Secondary attack rate and family clustering of SARS-CoV-2 infection in children of healthcare workers with confirmed COVID-19

Shamez N Ladhani,[1] Nick Andrews,[1] Felicity Aiano,[1] Frances Baawuah,[1] Zahin Amin-Chowdhury,[1] Kevin E Brown,[1] Gayatri Amirthalingam,[1] Mary E Ramsay,[1] Thomas Waterfield,[2] and the RAPID-19 Investigation team*

***RAPID-19 Investigation Team is listed in the acknowledgement section**

[1] Immunisation and Countermeasures Division, 61 Colindale Avenue, London NW9 5EQ, UK

[2] Thomas Waterfield, Centre For Experimental Medicine, Wellcome Wolfson Institute of Experimental Medicine, Queen's University Belfast, Belfast, UK

Corresponding Dr Shamez Ladhani, Immunisation and Countermeasures Division, 61 Colindale Avenue, London NW9 5EQ, UK. Email: shamez.ladhani@phe.gov.uk

ABSTRACT

We measured serum SARS-CoV-2 antibodies in 215 children of healthcare workers to estimate secondary attack rates (SAR). Twenty-one families had a parent with confirmed COVID-19. There was strong evidence of family clustering (P<0.001): 20/21 (95.2%) children were seropositive in 9 families and none of 23 children in 12 other families.

Keywords: COVID-19, children, secondary attack rates, healthcare workers

INTRODUCTION

Children are relatively protected against coronavirus disease 2019 (COVID-19) compared to adults.[1] Exposure to SARS-CoV-2, the virus responsible for COVID-19, typically results in asymptomatic infection or a mild, transient illness that rarely requires hospitalisation and is rarely fatal in children.[2] Systematic reviews of contact tracing studies estimate that children are 54% less likely to develop COVID-19 compared to adults,[3] while household transmission studies suggest a 3-fold lower risk of COVID-19 in children than in adults.[4] Such transmission studies, however, invariably utilised upper respiratory tract swabs to identify SARS-CoV-2 infection among contacts of confirmed cases, but this test relies on timing and technique of swabbing and is limited by the sensitivity of the RT-PCR assays for SARS-CoV-2,[5] which at least in part explains the heterogeneity of estimated secondary attack rates (SAR) in contacts of index cases, which have ranged from 4.6-90%.[4] Many studies also limited testing to symptomatic contacts only.[4] In contrast, serological studies have reported higher rates of SARS-CoV-2 infection than estimated through swabing.[6] and there is growing evidence that children are as likely as adults to be infected with SARS-CoV-2 and develop a robust antibody response.[7]

In London, England, COVID-19 cases began to increase rapidly in early March and peaked in mid-April before declining to low numbers by the end of May 2020.[8] Healthcare workers were disproportionately affected, with high rates of COVID-19, especially among clinical staff with direct patient contact.[9] We hypothesised that children of healthcare workers were more likely to be exposed to SARS-CoV-2 in a household setting, especially since most healthcare workers developed COVID-19 in March and England went into lockdown from 20 March until schools partially reopened on 01 June 2020, thus restricting opportunities for children to be exposed to SARS-CoV-2 outside the household.

The RAPID-19 study recruited children of healthcare workers in five UK cities from May 2020.[10] The study had multiple objectives, including monitoring SARS-CoV-2 infection, symptoms, illness severity, hospitalisation and seroprevalence over 4-6 months. For this analysis, we used the London cohort to estimate SAR using SARS-CoV-2 seropositivity to confirm virus exposure in a subset of children of healthcare workers with laboratory-confirmed COVID-19.

METHODS

The RAPID-19 study protocol is published online (www.clinicaltrials.gov; NCT04347408). For the London cohort, public health and National Health Service (NHS) hospital staff were informed of the study by email during May 2020 and, after parents provided written consent and completed a short questionnaire, a nasal swab and venous blood sample was taken. Nucleic acid was extracted and

analysed by an RT-PCR assay on an Applied Biosystems 7500 FAST system targeting a conserved region of the open reading frame (ORF1ab) gene of SARS-CoV-2 and an internal control.[11] Serology was performed using a chemiluminescent microparticle immunoglobulin G (IgG) immunoassay targeting the nucleoprotein (SARS-CoV-2 IgG, Abbott Commerce Chicago, USA). Data that did not follow a normal distribution were described as medians with interquartile ranges (IQR) and compared using the Mann Whitney U test. Proportions were compared using Fisher's Exact test. Family clustering of cases was assessed using random effects logistic regression (xtlogit, Stata v.15, StataCorp, Tx) with household as the random effect. The significance of the clustering parameter (rho) was tested using a likelihood ratio test.

RESULTS

A total of 126 families with 215 children from 126 families participated in the study. All nose and throat swabs tested negative for SARS-CoV-2. Twenty-one families (21/126, 16.7%) reported at least one parent who had developed COVID-19 symptoms (fever or new-onset cough) and tested positive for SARS-CoV-2 RNA by RT-PCR at the time of infection (n=19) or by serology (n=2) a few weeks later. Based on the date of symptom onset, a healthcare worker parent was the likely index case in all 21 households. At least one child had SARS-CoV-2 IgG in 9/21 (42.9%, 95%CI 21.8-66.0%) of the families with a positive parent and 20 (45.5%) of 44 children tested positive for SARS-CoV-2 IgG. There was, however, strong evidence of family clustering of seropositivity among children (rho, 0.965; 95%CI, 0.863-0.992; P<0.001) such that there were no seropositive children in 12 families and 20 (95.2%) of 21 children were seropositive in nine other families. One teenager had mild gastrointestinal symptoms 6 weeks prior to serological testing but was seronegative although his three siblings were all seropositive. In the random effects logistic regression model accounting for family clustering, the estimated overall SAR was 36.2% (9.0%-63.4%).

There were no significant differences in family size, ethnicity, source of infection (index case), degree of self-isolation by the index case between families with and without seropositive children (Table). The children in the seropositive families were more likely to be older and male and have a history of a COVID-19 like illness during the period between their parent's illness and the antibody test; all had mild, transient illness and none required hospitalisation. Overall, 58.3% (14/24) of symptomatic children were seropositive while 70.0% (14/20) of seropositive children developed symptoms.

DISCUSSION

Household studies provide a unique opportunity to study infection and transmission because there is often a more clear and fixed exposure of the infection source.[4,12,13] In children of healthcare workers with confirmed COVID-19, 20 (45.5%) of 44 children in 21 families were seropositive but there was evidence of strong family clustering, such that the SAR was 95.2% in 9 families with at least one seropositive child compared to none of the 23 children in 12 other families.

These findings are consistent with the stochastic pattern of SARS-CoV-2 transmission whereby a small proportion of cases are responsible for most of the secondary transmission.[14] One possible explanation for the familial clustering of cases is that, for wider transmission to occur, at least one child needed to become infected from the parent and that child then transmitted the virus to the other children.[15] Other potential contributing factors associated with increased household transmission include the symptoms (e.g. expectoration) and severity of illness in the parent with COVID-19,[16] as well as physical factors such as size of the home and number of rooms which may affect the ability of family members to self-isolate efficiently or maintain physical distancing within the home. Our results are consistent with the recent large-scale transmission study of 233 households in the UK where, although children were rarely the index case, they did have higher transmission rates within the household.[17] While these findings are in contrast with other household studies and especially in relation to younger children (<10 year-olds).[3] One explanation is that the authors of the UK study included possible cases which included symptomatic children who were either not tested or tested negative for SARS-CoV-2 by RT-PCR on the basis that children are more likely to have mild, transient and non-specific illness compared to adults.[17]

Detailed interviews revealed range of quarantine measures implemented by parents, with some parents isolating from their families as soon as they became symptomatic while others being unable to maintain social distancing because of the young age of their child, number of children in the family or the size of the home, for example. Interestingly, in a large Chinese household transmission study where secondary transmission ranged from 4% in children to 17% to adults, no secondary cases were reported in households where index cases implemented quarantine immediately after symptom appearance.[18]

The use of SARS-CoV-2 antibodies to assess past exposure to the virus will capture asymptomatic infections and overcomes the limitations of swabbing of symptomatic contacts to identify secondary cases, thus providing more robust SAR estimates. There are few other studies reporting serological assessments in household settings. In the Netherlands, none of the children aged <12 years

were seropositive initially and 21% (3/14) of 1-5 year-olds and 13% (4/31) of 6-11 year-olds became seropositive after 2-3 weeks later.[13] Older children and adults (9-19% seropositive) were more likely to be seropositive when the index case was diagnosed and to seroconvert 2-3 weeks later (31-43% seropositive).

A strength of this analysis is the use of serology to confirm previous SARS-CoV-2 infection in children. A limitation was that we did not perform serology on the parents which would have improved our sample size, especially since many parents were unable to get swab tests early in the pandemic despite being symptomatic. Additionally, we relied on retrospective parental recall of self-isolation practices and any symptoms in their children. The children were not tested for SARS-CoV-2 because of limited test availability but to avoid bias we did collect this information at the time of blood sampling when parents were not aware of their child's antibody status, which also explains the high rates of symptom reports in seronegative children. Other factors that might potentially contribute to an increased risk of household transmission include having respiratory symptoms. Finally, we used the timing of symptom onset to define the index case and infer the direction of transmission in household; the possibility of an asymptomatic index, therefore, cannot be excluded.

In conclusion, we found strong evidence of familial clustering of SARS-CoV-2 infection in children of healthcare workers with confirmed COVID-19. More detailed studies are needed to better understand infection and transmission involving children.

NOTES:

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REFERENCES

1. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020; 7;323(13):1239-1242.
2. Dong Y, Mo X, Hu Y, et al. Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China. Pediatrics 2020; doi: 10.1542/peds.2020-0702.
3. Viner RM, Mytton OT, Bonell C, Melendez-Torres GJ, Ward JL, Hudson L, Waddington C, Thomas J, Russell S, van der Klis F, Panovska-Griffiths J, Davies NG, Booy R, Eggo R. Susceptibility to and transmission of COVID-19 amongst children and adolescents compared with adults: a systematic review and meta-analysis. JAMA Pediatr. 2020 Sep 25. doi: 10.1001/jamapediatrics.2020.4573.
4. Lei H, Xu X, Xiao S, Wu X, Shu Y. Household transmission of COVID-19-a systematic review and meta-analysis. J Infect 2020 *(in press)*. Available at: https://www.journalofinfection.com/article/S0163-4453(20)30571-5/fulltext. Accessed: 13 October 2020.
5. Watson J, Whiting PF, Brush JE. Interpreting a covid-19 test result. BMJ 2020;369:m1808.
6. Alter G, Seder R. The Power of Antibody-Based Surveillance. N Engl J Med 2020; DOI: 10.1056/NEJMe2028079. Available at: https://www.nejm.org/doi/full/10.1056/NEJMe2028079. Accessed: 13 October 2020.
7. European Centre for Disease Prevention and Control (ECDC). COVID-19 in children and the role of school settings in COVID-19 transmission, 06 August 2020. Available at: https://www.ecdc.europa.eu/en/publications-data/children-and-school-settings-covid-19-transmission. Accessed: 13 October 2020.
8. Ladhani SN, Amin-Chowdhury Z, Davies HG, et al. COVID-19 in children: analysis of the first pandemic peak in England. Arch Dis Child 2020; archdischild-2020-320042: doi: 10.1136/archdischild-2020-320042.
9. Hunter E, Price DA, Murphy E, et al. First experience of COVID-19 screening of health-care workers in England. Lancet 2020;395:e77-e78.
10. Waterfield TW, C.; Moore, R.; et al. Seroprevalence of SARS-CoV-2 antibodies in children - A prospective multicentre cohort study. MedRxiv 02 September 2020; doi: https://doi.org/10.1101/2020.08.31.20183095.
11. Corman VM, Landt O, Kaiser M, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill 2020; 25(3):2000045.
12. Lipsitch M, Swerdlow DL, Finelli L. Defining the Epidemiology of Covid-19 - Studies Needed. N Engl J Med 2020;382:1194-6.
13. National Institute for Public Health and the Environment (RIVM). Children and COVID-19. 2020. Available at: https://www.rivm.nl/en/novel-coronavirus-covid-19/children-and-covid-19. Accessed: 13 October 2020.
14. Adam DC, Wu P, Wong JY, et al. Clustering and superspreading potential of SARS-CoV-2 infections in Hong Kong. Nat Med 2020; doi.org/10.1038/s41591-020-1092-0. Available at: https://www.nature.com/articles/s41591-020-1092-0.pdf. Accessed: 13 October 2020.

15. Okarska-Napierala M, Mandziuk J, Kuchar E. SARS-CoV-2 Cluster in Nursery, Poland. Emerg Infect Dis 2020;27. Available at: https://wwwnc.cdc.gov/eid/article/27/1/20-3849_article. Accessed: 13 October 2020.
16. Luo L, Liu D, Liao X, et al. Contact Settings and Risk for Transmission in 3410 Close Contacts of Patients With COVID-19 in Guangzhou, China : A Prospective Cohort Study. Ann Intern Med 2020.
17. Lopez Bernal JP, N.; Byers, C.; et al. Transmission dynamics of COVID-19 in household and community settings in the United Kingdom. MedRxiv 22 August 2020;https://doi.org/10.1101/2020.08.19.20177188
18. Li W, Zhang B, Lu J, et al. The characteristics of household transmission of COVID-19. Clin Infect Dis 2020; ciaa450, https://doi.org/10.1093/cid/ciaa450. Available at: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa450/5821281. Accessed 13 October 2020.

Table. Characteristics of families and children of healthcare workers with at least one parent who developed confirmed COVID-19 during the first peak of the pandemic in England

FAMILY CHARACTERISTICS	**Seronegative children (12 families)**	**At least one SeroPOSITIVE child (9 families)**	**P-value**
Index case			P=0.49
Father	5 (41.7)	5 (55.6)	
Mother	7 (58.3)	3 (33.3)	
Both	0 -	1 (11.1)	
Self-isolation by index case(s) *			P=0.36
Yes	4 (33.3)	3 (33.3)	
Partial	0 -	2 (22.2)	
No	8 (66.7)	4 (44.4)	
Median Number of Children	2 (1-3)	2 (2-3)	P=0.65
Number of children			P=0.67
1	4 (33.3)	3 (33.3)	
2	5 (41.7)	3 (33.3)	
3	3 (25.0)	1 (11.1)	
4	0	1 (11.1)	
5	0	1 (11.1)	
Ethnicity of children in the house hold			P=1.00**
White British	7 (58.3%)	5 (55.6%)	
White Other	1 (8.3%)	1 (11.1%)	
Black African	1 (8.3%)	0 -	
Asian	2 (16.7%)	1 (11.1%)	
Mixed	1 (8.3%)	2 (22.2%)	
Median interval (days) between parental SARS-CoV-2 test and child antibody test (IQR)	65 (36-70)	67 (60-79) *****	P=0.39
CHILD CHARACTERISTICS	**23 children**	**21 children**	**P-value*** **
Child Seropositivity			
Positive	0 -	20 (95.2)	
Negative	23 (100%)	1 (4.8)	
Child gender			P=0.014
Male	6 (26.1)	14 (66.7)	
Female	17 (73.9)	7 (33.3)	
Median child age (IQR)	6.3 (3.3-8.6)	9.1 (5.9-11.6)	P=0.044

Child Age Group			
<5y	9 (39.1)	5 (23.8)	P=0.010
5-10y	13 (56.5)	7 (33.3)	
11-15y	1 (4.4)	9 (42.9)	
Child Symptomatic ****			P=0.040
Yes	9 (39.1)	15 (71.4)	
No	14 (60.9)	6 (28.6)	

** The parent(s) with COVID-19 reported every attempt to self-isolate in the home as soon the first symptoms developed (YES), some attempt to self-isolate but admitting that this was not always possible with the children at home (PARTIAL) or no attempt to self-isolate from any family member*

*** white vs. non-white ethnicity*

**** the calculated P value does not allow for any clustering at the family level for these variables.*

***** parents were asked if their children had developed any symptoms typical of a viral illness, including respiratory (fever, cough, runny nose, sore throat, etc.) and gastrointestinal (vomiting, diarrhoea, etc.) infections – the children were not tested for SARS-CoV-2 infection at the time of their illness because of limited availability of testing at the time*

****** date of onset of infection was used for the two seropositive parents who were the index case in two households and did not have a swab test for SARS-CoV-2 during acute infection*