**Supplemental Information**

The Effect of Influenza Vaccination on Birth Outcomes in a Cohort of Pregnant Women in Lao PDR, 2014-2015

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**Methods**

Vaccine distribution: In 2014, Laos received 763,000 doses; 742,887 (97%) were administered, 38,738 of which were administered to pregnant women [9,899 (26%) targeted for pregnant women in Vientiane Capital and Luang Prabang Province; 4,825 of these went to the hospitals (3,875 to Vientiane central hospitals and 950 to Luang Prabang Hospital]).

Weeks of protection. Each week, a woman was considered protected if 1) she was vaccinated at least two weeks prior, 2) she was pregnant, and 3) influenza virus was circulating (same definition as high influenza activity). We then summed each week to get the total number of weeks of protection.

Statistical analysis: Covariates included mother’s age, parity, level of influenza activity, mother’s ethnic group as a proxy for access to health resources, mother’s education level, household income, number of antenatal care visits, number of people residing in the same household and distance from hospital.

Sensitivity analyses: We conducted sensitivity analyses to evaluate the association between vaccination and birth outcomes by (1) including May 2014 in the high influenza activity period, (2) defining preterm birth as <32 weeks gestation, and (3) including all births >28 weeks gestation (as predefined on the questionnaire). In addition, we repeated the primary analysis using a less restrictive dataset (n=5,965) that allowed for self-reported or unverified vaccination data (see supplement).

Results

We enrolled 6,668 pregnant women at delivery or miscarriage, 94% of which met the eligibility criteria (Figure 1). Of the 6,065 with a recorded vaccination status (yes/no), 52% were vaccinated. We excluded 54 persons without a full vaccination date, 46 with a vaccination date outside the campaign and reclassified 129 persons as unvaccinated who received the vaccine within two weeks of delivery. This dataset (n=5,965) was used for the sensitivity analysis. We further excluded 862 records for which the vaccine date was noted as self-reported (n=229) or verification missing (n=633); this dataset (n=5,103) was used for the primary analysis (Figure 1).

Other variables with an independence effect on primary outcomes: Greater parity (i.e., having previous live births) was associated with a decreased risk of SGA and increased mean birth weight. Having <4 antenatal visits was associated with an increased risk of preterm birth and lower mean birth weight (Supplemental Tables 1b and 1c). Lower income and less education increased risk of preterm birth and decreased mean birth weight, respectively, but only in infants born in periods of high influenza virus circulation. Mothers delivering in Luang Prabang had a decreased risk of preterm birth and a decreased mean birth weight but only in infants born in periods of high influenza virus circulation.

Sensitivity analyses: There were no substantial differences in the effect of vaccination on preterm during the high influenza activity period when we used the primary analytic dataset (n=5,103) but (1) included May 2014 in the high influenza activity period, (2) defined preterm birth as <32 weeks gestation, or (3) included all pregnancies that reached a gestational age ≥28 weeks (Supplemental Table 2). There were not enough fatal outcomes to assess this outcome separately. When we broadened the analytic dataset to include persons with self-reported or non-verified vaccination data (Figure 1, n=5,965), the results were similar to the primary analysis (Supplemental Table 3).

Viral data: Between April 2014 and Feb 2015, influenza B was the most commonly circulating influenza virus in Lao PDR (49.6%), followed by H3N2 (34.6%) then H1N1pdm09 (15.8%). Of a sample that were further characterized, all 12 influenza A (H1N1)pdm09 viruses and all 20 influenza B viruses were both antigenically similar to the components of 2014-2015 Northern Hemisphere vaccine (A/California/7/2009 and B/Massachusetts/02/2012). Of the 25 influenza A (H3N2) viruses, 5 were antigenically similar to the component in the vaccine (A/Texas/50/2012) and the others were low reactors. The vaccine would not have protected against these drifted H3N2 viruses.

Supplemental Table 1a. Adjusted risk ratios and 95% confidence intervals for small for gestational age among women with live births (n=4,854). Shaded cells indicate a statistically significant finding.

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| Variable | Small for Gestational Age | | |
| Whole period (n=3651)  Adjusted Risk Ratio (95% CI) | Low activity (n=565)  Adjusted Risk Ratio (95% CI) | High activity (n=3086)  Adjusted Risk Ratio (95% CI) |
| Maternal age (continuous) | 1.05 (1.01-1.09) | 1.08 (1.00-1.17) | 1.04 (1.00-1.09) |
| Parity/live deliveries (continuous) | 0.68 (0.54-0.86) | 0.39 (0.20-0.78) | 0.74 (0.58-0.96) |
| Influenza activity  Low  High | Reference  0.91 (0.60-1.36) | - | - |
| Province  Vientiane  Luang Prabang Province | Reference  1.07 (0.68-1.69) | Reference  1.18 (0.37-3.70) | Reference  1.05 (0.63-1.74) |
| Vaccinated  No  Yes | Reference  1.25 (0.91-1.71) | Reference  1.50 (0.71-3.17) | Reference  1.22 (0.86-1.74) |
| Ethnicity  Lao Loum  Other | Reference  1.50 (0.88-2.56) | Reference  1.10 (0.29-4.20) | Reference  1.66 (0.92-3.00) |
| Education  >Secondary school  <Secondary school | Reference  1.31 (0.94-1.83) | Reference  1.07 (0.49-2.33) | Reference  1.38 (0.96-2.01) |
| Monthly household income  <500,000M Kip (USD$62)  500,001-1,000,000  1,000,001-5,000,000  >5,000,000 | Reference  1.10 (0.55-2.20)  1.15 (0.63-2.09)  0.83 (0.39-1.78) | Reference  3.61 (0.81-16.04)  1.59 (0.35-7.15)  1.76 (0.29-10.59) | Reference  0.68 (0.30-1.54)  1.05 (0.55-2.01)  0.70 (0.30-1.63) |
| No antenatal visits  >4 visits  <4 visits | Reference  1.14 (0.67-1.93) | Reference  1.63 (0.56-4.74) | Reference  1.09 (0.59-2.00) |
| No people in household  <5 people  >5 people | Reference  0.70 (0.49-1.00) | Reference  1.62 (0.76-3.45) | Reference  0.57 (0.38-0.87) |
| Distance from hospital  <5km  >5-10km  >10km | Reference  1.03 (0.66-1.60)  1.20 (0.78-1.85) | Reference  1.86 (0.60-5.71)  2.43 (0.78-7.59) | Reference  0.94 (0.57-1.54)  1.01 (0.63-1.65) |

Supplemental Table 1b. Adjusted risk ratios and 95% confidence intervals for preterm birth among women with live births (n=4,854). Shaded cells indicate a statistically significant finding.

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| Variable | Preterm birth | | | Preterm birth |
| Whole period (n=3661)  Adjusted Risk Ratio (95% CI) | Low activity (n=567)  Adjusted Risk Ratio (95% CI) | High activity (n=3094)  Adjusted Risk Ratio (95% CI) | Whole period (n=3661) with propensity score adjustments  Adjusted Risk Ratio (95% CI) |
| Maternal age (continuous) | 0.97 (0.95-1.00) | 0.98 (0.93-1.04) | 0.97 (0.95-1.00) | 0.97 (0.95-1.00) |
| Parity/live deliveries (continuous) | 1.08 (0.96-1.22) | 0.94 (0.68-1.30) | 1.10 (0.96-1.25) | 1.04 (0.90-1.19) |
| Influenza activity  Low  High | Reference  1.00 (0.78-1.30) | - | - | Reference  0.96 (0.74-1.25) |
| Province  Vientiane  Luang Prabang Province | Reference  0.84 (0.62-1.15) | Reference  1.87 (1.00-3.51) | Reference  0.68 (0.48-0.98) | Reference  1.14 (0.66-1.97) |
| Vaccinated  No  Yes | Reference  0.70 (0.57-0.87) | Reference  0.83 (0.50-1.37) | Reference  0.69 (0.55-0.87) | Reference  0.71 (0.58-0.88) |
| Ethnicity  Lao Loum  Other | Reference  0.69 (0.48-1.01) | Reference  0.55 (0.23-1.32) | Reference  0.74 (0.49-1.13) | Reference  0.58 (0.36-0.93) |
| Education  >Secondary school  <Secondary school | Reference  1.14 (0.93-1.40) | Reference  1.12 (0.68-1.79) | Reference  1.14 (0.91-1.43) | Reference  1.02 (0.79-1.33) |
| Monthly household income  <500,000M Kip (USD$62)  500,001-1,000,000  1,000,001-5,000,000  >5,000,000 | Reference  1.15 (0.81-1.63)  0.88 (0.63-1.22)  0.52 (0.32-0.85) | Reference  0.84 (0.34-2.10)  1.34 (0.62-2.90)  0.73 (0.22-2.42) | Reference  1.18 (0.80-1.73)  0.79 (0.55-1.13)  0.48 (0.29-0.82) | Reference  0.84 (0.46-1.51)  0.73 (0.47-1.12)  0.45 (0.26-0.77) |
| No antenatal visits  >4 visits  <4 visits | Reference  2.18 (1.72-2.76) | Reference  1.91 (1.01-3.62) | Reference  2.23 (1.72-2.87) | Reference  0.76 (0.14-3.85) |
| No people in household  <5 people  >5 people | Reference  1.05 (0.86-1.29) | Reference  1.02 (0.63-1.67) | Reference  1.04 (0.84-1.30) | Reference  0.97 (0.76-1.23) |
| Distance from hospital  <5km  >5-10km  >10km | Reference  1.27 (0.96-1.68)  1.22 (0.92-1.61) | Reference  2.35 (1.19-4.64)  2.42 (1.16-5.05) | Reference  1.10 (0.81-1.49)  1.09 (0.81-1.47) | Reference  1.18 (0.88-1.59)  0.98 (0.64-1.51) |

Supplemental Table 1c. Adjusted risk ratios and 95% confidence intervals for mean birth weight among women with live births (n=4,854). Shaded cells indicate a statistically significant finding.

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| --- | --- | --- | --- |
| Variable | Birth Weight | | |
| Whole period (n=4770)  β (95% CI) | Low activity (n=757)  β (95% CI) | High activity (n=4013)  β (95% CI) |
| Maternal age (continuous) | 2.33 (-0.74-5.40) | 0.10 (-7.01-7.21) | 2.56 (-0.84-5.96) |
| Parity/live deliveries (continuous) | 55.51 (41.01-70.00) | 72.35 (41.14-103.56) | 52.19 (35.83-68.55) |
| Influenza activity  Low  High | Reference  28.08 (-6.37-62.54) | - | - |
| Province  Vientiane  Luang Prabang Province | Reference  -44.88 (-81.17- -8.58) | Reference  -60.55 (-141.69-20.59) | Reference  -42.05 (-82.59- -1.51) |
| Vaccinated  No  Yes | Reference  1.54 (-25.10-28.18) | Reference  -38.57 (-104.04-26.89) | Reference  8.74 (-20.43-37.90) |
| Ethnicity  Lao Loum  Other | Reference  30.62 (-12.89-74.13) | Reference  20.25 (-79.35-119.84) | Reference  33.59 (-14.67-81.85) |
| Education  >Secondary school  <Secondary school | Reference  -50.58 (-78.33- -22.83) | Reference  -10.11 (-75.27-55.04) | Reference  -57.77 (-88.43- -27.10) |
| Monthly household income  <500,000M Kip (USD$62)  500,001-1,000,000  1,000,001-5,000,000  >5,000,000 | Reference  6.23 (-46.75-59.21)  23.43 (-22.66-69.52)  88.28 (31.29-145.28) | Reference  21.07 (-89.78-131.92)  42.36 (-56.14-140.87)  79.95 (-51.33-211.23) | Reference  0.71 (-59.45-60.86)  17.18 (-34.99-69.36)  86.46 (22.89-150.021) |
| No antenatal visits  >4 visits  <4 visits | Reference  -135.50 (-172.96- -98.03) | Reference  -175.35 (-255.10- -89.60) | Reference  -127.89 (-169.80- -85.98) |
| No people in household  <5 people  >5 people | Reference  0.71 (-26.13-27.55) | Reference  -41.21 (-106.28-23.86) | Reference  8.27 (-21.16-37.70) |
| Distance from hospital  <5km  >5-10km  >10km | Reference  2.70 (-33.31-38.72)  8.11 (-27.58-43.80) | Reference  17.69 (-66.24-101.62)  -60.14 (-143.98-23.69) | Reference  0.72 (-39.21-40.65)  20.91 (-18.65-60.46) |

Supplemental Table 2. Sensitivity analysis using the main analytic dataset (n=5,103) to assess the effect of vaccination on preterm birth.

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| Effect on preterm birth in high influenza period | Adjusted RR to vaccinated (95% CI) |
| Among live births  Included May 2014 in high influenza activity period  Preterm birth defined as <32 weeks | 0.67 (0.53-0.84)  0.68 (0.28-1.69) |
| Among births >28 weeks gestation | 0.69 (0.55-0.87) |

Supplemental Table 3. Analysis of birth outcomes by maternal vaccination status influenza activity among women who had live births (n=5,965)

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| Outcome | Total  N (%) | Vaccinated  N (%) | Unvaccinated  N (%) | p-value | Crude risk to vaccinated (95% CI) | Adjusteda RR to vaccinated (95% CI) |
| Proportion SGA  High influenza activity  Low influenza activity | 184/4367 (4.2)  138/3297 (4.2)  46/1070 (4.4) | 108/2360 (4.6)  80/1700 (4.7)  28/660 (4.2) | 76/2007 (3.8)  58/1597 (3.6)  18/410 (4.4) | 0.20  0.12  0.91 | 1.21 (0.91-1.61)  1.30 (0.93-1.80)  0.97 (0.54-1.72) | 1.17 (0.85-1.62)  1.24 (0.88-1.74)  0.95 (0.37-2.43) |
| Proportion preterm  High influenza activity  Low influenza activity | 443/4377 (10.1)  328/3305 (9.9)  115/1072 (10.7) | 189/2368 (8.0)  123/1706 (7.2)  66/662 (10.0) | 254/2009 (12.6)  205/1599 (12.8)  49/410 (12.0) | <0.001  <0.001  0.31 | 0.63 (0.53-0.76)  0.56 (0.46-0.70)  0.83 (0.59-1.18) | 0.72 (0.59-0.89)  0.68 (0.55-0.85)  1.13 (0.56-2.27) |
|  |  |  |  |  | Difference in means (vaccinated-unvaccinated) | Difference in marginal means (vaccinated-unvaccinated |
| Mean birth weight in grams (SD)  High influenza activity (n=4079)  Low influenza activity (n=767) | 3070g (451)  3077g (454)  3048g (442) | 3080g (433)  3092g (432)  3050g (435) | 3061g (469)  3065g (473)  3046g (452) | 0.11  0.05  0.87 | +19 grams  +27 grams  +4 grams | +2 gramsb  +7 gramsc  -76 gramsd |

aAdjusted for mother’s age, parity, province, ethnicity, education, income, number of antenatal visits, number of household members, and distance to hospital.

bMean and 95% Wald CI for vaccinated (3019 grams, 2986-3051) and unvaccinated (3017 grams, 2985-3050).

cMean and 95% Wald CI for vaccinated (3043 grams, 3011-3075) and unvaccinated (3036 grams, 3007-3064).

dMean and 95% Wald CI for vaccinated (2959 grams, 2875-3043) and unvaccinated (3035 grams, 2943-3126).