



Early View

Correspondence

Correspondence regarding recently published editorial: 'Will children reveal their secret? The coronavirus dilemma'

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Cristiani and colleagues have raised interesting questions in their editorial discussing the differences in coronavirus disease 2019 (COVID-19) morbidity and mortality between children and adults[1]. The authors proposed a number of possible reasons to explain why children suffer less severe illness, including age-related variation in ACE2-receptor expression, trained immunity, and differences in lymphocyte and natural killer cell abundance. Whilst these hypotheses may be correct, we wish to challenge the notion that greater morbidity and mortality in adults is a remarkable feature of COVID-19. This is, in fact, the typical situation for most infections occurring in the absence of prior immunity.

The novel COVID-19 virus emerged into a previously unexposed, and presumably fully susceptible population at the end of 2019, facilitating its rapid spread around the world. It has since been well documented that children with COVID-19 suffer a milder illness than adults with better clinical outcomes overall. Age-specific case fatality ratios appear to increase continuously from close to zero percent in children under 10 years old to around 13% in adults aged 80 years or more[2]. Globally, children suffer the greatest burden of most infectious diseases, particularly respiratory infections, hence the low burden of COVID-19 in children has been viewed by many as surprising.

However, for most common infectious diseases the relationships between age and disease severity are influenced by acquisition of immunity, and because immunity is dependent on exposure it therefore increases with age. When only susceptible individuals are considered, age-specific mortality rates are typically higher in adults than in children for most infectious diseases. This was observed for measles in historical first-contact island epidemics[3], and more recently for emerging infectious diseases including Severe Acute Respiratory Syndrome (SARS)[4], West Nile virus infection[5], and Severe Fever with Thrombocytopenia Syndrome (SFTS)[6]. Similar relationships are

clear even for common infections causing their greatest burden in childhood, such as primary varicella infection[7] and *Plasmodium falciparum* malaria [8], when individuals without prior immunity are considered. We believe that the greater burden of COVID-19 in adults primarily reflects the fact that the whole population is susceptible, rather than an unusual association between severity and age.

Until we have better epidemiological data to be certain about denominators (numbers of infections in different age groups), it will be difficult to discern whether the relationship between age and case-fatality ratio is monotonic or “J” shaped (with a higher case fatality ratio in the very youngest children compared with older children). However, comparisons between different age-groups may tell us more about age-related host-pathogen interactions in general, than about the pathogenesis of COVID-19 specifically.

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