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Assortative mixing among vaccination groups and biased estimation of reproduction numbers

Assortative mixing, wherein there is more mixing within infection risk groups than would be expected to occur at random, has long been known to affect epidemic dynamics. A classic example comes from sexually transmitted diseases, for which assortative mixing within groups that have different levels of sexual activity increases the initial growth rate of the infection and the basic reproduction number ($R_0$) compared to the same population with more random choices of sexual partners.1 Assortative mixing within age groups has also been shown to affect dynamics and statistical inference for diseases spread through respiratory droplets,2 which motivates the widespread use of age-structured contact matrices in epidemic models. More recent studies3–5 have shown that assortative mixing with respect to vaccination status can affect outbreak sizes and estimates of vaccine efficacy in network-based epidemic models.

We hypothesised that assortative mixing among vaccination groups (vaccinated and unvaccinated) might be a source of bias in population-level estimates of the effective reproduction number ($R_e$) for the delta (B.1.617.2) variant of SARS-CoV-2. With a fixed total rate of contact between individuals, a lower $R_e$ is required to explain a given incidence of new infections when unvaccinated individuals preferentially contact other unvaccinated individuals. The prevalence of vaccination varies greatly across rural and urban areas as well as other social groupings within which assortative mixing is likely. According to Ohio Department of Health (ODH) data,6 the prevalence of vaccination among adults in Ohio, USA, counties ranges from slightly under 20% to slightly under 70%, with an overall prevalence of approximately 55%. To explore the potential impact of assortative mixing on estimation of $R_e$ we modified an age-stratified Susceptible-Exposed-Infected-Removed model of SARS-CoV-2 transmission in the state of Ohio to allow for assortative mixing within vaccination groups. This model was parameterised and fit using data from the ODH,7 the Centers for Disease Control and Prevention (CDC),8 and the United States Census Bureau.9 The contact matrix for age groups and some other parameters were taken from Prem and colleagues8 and Bubar and colleagues.9 The model $R$ is the spectral radius of the next-generation matrix.9

To make the rate of between-group contact $\rho$ (≤1) times the rate of within-group contact, we multiply each within-group contact rate $\beta_i$ by $\alpha$ and each between-group contact rate $\beta_j$ by $\rho \alpha$. The factor $\alpha$ ensures that the total rate of contact is not changed, and it is found by solving the following equation, in which $n_0$ is the number of unvaccinated individuals and $n_1$ is the number of vaccinated individuals.

$$a \left( \frac{n_0}{2} \right) + a \left( \frac{n_1}{2} \right) + \alpha p n_0 n_1 = \left( \frac{n_0 + n_1}{2} \right)$$

For a sufficiently large $n$ that $\sqrt{n} = n^2 + 2$, we get

$$\alpha = \frac{(n_0 + n_1)^2}{n_0^2 + 2pn_0 n_1 + n_1^2}$$

As intended, this gives us $\alpha = 1$ when $p = 1$. For several choices of $\rho$, we fit ODH daily reported incident cases using a Bayesian inference approach in...
which posterior distributions were sampled using a hybrid Markov chain Monte Carlo scheme (appendix). Figure 1 shows a histogram of the posterior distribution of $R$ and the fit to daily ODH incidence data. Although the estimates of $R$ differ considerably, there is almost no difference in the fit of the model to daily incident cases reported to ODH.

Despite the potential importance of assortative mixing among vaccination groups in understanding SARS-CoV-2 transmission, there is almost no quantitative empirical research available on this topic. A search using the Google search engine for phrases such as “covid19 + assortative mixing + vaccination” on Oct 25, 2021, returned about 87,000 results, of which the most relevant referred to age-assortative mixing and its potential impact on vaccination strategies. A search for the same terms using Google Scholar on the same day returned more than 400 hits, with the most relevant emphasising the interplay between age-assortative mixing and vaccination.

Although the epidemic modelling community routinely incorporates age-structured mixing matrices, assortative mixing among groups defined by other risk factors for infection are potential sources of bias in estimating epidemic parameters and the impact of interventions. Vaccination is one of the most important determinants of the risk of infection with SARS-CoV-2 in regions where a vaccine is widely available. An overestimation of $R$ could lead to undue pessimism about our ability to control the COVID-19 pandemic through vaccination and physical distancing.

The POLYMOD study shows how social survey methods could be used to better understand mixing patterns in an epidemic.10 Our simple experiment shows that such surveys could address an important gap in our ability to analyse the population-level transmission of disease and, by extension, to design and evaluate public health interventions in future epidemics.

We declare no competing interests.

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Figure 1: Assortative mixing and estimation of $R$

(A) Posterior distributions of $R$ under different degrees of assortative mixing within vaccination groups. (B) Posterior means and pointwise 90% credible intervals for the predicted 7-day moving average of daily COVID-19 cases plotted over daily ODH data. ODH=Ohio Department of Health.
Effectiveness of BNT162b2 against COVID-19 in adolescents

In the UK, COVID-19 vaccination for adults began in December, 2020.1 Because children and adolescents have a low risk of severe COVID-19 and due to concerns about rare but potentially severe myocarditis after mRNA vaccination—mainly after the second dose in young adult males—the UK Joint Committee on Vaccination and Immunisation (JCVI) initially recommended one dose for 16–17-year-olds from Aug 4, 2021,2 and recommended against vaccinating 12–15-year-olds because of marginal benefits versus risk. UK ministers subsequently recommended vaccinating this group with BNT162b2 (Comirnaty, Pfizer-BioNTech) or mRNA-1273 (Spikevax, Moderna) from Sept 13, 2021, to prevent BNT162b2 (Comirnaty) or mRNA-1273 subsequently recommended vaccinating this group with because of marginal benefits versus risk. UK ministers recommended against vaccinating 12–15-year-olds later second dose.4 The UK strategy provided a unique by the first dose and higher antibody responses after a 3-week interval, the UK recommends 8–12 weeks dose for 16–17-year-olds from Aug 4, 2021,2 and and Immunisation (JCVI) initially recommended one vaccination—mainly after the second dose in young adult males—the UK Joint Committee on Vaccination and Immunisation (JCVI) initially recommended one dose for 16–17-year-olds from Aug 4, 2021, and recommended against vaccinating 12–15-year-olds because of marginal benefits versus risk. UK ministers subsequently recommended vaccinating this group with BNT162b2 (Comirnaty, Pfizer-BioNTech) or mRNA-1273 (Spikevax, Moderna) from Sept 13, 2021, to prevent education disruption.3 Contrary to the authorised 3-week interval, the UK recommends 8–12 weeks between doses, because of the high protection provided by the first dose and higher antibody responses after a later second dose.4 The UK strategy provided a unique opportunity to assess single-dose mRNA vaccine effectiveness in adolescents during a period of high community infection with the highly transmissible delta (B.1.617.2) variant and subsequently with the more transmissible, and now dominant, omicron (B.1.1.529) variant.

We used a test-negative, case-control design to estimate vaccine effectiveness after one BNT162b2 dose against PCR-confirmed symptomatic infection with the delta and omicron variants of SARS-COV-2 in England, as described previously.1 Vaccination status in symptomatic 12–15-year-olds and 16–17-year-olds with PCR-confirmed SARS-COV-2 infection was compared with vaccination status in symptomatic adolescents in the same age groups who had a negative SARS-COV-2 PCR test (appendix pp 1–3).

From Sept 13, 2021, onwards, there were 617,259 eligible tests for 12–15-year-olds and 225,670 for 16–17-year-olds with a test date within 10 days of symptom onset date that could be linked to the National Immunisation Management system (match rate 92.5%; appendix pp 4–6). Vaccine uptake to the National Immunisation Management system 10 days of symptom onset date that could be linked to the National Immunisation Management system (match rate 92.5%; appendix pp 4–6). Vaccine uptake and confirmed infections by age group and over time are summarised in the appendix (p 9).

After one vaccine dose in 12–15-year-olds, vaccine effectiveness against symptomatic disease caused by

![Figure: Vaccine effectiveness in 12–15-year-olds (A) and 16–17-year-olds (B) with symptomatic, PCR-confirmed COVID-19. Error bars are 95% CI.](https://example.com/figure.png)