

PEDIATRIC ASTHMA

Influenza-Like Illness Responsible for Severe Exacerbations in Asthmatic Children During H1N1 Pandemic: A Survey Before Vaccination

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Background. Asthma seems to be the more prevalent underlying condition in patients hospitalized for H1N1-related flu. **Methods.** A prospective survey was conducted during the early phase of H1N1 pandemic in France in asthmatic children before vaccination to assess whether severe exacerbations in childhood asthma are associated with influenza-like illness (ILI, the definition of H1N1-related flu in a pandemic). Eight pediatricians in primary care distributed in three localities (Paris, south suburb, and west suburb) conducted the survey (4 weeks/locality from week 36 to 47). At each visit, the pediatrician filled a questionnaire entering the information regarding asthma treatment, severe exacerbation (at least 3 days' use of systemic corticosteroids), and ILI (temperature $\geq 37.8^{\circ}\text{C}$, cough, and/or sore throat, in the absence of a known cause other than influenza) during the past 3 weeks. **Results.** The survey included 1155 asthmatic children (mean age [SD]: 7.5 years [4.1]); almost all visits were scheduled (99%). A severe exacerbation was recorded in 121 children [10.5%; 95% confidence interval (CI): 8.7–12.2%], which was concomitant with ILI in 20 children (16.5%; 95% CI: 9.9–23.2%), whereas 1034 children did not exhibit any exacerbation. In these latter children, 40 ILI were observed (3.9%; 95% CI: 2.7–5.0%), which constituted a significantly lesser percentage as compared with children with both exacerbation and ILI ($p < .0001$). This result remained significant in each locality. Overall, 60/1155 (5.2%; 95% CI: 3.9–6.5%) asthmatic children had an ILI. **Conclusions.** Our survey shows that severe exacerbation and ILI are strongly associated during the H1N1 pandemic in asthmatic children.

Keywords asthma, exacerbation, influenza, childhood

INTRODUCTION

In a pattern similar to that in patients with seasonal influenza, the patients with H1N1 influenza have a high prevalence of underlying medical conditions. For instance, in the recent study of Jain et al. (1), on 272 patients who were hospitalized for at least 24 hours for influenza-like illness (ILI) and who tested positive for the 2009 H1N1 virus, asthma was the most common condition seen in both children (29%) and adults (27%). Similarly other recent studies report that asthma is the more prevalent underlying condition in patients hospitalized for H1N1-related flu (2, 3). Consequently, it seems that asthma constitutes a specific underlying condition with a high risk of clinical expression of the H1N1-related flu. Nevertheless, whether influenza is responsible

for severe asthma exacerbations is still debated. Some investigators found that there is no evidence that influenza virus infection is a major trigger of airway hyperreactivity or exacerbation of asthma in children (4, 5), explaining that influenza-related asthma exacerbation is usually a rare event in an epidemic setting (1.8% of all asthma exacerbations in children) (6). Other investigators showed that influenza-infected asthmatic children experienced a high rate of exacerbations (51–68%) (7). During a pandemic, we hypothesized that the incidence of ILI in asthmatic children would be higher than in the general population, making easier the evaluation of the consequence of ILI on asthma exacerbation. Consequently, we conducted a survey during the early phase (from August to November) of H1N1 pandemic in France in asthmatic children before H1N1 vaccination to assess whether severe exacerbations in childhood asthma were associated with ILI. We hypothesized that if ILI causes severe exacerbation, the percentage of asthmatic children with exacerbation and ILI would be increased as compared with the percentage of asthmatic children without exacerbation but with ILI.

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Patients and Methods

The survey involved eight pediatricians specialized in pulmonology distributed in three localities (Paris, South and West suburbs) because the pandemic spread was local then regional. They filled a questionnaire for all consecutive asthmatic children (diagnosis based on standard criteria) (8) referred for both scheduled and unscheduled visits (which was recorded). Each child was included only once.

In each locality (the order of the localities was randomly selected), questionnaires were filled for 1 week every 3 weeks from week 36 to 47 (4 weeks of survey/locality). At each visit, the child (and the parent) was questioned about ILI (defined as a temperature of $\geq 37.8^{\circ}\text{C}$, oral or equivalent, and cough and/or sore throat, in the absence of a known cause other than influenza) (9) and severe exacerbation of asthma (at least 3 days' use of systemic corticosteroids) (10) for the past 3 weeks. Thus, the questionnaire was administered through a 12-week period, but the total period surveyed was from week 33 to 47. To avoid random variability related to the low number of children included per week, data from 3 consecutive weeks of the survey were pooled in four periods that partially overlapped (see Figure 1). The Institutional Review Board of the French learned society for respiratory medicine—Société de Pneumologie de Langue Française—approved the protocol. No consent

was required for the survey according to the French Law of Bioethics because the data were analyzed anonymously.

Statistical Analysis

Our hypothesis was that ILI in the context of H1N1 pandemic would induce a dramatic increase in the exacerbation rate as compared with the epidemic flu-related exacerbation rate. Flu-related exacerbations represent 2% of all asthma exacerbations (6); to demonstrate a 10-fold increase in H1N1-related exacerbation rate, 116 exacerbations needed to be included (90% power and a two-sided alpha level of 5%). We then hypothesized that the seasonal epidemic exacerbation rate would be increased at least 2–3-fold by pandemic (hypothesizing an exacerbation rate of 2.0/year/patient) (12). A total of 1000 asthmatic children needed to be enrolled in the survey. Based on the number of asthmatic children followed up by each practitioner, we calculated that a 4-week survey/practitioner would be necessary to enroll 1000 patients.

Quantitative variables are expressed as mean $\pm$ SD. Chi-square test was used for the comparison of qualitative variables (Fisher's correction when necessary). A value of $p < .05$ was considered statistically significant. Statistical analyses were performed using Statview® software (SAS Institute Inc., Cary, NC, USA).

RESULTS

During the 12 weeks of the study, 1155 children were included and their characteristics are described in Table 1. Almost all visits were for regular follow-up of asthma because only 13 visits were unscheduled (10 with recent exacerbation and 4 with ILI). None of the children has been vaccinated for H1N1 virus.

Severe exacerbations occurred in 121 children [10.5%; 95% confidence interval (CI): 8.7–12.2%] and were more frequent in younger children (infants: 21%; preschool: 17%; junior school: 9%; high school: 6%; $p < .0001$) and in children with the highest inhaled corticosteroid (ICS) doses (no ICS: 9%; low dose: 10%; medium dose: 16%; high dose: 15%; $p = .044$). Eight children were hospitalized. Exacerbation rates were similar irrespective of the locality ($p = .49$).

Overall, 60/1155 (5.2%; 95% CI: 3.9–6.5%) asthmatic children had suffered from an ILI. Figure 1 shows the exacerbation and ILI rates of the four periods of the survey, suggesting the increasing proportion of ILI among exacerbations in this early phase of pandemic.

Figure 2 summarizes the main result, which is a highly significant statistical association between severe exacerbation and ILI in asthmatic children (this remained significant when excluding the 13 unscheduled visits). A significantly higher ILI rate was observed in the Paris locality as compared with the two suburb localities (versus west, $p = .025$; versus south, $p < .001$, see Figure 2). Nevertheless, in each locality the association between ILI and exacerbation remained significant: Paris, $p = .0022$;

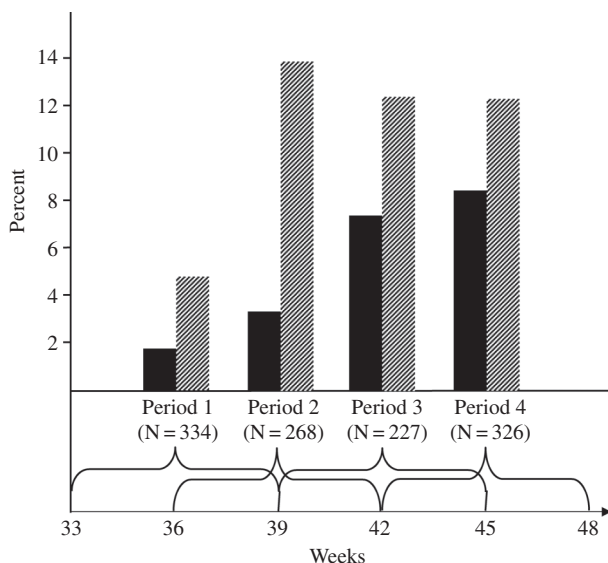


FIGURE 1.—Percentages of exacerbations and influenza-like illness (ILI) over time (weeks). The percentages (related to the total number of asthmatic children in parentheses enrolled during the period) of children who suffered from a severe exacerbation (shaded bars) or an ILI (black bars) are given for the four periods of the survey. The number of both exacerbations and ILI was significantly different for the four periods ($p = .0008$ and $p = .0002$, respectively). These periods overlapped (the study was not designed to assess the incidence of exacerbations and ILI) due to the design of the study (retrospective assessment at the time of visit for the 3 past weeks). Nevertheless, the risk exposure of a single child lasted 3 weeks for all children. The earlier increase in exacerbation rate as compared with ILI rate may represent the usual effect of September epidemic that is related to other viruses than influenza (11).

TABLE 1.—Characteristics of the asthmatic children.

	N = 1155
Mean age ^a (SD) (years)	7.5 (4.1)
Sex ratio ^b (F/M)	391/713
Infants (F/M)	21/75
Preschool (F/M)	137/221
Junior school (F/M)	133/213
High school (F/M)	98/195
Asthma treatment	
Beta-agonist on demand	496
Low ICS dose	203
Medium ICS dose	350
High ICS dose	106
Long-acting beta-agonist	381

Notes: M, male; F, female; ICS, inhaled corticosteroid. The three classes of ICS doses were those defined in GINA guidelines (8).

^aAge was available for 1137 children; ^bgender was available for 1104 children.

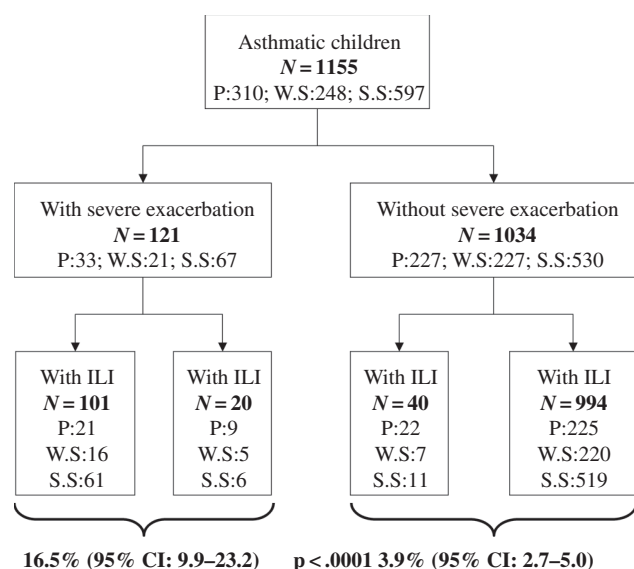


FIGURE 2.—Flowchart of the asthmatic children according to severe exacerbation and ILI. The number of children enrolled in each locality is provided. P, Paris; W.S, West suburb; S.S, South suburb, ILI, influenza-like illness.

West suburb, $p = .0014$; South suburb, $p = .0073$ (see Figure 2).

DISCUSSION

Our survey suggests that both ILI and severe exacerbation rates were high in asthmatic children and demonstrates that in the context of H1N1-related flu pandemic, ILI and severe exacerbations were strongly associated.

Our study was not designed for the estimation of the incidence rate of ILI in asthma because the survey design (see Figure 1) and the recruitment of pediatrician specialized in pulmonology may have obviously been biased. The number of unscheduled visits was low, which may be in agreement with the low impact on health-care services in France during the study period as stated by the WHO (13). The weekly percentage of outpatient visits for ILI reported by the US Outpatient ILI Surveillance Network increased from 3.5% in the week 36 to 7.7% in the week 44 (9). ILI activity has remained above the

national baseline during this entire period (9). The WHO stated that for the same period in Europe, widespread and increasing transmission of pandemic influenza virus was observed across much of the continent. Over 99% of all subtyped influenza A viruses reported in Europe were 2009 H1N1 viruses (13). In France, the Institut National de Veille Sanitaire declared that from week 33 to 47 the incidence increased from 36 to 693 ILI/100,000 consultations and on 24 November 357 severe cases of suspected or confirmed H1N1-related flu have been hospitalized, of whom 16% were with underlying asthma (14). Sixty over 1155 asthmatic children suffered from an ILI, because each patient was “surveyed” for 3 weeks. A weekly rate of approximately 1700/100,000 consultations of asthmatic children can be estimated, which is higher than the rate observed in the general population for the same period, but is consistent with an excess risk due to asthma (a 3–4-fold increased risk may be inferred from the results of Jain et al. (1)).

Our observed severe exacerbation rate (10.5%, which gives an annualized rate of 1.8/patient/year) was high, even for the fall season. For instance, we recently observed in a multicenter trial in children and young adults an exacerbation rate of 0.09/patient/year (95% CI: 0.02–0.23%) (15). We found the usual deleterious effect of young age and high dose of ICS on exacerbation rate (16), further demonstrating that the pattern of ILI-induced exacerbation was similar in the context of pandemic than in the usual epidemic season.

More interestingly, severe exacerbations were clearly associated with ILI in our asthmatic population, a finding that was similar irrespective of the locality. The WHO stated that ILI activity in France was local on weeks 36–43 and regional until week 44 (13), which may explain that the rate of ILI was significantly higher in Paris as compared with its suburbs. ILI was associated with 16.5% of all exacerbations in this pandemic context. Whether ILI were related to H1N1 virus was beyond the scope of this survey, but data from the French Groupes Régionaux d’Observation de la Grippe have shown that during the study period H1N1 virus was responsible from 3% (week 36) to 39% (week 47) of all acute respiratory

infections (17). It remains that the 16.5% ILI-induced exacerbation rate in this pandemic setting represents an eightfold augmentation as compared with an approximately 2% influenza-related exacerbation rate in seasonal epidemics (6).

Our study has limitations. It was not designed to determine the exacerbation and ILI rates in asthmatic children because our recruitment can be biased. The diagnosis of ILI and severe exacerbation was obtained through retrospective interview. Furthermore, even if we tried to determine whether the visit was scheduled, it is possible that some children consulted because of a recent ILI and/or exacerbation. Nevertheless, despite potential different degrees of availability of the investigators for unscheduled visits, the relationship between ILI and exacerbation was significant in all localities.

In conclusion, our survey shows that ILI and severe exacerbation are strongly associated in the H1N1 influenza pandemic in asthmatic children. In this context, an up to 10-fold increase in severe exacerbations may be observed, especially in younger children and in asthmatic children under medium- to high-dose ICS.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

AUTHORS' CONTRIBUTIONS

All the authors had substantial contribution to the conception and design or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and the final approval of the version to be published.

Specifically, Bruno Mahut and Christophe Delclaux made the initial design and draft of the study and are responsible for the integrity of the data in the study. Gilles Chatellier helped to design the study and was responsible for the statistical analysis.

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