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ORIGINAL ARTICLE

# Effectiveness of pandemic influenza A/H1N1 vaccine for prevention of otitis media in children

**Bahar Çuhaci Çakir · Ufuk Beyazova · Yusuf Kemal Kemaloğlu · Seçil Özkan · Bülent Gündüz · Ali Özdek**

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**Abstract** Our aim was to evaluate effectiveness of pandemic influenza A/H1N1 vaccine in preventing acute otitis media (AOM) and/or otitis media with effusion (OME), in a randomized, prospective and single-blind study conducted in the children aged of 6–60 months. This study was done between December 1, 2009 and April 30, 2010 during the pandemia between June 2009 and May 2010. On the healthy children, vaccinated against pandemic influenza A/H1N1 and age-matched unvaccinated controls, the rate of AOM, OME, and any otitis media (OM) attack (sum of AOM and OME attacks) confirmed by otoscopic and tympanometric examination, and their associations with risk factors were looked for. Otoscopic and tympanometric evaluation was done twice within the follow-up period of 4–8 weeks. Totally 46 vaccinated and 46 unvaccinated healthy children were enrolled. No difference in rates of AOM, OME, or OM was found between vaccinated and unvaccinated children. But logistic regression analysis revealed that unvaccinated children had 2.9-folds more risk for OME and OM, but not for AOM. Further, male gender and bottle feeding and/or using pacifier revealed significant relationships with AOM. *Conclusion*: We conclude that pandemic influenza A/H1N1 vaccine prevented OME rather than AOM attacks in children with 6–60 months of age.

**Keywords** Pandemic influenza A/H1N1 · Vaccine · Acute otitis media · Otitis media with effusion · Upper respiratory tract infection

B. Çuhaci Çakir (✉)
Ankara Child Diseases Hematology Oncology Training and Research Hospital, Well-Child Clinic, Ankara, Turkey
e-mail: baharcc44@yahoo.com

U. Beyazova
Department of Pediatrics, Gazi University Faculty of Medicine, Ankara, Turkey

Y. K. Kemaloğlu
Department of ORL-HNS, Gazi University Faculty of Medicine, Ankara, Turkey

S. Özkan
Public Health Department, Gazi University Faculty of Medicine, Ankara, Turkey

B. Gündüz
Department of ORL-HNS, Audiology Subdivision, Gazi University Faculty of Medicine, Ankara, Turkey

A. Özdek
Department of Otolaryngology, Head and Neck Surgery, Yildirim Beyazit Training and Research Hospital, Ankara, Turkey

## Introduction

Otitis media is one of the most common diseases during the childhood causing either infective or non-infective complications and sequels such as meningitis, abscess, permanent hearing disorders, speech problems, etc. [5]. Acute otitis media (AOM) is the second most common infectious diseases among infants and young children while otitis media with effusion (OME) is the most common otologic disorder causing hearing impairment and serious sequel in long-term during childhood. It has been reported that OME could be associated with significant effects on the development of speech, language, and cognitive abilities [5, 24].

Bacteria play a major role in the etiology of AOM [5]. Although it is mainly bacterial, some respiratory viruses like respiratory syncytial virus, rhinovirus, and influenza A virus are known to predispose to AOM [7, 15]. In many cases, AOM follow an upper respiratory infection due to viruses [11, 12, 14]. A viral upper respiratory infection can lead to

congestion of the respiratory mucosa. This congestion causes tubal dysfunction with impaired clearance and pressure regulation of the middle ear [5, 20]. As a consequence of tubal dysfunction in contribution with many other anatomical, immunological factors and allergy, OME, with or without bacterial infection, is one of the most frequent diseases during the childhood [5].

It has been reported that the administration of influenza vaccines decrease influenza-associated AOM and/or OME. [3, 4, 8, 13, 17–19]. Block et al. documented that attenuated influenza vaccine was more efficient against influenza-associated AOM compared with trivalent inactivated influenza vaccine [4]. On the other hand, Hoberman et al. found that influenza vaccine did not reduce burden of AOM during the influenza season [16]. In Turkey, previously we documented that inactivated influenza vaccine is effective in reducing otitis media (OM) episodes (either AOM or OME) in healthy day care children aged 6–60 months [19].

On June 2009, the World Health Organization declared the global spread of a novel influenza A (H1N1) pandemic [6], and it has been reported that the viruses were antigenically homogeneous and similar to North American swine A (H1N1) viruses but distinct from seasonal human A(H1N1) [9]. In Turkey, the first pandemic case was reported in June 2009, and since September 2009 (school opening) number of the reported cases has shown gradual increase with a peak value between November 9 and 29 (46–48 weeks of the year). During pandemic period, totally 10,700 patients were hospitalized in Turkey. The vaccination program in Turkey was started from November 2009 [1, 2], and the Turkish Ministry of Health recommended vaccination of children between the ages of 6 months through 5 years. The number of the subjects was found to be decreased gradually from December. The last reported case was in May 2009 [1, 2]. In this study, we aimed to determine the effect of the pandemic Influenza A/H1N1 vaccine against OM attacks in the healthy children.

## Materials and methods

### Study population and design

This prospective, randomized, single-blind case–control study was conducted between December 1, 2009 and April 30, 2010, in two reference hospitals (Gazi University Faculty of Medicine, Department of Social Pediatrics and Ankara Child Diseases Hematology Oncology Training and Research Hospital, in Ankara, Turkey). Written informed consent was obtained from the parents and the study was approved by the Gazi University ethics committee.

The children between 6 and 60 months of age, who were free of acquired or congenital immunodeficiency, any craniofacial abnormality or chronic diseases, were prospectively included to the study. Further, the subjects presenting symptoms of H1N1 pandemic infection from June 2009 were excluded from the study group. In enrolling process, a consecutive manner was followed. First, the subjects vaccinated by pandemic influenza A/H1N1 vaccine (Focetria of Novartis, contained 7.5 μ dose of monovalent influenza A/California/7/2009 (H1N1) MF59-adjuvanted surface-antigen vaccine) were enrolled and after enrolling of each vaccinated case, the first following unvaccinated age-matched case on the same day was taken to the control group. The vaccine dosage was 0.5 mL for children and two doses of vaccine were given 3 weeks apart.

During the study process, first, a survey were given to the parents and these data were used to determine the following risk factors related with gender, bottle feeding, use of pacifier, history of frequent upper respiratory tract infection (URTI), sibling history of URTI, sibling history of school or day care attendance, asthma and allergy, previous history of OM, passive smoking, and day care attendance.

Then, visual otoscopic examination and tympanometry were performed in all children. The first examination was done at the study entry, and then a second one was scheduled within the following 4–8 weeks. According to the otoscopic and tympanometric findings, the following definitions were done as in our previous study [19]:

> Normal ear: Normal otoscopic findings and type A or C1 curve detected by tympanometry.
> AOM: Hyperemia, opacity, bulging, or immobility of the tympanic membrane in addition to any combination of the following clinical findings: fever, earache, irritability, and vomiting.
> OME: Immobility, bulging, opacification, or retraction of the tympanic membrane without clinical signs and symptoms of acute infection and C2 or B curve on tympanometry.
> OM: Presence of any type of otitis media (either AOM or OME).

In the subjects in which otoscopic and tympanometric findings presented ambivalency or inconsistency, visual otoscopy was re-performed by another physician (any of the authors of this study) in a blind manner, and then tympanometry was repeated. In case of continuing the ambivalancy or inconsistency, this subject was excluded from the study groups.

### Statistical analysis

We used the Statistical Package for Social Sciences (SPSS/PC 13.0) software. Differences between groups were assessed by the $\chi^2$ test for categorical variables. Statistical

significance was defined as $p<0.05$. The vaccinated and unvaccinated groups were first compared with each other according to the number of at least one OME or AOM episodes separately; then, rates of the subjects presenting any type of OM (either AOM or OME) and pathologic tympanometric curves were also compared between the groups. Besides, the univariate analyses were performed to identify variables associated with OME, AOM, and OM using chi-square and Fisher's exact tests. For the multivariate analysis, the possible factors [unvaccinated by pandemic influenza A/H1N1 vaccine, sex, age, use of bottle feeding and/or pacifiers, sibling history of frequent URTI, presence of sibling history of school or day care attendance, previous OM history, passive smoking, unvaccinated by heptavalent pneumococcal conjugated vaccine (PCV7), day care attendance and frequent URTIs] identified with univariate analysis were further entered into the logistic regression (backward LR model) analysis to determine independent predictors of OME, AOM, and OM. The last step data of the logistic regression analysis was taken to the results.

## Results

In this study, we totally enrolled 46 vaccinated (mean age, 27.73±14.77 months; min, 7 months; max, 59 months) and 46 unvaccinated (mean age, 28.26±13.52 months; min, 8; max, 57 months) children (Table 1). Statistically, no age difference was found between the groups. The second otoscopic examination and tympanometry were done in 28 (60.86 %) cases in each group; the rest was unfortunately out of follow-up. Totally, 74 otoscopic examination and tympanograms were taken from each group and the data were analyzed.

It was documented that 12 cases (26.1 %) in vaccine group were vaccinated with single dose pandemic Influenza A/H1N1 vaccine. The second otoscopic examination and tympanometry were done in seven of them, while five of the single-vaccinated children left the study. As seen in Table 1, $\chi^2$ analysis presented no difference regarding presence or absence of any risk factors included to this study between vaccinated and unvaccinated cases.

In Table 2, rates of the subjects presenting at least one episode of AOM or OME are seen. In the vaccinated group, in either the first or second examination, only 6.5 % presented AOM while this rate was 17.4 % in unvaccinated cases. Rates of the subjects with at least one episode of OME were almost similar in both groups. Statistical analysis revealed no difference between the groups. Furthermore, the numbers of subjects presenting at least one episode of any type of OM (either AOM or OM) were also not found to be significantly different (Table 2). Similarly, rate of detection of at least one abnormal tympanogram curve (C2 or B) in any ear was found not to be significant between vaccinated and unvaccinated children (Table 2).

Moreover, when we compared single vaccinated cases with the double vaccinated ones, no difference was found. Mean numbers of OME and AOM in 12 single vaccinated groups were found to be 16.67 and 0 %, respectively, while these rates in 34 double-vaccinated children suffered were 11.77 and 5.88 %, respectively. Hence, in further statistical comparisons with unvaccinated ones, single and double vaccinated children were taken account as one group.

Multivariate analysis was performed to determine related risk factors for OME, AOM, and OM, and "being not vaccinated with pandemic Influenza A/H1N1 vaccine" was added to the list of independent variables as another risk factor. It was found that unvaccinated children had 2.9 times more risk for OME and OM than vaccinated ones (95 % CI: 1.03–8.56 % and 1.03–8.56 %; $p=0.044$ and $p=0.043$, respectively). Although unvaccination was appeared to be associated with 9.5-fold increased risk of AOM, it was not significant ($p>0.05$). Further, male gender (12.3-fold; 95 % CI: 1.12–136.63 %, $p=0.040$) and bottle feeding and/or

**Table 1** Characteristics and risk factors of the vaccinated and unvaccinated children

| | Vaccinated children *n* (%) | Unvaccinated children *n* (%) | *p*[a] |
|---|---|---|---|
| Gender (male/female) | 27/19 (58.7/41.3) | 26/20 (56.5/43.5) | 1.00 |
| Bottle feeding | 31 (67.4) | 32 (69.6) | 1.00 |
| Use of pacifier | 15 (32.6) | 19 (41.3) | 0.51 |
| History of frequent URTI | 11 (23.9) | 15 (28.3) | 0.48 |
| Sibling history of URTI | 6 (13) | 2 (4.3) | 0.10 |
| Sibling history of school or day care attendance | 17 (37) | 9 (19.6) | 0.11 |
| Asthma and allergy | 4 (8.7) | 0 (0) | 0.117 |
| Previous history of OM | 9 (19.6) | 14 (30.4) | 0.33 |
| Passive smoking | 16 (34.8) | 23 (50) | 0.20 |
| Vaccinated with PCV7 | 34 (73.9) | 14 (30.4) | 0.00 |
| Day care attendance | 8 (17.4) | 3 (6.5) | 0.19 |

*OM* otitis media, *PCV7* heptavalent pneumococcal conjugated vaccine, *URTI*, upper respiratory tract infection

[a] $\chi^2$ test

**Table 2** Number and rates of the vaccinated and unvaccinated children in which at least one episode of AOM, OME and OM, and at least one episode of abnormal tympanogram (C2 and B) were detected

| Children with | Vaccinated *n* (%) | Unvaccinated *n* (%) | *p*[a] |
|---|---|---|---|
| AOM | 3 (6.5) | 8 (17.4) | >0.05 |
| OME | 11 (23.9) | 12 (26.1) | |
| OM (AOM and/or OME) | 12 (26.1) | 18 (39.1) | |
| Abnormal timpanogram in any ear | 23 (50) | 32 (69.6) | |

*AOM* acute otitis media, *OM* otitis media, *OME* otitis media with effusion

[a] $\chi^2$ test

using pacifier (19.3-fold; 95 % CI: 1.61–233.03 %, $p$= 0.020) were reported to be other associated risk factors.

## Discussion

In this study, we reported that pandemic influenza A/H1N1 vaccine could have a potential positive effect on prevention of OME. Although our data did not present any clear group differences, multivariate analysis revealed that the children who were not vaccinated with pandemic Influenza A/H1N1 vaccine had 2.9 times more risk for OME.

Regarding the fact that OM, either AOM or OM, is a common childhood disease, particularly prevalent in early ages, this data could be optimistic for the future studies focusing on prevention OM. It has been known that developmental anatomic problems related with the Eustachian tube have been main underlying cause in OM tendency during the childhood [5]. Recently, the evolutionary aspects of this relationship have been explored. Specifically, flattening of the face in contemporary humans may be associated with an impaired tubal function by changing palatal anatomy and, thus, the orientation and function of Eustachian tube muscles [23]. However, it is also known that in the contemporary human deterioration of poor tubal function by viral infections, in addition to their impacts on immunological protection increased prevalence of AOM or OME during childhood. [5, 12, 14, 20].

Recently, Winther et al. pointed out that oseltamivir treatment significantly reduced the emergence of new AOM infections in children with laboratory confirmed influenza [26]. However, protection from influenza by using vaccine, if possible, has been a better alternative for most of the physicians [12]. Particularly, in comparison to relatively poor impact of pneumoccal vaccines on prevention of AOM [22], the studies with seasonal influenza vaccines documented more optimistic data [3, 4, 8, 17–19]. Vesikari et al. reported that vaccine efficacy against A/H1N1 was about 92 and 90 % in the first and second years of vaccination, respectively, and that efficacy against all episodes of AOM associated with culture-confirmed influenza was about 91 % in year1 and 97 % in year 2 [25]. The studies revealed a high protection rates against both AOM and OME by seasonal influenza vaccines [3, 4, 8, 17–19]. Previously, we documented that efficacy of influenza vaccine for protection against AOM and OME were about 51 and 18 % [19]. In accordance with this finding, higher efficacy of influenza vaccine on frequency of AOM rather than frequency or duration OME was reported by the researchers investigated both AOM and OME episodes [8, 17, 18].

In children with a recent history of recurrent AOM, Marchisio et al. reported very high efficacies of both intranasal, inactivated, virosomal subunit influenza vaccine and injectable trivalent virosomal-adjuvanted inactivated influenza vaccine [17, 18]. They pointed out the higher success rate in their study could be related with that their study group consisted of the children with documented prior AOM before vaccination because it has been demonstrated that pneumococcal vaccines were less efficient in children without documented prior AOM before vaccination [22]. However, as in our previous study [19], we found that previous OM history was not found to be an associated factor. But, it could be underlined that in this study we did not include any case with URTI during the last 4 months to prevent inclusion of the cases infected by novel H1N1 influenza during the pandemic period to the control group. This exclusion criteria could be an explanation about our finding that efficacy of pandemic Influenza A/H1N1 vaccine was evident for OME, but not AOM. Although a relatively higher incidence of AOM in unvaccinated group was detected, it was not statistically significant.

In studies of Marchisio et al., they also pointed out that cumulative duration of middle ear effusion was significantly less in vaccinated cases [17, 18]. However, Clements et al. reported no effect of trivalent subvirion influenza virus vaccine on OME [8].

We may speculate that this data could be related with either size of the study group or exclusion criteria mentioned above, and in a large sample higher efficacy might be detected. However, in another view of the aspect, it might be said that novel H1N1 may cause URTI and congestion of the Eustachian tube, but not a tendency to AOM. It is known that seasonal influenza vaccines in which efficacy against AOM was confirmed previously include not only influenza A/H1N1, but also influenza A/H3N2, and B subtypes. But the vaccine used in this study includes only a novel H1N1-2009 virus. This novel H1N1 infection may cause tubal congestion and edema, which triggers poor middle ear ventilation and negative middle ear pressure, ultimately causing OME, as detected in other respiratory viruses [27]. Giebink and Wright reported that tympanic membrane inflammation

was observed in only four of the 11 animals infected by H1N1, while this rate was nine of 10 animals infected by H3N2. Besides, negative middle ear pressure was detected in 77 and 100 % of the ears infected by H1N1 and H3N2, respectively [10]. Although this data is in accordance with our assumption, more detailed designed studies are necessary.

Our study also revealed clear mathematical associations between episodes AOM or OME and male gender, bottle feeding and/or using pacifier were documented as previously reported [5, 21, 24].

There are several studies that showed how OME has no impact in long-term follow-up and it causes only transients problems that tend to spontaneously cure in long term. Although, this means that a vaccination to prevent only OME has no sense at all, but, by using our data in this study, we conclude that pandemic Influenza A/H1N1 vaccine prevented OME rather than AOM attacks in children with 6–60 months of age.

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