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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Sullender WM, Fowler KB, Gupta V, et al. Efficacy of inactivated trivalent influenza vaccine in rural India: a 3-year cluster-randomised controlled trial. *Lancet Glob Health* 2019; **7:** e940–50.

Table S1. Demographic characteristics of vaccinees and non-vaccinees by vaccination group and year.

	Year 1		Year 2		Year 3	
Study Group	**IIV3***	**IPV†**	**IIV3**	**IPV**	**IIV3**	**IPV**
Households (n)	794	795	831	822	832	789
Vaccinees (n of individuals)	1572	1633	1705	1814	1670	1786
Household makeup, (Mean±standard deviation)						
Adults	4.4 ± 2.5‡	4.4 ± 2.5	4.6 ± 2.6	4.7 ± 2.6	4.9 ± 2.7	4.9 ± 2.8
Children	3.6 ± 1.7	3.6 ± 1.8	3.6 ± 1.8	3.7 ± 1.8	3.6 ± 1.8	3.9 ± 1.9
Total in household	8.0 ± 3.7	8.0 ± 3.7	8.2 ± 3.8	8.4 ± 3.9	8.5 ± 3.9	8.8 ± 4.1
Vaccinated children in household	2.7 ± 1.3	2.7 ± 1.3	2.7 ± 1.4	2.8 ± 1.4	2.7 ± 1.5	2.9 ± 1.5
Age in years of vaccinees (Mean±standard deviation)	5.7 ± 3.0	5.7 ± 2.9	5.8 ± 3.1	5.7 ± 3.0	5.7 ± 3.1	5.9 ± 3.0
Sex (n,%)						
Female	707 (45)§	709 (43)	767 (45)	821 (45)	782 (47)	816 (46)
Male	865 (55)	924 (57)	938 (55)	993 (55)	888 (53)	970 (54)
Enrolled in school (n,%)						
Yes	975 (62)	1028 (63)	1165 (68)	1289 (71)	1094 (66)	1157 (65)
No	520 (33)	536 (33)	333 (20)	367 (20)	480 (29)	470 (26)
Unknown	77 (5)	69 (4)	207 (12)	158 (9)	96 (6)	159 (9)
Weeks in surveillance after vaccination (Mean±standard deviation)	38.7 ± 5.4	38.8 ± 4.5	46.8 ± 4.3	46.9 ± 3.6	21.3 ± 1.2	21.2 ± 1.3
Non-vaccinees						
Households (n)	794	795	831	822	832	789
Non-vaccinees (n of individuals)	4154	4153	4331	4324	4371	4173
Adults	4.2±2.3‡	4.2±2.4	4.1±2.2	4.2±2.4	4.3±2.3	4.3±2.4
Children	3.1±1.6	3.2±1.5	3.1±1.6	3.3±1.6	3.0±1.6	3.3±1.6
Total in household	7.3±3.3	7.4±3.3	7.3±3.2	7.5±3.4	7.3±3.2	7.6±3.4
Vaccinated children in household	2.0±1.1	2.2±1.1	2.1±1.2	2.2±1.2	2.0±1.2	2.3±1.2
Individual-Level Characteristics of non-vaccinees						

Age years, (Mean±standard deviation)	32±18	32±18	32±18	32±18	33±17	32±17
Age years median, range	29, 0-94	29, 0-94	30, 0-95	30, 0-95	30, 0-96	30, 0-96
Age groups (n)						
<6 mo[¶]	155	185	162	226	111	132
6 mo - 10 y and not in vaccine cohort	80	105	66	84	53	70
11 - 17 years	670	575	689	587	645	610
18 - 49 years	2564	2578	2660	2693	2759	2654
50 - 64 years	459	460	504	473	547	462
≥ 65 years	226	250	250	261	256	245
Sex (n,%)						
Female	2062 (50)[¶]	2103 (51)	2147 (50)	2171 (50)	2140 (49)	2091 (50)
Male	2092 (50)	2050 (49)	2184 (50)	2153 (50)	2231 (51)	2082 (50)
Weeks in surveillance (Mean±standard deviation)	39.8±10.1	39.7±9.9	48.7±8.8	48.4±9.2	24.8±3.2	24.8±3.2

Includes households where at least one child received one or more doses of vaccine.
*IIV3, trivalent inactivated influenza vaccine
[†]IPV, inactivated poliovirus vaccine
[‡]Plus-minus values are means ± SD
[§] Numbers followed by a parenthesis are n (%).
[¶]Includes under 6 months of age at time vaccinations began plus those who were born during observation period

Table S2. Sensitivity Analysis for total efficacy of vaccination with trivalent inactivated influenza vaccine for the prevention of laboratory-confirmed influenza, using Poisson model of household-level incidence rate ratio (IRR) between intervention groups.

	Efficacy	95% Confidence Interval	p-value
Any influenza infection			
Year 1 (2009-2010)	27.7	10.9 -- 41.4	0.0024
Year 2 (2010-2011)	44.8	26.6 -- 58.5	<0.0001
Year 3 (2011-2012)	76.9	59.6 -- 86.8	<0.0001
All study years	45.1	35.2 -- 53.5	<0.0001

Table S3. Hemagglutination inhibition antibody responses of children vaccinated with IIV3 and IPV in years 1 and 2 of study.

	Year 1 (2009-2010)			Year 2 (2010)		
Virus	**Pre Vaccine**	**After dose 1**	**After dose 2**	**Pre Vaccine**	**After dose 1**	**After dose 2**
A/H1N1*	**Seroprotected No./No. tested (%; 95% CI)**			**Seroprotected No./ No. tested (%; 95% CI)**		
IIV3	16/76 (21.0; 12.5 -31.9)	30/41†‡ (73.2; 57.1, 85.8)	29/35†‡ (82.9; 66.3, 93.4)	94/176 (53.4; 45.7, 60.9)	57/87§¶ (65.5; 54.6, 75.4)	83/89 (93.3; 85.9, 97.5)
IPV	11/84 (13.1; 6.7, 22.2)	12/50 (24.0; 13.1, 38.2)	4/34 (11.8; 3.3, 27.4)	113/195 (57.9; 50.7, 65.0)	62/107§ (57.9; 48.0, 67.4)	45/88 (51.1; 40.2, 61.9)
	Seroconversion No./No. tested (%, 95% CI)			**Seroconversion No./No. tested (%, 95% CI)**		
IIV3		30/41† (73.2; 57.1, 85.8)	29/35 (82.9; 66.3, 93.4)		54/87 (62.1; 51.0, 72.3)	80/89 (89.9; 81.9, 95.3)
IPV		1/50 (2.0; 0.05, 10.6)	0/34 (0.0; 0.0, 10.3)		1/107 (0.9; 0.02, 5.1)	2/89 (2.3; 0.3, 8.0)
	Geometric mean titer (95% CI)			**Geometric mean titer (95% CI)**		
IIV3	1:15 (1:13, 1:17)	1:192†‡ (1:104, 1:352)	1:149 (1:85, 1:261)	1:39 (1:32, 1:49)	1:187¶ (1:118, 1:297)	1:367 (1:270, 1:499)
IPV	1:14 (1:12, 1:16)	1:15 (1:12, 1:18)	1:11 (1:6, 1:21)	1:42 (1:34, 1:51)	1:43 (1:33, 1:57)	1:37 (1:28, 1:50)

A/H3N2 **	**Pre Vaccine**	**Dose 1**	**Dose 2**	**Pre Vaccine**	**Dose 1**	**Dose 2**
	Seroprotected No./No. tested (%, 95% CI)			**Seroprotected No./No. tested (%, 95% CI)**		
IIV3	50/76 (65.8; 54.0, 76.3)	38/41‡, ‡‡ (92.7; 80.1, 98.5)	31/35 (88.6; 73.3, 96.8)	147/176 (83.5; 77.2, 88.7)	86/87††, ¶ (98.9; 93.8 , 100)	89/89 (100; 95.9,100)
IPV	45/84 (53.6; 42.3, 64.5)	25/50‡‡ (50.0; 42.3, 64.5)	19/34 (55.9; 37.9, 72.8)	113/195 (57.9; 50.7, 65.0)	55/107†† (51.4; 41.5, 61.2)	55/88 (62.5; 51.5, 72.6)
	Seroconversion No./No. tested (%, 95% CI)			**Seroconversion No./No. tested (%, 95% CI)**		
IIV3		33/41 (80.5; 65.1, 91.2)	27/35 (77.1; 59.9, 89.6)		74/87 (85.1; 75.8, 91.8)	73/89 (82.0; 72.4, 89.4)
IPV		2/50 (4.0; 0.5, 13.7)	0/34 (0.0; 0.0, 10.3)		1/107 (0.9; 0.02, 5.1)	1/88 (1.1; 0.03, 6.2)
	Geometric mean titer			**Geometric mean titer**		

		(95% CI)			**(95% CI)**	
IIV3	1:43 (1:33, 1:56)	1:288‡ (1:195, 1:426)	1:242 (1:147, 1:397)	1:109 (1:90, 1:132)	1:799¶ (1:660, 1:968)	1:620 (1:534, 1:720)
IPV	1:36 (1:27, 1:48)	1:34 (1:23, 1:49)	1:38 (1:25, 1:59)	1:42 (1:35, 1:51)	1:39 (1:30, 1:50)	1:42 (1:33, 55)

B§§	**Pre Vaccine**	**Dose 1**	**Dose 2**	**Pre Vaccine**	**Dose 1**	**Dose 2**
		Seroprotected No./No. tested (%, 95% CI)			**Seroprotected No./No. tested (%, 95% CI)**	
IIV3	11/76 (14.5; 7.4, 24.4)	24/41‡ (58.5; 42.1, 73.7)	30/35 (85.7; 69.7, 95.2)	136/176 (77.3; 70.4, 83.2)	86/87¶ (98.9; 93.8, 100)	89/89 (100; 95.9, 100)
IPV	10/84 (11.9; 5.9, 20.8)	5/50 (10.0; 3.3, 21.8)	7/34 (20.6; 8.7, 37.9)	83/195 (42.6; 35.5, 49.8)	47/107¶¶ (43.9; 34.3, 53.8)	36/88§§ (40.9; 30.5, 51.9)
		Seroconversion No./No. tested (%, 95% CI)			**Seroconversion No./No. tested (%, 95% CI)**	
IIV3		24/41 (58.5; 42.1, 73.7)	30/35 (85.7; 69.7, 95.2)		42/87 (48.3; 37.4, 59.2)	44/89 (49.4; 38.7, 60.2)
IPV		1/50 (2.0; 0.05, 10.6)	0/34 (0.0; 0.0, 10.3)		3/107 (2.8; 0.6, 8.0)	4/89 (4.5; 1.2, 11.2)
		Geometric mean titer (95% CI)			**Geometric mean titer (95% CI)**	
IIV3	1:12 (1:11, 1:15)	1:102‡ (1:55, 1:190)	1:156 (1:94, 1:258)	1:111 (1:87, 1:140)	1:325¶ (1:265, 1:400)	1:368 (1:308, 1:440)
IPV	1:12 (1:11, 1:14)	1:11 (1:10, 1:14)	1:14 (1:6, 1:19)	1:30 (1:25, 1:37)	1:32 (1:25, 1:42)	1:27 (1:21, 1:35)

95% CI, 95% confidence interval

* Influenza A(H1N1) used for antibody measurements in 2009-2010 was seasonal influenza A/Brisbane/59/2007 and in 2010-2011 was pandemic strain influenza A(H1N1)pdm09, reflecting vaccine composition these years as did other antigens as described in Methods.

† Reverted A/H1N1 titers occurred between pre-vaccination and post-vaccination in 1 child in the IIV3 group (1:80 to < 1:10) and 2 children in the IPV group (1:160 to < 1:10 & 1:40 to 1:20)

‡ For 3 children in the IIV3 group, specimens were collected 8 weeks post vaccination

§ Reverted A/H1N1 titers occurred between pre-vaccination and post-vaccination in 3 children in the IIV3 group (1:80 to < 1:10, 1:320 to 1:10, 1:160 to < 1:10) and 10 children in the IPV group (1:80 to < 1:10 (2); 1:80 to 1:20 (1); 1:80 to 1:10 (1); 1:40 to 1:20 (4); 1:40 to 1:10 (2))

¶ For 1 child in the IIV3 group, specimens were collected 8 weeks post vaccination

** Influenza A (H3N2) virus used for antibody measurements in 2009-2010 was A/Brisbane/10/2007 and in 2010-2011 was A/Perth/16/2009, reflecting vaccine composition these years.

†† Reverted A/H3N2 titers occurred between pre-vaccination and post-vaccination in 1 child in the IIV3 group (1:320 to < 1:10) and 6 children in the IPV group (1:160 to < 1:10; 1:80 to 1:20; 1:80 to < 1:10; 1:40 to 1:20 (2); & 1:40 to < 1:10).

[##]Reverted A/H3N2 titers occurred between pre-vaccination and post-vaccination in 3 children in the IPV group (1:160 to < 1:10 & 1:40 to 1:20 (2))
[§§]Influenza B used for antibody determinations was B/Brisbane/60/2008 (Victoria lineage).
[¶¶] Reverted B titers occurred between pre-vaccination and post-vaccination in 8 children in the IPV group (1:320 to 1:20; 1:80 to 1:20; 1:40 to 1:20 (2); 1:40 to 1:10 (2) & 1:40 to < 1:10 (2)

Statistical Analysis Plan (SAP) Version: 1

Direct and Indirect Protection by Influenza Vaccine Given to Children in India

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Date: 25-AUG-2010

CONTENTS

1. Introduction

Influenza is an important cause of illness among children and adults in the United States. Influenza is likely also an important cause of illness in India, but published data on influenza infections in India are limited, especially for children. Although influenza vaccines are used routinely in the United States, including in young children, influenza vaccines have not seen widespread use in India. This is likely due to the lack of information from India about disease burden due to influenza and because the influenza vaccines have never been tested for efficacy in India, or in any developing country. In addition, because young children are thought to be important in the spread of influenza in families, it is possible immunization of children against influenza will reduce influenza infections among older children and adults in the home. The study is important to conduct in India in order to demonstrate that the vaccine is effective in this population of Indian children. This might allow consideration of influenza as a national vaccine.

1.1 Study Objectives

1.1.1 Primary Objective

Measure the efficacy of trivalent inactivated influenza vaccine in reducing symptomatic influenza infections among immunized children

1.1.2 Secondary Objective

Measure the indirect protective effects of trivalent inactivated influenza vaccine against symptomatic influenza infections for unvaccinated persons in the households of immunized children

1.2 Study Design

The study is located in three villages (Dayalpur, Atali, and Chandawali) within Ballabgarh, Haryana state, India. Study villages were selected on the basis of sample size requirements, presence of a health facility, and proximity to the Ballabgarh health center. These three villages are part of a broader Comprehensive Rural Health Services Project
(CRHSP) in Ballabgarh, where each person is registered and has a unique health information system number.

This is a prospective, household-randomized, controlled, participant and observer blinded study. Households are defined as dwellings (compounds) that share a courtyard, to capture salient patterns in social interaction and transmission risk.

All inhabitants of the study villages are eligible to participate in the surveillance component of the study; there are no exclusion criteria for surveillance activities. Children 6 months through 10 years of age are eligible to participate in the vaccination component of the study. Exclusion criteria for vaccination are: known allergy to eggs, hypersensitivity to the vaccines or components of the vaccines, acute severe febrile illness (temporary exclusion) or any other condition that would impose a health risk.

Randomization was performed by the study statistician, with allocation fixed for the duration of study. Allocations used a set of four-character codes for each study arm; these codes were applied by the study pharmacist to labels that were applied over the product labels for each study arm. Vaccine administrators not involved in randomization or vaccine masking were hired specifically for vaccination activities.

1.3 Study time points

This is a three-year study, with annual (fall) vaccination as follows: December 2009-January 2010 (Year 1), October-November 2010 (Year 2), and October-November 2011 (Year 3). For children requiring two doses of vaccine per age and vaccination history, second dose will be administered ≥ four weeks post-dose one.

Household surveillance for influenza-associated illness episodes is conducted year-round throughout the entire study period. Annual and multi-year estimates will be calculated for efficacy and effectiveness outcomes.

2. Study Populations

Modified intent-to-treat (MITT) population: all randomized children who received at least one dose of influenza or control vaccine; primary study population for analyses

Safety population: all children from the ITT population who received at least one dose of influenza or control vaccine (equivalent to MITT population)

Indirect effectiveness population: all unvaccinated individuals 11 years and older who are enrolled and provide consent for surveillance activities who reside in a household that has been randomized to receive either influenza or control vaccine

3. Definitions and derived variables

3.1 Febrile acute respiratory illness (FARI)

FARI will be used to screen study populations for laboratory-confirmed influenza. It is defined as reported fever plus one or more respiratory complaints (such as cough, sore throat, nasal congestion, runny nose, earache, or difficulty breathing) within the past 7 days.

4. Efficacy/effectiveness Parameters

4.1 Primary Efficacy Endpoint

Difference in PCR-confirmed influenza infection among FARI episodes during the surveillance period between children receiving influenza vaccine and those receiving inactivated polio vaccine in the MITT population,

4.2 Secondary Effectiveness Endpoints

PCR-confirmed influenza infection among FARI episodes during the surveillance period between households receiving influenza vaccine and household receiving inactivated polio vaccine in the Indirect Effectiveness population

5. Safety Parameters

Safety data will be summarized for all subjects in the Safety population. Safety will be assessed through summary of adverse events that occur in the first month following each dose of study vaccine and summarized by treatment group for the following:

- All adverse events

- All serious adverse events
- Events judged to be related to vaccination

6. Statistical Methodology

6.1 Statistical and Analytical Issues

6.1.1 Statistical Methods

All statistical methods are based on the International Conference on Harmonization (ICH) document "Statistical Principles for Clinical Trials."

Data will be summarized by treatment group. For baseline demographic characteristics and safety outputs, total columns will be included to summarize all subjects.

In summary tables of continuous variables, the minimum and maximum statistics, the arithmetic mean and median, the 95% confidence interval, standard deviation, and standard error will be presented will to the same number of decimal places as the original data.

In summary tables of categorical variables, counts and percentages will be used. The denominator for each percentage will be the number of subjects within the population treatment group unless otherwise specified.

All hypothesis testing will be carried out at the 5% (2-sided) significance level unless otherwise specified.

P-values will be rounded to three decimal places. P-values less than 0.001 will be reported as <0.001 in tables.

6.1.2 Handling of dropouts and missing data

All individuals who drop out of FARI surveillance during the study period will be included up until their last week of completed surveillance. Missing or incomplete surveillance results will be excluded from incidence calculations, and from person-time denominator. No imputation will be performed.

6.1.3 Determination of sample size

For primary study objective of vaccine efficacy, it was assumed that the laboratory confirmed influenza attack rate would be 5% per year (or 5 per 100 person/years) in the unvaccinated group. We set the minimum detectable effectiveness at 50%. To assess total protection, 785 households are required per study group for 95% power. This was based on a conservative assumption of a coefficient of variation of 0.25 for the rates; with about 2 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.

For indirect effectiveness, we set the minimum detectable effectiveness as 25%, which we judged would be a minimum effect of public health importance. With 893 households per group the study would have 80% power for 25% effectiveness.

Parameter	Efficacy	Indirect Effect
Influenza attack rate (control households)	0.05	0.05
Influenza attack rate (vaccinated households)	0.025	0.0375

Coefficient of variation	0.25	0.25
Cluster size	2	5
Power	95%	80%
Clusters (households) required	785	893
Subjects per intervention arm	1570	4465

6.2 Subject Characteristics

6.2.1 Subject Disposition

The subject disposition tables will summarize the following information, by treatment group:

- The number of households randomized
- The number (%) of subjects living in randomized households
- The number (%) of subjects vaccinated
- The number (%) of unvaccinated household members in surveillance
- The number (%) of subjects in MITT analysis
- The number (%) of unvaccinated household members in indirect effectiveness analysis

The number (%) of subjects who complete and withdraw from the study and the primary reason for withdrawal will be summarized by treatment group and overall for all subjects.

6.2.2 Background and Demographic Characteristics

Demographic data presented will be age and gender for MITT and Indirect VE populations. School attendance, and household size will also be collected at baseline and presented for MITT population. Data will be summarized using summary statistics for continuous variables (number of subjects, mean, standard deviation, median, minimum, and maximum).

6.3 Efficacy Analysis

6.3.1 Primary Efficacy Variables

The primary efficacy variable is the incidence rate ratio (IRR) of laboratory-confirmed influenza between intervention arms in the MITT population. IRR will be calculated at the household level as the sum of laboratory confirmed influenza episodes among vaccinated individuals divided by the total number of person weeks at risk. IRR will beanalyzed each year using a Poisson model with a Pearson residual-estimated scale parameter. For the multi-year analysis, the model will also adjust for study year, and household will be added as a repeated measure. In the case where >10% of individuals have multiple influenza outcomes, a mixed effects Poisson model will be used with random effects for household and individual correlationsVE will be calculated as (1 – IRR) x 100%.

6.3.2 Secondary Effectiveness Variables

The indirect effectiveness variable is the incidence rate ratio (IRR) of laboratory-confirmed influenza between intervention arms in the Indirect Effectiveness population. The same models will be applied as in the primary efficacy analysis.

6.4 Safety Analysis

Safety analysis will be performed using the Safety population. All outputs will be summarized by actual treatment received.

6.4.1 Adverse Events

All adverse events (AEs) for a subject are recorded as separate events. The following is a list of solicited adverse events about which the study team will inquire directly to the subjects and their caretakers at follow up:

- Redness
- Swelling
- Tenderness at site
- Vomiting
- Diarrhea
- Headache
- Body ache
- Fever
- Irritability
- Lethargy
- Decreased feeding
- Abnormal cry

Solicited and unsolicited AEs will be classified as Grade 1 (mild, easily tolerated), Grade 2 (moderate, interferes with normal daily behavior/activities), or Grade 3 (severe, preventing daily behavior/activities). Serious adverse events (SAEs) are those resulting in death, requiring inpatient hospitalization or prolongation of existing hospitalization, or resulting in persistent or significant disability/incapacity.

The number of subjects having at least one adverse event (solicited or unsolicited) will be tabulated using counts and percentages, and the number of each will be tabulated. The number of subjects with any SAE or severe (Grade 3) AE will be presented separately.

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Statistical Analysis Plan (SAP) Version: 2

Direct and Indirect Protection by Influenza Vaccine Given to Children in India

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Date: 22-MAR-2013

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Indirect Effectiveness population: all unvaccinated individuals of any age who are enrolled and provide consent for surveillance activities who reside in a household where at least one child has received at least one dose of influenza or control vaccine

3. Definitions and derived variables

3.1 Febrile acute respiratory illness (FARI)

FARI will be used to screen study populations for laboratory-confirmed influenza. It is defined as reported fever plus one or more respiratory complaints (such as cough, sore throat, nasal congestion, runny nose, earache, or difficulty breathing) within the past 7 days.

4. Efficacy/effectiveness Parameters

4.1 Primary Efficacy Endpoint

Difference in PCR-confirmed influenza infection among FARI episodes during the surveillance period between children receiving influenza vaccine and those receiving inactivated polio vaccine in the MITT population,

4.2 Secondary Effectiveness Endpoints

PCR-confirmed influenza infection among FARI episodes during the surveillance period between households receiving influenza vaccine and household receiving inactivated polio vaccine in the Indirect Effectiveness population

5. Safety Parameters

Safety data will be summarized for all subjects in the Safety population. Safety will be assessed through summary of adverse events that occur in the first month following each dose of study vaccine and summarized by treatment group for the following:

- All adverse events
- All serious adverse events
- Events judged to be related to vaccination

6. Statistical Methodology

6.1 Statistical and Analytical Issues

6.1.1 Statistical Methods

All statistical methods are based on the International Conference on Harmonization (ICH) document "Statistical Principles for Clinical Trials."

Data will be summarized by treatment group. For baseline demographic characteristics and safety outputs, total columns will be included to summarize all subjects.

In summary tables of continuous variables, the minimum and maximum statistics, the arithmetic mean and median, the 95% confidence interval, standard deviation, and standard error will be presented will to the same number of decimal places as the original data.

In summary tables of categorical variables, counts and percentages will be used. The denominator for each percentage will be the number of subjects within the population treatment group unless otherwise specified.

All hypothesis testing will be carried out at the 5% (2-sided) significance level unless otherwise specified.

P-values will be rounded to three decimal places. P-values less than 0.001 will be reported as <0.001 in tables.

6.1.2 Handling of dropouts and missing data

All individuals who drop out of FARI surveillance during the study period will be included up until their last week of completed surveillance. Missing or incomplete surveillance results will be excluded from incidence calculations, and from person-time denominator. No imputation will be performed.

6.1.3 Determination of sample size

For primary study objective of vaccine efficacy, it was assumed that the laboratory confirmed influenza attack rate would be 5% per year (or 5 per 100 person/years) in the unvaccinated group. We set the minimum detectable effectiveness at 50%. To assess total protection, 785 households are required per study group for 95% power. This was based on a conservative assumption of a coefficient of variation of 0.25 for the rates; with about 2 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.

For indirect effectiveness, we set the minimum detectable effectiveness as 25%, which we judged would be a minimum effect of public health importance. With 893 households per group the study would have 80% power for 25% effectiveness.

Parameter	Efficacy	Indirect Effect
Influenza attack rate (control households)	0.05	0.05
Influenza attack rate (vaccinated households)	0.025	0.0375
Coefficient of variation	0.25	0.25
Cluster size	2	5
Power	95%	80%
Clusters (households) required	785	893
Subjects per intervention arm	1570	4465

6.2 Subject Characteristics

6.2.1 Subject Disposition

The subject disposition tables will summarize the following information, by treatment group:

- The number of households randomized
- The number (%) of subjects living in randomized households
- The number (%) of subjects vaccinated
- The number (%) of unvaccinated household members in surveillance
- The number (%) of subjects in MITT analysis
- The number (%) of unvaccinated household members in indirect effectiveness analysis

The number (%) of subjects who complete and withdraw from the study and the primary reason for withdrawal will be summarized by treatment group and overall for all subjects.

6.2.2 Background and Demographic Characteristics

Demographic data presented will be age and gender for MITT and Indirect Effectiveness populations. School attendance, and household size will also be collected at baseline and presented for MITT population. Data will be summarized using summary statistics for continuous variables (number of subjects, mean, standard deviation, median, minimum, and maximum).

6.3 Efficacy Analysis

6.3.1 Primary Efficacy Variables

The primary efficacy variable is the hazard ratio (HR) of laboratory-confirmed influenza between intervention arms in the MITT population. Hazard ratio will be estimated using a Cox Proportional Hazards model with a household-level random effect. Model start time will be defined yearly, as 15 days following receipt of last dose of vaccine that year. End time will be the first of the following censoring events: laboratory-confirmed influenza infection, loss-to-follow up (due to withdrawal from surveillance, migration, or death), or the end of the surveillance year. Ties in outcome data will be handled using Efron's likelihood method. VE will be calculated as (1 – HR) x 100.

6.3.2 Secondary Effectiveness Variables

The indirect effectiveness variable is the hazard ratio (HR) of laboratory-confirmed influenza between intervention arms in the Indirect Effectiveness population. The same models will be applied as in the primary efficacy analysis. Model start time will be defined at the household level each year, as 15 days after all children in the household have received their last dose of vaccine that year. End time will be defined individually, as the first of the following censoring events: laboratory-confirmed influenza infection, loss-to-follow up (due to withdrawal from surveillance, migration, or death), or the end of the surveillance year.

6.3.3 Sensitivity Analysis

As a sensitivity analysis, efficacy will be analyzed as the incidence rate ratio (IRR) of laboratory-confirmed influenza between intervention arms in the MITT population. IRR will be calculated at the household level as the sum of laboratory confirmed influenza episodes among vaccinated individuals divided by the total number of person weeks at risk. IRR will be analyzed using a Poisson model with a Pearson residual-estimated scale parameter. For the multi-year analysis, the model will also adjust for study year, and household will be added as a repeated measure. In the case where >10% of individuals

have multiple influenza outcomes, a mixed effects Poisson model will be used with random effects for household and individual correlations. VE will be calculated as (1 – IRR) x 100%.

6.4 Safety Analysis

Safety analysis will be performed using the Safety population. All outputs will be summarized by actual treatment received.

6.4.1 Adverse Events

All adverse events (AEs) for a subject are recorded as separate events. The following is a list of solicited adverse events about which the study team will inquire directly to the subjects and their caretakers at follow up:

- Redness
- Swelling
- Tenderness at site
- Vomiting
- Diarrhea
- Headache
- Body ache
- Fever
- Irritability
- Lethargy
- Decreased feeding
- Abnormal cry

Solicited and unsolicited AEs will be classified as Grade 1 (mild, easily tolerated), Grade 2 (moderate, interferes with normal daily behavior/activities), or Grade 3 (severe, preventing daily behavior/activities). Serious adverse events (SAEs) are those resulting in death, requiring inpatient hospitalization or prolongation of existing hospitalization, or resulting in persistent or significant disability/incapacity.

The number of subjects having at least one adverse event (solicited or unsolicited) will be tabulated using counts and percentages, and the number of each will be tabulated. The number of subjects with any SAE or severe (Grade 3) AE will be presented separately.

6.5 Modifications to Statistical Analysis Plan

The following modifications have been made:

1.3 Study Time Points:

- Multi-year estimates will not be presented for the primary or secondary analyses. Per discussion with CDC statistical team, year-by-year variability undermines interpretability of a pooled multi-year point estimate of vaccine efficacy or effectiveness.

2. Study Populations:

- Indirect effectiveness population will only include households where at least one child received vaccine, so that MITT and Indirect effectiveness analyses utilize individuals from the same set of households. Due to the delay between initial randomization and vaccination, a large number of households were randomized (intent-to-treat) but did not receive any vaccines. This will allow for cleaner comparison between direct efficacy and indirect effectiveness.

- Indirect effectiveness population will unvaccinated individuals of all ages, instead of just those 11 years and older. This will increase sample size and to allow for exploration of indirect effects among unvaccinated children.

6.3 Efficacy Analysis:

- Statistical model for direct and indirect vaccine effects has been changed from Poisson model to Cox Proportional Hazards model, per input from CDC statistical team. This model is consistent with other analyses looking specifically at influenza vaccine protection, and can account for time-varying protection at the individual and household level at the beginning of each study year, when vaccination is ongoing but viruses are actively circulating. Poisson model from original analysis plan (SAP v1) is now described in 6.3.3, Sensitivity Analysis.

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