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

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

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Keywords: case-control study, pandemic vaccine, AESI

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Abstract

Objective: to verify whether the vaccination against the A-H1N1 virus in the paediatric population was effective in preventing the occurrence of Influenza Like Illness (ILI) and was associated with Adverse Events of Special Interest (AESI).

Design, setting and patients: a case control analysis was performed in a surveillance of children hospitalized through the Emergency Departments of eight paediatric hospitals/wards for: ILI; neurological disorders; non-infectious muco-cutaneous diseases and vasculitis; thrombocytopenia; and gastroduodenal lesions.

Results: among 736 children enrolled from November 2009 to August 2010, only 25 were vaccinated with the pandemic vaccine. Out of 268 children admitted for a diagnosis compatible with AESI, 6 had received the A-H1N1 vaccine, though none occurred within the predefined risk windows. Only 35 children performed the laboratory test: 11 resulted 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 0.1-5.5).

Conclusions: the study provides further evidence of a positive benefit-risk profile of the pandemic vaccine. No sign of risk associated with the anti A-H1N1 vaccine used in Italy was pointed out. Several limitations were observed: in Italy, the 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 less than 10% of children). This study supports the importance of 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 (AESI) in the paediatric population.

Key messages

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

Strengths and limitations of this study

The study focused on events of Influenza Like Illness (ILI) and of AESI that were sufficiently severe to cause hospitalization in children. It was possible to provide supporting evidence for a positive benefit-risk profile of the pandemic vaccine.

The A-H1N1 vaccination coverage in Italy during the influenza season 2009-2010 was very low: around 4% of the general population and 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 influenza were lower than expected.

Background

A great concern about the severity of the A-H1N1 influenza epidemic in the paediatric population was raised in 2009 at international level.[1,2] The development and access to the new vaccines against the A-H1N1 virus were considered as the main public health response. There were, however, diffused uncertainties about both efficacy and safety due to the limited data availability on the pandemic vaccines that could not be solved in the short time before the approval, even though the procedures were predefined by regulatory agencies to be ready in case of a new epidemic.[3]

To ensure public safety during the influenza outbreak, special attention and care was offered to population subgroups normally considered at higher risk, such as pregnant women, young infants and immune-compromised patients for a rapid access to the new influenza A-H1N1 vaccines. There were also specific concerns related to 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.

To fill the gap of evidence supporting the vaccine use during the pandemic emergency, regulatory agencies around the world required companies to carry out post marketing surveillance studies on the newly developed influenza vaccines. The limited time available suggested to be an efficient strategy to invite also research groups already involved in the area of efficacy and safety assessment of drugs and vaccines, to focus their activities on the pandemic vaccines.[4] In Italy, a national pharmacovigilance pandemic plan, including as a specific focus safety in the paediatric population, was implemented.[5]

An active surveillance on the role of drugs and vaccines in the occurrence of selected clinical conditions responsible for paediatric hospitalisation is conducted in Italy since 1999. The surveillance provided so far useful contributions in the detection , description and evaluation of risk signals associated with drugs and vaccines use in children.[6-8] During the pandemic season 2009-2010, following the launch of the vaccination campaign by the Italian Ministry of Health,[5] the study protocol of the already active surveillance was adapted to focus on and include the evaluation of safety and efficacy of the A-H1N1 vaccine. In Italy the immunization campaign started in October in healthcare workers and subsequently extended to pregnant women and at risk subjects, including children. After some weeks the 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 the influenza A-H1N1 vaccination in the paediatric population in preventing the occurrence of Influenza Like Illnesses (ILI) and 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 represents an active surveillance on children hospitalised through the Emergency Departments of eight clinical centres for selected conditions, regardless of their previous drug and vaccine use. The period of interest for the present report extends from November 2009 to August 2010. For the safety objective, the study population consisted of all children (age range, 1 month – 18 years) admitted for the four following conditions: i) neurological disorders; ii) non-infectious muco-cutaneous diseases and vasculitis; iii) thrombocytopenia; iv) confirmed gastroduodenal lesions (and/or clinically defined haematemesis or melena). All the conditions considered in this surveillance, but the upper gastrointestinal lesions, account for almost all the 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 at the emergency department, were also enrolled in the study to estimate the effectiveness of the influenza A-H1N1vaccination. For children >5 years the following definition of ILI was adopted: sudden onset of fever >=38° C (for at least 24 hours), 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, in association with fever >38° C, the following general sign and symptoms were considered: inadequate drinking or feeding, vomiting and/or diarrhoea, respiratory symptoms.[9]

Assessment via laboratory test for influenza A virus was not an inclusion requirement. Following a recommendation of the Italian Ministry of Health, laboratory confirmation of A-H1N1 virus was routinely performed only during the epidemic phase (mid October – mid December 2009). In order to limit selection bias (i.e. selective enrolment of vaccinated children) participating centres were given the indication to enrol ILI cases on a given day of the week, up to 3-4 cases per week, blindly with regard to the vaccination status.

Data source

Parents were interviewed by a trained investigator, using a structured questionnaire, during the hospital admission of the child, after having granted their informed consent. For drug exposure, the time window of interest was represented by the three weeks prior to the onset of symptoms related to the hospital admission. With regard to vaccine exposure, the twelve weeks preceding the hospitalisation were considered of interest for all non-influenza vaccines. For the assessment of vaccine effectiveness, related to both A-H1N1 and seasonal influenza vaccines, children were considered exposed if vaccinated any time before admission. To evaluate any possible relation between vaccination and AESIs, a time window specific for each AESI were considered: e.g. 0-2 days for urticaria¸ 0-14 days for convulsions; 0-42 days for thrombocytopenia, vasculitis, neuropathies, etc.[10-11]

Data analysis

To estimate the odds ratios (OR), two different comparisons were conducted to assess vaccines effectiveness. For the first one, all children hospitalised for ILI were considered as “cases” whereas children (more than 5 months old) enrolled for any of the four clinical condition previously described represented the “control” group. For the second comparison, the analysis was restricted to all children admitted for ILI and tested for the A-H1N1 virus. ILI patients with a positive test were considered as “cases”, while those with negative test acted as “controls”. The purpose of the first analysis was to provide an estimate of the effectiveness of the vaccines in preventing the hospitalisation for any ILI during the influenza season. The second analysis was aimed at estimating the potential of the A-H1N1 vaccine to prevent the occurrence of confirmed episodes of pandemic influenza.

Assuming a proportion of vaccinated children of 50%, a power of 90% and an alfa error of 0.05, a sample size of 194 hospitalizations for ILI was required to estimate a reduction of at least 50% in the occurrence of ILI among vaccinated children (OR<= 0.5).

Adjusted ORs and related 95% Confidence Intervals (CI) were calculated through a multivariate logistic model. Data were analysed with SPSS® (version 17; SPSS Inc., Chicago, Ill., USA).

Study sites

The following paediatric hospitals and departments were participating: Giannina Gaslini Paediatric Hospital (Genova); Regina Margherita Paediatric Hospital (Torino); Department of Paediatrics, University of Padova (Padova); Anna Meyer Children's University Hospital (Firenze); Pharmacology and Paediatrics and Developmental Neuroscience, Università Cattolica Sacro Cuore (Roma); Emergency Department, Bambino Gesù Children Hospital (Roma); Santobono-Pausilipon

Paediatric Hospital (Napoli); Giovanni Di Cristina Paediatric Hospital (Palermo). The protocol of the study was submitted to the Ethical Committee of each clinical centre for approval. The eight centres account for around 350,000 Emergency Department (ED) visits per year (around 50,000 children are subsequently hospitalised through the ED) and are located in the 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, a total of 736 children, median age 4 years (range 1 month-18 years) have been enrolled. 492 children were admitted to the hospital due to at least one of the four conditions of interest for this study: 241 (49%) for neurological disorders, 144 (29%) for muco-cutaneous diseases, 60 (12%) for thrombocytopenia, and 47 (10%) for gastro-duodenal lesions. 244 children were admitted with a diagnosis of ILI (Table 1). The male to female ratio was largely overlapping in the different groups of diagnosis.

Among the neurological conditions, convulsion was the most frequent cause for admission (N=91; 38%), followed by disturbances of vigilance and consciousness - e.g., numbness, somnolence, lipothymia – (N=39; 16%), and by episodes of Apparent Life Threatening Events (N=30; 12%). Serious clinical conditions were admitted: 8 children with peripheral neuropathies and 5 with Guillain-Barré syndrome. Within the muco-cutaneous diseases, more than half were represented by Shoenlein-Henoch purpura or other vasculitis (N=80; 55%), followed by urticaria (N=32; 22%) and erythema (N=15; 10%).

Seventy-one percent of children enrolled in the study had assumed at least one drug in the three weeks preceding the hospital admission. A total of 173 children (24%) have been vaccinated before the hospitalisation either at any time for the influenza vaccines or during the preceding 12 weeks for the other vaccines. Hexavalent vaccine was the most frequently reported immunisation (55 children), followed the antipneumococcal (37 children) and MMR (24 children) vaccines.

For the influenza vaccine analysis the denominator is limited to the 683 children of at least 6 months (according to the vaccination schedule for the pandemic vaccine). In this population (244 for ILI and 439 for the other conditions), 25 children (3.7%) had received the pandemic vaccine (9 children received two doses), whereas 45 (6.6%) had received the vaccination against the seasonal influenza. Eleven children received both vaccines and in 9 children the type of influenza vaccine was not specified.

Out of 268 children admitted for a diagnosis compatible with AESI, only 6 were previously vaccinated with the A-H1N1 vaccine (2 cases of urticaria, 2 convulsions, 1 vasculitis and 1 Shoenlein-Henoch purpura), however, all admissions occurred outside the predefined risk windows (Table 2).

With regard to the evaluation of the pandemic vaccine effectiveness in the prevention of any ILI episodes, regardless to positive laboratory test, all estimates were higher than 1 (Table 3). Specifically, the adjusted ORs were 2.1 (1.1-4.1) for the seasonal vaccine and 1.3 (0.6-3.1) for the pandemic vaccine.

Among the 35 children who underwent to the laboratory testing, 11 resulted positive and 24 negative for the A-H1N1 virus. Since none of the A-H1N1 positive children had a positive history for A-H1N1vaccination it was not possible to obtain an estimate of the vaccine effectiveness. However, even though less specific, the OR of ILI associated with any influenza vaccination was still slightly lower than one (OR=0.9; 95% CI 0.1-5.5).

Discussion

One of the main strengths of the study was represented by the promptness to adapt the protocol of an existing study involving a network of hospitals to respond to the health alert created by the pandemic emergency. Despite the quite large enrolment in the Italian paediatric population, the results related to the evaluation of the safety and effectiveness of the pandemic vaccine were partly inconclusive. Several reasons may have contributed to this outcome. The A-H1N1 vaccination coverage in Italy during the influenza season 2009-2010 was very low: around 4% of the population[12] and 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 influenza were lower than expected. As a consequence, the Italian population did not adhere to the second part of the immunisation campaign, that was envisaged in January 2010. To further complicate the picture, since the A-H1N1 laboratory test was performed only during the epidemic phase, less than 10% of children hospitalized for ILI during the study period were tested.

It was possible however to provide supporting evidence for a positive benefit-risk profile of the pandemic vaccine. No report of AESI associated with the vaccine use in paediatrics was observed. These findings are coherent with those reported by experimental and observational studies, including analysis of spontaneous reporting systems.[13-17] In conclusion regarding safety, even within the limitation of a low level of immunisation, no sign of risk associated with the A-H1N1 vaccine used in Italy was described. Among the clinical diagnosis compatible with AESI none was reported related to vaccination in the predefined risk period.

With regard to effectiveness, as in other studies conducted in the adult population, a strong confounding effect was observed.[18-19] For instance, the immunisation with the seasonal vaccine was associated with a crude OR value greater than 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 the 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 the A-H1N1 vaccination. The crude OR was adjusted by age and presence of chronic diseases; the OR of A-H1N1 and 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 not able to control for, due to the limited power of the study.

A sample size of 194 children hospitalized for ILI was estimated in the protocol. Despite the fact that 244 children with this diagnosis were enrolled, the power resulted 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 derived from the comparison between test-positive and test-negative ILIs.[14] Considering the reasonable hypothesis that the 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 represent a valid control group (the source population of cases). Cases and controls would be impossible to differentiate on the basis of the clinical symptoms that prompted the admission. Moreover, children hospitalised for an episode of ILI would more likely share similar risk factors for influenza. Finally, since the information of 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 the study, we reported that given the low number of children affected by ILI who underwent the laboratory test, we could not estimate the effectiveness (only 35 children were tested and no child who tested positive for A-H1N1 was vaccinated against the H1N1 virus). This may also be interpreted as a sign of beneficial effect of the vaccination, especially when considering that the

estimate of the OR was lower than 1 even when combining the vaccination with both seasonal and pandemic vaccines (OR=0.9; 95% CI 0.1-5.5).

We consider it was worth to conduct the study even though the findings might be considered only exploratory. Had the influenza pandemic been more severe and prolonged, we would have been able to capture safety signals as well as to estimate the vaccine effectiveness. Moreover, our findings may contribute to pooled estimates together with those of similar investigations. Last but not least, this study further supports the importance of an active hospital-based surveillance which may easily be adapted to capture potential signals of safety and effectiveness of new influenza vaccines or new drugs.

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Table 1. Distribution of children hospitalized 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)
Thrombocytopenia	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)
ILI	244	3 (3)	108 (44)	170 (70)	77 (32)	58 (24)

IQR: interquartile range

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
Shoenlein-Henoch	47	No
Urticaria	60	No
Vasculitis	128	No
Convulsions	149	No
Convulsions	188	No

Table 3. OR of ILI in association with the immunisation status

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

Cases: all children hospitalised for ILI. Controls: children hospitalised for thrombocytopenia, gastroduodenal lesions, mucocutaneous and neurological conditions; only children older than 6 months are included).

[§] In 7 case and 2 controls the type of vaccine was not specified.

*Adjusted by age and chronic diseases; the OR of A-H1N1 and seasonal vaccine were also adjusted for the other influenza vaccine.

Table 4. OR of ILI in patients who tested positive to A-H1N1 virus

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

Cases: ILI patients who tested positive to the A-H1N1 virus. Controls: ILI patients who tested negative to the A-H1N1 virus.

[§] In 1 case and 1 control the type of vaccine was not specified.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *case-control studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	*(*a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	4-5
		(*b*) For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	5, 7
Study size	10	Explain how the study size was arrived at	5, 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	--
		(*d*) If applicable, explain how matching of cases and controls was addressed	NA
		(*e*) Describe any sensitivity analyses	--
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6, 12
		(b) Give reasons for non-participation at each stage	--
		(c) Consider use of a flow diagram	--
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	14-15
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	12, 14-15
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6, 14-15
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6, 15
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7-8
Generalisability	21	Discuss the generalisability (external validity) of the study results	7-8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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

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

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Abstract

Objective: to verify whether the vaccination against the A-H1N1 virus in the paediatric population was effective in preventing the occurrence of Influenza Like Illness (ILI) and was associated with Adverse Events of Special Interest (AESI).

Design, setting and patients: a case control analysis was performed in a surveillance of children hospitalized through the Emergency Departments of eight paediatric hospitals/wards for: ILI; neurological disorders; non-infectious muco-cutaneous diseases and vasculitis; thrombocytopenia; and gastroduodenal lesions.

Results: among 736 children enrolled from November 2009 to August 2010, only 25 were vaccinated with the pandemic vaccine. Out of 268 children admitted for a diagnosis compatible with AESI, 6 had received the A-H1N1 vaccine, though none occurred within the predefined risk windows. Only 35 children, out of 244 admitted with a diagnosis of ILI, performed the laboratory test: 11 resulted 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 0.1-5.5).

Conclusions: the study provides additional information on the benefit-risk profile of the pandemic vaccine. No sign of risk associated with the anti A-H1N1 vaccine used in Italy was pointed out. Several limitations were observed: in Italy, the 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 less than 10% of children). This study supports the importance of 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 (AESI) in the paediatric population.

Key messages

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

Strengths and limitations of this study

The study focused on events of Influenza Like Illness (ILI) and of AESI that were sufficiently severe to cause hospitalisation in children. It was possible to provide additional information on the benefit-risk profile of the pandemic vaccine.

The A-H1N1 vaccination coverage in Italy during the influenza season 2009-2010 was very low: around 4% of the general population and 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 influenza were lower than expected.

Background

A great concern about the severity of the A-H1N1 influenza epidemic in the paediatric population was raised in 2009 at international level.[1,2] The development and access to the new vaccines against the A-H1N1 virus were considered as the main public health response. There were, however, diffused uncertainties about both efficacy and safety due to the limited data availability on the pandemic vaccines that could not be solved in the short time before the approval, even though the procedures were predefined by regulatory agencies to be ready in case of a new epidemic.[3]

To ensure public safety during the influenza outbreak, special attention and care was offered to population subgroups normally considered at higher risk, such as pregnant women, young infants and immune-compromised patients for a rapid access to the new influenza A-H1N1 vaccines. There were also specific concerns related to 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.

To fill the gap of evidence supporting the vaccine use during the pandemic emergency, regulatory agencies around the world required companies to carry out post marketing surveillance studies on the newly developed influenza vaccines. The limited time available suggested to be an efficient strategy to invite also research groups already involved in the area of efficacy and safety assessment of drugs and vaccines, to focus their activities on the pandemic vaccines.[4] In Italy, a national pharmacovigilance pandemic plan, including as a specific focus safety in the paediatric population, was implemented.[5]

An active surveillance on the role of drugs and vaccines in the occurrence of selected clinical conditions responsible for paediatric hospitalisation is conducted in Italy since 1999. The surveillance provided so far useful contributions in the detection, description and evaluation of risk signals associated with drugs and vaccines use in children.[6-8] During the pandemic season 2009-2010, following the launch of the vaccination campaign by the Italian Ministry of Health,[5] the study protocol of the already active surveillance was adapted to focus on and include the evaluation of safety and efficacy of the A-H1N1 vaccine. In Italy the immunization campaign started in October in healthcare workers and subsequently extended to pregnant women and at risk subjects, including children. After some weeks the 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 the influenza A-H1N1 vaccination in the paediatric population in 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 represents an active surveillance on children hospitalised through the Emergency Departments of eight clinical centres for selected conditions, regardless of their previous drug and vaccine use. The period of interest for the present report extends from November 2009 to August 2010. For the safety objective, the study population consisted of all children (age range, 1 month – 18 years) admitted for the four following conditions: i) neurological disorders; ii) non-infectious muco-cutaneous diseases and vasculitis; iii) thrombocytopenia; iv) confirmed gastroduodenal lesions (and/or clinically defined haematemesis or melena). All the conditions considered in this surveillance, but the upper gastrointestinal lesions, account for almost all the 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 at the emergency department, were also enrolled in the study to estimate the effectiveness of the influenza A-H1N1vaccination. For children >5 years the following definition of ILI was adopted: sudden onset of fever >=38° C (for at least 24 hours), 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, in association with fever >38° C, the following general sign and symptoms were considered: inadequate drinking or feeding, vomiting and/or diarrhoea, respiratory symptoms.[9]

Assessment via laboratory test for influenza A-H1N1 virus 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 the participating hospitals. Moreover, following a recommendation of the Italian Ministry of Health, laboratory confirmation of A-H1N1 virus was not routinely suggested after the declining phase of the epidemic (mid December 2009). In order to limit selection bias (i.e. selective enrolment of vaccinated children) participating centres were given the indication to enrol ILI cases on a given day of the week, up to 3-4 cases per week, blindly with regard to the vaccination status. This recruitment strategy applied to all ILI cases and was independent from the decision to perform laboratory confirmation.

Data source

Parents were interviewed by a trained investigator, using a structured questionnaire, during the hospital admission of the child, after having granted their informed consent. The interview was aimed at acquiring the anamnesis and at ascertaining drug use and vaccination status. As reported in the study protocol, no validation of the information on drug and vaccine exposure was conducted..

For drug exposure, the time window of interest was represented by the three weeks prior to the onset of symptoms related to the hospital admission. With regard to vaccine exposure, the twelve weeks preceding the hospitalisation were considered of interest for all non-influenza vaccines. For the assessment of vaccine effectiveness, related to both A-H1N1 and seasonal influenza vaccines, children were considered exposed if vaccinated any time before admission. To evaluate any possible relation between vaccination and AESIs, a time window specific for each AESI were considered: e.g. 0-2 days for urticaria¸ 0-14 days for convulsions; 0-42 days for thrombocytopenia, vasculitis, neuropathies, etc.[11-12]

Data analysis

To estimate the odds ratios (OR), two different comparisons were conducted to assess vaccines effectiveness. For the first one, all children hospitalised for ILI were considered as “cases” whereas children (more than 5 months old) enrolled for any of the four clinical conditions previously described represented the “control” group. For the second comparison, the analysis was restricted to all children admitted for ILI and tested for the A-H1N1 virus. ILI patients with a positive test were considered as “cases”, while those with negative test acted as “controls”. The purpose of the first analysis was to provide an estimate of the effectiveness of the vaccines in preventing the hospitalisation for any ILI during the influenza season. The second analysis was aimed at estimating the potential of the A-H1N1 vaccine to prevent the occurrence of confirmed episodes of pandemic influenza.

Assuming a proportion of vaccinated children of 50%, a power of 90% and an alfa 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<= 0.5).

Adjusted ORs and related 95% Confidence Intervals (CI) were calculated through a multivariate logistic model. Data were analysed with SPSS® (version 17; SPSS Inc., Chicago, Ill., USA).

Study sites

The following paediatric hospitals and departments were participating: Giannina Gaslini Paediatric Hospital (Genova); Regina Margherita Paediatric Hospital (Torino); Department of Paediatrics, University of Padova (Padova); Anna Meyer Children's University Hospital (Firenze); Pharmacology and Paediatrics and Developmental Neuroscience, Università Cattolica Sacro Cuore (Roma); Emergency Department, Bambino Gesù Children Hospital (Roma); Santobono-Pausilipon Paediatric Hospital (Napoli); Giovanni Di Cristina Paediatric Hospital (Palermo). The protocol of the study was submitted to the Ethical Committee of each clinical centre for approval. The eight centres account for around 350,000 Emergency Department (ED) visits per year (around 50,000 children are subsequently hospitalised through the ED) and are located in the 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, a total of 736 children, median age 4 years (range 1 month-18 years) have been enrolled. 492 children were admitted to the hospital due to at least one of the four conditions of interest for this study: 241 (49%) for neurological disorders, 144 (29%) for muco-cutaneous diseases, 60 (12%) for thrombocytopenia, and 47 (10%) for gastro-duodenal lesions. 244 children were admitted with a diagnosis of ILI (Table 1). The male to female ratio was largely overlapping in the different groups of diagnosis.

Among the neurological conditions, convulsion was the most frequent cause for admission (N=91; 38%), followed by disturbances of vigilance and consciousness - e.g., numbness, somnolence, lipothymia – (N=39; 16%), and by episodes of Apparent Life Threatening Events (N=30; 12%). Serious clinical conditions were admitted: 8 children with peripheral neuropathies and 5 with Guillain-Barré syndrome. Within the muco-cutaneous diseases, more than half were represented by Shoenlein-Henoch purpura or other vasculitis (N=80; 55%), followed by urticaria (N=32; 22%) and erythema (N=15; 10%).

Seventy-one percent of children enrolled in the study had assumed at least one drug in the three weeks preceding the hospital admission. A total of 173 children (24%) have been vaccinated before the hospitalisation (either at any time for the influenza vaccines or during the preceding 12 weeks for the other vaccines). Hexavalent vaccine was the most frequently reported immunisation (55 children), followed the antipneumococcal (37 children) and MMR (24 children) vaccines.

For the influenza vaccine analysis the denominator is limited to the 683 children of at least 6 months (according to the vaccination schedule for the pandemic vaccine). In this population (244 for ILI and 439 for the other conditions), 25 children (3.7%) had received the pandemic vaccine (9 children received two doses), whereas 45 (6.6%) had received the vaccination against the seasonal influenza. Eleven children received both vaccines and in 9 children the type of influenza vaccine was not specified. All immunised children (both cases of ILI and controls) had received the influenza vaccines more than 14 days prior to the hospitalisation.

Out of 268 children admitted for a diagnosis compatible with AESI, only 6 were previously vaccinated with the A-H1N1 vaccine (2 cases of urticaria, 2 convulsions, 1 vasculitis and 1 Shoenlein-Henoch purpura), however, all admissions occurred outside the predefined risk windows (Table 2).

With regard to the evaluation of the pandemic vaccine effectiveness in the prevention of any ILI episodes, regardless to positive laboratory test, all estimates were higher than 1 (Table 3). Specifically, the adjusted ORs were 2.1 (1.1-4.1) for the seasonal vaccine and 1.3 (0.6-3.1) for the

pandemic vaccine. No difference in the OR estimates was observed when the analysis was restricted to the pandemic period (i.e., October 2009 – January 2010).

Among the 35 children who underwent the laboratory testing, 11 resulted positive and 24 negative for the A-H1N1 virus. Since none of the A-H1N1 positive children had a positive history for A-H1N1vaccination it was not possible to obtain an estimate of the 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 one (OR=0.9; 95% CI 0.1-5.5).

Discussion

One of the main strengths of the study was represented by the promptness to adapt the protocol of an existing study involving a network of hospitals to respond to the health alert created by the pandemic emergency. Despite the quite large enrolment in the Italian paediatric population, the results related to the evaluation of the safety and effectiveness of the pandemic vaccine were partly inconclusive. Several reasons may have contributed to this outcome. The A-H1N1 vaccination coverage in Italy during the influenza season 2009-2010 was very low: around 4% of the population [13] and 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 influenza were lower than expected. As a consequence, the Italian population did not adhere to the second part of the immunisation campaign, that was envisaged in January 2010. The epidemic curve during the influenza season 2009-2010 in Italy and the starting point of the vaccination campaign are represented in Figure 1. To further complicate the picture, since the A-H1N1 laboratory test was performed only during the epidemic phase, less than 10% of children hospitalized for ILI during the study period were tested.

These difficulties were observed in other European Countries. A very low level of vaccination was found, for instance, in the multinational study "Influenza monitoring vaccine effectiveness in Europe (I-Move)", [14] which was a practitioner-based outpatient surveillance conducted in seven Countries. Five of the seven Countries were not able to contribute with more than 1 vaccinated patient with confirmed A-H1N1 influenza. Only the pooled analysis derived from the international collaboration was able to estimate the effectiveness.

Despite the limitations, our study provided additional information on the benefit-risk profile of the pandemic vaccine. No report of AESI associated with the vaccine use in paediatrics was observed. These findings are coherent with those reported by experimental and observational studies, including analysis of spontaneous reporting systems.[15-18] In conclusion regarding safety, even within the limitation of a low level of immunisation, no sign of risk associated with the A-H1N1 vaccine used in Italy was described. Among the clinical diagnosis compatible with AESI none was reported related to vaccination in the predefined risk period.

With regard to effectiveness, as in other studies conducted in the adult population, a strong confounding effect was observed.[19-20] For instance, the immunisation with the seasonal vaccine was associated with a crude OR value greater than 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 the 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 the A-H1N1 vaccination. The crude OR was adjusted by age and presence of chronic diseases; the OR of A-H1N1 and 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 not able to control for, due to the limited power of the study.

A sample size of 194 children hospitalized for ILI was estimated in the protocol. Despite the fact that 244 children with this diagnosis were enrolled, the power resulted 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 derived from the comparison between test-positive and test-negative ILIs.[16] Considering the reasonable hypothesis that the 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 represent a valid control group (the source population of cases). Cases and controls would be impossible to differentiate on the basis of the clinical symptoms that prompted the admission. Moreover, children hospitalised for an episode of ILI would more likely share similar risk factors for influenza. Finally, since the information of 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 the study, we reported that given the low number of children affected by ILI who underwent the laboratory test, we could not estimate the effectiveness (only 35 children were tested and no child who tested positive for A-H1N1 was vaccinated against the H1N1 virus). This may also be interpreted as a sign of beneficial effect of the vaccination, especially when considering that the estimate of the OR was lower than 1 even when combining the vaccination with both seasonal and pandemic vaccines (OR=0.9; 95% CI 0.1-5.5).

We consider it was worth to conduct the study even though the findings might be considered only exploratory. One of the main results of this experience was to test the usefulness of an integrated model for conducting evaluations of 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 to estimate the vaccine effectiveness. Moreover, our findings may contribute to pooled estimates together with those of similar investigations. Last but not least, this study further supports the importance of an active hospital-based surveillance which may easily be adapted to capture potential signals of safety and effectiveness of new influenza vaccines or new drugs.

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Table 1. Distribution of children hospitalized 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)
Thrombocytopenia	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)
ILI	244	3 (3)	108 (44)	170 (70)	77 (32)	58 (24)

IQR: interquartile range

** All vaccines administered to the study subjects, and not only influenza ones, are included.*

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
Shoenlein-Henoch	47	No
Urticaria	60	No
Vasculitis	128	No
Convulsions	149	No
Convulsions	188	No

Table 3. OR of ILI in association with the immunisation status

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

Cases: all children hospitalised for ILI. Controls: children hospitalised for thrombocytopenia, gastroduodenal lesions, mucocutaneous and neurological conditions; only children older than 6 months are included).

[§] In 7 case and 2 controls the type of vaccine was not specified.

*Adjusted by age and chronic diseases; the OR of A-H1N1 and seasonal vaccine were also adjusted for the other influenza vaccine.

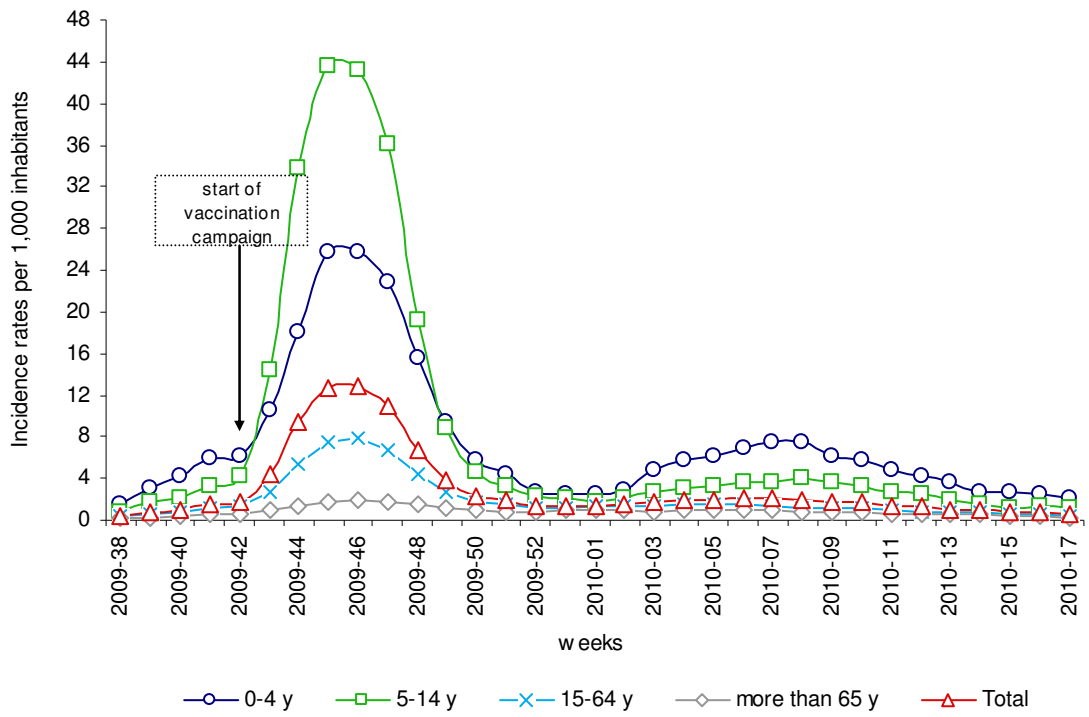
Table 4. OR of ILI in patients who tested positive to A-H1N1 virus

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

Cases: ILI patients who tested positive to the A-H1N1 virus. Controls: ILI patients who tested negative to the A-H1N1 virus.

[§] In 1 case and 1 control the type of vaccine was not specified.

Figure 1. Incidence of ILI in Italy by age group, season 2009-2010



Adapted from www.iss.it/iflu/

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *case-control studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	*(*a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	4-5
		(*b*) For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	5, 7
Study size	10	Explain how the study size was arrived at	5, 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	--
		(*d*) If applicable, explain how matching of cases and controls was addressed	NA
		(*e*) Describe any sensitivity analyses	--
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6, 12
		(b) Give reasons for non-participation at each stage	--
		(c) Consider use of a flow diagram	--
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	14-15
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	12, 14-15
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6, 14-15
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6, 15
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7-8
Generalisability	21	Discuss the generalisability (external validity) of the study results	7-8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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

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Primary Subject Heading:	Epidemiology
Keywords:	pandemic vaccine, Adverse events < THERAPEUTICS, PAEDIATRICS

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*

Keywords: case-control study, pandemic vaccine, adverse events, paediatrics

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Abstract

Objective: to verify whether the vaccination against the A-H1N1 virus in the paediatric population was effective in preventing the occurrence of Influenza Like Illness (ILI) and was associated with Adverse Events of Special Interest (AESI).

Design, setting and patients: a case control analysis was performed in a surveillance of children hospitalized through the Emergency Departments of eight paediatric hospitals/wards for: ILI; neurological disorders; non-infectious muco-cutaneous diseases and vasculitis; thrombocytopenia; and gastroduodenal lesions.

Results: among 736 children enrolled from November 2009 to August 2010, only 25 were vaccinated with the pandemic vaccine. Out of 268 children admitted for a diagnosis compatible with AESI, 6 had received the A-H1N1 vaccine, though none occurred within the predefined risk windows. Only 35 children, out of 244 admitted with a diagnosis of ILI, performed the laboratory test: 11 resulted 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 0.1-5.5).

Conclusions: the study provides additional information on the benefit-risk profile of the pandemic vaccine. No sign of risk associated with the anti A-H1N1 vaccine used in Italy was pointed out. Several limitations were observed: in Italy, the 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 less than 10% of children). This study supports the importance of 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 (AESI) in the paediatric population.

Key messages

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

Strengths and limitations of this study

The study focused on events of Influenza Like Illness (ILI) and of AESI that were sufficiently severe to cause hospitalisation in children. It was possible to provide additional information on the benefit-risk profile of the pandemic vaccine.

The A-H1N1 vaccination coverage in Italy during the influenza season 2009-2010 was very low: around 4% of the general population and 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 influenza were lower than expected.

Background

A great concern about the severity of the A-H1N1 influenza epidemic in the paediatric population was raised in 2009 at international level.[1,2] The development and access to the new vaccines against the A-H1N1 virus were considered as the main public health response. There were, however, diffused uncertainties about both efficacy and safety due to the limited data availability on the pandemic vaccines that could not be solved in the short time before the approval, even though the procedures were predefined by regulatory agencies to be ready in case of a new epidemic.[3]

To ensure public safety during the influenza outbreak, special attention and care was offered to population subgroups normally considered at higher risk, such as pregnant women, young infants and immune-compromised patients for a rapid access to the new influenza A-H1N1 vaccines. There were also specific concerns related to 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.

To fill the gap of evidence supporting the vaccine use during the pandemic emergency, regulatory agencies around the world required companies to carry out post marketing surveillance studies on the newly developed influenza vaccines. The limited time available suggested to be an efficient strategy to invite also research groups already involved in the area of efficacy and safety assessment of drugs and vaccines, to focus their activities on the pandemic vaccines.[4] In Italy, a national pharmacovigilance pandemic plan, including as a specific focus safety in the paediatric population, was implemented.[5]

An active surveillance on the role of drugs and vaccines in the occurrence of selected clinical conditions responsible for paediatric hospitalisation is conducted in Italy since 1999. The surveillance provided so far useful contributions in the detection, description and evaluation of risk signals associated with drugs and vaccines use in children.[6-8] During the pandemic season 2009-2010, following the launch of the vaccination campaign by the Italian Ministry of Health,[5] the study protocol of the already active surveillance was adapted to focus on and include the evaluation of safety and efficacy of the A-H1N1 vaccine. In Italy the immunization campaign started in October in healthcare workers and subsequently extended to pregnant women and at risk subjects, including children. After some weeks the 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 the influenza A-H1N1 vaccination in the paediatric population in 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 represents an active surveillance on children hospitalised through the Emergency Departments of eight clinical centres for selected conditions, regardless of their previous drug and vaccine use. The period of interest for the present report extends from November 2009 to August 2010. For the safety objective, the study population consisted of all children (age range, 1 month – 18 years) admitted for the four following conditions: i) neurological disorders; ii) non-infectious muco-cutaneous diseases and vasculitis; iii) thrombocytopenia; iv) confirmed gastroduodenal lesions (and/or clinically defined haematemesis or melena). All the conditions considered in this surveillance, but the upper gastrointestinal lesions, account for almost all the 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 at the emergency department, were also enrolled in the study to estimate the effectiveness of the influenza A-H1N1vaccination. For children >5 years the following definition of ILI was adopted: sudden onset of fever >=38° C (for at least 24 hours), 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, in association with fever >38° C, the following general sign and symptoms were considered: inadequate drinking or feeding, vomiting and/or diarrhoea, respiratory symptoms.[9]

Assessment via laboratory test for influenza A-H1N1 virus 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 the participating hospitals. Moreover, following a recommendation of the Italian Ministry of Health, laboratory confirmation of A-H1N1 virus was not routinely suggested after the declining phase of the epidemic (mid December 2009). In order to limit selection bias (i.e. selective enrolment of vaccinated children) participating centres were given the indication to enrol ILI cases on a given day of the week, up to 3-4 consecutive cases per week, blindly with regard to the vaccination status. This recruitment strategy applied to all ILI cases and was independent from the decision to perform laboratory confirmation.

Data source

Parents were interviewed by a trained investigator, using a structured questionnaire, during the hospital admission of the child, after having granted their informed consent. The interview was aimed at acquiring the anamnesis and at ascertaining drug use and vaccination status. As reported in the study protocol, no validation of the information on drug and vaccine exposure was conducted..

For drug exposure, the time window of interest was represented by the three weeks prior to the onset of symptoms related to the hospital admission. With regard to vaccine exposure, the twelve weeks preceding the hospitalisation were considered of interest for all non-influenza vaccines. For the assessment of vaccine effectiveness, related to both A-H1N1 and seasonal influenza vaccines, children were considered exposed if vaccinated any time before admission. To evaluate any possible relation between vaccination and AESIs, a time window specific for each AESI were considered: e.g. 0-2 days for urticaria¸ 0-14 days for convulsions; 0-42 days for thrombocytopenia, vasculitis, neuropathies, etc.[11-12]

Data analysis

To estimate the odds ratios (OR), two different comparisons were conducted to assess vaccine effectiveness. For the first one, all children hospitalised for ILI were considered as “cases” whereas children (more than 5 months old) enrolled for any of the four clinical conditions previously described represented the “control” group. For the second comparison, the analysis was restricted to all children admitted for ILI and tested for the A-H1N1 virus. ILI patients with a positive test were considered as “cases”, while those with negative test acted as “controls”. The purpose of the first analysis was to provide an estimate of the effectiveness of the vaccines in preventing the hospitalisation for any ILI during the influenza season. The second analysis was aimed at estimating the potential of the A-H1N1 vaccine to prevent the occurrence of confirmed episodes of pandemic influenza.

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Assuming a proportion of vaccinated children of 50%, a power of 90% and an alfa 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<= 0.5).

Adjusted ORs and related 95% Confidence Intervals (CI) were calculated through a multivariate logistic model. Data were analysed with SPSS® (version 17; SPSS Inc., Chicago, Ill., USA).

Study sites

The following paediatric hospitals and departments were participating: Giannina Gaslini Paediatric Hospital (Genova); Regina Margherita Paediatric Hospital (Torino); Department of Paediatrics, University of Padova (Padova); Anna Meyer Children's University Hospital (Firenze); Pharmacology and Paediatrics and Developmental Neuroscience, Università Cattolica Sacro Cuore (Roma); Emergency Department, Bambino Gesù Children Hospital (Roma); Santobono-Pausilipon Paediatric Hospital (Napoli); Giovanni Di Cristina Paediatric Hospital (Palermo). The protocol of the study was submitted to the Ethical Committee of each clinical centre for approval. The eight centres account for around 350,000 Emergency Department (ED) visits per year (around 50,000 children are subsequently hospitalised through the ED) and are located in the 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, a total of 736 children, median age 4 years (range 1 month-18 years) have been enrolled. 492 children were admitted to the hospital due to at least one of the four conditions of interest for this study: 241 (49%) for neurological disorders, 144 (29%) for muco-cutaneous diseases, 60 (12%) for thrombocytopenia, and 47 (10%) for gastro-duodenal lesions. 244 children were admitted with a diagnosis of ILI (Table 1). The male to female ratio was largely overlapping in the different groups of diagnosis.

Among the neurological conditions, convulsion was the most frequent cause for admission (N=91; 38%), followed by disturbances of vigilance and consciousness - e.g., numbness, somnolence, lipothymia – (N=39; 16%), and by episodes of Apparent Life Threatening Events (N=30; 12%). Serious clinical conditions were admitted: 8 children with peripheral neuropathies and 5 with Guillain-Barré syndrome. Within the muco-cutaneous diseases, more than half were represented by Shoenlein-Henoch purpura or other vasculitis (N=80; 55%), followed by urticaria (N=32; 22%) and erythema (N=15; 10%).

Seventy-one percent of children enrolled in the study had assumed at least one drug in the three weeks preceding the hospital admission. A total of 173 children (24%) have been vaccinated before the hospitalisation (either at any time for the influenza vaccines or during the preceding 12 weeks for the other vaccines). Hexavalent vaccine was the most frequently reported immunisation (55 children), followed the antipneumococcal (37 children) and MMR (24 children) vaccines.

For the influenza vaccine analysis the denominator is limited to the 683 children of at least 6 months (according to the vaccination schedule for the pandemic vaccine). In this population (244 for ILI and 439 for the other conditions), 25 children (3.7%) had received the pandemic vaccine (9 children received two doses), whereas 45 (6.6%) had received the vaccination against the seasonal influenza. Eleven children received both vaccines and in 9 children the type of influenza vaccine was not specified. All immunised children (both cases of ILI and controls) had received the influenza vaccines more than 14 days prior to the hospitalisation.

Out of 268 children admitted for a diagnosis compatible with AESI, only 6 were previously vaccinated with the A-H1N1 vaccine (2 cases of urticaria, 2 convulsions, 1 vasculitis and 1 Shoenlein-Henoch purpura), however, all admissions occurred outside the predefined risk windows (Table 2).

With regard to the evaluation of the pandemic vaccine effectiveness in the prevention of any ILI episodes, regardless to positive laboratory test, all estimates were higher than 1 (Table 3). Specifically, the adjusted ORs were 2.1 (1.1-4.1) for the seasonal vaccine and 1.3 (0.6-3.1) for the

pandemic vaccine. No difference in the OR estimates was observed when the analysis was restricted to the pandemic period (i.e., October 2009 – January 2010).

Among the 35 children who underwent the laboratory testing, 11 resulted positive and 24 negative for the A-H1N1 virus. Since none of the A-H1N1 positive children had a positive history for A-H1N1vaccination it was not possible to obtain an estimate of the 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 one (OR=0.9; 95% CI 0.1-5.5).

Discussion

One of the main strengths of the study was represented by the promptness to adapt the protocol of an existing study involving a network of hospitals to respond to the health alert created by the pandemic emergency. Despite the quite large enrolment in the Italian paediatric population, the results related to the evaluation of the safety and effectiveness of the pandemic vaccine were partly inconclusive. Several reasons may have contributed to this outcome. The A-H1N1 vaccination coverage in Italy during the influenza season 2009-2010 was very low: around 4% of the population [13] and 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 influenza were lower than expected. As a consequence, the Italian population did not adhere to the second part of the immunisation campaign, that was envisaged in January 2010. The epidemic curve during the influenza season 2009-2010 in Italy and the starting point of the vaccination campaign are represented in Figure 1. To further complicate the picture, since the A-H1N1 laboratory test was performed only during the epidemic phase, less than 10% of children hospitalized for ILI during the study period were tested.

These difficulties were observed in other European Countries. A very low level of vaccination was found, for instance, in the multinational study "Influenza monitoring vaccine effectiveness in Europe (I-Move)", [14] which was a practitioner-based outpatient surveillance conducted in seven Countries. Five of the seven Countries were not able to contribute with more than 1 vaccinated patient with confirmed A-H1N1 influenza. Only the pooled analysis derived from the international collaboration was able to estimate the effectiveness.

Despite the limitations, our study provided additional information on the benefit-risk profile of the pandemic vaccine. No report of AESI associated with the vaccine use in paediatrics was observed. These findings are coherent with those reported by experimental and observational studies, including analysis of spontaneous reporting systems.[15-18] In conclusion regarding safety, even within the limitation of a low level of immunisation, no sign of risk associated with the A-H1N1 vaccine used in Italy was described. Among the clinical diagnosis compatible with AESI none was reported related to vaccination in the predefined risk period.

With regard to effectiveness, as in other studies conducted in the adult population, a strong confounding effect was observed.[19-20] For instance, the immunisation with the seasonal vaccine was associated with a crude OR value greater than 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 the 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 the A-H1N1 vaccination. The crude OR was adjusted by age and presence of chronic diseases; the OR of A-H1N1 and 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 not able to control for, due to the limited power of the study.

A sample size of 194 children hospitalized for ILI was estimated in the protocol. Despite the fact that 244 children with this diagnosis were enrolled, the power resulted 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 the 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 represent a valid control group (the source population of cases). Cases and controls would be impossible to differentiate on the basis of the clinical symptoms that prompted the admission. Moreover, children hospitalised for an episode of ILI would more likely share similar risk factors for influenza. Finally, since the information of 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 the study, we reported that given the low number of children affected by ILI who underwent the laboratory test, we could not estimate the effectiveness (only 35 children were tested and no child who tested positive for A-H1N1 was vaccinated against the H1N1 virus). To support the assumption of a beneficial effect of the pandemic vaccination, our findings need to be corroborated by those of similar studies.

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We consider it was worth to conduct the study even though the findings might be considered only exploratory. One of the main results of this experience was to test the usefulness of an integrated model for conducting evaluations of 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 to estimate the vaccine effectiveness. Moreover, our findings may contribute to pooled estimates together with those of similar investigations. Last but not least, this study further supports the importance of an active hospital-based surveillance which may easily be adapted to capture potential signals of safety and effectiveness of new influenza vaccines or new drugs.

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Table 1. Distribution of children hospitalized 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)
Thrombocytopenia	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)
ILI	244	3 (3)	108 (44)	170 (70)	77 (32)	58 (24)

IQR: interquartile range

* All vaccines administered to the study subjects, and not only influenza ones, are included; 25 children exposed to the pandemic vaccine were distributed as follows: 6 cases (2.5%) were hospitalized for neurological disorders; 4 (2.8%) for muco-cutaneous diseases and vasculitis; 2 (4.3%) for gastroduodenal lesions; and 13 (5.3%) for ILI.

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
Shoenlein-Henoch	47	No
Urticaria	60	No
Vasculitis	128	No
Convulsions	149	No
Convulsions	188	No

Table 3. OR of ILI in association with the immunisation status

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

Cases: all children hospitalised for ILI. Controls: children hospitalised for thrombocytopenia, gastroduodenal lesions, mucocutaneous and neurological conditions; only children older than 6 months are included).

[§] In 7 cases and 2 controls the type of vaccine was not specified.

*Adjusted by age and chronic diseases; the OR of A-H1N1 and seasonal vaccine were also adjusted for the other influenza vaccine.

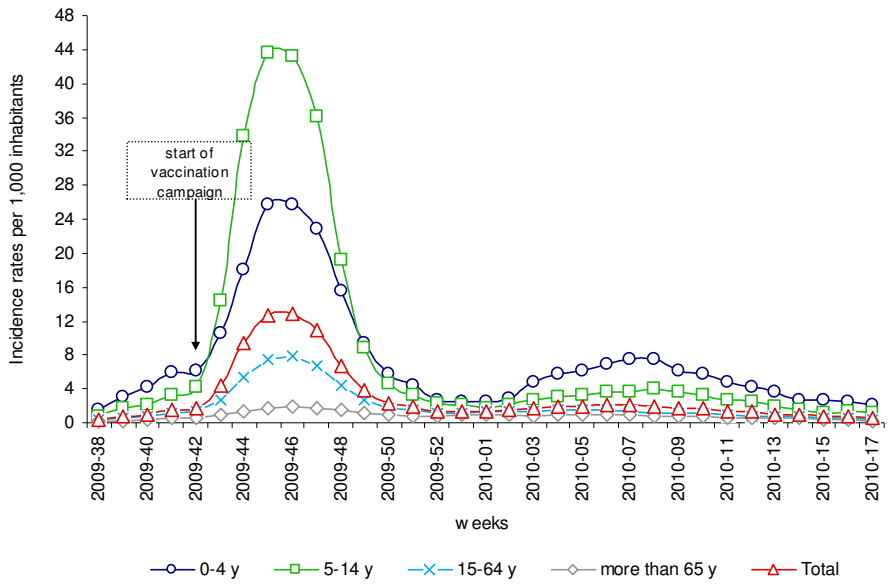
Table 4. OR of ILI in patients who tested positive to A-H1N1 virus

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

Cases: ILI patients who tested positive to the A-H1N1 virus. Controls: ILI patients who tested negative to the A-H1N1 virus.

[§] In 1 case and 1 control the type of vaccine was not specified.

Figure 1. Incidence of ILI in Italy by age group, season 2009-2010



Adapted from www.iss.it/iflu/

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *case-control studies*

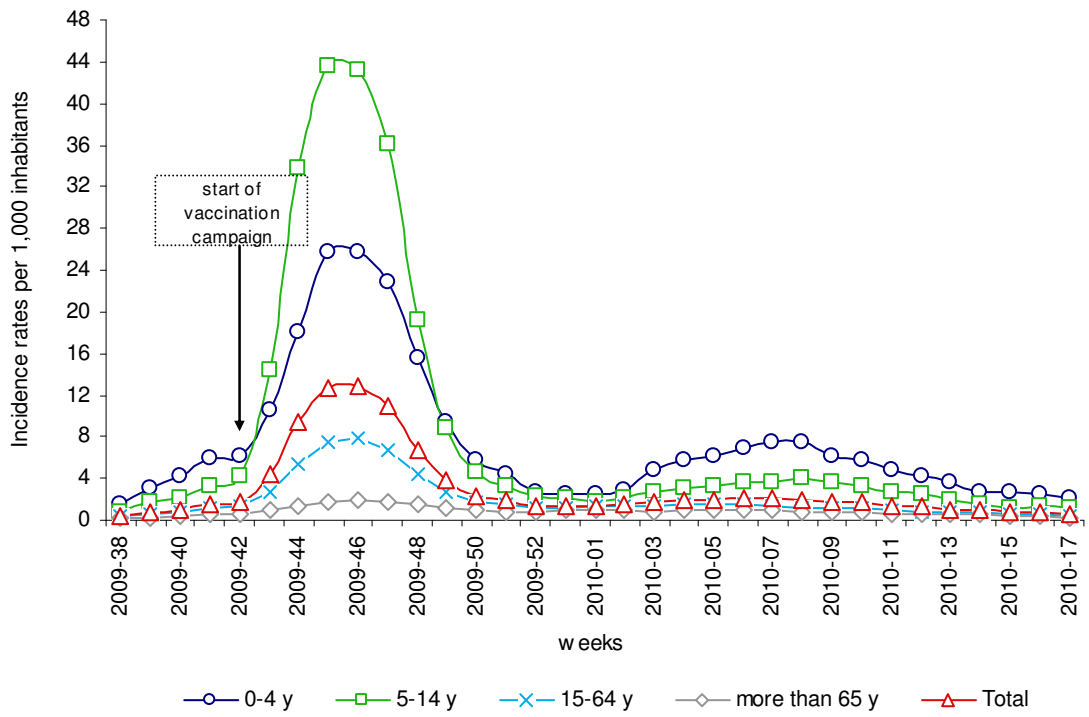
Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	*(*a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	4-5
		(*b*) For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	5, 7
Study size	10	Explain how the study size was arrived at	5, 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	--
		(*d*) If applicable, explain how matching of cases and controls was addressed	NA
		(*e*) Describe any sensitivity analyses	--
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6, 12
		(b) Give reasons for non-participation at each stage	--
		(c) Consider use of a flow diagram	--
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	14-15
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	12, 14-15
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6, 14-15
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6, 15
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7-8
Generalisability	21	Discuss the generalisability (external validity) of the study results	7-8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Figure 1. Incidence of ILI in Italy by age group, season 2009-2010



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