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Complications and factors associated with severity of influenza in hospitalized children and adults during the pandemic wave of A(H1N1)pdm2009 infections—The Fluco French cohort

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ABSTRACT

Background: The emergence of novel A(H1N1)pdm2009 virus threatened to lead to frequent severe manifestations.
Objectives: To describe the clinical, virological, and biological characteristics of the disease and identify the factors associated with severe presentations.
Study design: This prospective multicenter study recruited consecutive hospitalized patients with confirmed A(H1N1)pdm2009 disease. Clinical, virological and biological assessments were carried out at inclusion and 30 days post-inclusion. Disease manifestations were assessed by an adjudication committee using pre-identified definitions of complications and severity scores.
Results: The study analyzed from November 30th, 2009 to February 8th, 2010, 40 hospitalized patients, 21 children and 19 adults. Eighteen (45%) were considered to have severe presentations. Except age, main characteristics in children and adults did not differ. The majority (18/21) of children and all adults had a respiratory presentation; extra-respiratory manifestations tended to be more frequent in children (12 vs. 6, $P = 0.10$). Two children against 5 adults presented acute respiratory distress syndrome (ARDS, $P = 0.23$), but more children suffered respiratory failure (7 vs. 1, $P = 0.046$) without ARDS. At day 30, one death had occurred in each group. The main factor associated with non-severe presentation was an early (<48 h) implementation of oseltamivir treatment ($P = 0.038$).
Conclusions: Although the study failed to achieve its main objective, due mainly to the difficulty of carrying a study of this nature in the midst of a pandemic, it allowed the description of a panel of unusual and complicated forms and confirmed the added value of early oseltamivir treatment in limiting severity in hospitalized children and adults.

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1. Background

Although influenza is commonly considered a self-limited benign disease, lower respiratory tract and extra-respiratory presentations can lead to increased complications, sequelae and death in children as well as in adults [1–3].

With the emergence, mid-April 2009, of the A(H1N1)pdm2009 virus in California [4–7] and Mexico [8] among immunologically naive populations, severe manifestations were anticipated, especially in at-risk subpopulations with pre-existing comorbidities [9].

Consequently, the French health authorities decided in May 2009 to implement clinical studies in order to achieve a better understanding and management of the disease.

2. Objectives

Fluco was a multicenter national study designed to identify risk factors of severity, based on the description of clinical presentations and severe forms in children and adults with confirmed A(H1N1)pdm2009 influenza infection. This paper covers the description of severe and non-severe forms in hospitalized children and adults recruited during the A(H1N1)pdm2009 pandemic in France.

3. Study design

3.1. Patients' characteristics and follow-up

The Fluco study was a prospective multicenter study, the design of which started on May 5th, 2009, following the alert in USA and Mexico [7,8]. Patients were eligible if they attended the hospital for clinical manifestations compatible with influenza [1–3], had a positive A(H1N1)pdm2009 PCR, and gave informed consent.

Clinical data were recorded from day 1 and every other day during hospital stay. A final assessment was scheduled 30 days after inclusion. Collected data included demographic characteristics, history of influenza and pneumococcal vaccination, underlying medical conditions, as well as clinical signs and symptoms. Nasal swabs or washes were collected at inclusion and processed for detection of A(H1N1)pdm2009 virus by RT-PCR [10]. Leucocytes counts, C Reactive Protein (CRP) levels and radiological investigations were carried out.

3.2. Medical record review

Patients' case report forms and anonymized hospital medical records were analyzed by an adjudication committee (including intensivists, infectious diseases and internal medicine practitioners). This committee reviewed the clinical presentation, biological characteristics, medical imaging and validated the diagnosis. It classified complications, and distinguished those probably related to viral infection, those related to bacterial respiratory infection or other bacterial co-infection, those related to intercurrent events and those related to adverse effects of treatment, and validated disease severity, based on standardized pre-identified definitions of complications and severity scores: PELOD for children or FINE, SOFA or IGS2 for adults. Patients with upper or lower respiratory tract manifestations were diagnosed with a respiratory form, while those with manifestations involving non-respiratory tract organs (heart, CNS, etc.) were diagnosed with an extra-respiratory form. Bacterial respiratory infections were recognized on alveolar infiltrates, leucocytes counts greater than 10 000/mm^3 and/or CRP levels greater than 100 mg/dl, and/or sputum bacteriological analyses [11]. A case was considered severe when data (including oxygen requirements and PaO_2 values) suggested respiratory or other organ failure. Patients were separated into two groups, according to the time of oseltamivir treatment administration: patients treated earlier than 48 h after onset of symptoms and other patients treated later or left untreated.

3.3. Ethics

The study protocol was approved by the Institutional Review Board (IRB), *Comité de Protection des Personnes d'Ile de France 1, Paris, France, on October 7th, 2009*. A written informed consent was obtained from all patients or from parents (for children).

3.4. Study course and termination – statistical analysis

The study recruited patients in 18 centers from November 30th, 2009 to February 8th, 2010. On February 8th, 2010, the steering committee decided to terminate the study due to the low number of inclusions and the end of the A(H1N1)pdm2009 pandemic. Qualitative variables were analyzed using the Chi-square test, or Fisher exact test where needed; quantitative variables were compared using Mann–Whitney *U*-tests. All data analyses were carried out using SPSS version 17.0 (SPSS, Inc., Chicago IL).

4. Results

4.1. Study implementation and recruitment

The study conception started on April 30th, as soon as the alert had been announced to the public health institutions by the Health Ministry. As shown in Fig. 1, while the epidemic developed, several steps of implementation were conducted in parallel, in an attempt to rapidly start the study: protocol draft validations, submissions to the IRB and National Drug Agency (AFFSAPS), lead to a final agreement on October 7th. Financial negociations allowed definitive convention with the CRO on November 20th, after the epidemic's peak. During the study period, 42 patients were recruited; 22 children and 20 adult patients, among whom 21 children and 19 adults agreed to participate (see Fig. 2).

4.2. Patients characteristics

The characteristics of the patients are presented in Table 1. The mean (±SD) age was 3 (±5) years in children and 42 (±12) years in adults. Male patients were predominant in both groups (55%). Overall, 21 (53%) of the patients (9 children and 12 adults ($P = 0.20$)) had recognized risk factors for severe influenza. Exposure to tobacco was observed in 38% of children and 47% of adults ($P = 0.55$). Five percent of children and adults had been vaccinated against the current pandemic flu ($P = 0.99$), 10% and 16% against seasonal flu 2009/2010 ($P = 0.51$), and 48% and 5% against *Streptococcus pneumoniae* respectively (7-valent conjugate in children vs. polysaccharide pneumococcal vaccine in adults, $P = 0.004$).

4.3. Clinical presentation and complications

The delay between onset of symptoms and first medical contact was not significantly different between children and adults (2.1 ± 4.3 vs. 2.3 ± 2.4 days; $P = 0.17$), neither was the number of previous visits to a primary care center before hospital admission (1.8 ± 1.0 vs. 1.43 ± 0.7 visits; $P = 0.14$). Purely respiratory forms of influenza were identified in 22 patients, 9 (43%) children and 13 (68%) adults ($P = 0.10$), while 3 (14%) children had a clinical picture without any respiratory manifestation, isolated fever in neonates ($n = 2$) or neurological signs of encephalitis ($n = 1$). Mixed forms with respiratory and extra-respiratory manifestations, were identified in 15 patients, 9 (43%) children and 6 (32%) adults ($P = 0.10$). They

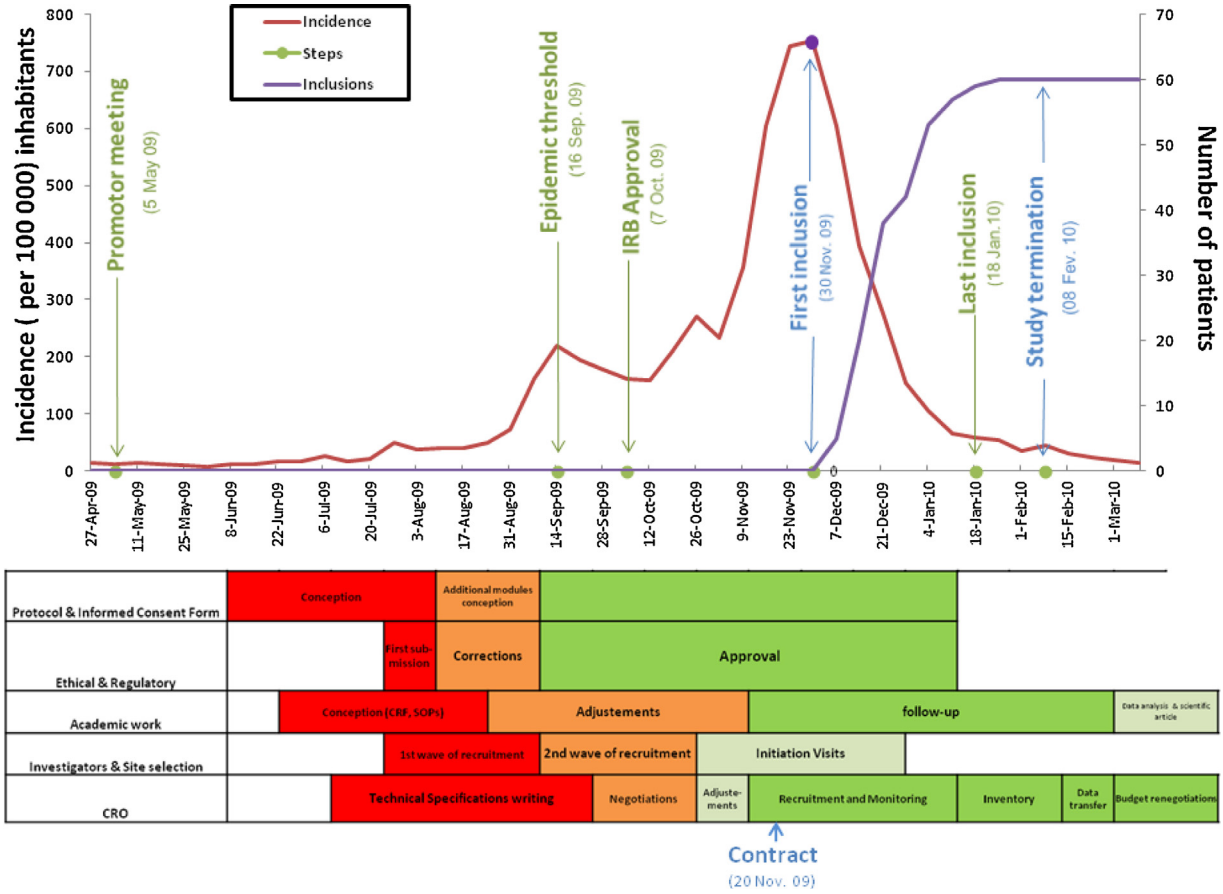

Fig. 1. Critical points of development of the Fluco study – 42 consecutive patients hospitalized for A(H1N1)pdm2009 influenza infection in France.

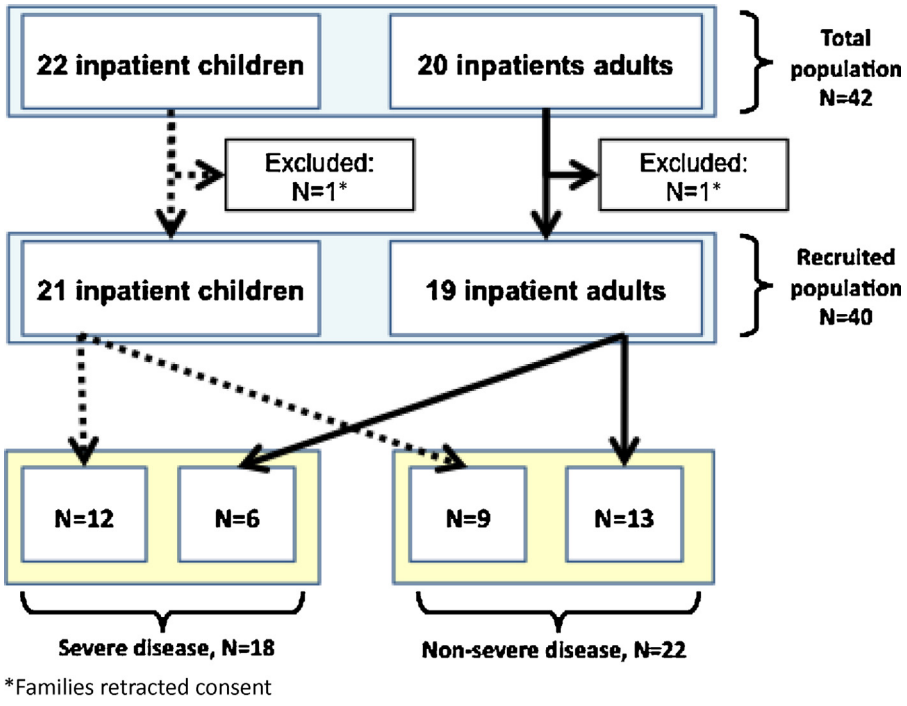

Fig. 2. Study flow chart of the sample survey 42 consecutive patients hospitalized for A(H1N1)pdm2009 influenza infection in France.

Table 1
Characteristics of the study population, disease presentation and management in 40 children and adult patients hospitalized for A(H1N1)pdm2009 influenza infection in France.

Characteristics	Children ($N=21$)	Adults ($N=19$)	P-value[a]
Patient characteristics			
Age	3 ± 5 [0–16]	42 ± 12 [21–65]	<0.001
Male	11 (52%)	11 (58%)	0.73
Risk factors for severe influenza[b]	9 (43%)	12 (63%)	0.20
Cardiovascular and respiratory risk factors	5 (24%)	6 (32%)	0.58
Immunodeficiency	2 (10%)	4 (21%)	0.40
Other risk factors[c]	4 (19%)	6 (32%)	0.47
Clinical presentation			
Patients with respiratory manifestations	18 (86%)	19 (100%)	0.23
Respiratory insufficiency[d]	7 (33%)	1 (5%)	0.046
Acute respiratory distress syndrome	2 (10%)	5 (26%)	0.40
Patients with extra respiratory manifestations	12 (57%)	6 (32%)	0.10
Patients with one or more complication(s)	17 (81%)	13 (68%)	0.23
Patients with severe (respiratory or not) disease	12 (57%)	6 (32%)	0.10
Death or sequelae at day 30	9 (43%)	8 (42%)	0.96
Clinical management			
Days between onset of symptoms and medical contact	2.1 ± 4.3 [0–19]	2.3 ± 2.4 [0–9]	0.17
Admission in intensive care unit	7 (33%)	6 (32%)	0.91
O_2 administration during hospital stay	11 (52%)	12 (63%)	0.49
Invasive ventilation	1 (5%)	6 (32%)	0.04
Non-invasive ventilation (cpap or optiflow)	5 (24%)	0 (0%)	0.05
Mask or lunettes	5 (24%)	6 (32%)	0.58
Oseltamivir treatment	19 (91%)	19 (100%)	0.49
Days between onset of symptoms and oseltamivir treatment	6.5 ± 9.7 [1–43]	4.3 ± 3.0 [0–11]	0.88
Patients treated with oseltamivir within 48 h after onset of symptoms	9 (47%)	7 (37%)	0.70
Antibiotics	14 (67%)	16 (84%)	0.28

Values are expressed either in n (%) or in mean ± SD, [min–max]

[a] Two sided tests

[b] Each patient can have more than one risk factor

[c] In children, the other risk factors observed were epilepsy (1), metastatic neuroblastoma with veno-occlusive disease and kidney failure (1), psychomotor retardation (1), and prematurity (1). In adults, other risk factors were myasthenia and alpha1 anti-trypsin deficiency (1), diabetes mellitus and pregnancy (1), hemiparesis (brain tumor sequela) (1), renal transplant and scalp cancer (1), HIV infection (1), systemic lupus with kidney failure (1) and obesity with a BMI value of 42 (1)

[d] Respiratory insufficiency other than acute respiratory distress syndrome

were related to neonatal fever in one child, and otherwise to extra-respiratory complications and/or co-morbidities described below and in Table 1.

Complications (1 to 3 per patient) occurred in 30 (75%) patients, 17 (81%) children and 13 (68%) adults ($P=0.47$). Complications were related to viral infection (15/21 – 71% in children and 9/19 – 47% in adults respectively), bacterial infection (9/21 – 43%, and 9/19 – 47%), intercurrent events (5/21 – 24%, and 5/19 – 26%), adverse effects (3/21 – 14%, and 4/19 – 21%). Among the 17 children with complications, respiratory diagnoses were viral pneumonia in 14 (82%), acute expiratory obstructive syndrome in 5 (29%, bronchiolitis in 4 and exacerbation of asthma in 1); and extra-respiratory diagnoses were encephalitis in 2 (12%), febrile seizures in 1 (6%), gastroenteritis in 1 (6%), apparent life-threatening event in 1 (6%), and/or decompensation of comorbidities in 3 (18%), diabetes mellitus in 1, aplasia in 1, acute leukemia in 1. Among the 14 children with viral pneumonia, 8 (57%) had bacterial respiratory infection, including 1 pleuropneumonia requiring surgery, 7 (50%) had respiratory failure (including 1 pneumothorax), and 2 (14%) had ARDS, associated with bacterial infection for both. One child had an identified bacterial co-infection presenting as *Nesseiria meningitidis* septicemia with purpura and arthritis. Identified bacterial respiratory infection involved *S. pneumoniae* ($n=4$) or *Staphylococcus aureus* ($n=3$). Among the 13 adults with complications, respiratory diagnoses were viral pneumonia in 9 (69%), acute expiratory obstructive syndrome in 3 (23%), exacerbation of asthma in 1, and of chronic obstructive broncho-pulmonary disease in 2, and acutisation of myasthenia in 1 (7%); and extra-respiratory diagnoses were cardiac failure in 2 (15%, including myocarditis in 1), kidney failure in 2 (15%), deep vein thrombosis in 1 (7%), central line bacterial infection in 1 (7%), and/or digestive hemorrhage in 1 (7%). Among the 9 adults with viral pneumonia, all 9 had bacterial infection, 1 had respiratory failure, and 5 (56%) had an ARDS, 3 of whom presenting with bacterial infection. Identified bacterial respiratory infection involved *S. pneumoniae* ($n=1$), *S. aureus* ($n=1$) or *Bramanella catarrhalis* ($n=1$).

4.4. Severity and medical management of the disease

Severe disease presentation was observed in 18 (45%) patients, 12 children and 6 adults ($P=0.10$). Death occurred in 2 (5%) of the 40 patients, one child from encephalopathy with status epilepticus and refractory intracranial hypertension, and one adult from viral myocarditis and ARDS. Among the patients with respiratory failure, the proportion of ARDS was significantly lower in children than in adults (2/9, 22% vs. 5/6, 83%, $P=0.04$). The patients with bacterial respiratory infections suffered more frequently of respiratory failure including ARDS than those with no bacterial respiratory infection (10/17, 59% vs. 5/23, 22%, $P=0.02$). Oxygen supply using different modes of ventilation was required in 11 (52%) children and 12 (63%) adults ($P=0.49$; see Table 1). All patients were given oseltamivir except 2 children who were admitted 6 and 11 days after onset of symptoms, for respectively gastroenteritis with vomiting and pleuresia as main presentations. Mean duration of treatment was the same in children and adults (6.3 ± 2.6 and 6.5 ± 3.6 days; $P=0.88$). Fourteen (67%) children and 16 (84%) adults received antibiotics ($P=0.28$).

4.5. Factors associated with severe disease

They are shown in Table 2. As expected, complicated forms were more frequent in severe than in nonsevere disease ($P<0.001$).

Table 2
Factors associated with severe disease in 40 children and adult patients hospitalized for A(H1N1)pdm2009 influenza infection in France.

Studied factors	Severe disease ($N=18$)	Nonsevere disease ($N=22$)	P-value[a]
Clinical presentation			
Patients with respiratory manifestations	17 (94%)	20 (91%)	0.99
Patients with extra-respiratory manifestations	11 (61%)	7 (32%)	0.064
Patients with complications	18 (100%)	12 (55%)	0.001
Patients with bacterial infections	12 (67%)	6 (33%)	0.02
Sequelae at day 30 or death	11 (61%)	6 (27%)	0.031
Risk factors for severe influenza			
At least one risk factor	9 (50%)	12 (55%)	0.78
Cardiovascular and respiratory risk factors	4 (22%)	7 (32%)	0.72
Other risk factors	5 (28%)	5 (23%)	0.73
Biological factors			
CRP (mg/L) at inclusion ($n=35$)	156 ± 89 [1–298]	79 ± 102 [1–321]	0.016
Viral load (10^6 copies/mL) at inclusion ($n=34$)	31 ± 62 [5–227]	140 ± 386 [5–1819]	0.36
Clinical management			
Days between onset of symptoms and hospitalization	6.9 ± 9.3 [1–42]	3.3 ± 2.9 [0–9]	0.072
Patients treated with oseltamivir within 48 h after symptom onset	4 (22%)	12 (55%)	0.038

Values are expressed either in n (%) or in mean ± SD, [min–max]; as some biological data were missing, number of patients is indicated for each variable. and provided in parentheses for variables with missing data.
[a] Two sided tests.

And bacterial infection was more frequent in severe forms (12/18, 67% versus 6/22, 27%, $P=0.02$). Patients with severe forms more often required hospitalization in intensive care unit (61% vs. 10%, $P<0.001$) and had sequelae at day 30 ($P=0.031$). The baseline viral load was not different in severe and non-severe forms ($P=0.36$), while C-Reactive Protein levels were higher in severe forms ($P=0.016$).

Delay between onset of symptoms and hospitalization or implementation of oseltamivir treatment tended to be longer in complicated and severe forms, as compared to noncomplicated (data not shown; $P=0.10$) or non-severe forms ($P=0.07$). The proportion of patients with early treatment (earlier than 48 h) was lower in severe forms (22% versus 55%, $P=0.038$).

5. Discussion

These results show that implementation of a clinical trial during an ongoing pandemic is indeed a daunting challenge. Initial perception of the health emergency allowed no delay in initial reactivity of numerous scientists, investigators, surveillance, and research reglementary institutions. However the study failed to include a sufficient number of patients for an optimal statistical analysis, as a 7-month long preparation prevented inclusions until shortly after the epidemic peak in France (see Fig. 1). We propose that a preliminary mock-up protocol be prepared now, to be used and adapted to future emerging infectious agents, in order to reduce as much as possible the delay until scientific validation. This simulation exercise could help also in anticipating logistics, ethical, administrative and financial preparation, and thus facilitate relationships between the concerned actors and institutions.

We acknowledge the fact that the patients hospitalized for influenza represent a small proportion of all patients with A(H1N1)pdm2009 flu who, in most cases, presented with a classical upper respiratory illness [4,5]. Thus, it was anticipated that, in our study, hospitalized patients were more likely to present complicated or severe manifestations. Extra-respiratory manifestations, very rarely reported in seasonal influenza, were observed in nearly half of the recruited patients. They appeared more frequent in children than in adults, especially neurological forms as previously published in children [3,14,15]. They tended to be associated with a more severe disease and contributed to two fatal outcomes in our sample. It is rather uncommon that a respiratory disease should lead to an ARDS in seasonal influenza [2], whereas it appeared less unusual in A(H1N1)pdm2009 influenza pandemic [12]. In the present study, ARDS presentation appeared more frequent in adults, whereas children had more often a respiratory failure without signs of ARDS. These differences may suggest less severe respiratory involvement in the pediatric population, translating in different requirements for oxygen supplementation. Indeed, most children could be ventilated with a non-invasive supply while the majority of adults required intubation. This difference in management of influenza according to age did not seem to markedly affect outcome in this study, but is difficult to compare with previous experience since literature comparing children and adults with influenza is rare [13]. These unusual ARDS and extra-respiratory presentations of influenza during the A(H1N1)pdm2009 pandemic may be associated to the greater number of persons affected by influenza during that period, the naïve status of a large part of the population and/or an intrinsic higher virulence or pulmonary tropism of the virus [9,16].

Although a similar proportion of children and adults had a well-identified factor associated with poor outcome in seasonal flu, it did not appear associated with severity in the present study, probably due to its limited size. Additionally, as described in other series of patients specifically infected with the A(H1N1)pdm2009 [17], approximately half of the study population had no identified predisposing factor for severe flu. The lack of association between nasal viral load and severity may be due to the small size of the study population, but also to the difference between upper and lower respiratory viral loads in severe presentations. It has been previously reported that discrepant viral loads may be detected in severe cases [16]. As expected [18], vaccination status for pneumococcal vaccine differed according to age. The main factors associated with severity were complications of influenza, and bacterial infections in particular. Even though bacterial infections frequencies in patients with influenza have varied widely in previous series, they have always been reported as a major factor influencing the prognosis [17,19–22]. Higher levels of CRP in patients with severe disease probably also reflect the role of bacterial infections, as previously suggested [23]. The limitations made on the wide use of antibiotics are generally advocated to contain the extension of bacterial resistance, including among patients with seasonal flu. In the context of an influenza pandemic, however, the important role of bacterial infection in severe disease suggests the potential benefit of an open and early probabilist implementation of antibiotics in hospitalized patients with influenza [22,24]. Whether high levels of CRP,

as suggested for procalcitonin, may help to define the therapeutic strategy to limit impairment of the respiratory function remains to be demonstrated [25].

It is interesting to note that, within this limited study population, nonsevere forms of the disease were associated to an initiation of oseltamivir treatment earlier than 48 h after the onset of symptoms, as already reported in several studies [5,13,17,19,21,26]. It is a hypothesis that the trend toward later admission can partly explain the development of severe disease in some patients. Although these data have to be interpreted with caution, they contribute to reinforce the message that every effort should be made to start oseltamivir, as soon as possible when indicated, to limit disease progression and the number of severe forms and deaths [12,22].

Pandemic preparedness planning has been recognized as an important step to mitigate the impact of a pandemic. Within pandemic planning, the research component, including epidemio-clinical research, has not been sufficiently addressed. Our experience in implementing a nation-wide clinical research protocol on the A(H1N1)pdm2009 influenza has clearly demonstrated the crucial need in future of protocol preparedness and funding planning during inter-pandemic periods. Such strategies are mandatory to allow an urgent deployment of the protocols in case of an emerging infectious disease threat [12].

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Competing interests

D. Ploin contributed as the French coordinator of a PK study of oseltamivir in children in the first year of life, and as investigator of an epidemiologic study of resistance of influenza virus in children, promoted by Roche. B. Lina contributed to a clinical trial and scientific advisory board, promoted by Roche. F. Carrat, C. Chidiac, B. Cohen, J.-C. Desenclos, E. Javouhey, C. Leport, M. Leruez, C. Mayaud declare no conflict of interest.

Ethical approval

The study protocol was approved by the Institutional Review Board, Comité de Protection des Personnes d'Ile de France 1, Paris, France, on October 7th, 2009.

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