# Efficacy of inactivated trivalent influenza vaccine in rural India: a 3-year cluster-randomised controlled trial

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## Summary

**Background** Paediatric vaccination against influenza can result in indirect protection, by reducing transmission to their unvaccinated contacts. We investigated whether influenza vaccination of children would protect them and their household members in a resource-limited setting.

**Methods** We did a cluster-randomised, blinded, controlled study in three villages in India. Clusters were defined as households (ie, dwellings that shared a courtyard), and children aged 6 months to 10 years were eligible for vaccination as and when they became age-eligible throughout the study. Households were randomly assigned (1:1) by a computer-based system to intramuscular trivalent inactivated influenza vaccine (IIV3) or a control of inactivated poliovirus vaccine (IPV) in the beginning of the study; vaccination occurred once a year for 3 years. The primary efficacy outcome was laboratory-confirmed influenza in a vaccinated child with febrile acute respiratory illness, analysed in the modified intention-to-treat population (ie, children who received at least one dose of vaccine, were under surveillance, and had not an influenza infection within 15 days of last vaccine dose). The secondary outcome for indirect effectiveness (surveillance study) was febrile acute respiratory illness in an unvaccinated household member of a vaccine study participant. Data from each year (year 1: November, 2009, to October, 2010; year 2: October, 2010, to October, 2011; and year 3: October, 2011, to May, 2012) were analysed separately. Safety was analysed among all participants who were vaccinated with at least one dose of the vaccine. This trial is registered with ClinicalTrials.gov, number NCT00934245.

**Findings** Between Nov 1, 2009, to May 1, 2012, we enrolled 3208 households, of which 1959 had vaccine-eligible children. 1010 households were assigned to IIV3 and 949 households were assigned to IPV. In 3 years, we vaccinated 4345 children (2132 with IIV3 and 2213 with IPV) from 1868 households (968 with IIV3 and 900 with IPV) with 10 813 unvaccinated household contacts. In year 1, influenza virus was detected in 151 (10%) of 1572 IIV3 recipients and 206 (13%) of 1633 of IPV recipients (total IIV3 vaccine efficacy 25·6% [95% CI 6·8–40·6]; p=0·010). In year 2, 105 (6%) of 1705 IIV3 recipients and 182 (10%) of 1814 IPV recipients had influenza (vaccine efficacy 41·0% [24·1–54·1]; p<0·0001). In year 3, 20 (1%) of 1670 IIV3 recipients and 81 (5%) of 1786 IPV recipients had influenza (vaccine efficacy 74·2% [57·8–84·3]; p<0·0001). In year 1, total vaccine efficacy against influenza A(H1N1)pdm09 was 14·5% (–20·4 to 39·3). In year 2, total vaccine efficacy against influenza A(H3N2) was 64·5% (48·5–75·5). Total vaccine efficacy against influenza B was 32·5% (11·3–48·6) in year 1, 4·9% (–38·9 to 34·9) in year 2, and 76·5% (59·4–86·4) in year 3. Indirect vaccine effectiveness was statistically significant only in year 3 (38·1% [7·4–58·6], p=0·0197) when influenza was detected in 39 (1%) of 4323 IIV3-allocated and 60 (1%) of 4121 IPV-allocated household unvaccinated individuals. In the IIV3 group, 225 (12%) of 1632 children in year 1, 375 (22%) of 1718 in year 2, and 209 (12%) of 1673 in year 3 had an adverse reaction (compared with 216 [13%] of 1730, 380 [21%] of 1825, and 235 [13%] of 1796, respectively, in the IPV group). The most common reactions in both groups were fever and tenderness at site. No vaccine-related deaths occurred in either group.

**Interpretation** IIV3 provided variable direct and indirect protection against influenza infection. Indirect protection was significant during the year of highest direct protection and should be considered when quantifying the effect of vaccination programmes.

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## Introduction

The global burden of illness due to influenza virus infection among children is substantial. In 2008, influenza was estimated to be associated with 20 million cases of paediatric acute lower respiratory infections, with 99% of paediatric influenza-associated deaths estimated to occur in developing countries.[1] WHO recommends influenza vaccination for children (aged 6–59 months) as a high-risk target group.[2] In India, influenza virus is an important cause of morbidity with an incidence of 6–48 hospital admissions per 10 000 person-years, varying by age group, year, and study site.[3,4] Children are also

## Research in context

### Evidence before this study

We searched PubMed, on Jan 7, 2007, for studies done in developing countries on influenza vaccine efficacy in children and indirect protection after influenza vaccination of children. We used the search terms "influenza vaccine", "child", and "developing country", for studies since database inception, for articles published in English.

We found no such studies. Subsequently a study of cold-adapted influenza vaccine, trivalent against culture-confirmed influenza in children showed efficacy during two consecutive influenza seasons at multiple sites in Asia. A randomised controlled trial of children aged 3–8 years in several low-resource countries administered a quadrivalent influenza vaccine (IIV4) containing both influenza B lineages. Efficacy for the IIV4 vaccinated cohort was 39%. Two studies of Russian-backbone live-attenuated influenza vaccine, from Senegal and Bangladesh, reported that vaccine efficacy for vaccine-matched strains was 58% in Bangladesh, whereas no efficacy was shown in Senegal.

Thus, information about influenza vaccine efficacy in developing countries is scarce. Similarly, although vaccination of children against influenza is thought to reduce influenza transmission to other susceptible individuals, resulting in indirect protection, studies to estimate indirect effects are very scarce. In one randomised controlled trial done among Hutterite communities in Canada, among non-vaccinated individuals, vaccine effectiveness was 61% against real-time RT-PCR-confirmed influenza infections.

### Added value of this study

We did a randomised controlled study in rural India over 3 years to measure total (direct and indirect) vaccine efficacy of IIV3 among children and indirect protection of household members of all ages. This trial is the first randomised control trial designed to investigate indirect effects at household-level in any setting. Influenza virus was detected by sensitive and specific molecular assays. Total protection varied by year and by type of influenza that was circulating. Indirect protection was shown in only 1 of the 3 years.

### Implications of all the available evidence

In a resource-limited country, IIV3 can prevent influenza virus infections among children and reduce infections among others in the households of the vaccinated children. Significant household-level indirect protection was observed during 1 year of high direct protection and should be considered as a potential effect of vaccination.

known sources of influenza to others and paediatric vaccination against influenza has been shown to reduce influenza transmission, resulting in indirect protection.[5,6]

Evidence of the benefits of influenza vaccination in children is often derived from observational data; randomised controlled trials using virological outcomes, as well as those exploring indirect protection, are uncommon.[7] Influenza vaccination uptake remains low and very few vaccine efficacy estimates are available from many developing countries,[8] where factors, such as untreated comorbidities or infections, malnutrition, and household crowding, might influence influenza transmission and modify vaccine efficacy.[9]

In this study, we aimed to measure total influenza vaccine efficacy against symptomatic laboratory-confirmed influenza-associated febrile acute respiratory illness (FARI) among vaccinated children (vaccination study; primary outcome), and its indirect protection among unvaccinated household members (surveillance study; secondary outcome), in rural India.

## Methods

### Study design

This study was a prospective, household-randomised, controlled trial, done in three villages in northern India (Dayalpur, Atali, and Chandawali). Clusters were defined as individual households—ie, dwellings (compounds) that shared a courtyard—situated within these villages. A cluster design was intentionally selected to measure household-level effects of vaccine. The protocol has been published.[10] The All India Institute of Medical Sciences (AIIMS) Ethics Committee and University of Alabama Birmingham Institutional Review Board reviewed and approved the study. An independent data safety and monitoring board (DSMB) assessed safety during annual meetings.

### Participants

All residents of three study villages in northern India were eligible to participate in surveillance for FARI. For the vaccination component of the study, only children aged between 6 months and 10 years were eligible. Exclusion criteria from the vaccine component of the study were known allergy to eggs, vaccine or vaccine component hypersensitivity, acute severe febrile illness (temporary exclusion), or any other condition that would impose a health risk. Written or oral informed consent was obtained for both surveillance and vaccine study participants; parental consent was obtained for children, and depending on their age, the child's assent was also requested. Families without vaccine-eligible children participated in the virological surveillance component of the study.[10]

### Randomisation and masking

Households were randomly assigned to either the trivalent influenza vaccine (IIV3; intervention) or inactivated poliovirus vaccine (IPV; control) group (1:1), via a computer-based randomisation program in STATA. Randomisation

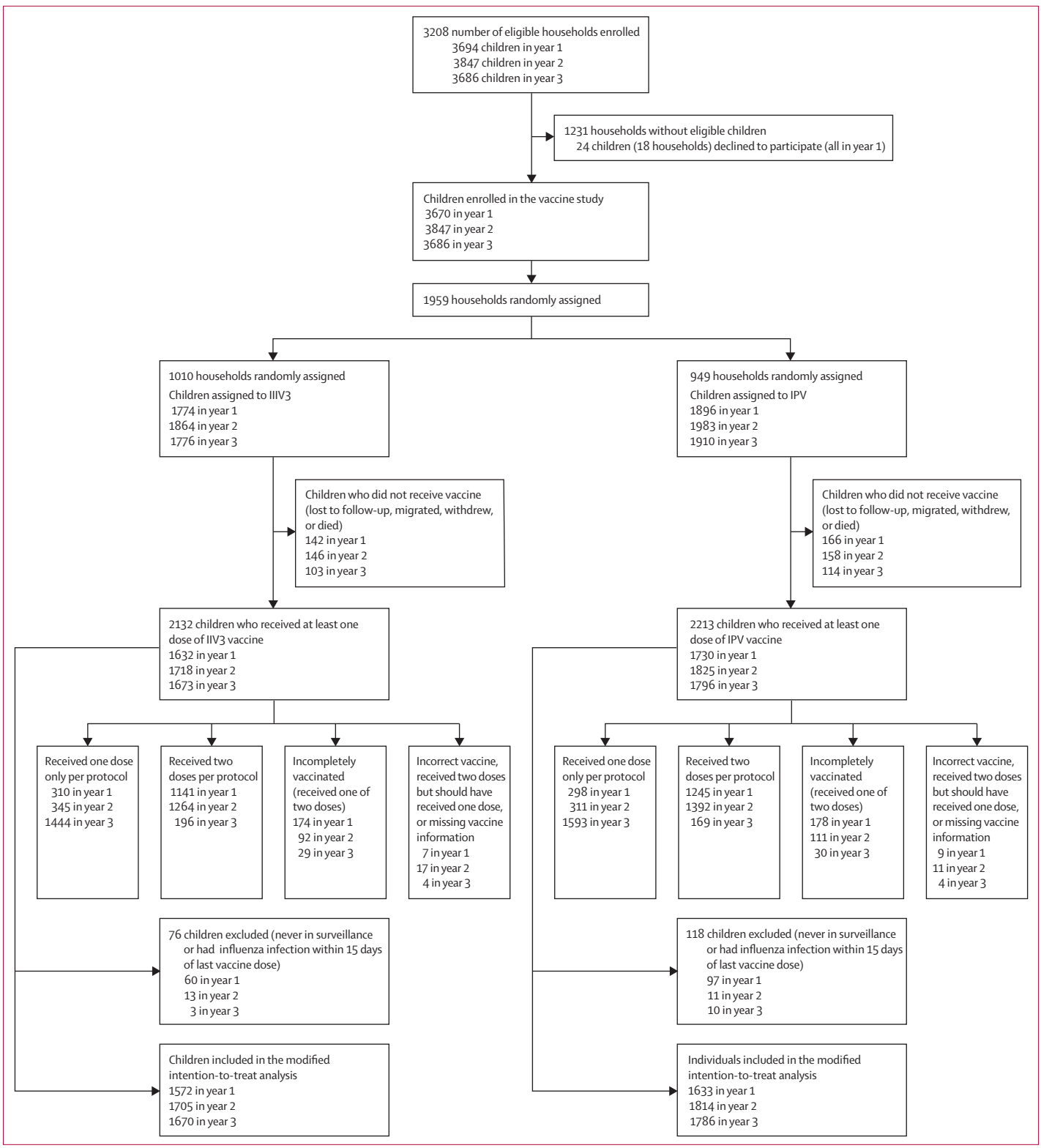


***Figure 1:*** **Trial profile**
Randomised childhood vaccination study analysing total protection.

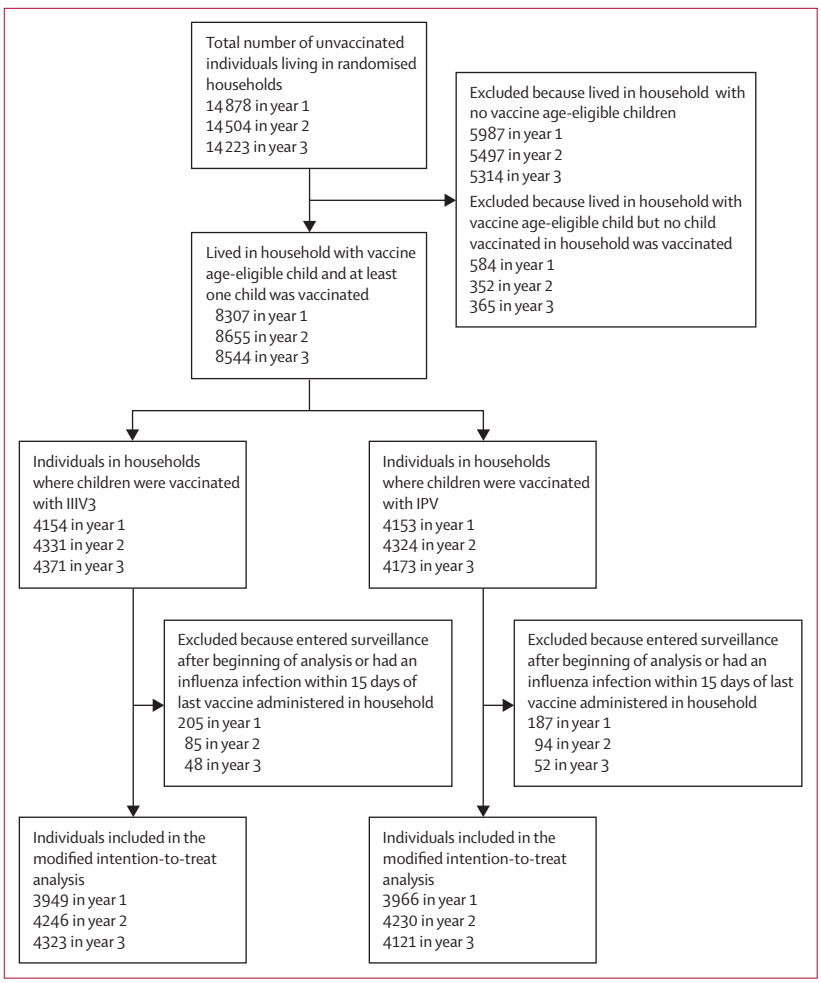


***Figure 2:*** **Trial profile**
Unvaccinated individuals in indirect protection analysis. Number of eligible households enrolled and randomly assigned to each group are shown in figure 1.

was done for all households in the villages irrespective of presence of children and before enrolment. This approach allowed families who might have had children after enrolment to be eligible for vaccination and inclusion. The allocation to IIV3 or IPV remained fixed throughout the entire study period. No stratification or restriction criteria were used. To reduce risk of unblinding, an AIIMS statistician developed multiple vaccine codes for each vaccine allocation. One vaccine code was assigned to each randomised vaccine-eligible child for each vaccination round. The vaccine codes represented either IPV or IIV3 and, therefore, were based on the household randomisation. Each child received vaccine and individual codes so that they could be correctly identified during immunisation. Lists containing vaccine codes and child identifiers were provided to a dedicated team responsible for the vaccination. The study statistician had no direct contact with either vaccination or surveillance teams and provided data to the DSMB in sealed envelopes for their review of adverse events. People delivering vaccination were hired solely for the vaccination campaign and were separate from the field assessment teams. Labels were applied by a pharmacist not involved in other aspects of the study that showed the vaccine code and obscured the underlying labels of the pre-filled vaccine syringes. All investigators, observers, laboratory staff, and participants were masked to the vaccine assignment.

## Procedures

At the time of study initiation, influenza virus circulation in India was poorly understood.[11] Furthermore, only influenza vaccines with a northern hemisphere formulation were available in India; therefore, we used northern hemisphere vaccine formulations for the study. Enrolled children were vaccinated in the following periods: year 1 (Nov 24, 2009, to Jan 17, 2010), year 2 (Oct 13, 2010, to Dec 13, 2010), and year 3 (Oct 7, 2011, to Dec 18, 2011). Children were re-vaccinated in years 2 and 3 if they remained in the eligible study age range. Intramuscular, northern hemisphere seasonal inactivated split-virion IIV3 (Vaxigrip Junior [0·25 mL dose, 7·5 µg of each haemagglutinin antigen for children aged 6–35 months] or Vaxigrip [0·5 mL dose, 15 µg of each haemagglutinin antigen for children aged 3–10 years]), and IPV (Imovax Polio, 0·5 mL dose for all children) were purchased from Sanofi Pasteur (India).[10] Two doses of the study vaccines were planned for year 1 (2009–10) and one dose in subsequent years for patients aged between 6 months and 8 years, and only one dose yearly for those aged 9–10 years. However, in response to the 2009 emergence of influenza A/California/7/2009 (H1N1pdm09) virus, two doses of vaccine (for both IIV3 and IPV groups) were administered to children between 6 months and 8 years of age in year 2 (2010), even if vaccinated in year 1.[11] In year 1 (2009–10), vaccine comprised influenza A/Brisbane/59/2007 (H1N1), A/Brisbane/10/2007 (H3N2), and B/Brisbane/60/2008 (Victoria lineage) strains, and in years 2 and 3, influenza A/California/7/2009 (H1N1pdm09), A/Perth/16/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage).[2]

Adverse events (both expected and unexpected), including serious events, were monitored and recorded. At time of vaccination, children were observed for immediate adverse events for 30 min and received follow-up visits by study staff at days 1, 7, and 30 after vaccination. Any reports of a child's admission to hospital or death during the entire study period were evaluated and assessed for a relationship with vaccination.

Year-round active surveillance for FARI was done via weekly household visits from November, 2009, until April, 2012.[11] Year 3 included only a partial year of surveillance (ended on May 1, 2012), because of the initiation of a second phase of this study with pre-monsoon (June) vaccination beginning in 2012.[11] FARI was defined as reported fever and any respiratory complaint (cough, sore throat, nasal congestion, runny nose, earache, or difficulty breathing) with onset in the

previous week; measurement of temperature was not required. An episode of FARI was considered a new event if 2 weeks had passed from the onset of a previous episode. Throat and nasal swabs were collected (nasal swabs alone in infants), from all participants with FARI, placed in transport medium, and maintained at 4°C for up to 24 h until transported to the laboratory.

Specimens were tested by real-time RT-PCR for influenza A and B viruses,[12] and, if positive, the subtype was determined with the same method. A subset of influenza B viruses were classified into Victoria and Yamagata lineages by real-time RT-PCR as previously described.[12] A third of the real-time RT-PCR-positive specimens were inoculated into Madin-Darby Canine Kidney cells for virus isolation; isolates were subtyped by use of WHO kits for haemagglutination inhibition and guinea pig red blood cells.[13]

In year 1 and 2, a subset of children aged 3–6 years were enrolled in a post-hoc analysis (ie, not included in the protocol, but decided before starting the study) immunogenicity study (appendix). The first 531 age-eligible children in the three villages whose parents consented to blood draw were selected to participate in this substudy and 1–2 mL of venous blood was collected before vaccination. Approximately half of the children provided a second blood sample 4 weeks after the first dose, and the other half 4 weeks after the second dose of the vaccine. Serum samples were tested for influenza antibodies by use of a haemagglutination inhibition assay with turkey red blood cells and vaccine-matched antigens following WHO protocols.[13] For influenza B virus, ether-treated antigen was used. Seroprotection was defined as a titre of 1:40 or more, seroconversion as a prevaccination titre of less than 1:10, and a post-vaccination titre of 1:40 or more; or a prevaccination titre of 1:10 or more and at least a 4-fold rise in post-vaccination antibody titre.[14]

## Outcomes

The primary outcome for total efficacy was laboratory-confirmed influenza in a vaccinated child with FARI. Total efficacy reflects both the direct protection provided by vaccination and an indirect effect from vaccination of other children in the household and community.[15] The secondary outcome for indirect effectiveness (surveillance study) was FARI with laboratory-confirmed influenza in an unvaccinated household member of a vaccine study participant.

## Statistical analysis

Three sets of data were linked through unique identifiers: electronic database with demographic information for residents, field data forms scanned into a database (TeleForm software, Hewlett Packard, Palo Alto, CA, USA), and laboratory data.[16] All data were uploaded to a study server in India. Data were maintained in SAS (version 9) for management and analyses.

| | IIV3 | IPV |
|---|---|---|
| Households (n) | 968 | 900 |
| Adults per household | 4 (2–6) | 4 (2–6) |
| Children per household | 3 (2–4) | 3 (2–4) |
| Total in household | 6 (5–9) | 6 (5–9) |
| Vaccinated children in household | 2 (1–2) | 2 (1–3) |
| Vaccinees (n) | 2132 | 2213 |
| Age, years | 5 (2–8) | 5 (1–8) |
| Sex | | |
| Female | 967 (45%) | 1005 (45%) |
| Male | 1165 (55%) | 1208 (55%) |
| Enrolled in school | | |
| Yes | 1109 (52%) | 1212 (55%) |
| No | 865 (41%) | 873 (39%) |
| Unknown | 158 (7%) | 128 (6%) |
| Non-vaccinees (n) | 5580 | 5233 |
| Median age, years | 27 (17–39) | 27 (16–38) |
| Age range, years | 0–94 | 0–94 |
| Age groups | | |
| <6 months* | 362 (6%) | 427 (8%) |
| 6 months to 10 years and not in vaccine cohort† | 155 (3%) | 191 (3%) |
| 11–17 years | 935 (17%) | 813 (15%) |
| 18–49 years | 3261 (58%) | 3014 (54%) |
| 50–64 years | 589 (11%) | 509 (9%) |
| ≥65 years | 278 (5%) | 279 (5%) |
| Sex | | |
| Female | 2761 (49%) | 2639 (50%) |
| Male | 2819 (51%) | 2594 (50%) |

Data are median (IQR) or n (%), unless otherwise specified. Number of households, vaccinees, and non-vaccinees are a sum of the participants per group during the 3 years of the study. All demographic data (including age) was calculated at the time of enrolment into the study. IIV3=trivalent inactivated influenza vaccine. IPV=inactivated poliovirus vaccine. *Includes children younger than 6 months at the time that vaccinations began and those who were born during the 3 years of the study. †Age-eligible children did not receive vaccine if they were temporarily absent during the vaccination campaign, were ill, were allergic to vaccine components, refused the vaccine, died, or had other unknown reasons.

***Table 1:*** **Demographic characteristics of vaccinees and non-vaccinees by vaccination group**

See Online for appendix

A modified intention-to-treat analysis was used to calculate total (direct and indirect) vaccine efficacy and indirect vaccine effectiveness.[15] A child was analysed as part of the IIV3 or IPV group according to the vaccine that the child first received in the study, irrespective of which vaccine they received later (eg, even in the cases of receiving the wrong vaccine through inadvertent protocol deviation or missed doses). Eligible children who did not receive any vaccine, those who were never in surveillance, and those who had an influenza infection within 15 days of last vaccine dose were not included in the analysis. Sample size estimations (assuming influenza attack rate of 5% per year in the control group, minimum detectable efficacy of 50%, minimum detectable indirect effectiveness of 25%, α of 0·05, and statistical power of 80%)[10] were 785 households

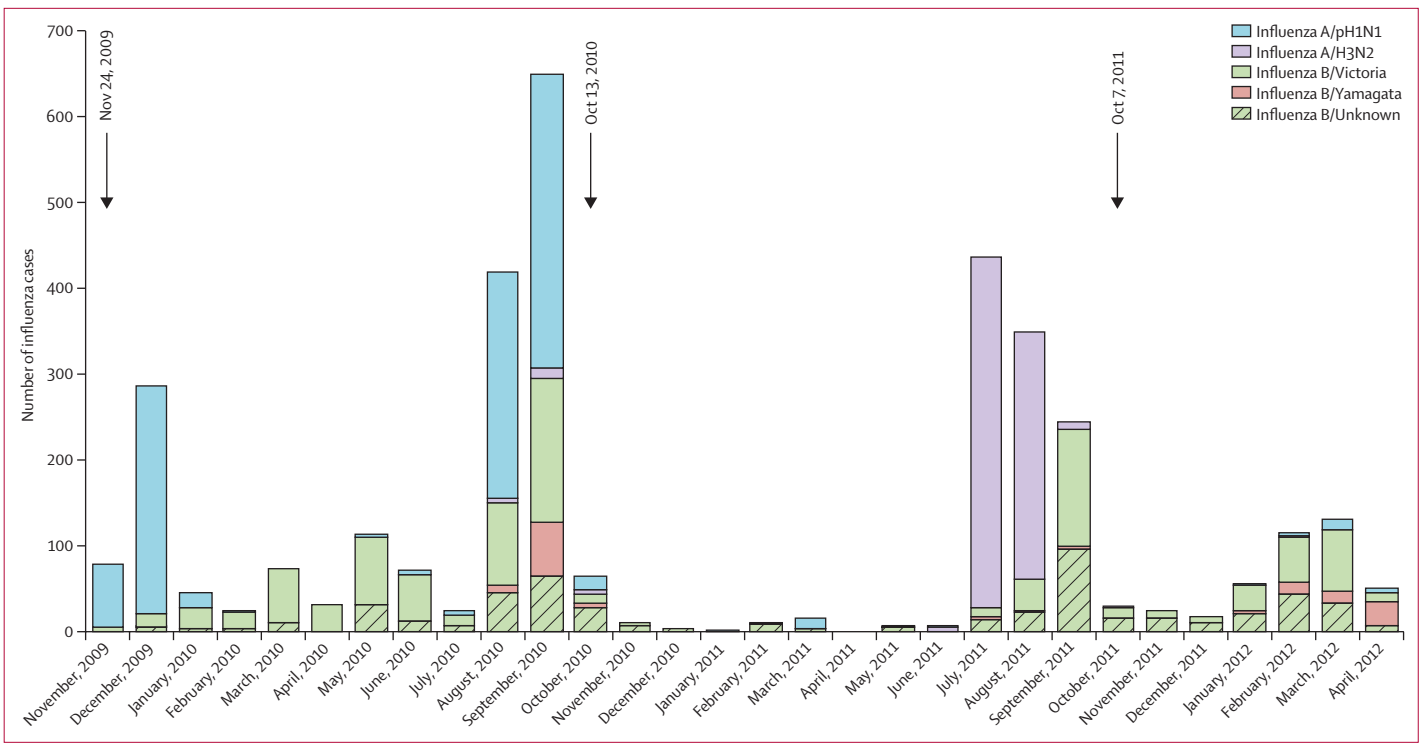


***Figure 3:*** **Number of laboratory-confirmed influenza cases by month and year, from November, 2009, to April, 2012, among vaccinated children and unvaccinated individuals**
Viruses were typed and subtyped by real-time RT-PCR and haemagglutination inhibition. Vertical arrows indicate start dates of vaccination each year. This analysis includes 15 158 participants (4345 vaccinated and 10 813 unvaccinated).

or 1570 individuals per group to assess total protection and 893 households or 4465 individuals for indirect protection. These estimates were based on a conservative assumption of an intracluster coefficient of variation of 0.25; with about two vaccine-eligible children per household, only a small proportion of households were expected to have more than one confirmed child case, with resulting low within-household correlation. Vaccine efficacy was estimated for each year separately using a Cox proportional hazards model accounting for random-effect clustering by household (frailty model).[17,18] The initial statistical analysis plan included a pooled multi-year estimate, as well as use of a Poisson model for vaccine efficacy estimation, but was changed per input from the US Centers for Disease Control and Prevention (CDC) statistician (PG; appendix). Both statistical analysis plan and results of the Poisson model are provided in the appendix.

Children were included in the analysis 15 days after receiving their last dose of vaccine that year, until the first of the following censoring events: infection with influenza virus (censored by any influenza infection for analysis of protection against any influenza infection, or by the specific virus type or subtype for analysis of virus type-specific and subtype-specific protection), last follow-up visit of that year, death, reaching 11 years of age, receiving a vaccination for the subsequent study year, or end of observation period. Vaccine efficacy estimates were stratified by predetermined subgroups: age group, sex, and time from vaccination (first and second halves of each annual surveillance period). Age was stratified into three groups: 6–35 months (two doses of 0·25 mL of IIV3), 36 months to 8 years (two doses of 0·5 mL of IIV3), and 9–10 years (one dose of 0·5 mL of IIV3). Indirect effectiveness was analysed similarly; unvaccinated individuals were included in the analysis if they belonged to a household in which at least one child received one or more doses of vaccine for a given study year. The analysis period for all unvaccinated individuals began 15 days after the last dose of vaccine was received among all vaccinated children in the household that year. No correction for multiple comparisons was made. The analysis code was written (in SAS Enterprise) and applied blindly first to all the data with no information on vaccine allocation to generate tables and examine balance between subgroups and categories. Then the code was applied to the unblinded data with no further modification to the code for exploratory analyses.

This trial is registered with ClinicalTrials.gov, number NCT00934245.

## Role of the funding source

The US CDC provided funding and participated in the study design, data analysis, data interpretation, and writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

| | Year 1 (2009–10) | | | | Year 2 (2010–11) | | | | Year 3 (2011–12) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n/N (%) | | Mean vaccine efficacy (95% CI) | p value | n/N (%) | | Mean vaccine efficacy (95% CI) | p value | n/N (%) | | Mean vaccine efficacy (95% CI) | p value |
| | IIV3 | IPV | | | IIV3 | IPV | | | IIV3 | IPV | | |
| Any influenza infection | 151/1572 (10%) | 206/1633 (13%) | 25·6% (6·8 to 40·6) | 0·010 | 105/1705 (6%) | 182/1814 (10%) | 41·0% (24·1 to 54·1) | <0·0001 | 20/1670 (1%) | 81/1786 (5%) | 74·2% (57·8 to 84·3) | <0·0001 |
| Sex | | | | | | | | | | | | |
| Female | 66/707 (9%) | 92/709 (13%) | 28·6% (1·0 to 48·5) | 0·043 | 47/767 (6%) | 79/821 (10%) | 39·0% (11·0 to 58·1) | 0·0104 | 12/782 (2%) | 35/816 (4%) | 64·6% (30·7 to 81·9) | 0·0024 |
| Male | 85/865 (10%) | 114/924 (12%) | 24·8% (–1·7 to 44·4) | 0·064 | 58/938 (6%) | 103/993 (10%) | 42·7% (19·2 to 59·4) | 0·0015 | 8/888 (1%) | 46/970 (5%) | 81·5% (60·3 to 91·3) | <0·0001 |
| Age group | | | | | | | | | | | | |
| 6–35 months | 44/367 (12%) | 52/374 (14%) | 13·0% (–31·6 to 42·5) | 0·51 | 39/410 (10%) | 65/427 (15%) | 39·3% (6·9 to 60·4) | 0·022 | 6/416 (1%) | 19/391 (5%) | 70·5% (24·2 to 88·5) | 0·011 |
| 36 months to 8 years | 82/897 (9%) | 119/969 (12%) | 27·3% (2·7 to 45·7) | 0·032 | 55/938 (6%) | 99/1068 (9%) | 40·1% (14·7 to 57·9) | 0·0045 | 10/897 (1%) | 47/1043 (5%) | 74·7% (48·9 to 87·5) | 0·0001 |
| 9–10 years | 25/308 (8%) | 35/290 (12%) | 35·7% (–8·5 to 61·9) | 0·098 | 11/357 (3%) | 18/319 (6%) | 46·2% (–13·9 to 74·6) | 0·11 | 4/357 (1%) | 15/352 (4%) | 74·1% (21·8 to 91·4) | 0·017 |
| Time after vaccination | | | | | | | | | | | | |
| 0–5 months | 19/1572 (1%) | 30/1633 (2%) | 36·1% (–14·9 to 64·5) | 0·13 | 4/1707 (<1%) | 3/1814 (<1%) | –41·9% (–534·0 to 68·2) | 0·65 | .. | .. | .. | .. |
| 6–11 months | 132/1545 (9%) | 176/1590 (11%) | 23·1% (1·6 to 39·9) | 0·037 | 101/1684 (6%) | 179/1803 (10%) | 42·1% (25·5 to 55·0) | <0·0001 | .. | .. | .. | .. |
| Influenza A (H1N1) pdm09 | 68/1580 (4%) | 81/1642 (5%) | 14·5% (–20·4 to 39·3) | 0·37 | .. | .. | .. | .. | .. | .. | .. | .. |
| Influenza A (H3N2) | .. | .. | .. | .. | 41/1706 (2%) | 124/1817 (7%) | 64·5% (48·5 to 75·5) | <0·0001 | .. | .. | .. | .. |
| Influenza B | 88/1608 (5%) | 137/1710 (8%) | 32·5% (11·3 to 48·6) | 0·0048 | 63/1705 (4%) | 68/1814 (5%) | 4·9% (–38·9 to 34·9) | 0·79 | 17/1670 (1%) | 80/1786 (4%) | 76·5% (59·4 to 86·4) | <0·0001 |

IIV3=trivalent inactivated influenza vaccine. IPV=inactivated poliovirus vaccine. *Efficacy calculation included all children who received at least one dose of vaccine, irrespective of whether they were assigned to receive one or two doses; exclusions listed in figure 1.

*Table 2:* **Total efficacy of any vaccination* with trivalent inactivated influenza vaccine for the prevention of laboratory-confirmed influenza**

## Results

From Sept 3, 2009, to May 1, 2012, a total of 3208 households were enrolled in the surveillance study, of which 1959 households had vaccine-eligible children. In year 1, 1680 households in the three villages had vaccine-eligible children, with 835 households allocated to IIV3 and 845 households allocated to IPV. Similarly, 1713 (859 IIV3 and 854 IPV) households had vaccine-eligible children in year 2 and 1686 (864 IIV3 and 822 IPV) in year 3 of the study. The number of children eligible for vaccination was similar in all years (figures 1, 2). At time of enrolment, children and household members in the IIV3 and IPV groups were similar in age, sex, household make-up, number of vaccinated children in the household, and school participation (table 1). Year-to-year comparison of vaccinated children and other household members in the IIV3 and IPV groups are provided in the appendix.

Influenza A(H1N1)pdm09 virus emerged during year 1, and was not a component of the 2009–10 vaccine administered that year (figure 3). Influenza A(H1N1) pdm09 virus did not occur substantially in years 2 or 3 (figure 3). Influenza A(H3N2) virus was observed primarily in year 2 and influenza B virus was detected throughout the 3 study years (figure 3). Of 493 identified influenza B virus strains among vaccine recipients, 337 (68%) were further characterised and, of these, 287 (85%) were B/Victoria-like (antigenically similar to vaccine strain), and the remainder were of Yamagata lineage. Distribution of influenza virus types was similar among those in the indirect protection group (data not shown).

In year 1, influenza virus was detected in 151 (10%) of 1572 IIV3 recipients and 206 (13%) of 1633 of IPV recipients, with a total vaccine efficacy of 25·6% (95% CI 6·8–40·6, p=0·010; table 2) against FARI due to any influenza virus. In year 2, influenza virus was detected in 105 (6%) of 1705 IIV3 recipients and 182 (10%) of 1814 IPV recipients; total vaccine efficacy was 41·0% (24·1–54·1; p<0·0001). In year 3, influenza virus was detected in 20 (1%) of 1670 IIV3 recipients and 81 (5%) of 1786 IPV recipients; total vaccine efficacy was 74·2% (57·8–84·3; p<0·0001). Poisson analysis provided similar results (appendix). In year 1, total vaccine efficacy against influenza A(H1N1)pdm09 virus was not statistically significant. In year 2, however, total vaccine efficacy against antigenically matched influenza A(H3N2) virus was statistically significant. Total vaccine efficacy against influenza B virus varied by year, despite an antigenic

| | Year 1 (2009–10) | | | | Year 2 (2010–11) | | | | Year 3 (2011–12) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n/N (%) | | Mean vaccine efficacy (95% CI) | p value | n/N (%) | | Mean vaccine efficacy (95% CI) | p value | n/N (%) | | Mean vaccine efficacy (95% CI) | p value |
| | IIV3 | IPV | | | IIV3 | IPV | | | IIV3 | IPV | | |
| Any influenza infection | 214/3949 (5%) | 218/3966 (5%) | 1·7% (–18·8 to 18·6) | 0·86 | 150/4246 (4%) | 175/4230 (4%) | 14·9% (–5·8 to 31·6) | 0·15 | 39/4323 (1%) | 60/4121 (1%) | 38·1% (7·4 to 58·6) | 0·020 |
| Sex | | | | | | | | | | | | |
| Female | 128/1959 (7%) | 136/2005 (7%) | 2·6% (–24·0 to 23·5) | 0·83 | 88/2106 (4%) | 99/2125 (5%) | 10·1% (–19·8 to 32·6) | 0·47 | 24/2118 (1%) | 41/2064 (2%) | 35·9% (–4·3 to 60·5) | 0·073 |
| Male | 86/1990 (4%) | 82/1961 (4%) | –1·7 (–37·6 to 24·9) | 0·91 | 62/2140 (3%) | 76/2105 (4%) | 20·5% (–11·2 to 43·2) | 0·18 | 12/2205 (1%) | 19/2057 (1%) | 41·2% (–21·2 to 71·4) | 0·15 |
| Age group | | | | | | | | | | | | |
| <6 months | 12/151 (8%) | 23/183 (13%) | 43·3% (–14·0 to 71·8) | 0·11 | 17/167 (10%) | 23/233 (10%) | 7·8% (–72·6 to 50·7) | 0·80 | 2/110 (2%) | 3/131 (2%) | 17·5% (–393·7 to 86·2) | 0·83 |
| 6 months to 10 years | 9/58 (16%) | 4/77 (5%) | –204·9% (–890·3 to 6·1) | 0·064 | 1/45 (2%) | 6/65 (9%) | 77·2% (–89·5 to 97·3) | 0·17 | 2/45 (4%) | 1/62 (2%) | –184·7% (–3040·0 to 74·2) | 0·39 |
| 11–17 years | 57/631 (9%) | 42/548 (8%) | –19·2% (–77·5 to 20·0) | 0·39 | 22/681 (3%) | 25/573 (4%4) | 25·6% (–31·9 to 58·1) | 0·31 | 16/642 (2%) | 14/606 (2%) | –8·3% (–121·8 to 47·2) | 0·83 |
| 18–49 years | 116/2448 (5%) | 120/2469 (5%) | 1·8% (–26·8 to 23·9) | 0·89 | 67/2612 (3%) | 90/2645 (3%) | 24·3% (–3·8 to 44·8) | 0·084 | 17/2736 (1%) | 31/2627 (1%) | 47·3% (4·8 to 70·8) | 0·034 |
| 50–64 years | 15/446 (3%) | 21/447 (5%) | 29·5% (–36·7 to 63·7) | 0·30 | 30/499 (6%) | 19/460 (4%) | –47·2% (–161·6 to 17·1) | 0·19 | 2/542 (<1%) | 7/454 (2%) | 76·2% (–14·7 to 95·0) | 0·074 |
| ≥65 years | 5/215 (2%) | 8/242 (3%) | 30·4% (–112·9 to 77·2) | 0·52 | 13/242 (5%) | 12/254 (5%) | –16·5% (–155·3 to 46·8) | 0·70 | 0/248 | 4/241 (2%) | NA | .. |
| Influenza A (H1N1) pdm09 | 113/3951 (3%) | 115/3970 (3%) | 1·4% (–27·8 to 24·0) | 0·91 | 5/4246 (<1%) | 0/4230 | NA | .. | 4/4323 (<1%) | 5/4121 (<1%) | 23·9% (–183·6 to 79·6) | 0·69 |
| Influenza A (H3N2) | 5/3975 (<1%) | 2/4001 (<1%) | –151·2% (–1194·6 to 51·3) | 0·27 | 118/4246 (3%) | 128/4230 (3) | 8·4% (–17·6 to 28·7) | 0·49 | 0/4323 | 0/4121 | NA | .. |
| Influenza B | 104/3973 (3%) | 112/3997 (3%) | 6·7% (–21·9 to 28·6) | 0·61 | 31/4246 (1%) | 48/4230 (1%) | 36·2% (–0·23 to 59·4) | 0·051 | 35/4323 (<1%) | 55/4121 (1%) | 39·4% (7·4 to 60·3) | 0·021 |

IIV3=trivalent inactivated influenza vaccine. IPV=inactivated poliovirus vaccine. NA=not applicable (ie, not possible to calculate vaccine efficacy in our model if one trial group has zero cases).

***Table 3:*** **Indirect effectiveness of vaccination with trivalent inactivated influenza vaccine for the prevention of laboratory-confirmed influenza**

match of the predominant B/Victoria lineage with the vaccine in all 3 years.

Total vaccine efficacy was similar between boys and girls. Among age groups, total vaccine efficacy was statistically significant for patients aged between 36 months and 8 years for the 3 years of the study; vaccine efficacy was also significant for children aged 6–35 months during years 2 and 3, and for those aged 9–10 years for year 3 (table 2). In year 1, total vaccine efficacy for all vaccinees was not statistically significant for the period up to 5 months after vaccination (table 2) when influenza A(H1N1)pdm09 virus was circulating, whereas for the period 6–11 months after vaccination, during which influenza B was circulating, total vaccine efficacy was statistically significant (table 2). Total vaccine efficacy stratified by time after vaccination could not be estimated in year 2 because too few infections occurred in year 3 since the observation period was truncated in April, 2012 (table 2).

Overall, indirect vaccine effectiveness was statistically significant only in year 3, with influenza virus detected in 39 (1%) of 4323 household members in the IIV3 group and 60 (1%) of 4121 household members in the IPV group. This indirect effect in year 3 was also significant for influenza B virus. The indirect vaccine effectiveness in year 2 for influenza B virus was similar to the efficacy in year 3, although the the 95% CIs narrowly crossed zero (36·2% [95% CI –0·2 to 59·4]; table 3). In years 1 and 2, no statistically significant indirect vaccine effectiveness was observed in any age group. In year 3, among household members aged 18–49 years, influenza virus was detected in 17 (1%) of 2736 in the IIV3 group and 31 (1%) of 2627 in the IPV group for an indirect vaccine effectiveness of 47·3% (95% CI 4·8–70·8; table 3). Indirect vaccine effectiveness was not observed when analysed by sex in any study year (table 3).

Safety was analysed among all participants who received with at least one dose of the vaccine. Local and systemic reactions were uncommon and similar between the IIV3 and IPV groups (table 4). In the IIV3 group, 225 (14%) of 1632 children in year 1, 375 (22%) of 1718 in year 2, and 209 (12%) of 1673 in year 3 had an adverse reaction (compared with 216 [12%] of 1730, 380 [21%] of 1825, and 235 [13%] of 1796, respectively, in the IPV group). The most common reactions in both groups were fever and tenderness at site. No serious adverse events were reported. Over the study, eight deaths occurred in the IIV3 cohort and seven in the IPV group; vaccine

efficacy against any influenza virus infection did not change when these deaths were excluded from the analysis (data not shown).

In year 1, few children in the IIV3 and IPV groups had seroprotective antibody titres against seasonal influenza A(H1N1; appendix) and influenza B viruses before vaccination, but more than half had seroprotective titres against influenza A(H3N2) virus before vaccination (appendix). After two doses of vaccine in year 1, 82·9% (95% CI 66·3–93·4) of children in the IIV3 group showed seroprotective titres against the three influenza vaccine viruses. In year 2, 93·3% (85·9–97·5) of the children in the IIV3 group had titres of 1:40 or more after two doses of vaccine.

## Discussion

This randomised controlled study among children in rural India showed a significant total (direct and indirect) vaccine efficacy of IIV3 against influenza-associated FARI, although with year-to-year variability. We also found significant indirect protection in year 3, the year when the vaccine-matched influenza B (Victoria lineage) predominated and when the vaccine efficacy among vaccinees was highest. Immunogenicity of influenza vaccination was also shown in this population. Despite these significant findings, total vaccine efficacy varied substantially between years, even when vaccine was well matched (eg, vaccine efficacy against influenza B in year 2). One possible factor was the timing of vaccination in concordance with temperate northern hemisphere influenza seasonality, which is now known to be suboptimal for most regions in India.[11] This variability in total and indirect protection from year to year emphasises the importance of multiple year studies in assessing the true effect of influenza vaccines and informing public health policy in India.

The effectiveness of inactivated influenza vaccines in children has been shown to vary by year and study, hence direct comparisons of vaccine efficacy are challenging, particularly between countries with different seasonality. This variability is driven by many factors, including vaccination timing, how well matched the vaccine is to circulating viruses, and the age and underlying health status of the study population.[19] A review[7] published in 2011 reported only one randomised controlled trial of IIV3 in children as young as 6 months that used specific and sensitive tests for influenza virus. In this US study, IIV3 efficacy against acute otitis media was 66% in the first year; in the second year attack rates were very low and efficacy was difficult to evaluate.[20] A more recent randomised controlled trial was done with children aged between 6 months and 72 months, in which one group received IIV3 alone. Efficacy against all strains was 43% and against vaccine-matched strains was 45%; our results (range 25·66–74·2%) are similar.[21] Similarly, a randomised controlled trial[22] of children aged 3–8 years in several low-resourced countries showed a vaccine efficacy of 59% from a quadrivalent influenza vaccine (IIV4) containing both influenza B virus lineages compared with a control vaccine. A study[23] of trivalent cold-adapted influenza vaccine against culture-confirmed influenza in children showed efficacy during two consecutive influenza seasons at multiple sites in Asia (70% in year 1 and 64% in year 2, against any influenza strains). Two studies[24,25] of Russian-backbone live attenuated influenza vaccine, from Senegal and Bangladesh, reported that vaccine efficacy for vaccine-matched strains was 58% in Bangladesh, whereas no efficacy was shown in Senegal.

Vaccination of school children during an influenza outbreak has been shown to reduce illness in families compared with communities in which schoolchildren were not vaccinated.[5,26] In Japan, an ecological study suggested that all-age mortality due to pneumonia and influenza was reduced when mandatory influenza vaccination of school children was introduced and increased after vaccination was made optional.[27]

| | Year 1 | | Year 2 | | Year 3 | |
|---|---|---|---|---|---|---|
| | IPV (n=1730) | IIV3 (n=1632) | IPV (n=1825) | IIV3 (n=1718) | IPV (n=1796) | IIV3 (n=1673) |
| Any reactions | 216 (13%) | 225 (14%) | 380 (21%) | 375 (22%) | 235 (13%) | 209 (12%) |
| Redness | 3 (<1%) | 3 (<1%) | 14 (1%) | 14 (1%) | 3 (<1%) | 1 (<1%) |
| Swelling | 13 (1%) | 21 (1%) | 48 (3%) | 71 (4%) | 11 (1%) | 16 (1%) |
| Tenderness at injection site | 72 (4%) | 77 (5%) | 229 (13%) | 236 (14%) | 145 (8%) | 118 (7%) |
| Vomiting | 8 (<1%) | 17 (1%) | 14 (1%) | 18 (1%) | 11 (1%) | 9 (1%) |
| Diarrhoea | 15 (1%) | 18 (1%) | 22 (1%) | 14 (1%) | 15 (1%) | 9 (1%) |
| Headache | 4 (<1%) | 11 (1%) | 3 (<1%) | 7 (<1%) | 0 | 1 (<1%) |
| Body ache | 3 (<1%) | 14 (1%) | 3 (<1%) | 7 (<1%) | 0 | 2 (<1%) |
| Fever | 113 (7%) | 122 (7%) | 161 (9%) | 154 (9%) | 93 (5%) | 99 (6%) |
| Irritability | 11 (1%) | 8 (<1%) | 9 (<1%) | 6 (<1%) | 2 (<1%) | 0 |
| Lethargy | 3 (<1%) | 4 (<1%) | 8 (<1%) | 12 (1%) | 2 (<1%) | 0 |
| Decreased feeding | 3 (<1%) | 2 (<1%) | 7 (<1%) | 9 (1%) | 1 (<1%) | 0 |
| Abnormal cry | 5 (<1%) | 3 (<1%) | 1 (<1%) | 5 (<1%) | 1 (<1%) | 1 (<1%) |
| Any serious adverse events | 0 | 0 | 0 | 0 | 0 | 0 |
| Any grade 2 or 3 reactions | 123 (7%) | 124 (8%) | 192 (11%) | 181 (11%) | 104 (6%) | 104 (6%) |
| Any grade 3 reactions | 64 (4%)* | 51 (3%)† | 65 (4%)‡ | 42 (2%)§ | 32 (2%)¶ | 40 (2%)‖ |
| Deaths** | 4 (<1%) | 5 (<1%) | 2 (<1%) | 3 (<1%) | 1 (<1%) | 0 |

Data are n (%). IPV=inactivated poliovirus vaccine. IIV3=trivalent inactivated influenza vaccine. *69 grade 3 reactions among 64 children: fever (n=47), tenderness at injection site (n=8), abnormal cry (n=5), vomiting (n=4), diarrhoea (n=3), headache (n=1), and irritability (n=1). †64 grade 3 reactions among 51 children: fever (n=35), body ache (n=5), vomiting (n=5), diarrhoea (n=5), tenderness at injection site (n=4), swelling (n=3), abnormal cry (n=3), headache (n=3), and irritability (n=1). ‡70 grade 3 reactions among 65 children: fever (n=37), tenderness at injection site (n=23), vomiting (n=3), diarrhoea (n=2), headache (n=1), body ache (n=1), irritability (n=1), decreased feeding (n=1), and abnormal cry (n=1). §47 grade 3 reactions among 42 children: fever (n=19), tenderness at injection site (n=18), abnormal cry (n=5), vomiting (n=2), diarrhoea (n=1), headache (n=), body ache (n=1), and decreased feeding (n=1). ¶34 grade 3 reactions among 32 children: fever (n=16), tenderness at injection site (n=11), vomiting (n=3), diarrhoea (n=3), and abnormal cry (n=1). ‖46 grade 3 reactions among 40 children: fever (n=24), tenderness at injection site (n=14), vomiting (n=3), diarrhoea (n=3), swelling (n=1), and abnormal cry (n=1). **No deaths were vaccine-related.

***Table 4:*** **Local and systemic adverse events following any dose of trivalent inactivated influenza vaccine or inactivated polio vaccine**

Community-level protection (indirect effectiveness 61%) was shown in a cluster-randomised trial[6] of IIV3 among children aged 36 months to 15 years in Hutterite communities in Canada, when using real-time RT-PCR for influenza virus detection. In our study, total protection in year 3, measured for only half a year, was roughly double that seen for indirect vaccine effectiveness (total 74·2% *vs* indirect 38·1%). This result might suggest a threshold level of protection was needed to show indirect effects, but in year 2, total vaccine efficacy for influenza A(H3N2) virus was 64·5% and no indirect vaccine effectiveness was observed. However, variability in factors affecting indirect vaccine effectiveness, such as social mixing patterns, makes comparison of these estimates across studies challenging. Randomisation at the community level would lead to an estimate of the maximal indirect vaccine effectiveness because the immediately surrounding population would be vaccinated (or unvaccinated). We deliberately randomised by household because we believed that, in a vaccination programme, vaccinated individuals would tend to cluster in households because of a care-giver decision to vaccinate; however, this approach probably leads to a lower indirect vaccine effectiveness estimate than if a whole community was vaccinated because of opportunities for exposure to influenza-infected individuals from nearby households in which children were not vaccinated against influenza.[6]

A subset of children were tested for antibodies to influenza A(H1N1), influenza A(H3N2), and influenza B. Among the IIV3 recipients, a large majority seroconverted and developed seroprotective antibody titres with rises in geometric mean titres. Seroprotection was defined as haemagglutination titres of 1:40 or more, which, in adults, corresponds to a 50% reduction the risk of influenza virus infection. This standard definition might be too low to be an accurate correlate of protection for children.[14,19,28] Our subset of children tested for immunogenicity was too small to analyse correlates of protection.

Our study has several limitations. In year 1, vaccination took place during the winter, when influenza A(H1N1) pdm09 virus was already emerging as the predominant strain, and was not included in the study vaccine. Neither protection nor increased risk of influenza A(H1N1)pdm09 infection was seen among vaccinees. Because influenza seasonality in India was not well understood at the time, vaccination occurred 8–9 months before peak influenza circulation throughout the study, which probably affected vaccine efficacy. In year 3, we were not able to analyse the possibility of declining protection over time from vaccination because the follow-up period stopped by May 1, 2012, with the start of a study of pre-monsoon influenza vaccination. The lower number of events in year 3 than years 1 and 2, therefore, might have led to a lack of power to detect efficacy. Timing of influenza virus circulation might also be a factor in the poor total efficacy against an antigenically matched influenza B virus in year 2, which is otherwise difficult to explain. However, the indirect effects appeared quite high (although were not statistically significant) against influenza B virus that year. Since influenza B virus circulation occurred primarily at the end of the study year, children might have had waning of immunity.[29] However, reduced protection for longer than 5 months after vaccination was not observed in year 1 for influenza B or in year 2 for influenza A(H3N2) viruses.

Vaccines are the primary tools in the prevention of influenza virus infection in young children. In a rural setting in India, we showed immunogenicity of IIV3, and moderate total and indirect vaccine effectiveness, which varied by study year, virus type, and virus subtype. Prevention of influenza virus infection in India and similar tropical climates requires innovative approaches and recognition that optimal timing of vaccination differs from temperate parts of the world, and might also differ within the country by locality because of differences in climate and virus seasonality within a country.[19] These data together with cost-effectiveness and burden estimates of influenza can inform policy in India, especially regarding the existing WHO recommendations for influenza vaccination of young children. However, further studies are required to better understand variability in vaccine efficacy in tropical settings and to inform global and national policy for influenza vaccination, particularly in children.

#### Contributors

WMS, KBF, VG, AK, KEL, RL, M-AW, and SB contributed to the study design. WMS, KBF, VG, AK, KEL, RL, M-AW, and SB discussed, critically revised, and approved the final study protocol. VG, AK, DRP, SS, and SB were responsible for organisation and conduct of the field trial. KBF managed the study data. SB led the laboratory testing and analysis of laboratory results, with assistance from RSVLN and RL. FSP was responsible for the data analysis, with input from WMS, KBF, VG, AK, KEL, SS, PG, SJ, RL, M-AW, and SB. WMS, KBF, VG, AK, KEL, SS, SJ, M-AW, and SB contributed for the manuscript writing. Editorial review was provided by the US Centers for Disease Control and Prevention (CDC). All authors discussed, critically revised, and approved the final version of the report for publication.

#### Declaration of interests

WMS, KBF, VG, AK, DRP, RSVLN, and SB report a grant from the US CDC during the conduct of the study. All other authors declare no competing interests.

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