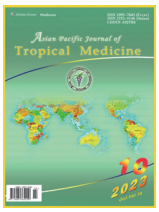

Letter to Editor

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Protection against symptomatic SARS-CoV-2 infection during the second wave among individuals with pre-existing binding antibodies to SARS-CoV-2: A population-based study from Puducherry, India

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During the COVID-19 pandemic, several studies have shown that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with a substantial reduction in the risk of subsequent reinfection with antigenically-related variants of the virus for at least 6 months[1,2]. However, most of these studies focused on people who had recovered from symptomatic SARS-CoV-2 infection[3], which tends to have higher antibody titres than asymptomatic infection. However, a comparison of the seropositivity rates in populations and of the cumulative COVID-19 case around the world indicate that a large majority of SARS-CoV-2 infections have been either asymptomatic or mildly symptomatic[4]. It remains unclear whether seropositive individuals who have never had symptomatic COVID-19 also have a lowered risk of SARS-CoV-2 reinfection[5].

India has experienced three waves of COVID-19, *i.e.* in August-October 2020, April-May 2021, and January-February 2022, related to alpha (B.1.1.7), delta (B.1.617.2) and omicron (B.1.1.529) variants, respectively[6]. During the pandemic, we had conducted six serial population-based surveys for anti-SARS-CoV-2 antibody prevalence in Puducherry district, located in southern India from August 2020 to March 2021[4]. This provided us an opportunity to follow-up the cohorts of sero-positive and sero-negative persons in the last two of these surveys and compare the frequency of subsequent SARS-CoV-2 infection in these.

Our sero-prevalence surveys had enrolled randomly-selected adults (aged 18 years and above) from 21 urban and 9 rural clusters for anti-SARS-CoV-2 antibodies using a commercial immunoassay (Elecsys® anti-SARS-CoV-2; Roche, with a reported 99.5% sensitivity and 99.8% specificity at >14 days after exposure to the virus)[4]. The participants in the last 2 surveys carried out during January 2021 [422/889 (47%) seropositive] and March 2021 [403/881 (45%) sero-positive], were contacted 6-8 months after the initial survey (in August 2021 and September 2021, respectively).

For each subject, demographic details such as age, sex, education, employment, comorbidity details and adherence to COVID-19 appropriate behaviour had been captured during the sero-prevalence study. In the current study, additional data, such as the occurrence of symptoms suggestive of SARS-CoV-2 infection, details and results on any tests for SARS-CoV-2 infection, disease severity, and vaccination status were collected through a telephonically-administered questionnaire.

Vaccination with Covishield started in Puducherry on 16th January 2021 in a phased manner. The protective effect of vaccine doses taken as beginning 21 days after vaccination for recipients of one dose and 14 days for recipients of two doses.

Data were captured using EpiCollect5 application and analysed using STATA v14.2. Cumulative incidence of SARS-CoV-2 infection was compared between seropositive and seronegative persons using Kaplan-Meier survival curves and log-rank test, treating the first positive test (antigen test or RT-PCR) for SARS-CoV-2 infection as the event of interest. Those who tested negative for SARS-CoV-2 were considered as right censored. In addition, a Cox regression

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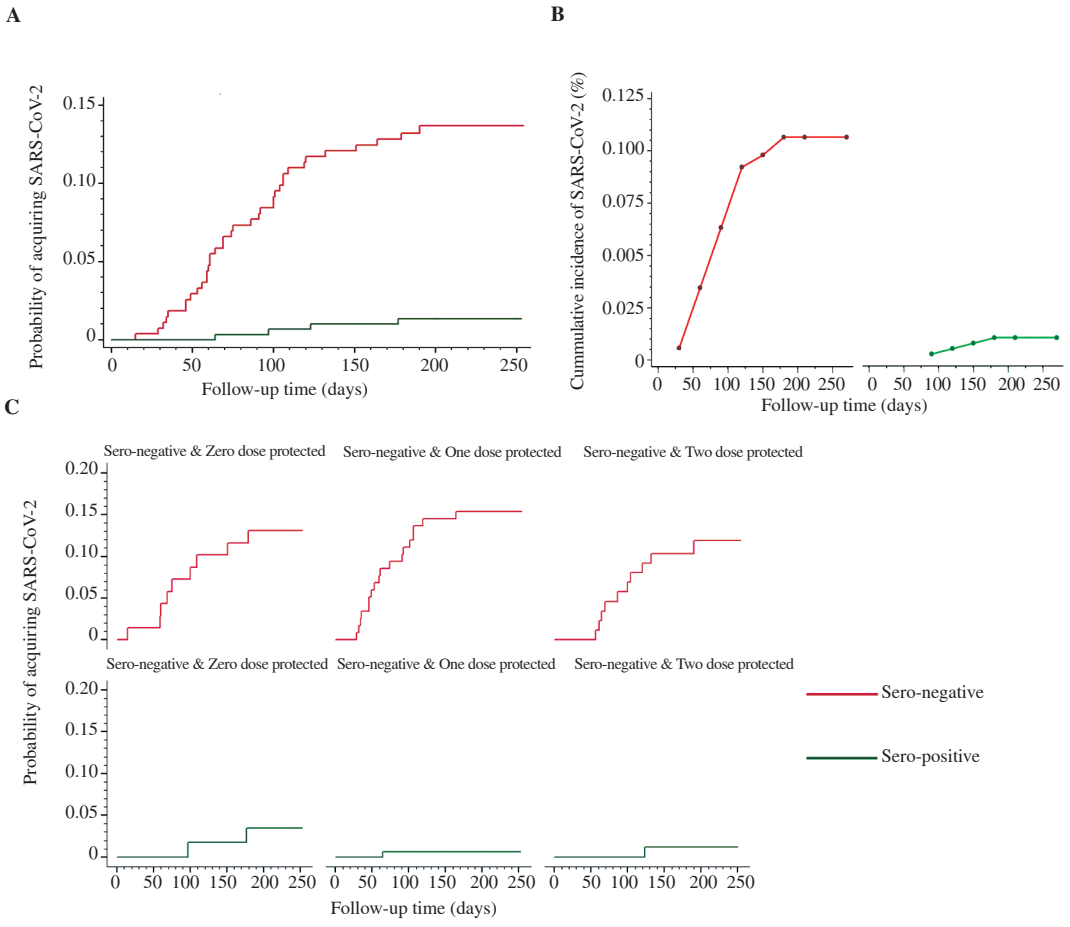

Figure 1. Kaplan-Meier curve showing time to positivity for SARS-CoV-2 disease between sero-positive and sero-negative (A). Cumulative incidence of SARS-CoV-2 infection among sero-positive and sero-negative (B). Kaplan-Meier curve showing time to positivity for SARS-CoV-2 disease between sero-positive and sero-negative stratified by vaccination status (C). blue=baseline sero-positive, red=baseline-sero-negative.

(proportional hazard regression) model was used to estimate hazard ratios (*HR*) and the corresponding 95% *CI* for seropositivity and vaccine protection status. Proportionality assumption was tested using Schoenfeld residuals test.

Of the 1770 eligible participants in the two surveys, 825 (46.6%) had been sero-positive and the remaining 945 were seronegative. Of these, we could recruit 380 seropositive and 347 seronegative individuals in the present study. A lower proportion of sero-positive than sero-negative reported having had COVID-19 symptoms *i.e.*, 18/380 (4.7%) *v.s.* 57/347 (16.4%), *P*-value <0.001. Furthermore, a lower proportion of sero-positive subjects had been diagnosed with COVID-19 than the sero-positive persons *i.e.*, 4/380 (1.1%) *v.s.* 37/347 (10.7%), *P*-value <0.001. For detailed characteristics see Supplementary Figure 1. These participants were followed up for a median period since initial serological testing of 214 days (65 312 person-days) and 193 days (52 068 person-days), respectively. Age and sex distribution, and other baseline characteristics (Supplementary Table 1) were similar in the two groups. Nearly 28.6% of the participants had at least one comorbidity.

The proportion of participants developing SARS-CoV-2 infection during the follow-up was 10.4% among the seronegative and 0.8% among the seropositive persons, with 69.1 and 6.1 events per 100 000 person-days, respectively (Figure 1A). On Kaplan-Meier analysis, the seronegative persons had a higher hazard of developing SARS-CoV-2 infection compared to those who were seropositive (*P*<0.001, log rank test).

Among the sero-negative, vaccinated were at lesser risk of developing SARS-CoV-2 disease than unvaccinated. There was no case among the sero-positive persons who had also been vaccinated against SARS-CoV-2. Kaplan-Meier curves comparing the COVID-19 disease incidence between the serological status and vaccination status was presented in Figure 1C.

In the multivariable analysis, seropositive status was associated with 85% reduction in the hazard of subsequent SARS-CoV-2 infection compared to seronegative status (adjusted hazard ratio 0.15, 95% *CI* 0.05-0.42, *P*<0.001). One dose and two dose protected with

90% and 94% reduction in the hazard of subsequent SARS-CoV-2 infection compared to no vaccination, respectively [0.10 (0.03-0.27); P<0.001 and 0.06 (0.01-0.45); P=0.01]. Cumulative incidence of SARS-CoV-2 infection among sero-positive and sero-negative were depicted in Figure 1B.

Our study found a significantly reduced risk of SARS-CoV-2 reinfection among sero-positive participants in 6-month follow-up period. Delta variant was the predominant strain in this period, whereas the alpha variant had previously dominated the first wave of COVID-19. The antibodies resulting from prior exposure to alpha variant provided substantial protection against reinfection with the delta variant[7].

Prior asymptomatic exposure to SARS-CoV-2 during the first wave of COVID-19 in India was associated with substantial protection against infection during the second wave, vaccination appeared to offer incremental protection even in individuals with such exposure to SARS-CoV-2[8].

Conflict of interest statement

The authors declare that they have no conflict of interest.

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Reference

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