The impact of SARS-CoV-2 vaccination on Alpha & Delta variant transmission

David W Eyre[1,2], Donald Taylor[3], Mark Purver[3], David Chapman[4], Tom Fowler[3,5], Koen B Pouwels[2,6], A Sarah Walker[2,7], Tim EA Peto[2,7]

[1]Big Data Institute, Nuffield Department of Population Health, University of Oxford, Oxford, UK

[2]NIHR Health Protection Research Unit in in Healthcare Associated Infections and Antimicrobial Resistance, University of Oxford, Oxford, UK

[3]Department of Health and Social Care, UK Government, London, UK

[4]Deloitte MCS Ltd, London, UK

[5]William Harvey Research Institute, Queen Mary University of London, London UK

[6]Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, Oxford, UK

[7]Nuffield Department of Medicine, University of Oxford

Abstract

Background

Pre-Delta, vaccination reduced transmission of SARS-CoV-2 from individuals infected despite vaccination, potentially via reducing viral loads. While vaccination still lowers the risk of infection, similar viral loads in vaccinated and unvaccinated individuals infected with Delta question how much vaccination prevents onward transmission.

Methods

We performed a retrospective observational cohort study of contacts of SARS-CoV-2-infected index cases using contact testing data from England. We used multivariable logistic regression to investigate the impact of index case and contact vaccination on transmission, and how this varies with Alpha and Delta variants (classified using S-gene detection/calendar trends) and time since second vaccination.

Results

51,798/139,164(37.2%) contacts tested were PCR-positive. Two doses of BNT162b2 or ChAdOx1 vaccines in Alpha variant index cases independently reduced PCR-positivity in contacts (aOR, adjusted odds ratio vs. unvaccinated=0.18[95%CI 0.12-0.29] and 0.37[0.22-0.63] respectively). The Delta variant attenuated vaccine-associated reductions in transmission: two BNT162b2 doses reduced Delta transmission (aOR=0.35[0.26-0.48]), more than ChAdOx1 (aOR=0.64[0.57-0.72]; heterogeneity p<0.001). Variation in viral load (Ct values) explained only a modest proportion of vaccine-associated transmission reductions.

Transmission reductions declined over time since second vaccination, for Delta reaching similar levels to unvaccinated individuals by 12 weeks for ChAdOx1 and attenuating substantially for BNT162b2. Protection from vaccination in contacts also declined in the 3 months after second vaccination.

Conclusions

Vaccination reduces transmission of Delta, but by less than the Alpha variant. The impact of vaccination decreased over time. Factors other than PCR-measured viral load are important in vaccine-associated transmission reductions. Booster vaccinations may help control transmission together with preventing infections.

Introduction

SARS-CoV-2 vaccines have been shown in randomised controlled trials[1–3] and real-world population studies[4,5] to prevent infection and adverse outcomes from several SARS-CoV-2 variants including Alpha (B.1.1.7) and Delta (B.1.617.2).[6–8]

Vaccination also potentially prevents onward transmission by at least two mechanisms. Firstly, by reducing symptomatic and asymptomatic infections and therefore the number of infectious individuals, and secondly via reduced onward spread from those who become infected despite vaccination. Household studies have demonstrated vaccination reduces onward transmission of the Alpha variant from those infected despite vaccination in the UK,[9] Israel[10,11] and Finland.[12] One hypothesised mechanism is lower viral loads observed in post-vaccination Alpha infections[7,13] compared in unvaccinated individuals, as viral load is associated with the likelihood of infection in contacts.[14,15]

However, viral loads in Delta variant infections occurring after vaccination are similar in vaccinated and unvaccinated individuals,[8,16] although the duration of viral shedding may be reduced.[17,18] This questions whether vaccination can control Delta spread as effectively as Alpha, and whether, with increased transmissibility,[19] this explains the rapid global dissemination of Delta despite rising vaccination coverage.

We use national contact testing data from England to investigate the impact of vaccination on onward transmission of SARS-CoV-2, and how this varies with Alpha and Delta variants

and time since second vaccination. We also investigate how much reductions in transmission after vaccination are explained by variation in PCR cycle threshold (Ct) values.

Methods

Setting and variants

We performed a retrospective observational cohort study of contacts of symptomatic and asymptomatic SARS-CoV-2-infected index cases. Data were obtained from the national contact tracing and testing service in England, NHS Test and Trace. Contacts were eligible for inclusion if they accessed NHS Test and Trace PCR testing 1-10 days after the index case's PCR test (typically following symptoms, but also after positive asymptomatic antigen screening tests), i.e. including contact pairs where the index case was the most likely source for any infection in the contact.[15] Only index cases with PCR tests performed by three national "lighthouse" laboratories (Milton Keynes, Alderley Park, Glasgow) were included, as these tests used the same standardised workflow and PCR assay (Thermo Fisher TaqPath, assessing for S gene, N gene and ORF1ab targets). Contacts could be tested by any community/hospital laboratory reporting results to NHS Test and Trace. Vaccination status in cases and contacts was obtained from National Immunisation Management Service (see Supplement).

Contacts of index cases tested between 01-January-2021 and 31-July-2021 were included as follows. Index cases were classified as the Alpha (B.1.1.7) variant based on S-gene target failure (SGTF), while this was considered a reliable proxy for Alpha, namely to 06-June-2021 (after which <5% cases had SGTF). From 10-May-2021 national spread of Delta meant that

>98% of sequenced cases were either due to the Alpha or Delta variants,[19] such that we used detection of S-gene on or after 10-May-2021 as a proxy for Delta (see Supplement).

We restricted our analysis to contacts undergoing testing, excluding untested contacts, to control as much as possible for biases related to health-seeking behaviour (including differences before and after vaccination), access to testing, and case ascertainment.[20]

Statistical analysis

We used multivariable logistic regression to investigate how onward transmission, i.e., SARS-CoV-2 PCR-positive tests in contacts, varied with index case vaccination status. Index case vaccination status was defined using administrative classifications as: unvaccinated, partially vaccinated (from day of first vaccine to 13 days after second vaccine), or fully vaccinated (≥14 days after second vaccine), further considering whether vaccination was AstraZeneca ChAdOx1 or Pfizer-BioNTech BNT162b2. We also investigated how onward transmission varied with Alpha vs. Delta index cases and whether any effects varied by vaccine by including pre-specified interaction terms. We additionally included a model term for time since 14 days after second BNT162b2 or ChAdOx1 vaccine to estimate the effect of time since second vaccine.

We adjusted for the following additional covariates: contact event type; index case factors - age, sex, and symptom status; contact factors - age, sex, vaccination status and time since vaccination (as above); local deprivation, local SARS-CoV-2 incidence, and calendar time (to capture changes in behaviour/social distancing, the likelihood of acquisition from a third party, population-wide vaccine uptake, and the percentage of unvaccinated people

previously infected) (Table S1). We used natural cubic splines and log transformation to account for non-linearity and tested for interactions (see Supplement).

We refitted models including index case Ct values to investigate whether the effect of index case vaccination status was explained by viral load (approximated Ct value[21]).

Ethics

The study was performed as public health surveillance and NHS Test and Trace program quality assurance, under Section 251 of the NHS Act 2006 with approvals from Public Health England (PHE), the Department of Health and Social Care and NHS Test and Trace. PHE's Research Ethics and Governance Group (PHE's Research Ethics Committee) reviewed the study protocol and confirmed compliance with all regulatory requirements. As no regulatory or ethical issues were identified, it was agreed that full ethical review was not needed, and the protocol was approved.

Results

151,821 contacts of 99,597 index cases underwent PCR testing between 02-January-2021 and 02-August-2021. 12,657 contacts were excluded with incomplete data (8.3%, see Supplement). Of the remaining 139,164 contacts (95,716 index cases), 51,798(37.2%) tested PCR-positive. The median(IQR)[range] index case and contact ages were 38(26-50)[0-102] and 38(23-50)[0-104] years respectively. 50,356(53%) index cases and 77,277(56%) contacts were female (see Table S1-S2 for details by case and contact vaccine status). Contact events

were predominantly within households (97,387;70%), but also in household visitors (14,066;10%), at events and activities (14,270;10%) and at work/education (13,441;10%).

Index case vaccination and onward transmission

27,666/55,977(49%) contacts of unvaccinated index cases tested PCR-positive, as did 5,256/14,398(37%) and 9,623/36,085(27%) contacts of partially ChAdOx1 and BNT162b2 vaccinated cases, and 7,559/25,422(30%) and 1,694/7,282(23%) contacts of fully ChAdOx1 and BNT162b2 vaccinated cases. For index cases vaccinated twice with BNT162b2 or ChAdOx1 the median(IQR) days from second vaccine to an Alpha variant PCR-positive test was 41(26-62) or 27(18-43) respectively and 89(69-110) and 50(34-69) for Delta.

In a multivariable model (Tables 1, S4), BNT162b2 vaccination in Alpha variant index cases independently reduced PCR-positive results in contacts, with two doses (aOR, adjusted odds ratio at 14 days post-second vaccine vs. unvaccinated=0.18[95%CI 0.12-0.29]) reducing onward transmission more than one (aOR=0.74[0.70-0.80]). There was weak evidence that ChAdOx1 was less effective than BNT162b2 at preventing transmission after one (aOR vs. unvaccinated=0.82[0.76-0.88], p=0.11 vs BNT162b2) and two doses (aOR=0.37[0.22-0.63], p=0.085 vs BNT162b2).

The Delta variant was associated with increased onward transmission vs. Alpha for symptomatic index cases (aOR=1.30[1.10-1.54]) and to a greater extent for asymptomatic index cases (aOR=2.14[1.75-2.60]). Post-second dose vaccine-associated reductions on onward transmission were also attenuated with Delta, for both BNT162b2 by 1.9-fold (aOR=1.93[1.25-2.99]) and ChAdOx1 by 1.7-fold (aOR=1.71[1.01-2.90]). This resulted in two

BNT162b2 doses reducing onward transmission of Delta by a greater extent than ChAdOx1 (aOR=0.35[0.26-0.48] vs aOR=0.64[0.57-0.72], respectively, heterogeneity p<0.001).

Vaccination in contacts

The estimated effect of contact vaccination status does not reflect overall vaccine effectiveness, as study inclusion was conditional on the contact being tested (typically after developing symptoms). However, as expected, PCR-positivity was highest in unvaccinated contacts (34,137/70,370(49%)), followed by those partially vaccinated with ChAdOx1, (3,401/10,325(33%)) and BNT162b2 (5,809/18,017(32%)); those fully vaccinated with ChAdOx1 (6,163/27,343(23%)) and BNT162b2 (2,288/13,109(17%)) had the lowest rates. In a multivariable model (Tables 1, S4), with Alpha contacts fully vaccinated with BNT162b2 had lower rates of PCR-positive tests than ChAdOx1 (aOR at 14 days post second vaccine vs. unvaccinated=0.06[0.04-0.10] vs. aOR=0.29[0.17-0.49] respectively, heterogeneity p<0.001). With Delta, more BNT162b2 vaccinated contacts tested PCR-positive than with Alpha, but there was no evidence that PCR-positivity changed in fully ChAdOx1 vaccinated contacts. Nevertheless, two doses of BNT162b2 remained more effective against Delta than ChAdOx1 (aOR vs. unvaccinated=0.10[0.08-0.13] vs aOR=0.28[0.25-0.32], respectively, heterogeneity p<0.001).

Duration of protection and transmission reductions

Vaccine-associated reductions in onward transmission declined over time since second vaccination in index cases (Figure 1A, Table S4). Independently of contact vaccination status, for each doubling of weeks since 14 days after second vaccination in index cases, the odds of a contact testing PCR-positive increased 1.13-fold (95%CI 1.09-1.17) for ChAdOx1 and

1.20-fold (1.10-1.31) for BNT162b2 with no evidence of a difference between vaccines (p=0.19). There was no evidence that fitting different rates by variant improved model fit. However, higher probabilities of PCR-positive results in contacts 14 days after second vaccination for Delta vs. Alpha meant that by 12 weeks post second ChAdOx1 dose there was no evidence that onward Delta transmission rates differed between those not vaccinated and those having received two ChAdOx1 doses and the impact of BNT162b2 had also attenuated substantially.

Although 14 days post second vaccination in contacts, those receiving BNT162b2 vs. ChAdOx1 were at lower risk of testing positive, the protective effect of vaccination in contacts waned faster for BNT162b2 than ChAdOx1 (Figure 1B, aOR per doubling of weeks since 14 days after second vaccination=1.37[95%CI 1.27-1.48] vs. 1.16[1.11-1.21] for ChAdOx1; heterogeneity p=0.002).

Other transmission risk factors

Multiple other factors were associated with contacts testing positive (Figure 2, Table S4, Figures S2-S4), including contact event type and index case age, with the highest rates of PCR-positivity after household contact with index cases aged ≥30 years and the lowest rates following contact with index cases <20 years at work or education (Figure 2A). Contacts in their 30s, 40s and 70s had the highest rates of positive tests after household contact, while contacts in their 20s had the highest rates after contact events outside their own home (Figure 2B). Contacts of index cases of the opposite sex were more likely to test positive, except for children where contacts of girls were more likely to test positive (Figure 2C). Male contacts were more likely than female contacts to be infected outside the home (Figure S2).

Case-contact pairs of similar ages were most likely to test positive, particularly with increasing age (Figure 2D). Contacts of asymptomatic index cases were less likely to test positive (aOR for Alpha=0.28[95%CI 0.26-0.30], Delta=0.61[0.50-0.73]) likely related to both lower viral loads (Figure 3) and symptoms. Contacts living in more deprived areas and areas with higher SARS-CoV-2 incidence (Figure S3) were more likely to test positive. Positivity also varied by calendar time (Figure S4).

Extent of vaccine impact on transmission explained by viral load

Consistent with previous reports, vaccination with BNT162b2 or ChAdOx1 was associated with lower viral loads in Alpha index cases at the time of their positive test, e.g. after two vaccinations in the presence of symptoms, median Ct values (IQR) were 27.9(19.7-32.8) and 25.5(18.1-33.0) vs. 18.4(15.8-22.8) if unvaccinated. However, Delta variant infections had similar viral loads independent of vaccination status (Figure 3), and higher viral loads than Alpha in both symptomatic and asymptomatic infections.

We investigated if adjusting for index case Ct values could explain the attenuated reductions in onward transmission after vaccination seen with the Delta variant. Estimates, adjusted for Ct value, of the impact of index case vaccination status and variants showed variation in measured Ct value accounted for only a modest proportion of the impact of vaccination overall (Figure 4A). This potentially explains why vaccination still reduces onward transmission of Delta despite Ct values at the index positive test being similar regardless of vaccination status. Higher viral loads (lower Ct values) were independently associated with increased transmission for both Alpha and Delta, but with a greater reduction in transmission of Alpha vs. Delta at lower viral loads (Figure 4B).

239

240 Discussion

241 Using large-scale contact tracing data, we show that BNT162b2 and ChAdOx1 vaccination
242 both reduce onward transmission of SARS-CoV-2 from individuals infected despite
243 vaccination. However, reductions in transmission are lower for both vaccines for the Delta
244 variant compared to Alpha. Vaccines continue to provide protection against infection with
245 Delta, but to a lesser degree than with Alpha, particularly considering symptomatic
246 infections or infections with moderate/high viral loads.[8] Therefore, Delta erodes vaccine-
247 associated protection against transmission by both making infection more common and
248 increasing the likelihood of transmission from vaccinated individuals who become infected.
249

250 It has been hypothesised that vaccines reduce onward transmission from infected
251 vaccinated individuals by reducing viral loads, as higher viral loads are associated with
252 transmission.[14,15] Therefore, it is perhaps surprising we found that most of the effect of
253 vaccines persisted after adjusting for Ct values, i.e., factors other than PCR-measured viral
254 load at diagnosis are important in vaccine-associated transmission reductions. The single
255 measured Ct value only approximates viral load at the time of transmission, as viral loads
256 are dynamic over time.[22] Hence, observed viral loads may not be representative of viral
257 loads at transmission, however, the strong relationship between measured Ct values and
258 risk of onward transmission argues against this[15] (replicated here, Figure 4B). Therefore, it is
259 possible vaccination acts by facilitating faster clearance of viable infectious virions,[17,18] but
260 leaving damaged ineffective virions behind that still contain PCR-detectable RNA. This may

mean antigen assays have advantages in predicting the risk of onward transmission in those vaccinated, but this needs further study.

We found that index cases infected with the Delta variant and vaccinated with BNT162b2 had lower odds of having PCR-positive contacts compared to index cases receiving ChAdOx1, with potentially insufficient power to resolve differences for Alpha. Contacts vaccinated twice with BNT162b2 also had lower rates of Alpha and Delta infections than those vaccinated with ChAdOx1.

Protection against onward transmission waned within 3 months post second vaccination. For Alpha this still left good levels of protection against transmission, but for Delta this eroded much of the protection against onward transmission, particularly for ChAdOx1, which by 3 months post second vaccine had no evidence of difference in transmission compared to that seen in unvaccinated individuals. "Waning" of protective behaviour over time may also underlie some of the differences seen, with vaccination facilitating reduced social distancing and mask wearing. However, reductions in antibody levels[23] and vaccine effectiveness[8] over time suggest biological explanations for increasing transmission over time are likely important. Additionally, some of the observed decline may be attributable to the fact that those clinically vulnerable with weaker immune systems were vaccinated longer ago. We also find that the probability of a contact testing positive increased with time since their second vaccination. Although BNT162b2 provided higher levels of protection for contacts throughout the 3 months post-second vaccine, protection against infection waned faster for BNT162b2 than ChAdOx1, as also seen in a representative UK survey.[8]

285

286 This study has several limitations. We considered only contacts who underwent PCR testing,
287 to minimise bias introduced by differences in testing behaviour that may occur for multiple
288 reasons including vaccination of contacts. This means we cannot estimate secondary attack
289 rates by case and contact vaccination status, and that absolute protective effects of
290 vaccination on transmission may be under-estimated as vaccine-protected uninfected
291 contacts may not have sought testing. Our approach is also not likely to eliminate bias,
292 particularly if test-seeking behaviour is related to perceived vaccine efficacy, given non-
293 specificity of many symptoms.[24] We did not have sufficient data to consider the impact of
294 previous infection status, which is also imperfectly ascertained in national testing programs.
295 It is likely that part of the explanation for the declines over time in the adjusted probability
296 of contacts testing positive (Figure S4), is increasing prevalence of prior infection in the
297 unvaccinated group, along with changes in test seeking behaviour and the incidence of
298 other infections causing similar symptoms.[25] We also had to use SGTF and time as a proxy
299 for Alpha vs. Delta infection rather than sequencing, which means some low viral load Delta
300 infections with SGTF may have been misclassified as Alpha, however we restricted the time
301 period of our dataset to minimise this. As we considered all PCR results in contacts, not just
302 those tested with assays including an S-gene target, we could not assess SGTF concordance
303 as supporting evidence for transmission between case-contact pairs. Finally, we did not
304 have data to adjust for comorbidities; with clinically vulnerable individuals and healthcare
305 workers vaccinated earlier, this may have partly impacted some of our findings, particularly
306 on waning over time and differences by vaccine type.

307

The Delta variant has spread globally and caused resurgences of infection even in the setting of high vaccination coverage. Increased onward transmission from individuals who become infected despite vaccination is an important reason for its spread. Booster vaccination campaigns being considered and implemented[26] are likely to help control transmission as well as preventing infections.

Data availability

Applications to use the data in this study can be made to NHS Digital's Data Access Request Service, please see https://digital.nhs.uk/services/data-access-request-service-dars for more details.

Declarations

DWE declares lecture fees from Gilead outside the submitted work. No other author has a conflict of interest to declare.

Funding

This study was funded by the UK Government's Department of Health and Social Care. This work was supported by the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Healthcare Associated Infections and Antimicrobial Resistance at Oxford University in partnership with Public Health England (PHE) (NIHR200915), and the NIHR Biomedical Research Centre, Oxford. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health

330 Research, the Department of Health or Public Health England. DWE is a Robertson
331 Foundation Fellow and an NIHR Oxford BRC Senior Fellow. ASW is an NIHR Senior
332 Investigator.

333

References

1 Polack FP, Thomas SJ, Kitchin N, *et al.* Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *New Engl J Med* 2020; 383: 2603–15.

2 Voysey M, Clemens SAC, Madhi SA, *et al.* 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. *Lancet* 2021; 397: 99–111.

3 Baden LR, Sahly HME, Essink B, *et al.* Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *New Engl J Med* 2020; 384: 403–16.

4 Bernal JL, Andrews N, Gower C, *et al.* Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. *Bmj* 2021; 373: n1088.

5 Dagan N, Barda N, Kepten E, *et al.* BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. *New Engl J Med* 2021. DOI:10.1056/nejmoa2101765.

6 Bernal JL, Andrews N, Gower C, *et al.* Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. *New Engl J Med* 2021; 385: 585–94.

7 Pritchard E, Matthews PC, Stoesser N, *et al.* Impact of vaccination on new SARS-CoV-2 infections in the United Kingdom. *Nat Med* 2021; 27: 1370–8.

8 Pouwels KB, Pritchard E, Matthews PC, *et al.* Impact of Delta on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. *Medrxiv* 2021; : 2021.08.18.21262237.

354 9 Harris RJ, Hall JA, Zaidi A, Andrews NJ, Dunbar JK, Dabrera G. Effect of Vaccination on
355 Household Transmission of SARS-CoV-2 in England. *New Engl J Med* 2021; 385: 759–60.

356 10 Layan M, Gilboa M, Gonen T, *et al.* Impact of BNT162b2 vaccination and isolation on
357 SARS-CoV-2 transmission in Israeli households: an observational study. *Medrxiv* 2021; :
358 2021.07.12.21260377.

359 11 Prunas O, Warren JL, Crawford FW, *et al.* Vaccination with BNT162b2 reduces
360 transmission of SARS-CoV-2 to household contacts in Israel. *Medrxiv* 2021; :
361 2021.07.13.21260393.

362 12 Salo J, Hägg M, Kortelainen M, *et al.* The indirect effect of mRNA-based Covid-19
363 vaccination on unvaccinated household members. *Medrxiv* 2021; : 2021.05.27.21257896.

364 13 Levine-Tiefenbrun M, Yelin I, Katz R, *et al.* Initial report of decreased SARS-CoV-2 viral
365 load after inoculation with the BNT162b2 vaccine. *Nat Med* 2021; 27: 790–2.

366 14 Marks M, Millat-Martinez P, Ouchi D, *et al.* Transmission of COVID-19 in 282 clusters in
367 Catalonia, Spain: a cohort study. *Lancet Infect Dis* 2021; 21: 629–36.

368 15 Lee LYW, Rozmanowski S, Pang M, *et al.* SARS-CoV-2 infectivity by viral load, S gene
369 variants and demographic factors and the utility of lateral flow devices to prevent
370 transmission. *Clin Infect Dis* 2021; : ciab421-.

371 16 Brown CM, Vostok J, Johnson H, *et al.* Outbreak of SARS-CoV-2 Infections, Including
372 COVID-19 Vaccine Breakthrough Infections, Associated with Large Public Gatherings —

373 Barnstable County, Massachusetts, July 2021. *Morbidity Mortal Wkly Rep* 2021; 70: 1059–
374 62.

375 17 Singanayagam A, Hakki S, Dunning J, *et al.* Community Transmission and Viral Load
376 Kinetics of SARS-CoV-2 Delta (B.1.617.2)Variant in Vaccinated and Unvaccinated Individuals.
377 *Ssrn Electron J* 2021. DOI:10.2139/ssrn.3918287.

378 18 Chia PY, Ong SWX, Chiew CJ, *et al.* Virological and serological kinetics of SARS-CoV-2
379 Delta variant vaccine-breakthrough infections: a multi-center cohort study. *Medrxiv* 2021; :
380 2021.07.28.21261295.

381 19 Public Health England. SARS-CoV-2 variants of concern and variants under investigation
382 in England: Technical briefing 21. 2021; published online Aug 20.
383 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_
384 data/file/1012644/Technical_Briefing_21.pdf (accessed Sept 2, 2021).

385 20 Fukushima W, Hirota Y. Basic principles of test-negative design in evaluating influenza
386 vaccine effectiveness. *Vaccine* 2017; 35: 4796–800.

387 21 Public Health England. Understanding cycle threshold (Ct) in SARS-CoV-2 RT-PCR. 2020;
388 published online Oct 1.
389 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_
390 data/file/926410/Understanding_Cycle_Threshold__Ct__in_SARS-CoV-2_RT-PCR_.pdf
391 (accessed Sept 27, 2021).

392 22 He X, Lau EHY, Wu P, *et al.* Temporal dynamics in viral shedding and transmissibility of
393 COVID-19. *Nat Med* 2020; 26: 672–5.

394 23 Wei J, Stoesser N, Matthews PC, *et al.* Antibody responses to SARS-CoV-2 vaccines in
395 45,965 adults from the general population of the United Kingdom. *Nat Microbiol* 2021; 6:
396 1140–9.

397 24 Lewnard JA, Patel MM, Jewell NP, *et al.* Theoretical Framework for Retrospective Studies
398 of the Effectiveness of SARS-CoV-2 Vaccines. *Epidemiology* 2021; 32: 508–17.

399 25 Vihta K-D, Pouwels KB, Peto T, *et al.* Symptoms and SARS-CoV-2 positivity in the general
400 population in the UK. *Medrxiv* 2021; : 2021.08.19.21262231.

401 26 Bar-On YM, Goldberg Y, Mandel M, *et al.* Protection of BNT162b2 Vaccine Booster
402 against Covid-19 in Israel. *New Engl J Med* 2021. DOI:10.1056/nejmoa2114255.

403