**SUPPLEMENTARY MATERIALS**

TABLE 1S. Influenza seasons by research site

TABLE 2S. Characteristics of adults by influenza infection and vaccination status

Footnote: Research sites B and D enrolled only children, site A enrolled only adults and site C enrolled both children and adults; Immunosuppression included non-cancer immunosuppressive conditions, cancer (other than skin cancer) and HIV infection with CD4 count ≥200/mm3; chronic conditions encompass medical conditions associated with influenza-associated complications including cardiopulmonary disease, diabetes mellitus, blood disorders, chronic liver/kidney disease, immunosuppressive conditions (including cancer), and neuromuscular diseases.

TABLE 3S. Characteristics of children by influenza infection and vaccination status

Footnote: Research sites B and D enrolled only children, site A enrolled only adults and site C enrolled both children and adults; Immunosuppression included non-cancer immunosuppressive conditions, cancer (other than skin cancer) and HIV infection with CD4 count ≥200/mm3; chronic conditions encompass medical conditions associated with influenza-associated complications including cardiopulmonary disease, diabetes mellitus, blood disorders, chronic liver/kidney disease, immunosuppressive conditions (including cancer), and neuromuscular diseases. BMI categories for children were determined per CDC guidelines: Underweight (<5th BMI-for-age percentile), Normal (5th - <85th percentile), Overweight (85th - <95th percentile), and Obese (>=95th percentile).

TABLE 4S. Sequential regression adjustment from crude to fully adjusted odds ratio and vaccine effectiveness estimate

Footnote: Vaccine effectiveness was estimated as 1-adjusted odds ratios; where odds ratios compared the odds of vaccination between cases and controls while controlling for age, gender, race/ethnicity, presence of children at home, smoking status, insurance status, use of oxygen supplementation at home, timing of admission relative to disease onset, timing from beginning of the influenza season to admission, the specific influenza season, and the presence of immunosuppressive conditions and other chronic medical conditions associated with influenza-associated complications including cardiopulmonary disease, diabetes mellitus, chronic liver/kidney disease, and neurological disease. \*Parameter was modeled using restricted cubic splines to account for nonlinear effects

FIGURE 1S. Temporal distribution of cases and controls by research site

Footnote: note that influenza seasons were defined by epidemic week (Table 1S) for each site, but the figure displays counts by calendar month. Influenza seasons are represented with blue horizontal bars as reference, where the extension of the bars approximates the extension of the seasons for each site.

**TABLE 1S. Influenza seasons by research site**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Site A | | | Sites B, C | | | Site D | | |
| Season | week | Start date | End date | week | Start date | End date | week | Start date | End date |
| 2009-2010 | 1-20 | 1/3/2010 | 5/22/2010 | 1-20 | 1/3/2010 | 5/22/2010 | 1-19 | 1/3/2010 | 5/15/2010 |
| 2010-2011 | 34-20 | 8/22/2010 | 5/21/2011 | 28-24 | 7/11/2010 | 6/18/2011 | 37-22 | 9/12/2010 | 6/4/2011 |
| 2011-2012 | 48-26 | 11/27/2011 | 6/16/2012 | 28-26 | 7/10/2011 | 6/30/2012 | 43-25 | 10/23/2011 | 6/23/2012 |

**TABLE 2S. Characteristics of adults by influenza infection and vaccination status**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Controls - non influenza pneumonia (n=1296) | Cases - influenza pneumonia (n=94) | P value | Non-vaccinated (n=979) | Vaccinated (n=411) | P value |
| Sociodemographic characteristics |  |  |  |  |  |  |
| Overall age, median (IQR) | 55 (44, 68) | 52.5 (40, 63) | 0.03 | 53 (41.5, 64) | 63 (52, 74.5) | <0.001 |
| Female gender, % (n) | 52% (678) | 49% (46) | 0.53 | 51% (496) | 55% (228) | 0.10 |
| Race/ethnicity, % (n) |  |  | <0.002 |  |  | 0.001 |
| White | 47% (609) | 30% (28) |  | 42% (409) | 55% (228) |  |
| Black | 40% (516) | 46% (43) |  | 43% (423) | 33% (136) |  |
| Hispanic | 10% (130) | 19% (18) |  | 12% (113) | 9% (35) |  |
| Other | 3% (41) | 5% (5) |  | 3% (34) | 3% (12) |  |
| Children <5 years old at home, % (n) |  |  | 0.34 |  |  | 0.26 |
| 0 | 24% (310) | 21% (20) |  | 23% (221) | 27% (109) |  |
| 1 or more | 12% (149) | 7% (7) |  | 11% (109) | 11% (47) |  |
| Unknown | 65% (837) | 71% (67) |  | 66% (649) | 62% (255) |  |
| Children 5-17 years old at home, % (n) |  |  | 0.85 |  |  | 0.01 |
| 0 | 21% (278) | 21% (20) |  | 20% (192) | 26% (106) |  |
| 1 or more | 19% (245) | 21% (20) |  | 21% (202) | 15% (63) |  |
| Unknown | 60% (773) | 57% (54) |  | 60% (585) | 59% (242) |  |
| Research Site, % (n) |  |  | 0.03 |  |  | 0.001 |
| A | 55% (717) | 67% (63) |  | 60% (587) | 47% (193) |  |
| B | 0% (0) | 0% (0) |  | 0% (0) | 0% (0) |  |
| C | 45% (579) | 33% (31) |  | 40% (392) | 53% (218) |  |
| D | 0% (0) | 0% (0) |  | 0% (0) | 0% (0) |  |
| Influenza Season, % (n) |  |  | 0.12 |  |  | <0.001 |
| 2009-2010 | 10% (134) | 4% (4) |  | 13% (125) | 3% (13) |  |
| 2010-2011 | 56% (730) | 64% (60) |  | 55% (540) | 61% (250) |  |
| 2011-2012 | 33% (432) | 32% (30) |  | 32% (314) | 36% (148) |  |
| Smoking, % (n) |  |  | 0.07 |  |  | <0.001 |
| Non-smoking | 36% (464) | 34% (32) |  | 36% (353) | 35% (143) |  |
| Current smoking | 29% (374) | 39% (37) |  | 33% (326) | 21% (85) |  |
| Past smoking | 35% (458) | 27% (25) |  | 31% (300) | 45% (183) |  |
| Insurance, % (n) |  |  | 0.05 |  |  | <0.001 |
| Public | 45% (586) | 49% (46) |  | 42% (413) | 53% (219) |  |
| Private | 27% (355) | 23% (22) |  | 26% (256) | 29% (121) |  |
| Both | 10% (133) | 3% (3) |  | 8% (82) | 13% (54) |  |
| None/other | 17% (222) | 24% (23) |  | 23% (228) | 4% (17) |  |

**TABLE 2S. Characteristics of adults by influenza infection and vaccination status (continuation)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Controls - non influenza pneumonia (n=1296) | Cases - influenza pneumonia (n=94) | P value | Non-vaccinated (n=979) | Vaccinated (n=411) | P value |
| Comorbidities and risk factors |  |  |  |  |  |  |
| Need oxygen supplementation at home, % (n) | 11% (145) | 5% (5) | 0.08 | 7% (70) | 19% (80) | <0.001 |
| BMI (kg/m2), median (IQR) | 27.4 (23.0, 33.0) | 27.9 (25.1, 34.7) | 0.08 | 27.4 (23.1, 32.9) | 27.7 (23.0, 33.4) | 0.76 |
| Chronic condition | 77% (997) | 66% (62) | 0.02 | 70% (684) | 91% (375) | <0.001 |
| Asthma or Reactive Airway Disease | 26% (342) | 30% (28) | 0.47 | 24% (239) | 32% (131) | 0.004 |
| Chronic Obstructive Pulmonary Disease (COPD) | 22% (291) | 19% (18) | 0.46 | 17% (170) | 34% (139) | <0.001 |
| Coronary Artery Disease | 28% (358) | 26% (24) | 0.66 | 22% (211) | 42% (171) | <0.001 |
| Heart failure | 21% (268) | 9% (8) | 0.004 | 14% (141) | 33% (135) | <0.001 |
| Diabetes mellitus | 26% (333) | 20% (19) | 0.24 | 23% (224) | 31% (128) | 0.001 |
| Blood Disorder (e.g. sickle cell disease) | 11% (143) | 6% (6) | 0.16 | 9% (88) | 15% (61) | 0.001 |
| Chronic Kidney Disease | 16% (209) | 10% (9) | 0.09 | 12% (120) | 24% (98) | <0.001 |
| Chronic Liver Disease | 6% (80) | 9% (8) | 0.37 | 6% (59) | 7% (29) | 0.472 |
| Splenectomy | 2% (23) | 0% (0) | 0.19 | 1% (12) | 3% (11) | 0.053 |
| Non-cancer immunosuppressive condition | 17% (215) | 18% (17) | 0.71 | 13% (123) | 24% (97) | <0.001 |
| HIV | 3% (42) | 6% (6) | 0.11 | 2% (24) | 6% (24) | 0.002 |
| Cancer | 17% (225) | 13% (12) | 0.25 | 13% (127) | 27% (110) | <0.001 |
| Immunosuppression | 28% (368) | 29% (27) | 0.95 | 13% (130) | 25% (102) | <0.001 |
| Seizure disorder | 5% (63) | 5% (5) | 0.84 | 5% (48) | 5% (20) | 0.98 |
| Obstructive Sleep Apnea | 7% (86) | 3% (3) | 0.19 | 5% (45) | 11% (44) | <0.001 |
| Dementia | 2% (24) | 1% (1) | 0.58 | 1% (14) | 3% (11) | 0.11 |
| Stroke | 6% (72) | 2% (2) | 0.15 | 5% (45) | 7% (29) | 0.06 |
| Guillain-Barre Syndrome | 0% (4) | 1% (1) | 0.24 | 0% (2) | 1% (3) | 0.14 |
| Scoliosis | 0% (5) | 0% (0) | 0.55 | 0% (2) | 1% (3) | 0.64 |
| Down’s Syndrome | 0% (3) | 0% (0) | 0.64 | 0% (2) | 0% (1) | 0.89 |
| Currently on steroids | 13% (172) | 13% (12) | 0.89 | 10% (99) | 21% (85) | <0.001 |
| Influenza and vaccination status, and timing of admission |  |  |  |  |  |  |
| Verified influenza vaccination, % (n) | 30% (390) | 22% (21) | 0.20 |  |  |  |
| Influenza confirmed by RT-PCR, % (n) |  |  |  | 7% (73) | 5% (21) | 0.11 |
| Disease onset to admission, median (IQR) | 4 (2, 8) | 3.5 (2, 5) | 0.11 | 4 (2, 8.75) | 3 (1, 7) | 0.004 |
| Admission week in flu season, median (IQR) | 19 (11, 29) | 23.5 (16, 30) | 0.01 | 17 (9, 27) | 26 (19, 34) | <0.001 |
| Days from vaccination to admission, median (IQR) | 121.0 (74.2, 178.2) | 123.0 (91.0, 146.0) | 0.75 |  | 121 (76, 174) |  |
| Days from season start to admission, median (IQR) | 131 (72, 202) | 160 (105, 204) | 0.01 | 118.0 (61.5, 198.5) | 176.0 (128.0, 237.0) | <0.001 |

Footnote: Research sites B and D enrolled only children, site A enrolled only adults and site C enrolled both children and adults; Immunosuppression included non-cancer immunosuppressive conditions, cancer (other than skin cancer) and HIV infection with CD4 count ≥200/mm3; chronic conditions encompass medical conditions associated with influenza-associated complications including cardiopulmonary disease, diabetes mellitus, blood disorders, chronic liver/kidney disease, immunosuppressive conditions (including cancer), and neuromuscular diseases.

**TABLE 3S. Characteristics of children by influenza infection and vaccination status**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Controls - non influenza pneumonia (n=1309) | | Cases - influenza pneumonia (n=68) | | P value | | Non-vaccinated (n=994) | | Vaccinated (n=383) | P value | |
| Sociodemographic characteristics | |  |  |  | |  | |  | | |  |
| Overall age, median (IQR) | 3 (1, 6) | | 3 (1, 9) | | 0.23 | | 3 (1, 7) | | 2 (1, 6) | 0.14 | |
| Female gender, % (n) | 44% (581) | | 40% (27) | | 0.45 | | 45% (447) | | 42% (161) | 0.33 | |
| Race/ethnicity, % (n) |  | |  | | 0.19 | |  | |  | <0.001 | |
| White | 37% (487) | | 32% (22) | |  | | 36% (362) | | 38% (147) |  | |
| Black | 38% (500) | | 50% (34) | |  | | 44% (435) | | 26% (99) |  | |
| Hispanic | 18% (231) | | 10% (7) | |  | | 14% (136) | | 27% (102) |  | |
| Other | 7% (91) | | 7% (5) | |  | | 6% (61) | | 9% (35) |  | |
| Children <5 years old at home, % (n) |  | |  | | 0.19 | |  | |  | 0.05 | |
| 0 | 19% (253) | | 26% (18) | |  | | 21% (211) | | 16% (60) |  | |
| 1 or more | 76% (994) | | 72% (49) | |  | | 74% (736) | | 80% (307) |  | |
| Unknown | 5% (62) | | 1% (1) | |  | | 5% (47) | | 4% (16) |  | |
| Children 5-17 years old at home, % (n) |  | |  | | 0.28 | |  | |  | 0.003 | |
| 0 | 23% (299) | | 25% (17) | |  | | 22% (214) | | 27% (102) |  | |
| 1 or more | 71% (930) | | 74% (50) | |  | | 74% (731) | | 65% (249) |  | |
| Unknown | 6% (80) | | 1% (1) | |  | | 5% (49) | | 8% (32) |  | |
| Research Site, % (n) |  | |  | | 0.05 | |  | |  | <0.001 | |
| A | 0% (0) | | 0% (0) | |  | | 0% (0) | | 0% (0) |  | |
| B | 42% (544) | | 56% (38) | |  | | 50% (497) | | 22% (85) |  | |
| C | 33% (438) | | 22% (15) | |  | | 27% (272) | | 47% (181) |  | |
| D | 25% (327) | | 22% (15) | |  | | 23% (225) | | 31% (117) |  | |
| Influenza Season, % (n) |  | |  | | 0.02 | |  | |  | 0.01 | |
| 2009-2010 | 13% (171) | | 3% (2) | |  | | 14% (141) | | 8% (32) |  | |
| 2010-2011 | 42% (553) | | 54% (37) | |  | | 42% (414) | | 46% (176) |  | |
| 2011-2012 | 45% (585) | | 43% (29) | |  | | 44% (439) | | 46% (175) |  | |
| Insurance, % (n) |  | |  | | 0.42 | |  | |  | 0.002 | |
| Public | 62% (810) | | 66% (45) | |  | | 63% (622) | | 61% (233) |  | |
| Private | 33% (430) | | 26% (18) | |  | | 33% (325) | | 32% (123) |  | |
| Both | 3% (43) | | 3% (2) | |  | | 2% (22) | | 6% (23) |  | |
| None/other | 2% (26) | | 4% (3) | |  | | 3% (25) | | 1% (4) |  | |

**TABLE 3S. Characteristics of children by influenza infection and vaccination status (continuation)**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Controls - non influenza pneumonia (n=1309) | | Cases - influenza pneumonia (n=68) | | P value | | Non-vaccinated (n=994) | | Vaccinated (n=383) | P value | |
| Comorbidities and risk factors | |  |  |  | |  | |  | | |  |
| Need oxygen supplementation at home, % (n) | 3% (45) | | 7% (5) | | 0.09 | | 3% (26) | | 6% (24) | 0.001 | |
| BMI categories |  | |  | | 1.00 | |  | |  | 0.84 | |
| Underweight | 20% (149) | | 20% (8) | |  | | 19% (115) | | 20% (42) |  | |
| Normal | 55% (419) | | 54% (22) | |  | | 55% (324) | | 56% (117) |  | |
| Overweight | 11% (85) | | 12% (5) | |  | | 11% (65) | | 12% (25) |  | |
| Obese | 14% (108) | | 15% (6) | |  | | 15% (88) | | 12% (26) |  | |
| Morbidly Obese | 0% (0) | | 0% (0) | |  | | 0% (0) | | 0% (0) |  | |
| Chronic condition | 48% (631) | | 43% (29) | | 0.37 | | 48% (475) | | 48% (185) | 0.86 | |
| Asthma or Reactive Airway Disease | 39% (510) | | 37% (25) | | 0.72 | | 40% (396) | | 36% (139) | 0.23 | |
| Congenital Heart Disease | 7% (87) | | 0% (0) | | 0.03 | | 5% (51) | | 9% (36) | 0.004 | |
| Heart failure | 1% (11) | | 0% (0) | | 0.45 | | 0% (4) | | 2% (7) | 0.008 | |
| Diabetes mellitus | 0% (4) | | 0% (0) | | 0.65 | | 0% (3) | | 0% (1) | 0.9 | |
| Blood Disorder (e.g. sickle cell disease) | 4% (46) | | 3% (2) | | 0.80 | | 3% (32) | | 4% (16) | 0.39 | |
| Chronic Kidney Disease | 1% (12) | | 0% (0) | | 0.43 | | 1% (5) | | 2% (7) | 0.02 | |
| Chronic Liver Disease | 0% (2) | | 1% (1) | | 0.02 | | 1% (5) | | 2% (7) | 0.13 | |
| Splenectomy | 1% (8) | | 0% (0) | | 0.52 | | 0% (4) | | 1% (4) | 0.16 | |
| Non-cancer immunosuppressive condition | 2% (21) | | 1% (1) | | 0.93 | | 1% (11) | | 2% (9) | 0.08 | |
| HIV | 0% (1) | | 0% (0) | | 0.82 | | 0% (1) | | 0% (0) | 0.54 | |
| Cancer | 0% (5) | | 1% (1) | | 0.18 | | 0% (4) | | 1% (2) | 0.76 | |
| Immunosuppression | 2% (25) | | 1% (1) | | 0.80 | | 1% (12) | | 3% (10) | 0.06 | |
| Seizure disorder | 6% (74) | | 7% (5) | | 0.56 | | 5% (47) | | 8% (32) | 0.01 | |
| Cerebral Palsy | 3% (34) | | 4% (3) | | 0.37 | | 2% (21) | | 4% (16) | 0.03 | |
| Scoliosis | 1% (9) | | 1% (1) | | 0.46 | | 1% (6) | | 1% (4) | 0.39 | |
| Down’s Syndrome | 3% (35) | | 0% (0) | | 0.17 | | 2% (16) | | 5% (19) | <0.001 | |
| Other Chromosomal Abnormality | 3% (35) | | 3% (2) | | 0.89 | | 2% (22) | | 4% (15) | 0.08 | |
| Pre-term birth, % (n) | 7% (98) | | 1% (1) | | 0.06 | | 7% (71) | | 7% (28) | 0.91 | |
| Currently on steroids | 9% (117) | | 9% (6) | | 0.97 | | 9% (93) | | 8% (30) | 0.38 | |
| Influenza and vaccination status, and timing of admission |  | |  | |  | |  | |  |  | |
| Verified influenza vaccination, % (n) | 29% (376) | | 10% (7) | | 0.004 | |  | |  |  | |
| Influenza confirmed by RT-PCR, % (n) |  | |  | |  | | 6% (61) | | 2% (7) | <0.001 | |
| Disease onset to admission, median (IQR) | 3 (1, 6) | | 3 (2, 6) | | 0.29 | | 3 (1, 6) | | 3 (2, 6) | 0.04 | |
| Admission week in flu season, median (IQR) | 21 (14, 33) | | 29 (23, 35) | | 0.001 | | 20 (13, 31) | | 28 (19, 35) | <0.001 | |
| Days from vaccination to admission, median (IQR) | 98 (55, 144) | | 145 (88, 158) | | 0.34 | |  | | 99 (55, 146) |  | |
| Days from season start to admission, median (IQR) | 144.0 (96, 225.0) | | 197.0 (158.0, 239.0) | | 0.001 | | 135 (89, 212) | | 193 (126, 241) | <0.001 | |

Footnote: Research sites B and D enrolled only children, site A enrolled only adults and site C enrolled both children and adults; Immunosuppression included non-cancer immunosuppressive conditions, cancer (other than skin cancer) and HIV infection with CD4 count ≥200/mm3; chronic conditions encompass medical conditions associated with influenza-associated complications including cardiopulmonary disease, diabetes mellitus, blood disorders, chronic liver/kidney disease, immunosuppressive conditions (including cancer), and neuromuscular diseases. BMI categories for children were determined per CDC guidelines: Underweight (<5th BMI-for-age percentile), Normal (5th - <85th percentile), Overweight (85th - <95th percentile), and Obese (>=95th percentile).

**TABLE 4S. Sequential adjustment from crude to fully adjusted odds ratio and vaccine effectiveness estimates**

|  |  |  |
| --- | --- | --- |
| Parameters in the model | Adjusted Odds Ratio (95% CI) | Estimated vaccine effectiveness (95% CI) |
| Vaccination status (unadjusted) | 0.50 (0.33 , 0.76) | 49.8 (24.0 , 66.9) |
| added age\* and sex | 0.53 (0.35 , 0.81) | 47.2 (19.5 , 65.3) |
| added days since beginning of season\* | 0.41 (0.26 , 0.63) | 59.3 (37.3 , 73.6) |
| added season | 0.40 (0.26 , 0.62) | 59.9 (38.2 , 74.0) |
| added race | 0.40 (0.26 , 0.62) | 59.7 (37.8 , 73.9) |
| added smoking | 0.41 (0.27 , 0.64) | 58.9 (36.5 , 73.4) |
| added insurance | 0.42 (0.27 , 0.65) | 57.9 (34.6 , 72.9) |
| added chronic conditions | 0.43 (0.28 , 0.67) | 56.7 (32.7 , 72.2) |
| added home oxygen | 0.43 (0.28 , 0.67) | 57.1 (33.1 , 72.5) |
| added steroid use | 0.43 (0.27 , 0.67) | 57.2 (33.2 , 72.6) |
| added days from disease onset | 0.42 (0.27 , 0.66) | 57.6 (33.9 , 72.9) |
| added site | 0.44 (0.28 , 0.69) | 55.8 (30.6 , 71.9) |
| added immunosuppressive conditions | 0.43 (0.28 , 0.69) | 56.7 (31.9 , 72.5) |
| Final adjusted model (included all parameters listed in the table) | 0.43 (0.28 , 0.68) | 56.7 (31.9 , 72.5) |

Footnote: Vaccine effectiveness was estimated as (1-adjusted odds ratios)\*100; where odds ratios compared the odds of vaccination between cases and controls while controlling for age, gender, race/ethnicity, presence of children at home, smoking status, insurance status, use of oxygen supplementation at home, timing of admission relative to disease onset, timing from beginning of the influenza season to admission, the specific influenza season, and the presence of immunosuppressive conditions and other chronic medical conditions associated with influenza-associated complications including cardiopulmonary disease, diabetes mellitus, chronic liver/kidney disease, and neurological disease. \*Parameter was modeled using restricted cubic splines to account for nonlinear effects

**FIGURE 1S. Temporal distribution of cases and controls by research site**



Footnote: note that influenza seasons were defined by epidemic week (Table 1S) for each site, but the figure displays counts by calendar month. Influenza seasons are represented with blue horizontal bars as reference, where the extension of the bars approximates the extension of the seasons for each site.