[32] Bleier, B. S., et al. (2021). COVID-19 Vaccines May Not Prevent Nasal SARS-CoV-2 Infection and Asymptomatic Transmission. *Otolaryngology*, 164(2), 305–307. 10.1177/0194599820982633

- Commentary. Focussed on risk in specific health service settings
- Current COVID-19 vaccine candidates are administered by injection and designed to produce an IgG response, preventing viremia and the COVID-19 syndrome. However, systemic respiratory vaccines generally provide limited protection against viral shedding within the airway as this requires local mucosal secretory IgA response.
- preclinical studies of adenovirus and mRNA candidate vaccines demonstrated persistent virus in nasal swabs despite preventing COVID-19 suggests that systemically vaccinated patients, while asymptomatic, may still be become infected and transmit live virus from the upper airway.
- COVID-19 is known to spread through respiratory droplets and aerosols. Significant evidence has shown that many clinic and surgical endonasal procedures are aerosol generating. Until further knowledge is acquired regarding mucosal immunity following systemic vaccination, otolaryngology providers should maintain precautions against viral transmission to protect the proportion of persistently vulnerable patients who exhibit subtotal vaccine efficacy or waning immunity or who defer vaccination.

Media Reports

Novavax

[33] Wadman, M. (2021). Will a small, long-shot U.S. company end up producing the best coronavirus vaccine? *Science.* Nov 3

- … scientists noted strong results in a dozen monkeys injected with various doses of Novavax's vaccine and then infected with live coronavirus. The virus failed entirely to multiply in the animals' noses and replicated in the lungs of just one monkey that received the lowest dose; that animal shut down the infection after 4 days.
- "It's the only vaccine I've seen out of all the candidates that are further down the pipeline that actually had no viral replication in the nasal swabs of vaccinated animals," says Angela Rasmussen, a virologist at Columbia University. That's important, she says, because stopping viral replication in the nose can reduce the spread of infection among people who may be unaware they are sick. But she cautions that monkeys are not people. "We can't really conclude that this vaccine is going to be better in practice until we have some reliable safety and efficacy data in people."
- That's why researchers will be eager to see results from Novavax's phase III trials.

Pfizer

Aodha, G. N. Pfizer CEO says there is 'encouraging' data on whether its vaccine stops Covid transmission. *The Journal (Ireland).* **13 Jan 2021**

- THE CEO OF Pfizer has said that there is "encouraging" data on whether the Pfizer BioNTech vaccine stops transmission.
- Dr Albert Bourla said at the EPP Group health event that "more concrete data" would be available by February.
- Studies to date have shown that its vaccine is highly effective at preventing a person who gets SARS-CoV-2 from becoming seriously ill with Covid-19, but separate research needs to be carried out as to its effectiveness at preventing transmission itself.
- "Right now we want to see to the vaccine, in addition to protecting people, is also preventing transferring the virus," Dr Bourla said.
- "This is not conclusive yet. We know that in animals, [there is] significant protection from transferring the virus…. We haven't [proven that in] humans yet."

Ockenden W Coronavirus was running rampant in Israel. But a swift vaccination program is having dramatic results *ABC* (**7 Feb 2021**)

- Israel has managed to vaccinate more than half of its population against COVID-19 in just five weeks, having a dramatic impact on its infection rate.
- It's by far the highest percentage in the world, and most of the vaccines used in Israel so far have come from the pharmaceutical giant Pfizer.
- Since then, roughly 55 per cent of the population has received at least one shot from the two-shot regimen, according to Bloomberg's COVID vaccine tracker.
- Nearly 20 per cent of Israelis have received the full two doses, meaning they're fully vaccinated.

- Vaccinations started with older and more vulnerable patients.
- Israel has a universal healthcare system and every citizen has a digital health record.
- That has proven to be very attractive for Pfizer, which has signed an agreement with Israel for anonymised data on vaccine recipients, including age, gender and demographic information.
- It's hoped that the real-world data can add to the knowledge on how the vaccine is performing, and if objectives like herd immunity are achievable.
- It will also help scientists understand how new coronavirus variants will perform with the currently available vaccines.

Jeffay N Vaccinated people less likely to transmit coronavirus, Israeli study suggests *Times of Israel* (**8 Feb 2021**)

- Nation's largest testing lab publishes research showing older group's viral load fell compared to younger cohort once most Israelis 60+ had received Pfizer-BioNTech shot.
- A paper published online Monday (see [31] claims that positive test results of patients age 60 and over had up to 60 percent smaller viral loads on the test swab than the 40-59 age group, starting in mid-January, when most of Israel's population age 60-plus had already been vaccinated with at least one dose.
- The results are only based on partial data, because MyHeritage did not know if individual samples came from patients who had been vaccinated or not. But overall, the **results appear to show that once someone is vaccinated**, **even if they have the virus in their system, they are less likely to pass it on because they have fewer infectious SARS-CoV-2 droplets hanging around their noses and throats**.
- "Our result reflects great data, because it gives exactly what we want from a vaccine, namely that it reduces transmission," Prof. Yaniv Erlich, head of the MyHeritage lab, told The Times of Israel on Monday. "It shows, to some extent, that this reduces viral load in the nose and throat, which is the main channel for transmission of the virus."
- While the lab found a 60% reduction in viral load for those 60 and over, Ehrlich postulated that it could drop further once more people in the cohort are vaccinated. He emphasized that his research is at an early stage, and the topic needs more investigation.
- While there is strong data from Phase 3 trials of the Pfizer-BioNTech vaccine, and since, showing that vaccinated people are far less likely to become verified COVID-19 carriers, clinical trials didn't produce robust results on whether those who are vaccinated will still spread the virus.

AstraZeneca

CNN: (**3 Feb 2021**) AstraZeneca vaccine appears to substantially reduce transmission of the coronavirus, study shows

- The Oxford-AstraZeneca Covid-19 vaccine appears to substantially reduce transmission of the virus, rather than simply preventing symptomatic infections, UK researchers have suggested.
- The rate of positive PCR tests declined by about half after two doses, according to preliminary results by researchers at the University of Oxford that have yet to be peer reviewed. (See [28])
- The study did not measure transmission directly -- for example, by tracing contacts who were infected by study volunteers. But the researchers did collect regular nasal swabs from some participants and found that the rate of positive PCR tests fell by half after two doses of the vaccine. After one dose only, the rate of positive tests fell by 67%.
- "While transmission studies per se were not included in the analysis, swabs were obtained from volunteers every week in the UK study, regardless of symptoms, to allow assessment of the overall impact of the vaccine on risk of infection and thus a surrogate for potential onward transmission," the authors write.

- If the vaccine were simply making infections milder, PCR positivity would not change, the authors argued in the preprint analysis. "A measure of overall PCR positivity is appropriate to assess whether there is a reduction in the burden of infection."
- Coronavirus vaccine trials have primarily looked at prevention of symptomatic cases of Covid-19. Previously, there has been little other public data suggesting that vaccines could prevent people from passing the infection to others.
- Speaking to the UK's Science Media Centre (SMC), Helen Fletcher, professor of immunology at the London School of Hygiene and Tropical Medicine, said the data in the study "suggest a possibility that the vaccine could have an impact on transmission but further follow-up would be needed to confirm this."
- Dr. Doug Brown, chief executive of the British Society for Immunology, told the SMC the study "hints that the Oxford/AstraZeneca vaccine may be effective in stopping people being able to transmit the virus."
- Before January 15, only negligible differences in viral load between the age groups were seen, but after that date it began to drop for the 60-plus group.
- Before January 15, only negligible differences in viral load between the age groups were seen, but after that date it began to drop for the 60-plus group.
- Ehrlich said further research is needed to calculate the exact direct impact of vaccination on viral load, but his model suggests it could be reducing it to between 60% and 5% of the norm.
- “The results reflect a statistically significant reduction of viral load, and we know from many studies in virology that people will be less likely to transmit if their viral load is lower,” he said, “though it’s hard to estimate at this point to what extent.”

Nonspecific commentary

Smith B & Willis O Do COVID-19 vaccines prevent transmission of coronavirus — and how much does that matter? *ABC Health & Wellbeing*. (5 Feb 2021)

- The goal of vaccination is, first and foremost, to stop people getting sick, says Nigel McMillan, director of infectious diseases and immunology at Menzies Health.
- Sometimes, vaccines are also able to stop us from getting infected in the first place — and therefore prevent us from passing the virus onto others. This is known as **sterilising immunity**.
- With mass vaccination efforts rolling out overseas, we should soon see more data around transmission rates emerge, and in the not too distant future, says James Trauer, head of Monash University's Epidemiological Modelling Unit.
- "The proof will be actually observing the pandemic fall away as populations are vaccinated — that's going to be the strongest signal that we'll get," Dr Trauer says.
- Researchers tend to think of this as Phase 4 of the clinical trials.
- Untangling the effects of vaccines on transmission isn't a straightforward affair, but not impossible, Professor Sharon Lewin says. "Those sorts of data are quite difficult to interpret, because there are other things that happen that slow transmission, such as non-pharmaceutical interventions,"

Authors: Prof Caroline Miller, Dr Jo Dono (SAHMRI Health Policy Centre)
Searchers: Nikki May (SA Health Library Service)
Expert input: Prof Steve Wesselingh (SAHMRI)

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