PHE enhanced surveillance of household contacts: interim analysis

Version 2.0 July 20th 2020

1. Background

As an extension of the FF100 follow up, from March 20th 2020 the households of individuals (index cases) with a PCR confirmation of COVID-19 who were registered at practices contributing to the Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) were asked to participate in enhanced surveillance to document transmission under conditions of household exposure. From June 5th 2020, when RCGP RSC cases had declined to a low level, index cases were also recruited via Pillar 2 testing with emphasis on recruitment of index cases who were children.

The primary objectives of the household surveillance were based on the WHO generic household transmission protocol[1] and were to measure:

(i) The infection rate in household contacts by age (of the contact)
(ii) The proportion of individuals infected who develop symptoms by age
(iii) The proportion of infected individuals without symptoms with evidence of viral shedding
(iv) The proportion of confirmed cases that are still swab positive 7 days or more after symptom onset

2. Design

Households in which the index case had at least one household contact who was not already known to be PCR positive were recruited by PHE nurses who phoned the index case on receipt of the positive result (Day 1). The index case and household contacts were administered a questionnaire with solicited symptoms and medical history on Day 1 and again on Day 14. Packs containing nasal and oral fluid (OF) swabs to be taken on receipt (around Days 2-4) with a second nasal swab sample to be taken 7 days later were sent to each household member together with a symptom diary to be completed each day for 14 days (starting retrospectively on Day 1). The nasal swabs and OF samples were tested for SARS-CoV-2 virus by PCR and from May 19th 2020, nasal swabs were couriered to the Virus Reference Laboratory for culture in addition to PCR to check for viable virus. Blood samples were obtained from all consenting family members around Day 35 together with a second OF sample.

Serum was tested for IgG antibody to the SARS-CoV-2 nucleoprotein by the Abbott assay with test results ≥0.8 taken as antibody positive. Samples were also tested by an in-house IgG ELISA that measures antibody to the receptor binding domain (RBD) for which a positive result is taken as ≥5.0. In this report a serologically confirmed infection is defined as antibody positive by either assay; both have shown high specificity in serum samples taken before the emergence of COVID-19 (99.1% (98.4-99.6) for the Abbott assay and 98% (97-98.8) for the RBD) at the cut-offs used in this analysis.[2] Blood samples are also being tested for neutralising antibody by a plaque reduction neutralisation assay using live virus and also for IgG antibody to the spike protein by the EUROIMMUN assay (results not yet available). Suitable assays for measuring antibodies in OF are under development at PHE.

[1] Available at https://www.who.int/publications-detail/household-transmission-investigation-protocol-for-2019-novel-coronavirus-(2019-ncov)-infection
2 https://www.gov.uk/government/publications/national-covid-19-surveillance-reports

The study design allows the following additional questions to be addressed:

a) What is the serial interval distribution between onset of symptoms in the primary case and secondary cases?
b) Of those contacts reporting symptoms what proportion have evidence of infection (as defined by a nasal swab positive for SARS-CoV-2[3] and/or antibody to SARS-CoV-2 detected at the 35 day follow up), and for each symptom reported (the first time it was reported) in the contacts what proportion of individuals have evidence of infection (i.e the positive predictive value (PPV) of different symptoms)?
c) For those contacts with evidence of infection what proportion reported each symptom at the time of the first symptoms (sensitivity of symptoms).

3. Analysis methods

Index case, primary case, co-primary case and serial interval

Each family has an index case (the case that led to the household being recruited). In some households this individual is not the individual with the first symptoms. For calculation of secondary attack rates and serial intervals, contacts will be excluded if they are potentially the first case themselves (onset prior to the onset in the index case) or are co-primary (onset on the same day or the day after the index case). Contacts that are symptomatic but do not have antibodies or a PCR positive swab are assumed to be uninfected.

Age grouping

Ages of index cases and contacts were grouped into ≤18, 18-54, 55 years to broadly represent school age children, young adults and parents with young children, and older adults.

Asymptomatic infections

Asymptomatically infected contacts are assumed to be secondary cases, but this is not known as they may have been infected prior to onset or at the same time as the index case. Also, some Pillar 2 index cases are asymptomatic having been identified, for example, through testing in an outbreak situation. These asymptomatic index cases are predominantly under <18 years of age (12/15 so far). For infected individuals (index cases and contacts) who do not report symptoms on the Day 1 and Day 14 questionnaires or the daily dairies, an index date will be assigned as 3 days prior to the PCR test date. This will be used as a proxy "onset" date to allow identification of potential co-primary asymptomatic infections which will be excluded for the purposes of calculating secondary attack rates; for asymptomatic contacts who are PCR negative and identified as infected by serological testing alone exclusion of potential co-primary cases is not possible. Secondary attack rates with the exclusion of all asymptomatic infected contacts will also be calculated but will be an underestimate.

[3] PCR positive oral fluid swabs were also detected and in some instances were positive but the accompanying first nasal swab was negative. All infected contacts with an OF PCR positive/nasal swab negative test (n=4) are included in this analysis as they were also antibody positive. The day 35 OF swabs have not yet been tested for virus. The PCR data from OF swabs will be included in the final analysis with an evaluation of the sensitivity of this method of confirmation compared with nasal swabbing.

Missing symptom information

Where one or more solicited symptoms are recorded, it was assumed for this analysis that other solicited symptoms are absent even if not specifically stated as "No" on the Day 1 and 14 questionnaires. If stated as Not Known this was treated as missing data. For the final analysis missing and unknown symptom information from the Day 1 and Day 14 questionnaires will be cross checked against the 14 day symptom diaries and questionnaires updated where appropriate.

Selection of household members for different objectives

More household contacts are identified as a result of serology than PCR testing. Secondary attack rates that include contacts without a serology result will therefore be an underestimate. In this interim analysis, serology results are missing for 155 household contacts; 133 are in households not yet eligible for the blood sample or the result is awaited. For the remaining 22 individuals blood samples have been declined or there was a failed venepuncture; 20 are children.

The datasets used in this analysis are defined as follows.

A1: any contact with either a PCR or a serology result but excluding contacts that are co-primaries or with onset before the index case.

B1: contacts with a serology result but excluding contacts that are co-primaries or with onset before the index case.

Analyses for the different objectives are then based on these datasets as given below.

For objective (i): This will be based on datasets A1 and B1. In addition for this interim report this will also be done just based on using PCR as the end point when assessed by age of index. Also for age of index an additional restriction to just households where the index case is the primary case will be done.

For objective (ii): This will be based on the subset of dataset B1 who are infected

For objective (iii): This is based on all contacts with positive serology results and with a PCR test done

For objective (iv): For this analysis all index cases as well as contacts with a symptom onset date and evidence of infection (PCR or antibody positive) will be included. Interval will be divided into (-7 to -1),(0 to 3),(4 to 6),(7 to 10),(11 to 13),(14 to 20) and 21+ days. In the final report, this analysis will be restricted to those who are serologically confirmed contacts as inclusion of infected contacts identified solely on the basis of a positive PCR will overestimate the sensitivity of PCR. Similarly inclusion of index cases will also bias upwards the sensitivity estimate as index cases all have an initial PCR positive swab.

For additional objective a) This will be dataset A1. Those with no symptoms will be recorded as not known. Where intervals exceed 10 days evidence of tertiary infection will be assessed by looking at serial intervals between contacts within households.

For additional objective b) This will be all contacts who have symptoms and a serology result.

For additional objective c) This will be the contacts for whom an infection is identified.

4. Descriptive analysis

A total of 131 households are included in this interim analysis with 315 contacts. Occupations, where given, of the index cases are shown below. The proportion of children is biased by the preferential recruitment of Pillar 2 cases in children in recent weeks.

Table1: Index by occupation

Occupation	Count
HCW	24
Care Home or carer in community	24*
Other public facing worker[1]	10
Office worker	15
Teacher	2
Pre-school/school child	38
Other	17**
Not stated	1
Total	131

[1]Police, driver, cleaner, supermarket worker, postman

* Includes one 16 year old

** Includes a 17 year old

Numbers by household size are given below as well as numbers in datasets for analysis

Table 2: numbers by household size

Household size	Households	contacts total	contacts in A1	contacts in B1
2	42	42	34	28
3	26	52	41	19
4	38	114	97	29
5	20	80	74	34
6	4	20	18	8
8	1	7	4	1
total	131*	315	268	119

*In 15 of these households the index case was asymptomatic (total 37 contacts); 12 of these 15 index cases were ≤18 years

Numbers of index cases and contacts tabulated by age and sex of each are shown below

Table 3: Cases and contacts by age and sex

	index cases	contacts	contacts in A1	contacts in B1
Sex				
F	81	151	127	50
M	50	164	141	69
Age group				
<=18	40	123	114	45
18 to 54	67	150	124	57
>=55	24	42	30	17

When the number of contacts is tabulated by age of the index case (Table 4) there are currently relatively few contacts with serology in households with an index cases who is a child (dataset B1) due to the recent preferential recruitment of Pillar 2 index cases who are children; the 35 day blood samples from these recently recruited households are not yet due.

Table 4: numbers by age of index case

Age Index	cases	contacts	households in dataset A1	contacts in dataset_A1	households in dataset B1	contacts in dataset B1
<=18	40	120	38	111	3	5
18 to 54	67	160	58	130	50	93
>=55	24	35	21	27	18	21

Secondary attack rates (objective i)

Note that the 95% CIs given here do not allow for clustering. This will be done in the final report but are not expected to be much wider.

Table 5 shows secondary attack rates by the age of the contact among those that have had a serological follow up. The overall secondary attack rate showed little variation by age group.

Table 5: Secondary attack rates in contacts who have had serological follow up (dataset B1)

Age group contact	Infected	Uninfected	Total	% infected (95% CI)
<=18	21	24	45	46.7% (31.7-62.1)
18 to 54	29	28	57	50.9% (37.3-64.4)
>=55	7	10	17	41.2% (18.4-67.1)
Total	57	62	119	47.9% (38.7-57.2)

As indicated in Table 4, there is little serological data as yet to assess secondary attack rates by age of index case (Table 6).

Table 6: based on dataset B1 – by age of index case

Age group index case	Infected	Uninfected	Total	% infected (95% CI)
<=18*	2	3	5	40.0% (5.3-85.3)
18 to 54	47	46	93	50.5% (40-61.1)
>=55	8	13	21	38.1% (18.1-61.6)
Total	57	62	119	47.9% (38.7-57.2)

*Note that for the 3 households where the index case was <=18, two had earlier cases in the household before the index case and in one a contact was asymptomatic.

In the final report an analysis will be conducted restricted to households where the index case is also the primary case in the household and is symptomatic. Table 7 shows secondary attack rates based on PCR results alone for comparison with the results of other published household contact studies which have not included serology. Based just on the PCR results secondary attack rates appear lower in households with an index case who is a child. However these include asymptomatic index cases; there are at present insufficient index cases who are both the primary case and symptomatic (n=2) to assess transmission using serological outcomes. The 35 day blood samples from these recently recruited households with childhood index cases are not yet due.

Table 7: Secondary attack rates excluding serology and based on PCR only – by age of index case

age_group index case	PCR pos	PCR neg	Total	% infected
<=18	4	107	111	3.6% (1-9)
18 to 54	23	107	130	17.7% (11.6-25.4)
>=55	7	20	27	25.9% (11.1-46.3)
Total	34	234	268	12.7% (8.9-17.3)

Symptoms in those infected (objective ii)

Table 8 shows the proportion of infected contacts who reported symptoms. The proportion symptomatic was similar across age groups. In the final analysis, the types of symptoms reported by age group will be examined.

Table 8: proportions with symptoms in those infected (data B1 and infected)

age_group contact	yes	No	Total	% symptoms (95% CI)
<=18	16	5	21	76.2% (52.8-91.8)
18 to 54	22	7	29	75.9% (56.5-89.7)
>=55	4	3	7	57.1% (18.4-90.1)
Total	42	15	57	73.7% (60.3-84.5)

Proportion of individuals infected without symptoms but with evidence of viral shedding (objective iii)

Only around a third of contacts who were antibody positive were PCR positive on either the first and/or second nasal swab (Tables 9 and 10). This was similar whether or not they had symptoms (Table 9) and there was little difference in the proportion PCR positive by age group (Table 10).

Table 9: PCR detection in contacts with evidence of infection (these must be antibody positive)

symptoms	PCR pos	PCR neg	Total	% PCR+ (95% CI)
No	5	10	15	33.3% (11.8-61.6)
Yes	30	53	83	36.1% (25.9-47.4)
Total	35	63	98	35.7% (26.3-46)

Table 10: PCR detection in contacts with evidence of infection by age (these must be antibody positive) irrespective of symptoms

Age of contact	PCR pos	PCR neg	Total	% PCR+ (95% CI)
<=18	11	17	28	39.3% (21.5-59.4)
18 to 54	17	36	53	32.1% (19.9-46.3)
>=55	7	10	17	41.2% (18.4-67.1)
Total	35	63	98	35.7% (26.3-46)

PCR positivity in infected contacts and index cases by time since symptom onset (objective iv)

Table 11 shows PCR positivity among confirmed cases (by serology or PCR) by interval from symptom onset to date of either first or second swab). Around half were PCR positive from a few days before symptom onset to 9 days after. From day 10 onwards, the proportion positive drops steadily.

Table 11 – PCR positive nasal swab by time since onset of symptoms in infected contacts and index cases– first and second nasal swab combined.

interval from onset (days)	Pos	neg	Tot	% Pos (95% CI)*
-7 to -1	3	3	6	50% (11.8-88.2)
0 to 2	2	2	4	50% (6.8-93.2)
3 to 6	10	10	20	50% (27.2-72.8)
7 to 9	21	17	38	55.3% (38.3-71.4)
10 to 13	26	58	84	31% (21.3-42)
14 to 20	21	127	148	14.2% (9-20.9)
21 to 27	4	66	70	5.7% (1.6-14)
28+	3	24	27	11.1% (2.4-29.2)
Total	90	307	397	22.7% (18.6-27.1)

*95% CI does not account for repeated measures

Note that this analysis will be done in the final report just in those with serology with addition of median CT values and where available the results of virus culture. If data allow the -7 to -1 group will be further stratified.

Serial Intervals

Intervals are shown from the index case onset to contacts' onsets (PCR positive or serology positive). By definition they must be at least 2 days. For longer intervals (10 days or more) the possibility of tertiary cases in the household was assessed and these are shown separately in Table 12. The median serial interval is 4 days and IQR 3 to 8 days

Table 12: Serial intervals. These are shown separately in households where there is evidence of a tertiary case

Interval (days)	count (no tertiary households)
2	2
3	13
4	10
5	5
6	0
7	1
8	2
9	3
10	1
11	1
12	0
13	3
14	0
15	2
16	0
17	0
20	1
Intervals from index	Households with putative tertiary cases
9, 10, 13	1 with 3 contacts
5,23	1 with 2 contacts
total contacts	49

Symptoms

Positive predictive value of symptoms:

Table 13 shows the proportion of those with each symptom where there is evidence of infection. For this analysis only symptoms reported at the time the first symptoms were reported on either the day 1 or day 14 questionnaire were included. This analysis is restricted to contacts who have had a serological result, and includes all such contacts even if a co-primary or with onset before the index

case. Given the high secondary infection rate in the contacts the PPV value of individual symptoms will be substantially higher than in the general population.

Table 13: Infection rate in those contacts with symptoms

Symptom	n infected / N with symptom	% (95% CI)
Any symptom	83/110	75.5% (66.3-83.2)
Fever	33/34	97.1% (84.7-99.9)
Runny nose	27/30	90% (73.5-97.9)
Cough	54/62	87.1% (76.1-94.3)
dry_cough	38/45	84.4% (70.5-93.5)
prod_cough	13/13	100% (75.3-100)
Short of breath	24/29	82.8% (64.2-94.2)
Sore throat	31/38	81.6% (65.7-92.3)
Loss taste/smell	37/40	92.5% (79.6-98.4)
Nausea	8/9	88.9% (51.8-99.7)
Diarrhoea	13/17	76.5% (50.1-93.2)
Headache	24/30	80% (61.4-92.3)
Muscle/bodypain	18/18	100% (81.5-100)
Fatigue	59/72	81.9% (71.1-90)

Comments

The results of this provisional analysis need to be interpreted with caution given the lack of serological outcome data for the most recently recruited households which will predominantly affect household contacts who have been exposed to an index case who is a child. Basing the analysis solely on PCR test results in contacts (Table 7) suggests a lower secondary attack rate in those exposed to an index case ≤18 years but no definitive conclusions should be drawn until the serological outcome data are available and there are sufficient primary symptomatic index cases in ≤18 year olds for analysis. As shown in Table 11 self-swabbing with a single nasal swab in this population appears to have a relatively low sensitivity in detecting infected contacts even if swabbed within a few days of onset of symptoms (around 50% PCR positive).

From the serological and PCR data for contacts so far available there is no indication that children with household exposure are less likely to be infected than adults (Table 5) nor that if infected they are more likely to be asymptomatic (Table 8).

The proportion of infected contacts who were PCR positive was similar in those with and without symptoms (Table 9) and was not lower in infected children than adults (Table 10). However, these analyses are dependent on having a serological outcome in the contact for whom numbers are still relatively limited.

In the household surveillance it was not feasible to obtain acute serum samples to allow identification of 4-fold rises in titre. Confirmation of infection was therefore based on detection of SARS-CoV-2 antibodies by a sensitive and specific assay. Given the high specificity of the two assays used the PPV of a positive antibody test in this household contact population, of whom a substantial proportion is infected, will be very high. The sensitivity of the Abbott and RBD assays for samples taken within 3-6 weeks of onset in PCR confirmed cases is currently estimated to over 90%,[4] which would allow the majority of infected contacts to be identified irrespective of their PCR result. Among the 88 index cases in this interim analysis for whom an antibody result is available, 85 (96.6%) were antibody positive with the Abbott and/or the RBD assay confirming the high sensitivity in this household population. Paired acute and convalescent oral fluid samples were obtained which may allow confirmation of additional PCR negative infected contacts who failed to provide blood samples. Of those contacts without blood samples, the majority are children. The acute OF sample may also allow the identification of contacts who were infected prior to the index case.

Table 13 shows that while the use of clinical case definitions alone in household contact studies may accurately identify secondary cases, they lack sensitivity (Table 14); the only individual symptoms present in more than half the infected contacts were cough and fatigue. Further analysis of the PPV and sensitivity of symptoms will be conducted when all the available symptom data has been cross checked. Further analyses on outcome and clinical presentation will also be conducted using data collected on subjects' co-morbidities.

4 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/890566/Evaluation_of_Abbott_SARS_CoV_2_IgG_PHE.pdf

Of the household contact studies from China so far published [5,6,7] none has had serological follow up of contacts, just PCR swabbing. This interim analysis shows that secondary attack rates based on PCR alone may be a substantial underestimate. A small household contact study from the Netherlands had serological follow up with evidence of infection found in 16% of children and 24% of adults[8]; however serum samples were taken within 2-3 weeks which may be too soon for antibody development if using an assay based on the S1 antigen[2]. Few index cases in this study were children.

In order to compare secondary attack rates in households with index cases who are children with those with an adult index case it is important to have index cases who are both the primary case and are symptomatic; in this interim analysis a greater proportion of the index cases in children are asymptomatic (12/40) compared with 3/91 in adults. It is estimated that to obtain secondary attack rates with a precision of +/- 10% around 40 symptomatic primary index cases in children are required, assuming that each provides around 3 household contacts and assuming 80% have a serological result. Recruitment will continue to ensure that this minimum number is reached.

Nick Andrews, Pauline Kaye, Jamie Lopez-Bernal, Liz Miller 20/7/2020

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[8] Van der Hoek W et al. The role of children in transmission of SARS-CoV-2. NED TIJDSCHR GENEESKD. 2020;164:D5140