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Review

Household Transmission of Influenza Virus

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Human influenza viruses cause regular epidemics and occasional pandemics with a substantial public health burden. Household transmission studies have provided valuable information on the dynamics of influenza transmission. We reviewed published studies and found that once one household member is infected with influenza, the risk of infection in a household contact can be up to 38%, and the delay between onset in index and secondary cases is around 3 days. Younger age was associated with higher susceptibility. In the future, household transmission studies will provide information on transmission dynamics, including the correlation of virus shedding and symptoms with transmission, and the correlation of new measures of immunity with protection against infection.

Trends

Historically, household cohort studies have provided valuable information on the incidence of respiratory infections and risk factors for infection. However, these studies require substantial resources and can provide limited information on transmission dynamics.

Household transmission studies provide an efficient approach to describing the risk of influenza transmission and factors affecting transmission. In these studies, households with at least one member infected by influenza are eligible and are followed intensively for 1–2 weeks to observe secondary transmission within the household.

Transmission studies also provide a model for evaluation of interventions in randomized controlled trials, and have been used to determine the efficacy of antiviral drugs for treatment and prophylaxis, and nonpharmaceutical interventions such as face masks and hand hygiene.

Transmission of Human Influenza Viruses

Human influenza viruses cause regular epidemics and occasional pandemics. During influenza epidemics, high attack rates of generally mild and self-limiting illnesses cause a substantial public health burden, and a small fraction of infections are severe, requiring hospitalization [1]. Community-based studies of influenza virus infection and transmission have provided detailed information on influenza epidemiology since the 1920s [2], with a series of seminal studies in the 1950s, 1960s, and 1970s, the most comprehensive of which was the 10-year Tecumseh study of acute respiratory infections in households [3,4]. These studies conducted serologic and virologic testing of participants to determine the frequency of acute respiratory illnesses and identified the etiologic agents responsible. By enrolling entire households, these studies also examined transmission of respiratory pathogens, including influenza virus, identifying, for example, the importance of school-age children in introducing infections to the household [5].

More recently, an efficient study design known as the household transmission study has been increasingly used to study influenza virus transmission. During the 2009 influenza pandemic, this design was used to provide early estimates of transmission dynamics of the novel H1N1pdm09 strain, including the risk of infection among household contacts and the serial interval, defined as the time from symptom onset in the index case to the secondary case, and the severity of illnesses [6]. This review describes the methodology used in these transmission studies, the main findings of the studies on the transmission dynamics of human influenza viruses in households, and the potential for further research using this study design to provide answers to important outstanding questions on influenza.

Household Cohort Studies and Transmission Studies

Household cohort studies have been used to study influenza epidemiology for many years [4] and continue to provide useful insights on influenza epidemiology [7–17]. In a household cohort study, households are recruited prospectively from a sampling frame that typically includes the entire community, and some studies exclude households with one person. Participants in the

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study are then followed up prospectively across one or more influenza epidemic, or influenza season, to identify infections and illnesses. In many cohort studies, sera will be collected from participants before and after influenza epidemics, to permit identification of infections by, for example, the proportion of individuals with a 4-fold or greater rise in antibody titer against a particular strain across an epidemic of that strain [18,19]. During an influenza epidemic, or in some cases throughout follow-up regardless of influenza activity, participants may keep symptom diaries to permit estimation of the incidence of acute respiratory illnesses. Collection of nasal swabs or other respiratory specimens from ill participants, or at regular intervals from all participants regardless of illness [20], can permit virologic identification of specific pathogens causing those illnesses, including influenza viruses.

An advantage of household studies is the efficiency of simultaneously following up multiple individuals in households rather than separately following up the same number of people independently selected from the population. Compared with other types of close contacts, household contacts are easier to identify and follow up, and they provide a well-defined number of susceptible people that are likely to have been exposed to infection, compared with other settings such as schools, offices, or hospitals. Household cohort studies can also permit inference on the transmission dynamics of influenza in households, providing valuable data on transmission in the broader community because a substantial fraction of influenza virus transmission events do occur in households [21,22]. However, in many cohort studies infections are ascertained by serologic analysis, which can have imperfect sensitivity and specificity, and only provides what is known as final size data in which the number of infected and uninfected household members is known at the end of each epidemic [5]. Specialized methods have been developed to permit inference on transmission dynamics (who was infected by whom) based on final size data, allowing for the risks of acquiring infection from outside or inside the household [5,23,24]. It can be challenging to explore heterogeneities in transmission dynamics due to individual characteristics, for example age, when only final size data are available [7]. In addition, it is not possible to estimate the serial interval based on final size data, although this epidemiologic parameter, measuring the average time between illness onset in an infected person and a secondary case infected by that person, is an important parameter for mechanistic models (also called mathematical models) of influenza epidemics that are often used for policy planning [22,25]. Some of these limitations can be ameliorated by careful collection of respiratory specimens from ill individuals, although intense follow up for illnesses over a prolonged period is challenging and demands considerable resources [26,27].

While cohort studies can provide valuable data on influenza and other acute respiratory illnesses, there are a number of limitations, the greatest of which is the substantial resources required to establish and follow up a cohort of hundreds or typically thousands of participants over a series of influenza epidemics. Furthermore, in areas where influenza seasons are difficult to predict, for example in tropical and subtropical regions, collecting well-timed pre-epidemic and post-epidemic sera can be difficult [7–9,28–32], leading to difficulties in interpreting serological data. Cohort studies were established to determine the cumulative incidence of H1N1pdm09 infections in 2009, but most such studies could not be established quickly enough to collect baseline pre-epidemic sera [30]. Finally, as mentioned above, it is difficult to characterize heterogeneity in transmission dynamics using cohort studies.

One particular study design that has been introduced to characterize the risk of transmission and heterogeneity in transmission risk is the household transmission study, also known as the case ascertained study [6,33]. In a household transmission study of influenza, in contrast to a traditional cohort study as described above, households are eligible for enrolment only after at least one household member has been identified as having an acute influenza virus infection [34]. This case can be referred to as the index case, and the other members as household

contacts, with caveats on this terminology discussed below. In contrast to cohort studies, household transmission studies typically involve a short duration of follow-up of participants for 1 or 2 weeks, or in some cases 1 month to permit collection of convalescent sera. Collection of respiratory specimens, such as nasal swabs or sera, from household contacts permits ascertainment of secondary infections in the households with laboratory confirmation, and symptom diaries provide information on illnesses. Differences between the cohort and transmission study design are illustrated in Figure 1. In principle, the transmission study is also a cohort study because it involves a defined cohort of individuals, but it differs from the traditional cohort study because only households with at least one infected person are included, and in theory the same household can be enrolled more than once (Figure 1). Further complicating the distinction, it is also possible to effectively nest a transmission study within a cohort study, by intensively observing participants in a traditional cohort study and initiating additional investigations once one household member becomes infected [35].

In household transmission studies, information on the dates of illness onset in index and secondary cases allows estimation of the serial interval, and identification of factors associated with heterogeneity in transmission. One caveat of this design is that the identity of the person who first introduced infection into the household can be unclear, and may not necessarily be the person enrolled in the study as the 'index case'. For example, in one household, the first infected person may have very mild illness that is not apparent, but is sufficiently infectious to transmit infection to a second person who has a more serious illness, seeks care at an outpatient clinic, and is enrolled as the index case. Finally, it should be mentioned that the definition of a household

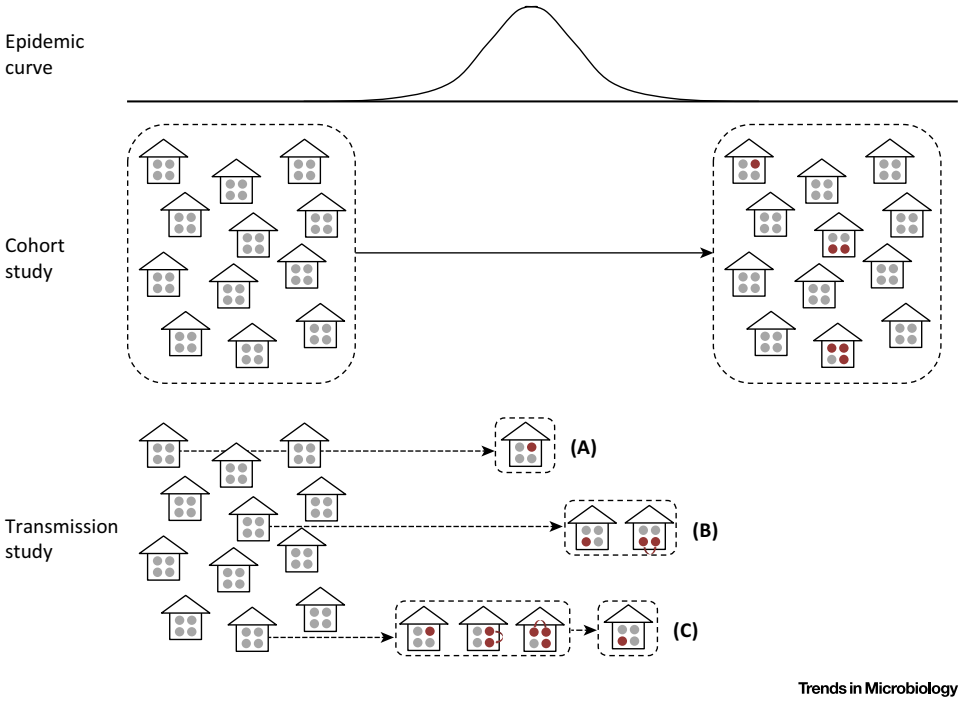

Figure 1. Comparison of the Design of Household Cohort Studies and Household Transmission Studies. In the cohort study, households are recruited before, and followed throughout, an epidemic, and some individuals are determined to have been infected by analysis of serological data (infected persons indicated as dark circles). By contrast, the household transmission study recruits households during the epidemic and includes only those households in which at least one person was infected. In this example, the index case in household A does not cause any secondary case, the index case in household B causes one secondary case, and household C is enrolled in the study twice – the first time when an index case causes two secondary cases, and the second time when another index case occurs (perhaps with a different type of influenza virus).

can vary between cultures. In western cultures, the household typically comprises a nuclear family, but in other cultures – and particularly in low- and middle-income countries – it is possible to find large extended families or social groups living together in compounds or small communities with substantial interactions that should not be ignored when analyzing transmission dynamics in the nuclear families.

What Can Be Learned from Household Transmission Studies?

The primary objective of a typical household transmission study is an estimate of the transmissibility of influenza viruses within the household, measured by the Secondary Infection Risk (SIR), that is, the proportion of household contacts that are infected during the study period. In a basic descriptive analysis, this is simply the proportion of household contacts that develop cases of confirmed influenza virus infection, or the proportion of household contacts that develop an acute respiratory illness. The SIR has frequently been referred to as the 'secondary attack rate' in the literature [36]. However, we note that infections do not necessarily cause more severe illness (attack) and the quantity in question is a risk, that is, a proportion, not an incidence rate with a person–time denominator. The term 'secondary infection risk' therefore seems preferable [6].

More complex statistical analyses can also be performed to take into account the potential for some contacts to acquire infection from outside the household, and other infections to be third-generation 'tertiary' cases rather than secondary cases [37]. These analyses make it possible to estimate the 'person-to-person' household transmission risk, that is, the probability of transmission from a case to a single household member. The person-to-person household transmission risk is usually lower than the SIR because of the additional risk of the household contact acquiring infection from another source apart from the index case [38]. Modeling studies and analyses of the homology in virus sequences between infections in index cases and household contact confirmed that almost all infections in household contacts in the short period after onset in an index case will have been acquired within households rather than from outside the household, confirming the feasibility and applicability of this study design to assess transmission within households [39–42].

Household transmission studies can also provide rich information on factors associated with higher or lower transmissibility. Heterogeneity in transmission could occur because of (i) variation in infectiousness, for example, if infected children were more infectious than infected adults to their family members; (ii) variation in susceptibility to infection, for example, if vaccinated contacts were less likely to contract infection in the household than unvaccinated contacts; or (iii) variation in the environment, for example, households with better ventilation might experience less within-household transmission.

As described in the previous section, household transmission studies can provide evidence on the serial interval, which is related to the generation time, the duration of infectiousness, and the incubation period. Serial intervals can be used to inform and characterize the speed with which an epidemic will spread, as well as the time during which people are infectious – with implications for isolation policies [43].

Control measures can be improved by identification of important factors affecting transmissions in households. Furthermore, experiments may be conducted with this design, for example, by randomly allocating interventions to different participants or different households to determine how effectively those interventions can control transmission. One factor of particular interest is the correlation of immune status with protection against infection.

Review of Transmissibility of Influenza Viruses in Households

We conducted a review of household transmission studies of influenza, explored the typical design and implementation of these studies, and contrasted and compared their major findings.

We identified 56 relevant published studies (see Tables S1 and S2 in the supplemental information online) [34,35,38,40,42,44–93]. In the following sections, we describe the key design features of transmission studies and summarize the scientific findings of these studies in terms of the basic transmissibility of influenza viruses in households, the factors affecting transmission, and the effectiveness of specific control measures in household settings.

Secondary Infection Risk

An estimate of the secondary infection risk can be made as the number of secondary cases divided by the total number of household contacts. The number of contacts with influenza-like illness (ILI), or the number of contacts with acute respiratory infection (ARI) in household contacts, can also be used to estimate the risk of secondary infections and illnesses. In published studies, there has been considerable heterogeneity in the reported secondary infection risks for laboratory-confirmed influenza and illness (Figure 2A). The secondary infection risks of PCR-confirmed infection among household contacts ranged from 1% to 38%, while those based on ILI ranged from 6% to 35%, and those based on ARI ranged from 3% to 31%. Some studies reported secondary infection risks based on more than one of these case definitions. Approaches to ascertaining index cases and then identifying infections and illnesses in household contacts likely contributed to the substantial heterogeneity in estimates of the secondary infection risk (Figure 2A). A previous review found that studies that collected respiratory specimens regardless of illness in household contacts reported higher secondary infection risks, compared with those studies that collected swab specimens only from symptomatic contacts [6]. Another potential explanation for the heterogeneity was that, in some studies, there was delay between symptom onset in index cases and the start of follow-up of households, and hence very small secondary infection risks were reported [56,91]. There is no reason to believe that there is a single true value of the secondary infection risk in a particular location since the degree of transmission that occurs in households will depend on the characteristics of the household members, the degree of contact between them, and the household environment.

Correlates of Susceptibility and Infectivity

Factors affecting susceptibility can be explored by comparing the number of secondary cases in household contacts with or without a particular characteristic, while factors affecting infectivity

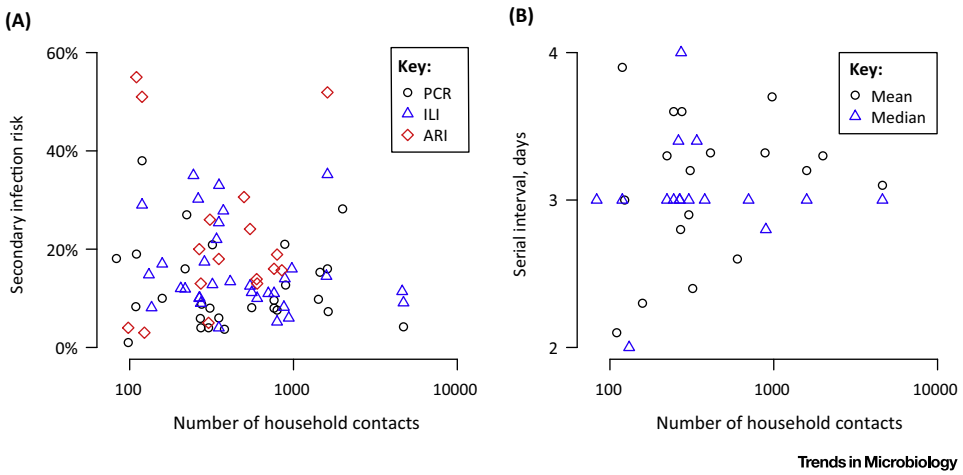

Figure 2. Estimates of Secondary Infection Risk and Serial Interval. (A) Estimates of the secondary infection risk determined by the proportion of household contacts with PCR-confirmed infection (circles), influenza-like illness (ILI, triangles), or acute respiratory illness (ARI, diamonds). (B) Estimates of the mean and median of serial intervals of influenza virus. Data in these graphs are in Tables S1 and S2 in the supplemental information online.

can be explored by comparing the number of secondary cases from index cases with or without a specific characteristic. Most studies explored the factors affecting susceptibility or infectivity using Fisher's exact test, Chi-squared tests, or logistic regression, with [35,45,47,58,64,65,71,76,82,90] or without [49–51,57,59–61,78,79,85] adjustment for clustering of secondary infections within households, although these approaches assumed that all infections in household contacts were secondary cases infected from index cases and ignored the possibility of tertiary cases or infections acquired from outside the household. In a few studies, more complex models were used to relax these assumptions, such as household transmission models that estimated the probability of person-to-person transmission in households and community infection acquired from outside the household [38,42,52,88] or other type of transmission models based on final size data [62,89].

Several factors have been investigated to understand their effect on susceptibility. The effect of age has often been explored, with a younger age associated with higher susceptibility. While children generally have a higher risk of infection than adults [94], some studies failed to detect this association. Possible reasons include smaller sample size and hence insufficient statistical power to identify small-to-moderate effects. While one potential explanation for the higher susceptibility among children was the lower immunity in children on average, an identified study reported that age still had a significant association with susceptibility after adjusting for antibody titers [88], which is also supported by another household cohort study [7].

Another frequently explored factor is gender, but only limited studies have found a significant difference in susceptibility by gender where women were more susceptible [57,90]. Other factors included underlying conditions, smoking, relationship of contacts to the index case, and intensity of exposure measured by time spent at home or having close contacts with the index case (shared bedroom or meal).

Two studies [54,88] explored the relationship between baseline antibody titer levels against PCR-confirmed infection and susceptibility, with one study reporting that antibody titers of 1:40 measured by the hemagglutination-inhibition assay were associated with 31% protection against PCR-confirmed infection, and confirming that antibody titers measured by virus neutralization were significantly correlated with protection [88]. While an antibody titer of 1:40 measured by hemagglutination inhibition is generally associated with 50% protection against infection [95–97], one study suggested that a hemagglutination-inhibition titer of 1:40 was only associated with 31% protection in the household setting [88], potentially because of exposures of greater duration or intensity in the confined setting of households. As more components of humoral immunity are quantified, by, for example, virus neutralization assays, neuraminidase-inhibition assays, or fusion-inhibition assays, the household transmission study may be a particularly efficient study design to validate the correlation of measurements from these assays with protection against infection or illness. In the same way, transmission studies could also be used to study cell-mediated immunity and innate immunity.

Household transmission studies have also included analyses on factors potentially associated with infectivity (Table 1). The most explored factor affecting infectivity was age. Some studies identified a significant association between age and infectivity, in each case finding that children were more infectious than adults [34,42,61,76]. While children are generally considered to be the main drivers of influenza transmission in the community, only a few household transmission studies have found that children were more infectious than adults to their household contacts. Other explored factors include the number of household contacts, and three studies reported that a lower number of household contacts was associated with a higher risk of transmission in households [35,47,62], while one study reported the converse association [61]. Some studies also explored whether the presence of particular symptoms was associated with higher

Table 1. Assessment of Factors Potentially Affecting Susceptibility and Infectivity in Household Transmission Studies

Outcome	Overall		PCR-Confirmed		Not PCR-Confirmed	
Factors	Number of Studies	Number of Studies Reporting Significant Association	Number of Studies	Number of Studies Reporting Significant Association	Number of Studies	Number of Studies Reporting Significant Association
Factors Affecting Susceptibility						
Age	37	27	16	7	21	20
Gender	18	2	8	0	10	2
Vaccination	12	2	5	1	7	1
Prophylactic antiviral	10	9	6	6	4	3
Intervention	7	0	5	0	2	0
Density of exposure	6	4	2	2	4	2
Underlying condition	6	2	1	0	5	2
Relationship to index	4	3	1	1	3	2
Smoking	4	0	1	0	3	0
Factors Affecting Infectivity						
Age	20	4	8	1	12	3
Number of household contacts	17	4	5	2	12	2
Antiviral	12	5	4	1	8	4
Cough	8	5	2	0	6	5
Gender	5	0	3	0	2	0
Diarrhea	4	2	0	0	4	2
Runny nose	4	1	1	0	3	1
Fever	3	1	1	0	2	1
Number of children	3	1	1	0	2	1
Vomiting	3	2	1	1	2	1

infectivity and reported that cough [48,49,51,71,98], diarrhea [40,48], fever [51], runny nose [98], or vomiting [40,48] were associated with higher infectivity. All studies that explored gender relative infectivity reported no association of gender with infectivity [47,49,53,55,82]. However, the association between particular symptoms and infectivity remains unclear as the number of studies exploring these was small (Table 1).

Serial Intervals

Serial intervals were computed by the time from symptom onset in index cases to symptom onset in secondary cases. The ranges of reported mean and median of serial intervals were 2.3–3.9 days and 2–4 days respectively (Figure 2B). These estimates were consistent with estimates from other settings [99]. It should be noted that serial intervals will not necessarily be the same in different settings because they depend on the infectivity profile of index cases, the intensity of exposure and contact patterns in households, the transmission dynamics in the community, and the incubation period [6,100].

Effectiveness of Control Measures

Household transmission studies can also be used to explore control measures against influenza. Control measures include nonpharmacological intervention (facemasks or hand hygiene),

antivirals (either treatment of index cases or prophylactic use among household contacts), or vaccination. Nonpharmacological interventions were found to give nonsignificant protection in both randomized controlled trials [45,53,55,73,82,85] and observational studies [79]. On the other hand, two randomized controlled trials did report significant protection from nonpharmacological intervention among the households in which the intervention was applied very early, within 36 hours of illness onset in the index cases [53,85]. Other control measures, such as home isolation, improved ventilation, or home humidification, can be explored. For example, one household cohort study reported that home humidification was associated with protection against infection in household members [101].

Use of prophylactic antivirals showed significant protection in both a randomized controlled trial [66] and observational studies [48,57,59,68,69,77,78,90], and only one study did not identify a significant effect [76]. In addition, antiviral treatment of index cases was found to be associated with lower infectivity in a randomized controlled trial [58] and four observational studies [61,76,78,87]. It suggested that treatment could reduce onwards transmission. In those observational studies that explored the protection associated with vaccination, only two studies reported significant protection among vaccinated persons [64,88]. Possible reasons included insufficient sample sizes to identify moderate vaccine effectiveness, mismatches between circulating strains and vaccine strains, or lower vaccine effectiveness against infection in the household setting.

Limitations of Household Transmission Studies

As discussed above, household transmission studies can provide rich data on transmission dynamics and epidemiology of influenza. However, some limitations of these studies should be noted. First, in a household transmission study, index cases are generally enrolled after presenting for medical attention and therefore are biased towards infections that cause more serious illness. If more severe illness was associated with greater transmissibility, then the estimates of transmissibility from household transmission studies may be overestimated. More generally, in household transmission studies it is not possible to estimate the total number of secondary infections in all settings caused by one index case (i.e., the reproductive number) because data are not collected outside the household. Second, because of the case ascertainment, households without any infections will not be enrolled (Figure 1), and it is not possible to estimate population-based rates of infection unless the transmission study is nested in a larger cohort study. Third, it is possible to characterize the mild end of clinical severity by assessing illnesses in household contacts, but severe disease is rare, and only very large transmission studies would be able to estimate, for example, the risk of hospitalization if infected with influenza.

Concluding Remarks

In summary, household transmission studies can provide valuable information on transmissibility, factors affecting transmission, effectiveness of control measures, and serial intervals, that could be useful for control and prevention of human influenza. As we have discussed above, once one household member is infected with influenza, the risk of infection in a household contact can be up to 38%, and the delay between onset in index and secondary cases is around 3 days (Figure 2B). As new innovative approaches for data collection become available [10,12,102], it should be possible to improve and simplify data collection in household transmission studies. Although not discussed in this review, household transmission studies can also provide information on the severity of typical influenza virus infections. Whereas index cases, ascertained either by presenting for medical attention or reporting symptoms, are not likely to be representative of all natural infections, because milder cases would have a lower probability of being ascertained, the infections among secondary cases may give a representative picture of the severity of natural infections [40,54,83,84]. The fraction of infections that was asymptomatic

Outstanding Questions

Why is there so much apparent variability in the risk of influenza transmission in different locations and years?

What are the mechanisms that may explain the dependence between the person-to-person risk of transmission and household size?

As new innovative approaches for data collection become available, how can we improve and simplify data collection in household transmission studies?

What are optimal designs for household transmission studies?

Which other infections could benefit from this type of study?

What components of adaptive and innate immunity protect persons again influenza virus infection, and illness if infected, and what is the strength of any such protection?

Does the strength of protection vary with the force of infection? For example, does protection vary depending on the duration of exposure in the household, or is protection different for high-intensity exposure in the household environment compared to exposure in the community?

Given that surgical face masks and enhanced hand hygiene appear to have limited efficacy, what other interventions might be more effective in controlling influenza transmission in households – other types of face mask, home humidification, improved ventilation, isolation of ill persons in bedrooms?

varied from 0% to 21% [40,42,54,66,70,82–84]. A major outstanding question in influenza epidemiology, which could be addressed in large transmission studies, is whether these asymptomatic cases can transmit infection.

Household transmission studies can also be used to assess the transmission of other respiratory pathogens. Two published studies have evaluated the potential of human-to-human transmission of avian influenza viruses based on assessment of infections among household contacts of confirmed cases [103,104]. One study found that the blood-related household contacts of index cases may face a higher risk of H5N1 infection but not H7N9 infection, and identified biases in case ascertainment towards more severe H7N9 cases [104]. Household transmission studies are also valuable tools in the assessment of transmissibility of novel pathogens such as the Middle East Respiratory Syndrome coronavirus [105].

In future, household transmission studies will continue to provide important insights on influenza epidemiology (see Outstanding Questions). In particular, household transmission studies are likely to be initiated early in the next pandemic to provide important early data on the transmissibility and severity of the new pandemic strain [6]. Household transmission studies of seasonal influenza will provide information on transmission dynamics, including the correlation of virus shedding and symptoms with transmission, and the correlation of new measures of immunity with protection against infection.

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Supplementary Information

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