Children are unlikely to have been the primary source of household SARS-CoV-2 infections

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ABSTRACT

BACKGROUND: Since its identification on the 7th of January 2020, SARS-CoV-2 has spread to more than 180 countries worldwide, causing >11,000 deaths. At present, viral disease and transmission amongst children is incompletely understood. Specifically, there is concern that children could be an important source of SARS-CoV-2 in household transmission clusters.

METHODS: We performed an observational study analysing literature published between December 2019 and March 2020 of the clinical features of SARS-CoV-2 in children and descriptions of household transmission clusters of SARS-CoV-2. In these studies the index case of each cluster defined as the individual in the household cluster who first developed symptoms.

FINDINGS: Drawing on studies from China, Singapore, South Korea, Japan, and Iran a broad range of clinical symptoms were observed in children. These ranged from asymptomatic to severe disease. Of the 31 household transmission clusters that were identified, 9.7% (3/31) were identified as having a paediatric index case. This is in contrast other zoonotic infections (namely H5N1 influenza virus) where 54% (30/56) of transmission clusters identified children as the index case.

INTERPRETATION: Whilst SARS-CoV-2 can cause mild disease in children, the data available to date suggests that children have not played a substantive role in the intra-household transmission of SARS-CoV-2.

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INTRODUCTION

On the 31st of December 2019, the World Health Organisation (WHO) was informed of a series of unknown pneumonia cases emerging in Wuhan City, Hubei Province, China. On the 7th of January, 2020 the causative agent of these infections was identified as a novel coronavirus subsequently named SARS-CoV-2. This virus eventually spread to more than 180 different countries worldwide and in March 2020 the WHO declared SARS-CoV-2 a pandemic. At the time of writing (22nd March, 2020) SARS-CoV-2 has infected >274,000 people resulting in >11,000 deaths.[1] Large data analyses have shown that the elderly are particularly susceptible to severe forms of COVID-19 (the clinical manifestation of SARS-CoV-2 infection).[2] However, disease severity and transmission amongst the paediatric population is less well defined. In an analysis of the 44,672 confirmed COVID-19 cases in China only 2·1% were found to be in children (≤19 years of age),[2] suggesting a reduced rate of infection in this age group. However, this observation remains controversial as others have suggested that the rate of SARS-CoV-2 infection in children under ten (7·4%) is similar to the population average (7·9%).[3] The current consensus is that clinical symptoms of COVID-19 are, on average, milder in children (although severe infections can still occur).[4–8] Such observations are consistent with the lower incidence of severe disease amongst children following infection with other coronaviruses including severe acute respiratory distress syndrome (SARS) or Middle East respiratory syndrome (MERS).[9,10] However, this lower incidence of clinical symptoms (and therefore lower incidence of detected disease) raises concerns that children could be an important source of SARS-CoV-2 in household transmission clusters.[8]

To address this question we performed an observational study using currently published literature of the clinical features of SARS-CoV-2 in children and descriptions of household transmission clusters of SARS-CoV-2.

METHODS

Data collection

We retrospectively investigated published and publically released, de-identified, data made available between Dec 1, 2019, and March 18, 2020. Information was accessed from World Health Organization news[11], local health authority's news releases, Google Scholar, PubMed, the Lancet COVID-19 resource centre[12], Clinical Infectious Disease Journal, New England Journal of Medicine, and three Chinese databases (CNKI, Wanfang, and CQVIP).

We performed the searching and reviewing using the terms (“severe acute respiratory syndrome coronavirus 2”[All Fields]) OR ("SARS-CoV-2"[All Fields]) OR (“COVID-19” [All Fields]) AND ("Children"[All Fields] OR "Paediatric"[All Fields]) OR ("Family"[MeSH Terms] OR "Family"[All Fields])”. To examine H5N1 avian influenza household transmission eventS, we used search queries “H5N1[All Fields] AND ("Children"[All Fields] OR "Paediatric"[All Fields]) AND (family cluster[All Fields])”. A total of 166 articles were retrieved and reviewed (available in either English or Chinese). Of these, 126 articles were excluded because i) they did not report paediatric infections ii) did not report sufficient individual case data and/or iii) did not report family clusters. Individual paediatric patient data was obtained from the reviewed studies and was only excluded if the individual was recorded as having leukaemia (n = 1) or if the blood panel data was descriptive, rather than numerical (e.g. 'elevated platelets') (n=10). The intra-household transmission clusters were also sourced from information provided by local health authority's news of China, Europe, France, Germany, Italy, Japan, and South Korea when available. Any intra-household cluster identified in these local sources was included in the study.

SARS-CoV-2 case definition and diagnosis

Case definitions and diagnosis, epidemiological investigation of SARS-CoV-2 cases and laboratory-confirmed test assays were according to the relevant national diagnostic criteria. The incubation period was defined as the time from exposure to the onset of illness, which was estimated among patients who could provide the exact date of close contact with individuals with confirmed SARS-CoV-2 infection.

Definitions of household transmission clusters

A household transmission cluster was defined as a group of ≥ 2 confirmed cases of SARS-CoV-2 or H5N1 influenza virus infection in co-habiting individuals in whom the onset of cases occurred within 2 weeks of each other. Co-habiting individuals were defined as parents, children, partners, siblings, grandparents, grandchildren, uncle/aunts, nieces/nephews, family-in-law and live-in employees. The index case of each cluster was defined as the individual in the household cluster who first developed symptoms. Adults were defined as individuals equal to or over the age of 18 whilst children were defined as individuals less than 18 years of age. The decision tree used to classify household transmission clusters is shown in Figure 1.

Role of the funding source – The sponsors of this study had no role in the study design, collection, analysis, and interpretation of data, report writing, or the decision to submit for publication.

RESULTS

We identified 166 articles that described SARS-CoV-2 infection in children, rejected 126 articles due to a lack of sufficient and or appropriate data and derived a total of 40 articles in addition to case information obtained from local news sources.

A broad range of disease severity was observed (Table 1). Whilst approximately 19% of paediatric cases were asymptomatic, severe cases (12%) were still observed. In children, the predominant symptoms associated with disease onset were fever (77%) and cough (59%), whilst only a minority of children were reported to display fatigue (2%). The majority of children showed abnormal chest computer tomography (CT) although almost 30% of cases had normal chest CTs. The mean incubation period across these studies was 7.74 d ± 3.22.

Mean complete blood counts were largely unremarkable, with the mean values falling within the normal reference ranges for children aged 6-12 years[46]. (Table 1). In contrast, blood chemistry analysis showed that the mean value of c-reactive protein (18.46 mg/L) was elevated compared to the 10mg/L suggested as the upper limit of the normal reference range for children[47]. Similarly, the mean level of lactate dehydrogenase level detected in the blood of children infected with SARS-CoV-2 (315.75U/L) was elevated relative to the recommended reference range for children aged 1 to 10 years (<305U/L)[48]. Together, these data suggest that SARS-CoV-2 induces a broad range of clinical symptoms in children and can manifest as either an asymptomatic, mild or severe infection.

Asymptomatic infections experienced by children infected with SARS-CoV-2 could have important implications for transmission. Specifically, a number of asymptomatic or mild paediatric cases could result in children driving the intra-household transmission of SARS-CoV-2.[8] To investigate this hypothesis, we examined the available published data on SARS-CoV-2 household transmission clusters. A total of 31 household transmission clusters were identified with sufficient information available to include in this analysis (Table 2). These cases were drawn from China, Singapore, the USA, Vietnam, and South Korea. Of these transmission clusters, only three (9·7%) were identified as having a paediatric index case (Table 2). Importantly, these data do not suggest that children are not becoming infected with SARS-CoV-2, as isolated paediatric SARS-CoV-2 infections would not be captured in reports of household transmission (and are indeed shown in Table 1). Rather, these data suggest that to date, children have not been the primary source of household SARS-CoV-2 infections.

The limited number of defined SARS-CoV-2 household clusters with children as the index case could have been influenced by the fact that disease in children can be asymptomatic. Accordingly, it is possible that within a household cluster children were not correctly identified as the index case of the infection (i.e. the first to develop symptoms) and were instead mistakenly identified as a contact case. To exclude this possibility, we reanalysed the data looking at the number of families where an adult was identified as the index but one or more children were identified as asymptomatically infected (Figure 1). However, even if we assume that all asymptomatic children in these families were in fact the index case, only 6/28 (21%) children were identified as the index case in the household cluster (Table 2). These data suggest that even if children are being mistakenly overlooked as the index case, they are still likely to only have accounted for a limited percentage of household cluster transmissions of SARS-CoV-2.

It is also possible that these data were influenced by the fact that early in the SARS-CoV-2 outbreak, infections were associated with travel to outbreak areas (i.e. initially to Wuhan itself and later to the entirety of the Hubei province). Travel is much more likely to be undertaken by an adult in the family, rather than a child under the age of 16 years, potentially cofounding the results. To control for this factor, we reanalysed the data only including household transmission clusters where the index case had no history of travel or the whole family was located in (or had a history of travel) to an outbreak area. This resulted in a total 23 cases, two of which (9%) were identified as having a child as the index case in the cluster.

Finally, we wished to determine if the limited number of paediatric index cases was specific to SARS-CoV-2 or if it was a typical phenomenon associated with zoonotic infections. To do so, we examined 56 family clusters of highly pathogenic H5N1 avian influenza transmission events (Table 3). Here, 54% (30/56) of transmission clusters identified children as the index case. These data suggest that whilst children can facilitate the intra-household transmission of some viral infections, the data available to date suggest that children have not played a substantive role in the intra-household transmission of SARS-CoV-2.

DISCUSSION

Understanding the pathogenesis and transmission of SARS-CoV-2 in children is of paramount importance to reducing the severity of the pandemic and implementing appropriate public health controls.

Here, we analyse previously published literature from China, Singapore, South Korea, Japan, and Iran to show that children infected with SARS-CoV-2 displayed a broad range of clinical characteristics. Whilst some children developed severe disease, others presented asymptomatically with normal chest CT findings. These data are consistent with current consensus is that clinical symptoms of COVID-19 are, on average, milder in children (although severe infections can still occur).[4–8] Similarly findings have been made in children infected with either SARS or MERS.[9,10] At present, it remains unclear why children may develop less severe forms of COVID-19. It has been suggested that the receptor for SARS-CoV-2, ACE2, may be expressed at a lower level in children than in adults.[16] Alternatively, these observations may reflect the fact that the paediatric immune system is more adept than that of adults at dealing with infections for which there is no pre-existing immunity.[58,59] This is reflected in the comparatively mild infections experienced by children upon infection with measles virus and varicella zoster virus.[60,61] Understanding age-dependent differences in the pathogenesis of SARS-CoV-2 remains a key priority for future research.

We showed that of the 31 recorded SARS-CoV-2 household transmission clusters there were only three incidences of children being identified as the index case in the family. This observation is supported by previous evidence from China, where a study of 66 family transmission clusters showed that children were never the first in the family to be diagnosed with COVID-19.[62] Similarly, a separate study of 419 household SARS-CoV-2 transmission clusters in China did not detect a single cluster where the index case was under the age of 15, and only three where the index case was under the age of 18.[63] Early observations from Wuhan also suggested that children were most likely to be diagnosed with SARS-CoV-2 following an exposure history to a household infection, indicating that even in epidemic areas children were more likely to be contact, rather than index cases.[64,65] The reasons for these observations remain unclear. These data may reflect an overall lower incidence of infection in children.[2] Alternatively, these data may reflect altered viral shedding (either in titre or duration) in children or an alternate, less efficient route of virus transmission from infected children to adults.[24,66] It is also possible that children simply have fewer interactions outside of the home than adults and are therefore less likely to be index cases. This may be magnified in countries which have implemented school closures in an attempt to control the outbreak. However, it is worth noting that Singapore did not mandate the closure of schools and yet still did not detect any household clusters of transmission of SARS-CoV-2 with children as the index case.[13,67] Similarly, should children have fewer interactions outside the home it would suggest that children would be unlikely to be the index case in any household transmission event. In contrast, our analysis of household transmission clusters of highly pathogenic H5N1 avian influenza show that children were frequently the index case. Whether this difference simply reflects the different route of transmission of these infections (poultry-to-human vs person-to-person spread) remains to be determined.

There is a growing body of evidence suggesting that asymptomatic individuals play an important role in the transmission of SARS-CoV-2 in the community[68-70]; However, such studies do not negate the results of the present study, as both children AND adults can present with an asymptomatic infection. This is perhaps best demonstrated by the outbreak of SARS-CoV-2 on board the Diamond Princess cruise ship[66]. Here, 634 individuals were infected. Of these infected individuals, only six were aged 0–19 years, 152 were aged 20–59 years and 476 were 60 years and older. Despite the near absence of children on the ship, 328 of the 634 infected individuals were asymptomatic. These data clearly indicate that asymptomatic infections are not limited to the paediatric population. Therefore, perhaps one of the most effective public health intervention strategies would be to identify and isolate asymptomatically infected adults, as it is these individuals who have numerous contacts outside the home and may be contributing to viral spread.

There are important caveats that need to be acknowledged when interpreting these data for public health policy. Our analysis of household transmission clusters was also based on the assumption that the incubation period for SARS-CoV-2 was approximately equivalent in children and adults. Whilst we did not observe any significant difference in the incubation time of infected children and their infected adult relatives (data not shown), others have suggested there might be a longer incubation period for SARS-CoV-2 in children[71]. It is also possible that the analysis performed herein was impaired by the policy within particular countries to only test contacts of a known COVID-19 patient when and if they become symptomatic. This could result in the number of asymptomatically infected individuals being underestimated. Importantly, China rapidly implemented a policy to test both symptomatic and non-symptomatic contacts, suggesting that this limitation would only apply to transmission clusters detected outside of China. Nevertheless, despite these important limitations, these data suggest that children are unlikely to be driving the household transmission of SARS-CoV-2.

As the global SARS-CoV-2 situation continues to evolve it will be important to validate these data with a larger number of case studies across a wider geographic distribution. It is also possible that as community spread of the virus becomes more common, the transmission dynamics and clinical characteristics of disease will change. However, in the interim our analyses show that, to date, children have not been the primary source of household transmission clusters.

RESEARCH IN CONTEXT

Evidence before this study

Before undertaking this study, evidence published between December 2019 and March 2020 in English or Chinese was considered from data made available between Dec 1, 2019, and March 18, 2020. Information was accessed from World Health Organization news[11], local health authority's news releases, Google Scholar, PubMed, the Lancet COVID-19 resource centre[12], Clinical Infectious Disease Journal, New England Journal of Medicine, and three Chinese databases (CNKI, Wanfang, and CQVIP).

We performed the searching and reviewing using the terms (“severe acute respiratory syndrome coronavirus 2”[All Fields]) OR ("SARS-CoV-2"[All Fields]) OR (“COVID-19” [All Fields]) AND ("Children"[All Fields] OR "Paediatric"[All Fields]) OR ("Family"[MeSH Terms] OR "Family"[All Fields])”. To examine H5N1 avian influenza household transmission event, we used search queries “H5N1[All Fields] AND ("Children"[All Fields] OR "Paediatric"[All Fields]) AND (family cluster[All Fields])”. A total of 166 articles were retrieved and reviewed. Of these, 126 articles were excluded because i) they did not report paediatric infections ii) did not report sufficient individual case data and/or iii) did not report family clusters. The intra-household transmission clusters were also sourced from information provided by local health authority's news of China, Europe, France, Germany, Italy, Japan, and South Korea when available. Any intra-household cluster identified in these local sources was included in the study.

Added value of this study

Our findings add value to the existing body of evidence by not only supporting previous suggestions that COVID-19 can have numerous different clinical manifestations in children but also suggesting that, to date, children have not driven the household transmission of SARS-CoV-2.

Implications of all the available evidence

Understanding the pathogenesis and transmission of SARS-CoV-2 in children is of paramount importance to reducing the severity of the pandemic and implementing appropriate public health controls. Specifically, our findings hold important implications for policies regarding school and day-care closures during this period. As the global SARS-CoV-2 situation continues to evolve it will be important to validate these data with a larger number of case studies across a wider geographic distribution

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CONTRIBUTIONS

YZ and KRS contributed to data acquisition; study design; data analysis; manuscript writing and revising. CJB contributed to data analysis; manuscript writing and revising. KDH contributed to data acquisition; data analysis; manuscript writing and revising. JES contributed to data acquisition; data analysis; manuscript revising. MT, LES, ECN, JL contributed to data acquisition; data analysis. KYC contributed to the study design; data acquisition; data analysis. JLP contributed to data interpretation and critical review of the manuscript. CG contributed to the contributed to critical review of the manuscript. ACB contributed to critical review of the manuscript and reviewed for clinical content.

DECLARATION OF INTERESTS

No conflict of interests to declare.

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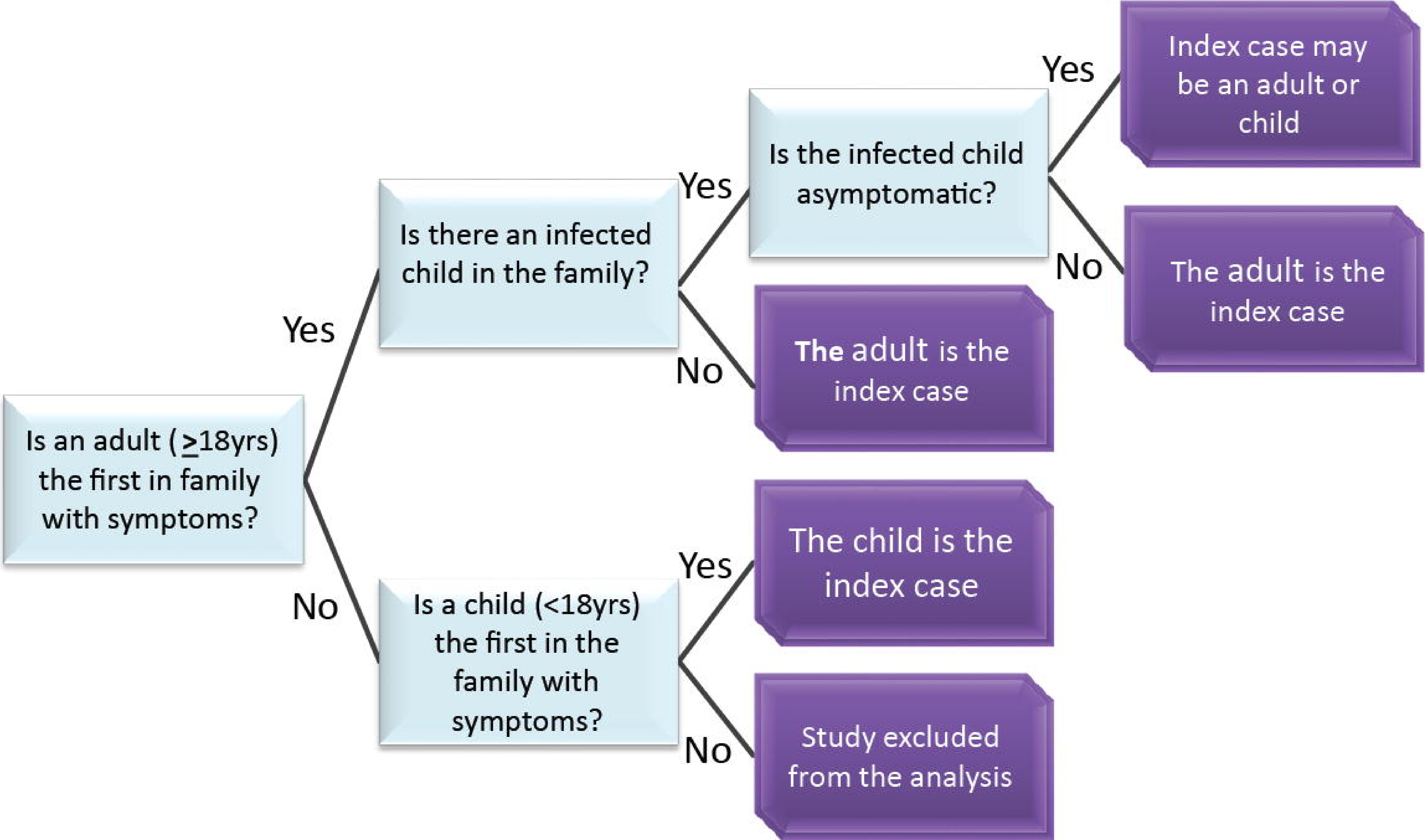
Is an adult ($\geq$18yrs) the first in family with symptoms?
Yes
No
Is there an infected child in the family?
Yes
No
Is the infected child asymptomatic?
Yes
No
Index case may be an adult or child
The adult is the index case
The adult is the index case
Is a child (<18yrs) the first in the family with symptoms?
Yes
No
The child is the index case
Study excluded from the analysis

Table 1: Clinical characteristics of SARS-CoV-2 in children

Characteristic	Value
Age (n = 103)	5.35 y ± 4.65 (n = 103)
Sex (n = 105)	56.19% female (n = 105)
Severity of infection (n = 102)	19% Asymptomatic
	69% Mild - Moderate
	12% Severe
Onset symptoms (n = 81)	77% Fever
	59% Cough
	17% Runny Nose/ Rhinorrhea
	12% Tachypnea
	12% Nausea/ vomiting
	12% Sore Throat
	11% Chills
	11% Retraction
	6% Diarrhoea
	2% Fatigue/ Myalgia/weakness
Temperature at hospital admission (n = 71)	37.5 °C ± 3.78
CT Findings (n = 89)	33.71% Opacities
	29.21% Normal
	29.21% Patch Shadows
	12.36% Consolidations
	3.37% Signs of Viral Infection/ Pneumonia
Average incubation period	7.74 d ± 3.22
Haemoglobin	15.88 ± 15.21 g/dL (n = 48)
White Blood Cells	7.63 ± 3.49 x 10^9/ L (n = 61)
Neutrophil Count	3.55 ± 2.96 x 10^9/ L (n = 47)
Lymphocyte Count	2.9 ± 1.8 x 10^9/ L (n = 48)
Platelet Count	262.16 ± 91 x 10^9/L (n = 44)
C-Reactive Protein Level	18.47 ± 25.74 mg/L (n = 48)
D-dimer	1.78 ± 7.44 µg/mL (n = 29)
Alanine Aminotransferase	29.95 ± 33.88 U/L (n = 38)
Creatinine	41.7 ± 37.11 µ/mol/L (n =31)
Lactate Dehydrogenase	315.75 ± 182.36 U/L (n = 35)

[1]Data sourced from multiple studies.[5,7,13,15,17–45]

Table 2: Household transmission clusters of SARS-CoV-2

Cluster	Country	Province (China) or city (outside China)	Age	Sex	Relation to Index case	Laboratory (L) or clinically (C)	Symptomatic infection?	History of travel?	Source
1	China	Guangdong	35 y	M	Index	L	Y	Yes – travel to Wuhan	[20]
1	China	Guangdong	33 y	F	Wife	L	N	Yes – travel to Wuhan	[20]
1	China	Guangdong	3 y	M	Son	L	N	Yes – travel to Wuhan	[20]
2	China	Hubei	9 y	M	Index	L	Y	No – local resident of Wuhan	[19]
2	China	Hubei	71 y	F	Grandmother	L	Y	No – local resident of Wuhan	[19]
2	China	Hubei	31 y	F	Mother	L	Y	No – local resident of Wuhan	[19]
3	China	Guangdong	65 y	F	Index	L	Y	Yes – travel to Wuhan	[33]
3	China	Guangdong	66 y	M	Father	L	Y	Yes – travel to Wuhan	[33]

3	China	Guangdong	37 y	F	Daughter	L	Y	Yes – travel to Wuhan	33
3	China	Guangdong	36 y	M	Son-in-law	L	Y	Yes – travel to Wuhan	33
3	China	Guangdong	10 y	M	Grandson	L	N	Yes – travel to Wuhan	33
3	China	Guangdong	7 y	F	Granddaughter	C	N	Yes – travel to Wuhan	33
3	China	Guangdong	63 y	F	Mother of son-in-law	L	Y	No	33
4	China	Guangdong	36 y	M	Index	L	Y	Yes – travel to Wuhan	49
4	China	Guangdong	38 y	F	Wife	L	Y	No	49
4	China	Guangdong	60 y	F	Mother	L	Y	No	49
4	China	Guangdong	62 y	M	Father	L	Y	No	49
4	China	Guangdong	3 y	M	Son	L	Y	No	49

5	China	Guangdong	58 y	F	Index	L	Y	Yes – travel to Hubei	49
5	China	Guangdong	38 y	M	Son	L	Y	No	49
5	China	Guangdong	33 y	F	Daughter-in-law	L	Y	No	49
5	China	Guangdong	16 m	M	Grandson	L	Y	Yes – travel to Hubei	49
6	China	Guangdong	59 y	M	Index	L	Y	No – local resident of Wuhan	49
6	China	Guangdong	10 m	F	Granddaughter	L	Y	No – local resident of Wuhan	49
6	China	Guangdong	57 y	F	Wife	L	Y	No – local resident of Wuhan	49
6	China	Guangdong	38 y	M	Son-in-law	L	N	No – local resident of Wuhan	49
7	China	Guangdong	32 y	F	Index	L	Y	No – local resident of Wuhan	49
7	China	Guangdong	6 y	M	Son	L	N	No – local resident of Wuhan	49

8	China	Zhejiang	29 y	M	Index	L	Y	No	40
8	China	Zhejiang	28 y	F	Wide	L	N	No	40
9	China	Zhejiang	42 y	M	Index	L	Y	No	40
9	China	Zhejiang	41 y	F	Wife	L	N	No	40
9	China	Zhejiang	12 y	M	Son	L	N	No	40
10	USA	Illinois	60-70 y	F	Index	L	Y	Yes – travel to Wuhan	50
10	USA	Illinois	..	M	Husband	L	Y	No	50
11	Vietnam	Ho Chi Minh City	65 y	M	Index	L	Y	Yes – travel to Wuhan	51
11	Vietnam	Ho Chi Minh City	27 y	M	Son	L	Y	No	51
12	Singapore	Singapore	28 y	F	Index	L	Y	No	52

12	Singapore	Singapore	45 y	M	Husband	L	Y	No	[52]
12	Singapore	Singapore	44 y	F	Domestic helper	L	Y	No	[52]
12	Singapore	Singapore	6 m	M	Son	L	Y	No	[52]
13	Singapore	Singapore	42 y	M	Index	L	Y	No	[52]
13	Singapore	Singapore	40 y	F	Sister	L	Y	No	[52]
13	Singapore	Singapore	65 y	F	Mother-in-law	L	Y	No	[52]
14	Singapore	Singapore	86 y	M	Index	L	Y	No	[13]
14	Singapore	Singapore	57 y	M	Family member	L	Y	No	[13]
14	Singapore	Singapore	80 y	F	Family member	L	Y	No	[13]
15	Singapore	Singapore	30 y	M	Index	L	Y	Yes – travel to France	[13]

15	Singapore	Singapore	62 y	F	Family member	L	Y	No	13
16	Japan	Saitama	40-50 y	M	Index	L	Y	Yes – travel to Wuhan	45
16	Japan	Saitama	3-6 y	M	Son	L	Y	Yes – travel to Wuhan	45
17	Japan	Nakafurano	<10 y	M	Index	L	Y	No	45
17	Japan	Nakafurano	10 y	M	Older brother	L	Y	No	45
18	South Korea	Seoul	Adult	M	Index	L	Y	Yes – travel to Wuhan	37
18	South Korea	Seoul	Adult	F	Sister	L	Y	No	37
18	South Korea	Seoul	10	F	Niece	L	Y	No	37
19	China	Sichuan	Adult	F	Index	C	Y	No	39
19	China	Sichuan	7 m	F	Daughter	C	Y	No	39

19	China	Sichuan	Adult	F	Mother-in-law	C	Y	No	39
19	China	Sichuan	Adult	M	Husband	C	N	No	39
20	China	Sichuan	Adult	M	Index	C	Y	Yes – chartered out of Wuhan	39
20	China	Sichuan	5 y	M	Son	C	Y	No	39
20	China	Sichuan	Adult	F	Wife	C	Y	No	39
21	China	Hunan	53 y	M	Index	C	Y	Yes – travel to Wuhan	32
21	China	Hunan	Adult	F	Wife	C	Y	No	32
21	China	Hunan	28 y	M	Son	C	Y	No	32
21	China	Hunan	28 y	F	Daughter-in-law	C	Y	No	32
21	China	Hunan	34 y	M	Son-in-law	C	Y	No	32

21	China	Hunan	32 y	F	Daughter	C	Y	No	32
21	China	Hunan	4 y	M	Grandson	C	Y	No	32
21	China	Hunan	4 y	F	Granddaughter	C	Y	No	32
22	China	Guangdong	43 y	F	Index	C	Y	Yes – chartered out of Wuhan	49
22	China	Guangdong	42 y	M	Husband	C	Y	No	49
22	China	Guangdong	15 y	M	Son	C	Y	No	49
23	China	Hainan	3 m 19 d	F	Index	L	Y	Exposure to an epidemic area	23
23	China	Hainan	Adult	M	Father	L	Y	··	23
23	China	Hainan	Adult	F	Mother	L	N	··	23
24	China	Henan	20 y	F	Index	L + C	N	Yes – chartered out of Wuhan	53

24	China	Henan	42-57 y	··	Family member	L + C	Y	No	53
25	Singapore	Singapore	64 y	M	Index	L	Y	No	13
25	Singapore	Singapore	59 y	F	Family member	L	Y	No	13
26	Singapore	Singapore	71 y	M	Index	L	Y	No	13
26	Singapore	Singapore	71 y	F	Family member	L	Y	No	13
27	Singapore	Singapore	62 y	M	Index	L	Y	No	13
27	Singapore	Singapore	30 y	M	Family member	L	Y	No	13
27	Singapore	Singapore	61 y	F	Family member	L	Y	No	13
28	Singapore	Singapore	23 y	F	Index	L	Y	Yes – travel to Malaysia	13
28	Singapore	Singapore	27 y	M	Family member	L	Y	Yes – travel to Malaysia	13

29	Singapore	Singapore	40 y	M	Index	L	Y	No	13
29	Singapore	Singapore	35 y	M	Family member	L	Y	No	13
30	Singapore	Singapore	27 y	M	Index	L	Y	Yes – travel to Indonesia	13
30	Singapore	Singapore	26 y	M	Family member	L	Y	Yes – travel to Indonesia	13
31	Singapore	Singapore	32 y	F	Index	L	Y	No	13
31	Singapore	Singapore	40 y	M	Husband	L	Y	No	13

*F, female; M, male; Y, Yes; N, No

Table 3: Household transmission clusters of highly pathogenic avian influenza H5N1

Cluster	Onset of index case	Country	Age(y)	Sex	Relation to Index Case	Source
1	Dec-97	China, HK	5	F	Index	54
1	Dec-97	China, HK	2	M	Cousin	54
2	Jan-03	China, HK	8	F	Index	55
2	Jan-03	China, HK	33	M	Father	55
2	Jan-03	China, HK	9	M	Sibling	55
3	Dec-03	Vietnam	12	F	Index	56,57
3	Dec-03	Vietnam	30	F	Mother	56,57
4	Dec-03	Vietnam	7	F	Index	56,57
4	Dec-03	Vietnam	5	M	Sibling	56,57
5	Jan-04	Vietnam	31	M	Index	56,57
5	Jan-04	Vietnam	30	F	Sibling	56,57
5	Jan-04	Vietnam	28	F	Wife	56,57
5	Jan-04	Vietnam	23	F	Sibling	56,57
6	Jan-04	Thailand	6	M	Index	56,57
6	Jan-04	Thailand	33	F	Mother	56,57
7	Jan-04	Vietnam	9	F	Index	56,57
7	Jan-04	Vietnam	4	M	Sibling	56,57
8	Jul-04	Vietnam	19	M	Index	56,57
8	Jul-04	Vietnam	22	F	Cousin	56,57
8	Jul-04	Vietnam	23	F	Sibling	56,57
9	Sep-04	Thailand	11	F	Index	56,57
9	Sep-04	Thailand	26	F	Mother	56,57

9	Sep-04	Thailand	32	F	Aunt	[56,57]
9	Sep-04	Thailand	6	M	Aunt's son	[56,57]
10	Dec-04	Vietnam	42	M	Index	[56,57]
10	Dec-04	Vietnam	36	M	Sibling	[56,57]
11	Jan-05	Vietnam	35	F	Index	[56,57]
11	Jan-05	Vietnam	13	F	Daughter	[56,57]
12	Jan-05	Cambodia	14	M	Index	[56,57]
12	Jan-05	Cambodia	25	F	Sibling	[56,57]
13	Feb-05	Vietnam	21	M	Index	[56,57]
13	Feb-05	Vietnam	14	F	Sibling	[56,57]
14	Mar-05	Vietnam	13	F	Index	[56,57]
14	Mar-05	Vietnam	5	M	Sibling	[56,57]
14	Mar-05	Vietnam	Adult	F	Aunt	[56,57]
15	Mar-05	Vietnam	35	M	Father	[56,57]
15	Mar-05	Vietnam	31	F	Mother	[56,57]
16	Mar-05	Vietnam	0.3	F	Index	[56,57]
16	Mar-05	Vietnam	3	F	Sibling	[56,57]
16	Mar-05	Vietnam	10	F	Sibling	[56,57]
17	Jun-05	Indonesia	8	F	Index	[56,57]
17	Jun-05	Indonesia	1	F	Sibling	[56,57]
17	Jun-05	Indonesia	38	M	Father	[56,57]
18	Oct-05	China	12	F	Index	[56,57]
18	Oct-05	China	9	M	Sibling	[56,57]
19	Oct-05	Thailand	48	M	Index	[56,57]
19	Oct-05	Thailand	7	M	Son	[56,57]

20	Aug-05	Indonesia	37	F	Index	[56,57]
20	Aug-05	Indonesia	9	M	Nephew	[56,57]
21	Sep-05	Indonesia	21	M	Index	[56,57]
21	Sep-05	Indonesia	5	M	Sibling	[56,57]
21	Sep-05	Indonesia	4	M	Nephew	[56,57]
22	Oct-05	Indonesia	19	F	Index	[56,57]
22	Oct-05	Indonesia	8	M	Sibling	[56,57]
23	Nov-05	Indonesia	7	M	Index	[56,57]
23	Nov-05	Indonesia	20	M	Sibling	[56,57]
23	Nov-05	Indonesia	16	M	Sibling	[56,57]
24	Dec-05	Turkey	14	M	Index	[56,57]
24	Dec-05	Turkey	15	F	Sibling	[56,57]
24	Dec-05	Turkey	12	F	Sibling	[56,57]
24	Dec-05	Turkey	5	M	Neighbour	[56,57]
25	Dec-05	Turkey	9	F	Index	[56,57]
25	Dec-05	Turkey	3	M	Sibling	[56,57]
26	Jan-06	Turkey	14	F	Index	[56,57]
26	Jan-06	Turkey	5	M	Sibling	[56,57]
27	Jan-06	Indonesia	13	F	Index	[56,57]
27	Jan-06	Indonesia	4	M	Sibling	[56,57]
27	Jan-06	Indonesia	14	F	Sibling	[56,57]
27	Jan-06	Indonesia	43	M	Father	[56,57]
28	Jan-06	Iraq	15	F	Index	[56,57]
28	Jan-06	Iraq	39	M	Uncle	[56,57]
30	Feb-06	Azerbaijan	24	M	Index	[56,57]

30	Feb-06	Azerbaijan	21	F	Sibling	56,57
31	Feb-06	Indonesia	12	F	Index	56,57
31	Feb-06	Indonesia	10	M	Sibling	56,57
32	Mar-06	Egypt	6	F	Index	56,57
32	Mar-06	Egypt	1.5	F	Sibling	56,57
33	Apr-06	Indonesia	37	F	Index	56,57
33	Apr-06	Indonesia	15	M	Son	56,57
33	Apr-06	Indonesia	17	M	Son	56,57
33	Apr-06	Indonesia	28	F	Sibling	56,57
33	Apr-06	Indonesia	1.5	F	Niece	56,57
33	Apr-06	Indonesia	25	M	Sibling	56,57
33	Apr-06	Indonesia	10	M	Nephew	56,57
33	Apr-06	Indonesia	32	M	Sibling	56,57
34	May-06	Indonesia	10	F	Index	56,57
34	May-06	Indonesia	18	M	Sibling	56,57
35	May-06	Indonesia	15	F	Index	56,57
35	May-06	Indonesia	27	M	Sibling	56,57
36	May-06	Indonesia	10	M	Index	56,57
36	May-06	Indonesia	7	F	Sibling	56,57
38	Sep-06	Indonesia	11	M	Index	56,57
38	Sep-06	Indonesia	21	F	Sibling	56,57
39	Sep-06	Indonesia	24	M	Index	56,57
39	Sep-06	Indonesia	20	M	Sibling	56,57
40	Dec-06	Egypt	30	F	Index	56,57
40	Dec-06	Egypt	26	M	Sibling	56,57

40	Dec-06	Egypt	16	F	Niece	[56,57]
41	Jan-07	Indonesia	37	F	Index	[56,57]
41	Jan-07	Indonesia	18	M	Son	[56,57]
42	Jan-07	Nigeria	52	F	Index	[56,57]
42	Jan-07	Nigeria	22	F	Daughter	[56,57]
43	Mar-07	Egypt	6	F	Index	[56,57]
43	Mar-07	Egypt	4	M	Sibling	[56,57]
44	Jul-07	Indonesia	5	F	Index	[56,57]
44	Jul-07	Indonesia	29	F	Mother	[56,57]
45	Oct-07	Pakistan	25	M	Index	[56,57]
45	Oct-07	Pakistan	22	M	Sibling	[56,57]
45	Oct-07	Pakistan	25	M	Sibling	[56,57]
45	Oct-07	Pakistan	32	M	Sibling	[56,57]
46	Nov-07	China	24	M	Index	[56,57]
46	Nov-07	China	51	M	Father	[56,57]
47	Jan-08	Indonesia	38	F	Index	[56,57]
47	Jan-08	Indonesia	15	F	Daughter	[56,57]
48	Dec-08	Vietnam	13	F	Index	[56,57]
48	Dec-08	Vietnam	8	F	Sibling	[56,57]
49	Dec-08	China	26	F	Index	[56,57]
49	Dec-08	China	2	F	Daughter	[56,57]
50	Feb-11	Cambodia	19	F	Index	[56,57]
50	Feb-11	Cambodia	1	M	Son	[56,57]
51	Feb-11	Indonesia	31	F	Index	[56,57]
51	Feb-11	Indonesia	2	F	Daughter	[56,57]

52	Sep-11	Indonesia	5	F	Index	56,57
52	Sep-11	Indonesia	10	M	Sibling	56,57
52	Sep-11	Indonesia	29	F	Mother	56,57
53	Nov-11	Egypt	27	F	Index	56,57
53	Nov-11	Egypt	1.5	F	Child	56,57
54	Dec-11	Indonesia	23	M	Index	56,57
54	Dec-11	Indonesia	5	F	Family contact	56,57
55	Jan-14	Cambodia	8	M	Index	56,57
55	Jan-14	Cambodia	3	F	Sibling	56,57
56	Mar-15	Indonesia	2	M	Index	56,57
56	Mar-15	Indonesia	40	M	Father	56,57

* F, female; M, male