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Effectiveness and safety of the A-H1N1 vaccine in children: a hospital-based case–control study

Italian Multicenter Study Group for Drug and Vaccine Safety in Children*

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*The members of the Italian Multicenter Study Group for Drug and Vaccine Safety in Children are listed in appendix 1.

Correspondence to
Dr Francesca Menniti-Ippolito;
francesca.menniti@iss.it

ABSTRACT

Objective: To verify whether vaccination against the A-H1N1 virus in the paediatric population was effective in preventing the occurrence of influenza-like illness (ILI) or was associated with adverse events of special interest.

Design, setting and patients: A case–control analysis was performed as part of surveillance of children hospitalised through the emergency departments of eight paediatric hospitals/wards for ILI, neurological disorders, non-infectious muco-cutaneous diseases and vasculitis, thrombocytopaenia and gastroduodenal lesions.

Results: Among 736 children enrolled from November 2009 to August 2010, only 25 had been vaccinated with the pandemic vaccine. Out of 268 children admitted for a diagnosis compatible with the adverse events of special interest, six had received the A-H1N1 vaccine, although none of the adverse events occurred within the predefined risk windows. Only 35 children out of 244 admitted with a diagnosis of ILI underwent laboratory testing: 11 were positive and 24 negative for the A-H1N1 virus. None of the A-H1N1 positive children had received the pandemic vaccine. The OR of ILI associated with any influenza vaccination was 0.9 (95% CI 0.1 to 5.5).

Conclusions: The study provides additional information on the benefit–risk profile of the pandemic vaccine. No sign of risk associated with the influenza A-H1N1 vaccine used in Italy was found, although several limitations were observed: in Italy, pandemic vaccination coverage was low, the epidemic was almost over by mid December 2009 and the A-H1N1 laboratory test was performed only during the epidemic phase (in <10% of children). This study supports the importance of the existing network of hospitals for the evaluation of signals relevant to new vaccines and drugs.

ARTICLE SUMMARY

Article focus

- To assess the effectiveness of the influenza A-H1N1 vaccine and the occurrence of adverse events of special interest in the paediatric population.

Key messages

- During the 2009–2010 influenza season, very limited information was available on the safety and effectiveness of the influenza A-H1N1 vaccine.
- Together with other post-marketing studies, our findings provide additional information on the benefit–risk profile of the pandemic vaccine.

Strengths and limitations of this study

- The study focused on influenza-like illness and adverse events of special interest that were sufficiently severe to cause hospitalisation in children and provided additional information on the benefit–risk profile of the pandemic vaccine.
- A-H1N1 vaccination coverage in Italy during the 2009–2010 influenza season was very low, with around 4% of the general population and only 3.7% of the children included in this study having been vaccinated.
- The influenza outbreak was almost over by the first half of December 2009, and both the incidence and severity of the disease were lower than expected.

BACKGROUND

Great concern about the severity of the A-H1N1 influenza epidemic in the paediatric population was expressed at international level in 2009.[1 2] The main public health response was considered to be the development of and access to new vaccines against the A-H1N1 virus. However, due to the limited availability of data, there was widespread uncertainty about the efficacy and safety of the pandemic vaccines, which could not be resolved in the short time available before vaccine approval, even though authorities had laid down the procedures to be completed in case of a new epidemic.[3]

To ensure public safety during the influenza outbreak, rapid access to the new influenza A-H1N1 vaccines was offered to high-risk groups such as pregnant women, young infants and immune-compromised patients. There were also specific concerns about the potential risks of adverse events

associated with the adjuvant included in some of the A-H1N1 vaccines and with the concomitant use of other influenza vaccines.

Regulatory agencies around the world require companies to carry out post-marketing surveillance studies on newly developed vaccines. However, because of the limited time available during this emergency, research groups already involved in the efficacy and safety assessment of drugs and vaccines were invited to focus their activities on the pandemic vaccines.[4] In Italy, a national pharmacovigilance pandemic plan, with specific focus on safety in the paediatric population, was implemented.[5]

Active surveillance of the role of drugs and vaccines in the occurrence of selected clinical conditions responsible for paediatric hospitalisation has been conducted in Italy since 1999. This surveillance so far has proved useful in the detection, description and evaluation of risk signals associated with drugs and vaccines used in children.[6–8] During the 2009–2010 pandemic season, following the launch of the vaccination campaign by the Italian Ministry of Health,[5] the study protocol of the existing surveillance system was adapted to focus on and include evaluation of the safety and efficacy of the A-H1N1 vaccine. In Italy the immunisation campaign started in October in healthcare workers and was subsequently extended to pregnant women and other at-risk groups, including children. After some weeks vaccination was offered to all citizens. Focetria, administered free of charge by the Italian NHS, was the only available pandemic vaccine.

The purpose of this study was to assess effectiveness of influenza A-H1N1 vaccination in the paediatric population for preventing the occurrence of influenza-like illnesses (ILI) requiring hospitalisation. Moreover, we assessed the safety of the vaccine, in particular by evaluating all the adverse events of special interest (AESI) reported in the exposed population.

METHODS

Study population

This study consisted of active surveillance of children hospitalised from November 2009 to August 2010 through the emergency departments (EDs) of eight clinical centres for selected conditions, regardless of their previous drug and vaccine exposure. The study population consisted of all children (aged 1 month–18 years) admitted for the four following conditions: (i) neurological disorders; (ii) non-infectious muco-cutaneous diseases and vasculitis; (iii) thrombocytopaenia; and (iv) confirmed gastroduodenal lesions (and/or clinically defined haematemesis or melena). The first three conditions cover nearly all diagnoses compatible with vaccine related AESI and were considered for vaccine safety evaluation.

Children older than 6 months hospitalised for ILI, as judged by the clinicians in the ED, were also enrolled in the study to estimate the effectiveness of influenza A-H1N1 vaccination. For children >5 years of age, the following definition of ILI was adopted: sudden onset of fever ≥38°C (for at least 24 h) in association with at least one respiratory symptom (cough, sore throat, coryza) and at least one general symptom (headache, asthenia, malaise). For children between 6 months and 5 years of age, in association with fever >38°C, the following general sign and symptoms were considered: inadequate drinking or feeding, vomiting and/or diarrhoea and respiratory symptoms.[9]

Assessment of the presence of influenza A-H1N1 virus by laboratory test was not an inclusion requirement. Both clinically defined and laboratory confirmed hospitalisations for ILI were considered of interest in evaluating the effectiveness of the influenza vaccines.[10] Given the non-interventional nature of the study design, we had to rely on the usual practice of participating hospitals. Moreover, following a recommendation of the Italian Ministry of Health, laboratory confirmation of A-H1N1 virus was not routinely suggested after the epidemic began to decline (mid December 2009) (figure 1). In order to limit selection bias (ie, selective enrolment of vaccinated children), participating centres were asked to enrol ILI cases on a specified day of the week (up to three or four consecutive cases per week) blind to vaccination status. This recruitment strategy applied to all ILI cases and was independent of the decision to carry out laboratory confirmation.

Data source

After providing informed consent, parents were interviewed by a trained investigator, using a structured questionnaire, during the hospital admission of the child. The interview sought to obtain the relevant history and to ascertain drug use and vaccination status. As reported in the study protocol, the information on drug and vaccine exposure was not validated.

For drug exposure, the time window of interest was the 3 weeks before the onset of symptoms related to the hospital admission. With regard to vaccine exposure, the 12 weeks preceding the hospitalisation were considered of interest for all non-influenza vaccines. For the assessment of the effectiveness of both the A-H1N1 and seasonal influenza vaccines, children were considered exposed if vaccinated any time before admission. To evaluate any possible relationship between vaccination and AESIs, time windows specific for each AESI were considered, for example 0–2 days for urticaria, 0–14 days for convulsions and 0–42 days for thrombocytopaenia, vasculitis, neuropathies, etc.[11 12]

Data analysis

Two different comparisons were conducted to assess vaccine effectiveness and estimate the ORs. For the first comparison, all children hospitalised for ILI were considered as cases, while children >5 months old enrolled for any of the four clinical conditions described above acted as controls. For the second comparison, the analysis was restricted to all children admitted for ILI

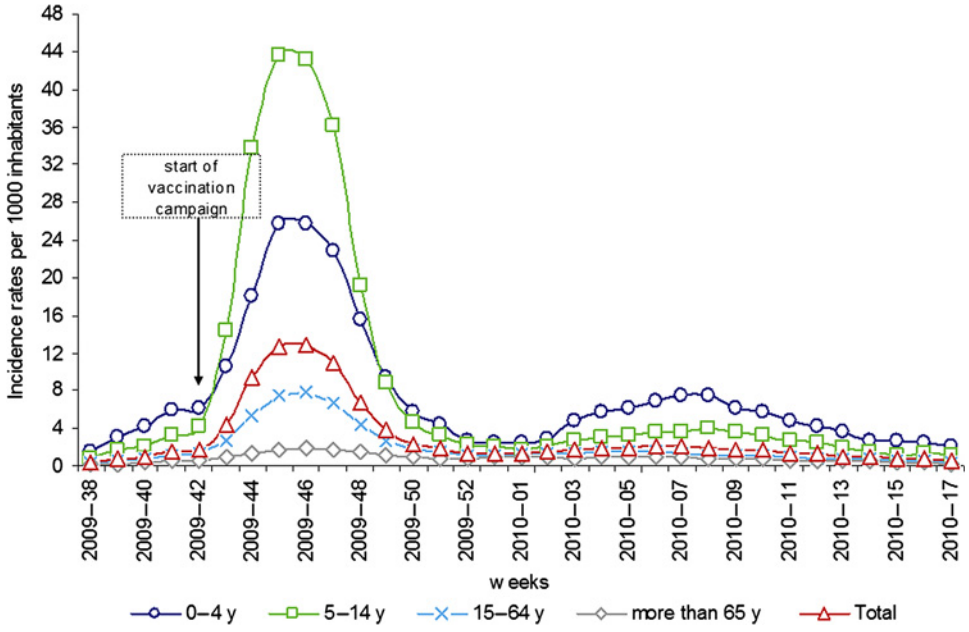

Figure 1 Effectiveness and safety of the A-H1N1 vaccine. y, years. Adapted from http://www.iss.it/binary/iflu/cont/2009_2010.pdf.

and tested for the A-H1N1 virus. ILI patients with a positive test were considered as cases, while those with a negative test acted as controls. The purpose of the first analysis was to provide an estimate of the effectiveness of the vaccines in preventing hospitalisation for any ILI during the influenza season. The second analysis was aimed at estimating the ability of the A-H1N1 vaccine to prevent the occurrence of confirmed episodes of pandemic influenza.

Assuming 50% of children were vaccinated, a power of 90% and an α error of 0.05, a sample size of 194 hospitalisations for ILI was required to estimate a reduction of at least 50% in the occurrence of ILI among vaccinated children (OR$\leq$0.5).

Adjusted ORs and related 95% CIs were calculated through a multivariate logistic model. Data were analysed with SPSS V.17.

Study sites

The following paediatric hospitals and departments participated in the study: Giannina Gaslini Paediatric Hospital (Genoa), Regina Margherita Paediatric Hospital (Turin), Department of Paediatrics, University of Padua (Padua), Anna Meyer Children's University Hospital (Florence), Pharmacology and Paediatrics and Developmental Neuroscience, Università Cattolica Sacro Cuore (Rome), Emergency Department, Bambino Gesù Children Hospital (Rome), Santobono-Pausilipon Paediatric Hospital (Naples) and Giovanni Di Cristina Paediatric Hospital (Palermo). The protocol of the study was submitted to the ethics committee of each clinical centre for approval. The eight centres account for around 350 000 ED visits annually (around 50 000 children are subsequently hospitalised through the ED) and are located in northern, central and southern Italy. The study was coordinated by the National Centre of Epidemiology of the National Institute of Health.

RESULTS

From 1 November 2009 to 31 August 2010, 736 children, with a median age of 4 years (range 1 month–18 years), were enrolled. Overall, 492 children were hospitalised for at least one of the four conditions of interest in this study: 241 (49%) for neurological disorders, 144 (29%) for muco-cutaneous diseases, 60 (12%) for thrombocytopaenia and 47 (10%) for gastro-duodenal lesions. A total of 244 children were admitted with a diagnosis of ILI (table 1). The male to female ratio was largely similar in the different diagnostic groups.

Among those with neurological conditions, convulsion was the most frequent cause of admission (N=91; 38%), followed by disturbances of vigilance and consciousness, for example, numbness, somnolence and lipothymia (N=39; 16%) and by apparent life threatening events (N=30; 12%). Some children with serious clinical conditions were admitted: eight with peripheral neuropathies and five with Guillain-Barré syndrome. More than half of those with muco-cutaneous diseases had Schoenlein-Henoch purpura or other vasculitis (N=80; 55%), followed by urticaria (N=32; 22%) and erythema (N=15; 10%).

Of the children enrolled in the study, 71% had been exposed to at least one drug in the 3 weeks preceding hospital admission. A total of 173 children (24%) had been vaccinated before hospitalisation (either at any time for the influenza vaccines or during the preceding 12 weeks for the other vaccines). Hexavalent vaccine was most frequently reported (55 children), followed by the antipneumococcal (37 children) and MMR (24 children) vaccines.

For the influenza vaccine analysis, the denominator was limited to the 683 children at least 6 months of age (according to the vaccination schedule for the pandemic vaccine). In this population (244 admitted for ILI and 439 for the other conditions), 25 children (3.7%) had

Table 1 Distribution of children hospitalised for the study conditions

Conditions	Patients, N (%)	Median age (IQR)	Female, N (%)	Exposed to drug(s), N (%)	Exposed to vaccine,* N (%)	Underlying chronic diseases, N (%)
Neurological disorders	241 (49)	4 (9)	112 (47)	166 (69)	53 (22)	35 (15)
Muco-cutaneous diseases and vasculitis	144 (29)	5 (5)	53 (37)	110 (76)	18 (13)	14 (10)
Thrombocytopaenia	60 (12)	4 (7)	21 (35)	40 (67)	17 (28)	10 (17)
Gastroduodenal lesions	47 (10)	5 (6)	20 (43)	33 (70)	8 (17)	6 (13)
Total	492 (100)	4 (7)	206 (42)	349 (71)	96 (20)	65 (13)
Influenza-like illness	244	3 (3)	108 (44)	170 (70)	77 (32)	58 (24)

*All vaccines administered to the study subjects, and not only those with influenza, are included; 25 children exposed to the pandemic vaccine were distributed as follows: six cases (2.5%) were hospitalised for neurological disorders, 4 (2.8%) for muco-cutaneous diseases and vasculitis, 2 (4.3%) for gastroduodenal lesions and 13 (5.3%) for influenza-like illness. IQR, interquartile range.

received the pandemic vaccine (nine children received two doses) and 45 (6.6%) had been vaccinated against seasonal influenza. Eleven children received both vaccines and in nine children the type of influenza vaccine was not specified. All immunised children (those with ILI and controls) had received the influenza vaccines more than 14 days before hospitalisation.

Out of 268 children admitted for a diagnosis compatible with AESI, only six had been previously vaccinated with the A-H1N1 vaccine (two cases of urticaria, two convulsions, one vasculitis and one Schoenlein-Henoch purpura), however, all admissions occurred outside the predefined risk windows (table 2).

Regarding evaluation of the effectiveness of the pandemic vaccine to prevent ILI episodes, regardless of any positive laboratory test, all estimates were above 1 (table 3). Specifically, the adjusted ORs were 2.1 (95% CI 1.1 to 4.1) for the seasonal vaccine and 1.3 (95% CI 0.6 to 3.1) for the pandemic vaccine. No difference in the OR estimates was observed when the analysis was restricted to the pandemic period (ie, October 2009–January 2010).

Among the 35 children who underwent laboratory testing, 11 were positive and 24 negative for the A-H1N1 virus (table 4). Since none of the A-H1N1 positive children had a positive history for A-H1N1 vaccination, it was not possible to obtain an estimate of vaccine effectiveness. Given the prevalence of exposure among controls, the likelihood of none of the 11 children with confirmed influenza having been immunised with the pandemic vaccine was 0.35. The OR of ILI associated with any influenza vaccination was slightly lower than 1 (OR 0.9; 95% CI 0.1 to 5.5).

Table 2 Children admitted with a diagnosis of AESI and vaccinated with the pandemic vaccine

Diagnosis	Interval (days)	Within the risk period
Urticaria	20	No
Schoenlein-Henoch purpura	47	No
Urticaria	60	No
Vasculitis	128	No
Convulsions	149	No
Convulsions	188	No

AESI, adverse events of special interest.

DISCUSSION

One of the main strengths of this study was the promptness in adapting the protocol of an existing study involving a network of hospitals to respond to the health alert created by the pandemic emergency. Despite the large Italian paediatric population enrolled, the results concerning the safety and effectiveness of the pandemic vaccine were partly inconclusive. Several reasons may have contributed to this outcome. A-H1N1 vaccination coverage in Italy during the 2009–2010 influenza season was very low at around 4% of the population[13] and only 3.7% of the children included in the study. The influenza outbreak was almost over by the first half of December 2009, and both the incidence and severity of the disease were lower than expected. As a consequence, the Italian population did not adhere to the second part of the immunisation campaign planned for January 2010. The epidemic curve during the 2009–2010 influenza season in Italy and the start of the vaccination campaign are shown in figure 1. To further complicate the picture, since A-H1N1 laboratory tests were performed only during the epidemic phase, less than 10% of children hospitalised for ILI during the study period were tested.

These difficulties were also observed in other European countries. A very low level of vaccination was found, for instance, in the multinational European study Influenza — Monitoring Vaccine Effectiveness (I-MOVE),[14] which was a practitioner-based outpatient surveillance study conducted in seven countries. Five of the seven countries were unable to contribute more than one vaccinated patient with confirmed A-H1N1 influenza. Only the pooled analysis derived from the international collaboration was able to estimate vaccine effectiveness.

Table 3 OR of influenza-like illness in association with immunisation status

Vaccines	Cases (244)	Controls (439)	Crude OR (CI 95%)	Adjusted* OR (CI 95%)
Any flu vaccines†	41	27	3.1 (1.8 to 5.3)	2.7 (1.6 to 4.7)
A-H1N1 vaccine	13	12	2.2 (0.9 to 5.3)	1.3 (0.6 to 3.1)
Seasonal vaccine	27	18	3.0 (1.6 to 5.9)	2.1 (1.1 to 4.1)
Not vaccinated	203	412	Reference	–

Cases: all children hospitalised for ILI; controls: children hospitalised for thrombocytopaenia, gastroduodenal lesions, muco-cutaneous or neurological conditions; only children above 6 months of age are included.
*Adjusted by age and chronic diseases; the ORs of A-H1N1 and seasonal vaccine were also adjusted for the other influenza vaccine.
†In seven cases and two controls, the type of vaccine was not specified.

Despite the limitations, our study provided additional information on the benefit–risk profile of the pandemic vaccine. There were no reports of AESI associated with vaccine use in children. These findings are consistent with those reported by experimental and observational studies, including analysis of spontaneous reporting systems.[15–18] In conclusion, even with the limitation of a low level of immunisation, no risk associated with the A-H1N1 vaccine used in Italy was described. Among the clinical diagnoses compatible with AESI, none was reported in relation to vaccination in the predefined risk period.

Regarding effectiveness, as in other studies conducted in adult populations, a strong confounding effect was observed.[19 20] For instance, immunisation with the seasonal vaccine was associated with a crude OR of >3. Since the viruses included in the seasonal vaccine were not circulating in the 2009–2010 season, this OR may simply represent the effect of a greater prevalence of influenza risk factors, mainly fragile patients, among those immunised. Of note, when a protective effect was expected, as for the pandemic vaccine, we observed a wide difference between the crude and the adjusted ORs (2.2 vs 1.3) associated with A-H1N1 vaccination. The crude OR was adjusted by age and presence of chronic diseases; the OR of A-H1N1 and the seasonal vaccine were also adjusted for the other influenza vaccine. The fact that even the adjusted OR remains above unity is compatible with the presence of residual confounding factors that we were unable to control for due to the limited power of the study.

Table 4 OR of influenza-like illness in patients who tested positive for A-H1N1 virus

	Cases (11)	Controls (24)	Crude OR (CI 95%)
Any flu vaccines*	3	7	0.9 (0.1 to 5.5)
A-H1N1 vaccine	0	3	–
Seasonal vaccine	2	6	0.7 (0.1 to 5.3)
Not vaccinated	8	17	Reference

Cases: patients with influenza-like illness (ILI) who tested positive for the A-H1N1 virus; controls: ILI patients who tested negative for the A-H1N1 virus.
*In one case and one control, the type of vaccine was not specified.

A required sample size of 194 children hospitalised for ILI was estimated in the protocol. Despite the fact that 244 children with this diagnosis were enrolled, the power proved inadequate given the low level of vaccination. However, the sample size estimate, based on the hypothesis that at least 50% of the paediatric population had been vaccinated, was reliable at the time the protocol was written.

As foreseen in the study protocol, a more valid estimate of vaccine effectiveness was derived from the comparison between test-positive and test-negative ILIs.[16] Considering the reasonable hypothesis that effectiveness is limited to the strains included in the vaccine, cases of interest should concern hospitalisations for ILI attributable to the influenza viruses against which the vaccine was developed. Test-negative ILIs are therefore a valid control group (the source population of cases). It would be impossible to differentiate between cases and controls on the basis of the clinical symptoms that prompted admission. Moreover, children hospitalised for an episode of ILI would more likely share similar risk factors for influenza. Finally, since information on vaccine status was collected in a similar way and in the same setting for both cases and controls, recall bias can be reasonably excluded.

In this study, we reported that given the low number of children affected by ILI who underwent laboratory testing, we could not estimate vaccine effectiveness (only 35 children were tested and no child who tested positive for A-H1N1 had been vaccinated against the H1N1 virus). To support the assumption of a beneficial effect of pandemic vaccination, our findings need to be corroborated by those of similar studies.

We consider it was worthwhile conducting the study even though the findings might be considered only exploratory. One of the main results of this process was to test the usefulness of an integrated model for conducting evaluations of the benefit–risk profile of vaccines in children.

Had the influenza pandemic been more severe and prolonged, we would have been able to capture safety signals as well as estimate vaccine effectiveness. However, our findings may contribute to pooled estimates together with those of similar investigations. Last but not least, this study further supports the importance of active hospital-based surveillance which can easily be adapted

to capture safety and effectiveness signals for new influenza vaccines or new drugs.

Correction notice The "To cite: …" information and running footer in this article have been updated with the correct volume number (volume 1).

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Competing interests None.

Ethics approval The ethics committees of the participating centres approved this study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The authors express their willingness to share data within the framework of collaborative activity.

REFERENCES

1. Domìnguez-Cherit G, Lapinsky SE, Macias AE, *et al*. Critically Ill patients with 2009 influenza A(H1N1) in Mexico. *JAMA* 2010;302:1880–7.
2. Libster R, Bugna J, Coviello S, *et al*. Pediatric hospitalizations associated with 2009 pandemic influenza A (H1N1) in Argentina. *N Engl J Med* 2010;362:45–55.
3. WHO. *Regulatory Preparedness for Human Pandemic Influenza Vaccines*, 2007. http://www.who.int/biologicals/publications/trs/areas/vaccines/influenza/Human_pandemic_Influenza_Vaccines_BS2074_01Feb08.pdf.
4. European Medicines Agency (EMA), European Centre for Disease Prevention and Control (ECDC), Heads of Medicines Agencies (HMA). *European Strategy for Influenza A/H1N1 Vaccine Benefit-Risk Monitoring*, 2009. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/01/WC500044933.pdf.
5. Agenzia Italiana del Faramaco (AIFA). *Piano Nazionale Di Farmacovigilanza Per Il Monitoraggio Della Sicurezza Dei Vaccini Pandemici E Degli Antivirali in Corso Di Pandemia Influenzale*, 2009. http://www.agenziafarmaco.gov.it/allegati/piano_farmaco_09092009.pdf.
6. Menniti-Ippolito F, Sagliocca L, Da Cas R, *et al*. Niflumic acid and cutaneous reactions in children. *Arch Dis Child* 2001;84:430–1.
7. Menniti-Ippolito F, Traversa G, Da Cas R, *et al*. Extrapyramidal reactions in children treated with metoclopramide. *Ital J Pediatr* 2004;30:49–52.
8. Bertuola F, Morando C, Menniti-Ippolito F, *et al*. Association between drug and vaccine use and acute immune thrombocytopenia in childhood. A case control study in Italy. *Drug Saf* 2010;33:65–72.
9. European Center for Disease Prevention and Control (ECDC). *Influenza Case Definitions*, 2009. http://www.ecdc.europa.eu/en/activities/surveillance/eisn/surveillance/pages/influenza_case_definitions.aspx.
10. Jefferson T, Di Pietrantonj C, Al-Ansary LA, *et al*. Vaccines for preventing influenza in the elderly. *Cochrane Database Syst Rev* 2010;(2):CD004876.
11. Black S, Eskola J, Siegrist C, *et al*. Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines. *Lancet* 2009;374:2115–22.
12. Schattner A. Consequence or coincidence? The occurrence, pathogenesis and significance of autoimmune manifestations after viral vaccines. *Vaccine* 2005;23:3876–86.
13. National Centre of Epidemiology-Italian National Institute of Health (Cnesps-ISS). *EpiCentro. FLUNEWS*. Rome: Cnesps-ISS. http://www.epicentro.iss.it/focus/h1n1/archivioflunews.asp.
14. Valenciano M, Kissling E, Cohen JM, *et al*. Estimates of pandemic influenza vaccine effectiveness in Europe, 2009-2010: results of influenza monitoring vaccine effectiveness in Europe (I-MOVE) multicentre case-control study. *PLoS Med* 2011;9:e1000388.
15. European Medicines Agency (EMA). *Twenty-second Pandemic Pharmacovigilance Update*, 2010. www.ema.europa.eu/docs/en_GB/document_library/Report/2010/08/WC500095870.pdf.
16. Puig-Barberà J, Arnedo-Pena A, Pardo-Serrano F, *et al*. Effectiveness of seasonal 2008-2009, 2009-2010 and pandemic vaccines, to prevent influenza hospitalizations during the autumn 2009 influenza pandemic wave in Castellón, Spain. A test-negative, hospital-based, case–control study. *Vaccine* 2010;28:7460–7.
17. Wu J, Xu F, Lu L, *et al*. Safety and effectiveness of a 2009 H1N1 vaccine in Beijing. *N Engl J Med* 2010;363:2416–23.
18. Liang XF, Li L, Liu DW, *et al*. Safety of influenza A (H1N1) vaccine in postmarketing surveillance in China. *N Engl J Med* 2011;364:638–47.
19. Jackson LA, Nelson JC, Benson P. Functional status is a confounder of the association of influenza vaccine and risk of all cause mortality in seniors. *Int J Epidemiol* 2006;35:345–52.
20. Hak E, Verheij TJ, Grobbee DE, *et al*. Confounding by indication in non-experimental evaluation of vaccine effectiveness: the example of prevention of influenza complications. *J Epidemiol Community Health* 2002;56:951–5.

APPENDIX 1

Italian Multicenter Study Group for Drug and Vaccine Safety in Children

Francesca Menniti-Ippolito, Roberto Da Cas, Luciano Sagliocca, Giuseppe Traversa (National Centre for Epidemiology, National Institute of Health, Rome); Fernanda Ferrazin, Carmela Santuccio, Loriana Tartaglia, Francesco Trotta (Italian Medicines Agency, Rome); Pasquale Di Pietro, Salvatore Renna, Rossella Rossi, Bianca Domenichini, Stefania Gamba, Francesco Trovato (Giannina Gaslini Paediatric Hospital, Genoa); Pier-Angelo Tovo, Manuela Bianciotto, Carmelina Calitri, Clara Gabiano, Irene Raffaldi, Antonio Urbino (Regina Margherita Paediatric Hospital, Turin); Liviana Da Dalt, Valentina Favero, Laura Giordano, Maura Baraldi, Federica Bertuola, Eleonora Lorenzon, Francesca Parata, Giorgio Perilongo, Silvia Vendramin (Department of Paediatrics, University of Padua, Padua); Monica Frassineti, Anna Maria Calvani, Elena Chiappini, Maurizio De Martino, Claudia Fancelli, Francesco Mannelli, Rachele Mazzantini, Sara Sollai, Elisabetta Venturini (Anna Meyer Children's University Hospital, Florence); Nicola Pirozzi, Umberto Raucci, Antonino Reale, Rossella Rossi (Emergency Department, Bambino Gesù Children Hospital, Rome); Nadia Mores, Giulia Bersani, Alessia De Nisco, Antonio Chiaretti, Riccardo Riccardi, Costantino Romagnoli (Pharmacology and Paediatrics and Developmental Neuroscience, Università Cattolica Sacro Cuore, Rome); Vincenzo Tipo, Michele Dinardo, Teresa Pisapia (Santobono Paediatric Hospital, Naples); Annalisa Capuano, Elisabetta Parretta, Concita Rafaniello (Department of Experimental Medicine, Section of Pharmacology 'L. Donatelli', Second University of Naples, Naples); Fortunata Fucà, Eleonora Di Rosa (Giovanni Di Cristina Paediatric Hospital, Palermo).