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Results of a population-based survey to estimate the seroprevalence of SARS-CoV-2 specific IgG antibodies in Kashmir, India, seven months after the appearance of the first COVID-19 case

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3 **Results of a population-based survey to estimate the seroprevalence of SARS-CoV-2 specific IgG**
4 **antibodies in Kashmir, India, seven months after the appearance of the first COVID-19 case**
5

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ABSTRACT

Objectives: We designed a population-based survey in Kashmir to estimate the seroprevalence of SARS-CoV-2 specific IgG antibodies in the general population aged 18 years and above.

Setting: The survey was conducted among 110 villages and urban wards across ten districts in Kashmir from 17 Oct 2020 to 04 Nov 2020.

Participants: Individuals aged 18 years and above were eligible to be included in the survey. Serum samples were tested for the presence of SARS-CoV-2 specific IgG antibodies using the Abbott SARS-CoV-2 IgG assay.

Primary and secondary outcome measures: We labeled assay results equal to or above the cut-off index value of 1.4 as positive for SARS-CoV-2 specific IgG antibodies. Seroprevalence estimates were adjusted for the sampling design and assay characteristics.

Results: Out of 6397 eligible individuals enumerated, 6315 (98.7%) agreed to participate. The final analysis was done on 6230 participants. Seroprevalence adjusted for the sampling design and assay characteristics was 36.7% (95% CI 34.3%-39.2%). Seroprevalence was higher among the older population. Only one-half of symptomatic individuals reported having been tested. One out of every ten seropositive individuals reported a history of COVID-19 like symptoms. We estimated an infection fatality rate of 342 deaths per million infections.

Conclusions: During the first seven months of the COVID-19 epidemic in Kashmir valley, approximately 37% of individuals were infected. There is still a significant pool of susceptible people in Kashmir. The number of infections will continue to rise unless infection prevention measures are practiced by the population.

ARTICLE SUMMARY

Strengths and limitations of this study

- The findings of our study are based on a representative sample of the population.
- The laboratory test used for the detection of SARS-CoV-2 specific IgG antibodies in serum samples provides valid results.
- We report seroprevalence estimates adjusted for sampling design and test performance.
- Even though we adjusted the weighted seroprevalence estimates for test performance using manufacturer-provided sensitivity and specificity (100% and 99.63% respectively), we did not quantify the test validity in-house.
- Because of lack of age- and gender-specific mortality data we could not estimate age- and gender-specific infection fatality rate.

INTRODUCTION

On 11 Feb 2020, the World Health Organization announced that the disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) will be named coronavirus disease (COVID-19).[1] In Kashmir, the first case of COVID-19 was confirmed in Srinagar city on 18 Mar 2020.[2] The government imposed the first phase of the lockdown in Kashmir on 24 March 2020. During this phase, inter-state travel remained suspended. People were barred from moving outside except in an emergency. Except

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3 for essential services, all government and private offices were advised to work from home. Universal
4 masking was made mandatory. The lockdown was extended till 31 May 2020 and later relaxed in a
5 phased manner.
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7 Mild or asymptomatic infections are common in Coronavirus disease 2019 (COVID-19) and are an
8 important source of infection transmission.[3,4] Such cases are less likely to be detected by a
9 surveillance system based on reverse-transcriptase polymerase chain reaction (RT-PCR) testing. The
10 number of reported RT-PCR positive cases are an underestimate of the true number of infections in a
11 population.
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14 Seroprevalence surveys have been conducted in various countries at different stages of the current
15 epidemic among various population groups.[5–14] Seroprevalence surveys provide a more accurate
16 estimate of past infection, improve understanding of the infection transmission dynamics, and guide
17 public health response.[15]
18

19 We designed this survey to estimate the seroprevalence of severe acute respiratory syndrome
20 coronavirus 2 (SARS-CoV-2) specific IgG antibodies in the adult population of Kashmir valley.
21
22

23 **METHODS**

24 We designed a population-based cross-sectional study. The study covered all the ten districts of
25 Kashmir, a valley in northern India. We completed data collection in three weeks, from 17 Oct 2020 to
26 04 Nov 2020.
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28

29 **Ethics**

30 We obtained written informed consent from all study participants. The study was approved by the
31 Institutional Ethics Committee of Government Medical College Srinagar. We used anonymized
32 participant data for analysis.
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34

35 **Patient and Public Involvement**

36 No patients were involved in this study.
37
38

39 **Sample size**

40 We calculated the minimum sample size based on an anticipated seroprevalence of 20%, an absolute
41 error of 2%, and a design effect of 2. To obtain precise estimates for district Srinagar, sample size
42 estimation was made for the district separately. We targeted a total sample size of 6400.
43
44

45 **Participants**

46 All adults ≥ 18 years of age were eligible to participate in the study. We selected eligible participants
47 using a three-stage stratified cluster sampling technique. We listed all clusters in the valley using the
48 Census 2011 data.[16] Within each of the ten districts in the valley, clusters were stratified into urban
49 and rural clusters. We selected clusters within each of the 20 strata by probability proportionate to size
50 (PPS) sampling. Except for district Srinagar which we oversampled to obtain precise seroprevalence
51 estimates for, ten clusters were randomly selected from each district. We selected 20 clusters from
52 district Srinagar. Within each selected cluster we identified four random locations and approached
53 consecutive households to enroll at least ten eligible participants. We thus identified a total of 440
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3 random locations within 110 clusters in ten districts. We invited all eligible adults in a household for
4 participation.
5

6 **Variables**

7
8 The main outcome variable of interest was SARS-CoV-2 specific IgG antibodies. We obtained information
9 from participants about their age, gender, history of COVID-19 like symptoms in the three months
10 before the interview date, history of contact with a known COVID-19 patient, and history of COVID-19
11 testing.
12

13 **Procedure**

14
15 We informed eligible adults about the purpose and the procedure of the study. Study participation was
16 voluntary. Participants were interviewed by health personnel specifically trained for the interview.
17 Interview responses were recorded in an Epicollect5 form.[17] Once the interview was completed, a
18 trained phlebotomist collected 3-5 mL of venous blood from the antecubital vein under aseptic
19 precautions into a red-top collection tube containing a clot activator. The tube was left standing,
20 undisturbed, for at least 30 minutes for clot formation. The sample was later transported to a central
21 facility for centrifugation. Centrifuged samples were transported to a central laboratory for further
22 processing and analysis. Serum samples were tested for the presence of SARS-CoV-2 specific IgG
23 antibodies using the Abbott SARS-CoV-2 IgG assay. The assay uses chemiluminescence to detect IgG
24 antibodies against the SARS-CoV-2 nucleocapsid protein. The reported sensitivity and specificity of the
25 assay are 100% and 99.63%, respectively.[18] As recommended by the manufacturer, we labeled assay
26 results equal to or above the cut-off index value of 1.4 as positive for SARS-CoV-2 specific IgG antibodies.
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31 **Statistical methods**

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33 We report unweighted seroprevalence estimates in percentages. We used the Agresti-Coull procedure
34 to calculate a 95% confidence interval (CI) for seroprevalence estimates. A weighted estimate of
35 seroprevalence is provided. To calculate survey weights (inverse of sampling probability) we used the
36 estimated population of the districts. We used the census 2011 data and growth rates from Sample
37 Registration System to estimate the population of the districts in 2020.[16,19] Survey weights so
38 obtained was further adjusted for non-response and age and sex structure (post-stratification weights).
39 We further adjusted the weighted seroprevalence estimates for test performance to calculate
40 “weighted seroprevalence adjusted for test performance”. We did this using the formula:

41
42 *Weighted seroprevalence adjusted for test performance* =
43 $(\text{Weighted seroprevalence} + \text{Test specificity} - 1) / (\text{Test sensitivity} + \text{Test specificity} - 1)$. [20]
44

45 We used the manufacturer-provided sensitivity and specificity in the above formula.[18]
46

47 We analyzed the difference in seroprevalence estimates across levels of a categorical variable using a
48 Chi-square test adjusted for the sampling design.
49

50 We estimated the number of SARS-CoV-2 infections by multiplying the weighted seroprevalence
51 adjusted for test performance with the estimated population of the valley. To estimate the number of
52 infections per reported case, we divided the estimated number of SARS-CoV-2 infections by the
53 reported number of COVID-19 cases two weeks before the survey date. We calculated the infection
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fatality rate by dividing the reported number of deaths by the number of estimated infections, assuming a three-week lag time from infection to death.[21]

We analyzed the data using Stata version 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP.).

RESULTS

We enumerated 6 397 individuals ≥ 18 years from 3 077 households and 110 clusters (34 urban clusters and 76 rural clusters) between 17 Oct 2020 and 04 Nov 2020. Out of the 6 397 eligible individuals, 6 315 (98.7%) agreed to participate and were enrolled. The final analysis was done on a sample of 6 230 participants. (Figure 1)

Of the 6 230 participants, 1 513 (24.3%) were between 18 and 30 years of age, 2 672 (42.9%) were aged 30-49 years, 1 643 (26.4%) were aged 50-69 years, and 402 (6.4%) were 70 years and older. (Table 1). There was equal representation from males and females, and 3 364 (54.0%) resided in a rural area. Of the 3 104 females, 56 (1.8%) reported pregnant at the time of the survey. Four hundred seventy-four (7.6%) reported COVID-19 like symptoms in the three months preceding the survey and 439 (7.0%) reported to have ever come in contact with a known COVID-19 case. One thousand ninety-two (17.5%) reported having been tested for COVID-19 using RT-PCR or a Rapid Antigen Test (RAT) previously, of whom 176 (16.2%) reported to have tested positive for the disease.

Table 1: Characteristics of study participants

	Frequency	Percent
Total	6230	..
Age, years
18-29	1513	24.3
30-49	2672	42.9
50-69	1643	26.4
≥ 70	402	6.5
Gender
Male	3126	50.2
Female	3104	49.8
Residence
Urban	2866	46.0
Rural	3364	54.0
Pregnant (n=3104)	56	1.8
Self-reported history of chronic disease	1145	18.4
History of COVID-19 like symptoms	474	7.6
History of contact with a known COVID-19 case	439	7.0
Ever tested for COVID-19 (RT-PCR)	1092	17.5
RT-PCR result (n=1088*)
Positive	176	16.2
Negative	912	83.8

COVID-19: Coronavirus disease; RT-PCR: Reverse transcriptase polymerase chain reaction

*RT-PCR result not known in four participants

We found an overall unweighted seroprevalence of 38.8% (95% CI 37.6 – 40.0). The seroprevalence ranged from 28.2% in district Kulgam to 41.7% in district Badgam. The overall weighted seroprevalence (adjusted for sampling design) was 36.9% (95% CI 34.5 – 39.4). The weighted seroprevalence adjusted for test performance was 36.7% (95% CI 34.3 – 39.2). (Table 1)

Seroprevalence was lowest among participants aged 18-29 years [33.5% (95% CI 29.8 – 37.4)] and was higher in older age groups. Seroprevalence was highest in those aged 70 years and above [45.1% (95% CI 37.6 – 52.8)]. Seroprevalence was not significantly different among males and females ($p=0.34$). The seroprevalence among urban residents was 40.0% (95% CI 36.1 – 43.9), slightly but not significantly, higher than rural residents [35.3% (95% CI 32.2 – 38.5), $p=0.07$]. (Table 2)

Table 2: Seroprevalence of SARS-CoV-2 specific IgG antibodies by participant characteristics

	Number tested, n	Number seropositive, n	Unweighted seroprevalence, % (95% CI)	Weighted seroprevalence, % (95% CI)	Weighted seroprevalence adjusted for test performance, % (95% CI)	Design-based F, p-value
Total	6230	2415	38.8 (37.6-40.0)	36.9 (34.5-39.4)	36.7 (34.3-39.2)	..
Age, years
18-29	1513	538	35.6 (33.2-38.0)	33.7 (30.1-37.6)	33.5 (29.8-37.4)	6.42, 0.0006
30-49	2672	1000	37.4 (35.6-39.3)	36.3 (33.5-39.3)	36.1 (33.3-39.1)	..
50-69	1643	691	42.1 (39.7-44.5)	42.5 (38.8-46.2)	42.3 (38.6-46.0)	..
≥70	402	186	46.3 (41.5-51.2)	45.3 (37.8-53.0)	45.1 (37.6-52.8)	..
Gender
Male	3126	1166	37.3 (35.6-39.0)	36.1 (33.5-38.9)	35.9 (33.3-38.7)	0.94, 0.34
Female	3104	1249	40.2 (38.5-42.0)	37.8 (34.5-41.3)	37.6 (34.3-41.1)	..
Residence
Urban	2866	1180	41.2 (39.4-43.0)	40.2 (36.3-44.1)	40.0 (36.1-43.9)	3.43, 0.07
Rural	3364	1235	36.7 (35.1-38.4)	35.5 (32.5-38.7)	35.3 (32.2-38.5)	..

Self-reported history of chronic disease
Yes	1145	495	43.2 (40.4-46.1)	41.9 (37.4-46.6)	41.7 (37.2-46.4)	6.14, 0.02
No	5085	1920	37.8 (36.4-39.1)	36.2 (33.7-38.9)	36.0 (33.5-38.7)	
History of COVID-19 like symptoms
Yes	474	247	52.1 (47.6-56.6)	47.4 (37.9-57.1)	47.2 (37.7-56.9)	5.53, 0.02
No	5756	2168	37.7 (36.4-38.9)	36.3 (33.9-38.8)	36.1 (33.7-38.6)	..
History of contact with a known COVID-19 case
Yes	439	219	49.9 (45.2-54.5)	45.2 (38.3-52.2)	45.0 (38.1-52.0)	7.13, 0.01
No	5791	2196	37.9 (36.7-39.2)	36.5 (34.1-39.0)	36.3 (33.9-38.8)	..
Ever tested for COVID-19 (RT-PCR)
Yes	1092	485	44.4 (41.5-47.4)	41.0 (35.4-46.9)	40.8 (35.2-46.7)	2.17, 0.14
No	5138	1930	37.6 (36.2-38.9)	36.2 (33.5-39.0)	36.0 (33.3-38.8)	..
RT-PCR result (n=1088*)
Positive	176	140	79.5 (73.0-84.9)	81.8 (74.8-87.1)	81.7 (74.7-87.1)	74.93, <0.0001
Negative	912	345	37.8 (34.7-41.0)	38.8 (33.3-44.7)	38.6 (33.1-44.5)	..

COVID-19: Coronavirus disease; RT-PCR: Reverse transcriptase polymerase chain reaction

*RT-PCR result not known in four participants

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3 One in five participants (1145/6230, 18.4%) self-reported a history of at least one chronic disease (Table
4 1). Hypertension (815/6230, 13.1%) and diabetes mellitus (314/6230, 5.0%) were the most commonly
5 reported chronic diseases (Supplementary File 1). Seroprevalence was significantly higher in participants
6 who self-reported history of chronic disease (41.7%, 95% CI 37.2 – 46.4) as compared to those who did
7 not report a history of chronic disease (36.0%, 95% CI 33.5 - 38.7) (Table 2).
8
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10 Among participants who reported a history of COVID-19 like symptoms, seroprevalence was 47.2% (95%
11 CI 37.7 – 56.9) compared with 36.1% (95% CI 33.7 – 38.6) among participants who did not report such
12 symptoms. Seroprevalence was higher among those who reported contact with a known COVID-19 case
13 [45.0% (95% CI 38.1 – 52.0)] than participants who did not report any history of such contact [36.3%
14 (95% CI 33.9 – 38.8)]. (Table 2)
15

16 Seroprevalence was not significantly related to being tested for COVID-19 (RT-PCR). However, those who
17 reported a positive RT-PCR COVID-19 test had significantly higher seroprevalence (81.7%, 95% CI 74.7 –
18 87.1) as compared to those who reported a negative RT-PCR COVID-19 test (38.6%, 95% CI 33.1 – 44.5).
19 (Table 2)
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22 Among 2 415 seropositive individuals, only 247 (10.2%) reported a history of COVID-19 like symptoms.
23 Among 474 who reported a history of COVID-19 like symptoms, 233 (49.2%) were tested for COVID-19
24 (RT-PCR).
25

26 Among 36 participants who reported a positive RT-PCR COVID-19 test but were seronegative, the
27 duration between COVID-19 RT-PCR test and serological testing ranged from 9 days to 101 days. In only
28 four of these 36 participants, the duration between the COVID-19 RT-PCR test and the serological test
29 was 14 days or less. Of the remaining 32 participants, 21 did not report a history of COVID-19 like
30 symptoms, nine did not report a history of contact with a known COVID-19 case, and eight reported
31 neither a history of COVID-19 like symptoms nor a history of contact with a known COVID-19 case.
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34 We estimated that there were 1 673 484 (95% CI 1 564 047 – 1 787 482) cumulative number of
35 infections among adults aged ≥ 18 years in the valley by 03 Oct 2020, two weeks before the start of the
36 survey. If we assume that the seroprevalence was similar to the overall seroprevalence in the population
37 not included in our study (< 18 years of age) then the estimated cumulative number of infections in the
38 valley by 03 Oct 2020 was 2 791 933 (95% CI 2 609 354 – 2 982 119). Considering that the cumulative
39 number of reported COVID-19 cases was 47 071 by 03 Oct 2020, we estimate the number of infections
40 per reported case as 59.3 (95% CI 55.4 – 63.4). The number of reported COVID-19 deaths after a three-
41 week lag period (on 24 Oct 2020) was 955. Thus, we estimated the infection fatality rate as 342.1 deaths
42 per million infections (95% CI 320.2 – 366.0).
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46 DISCUSSION

47 The results of our study indicate that by the first week of October 2020, nearly seven months after the
48 appearance of the first laboratory-confirmed COVID-19 case on 18 March 2020, close to 37% of the
49 valley's population aged ≥ 18 years had been infected. Our results suggest that the cumulative number of
50 SARS-CoV-2 infections by the first week of October 2020 was nearly 2.8 million with an estimated
51 infection fatality rate of 342.1 deaths per million infections. Seroprevalence did not differ by gender but
52 was higher in older age groups.
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3 The findings of our study are based on a representative sample of the population. The laboratory test
4 used for the detection of SARS-CoV-2 specific IgG antibodies in serum samples provides valid
5 results.[18,22] We report seroprevalence estimates adjusted for sampling design and test performance.
6

7 The overall adjusted seroprevalence of around 37% indicates that a large proportion of the valley's
8 population has been infected with the virus. Easing of lockdown, being fed up with the restrictions, and
9 non-adherence to prevention norms are the possible reasons. Even though a large proportion of the
10 population has been infected, the transmission of infection is expected to continue till most of the
11 susceptible population becomes immune. Herd immunity in the context of COVID-19 is a matter of
12 debate as reports of a second infection continue to pour in.[23] Several factors potentially influence the
13 seroprevalence rates. These include population density, social and demographic structure of the
14 population, governmental policies and the extent of their implementation, immunity level of the
15 population, time since the start of infection transmission, adherence to infection prevention guidelines,
16 quality of contact tracing and quarantine, and possibly the geography and environment of an area.
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20 The seroprevalence of SARS-CoV-2 IgG antibodies was higher in older age groups. During the early
21 period of the pandemic, people were adherent to social distancing and other non-pharmaceutical
22 interventions because of a fear of the disease and administrative restrictions. With time, administrative
23 restrictions were relaxed, fear of the disease attenuated, and people became sort of fed up with the
24 social restrictions. This not only led to an increase in the number of reported COVID-19 cases but also
25 provided the population, including older age groups, an opportunity to contract the infection. That older
26 people have an increased risk of symptomatic and more severe disease is now well known.[24,25]
27 However, age-based differential susceptibility to SARS-CoV-2 infection antibody response and the
28 reasons thereof are still a grey area and need further understanding. Existing literature might suggest
29 that the young who are more mobile and socially active have a higher risk of infection.[6,7] However,
30 this should not imply that the elderly have a decreased susceptibility to SARS-CoV-2 infection or a
31 decreased antibody response.[26] On the contrary, several studies suggest that the seroprevalence of
32 SARS-CoV-2 specific IgG antibodies is higher in the older age groups and particularly so in more dense
33 population groups.[4,5,8–11,13] Furthermore, SARS-CoV-2 antibody levels have been reported to be
34 higher in older people.[12]
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39 The seroprevalence of SARS-CoV-2 specific IgG antibodies did not differ significantly by gender, though
40 the figure was slightly higher for females. These findings are consistent with the available
41 literature.[6,13] Difference in seroprevalence by gender has been suggested by some studies and
42 females have been reported to have lower antibody levels.[5,7,9,11,12,14,27]
43

44 Urban areas are more densely populated as compared to rural areas which accelerate the transmission
45 of infections in the population. Seroprevalence of SARS-CoV-2 specific IgG antibodies is thus expected to
46 be higher in urban areas especially during the early phases of an epidemic. As the epidemic progresses
47 the seroprevalence gap between urban and rural areas will wane off. We estimated an adjusted
48 seroprevalence of 40.0% (95% CI 36.1 – 43.9) in urban areas as compared to 35.3% (95% CI 32.2 – 38.5)
49 in rural areas (p=0.07).
50
51

52 People with a chronic disease experience more severe COVID-19 symptoms and are more likely to die
53 when compared to people with no chronic disease.[28] We found a higher proportion of symptomatic
54 infection among participants with a self-reported history of chronic disease (78/1145, 6.8%) as
55 compared to participants with no chronic disease (169/5085, 3.3%) (Supplementary File 2). Little is,
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3 however, known about the risk of infection in chronic disease patients. We found a significantly higher
4 seroprevalence among participants with a self-reported history of chronic disease (Table 2). This finding
5 needs further research for corroboration and possible explanations.
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8 People with a self-reported history of COVID-19 related symptoms, contact with a known COVID-19
9 case, or a positive COVID-19 RT-PCR had a higher seroprevalence as compared to their complement.
10 Among seropositive individuals, only 10·2% reported being symptomatic. The percentage of
11 asymptomatic infections, thus, was 90%. However, only 49% of individuals with a history of COVID-19
12 like symptoms were tested using RT-PCR. We also estimated that only one out of almost 59 infections
13 gets reported. This reflects the necessity of improving the efficiency of RT-PCR testing so that more
14 symptomatic individuals receive the test. Not all individuals with a known RT-PCR positive result showed
15 the presence of IgG antibodies. Around 20% of RT-PCR positive individuals were seronegative and in a
16 large majority of them (32 out of 36) the duration since RT-PCR positivity was more than two weeks. This
17 may be attributed to a poor B cell response or a false negative antibody test.[29] Around 38% of RT-PCR
18 negative individuals were seropositive suggesting a false-negative RT-PCR or infection acquisition at a
19 date later than the RT-PCR test.
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23 We estimated an infection fatality rate of 342·1 per million infections (95% CI 320·2 – 366·0). In
24 developed nations like the United States and many European countries, a higher infection fatality rate
25 has been reported.[24,30] The infection fatality rate is, however, known to be lower in developing
26 nations.[24,31]
27

28
29 One important limitation of our study is that even though we adjusted the weighted seroprevalence
30 estimates for test performance using manufacturer-provided sensitivity and specificity (100% and
31 99·63% respectively), we did not quantify the test validity in-house. Another limitation of our study
32 estimates is that we excluded people <18 years of age. The results of our study may not thus be
33 generalizable to this group of the population. Further, because of lack of age- and gender-specific
34 mortality data we could not estimate age- and gender-specific infection fatality rate.
35

36 **CONCLUSIONS**

37
38 We conclude that nearly 37% of individuals aged 18 years and above were infected with SARS-CoV-2 in
39 Kashmir by October 2020. The infection fatality rate in the valley is around 342 deaths per million
40 infections. A majority of cases go unreported. Given the current adherence to COVID-19 prevention
41 measures in the valley, the seroprevalence is going to increase. Since almost half of the symptomatic
42 individuals go unreported, testing of symptomatic individuals and effective contact tracing needs to
43 continue. We further recommend that adherence to COVID-19 prevention measures should be ensured
44 at least till a large proportion of the population gets vaccinated.
45
46

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13 14 **COMPETING INTERESTS**

15
16 We declare no competing interests, financial or otherwise.

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40
41 S Muhammad Salim Khan, Mariya Amin Qurieshi, Inaamul Haq, and Sabhiya Majid have verified the
42 underlying data.

43 44 45 **DATA SHARING**

46
47 Anonymized data collected for the study, including individual participant data and a data dictionary
48 defining each field in the set, will be made available to interested researchers on request by Inaamul
49 Haq (haqinaam@yahoo.co.in) for two years from publication. The study protocol, statistical analysis
50 plan, and informed consent forms are also available from Inaamul Haq.

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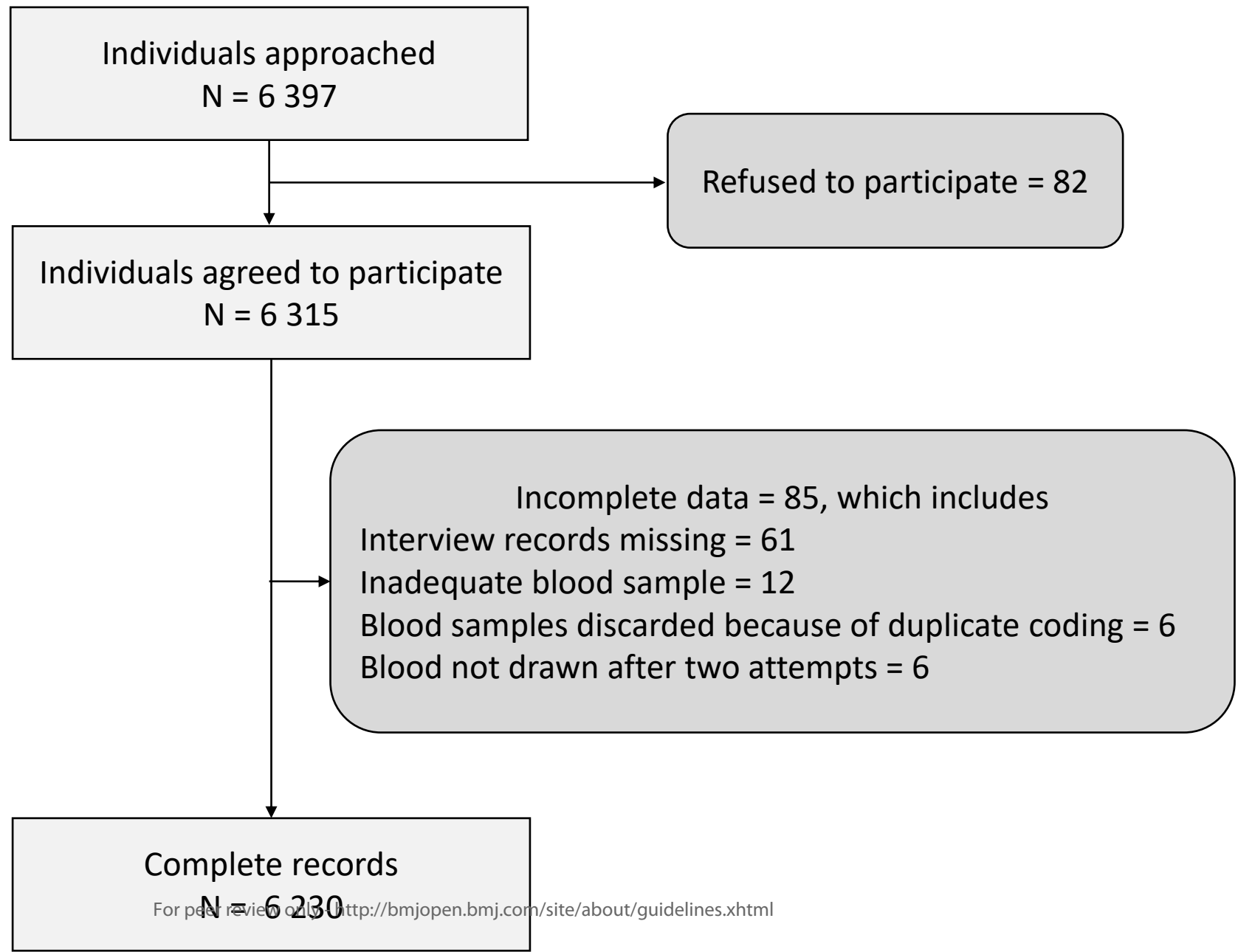
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8 **Figure 1 legend:**

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10 Figure 1: Participant flow.
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Figure 1: Participant flow



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Chronic disease and SARS-CoV-2 infection in the study population

Of the 6230 participants, 1145 reported a history of at least one chronic disease. Two hundred ninety-eight reported a history of more than one chronic disease.

Supplementary Table 1: Chronic disease in the study population

Chronic disease (n = 1145)	Number (%)
Hypertension	815 (13.1%)
Diabetes	314 (5.0%)
Chronic Obstructive Pulmonary Disease	39 (0.6%)
Coronary Heart Disease	35 (0.6%)
Cerebrovascular Disease	16 (0.3%)
Asthma	15 (0.2%)
Chronic Kidney Disease	10 (0.2%)
Chronic Liver Disease	5 (0.1%)
Cancer	4 (0.1%)

Supplementary Table 2: History of COVID-19 like symptoms and seropositivity vis-à-vis history of chronic disease

		History of COVID-19 like symptoms	
		Yes	No
..	..		
Reported history of chronic disease (n=1145)	Seropositive	78	417
..	Seronegative	63	587
Did not report any history of chronic disease (n=5085)	Seropositive	169	1751
..	Seronegative	164	3001

Of the 1154 participants who reported a history of chronic disease 78 (6.8%) reported a history of COVID-19 like symptoms within three months of the interview date and were seropositive for SARS-CoV-2 specific IgG (symptomatic infection). The proportion of symptomatic infection among participants who did not report any history of chronic disease was 3.3% (169/5085).

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1, 3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4, 5
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	4, 5
		(b) Describe any methods used to examine subgroups and interactions	5
		(c) Explain how missing data were addressed	5
		(d) If applicable, describe analytical methods taking account of sampling strategy	4, 5
		(e) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 1, and page 5
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1, Figure 1
Outcome data	15*	Report numbers of outcome events or summary measures	Table 2

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Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2
		(b) Report category boundaries when continuous variables were categorized	Table 1, 2
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 2
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9, 10
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for exposed and unexposed groups.

BMJ Open

Seroprevalence of SARS-CoV-2 specific IgG antibodies in Kashmir, India, seven months after the first reported local COVID-19 case: results of a population-based seroprevalence survey from October-November, 2020

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3 **Seroprevalence of SARS-CoV-2 specific IgG antibodies in Kashmir, India, seven months after the first**
4 **reported local COVID-19 case: results of a population-based seroprevalence survey from October-**
5 **November, 2020**
6

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ABSTRACT

Objectives: We designed a population-based survey in Kashmir to estimate the seroprevalence of SARS-CoV-2 specific IgG antibodies in the general population aged 18 years and above.

Setting: The survey was conducted among 110 villages and urban wards across ten districts in Kashmir from 17 Oct 2020 to 04 Nov 2020.

Participants: Individuals aged 18 years and above were eligible to be included in the survey. Serum samples were tested for the presence of SARS-CoV-2 specific IgG antibodies using the Abbott SARS-CoV-2 IgG assay.

Primary and secondary outcome measures: We labeled assay results equal to or above the cut-off index value of 1.4 as positive for SARS-CoV-2 specific IgG antibodies. Seroprevalence estimates were adjusted for the sampling design and assay characteristics.

Results: Out of 6397 eligible individuals enumerated, 6315 (98.7%) agreed to participate. The final analysis was done on 6230 participants. Seroprevalence adjusted for the sampling design and assay characteristics was 36.7% (95% CI 34.3%-39.2%). Seroprevalence was higher among the older population. Among seropositive individuals, 10.2% (247/2415) reported a history of COVID-19 like symptoms. Out of 474 symptomatic individuals, 233 (49.2%) reported having been tested. We estimated an infection fatality rate of 0.034%.

Conclusions: During the first seven months of the COVID-19 epidemic in Kashmir valley, approximately 37% of individuals were infected. A large proportion of the population remains susceptible to the infection. The experience of a second wave of COVID-19 in April-June 2021, the appearance of virus variants, and the introduction of vaccination programs warrant robust surveillance of the epidemic.

ARTICLE SUMMARY

Strengths and limitations of this study

- The findings of our study are based on a representative sample of the population.
- The laboratory test used for the detection of SARS-CoV-2 specific IgG antibodies in serum samples provides valid results.
- We report seroprevalence estimates adjusted for sampling design and test performance.
- Even though we adjusted the weighted seroprevalence estimates for test performance using manufacturer-provided sensitivity and specificity (100% and 99.63% respectively), we did not quantify the test validity in-house.
- Because of lack of age- and gender-specific mortality data we could not estimate age- and gender-specific infection fatality rates.

INTRODUCTION

On 11 Feb 2020, the World Health Organization announced that the disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) will be named coronavirus disease (COVID-19).[1] In Kashmir, the first case of COVID-19 was confirmed in Srinagar city on 18 Mar 2020.[2] The government imposed the first phase of the lockdown in Kashmir on 24 March 2020. During this phase, inter-state travel remained suspended. People were barred from moving outside except in an emergency. Except

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3 for essential services, all government and private offices were advised to work from home. Universal
4 masking was made mandatory. The lockdown was extended till 31 May 2020 and later relaxed in a
5 phased manner.
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7 Mild or asymptomatic infections are common in Coronavirus disease 2019 (COVID-19) and are an
8 important source of infection transmission.[3,4] Such cases are less likely to be detected by a
9 surveillance system based on reverse-transcriptase polymerase chain reaction (RT-PCR) testing. The
10 number of reported RT-PCR positive cases are an underestimate of the true number of infections in a
11 population.
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14 Seroprevalence surveys have been conducted in various countries at different stages of the current
15 epidemic among various population groups.[5–14] Seroprevalence surveys provide a more accurate
16 estimate of past infection, improve understanding of the infection transmission dynamics, and guide
17 public health response.[15]
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19 We designed this survey with the primary objective to estimate the seroprevalence of severe acute
20 respiratory syndrome coronavirus 2 (SARS-CoV-2) specific IgG antibodies in the adult population of
21 Kashmir valley.
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24 **METHODS**

25
26 We designed a population-based cross-sectional study. The study covered all the ten districts of
27 Kashmir, a valley in northern India. (Figure 1) We completed data collection in three weeks, from 17 Oct
28 2020 to 04 Nov 2020.
29

30 **Ethics**

31
32 We obtained written informed consent from all study participants. The study was approved by the
33 Institutional Ethics Committee of Government Medical College Srinagar (reference number:
34 1004/ETH/GMC). We used anonymized participant data for analysis.
35

36 **Sample size**

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38 Based on the results of a previous study conducted in July 2020, we speculated that, by October 2020,
39 the prevalence would have increased to around 20%.[16] We calculated the minimum sample size based
40 on an anticipated seroprevalence of 20%, an absolute precision of 2%, and a design effect of 2. We used
41 OpenEpi to make sample size calculations.[17] We adjusted the sample size for a possible non-response
42 of 10% to obtain a minimum size of 3376. We decided to select 3600 individuals from nine of the ten
43 districts (except district Srinagar). To obtain precise estimates for district Srinagar, sample size
44 estimation was made for the district separately. We used a design effect of 1.5, an anticipated
45 seroprevalence of 20%, and absolute precision of 2% to obtain a sample size of 2302 for the district,
46 which was further increased to 2400 to account for non-response. We thus targeted a total sample size
47 of 6000 (3600 + 2400).
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51 **Participants**

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53 All adults ≥ 18 years of age were eligible to participate in the study. We selected eligible participants
54 using a three-stage stratified cluster sampling technique. We listed all clusters in the valley using the
55 Census 2011 data.[18] Within each of the ten districts in the valley, clusters were stratified into urban
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3 and rural clusters. We selected clusters within each of the 20 strata by probability proportionate to size
4 (PPS) sampling. Except for district Srinagar which we oversampled to obtain precise seroprevalence
5 estimates for, ten clusters were randomly selected from each district. We selected 20 clusters from
6 district Srinagar. We divided each selected cluster into four equal areas and chose a central location
7 within each of the four areas as the starting point. Thereafter, we approached consecutive households
8 to enroll at least ten eligible participants. We thus identified a total of 440 random locations within 110
9 clusters in ten districts. We invited all eligible adults in a household for participation.
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12 **Variables**

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14 The main outcome variable of interest was SARS-CoV-2 specific IgG antibodies. We obtained information
15 from participants about their age, gender, history of COVID-19 like symptoms in the three months
16 before the interview date, history of contact with a known COVID-19 patient, and history of COVID-19
17 testing.
18

19 **Procedure**

20
21 We informed eligible adults about the purpose and the procedure of the study. Study participation was
22 voluntary. Participants were interviewed by health personnel specifically trained for the interview.
23 Interview responses were recorded in an Epicollect5 form.[19] Once the interview was completed, a
24 trained phlebotomist collected 3-5 mL of venous blood from the antecubital vein under aseptic
25 precautions into a red-top collection tube containing a clot activator. The tube was left standing,
26 undisturbed, for at least 30 minutes for clot formation. The sample was later transported to a central
27 facility for centrifugation. Centrifuged samples were transported to a central laboratory for further
28 processing and analysis. Serum samples were tested for the presence of SARS-CoV-2 specific IgG
29 antibodies using the Abbott SARS-CoV-2 IgG assay. The assay uses chemiluminescence to detect IgG
30 antibodies against the SARS-CoV-2 nucleocapsid protein. The reported sensitivity and specificity of the
31 assay are 100% (95% CI 95.89-100.00) and 99.63% (99.05-99.90), respectively.[20] As recommended by
32 the manufacturer, we labeled assay results equal to or above the cut-off index value of 1.4 as positive
33 for SARS-CoV-2 specific IgG antibodies.
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38 **Statistical methods**

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40 We report unweighted seroprevalence estimates in percentages. We used the Agresti-Coull procedure
41 to calculate a 95% confidence interval (CI) for seroprevalence estimates.[21] A weighted estimate of
42 seroprevalence is provided. To calculate survey weights (inverse of sampling probability) we used the
43 estimated population of the districts. We used the census 2011 data and growth rates from Sample
44 Registration System to estimate the population of the districts in 2020.[18,22] Survey weights so
45 obtained were further adjusted for non-response and age and sex structure (post-stratification weights).
46 We further adjusted the weighted seroprevalence estimates for test performance to calculate
47 “weighted seroprevalence adjusted for test performance”. We did this using the formula:
48 *Weighted seroprevalence adjusted for test performance* =
49 $(\text{Weighted seroprevalence} + \text{Test specificity} - 1) / (\text{Test sensitivity} + \text{Test specificity} - 1)$. [23]
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52 We used the manufacturer-provided sensitivity and specificity in the above formula.[20] We used the
53 lower and upper bounds of the manufacturer-provided test performance to report sensitivity analyses.
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We analyzed the difference in seroprevalence estimates across levels of a categorical variable using a Chi-square test adjusted for the sampling design.

We estimated the number of SARS-CoV-2 infections by multiplying the weighted seroprevalence adjusted for test performance with the estimated population of the valley. To estimate the number of infections per reported case, we divided the estimated number of SARS-CoV-2 infections by the reported number of COVID-19 cases two weeks before the survey date. We calculated the infection fatality rate by dividing the reported number of deaths by the number of estimated infections, assuming a three-week lag time from infection to death.[24]

We analyzed the data using Stata version 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP.).

Patient and Public Involvement

No patients or members of the public were involved in this study.

RESULTS

We enumerated 6 397 individuals ≥ 18 years from 3 077 households and 110 clusters (34 urban clusters and 76 rural clusters) between 17 Oct 2020 and 04 Nov 2020. Out of the 6 397 eligible individuals, 6 315 (98.7%) agreed to participate and were enrolled. The final analysis was done on a sample of 6 230 participants. (Figure 2)

Of the 6 230 participants, 1 513 (24.3%) were between 18 and 30 years of age, 2 672 (42.9%) were aged 30-49 years, 1 643 (26.4%) were aged 50-69 years, and 402 (6.4%) were 70 years and older. (Table 1). There was equal representation from males and females, and 3 364 (54.0%) resided in a rural area. Of the 3 104 females, 56 (1.8%) reported pregnant at the time of the survey. Four hundred seventy-four (7.6%) reported COVID-19 like symptoms in the three months preceding the survey and 439 (7.0%) reported to have ever come in contact with a known COVID-19 case. One thousand ninety-two (17.5%) reported having been tested for COVID-19 using RT-PCR or a Rapid Antigen Test (RAT) previously, of whom 176 (16.2%) reported to have tested positive for the disease.

Table 1: Characteristics of study participants

	Frequency	Percent
Total	6230	
Age, years		
18-29	1513	24.3
30-49	2672	42.9
50-69	1643	26.4
≥ 70	402	6.5
Gender		
Male	3126	50.2
Female	3104	49.8
Residence		
Urban	2866	46.0
Rural	3364	54.0

Pregnant (n=3104)	56	1.8
Self-reported history of chronic disease	1145	18.4
History of COVID-19 like symptoms	474	7.6
History of contact with a known COVID-19 case	439	7.0
Ever tested for COVID-19 (RT-PCR)	1092	17.5
RT-PCR result (n=1088*)		
Positive	176	16.2
Negative	912	83.8

COVID-19: Coronavirus disease; RT-PCR: Reverse transcriptase-polymerase chain reaction

*RT-PCR result not known in four participants

We found an overall unweighted seroprevalence of 38.8% (95% CI 37.6 – 40.0). The seroprevalence ranged from 28.5% in district Kulgam to 43.1% in district Pulwama. (Figure 1 and online supplemental file 1) The overall weighted seroprevalence (adjusted for sampling design) was 36.9% (95% CI 34.5 – 39.4). The weighted seroprevalence adjusted for test performance was 36.7% (95% CI 34.3 – 39.2). (Table 2) Upon sensitivity analyses, the weighted seroprevalence adjusted for test performance ranged from 36.3% (95% CI 33.9 – 38.8) to 38.4% (95% CI 35.9 – 41.0). (Table 3)

Table 2: Seroprevalence of SARS-CoV-2 specific IgG antibodies by participant characteristics

	Number tested	Number seropositive	Unweighted seroprevalence, % (95% CI)	Weighted seroprevalence, % (95% CI)	Weighted seroprevalence adjusted for test performance, % (95% CI)	Design-based F, p-value
Total	6230	2415	38.8 (37.6-40.0)	36.9 (34.5-39.4)	36.7 (34.3-39.2)	
Age, years						
18-29	1513	538	35.6 (33.2-38.0)	33.7 (30.1-37.6)	33.5 (29.8-37.4)	6.42, 0.0006
30-49	2672	1000	37.4 (35.6-39.3)	36.3 (33.5-39.3)	36.1 (33.3-39.1)	
50-69	1643	691	42.1 (39.7-44.5)	42.5 (38.8-46.2)	42.3 (38.6-46.0)	
≥70	402	186	46.3 (41.5-51.2)	45.3 (37.8-53.0)	45.1 (37.6-52.8)	
Gender						
Male	3126	1166	37.3 (35.6-39.0)	36.1 (33.5-38.9)	35.9 (33.3-38.7)	0.94, 0.34
Female	3104	1249	40.2 (38.5-42.0)	37.8 (34.5-41.3)	37.6 (34.3-41.1)	
Residence						
Urban	2866	1180	41.2 (39.4-43.0)	40.2 (36.3-44.1)	40.0 (36.1-43.9)	3.43, 0.07
Rural	3364	1235	36.7 (35.1-38.4)	35.5 (32.5-38.7)	35.3 (32.2-38.5)	

Self-reported history of chronic disease						
Yes	1145	495	43.2 (40.4-46.1)	41.9 (37.4-46.6)	41.7 (37.2-46.4)	6.14, 0.02
No	5085	1920	37.8 (36.4-39.1)	36.2 (33.7-38.9)	36.0 (33.5-38.7)	
History of COVID-19 like symptoms						
Yes	474	247	52.1 (47.6-56.6)	47.4 (37.9-57.1)	47.2 (37.7-56.9)	5.53, 0.02
No	5756	2168	37.7 (36.4-38.9)	36.3 (33.9-38.8)	36.1 (33.7-38.6)	
History of contact with a known COVID-19 case						
Yes	439	219	49.9 (45.2-54.5)	45.2 (38.3-52.2)	45.0 (38.1-52.0)	7.13, 0.01
No	5791	2196	37.9 (36.7-39.2)	36.5 (34.1-39.0)	36.3 (33.9-38.8)	
Ever tested for COVID-19 (RT-PCR)						
Yes	1092	485	44.4 (41.5-47.4)	41.0 (35.4-46.9)	40.8 (35.2-46.7)	2.17, 0.14
No	5138	1930	37.6 (36.2-38.9)	36.2 (33.5-39.0)	36.0 (33.3-38.8)	
RT-PCR result (n=1088*)						
Positive	176	140	79.5 (73.0-84.9)	81.8 (74.8-87.1)	81.7 (74.7-87.1)	74.93, <0.0001
Negative	912	345	37.8 (34.7-41.0)	38.8 (33.3-44.7)	38.6 (33.1-44.5)	

COVID-19: Coronavirus disease; RT-PCR: Reverse transcriptase-polymerase chain reaction

*RT-PCR result not known in four participants

Table 3: Sensitivity analyses for seroprevalence at extremes of test performance

	Weighted seroprevalence, % (95% CI)	Weighted seroprevalence adjusted for test performance, % (95% CI) [Sensitivity 100.00%, Specificity 99.63%]	Weighted seroprevalence adjusted for test performance, % (95% CI) [Sensitivity 95.89%, Specificity 99.90%]	Weighted seroprevalence adjusted for test performance, % (95% CI) [Sensitivity 100.00%, Specificity 99.05%]
Overall	36.9 (34.5-39.4)	36.7 (34.3-39.2)	38.4 (35.9-41.0)	36.3 (33.9-38.8)
Age, years				
18-29	33.7 (30.1-37.6)	33.5 (29.8-37.4)	35.1 (31.3-39.1)	33.1 (29.4-37.0)
30-49	36.3 (33.5-39.3)	36.1 (33.3-39.1)	37.8 (34.9-40.9)	35.7 (32.9-38.7)

50-69	42.5 (938.8-46.2)	42.3 (38.6-46.0)	44.3 (40.4-48.1)	41.9 (38.2-45.7)
≥70	45.3 (937.8-53.0)	45.1 (37.6-52.8)	47.2 (39.4-55.2)	44.8 (37.2-52.5)
Gender				
Male	36.1 (33.5-38.9)	35.9 (33.3-38.7)	37.6 (34.9-40.5)	35.5 (32.9-38.3)
Female	37.8 (34.5-41.3)	37.6 (34.3-41.1)	39.4 (35.9-43.0)	37.2 (33.9-40.7)
Residence				
Urban	40.2 (36.3-44.1)	40.0 (36.1-43.9)	41.9 (37.8-45.9)	39.6 (35.7-43.6)
Rural	35.5 (32.5-38.7)	35.3 (32.2-38.5)	37.0 (33.8-40.3)	34.9 (31.9-38.1)
Self-reported history of chronic disease				
Yes	43.2 (40.4-46.1)	41.9 (37.4-46.6)	43.6 (38.9-48.5)	41.3 (36.8-46.1)
No	37.8 (36.4-39.1)	36.2 (33.7-38.9)	37.7 (35.1-40.5)	35.6 (33.1-38.3)
History of COVID-19 like symptoms				
Yes	52.1 (47.6-56.6)	47.4 (37.9-57.1)	49.4 (39.5-59.5)	46.9 (37.3-56.7)
No	37.7 (36.4-38.9)	36.3 (33.9-38.8)	37.8 (35.3-40.4)	35.7 (33.3-38.2)
History of contact with a known COVID-19 case				
Yes	49.9 (45.2-54.5)	45.2 (38.3-52.2)	47.1 (39.9-54.4)	44.7 (37.7-51.7)
No	37.9 (36.7-39.2)	36.5 (34.1-39.0)	38.0 (35.5-40.6)	35.9 (33.5-38.4)
Ever tested for COVID-19 (RT-PCR)				
Yes	44.4 (41.5-47.4)	41.0 (35.4-46.9)	42.7 (36.9-48.9)	40.4 (34.8-46.4)
No	37.6 (36.2-38.9)	36.2 (33.5-39.0)	37.7 (34.9-40.6)	35.6 (32.9-38.4)
RT-PCR result (n=1088*)				
Positive	79.5 (73.0-84.9)	81.8 (74.8-87.1)	85.3 (78.0-90.8)	81.6 (74.6-87.0)
Negative	37.8 (34.7-41.0)	38.8 (33.3-44.7)	40.4 (34.7-46.6)	38.2 (32.7-44.2)

Seroprevalence was lowest among participants aged 18-29 years [33.5% (95% CI 29.8 – 37.4)] and was higher in older age groups. Seroprevalence was highest in those aged 70 years and above [45.1% (95% CI 37.6 – 52.8)]. Seroprevalence was not significantly different among males and females ($p=0.34$). The seroprevalence among urban residents was 40.0% (95% CI 36.1 – 43.9), slightly but not significantly, higher than rural residents [35.3% (95% CI 32.2 – 38.5), $p=0.07$]. (Table 2)

One in five participants (1145/6230, 18.4%) self-reported a history of at least one chronic disease (Table 1). Hypertension (815/6230, 13.1%) and diabetes mellitus (314/6230, 5.0%) were the most commonly reported chronic diseases (online supplemental file 2). Seroprevalence was significantly higher in participants who self-reported history of chronic disease (41.7%, 95% CI 37.2 – 46.4) as compared to those who did not report a history of chronic disease (36.0%, 95% CI 33.5 - 38.7) (Table 2).

Among participants who reported a history of COVID-19 like symptoms, seroprevalence was 47.2% (95% CI 37.7 – 56.9) compared with 36.1% (95% CI 33.7 – 38.6) among participants who did not report such

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3 symptoms. Seroprevalence was higher among those who reported contact with a known COVID-19 case
4 [45.0% (95% CI 38.1 – 52.0)] than participants who did not report any history of such contact [36.3%
5 (95% CI 33.9 – 38.8)]. (Table 2)
6

7 Seroprevalence was not significantly related to being tested for COVID-19 (RT-PCR). However, those who
8 reported a positive RT-PCR COVID-19 test had significantly higher seroprevalence (81.7%, 95% CI 74.7 –
9 87.1) as compared to those who reported a negative RT-PCR COVID-19 test (38.6%, 95% CI 33.1 – 44.5).
10 (Table 2)
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12
13 Among 2 415 seropositive individuals, only 247 (10.2%) reported a history of COVID-19 like symptoms.
14 Only 20.1% (485/2415) of the seropositive individuals were tested for COVID-19 (RT-PCR). Among 474
15 who reported a history of COVID-19 like symptoms, 233 (49.2%) were tested for COVID-19 (RT-PCR).
16 Among 4897 individuals who did not report a history of COVID-19 like symptoms and were never tested
17 for COVID-19 (RT-PCR), 1825 (37.3%) were seropositive. (Figure 3)
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19
20 Among 36 participants who reported a positive RT-PCR COVID-19 test but were seronegative, the
21 duration between COVID-19 RT-PCR test and serological testing ranged from 9 days to 101 days. In only
22 four of these 36 participants, the duration between the COVID-19 RT-PCR test and the serological test
23 was 14 days or less. Of the remaining 32 participants, 21 did not report a history of COVID-19 like
24 symptoms, nine did not report a history of contact with a known COVID-19 case, and eight reported
25 neither a history of COVID-19 like symptoms nor a history of contact with a known COVID-19 case.
26

27 We estimated that there were 1 673 484 (95% CI 1 564 047 – 1 787 482) cumulative number of
28 infections among adults aged ≥ 18 years in the valley by 03 Oct 2020, two weeks before the start of the
29 survey. If we assume that the seroprevalence was similar to the overall seroprevalence in the population
30 not included in our study (< 18 years of age) then the estimated cumulative number of infections in the
31 valley by 03 Oct 2020 was 2 791 933 (95% CI 2 609 354 – 2 982 119). Considering that the cumulative
32 number of reported COVID-19 cases was 47 071 by 03 Oct 2020 (Figure 4), we estimate the number of
33 infections per reported case as 59.3 (95% CI 55.4 – 63.4). The number of reported COVID-19 deaths after
34 a three-week lag period (on 24 Oct 2020) was 955. Thus, we estimated the infection fatality rate as
35 0.034% (95% CI 0.032 – 0.037).
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39 DISCUSSION

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41 The results of our study indicate that by the first week of October 2020, nearly seven months after the
42 appearance of the first laboratory-confirmed COVID-19 case on 18 March 2020, close to 37% of the
43 valley's population aged ≥ 18 years had been infected. Our results suggest that the cumulative number of
44 SARS-CoV-2 infections by the first week of October 2020 was nearly 2.8 million with an estimated
45 infection fatality rate of 0.034%. Seroprevalence did not differ by gender but was higher in older age
46 groups.
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49 The findings of our study are based on a representative sample of the population. The laboratory test
50 used for the detection of SARS-CoV-2 specific IgG antibodies in serum samples provides valid
51 results.[20,25] We report seroprevalence estimates adjusted for sampling design and test performance.
52

53 The overall adjusted seroprevalence of around 37% indicates that a large proportion of the valley's
54 population has been infected with the virus. Easing of lockdown, being fed up with the restrictions, and
55 non-adherence to prevention norms are the possible reasons. Even though a large proportion of the
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3 population has been infected, the transmission of infection is expected to continue till most of the
4 susceptible population becomes immune. Herd immunity in the context of COVID-19 is a matter of
5 debate as reports of a second infection continue to pour in.[26] The emergence of several Variants of
6 Concern and the introduction of COVID-19 vaccination will also influence population immunity. Several
7 factors potentially influence the seroprevalence rates. These include population density, social and
8 demographic structure of the population, governmental policies and the extent of their implementation,
9 immunity level of the population, time since the start of infection transmission, adherence to infection
10 prevention guidelines, quality of contact tracing and quarantine, and possibly the geography and
11 environment of an area.
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15 Comparison with previous reports suggests that the seroprevalence has increased almost ten-fold since
16 July 2020.[16,27] The second of the three nationwide seroprevalence surveys in India conducted in
17 August-September 2020 reports an overall seroprevalence of 6.6% ranging from 5.2% in rural areas to
18 16.9% in urban slums.[28] A nationwide survey conducted in December 2020-January 2021 reported an
19 overall seroprevalence of 24.1% ranging from 4.9% - 44.4% across districts.[29] Kashmir is thus not a
20 low-infection area. Being an oft-visited tourist area, Kashmir is at an increased risk of infection
21 transmission. Adherence to COVID appropriate behavior (use of face masks in public, frequent
22 handwashing, physical and social distancing) has been poor. With the introduction of the COVID-19
23 vaccination program in January 2021 and the emergence of a 'second wave' in Kashmir in April 2021, the
24 seroprevalence estimates are expected to increase in the future.
25
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27
28 The seroprevalence of SARS-CoV-2 IgG antibodies was higher in older age groups. During the early
29 period of the pandemic, people were adherent to social distancing and other non-pharmaceutical
30 interventions because of a fear of the disease and administrative restrictions. With time, administrative
31 restrictions were relaxed, fear of the disease attenuated, and people became sort of fed up with the
32 social restrictions. This not only led to an increase in the number of reported COVID-19 cases but also
33 provided the population, including older age groups, an opportunity to contract the infection. That older
34 people have an increased risk of symptomatic and more severe disease is now well known.[30,31]
35 However, age-based differential susceptibility to SARS-CoV-2 infection antibody response and the
36 reasons thereof are still a grey area and need further understanding. Existing literature might suggest
37 that the young who are more mobile and socially active have a higher risk of infection.[6,7] However,
38 this should not imply that the elderly have a decreased susceptibility to SARS-CoV-2 infection or a
39 decreased antibody response.[32] On the contrary, several studies suggest that the seroprevalence of
40 SARS-CoV-2 specific IgG antibodies is higher in the older age groups and particularly so in more dense
41 population groups.[4,5,8-11,13] Furthermore, SARS-CoV-2 antibody levels have been reported to be
42 higher in older people.[12]
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46
47 The seroprevalence of SARS-CoV-2 specific IgG antibodies did not differ significantly by gender, though
48 the figure was slightly higher for females. These findings are consistent with the available
49 literature.[6,13] Difference in seroprevalence by gender has been suggested by some studies and
50 females have been reported to have lower antibody levels.[5,7,9,11,12,14,33]
51

52
53 Urban areas are more densely populated as compared to rural areas which accelerate the transmission
54 of infections in the population. The seroprevalence of SARS-CoV-2 specific IgG antibodies is thus
55 expected to be higher in urban areas especially during the early phases of an epidemic. As the epidemic
56 progresses the seroprevalence gap between urban and rural areas will wane off. We estimated an
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3 adjusted seroprevalence of 40.0% (95% CI 36.1 – 43.9) in urban areas as compared to 35.3% (95% CI
4 32.2 – 38.5) in rural areas ($p=0.07$).

6 People with a chronic disease experience more severe COVID-19 symptoms and are more likely to die
7 when compared to people with no chronic disease.[34] We found a higher proportion of symptomatic
8 infection among participants with a self-reported history of chronic disease (78/1145, 6.8%) as
9 compared to participants with no chronic disease (169/5085, 3.3%) (online supplemental file 3). Little is,
10 however, known about the risk of infection in chronic disease patients. We found a significantly higher
11 seroprevalence among participants with a self-reported history of chronic disease (Table 2). This finding
12 needs further research for corroboration and possible explanations.

15 People with a self-reported history of COVID-19 related symptoms, contact with a known COVID-19
16 case, or a positive COVID-19 RT-PCR had a higher seroprevalence as compared to their complement.
17 Among seropositive individuals, only 10.2% reported being symptomatic. The percentage of
18 asymptomatic infections, thus, was 90%. However, only 49% of individuals with a history of COVID-19
19 like symptoms were tested using RT-PCR. We also estimated that only one out of almost 59 infections
20 gets reported. This reflects the necessity of improving the efficiency of RT-PCR testing so that more
21 symptomatic individuals receive the test. Not all individuals with a known RT-PCR positive result showed
22 the presence of IgG antibodies. Around 20% of RT-PCR positive individuals were seronegative and in a
23 large majority of them (32 out of 36) the duration since RT-PCR positivity was more than two weeks. This
24 may be attributed to a poor B cell response or a false negative antibody test.[35] Around 38% of RT-PCR
25 negative individuals were seropositive suggesting a false-negative RT-PCR or infection acquisition at a
26 date later than the RT-PCR test.

30 We estimated an infection fatality rate of 0.034% (95% CI 0.032 – 0.037). The infection fatality rate in
31 SARS-CoV-2 infection has been reported to range from as low as 0.00% to 1.63%.[36] Our estimates of
32 the infection fatality rate are low as compared to estimates from several Indian studies.[5,28,37] Under-
33 reporting of COVID-19 deaths because of non-uniform definition for a 'COVID-19 death' may falsely
34 lower the infection fatality rates.[38] The infection fatality rate is, however, known to be lower in
35 developing nations.[30,39] In developed nations like the United States and many European countries, a
36 higher infection fatality rate has been reported.[30,40]

39 Limitations

41 One important limitation of our study is that even though we adjusted the weighted seroprevalence
42 estimates for test performance using manufacturer-provided sensitivity and specificity (100% and
43 99.63% respectively), we did not quantify the test validity in-house. Another limitation of our study
44 estimates is that we excluded people <18 years of age. The results of our study may not thus be
45 generalizable to this group of the population.

48 Our estimated seroprevalence was much higher than we anticipated at the designing stage. This has
49 impacted the precision of our estimates to some extent. However, we believe we still have been able to
50 estimate the seroprevalence with reasonable precision.

52 Lack of reliable death counts is another potential limitation. This may have led to an underestimation of
53 the infection fatality rate. We did not perform any adjustment for death counts. Further, because of lack
54

of age- and gender-specific mortality data we could not estimate age- and gender-specific infection fatality rates.

CONCLUSIONS

We conclude that nearly 37% of individuals aged 18 years and above were infected with SARS-CoV-2 in Kashmir by October 2020. The infection fatality rate in the valley is around 0.034%. A majority of cases go unreported. For every reported case there are 59 unreported infections in the population. Since almost half of the symptomatic individuals go unreported, testing of symptomatic individuals and effective contact tracing needs to continue. Given the emergence of mutant Variants of Concern, increasing the population immunity through augmented and sustained vaccination is needed. We further recommend that adherence to COVID-19 prevention measures should be ensured at least till a large proportion of the population gets vaccinated.

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COMPETING INTERESTS

We declare no competing interests, financial or otherwise.

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CONTRIBUTORS

S Muhammad Salim Khan: Conceptualization, Funding acquisition, Methodology, Writing-review & editing.

Mariya Amin Qurieshi, Inaamul Haq, Sabhiya Majid: Formal analysis, Data curation, Methodology, Project administration, Writing-original draft, Writing-review & editing.

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11 Writing-review & editing.

12
13
14 S Muhammad Salim Khan, Mariya Amin Qurieshi, Inaamul Haq, and Sabhiya Majid have verified the
15 underlying data.

16 17 **DATA SHARING**

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19 Anonymized data collected for the study, including individual participant data and a data dictionary
20 defining each field in the set, will be made available to interested researchers on request by Inaamul
21 Haq (haqinaam@yahoo.co.in) for two years from publication. The study protocol, statistical analysis
22 plan, and informed consent forms are also available from Inaamul Haq.
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Figure 1 legend:

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40 Figure 1: Location of the ten districts and seroprevalence (%) by district. Figures in parentheses indicate
41 a 95% Confidence Interval for seroprevalence.
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Figure 2 legend:

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45 Figure 2: Participant flow.
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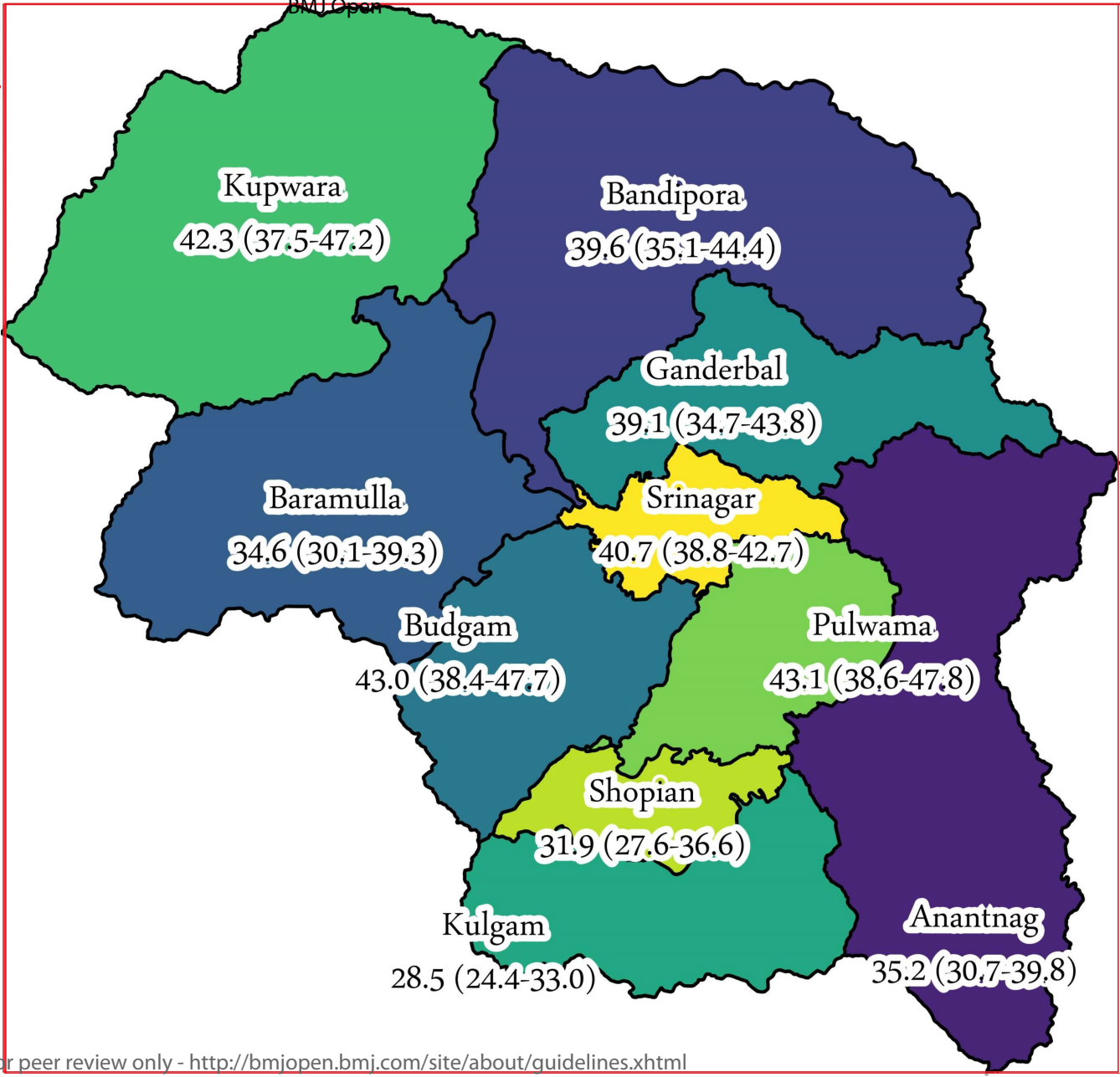
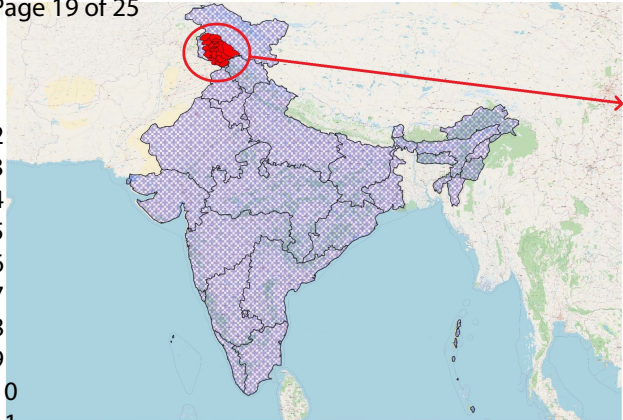
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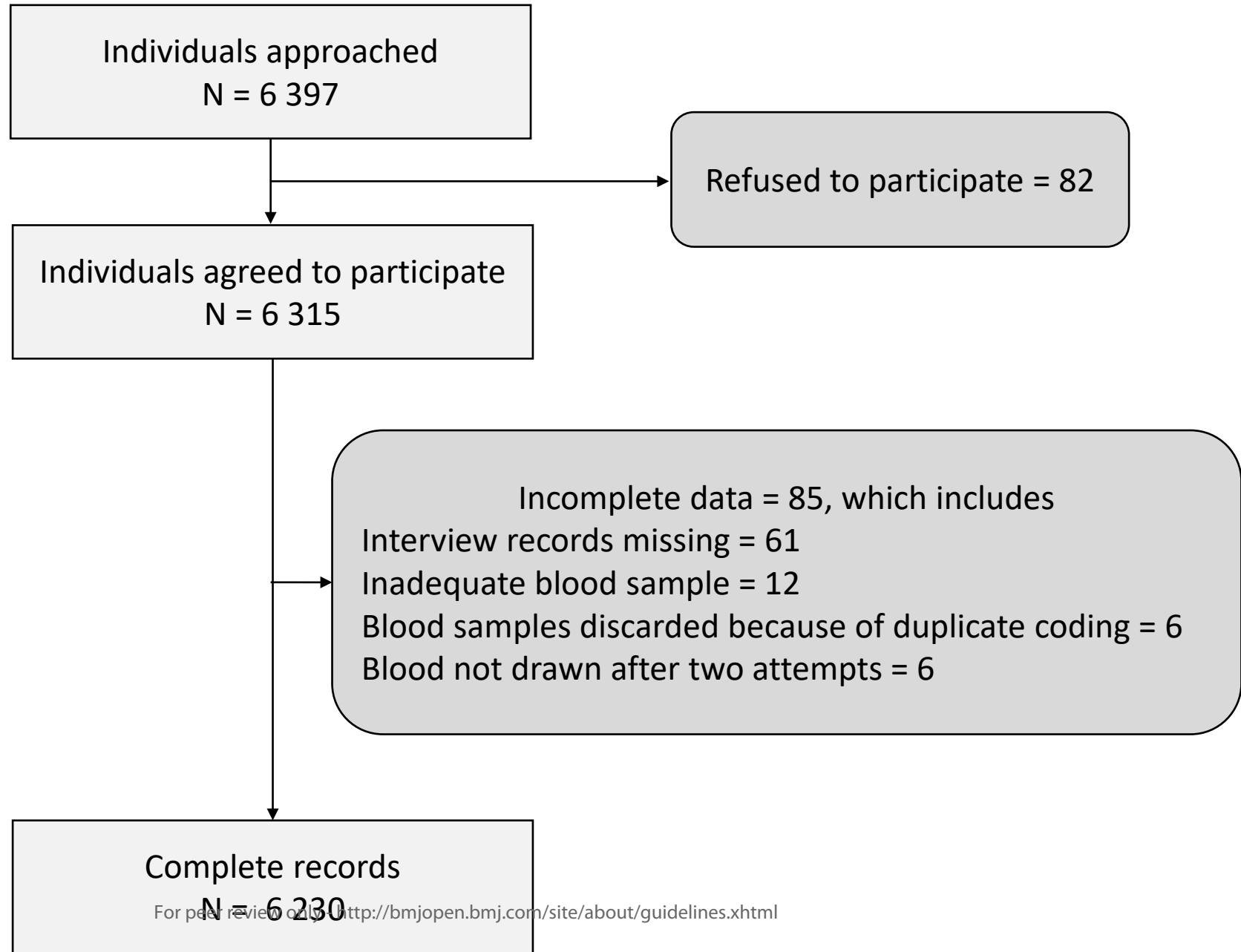
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49 Figure 3: A. Seropositivity by the history of COVID-19 like symptoms, RT-PCR testing, and test result. B.
50 History of COVID-19 like symptoms by seropositivity, RT-PCR testing, and test result.
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Figure 4 legend:

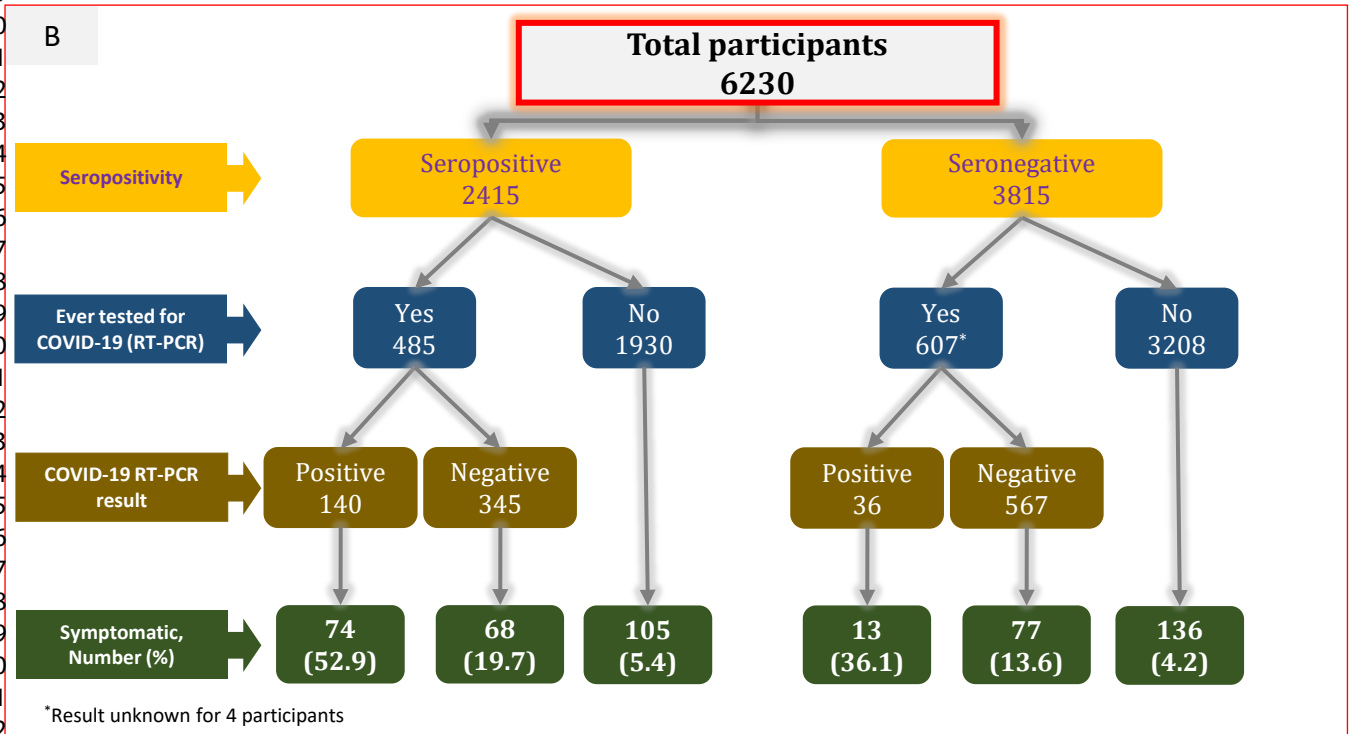
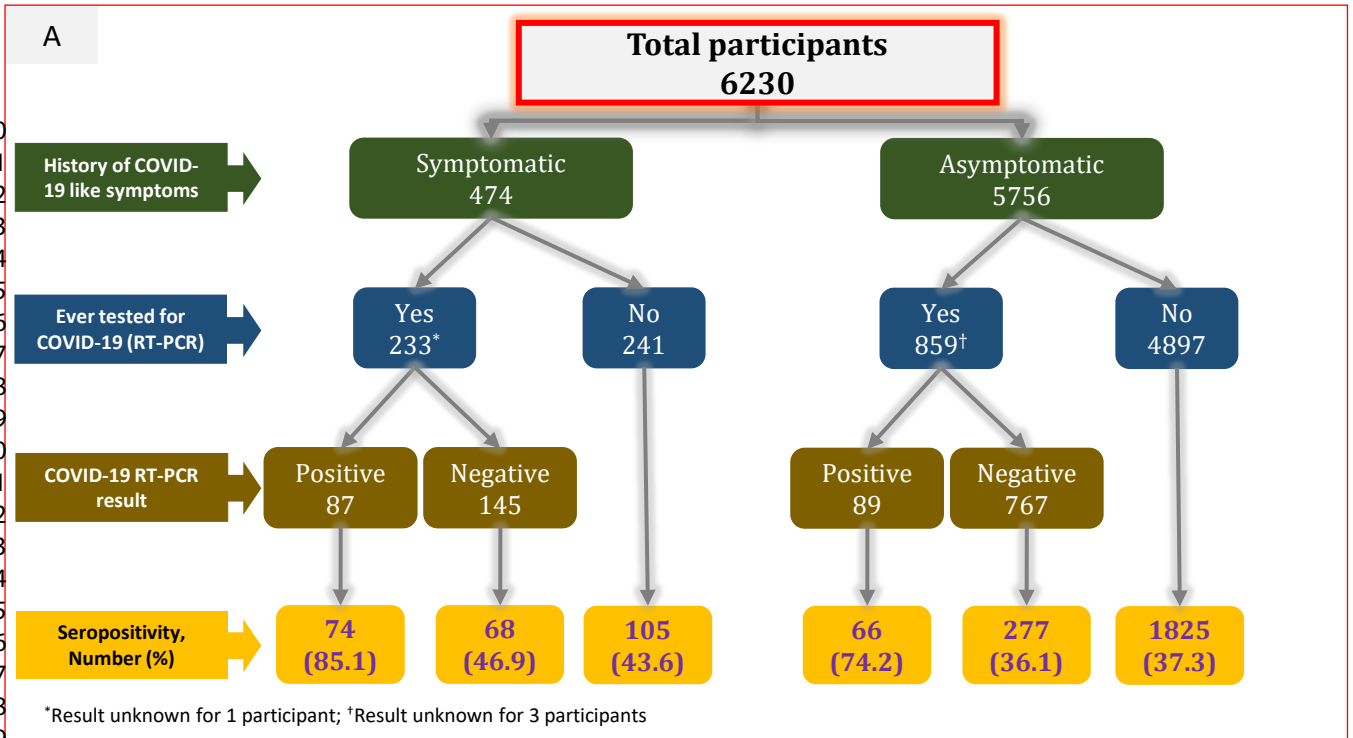
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54 Figure 4: A. Daily cases and deaths in Kashmir since the start of the COVID-19 pandemic; B. Cumulative
55 number of cases and deaths in Kashmir.
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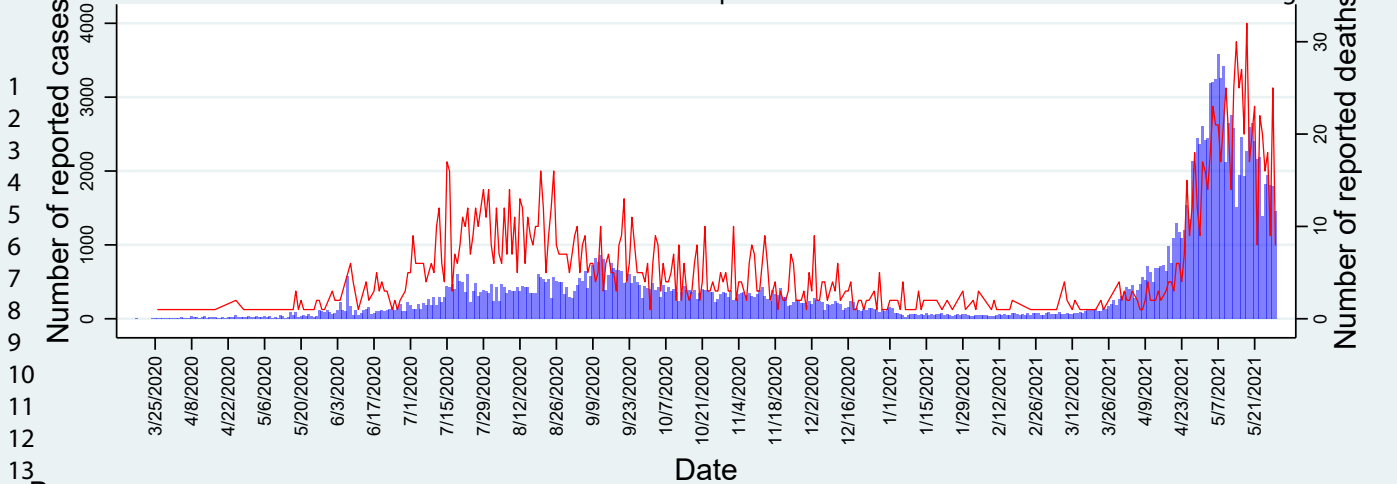


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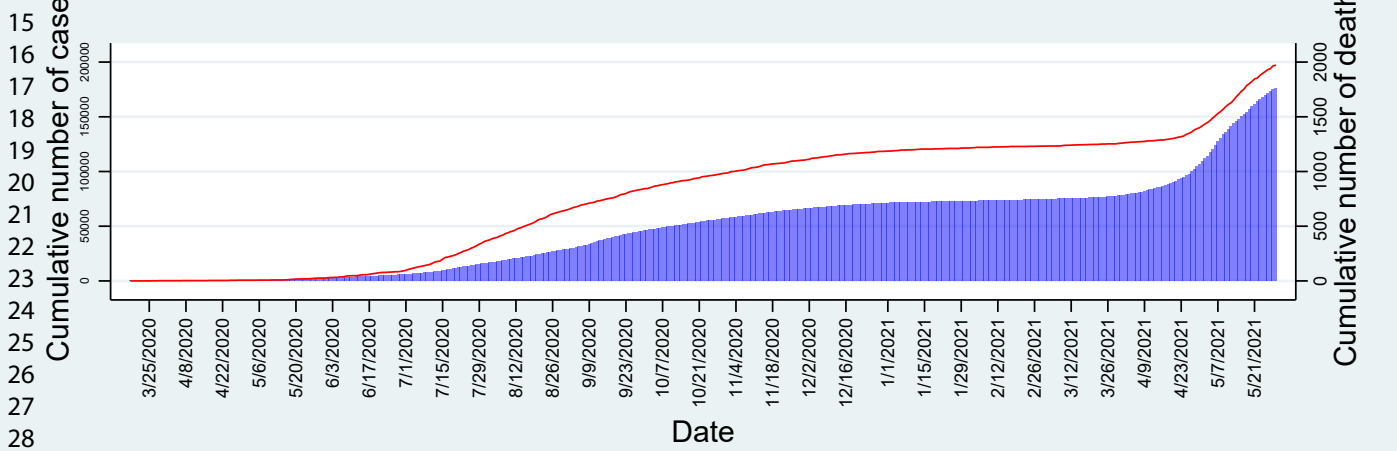


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Supplemental Table 1: Participant characteristics by district

District	Total	Age (years)				Gender		Residence	
		<30	30-49	50-69	70+	Female	Male	Rural	Urban
Anantnag	421	84	197	113	27	214	207	295	126
Budgam	442	113	190	105	34	263	179	354	88
Bandipora	424	106	174	114	30	227	197	341	83
Baramulla	405	113	176	98	18	214	191	325	80
Ganderbal	442	92	210	123	17	233	209	346	96
Kulgam	428	102	194	113	19	257	171	346	82
Kupwara	400	81	171	105	43	215	185	360	40
Pulwama	443	102	176	126	39	218	225	396	47
Shopiyan	407	119	152	90	46	211	196	368	39
Srinagar	2418	601	1032	656	129	1052	1366	233	2185
Total	6230	1513	2672	1643	402	3104	3126	3364	2866

Supplemental Table 2: Seroprevalence (unadjusted) by district and participant characteristics

District	Overall	Age (years)				Gender		Residence	
		<30	30-49	50-69	70+	Male	Female	Urban	Rural
Anantnag	35.2 (30.7-39.8)	29.8 (21-40.4)	34.5 (28.2-41.4)	38.9 (30.4-48.2)	40.7 (24.2-59.7)	36.2 (30-43)	34.1 (28.1-40.7)	42.9 (34.5-51.6)	31.9 (26.8-37.4)
Budgam	43 (38.4-47.7)	44.2 (35.4-53.5)	37.9 (31.3-45)	48.6 (39.2-58.1)	50 (33.8-66.2)	41.9 (34.9-49.3)	43.7 (37.8-49.8)	38.6 (29.1-49.2)	44.1 (39-49.3)
Bandipora	39.6 (35.1-44.4)	37.7 (29-47.3)	42 (34.8-49.4)	40.4 (31.8-49.6)	30 (16.4-48.3)	37.6 (31.1-44.5)	41.4 (35.2-47.9)	55.4 (44.6-65.7)	35.8 (30.9-41)
Baramulla	34.6 (30.1-39.3)	27.4 (20-36.4)	32.4 (25.9-39.6)	44.9 (35.4-54.8)	44.4 (24-67)	39.3 (32.6-46.4)	30.4 (24.6-36.9)	36.3 (26.5-47.3)	34.2 (29.2-39.5)
Ganderbal	39.1 (34.7-43.8)	34.8 (25.8-45)	40.5 (34-47.3)	39.8 (31.6-48.7)	41.2 (21-64.8)	39.2 (32.8-46)	39.1 (33-45.5)	42.7 (33.2-52.8)	38.2 (33.2-43.4)
Kulgam	28.5 (24.4-33)	27.5 (19.7-36.9)	26.8 (21-33.5)	31 (23.1-40.1)	36.8 (18.7-59.7)	25.1 (19.2-32.2)	30.7 (25.4-36.6)	37.8 (28-48.7)	26.3 (21.9-31.2)
Kupwara	42.3 (37.5-47.2)	33.3 (24-44.2)	39.8 (32.7-47.3)	50.5 (41-59.9)	48.8 (34.4-63.4)	41.6 (34.7-48.9)	42.8 (36.3-49.5)	50 (35-65)	41.4 (36.4-46.6)
Pulwama	43.1 (38.6-47.8)	35.3 (26.7-45)	42.6 (35.5-50)	45.2 (36.8-54)	59 (43.2-73.1)	39.6 (33.4-46.1)	46.8 (40.3-53.4)	40.4 (27.5-54.9)	43.4 (38.6-48.4)
Shopiyan	31.9 (27.6-36.6)	28.6 (21.2-37.3)	29.6 (22.9-37.3)	41.1 (31.4-51.5)	30.4 (18.9-45.1)	31.1 (25-37.9)	32.7 (26.7-39.3)	38.5 (24.7-54.4)	31.3 (26.7-36.2)
Srinagar	40.7 (38.8-42.7)	39.1 (35.3-43.1)	39.2 (36.3-42.3)	41.9 (38.2-45.7)	53.5 (44.9-61.9)	37.7 (35.2-40.3)	44.6 (41.6-47.6)	40.8 (38.7-42.9)	39.9 (33.8-46.3)

Chronic disease and SARS-CoV-2 infection in the study population

Of the 6230 participants, 1145 reported a history of at least one chronic disease. Two hundred ninety-eight reported a history of more than one chronic disease.

Supplementary Table 3: Chronic disease in the study population

Chronic disease (n = 1145)	Number (%)
Hypertension	815 (13.1%)
Diabetes	314 (5.0%)
Chronic Obstructive Pulmonary Disease	39 (0.6%)
Coronary Heart Disease	35 (0.6%)
Cerebrovascular Disease	16 (0.3%)
Asthma	15 (0.2%)
Chronic Kidney Disease	10 (0.2%)
Chronic Liver Disease	5 (0.1%)
Cancer	4 (0.1%)

Supplementary Table 4: History of COVID-19 like symptoms and seropositivity vis-à-vis history of chronic disease

		History of COVID-19 like symptoms	
		Yes	No
Reported history of chronic disease (n=1145)	Seropositive	78	417
	Seronegative	63	587
Did not report any history of chronic disease (n=5085)	Seropositive	169	1751
	Seronegative	164	3001

Of the 1154 participants who reported a history of chronic disease 78 (6.8%) reported a history of COVID-19 like symptoms within three months of the interview date and were seropositive for SARS-CoV-2 specific IgG (symptomatic infection). The proportion of symptomatic infection among participants who did not report any history of chronic disease was 3.3% (169/5085).

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1, 3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3 and Figure 1
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	3, 4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4, 5
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	4, 5
		(b) Describe any methods used to examine subgroups and interactions	5
		(c) Explain how missing data were addressed	5
		(d) If applicable, describe analytical methods taking account of sampling strategy	4, 5
		(e) Describe any sensitivity analyses	6, Table 3
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 2, and page 5
		(b) Give reasons for non-participation at each stage	Figure 2
		(c) Consider use of a flow diagram	Figure 2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1, Figure 2
Outcome data	15*	Report numbers of outcome events or summary measures	Table 2

1			
2	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted
3			estimates and their precision (eg, 95% confidence interval). Make
4			clear which confounders were adjusted for and why they were
5			included
6			
7			(b) Report category boundaries when continuous variables were
8			categorized
9			
10			(c) If relevant, consider translating estimates of relative risk into
11			absolute risk for a meaningful time period
12	Other analyses	17	Report other analyses done—eg analyses of subgroups and
13			interactions, and sensitivity analyses
14			
15	Discussion		
16	Key results	18	Summarise key results with reference to study objectives
17			
18	Limitations	19	Discuss limitations of the study, taking into account sources of
19			potential bias or imprecision. Discuss both direction and magnitude
20			of any potential bias
21	Interpretation	20	Give a cautious overall interpretation of results considering
22			objectives, limitations, multiplicity of analyses, results from similar
23			studies, and other relevant evidence
24			
25	Generalisability	21	Discuss the generalisability (external validity) of the study results
26			
27	Other information		
28	Funding	22	Give the source of funding and the role of the funders for the present
29			study and, if applicable, for the original study on which the present
30			article is based
31			

*Give information separately for exposed and unexposed groups.

BMJ Open

Seroprevalence of SARS-CoV-2 specific IgG antibodies in Kashmir, India, seven months after the first reported local COVID-19 case: results of a population-based seroprevalence survey from October-November, 2020

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3 **Seroprevalence of SARS-CoV-2 specific IgG antibodies in Kashmir, India, seven months after the first**
4 **reported local COVID-19 case: results of a population-based seroprevalence survey from October-**
5 **November, 2020**
6

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ABSTRACT

Objectives: We designed a population-based survey in Kashmir to estimate the seroprevalence of SARS-CoV-2 specific IgG antibodies in the general population aged 18 years and above.

Setting: The survey was conducted among 110 villages and urban wards across ten districts in Kashmir from 17 Oct 2020 to 04 Nov 2020.

Participants: Individuals aged 18 years and above were eligible to be included in the survey. Serum samples were tested for the presence of SARS-CoV-2 specific IgG antibodies using the Abbott SARS-CoV-2 IgG assay.

Primary and secondary outcome measures: We labeled assay results equal to or above the cut-off index value of 1.4 as positive for SARS-CoV-2 specific IgG antibodies. Seroprevalence estimates were adjusted for the sampling design and assay characteristics.

Results: Out of 6397 eligible individuals enumerated, 6315 (98.7%) agreed to participate. The final analysis was done on 6230 participants. Seroprevalence adjusted for the sampling design and assay characteristics was 36.7% (95% CI 34.3%-39.2%). Seroprevalence was higher among the older population. Among seropositive individuals, 10.2% (247/2415) reported a history of COVID-19 like symptoms. Out of 474 symptomatic individuals, 233 (49.2%) reported having been tested. We estimated an infection fatality rate of 0.034%.

Conclusions: During the first seven months of the COVID-19 epidemic in Kashmir valley, approximately 37% of individuals were infected. A large proportion of the population remains susceptible to the infection. The experience of a second wave of COVID-19 in April-June 2021, the appearance of virus variants, and the introduction of vaccination programs warrant robust surveillance of the epidemic.

ARTICLE SUMMARY

Strengths and limitations of this study

- The findings of our study are based on a representative sample of the population.
- The laboratory test used for the detection of SARS-CoV-2 specific IgG antibodies in serum samples provides valid results.
- We report seroprevalence estimates adjusted for sampling design and test performance.
- Even though we adjusted the weighted seroprevalence estimates for test performance using manufacturer-provided sensitivity and specificity (100% and 99.63% respectively), we did not quantify the test validity in-house.
- Because of lack of age- and gender-specific mortality data we could not estimate age- and gender-specific infection fatality rates.

INTRODUCTION

On 11 Feb 2020, the World Health Organization announced that the disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) will be named coronavirus disease (COVID-19).[1] In Kashmir, the first case of COVID-19 was confirmed in Srinagar city on 18 Mar 2020.[2] The government imposed the first phase of the lockdown in Kashmir on 24 March 2020. During this phase, inter-state travel remained suspended. People were barred from moving outside except in an emergency. Except

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2
3 for essential services, all government and private offices were advised to work from home. Universal
4 masking was made mandatory. The lockdown was extended till 31 May 2020 and later relaxed in a
5 phased manner.
6

7 Mild or asymptomatic infections are common in Coronavirus disease 2019 (COVID-19) and are an
8 important source of infection transmission.[3,4] Such cases are less likely to be detected by a
9 surveillance system based on reverse-transcriptase polymerase chain reaction (RT-PCR) testing. The
10 number of reported RT-PCR positive cases are an underestimate of the true number of infections in a
11 population.
12
13

14 Seroprevalence surveys have been conducted in various countries at different stages of the current
15 epidemic among various population groups.[5–14] Seroprevalence surveys provide a more accurate
16 estimate of past infection, improve understanding of the infection transmission dynamics, and guide
17 public health response.[15]
18

19 We designed this survey with the primary objective to estimate the seroprevalence of severe acute
20 respiratory syndrome coronavirus 2 (SARS-CoV-2) specific IgG antibodies in the adult population of
21 Kashmir valley.
22
23

24 **METHODS**

25
26 We designed a population-based cross-sectional study. The study covered all the ten districts of
27 Kashmir, a valley in northern India. (Figure 1) We completed data collection in three weeks, from 17 Oct
28 2020 to 04 Nov 2020.
29

30 **Ethics**

31
32 We obtained written informed consent from all study participants. The study was approved by the
33 Institutional Ethics Committee of Government Medical College Srinagar (reference number:
34 1004/ETH/GMC). We used anonymized participant data for analysis.
35

36 **Sample size**

37
38 Based on the results of a previous study conducted in July 2020, we speculated that, by October 2020,
39 the prevalence would have increased to around 20%.[16] We calculated the minimum sample size based
40 on an anticipated seroprevalence of 20%, an absolute precision of 2%, and a design effect of 2. We used
41 OpenEpi to make sample size calculations.[17] We adjusted the sample size for a possible non-response
42 of 10% to obtain a minimum size of 3376. We decided to select 3600 individuals from nine of the ten
43 districts (except district Srinagar). To obtain precise estimates for district Srinagar, sample size
44 estimation was made for the district separately. We used a design effect of 1.5, an anticipated
45 seroprevalence of 20%, and absolute precision of 2% to obtain a sample size of 2302 for the district,
46 which was further increased to 2400 to account for non-response. We thus targeted a total sample size
47 of 6000 (3600 + 2400).
48
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51 **Participants**

52
53 All adults ≥ 18 years of age were eligible to participate in the study. We selected eligible participants
54 using a three-stage stratified cluster sampling technique. We listed all clusters in the valley using the
55 Census 2011 data.[18] Within each of the ten districts in the valley, clusters were stratified into urban
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3 and rural clusters. We selected clusters within each of the 20 strata by probability proportionate to size
4 (PPS) sampling. Except for district Srinagar which we oversampled to obtain precise seroprevalence
5 estimates for, ten clusters were randomly selected from each district. We selected 20 clusters from
6 district Srinagar. We divided each selected cluster into four equal areas and chose a central location
7 within each of the four areas as the starting point. Thereafter, we approached consecutive households
8 to enroll at least ten eligible participants. We thus identified a total of 440 random locations within 110
9 clusters in ten districts. We invited all eligible adults in a household for participation.
10
11

12 **Variables**

13
14 The main outcome variable of interest was SARS-CoV-2 specific IgG antibodies. We obtained information
15 from participants about their age, gender, history of COVID-19 like symptoms in the three months
16 before the interview date, history of contact with a known COVID-19 patient, and history of COVID-19
17 testing.
18

19 **Procedure**

20
21 We informed eligible adults about the purpose and the procedure of the study. Study participation was
22 voluntary. Participants were interviewed by health personnel specifically trained for the interview.
23 Interview responses were recorded in an Epicollect5 form.[19] Once the interview was completed, a
24 trained phlebotomist collected 3-5 mL of venous blood from the antecubital vein under aseptic
25 precautions into a red-top collection tube containing a clot activator. The tube was left standing,
26 undisturbed, for at least 30 minutes for clot formation. The sample was later transported to a central
27 facility for centrifugation. Centrifuged samples were transported to a central laboratory for further
28 processing and analysis. Serum samples were tested for the presence of SARS-CoV-2 specific IgG
29 antibodies using the Abbott SARS-CoV-2 IgG assay. The assay uses chemiluminescence to detect IgG
30 antibodies against the SARS-CoV-2 nucleocapsid protein. The reported sensitivity and specificity of the
31 assay are 100% (95% CI 95.89-100.00) and 99.63% (99.05-99.90), respectively.[20] As recommended by
32 the manufacturer, we labeled assay results equal to or above the cut-off index value of 1.4 as positive
33 for SARS-CoV-2 specific IgG antibodies.
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38 **Statistical methods**

39
40 We report unweighted seroprevalence estimates in percentages. We used the Agresti-Coull procedure
41 to calculate a 95% confidence interval (CI) for seroprevalence estimates.[21] A weighted estimate of
42 seroprevalence is provided. To calculate survey weights (inverse of sampling probability) we used the
43 estimated population of the districts. We used the census 2011 data and growth rates from Sample
44 Registration System to estimate the population of the districts in 2020.[18,22] Survey weights so
45 obtained were further adjusted for non-response and age and sex structure (post-stratification weights).
46 We further adjusted the weighted seroprevalence estimates for test performance to calculate
47 “weighted seroprevalence adjusted for test performance”. We did this using the formula:
48 *Weighted seroprevalence adjusted for test performance* =
49 $(\text{Weighted seroprevalence} + \text{Test specificity} - 1) / (\text{Test sensitivity} + \text{Test specificity} - 1)$. [23]
50
51

52 We used the manufacturer-provided sensitivity and specificity in the above formula.[20] We used the
53 lower and upper bounds of the manufacturer-provided test performance to report sensitivity analyses.
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We analyzed the difference in seroprevalence estimates across levels of a categorical variable using a Chi-square test adjusted for the sampling design.

We estimated the number of SARS-CoV-2 infections by multiplying the weighted seroprevalence adjusted for test performance with the estimated population of the valley. To estimate the number of infections per reported case, we divided the estimated number of SARS-CoV-2 infections by the reported number of COVID-19 cases two weeks before the survey date. We calculated the infection fatality rate by dividing the reported number of deaths by the number of estimated infections, assuming a three-week lag time from infection to death.[24]

We analyzed the data using Stata version 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP.).

Patient and Public Involvement

No patients or members of the public were involved in this study.

RESULTS

We enumerated 6 397 individuals ≥ 18 years from 3 077 households and 110 clusters (34 urban clusters and 76 rural clusters) between 17 Oct 2020 and 04 Nov 2020. Out of the 6 397 eligible individuals, 6 315 (98.7%) agreed to participate and were enrolled. The final analysis was done on a sample of 6 230 participants. (Figure 2)

Of the 6 230 participants, 1 513 (24.3%) were between 18 and 30 years of age, 2 672 (42.9%) were aged 30-49 years, 1 643 (26.4%) were aged 50-69 years, and 402 (6.4%) were 70 years and older. (Table 1). There was equal representation from males and females, and 3 364 (54.0%) resided in a rural area. Of the 3 104 females, 56 (1.8%) reported pregnant at the time of the survey. Four hundred seventy-four (7.6%) reported COVID-19 like symptoms in the three months preceding the survey and 439 (7.0%) reported to have ever come in contact with a known COVID-19 case. One thousand ninety-two (17.5%) reported having been tested for COVID-19 using RT-PCR or a Rapid Antigen Test (RAT) previously, of whom 176 (16.2%) reported to have tested positive for the disease.

Table 1: Characteristics of study participants

	Frequency	Percent
Total	6230	
Age, years		
18-29	1513	24.3
30-49	2672	42.9
50-69	1643	26.4
≥ 70	402	6.5
Gender		
Male	3126	50.2
Female	3104	49.8
Residence		
Urban	2866	46.0
Rural	3364	54.0

Pregnant (n=3104)	56	1.8
Self-reported history of chronic disease	1145	18.4
History of COVID-19 like symptoms	474	7.6
History of contact with a known COVID-19 case	439	7.0
Ever tested for COVID-19 (RT-PCR)	1092	17.5
RT-PCR result (n=1088*)		
Positive	176	16.2
Negative	912	83.8

COVID-19: Coronavirus disease; RT-PCR: Reverse transcriptase-polymerase chain reaction

*RT-PCR result not known in four participants

We found an overall unweighted seroprevalence of 38.8% (95% CI 37.6 – 40.0). The seroprevalence ranged from 28.5% in district Kulgam to 43.1% in district Pulwama. (Figure 1 and online supplemental file 1) The overall weighted seroprevalence (adjusted for sampling design) was 36.9% (95% CI 34.5 – 39.4). The weighted seroprevalence adjusted for test performance was 36.7% (95% CI 34.3 – 39.2). (Table 2) Upon sensitivity analyses, the weighted seroprevalence adjusted for test performance ranged from 36.3% (95% CI 33.9 – 38.8) to 38.4% (95% CI 35.9 – 41.0). (Table 3)

Table 2: Seroprevalence of SARS-CoV-2 specific IgG antibodies by participant characteristics

	Number tested	Number seropositive	Unweighted seroprevalence, % (95% CI)	Weighted seroprevalence, % (95% CI)	Weighted seroprevalence adjusted for test performance, % (95% CI)	Design-based F, p-value
Total	6230	2415	38.8 (37.6-40.0)	36.9 (34.5-39.4)	36.7 (34.3-39.2)	
Age, years						
18-29	1513	538	35.6 (33.2-38.0)	33.7 (30.1-37.6)	33.5 (29.8-37.4)	6.42, 0.0006
30-49	2672	1000	37.4 (35.6-39.3)	36.3 (33.5-39.3)	36.1 (33.3-39.1)	
50-69	1643	691	42.1 (39.7-44.5)	42.5 (38.8-46.2)	42.3 (38.6-46.0)	
≥70	402	186	46.3 (41.5-51.2)	45.3 (37.8-53.0)	45.1 (37.6-52.8)	
Gender						
Male	3126	1166	37.3 (35.6-39.0)	36.1 (33.5-38.9)	35.9 (33.3-38.7)	0.94, 0.34
Female	3104	1249	40.2 (38.5-42.0)	37.8 (34.5-41.3)	37.6 (34.3-41.1)	
Residence						
Urban	2866	1180	41.2 (39.4-43.0)	40.2 (36.3-44.1)	40.0 (36.1-43.9)	3.43, 0.07
Rural	3364	1235	36.7 (35.1-38.4)	35.5 (32.5-38.7)	35.3 (32.2-38.5)	

Self-reported history of chronic disease						
Yes	1145	495	43.2 (40.4-46.1)	41.9 (37.4-46.6)	41.7 (37.2-46.4)	6.14, 0.02
No	5085	1920	37.8 (36.4-39.1)	36.2 (33.7-38.9)	36.0 (33.5-38.7)	
History of COVID-19 like symptoms						
Yes	474	247	52.1 (47.6-56.6)	47.4 (37.9-57.1)	47.2 (37.7-56.9)	5.53, 0.02
No	5756	2168	37.7 (36.4-38.9)	36.3 (33.9-38.8)	36.1 (33.7-38.6)	
History of contact with a known COVID-19 case						
Yes	439	219	49.9 (45.2-54.5)	45.2 (38.3-52.2)	45.0 (38.1-52.0)	7.13, 0.01
No	5791	2196	37.9 (36.7-39.2)	36.5 (34.1-39.0)	36.3 (33.9-38.8)	
Ever tested for COVID-19 (RT-PCR)						
Yes	1092	485	44.4 (41.5-47.4)	41.0 (35.4-46.9)	40.8 (35.2-46.7)	2.17, 0.14
No	5138	1930	37.6 (36.2-38.9)	36.2 (33.5-39.0)	36.0 (33.3-38.8)	
RT-PCR result (n=1088*)						
Positive	176	140	79.5 (73.0-84.9)	81.8 (74.8-87.1)	81.7 (74.7-87.1)	74.93, <0.0001
Negative	912	345	37.8 (34.7-41.0)	38.8 (33.3-44.7)	38.6 (33.1-44.5)	

COVID-19: Coronavirus disease; RT-PCR: Reverse transcriptase-polymerase chain reaction

*RT-PCR result not known in four participants

Table 3: Sensitivity analyses for seroprevalence at extremes of test performance

	Weighted seroprevalence, % (95% CI)	Weighted seroprevalence adjusted for test performance, % (95% CI) [Sensitivity 100.00%, Specificity 99.63%]	Weighted seroprevalence adjusted for test performance, % (95% CI) [Sensitivity 95.89%, Specificity 99.90%]	Weighted seroprevalence adjusted for test performance, % (95% CI) [Sensitivity 100.00%, Specificity 99.05%]
Overall	36.9 (34.5-39.4)	36.7 (34.3-39.2)	38.4 (35.9-41.0)	36.3 (33.9-38.8)
Age, years				
18-29	33.7 (30.1-37.6)	33.5 (29.8-37.4)	35.1 (31.3-39.1)	33.1 (29.4-37.0)
30-49	36.3 (33.5-39.3)	36.1 (33.3-39.1)	37.8 (34.9-40.9)	35.7 (32.9-38.7)

50-69	42.5 (938.8-46.2)	42.3 (38.6-46.0)	44.3 (40.4-48.1)	41.9 (38.2-45.7)
≥70	45.3 (937.8-53.0)	45.1 (37.6-52.8)	47.2 (39.4-55.2)	44.8 (37.2-52.5)
Gender				
Male	36.1 (33.5-38.9)	35.9 (33.3-38.7)	37.6 (34.9-40.5)	35.5 (32.9-38.3)
Female	37.8 (34.5-41.3)	37.6 (34.3-41.1)	39.4 (35.9-43.0)	37.2 (33.9-40.7)
Residence				
Urban	40.2 (36.3-44.1)	40.0 (36.1-43.9)	41.9 (37.8-45.9)	39.6 (35.7-43.6)
Rural	35.5 (32.5-38.7)	35.3 (32.2-38.5)	37.0 (33.8-40.3)	34.9 (31.9-38.1)
Self-reported history of chronic disease				
Yes	43.2 (40.4-46.1)	41.9 (37.4-46.6)	43.6 (38.9-48.5)	41.3 (36.8-46.1)
No	37.8 (36.4-39.1)	36.2 (33.7-38.9)	37.7 (35.1-40.5)	35.6 (33.1-38.3)
History of COVID-19 like symptoms				
Yes	52.1 (47.6-56.6)	47.4 (37.9-57.1)	49.4 (39.5-59.5)	46.9 (37.3-56.7)
No	37.7 (36.4-38.9)	36.3 (33.9-38.8)	37.8 (35.3-40.4)	35.7 (33.3-38.2)
History of contact with a known COVID-19 case				
Yes	49.9 (45.2-54.5)	45.2 (38.3-52.2)	47.1 (39.9-54.4)	44.7 (37.7-51.7)
No	37.9 (36.7-39.2)	36.5 (34.1-39.0)	38.0 (35.5-40.6)	35.9 (33.5-38.4)
Ever tested for COVID-19 (RT-PCR)				
Yes	44.4 (41.5-47.4)	41.0 (35.4-46.9)	42.7 (36.9-48.9)	40.4 (34.8-46.4)
No	37.6 (36.2-38.9)	36.2 (33.5-39.0)	37.7 (34.9-40.6)	35.6 (32.9-38.4)
RT-PCR result (n=1088*)				
Positive	79.5 (73.0-84.9)	81.8 (74.8-87.1)	85.3 (78.0-90.8)	81.6 (74.6-87.0)
Negative	37.8 (34.7-41.0)	38.8 (33.3-44.7)	40.4 (34.7-46.6)	38.2 (32.7-44.2)

Seroprevalence was lowest among participants aged 18-29 years [33.5% (95% CI 29.8 – 37.4)] and was higher in older age groups. Seroprevalence was highest in those aged 70 years and above [45.1% (95% CI 37.6 – 52.8)]. Seroprevalence was not significantly different among males and females ($p=0.34$). The seroprevalence among urban residents was 40.0% (95% CI 36.1 – 43.9), slightly but not significantly, higher than rural residents [35.3% (95% CI 32.2 – 38.5), $p=0.07$]. (Table 2)

One in five participants (1145/6230, 18.4%) self-reported a history of at least one chronic disease (Table 1). Hypertension (815/6230, 13.1%) and diabetes mellitus (314/6230, 5.0%) were the most commonly reported chronic diseases (online supplemental file 2). Seroprevalence was significantly higher in participants who self-reported history of chronic disease (41.7%, 95% CI 37.2 – 46.4) as compared to those who did not report a history of chronic disease (36.0%, 95% CI 33.5 - 38.7) (Table 2).

Among participants who reported a history of COVID-19 like symptoms, seroprevalence was 47.2% (95% CI 37.7 – 56.9) compared with 36.1% (95% CI 33.7 – 38.6) among participants who did not report such

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3 symptoms. Seroprevalence was higher among those who reported contact with a known COVID-19 case
4 [45.0% (95% CI 38.1 – 52.0)] than participants who did not report any history of such contact [36.3%
5 (95% CI 33.9 – 38.8)]. (Table 2)
6

7 Seroprevalence was not significantly related to being tested for COVID-19 (RT-PCR). However, those who
8 reported a positive RT-PCR COVID-19 test had significantly higher seroprevalence (81.7%, 95% CI 74.7 –
9 87.1) as compared to those who reported a negative RT-PCR COVID-19 test (38.6%, 95% CI 33.1 – 44.5).
10 (Table 2)
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13 Among 2 415 seropositive individuals, only 247 (10.2%) reported a history of COVID-19 like symptoms.
14 Only 20.1% (485/2415) of the seropositive individuals were tested for COVID-19 (RT-PCR). Among 474
15 who reported a history of COVID-19 like symptoms, 233 (49.2%) were tested for COVID-19 (RT-PCR).
16 Among 4897 individuals who did not report a history of COVID-19 like symptoms and were never tested
17 for COVID-19 (RT-PCR), 1825 (37.3%) were seropositive. (Figure 3)
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20 Among 36 participants who reported a positive RT-PCR COVID-19 test but were seronegative, the
21 duration between COVID-19 RT-PCR test and serological testing ranged from 9 days to 101 days. In only
22 four of these 36 participants, the duration between the COVID-19 RT-PCR test and the serological test
23 was 14 days or less. Of the remaining 32 participants, 21 did not report a history of COVID-19 like
24 symptoms, nine did not report a history of contact with a known COVID-19 case, and eight reported
25 neither a history of COVID-19 like symptoms nor a history of contact with a known COVID-19 case.
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27 We estimated that there were 1 673 484 (95% CI 1 564 047 – 1 787 482) cumulative number of
28 infections among adults aged ≥ 18 years in the valley by 03 Oct 2020, two weeks before the start of the
29 survey. If we assume that the seroprevalence was similar to the overall seroprevalence in the population
30 not included in our study (< 18 years of age) then the estimated cumulative number of infections in the
31 valley by 03 Oct 2020 was 2 791 933 (95% CI 2 609 354 – 2 982 119). Considering that the cumulative
32 number of reported COVID-19 cases was 47 071 by 03 Oct 2020 (Figure 4), we estimate the number of
33 infections per reported case as 59.3 (95% CI 55.4 – 63.4). The number of reported COVID-19 deaths after
34 a three-week lag period (on 24 Oct 2020) was 955. Thus, we estimated the infection fatality rate as
35 0.034% (95% CI 0.032 – 0.037).
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39 Figure 5 depicts the relationship between the estimated number of SARS-CoV-2 infected persons,
40 reported COVID-19 cases, and reported COVID-19 deaths. Of the total estimated SARS-CoV-2 infected
41 persons, only 1.69% were reported. Of the total reported COVID-19 cases, 2.03% died.**DISCUSSION**
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43 The results of our study indicate that by the first week of October 2020, nearly seven months after the
44 appearance of the first laboratory-confirmed COVID-19 case on 18 March 2020, close to 37% of the
45 valley's population aged ≥ 18 years had been infected. Our results suggest that the cumulative number of
46 SARS-CoV-2 infections by the first week of October 2020 was nearly 2.8 million with an estimated
47 infection fatality rate of 0.034%. Seroprevalence did not differ by gender but was higher in older age
48 groups.
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51 The findings of our study are based on a representative sample of the population. The laboratory test
52 used for the detection of SARS-CoV-2 specific IgG antibodies in serum samples provides valid
53 results.[20,25] We report seroprevalence estimates adjusted for sampling design and test performance.
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3 The overall adjusted seroprevalence of around 37% indicates that a large proportion of the valley's
4 population has been infected with the virus. Easing of lockdown, being fed up with the restrictions, and
5 non-adherence to prevention norms are the possible reasons. Even though a large proportion of the
6 population has been infected, the transmission of infection is expected to continue till most of the
7 susceptible population becomes immune. Herd immunity in the context of COVID-19 is a matter of
8 debate as reports of a second infection continue to pour in.[26] The emergence of several Variants of
9 Concern and the introduction of COVID-19 vaccination will also influence population immunity. Several
10 factors potentially influence the seroprevalence rates. These include population density, social and
11 demographic structure of the population, governmental policies and the extent of their implementation,
12 immunity level of the population, time since the start of infection transmission, adherence to infection
13 prevention guidelines, quality of contact tracing and quarantine, and possibly the geography and
14 environment of an area.
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18 Comparison with previous reports suggests that the seroprevalence has increased almost ten-fold since
19 July 2020.[16,27] The second of the three nationwide seroprevalence surveys in India conducted in
20 August-September 2020 reports an overall seroprevalence of 6.6% ranging from 5.2% in rural areas to
21 16.9% in urban slums.[28] A nationwide survey conducted in December 2020-January 2021 reported an
22 overall seroprevalence of 24.1% ranging from 4.9% - 44.4% across districts.[29] Kashmir is thus not a
23 low-infection area. Being an oft-visited tourist area, Kashmir is at an increased risk of infection
24 transmission. Adherence to COVID appropriate behavior (use of face masks in public, frequent
25 handwashing, physical and social distancing) has been poor. With the introduction of the COVID-19
26 vaccination program in January 2021 and the emergence of a 'second wave' in Kashmir in April 2021, the
27 seroprevalence estimates are expected to increase in the future.
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31 The seroprevalence of SARS-CoV-2 IgG antibodies was higher in older age groups. During the early
32 period of the pandemic, people were adherent to social distancing and other non-pharmaceutical
33 interventions because of a fear of the disease and administrative restrictions. With time, administrative
34 restrictions were relaxed, fear of the disease attenuated, and people became sort of fed up with the
35 social restrictions. This not only led to an increase in the number of reported COVID-19 cases but also
36 provided the population, including older age groups, an opportunity to contract the infection. That older
37 people have an increased risk of symptomatic and more severe disease is now well known.[30,31]
38 However, age-based differential susceptibility to SARS-CoV-2 infection antibody response and the
39 reasons thereof are still a grey area and need further understanding. Existing literature might suggest
40 that the young who are more mobile and socially active have a higher risk of infection.[6,7] However,
41 this should not imply that the elderly have a decreased susceptibility to SARS-CoV-2 infection or a
42 decreased antibody response.[32] On the contrary, several studies suggest that the seroprevalence of
43 SARS-CoV-2 specific IgG antibodies is higher in the older age groups and particularly so in more dense
44 population groups.[4,5,8-11,13] Furthermore, SARS-CoV-2 antibody levels have been reported to be
45 higher in older people.[12]
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50 The seroprevalence of SARS-CoV-2 specific IgG antibodies did not differ significantly by gender, though
51 the figure was slightly higher for females. These findings are consistent with the available
52 literature.[6,13] Difference in seroprevalence by gender has been suggested by some studies and
53 females have been reported to have lower antibody levels.[5,7,9,11,12,14,33]
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3 Urban areas are more densely populated as compared to rural areas which accelerate the transmission
4 of infections in the population. The seroprevalence of SARS-CoV-2 specific IgG antibodies is thus
5 expected to be higher in urban areas especially during the early phases of an epidemic. As the epidemic
6 progresses the seroprevalence gap between urban and rural areas will wane off. We estimated an
7 adjusted seroprevalence of 40.0% (95% CI 36.1 – 43.9) in urban areas as compared to 35.3% (95% CI
8 32.2 – 38.5) in rural areas (p=0.07).

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11 People with a chronic disease experience more severe COVID-19 symptoms and are more likely to die
12 when compared to people with no chronic disease.[34] We found a higher proportion of symptomatic
13 infection among participants with a self-reported history of chronic disease (78/1145, 6.8%) as
14 compared to participants with no chronic disease (169/5085, 3.3%) (online supplemental file 3). Little is,
15 however, known about the risk of infection in chronic disease patients. We found a significantly higher
16 seroprevalence among participants with a self-reported history of chronic disease (Table 2). This finding
17 needs further research for corroboration and possible explanations.

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20 People with a self-reported history of COVID-19 related symptoms, contact with a known COVID-19
21 case, or a positive COVID-19 RT-PCR had a higher seroprevalence as compared to their complement.
22 Among seropositive individuals, only 10.2% reported being symptomatic. The percentage of
23 asymptomatic infections, thus, was 90%. However, only 49% of individuals with a history of COVID-19
24 like symptoms were tested using RT-PCR. We also estimated that only one out of almost 59 infections
25 gets reported. This reflects the necessity of improving the efficiency of RT-PCR testing so that more
26 symptomatic individuals receive the test. Not all individuals with a known RT-PCR positive result showed
27 the presence of IgG antibodies. Around 20% of RT-PCR positive individuals were seronegative and in a
28 large majority of them (32 out of 36) the duration since RT-PCR positivity was more than two weeks. This
29 may be attributed to a poor B cell response or a false negative antibody test.[35] Around 38% of RT-PCR
30 negative individuals were seropositive suggesting a false-negative RT-PCR or infection acquisition at a
31 date later than the RT-PCR test.

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35 We estimated an infection fatality rate of 0.034% (95% CI 0.032 – 0.037). The infection fatality rate in
36 SARS-CoV-2 infection has been reported to range from as low as 0.00% to 1.63%.[36] Our estimates of
37 the infection fatality rate are low as compared to estimates from several Indian studies.[5,28,37] Under-
38 reporting of COVID-19 deaths because of non-uniform definition for a 'COVID-19 death' may falsely
39 lower the infection fatality rates.[38] Many other factors can influence the infection fatality rate in SARS-
40 CoV-2 infection – the quality of available health facilities, the age structure of the population, and
41 COVID-19 epidemic intensity.[39,40] Developing countries usually have a younger population as
42 compared to the developed countries and Kashmir is not an exception. However, because of the
43 possibility of under-reporting of COVID-19 deaths, the true infection fatality rate in Kashmir may be
44 higher than our estimates. The infection fatality rate is, however, known to be lower in developing
45 nations.[30,41] In developed nations like the United States and many European countries, a higher
46 infection fatality rate has been reported.[30,42]

50 51 **Limitations**

52 One important limitation of our study is that even though we adjusted the weighted seroprevalence
53 estimates for test performance using manufacturer-provided sensitivity and specificity (100% and
54 99.63% respectively), we did not quantify the test validity in-house. Another limitation of our study
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3 estimates is that we excluded people <18 years of age. The results of our study may not thus be
4 generalizable to this group of the population.
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6 Our estimated seroprevalence was much higher than we anticipated at the designing stage. This has
7 impacted the precision of our estimates to some extent. However, we believe we still have been able to
8 estimate the seroprevalence with reasonable precision.
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10 Lack of reliable death counts is another potential limitation. This may have led to an underestimation of
11 the infection fatality rate. We did not perform any adjustment for death counts. Further, because of lack
12 of age- and gender-specific mortality data we could not estimate age- and gender-specific infection
13 fatality rates.
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16 **CONCLUSIONS**

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18 We conclude that nearly 37% of individuals aged 18 years and above were infected with SARS-CoV-2 in
19 Kashmir by October 2020. The infection fatality rate in the valley is around 0.034%. A majority of cases
20 go unreported. For every reported case there are 59 unreported infections in the population. Since
21 almost half of the symptomatic individuals go unreported, testing of symptomatic individuals and
22 effective contact tracing needs to continue. Given the emergence of mutant Variants of Concern,
23 increasing the population immunity through augmented and sustained vaccination is needed. We
24 further recommend that adherence to COVID-19 prevention measures should be ensured at least till a
25 large proportion of the population gets vaccinated.
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27

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50 **COMPETING INTERESTS**

51
52 We declare no competing interests, financial or otherwise.
53

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5

6 **CONTRIBUTORS**

7
8 S Muhammad Salim Khan: Conceptualization, Funding acquisition, Methodology, Writing-review &
9 editing.
10

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12 Project administration, Writing-original draft, Writing-review & editing.
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22 Writing-review & editing.
23

24 S Muhammad Salim Khan, Mariya Amin Qurieshi, Inaamul Haq, and Sabhiya Majid have verified the
25 underlying data.
26
27

28 **DATA SHARING**

29
30 Anonymized data collected for the study, including individual participant data and a data dictionary
31 defining each field in the set, will be made available to interested researchers on request by Inaamul
32 Haq (haqinaam@yahoo.co.in) for two years from publication. The study protocol, statistical analysis
33 plan, and informed consent forms are also available from Inaamul Haq.
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46 **Figure 1 legend:**

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48 Figure 1: Location of the ten districts and seroprevalence (%) by district. Figures in parentheses indicate
49 a 95% Confidence Interval for seroprevalence.
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51 **Figure 2 legend:**

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53 Figure 2: Participant flow.
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55 **Figure 3 legend:**

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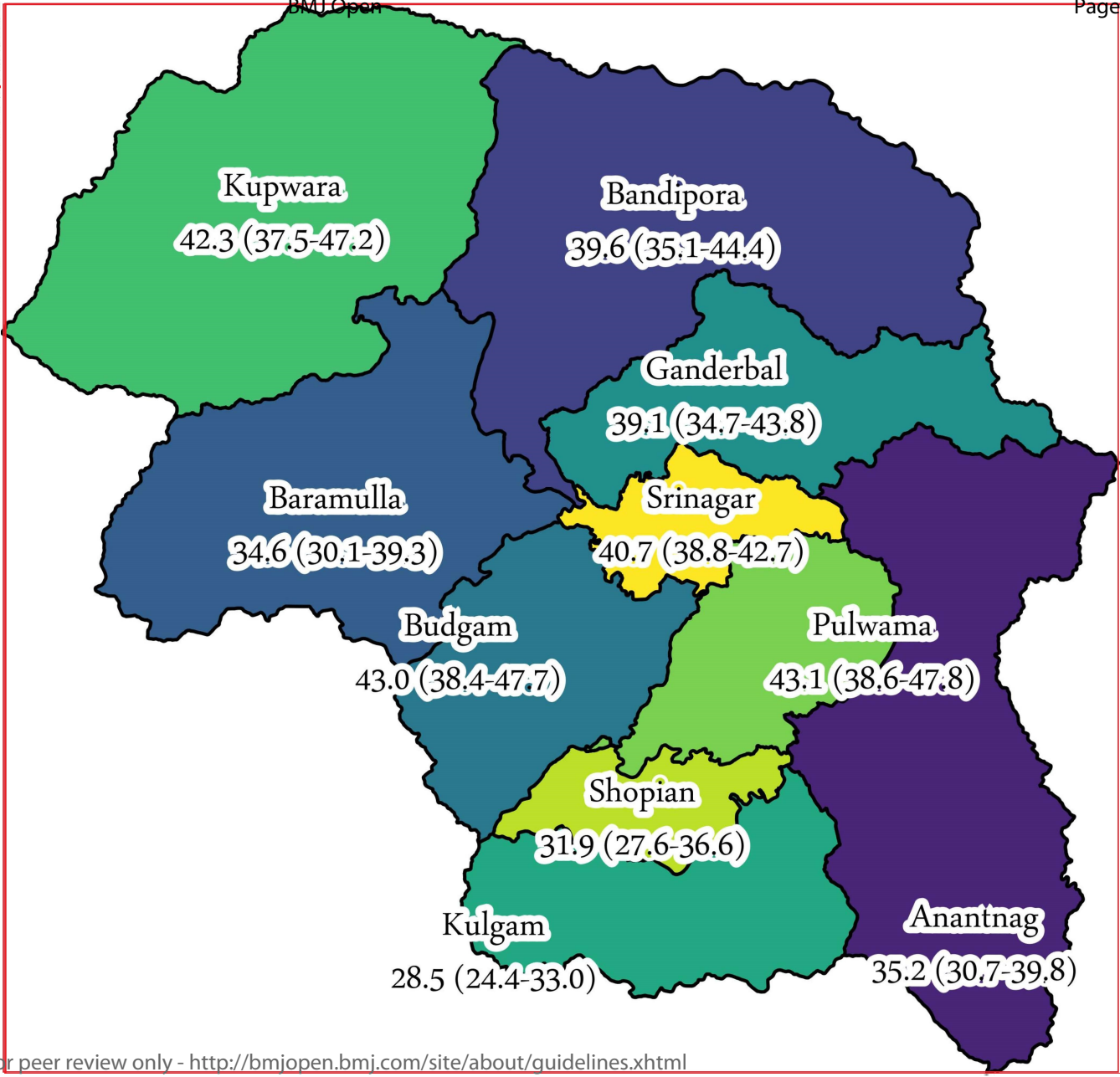
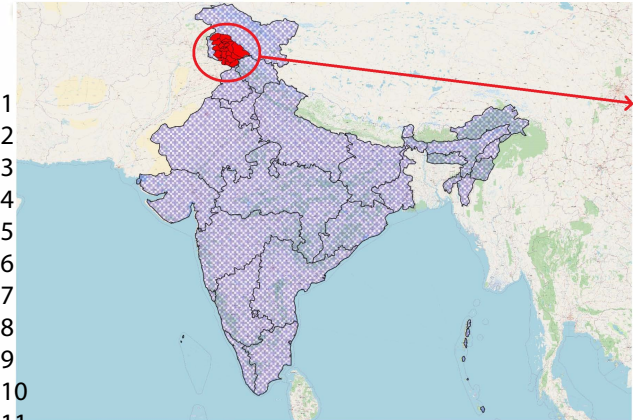
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3 Figure 3: A. Seropositivity by the history of COVID-19 like symptoms, RT-PCR testing, and test result. B.
4 History of COVID-19 like symptoms by seropositivity, RT-PCR testing, and test result.
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6 **Figure 4 legend:**
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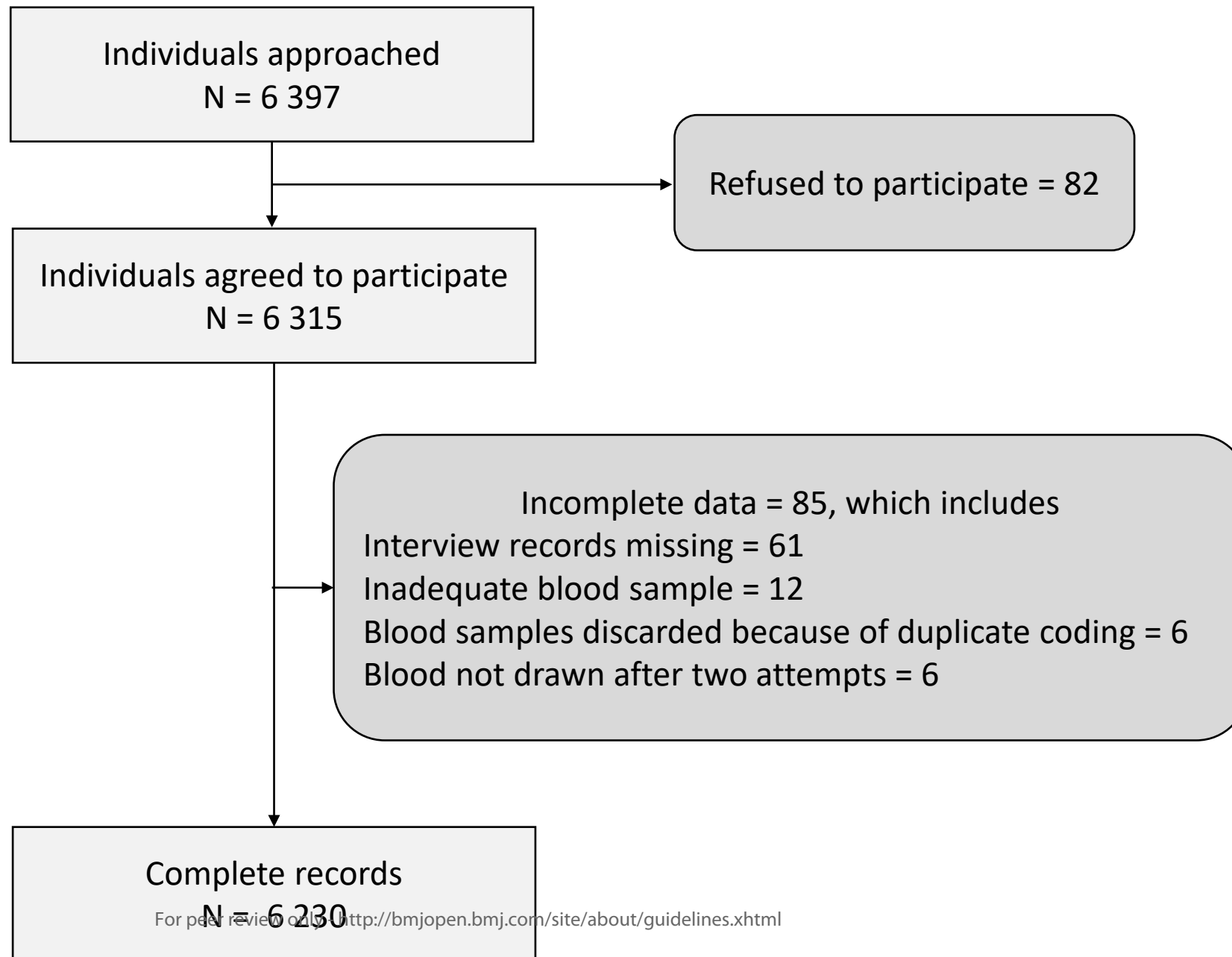
8 Figure 4: A. Daily cases and deaths in Kashmir since the start of the COVID-19 pandemic; B. Cumulative
9 number of cases and deaths in Kashmir.
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11 **Figure 5 legend:**
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13 Figure 5: Cumulative estimated SARS-CoV-2 infections, reported cases, and deaths in Kashmir, October-
14 November 2020. The bars represent the number of persons at each step. The percentages above the
15 bars represent the percentage out of the total population. The percentages within the triangles
16 represent percentages out of the previous step who proceed to the next step.
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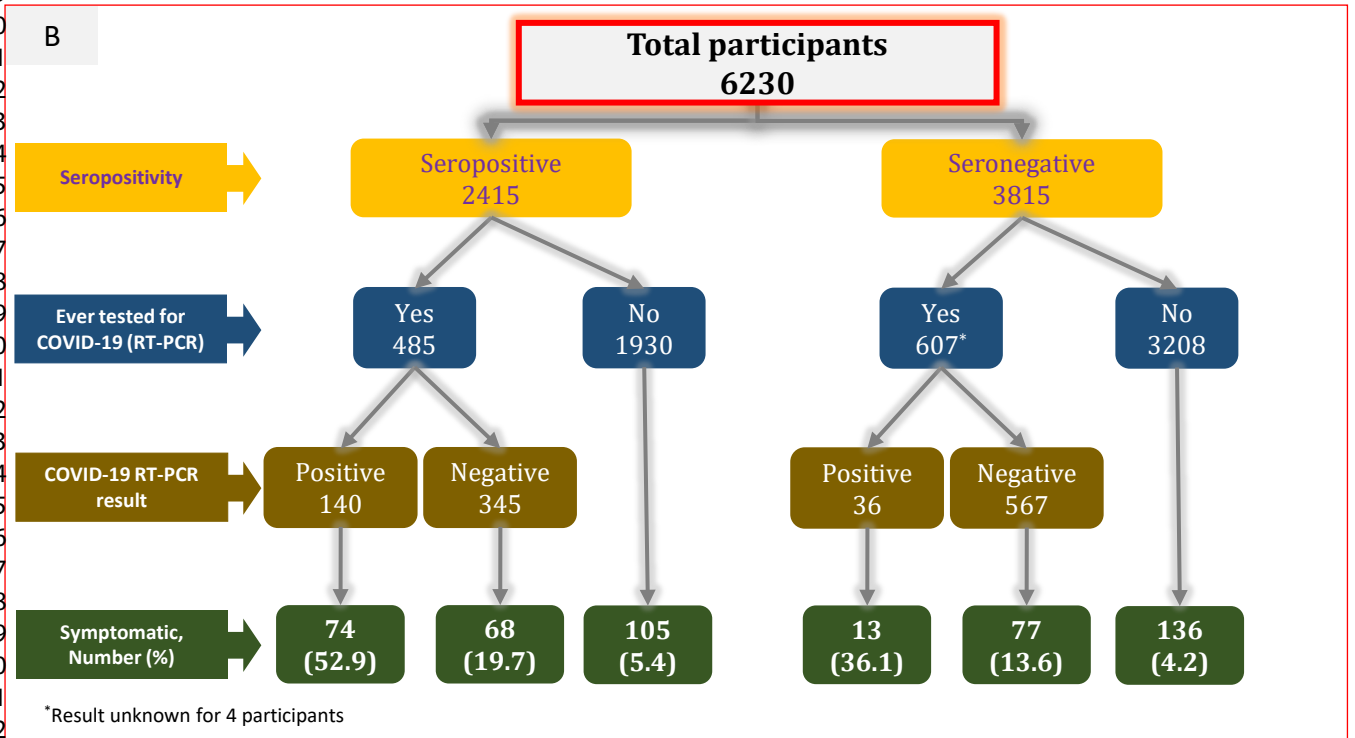
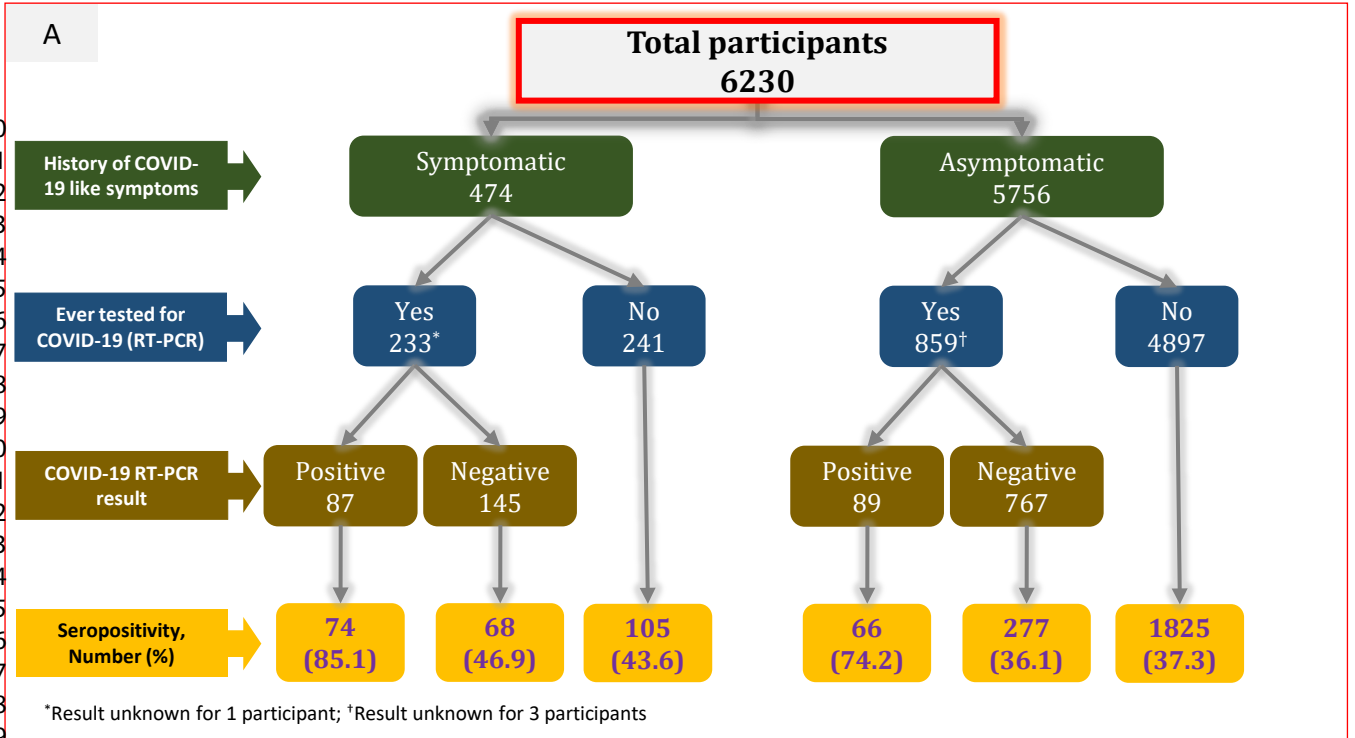


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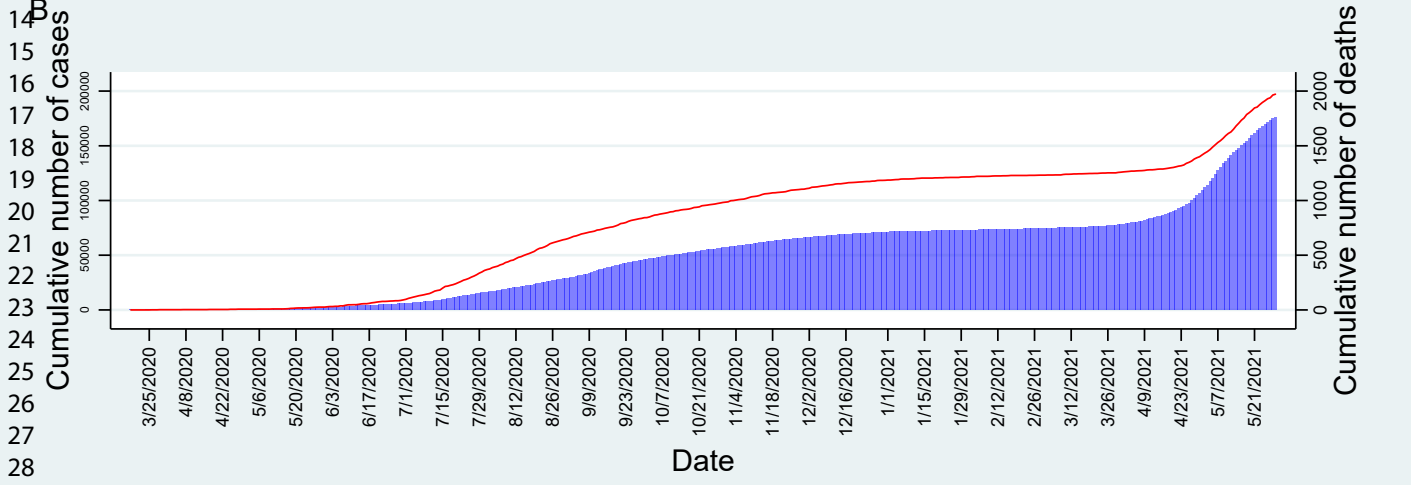
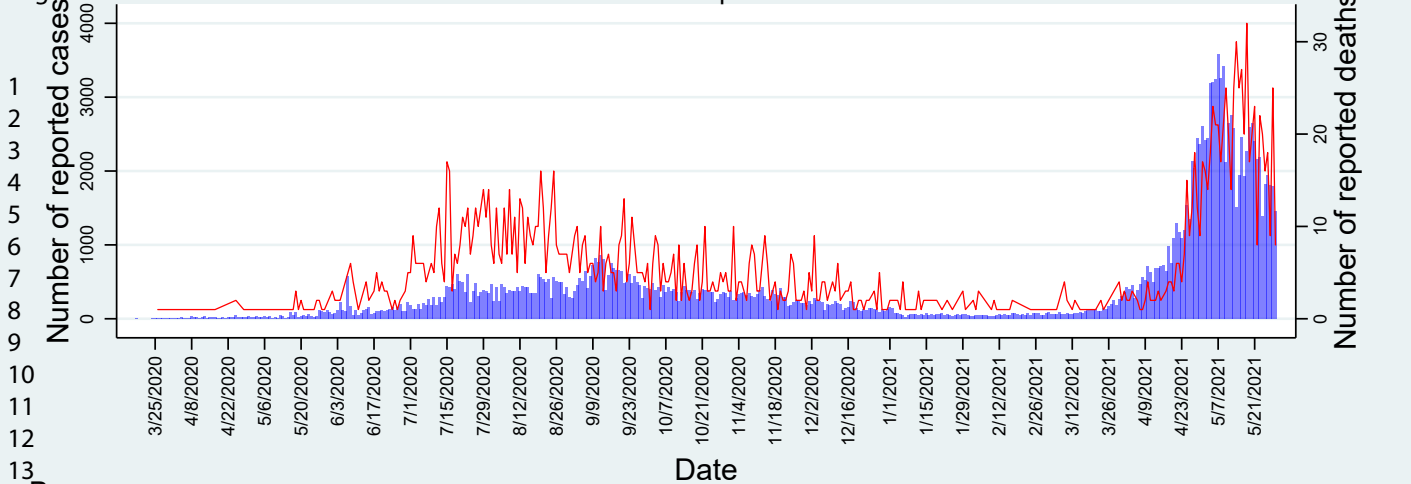


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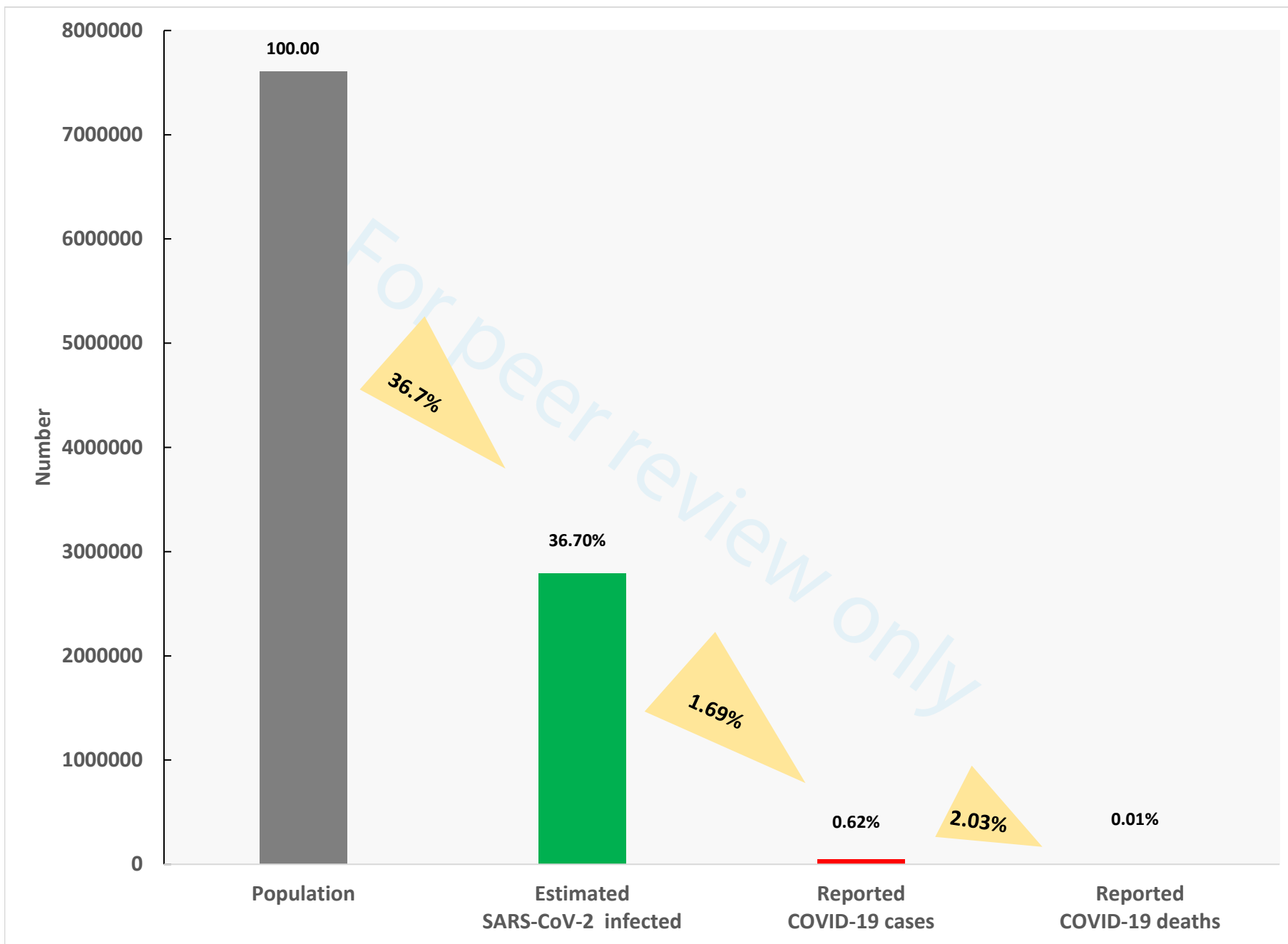
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Supplemental Table 1: Participant characteristics by district

District	Total	Age (years)				Gender		Residence	
		<30	30-49	50-69	70+	Female	Male	Rural	Urban
Anantnag	421	84	197	113	27	214	207	295	126
Budgam	442	113	190	105	34	263	179	354	88
Bandipora	424	106	174	114	30	227	197	341	83
Baramulla	405	113	176	98	18	214	191	325	80
Ganderbal	442	92	210	123	17	233	209	346	96
Kulgam	428	102	194	113	19	257	171	346	82
Kupwara	400	81	171	105	43	215	185	360	40
Pulwama	443	102	176	126	39	218	225	396	47
Shopiyan	407	119	152	90	46	211	196	368	39
Srinagar	2418	601	1032	656	129	1052	1366	233	2185
Total	6230	1513	2672	1643	402	3104	3126	3364	2866

Supplemental Table 2: Seroprevalence (unadjusted) by district and participant characteristics

District	Overall	Age (years)				Gender		Residence	
		<30	30-49	50-69	70+	Male	Female	Urban	Rural
Anantnag	35.2 (30.7-39.8)	29.8 (21-40.4)	34.5 (28.2-41.4)	38.9 (30.4-48.2)	40.7 (24.2-59.7)	36.2 (30-43)	34.1 (28.1-40.7)	42.9 (34.5-51.6)	31.9 (26.8-37.4)
Budgam	43 (38.4-47.7)	44.2 (35.4-53.5)	37.9 (31.3-45)	48.6 (39.2-58.1)	50 (33.8-66.2)	41.9 (34.9-49.3)	43.7 (37.8-49.8)	38.6 (29.1-49.2)	44.1 (39-49.3)
Bandipora	39.6 (35.1-44.4)	37.7 (29-47.3)	42 (34.8-49.4)	40.4 (31.8-49.6)	30 (16.4-48.3)	37.6 (31.1-44.5)	41.4 (35.2-47.9)	55.4 (44.6-65.7)	35.8 (30.9-41)
Baramulla	34.6 (30.1-39.3)	27.4 (20-36.4)	32.4 (25.9-39.6)	44.9 (35.4-54.8)	44.4 (24-67)	39.3 (32.6-46.4)	30.4 (24.6-36.9)	36.3 (26.5-47.3)	34.2 (29.2-39.5)
Ganderbal	39.1 (34.7-43.8)	34.8 (25.8-45)	40.5 (34-47.3)	39.8 (31.6-48.7)	41.2 (21-64.8)	39.2 (32.8-46)	39.1 (33-45.5)	42.7 (33.2-52.8)	38.2 (33.2-43.4)
Kulgam	28.5 (24.4-33)	27.5 (19.7-36.9)	26.8 (21-33.5)	31 (23.1-40.1)	36.8 (18.7-59.7)	25.1 (19.2-32.2)	30.7 (25.4-36.6)	37.8 (28-48.7)	26.3 (21.9-31.2)
Kupwara	42.3 (37.5-47.2)	33.3 (24-44.2)	39.8 (32.7-47.3)	50.5 (41-59.9)	48.8 (34.4-63.4)	41.6 (34.7-48.9)	42.8 (36.3-49.5)	50 (35-65)	41.4 (36.4-46.6)
Pulwama	43.1 (38.6-47.8)	35.3 (26.7-45)	42.6 (35.5-50)	45.2 (36.8-54)	59 (43.2-73.1)	39.6 (33.4-46.1)	46.8 (40.3-53.4)	40.4 (27.5-54.9)	43.4 (38.6-48.4)
Shopiyan	31.9 (27.6-36.6)	28.6 (21.2-37.3)	29.6 (22.9-37.3)	41.1 (31.4-51.5)	30.4 (18.9-45.1)	31.1 (25-37.9)	32.7 (26.7-39.3)	38.5 (24.7-54.4)	31.3 (26.7-36.2)
Srinagar	40.7 (38.8-42.7)	39.1 (35.3-43.1)	39.2 (36.3-42.3)	41.9 (38.2-45.7)	53.5 (44.9-61.9)	37.7 (35.2-40.3)	44.6 (41.6-47.6)	40.8 (38.7-42.9)	39.9 (33.8-46.3)

Chronic disease and SARS-CoV-2 infection in the study population

Of the 6230 participants, 1145 reported a history of at least one chronic disease. Two hundred ninety-eight reported a history of more than one chronic disease.

Supplementary Table 3: Chronic disease in the study population

Chronic disease (n = 1145)	Number (%)
Hypertension	815 (13.1%)
Diabetes	314 (5.0%)
Chronic Obstructive Pulmonary Disease	39 (0.6%)
Coronary Heart Disease	35 (0.6%)
Cerebrovascular Disease	16 (0.3%)
Asthma	15 (0.2%)
Chronic Kidney Disease	10 (0.2%)
Chronic Liver Disease	5 (0.1%)
Cancer	4 (0.1%)

Supplementary Table 4: History of COVID-19 like symptoms and seropositivity vis-à-vis history of chronic disease

		History of COVID-19 like symptoms	
		Yes	No
Reported history of chronic disease (n=1145)	Seropositive	78	417
	Seronegative	63	587
Did not report any history of chronic disease (n=5085)	Seropositive	169	1751
	Seronegative	164	3001

Of the 1154 participants who reported a history of chronic disease 78 (6.8%) reported a history of COVID-19 like symptoms within three months of the interview date and were seropositive for SARS-CoV-2 specific IgG (symptomatic infection). The proportion of symptomatic infection among participants who did not report any history of chronic disease was 3.3% (169/5085).

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1, 3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3 and Figure 1
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	3, 4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4, 5
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	4, 5
		(b) Describe any methods used to examine subgroups and interactions	5
		(c) Explain how missing data were addressed	5
		(d) If applicable, describe analytical methods taking account of sampling strategy	4, 5
		(e) Describe any sensitivity analyses	6, Table 3
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 2, and page 5
		(b) Give reasons for non-participation at each stage	Figure 2
		(c) Consider use of a flow diagram	Figure 2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1, Figure 2
Outcome data	15*	Report numbers of outcome events or summary measures	Table 2

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2	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted
3			estimates and their precision (eg, 95% confidence interval). Make
4			clear which confounders were adjusted for and why they were
5			included
6			
7			(b) Report category boundaries when continuous variables were
8			categorized
9			
10			(c) If relevant, consider translating estimates of relative risk into
11			absolute risk for a meaningful time period
12	Other analyses	17	Report other analyses done—eg analyses of subgroups and
13			interactions, and sensitivity analyses
14			
15	Discussion		
16	Key results	18	Summarise key results with reference to study objectives
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18	Limitations	19	Discuss limitations of the study, taking into account sources of
19			potential bias or imprecision. Discuss both direction and magnitude
20			of any potential bias
21	Interpretation	20	Give a cautious overall interpretation of results considering
22			objectives, limitations, multiplicity of analyses, results from similar
23			studies, and other relevant evidence
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25	Generalisability	21	Discuss the generalisability (external validity) of the study results
26			
27	Other information		
28	Funding	22	Give the source of funding and the role of the funders for the present
29			study and, if applicable, for the original study on which the present
30			article is based
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*Give information separately for exposed and unexposed groups.

BMJ Open

Seroprevalence of SARS-CoV-2 specific IgG antibodies in Kashmir, India, seven months after the first reported local COVID-19 case: results of a population-based seroprevalence survey from October-November, 2020

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Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Epidemiology
Keywords:	COVID-19, EPIDEMIOLOGY, Epidemiology < INFECTIOUS DISEASES

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3 **Seroprevalence of SARS-CoV-2 specific IgG antibodies in Kashmir, India, seven months after the first**
4 **reported local COVID-19 case: results of a population-based seroprevalence survey from October-**
5 **November, 2020**
6

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ABSTRACT

Objectives: We designed a population-based survey in Kashmir to estimate the seroprevalence of SARS-CoV-2 specific IgG antibodies in the general population aged 18 years and above.

Setting: The survey was conducted among 110 villages and urban wards across ten districts in Kashmir from 17 Oct 2020 to 04 Nov 2020.

Participants: Individuals aged 18 years and above were eligible to be included in the survey. Serum samples were tested for the presence of SARS-CoV-2 specific IgG antibodies using the Abbott SARS-CoV-2 IgG assay.

Primary and secondary outcome measures: We labeled assay results equal to or above the cut-off index value of 1.4 as positive for SARS-CoV-2 specific IgG antibodies. Seroprevalence estimates were adjusted for the sampling design and assay characteristics.

Results: Out of 6397 eligible individuals enumerated, 6315 (98.7%) agreed to participate. The final analysis was done on 6230 participants. Seroprevalence adjusted for the sampling design and assay characteristics was 36.7% (95% CI 34.3%-39.2%). Seroprevalence was higher among the older population. Among seropositive individuals, 10.2% (247/2415) reported a history of COVID-19 like symptoms. Out of 474 symptomatic individuals, 233 (49.2%) reported having been tested. We estimated an infection fatality rate of 0.034%.

Conclusions: During the first seven months of the COVID-19 epidemic in Kashmir valley, approximately 37% of individuals were infected. The reported number of COVID-19 cases was only a small fraction of the estimated number of infections. A more efficient surveillance system with strengthened reporting of COVID-19 cases and deaths is warranted.

ARTICLE SUMMARY

Strengths and limitations of this study

- The findings of our study are based on a representative sample of the population.
- The laboratory test used for the detection of SARS-CoV-2 specific IgG antibodies in serum samples provides valid results.
- We report seroprevalence estimates adjusted for sampling design and test performance.
- Even though we adjusted the weighted seroprevalence estimates for test performance using manufacturer-provided sensitivity and specificity (100% and 99.63%, respectively), we did not quantify the test validity in-house.
- Because of lack of age- and gender-specific mortality data, we could not estimate age- and gender-specific infection fatality rates.

INTRODUCTION

On 11 Feb 2020, the World Health Organization announced that the disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) would be named coronavirus disease (COVID-19).[1] In Kashmir, the first case of COVID-19 was confirmed in Srinagar city on 18 Mar 2020.[2] The government imposed the first phase of the lockdown in Kashmir on 24 March 2020. During this phase, inter-state travel remained suspended. People were barred from moving outside except in an

1
2
3 emergency. Except for essential services, all government and private offices were advised to work from
4 home. Universal masking was made mandatory. The lockdown was extended till 31 May 2020 and later
5 relaxed in a phased manner.
6

7 Mild or asymptomatic infections are common in Coronavirus disease 2019 (COVID-19) and are an
8 important source of infection transmission.[3,4] Such cases are less likely to be detected by a
9 surveillance system based on reverse-transcriptase polymerase chain reaction (RT-PCR) testing.
10 Therefore, the number of reported RT-PCR positive cases are an underestimate of the true number of
11 infections in a population.
12
13

14 Seroprevalence surveys have been conducted in various countries at different stages of the current
15 epidemic among various population groups.[5–14] Seroprevalence surveys provide a more accurate
16 estimate of past infection, improve understanding of the infection transmission dynamics, and guide
17 public health response.[15]
18

19 We designed this survey with the primary objective to estimate the seroprevalence of severe acute
20 respiratory syndrome coronavirus 2 (SARS-CoV-2) specific IgG antibodies in the adult population of
21 Kashmir valley.
22
23

24 **METHODS**

25
26 We designed a population-based cross-sectional study. The study covered all the ten districts of
27 Kashmir, a valley in northern India. (Figure 1) We completed data collection in three weeks, from 17 Oct
28 2020 to 04 Nov 2020.
29

30 **Ethics**

31
32 We obtained written informed consent from all study participants. The study was approved by the
33 Institutional Ethics Committee of Government Medical College Srinagar (reference number:
34 1004/ETH/GMC). We used anonymized participant data for analysis.
35

36 **Sample size**

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38 Based on the results of a previous study conducted in July 2020, we speculated that, by October 2020,
39 the prevalence would have increased to around 20%.[16] We calculated the minimum sample size based
40 on an anticipated seroprevalence of 20%, an absolute precision of 2%, and a design effect of 2. We used
41 OpenEpi to make sample size calculations.[17] We adjusted the sample size for a possible non-response
42 of 10% to obtain a minimum size of 3376. We decided to select 3600 individuals from nine of the ten
43 districts (except district Srinagar). To obtain precise estimates for district Srinagar, sample size
44 estimation was made for the district separately. We used a design effect of 1.5, an anticipated
45 seroprevalence of 20%, and absolute precision of 2% to obtain a sample size of 2302 for the district,
46 further increasing to 2400 to account for non-response. We thus targeted a total sample size of 6000
47 (3600 + 2400).
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51 **Participants**

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53 All adults ≥ 18 years of age were eligible to participate in the study. We selected eligible participants
54 using a three-stage stratified cluster sampling technique. We listed all clusters in the valley using the
55 Census 2011 data.[18] Within each of the ten districts in the valley, clusters were stratified into urban
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3 and rural clusters. We selected clusters within each of the 20 strata by probability proportionate to size
4 (PPS) sampling. Except for district Srinagar which we oversampled to obtain precise seroprevalence
5 estimates for, ten clusters were randomly selected from each district. We selected 20 clusters from
6 district Srinagar. We divided each selected cluster into four equal areas and chose a central location
7 within each of the four areas as the starting point. Thereafter, we approached consecutive households
8 to enroll at least ten eligible participants. We thus identified a total of 440 random locations within 110
9 clusters in ten districts. We invited all eligible adults in a household for participation.
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11

12 **Variables**

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14 The primary outcome variable of interest was SARS-CoV-2 specific IgG antibodies. In addition, we
15 obtained information from participants about their age, gender, history of COVID-19 like symptoms in
16 the three months before the interview date, history of contact with a known COVID-19 patient, and
17 history of COVID-19 testing.
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20 **Procedure**

21 We informed eligible adults about the purpose and the procedure of the study. Study participation was
22 voluntary. Participants were interviewed by health personnel specifically trained for the interview.
23 Interview responses were recorded in an Epicollect5 form.[19] Once the interview was completed, a
24 trained phlebotomist collected 3-5 mL of venous blood from the antecubital vein under aseptic
25 precautions into a red-top collection tube containing a clot activator. The tube was left standing,
26 undisturbed, for at least 30 minutes for clot formation. The sample was later transported to a central
27 facility for centrifugation. Centrifuged samples were transported to a central laboratory for further
28 processing and analysis. Serum samples were tested for the presence of SARS-CoV-2 specific IgG
29 antibodies using the Abbott SARS-CoV-2 IgG assay. The assay uses chemiluminescence to detect IgG
30 antibodies against the SARS-CoV-2 nucleocapsid protein. The reported sensitivity and specificity of the
31 assay are 100% (95% CI 95.89-100.00) and 99.63% (99.05-99.90), respectively.[20] As recommended by
32 the manufacturer, we labeled assay results equal to or above the cut-off index value of 1.4 as positive
33 for SARS-CoV-2 specific IgG antibodies.
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38 **Statistical methods**

39 We report unweighted seroprevalence estimates in percentages. We used the Agresti-Coull procedure
40 to calculate a 95% confidence interval (CI) for seroprevalence estimates.[21] A weighted estimate of
41 seroprevalence is provided. To calculate survey weights (inverse of sampling probability), we used the
42 estimated population of the districts. We used the census 2011 data and growth rates from Sample
43 Registration System to estimate the population of the districts in 2020.[18,22] Survey weights obtained
44 were further adjusted for non-response and age and sex structure (post-stratification weights). We
45 further adjusted the weighted seroprevalence estimates for test performance to calculate “weighted
46 seroprevalence adjusted for test performance”. We did this using the formula:
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48

49 *Weighted seroprevalence adjusted for test performance* =
50 $(\text{Weighted seroprevalence} + \text{Test specificity} - 1) / (\text{Test sensitivity} + \text{Test specificity} - 1)$. [23]
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52 We used the manufacturer-provided sensitivity and specificity in the above formula.[20] We used the
53 extremes of the manufacturer-provided 95% CI of the test sensitivity and specificity (upper limit of
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sensitivity, lower limit of specificity; and lower limit of sensitivity, upper limit of specificity) to report sensitivity analyses.

We analyzed the difference in seroprevalence estimates across levels of a categorical variable using a Chi-square test adjusted for the sampling design.

We estimated the number of SARS-CoV-2 infections by multiplying the weighted seroprevalence adjusted for test performance with the estimated population of the valley. To estimate the number of infections per reported case, we divided the estimated number of SARS-CoV-2 infections by the reported number of COVID-19 cases two weeks before the survey date. We calculated the infection fatality rate by dividing the reported number of deaths by the number of estimated infections, assuming a three-week lag time from infection to death.[24]

We analyzed the data using Stata version 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP.).

Patient and Public Involvement

No patients or members of the public were involved in this study.

RESULTS

We enumerated 6 397 individuals ≥ 18 years from 3 077 households and 110 clusters (34 urban clusters and 76 rural clusters) between 17 Oct 2020 and 04 Nov 2020. Of the 6 397 eligible individuals, 6 315 (98.7%) agreed to participate and were enrolled. The final analysis was done on a sample of 6 230 participants. (Figure 2)

Of the 6 230 participants, 1 513 (24.3%) were between 18 and 30 years of age, 2 672 (42.9%) were aged 30-49 years, 1 643 (26.4%) were aged 50-69 years, and 402 (6.4%) were 70 years and older. (Table 1). There was equal representation from males and females, and 3 364 (54.0%) resided in a rural area. Of the 3 104 females, 56 (1.8%) reported being pregnant at the time of the survey. Four hundred seventy-four (7.6%) reported COVID-19 like symptoms in the three months preceding the survey, and 439 (7.0%) reported to have ever come in contact with a known COVID-19 case. One thousand ninety-two (17.5%) reported having been tested for COVID-19 using RT-PCR or a Rapid Antigen Test (RAT) previously, of whom 176 (16.2%) reported to have tested positive for the disease.

Table 1: Characteristics of study participants

	Frequency	Percent
Total	6230	
Age, years		
18-29	1513	24.3
30-49	2672	42.9
50-69	1643	26.4
≥ 70	402	6.5
Gender		
Male	3126	50.2
Female	3104	49.8

Residence		
Urban	2866	46.0
Rural	3364	54.0
Pregnant (n=3104)	56	1.8
Self-reported history of chronic disease	1145	18.4
History of COVID-19 like symptoms	474	7.6
History of contact with a known COVID-19 case	439	7.0
Ever tested for COVID-19 (RT-PCR)	1092	17.5
RT-PCR result (n=1088*)		
Positive	176	16.2
Negative	912	83.8

COVID-19: Coronavirus disease; RT-PCR: Reverse transcriptase-polymerase chain reaction

*RT-PCR result not known in four participants

We found an overall unweighted seroprevalence of 38.8% (95% CI 37.6 – 40.0). The seroprevalence ranged from 28.5% in district Kulgama to 43.1% in district Pulwama. (Figure 1 and online supplemental file 1) The overall weighted seroprevalence (adjusted for sampling design) was 36.9% (95% CI 34.5 – 39.4). The weighted seroprevalence adjusted for test performance was 36.7% (95% CI 34.3 – 39.2). (Table 2) Upon sensitivity analyses, the weighted seroprevalence adjusted for test performance ranged from 36.3% (95% CI 33.9 – 38.8) to 38.4% (95% CI 35.9 – 41.0). (Table 3)

Table 2: Seroprevalence of SARS-CoV-2 specific IgG antibodies by participant characteristics

	Number tested	Number seropositive	Unweighted seroprevalence, % (95% CI)	Weighted seroprevalence, % (95% CI)	Weighted seroprevalence adjusted for test performance, % (95% CI)	Design-based F, p-value
Total	6230	2415	38.8 (37.6-40.0)	36.9 (34.5-39.4)	36.7 (34.3-39.2)	
Age, years						
18-29	1513	538	35.6 (33.2-38.0)	33.7 (30.1-37.6)	33.5 (29.8-37.4)	6.42, 0.0006
30-49	2672	1000	37.4 (35.6-39.3)	36.3 (33.5-39.3)	36.1 (33.3-39.1)	
50-69	1643	691	42.1 (39.7-44.5)	42.5 (38.8-46.2)	42.3 (38.6-46.0)	
≥70	402	186	46.3 (41.5-51.2)	45.3 (37.8-53.0)	45.1 (37.6-52.8)	
Gender						
Male	3126	1166	37.3 (35.6-39.0)	36.1 (33.5-38.9)	35.9 (33.3-38.7)	0.94, 0.34
Female	3104	1249	40.2 (38.5-42.0)	37.8 (34.5-41.3)	37.6 (34.3-41.1)	
Residence						
Urban	2866	1180	41.2 (39.4-43.0)	40.2 (36.3-44.1)	40.0 (36.1-43.9)	3.43, 0.07

Rural	3364	1235	36.7 (35.1-38.4)	35.5 (32.5-38.7)	35.3 (32.2-38.5)	
Self-reported history of chronic disease						
Yes	1145	495	43.2 (40.4-46.1)	41.9 (37.4-46.6)	41.7 (37.2-46.4)	6.14, 0.02
No	5085	1920	37.8 (36.4-39.1)	36.2 (33.7-38.9)	36.0 (33.5-38.7)	
History of COVID-19 like symptoms						
Yes	474	247	52.1 (47.6-56.6)	47.4 (37.9-57.1)	47.2 (37.7-56.9)	5.53, 0.02
No	5756	2168	37.7 (36.4-38.9)	36.3 (33.9-38.8)	36.1 (33.7-38.6)	
History of contact with a known COVID-19 case						
Yes	439	219	49.9 (45.2-54.5)	45.2 (38.3-52.2)	45.0 (38.1-52.0)	7.13, 0.01
No	5791	2196	37.9 (36.7-39.2)	36.5 (34.1-39.0)	36.3 (33.9-38.8)	
Ever tested for COVID-19 (RT-PCR)						
Yes	1092	485	44.4 (41.5-47.4)	41.0 (35.4-46.9)	40.8 (35.2-46.7)	2.17, 0.14
No	5138	1930	37.6 (36.2-38.9)	36.2 (33.5-39.0)	36.0 (33.3-38.8)	
RT-PCR result (n=1088*)						
Positive	176	140	79.5 (73.0-84.9)	81.8 (74.8-87.1)	81.7 (74.7-87.1)	74.93, <0.0001
Negative	912	345	37.8 (34.7-41.0)	38.8 (33.3-44.7)	38.6 (33.1-44.5)	

COVID-19: Coronavirus disease; RT-PCR: Reverse transcriptase-polymerase chain reaction

*RT-PCR result not known in four participants

Table 3: Sensitivity analyses for seroprevalence at extremes of test performance

	Weighted seroprevalence, % (95% CI)	Weighted seroprevalence adjusted for test performance, % (95% CI) [Sensitivity 100.00%, Specificity 99.63%]	Weighted seroprevalence adjusted for test performance, % (95% CI) [Sensitivity 95.89%, Specificity 99.90%]	Weighted seroprevalence adjusted for test performance, % (95% CI) [Sensitivity 100.00%, Specificity 99.05%]
Overall	36.9 (34.5-39.4)	36.7 (34.3-39.2)	38.4 (35.9-41.0)	36.3 (33.9-38.8)
Age, years				
18-29	33.7 (30.1-37.6)	33.5 (29.8-37.4)	35.1 (31.3-39.1)	33.1 (29.4-37.0)

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30-49	36.3 (33.5-39.3)	36.1 (33.3-39.1)	37.8 (34.9-40.9)	35.7 (32.9-38.7)
50-69	42.5 (38.8-46.2)	42.3 (38.6-46.0)	44.3 (40.4-48.1)	41.9 (38.2-45.7)
≥70	45.3 (41.8-48.8)	45.1 (41.6-48.6)	47.2 (43.4-51.0)	44.8 (41.2-48.4)
Gender				
Male	36.1 (33.5-38.9)	35.9 (33.3-38.7)	37.6 (34.9-40.5)	35.5 (32.9-38.3)
Female	37.8 (34.5-41.3)	37.6 (34.3-41.1)	39.4 (35.9-43.0)	37.2 (33.9-40.7)
Residence				
Urban	40.2 (36.3-44.1)	40.0 (36.1-43.9)	41.9 (37.8-45.9)	39.6 (35.7-43.6)
Rural	35.5 (32.5-38.7)	35.3 (32.2-38.5)	37.0 (33.8-40.3)	34.9 (31.9-38.1)
Self-reported history of chronic disease				
Yes	43.2 (40.4-46.1)	41.9 (37.4-46.6)	43.6 (38.9-48.5)	41.3 (36.8-46.1)
No	37.8 (36.4-39.1)	36.2 (33.7-38.9)	37.7 (35.1-40.5)	35.6 (33.1-38.3)
History of COVID-19 like symptoms				
Yes	52.1 (47.6-56.6)	47.4 (37.9-57.1)	49.4 (39.5-59.5)	46.9 (37.3-56.7)
No	37.7 (36.4-38.9)	36.3 (33.9-38.8)	37.8 (35.3-40.4)	35.7 (33.3-38.2)
History of contact with a known COVID-19 case				
Yes	49.9 (45.2-54.5)	45.2 (38.3-52.2)	47.1 (39.9-54.4)	44.7 (37.7-51.7)
No	37.9 (36.7-39.2)	36.5 (34.1-39.0)	38.0 (35.5-40.6)	35.9 (33.5-38.4)
Ever tested for COVID-19 (RT-PCR)				
Yes	44.4 (41.5-47.4)	41.0 (35.4-46.9)	42.7 (36.9-48.9)	40.4 (34.8-46.4)
No	37.6 (36.2-38.9)	36.2 (33.5-39.0)	37.7 (34.9-40.6)	35.6 (32.9-38.4)
RT-PCR result (n=1088*)				
Positive	79.5 (73.0-84.9)	81.8 (74.8-87.1)	85.3 (78.0-90.8)	81.6 (74.6-87.0)
Negative	37.8 (34.7-41.0)	38.8 (33.3-44.7)	40.4 (34.7-46.6)	38.2 (32.7-44.2)

Seroprevalence was lowest among participants aged 18-29 years [33.5% (95% CI 29.8 – 37.4)] and was higher in older age groups. Seroprevalence was highest in those aged 70 years and above [45.1% (95% CI 37.6 – 52.8)]. Seroprevalence was not significantly different among males and females ($p=0.34$). The seroprevalence among urban residents was 40.0% (95% CI 36.1 – 43.9), slightly but not significantly, higher than rural residents [35.3% (95% CI 32.2 – 38.5), $p=0.07$]. (Table 2)

One in five participants (1145/6230, 18.4%) self-reported history of at least one chronic disease (Table 1). Hypertension (815/6230, 13.1%) and diabetes mellitus (314/6230, 5.0%) were the most commonly reported chronic diseases (online supplemental file 2). Seroprevalence was significantly higher in participants who self-reported history of chronic disease (41.7%, 95% CI 37.2 – 46.4) as compared to those who did not report a history of chronic disease (36.0%, 95% CI 33.5 - 38.7) (Table 2).

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3 Among participants who reported a history of COVID-19 like symptoms, seroprevalence was 47.2% (95%
4 CI 37.7 – 56.9) compared with 36.1% (95% CI 33.7 – 38.6) among participants who did not report such
5 symptoms. Seroprevalence was higher among those who reported contact with a known COVID-19 case
6 [45.0% (95% CI 38.1 – 52.0)] than participants who did not report any history of such contact [36.3%
7 (95% CI 33.9 – 38.8)]. (Table 2)
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10 Seroprevalence was not significantly related to being tested for COVID-19 (RT-PCR). However, those who
11 reported a positive RT-PCR COVID-19 test had significantly higher seroprevalence (81.7%, 95% CI 74.7 –
12 87.1) as compared to those who reported a negative RT-PCR COVID-19 test (38.6%, 95% CI 33.1 – 44.5).
13 (Table 2)
14

15 Among 2 415 seropositive individuals, only 247 (10.2%) reported a history of COVID-19 like symptoms.
16 Only 20.1% (485/2415) of the seropositive individuals were tested for COVID-19 (RT-PCR). Among 474
17 who reported a history of COVID-19 like symptoms, 233 (49.2%) were tested for COVID-19 (RT-PCR).
18 Among 4897 individuals who did not report a history of COVID-19 like symptoms and were never tested
19 for COVID-19 (RT-PCR), 1825 (37.3%) were seropositive. (Figure 3)
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21

22 Among 36 participants who reported a positive RT-PCR COVID-19 test but were seronegative, the
23 duration between COVID-19 RT-PCR test and serological testing ranged from 9 days to 101 days. In only
24 four of these 36 participants, the duration between the COVID-19 RT-PCR test and the serological test
25 was 14 days or less. Of the remaining 32 participants, 21 did not report a history of COVID-19 like
26 symptoms, nine did not report a history of contact with a known COVID-19 case, and eight reported
27 neither a history of COVID-19 like symptoms nor a history of contact with a known COVID-19 case.
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30 We estimated that there were 1 673 484 (95% CI 1 564 047 – 1 787 482) cumulative number of
31 infections among adults aged ≥ 18 years in the valley by 03 Oct 2020, two weeks before the start of the
32 survey. If we assume that the seroprevalence was similar to the overall seroprevalence in the population
33 not included in our study (< 18 years of age) then the estimated cumulative number of infections in the
34 valley by 03 Oct 2020 was 2 791 933 (95% CI 2 609 354 – 2 982 119). Considering that the cumulative
35 number of reported COVID-19 cases was 47 071 by 03 Oct 2020 (Figure 4), we estimate the number of
36 infections per reported case as 59.3 (95% CI 55.4 – 63.4). The number of reported COVID-19 deaths after
37 a three-week lag period (on 24 Oct 2020) was 955. Thus, we estimated the infection fatality rate as
38 0.034% (95% CI 0.032 – 0.037).
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41 Figure 5 depicts the relationship between the estimated number of SARS-CoV-2 infected persons,
42 reported COVID-19 cases, and reported COVID-19 deaths. Of the total estimated SARS-CoV-2 infected
43 persons, only 1.69% were reported. Of the total reported COVID-19 cases, 2.03% died.
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46 DISCUSSION

47 We report the results of a seroprevalence survey conducted in Kashmir from October-November 2020,
48 seven months after the appearance of the first local COVID-19 case. The COVID-19 pandemic is rapidly
49 evolving worldwide. In Kashmir, several important events happened since we completed our survey.
50 From 16 Jan 2021, COVID-19 vaccination was introduced in a phased manner. Healthcare workers were
51 given preference during the first phase. From 01 Mar 2021, the vaccine was made available for people
52 ≥ 60 years of age and those with chronic diseases in the age group of 45-59 years. However, especially
53 during the early phases of the COVID-19 vaccination campaign, many people were hesitant to receive
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3 the vaccine doses. During the same time, SARS-CoV-2 Variants of Concern began to emerge and
4 circulate. The daily number of COVID-19 cases started to rise again. The 'second wave' in April 2021 was
5 more explosive than the 'first wave' at the beginning of the pandemic. The fear of the disease had
6 diminished, and COVID appropriate behaviour was no more a norm. The government and the people
7 were caught unawares. There were several reports of a possible 'second infection' and reports of cases
8 among previously vaccinated individuals. Given these developments, the current seroprevalence in
9 Kashmir will be higher than what we report in this study.
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12 The results of our study indicate that by the first week of October 2020, nearly seven months after the
13 appearance of the first laboratory-confirmed COVID-19 case on 18 March 2020, close to 37% of the
14 valley's population aged ≥ 18 years had been infected. Our results suggest that the cumulative number of
15 SARS-CoV-2 infections by the first week of October 2020 was nearly 2.8 million, with an estimated
16 infection fatality rate of 0.034%. Seroprevalence did not differ by gender but was higher in older age
17 groups.
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20 The findings of our study are based on a representative sample of the population. The laboratory test
21 used for the detection of SARS-CoV-2 specific IgG antibodies in serum samples provides valid
22 results.[20,25] We report seroprevalence estimates adjusted for sampling design and test performance.
23

24 The overall adjusted seroprevalence of around 37% indicates that, by October 2020, a large proportion
25 of the valley's population had been infected with the virus. Easing of lockdown, being fed up with the
26 restrictions, and non-adherence to prevention norms are the possible reasons. Using several
27 assumptions about the test sensitivity and specificity to calculate adjusted seroprevalence estimates
28 yielded small differences.
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31 Several factors potentially influence the seroprevalence rates. These include population density, social
32 and demographic structure of the population, governmental policies and the extent of their
33 implementation, immunity level of the population, time since the start of infection transmission,
34 adherence to infection prevention guidelines, quality of contact tracing and quarantine, and possibly the
35 geography and environment of an area. The emergence of several Variants of Concern and the
36 introduction of COVID-19 vaccination will also influence population immunity. Herd immunity in the
37 context of COVID-19 is a matter of debate as reports of a second infection continue to pour in.[26]
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40 Comparison with previous reports suggests that, by October 2020, the seroprevalence had increased
41 almost ten-fold since July 2020.[16,27] The second of the three nationwide seroprevalence surveys in
42 India conducted in August-September 2020 reports an overall seroprevalence of 6.6%, ranging from
43 5.2% in rural areas to 16.9% in urban slums.[28] A nationwide survey conducted in December 2020-
44 January 2021 reported an overall seroprevalence of 24.1% ranging from 4.9% - 44.4% across
45 districts.[29] Kashmir is thus not a low-infection area. Being an oft-visited tourist area, Kashmir is at an
46 increased risk of infection transmission. Adherence to COVID appropriate behavior (use of face masks in
47 public, frequent handwashing, physical and social distancing) has been poor. The experience of a
48 'second wave' of COVID-19 in April-June 2021, the appearance of virus variants, and the introduction of
49 vaccination programs warrant robust surveillance of the epidemic.
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53 The seroprevalence of SARS-CoV-2 IgG antibodies was higher in older age groups. During the early
54 period of the pandemic, people were adherent to social distancing and other non-pharmaceutical
55 interventions because of a fear of the disease and administrative restrictions. With time, administrative
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3 restrictions were relaxed, fear of the disease attenuated, and people became fed up with the social
4 restrictions. This led to an increase in the number of reported COVID-19 cases and provided the
5 population, including older age groups, an opportunity to contract the infection. That older people have
6 an increased risk of symptomatic and more severe disease is now well known.[30,31] However, age-
7 based differential susceptibility to SARS-CoV-2 infection antibody response and the reasons thereof are
8 still a grey area and need further understanding. Existing literature might suggest that the more mobile
9 and socially active young have a higher risk of infection.[6,7] However, this should not imply that the
10 elderly have a decreased susceptibility to SARS-CoV-2 infection or a decreased antibody response.[32]
11 On the contrary, several studies suggest that the seroprevalence of SARS-CoV-2 specific IgG antibodies is
12 higher in the older age groups and particularly so in more dense population groups.[4,5,8–11,13]
13 Furthermore, SARS-CoV-2 antibody levels have been reported to be higher in older people.[12]

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17 The seroprevalence of SARS-CoV-2 specific IgG antibodies did not differ significantly by gender, though
18 the figure was slightly higher for females. These findings are consistent with the available
19 literature.[6,13] Difference in seroprevalence by gender has been suggested by some studies, and
20 females have been reported to have lower antibody levels.[5,7,9,11,12,14,33]

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23 Urban areas are more densely populated than rural areas, accelerating the transmission of infections in
24 the population. The seroprevalence of SARS-CoV-2 specific IgG antibodies is thus expected to be higher
25 in urban areas, especially during the early phases of an epidemic. However, as the epidemic progresses,
26 the seroprevalence gap between urban and rural areas will wane off. We estimated an adjusted
27 seroprevalence of 40·0% (95% CI 36·1 – 43·9) in urban areas as compared to 35·3% (95% CI 32·2 – 38·5)
28 in rural areas (p=0·07).

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31 People with a chronic disease experience more severe COVID-19 symptoms and are more likely to die
32 when compared to people with no chronic disease.[34] We found a higher proportion of symptomatic
33 infection among participants with a self-reported history of chronic disease (78/1145, 6·8%) as
34 compared to participants with no chronic disease (169/5085, 3·3%) (online supplemental file 3). Little is,
35 however, known about the risk of infection in chronic disease patients. We found a significantly higher
36 seroprevalence among participants with a self-reported history of chronic disease (Table 2). This finding
37 needs further research for corroboration and possible explanations.

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40 People with a self-reported history of COVID-19 related symptoms, contact with a known COVID-19
41 case, or a positive COVID-19 RT-PCR had a higher seroprevalence as compared to their complement.
42 Among seropositive individuals, only 10·2% reported being symptomatic. The percentage of
43 asymptomatic infections, thus, was 90%. However, only 49% of individuals with a history of COVID-19
44 like symptoms were tested using RT-PCR. We also estimated that only one out of almost 59 infections
45 gets reported. This reflects the necessity of improving the efficiency of RT-PCR testing so that more
46 symptomatic individuals receive the test. Not all individuals with a known RT-PCR positive result showed
47 the presence of IgG antibodies. Around 20% of RT-PCR positive individuals were seronegative, and in a
48 large majority of them (32 out of 36), the duration since RT-PCR positivity was more than two weeks.
49 This may be attributed to a poor B cell response or a false negative antibody test.[35] Around 38% of RT-
50 PCR negative individuals were seropositive, suggesting a false-negative RT-PCR or infection acquisition at
51 a date later than the RT-PCR test.

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54 We estimated an infection fatality rate of 0·034% (95% CI 0·032 – 0·037). The infection fatality rate in
55 SARS-CoV-2 infection has been reported to range from as low as 0·00% to 1·63%.[36] Our estimates of
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3 the infection fatality rate are low as compared to estimates from several Indian studies.[5,28,37] Under-
4 reporting COVID-19 deaths because of the non-uniform definition for a 'COVID-19 death' may falsely
5 lower the infection fatality rates.[38] Many other factors can influence the infection fatality rate in SARS-
6 CoV-2 infection – the quality of available health facilities, the age structure of the population, and
7 COVID-19 epidemic intensity.[39,40] Developing countries usually have a younger population as
8 compared to the developed countries, and Kashmir is not an exception. However, because of the
9 possibility of under-reporting of COVID-19 deaths, the true infection fatality rate in Kashmir may be
10 higher than our estimates. The infection fatality rate is, however, known to be lower in developing
11 nations.[30,41] In developed nations like the United States and many European countries, a higher
12 infection fatality rate has been reported.[30,42]
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16 **Limitations**

17
18 One important limitation of our study is that even though we adjusted the weighted seroprevalence
19 estimates for test performance using manufacturer-provided sensitivity and specificity (100% and
20 99-63% respectively), we did not quantify the test validity in-house. Another limitation of our study
21 estimates is that we excluded people <18 years of age. The results of our study may not thus be
22 generalizable to this group of the population.
23

24 Our estimated seroprevalence was much higher than we anticipated at the designing stage. This has
25 impacted the precision of our estimates to some extent. However, we believe we still have been able to
26 estimate the seroprevalence with reasonable precision.
27

28 Lack of reliable death counts is another potential limitation. This may have led to an underestimation of
29 the infection fatality rate. We did not perform any adjustment for death counts. Further, because of lack
30 of age- and gender-specific mortality data, we could not estimate age- and gender-specific infection
31 fatality rates.
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33

34 **CONCLUSIONS**

35
36 We conclude that nearly 37% of individuals aged 18 years and above were infected with SARS-CoV-2 in
37 Kashmir by October 2020. The infection fatality rate in the valley is around 0.034%. A majority of cases
38 go unreported. For every reported case, there are 59 unreported infections in the population. Since
39 almost half of the symptomatic individuals go unreported, testing of symptomatic individuals and
40 effective contact tracing needs to continue. Given the emergence of mutant Variants of Concern,
41 increasing the population immunity through augmented and sustained vaccination is necessary. We
42 further recommend that adherence to COVID-19 prevention measures should be ensured until a large
43 proportion of the population gets vaccinated.
44
45

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13 Naveed Manzoor, Mubeena.
14

15 **COMPETING INTERESTS**

16
17 We declare no competing interests, financial or otherwise.
18

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20
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22 in study designing, implementation, analysis, or interpretation of the study findings.
23

24 **CONTRIBUTORS**

25
26 S Muhammad Salim Khan: Conceptualization, Funding acquisition, Methodology, Writing-review &
27 editing.
28

29 Mariya Amin Qurieshi, Inaamul Haq, Sabhiya Majid: Formal analysis, Data curation, Methodology,
30 Project administration, Writing-original draft, Writing-review & editing.
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32 Javid Ahmad, Taha Ayub, Anjum Bashir, Ashfaq Ahmad Bhat, Abdul Majeed Ganai, Yasmeen Jan, Rauf-
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35 review & editing.
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40 Writing-review & editing.
41

42
43 S Muhammad Salim Khan, Mariya Amin Qurieshi, Inaamul Haq, and Sabhiya Majid have verified the
44 underlying data.
45

46 **DATA SHARING**

47
48 Anonymized data collected for the study, including individual participant data and a data dictionary
49 defining each field in the set, will be made available to interested researchers on request by Inaamul
50 Haq (haqinaam@yahoo.co.in) for two years from publication. The study protocol, statistical analysis
51 plan, and informed consent forms are also available from Inaamul Haq.
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Figure 1 legend:

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48 Figure 1: Location of the ten districts and seroprevalence (%) by district. Figures in parentheses indicate
49 a 95% Confidence Interval for seroprevalence.
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Figure 2 legend:

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53 Figure 2: Participant flow.
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Figure 3 legend:

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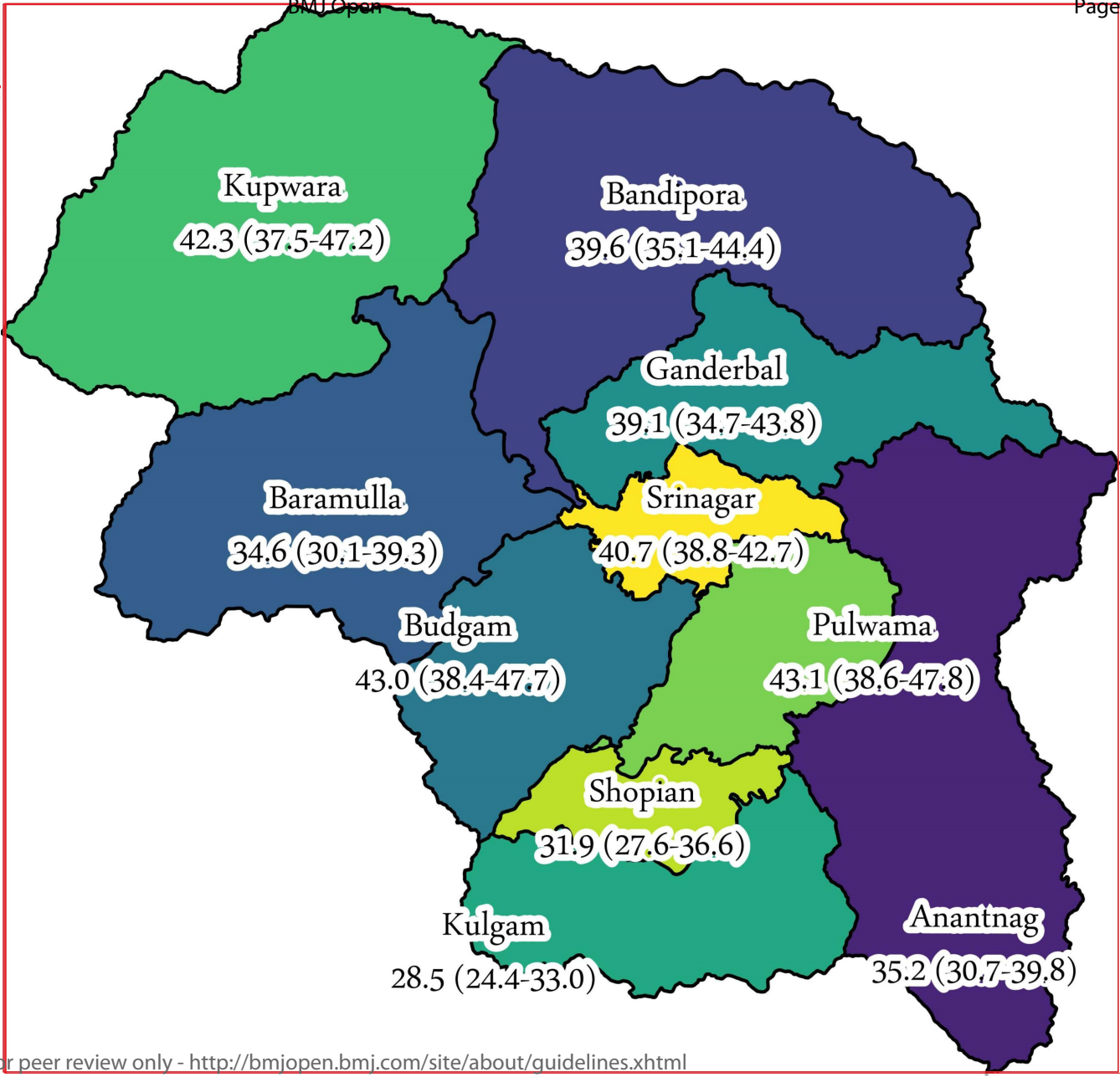
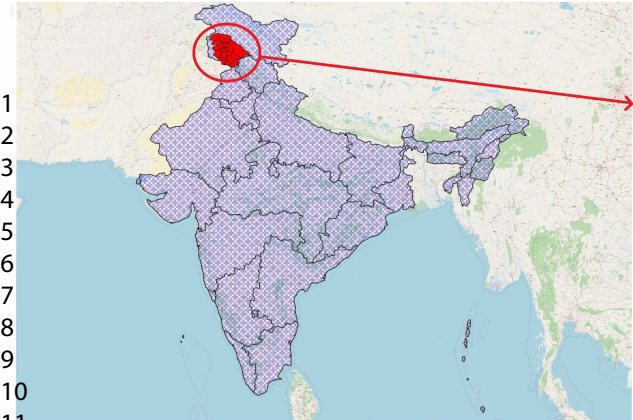
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3 Figure 3: A. Seropositivity by the history of COVID-19 like symptoms, RT-PCR testing, and test result. B.
4 History of COVID-19 like symptoms by seropositivity, RT-PCR testing, and test result.
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6 **Figure 4 legend:**
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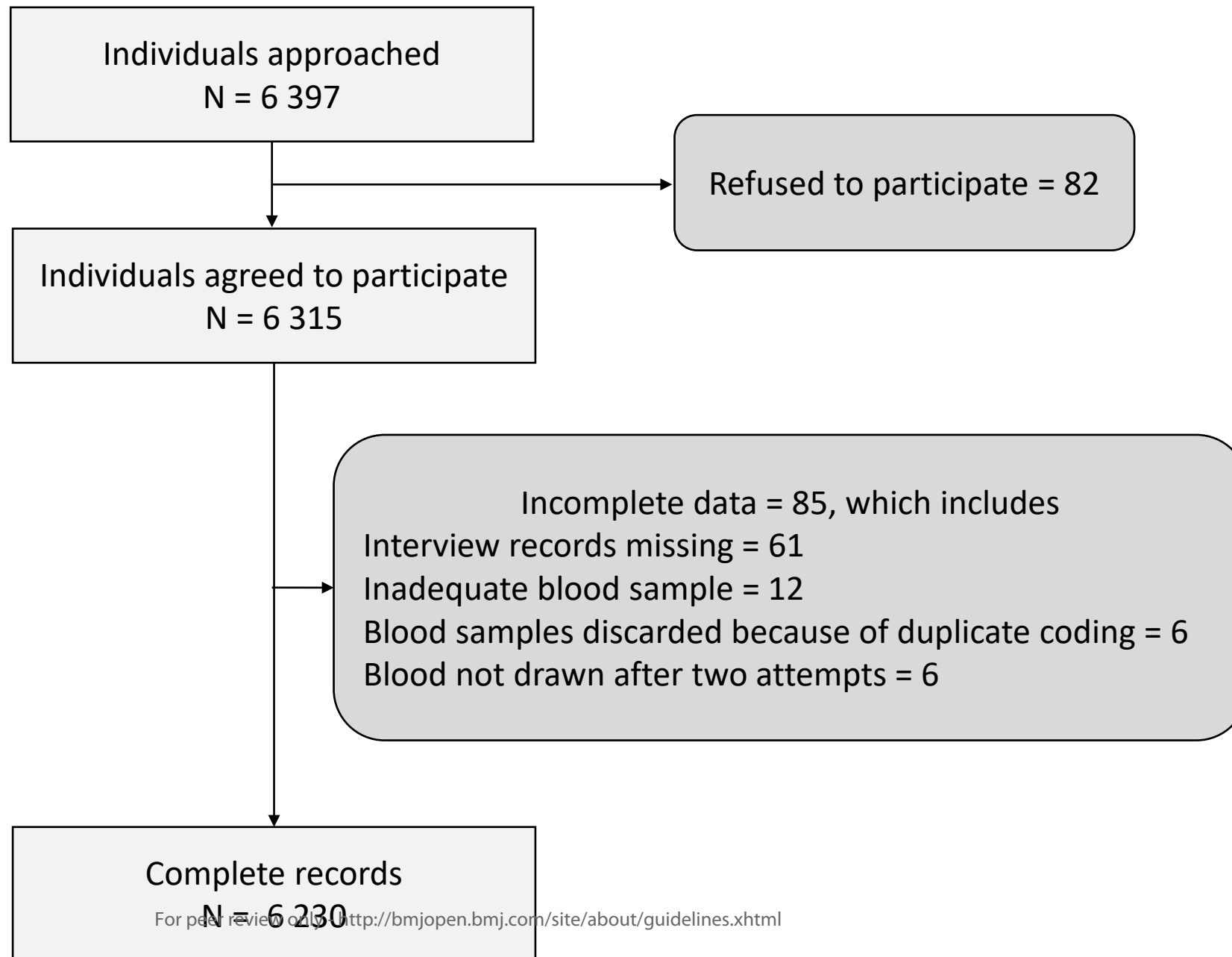
8 Figure 4: A. Daily cases and deaths in Kashmir since the start of the COVID-19 pandemic; B. Cumulative
9 number of cases and deaths in Kashmir.
10

11 **Figure 5 legend:**
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13 Figure 5: Cumulative estimated SARS-CoV-2 infections, reported cases, and deaths in Kashmir, October-
14 November 2020. The bars represent the number of persons at each step. The percentages above the
15 bars represent the percentage out of the total population. The percentages within the triangles
16 represent percentages out of the previous step who proceed to the next step. (Adapted from Holtgrave
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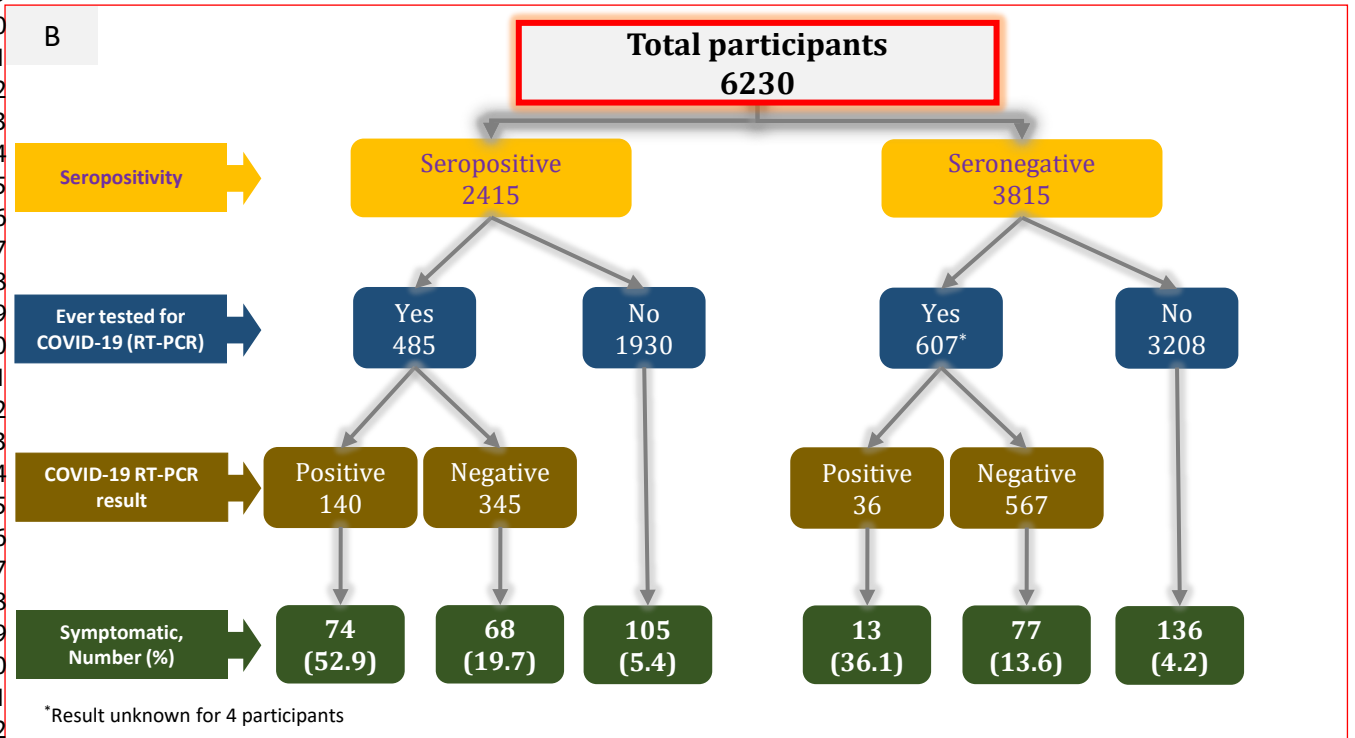
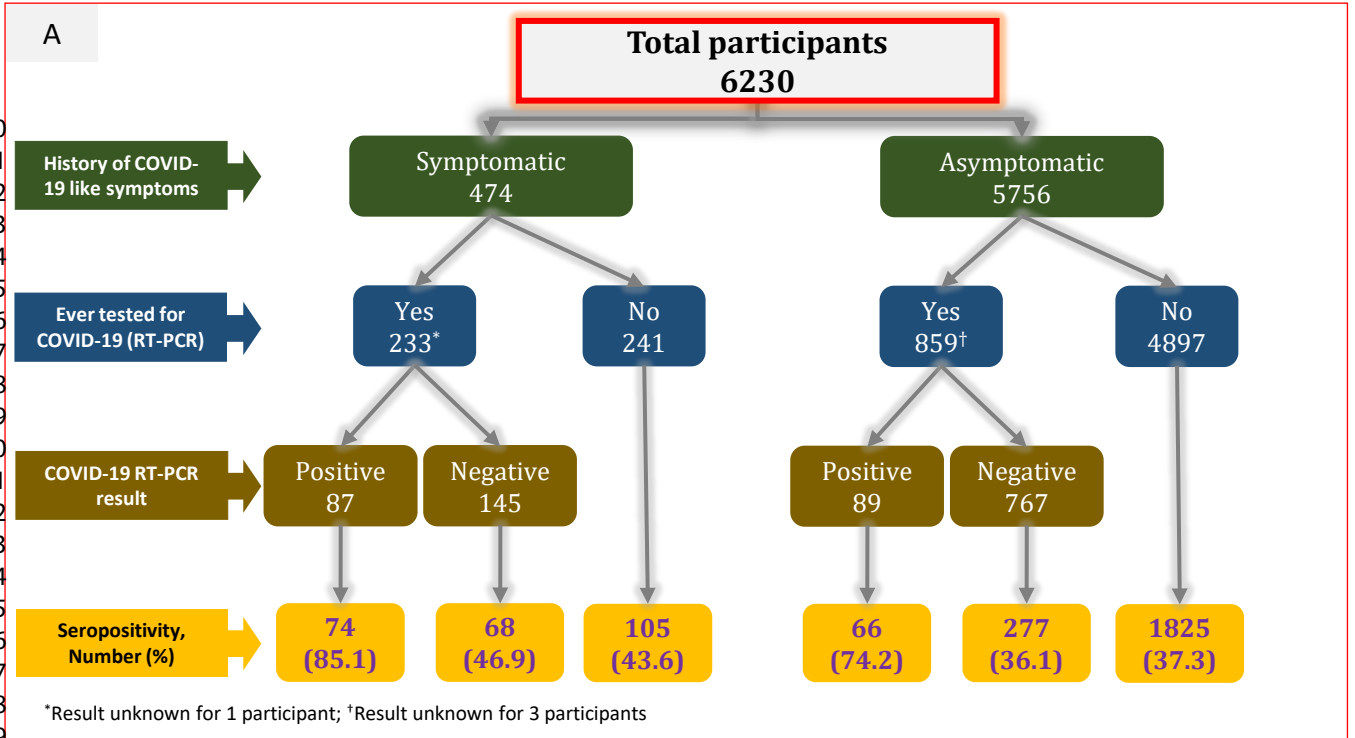


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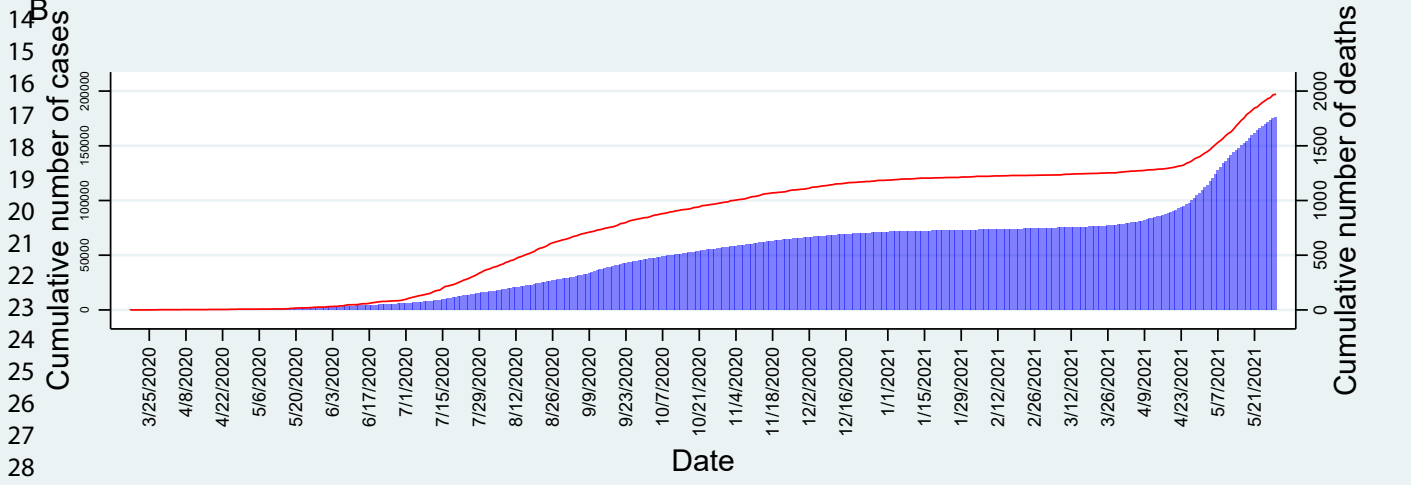
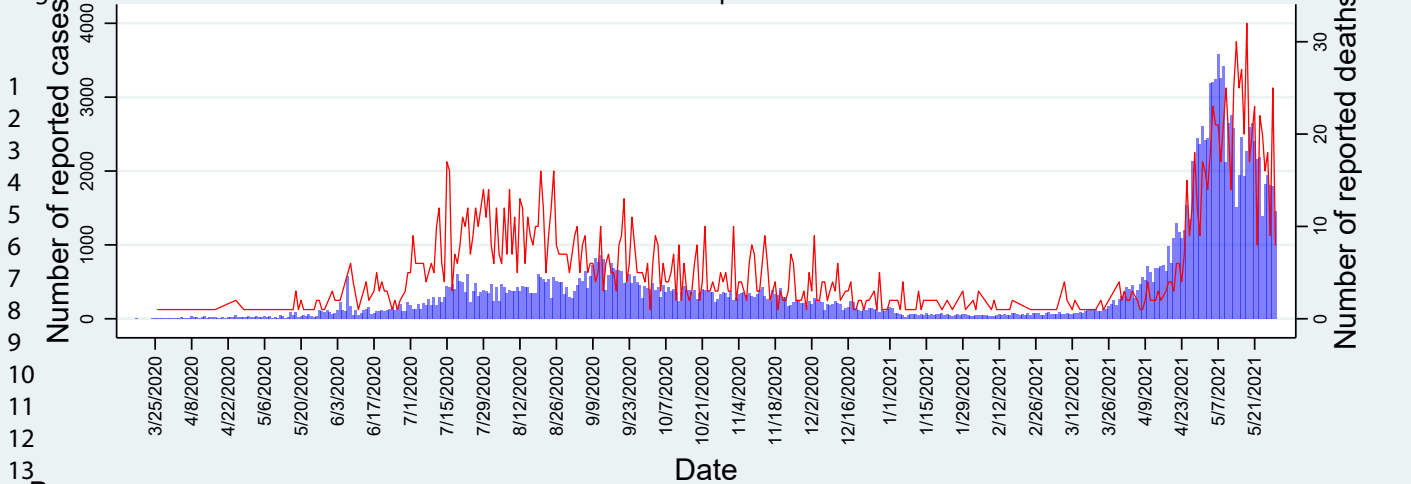


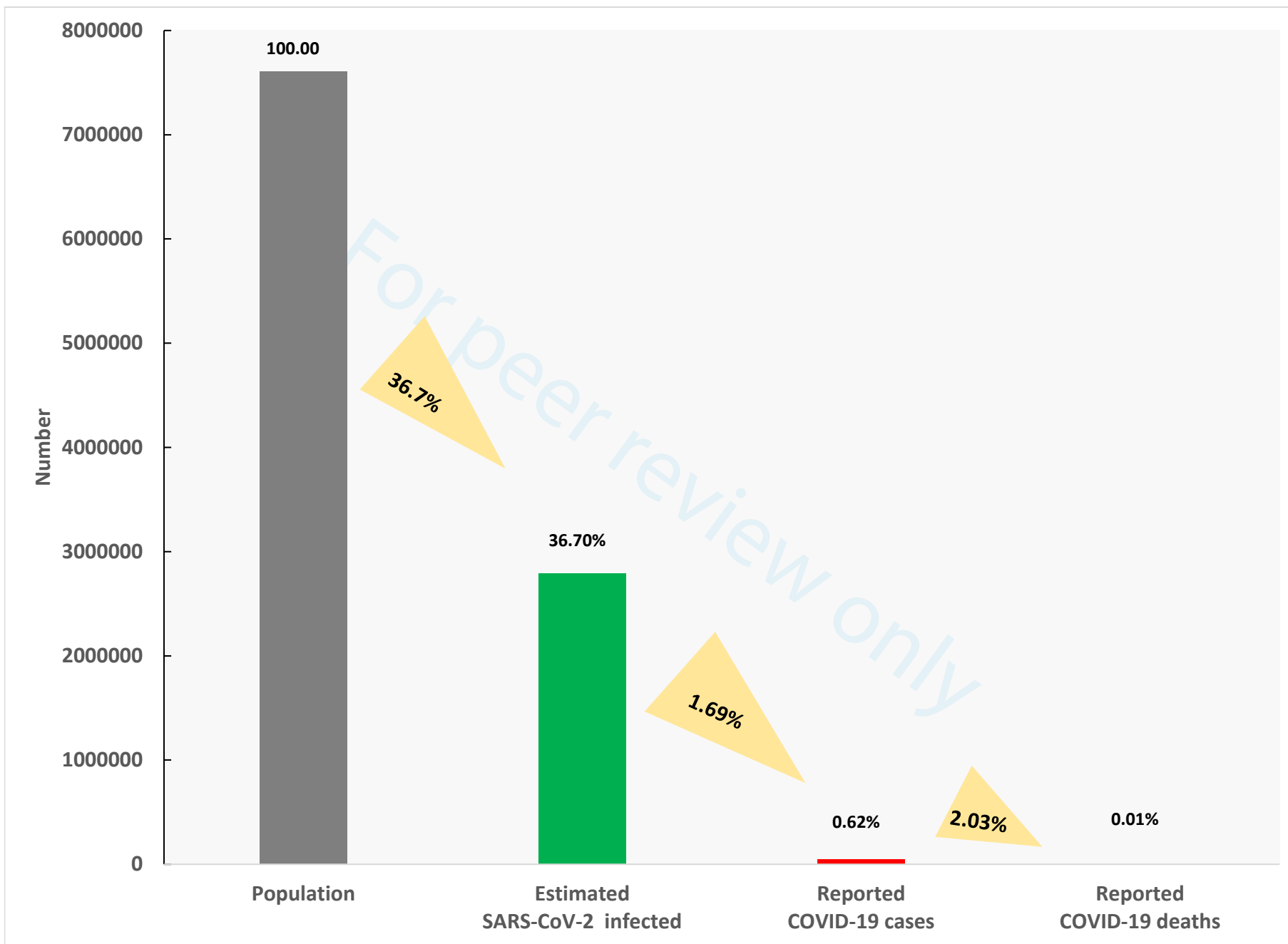
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Supplemental Table 1: Participant characteristics by district

District	Total	Age (years)				Gender		Residence	
		<30	30-49	50-69	70+	Female	Male	Rural	Urban
Anantnag	421	84	197	113	27	214	207	295	126
Budgam	442	113	190	105	34	263	179	354	88
Bandipora	424	106	174	114	30	227	197	341	83
Baramulla	405	113	176	98	18	214	191	325	80
Ganderbal	442	92	210	123	17	233	209	346	96
Kulgam	428	102	194	113	19	257	171	346	82
Kupwara	400	81	171	105	43	215	185	360	40
Pulwama	443	102	176	126	39	218	225	396	47
Shopiyan	407	119	152	90	46	211	196	368	39
Srinagar	2418	601	1032	656	129	1052	1366	233	2185
Total	6230	1513	2672	1643	402	3104	3126	3364	2866

Supplemental Table 2: Seroprevalence (unadjusted) by district and participant characteristics

District	Overall	Age (years)				Gender		Residence	
		<30	30-49	50-69	70+	Male	Female	Urban	Rural
Anantnag	35.2 (30.7-39.8)	29.8 (21-40.4)	34.5 (28.2-41.4)	38.9 (30.4-48.2)	40.7 (24.2-59.7)	36.2 (30-43)	34.1 (28.1-40.7)	42.9 (34.5-51.6)	31.9 (26.8-37.4)
Budgam	43 (38.4-47.7)	44.2 (35.4-53.5)	37.9 (31.3-45)	48.6 (39.2-58.1)	50 (33.8-66.2)	41.9 (34.9-49.3)	43.7 (37.8-49.8)	38.6 (29.1-49.2)	44.1 (39-49.3)
Bandipora	39.6 (35.1-44.4)	37.7 (29-47.3)	42 (34.8-49.4)	40.4 (31.8-49.6)	30 (16.4-48.3)	37.6 (31.1-44.5)	41.4 (35.2-47.9)	55.4 (44.6-65.7)	35.8 (30.9-41)
Baramulla	34.6 (30.1-39.3)	27.4 (20-36.4)	32.4 (25.9-39.6)	44.9 (35.4-54.8)	44.4 (24-67)	39.3 (32.6-46.4)	30.4 (24.6-36.9)	36.3 (26.5-47.3)	34.2 (29.2-39.5)
Ganderbal	39.1 (34.7-43.8)	34.8 (25.8-45)	40.5 (34-47.3)	39.8 (31.6-48.7)	41.2 (21-64.8)	39.2 (32.8-46)	39.1 (33-45.5)	42.7 (33.2-52.8)	38.2 (33.2-43.4)
Kulgam	28.5 (24.4-33)	27.5 (19.7-36.9)	26.8 (21-33.5)	31 (23.1-40.1)	36.8 (18.7-59.7)	25.1 (19.2-32.2)	30.7 (25.4-36.6)	37.8 (28-48.7)	26.3 (21.9-31.2)
Kupwara	42.3 (37.5-47.2)	33.3 (24-44.2)	39.8 (32.7-47.3)	50.5 (41-59.9)	48.8 (34.4-63.4)	41.6 (34.7-48.9)	42.8 (36.3-49.5)	50 (35-65)	41.4 (36.4-46.6)
Pulwama	43.1 (38.6-47.8)	35.3 (26.7-45)	42.6 (35.5-50)	45.2 (36.8-54)	59 (43.2-73.1)	39.6 (33.4-46.1)	46.8 (40.3-53.4)	40.4 (27.5-54.9)	43.4 (38.6-48.4)
Shopiyan	31.9 (27.6-36.6)	28.6 (21.2-37.3)	29.6 (22.9-37.3)	41.1 (31.4-51.5)	30.4 (18.9-45.1)	31.1 (25-37.9)	32.7 (26.7-39.3)	38.5 (24.7-54.4)	31.3 (26.7-36.2)
Srinagar	40.7 (38.8-42.7)	39.1 (35.3-43.1)	39.2 (36.3-42.3)	41.9 (38.2-45.7)	53.5 (44.9-61.9)	37.7 (35.2-40.3)	44.6 (41.6-47.6)	40.8 (38.7-42.9)	39.9 (33.8-46.3)

Chronic disease and SARS-CoV-2 infection in the study population

Of the 6230 participants, 1145 reported a history of at least one chronic disease. Two hundred ninety-eight reported a history of more than one chronic disease.

Supplementary Table 3: Chronic disease in the study population

Chronic disease (n = 1145)	Number (%)
Hypertension	815 (13.1%)
Diabetes	314 (5.0%)
Chronic Obstructive Pulmonary Disease	39 (0.6%)
Coronary Heart Disease	35 (0.6%)
Cerebrovascular Disease	16 (0.3%)
Asthma	15 (0.2%)
Chronic Kidney Disease	10 (0.2%)
Chronic Liver Disease	5 (0.1%)
Cancer	4 (0.1%)

Supplementary Table 4: History of COVID-19 like symptoms and seropositivity vis-à-vis history of chronic disease

		History of COVID-19 like symptoms	
		Yes	No
Reported history of chronic disease (n=1145)	Seropositive	78	417
	Seronegative	63	587
Did not report any history of chronic disease (n=5085)	Seropositive	169	1751
	Seronegative	164	3001

Of the 1154 participants who reported a history of chronic disease 78 (6.8%) reported a history of COVID-19 like symptoms within three months of the interview date and were seropositive for SARS-CoV-2 specific IgG (symptomatic infection). The proportion of symptomatic infection among participants who did not report any history of chronic disease was 3.3% (169/5085).

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1, 3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3 and Figure 1
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	3, 4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4, 5
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	4, 5
		(b) Describe any methods used to examine subgroups and interactions	5
		(c) Explain how missing data were addressed	5
		(d) If applicable, describe analytical methods taking account of sampling strategy	4, 5
		(e) Describe any sensitivity analyses	6, Table 3
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 2, and page 5
		(b) Give reasons for non-participation at each stage	Figure 2
		(c) Consider use of a flow diagram	Figure 2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1, Figure 2
Outcome data	15*	Report numbers of outcome events or summary measures	Table 2

1				
2	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2
3				
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7			(b) Report category boundaries when continuous variables were categorized	Table 1, 2
8				
9				
10			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
11				
12	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 2, Table 3
13				
14				
15	Discussion			
16	Key results	18	Summarise key results with reference to study objectives	9
17				
18	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11, 12
19				
20				
21	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9, 10, 11
22				
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24				
25	Generalisability	21	Discuss the generalisability (external validity) of the study results	11
26				
27	Other information			
28	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12
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*Give information separately for exposed and unexposed groups.

BMJ Open

Seroprevalence of SARS-CoV-2 specific IgG antibodies in Kashmir, India, seven months after the first reported local COVID-19 case: results of a population-based seroprevalence survey from October-November, 2020

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3 **Seroprevalence of SARS-CoV-2 specific IgG antibodies in Kashmir, India, seven months after the first**
4 **reported local COVID-19 case: results of a population-based seroprevalence survey from October-**
5 **November, 2020**
6

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ABSTRACT

Objectives: We designed a population-based survey in Kashmir to estimate the seroprevalence of SARS-CoV-2 specific IgG antibodies in the general population aged 18 years and above.

Setting: The survey was conducted among 110 villages and urban wards across ten districts in Kashmir from 17 Oct 2020 to 04 Nov 2020.

Participants: Individuals aged 18 years and above were eligible to be included in the survey. Serum samples were tested for the presence of SARS-CoV-2 specific IgG antibodies using the Abbott SARS-CoV-2 IgG assay.

Primary and secondary outcome measures: We labeled assay results equal to or above the cut-off index value of 1.4 as positive for SARS-CoV-2 specific IgG antibodies. Seroprevalence estimates were adjusted for the sampling design and assay characteristics.

Results: Out of 6397 eligible individuals enumerated, 6315 (98.7%) agreed to participate. The final analysis was done on 6230 participants. Seroprevalence adjusted for the sampling design and assay characteristics was 36.7% (95% CI 34.3%-39.2%). Seroprevalence was higher among the older population. Among seropositive individuals, 10.2% (247/2415) reported a history of COVID-19 like symptoms. Out of 474 symptomatic individuals, 233 (49.2%) reported having been tested. We estimated an infection fatality rate of 0.034%.

Conclusions: During the first seven months of the COVID-19 epidemic in Kashmir valley, approximately 37% of individuals were infected. The reported number of COVID-19 cases was only a small fraction of the estimated number of infections. A more efficient surveillance system with strengthened reporting of COVID-19 cases and deaths is warranted.

ARTICLE SUMMARY

Strengths and limitations of this study

- The findings of our study are based on a representative sample of the population.
- The laboratory test used for the detection of SARS-CoV-2 specific IgG antibodies in serum samples provides valid results.
- We report seroprevalence estimates adjusted for sampling design and test performance.
- Even though we adjusted the weighted seroprevalence estimates for test performance using manufacturer-provided sensitivity and specificity (100% and 99.63%, respectively), we did not quantify the test validity in-house.
- Because of lack of age- and gender-specific mortality data, we could not estimate age- and gender-specific infection fatality rates.

INTRODUCTION

On 11 Feb 2020, the World Health Organization announced that the disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) would be named coronavirus disease (COVID-19).[1] In Kashmir, the first case of COVID-19 was confirmed in Srinagar city on 18 Mar 2020.[2] The government imposed the first phase of the lockdown in Kashmir on 24 March 2020. During this phase, inter-state travel remained suspended. People were barred from moving outside except in an

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3 emergency. Except for essential services, all government and private offices were advised to work from
4 home. Universal masking was made mandatory. The lockdown was extended till 31 May 2020 and later
5 relaxed in a phased manner.
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7 Mild or asymptomatic infections are common in Coronavirus disease 2019 (COVID-19) and are an
8 important source of infection transmission.[3,4] Such cases are less likely to be detected by a
9 surveillance system based on reverse-transcriptase polymerase chain reaction (RT-PCR) testing.
10 Therefore, the number of reported RT-PCR positive cases are an underestimate of the true number of
11 infections in a population.
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14 Seroprevalence surveys have been conducted in various countries at different stages of the current
15 epidemic among various population groups.[5–14] Seroprevalence surveys provide a more accurate
16 estimate of past infection, improve understanding of the infection transmission dynamics, and guide
17 public health response.[15]
18

19 We designed this survey with the primary objective to estimate the seroprevalence of severe acute
20 respiratory syndrome coronavirus 2 (SARS-CoV-2) specific IgG antibodies in the adult population of
21 Kashmir valley.
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23

24 **METHODS**

25
26 We designed a population-based cross-sectional study. The study covered all the ten districts of
27 Kashmir, a valley in northern India. (Figure 1) We completed data collection in three weeks, from 17 Oct
28 2020 to 04 Nov 2020.
29

30 **Ethics**

31
32 We obtained written informed consent from all study participants. The study was approved by the
33 Institutional Ethics Committee of Government Medical College Srinagar (reference number:
34 1004/ETH/GMC). We used anonymized participant data for analysis.
35

36 **Sample size**

37
38 Based on the results of a previous study conducted in July 2020, we speculated that, by October 2020,
39 the prevalence would have increased to around 20%.[16] We calculated the minimum sample size based
40 on an anticipated seroprevalence of 20%, an absolute precision of 2%, and a design effect of 2. We used
41 OpenEpi to make sample size calculations.[17] We adjusted the sample size for a possible non-response
42 of 10% to obtain a minimum size of 3376. We decided to select 3600 individuals from nine of the ten
43 districts (except district Srinagar). To obtain precise estimates for district Srinagar, sample size
44 estimation was made for the district separately. We used a design effect of 1.5, an anticipated
45 seroprevalence of 20%, and absolute precision of 2% to obtain a sample size of 2302 for the district,
46 further increasing to 2400 to account for non-response. We thus targeted a total sample size of 6000
47 (3600 + 2400).
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51 **Participants**

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53 All adults ≥ 18 years of age were eligible to participate in the study. We selected eligible participants
54 using a three-stage stratified cluster sampling technique. We listed all clusters in the valley using the
55 Census 2011 data.[18] Within each of the ten districts in the valley, clusters were stratified into urban
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3 and rural clusters. We selected clusters within each of the 20 strata by probability proportionate to size
4 (PPS) sampling. Except for district Srinagar which we oversampled to obtain precise seroprevalence
5 estimates for, ten clusters were randomly selected from each district. We selected 20 clusters from
6 district Srinagar. We divided each selected cluster into four equal areas and chose a central location
7 within each of the four areas as the starting point. Thereafter, we approached consecutive households
8 to enroll at least ten eligible participants. We thus identified a total of 440 random locations within 110
9 clusters in ten districts. We invited all eligible adults in a household for participation.
10
11

12 **Variables**

13
14 The primary outcome variable of interest was SARS-CoV-2 specific IgG antibodies. In addition, we
15 obtained information from participants about their age, gender, history of COVID-19 like symptoms in
16 the three months before the interview date, history of contact with a known COVID-19 patient, and
17 history of COVID-19 testing.
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19

20 **Procedure**

21 We informed eligible adults about the purpose and the procedure of the study. Study participation was
22 voluntary. Participants were interviewed by health personnel specifically trained for the interview.
23 Interview responses were recorded in an Epicollect5 form.[19] Once the interview was completed, a
24 trained phlebotomist collected 3-5 mL of venous blood from the antecubital vein under aseptic
25 precautions into a red-top collection tube containing a clot activator. The tube was left standing,
26 undisturbed, for at least 30 minutes for clot formation. The sample was later transported to a central
27 facility for centrifugation. Centrifuged samples were transported to a central laboratory for further
28 processing and analysis. Serum samples were tested for the presence of SARS-CoV-2 specific IgG
29 antibodies using the Abbott SARS-CoV-2 IgG assay. The assay uses chemiluminescence to detect IgG
30 antibodies against the SARS-CoV-2 nucleocapsid protein. The reported sensitivity and specificity of the
31 assay are 100% (95% CI 95.89-100.00) and 99.63% (99.05-99.90), respectively.[20] As recommended by
32 the manufacturer, we labeled assay results equal to or above the cut-off index value of 1.4 as positive
33 for SARS-CoV-2 specific IgG antibodies.
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38 **Statistical methods**

39 We report unweighted seroprevalence estimates in percentages. We used the Agresti-Coull procedure
40 to calculate a 95% confidence interval (CI) for seroprevalence estimates.[21] A weighted estimate of
41 seroprevalence is provided. To calculate survey weights (inverse of sampling probability), we used the
42 estimated population of the districts. We used the census 2011 data and growth rates from Sample
43 Registration System to estimate the population of the districts in 2020.[18,22] Survey weights obtained
44 were further adjusted for non-response and age and sex structure (post-stratification weights). We
45 further adjusted the weighted seroprevalence estimates for test performance to calculate “weighted
46 seroprevalence adjusted for test performance”. We did this using the formula:
47
48

49 *Weighted seroprevalence adjusted for test performance =*
50 *(Weighted seroprevalence + Test specificity – 1)/(Test sensitivity + Test specificity – 1).[23]*
51

52 We used the manufacturer-provided sensitivity and specificity in the above formula.[20] We used the
53 extremes of the manufacturer-provided 95% CI of the test sensitivity and specificity (upper limit of
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sensitivity, lower limit of specificity; and lower limit of sensitivity, upper limit of specificity) to report sensitivity analyses.

We analyzed the difference in seroprevalence estimates across levels of a categorical variable using a Chi-square test adjusted for the sampling design.

We estimated the number of SARS-CoV-2 infections by multiplying the weighted seroprevalence adjusted for test performance with the estimated population of the valley. To estimate the number of infections per reported case, we divided the estimated number of SARS-CoV-2 infections by the reported number of COVID-19 cases two weeks before the survey date. We calculated the infection fatality rate by dividing the reported number of deaths by the number of estimated infections, assuming a three-week lag time from infection to death.[24]

We analyzed the data using Stata version 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP.).

Patient and Public Involvement

No patients or members of the public were involved in this study.

RESULTS

We enumerated 6 397 individuals ≥ 18 years from 3 077 households and 110 clusters (34 urban clusters and 76 rural clusters) between 17 Oct 2020 and 04 Nov 2020. Of the 6 397 eligible individuals, 6 315 (98.7%) agreed to participate and were enrolled. The final analysis was done on a sample of 6 230 participants. (Figure 2)

Of the 6 230 participants, 1 513 (24.3%) were between 18 and 30 years of age, 2 672 (42.9%) were aged 30-49 years, 1 643 (26.4%) were aged 50-69 years, and 402 (6.4%) were 70 years and older. (Table 1). There was equal representation from males and females, and 3 364 (54.0%) resided in a rural area. Of the 3 104 females, 56 (1.8%) reported being pregnant at the time of the survey. Four hundred seventy-four (7.6%) reported COVID-19 like symptoms in the three months preceding the survey, and 439 (7.0%) reported to have ever come in contact with a known COVID-19 case. One thousand ninety-two (17.5%) reported having been tested for COVID-19 using RT-PCR or a Rapid Antigen Test (RAT) previously, of whom 176 (16.2%) reported to have tested positive for the disease.

Table 1: Characteristics of study participants

	Frequency	Percent
Total	6230	
Age, years		
18-29	1513	24.3
30-49	2672	42.9
50-69	1643	26.4
≥ 70	402	6.5
Gender		
Male	3126	50.2
Female	3104	49.8

Residence		
Urban	2866	46.0
Rural	3364	54.0
Pregnant (n=3104)	56	1.8
Self-reported history of chronic disease	1145	18.4
History of COVID-19 like symptoms	474	7.6
History of contact with a known COVID-19 case	439	7.0
Ever tested for COVID-19 (RT-PCR)	1092	17.5
RT-PCR result (n=1088*)		
Positive	176	16.2
Negative	912	83.8

COVID-19: Coronavirus disease; RT-PCR: Reverse transcriptase-polymerase chain reaction

*RT-PCR result not known in four participants

We found an overall unweighted seroprevalence of 38.8% (95% CI 37.6 – 40.0). The seroprevalence ranged from 28.5% in district Kulgam to 43.1% in district Pulwama. (Figure 1 and online supplemental file 1) The overall weighted seroprevalence (adjusted for sampling design) was 36.9% (95% CI 34.5 – 39.4). The weighted seroprevalence adjusted for test performance was 36.7% (95% CI 34.3 – 39.2). (Table 2) Upon sensitivity analyses, the weighted seroprevalence adjusted for test performance ranged from 36.3% (95% CI 33.9 – 38.8) to 38.4% (95% CI 35.9 – 41.0). (Table 3)

Table 2: Seroprevalence of SARS-CoV-2 specific IgG antibodies by participant characteristics

	Number tested	Number seropositive	Unweighted seroprevalence, % (95% CI)	Weighted seroprevalence, % (95% CI)	Weighted seroprevalence adjusted for test performance, % (95% CI)	Design-based F, p-value
Total	6230	2415	38.8 (37.6-40.0)	36.9 (34.5-39.4)	36.7 (34.3-39.2)	
Age, years						
18-29	1513	538	35.6 (33.2-38.0)	33.7 (30.1-37.6)	33.5 (29.8-37.4)	6.42, 0.0006
30-49	2672	1000	37.4 (35.6-39.3)	36.3 (33.5-39.3)	36.1 (33.3-39.1)	
50-69	1643	691	42.1 (39.7-44.5)	42.5 (38.8-46.2)	42.3 (38.6-46.0)	
≥70	402	186	46.3 (41.5-51.2)	45.3 (37.8-53.0)	45.1 (37.6-52.8)	
Gender						
Male	3126	1166	37.3 (35.6-39.0)	36.1 (33.5-38.9)	35.9 (33.3-38.7)	0.94, 0.34
Female	3104	1249	40.2 (38.5-42.0)	37.8 (34.5-41.3)	37.6 (34.3-41.1)	
Residence						
Urban	2866	1180	41.2 (39.4-43.0)	40.2 (36.3-44.1)	40.0 (36.1-43.9)	3.43, 0.07

Rural	3364	1235	36.7 (35.1-38.4)	35.5 (32.5-38.7)	35.3 (32.2-38.5)	
Self-reported history of chronic disease						
Yes	1145	495	43.2 (40.4-46.1)	41.9 (37.4-46.6)	41.7 (37.2-46.4)	6.14, 0.02
No	5085	1920	37.8 (36.4-39.1)	36.2 (33.7-38.9)	36.0 (33.5-38.7)	
History of COVID-19 like symptoms						
Yes	474	247	52.1 (47.6-56.6)	47.4 (37.9-57.1)	47.2 (37.7-56.9)	5.53, 0.02
No	5756	2168	37.7 (36.4-38.9)	36.3 (33.9-38.8)	36.1 (33.7-38.6)	
History of contact with a known COVID-19 case						
Yes	439	219	49.9 (45.2-54.5)	45.2 (38.3-52.2)	45.0 (38.1-52.0)	7.13, 0.01
No	5791	2196	37.9 (36.7-39.2)	36.5 (34.1-39.0)	36.3 (33.9-38.8)	
Ever tested for COVID-19 (RT-PCR)						
Yes	1092	485	44.4 (41.5-47.4)	41.0 (35.4-46.9)	40.8 (35.2-46.7)	2.17, 0.14
No	5138	1930	37.6 (36.2-38.9)	36.2 (33.5-39.0)	36.0 (33.3-38.8)	
RT-PCR result (n=1088*)						
Positive	176	140	79.5 (73.0-84.9)	81.8 (74.8-87.1)	81.7 (74.7-87.1)	74.93, <0.0001
Negative	912	345	37.8 (34.7-41.0)	38.8 (33.3-44.7)	38.6 (33.1-44.5)	

COVID-19: Coronavirus disease; RT-PCR: Reverse transcriptase-polymerase chain reaction

*RT-PCR result not known in four participants

Table 3: Sensitivity analyses for seroprevalence at extremes of test performance

	Weighted seroprevalence, % (95% CI)	Weighted seroprevalence adjusted for test performance, % (95% CI) [Sensitivity 100.00%, Specificity 99.63%]	Weighted seroprevalence adjusted for test performance, % (95% CI) [Sensitivity 95.89%, Specificity 99.90%]	Weighted seroprevalence adjusted for test performance, % (95% CI) [Sensitivity 100.00%, Specificity 99.05%]
Overall	36.9 (34.5-39.4)	36.7 (34.3-39.2)	38.4 (35.9-41.0)	36.3 (33.9-38.8)
Age, years				
18-29	33.7 (30.1-37.6)	33.5 (29.8-37.4)	35.1 (31.3-39.1)	33.1 (29.4-37.0)

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30-49	36.3 (33.5-39.3)	36.1 (33.3-39.1)	37.8 (34.9-40.9)	35.7 (32.9-38.7)
50-69	42.5 (38.8-46.2)	42.3 (38.6-46.0)	44.3 (40.4-48.1)	41.9 (38.2-45.7)
≥70	45.3 (41.8-48.8)	45.1 (41.6-48.6)	47.2 (43.5-50.9)	44.8 (41.3-48.3)
Gender				
Male	36.1 (33.5-38.9)	35.9 (33.3-38.7)	37.6 (34.9-40.5)	35.5 (32.9-38.3)
Female	37.8 (34.5-41.3)	37.6 (34.3-41.1)	39.4 (35.9-43.0)	37.2 (33.9-40.7)
Residence				
Urban	40.2 (36.3-44.1)	40.0 (36.1-43.9)	41.9 (37.8-45.9)	39.6 (35.7-43.6)
Rural	35.5 (32.5-38.7)	35.3 (32.2-38.5)	37.0 (33.8-40.3)	34.9 (31.9-38.1)
Self-reported history of chronic disease				
Yes	43.2 (40.4-46.1)	41.9 (37.4-46.6)	43.6 (38.9-48.5)	41.3 (36.8-46.1)
No	37.8 (36.4-39.1)	36.2 (33.7-38.9)	37.7 (35.1-40.5)	35.6 (33.1-38.3)
History of COVID-19 like symptoms				
Yes	52.1 (47.6-56.6)	47.4 (37.9-57.1)	49.4 (39.5-59.5)	46.9 (37.3-56.7)
No	37.7 (36.4-38.9)	36.3 (33.9-38.8)	37.8 (35.3-40.4)	35.7 (33.3-38.2)
History of contact with a known COVID-19 case				
Yes	49.9 (45.2-54.5)	45.2 (38.3-52.2)	47.1 (39.9-54.4)	44.7 (37.7-51.7)
No	37.9 (36.7-39.2)	36.5 (34.1-39.0)	38.0 (35.5-40.6)	35.9 (33.5-38.4)
Ever tested for COVID-19 (RT-PCR)				
Yes	44.4 (41.5-47.4)	41.0 (35.4-46.9)	42.7 (36.9-48.9)	40.4 (34.8-46.4)
No	37.6 (36.2-38.9)	36.2 (33.5-39.0)	37.7 (34.9-40.6)	35.6 (32.9-38.4)
RT-PCR result (n=1088*)				
Positive	79.5 (73.0-84.9)	81.8 (74.8-87.1)	85.3 (78.0-90.8)	81.6 (74.6-87.0)
Negative	37.8 (34.7-41.0)	38.8 (33.3-44.7)	40.4 (34.7-46.6)	38.2 (32.7-44.2)

Seroprevalence was lowest among participants aged 18-29 years [33.5% (95% CI 29.8 – 37.4)] and was higher in older age groups. Seroprevalence was highest in those aged 70 years and above [45.1% (95% CI 37.6 – 52.8)]. Seroprevalence was not significantly different among males and females ($p=0.34$). The seroprevalence among urban residents was 40.0% (95% CI 36.1 – 43.9), slightly but not significantly, higher than rural residents [35.3% (95% CI 32.2 – 38.5), $p=0.07$]. (Table 2)

One in five participants (1145/6230, 18.4%) self-reported history of at least one chronic disease (Table 1). Hypertension (815/6230, 13.1%) and diabetes mellitus (314/6230, 5.0%) were the most commonly reported chronic diseases (online supplemental file 2). Seroprevalence was significantly higher in participants who self-reported history of chronic disease (41.7%, 95% CI 37.2 – 46.4) as compared to those who did not report a history of chronic disease (36.0%, 95% CI 33.5 - 38.7) (Table 2).

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3 Among participants who reported a history of COVID-19 like symptoms, seroprevalence was 47.2% (95%
4 CI 37.7 – 56.9) compared with 36.1% (95% CI 33.7 – 38.6) among participants who did not report such
5 symptoms. Seroprevalence was higher among those who reported contact with a known COVID-19 case
6 [45.0% (95% CI 38.1 – 52.0)] than participants who did not report any history of such contact [36.3%
7 (95% CI 33.9 – 38.8)]. (Table 2)
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10 Seroprevalence was not significantly related to being tested for COVID-19 (RT-PCR). However, those who
11 reported a positive RT-PCR COVID-19 test had significantly higher seroprevalence (81.7%, 95% CI 74.7 –
12 87.1) as compared to those who reported a negative RT-PCR COVID-19 test (38.6%, 95% CI 33.1 – 44.5).
13 (Table 2)
14

15 Among 2 415 seropositive individuals, only 247 (10.2%) reported a history of COVID-19 like symptoms.
16 Only 20.1% (485/2415) of the seropositive individuals were tested for COVID-19 (RT-PCR). Among 474
17 who reported a history of COVID-19 like symptoms, 233 (49.2%) were tested for COVID-19 (RT-PCR).
18 Among 4897 individuals who did not report a history of COVID-19 like symptoms and were never tested
19 for COVID-19 (RT-PCR), 1825 (37.3%) were seropositive. (Figure 3)
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22 Among 36 participants who reported a positive RT-PCR COVID-19 test but were seronegative, the
23 duration between COVID-19 RT-PCR test and serological testing ranged from 9 days to 101 days. In only
24 four of these 36 participants, the duration between the COVID-19 RT-PCR test and the serological test
25 was 14 days or less. Of the remaining 32 participants, 21 did not report a history of COVID-19 like
26 symptoms, nine did not report a history of contact with a known COVID-19 case, and eight reported
27 neither a history of COVID-19 like symptoms nor a history of contact with a known COVID-19 case.
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30 We estimated that there were 1 673 484 (95% CI 1 564 047 – 1 787 482) cumulative number of
31 infections among adults aged ≥ 18 years in the valley by 03 Oct 2020, two weeks before the start of the
32 survey. If we assume that the seroprevalence was similar to the overall seroprevalence in the population
33 not included in our study (< 18 years of age) then the estimated cumulative number of infections in the
34 valley by 03 Oct 2020 was 2 791 933 (95% CI 2 609 354 – 2 982 119). Considering that the cumulative
35 number of reported COVID-19 cases was 47 071 by 03 Oct 2020 (Figure 4), we estimate the number of
36 infections per reported case as 59.3 (95% CI 55.4 – 63.4). The number of reported COVID-19 deaths after
37 a three-week lag period (on 24 Oct 2020) was 955. Thus, we estimated the infection fatality rate as
38 0.034% (95% CI 0.032 – 0.037). Of the total estimated SARS-CoV-2 infected persons, only 1.69% (47
39 071/2 791 933) were reported. Of the total reported COVID-19 cases, 2.03% (955/47 071) died.
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43 DISCUSSION

44 We report the results of a seroprevalence survey conducted in Kashmir from October-November 2020,
45 seven months after the appearance of the first local COVID-19 case. The COVID-19 pandemic is rapidly
46 evolving worldwide. In Kashmir, several important events happened since we completed our survey.
47 From 16 Jan 2021, COVID-19 vaccination was introduced in a phased manner. Healthcare workers were
48 given preference during the first phase. From 01 Mar 2021, the vaccine was made available for people
49 ≥ 60 years of age and those with chronic diseases in the age group of 45-59 years. However, especially
50 during the early phases of the COVID-19 vaccination campaign, many people were hesitant to receive
51 the vaccine doses. During the same time, SARS-CoV-2 Variants of Concern began to emerge and
52 circulate. The daily number of COVID-19 cases started to rise again. The 'second wave' in April 2021 was
53 more explosive than the 'first wave' at the beginning of the pandemic. The fear of the disease had
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3 diminished, and COVID appropriate behaviour was no more a norm. The government and the people
4 were caught unawares. There were several reports of a possible 'second infection' and reports of cases
5 among previously vaccinated individuals. Given these developments, the current seroprevalence in
6 Kashmir will be higher than what we report in this study.
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9 The results of our study indicate that by the first week of October 2020, nearly seven months after the
10 appearance of the first laboratory-confirmed COVID-19 case on 18 March 2020, close to 37% of the
11 valley's population aged ≥ 18 years had been infected. Our results suggest that the cumulative number of
12 SARS-CoV-2 infections by the first week of October 2020 was nearly 2.8 million, with an estimated
13 infection fatality rate of 0.034%. Seroprevalence did not differ by gender but was higher in older age
14 groups.
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17 The findings of our study are based on a representative sample of the population. The laboratory test
18 used for the detection of SARS-CoV-2 specific IgG antibodies in serum samples provides valid
19 results.[20,25] We report seroprevalence estimates adjusted for sampling design and test performance.
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22 The overall adjusted seroprevalence of around 37% indicates that, by October 2020, a large proportion
23 of the valley's population had been infected with the virus. Easing of lockdown, being fed up with the
24 restrictions, and non-adherence to prevention norms are the possible reasons. Using several
25 assumptions about the test sensitivity and specificity to calculate adjusted seroprevalence estimates
26 yielded small differences.
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29 Several factors potentially influence the seroprevalence rates. These include population density, social
30 and demographic structure of the population, governmental policies and the extent of their
31 implementation, immunity level of the population, time since the start of infection transmission,
32 adherence to infection prevention guidelines, quality of contact tracing and quarantine, and possibly the
33 geography and environment of an area. The emergence of several Variants of Concern and the
34 introduction of COVID-19 vaccination will also influence population immunity. Herd immunity in the
35 context of COVID-19 is a matter of debate as reports of a second infection continue to pour in.[26]
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38 Comparison with previous reports suggests that, by October 2020, the seroprevalence had increased
39 almost ten-fold since July 2020.[16,27] The second of the three nationwide seroprevalence surveys in
40 India conducted in August-September 2020 reports an overall seroprevalence of 6.6%, ranging from
41 5.2% in rural areas to 16.9% in urban slums.[28] A nationwide survey conducted in December 2020-
42 January 2021 reported an overall seroprevalence of 24.1% ranging from 4.9% - 44.4% across
43 districts.[29] Kashmir is thus not a low-infection area. Being an oft-visited tourist area, Kashmir is at an
44 increased risk of infection transmission. Adherence to COVID appropriate behavior (use of face masks in
45 public, frequent handwashing, physical and social distancing) has been poor. The experience of a
46 'second wave' of COVID-19 in April-June 2021, the appearance of virus variants, and the introduction of
47 vaccination programs warrant robust surveillance of the epidemic.
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50 The seroprevalence of SARS-CoV-2 IgG antibodies was higher in older age groups. During the early
51 period of the pandemic, people were adherent to social distancing and other non-pharmaceutical
52 interventions because of a fear of the disease and administrative restrictions. With time, administrative
53 restrictions were relaxed, fear of the disease attenuated, and people became fed up with the social
54 restrictions. This led to an increase in the number of reported COVID-19 cases and provided the
55 population, including older age groups, an opportunity to contract the infection. That older people have
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3 an increased risk of symptomatic and more severe disease is now well known.[30,31] However, age-
4 based differential susceptibility to SARS-CoV-2 infection antibody response and the reasons thereof are
5 still a grey area and need further understanding. Existing literature might suggest that the more mobile
6 and socially active young have a higher risk of infection.[6,7] However, this should not imply that the
7 elderly have a decreased susceptibility to SARS-CoV-2 infection or a decreased antibody response.[32]
8 On the contrary, several studies suggest that the seroprevalence of SARS-CoV-2 specific IgG antibodies is
9 higher in the older age groups and particularly so in more dense population groups.[4,5,8–11,13]
10 Furthermore, SARS-CoV-2 antibody levels have been reported to be higher in older people.[12]
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13 The seroprevalence of SARS-CoV-2 specific IgG antibodies did not differ significantly by gender, though
14 the figure was slightly higher for females. These findings are consistent with the available
15 literature.[6,13] Difference in seroprevalence by gender has been suggested by some studies, and
16 females have been reported to have lower antibody levels.[5,7,9,11,12,14,33]
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19 Urban areas are more densely populated than rural areas, accelerating the transmission of infections in
20 the population. The seroprevalence of SARS-CoV-2 specific IgG antibodies is thus expected to be higher
21 in urban areas, especially during the early phases of an epidemic. However, as the epidemic progresses,
22 the seroprevalence gap between urban and rural areas will wane off. We estimated an adjusted
23 seroprevalence of 40.0% (95% CI 36.1 – 43.9) in urban areas as compared to 35.3% (95% CI 32.2 – 38.5)
24 in rural areas ($p=0.07$).
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26
27 People with a chronic disease experience more severe COVID-19 symptoms and are more likely to die
28 when compared to people with no chronic disease.[34] We found a higher proportion of symptomatic
29 infection among participants with a self-reported history of chronic disease (78/1145, 6.8%) as
30 compared to participants with no chronic disease (169/5085, 3.3%) (online supplemental file 3). Little is,
31 however, known about the risk of infection in chronic disease patients. We found a significantly higher
32 seroprevalence among participants with a self-reported history of chronic disease (Table 2). This finding
33 needs further research for corroboration and possible explanations.
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36 People with a self-reported history of COVID-19 related symptoms, contact with a known COVID-19
37 case, or a positive COVID-19 RT-PCR had a higher seroprevalence as compared to their complement.
38 Among seropositive individuals, only 10.2% reported being symptomatic. The percentage of
39 asymptomatic infections, thus, was 90%. However, only 49% of individuals with a history of COVID-19
40 like symptoms were tested using RT-PCR. We also estimated that only one out of almost 59 infections
41 gets reported. This reflects the necessity of improving the efficiency of RT-PCR testing so that more
42 symptomatic individuals receive the test. Not all individuals with a known RT-PCR positive result showed
43 the presence of IgG antibodies. Around 20% of RT-PCR positive individuals were seronegative, and in a
44 large majority of them (32 out of 36), the duration since RT-PCR positivity was more than two weeks.
45 This may be attributed to a poor B cell response or a false negative antibody test.[35] Around 38% of RT-
46 PCR negative individuals were seropositive, suggesting a false-negative RT-PCR or infection acquisition at
47 a date later than the RT-PCR test.
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51 We estimated an infection fatality rate of 0.034% (95% CI 0.032 – 0.037). The infection fatality rate in
52 SARS-CoV-2 infection has been reported to range from as low as 0.00% to 1.63%.[36] Our estimates of
53 the infection fatality rate are low as compared to estimates from several Indian studies.[5,28,37] Under-
54 reporting COVID-19 deaths because of the non-uniform definition for a 'COVID-19 death' may falsely
55 lower the infection fatality rates.[38] Many other factors can influence the infection fatality rate in SARS-
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CoV-2 infection – the quality of available health facilities, the age structure of the population, and COVID-19 epidemic intensity.[39,40] Developing countries usually have a younger population as compared to the developed countries, and Kashmir is not an exception. However, because of the possibility of under-reporting of COVID-19 deaths, the true infection fatality rate in Kashmir may be higher than our estimates. The infection fatality rate is, however, known to be lower in developing nations.[30,41] In developed nations like the United States and many European countries, a higher infection fatality rate has been reported.[30,42]

Limitations

One important limitation of our study is that even though we adjusted the weighted seroprevalence estimates for test performance using manufacturer-provided sensitivity and specificity (100% and 99-63% respectively), we did not quantify the test validity in-house. Another limitation of our study estimates is that we excluded people <18 years of age. The results of our study may not thus be generalizable to this group of the population.

Our estimated seroprevalence was much higher than we anticipated at the designing stage. This has impacted the precision of our estimates to some extent. However, we believe we still have been able to estimate the seroprevalence with reasonable precision.

Lack of reliable death counts is another potential limitation. This may have led to an underestimation of the infection fatality rate. We did not perform any adjustment for death counts. Further, because of lack of age- and gender-specific mortality data, we could not estimate age- and gender-specific infection fatality rates.

CONCLUSIONS

We conclude that nearly 37% of individuals aged 18 years and above were infected with SARS-CoV-2 in Kashmir by October 2020. The infection fatality rate in the valley is around 0.034%. A majority of cases go unreported. For every reported case, there are 59 unreported infections in the population. Since almost half of the symptomatic individuals go unreported, testing of symptomatic individuals and effective contact tracing needs to continue. Given the emergence of mutant Variants of Concern, increasing the population immunity through augmented and sustained vaccination is necessary. We further recommend that adherence to COVID-19 prevention measures should be ensured until a large proportion of the population gets vaccinated.

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11 **COMPETING INTERESTS**

12
13 We declare no competing interests, financial or otherwise.

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15
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18 **CONTRIBUTORS**

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20 S Muhammad Salim Khan: Conceptualization, Funding acquisition, Methodology, Writing-review &
21 editing.

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35
36 S Muhammad Salim Khan, Mariya Amin Qurieshi, Inaamul Haq, and Sabhiya Majid have verified the
37 underlying data.

38 **DATA SHARING**

39
40 Anonymized data collected for the study, including individual participant data and a data dictionary
41 defining each field in the set, will be made available to interested researchers on request by Inaamul
42 Haq (haqinaam@yahoo.co.in) for two years from publication. The study protocol, statistical analysis
43 plan, and informed consent forms are also available from Inaamul Haq.

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46 **Figure 1 legend:**

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48 Figure 1: Location of the ten districts and seroprevalence (%) by district. Figures in parentheses indicate
49 a 95% Confidence Interval for seroprevalence.
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51 **Figure 2 legend:**

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53 Figure 2: Participant flow.
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55 **Figure 3 legend:**

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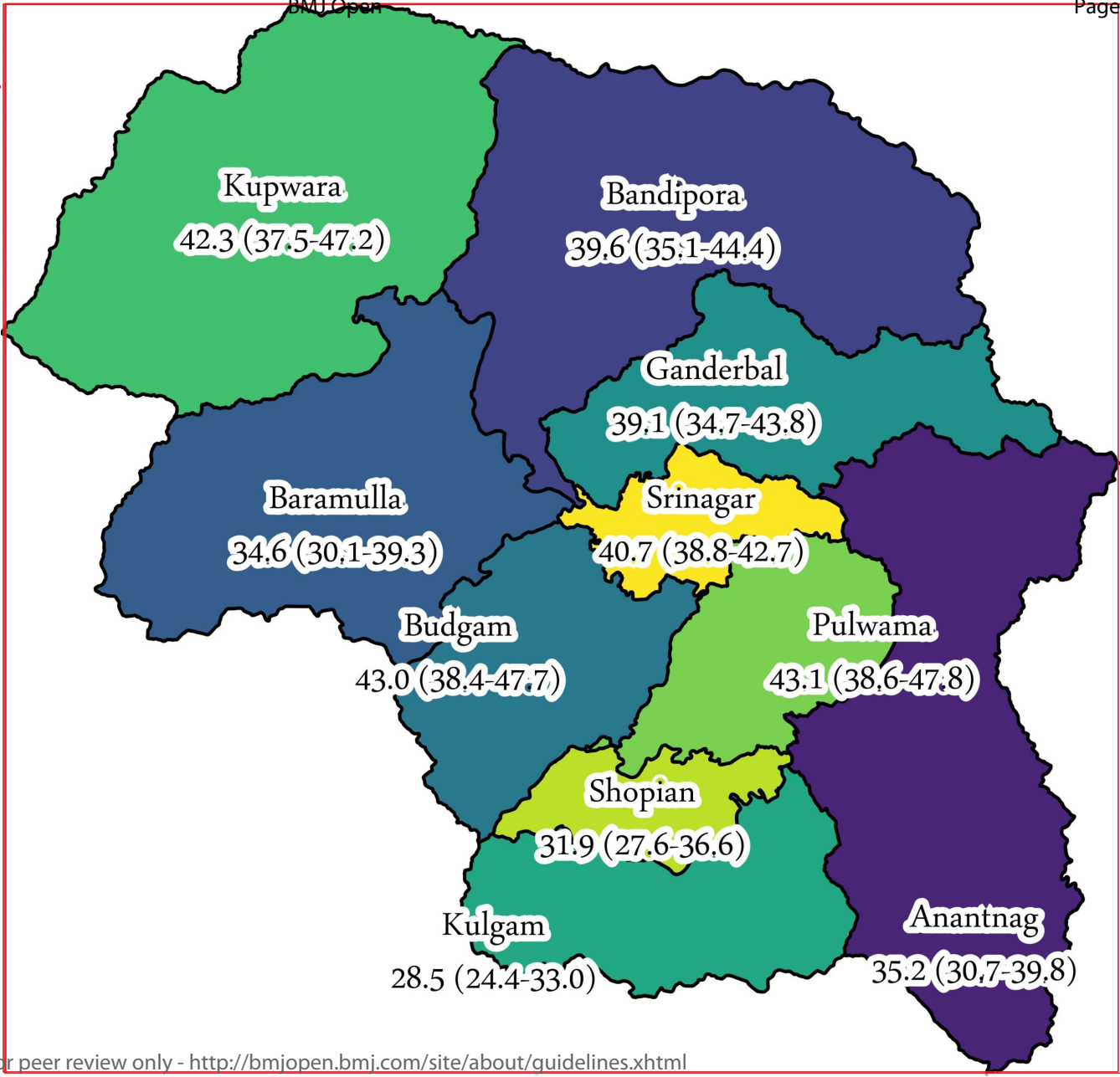
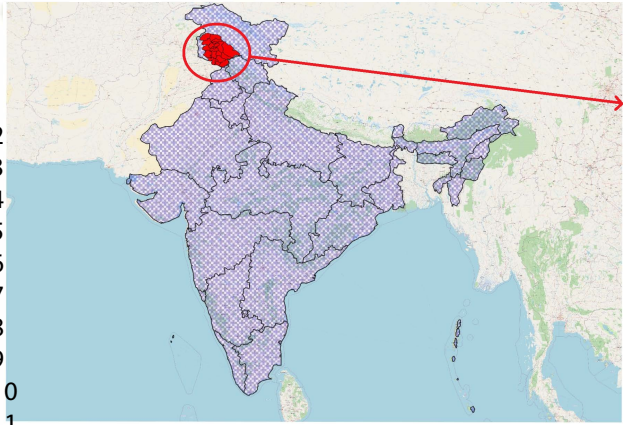
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3 Figure 3: A. Seropositivity by the history of COVID-19 like symptoms, RT-PCR testing, and test result. B.
4 History of COVID-19 like symptoms by seropositivity, RT-PCR testing, and test result.
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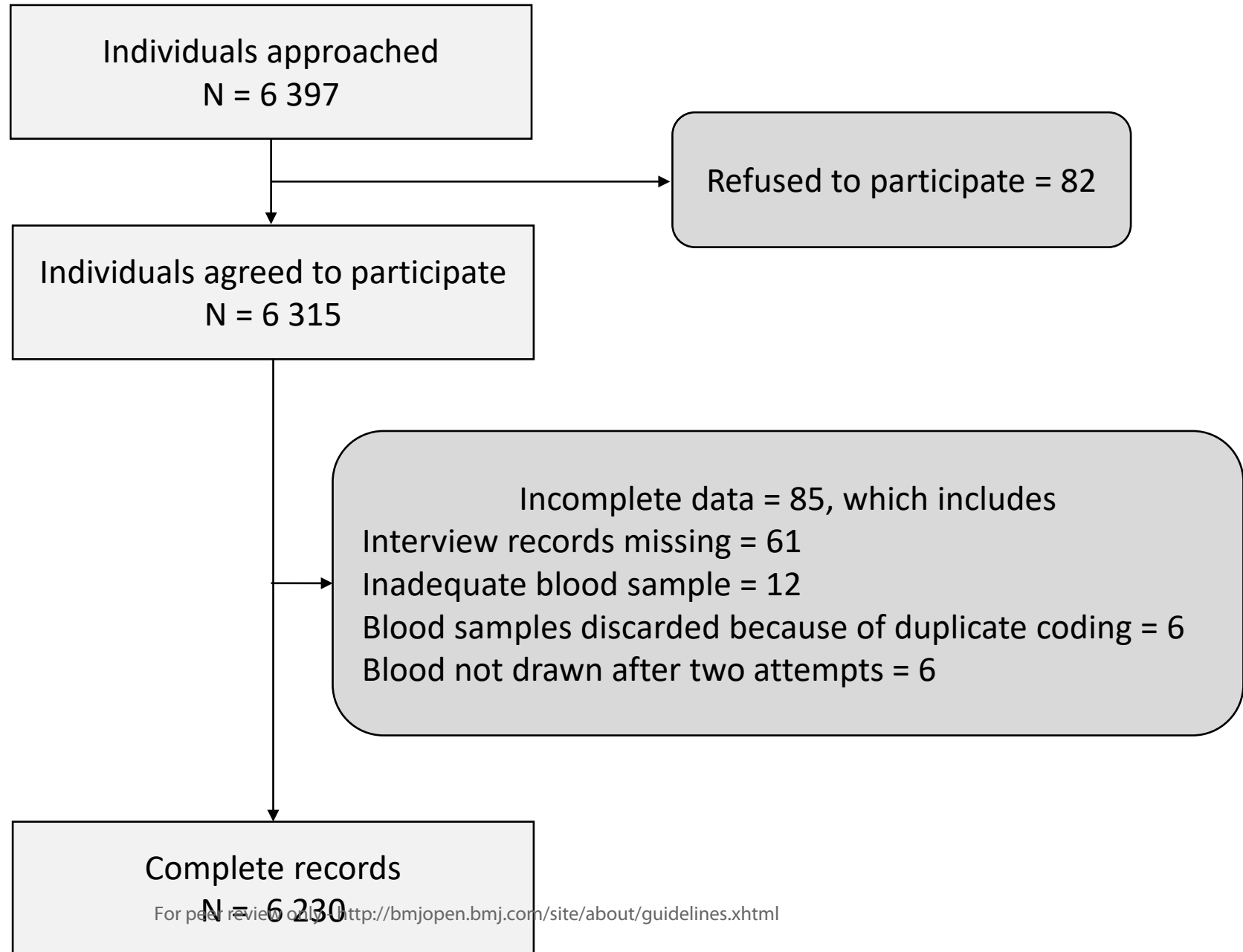
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8 Figure 4: A. Daily cases and deaths in Kashmir since the start of the COVID-19 pandemic; B. Cumulative
9 number of cases and deaths in Kashmir.
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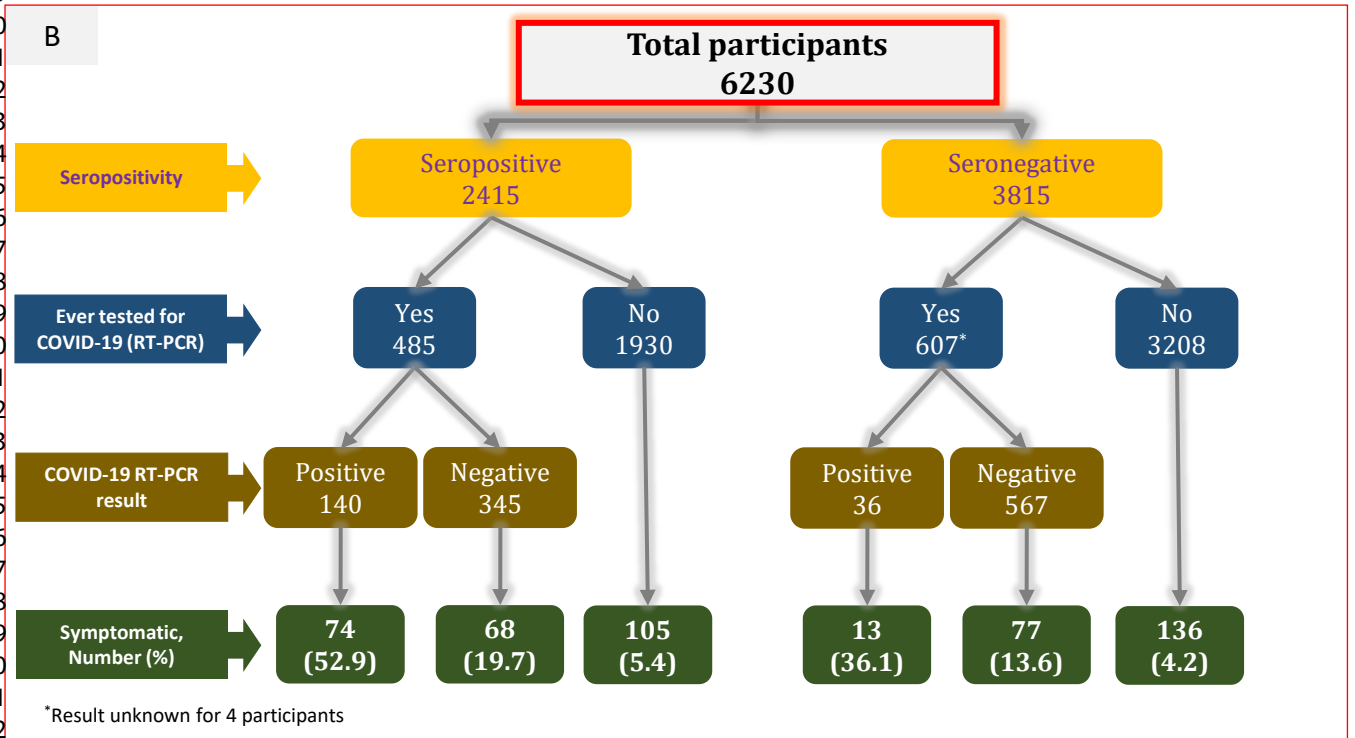
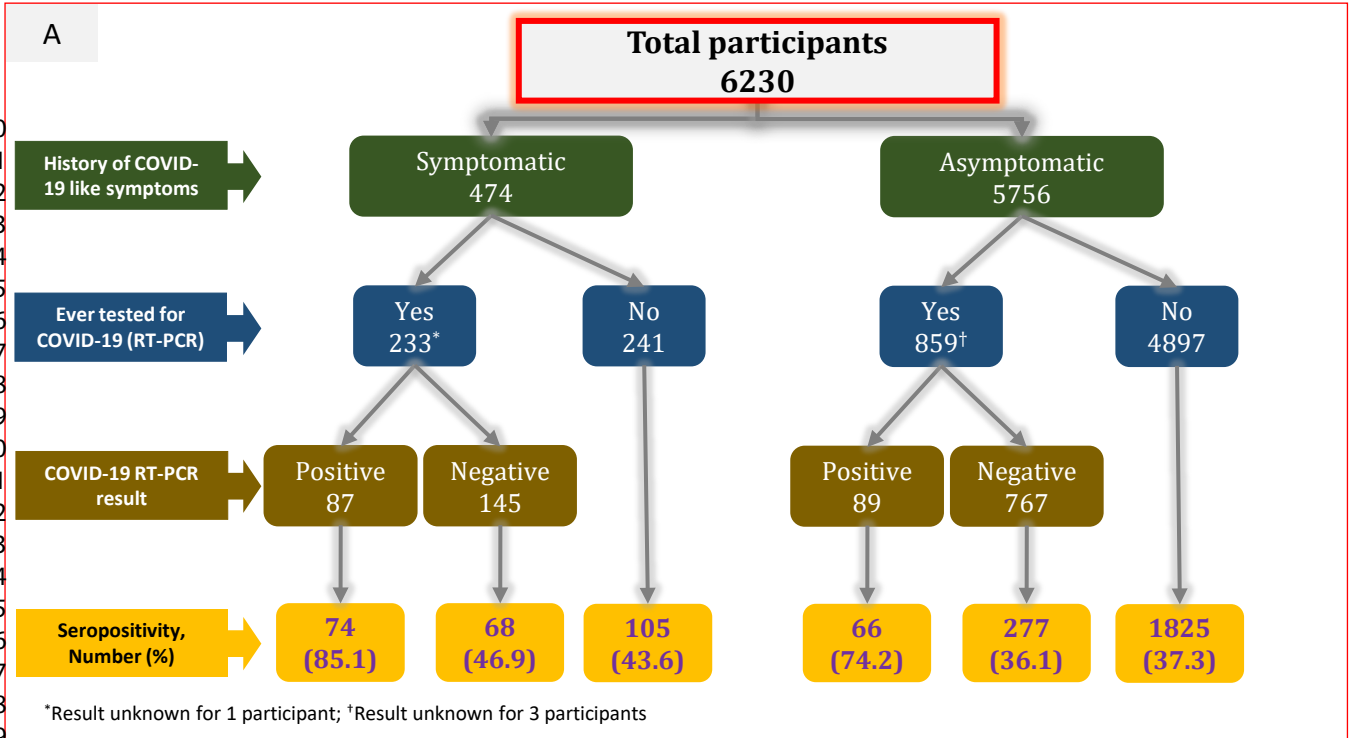
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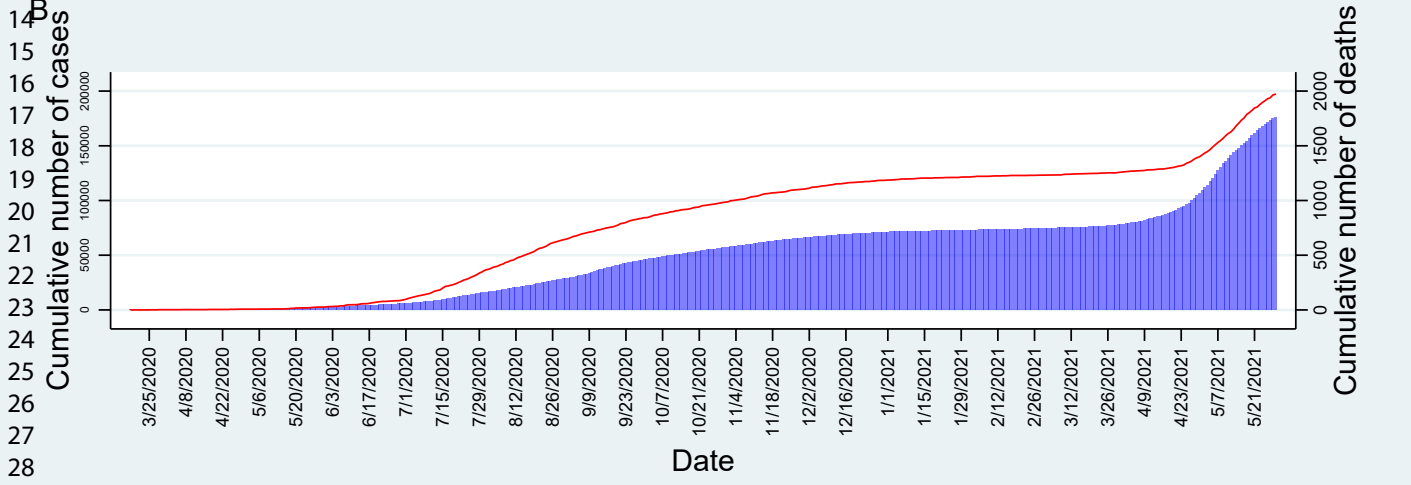
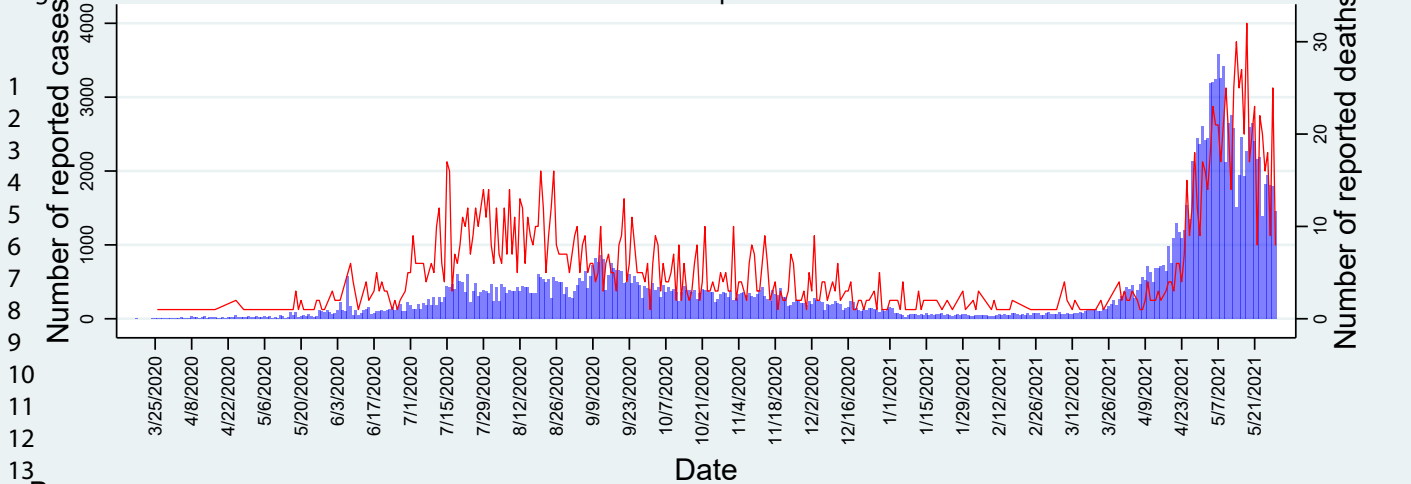


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Supplemental Table 1: Participant characteristics by district

District	Total	Age (years)				Gender		Residence	
		<30	30-49	50-69	70+	Female	Male	Rural	Urban
Anantnag	421	84	197	113	27	214	207	295	126
Budgam	442	113	190	105	34	263	179	354	88
Bandipora	424	106	174	114	30	227	197	341	83
Baramulla	405	113	176	98	18	214	191	325	80
Ganderbal	442	92	210	123	17	233	209	346	96
Kulgam	428	102	194	113	19	257	171	346	82
Kupwara	400	81	171	105	43	215	185	360	40
Pulwama	443	102	176	126	39	218	225	396	47
Shopiyan	407	119	152	90	46	211	196	368	39
Srinagar	2418	601	1032	656	129	1052	1366	233	2185
Total	6230	1513	2672	1643	402	3104	3126	3364	2866

Supplemental Table 2: Seroprevalence (unadjusted) by district and participant characteristics

District	Overall	Age (years)				Gender		Residence	
		<30	30-49	50-69	70+	Male	Female	Urban	Rural
Anantnag	35.2 (30.7-39.8)	29.8 (21-40.4)	34.5 (28.2-41.4)	38.9 (30.4-48.2)	40.7 (24.2-59.7)	36.2 (30-43)	34.1 (28.1-40.7)	42.9 (34.5-51.6)	31.9 (26.8-37.4)
Budgam	43 (38.4-47.7)	44.2 (35.4-53.5)	37.9 (31.3-45)	48.6 (39.2-58.1)	50 (33.8-66.2)	41.9 (34.9-49.3)	43.7 (37.8-49.8)	38.6 (29.1-49.2)	44.1 (39-49.3)
Bandipora	39.6 (35.1-44.4)	37.7 (29-47.3)	42 (34.8-49.4)	40.4 (31.8-49.6)	30 (16.4-48.3)	37.6 (31.1-44.5)	41.4 (35.2-47.9)	55.4 (44.6-65.7)	35.8 (30.9-41)
Baramulla	34.6 (30.1-39.3)	27.4 (20-36.4)	32.4 (25.9-39.6)	44.9 (35.4-54.8)	44.4 (24-67)	39.3 (32.6-46.4)	30.4 (24.6-36.9)	36.3 (26.5-47.3)	34.2 (29.2-39.5)
Ganderbal	39.1 (34.7-43.8)	34.8 (25.8-45)	40.5 (34-47.3)	39.8 (31.6-48.7)	41.2 (21-64.8)	39.2 (32.8-46)	39.1 (33-45.5)	42.7 (33.2-52.8)	38.2 (33.2-43.4)
Kulgam	28.5 (24.4-33)	27.5 (19.7-36.9)	26.8 (21-33.5)	31 (23.1-40.1)	36.8 (18.7-59.7)	25.1 (19.2-32.2)	30.7 (25.4-36.6)	37.8 (28-48.7)	26.3 (21.9-31.2)
Kupwara	42.3 (37.5-47.2)	33.3 (24-44.2)	39.8 (32.7-47.3)	50.5 (41-59.9)	48.8 (34.4-63.4)	41.6 (34.7-48.9)	42.8 (36.3-49.5)	50 (35-65)	41.4 (36.4-46.6)
Pulwama	43.1 (38.6-47.8)	35.3 (26.7-45)	42.6 (35.5-50)	45.2 (36.8-54)	59 (43.2-73.1)	39.6 (33.4-46.1)	46.8 (40.3-53.4)	40.4 (27.5-54.9)	43.4 (38.6-48.4)
Shopiyan	31.9 (27.6-36.6)	28.6 (21.2-37.3)	29.6 (22.9-37.3)	41.1 (31.4-51.5)	30.4 (18.9-45.1)	31.1 (25-37.9)	32.7 (26.7-39.3)	38.5 (24.7-54.4)	31.3 (26.7-36.2)
Srinagar	40.7 (38.8-42.7)	39.1 (35.3-43.1)	39.2 (36.3-42.3)	41.9 (38.2-45.7)	53.5 (44.9-61.9)	37.7 (35.2-40.3)	44.6 (41.6-47.6)	40.8 (38.7-42.9)	39.9 (33.8-46.3)

Chronic disease and SARS-CoV-2 infection in the study population

Of the 6230 participants, 1145 reported a history of at least one chronic disease. Two hundred ninety-eight reported a history of more than one chronic disease.

Supplementary Table 3: Chronic disease in the study population

Chronic disease (n = 1145)	Number (%)
Hypertension	815 (13.1%)
Diabetes	314 (5.0%)
Chronic Obstructive Pulmonary Disease	39 (0.6%)
Coronary Heart Disease	35 (0.6%)
Cerebrovascular Disease	16 (0.3%)
Asthma	15 (0.2%)
Chronic Kidney Disease	10 (0.2%)
Chronic Liver Disease	5 (0.1%)
Cancer	4 (0.1%)

Supplementary Table 4: History of COVID-19 like symptoms and seropositivity vis-à-vis history of chronic disease

		History of COVID-19 like symptoms	
		Yes	No
Reported history of chronic disease (n=1145)	Seropositive	78	417
	Seronegative	63	587
Did not report any history of chronic disease (n=5085)	Seropositive	169	1751
	Seronegative	164	3001

Of the 1154 participants who reported a history of chronic disease 78 (6.8%) reported a history of COVID-19 like symptoms within three months of the interview date and were seropositive for SARS-CoV-2 specific IgG (symptomatic infection). The proportion of symptomatic infection among participants who did not report any history of chronic disease was 3.3% (169/5085).

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1, 3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3 and Figure 1
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	3, 4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4, 5
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	4, 5
		(b) Describe any methods used to examine subgroups and interactions	5
		(c) Explain how missing data were addressed	5
		(d) If applicable, describe analytical methods taking account of sampling strategy	4, 5
		(e) Describe any sensitivity analyses	6, Table 3
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 2, and page 5
		(b) Give reasons for non-participation at each stage	Figure 2
		(c) Consider use of a flow diagram	Figure 2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1, Figure 2
Outcome data	15*	Report numbers of outcome events or summary measures	Table 2

1			
2	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted
3			estimates and their precision (eg, 95% confidence interval). Make
4			clear which confounders were adjusted for and why they were
5			included
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7			(b) Report category boundaries when continuous variables were
8			categorized
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10			(c) If relevant, consider translating estimates of relative risk into
11			absolute risk for a meaningful time period
12	Other analyses	17	Report other analyses done—eg analyses of subgroups and
13			interactions, and sensitivity analyses
14			
15	Discussion		
16	Key results	18	Summarise key results with reference to study objectives
17			
18	Limitations	19	Discuss limitations of the study, taking into account sources of
19			potential bias or imprecision. Discuss both direction and magnitude
20			of any potential bias
21	Interpretation	20	Give a cautious overall interpretation of results considering
22			objectives, limitations, multiplicity of analyses, results from similar
23			studies, and other relevant evidence
24			
25	Generalisability	21	Discuss the generalisability (external validity) of the study results
26			
27	Other information		
28	Funding	22	Give the source of funding and the role of the funders for the present
29			study and, if applicable, for the original study on which the present
30			article is based
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33 *Give information separately for exposed and unexposed groups.

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