Implications of the age profile of the novel coronavirus

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The role of children in the transmission of SARS-CoV-2 remains unclear, and existing data are yet to provide a consistent explanation for the markedly skewed age distribution of COVID-19 cases. Whereas early data from symptomatic case confirmations suggested a lack of disease in children, subsequent contact tracing studies have found that children are likely to be infected. Governments are now facing immense pressure to weigh the public health benefit of interventions such as school closure against the significant economic disruption they impose. To motivate the discussion of age-stratified social distancing measures, we discuss potential biological mechanisms by which a skewed age distribution of cases may be generated and show through mathematical modelling how different age-targeted interventions are likely to affect the epidemic final size. We propose that identifying age-dependent transmissibility, in addition to susceptibility, will be essential to understand which social distancing measures are likely to be the most impactful going forward.

SARS-CoV-2 | COVID-19 | Children | Transmission

Case reports associated with the pandemic SARS-CoV-2 virus are strikingly skewed to older ages (Figure 1B). This contradicts the role of social mixing in communicable disease dynamics: typically, age groups with high contact rates (children) experience higher rates of exposure than age groups with fewer contacts (the elderly) (Figure 1C). Understanding why COVID-19 (the disease caused by SARS-CoV-2) deviates from this expectation is crucial for implementing and subsequently relaxing appropriate interventions. If children are contributing to transmission, then school closure is likely to be impactful in slowing the spread of SARS-CoV-2. If transmission is driven predominantly by adults, then focus should be on reducing their contacts. These critical decisions are being made now, and communities are enacting social distancing measures to varying degrees. Some countries now face the additional challenge of deciding which interventions should be relaxed to minimize economic disruption. We consider different hypotheses for the role of children in transmission and the extent to which social distancing among adults, with or without school closures, is expected to reduce the epidemic final size.

The impact of social distancing measures will depend on the role of different age groups in transmission. There are several potential, non-mutually exclusive, explanations for the age profile of COVID-19 cases: (i) contacts are far more frequent among adults than children in affected communities; (ii) age groups demonstrate differential susceptibility to infection, either decreased in children or increased in the elderly; (iii) children are acquiring and participating in transmission of the virus but are largely asymptomatic and thus not tested; (iv) older individuals transmit significantly more than children per contact, leading to relatively skewed onward transmission.

Intuitively, low contact rates in children and high rates in the elderly seem unlikely given that contact patterns are ubiquitously shown to feature highest rates among children (Figure 1C) (1). However, in China, the coincident timing of the Lunar New Year followed by timely social distancing measures massively reduced contacts made between children (i.e., because of breaks from school), and possibly increased contacts between children and older age groups (2). Although a likely contributor, this change in social structure is unlikely to explain the skewed age distribution on its own (Figure 1E), particularly as these patterns have now been seen elsewhere.

The second scenario (children are less susceptible to acquisition) may arise from pre-existing, cross-reactive immunity. Cross-protective immunity from previous seasonal coronavirus is a tempting but unsupported hypothesis for children, wherein early-life exposure could afford antigenically broad, transient immunity. Alternatively, antibody-dependent enhancement (ADE) may arise through reactive but not neutralizing antibodies in older individuals that enhance viral entry and exacerbate disease. Although ADE is well described in terms of disease severity, it has not been considered in terms of enhancing susceptibility. Testing contacts of confirmed cases in China have found contrasting results: one not-yet-published study found that secondary attack rates were fairly uniform across all ages with a slight general increasing trend with age, whereas another found reduced risk of infection in younger individuals (2, 3). It is therefore currently unclear if children have superior protection from acquisition than adults given exposure to the same infectious dose. It is important to note that even if acquisition rates are lower in children than adults, overall transmission from infected children may still be significant.

The third scenario (children are asymptomatic) is plausible given emerging case series data, which suggest that COVID-19 disease is typically, but not exclusively, mild in children (4). Milder cases are less likely to be picked up if detection depends on disease severity, lending support to this hypothesis. If this is the case, many of the conclusions oncontrolling transmission emerging from the large body of work attributable to pandemic influenza, including the impacts of school closures, will be portable to COVID-19 control efforts. However, samples from influenza-like-illness surveillance suggested that the number of infected children may be genuinely low (5). Clarification on the conclusions drawn by the WHO on these data will

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be important to understand if incidence in children truly is low, or an artefact of surveillance following substantial control measures.

Increased transmissibility in older ages could result from transmissibility increasing as a function of disease severity. Individuals with more severe disease may shed more virus, or shed virus through a more transmissible route, increasing the likelihood that they infect susceptible contacts. Again, support for this hypothesis is limited, as early clinical findings suggest that children and asymptomatic individuals shed significant amounts of virus through respiratory and fecal routes (4). However, the experience of the cruise ships, with an older demographic, shows that rapid spread in the absence of children is feasible. It will be important to consider this hypothesis should serosurveys find lower infection rates in children, as age-dependent transmissibility has profound implications for longer term control measures.

Although we do not have definitive data to discriminate between these hypotheses, underreporting of infected children or age-dependent transmissibility currently seem the most plausible drivers of the age-distribution of COVID-19 cases. It has been suggested that the apparent low rate of infection among children means school closures will have little impact (6), but the true incidence in younger ages is likely greater than initial estimates which were skewed towards invasive disease (3). If transmissibility does not vary by age, and only disease severity does, then school closures in addition to a substantial reduction in contacts made by adults would be necessary to reduce the effective reproductive number to below 1 (Figure 2A&B). However, if transmission is being primarily driven by adults, then reducing contacts between these age groups becomes more important (Figure 2C&D). Some viruses do demonstrate incidence that is highly skewed towards older ages (e.g., herpes zoster), though we are unaware of any such viral respiratory pathogen. Extremely low transmissibility in children that drastically increases in older adults is required to generate incidence patterns comparable to the distribution of COVID-19 cases (Figure 1D&E). Given the transmission route of SARS-CoV-2, a lack of transmission in children would be surprising.

Distinguishing between these hypotheses will be achieved using a combination of serological surveillance, clinical observations and household studies. In the longer term, contact tracing studies to discern the relative contributions of children and adults to overall transmission (Figure 2E&F) will also be important to understand when different interventions may be relaxed. Existing contact tracing data are limited in this regard, as the majority of index cases are clinically detectable infections and therefore predominantly adults. To understand if the probability of transmission per contact varies between infected children and adults, data are needed with younger index cases, many of whom may be asymptomatic. As SARS-CoV-2 continues to gain traction at the community level, it will be important for epidemiologists and public health policy makers to reconcile epidemiological observations that deviate from expectation via an increased understanding of its biology.

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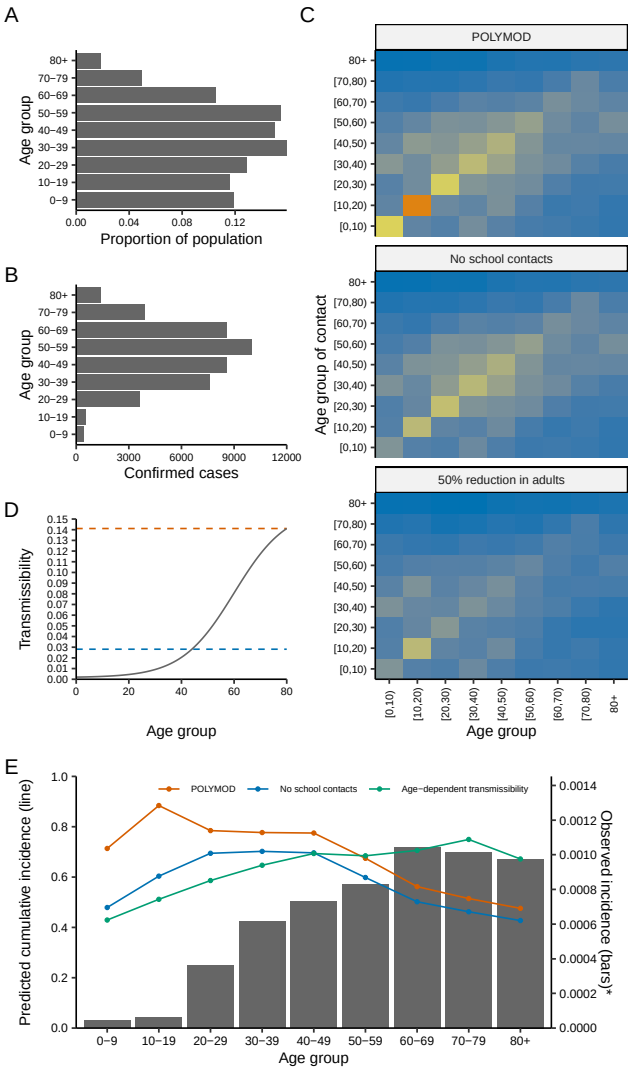

Fig. 1. (A) Age distribution of China (7); (B) Age distribution of confirmed COVID-19 cases in China as of 11th February 2020 (8); (C) Contact matrices based on POLYMOD data generated using the *socialmixr* package (9–11): unmodified, with school closures and with school closures plus 50% of all contacts made by ages 20+ removed. Blue shows low contact rates and orange shows high contact rates (10, 11). (D) Age-dependent transmissibility required to generate a marked reduction of incidence in children. Blue dashed line shows transmissibility required for an R_0 of 2 with no age-dependent transmissibility. Orange line shows maximum transmissibility. (E) We implemented an SIR model with 9 age classes (10-year intervals) using the POLYMOD contact matrix, the age-distribution of China, the population of Wuhan and an incubation period of 5 days. Bar chart shows observed incidence by age in Hubei, assuming that 75% of the confirmed cases were in Hubei and that the population of Hubei is 58.5 million. Orange line shows the results of simulating the SIR model with an entirely susceptible population and a basic reproductive number (R_0) of 2. The blue line shows the same simulation, but after removing all contacts made in school. The green line shows the same simulation assuming POLYMOD contact data, but with transmissibility increasing as a function of age.

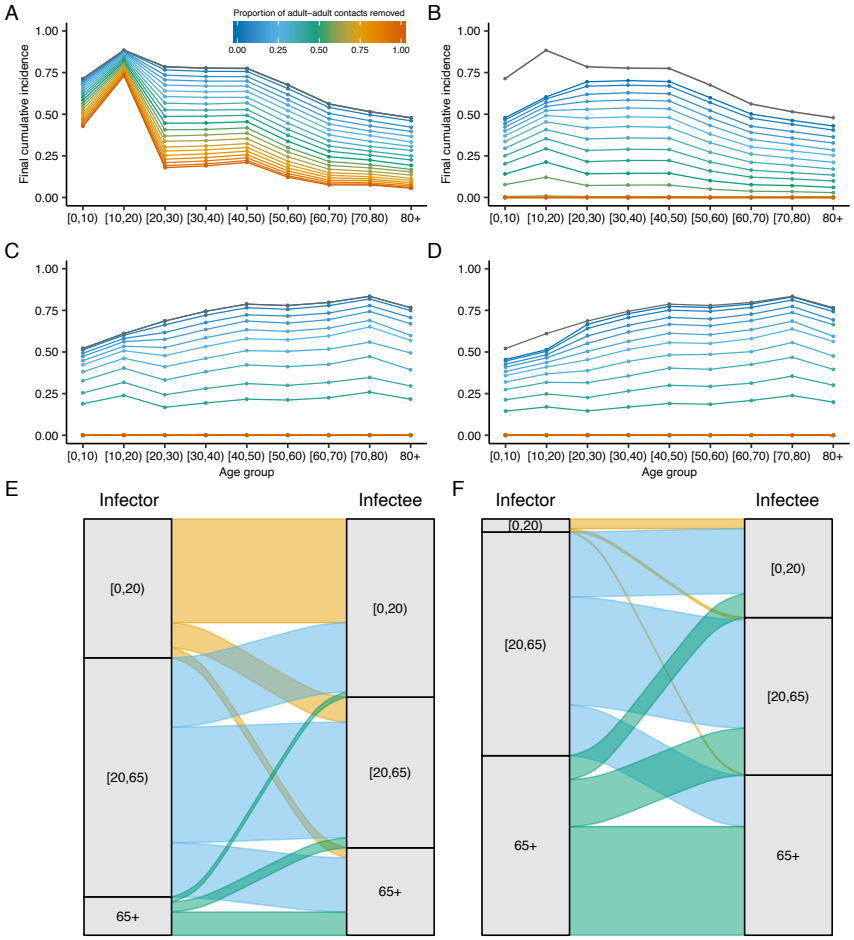

Fig. 2. (A) Impact of reducing contacts between 20+ year olds with no school closure. Top line shows age-stratified final cumulative incidence assuming POLYMOD mixing as in Figure 1. Each subsequent colored line shows the final size incidence by age if an increasing proportion (0.05 increments) of contacts made between 20+ year olds are removed. (B) Same as (A), but with all contacts made in school removed. When children are involved in transmission, fewer adult-adult transmission pairs must be removed in addition to school closure to achieve marked reductions in the proportion infected. (C) Same as (A), but assuming that transmissibility is low in children and increases into older age classes, as in Figure 1D. (D) Same as (C), but with all contacts made in school removed. When transmissibility is largely driven by older age groups, significant reductions in contacts made between 20+ year olds are required to reduce incidence. (E) Relative contribution of age-specific transmission pairs assuming POLYMOD contact mixing and no age-dependent transmissibility. Alluvial plot shows the relative contribution of each transmission pair type. (F) Same as (E), but assuming that transmissibility is low in children and increases into older ages, as in Figure 1D.

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