

ORIGINAL ARTICLE

# Effectiveness of Maternal Influenza Immunization in Mothers and Infants

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## ABSTRACT

### BACKGROUND

Young infants and pregnant women are at increased risk for serious consequences of influenza infection. Inactivated influenza vaccine is recommended for pregnant women but is not licensed for infants younger than 6 months of age. We assessed the clinical effectiveness of inactivated influenza vaccine administered during pregnancy in Bangladesh.

### METHODS

In this randomized study, we assigned 340 mothers to receive either inactivated influenza vaccine (influenza-vaccine group) or the 23-valent pneumococcal polysaccharide vaccine (control group). Mothers were interviewed weekly to assess illnesses until 24 weeks after birth. Subjects with febrile respiratory illness were assessed clinically, and ill infants were tested for influenza antigens. We estimated the incidence of illness, incidence rate ratios, and vaccine effectiveness.

### RESULTS

Mothers and infants were observed from August 2004 through December 2005. Among infants of mothers who received influenza vaccine, there were fewer cases of laboratory-confirmed influenza than among infants in the control group (6 cases and 16 cases, respectively), with a vaccine effectiveness of 63% (95% confidence interval [CI], 5 to 85). Respiratory illness with fever occurred in 110 infants in the influenza-vaccine group and 153 infants in the control group, with a vaccine effectiveness of 29% (95% CI, 7 to 46). Among the mothers, there was a reduction in the rate of respiratory illness with fever of 36% (95% CI, 4 to 57).

### CONCLUSIONS

Inactivated influenza vaccine reduced proven influenza illness by 63% in infants up to 6 months of age and averted approximately a third of all febrile respiratory illnesses in mothers and young infants. Maternal influenza immunization is a strategy with substantial benefits for both mothers and infants. (ClinicalTrials.gov number, NCT00142389.)

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**I**NFECTION WITH INFLUENZA VIRUS IS ASSOCIATED with serious illness and hospitalization among pregnant women<sup>1-3</sup> and young infants, including neonates.<sup>4-6</sup> Maternal influenza infection has been associated with an increased risk of maternal hospitalization, fetal malformation, and other illnesses.<sup>7,8</sup> Influenza infection in young infants often prompts hospitalization and can predispose the infants to bacterial pneumonia or otitis media.<sup>9,10</sup> Studies from North America<sup>11</sup> and Hong Kong<sup>12</sup> have shown high rates of hospitalization among infants with influenza, especially those under 6 months of age.<sup>13</sup> The rate of hospitalization for such infants is higher than that for other high-risk groups. A national survey in the United States showed that childhood deaths associated with influenza are most frequent in infants under the age of 6 months.<sup>14</sup>

Natural maternal influenza antibodies protect infants during the first few months of life.<sup>15,16</sup> A study of influenza immunization of pregnant women showed that active transport of immunoglobulin G produced umbilical-cord antibody levels that were higher than those in maternal serum.<sup>17</sup> Epidemiologic data suggest that breastfeeding is also protective against influenza in young infants.<sup>18</sup>

Immunization of pregnant women with inactivated trivalent influenza vaccine has been recommended in the United States for more than a decade<sup>19</sup> and by the World Health Organization (WHO) since 2005.<sup>20</sup> However, few mothers receive the vaccine.<sup>7</sup> The general safety of this strategy has been shown,<sup>21,22</sup> but there has been no randomized, prospective evaluation of its clinical effectiveness.<sup>19,23</sup> Antiviral drugs are not recommended for use in early pregnancy.<sup>19</sup>

Since 2003 in the United States, influenza immunization has been recommended for infants between the ages of 6 months and 23 months,<sup>19</sup> although vaccine immunogenicity may be reduced in children under the age of 2 years.<sup>24,25</sup> Influenza vaccines are not licensed in the United States for use in infants under the age of 6 months, and antiviral drugs for influenza therapy are not licensed for infants under the age of 1 year.<sup>19,26</sup>

The Mother's Gift project is a randomized trial of the strategy of maternal immunization, with the primary goal of assessing the safety and immunogenicity of sequential maternal and infant immunization with pneumococcal vaccines in Bangladesh. In our study of influenza vaccine, mothers in the control group received

pneumococcal vaccine only. No infants received the influenza vaccine. We made use of the opportunity afforded by the randomized, blinded design to assess the influenza-related illnesses of the mothers who had received the influenza vaccine and their infants, as compared with those who received only pneumococcal vaccine. We report here estimates of the clinical effectiveness of maternal immunization with inactivated influenza vaccine on influenza illness in infants and mothers.

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## METHODS

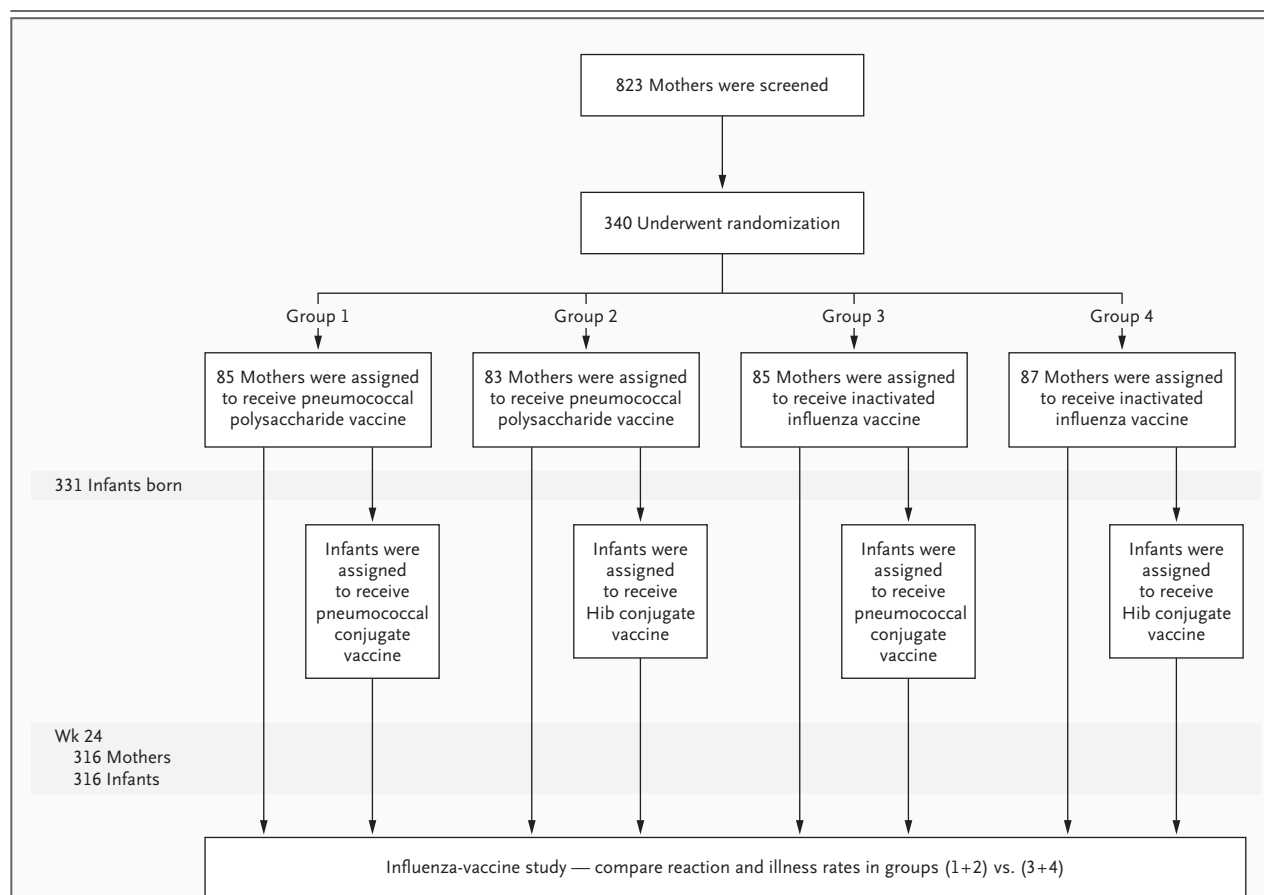
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### STUDY DESIGN

We conducted a prospective, controlled, blinded, randomized trial to assess the safety and immunogenicity of pneumococcal vaccines, as well as the clinical effectiveness of influenza vaccine (Fig. 1). The primary outcome in infants was the first episode of laboratory-confirmed influenza before 24 weeks of age. Other outcomes in the infants were the confirmation of influenza-like illness by a clinician and confirmation by obtaining a throat swab for influenza antigen testing. Study outcomes for both mothers and infants were the numbers of episodes of respiratory illness with fever or of documented fever of more than 38°C, clinic visits with respiratory illness, and episodes of diarrhea (nonrespiratory end point for both groups).

Exclusion criteria for mothers were a history of systemic disease, previous complicated pregnancy or preterm delivery, spontaneous or medical abortion, congenital anomaly, and hypersensitivity to or receipt of a study vaccine in the previous 3 years. After providing written informed consent, pregnant women were randomly assigned to one of four groups for the primary study, with women in groups 1 and 2 receiving pneumococcal vaccine and those in groups 3 and 4 receiving influenza vaccine. For our analysis of the effect of maternal influenza immunization, the mothers and their infants were analyzed in two groups: those who received influenza vaccine and the control group (see the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org)).

The randomization sequence was computer-generated, stratified according to clinic, and blocked in groups of four; sequentially numbered opaque envelopes with data regarding assignments to study groups were provided to each clinic.



**Figure 1. Original Study Design, Showing Subgroups of Mothers and Infants Included in the Current Analysis.**

After undergoing screening, 340 pregnant women were randomly assigned to one of four groups for the primary study of the safety and immunogenicity of sequential maternal and infant immunization with pneumococcal vaccines, with mothers in groups 1 and 2 receiving pneumococcal vaccine and those in groups 3 and 4 receiving influenza vaccine. For our current analysis of the effect of maternal influenza immunization, the mothers and their infants were analyzed in two larger groups: mothers who received inactivated influenza vaccine and those who received pneumococcal vaccine only (control group). None of the infants received the vaccine against influenza virus. Hib denotes *Haemophilus influenzae* type b, a bacterium that causes a range of severe infections, including meningitis.

Mothers, families, and study staff who collected data regarding illnesses and adverse events were unaware of the study-group assignments. Blood was collected from mothers before and after immunization; for infants, cord blood was collected at birth, and samples were taken at 6, 10, 14, and 18 weeks and between 22 and 24 weeks for serologic assessment. All infants received the local routine childhood immunizations at 6, 10, and 14 weeks. Infants in the primary immunogenicity study received either three doses of pneumococcal conjugate vaccine (Prennar, Wyeth) or *Haemophilus influenzae* type b conjugate vaccine (Hiberix, Glaxo-SmithKline) at 6, 10, and 14 weeks.

The project protocol was reviewed and ap-

proved by the institutional review boards at the International Centre for Diarrheal Disease Research, Bangladesh, and the Bloomberg School of Public Health at Johns Hopkins University, Baltimore. Use of study vaccines was approved by the Directorate of Drug Administration, the Government of the People's Republic of Bangladesh. All the authors vouch for the completeness of the data and the analyses presented.

#### STUDY VACCINES

Mothers were randomly assigned to receive an inactivated influenza virus vaccine, Fluarix (lot number, AFLUA004BC), containing strains for 2004 (including A/New Caledonia/20/99 [H1N1],

A/Fujian/411/2002 [H3N2], and B/Hong Kong/330/2001), as recommended by the WHO for the southern hemisphere, or the 23-valent polysaccharide pneumococcal vaccine, Pneumovax (lot number, 0987N). All study vaccines were purchased from the manufacturer. Clinic staff members who were not involved with study-outcome assessments administered all doses of vaccine by intramuscular injection.

#### SURVEILLANCE

All mothers were interviewed 8, 24, 48, and 72 hours after immunization and then 1 week later by telephone or home interview to record local and systemic side effects. Most mothers were followed from 2 weeks after immunization through pregnancy and delivery, and all mothers were interviewed once a week from the birth of the infant through 24 weeks of age to assess the occurrence of illnesses in themselves and their infants. Of the 340 mothers who underwent randomization, 331 mothers and their infants (97.4%) began surveillance after delivery, and 316 mother–infant pairs (92.9%) completed the 24 weeks of study surveillance.

Mothers were given digital thermometers and were taught to record axillary temperatures of their infants. Families were asked to bring infants who were ill to the study clinic for evaluation, influenza-antigen testing, and treatment. For clinician-confirmed acute febrile respiratory illness in infants, throat swabs were collected and tested within 24 hours after collection by laboratory technicians at the International Centre for Diarrheal Disease Research in Dhaka, using a rapid test for both influenza A and B (Zstat, ZymeTx). Test results were provided to the clinicians to guide treatment of the patients. Because of a shortage of rapid tests, episodes of respiratory illness with fever in infants from August 2004 through October 2004 could not be tested, and maternal illnesses were not tested. An independent data and safety monitoring board and both institutional review boards reviewed all severe adverse events (for details, see the Supplementary Appendix).

#### STATISTICAL ANALYSIS

The numbers of subjects that were needed for the primary study were calculated to detect a specified difference in the mean pneumococcal antibody titer in the two groups<sup>27</sup> (see the Supplementary Appendix for details). The sample size had

a power of 80% to detect a difference in illness rate of 30% or more. For a comparison of study groups, we assessed group means with Student's *t*-test and proportions with the chi-square test and Fisher's exact test; all tests were two-sided. Intention-to-treat analysis was performed on the outcome data. Incidence rate ratios (IRRs) were calculated for the study outcomes with the use of Poisson regression models (see the Supplementary Appendix for details). Estimates of clinical effectiveness were calculated with the formula  $(1 - \text{IRR}) \times 100$ . We used a post hoc analysis with an interaction term to assess the effect of all infant vaccines that did not contain the inactivated influenza virus. There were no interim analyses of the data. All *P* values are two-sided and not adjusted for multiple testing. Associations with a *P* value of less than 0.05 or effectiveness confidence intervals that did not include 0 were considered to have statistical significance.

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## RESULTS

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#### POPULATION AND ADVERSE EVENTS

A total of 340 women in the third trimester of pregnancy who met the inclusion criteria agreed to participate in the study. The mothers and infants in the two study groups were similar in both demographic and other characteristics (Table 1). Minor local and systemic side effects that occurred during the first 7 days after immunization were similar in the two groups of mothers except for local pain, which was more frequent among the mothers who received pneumococcal vaccine. The difference in the rate of severe adverse events between the two groups was not significant (for details, see the Supplementary Appendix).

#### EFFECTIVENESS

Mothers were recruited and immunized from August 2004 through May 2005, and cohorts of mother–infant pairs were observed through November 2005, for a total of 1651 person-months in the group of infants and 2165 person-months in the group of mothers. Of the mother–infant pairs, 316 were observed for the full 24-week period. During this time, 22 infants had at least one laboratory-confirmed influenza infection (Fig. 2).

Maternal influenza immunization significantly reduced the rate of laboratory-confirmed influenza in the infants (Table 2). Among the 159 infants whose mothers received influenza vac-

**Table 1. Characteristics of the Patients.**

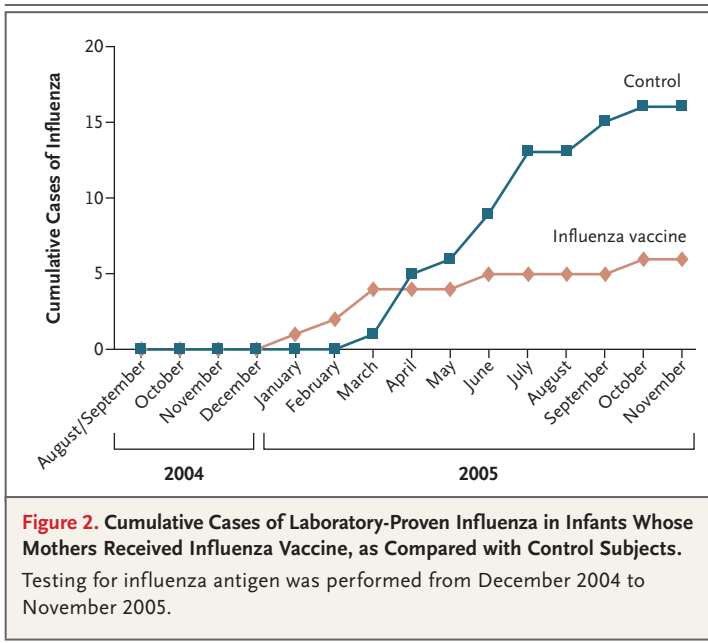
Characteristic	Control (N=168)	Influenza Vaccine (N=172)	P Value*
Maternal age (yr)			0.63
Mean	24.9	25.1	
Range	18.0–36.0	18.0–36.0	
Maternal education (yr)			0.42
Mean	10.9	11.2	
Range	0–16.0	0–16.0	
Gravidity			0.93
Mean	2	2	
Range	1–7	1–6	
Parity			0.80
Mean	1.2	1.1	
Range	0–4.0	0–4.0	
Rooms in house (no.)			0.97
Mean	4	4	
Range	1–10	1–10	
Smoker in family (%)	45	40	0.32
Maternal height (cm)			0.64
Mean	153	153	
Range	126–168	140–168	
Interval between vaccination and birth (days)			0.41
Mean	56	54†	
Range	13–94	0–89	
Gestational age at birth (wk)			0.55
Mean	39.3	39.4	
Range	32.2–43.2	32.3–43.9	
Gestational age <37 wk (%)	8.4	6.5	0.54
Delivery in hospital or clinic (%)	92.2	92.3	1.0
Cesarean delivery (%)‡	47.3	45.6	0.83
Birth weight (kg)			0.08
Mean	3.0	3.1	
Range	1.9–4.6	1.8–5.0	
Birth weight <2.5 kg (%)	7.8	4.1	0.17
Mean Apgar score at 1 min and 5 min§	7.5 and 8.5	7.3 and 8.5	0.50 and 0.77
Sex of infant female (%)	43.1	46.1	0.58
Duration of exclusive breast-feeding (wk)			0.18
Mean	15	14	
Range	1–25	1–25	

\* Means were compared with the use of Student's t-test, and proportions were compared with the use of Fisher's exact test. None of the differences between the two study groups were significant.

† One mother in the influenza-vaccine group began labor about 8 hours after receiving a dose of the vaccine. The delivery was uneventful, and the infant weighed 2400 g at an estimated gestational age of 34 weeks. This mother–infant pair was included in the intention-to-treat analyses.

‡ The rate of cesarean delivery was typical for the population of patients at the study centers.

§ The Apgar score ranges from 0 to 10, with scores above 7 indicating that the baby's condition is good to excellent.



cine, 6 had laboratory-confirmed influenza, as compared with 16 among the 157 infants whose mothers were in the control group, an effectiveness of 63% (95% confidence interval, 5 to 85). Influenza immunization also had substantial effectiveness against the other clinical outcomes in the infants, including a reduction of 29% in the rate of respiratory illness with fever, a reduction of 42% in the rate of infant clinic visits for respiratory illness with fever, and a reduction of 49% in the rate of clinician testing for influenza. Antigen-test-positive influenza was detected from January through October 2005, and vaccine effectiveness appeared to vary somewhat during the 15 months of observation, with apparent increased effectiveness from March through November 2005 (Fig. 2).

Mothers who received influenza vaccine were significantly less likely to have respiratory illness with fever, as compared with the control group, and had fewer respiratory illnesses with a temperature of more than 38°C and fewer clinic visits (Table 2). We observed clinical effectiveness in the reduction of febrile respiratory illness in infants up to 5 and 6 months of age (Fig. 3 and 4). Reported diarrheal illness in mothers and infants was similar in both study groups. The post hoc analysis that was performed with the use of Poisson regression including an interaction term accounting for the noninfluenza childhood

vaccines did not show a significant interaction for the infant end-point data ( $P=0.80$ ), suggesting the effectiveness of maternal influenza immunization did not vary according to infant immunization with *H. influenzae* type b vaccine or pneumococcal vaccine.

#### INFLUENZA DISEASE AND IMMUNIZATION IN SOUTH ASIA

The frequent, close observation of our Bangladeshi subjects provided unique, serendipitous descriptive data on the natural history of influenza in this South Asian environment, although these observations were not a primary objective of our study. In tropical and subtropical regions, influenza viruses may be perennial with some seasonal variation, causing disease for much of the year.<sup>12,28,29</sup> Limited data regarding influenza are available for Dhaka, which is located at 23.5°N, virtually on the Tropic of Cancer.<sup>30,31</sup> Our surveillance in Dhaka showed evidence of the circulation of influenza virus for 10 of 11 months of observation. Our preliminary data for infants showed that in the control group, the incidence of laboratory-proven influenza illness was at least 10% in the first 6 months of life. In addition, we observed that one infant in each study group had two episodes of laboratory-confirmed influenza (at 1 and 12 weeks in the influenza-vaccine group and at 9 and 28 weeks in the control group). In the mothers, the observed effect of influenza vaccine on febrile illnesses suggested that at least 36% of all maternal febrile respiratory illnesses are attributable to influenza up to 6 months post partum.<sup>32,33</sup>

#### DISCUSSION

Our study showed that maternal immunization with influenza vaccine had significant clinical effectiveness, with a reduction of 63% in laboratory-proven influenza illness in infants up to 6 months of age and reductions of 29% and 36% in rates of respiratory illness with fever in infants and mothers, respectively. Although the confidence limits for the effectiveness of passive immunization were wide, the point estimates of effectiveness against both laboratory-proven influenza and multiple clinical end points in the infants were similar to those reported in trials of active influenza vaccine in infants older than 6 months of age.<sup>25</sup> However, our findings differ from those of some non-

**Table 2. Clinical Effectiveness of Influenza Vaccine in Infants and Mothers.\***

Variable	Episodes		Clinical Effectiveness (95% CI)†	Risk Difference (95% CI)‡
	Control	Influenza Vaccine no.		
<b>Infants</b>				
Person-months	870	881		
Respiratory illness with fever				
Any fever	153	110	28.9 (6.9 to 45.7)	-28.1 (-48.2 to -8.0)§
Temperature >38°C	77	56	28.1 (-4.6 to 50.6)	-13.7 (-28.0 to 0.5)
Diarrheal disease	138	137	1.9 (-30.0 to 26.0)	-1.6 (-22.1 to 18.9)
Clinic visit	92	54	42.0 (18.2 to 58.8)	-24.5 (-39.5 to -9.5)§
Influenza test ordered	79	41	48.7 (25.4 to 64.7)	-24.4 (-38.0 to -10.8)§
Influenza test positive	16	6	62.8 (5.0 to 85.4)	-6.4 (-12.2 to -0.5)§
<b>Mothers</b>				
Person-months	1076	1089		
Respiratory illness with fever				
Any fever	77	50	35.8 (3.7 to 57.2)	-14.2 (-25.5 to -2.9)§
Temperature >38°C	33	19	43.1 (-9.0 to 70.3)	-7.3 (-14.5 to -0.1)§
Diarrheal disease	60	49	19.3 (-24.6 to 47.8)	-5.9 (-16.4 to 4.5)
Clinic visit	25	19	24.9 (-43.9 to 60.8)	-3.2 (-9.8 to 3.4)

\* A total of 300 mothers were followed from 2 weeks after antenatal immunization to delivery, and 316 were followed from delivery until their infants were 24 weeks of age. For case definitions, see the Supplementary Appendix.

† Clinical effectiveness was calculated according to the formula  $(1 - \text{incidence rate ratio}) \times 100$ . The incidence rate ratio was calculated with the use of Poisson regression.

‡ The risk difference was calculated as the difference in the incidence of influenza per 100 subjects at 6 months among infants and mothers in the influenza-vaccine group, as compared with those in the control group, according to the formula  $([\text{episodes in influenza group/person/day}] \times 168 \times 100) - ([\text{episodes in control group/person/day}] \times 168 \times 100)$ .

§  $P < 0.05$ .

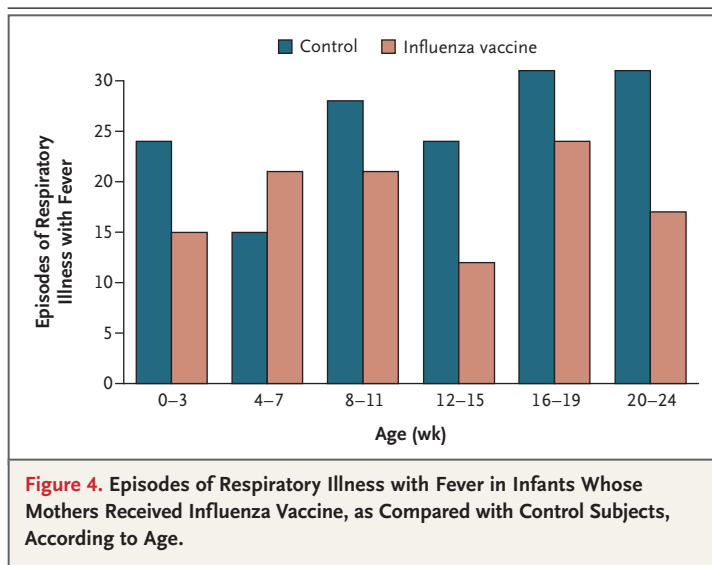
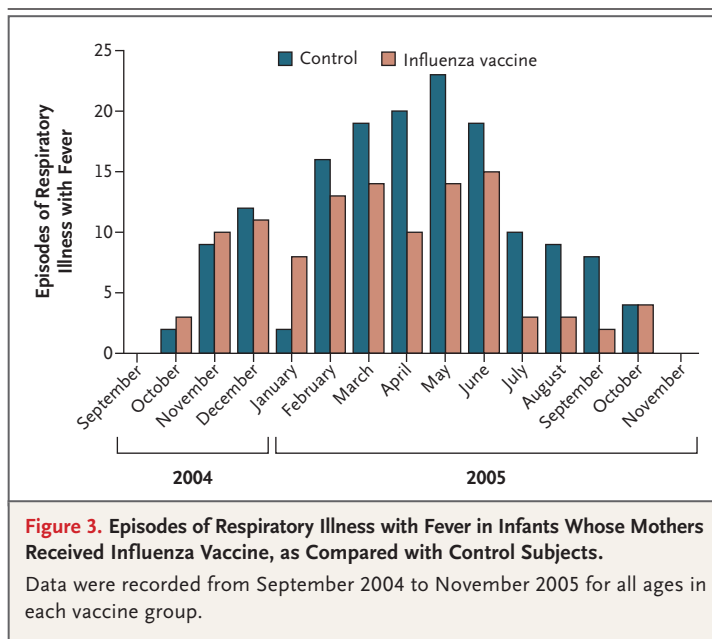
randomized, retrospective studies involving a review of patient records.<sup>34,35</sup>

The randomized and masked nature of the intervention, with the prospective weekly surveillance, allowed us to measure the clinical effects of influenza immunization in both mothers and infants with minimal bias, as evidenced by similar rates in study groups for reported diarrheal disease. The observed vaccine effect in the context of perennial circulation of a variety of influenza virus strains provides a generalizable estimate of the clinical effectiveness of the strategy of maternal immunization in this setting. These data also suggest that infants were protected from clinical illness up to the age of 5 to 6 months, somewhat longer than earlier estimates of passive protection.<sup>16,17</sup>

The rapid test that we used detects influenza neuraminidase and is reported to have a specificity of 80 to 90% and a sensitivity of 70 to 72% for

both type A and type B influenza.<sup>36,37</sup> These sensitivity data suggest that perhaps a quarter of true influenza cases were not detected. The test probably was performed in a similar fashion in the two study groups, so that the observed relative reduction or effectiveness would be unaffected, but the absolute incidence of influenza illness in study subjects was underestimated. An independent community surveillance for influenza illness, carried out in Dhaka by the International Centre for Diarrheal Disease Research and the Centers for Disease Control and Prevention during the same period as this study, corroborated the perennial local presence of influenza viruses during the study period and documented the variety of influenza virus strains in circulation.<sup>30</sup>

The study was randomized and controlled, but the analytic comparison was between groups who had received maternal influenza vaccine or another active noninfluenza vaccine, not between



active immunization and placebo. It is possible that in the control group, infants of mothers who received pneumococcal vaccine had a reduced incidence of pneumococcus-associated respiratory illness with fever and a reduced number of clinic visits.<sup>38,39</sup> Such a possibility would reduce the apparent effectiveness of maternal influenza vaccine. In addition, infants were randomly assigned to receive either haemophilus conjugate or pneumococcus conjugate vaccine (Fig. 1), which after several doses may have reduced cases of respira-

tory illness with fever and clinic visits during the fourth and fifth months of life.<sup>40</sup> However, the randomization of infants ensured that the clinical effect of the infant immunizations would have been similar in the two study groups, with minimal influence on the apparent effectiveness of maternal influenza vaccine. The post hoc interaction analysis was consistent with the lack of effect of infant noninfluenza immunization on influenza-associated illness. Overall, the assessment of these factors suggests that the effect of influenza vaccine we observed in this study underestimated the true effect of maternal influenza immunization.

Our study had several potential limitations. The project did not have resources for carrying out virologic studies, so we had no study data on the strains of influenza virus that were prevalent during the study period, though independent local data describing the variety of influenza viruses in Dhaka during the study period were reported previously.<sup>30</sup> Our study did not have statistical power to assess the infrequent outcomes of influenza, including hospitalization and severe illness. However, the substantial reduction of laboratory-proven influenza illness suggests that a proportion of infrequent serious outcomes of influenza infection would have been averted also. The influenza rapid diagnostic tests were received late and were in short supply, so we tested only some of the infants; this suggests that some episodes of laboratory-proven influenza were not detected in both mothers and infants. However, we did record in detail all illnesses each week throughout the entire project, providing a measure of illnesses that were prevented by the influenza vaccine.

The study surveillance continued for 15 months, representing a relatively brief assessment of the strategy of maternal immunization in this setting. Since a variety of influenza viruses circulated during at least 10 of those months, we suggest that the effectiveness data are representative for this Asian region and are probably generalizable elsewhere as a biologic effect of influenza immunization in pregnant women.

Our data show that a single dose of maternal influenza vaccine provides a considerable two-for-one benefit to both mothers and their young infants. The absolute reduction in the rate of illness showed that every 100 influenza immunizations in pregnancy prevented respiratory illness with fever of more than 38°C in 14 infants and

7 mothers. In other words, five pregnant women would need to be vaccinated to prevent a single case of respiratory illness with fever in a mother or infant.<sup>41</sup> These study data also indicate that influenza immunization of fewer than 16 mothers prevented one laboratory-proven influenza illness in the young infants.

In summary, the clinical effectiveness of influenza vaccine against both laboratory-proven influenza and several other respiratory illnesses shown in this randomized study is unique evidence supporting the strategy of maternal immunization to prevent influenza infection in young infants and their mothers. In a tropical setting of perennial transmission of influenza virus, maternal influenza immunization for much of the year had a substantial protective effect in both mothers and their young infants. In regions with limited financial resources, the strategy of maternal immunization is widely used for tetanus prevention, and antenatal-immunization systems are in place. Our study suggests that the antenatal-immunization strategy should be eval-

uated further for the prevention of influenza. Additional, larger studies will need to be carried out for several years with annual new formulations of influenza vaccine to show the full effect of the strategy of maternal influenza immunization in tropical and subtropical regions.

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**CORRECTION**

**Effectiveness of Maternal Influenza Immunization in Mothers and Infants**

Effectiveness of Maternal Influenza Immunization in Mothers and Infants . In the author list, Robert Breiman's middle initial should have been F., and in the affiliations, R.E.B. should have been R.F.B. The article has been corrected at NEJM.org.