

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Zaman K, Roy E, Arifeen SE, et al. Effectiveness of maternal influenza immunization in mothers and infants. *N Engl J Med* 2008;359:1555-64. DOI: 10.1056/NEJMoa0708630.

Definitions of influenza illness in infants:

Laboratory-confirmed influenza illness was an acute respiratory illness more than 7 days after a previous respiratory illness, with a positive rapid test for influenza virus.

Standard influenza-like illness (ILI) definitions (19) were modified for the young infants; we defined infant respiratory illness with fever (RIF) as a maternal report of infant illness, occurring more than 7 days after previous illness, with respiratory symptoms including runny nose, nasal congestion, cough, difficulty swallowing or difficulty breathing with fever;

RIF $>38^{\circ}\text{C}$ was RIF with an axillary temperature $>38^{\circ}\text{C}$ documented with a digital thermometer, and

Clinic visit was a visit to the study clinic with a respiratory illness.

Diarrheal illness was defined as maternal report of increased stool frequency with change in stool character.

Sample Size:

The sample size of the study was calculated to answer the primary study question: to detect a specified difference between infant study groups of the geometric mean IgG antibody titers for selected pneumococcal polysaccharides. Using standard formulae, and reported local antibody variance data (27), setting 2-sided $\alpha = 0.05$, and $\beta = 0.20$ and assuming 25% of enrolled subjects might not complete the study, 336 subjects were needed for the primary pneumococcal vaccine immunogenicity study. This

study size was also sufficient to detect a 30% or greater difference in illness rates between the two groups of children in the influenza vaccine effectiveness assessment.

Analysis:

The natural logarithm of person-months of observation in each study group was used as the offset term in the regression models. For estimation of effectiveness against the primary outcome of laboratory-proven influenza in infants, the first laboratory test-positive event in an infant and the person-time of observation up to that episode were included in the analysis. For all other outcomes in mothers and infants, multiple events were included in the analysis and were assumed to be auto-correlated within each study subject (infant or mother) and independent between subjects. Therefore, the confidence intervals for outcomes with multiple events were based on robust (Huber/White/sandwich) estimation of variance.

Appendix Table 1. Screening and Enrollment Data

	number	%
Subjects screened	823	100.0%
Subjects enrolled	340	41.3%
Subjects not enrolled	483	58.7%
<u>Reasons for not enrolling</u>		
Declined, not interested	166	34.4%
Refusal	106	21.9%
Not planning to stay in Dhaka for/after delivery	77	15.9%
Obstetric high risk group	68	14.1%
Did not return to clinic after initial discussion	26	5.4%
History of Allergy	17	3.5%
Mismatch between clinical examination and LMP dates	17	3.5%
Medical contraindication	6	1.2%
Subtotal	483	

Appendix Table 2. Reactions in mothers (0-7 days after immunization

	<u>vaccine</u>		
	<u>influenza</u>	<u>pneumococcal</u>	
	<u>(n=172)</u>	<u>(n=168)</u>	<u>p-value</u>
minor local and systemic reactions	13 (7.6%)	20 (12.0%)	0.17
local pain	7 (4.1%)	19 (11.4%)	0.01
fewer within 72 hours	23 (13.4%)	21 (12.6%)	0.81

Appendix Table 3. Adverse Events

Deaths				
age group	vaccine	cause	number	related*
fetal				
	influenza	stillbirth	3	no
perinatal				
	pneumococcal	severe perinatal asphyxia	2	no
	influenza	preterm low birth weight, and Rh incompatibility	1	no
mother				
	pneumococcal	anesthesia complications	1	no
Hospitalization				
mother				
peri partum	pneumococcal	hypertension	1	no
	influenza	fever	1	no
	influenza	reduced fetal activity	1	no
	influenza	antenatal complications	1	no
	pneumococcal	abdominal pain, diarrhea	1	no
newborn				
0-28 days	pneumococcal	transient tachypnea	2	no
	pneumococcal	meconium aspiration	1	no
	influenza	low birth weight	1	no
	pneumococcal	low birth weight	2	no
	pneumococcal	jaundice	1	no
	influenza	asphyxia	4	no
	pneumococcal	asphyxia	5	no
infants				
5-24 weeks	pneumococcal	gastroenteritis	3	no
	influenza	gastroenteritis	3	no
	pneumococcal	pneumonia	3	no
	influenza	pneumonia	2	no
	influenza	septicemia	4	no
	pneumococcal	septicemia	1	no
	influenza	meningitis	1	no
	pneumococcal	meningitis	1	no
mother				
post partum	influenza	appendicitis	1	no

*to vaccine or to participation in study, as determined by DSMB

a) There were no statistical differences in the numbers of death or hospitalizations between the 2 vaccine groups. These observed rates of maternal, neonatal and infant mortality are not significantly different from national Bangladesh rates. (http://www.who.int/whr/2005/annex/annexe8_en.pdf)