Transmission of B.1.617.2 Delta Variant Between Vaccinated Healthcare Workers

Steven A. Kemp

University of Cambridge

Mark TK Cheng

University of Cambridge

Will Hamilton

University of Cambridge

Kimia Kamelian

Public Health Agency of Canada, National Microbiology Laboratory

Sujeet Singh

National Centre for Disease Control

Partha Rakshit

National Centre for Disease Control

Anurag Aggrawal

CSIR Institute of Genomics and Integrative Biology

Christopher J.R. Illingworth

MRC-University of Glasgow Centre for Virus Research

Ravindra K. Gupta (✉ rkg20@cam.ac.uk)

University of Cambridge

Research Article

Keywords: transmission, vaccinated healthcare workers, delta

Posted Date: January 24th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1166169/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

---

1   **Transmission of B.1.617.2 Delta Variant between vaccinated healthcare workers**

2
3   Steven A. Kemp^{1,2†}, Mark TK Cheng^{1†}, Will Hamilton², Kimia Kamelian³, INSACOG Consortium, Sujit
4   Singh,⁴ Partha Rakshit⁴, Anurag Aggrawal⁵, Christopher J.R. Illingworth^{6,7,8†} & Ravindra K. Gupta^{1,2,9†*}

- 5
6   1.   Cambridge Institute of Therapeutic Immunology & Infectious Disease (CITIID), Cambridge, UK.
7   2.   Department of Medicine, University of Cambridge, Cambridge, UK.
8   3.   Public Health Agency of Canada, National Microbiology Laboratory, Winnipeg, Manitoba,
9   Canada
10   4.   National Centre for Disease Control, Delhi, India
11   5.   CSIR Institute of Genomics and Integrative Biology, Delhi, India
12   6.   MRC-University of Glasgow Centre for Virus Research, Garscube Campus, 464 Bearsden Road,
13   Glasgow, UK
14   7.   MRC Biostatistics Unit, University of Cambridge, East Forvie Building, Forvie Site, Robinson
15   Way, Cambridge, UK
16   8.   Department of Applied Mathematics and Theoretical Physics, University of Cambridge,
17   Cambridge, UK
18   9.   Africa Health Research Institute, Durban, South Africa.

19
20   [†]Authors contributed equally

21   ^{*}Corresponding Author

22
23   Ravindra K Gupta: Jeffrey Cheah Biomedical Centre, Cambridge, CB5 8UB, United Kingdom

24   rkg20@cam.ac.uk

25
26   Keywords: transmission, vaccinated healthcare workers, delta
27
28
29

Abstract

Breakthrough infections with SARS-CoV-2 Delta variant have been reported in vaccine recipients and in individuals infected with previous variants. Studies of viral spread within hospital settings have highlighted the potential for transmission between patients and health care workers, and highlighted the benefits of high-grade respiratory protection for health care workers. However the extent to which vaccination is preventative of viral spread in health care settings is less well studied. We here analyse data from health care workers in two hospitals in India, constructing probable transmission networks from epidemiological and virus genome sequence data using a suite of computational approaches. A maximum likelihood reconstruction of transmission involving known cases of infection suggests a high probability that doubly vaccinated health care workers transmitted SARS-CoV-2 between each other, and highlights potential cases of virus transmission between individuals who had received two doses of vaccine. Our findings support the need for ongoing infection control measures even in highly vaccinated populations.

Introduction

The B.1.617.2 (Delta) variant is now the most common lineage circulating in India and worldwide. Vaccine efficacy (VE) for the Delta variant is estimated at around 50% for mild symptomatic infection after two doses of either mRNA or adenovirus-based vaccine platforms¹. However, VE for moderately-severe and severe disease is estimated as 95%². Breakthrough infections of the Delta variant have been reported in vaccine recipients, as well as re-infection of individuals infected with previously circulating variants³⁻⁵. We previously reported 155 occurrences of vaccine breakthrough infections⁶ amongst frontline Delhi healthcare workers (HCW), all of whom had one or two doses of the Covishield (ChAdOx1) vaccine, the majority of whom were vaccinated >21 days prior to symptomatic presentation.

Existing literature suggests that there are similar viral loads between vaccinated and unvaccinated^{7,8}, but with steeper decay⁹ over time in vaccinated persons. Furthermore the probability of culturing virus appears lower in the vaccinated. Contact tracing data suggests a reduced probability of household transmission from individuals who been vaccinated¹⁰.

A variety of studies have highlighted the need to better understand and prevent SARS-CoV-2 transmission in hospital settings¹¹. Newly infected patients pose a risk both to other patients and to health care workers¹². Infection of patients by HCWs is potentially a rarer event, though HCWs pose a risk to each other¹³. Distinct approaches have been taken to reduce the risk to HCWs of infection at work. A study of the use of FFP3 respirators by HCWs in one hospital showed that these provided at least a 52% improvement in protection against infection compared to fluid resistant surgical masks¹⁴. HEPA filters have suggested as a further measure in protecting patients and staff¹⁵. The use of virus genome sequencing has prompted the development of new approaches for the rapid assessment of cases of hospital infection^{16,17}. Genome sequence data is of demonstrated benefit in health care settings^{18,19}.

Vaccination has been proven to provide substantial protection against infection and against the worst clinical consequences of infection²⁰ and a single dose of vaccine had demonstrable value in reducing infection among health care workers²¹. However, the Delta variant has some ability to escape antibody responses that targeted the original pandemic viral strain²².

Here we evaluated cases of SARS-CoV-2 infection among vaccinated and unvaccinated HCW in Indian hospitals. Applying *in silico* approaches to genomic and epidemiological data we identified potential

transmission networks involving HCWs. Our results suggest that transmission of the Delta variant of SARS-CoV-2 may have occurred from and between doubly-vaccinated HCWs, supporting the ongoing use of infection control measures beyond vaccination, and within highly vaccinated populations.

Results

ChAdOx1 nCoV-19 Breakthrough Infection

All symptomatic HCWs in two hospitals who had received one or two doses of the ChAdOx1 nCoV-19 mRNA vaccine (AZD1222), in addition to a set of unvaccinated HCWs, underwent RT-PCR testing within one day of symptom onset as part of a hospital staff symptomatic testing program. From these cases we identified breakthrough infection in staff who had received two doses of the vaccine. In hospital A, there were 81 breakthrough infections amongst 1100 HCWs, and in hospital B, 32 infections amongst 4000 HCWs, as previously reported⁶.

Among the 113 cases from hospitals A and B, 12.4% were administrative staff, 31.9% were nurses, 40.7% were primary physicians, 7.1% were paramedics and 3.5% were pharmacists. The remaining 3.5% of breakthrough infections consisted of medical interns (1.8%), and laboratory workers (1.8%) (**Table 1**). The median interval between receiving a second vaccination and date of positive RT-PCR test was 45 days (range 3-78 days). Amongst the breakthrough infections of doubly-vaccinated HCW, 90.7% were infected with B.1.617.2, 5.3% by B.1.1.7-like, 1.3% by B.1.538. (**Table 2**). The most commonly reported symptoms were fever (82.3% of all cases), cough (43.4%), myalgia (20.4%), and loss of smell/taste (14.2%) (**Table 3**).

Whole genome sequencing was used to characterise staff nose and throat swab samples. In hospital A, 66 sequences with high quality whole genome coverage of >90% were generated, including 43 cases of breakthrough infection. In hospital B, high quality genome sequences were generated from 52 samples, including all 32 symptomatic breakthrough infections.

Community Sequencing

Between April – May 2021, >99% of SARS-CoV-2 sequences in India were assigned Delta (B.1.616.2) lineages. However, since August 2021, the Delta sub-lineages have proliferated - predominantly AY.12 – across India and elsewhere²³. To determine the relationship between community and HCW sequences, we inferred a maximum-likelihood phylogeny to estimate dispersion (**Figure 1**). The analysis suggested multiple introductions into hospitals A and B, with subsequent intra-hospital transmission. We found significant partitioning of the inferred phylogeny, separating the sequences

into distinct clades. Mutations relative to the Delta consensus that were found in these cases were spread across the SARS-CoV-2 genome. None of the identified SNPs were in homoplastic regions of the genome. We note that the individuals 115, 127, and 305 in hospital A had identical virus genomes.

Characterisation of Delta variant infection dynamics

As a preliminary step towards an analysis of virus transmission we used published data to parameterise distributions describing the incubation period and the infectivity profile of the Delta variant²⁴. Data describing the incubation period and the serial interval of the virus were taken from a study of an outbreak of Delta variant SARS-CoV-2 in Guangdong province. Following previous approaches to characterising infection dynamics²⁵⁻²⁷ we inferred parameters describing the time t_s to symptom onset of the virus as a lognormal distribution

$$P_{LN}(t_s|\mu, \sigma) = \frac{1}{x\sigma\sqrt{2\pi}} \exp\left(-\frac{(\ln t_s - \mu)^2}{2\sigma^2}\right)$$

with parameters $\mu = 1.39599$ and $\sigma = 0.41354$, and the infectivity profile of the virus as an offset gamma distribution

$$P_\gamma(t|a, b, o) = \frac{b^a(t - o)^{a-1} \exp(-b(t - o))}{\Gamma(a)}$$

with parameters $\alpha = 38.4805$, $\beta = 0.468049$, and $o=20$.

Linkage between vaccinated HCW and transmission networks

Integrating our derived parameters into the A2B-COVID¹⁶ software package, we identified a number of putative transmission pairs between HCWs. The A2B-COVID package combines dates of symptom onset with virus genomes to identify pairs of individuals for whom the data are consistent with direct transmission. Within our data we identified 35 putative transmission events involving 14 HCWs in hospital A, and 26 putative events involving 13 patients in hospital B (**Supplementary Figures 1, 2**).

Potential transmission networks connecting these cases were inferred using the A2B-Network software package¹³. Given a set of cases infected which are potentially related by transmission, this identifies potential networks of transmission events connecting the cases, and calculates a probability for each specific network, conditional upon the cases being linked by direct transmission. To reduce excessive computational load, potential transmission events in hospital A were filtered to remove those involving the gain of more than one SNP (**Supplementary Figure 5**); none of the statistics we go on to derive could have been altered by this step. From the cases remaining we identified a set of

possible networks involving six HCWs, two of whom had received their second dose of vaccine at least 14 days prior to reporting symptoms (**Figure 2**). A total of 1381 possible transmission networks were identified. Conditional upon these individuals being linked by direct transmission, there was a 92.1% chance that one of the two individuals receiving a second vaccine 14 days prior to infection was the source of transmission to another individual in the network. If this criterion was relaxed to 7 days between second vaccination and infection, we estimated a 99.9% chance that at least one of the three such individuals infected another individual in the network, with a 98.7% probability of direct virus transmission between these three individuals. Other unrelated networks in hospital A were identified, but did not involve transmission from vaccinated HCWs to unvaccinated HCWs (**Supplementary Figure 4**).

The inferred transmission networks involved a variety of medical staff. In hospital A, a common genome sequence was shared by the junior medical staff member P115, the nursing student P127, and by P305, a member of the nursing staff, who collectively became symptomatic over a period of six days. Three other staff had virus genomes which differed from this by a single SNP each. The ophthalmologic junior medical staff P142 became symptomatic a day after P305; the SNP 8016T causes a nonsynonymous change in ORF1ab, A2584V. P155 was also a member of the nursing staff; the SNP C9509T leads to the nonsynonymous substitution T3082I in ORF1ab. Finally, P164 was a paramedic; the SNP A19298G represents a nonsynonymous change in the ORF1ab (Y6345C).

An analysis of potential transmission events in hospital B identified a network involving eight HCWs, four of whom had received their second dose of vaccine at least 14 days prior to reporting symptoms (**Figure 2**). A total of 128 possible transmission networks between these individuals were identified, all of which implied that one of the four individuals who received a second vaccine at least 14 days prior to infection was the source of transmission to another individual in the network. Among the five individuals who were infected more than seven days post second vaccination, we found a 97.8% chance of a transmission event having occurred between individuals vaccinated with two doses. In hospital B, the individuals P205, P207, and P240 all received their second dose of vaccine at least 14 days before testing positive. P205 was a paediatrician, P207 and P240 both adult physicians. Further details of symptoms, job titles, symptoms, and positive test dates, where known, are shown in **Table 4**. Full details of SNPs are given in **Supplementary Figure 5 and 6**.

A simulation-based validation procedure, used to assess the potential influence of missing data upon the derived networks, suggested that the network inferred using data from hospital A was self-

consistent, but that the network inferred for hospital B was likely affected by missing data (**Figure 3**). Missing data is a key limitation of our study; the algorithm used in our study for network reconstruction builds networks only from the cases of infection that are known to have occurred. In our dataset, while symptomatic HCWs were surveyed for infection, there is the potential that asymptomatic HCWs or patients could form unobserved parts of the original transmission networks. We therefore compared the networks derived from hospital data to ensembles of simulations describing identical networks of transmission events, comparing the genetic properties of the hospital networks to the statistics of simulated viral populations; an excess of genetic substitutions in a network, relative to simulations, can indicate the presence of missing parts of its inferred evolutionary history as would arise from missing data (**Supplementary Figure 7**).

Discussion

Given the substantial global influence of the Delta variant, information on transmission amongst fully vaccinated individuals is needed to dictate the need for future infection control and vaccination boost strategies. Our study highlights the potential for Delta variant transmission in a healthcare setting from and between fully vaccinated individuals. Our study has caveats; firstly by only considering symptomatic cases, we exclude HCWs who are asymptomatic or fail to report their infection status, or patients who could have been the source of some infections. Secondly, the number of valid samples is further reduced by incomplete sampling and subsequent sequence filtering, likely resulting in incomplete transmission chains. Calculations suggested that the networks inferred for hospital B are likely to be affected by missing data, though the data from hospital A was not clearly affected.

Although vaccination is still highly effective for Delta in protecting against severe disease²⁸, we have demonstrated that breakthrough infections still occur in healthcare settings in individuals within 60 days of the second dose when circulating neutralising antibody levels are at their highest²⁹. Given the risk of onward transmission to potentially very vulnerable patients (including people in whom vaccination is less effective, such as those with compromised immune systems), our findings highlight the need for ongoing infection control measures even in highly vaccinated populations, and mask wearing in individuals who have received two doses of vaccine, in order to limit onward transmission.

Methods

Study Design

From 25th March – 10th May 2021 all frontline healthcare workers who presented with symptoms consistent with SARS-CoV-2 were diagnostically tested for the presence of SARS-CoV-2 by means of

reverse transcriptase polymerase chain reaction (RT-PCR) using TRUENAT or CBNAAT (GENEXPERT). Findings were expressed as the cycle threshold (Ct) for the gene encoding the nucleocapsid protein (N gene) for hospital A, and the gene encoding for the envelope protein (E gene) for hospital V. A Ct value of less than 30 was considered to be infective. A vaccine breakthrough infection was defined as detection of SARS-CoV-2 in a sample collected from an individual 21 days after receipt of a second dose of ChAdOx1.

Ethical approval for this study and specifically the investigation of vaccine-elicited antibodies in sera from vaccinees was obtained from the East of England Cambridge Central Research Ethics Committee, University of Cambridge, Cambridge, United Kingdom (REC ref. 17/EE/0025). Studies involving HCWs (including testing and sequencing of respiratory samples) were reviewed and approved by The Institutional Human Ethics Committees of the National Centre for Disease Control (NCDC) and Council Of Scientific And Industrial Research–Institute Of Genomics And Integrative Biology, India (CSIR IGIB) (NCDC/2020/NERC/14 and CSIRIGIB/IHEC/202021/01). Participants provided informed consent.

All methods followed in this manuscript were performed in accordance with the relevant guidelines stipulated by the ethical approval committee, as reviewed.

Bioinformatics and Phylogenetic analysis

Fasta consensus sequences were obtained from two separate Hospitals in Delhi, India. All sequences were concatenated into a single fasta and aligned to reference strain MN908947.3 with mafft v7.847³⁰ using the --keeplength and --addfragments options. Following this, all sequences were screened for number of gaps and N-regions using the Nextclade v1.5.4 (<https://clades.nextstrain.org/>) server. All sequences were assigned a lineage with Pangolin v3.1.11³¹, pangoleARN (dated 9th August 2021) and scorio v0.0.14. Sequences that could not be assigned a lineage were discarded. After assigning lineages, all sequences with more than 5% N-regions were also discarded.

To contextualise outbreak sequences, all sequences from India with lineage defined as B.1.617.2 from the month of April 2021 were downloaded from the Global Initiative on Sharing Avian Influenza Data (GISAID) EpiCoV database. Incomplete (<29,000 base pair), duplicate, and low-quality sequences (defined as equal to or more than 5% Ns; less than 95% genome coverage) were excluded.

SNP distance, variant calling and annotation

Single-nucleotide polymorphisms (SNPs), relative to the Delta variant strain, were identified by re-alignment of groupings of sequences based on each hospital to the Delta variant consensus reference (MZ359841.1) using mafft v7.8477 with the --keeplength and --addfragments parameters. Initial analysis of pairwise SNP distance between each patient was conducted using snp-dists v0.8.2 with default parameters.

Following this, a VCF of acquired mutations of each patient with respect to the reference strain MN908947.3 (Wuhan-Hu-1) is calculated by snp-sites v2.5.1³² using the -v and -c option. Multiallelic variants are broken down into biallelic variant representations and are subsequently annotated by snpEff v5.0e³³ with reference to MN908947.3. The nucleotide and amino acid variants between each transmission pairs are extracted from the VCF, and SNP number verified using an in-house script (https://github.com/TKMarkCheng/Indian_HCW). The VCFs were manually scanned to identify homoplasic/problematic sites (https://github.com/W-L/ProblematicSites_SARS-CoV2).

Estimating transmission dynamics for the Delta variant

In order to evaluate potential transmission events involving the Delta strain of SARS-CoV-2 we used data published on an early study involving this virus (new ref) to re-derive parameters for these two distributions.

Incubation period of the virus

The incubation period of the virus is modelled in A2B-COVID by a lognormal distribution, described as follows:

$$P_{LN}(x|\mu, \sigma) = \frac{1}{x\sigma\sqrt{2\pi}} \exp\left(-\frac{(\ln x - \mu)^2}{2\sigma^2}\right)$$

Zhang et al report a mean for the incubation period of 4.4 days, with a standard deviation of 1.9 days²⁴.

We note that the mean and standard deviation of x in the lognormal distribution are given respectively by

$$\bar{x} = \exp\left(\mu + \frac{\sigma^2}{2}\right)$$

and

$$Std(x) = (\exp(\sigma^2) - 1) \exp(2\mu + \sigma^2)$$

These equations allow for numerical solution, which was performed using the Mathematica software package, providing the values $\mu = 1.39599$ and $\sigma = 0.41354$.

Serial interval

The serial interval (time between symptom onsets) is modelled by He et al using an offset gamma distribution²⁵, with parameters a , b , and o .

$$P_\gamma(x|a, b, o) = \frac{b^a (x - o)^{a-1} \exp(-b(x - o))}{\Gamma(a)}$$

Zhang et al report a mean for this distribution of 2.3 days, with a standard deviation of 3.4 days²⁴. We note that the mean and standard deviation of this distribution are given by

$$\bar{x} = ab + o$$

and

$$Std(x) = a\sqrt{b}$$

These equations allow for straightforward solution. Here the offset is included to account for negative intervals, whereby individual A infects individual B, but B becomes symptomatic before A. Setting the value of the offset o to 20 days (changing this does not greatly affect the shape of the final distribution), the mean and standard deviation are satisfied by the values $a = 43.0182$ and $b = 0.518386$.

Infectivity profile

Finally, to derive an infectivity profile for the Delta strain of SARS-CoV-2, assuming it to follow an offset gamma distribution with parameters α , β , and the offset $o=20$ days. We used numerical methods to find parameters α and β so as to minimise the distance metric

$$D = \sqrt{\sum_{x=-40}^{30} \left[P_\gamma(x|a, b, o) - \int_{-\infty}^{\infty} P_{LN}(x - y|\mu, \sigma) P_\gamma(y|\alpha, \beta, o) dy \right]^2}$$

In other words, we derived parameters for an infectivity profile such that the compound of it and the distribution describing the incubation period of the virus provided the closest possible fit to the inferred serial interval. From this calculation we obtained the values $\alpha = 38.4805$ and $\beta = 0.468049$. Inferred distributions are shown in **Supplementary Figure 8**.

Identifying plausible cases of person-to-person transmission

As an initial assessment of whether participants in the study had passed an infection to another, we utilised A2B-COVID¹⁶. This software considers data from individuals in a pairwise fashion, considering the timing of symptom onset and virus genome sequences in order to assess for each pair of individuals A and B whether the data are consistent with an underlying model of direct virus transmission from A to B. Data from each pair are described as ‘consistent’ with transmission, ‘borderline’, or ‘unlikely’ to have been produced given direct transmission.

Estimating likelihood of person-to-person transmission

Network reconstruction was performed using the A2B-Network software¹³. Again using dates of symptom onset and virus genome sequences, this identifies plausible networks via which all of the individuals in a set could have transmitted the virus between themselves, and assesses the probability of each such network having occurred, given our model assumptions. In this manner, the code produces ensembles of networks, describing the extent to which the data constrain the possible routes of transmission of the virus. The probabilities we report were calculated by summing network likelihoods. For example, the probability that a network contains a transmission event between doubly vaccinated individuals is the sum of the probabilities of the networks which contain at least one such transmission event. Our model assumes a set of underlying parameters describing the transmission dynamics and rate of evolution of the SARS-CoV-2 virus. The network probabilities we report are conditional on these parameters and upon the assumption that the individuals to whom we apply the model are connected by a transmission network.

Network validation

Transmission networks were validated for self-consistency using a model of simulated SARS-CoV-2 outbreaks. Simulations used identical parameters to the network inference model to describe the transmission dynamics and rate of evolution of the SARS-CoV-2 virus, and exploited the fact that missing data can lead to missing time in the evolutionary tree (**Supplementary Figure 7**). A total of 10^5 networks were chosen at random from the ensemble of networks inferred for the hospitals, with

346 the probability that a specific network was chosen being identical to its probability within the
347 inference. Across these networks we then calculated distributions of the total number of unique
348 mutations, which evolves proportional to the time within the transmission tree, and the number of
349 individuals with mutations observed in no other individual, which measures the time in the tree after
350 the last transmission from an individual to someone else.

351

352

353

354

References

1. Pramod S, Govindan D, Ramasubramani P, et al. Effectiveness of Covishield vaccine in preventing Covid-19 – A test-negative case-control study. medRxiv 2021:2021.07.19.21260693. DOI: 10.1101/2021.07.19.21260693.
2. Tang P, Hasan MR, Chemaitelly H, et al. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the SARS-CoV-2 Delta variant in Qatar. Nature Medicine 2021. DOI: 10.1038/s41591-021-01583-4.
3. Jolly B, John N, Bhoyar RC, et al. Genomic survey of SARS-CoV-2 vaccine breakthrough infections in healthcare workers from Kerala, India. Journal of Infection 2021;83(2):237-279.
4. Tyagi K, Ghosh A, Nair D, et al. Breakthrough COVID19 infections after vaccinations in healthcare and other workers in a chronic care medical facility in New Delhi, India. Diabetes & Metabolic Syndrome: Clinical Research & Reviews 2021;15(3):1007-1008.
5. Dhar MS, Marwal R, VS R, et al. Genomic characterization and epidemiology of an emerging SARS-CoV-2 variant in Delhi, India. Science;0(0):eabj9932. DOI: doi:10.1126/science.abj9932.
6. Mlcochova P, Kemp S, Dhar MS, et al. SARS-CoV-2 B.1.617.2 Delta variant replication and immune evasion. Nature 2021. DOI: 10.1038/s41586-021-03944-y.
7. Riemersma KK, Grogan BE, Kita-Yarbro A, et al. Vaccinated and unvaccinated individuals have similar viral loads in communities with a high prevalence of the SARS-CoV-2 delta variant. medRxiv 2021:2021.07.31.21261387. DOI: 10.1101/2021.07.31.21261387.
8. Pouwels KB, Pritchard E, Matthews PC, et al. Effect of Delta variant on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. Nature Medicine 2021. DOI: 10.1038/s41591-021-01548-7.
9. Chia PY, Xiang Ong SW, Chiew CJ, et al. Virological and serological kinetics of SARS-CoV-2 Delta variant vaccine-breakthrough infections: a multi-center cohort study. medRxiv 2021:2021.07.28.21261295. DOI: 10.1101/2021.07.28.21261295.
10. Eyre DW, Taylor D, Purver M, et al. The impact of SARS-CoV-2 vaccination on Alpha & Delta variant transmission. medRxiv 2021:2021.09.28.21264260. DOI: 10.1101/2021.09.28.21264260.
11. Richterman A, Meyerowitz EA, Cevik M. Hospital-Acquired SARS-CoV-2 Infection: Lessons for Public Health. JAMA 2020;324(21):2155-2156. DOI: 10.1001/jama.2020.21399.
12. Mo Y, Deng L, Zhang L, et al. Work stress among Chinese nurses to support Wuhan in fighting against COVID-19 epidemic. Journal of Nursing Management 2020;28(5):1002-1009. (<https://doi.org/10.1111/jonm.13014>). DOI: <https://doi.org/10.1111/jonm.13014>.

- 388 13. Illingworth CJR, Hamilton WL, Warne B, et al. Superspreaders drive the largest outbreaks of
389 hospital onset COVID-19 infections. *Elife* 2021;10:e67308. DOI: 10.7554/eLife.67308.
- 390 14. Ferris M, Ferris R, Workman C, et al. Efficacy of FFP3 respirators for prevention of SARS-CoV-
391 2 infection in healthcare workers. *Elife* 2021;10:e71131. DOI: 10.7554/eLife.71131.
- 392 15. Conway Morris A, Sharrocks K, Bousfield R, et al. The removal of airborne SARS-CoV-2 and
393 other microbial bioaerosols by air filtration on COVID-19 surge units. *Clinical Infectious*
394 *Diseases* 2021. DOI: 10.1093/cid/ciab933.
- 395 16. Illingworth CJR, Hamilton WL, Jackson C, et al. A2B-COVID: A method for evaluating potential
396 SARS-CoV-2 transmission events. *medRxiv* 2021:2020.10.26.20219642. DOI:
397 10.1101/2020.10.26.20219642.
- 398 17. Stirrup O, Hughes J, Parker M, et al. Rapid feedback on hospital onset SARS-CoV-2 infections
399 combining epidemiological and sequencing data. *Elife* 2021;10:e65828. DOI:
400 10.7554/eLife.65828.
- 401 18. Hamilton WL, Fieldman T, Jahun A, et al. Applying prospective genomic surveillance to support
402 investigation of hospital-onset COVID-19. *The Lancet Infectious Diseases* 2021;21(7):916-917.
403 DOI: 10.1016/S1473-3099(21)00251-6.
- 404 19. Meredith LW, Hamilton WL, Warne B, et al. Rapid implementation of SARS-CoV-2 sequencing
405 to investigate cases of health-care associated COVID-19: a prospective genomic surveillance
406 study. *The Lancet Infectious diseases* 2020;20(11):1263-1271. DOI: 10.1016/S1473-
407 3099(20)30562-4.
- 408 20. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19
409 Vaccine. *New England Journal of Medicine* 2020;383(27):2603-2615. DOI:
410 10.1056/NEJMoa2034577.
- 411 21. Jones NK, Rivett L, Seaman S, et al. Single-dose BNT162b2 vaccine protects against
412 asymptomatic SARS-CoV-2 infection. *Elife* 2021;10:e68808. DOI: 10.7554/eLife.68808.
- 413 22. Planas D, Veyer D, Baidaliuk A, et al. Reduced sensitivity of SARS-CoV-2 variant Delta to
414 antibody neutralization. *Nature* 2021;596(7871):276-280. DOI: 10.1038/s41586-021-03777-9.
- 415 23. INSACOG. INSACOG WEEKLY BULLETIN. 23/08/21 2021.
416 ([https://dbtindia.gov.in/sites/default/files/INSACOG%20WEEKLY%20BULLETIN%2023-08-](https://dbtindia.gov.in/sites/default/files/INSACOG%20WEEKLY%20BULLETIN%2023-08-2021_.pdf)
417 [2021_.pdf](https://dbtindia.gov.in/sites/default/files/INSACOG%20WEEKLY%20BULLETIN%2023-08-2021_.pdf)).
- 418 24. Meng Z, Jianpeng X, Aiping D, et al. Transmission Dynamics of an Outbreak of the COVID-19
419 Delta Variant B.1.617.2 — Guangdong Province, China, May–June 2021. *China CDC Weekly*
420 2021;3(27):584-586. DOI: 10.46234/ccdcw2021.148.

25. He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med* 2020;26(5):672-675. DOI: 10.1038/s41591-020-0869-5.
26. Ashcroft P, Huisman JS, Lehtinen S, et al. COVID-19 infectivity profile correction. *arXiv preprint arXiv:200706602* 2020.
27. Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. *New England Journal of Medicine* 2020;382(13):1199-1207. DOI: 10.1056/NEJMoa2001316.
28. Tartof SY, Slezak JM, Fischer H, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. *Lancet* 2021;398(10309):1407-1416. DOI: 10.1016/S0140-6736(21)02183-8.
29. Wall EC, Wu M, Harvey R, et al. Neutralising antibody activity against SARS-CoV-2 VOCs B.1.617.2 and B.1.351 by BNT162b2 vaccination. *Lancet* 2021;397(10292):2331-2333. DOI: 10.1016/S0140-6736(21)01290-3.
30. Katoh K, Standley DM. MAFFT multiple sequence alignment software version 7: improvements in performance and usability. *Mol Biol Evol* 2013;30(4):772-80. DOI: 10.1093/molbev/mst010.
31. Rambaut A, Holmes EC, O'Toole A, et al. A dynamic nomenclature proposal for SARS-CoV-2 lineages to assist genomic epidemiology. *Nat Microbiol* 2020;5(11):1403-1407. DOI: 10.1038/s41564-020-0770-5.
32. Page AJ, Taylor B, Delaney AJ, et al. SNP-sites: rapid efficient extraction of SNPs from multi-FASTA alignments. *Microbial Genomics* 2016;2(4). DOI: <https://doi.org/10.1099/mgen.0.000056>.
33. Cingolani P, Platts A, Wang LL, et al. A program for annotating and predicting the effects of single nucleotide polymorphisms, SnpEff. *Fly* 2012;6(2):80-92. DOI: 10.4161/fly.19695.

Acknowledgements

We are grateful to all participants and medical staff involved in sample collection and sequencing efforts. R.K.G. is supported by a Wellcome Trust Senior Fellowship in Clinical Science (WT108082AIA). S.A.K. is supported by the Bill and Melinda Gates Foundation via PANGEA grant (OPP1175094). CJRI was supported by the Medical Research Council (MC_UU_12014).

Table 1: Job roles of vaccinated HCWs in hospitals A and B

Job Description	Count	
Administrative	14	12.4%
Nursing	36	31.9%
Medical Physician	46	40.7%
Paramedics	8	7.1%
Pharmacist	4	3.5%
Healthcare assistant	2	1.8%
Intern	2	1.8%
Laboratory worker	1	0.9%
Total	113	

Table 2: Lineage assignments of all sequences using the Pangolin tool.

Lineage	Count	Percentage
Alpha (B.1.1.7-like)	4	
B.1.1.7	3	4.0%
Q.1	1	1.3%
B.1.617.1-like	2	
B.1.617.1	2	2.7%
Delta (B.1.617.2-like)	68	
B.1.617.2	68	90.7%
Others	1	
B.1.538	1	1.3%
Total	75	

Table 3: Symptom prevalence amongst vaccinated HCWs in both hospitals.

Symptoms	Number of cases	% of total
Asymptomatic	2	1.8%
Weakness	2	1.8%
Nausea and/or vomiting	3	2.7%
Dyspnoea	3	2.7%
Congestion	5	4.4%
Diarrhoea	5	4.4%
Headache	12	10.6%
Anosmia and/or ageusia	16	14.2%
Sore throat	32	28.3%
Myalgia (including backache)	23	20.4%
Cough	49	43.4%
Fever	93	82.3%

Table 4: Details of cases in the inferred transmission networks

Individual	Job description	Symptom onset DD/MM/YY	Test date DD/MM/YY	CT value	Symptoms
<i>Hospital A</i>					
P115	Junior medical staff	12/04/21	13/04/21	22.8	Fever, myalgia, sore throat, abdominal cramps
P127	Nursing student	14/04/21	15/04/21	35.2	Throat irritation
P305	Nursing staff	17/04/21	19/04/21	25	Anosmia, conjunctivitis, rhinorrhoea
P142	Junior medical staff (ophthalmology)	18/04/21	19/04/21	29.6	Fever, cold cough
P155	Nursing staff	20/04/21	21/04/21	29	Rashes, fever, myalgia, headache
P164	Paramedic	24/04/21	25/04/21	21.1	Fever, cough, sore throat
<i>Hospital B</i>					
P232	Medical officer	09/04/21	12/04/21	15.5	Fever, rhinorrhoea, sore throat
P205	Paediatrician	12/04/21	19/04/21	17.1	Fever, myalgia, anosmia, ageusia
P215	Chief health director / Physician	13/04/21	14/04/21	18.5	Fever
P240	Doctor (pathology labs, COVID wards)	16/04/21	17/04/21	12.8	Fever, cough, myalgia
P207	Physician	17/04/21	19/04/21	16.8	Cough, rhinorrhoea, sore throat
P199	Physician	22/04/21	22/04/21	16.3	Fever, myalgia
P196	OT Assistant	24/04/21	26/04/21	14.6	Fever, sore throat, myalgia
P249	Nursing staff	28/04/21	28/04/21	14.6	Fever, rhinorrhoea

Figure 1. Maximum-likelihood phylogenies of double-vaccinated individuals in Hospitals A and B, with 100 randomly selected community-origin Delta variant SARS-CoV-2 genomes from the state of Delhi, India. Pangolin lineages of all sequences are indicated by the adjacent heatmap. Vaccination status of HCW is indicated by the far-right heatmap. Community sequences have unknown vaccination status.

Figure 2. Potential transmission networks between HCWs. Individual labels are coloured according to vaccine status, including the timing prior to infection at which the second vaccine was given, where relevant. The thickness of lines between individuals show the probabilities of distinct pairwise transmission events between individuals; these probabilities are conditional on transmission having occurred between the individuals observed in each network. Labels show the relative dates on which individuals became symptomatic, and respective gains of nucleotides in sequences collected from each individual with respect to the mutual consensus.

Figure 3. Assessments of network consistency. Data from simulations conducted on the transmission networks inferred for (A, B) hospital A and (C, D) hospital B. Simulations used the evolutionary model for the Delta variant of SARS-CoV-2 used to infer transmission networks. Simulated data were assessed to measure the total number of independent SNPs arising across the course of the transmission network, and the number of individuals in the network with SNPs that were unique to themselves. Data from the networks inferred for hospital 2 were consistent with the statistics of the simulations, though the data from hospital 3 was a significant outlier in terms of the number of individuals in the network with unique SNPs. These results provide evidence that the networks derived for hospital B is affected by missing data, though no such conclusion could be made for the networks derived for hospital A.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [naturescirepFinalSuppFigures.pdf](#)