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Epidemiology and transmission dynamics of COVID-19 in two Indian states

Ramanan Laxminarayan^{1,2,3}, Brian Wahl^{3,4}, Shankar Reddy Dudala⁵, K. Gopal⁶, Chandra Mohan⁷, S. Neelima⁸, K. S. Jawahar Reddy⁹, J. Radhakrishnan¹⁰, Joseph A. Lewnard^{11,12*}

¹Center for Disease Dynamics, Economics and Policy, New Delhi, India. ²Princeton Environmental Institute, Princeton University, Princeton, NJ, USA. ³Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA. ⁴International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA. ⁵Department of Community Medicine, Government Medical College, Kadapa, Andhra Pradesh, India. ⁶Animal Husbandry, Dairying and Fisheries Department, Government of Tamil Nadu, Chennai, Tamil Nadu, India. ⁷Backward Classes, Most Backward Classes, and Minorities Welfare Department, Government of Tamil Nadu, Chennai, Tamil Nadu, India. ⁸Department of Community Medicine, Guntur Medical College, Guntur, Andhra Pradesh, India. ⁹Department of Health, Family Welfare, and Medical Education, Government of Andhra Pradesh, Amaravati, Andhra Pradesh, India. ¹⁰Health and Family Welfare Department, Government of Tamil Nadu, Chennai, Tamil Nadu, India. ¹¹Division of Epidemiology, School of Public Health, University of California, Berkeley, CA, USA. ¹²Center for Computational Biology, College of Engineering, University of California, Berkeley, CA, USA.

*Corresponding author. Email: jlewnard@berkeley.edu

Although most COVID-19 cases have occurred in low-resource countries, little is known about the epidemiology of the disease in such contexts. Data from the Indian states of Tamil Nadu and Andhra Pradesh provide a detailed view into SARS-CoV-2 transmission pathways and mortality in a high-incidence setting. Reported cases and deaths have been concentrated in younger cohorts than expected from observations in higher-income countries, even after accounting for demographic differences across settings. Among 575,071 individuals exposed to 84,965 confirmed cases, infection probabilities ranged from 4.7–10.7% for low-risk and high-risk contact types. Same-age contacts were associated with the greatest infection risk. Case-fatality ratios spanned 0.05% at ages 5–17 years to 16.6% at ages ≥ 85 years. Primary data are urgently needed from low-resource countries to guide control measures.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), has spread rapidly around the world since emerging in Wuhan, China in late 2019 (1). Current understanding of COVID-19 comes largely from disease surveillance and epidemiologic studies undertaken in early phases of the pandemic in China (1–3) and high-income countries of Europe (4, 5) and North America (6–8). However, most confirmed cases of COVID-19 have now occurred in low- and middle-income countries (LMICs), where a substantial proportion of individuals may be at increased risk of severe outcomes and face barriers to accessing quality health services (9–11). While multiple modeling studies have sought to assess how COVID-19 might affect individuals and communities in such settings (12–14), almost no primary studies of the transmission dynamics and clinical outcomes of COVID-19 in LMICs are available to validate these models and inform intervention strategies (15).

Over 1.3 billion people are at risk of SARS-CoV-2 infection in India, where concerns over COVID-19 have prompted large-scale containment strategies at the national, state, and local levels (16). The country's first known COVID-19 case, documented on 30 January 2020, was an Indian national

evacuated from China (17). Andhra Pradesh and Tamil Nadu are two states in the south of India whose 127.8 million residents collectively account for approximately 10% of the country's total population. Although they are not the wealthiest states in India, Andhra Pradesh and Tamil Nadu are among the states with the largest healthcare workforces and public health expenditures per capita, and are known for their effective primary healthcare delivery models (18–20). Both states initiated rigorous disease surveillance and contact tracing early in response to the pandemic. Procedures include syndromic surveillance and SARS-CoV-2 testing for all individuals seeking care for severe acute respiratory illness or influenza-like illness at healthcare facilities; delineation of 5km “containment zones” surrounding cases for daily house-to-house surveillance to identify individuals with symptoms; and daily follow-up of all contacts of laboratory-confirmed or suspect COVID-19 cases, with the aim of testing these individuals 5–14 days after their contact with a primary case, irrespective of symptoms, to identify onward transmission (21, 22). We analyzed comprehensive surveillance and contact tracing data from these programs aiming to understand transmission dynamics and clinical outcomes of COVID-19 in South India, and to pro-

vide insights into control of SARS-CoV-2 in similar LMIC settings.

Expansion of SARS-CoV-2

In India, surveillance of COVID-19 was initiated with airport screening for severe acute respiratory infection, especially for travelers from China. Tamil Nadu further instituted thermal and clinical screening at land borders with other states on 4 March 2020. Nationwide, testing was initially prioritized for symptomatic individuals with history of travel or contact with a confirmed COVID-19 case within the previous 14 days, and was expanded to include all symptomatic individuals and asymptomatic contacts of confirmed cases in states between 20–28 March 2020. We detail the timeline of changes in surveillance practices at federal and state levels in the materials and methods.

Tamil Nadu and Andhra Pradesh each recorded their first laboratory-confirmed COVID-19 cases on 5 March. Under-ascertainment of cases during March and early April was likely due to limited testing availability and testing algorithms; the proportion of tests yielding positive results peaked at 39.7% in Tamil Nadu and 33.5% in Andhra Pradesh on 30 and 31 March 2020, respectively, when the daily number of tests performed was low in the two states (range: 379–469 tests; Fig. 1). Throughout early April, increases in the number of tests performed daily coincided with a reduction in the proportion of tests yielding positive results. Our analyses include data collected through 1 August, at which time Tamil Nadu and Andhra Pradesh had identified 263,330 and 172,209 cases, respectively (table S1). (As testing and contact tracing constitute routine public health activities, data collection was not governed by an institutional review board.)

The earliest clusters of locally acquired cases emerged in March in Chennai and surrounding coastal districts of eastern Tamil Nadu. Of all districts, Chennai ultimately experienced the highest cumulative incidence of COVID-19, totaling 102,199 cases (204.6 per 10,000 population) by 1 August, 2020. An outbreak beginning 28 April caused 1,142 cases by 15 May in the adjoining districts of Ariyalur, Cuddalore, Perambalur, and Villuppuram in Tamil Nadu; thereafter, few cases were identified in these districts until early June (fig. S1). Though limited in March and April, incidence in southern districts of Tamil Nadu surrounding Madurai increased during June and reached rates commensurate with incidence in the northern districts of Chennai, Kancheepuram, and Tiruvallur by 1 August, with 1–4 new positive detections per 10,000 population daily. Similar increases in incidence occurred throughout all districts of Andhra Pradesh in June, where the numerical and geographic extent of cases remained limited during April and May despite similar levels of testing in comparison to Tamil Nadu.

Statewide estimates of the time-varying reproduction number R_t , describing the number of secondary infections each infected individual would be expected to generate (23), declined from a range of 1.7–3.0 in Tamil Nadu and 1.4–4.3 in Andhra Pradesh over the period of 10–23 March to a range of 1.0–1.3 in both states by the third week of the initial country-wide lockdown (fig. S3). Expansions in testing over this same period, however, are likely to bias analyses of changes in R_t over time (24). Estimates of R_t held in the range 1.1–1.4 from 15 May onward within both states, although incidence trajectories differed over time by district (fig. S1), likely reflecting changes in both the uptake and enforcement of social distancing interventions as well as the effectiveness of contact tracing efforts.

Contact tracing

Contact tracing efforts in the states reached 3,084,885 known exposed contacts of confirmed cases by 1 August, 2020 (table S2); individual-level epidemiological data on cases and contacts, as well as laboratory test results, were available from 575,071 tested contacts of 84,965 confirmed case. Traced contacts tended to be younger and were more often female than their linked index cases (table S3). Additionally, test-positive individuals identified through contact tracing were, on average, 1.3 years (bootstrap 95% confidence interval: 1.1–1.5 years) younger and 4.5% (3.7–5.4%) less likely to be male than the overall population of COVID-19 cases in the two states (table S4). As studies in other settings have shown the risk of symptomatic disease to be higher among older age groups and among males (25), these findings may indicate the identification of less-severe infections through active case-finding.

The mean number of contacts tested per index case was 7.3 (interquartile range: 2–9) and 0.2% of index cases were linked to >80 tested contacts (range: 1–857; Fig. 2A); numbers of contacts tested varied by district, and the geographic distribution of index cases included in our analyses did not necessarily reflect the geographic distribution of all reported cases (table S5). No positive contacts were identified for 70.7% of index cases for whom reliable contact-tracing data, including test results, were available (Fig. 2A). The distribution of the number of positive contacts linked to each index case was heavily right-skewed, and we estimated a negative binomial dispersion parameter for the distribution of the number of infected contacts traced to each index case of 0.51 (95% confidence interval: 0.49–0.52). On average, 9.2 contacts were tested for each index case with ≥ 1 contact identified, as compared to 5.7 tested for each index case without positive contacts identified (two-sided bootstrap $p < 0.001$; fig. S4). While our analysis is limited in that it does not necessarily capture all secondary infections (e.g., among contacts who were not reported), these observations are

consistent with the presence of super-spreading related to differences in individual contact patterns (26).

Assuming test-positive contacts were infected by the index case to whom they were traced, we estimated that the overall secondary attack rate (or risk of transmission from an index case to an exposed contact) was 10.7% (10.5-10.9%) for high-risk contacts, who had close social contact or direct physical contact with index cases without protective measures, and 4.7% (4.6-4.8%) for low-risk contacts, who were in the proximity of index cases but did not meet these criteria for high-risk exposure (tables S6 and S7). Data on exposure settings, available for 18,485 contacts of 1,343 index cases, revealed considerable differences in transmission risk associated with differing types of interaction. Secondary attack rate estimates ranged from 1.2% (0.0-5.1%) in healthcare settings to 2.6% (1.6-3.9%) in the community and 9.0% (7.5-10.5%) in the household. Among 78 individuals with high-risk travel exposures—defined as close proximity to an infected individual in a shared conveyance for ≥ 6 hours—we estimated a secondary attack rate of 79.3% (52.9-97.0%).

Whereas secondary attack rate estimates did not differ considerably by the sex of cases and their contacts (Fig. 2B), analyses stratified by case and contact age identified the highest probability of transmission, given exposure, within case-contact pairs of similar age (Fig. 2C and table S8). These patterns of enhanced transmission risk in similar-age pairs were strongest among children ages 0-14 years and among adults ages ≥ 65 years, and may reflect differences in the nature of intragenerational and intergenerational social and physical interactions in India (27). Nonetheless, the greatest proportion of test-positive contacts within most age groups were exposed to index cases ages 20-44 years (Fig. 2C, fig. S5, and table S8). As serological surveys in other settings have demonstrated that case-based surveillance may lead to under-estimation of SARS-CoV-2 infection prevalence among children (28, 29), it remains crucial to establish whether the role of children in transmission is underestimated in studies such as ours using case-based surveillance to identify index infections.

Mortality among COVID-19 cases

In a sub-cohort of 102,569 cases in Tamil Nadu and 22,315 cases in Andhra Pradesh who tested positive at least 30 days before the end of the study follow-up period, the overall case-fatality ratio was 2.06% (1.98-2.14%; Fig. 3). Age-specific estimates ranged from 0.05% (0.012-0.11%) at ages 5-17 years to 16.6% (13.4-19.9%) at ages ≥ 85 years. Risk of death was higher among male cases than among female cases overall, and the magnitude of this difference widened in the oldest age groups. Higher mortality in older age groups and among males have similarly been observed in high-

income settings (1-7, 30-32).

Half of the cases ascertained before death in Tamil Nadu and Andhra Pradesh succumbed within ≤ 6 days of testing (interquartile range: 3-12 days), and 1,042 fatal cases (18.2% of 5,733 observed) were identified either ≤ 24 hours before death or posthumously. Our estimates of time-to-death in Tamil Nadu and Andhra Pradesh are below what has been observed internationally: in the United States, median time-to-death from the date of hospital admission was 13 days (8), and the World Health Organization estimated time to death following onset of symptoms could range from two to eight weeks based on data from China (33). Our observations likely indicate a substantial proportion of patients in Tamil Nadu and Andhra Pradesh are diagnosed late in their disease course, although differences in patients' health status, healthcare systems capacity, and approaches to end-of-life care may also contribute to variation in time to death.

In a survival analysis of the full cohort, mortality by 1 August, 2020 was independently associated with older age, with stepwise increases in the adjusted hazard ratio of time-to-death for each successive age group besides children ages 0-4 years, consistent with our estimates of the case-fatality ratio (Fig. 3). Additional predictors of mortality included being male (adjusted hazard ratio: 1.62 [1.52-1.73] compared with being female), receipt of a test early in the epidemic (0.87 [0.72-1.07] for being tested between May 1 and June 30, and 0.74 [0.61-0.91] for being tested between July 1 and August 1, both compared with testing between March 1 and April 30), and state of residence (1.08 [1.01-1.16] for residents of Tamil Nadu compared with those in Andhra Pradesh.

Among decedents in the two Indian states, the most prevalent comorbid conditions were diabetes (45.0%), sustained hypertension (36.2%), coronary artery disease (12.3%), and renal disease (8.2%; table S9). While prevalence of any comorbidity was highest among decedents at older ages, this pattern differed across conditions; diabetes was most prevalent among decedents ages 50-64 years, and liver disease and renal disease were most prevalent in fatal cases at ages 0-17 years and 18-29 years, respectively. At least one comorbid condition was noted among 62.5% of fatalities, in comparison to 22% of fatalities in the United States as of 30 May, 2020 (34).

Epidemiological comparison to high-income settings

Cases in Tamil Nadu and Andhra Pradesh showed a younger age distribution than cases reported in the United States as of 21 August, 2020 (Fig. 4) (35). Comparing cumulative COVID-19 incidence across ages revealed the observed differences surpassed expectations based on population age distributions alone, as signaled by the absence of parallel

trends in age-specific incidence (table S10). Although lower across all age groups in Tamil Nadu and Andhra Pradesh in comparison to the United States, age-specific COVID-19 incidence increased sharply in both settings between the 5–17 year and 18–29 year age groups. Whereas incidence declined steadily at ages older than 30–39 years in the two Indian states, incidence increased at ages ≥ 65 years in the United States.

In the two Indian states, only 17.9% of COVID-19 deaths occurring on or before 1 August, 2020 were among individuals ages ≥ 75 years, compared with 58.1% of COVID-19 deaths in the United States (Fig. 4 and table S10). Age-specific COVID-19 mortality was lower in Tamil Nadu and Andhra Pradesh compared with the United States, consistent with the lower reported incidence of disease. While COVID-19 mortality trended upward across ages in the two Indian states, mortality plateaued at ages ≥ 65 years, in contrast to observations in the United States where COVID-19 mortality reached 69.6 deaths per 10,000 individuals ages ≥ 85 years; this observation was consistent with the relatively lower incidence of disease at the oldest ages within the two Indian states.

Discussion

Our findings provide insight into the epidemiology of COVID-19 in resource-limited populations based on comprehensive surveillance and contact tracing data from the Indian states of Tamil Nadu and Andhra Pradesh. Our analysis suggests substantial variation in individuals' likelihood of transmitting: no secondary infections were linked to 71% of cases whose contacts were traced and tested. While the role of children in transmission has been debated (36, 37), we identify high prevalence of infection among children who were contacts of cases around their own age; this finding of enhanced infection risk among individuals exposed to similar-age cases was also apparent among adults. School closures and other non-pharmaceutical interventions during the study period may have contributed to reductions in contact among children. Nonetheless, our analyses suggest social interactions among children may be conducive to transmission in this setting. Last, our analyses of fatal outcomes reveal an overall case-fatality ratio of 2.1%. While our estimates of age-specific case-fatality ratios are similar to those in other settings, such comparisons are limited by uncertainty in the proportion of infections ascertained as cases (30, 38). Lower relative incidence of COVID-19 among older adults in Tamil Nadu and Andhra Pradesh has contributed to stark differences in the overall case fatality ratio and age distribution of decedents relative to observations in the United States and other high-income countries (32).

Several factors may contribute to our observation of limited COVID-19 incidence and mortality among older

adults in Tamil Nadu and Andhra Pradesh. Imperfect surveillance systems may have contributed to underascertainment of cases among older adults, although this circumstance is unexpected given strong public and clinical awareness of COVID-19 and the predisposition of older adults to severe disease. Case-based surveillance may likewise under-estimate attack rates among younger adult age groups in high-income settings (28, 29). It is plausible that stringent stay-at-home orders for older Indian adults, coupled with delivery of essentials through social welfare programs and regular community health worker interactions, contributed to lower exposure to infection within this age group in Tamil Nadu and Andhra Pradesh. Our finding may also reflect survivorship bias if older adults in India are at disproportionately low risk for SARS-CoV-2 infection in comparison to the general population, for instance as a result of higher socioeconomic status (39). Life expectancy at birth is 69 years in India, in comparison to 77 years in China, 79 years in the United States, and 83 years in Italy and South Korea (40); as such, socioeconomic factors distinguishing individuals who survive to old age from the general population are likely more pronounced in India than in higher-income settings with longer average life expectancies (41, 42).

Prospective testing of a large sample of exposed individuals through integrated active surveillance and public health interventions in Tamil Nadu and Andhra Pradesh provided an opportunity to characterize secondary attack rates as a function of both case and contact age, identify risk factors for transmission, and account for deaths outside of healthcare settings—a limitation of mortality surveillance in other settings (30, 43, 44). However, several limitations should be considered. The contact tracing data analyzed included only 20% of all reported cases as index cases and represented only 19% of all contacts traced; case-finding effort further varied by district and over time within Tamil Nadu and Andhra Pradesh. Contacts who complete testing and supply personal information to tracing teams may not be representative of the full population. Another limitation was the lack of data on timing of exposure and symptoms onset in relation to testing dates; this necessitated assumptions about identification of true index cases. More robust temporal data would reduce the dependence on such assumptions, provide greater insight into the directionality of transmission, and reduce risk for misclassification of infection status among contacts with positive or negative results at the time of testing (45, 46). The lack of temporal data also prevented us from estimating several epidemiologic parameters of interest. Current estimates of both the incubation period (c. 4–6 days) and the serial interval (c. 3–5 days) come from China (1, 47–51). Several factors can modify the incubation period of respiratory viral infections, including the

route of acquisition, the infectious dose, and the period of exposure to infected cases (52). The serial interval between successive infections is expected to be lower in high-transmission settings. Data allowing estimation of these parameters for SARS-CoV-2 in LMICs are needed to inform quarantine policies and other epidemic response efforts. Some true positives might have been misclassified due to imperfect test sensitivity, particularly among contacts tested as few as 5 days after exposure to a confirmed case. Imperfect test sensitivity has been attributed to inadequate sample collection procedures and low viral load in the upper respiratory tract, particularly for pre-symptomatic or asymptomatic cases (53). This limitation could lead to an overall underestimate of transmission risk within case-contact pairs. Finally, while comorbidities data collected as part of COVID-19 mortality surveillance revealed clinical and epidemiological attributes of fatal cases, the fact that such data were not collected for all diagnosed cases prevented inference of the contribution of comorbidities to fatal outcomes.

Surveillance and contact tracing are critical components of an effective public health response to COVID-19 (54, 55). In our study, data generated by these activities within two states of South India provided key insights into the local epidemiology and transmission dynamics SARS-CoV-2, without competing with emergency response activities for limited resources: a high priority in many LMICs where health workers and diagnostic equipment are already in short supply (15). Similar studies are necessary to inform the successful adaption of epidemic control measures in low-resource settings globally.

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56. De-identified data and code for replication of the analyses is available from <https://doi.org/10.5281/zenodo.4003365>.

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SUPPLEMENTARY MATERIALS

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Materials and Methods

Figs. S1 to S5

Tables S1 to S10

MDAR Reproducibility Checklist

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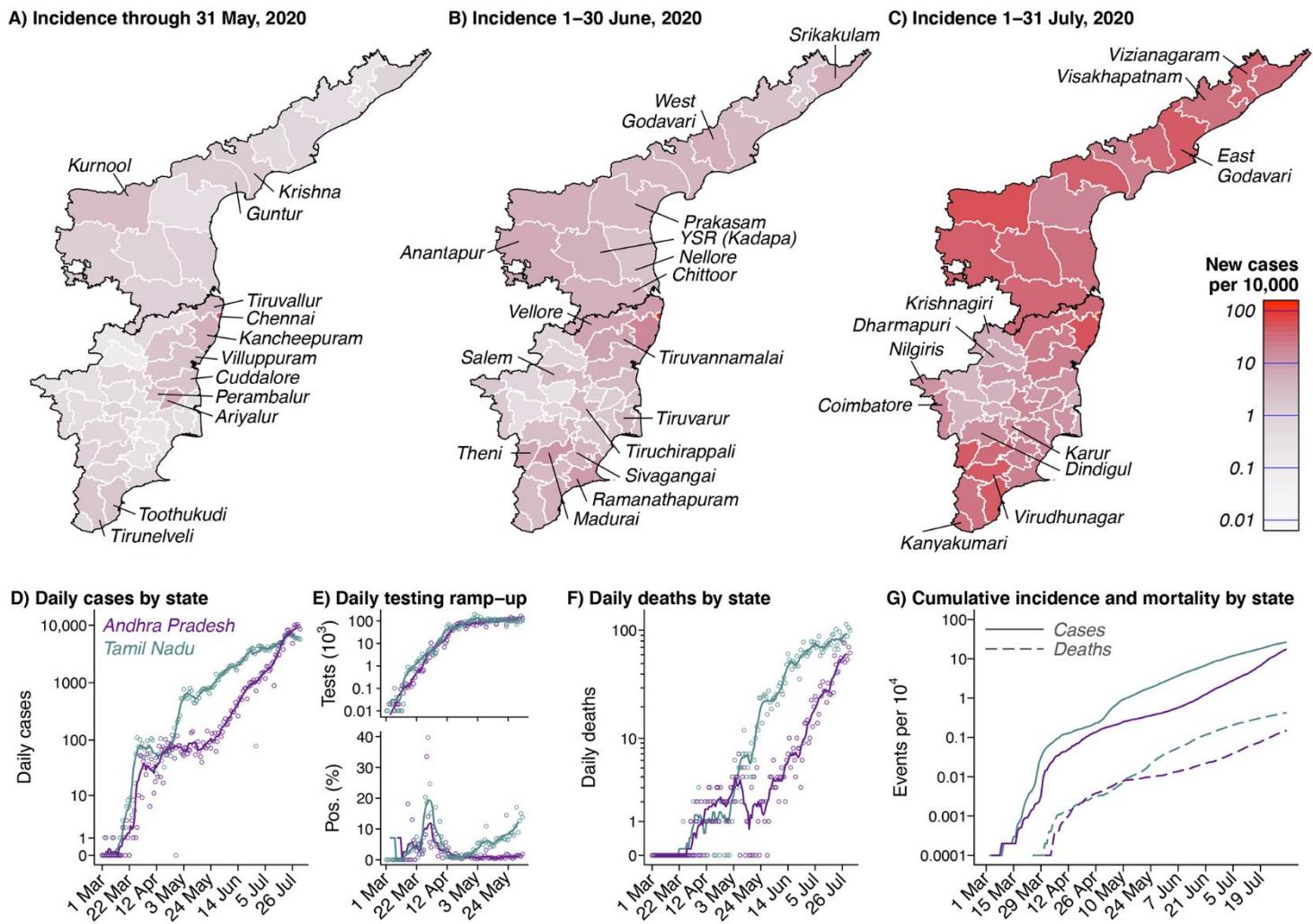


Fig. 1. Incidence over time and across districts in Tamil Nadu and Andhra Pradesh. Red shading of regions on the choropleths map indicates higher incidence over each period: (A) 1 March to 31 May, 2020; (B) 1–30 June, 2020; and (C) 1–31 July, 2020. Districts are plotted according to 2019 administrative boundaries and do not reflect the recent bifurcation of Tirunelveli, Villupuram, Vellore, and Chengalpattu districts. (D) We plot cases detected each day in each state (points) and 7-day moving averages (lines). Cases are aggregated by testing date; data are plotted in blue and lavender for Tamil Nadu and Andhra Pradesh, respectively, for all figure panels. (E) We illustrate diagnostic tests conducted each day (top) and the proportion of tests yielding positive results (bottom), for the period of March through May when districts reported comprehensive testing information to the state governments. Points and lines again indicate daily counts and 7-day moving averages, respectively. The high proportion of positive tests from late-March to mid-April, while case number remained relatively stable, may indicate a period during which cases were undercounted due to limited testing capacity. (F) We plot daily deaths in the two states; points and lines again indicate daily counts and 7-day moving averages, respectively. (G) Last, we plot cumulative incidence (solid lines) and mortality (dashed lines) per 10,000 population.

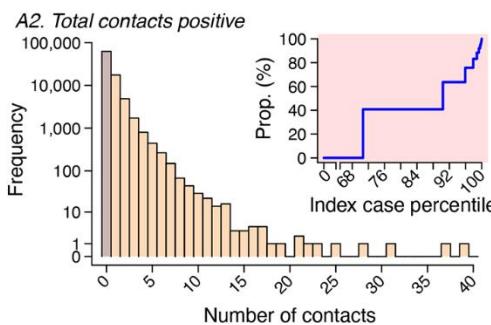
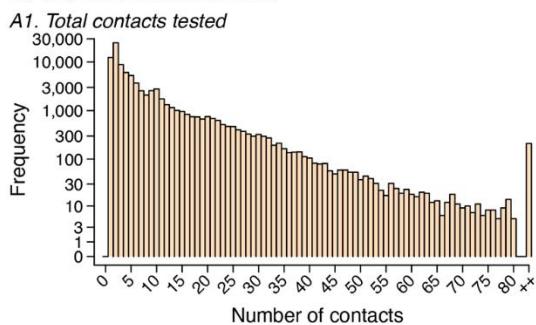
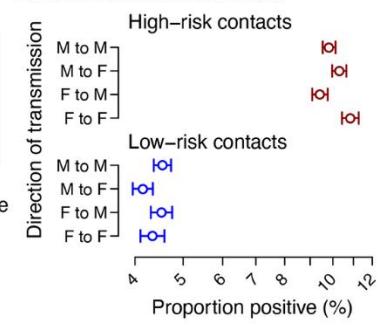
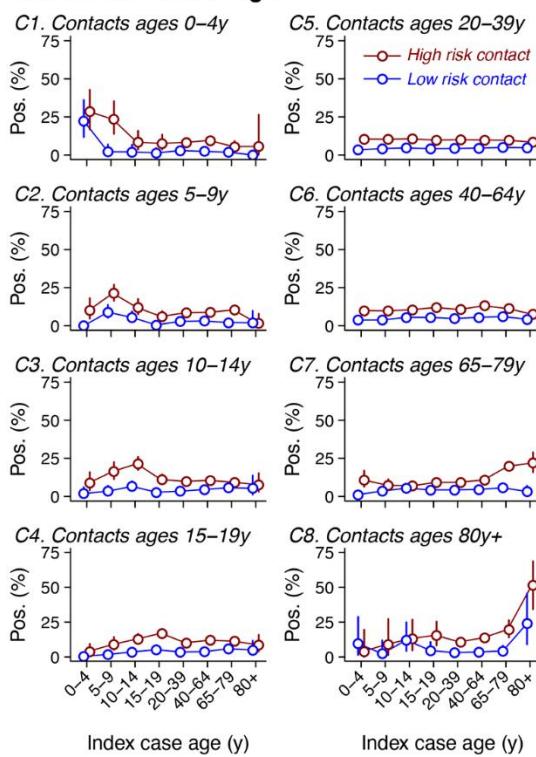
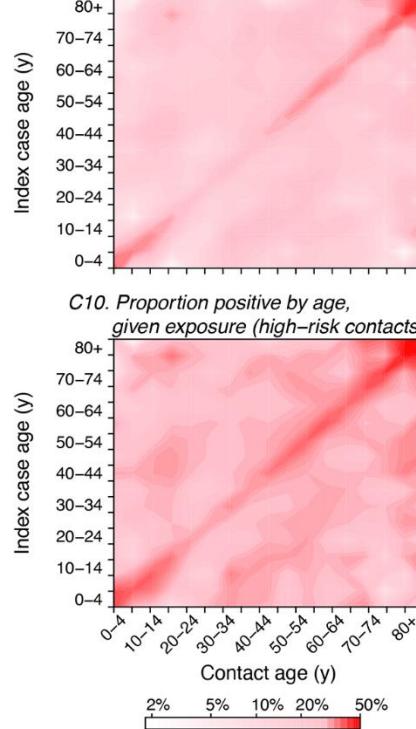
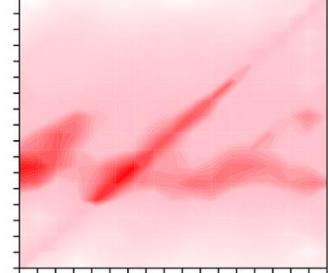
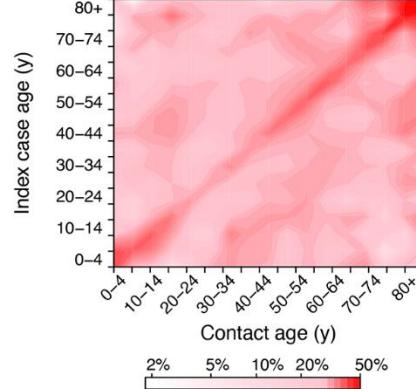
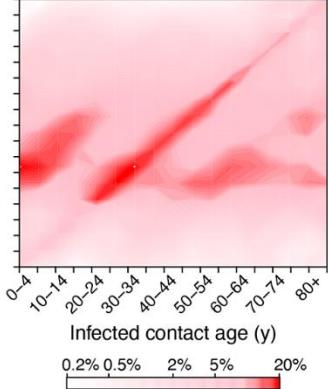
A. Contact distributions**B. Case and contact sex****C. Case and contact age****C9. Proportion positive by age, given exposure (all contacts)****C11. Age distribution of index cases, among all infected contacts****C10. Proportion positive by age, given exposure (high-risk contacts)****C12. Age distribution of index cases, among infected high-risk contacts**

Fig. 2. Analyses of contact tracing data for 575,071 tested contacts of 84,965 infected individuals, from whom test results were available together with individual-level detailed epidemiological data on both exposed contacts and index cases. (A) Left: Distribution of the number of contacts traced for each index case in Tamil Nadu and Andhra Pradesh, binning values ≥ 80 (0.2%). Right: Number of positive contacts traced from each index case, and (inset panel) the cumulative attributable proportion of secondary infections (y-axis) associated with quantiles (x-axis) of the distribution of the number of positive contacts traced per index case; 0%ile and 100%ile values indicate index cases with the fewest and the most positive contacts identified, respectively. (B) We plot adjusted estimates from Poisson regression models addressing the proportion of female and male contacts with a positive result, among those who were known to be exposed to female and male index cases; models further control for case and contact age groups (interacted) and state. We stratify for high-risk and low-risk contacts, as defined in table S6. Points and lines indicate mean estimates and 95% confidence intervals. (C) We indicate the proportion of contacts with a positive test result stratified by case and contact age, for high-risk and low-risk contacts. At right, contour plots indicate the proportion of exposed contacts with a positive test result by case and contact age for all contacts and high-risk contacts on a choropleth scale; we present raw counts in table S8. Positive test results among tested, exposed contacts are interpreted as evidence of probable transmission from the index case. Last, we plot the distribution of index cases ages for all infected contacts and for infected high-risk contacts.

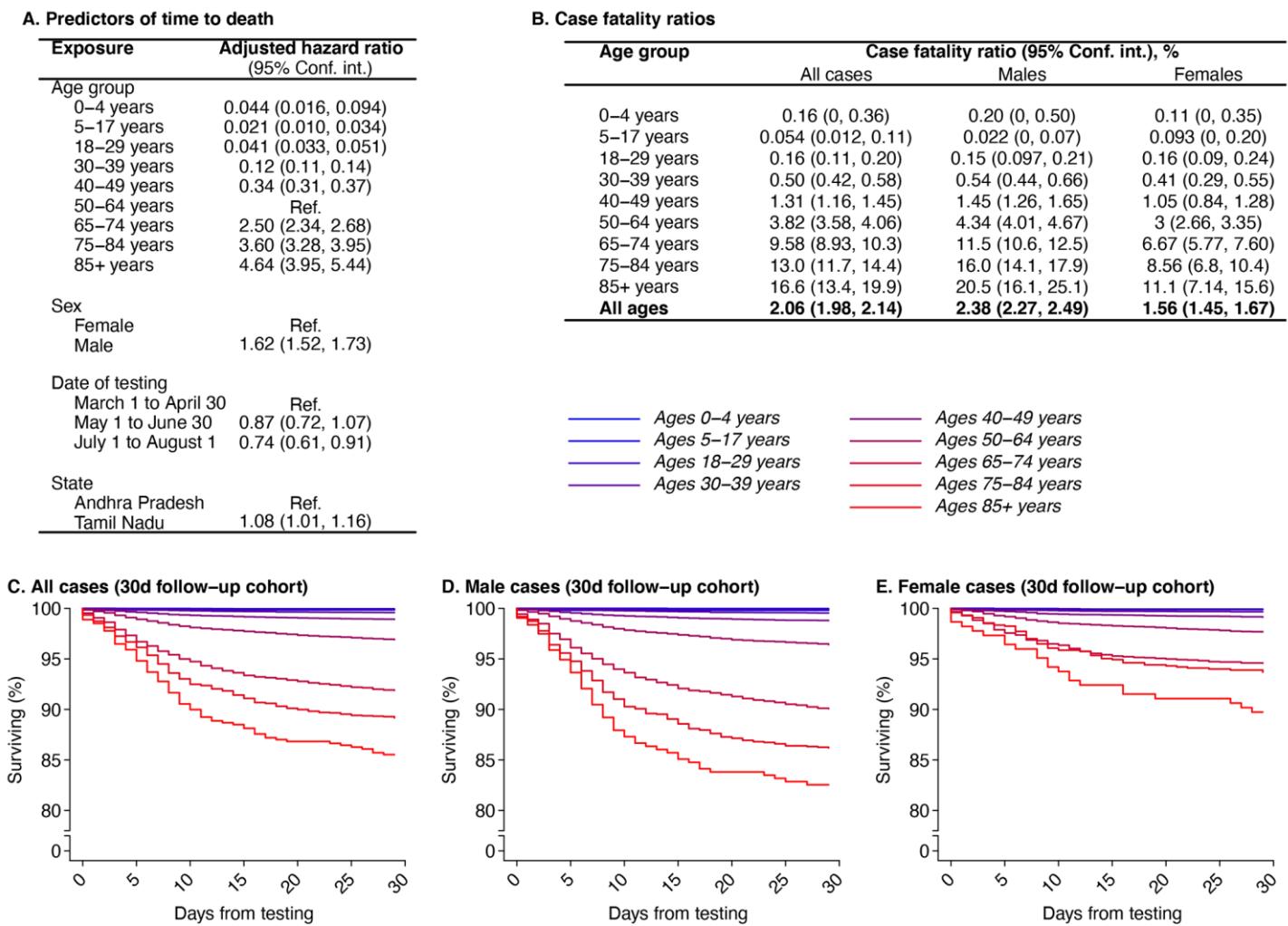


Fig. 3. Mortality among confirmed COVID-19 cases. (A) We present adjusted hazard ratios for mortality by 1 August, 2020 estimated via Cox proportional hazards models including all confirmed cases. (B) We present absolute case-fatality risk estimates, obtained via bootstrap resampling of individuals with confirmed infection by 1 July, 2020. Within this cohort, we plot survival probabilities by age over the 30 day period following testing for (C) all cases; (D) male cases; and (E) female cases. Blue-to-red coloration aligns with younger-to-older age group, for strata as defined in the above tables. Age bins were selected based on reporting of United States COVID-19 surveillance data (Fig. 4).

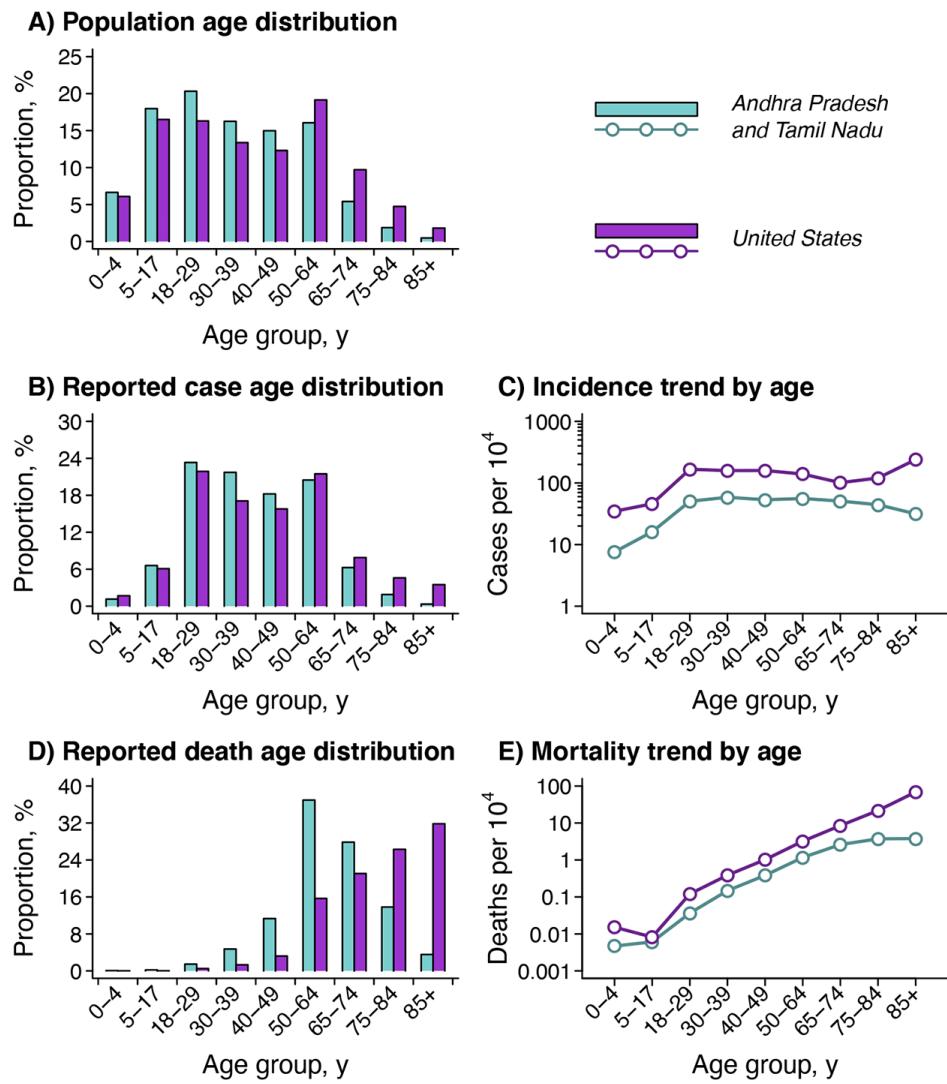


Fig. 4. Demographic comparison of populations, cases, and deaths for Tamil Nadu and Andhra Pradesh and the United States. (A) We illustrate the age distribution of the population of Tamil Nadu and Andhra Pradesh (blue) against the age distribution of the US population (purple) for comparison; underlying data are presented in table S10. Estimates are census extrapolations for the year 2020 in both settings. (B) We next illustrate the age distribution of cases and (C) cumulative incidence of COVID-19 by age in the two countries, and (D) the age distribution of deaths and (E) cumulative COVID-19 mortality by age. United States data include all cases and deaths reported by 21 August, 2020 (35).

Epidemiology and transmission dynamics of COVID-19 in two Indian states

Ramanan Laxminarayan, Brian Wahl, Shankar Reddy Dudala, K. Gopal, Chandra Mohan, S. Neelima, K. S. Jawahar Reddy, J. Radhakrishnan and Joseph A. Lewnard

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