On the effect of age on the transmission of SARS-CoV-2 in households, schools and the community

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Summary: Our literature review suggests that compared to younger/middle aged adults, susceptibility to SARS-CoV-2 infection for children aged <10y is relatively low, while susceptibility in adults aged >60y is higher. Mitigation measures should be implemented when opening schools, particularly secondary/high schools.

Abstract

Background: There is limited information on the effect of age on the transmission of SARS-CoV-2 infection in different settings.

Methods: We reviewed published studies/data on detection of SARS-CoV-2 infection in contacts of COVID-19 cases, serological studies, and studies of infections in schools.

Results: Compared to younger/middle aged adults, susceptibility to infection for children aged under 10y is estimated to be significantly lower, while estimated susceptibility to infection in adults aged over 60y is higher. Serological studies suggest that younger adults (particularly those aged under 35y) often have high cumulative incidence of SARS-CoV-2 infection in the community. There is some evidence that given limited control measures, SARS-CoV-2 may spread robustly in secondary/high schools, and to a lesser degree in primary schools, with class size possibly affecting that spread. There is also evidence of more limited spread in schools when some mitigation measures are implemented. Several potential biases that may affect these studies are discussed.

Conclusions: Mitigation measures should be implemented when opening schools, particularly secondary/high schools. Efforts should be undertaken to diminish mixing in younger adults, particularly individuals aged 18-35y to mitigate the spread of the epidemic in the community.

Keywords: SARS-CoV-2; susceptibility; seroprevalence; age; children; young adults; primary schools; secondary schools; high schools

Introduction

Among those infected with SARS-CoV-2, elderly patients have had the most severe outcomes, including the highest death rates, whereas infected younger persons, particularly children aged 1-18y, if symptomatic at all, are far more often mildly ill [1]. While this age-dependent pattern of illness severity has become well-established, the roles of different age groups in transmission has not been as clear. Recently, evidence has accumulated that susceptibility to infection generally increases with age, e.g. [2,3]. This, however, does not suggest that the oldest individuals necessarily have the highest SARS-CoV-2 incidence – in fact, serological studies suggest that younger adults, particularly those aged under 35y often experience the highest cumulative rates of infection [4-8], possibly due to age-related differences in mixing. Additionally, there is uncertainty as to how susceptibility to infection varies with age in children, and how it compares to susceptibility to infection in different age groups of adults. The effect of the ongoing and future openings of primary, secondary and high schools and higher-educational institutions on the spread of infection requires a better characterization of transmission dynamics in different age groups. Here, we review the relevant evidence based on household, school and community studies, and draw some conclusions regarding the relevant public health policies.

Age variation in susceptibility to infection given contact

We undertook a literature review using the Living Evidence on COVID-19, a database collecting COVID-19 related published articles from Pubmed and EMBASE and preprints from medRxiv and bioRxiv [9], with articles containing the words ((children) OR (age) OR (aged) OR (years old) OR (secondary)) AND ((household) OR (households) OR (contacts)) in the Title/Abstract published before October 5, 2020 examined for relevance. Studies were eligible for inclusion if they reported the estimates of either secondary attack rate, susceptibility to, or odds ratio for infection in different age groups, and where the setting for the contact (e.g. household or other), either was the same for all

contacts, or was adjusted for (as a covariate in a model) in those estimates (to reduce the effects of heterogeneity in exposure on those estimates).

Informed consent: We used published, de-identified data, with no informed consent from the participants sought.

Relative susceptibility to infection in different age groups

In this section we present the fourteen included studies that assess relative susceptibility for different age groups, describe some potential biases in those studies, and present evidence for lower susceptibility to infection in children aged under 10y, and higher susceptibility to infection in adults aged over 60y compared to young/middle aged adults.

PCR-based studies of SARS-CoV-2 infection in close contacts: Several studies found much lower secondary attack rates (measured by PCR-positive cases among contacts) in children as contacts – using different age cutoffs of children up to age 20y -- compared to adults. In a hospital-based study near Wuhan, China [10], the OR (odds ratio) for infection in contacts aged <18y relative to adults was 0.18 (95% CI (0.06,0.54)). In a Guangzhou, China study [2], the multivariable OR for infection in contacts aged under 20y vs. contacts aged over 60y was OR=0.23(0.11,0.46)), while for contacts aged 20-59y vs. contacts aged over 60y it was OR=0.64 (0.43,0.97). For household contacts of confirmed cases in Zhuhai, China [11], the OR for infection in children aged 4-18y relative to persons aged 19-60y was 0.09(0.01-0.73). In a Chinese study of close contacts [3], the multivariable OR for infection in children aged <15y compared to adults aged 15-64y was 0.34 (0.24 to 0.49). In a Hunan, China study [12] the multivariable odds ratio for infection in contacts aged under 15y vs. contacts aged 15-64y was 0.58 (0.34, 0.98). A study modeling transmission within household in Israel [13] found that susceptibility in children under the age of 20y was 0.45(0.40, 0.55) that of adults. For a

study of household contacts in New York State [14], the OR for infection in children aged <18y relative to adults aged 18-29y was 0.41 (0.17,0.99).

A few studies showed similar SAR (secondary attack rate) in children or adults. For a study of household contacts in Wisconsin and Utah [15], the OR for infection in children aged <18y relative to adults aged 18-49y was 0.88 (0.37,2.02). For the study in Shenzhen, China [16], infection rates in close contacts were similar across age groups. However, 298/391 of index cases in this study were travelers, with joint travel being associated with an odds ratio of 7.1 (1.4,34.9) for infection in close contacts, suggesting the possibility of acquisition of infection at the source of travel and making the interpretation of the estimates in [16] difficult. For a multivariable analysis involving contacts of COVID-19 cases in Guangzhou, China [17], the odds ratio for infection in contacts aged <18y relative to contacts aged 18-44y was 0.78 (0.41,1.50). For household contacts of COVID-19 cases in two Indian states [18], OR for infection in children aged <18y relative to adults aged 18-34y was 0.96(0.71,1.29). For a study of family members of SARS-CoV-2 cases in Greece [19], OR for infection in pediatric contacts vs. adult contacts was 1.69(0.7,4.2).

Serological studies of SARS-CoV-2 infection in close contacts: For a study of household contacts of hospitalized cases in Italy [20], the OR for infection in children aged <18y relative to adults was 0.77(0.27,2.17). For a study of household contacts in Utah and Wisconsin, USA [21] (not retrieved from [9]), the OR for infection in children aged <18y relative to adults was 1.39(0.55,3.53).

Potential biases for the estimates of susceptibility in children vs. adults: Estimates of relative susceptibility in children vs. adults based on household attack rates may be influenced (generally downward biased) due to contact patterns because certain adult-adult contacts may be more

sustained than adult-child contacts: that is, higher secondary attack rates in adults vs. children may reflect greater exposure in addition to differences in susceptibility given the same exposure. A serological study of a SARS-CoV-2 outbreak on a US Navy ship [22] found that cumulative incidence of infection was higher among persons who reported sharing the same sleeping berth with a crew member who had positive test results compared with those who did not, OR = 3.3 (1.8,6.1). This suggests that among contacts of an index case in a household, the spouse might face an additional risk for infection due to shared bed, or room. In fact, for adult contacts in the Wuhan study [10], the SAR among spouses of index cases was 27.8% (25/90), whereas the SAR among other adults in the household was 17.3% (35/202), with the relative risk (RR) for infection for a spouse of the index case vs. a non-spouse adult household contact being RR=1.60(1.02,2.51). In the Zhuhai study [11], 12/23 spouses of index cases were infected, compared to 31/89 of other adult contacts of index cases, with the relative risk for infection being RR=1.50(0.92,2.43).

A second source of bias in the estimated relative susceptibility of children vs. adults is the possibility of the following scenario (index misclassification): a child is infected first in a household and transmits to an adult, but because the child has no/mild symptoms, the child is not tested initially, and the adult is considered the household index. For example, in studies [10-12] (conducted early in the pandemic), hospitalized individuals/persons with pneumonia were identified as index cases, and given the underrepresentation of children among severe cases compared to all SARS-CoV-2 infections, pediatric index cases could have been missed in those studies. For studies based on PCR detection of contacts, this error would bias the SAR estimates in children downward if the true index child is classified as an uninfected pediatric contact, and upwards if the true index child is subsequently detected and misclassified as a secondary case. For serological studies of household contacts, this would bias the SAR estimate in children upward (because the index child is classified as an infected pediatric contact in the estimates of SAR). A further limitation related to serological

studies is that they cannot assess whether non-index cases were infected in the household (e.g. delay between infection in the index case and serological testing in [20]).

We note that the last two sources of bias may help explain why in studies based on PCR testing of contacts, the estimated susceptibility to infection in children is generally lower than in adults, while in the serological studies of household contacts [20,21] (where these biases are expected to be upwards for children), the differences in the estimated susceptibility to infection in children and adults are smaller.

Lower relative susceptibility to SARS-CoV-2 infection for children aged under 10y vs. adults: An approach that minimizes these potential biases is to compare infection in different age subgroups of children among household contacts. For one study we reviewed [13], the data are available to compare secondary attack rates in children aged 0-4y and 5-9y to those of older children; SAR in these younger groups are less than half those children aged 15-19y (Table 5 in [13]). Given that there is no evidence that 15-19y olds are more susceptible than adults, this within-childhood comparison can support the inference that children aged under 10y are at most half as susceptible as adults.

Elevated susceptibility to infection for adults aged over 60y compared to younger/middle-age adults: Study [2] estimates that for household contacts among persons aged 20-59y, the OR for infection is 0.64 (0.43,0.97) compared to household contacts aged over 60y. Study [3] estimates that for close contacts among persons aged over 65y, the OR for infection is 1.67 (1.12,1.92) compared to household contacts aged 15-64y. Study [12] estimates that for close contacts among persons aged over 65y, the OR for infection is 1.64 (1.02, 2.63) compared to household contacts aged 15-64y. For the multivariable analysis involving contacts of COVID-19 cases in Guangzhou, China [17], the OR for

infection in contacts aged over 60y relative to contacts aged 18-44y was 2.34 (1.39,3.97), whereas the odds ratio for infection in contacts aged 45-59y relative to contacts aged 18-44y was 1.16 (0.70,1.92). No significant differences in susceptibility for older vs. younger adults were found in [11,14,18].

Table 1 summarizes the above estimates for the relative susceptibilities/odds ratio for infection in different age groups.

Age variation in infectivity

There is limited evidence in the literature regarding age-related differences in infectivity, though point estimates in several studies suggest that infectivity may increase somewhat with age. For the household contacts examined in two Indian states [18], the OR for infection in contacts of a person aged <18y vs. 40-64y was 0.63(0.32,1.15); and OR=0.58(0.45,0.74) for infection in contacts of a person aged 18-39y vs. 40-64y. The Bnei Brak, Israel study [13] estimated the relative infectivity for children aged under 20y compared to adults as 0.85 (0.65,1.1). For the multivariable analysis in Hunan, China [12], the odds ratio for infection in contacts of persons aged 0-14y vs. contacts of persons aged 15-64y is OR=0.28 (0.04, 2.04), whereas the odds ratio for infection in contacts of persons aged over 65y vs. contacts of persons aged 15-64y is OR= 0.56 (0.22, 1.43). Data from 54 households in the Netherlands [23] yielded lower point estimates for transmissibility of infection to close contacts from children aged under 19y, and higher point estimates for adults aged over 70y compared to persons aged 19-69y. For the South Korean study [24], while the household SAR increases with the age of the index for adult index cases, for index cases aged 10-19y, the household SAR was significantly higher than for index cases aged 20-49y. However, a related study from South

Korea [25] adjusting for potential index misclassification in [24] finds a significantly lower SAR for pediatric indices compared to for adult indices.

Potential biases in infectivity studies: As in studies of age-specific susceptibility, there may be errors in ascertaining index cases, as well as conflation of differences in infectivity with differences in susceptibility and intensity of contacts.

Age variation in seroprevalence

We reviewed all seroprevalence studies in the Living Evidence on COVID-19 database [9] with words (seroprevalence) OR (((antibody) OR (serological)) AND (survey)) in the Abstract/Title.

Several serological studies estimate that younger adults, particularly those aged under 35y have the highest seroprevalence of all or nearly all age groups. Serological studies in US blood donors, in England, Rio de Janeiro, Brazil, Tokyo, Japan, as well as Heinsberg, Germany estimate that SARS-CoV-2 seroprevalence is highest in adults aged under 35y [4-7,26]. In Geneva Switzerland, persons aged 20-49 years had the highest estimated seroprevalence, followed by those aged 10-19 years [8].

A serological study in a slum community in Buenos Aires, Argentina found no difference in seroprevalence according to age among those over the age of 14 in multivariable analysis, although the highest seroprevalence was found in male adolescents aged 14-19y [27]. A study of Kenyan blood donors found the highest seroprevalence in persons aged 35-44y, followed by persons aged 15-34y [28]. Studies in Corsica [29] and three regions in France [30] found that seroprevalence

in persons aged under 50y was significantly higher than in persons aged over 50y. In a serological study in Brazil [32], the highest seroprevalence estimates belong to persons aged 20-59y. Serosurveillance of adults outside grocery stores in New York State found that rates of infection in individuals aged over 55y were significantly lower than in persons aged 18-54y [32]; the highest infection rates in New York State were in persons aged 45-54y. Serological studies in Los Angeles County and Karachi, Pakistan found similar seroprevalence estimates in different age groups of adults in each study [33,34]. A serological study in Mumbai, India in which infection rates were found to be high in slum populations, infection rates generally decreased with age in non-slum populations, and increased with age in the slum populations [35]. A serological study in Iceland has the highest estimate for the cumulative incidence of infection in persons aged 40-50y (Figure 2E in [36]), though a sizeable proportion of individuals with serologically confirmed infection were travelers, and rates of seropositivity in different age groups in this study were low. A study of seroprevalence in ten US locations [37] found that the age group with the highest seroprevalence estimate varies by location, with highest rates observed in adults aged 19-49y in three locations, adults aged 50-64y in three locations, adults aged 65+y in two locations, and those aged 0-18y in two locations.

For the serological study in Spain [38], the highest seroprevalence for the point-of-care test was in persons aged over 50y, while for the immunoassay, the highest estimates belong to younger adults. Additionally, serological studies in Hungary [39], Liguria and Lombardia, Italy [40], and Wuhan, China [41] had the highest seroprevalence estimates in persons aged over 60y.

Potential biases in seroprevalence studies: Participants in seroprevalence surveys are almost never fully representative of the source population, as convenience samples might be more likely to reach generally healthy people (e.g. blood donors, [4,5,26,28,41]), people who are not sheltering in place

(grocery store shoppers, [32]), or other groups with unrepresentative risks of exposure. Additionally, estimates of sensitivity and specificity for antibody tests are derived from groups of individuals that might be different from the general population in the serological studies. Overestimation of test sensitivity due to calibration on more severe cases and differences in test sensitivity by age [42] may also complicate interpretation of the estimates and produce downward biases. It is also worth remembering that age-seroprevalence data may reflect the unusual social dynamics of epidemic and/or lockdown periods, and contact patterns may change, leading to different age-specific attack rates, over time.

Transmission of SARS-CoV-2 in schools

We reviewed all studies related to school outbreaks in the Living Evidence on COVID-19 database [9].

There is some evidence, particularly from the Spring 2020 [43-45] that given no or limited mitigation measures (that is, for example, limited testing and quarantine of infected individuals and their contacts in schools, no reduction in class sizes, and limited mask use), robust spread of SARS-CoV-2 can occur in secondary/high schools. A cluster investigation linked to a high school in a town in northern France found high rates of seroprevalence for anti-SARS-CoV-2 antibodies among high school students. While even higher seroprevalence among the school staff was found following an outbreak in that school, much lower seroprevalence was identified among parents and siblings of pupils, suggesting that the school was likely the source of transmission [43]. An outbreak investigation in a regional public school in Jerusalem, Israel found high rates of PCR-detected SARS-CoV-2 infection in both the staff and students in grades 7-9 -- but not grades 10-12, suggesting that in-school, rather than just community transmission contributed to the rates of infection in students in grades 7-9 [44]. A serological study in Santiago, Chile [45] following an outbreak that led to a

school closure found high rates of anti-SARS-CoV-2 antibody seroprevalence among pre-school through secondary school students, with even higher seroprevalence rates among the staff.

There is evidence of a more limited spread of SARS-CoV-2 in primary schools compared to high schools ([43] vs. [46]), which agrees with the evidence about lower susceptibility to infection in children under the age of 10y compared to older children or adolescents [13]. Nonetheless, outbreaks have been reported in certain primary schools [45].

Classroom crowding and other factors related to social distancing in classrooms/schools may play a role in the spread of SARS-CoV-2 in schools. The Jerusalem school with an outbreak [44] reported crowded classes with 35–38 students per class. The school serological study in Santiago, Chile, [45] concerned a large private school with 14 grades (from pre-school to high school) and large class sizes (25-27 students in pre-school, 36-38 students in the rest of the school). Some of the infections recorded in this study [45] could have taken place after the school was closed on March 13. However, following the introduction of infection into a preschool by adults (parent/teacher), seroprevalence in pre-school and primary school students was higher than in high school students, suggesting infections in younger students before the school closure.

As suggested above, in-school transmission has likely contributed to the large outbreaks [43-45]. We note the importance of denominator when interpreting school outbreaks as larger outbreaks may be more readily detected, whereas smaller outbreaks where mitigation measures have helped prevent larger outbreaks are less likely to be reported.

There are several examples demonstrating that mitigation measures prevent large outbreaks. During the Spring wave of the SARS-CoV-2 epidemic in New South Wales, Australia, a small number of secondary infections were recorded in a small number of schools where cases were found [47], with

widespread testing in schools and schools getting closed for 24-48 hours following case detection with contacts of detected cases subsequently quarantined. In Baden-Württemberg, Germany, where halving of group sizes and other mitigation efforts (though not mask use) were implemented [48], out of 137 detected cases of infection in schoolchildren, only 6 were found to have caused further infections in the school setting despite extensive contact tracing (infecting a total of 11 out of 1155 close contacts). A national study of COVID-19 outbreaks in schools in Germany found that those outbreaks were small, with about half the cases being the school staff [49]. A variety of mitigation measures including staggering timetables and restricting class sizes were applied throughout Germany [49]. In Salt Lake County, Utah school study, where masks in schools were mandated, the vast majority of reported outbreaks in schools were small (under 15 cases, p. 10 in [50]), with a fewer, larger outbreaks mostly taking place in high schools.

Conclusions

We found evidence that compared to younger/middle aged adults, children aged under 10y have significantly lower estimated susceptibility to SARS-CoV-2 infection, while adults aged over 60y have elevated susceptibility to infection, and they merit extra efforts for protection against infection (such as allocating certain time slots for grocery shopping among the elderly only, etc.). Some uncertainty remains about the magnitude of the difference in susceptibility of children vs. adults due to presence of biases in several published studies. On the other hand, comparisons between younger and older children are arguably more robust and – in the one study that reports them [13] – reach the same conclusion. Future studies using both virological and serological testing of contacts, and stool specimens in addition to upper respiratory samples to decrease the likelihood of missed infections may help mitigate the biases we describe.

When there is a combination of limited mitigation of SARS-CoV-2 spread in schools and relatively high community transmission, there is evidence of robust SARS-CoV-2 spread in secondary/high schools, and more limited spread in primary schools, with factors such as classroom size possibly affecting that spread. Therefore community transmission levels and combination of mitigation efforts such as social distancing, avoiding crowding/reduction in class size, widespread/timely testing, quarantine for detected cases and their contacts, and mask wearing (especially by teachers) according to the WHO guidelines as well as measures to prevent staff to staff transmission (preventing crowding in teacher rooms, mask wearing) should be considered when opening schools, particularly secondary/high schools.

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Study description	Odds ratios for infection in close contacts of an infected person or relative susceptibility to infection in close contacts of an infected person for contacts in different age groups relative to one (reference) age group				
***(3)* PCR**	<15y		15-64y		Over 65y
H+C	OR=0.34 (0.24, 0.49)		OR=1 (ref.)		OR=1.67 (1.12,1.92)
***(2)* PCR**	<20y		20-59y		Over 60y
H+C	OR=0.23 (0.11,0.46)		OR=0.64 (0.43,0.97)		OR=1 (ref.)
***(12)* PCR**	0-14y		15-64y		Over 65y
H+C	OR=0.28 (0.04, 2.04)		OR=1 (ref.)		OR= 1.64 (1.02, 2.63)
***(11)* PCR**	0-3y	4-18y	19-60y		Over 60y
H	OR=1.13 (0.29-4.48)	OR=0.09 (0.01-0.73)	OR=1 (ref.)		OR=1.23 (0.51-2.98)
***(14)* PCR**	<18y	18-29y	30-49y	50-64y	Over 65y
H	OR=0.41 (0.17,0.99)	OR=1 (ref)	OR=1.74 (0.70,4.32)	OR=2.23 (0.87,5.75)	OR=1.99 (0.67,6.0)
***(10)* PCR**	<18y		Over 18y		
H	OR= 0.18 (0.06,0.54)		OR=1 (ref.)		
***(13)* PCR**	<20y		Over 20y		
H	Susceptibility = 0.45 (0.40,0.55)		Susceptibility=1 (ref.)		
***(17)* PCR**	0-17y	18-44y	45-59y		Over 60y
H+C	OR=0.78(0.41,1.50)	OR=1 (ref.)	OR=1.16(0.70,1.92)		OR=2.34(1.39,3.97)

***(18)* PCR**	0-17y	18-39y	40-64y	Over 65y
H	OR=0.96(0.71,1.29)	OR=1 (ref.)	OR=0.89(0.67,1.19)	OR=1.31(0.75,2.19)
***(15)* PCR**	0-18y	18-49y	Over 50y	
H	OR=0.88 (0.37,2.02)	OR=1 (ref.)	OR=1.86 (0.73,4.65)	
(16)* PCR *H+C	No age-related differences in susceptibility were found			
***(19)* PCR**	<18y	Over 18y		
H	OR=1.69(0.7,4.2)	OR=1 (ref.)		
(20)	<18y	Over 18y		
Serology H	OR=0.77(0.27,2.17)	OR=1 (ref.)		
(21)	<18y	Over 18y		
Serology H	OR=1.39(0.55,3.53)	OR=1 (ref.)		

Table 1: Odds ratios for infection in close contacts of an infected person or relative susceptibility to infection in close contacts of an infected person for close contacts in different age groups relative to one (reference) age group for studies [*2,3,10-21*]. PCR: study based of PCR testing of close contacts; Serology: study based on serological testing of close contacts. H: household contacts; H+C: household + community contacts (multivariable analysis adjusting for contact setting, etc.). Also see the caveats in the *Potential biases for the estimates of susceptibility in children vs. adults* subsection.