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MAJOR ARTICLE

Association Between Population-Level Factors and Household Secondary Attack Rate of SARS-CoV-2: A Systematic Review and Meta-analysis

Can Wang,[1] Xiaotong Huang,[1] Eric H. Y. Lau,[1,2] Benjamin J. Cowling,[1,2] and Tim K. Tsang[1,2]

[1]WHO Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China, and [2]Laboratory of Data Discovery for Health Limited, Hong Kong Science and Technology Park, New Territories, Hong Kong Special Administrative Region, China

Background. Accurate estimation of household secondary attack rate (SAR) is crucial to understand the transmissibility of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The impact of population-level factors, such as transmission intensity in the community, on SAR estimates is rarely explored.

Methods. In this study, we included articles with original data to compute the household SAR. To determine the impact of transmission intensity in the community on household SAR estimates, we explored the association between SAR estimates and the incidence rate of cases by country during the study period.

Results. We identified 163 studies to extract data on SARs from 326 031 cases and 2 009 859 household contacts. The correlation between the incidence rate of cases during the study period and SAR estimates was 0.37 (95% CI, 0.24–0.49). We found that doubling the incidence rate of cases during the study period was associated with a 1.2% (95% CI, 0.5%–1.8%) higher household SAR.

Conclusions. Our findings suggest that the incidence rate of cases during the study period is associated with higher SAR. Ignoring this factor may overestimate SARs, especially for regions with high incidences, which further impacts control policies and epidemiological characterization of emerging variants.

Keywords. SARS-CoV-2; heterogeneity; population incidence; secondary attack rate.

Studying household transmission is important to evaluating the transmissibility of an emerging or re-emerging virus [1, 2]. Household secondary attack rate (SAR), which is used to characterize the risk and heterogeneity in the risk of transmission, has been broadly reported for coronavirus disease 2019 (COVID-19) [3–5]. Furthermore, the household is one of the most important settings for transmission of infectious diseases, including influenza and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2, 6]. Therefore, understanding household transmission dynamics of SARS-CoV-2 would provide valuable information to guide control policies.

Previous reviews on household transmission studies have suggested that household SAR estimates (hereafter referred to as household SAR unless otherwise specified) could be different due to emerging variants, study location, and period [3, 7]. A range of characteristics of household members that may impact SAR estimates has been proposed, including age of index cases and contacts, symptom status of index cases and contacts, and comorbidities of contacts [3, 4, 8]. However, other population-level factors including population immunity, mobility change, and the intensity of community transmission may impact SAR estimates. These unaccounted-for population-level factors are also commonly acknowledged as limitations in the work of evaluating epidemiology and transmission risk of SARS-CoV-2, as well as making public health decisions [3, 4, 9]. Here, we aim to systematically review and analyze published data from household transmission studies to characterize the epidemiological and population-level factors affecting household SAR estimates.

METHODS

Definition of Household Secondary Attack Rate

In this study, an index case was defined as the first detected case in a household, while secondary cases were defined as the identified infected household contacts of the index case. The secondary attack rate within a household or family was defined as the proportion of infected household/family contacts. Household or family contacts include those living in the same residence as the index/primary case and family members of the index/primary case.

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Correspondence: Tim K. Tsang, PhD, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 7 Sassoon Road, Pokfulam, Hong Kong Special Administrative Region, China (timtsang@connect.hku.hk).

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Search Strategy and Selection Criteria

This systematic review was conducted following the updated Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement [10]. A standardized search was done in PubMed, using search terms including "SARS-CoV-2," "COVID-19," "secondary attack rate," "household," "family transmission," or "close contacts" (Supplementary Data 1). Articles published before March 9, 2022, were identified from previous systematic reviews using the same search terms [3, 7]. Then we used the same search terms to identify articles published from March 9 to June 9, 2022. There were no restrictions on language or study location. Additional relevant articles from reference sections were also reviewed.

Two authors (C.W. and X.H.) independently screened the titles and full texts and extracted data from the included studies, with disagreement resolved by consensus together with a third author (T.K.T.). Studies identified from different sources were de-duplicated. We included studies that provided sufficient data for computing the empirical SAR. The following articles were excluded: (1) case reports or case series focusing on an individual household; (2) full text was not available.

Data were extracted from included studies into a standard form (Supplementary Table 3), including the following information: (1) study period, (2) study locations, (3) the number of infections among household contacts, (4) the number of all identified household contacts, (5) ascertainment method for infections (types of laboratory tests or symptom-based ascertainment), (6) test coverage among identified contacts, (7) predominant circulating viruses during the study period (ancestral strains or variants), and (8) precision of study period (days or months). When exact days were not available, we assumed the day was the 15th. To explore the relationship between household SAR estimates and preexisting population immunity or incidence rate of cases in a population during the study period, we obtained data on the population size, time series of number of COVID-19 cases and deaths, and the number of people fully vaccinated by countries from the Our World in Data and World Health Organization databases [11, 12].

Data Analysis

As most studies did not report variant-specific SAR, we grouped predominant circulating viruses during each study period into the following 4 categories (Supplementary Data 2): (1) ancestral strains, (2) any variants (except Omicron) with ancestral strains, (3) any variants (except Omicron) without ancestral strains, (4) Omicron. We obtained information on predominant circulating viruses during the study period from the Nextstrain website if such information was not available in the study [13]. When determining circulating viruses during the study period, we only included those dominant strains that accounted for >10% of all identified viruses.

For each study, we extracted the number of infections and household contacts during the study period, SAR estimates, and corresponding 95% CIs. Then, we conducted random-effects meta-analyses using the inverse variance method and restricted maximum likelihood estimator for heterogeneity to summarize SAR estimates for studies with different viruses, case ascertainment methods, or study periods [14, 15]. The Cochran Q test and the I^2 statistic were used to identify and quantify heterogeneity among included studies [16]. An I^2 value >75% indicated high heterogeneity [16]. A meta-analysis was conducted by the circulating viruses, test coverage, only polymerase chain reaction (PCR), or other case ascertainment methods for cases in households, as well as whether the study period was before June 1, 2020, to explore the impact of insufficient tests during the early pandemic period.

We explored differences in SAR estimates by predominant circulating viruses (hereafter referred to as the baseline model), as multiple reports suggested that the transmissibility of certain strains and variants could be different. To evaluate the impact of preexisting population immunity or incidence rate of cases in the population on SAR estimates, we adapted a meta-regression approach. Based on the location of each study, we computed the $\log_2$-transformed cumulative incidence of cases on the day before the beginning of the study. We also used cumulative incidence of deaths as an alternative measure since reporting of death was more stable and less sensitive to reporting bias [17]. In addition, we explored the effects of preexisting population immunity, reflected by the proportion of people fully vaccinated before the start of the study, on SAR estimates. Finally, as a proxy of intensity of transmission in the community, the $\log_2$-transformed incidence rate of cases or deaths during the study period was also computed to evaluate its impact on SAR estimates using the same meta-regression approach. In these analyses, SARs were adjusted by predominant circulating viruses since the SARs for different viruses could be different. We conducted a sensitivity analysis by repeating the same analysis but restricted to studies with accurate study periods. Statistical analyses were conducted using R, version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

In the systematic review, we updated the search from Madewell et al. [7] and identified 579 new studies with 2 duplicates. After screening the titles and abstracts of the remaining articles, we screened 111 full texts. On the basis of our selection criteria, we excluded 88 of those studies, and 23 met our inclusion criteria (Supplementary Table 1) [18–40]. Combined with 140 studies identified from previous reviews [5, 41–166], there were 163 studies included in our analysis (Supplementary Figure 1, Supplementary Table 2). Overall, 163 studies provided 179 estimates of household SAR, with 326 031 cases among 2 009 859

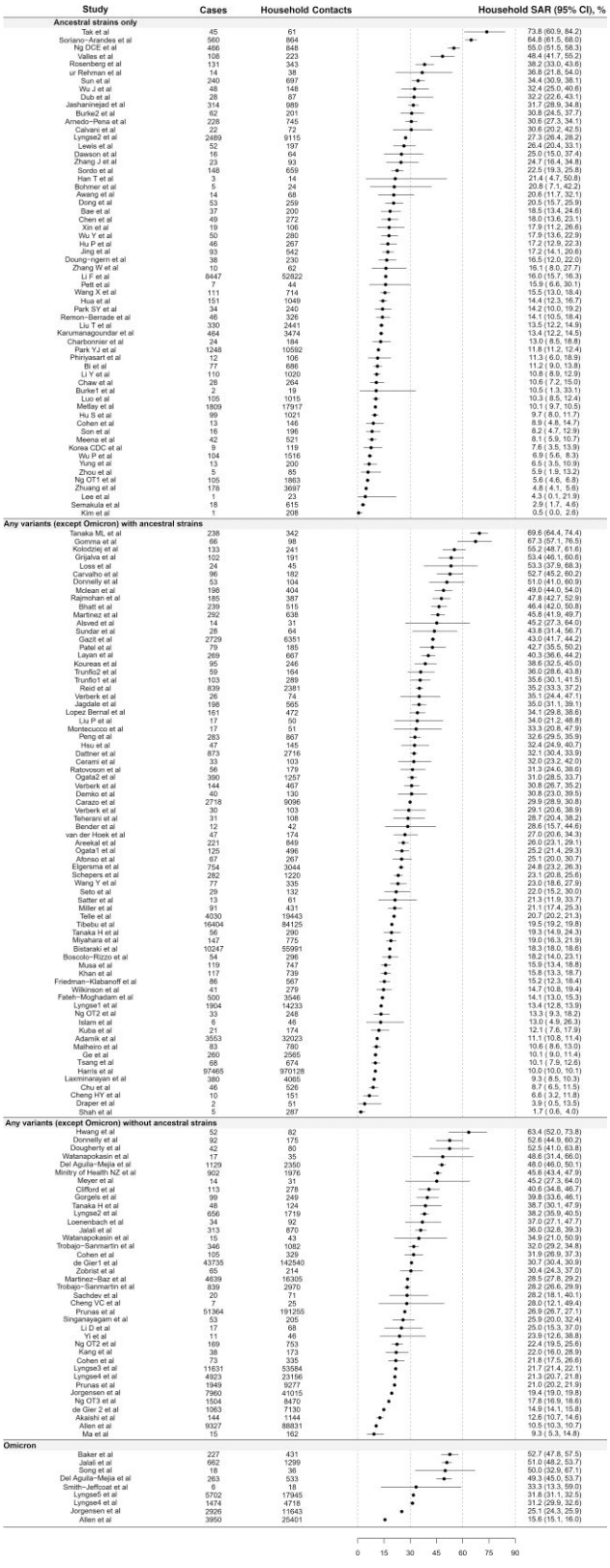

Figure 1. Estimates of household SAR for all studies grouped by circulating viruses during the study period. Dashed vertical lines represent 0%, 30%, 60%, and 90% household SAR estimates. Abbreviation: SAR, secondary attack rate.

household contacts (Figure 1). Among all included studies, 127 provided accurate study periods. Regarding case ascertainment methods among household contacts, almost all studies used PCR, while 29 studies additionally used symptoms, antigen, serology, or clinical criteria. Ten study used rapid tests [167–169], serology [19], antigen [169–171], or symptoms [172–174] instead of PCR. Four remaining studies had unknown ascertainment methods for secondary cases [175–178]. Regarding test coverage of household contacts, most studies (118 out of 163) tested all identified household contacts, while other studies provided test coverages ranging from 11% to 96% or only symptomatic individuals were tested. The remaining 15 studies did not provide information on test coverage among identified contacts. In terms of predominant circulating viruses, 60 estimates were based on cases infected by ancestral strains only, while the remaining 72, 38, and 9 estimates investigated infections by any variants (except Omicron) with ancestral strains, any variants (except Omicron) without ancestral strains, and Omicron, respectively.

Impact of Population-Level Incidence Rate of Cases During the Study Period and Cumulative Incidence of Cases Before the Study Period on Household SAR

Despite large heterogeneity in SAR estimates, we still observed a positive trend between the SAR and the incidence rate of cases (correlation, 0.37; 95% CI, 0.24–0.49; $P < .01$) or deaths (correlation, 0.34; 95% CI, 0.20–0.47; $P < .01$) (Figure 2). After accounting for predominant circulating viruses during the study period in the meta-regression, we found that doubling the incidence rate of cases and deaths during the study period was associated with 1.2% (95% CI, 0.5%–1.8%) and 1.3% (95% CI, 0.6%–1.9%) higher SAR (Table 1). In addition, we estimated that doubling the cumulative incidence of cases and deaths during the study period was related to 0.9% (95% CI, 0.5%–1.2%) and 1% (95% CI, 0.5%–1.4%) higher SAR, respectively. For studies that provided accurate study periods, we observed similar directions and magnitudes for the above factors.

Impact of Predominant Circulating Viruses and Epidemiological Factors

The SAR estimates ranged from 0.5% to 73.8% (Figure 3). These estimates varied substantially for different variants, study periods (before or after June 1, 2020), test coverages (whether all identified household contacts were tested), and case ascertainment methods (Figure 4; Supplementary Figure 2). The SARs for the Omicron variant were the highest among all virus categories (37.5%; 95% CI, 28.3%–46.7%), followed by any variants (except Omicron) with ancestral strains (30.3%; 95% CI, 26.4%–34.3%) and any variants (except Omicron) without ancestral strains (28.2%; 95% CI, 24.8%–31.7%), while the lowest estimate for ancestral strains only was 19.5% (95% CI, 15.9%–23.1%). Regarding the test coverage, we found that household SAR estimates for studies that tested all identified household

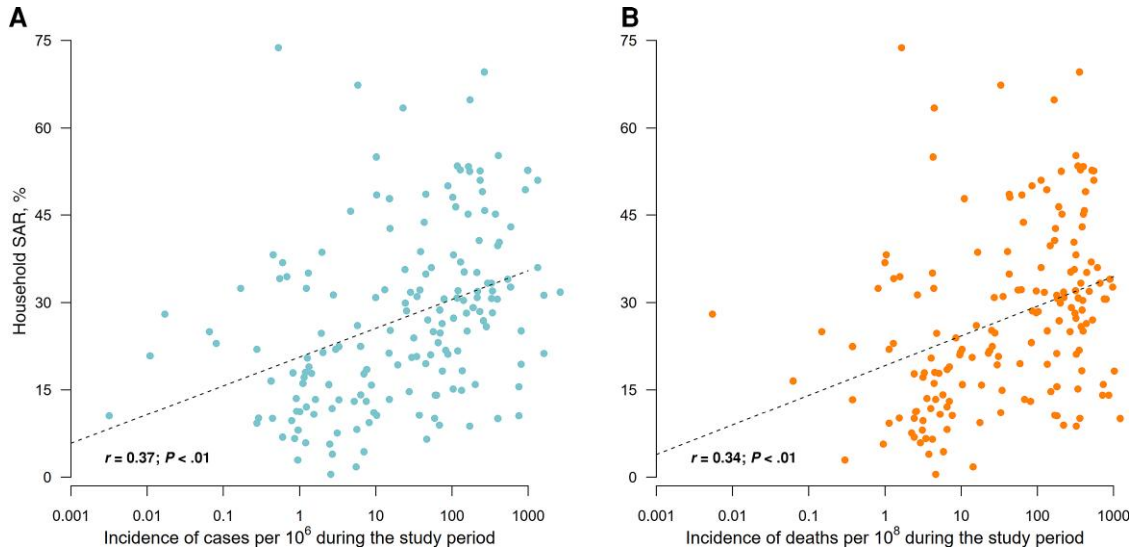

Figure 2. Household SAR estimates vs incidence rates of cases and deaths during the study period. *A*, Household SAR estimates vs the incidence rate of cases (per 1 000 000) during the study period (in log scale) by country. *B*, Household SAR estimates vs the incidence rate of deaths (per 100 000 000) during the study period (in log scale) by country. Results of Spearman correlation tests are provided (*r*). Only studies with positive incidence rates (in log scale) were selected to present the figures. Abbreviation: SAR, secondary attack rate.

contacts (27.5%; 95% CI, 24.9%–30.1%) were higher than for studies that did not conduct universal testing (22.5%; 95% CI, 18.7%–26.2%). For studies conducted before June 1, 2020, the household SAR estimate was 18.2% (95% CI, 15.4%–21.0%), which was significantly lower than the SAR derived from those conducted after June 1, 2020 (30.7%; 95% CI, 28.0%–33.5%). Finally, we detected a significantly lower household SAR (24.0%; 95% CI, 21.5%–26.4%) for studies that only used PCR for case ascertainment of secondary cases than those not (32.6%; 95% CI, 28.2%–37.0%). Restricting to estimates from studies with accurate study periods, we observed similar patterns and magnitudes regarding the above factors (Figure 3).

Based on meta-regression (Table 1), we found that compared with ancestral strains only, the SARs for any variants (except Omicron) with ancestral strains, any variants (except Omicron) without ancestral strains, or Omicron were 8.7% (95% CI, 3.8%–13.6%), 11.0% (95% CI, 5.2%–16.8%), and 18.0% (95% CI, 7.9%–28.1%) higher, respectively. The results were similar if only considering studies with accurate study periods. We found no association between the proportion of people fully vaccinated with primary doses in the population before the study period and SARs. Regarding the study period, we found that having a study period before June 1, 2020, was associated with a lower SAR after accounting for predominant circulating viruses, with −9.8% (95% CI, −15.4% to −4.1%) and −9.8% (95% CI, −16.3% to −3.4%) for all studies and studies with accurate study periods, respectively. We found that all secondary cases ascertained by PCR only was associated with a 6.6% (95% CI, 1.8%–11.3%) lower SAR vs using other ascertainment methods. Finally, testing all household members was associated with a 7.0% (95% CI, 1.2%–12.7%) higher SAR, restricting to studies with accurate study periods.

DISCUSSION

Accurate estimation of household SAR was crucial, as the household is one of the most important settings for transmission of many viruses including SARS-CoV-2 [6, 8]. Furthermore, household SAR was an important measure to determine the transmission potential of emerging viruses [2]. In this study, we synthesized SAR estimates from household transmission studies of SARS-CoV-2. We found that there was considerable heterogeneity in SAR estimates, and several factors may have impacts on SARs, which may have impacts on both public health decisions and scientific implications.

We found that a higher population-level incidence rate of cases or deaths during the study period was associated with higher SAR estimates. The SAR estimates did not account for the source of infection for secondary cases [2], and therefore some secondary cases may have been infected from the community rather than index cases within households. Our findings suggest that SAR estimates may be correlated with the community incidence rate, and therefore it might be possible to monitor the household SAR to determine the transmission intensity in communities. On the other hand, this finding could be a confounding result induced by other factors. For example, it may be explained by more advanced diagnostic or detection tools and testing frequencies for COVID-19 in some countries,

Table 1. Association Between Household SAR Estimates and Epidemiological and Population-Level Factors

Outcome	SAR (All Studies), %	SAR (Studies With Accurate Study Period), %
Baseline model: adjusted for SARS-CoV-2 variants		
Circulating virus	…	…
Ancestral strains	Ref	
Any variants (except Omicron) with ancestral strains	8.7 (3.8 to 13.6)[a]	7.0 (1.6 to 12.4)[a]
Any variants (except Omicron) without ancestral strains	11.0 (5.2 to 16.8)[a]	10.6 (4.0 to 17.2)[a]
Omicron	18.0 (7.9 to 28.1)[a]	12.1 (0.09 to 24.1)[a]
Model 1: Baseline model with incidence rate of cases/deaths during the study period		
Incidence rate of cases in $\log_2$ scale	1.2 (0.5 to 1.8)[a]	1.1 (0.4 to 1.8)[a]
Incidence rate of deaths in $\log_2$ scale	1.3 (0.6 to 1.9)[a]	1.2 (0.4 to 2.0)[a]
Model 2: Baseline model with cumulative incidence of cases/deaths before the study period		
Cumulative incidence of cases in $\log_2$ scale	0.9 (0.5 to 1.2)[a]	0.8 (0.3 to 1.2)[a]
Cumulative incidence of death in $\log_2$ scale	1.0 (0.5 to 1.4)[a]	0.9 (0.4 to 1.3)[a]
Model 3: Baseline model with adjustment for the proportion of people fully vaccinated before the study period		
Proportion of people fully vaccinated	−9.3 (−25.9 to 7.3)	−17.7 (−36.3 to 0.9)
Model 4: Baseline model with adjustment for epidemiological factors		
All household contacts were tested	4.8 (−0.2 to 9.8)	7.0 (1.2 to 12.7)[a]
Early period (before 2020-06-01)	−9.8 (−15.4 to −4.1)	−9.8 (−16.3 to −3.4)[a]
Ascertainment only by PCR for secondary cases	−6.6 (−11.3 to −1.8)[a]	−4.7 (−1.3 to 0.9)

Abbreviations: PCR, polymerase chain reaction; SAR, secondary attack rate; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Statistically significant ($P < .05$).

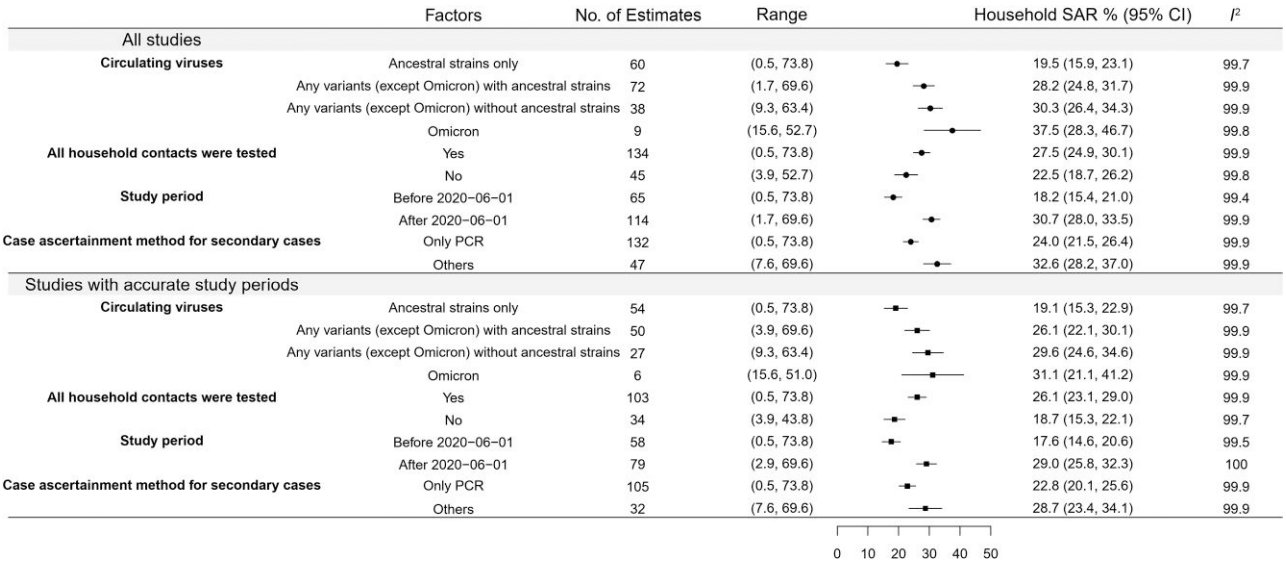

Figure 3. Pooled estimates of household SARs stratified by circulating viruses, study period, test coverage, and case ascertainment methods, with results of a sensitivity analysis restricting to studies with accurate study periods. Abbreviations: PCR, polymerase chain reaction; SAR, secondary attack rate.

and therefore both the population-level incidence and household SAR were higher. Also, less stringent public health and social measures (PHSMs) and lower levels of maintenance of good hygiene in countries may also contribute to higher incidence rates of cases. Household SAR by index cases' characteristics has been used to evaluate factors affecting infectiousness [8], and our results suggest that such an approach may be biased as SAR estimates did not account for the source of infection.

We also found that higher cumulative incidence of cases or deaths before the study was associated with higher SAR. This may be explained by the fact that there were repeated and denser exposures within households compared with in communities [8], and therefore transmission in countries with higher

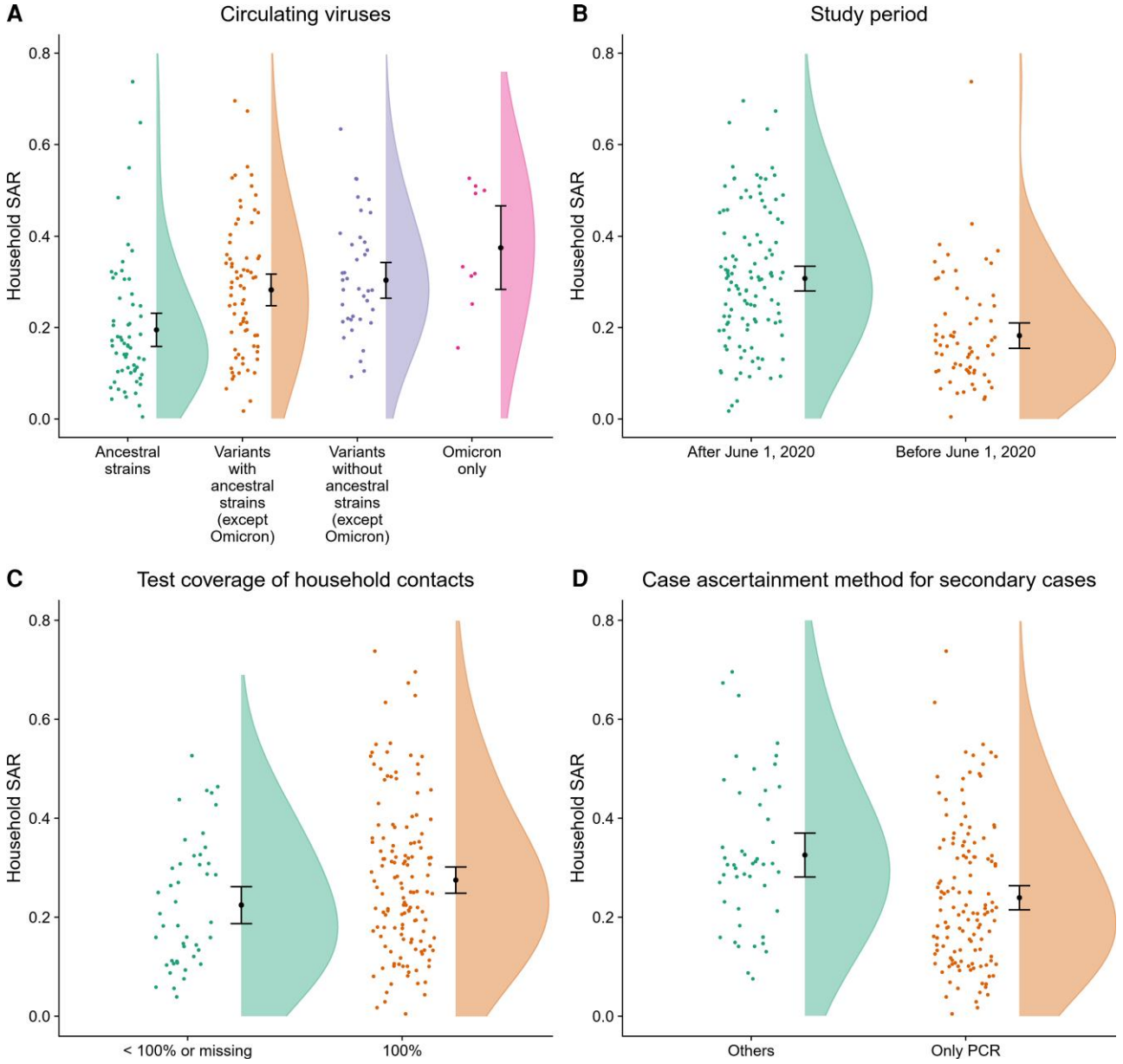

Figure 4. Distributions and pooled estimates of household SARs. *A*, By circulating virus. *B*, By study period. *C*, By test coverage of identified household contacts and *D*, By case ascertainment methods for secondary cases. Black dots are point estimates from mate analysis with bars representing 95% CIs. Abbreviations: PCR, polymerase chain reaction; SAR, secondary attack rate.

population immunity may be shifted from community settings to households. However, this may also be a confounding result caused by higher testing frequencies, better diagnostic or detection tools, or lower risk perceptions toward COVID-19 at the country level [179–182].

In addition, we found that SAR estimates vary substantially by the study period, predominant circulating viruses, and epidemiological factors including testing coverage and case ascertainment method [3, 7]. We found that the SARs for Omicron and other variants were higher than ancestral strains, consistent with previous reviews and modeling studies for estimating transmissibility of emerging variants [7, 52, 183, 184]. After accounting for differences in household SAR estimates by circulating viruses, we still detected a significantly higher SAR for studies conducted after June 1, 2020, potentially due to the improvement of detection or diagnostic approaches and relaxation of PHSMs. Similarly, we also found that testing all identified household contacts and using only PCR for case ascertainment for both index and secondary cases were associated with higher household SAR, indicating that such differences in testing or screening strategies contributed to the substantial heterogeneity of SAR estimates. We found that the proportion

of people fully vaccinated with primary doses was not associated with SAR, despite a negative point estimate. There could be large variations due to different vaccine types, effectiveness, and the waning effect of immunity induced by vaccination.

Our study is subject to several limitations. First, we included studies with family contacts who live outside the household of the index case. However, it is not likely that this was a significant factor contributing to the heterogeneity in household SAR as a previous study found that the SAR for household contacts was not significantly different from that for family contacts [4]. Second, there was a lack of detailed or accurate data on determining the study period and circulating viruses for some studies. Although we assumed a midday and obtained dominant viruses for those studies with missing information, data from the Nexstrain website may have uncertainties surrounding estimates of specific transmission dates [13, 185]. Still, our results were broadly consistent in a sensitivity analysis only including studies with accurate study periods. Finally, we did not consider within-household factors associated with household transmission that have been reported previously, such as age and sex of household members, symptom status of index cases, and household crowding, etc., as this individual-level information may not be publicly available [3, 8].

In conclusion, our findings suggested that population-level factors including the incidence rate in a country during the study period and testing strategies contributed to the high SAR estimates. Therefore, ignoring these factors could lead to inaccurate or even biased estimates of transmissibility. This may have impacts on informing control policies and epidemiological characterization of emerging viruses or variants.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. B.J.C. consults for AstraZeneca, Fosun Pharma GlaxoSmithKline, Moderna, Pfizer Roche, and Sanofi Pasteur. All other authors: no reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Patient consent. This study is a literature review and meta-analysis that does not include factors necessitating patient consent.

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