

The importance of increasing primary vaccinations against COVID-19 in Europe



Pierre-Yves Boëlle, Eugenio Valdano*

Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, F75012, Paris, France

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ABSTRACT

In the European Union, mass vaccination against COVID-19 staved off the strict restrictions that had characterized early epidemic response. Now, vaccination campaigns are focusing on booster doses, and primary vaccinations have all but halted. Still, 52 million European adults are unvaccinated.

We investigated if reaching the still unvaccinated population in future vaccination campaigns would substantially decrease the current burden of COVID-19, which is substantial. We focused on vaccination homophily, whereby those who are unvaccinated are mostly in contact with other unvaccinated, making COVID-19 circulation easier. We quantified vaccination homophily and estimated its impact on COVID-19 circulation.

We used an online survey of 1,055,286 people from 22 European countries during early 2022. We computed vaccination homophily as the association between reported vaccination status and perceived vaccination uptake among one's own social contacts, using a case-referent design and a hierarchical logistic model. We used this information in an analysis of the COVID-19 reproduction ratio to determine the impact of vaccine homophily in transmission.

Vaccination homophily was present and strong everywhere: the average odds ratio of being vaccinated for a 10-percentage-point increase in coverage among contacts was 1.66 (95% CI=(1.60, 1.72)). Homophily was positively associated with the strictness of COVID-19-related restrictions in 2020 (Pearson = 0.49, $P = .03$). In the countries studied, 12%-to-18% of the reproduction ratio would be attributable to vaccine homophily.

Reducing vaccination homophily may curb the reproduction ratio substantially even to the point of preventing recurrent epidemic waves. In addition to boosting those already vaccinated, increasing primary vaccination should remain a high priority in future vaccination campaigns, to reduce vaccination homophily: this combined strategy may decrease COVID-19 burden.

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* Corresponding author. Institut Pierre Louis d'Epidémiologie et de Santé Publique, INSERM & Sorbonne Université, site Hôpital St. Antoine, 27 rue Chaligny, 75012, Paris, France.

E-mail address: eugenio.valdano@inserm.fr (E. Valdano).

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1. Introduction

With mass vaccination, countries in the European Union (EU) are now managing COVID-19 without resorting to the pervasive closures and movement restrictions that characterized the first year and a half of the pandemic. Vaccine uptake in the EU is high: 86% of adults have received at least one dose (European Centre for Disease Prevention and Control - Data). There, COVID-19 is transitioning from being an emergent disease to an endemic respiratory disease imposing considerable morbidity and mortality (Telenti et al., 2021). Vaccines will likely remain the most effective public health tool for its routine management, as treatment options are limited (Cohen, 2022; Hammond et al., 2022), and pervasive non-pharmaceutical interventions are no longer sustainable or socially justifiable. But what should future vaccination campaigns against COVID-19 aim for? Two extreme targets could be envisioned: The first is to increase the number of primary vaccinations among those 52 million adults who never got vaccinated; the second is to boost immunity among those already vaccinated, to make up for the relatively short-lived immunity conferred by vaccines (Andrews et al., 2022) and to increase their efficacy against new SARS-CoV-2 variants and subvariants. Current campaigns are unquestionably pursuing the latter, as policies to increase primary vaccinations, like vaccine mandates and restrictions selectively targeting the unvaccinated, have been scaled down. Primary vaccinations have stalled since early 2022 and policymakers have little hope, and no plans, to persuade those still unvaccinated to get the jab. Giving up on primary vaccinations, however, may mean accepting the current burden of COVID-19 as part of its long-term management, in terms of incidence of severe disease (Bowe et al., 2022), mortality - the EU recorded 242,000 COVID-19-attributable deaths from January to October 2022 (European Centre for Disease Prevention and Control - Data) - and post-acute sequelae (Ballering et al., 2022; Bowe et al., 2022; Phillips & Williams, 2021). In this study we show that increasing the number of primary vaccinations would still be extremely beneficial in terms of epidemic control. This is because in all EU countries under study, those who are not vaccinated tend to be socially connected and cluster together - an effect that may be described as *vaccination homophily*. Vaccination homophily implies that those unvaccinated are in contact with other unvaccinated individuals, even if the overall vaccination coverage is high. This creates clusters with low vaccination uptake and favors more frequent and larger outbreaks, making population-level epidemic control harder. This phenomenon has already been reported for flu (Edge et al., 2019), measles (van den Hof et al., 2002; Parker et al., 2006; Phadke et al., 2016; Zucker et al., 2020) and pertussis (Aloe et al., 2017; Phadke et al., 2016) and explored in modeling studies (Burgio et al., 2022; Glasser et al., 2016; Gromis & Liu, 2021; Mbah et al., 2012). Here, we quantified vaccination homophily for COVID-19 and found that it contributes to a sizeable share of the reproduction ratio - the average number of secondary cases that a case generates. Also, we found that this share increases as the already vaccinated population is boosted. Our study implies that vaccination coverage as a metric of population protection may be misleading and that increasing primary vaccinations - with the consequence of reducing homophily - would have an effect beyond direct protection: It would help bring down incidence in the community, reducing the burden of COVID-19 below current levels.

2. Methods

2.1. Survey data and complementary data sources

Data on vaccination was obtained from *The University of Maryland Social Data Science Center Global COVID-19 Trends and Impact Survey (Global COVID)*. This survey collects questionnaires filled by Facebook users. We included in the study 21 out of 27 member countries of the European Union, excluding Cyprus, Estonia, Latvia, Lithuania, Luxembourg, Malta, for insufficient data (Supplemental File Table S1 reports the sample size in the excluded countries). We also included Norway, a member of the European Economic Area that participates to the network of the European Centre for Disease Prevention and Control (ECDC). Tables 1 and 2 list the number of questionnaires by country, demographics and vaccination status. Questionnaires were offered in different languages, to Facebook users aged 18 years or older. We included questionnaires from January 1st, 2022, to April 30th, 2022. In this period vaccination coverage was stable in all countries (see Supplemental File Fig. S1): the largest increase was in Germany where an additional 2.3% of the adult population received a first injection. Responders were solicited at most once per month. From each questionnaire, we obtained age (recoded as 18–34 years old, 35–64 years old, 65+ years old), gender and the two following questions: 1) “Have you had a COVID-19 vaccination?”, possible answers: “yes”, “no”; 2) “Thinking about your friends and family, how many have gotten a COVID-19 vaccine?”, possible answers: “None of the people”, “A few people”, “Some people”, “Most people”, “All of the people”. We excluded users who did not reply to either question. Tables 1 and 2 report the number of respondents in the study, by country, vaccination status, gender and age. To determine whether there was evidence of selection bias with respect to vaccination status, we used the individual weights that the data provider made available (described in Ref. (Barkay et al., 2020)), and which allowed computing population-level estimates from the survey data. Additional data to complement the analysis were country-level vaccination coverage and COVID-19-related deaths from ECDC (European Centre for Disease Prevention and Control - Data) and the Stringency Index from the COVID-19 Government Response Tracker (COVID-19 Government Response Tracker). For the latter, we averaged the daily reported values in each country over the period March 2020–December 2020, to compute the tightness of restrictions during the 1st year of the pandemic.

Table 1

Included survey respondents, by country and vaccination status. Percentages are computed on the total in each country, and the overall total in the last row.

country ISO code	country name	non vaccinated	vaccinated	total
AUT	Austria	4290 (17%)	20,573 (83%)	24,863
BEL	Belgium	2393 (10%)	22,215 (90%)	24,608
BGR	Bulgaria	5608 (37%)	9493 (63%)	15,101
CZE	Czechia	4488 (17%)	21,391 (83%)	25,879
DEU	Germany	16,353 (11%)	133,804 (89%)	150,157
DNK	Denmark	1510 (4%)	33,403 (96%)	34,913
ESP	Spain	3467 (5%)	60,309 (95%)	63,776
FIN	Finland	1344 (7%)	16,943 (93%)	18,287
FRA	France	16,126 (12%)	120,914 (88%)	137,040
GRC	Greece	3201 (11%)	25,857 (89%)	29,058
HRV	Croatia	2835 (26%)	7883 (74%)	10,718
HUN	Hungary	6306 (14%)	38,170 (86%)	44,476
IRL	Ireland	821 (6%)	11,983 (94%)	12,804
ITA	Italy	8616 (6%)	139,345 (94%)	147,961
NLD	Netherlands	4911 (11%)	38,313 (89%)	43,224
NOR	Norway	1691 (5%)	31,799 (95%)	33,490
POL	Poland	7484 (17%)	36,459 (83%)	43,943
PRT	Portugal	1981 (5%)	39,359 (95%)	41,340
ROU	Romania	7079 (21%)	26,548 (79%)	33,627
SVK	Slovakia	2930 (21%)	10,746 (79%)	13,676
SVN	Slovenia	1415 (23%)	4831 (77%)	6246
SWE	Sweden	5504 (5%)	94,595 (95%)	100,099
TOTAL		110,353 (10%)	944,933 (90%)	1,055,286

2.2. Inferring vaccination homophily

We defined *perceived coverage* for an individual as the fraction of those vaccinated among their friends and family. To measure vaccination homophily, we used a case-referent design, in which cases were vaccinated responders and referents were the unvaccinated, and the exposure was measured by perceived coverage. We assumed a logistic dependency between perceived coverage $\eta \in [0, 1]$ and vaccination status $v \in \{0, 1\}$ (with $v = 1$ meaning vaccinated) as follows:

$$\text{logit}P(v_{ik} = 1 | \eta, \mathbf{x}_i) = \alpha_i + \beta_i \eta_{ik} + \gamma \cdot \mathbf{x}_{ik}.$$

The indices indicate the country (i) and the k -th the individual of country i . Coefficient β_i is the log odds-ratio of perceived coverage for vaccination, i.e., $\exp(\beta_i \Delta \eta)$ is the odds-ratio of being vaccinated for a $\Delta \eta$ increase in perceived coverage. In the following, we will report odds ratios for an increase of 10 percentage points in perceived coverage ($\Delta \eta = 0.1$) and call it *vaccination odds ratio*. The variable \mathbf{x}_{ik} encodes the demographic characteristics of individual k , namely gender (Female vs. Male) and age in 3 classes ($<35, 35-64, \geq 65$) with γ the corresponding coefficients. We adopted a hierarchical description for α_i, β_i as:

$$(\alpha_i, \beta_i) \sim N \left((\alpha, \beta), \begin{pmatrix} \sigma_\alpha^2 & 0 \\ 0 & \sigma_\beta^2 \end{pmatrix} \right).$$

In the data, perceived coverage is available through the ordinal variable $J = \{\text{“None of the people”, “A few people”, “Some people”, “Most people”, “All of the people”}\}$. We modeled this as

$$P(J = j | \eta, \{c\}) = 1 \{c_{j-1} < \eta \leq c_j\},$$

where $1\{\cdot\}$ is the indicator function and $\{c\}$ is a set of 4 cutpoints to be estimated defining the boundaries for discretisation of η : $c_0 = 0 < c_1 < c_2 < c_3 < c_4 < c_5 = 1$. This finally gives the individual-level likelihood as follows:

$$L = \prod_i \prod_{k \in I} \frac{1}{c_{J_{ik}} - c_{J_{ik}-1}} \int_{c_{J_{ik}-1}}^{c_{J_{ik}}} d\eta \left(\frac{v_{ik} e^{\alpha_i + \beta_i \eta + \gamma \cdot \mathbf{x}_{ik}}}{1 + e^{\alpha_i + \beta_i \eta + \gamma \cdot \mathbf{x}_{ik}}} + \frac{1 - v_{ik}}{1 + e^{\alpha_i + \beta_i \eta + \gamma \cdot \mathbf{x}_{ik}}} \right).$$

The likelihood is explored using a Markov-Chain-Monte-Carlo (MCMC), with non-informative priors on $\alpha, \beta, \gamma, \sigma_\alpha^2, \sigma_\beta^2$ and $\{c\}$, implemented in Stan 2.1 interfaced with Python 3.8. More on the statistical inference is available in the Supplemental File. Model diagnostics (identifiability) and MCMC diagnostics are available in Supplemental File Fig. S2.

Table 2

Included survey respondents, by gender, age and vaccination status. Percentages are computed on the total of each row.

gender	age class	non vaccinated	vaccinated	total
F	18–34	16,358 (14%)	100,803 (86%)	117,161
F	35–54	35,456 (9%)	349,312 (91%)	384,768
F	65+	6409 (5%)	113,384 (95%)	119,793
M	18–34	11,441 (18%)	52,507 (82%)	63,948
M	35–54	34,077 (13%)	227,126 (87%)	261,203
M	65+	6612 (6%)	101,801 (94%)	108,413

2.3. Computing correlations with vaccination homophily

We computed the Pearson correlation of vaccination homophily in each country with some other quantities, e.g., the vaccination coverage reported by the ECDC. To account for uncertainty in homophily (coming from the uncertainty in β), we computed the Pearson correlation coefficients with each sample of the posterior distribution of the β s generated by the MCMC sampling. The median value of these coefficient was then reported as the measure of correlation. To compute P values, we repeated this approach with permutation of the countries (3000 permutations). The P value was then computed as the percentage of (permuted) correlation coefficients more extreme than the original measure. Statistical significance was set at the 0.05 threshold for P values.

2.4. Proportion of the reproduction ratio attributable to vaccination homophily

We computed the reproduction ratio for COVID-19 using the next-generation matrix (Diekmann et al., 2010) structured by age, gender and vaccine homophily. The next generation matrix holds the number of secondary cases that will be directly infected by a primary case in the population, accounting for the structure of the population. Here, we indexed the matrix according to vaccination status and age/gender characteristics (v, x) in the primary case and those in secondary cases (v', x') as $M(v, x; v', x')$. The largest eigenvalue of this matrix yields the reproduction ratio R (Ref. (Diekmann et al., 2010)). We wrote M as the sum of cases arising from contacts obeying vaccine homophily and those mixing randomly as $M = M_{homo} + M_{rand}$. We used this linear composition as the entries of both matrices encode the expected number of contacts per unit time established with a specific class, and guarantees that stochastic fluctuations around expected values are at most as large as the stochastic fluctuations of each component (see Supplemental File). Each matrix could in turn be split as arising from contacts in households and in the community, informed by age-, gender-stratified mixing matrices of household contacts ($C_H(x, x')$) and community contacts ($C_C(x, x')$) from the POLYMOD study (Mosson et al., 2008) and others (Béraud et al., 2015; Van Hoang et al., 2021). The final ingredient in $M_{homo} \cdot M_{rand}$ were the probabilities derived from the vaccine homophily analysis reported above. In the Supplemental File, we show that $M_{homo}(v, x; v', x') = (\varphi_H C_H(x, x') + \varphi_C \omega C_C(x, x')) P(v'|v, x, x')$ where φ_H (resp. φ_C) is the percentage of household (resp. community) contacts obeying homophily and $M_{rand}(v, x; v', x') = ((1 - \varphi_H) C_H(x, x') + (1 - \varphi_C) \omega C_C(x, x')) P(v'|x')$, where $\omega \in]0, 1]$ is the relative probability of transmission in community contacts relative to household contacts and $P(v|x) = \int_0^1 d\eta P(v|\eta, x) P(\eta|x)$ and $P(v'|v, x, x') = \int_0^1 d\eta P(v'|x) P(v|\eta, x) P(\eta|x) / P(v|x)$. We set $\omega = 0.3$ (Ref. (Faucher et al., 2022)), $\varphi_H = 1$ (i.e. all household contacts obey homophily) and $\varphi_C = 0.25$ and investigated alternative choices in the Supplemental File. We assumed leaky vaccine protection reducing susceptibility by a factor E (vaccine efficacy) and testing $E = 25\%$, $E = 50\%$, $E = 75\%$. Finally, to estimate how vaccine homophily impacts transmission, we considered the case where transmission would be purely random, i.e., $\varphi_H = \varphi_C = 0$ and computed the corresponding reproduction ratio $R^{(rand\ only)}$. The increase in reproduction ratio due to vaccination homophily is then computed as $(R - R^{(rand\ only)})/R$.

3. Results

3.1. Vaccination homophily

The statistical model provided a good fit for the probability of being vaccinated, given age, gender, and reported perceived coverage among friends and family (Fig. 1A and Supplemental File Fig. S3). We found strong, statistically significant, vaccine homophily in all countries (Fig. 1B and C), as measured by the vaccination odds ratio, i.e., the odds ratio of being vaccinated for an increase in perceived coverage of 10 percentage points. Sweden had the strongest homophily: vaccination O.R. was 1.88 CI=(1.84, 1.91). Hungary had the weakest homophily: vaccination O.R. was 1.44 CI=(1.42, 1.46). The Supplemental File Tables S2–S4 report the estimated values of the parameters of the statistical model. Also, Supplemental File Figs. S4 and S5 show that our estimates were insensitive to changing the parametrization of the prior distributions, suggesting that the data are providing most information and the priors are noninformative. There was no apparent association between homophily and vaccination coverage (Fig. 1D). In particular, countries in Western and Northern Europe spanned all the observed range of homophily, while all having coverage between 80% and 100%, and most around 90%. Among those countries, however, there was a positive association between homophily and the severity of the first waves of COVID-19, as measured by the total number of COVID-19-attributable deaths in 2020 per 100,000 inhabitants (see Supplemental File Fig. S6): Pearson correlation

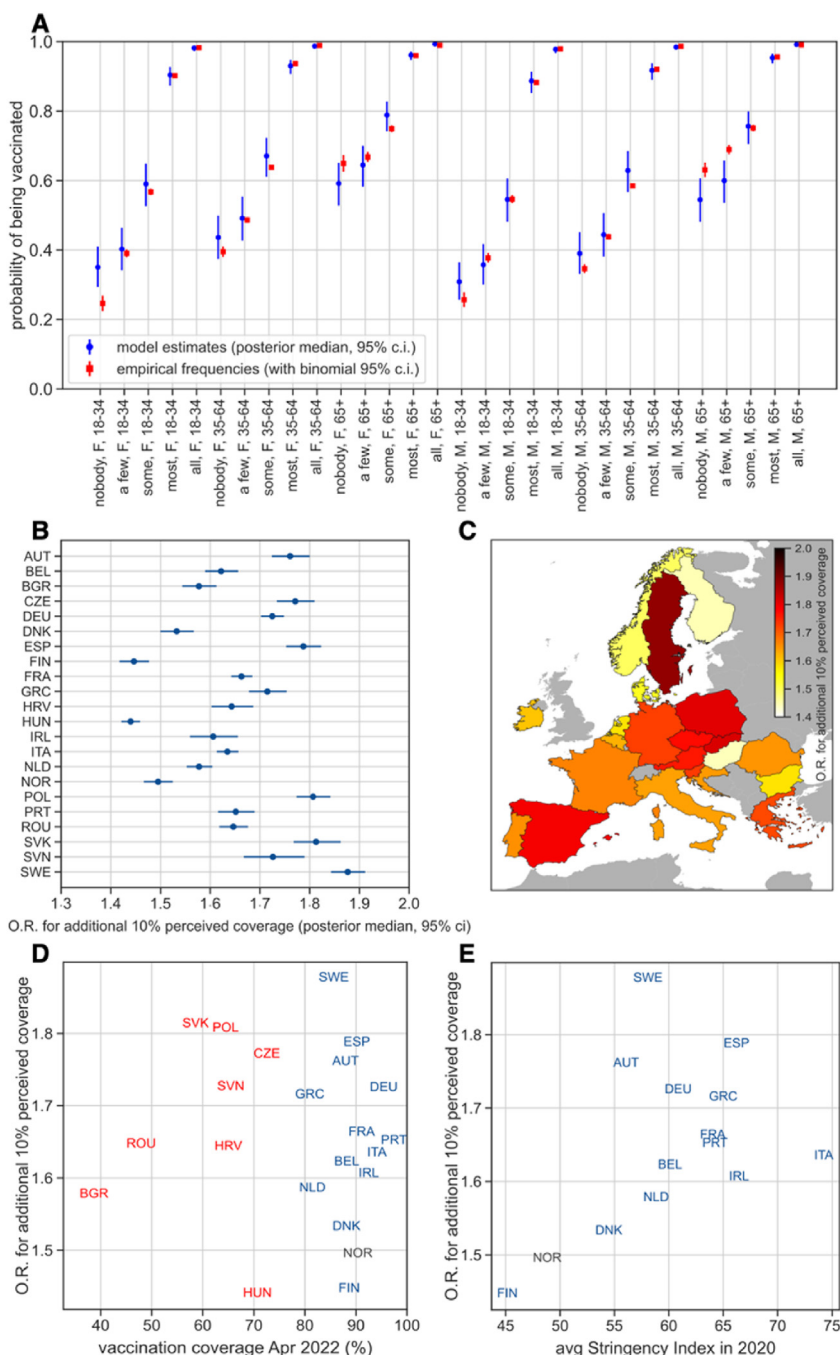


Fig. 1. Vaccination homophily. (A) Probability of being vaccinated conditioned on gender, age and reported perceived coverage across the countries under study (see Supplemental File for computation and Supplemental File Fig. S3 for country-specific probabilities): in blue model estimates reporting posterior median and 95% credibility interval; in red empirical frequencies with binomial 95% confidence intervals. (B) and (C) Posterior estimates of vaccination homophily in terms of posterior vaccination odds ratio for 10% increase in perceived coverage for each country under study: we report median values in B,C and 95% credibility intervals in B. (D) Scatter plot of vaccination coverage (April 2022) vs vaccination homophily. Countries in blue joined the EU before 2004 (Western Europe), those in red in 2004 or after (Eastern Europe). Countries in gray are in the ECDC network but not members of the EU. (E) Scatter plot of Stringency Index (averaged over March–December 2020) and vaccination homophily. Color code is the same as in (D).

with homophily was 0.46 ($P = .047$). Notably, the Pearson correlation between homophily and the tightness of restrictions put in place in 2020 (measured by the Stringency Index) was 0.49 ($P = .039$) – even stronger than that with surveillance indicators, revealing possible mechanisms linking homophily to the early response against the new pandemic (Fig. 1E). Instead, no correlation existed between mortality and vaccination coverage (Pearson -0.01 , $P = .97$), or tightness of restrictions and

vaccination coverage (Pearson 0.18, $P = .52$). We found no evidence that our estimates of homophily are sensitive to urbanization and geography. Firstly, adding the type of settlement (urban v rural) to the model had no impact on homophily estimates (Supplemental File Fig. S7). Secondly, the predictive performance of our model was similar across regions of the same country, showing that our country-level estimates of homophily are representative across geographic communities (Supplemental File Fig. S8). We found some evidence that patterns of individual beliefs, which are themselves known to exhibit homophily, may be associated with vaccination homophily. Specifically, adjusting for declared trust in politicians as a reliable source of COVID-19 information caused an overall increase in the estimated vaccination homophily, albeit modest and rarely statistically significant: in Poland, the country with the largest increase, vaccination O.R. went from 1.8 to 1.9 (see Supplemental File Fig. S7). Finally, we checked that a possible difference in the likelihood of responding to the survey given the vaccination status did not bias our findings (selection bias). To do this, we compared vaccination coverage stratified by country, gender, age in our sample, with population-level averages computed through the weights provided by the data owner. Sample coverage and estimated population coverage were statistically compatible in most countries and demographic classes. Only in Poland and Romania there seemed to be a consistent overrepresentation of people who got vaccinated, but even there the excess coverage was no larger than 4 percentage points (see Supplemental File Fig. S9).

3.2. Proportion of the reproduction ratio attributable to vaccination homophily

Our model estimated, in each country, the relative difference in the community reproduction ratio of COVID-19 at measured levels of vaccination homophily, and a counterfactual scenario with no homophily, i.e., in which the individual vaccination status is not correlated with the vaccination status of one's own contacts. Vaccination homophily was responsible for a sizeable fraction of the reproduction ratio in all the countries under study (Fig. 2A). The impact was lowest in Bulgaria (12% of the reproduction ratio), highest in Ireland (18%), at current levels of vaccination coverage, and assuming vaccine to be 50% effective in preventing infection (Ssentongo et al., 2022). To estimate this, we used social mixing data from the POLYMOD project (Mosson et al., 2008), and assumed that vaccination homophily was present among household contacts, and $\frac{1}{4}$ of community (non-household) contacts, to match the survey question “among your friends and family”. We also explored alternatives to these various assumptions. Alternative social mixing data from Ref. (Béraud et al., 2015; Mosson et al., 2008; Van Hoang et al., 2021) did not significantly change the ranking among countries, and caused the impact of homophily on the reproduction number R_t to increase or decrease by roughly 2 percentage points in each country (Supplemental File Fig. S10A). Assuming that only household contacts experienced homophily decreased its impact on R_t by roughly 3.5 percentage points in each country (Supplemental File Fig. S10B). Conversely, assuming that $\frac{1}{2}$ of community contacts experienced homophily increased its impact on R_t by roughly 3.5 percentage points in each country (Supplemental File Fig. S10B). The strength of vaccine protection had a strong effect: Very low efficacy (25%) was associated with a low impact of vaccine homophily: 4.5%–to-6.5% of R_t . High efficacy (75%) raised that to between 22% and 42%. Also, at high vaccine efficacy, the impact on R_t increased with vaccine coverage (Fig. 2B).

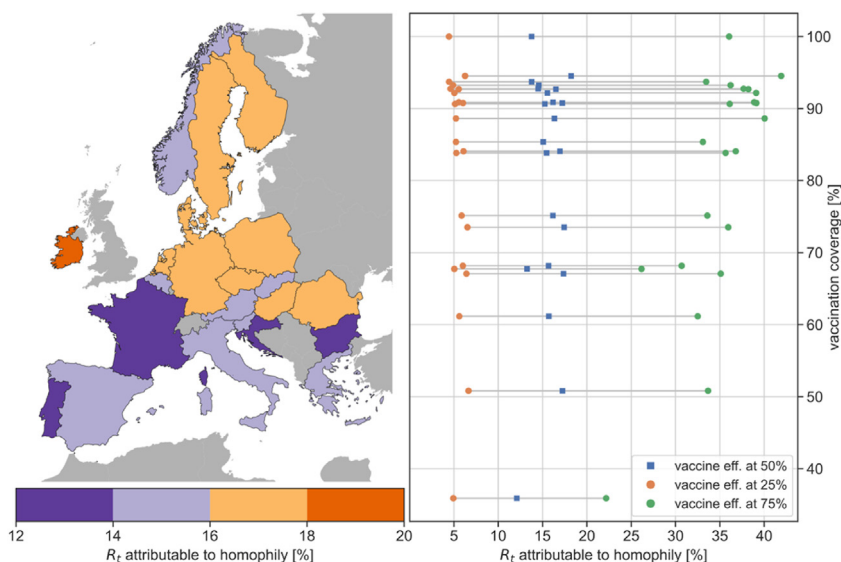


Fig. 2. Impact of vaccination homophily on the reproduction ratio. (A) Percentage of the reproduction ratio attributable to vaccination homophily, assuming that vaccination is 50% effective in protecting from infection, contact matrices from the POLYMOD study and that homophily applies to $\frac{1}{4}$ of non-household contacts. (B) Percentage of the reproduction ratio attributable to vaccination homophily at varying vaccination efficacy.

4. Discussion

Vaccination homophily, whereby the contacts of those unvaccinated are themselves likely unvaccinated, characterized all 22 European countries in the first four months of 2022, when primary vaccination campaigns were likely to have reached the *vaccine compliant* fraction of the population (Neumann-Böhme et al., 2020). Despite the high overall vaccination uptake, homophily was strong and unveiled the presence of clusters of unvaccinated people. Vaccination homophily was present in all European countries albeit with different strength. Sweden was the country where homophily was the highest. There, young men reporting that none of their friends were vaccinated had a probability of being vaccinated as low as 20%; those who instead reported that all of those around them were vaccinated had a probability of being themselves vaccinated close to 100% (Supplemental File Fig. S3). While these differences decreased with less homophily, they were still substantial: in Hungary, where homophily was the lowest, the corresponding probabilities were 40% vs 90%. Vaccination coverage and vaccination homophily had no simple correlation. For instance, vaccination coverage was almost the same in Finland and Sweden, 91% vs 89%, but homophily values were on the opposite side of the spectrum (Fig. 1C). The early evolution of the COVID-19 pandemic may help to explain these differences: early experience with the epidemic could have influenced the willingness to get vaccinated later, although it is not clear in which direction. On the one hand, high incidence and mortality in 2020 could have increased the perception of the risk related to COVID-19, making people more willing to get vaccinated. On the other hand, the exposure to high death and hospitalization counts and the experience of strict restrictions on movement and activities were linked to psychological distress (Aknin et al., 2022), which in turn might have prompted vaccine hesitancy (Aknin et al., 2022; Murphy et al., 2021). The result of these, and possibly other, competing drives is that, in western Europe, neither early epidemic severity, nor tightness of restrictions, seemed to impact the final vaccination coverage. But interestingly, that was not the case with homophily: a high early burden of COVID-19, and tight restrictions in 2020 were both associated with higher homophily. A possible interpretation of this is that the aforementioned psychological and societal stress contributed to polarizing trust in governments and institutions, which is in turn associated with vaccine acceptance (Bollyky et al., 2022).

Vaccine homophily is a threat to the effectiveness of vaccination campaigns, because clusters of unvaccinated people facilitate viral re-emergence and its circulation in the community, as described for other diseases (Edge et al., 2019; van den Hof et al., 2002; Parker et al., 2006; Phadke et al., 2016; Zucker et al., 2020; Aloe et al., 2017). Here, we showed that vaccination homophily also drives the reproduction ratio (R) of the COVID-19 epidemic up, making control less easy. Our findings indicate that a sizeable fraction of the current reproduction ratio could be attributed to vaccination homophily, ranging from 10% to 20% of the reproduction ratio, assuming that vaccines offer a 50% protection against SARS-CoV-2 acquisition. Differences in homophily, and in age- and gender-stratified vaccination uptake, explained the different impact homophily had on R across countries. Importantly, this means that vaccination uptake alone fails to describe the level of protection in the population – even if stratified on geography, gender and age. Notably, the effect of homophily could be large enough to keep an epidemic wave above the epidemic threshold: if, for instance, homophily is responsible for 20% of the reproduction ratio, and the reproduction ratio is no larger than 1.25, then acting on homophily could stop the epidemic wave. The existence of homophily, and its effect on community circulation, is thus an obstacle to keeping the epidemic under control, but also hints at what public health action should aim at. Indeed, the effectiveness of past and current vaccination campaigns is indisputable: they have been saving lives (Watson et al., 2022) and relieving the pressure on the healthcare system without the need of closures and movement restrictions. But the burden of COVID-19 is still high: reported COVID-19 mortality in the period January–October 2022 in the countries under study ranged from 11 to 119 deaths per 100,000 people (European Centre for Disease Prevention and Control - Data) and excess mortality was around 10% compared with 2016–2019 (Excess mortality). Plus, to date, there is no evidence that morbidity and mortality will go down on their own with time as COVID-19 transitions to endemicity (Bowe et al., 2022). On top of this, post-acute sequelae of COVID-19 may add to its long-term burden (Ballering et al., 2022; Bowe et al., 2022; Phillips & Williams, 2021), if incidence of infections remains high. Current vaccination strategies have little chance to invert this trend and will not keep COVID-19 circulation consistently below the epidemic threshold ($R < 1$), as they focus solely on boosting those already vaccinated: primary vaccinations have stalled for months, and measures to encourage them have been scaled back. Our results instead show that prolonged efforts to increase primary vaccinations, in combination with booster campaigns, would greatly pay off. New primary vaccinations would break the clusters of unvaccinated individuals and reduce homophily, and that would bring down the reproduction ratio, possibly below the epidemic threshold, as our model shows. In addition, we also estimate that the fraction of R attributable to homophily increases if vaccines become more effective, and especially so where uptake is already high. This means that the more effective booster campaigns are, by reaching high coverage and vaccine efficacy (Khoury et al., 2022), the more it will make sense to concurrently target primary vaccinations, to slash the residual fraction of reproduction ratio and make waves smaller and shorter, or possibly avoid them altogether.

Our study has limitations. It relies on survey respondents accurately reporting their demographic profile, vaccination status and perceived coverage, which may be biased with respect to the actual coverage among one's own friends and family. The analyzed sample of survey respondents was however large and heterogeneous, decreasing the impact of a perception bias in specific geographic or sociodemographic population strata. There may also be a selection bias if those vaccinated were more or less likely to respond to the survey, although our analysis showed that it is likely to be negligible. Analogously, estimates of the reproduction ratio rely on age- and gender-stratified mixing matrices which themselves rely on survey data. Testing different matrices however gave similar results (Supplemental File Fig. S10). The estimate of the impact of homophily

on R also relied on correctly matching the two data and deciding which social contacts obey the observed homophily: mixing matrices are reported by location (household, community, ...), while reported coverage is “among one's own friends and family”. We tested various assumptions and found little impact on results (Supplemental File Fig. S10). Another factor impacting the fraction of R explained by homophily was vaccine efficacy in preventing acquisition of SARS-CoV-2. We assumed that protection was the same for all those vaccinated: in reality, it changes with the number of doses, time from last dose and viral variant (Ssentongo et al., 2022). We believe, however, that adding this feature to our model would not change its qualitative behavior, and make it over-reliant on data and estimates which are often poorly available. We instead decided to explore a wide range of overall vaccine efficacy to study the impact of booster campaigns (resulting in an increase in average efficacy) on the role of homophily. Our study excludes those younger than 18 years old, not covered by the survey. Their vaccine uptake, however, is much lower than those of adults - 33% vs 86% (European Centre for Disease Prevention and Control - Data) -, limiting the bias they might induce when estimating the effect of homophily on COVID-19 circulation. Plus, if this bias does exist, it is likely to underestimate the effect of homophily (Nguyen et al., 2022). Our model does not include protection from previous infection (Stein et al., 2023) as we do not need to explicitly compute the reproductive ratio, only the relative fraction attributable to homophily. Plus, higher protection from previous infection among those unvaccinated would effectively appear in our model as lower vaccine efficacy (which tunes the relative protection of those vaccinated with respect to those unvaccinated), which we explored and already discussed. Finally, our study suggests that increasing the uptake of primary vaccinations may substantially decrease the circulation and burden of COVID-19, by reducing homophily, but it does not quantify the relationship between new vaccinations and drops in homophily. However, it is reasonable to assume that many new primary vaccinations must occur within cliques of previously unvaccinated individuals, given that most of the population has already been vaccinated, and those vaccinated are surrounded mostly by vaccinated individuals. And vaccinating inside cliques of unvaccinated individuals is what decreases homophily (Alvarez-Zuzek et al., 2022; Glasser et al., 2016).

5. Conclusion

In Europe, COVID-19 is shifting from an emergent threat to an endemic disease. Vaccination campaigns are keeping the pressure on the healthcare system in check, but the burden of COVID-19 is still considerable, in terms of severe disease, deaths and post-COVID-19 condition. Broadly, the current strategy is to repeatedly boost those who already got vaccinated, giving up on persuading those who have so far refused to. Vaccination campaigns should instead target primary vaccinations too, as our study shows that this has the potential to substantially decrease the circulation of COVID-19 in communities, and its burden. It will not be easy, but the public health benefit may warrant the effort.

CRedit authorship contribution statement

Pierre-Yves Boëlle: Formal analysis, Methodology, Writing – review & editing. **Eugenio Valdano:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.idm.2023.11.008>.

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