Risk factors of influenza transmission in households

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SUMMARY

Background: Influenza transmission in households is a subject of renewed interest, as the vaccination of children is currently under debate and antiviral treatments have been approved for prophylactic use.

Aims: To quantify the risk factors of influenza transmission in households.

Design of study: A prospective study conducted during the 1999 to 2000 winter season in France.

Setting: Nine hundred and forty-six households where a member, the index patient, had visited their general practitioner (GP) because of influenza-like illness were enrolled in the study. Five hundred and ten of the index patients tested positive for influenza A (subtypes H3N2 and H1N1).

Methods: Secondary cases of influenza were those household contacts who had developed clinical influenza within 5 days of the disease onset in the index patient. Hazard ratios for individual clinical and demographic characteristics of the contact and their index patient were derived from a Cox regression model.

Results: Overall in the 279 households, 131 (24.1%) secondary cases occurred among the 543 household contacts. There was an increased risk of influenza transmission in preschool contacts (hazard ratio [HR] = 1.85, 95% confidence interval [CI] = 1.09 to 3.26) as compared with school-age and adult contacts. There was also an increased risk in contacts exposed to preschool index patients (HR = 1.93, 95% CI = 1.09 to 3.42) and school-age index patients (HR = 1.68, 95% CI = 1.07 to 2.65), compared with those exposed to adult index cases. No other factor was associated with transmission of the disease.

Conclusions: Our results support the major role of children in the dissemination of influenza in households. Vaccination of children or prophylaxis with neuraminidase inhibitors would prevent, respectively, 32-38% and 21-41% of secondary cases caused by exposure to a sick child in the household.

Keywords: antivirals; children; epidemiology; influenza; prospective studies; risk factors; vaccination.

Introduction

The epidemiology of influenza transmission in households has been the subject of great interest and investigation in the past, with the rationale that a better understanding of influenza transmission mechanisms could aid in the design of efficient control strategies. Several follow-up studies of families during one or several consecutive influenza seasons have described the occurrence and spread of infection in households in relation to age, family composition, crowding, circulating viral strains, exposure in the community, and prior immunity.

The current thinking regarding influenza transmission is that children play a major role in the early stages of the epidemic, with the assumption that they are more susceptible than older age groups, and that they contribute more extensively to the spreading of the virus in the population. Furthermore, children spend a great deal of time in communities where daily contact with other people is extensive; for example, in schools, play groups, and daycare centres, and it is assumed that close contact favours transmission. However, the extent to which these mechanisms contribute to transmission has not been quantified.

Recently, there has been renewed interest in the study of influenza transmission in families, especially in light of the recent debates about whether large-scale vaccination of healthy children in daycare would be beneficial to other age groups, and whether contact prophylaxis with neuraminidase inhibitors could effectively prevent transmission. However, no data are available on the quantitative evaluation of the predictors of influenza transmission in households.

In this work, we analyse a prospective study of influenza transmission in families conducted in France during the 1999 to 2000 influenza season, where influenza-positive index patients were identified by virological tests. From this study we assess the risk factors for influenza transmission associated with the individual characteristics of index patients and their household contacts.

Methods

Study design

This study, which is described in detail elsewhere, was conducted within the framework of the French Sentinel network. The Sentinel network is a computerised public health surveillance system compiled with the voluntary and unpaid participation of 1790 general practitioners (GPs) located all over France. Since November 1984 it has been collecting weekly reports on 10 communicable diseases, including influenza-like illness. In addition to the continuous surveillance of disease activity, the network is a setting for
thorough investigations conducted over limited time periods.10,11 One hundred and sixty-one of the GPs from the network volunteered to participate in this specific study of influenza transmission in households. They received training on the study protocol and virology sampling during a pilot phase in October 1999.

A household was enrolled when a member visited the GP and met the following inclusion criteria: the patient had had a fever >38°C within 48 hours of the visit, together with respiratory signs; there was at least one other member in the household; the consulting patient was the first case in the household; the patient was not hospitalised as a result of this visit. If the inclusion criteria were met, the patient was considered to be the index case of the household. Following discussion of this observational follow-up by the study scientific committee and jurists from the institutional sponsor, oral consent was obtained from the index patient (or the index patient’s parents if the index patient was a child). All studies conducted within the framework of the Sentinel network are approved by the French Commission Nationale de l’Informatique et des Libertés (approval no. 471 393).

Information concerning social and demographic characteristics of the household was collected upon enrollment in the study. Daily details about 13 symptoms (fever >38°C; feverishness; cough; sore throat; nasal congestion, rhinorrhea or sneezing; dysphonia; fatigue; headache; stiffness or myalgias; otalgias; ocular symptoms; loss of appetite; sleep disturbances), medication, visits to physicians, and missed days of work of each household member, were reported in a standardised questionnaire for the 15 days following the initial visit of the index patient to their GP. The initial visit was counted as day 0 of the follow-up. A daily severity score was calculated as the proportion of the 13 symptoms reported on a given day (ranging from 0 to 1) as described elsewhere.9 All participants who completed the questionnaire were included in the study.

Demographic characteristics
Between January 2000 and March 2000, 946 index patients and their household contacts were enrolled in the study. Nasal swabs were obtained from all index patients.

Respiratory syncytial virus, parainfluenzae virus and adenovirus infections were diagnosed with the immunofluorescence test.9 Influenza was diagnosed where one or more results with the immunofluorescence test, viral culture and the polymerase chain reaction (PCR) test were positive. Of the 946 index patients, 510 were influenza A (subtype H3N2)-positive and, of these, 395 (77%) completed the follow-up with their household contacts (Figure 1). The 510 influenza A-positive patients were located in 21 of the 21 administrative regions of France. The median number of index cases per region was 16, with a range of 2–61. At inclusion, the only difference between households that com-

Figure 1. Flow diagram of the study. Dotted boxes denote subjects included in the main analysis.
completed the study (n = 395) and those lost to follow-up (n = 115) was in the sex of the index patient: 19% of the households with a female index patient and 26% of those with a male index patient were lost to follow-up (P = 0.04). In particular, there was no difference regarding variables such as the age of the index patient, severity of the disease on the first day of illness, body temperature, and inclusion date.

We used a clinical definition of influenza, without laboratory testing, to identify secondary patients. Clinical influenza was defined as the presence of a fever > 38°C, or feverishness when the temperature was not taken, or at least two of the following symptoms: cough; sore throat; nasal congestion, rhinorrhea, or sneezing; fatigue; headache; stiffness; myalgias. This definition is based on the criteria that define influenza-like illness in clinical trials of neuraminidase inhibitors.7–13 Household contacts who developed clinical influenza within 5 days of the initial visit of the index patient were classified as secondary patients. To avoid ambiguity about the true introduction of infection in the household, we excluded households in which one or more contacts had developed clinical influenza on the day of the initial GP visit of the index patient (day 0) from the main analysis. The incubation period of influenza is around 1–1.5 days,14,15 therefore this procedure minimises the probability that the household members (index patient and contacts) were infected from a common source from outside the household and not by transmission within the household. Among the 395 households that completed the study, 116 reported potential co-existing primary patients and were excluded from the main analysis. We subsequently performed sensitivity analyses with an extended dataset that included those households where co-existing primary cases were reported on the day of the initial visit, and also a more specific definition of clinical influenza based on the combined presence of fever > 38°C and cough.16

In the remaining 279 households, the mean number of children per household under 15 years of age was 0.71. This is in line with the national figure of 0.68 for French households of two or more members.12 The mean age of index patients was 38.4 years (standard deviation [SD] = 19.4), 241 (86.4%) of them were adults (mean age = 43.1 years, SD = 16.6) and 38 (13.6%) were children aged ≤15 years (mean age = 9.1 years, SD = 4.7) of whom 10 (3.6%) were <5 years of age. Ten per cent of the index patients were vaccinated against influenza, and 14% had experienced clinical influenza in the preceding year.

In the 279 households there were 615 contact members. We disregarded 72 contacts with insufficient information on clinical follow-up, and in the final analysis included 543 contacts, with a mean age of 32.1 years (SD = 19.9), comprising 401 (73.8%) adults (mean age = 40.4 years, SD = 16.3) and 142 (26.2%) children (mean age = 8.7 years, SD = 4.1) of whom 36 (6.6%) were below 5 years of age. The proportion of children among the 72 contacts who did not fully complete the questionnaire was 28%. Seven per cent of the household contacts were vaccinated against influenza, and 9% had experienced clinical influenza in the preceding year.

**Statistical analysis**

Although occurrence of secondary transmission is the ultimate outcome of interest in this work, time to transmission is important as well, because the level of exposure to influenza in the household is not constant over time. Household members became sick and recovered during the study follow-up. Adjustment for factors that varied between households; for example, exposure to influenza and household structure, was needed to assess the true role of individual predictors of transmission. The Cox model is a popular regression model used to assess the relation of explanatory covariates to the time of occurrence of events, which in this study is the onset of clinical influenza in contacts. This model allows adjustment for time-dependent covariates; for example, the level of exposure to influenza in the household.

Extensions to the Cox model exist that deal with the dependence between observations, in particular for correlated household members. In this study, dependence between household contacts is due to shared household structure and exposure to the same index patient.17 Household contacts who had not developed clinical influenza within 5 days (412/543 [75.9%]) were considered as censored (for these contacts, transmission events had not occurred within 5 days but may occur later).

Similarly to previous studies of influenza transmission in families,18 we distinguished between preschool children (0–5 years old), school-age children (6–15 years old), and adults (>15 years) to quantify the effect of age. Size limitation did not allow for more refined subcategories, such as infants or adolescents. We included the following covariates separately in the model: age of the household contact (0–5, 6–15, >15 years); influenza vaccination of the contact; influenza-like illness of the contact in the previous year; history of chronic disease and tobacco consumption of the contact; duration of illness of the index patient (above or below the median); and severity of disease of the index patient on the first day of symptoms (above or below the median). We also adjusted for three household-specific parameters that could confound individual characteristics: the number of children ≤15 years in the household, the number of adults, and the level of exposure to influenza infection in the household. We used a daily index, calculated as the sum of the severity scores of the household members (the daily severity score was the proportion of symptoms reported on a given day among the 13 listed in the questionnaire and ranged from 0 to 1) as a proxy for the level of exposure to influenza.9

Upon completion of the study and data entry by trained personnel, less than 4% of the information was missing. Because of the low rate of missing values, these values were not replaced. All statistical analyses were carried out by statisticians.

**Results**

**Descriptive analysis**

Overall, 131 (24.1%) of the 543 contacts developed symptoms of influenza within 5 days of the onset of disease in the index patient, and hence were considered as secondary
Influenza transmission was observed in 97 (35%) households. Of the 97 households, 67 (69.1%) reported three. The median time lag between the onset of influenza in the index patient and the onset of symptoms in the secondary patient was 2 days (range = 1–5 days) (Figure 2). The demographic and medical data for the secondary patients and non-case household contacts are presented in Table 1. We found no significant differences in the individual characteristics of these two groups of contacts with regard to age, sex, smoking status, history of chronic disease, influenza vaccination, or previous influenza-like illness. However, clinical influenza was reported in 38.5% (10/26) of contacts in households where the index patient belonged to the 0–5 years age group, in 33.7% (28/83) of the 6–15 years age group and in 21.4% (93/434) of adults, (Cochran-Armitage trend test, \( \text{P}=0.004 \)). Note that these estimates are not adjusted on household structure. Households in which the index patient was a child had more children than those where the index patient was an adult (respective median number of children = 2 versus 1, \( \text{P}<0.001 \)).

**Risk factors of influenza transmission in households**

The Cox statistical analysis showed that transmission of influenza was clearly associated with the age of both the index patient and the contact. We found an increased risk of clinical influenza in preschool contacts compared with adults, with a hazard ratio (HR) of 1.85, 95% confidence interval (CI) = 1.09 to 3.26. There was no increased risk in school-age contacts (HR = 1.12, 95% CI = 0.73 to 1.71). There was also an increased risk of clinical influenza in contacts exposed to preschool index patients (HR = 1.93, 95% CI = 1.09 to 3.42) and school-age index patients (HR = 1.68, 95% CI = 1.07 to 2.65), compared with those exposed to adult index patients. No other factor related either to the contact or to the index patient was associated with influenza transmission (Table 2).

We tested the effect of discarding the households where co-existing primary cases were reported on the day of the initial visit to the GP from the analysis. We repeated the initial statistical analysis with an extended dataset comprising all households (\( n = 395 \)), in which 313 secondary cases were reported (secondary attack rate in contacts = 38.3%). We retrieved similar results, but all hazard ratio estimates

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**Table 1. Comparison of demographic data for household contacts \( n = 543 \), grouped by secondary cases and non-case contacts.**

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>Non-cases ( n = 412 )</th>
<th>Secondary cases ( n = 131 )</th>
<th>( \text{P-value} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
<td>32.1 (19.4)</td>
<td>32.0 (21.3)</td>
<td>0.95</td>
</tr>
<tr>
<td>Age (( n \ [%] ))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–5 years</td>
<td>22 (5.3)</td>
<td>14 (11.5)</td>
<td>0.09*</td>
</tr>
<tr>
<td>6–15 years</td>
<td>80 (19.4)</td>
<td>26 (19.9)</td>
<td></td>
</tr>
<tr>
<td>&gt;15 years</td>
<td>310 (75.2)</td>
<td>91 (68.9)</td>
<td></td>
</tr>
<tr>
<td>Male sex (( n \ [%] ))</td>
<td>191 (46.4)</td>
<td>65 (49.6)</td>
<td>0.51</td>
</tr>
<tr>
<td>Current smoker (( n \ [%] ))</td>
<td>75 (18.2)</td>
<td>18 (13.7)</td>
<td>0.24</td>
</tr>
<tr>
<td>Chronic diseases (( n \ [%] ))</td>
<td>45 (10.9)</td>
<td>20 (15.3)</td>
<td>0.14</td>
</tr>
<tr>
<td>Influenza vaccination (( n \ [%] ))</td>
<td>28 (6.8)</td>
<td>6 (4.6)</td>
<td>0.36</td>
</tr>
<tr>
<td>Influenza-like illness in the previous year (( n \ [%] ))</td>
<td>32 (7.8)</td>
<td>14 (10.7)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

*\( \text{P} \) for trend = 0.06. SD = standard deviation.

**Table 2. Hazard ratios for individual predictors of influenza household transmission, adjusted on a daily score for exposure to influenza infection, the number of children under 15 years old and the number of adults in the household.**

<table>
<thead>
<tr>
<th>Individual predictor</th>
<th>Hazard ratio (95% CI)</th>
<th>( \text{P-value} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Household contact</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;15 years</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>6–15 years</td>
<td>1.12 (0.73 to 1.71)</td>
<td>0.60</td>
</tr>
<tr>
<td>0–5 years</td>
<td>1.85 (1.09 to 3.26)</td>
<td>0.02</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>1.54 (0.89 to 2.64)</td>
<td>0.12</td>
</tr>
<tr>
<td>Influenza vaccination</td>
<td>0.83 (0.40 to 1.70)</td>
<td>0.61</td>
</tr>
<tr>
<td>Chronic diseases</td>
<td>1.31 (0.72 to 2.36)</td>
<td>0.38</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.20 (0.93 to 1.55)</td>
<td>0.15</td>
</tr>
<tr>
<td>Index patient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;15 years</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>6–15 years</td>
<td>1.68 (1.07 to 2.65)</td>
<td>0.02</td>
</tr>
<tr>
<td>0–5 years</td>
<td>1.93 (1.09 to 3.42)</td>
<td>0.02</td>
</tr>
<tr>
<td>Severity of disease on day 1 (( \geq ) median))</td>
<td>1.35 (0.91 to 1.99)</td>
<td>0.13</td>
</tr>
<tr>
<td>Duration of disease (( \geq ) median))</td>
<td>1.40 (0.96 to 2.03)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

*The median severity of disease on day 0 (proportion of 13 clinical symptoms reported on the day of the visit to the general practitioner) was 0.65 for index cases (range = 0–1). \( \text{P} \) for trend = 0.06. SD = standard deviation.
were somewhat closer to one than those of the main analy-
sis. There was an increased risk of clinical influenza in
school contacts (HR = 1.90, 95% CI = 1.35 to 2.67) but
not in school-age contacts (HR = 0.94, 95% CI = 0.71 to
1.26). There was also an increased risk of clinical influenza
in contacts exposed to young index patients, with a hazard
ratio of 1.62, 95% CI = 1.31 to 2.00 for preschool index
patients and a hazard ratio of 1.27, 95% CI = 1.03 to 1.57
for school-age index patients.

The additional sensitivity analysis using a more specific
definition of clinical influenza (based on fever and cough)
gave results in line with those from the main analysis. The
secondary attack rate in contacts was 18.1%. There was an
increased risk of clinical influenza in preschool contacts (HR
= 2.28, 95% CI = 1.46 to 3.59) but not in school-age con-
tacts (HR = 0.61, 95% CI = 0.37 to 1.01). Although no more
significant, the magnitude of risk and confidence intervals
associated with the age of the index patient was consistent
with the previous estimates (HR = 1.03, 95% CI = 0.42 to
2.54) for preschool index patients and HR = 1.44, 95% CI =
0.83 to 2.51 for school-age index patients.

Discussion

The present study identifies age of index patients and age of
contacts as the main predictors of influenza transmission in
families. These factors appear to be more important than
other individual variables, whether they are related to the
contact person or to the index patient. Based on our risk
estimates, 40–48% of the secondary cases exposed to a
child sick with influenza in the household are attributable
to transmission from the child.

Strengths and limitations

Two factors may have harmed the validity of our results. The
first is that the household contacts were not tested for
influenza infection to limit intervention bias.9 It is therefore
possible that some of the clinical infections detected here
may be due to respiratory viruses other than influenza.
However, there was little circulation of other respiratory
viruses in the community during the study period: only 25 of
the 946 (2.6%) index patients tested positive for respiratory
syncytial virus and none were found to be positive for
parainfluenzae virus or adenovirus. Furthermore, a recent
investigation of the genetic sequences of influenza viruses
recovered in families suggested that transmission from com-
mmunity sources was rare in families where an index patient
had tested positive for influenza A.19

Instead of laboratory tests, we used a broad clinical defin-
ition based on fever or respiratory signs to identify sec-
ondary cases. Indeed, 38% of contacts classified as sec-
condary patients did not report a fever. In patients consulting
physicians for a respiratory illness during an influenza epi-
demic period, the relative risk that fever >37.8°C is associ-
ated with an influenza diagnosis was 2.5 in one study (4.6 for
influenza A [H3N2] specifically),20 and 3.3 in another.18
However, syndromes associated with true influenza infection
do not necessarily always include fever. In the latter studies,
30–40% of patients with respiratory syndromes caused by
influenza were afebrile. Furthermore, by applying a specific
combination of cough and fever as case definition,16 we
found risk estimates consistent with those derived from our
original broader definition, although some of our risk esti-
mates were no longer significant due to lack of statistical
power.

The choice of a time period of 1–5 days from the inclusion
of index patients to the onset of symptoms in secondary
patients (mean delay = 2.4 days) minimised the risk of
infections from non-influenza pathogens and from extra-
household sources. Indeed, in the present study, we found
influenza transmission in 24.1% of the household contacts
and in 34.8% of the households. These figures are within
the range of previously published estimates in comparable
placebo groups of clinical trials.5,7,8

Overall, although we do not know the exact proportion of
patients with influenza among the contacts showing symp-
toms of clinical influenza, we can provide an estimate. It has
been reported that 75–80% of household transmissions
occur directly from the influenza-positive index patient or
from the same source of infection as the index patient.7,8 In
this group, all of the clinical secondary cases have an
influenza aetiology. The remaining 20–25% are due to trans-
mission from the community at large.7,8 In this second
group, the probability of infection by influenza equals the
prevalence of influenza in the community. From the propor-
tion of influenza infections in index patients at inclusion we
estimate the prevalence of influenza in the community at
54% in this study. A plausible range estimate of the propor-
tion of influenza infection among secondary patients is
therefore 88.5–90.8%.

Reasons for increased transmission from children

The role of children in the dissemination of influenza is com-
monly accepted,2,3 and can be explained by three different
and possibly complementary mechanisms. First, children are
believed to experience a large number of extra-household
contacts with their peers in schools or daycare centres,
although very little quantitative information is available on
the subject. Our study was not designed to test this mechanism.
Second, children are assumed to be more susceptible to
influenza infection because of lower immunity, although it
depends on virus (sub)types and setting.3,21 Accordingly, we
found evidence of increased susceptibility to clinical influen-
za in preschool children. We have no clear explanation as to
why there was no increased susceptibility in school-age chil-
dren, but influenza A (H3N2) infections usually have a wider
distribution of age-specific attack rates than influenza A
(H1N1) or influenza B infections.18 It is also possible that few
differences in susceptibility between adults and school-age
children occurred in this particular year, due to the circulation
of the same influenza viruses (A/Sydney/5/97-like viruses,
A/H3N2 subtype) for the third consecutive winter. Third, chil-
dren could also be more infectious both because of an
increased amount of virus shedding and an increased dura-
tion of the infectious period, as reported in recent clinical
studies.22–7 Our results are in line with these findings.

Strategies for limiting secondary transmission of
influenza in households
This work provides a quantification of the major role of children, and particularly younger children, in the transmission of influenza in families. Based on attributable fractions of exposure to sick children in the household of around 40–48% we can assess the potential impact of two intervention strategies. The first is the vaccination of children in advance of the epidemic season. The efficacy of influenza vaccine has been estimated to be around 80% in preventing the disease in children.23 Thus, 32–38% of the secondary household cases from exposure to a sick child could be averted by vaccinating children. The second is the prophylactic treatment of household contacts with neuraminidase inhibitors after exposure to a child sick with influenza. Parents usually consult a GP or a paediatrician if their child has symptoms of influenza-like illness, so the diagnostic of influenza needs to be established. Using rapid influenza tests during the visit would allow identification of 72–95% of influenza needs to be established. Using rapid influenza has symptoms of influenza-like illness, so the diagnostic of influenza would prevent 21–41% of cases in exposed household contacts. These figures should help clinicians choose adequate strategies for controlling the size of influenza epidemics within households.

References


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