**Epidemiology and Infection**

**Interactive effects of age and respiratory virus on severe lower respiratory infection - Supplementary Material**

N. Prasad, A. A. Trenholme, Q. S. Huang, M.G. Thompson, N. Pierse, MA. Widdowson, T. Wood, R. Seeds, S. Taylor, C.C. Grant, E. C. Newbern, SHIVERS team

**Supplementary Text S1: Additional information on laboratory testing methods as part of the** **Southern Hemisphere Influenza Vaccine Effectiveness Research and Surveillance project**

Two major public hospitals, the Auckland and Counties Manakau District Health Board hospitals (ADHB and CMDHB), served the central, eastern, and southern Auckland region in 2012-2016 and were the study sites of the SHIVERS surveillance. The performance of hospital assays from clinician ordered tests were compared to CDC’s real-time RT-PCR as a gold standard. Only results from assays with a sensitivity greater than 80% and a specificity greater than 95% were included in the SHIVERS study dataset.

**Supplementary Table S1: Performance of hospital assays (clinician ordered tests) in detecting different respiratory viruses 2012-2016**

|  |  |  |  |
| --- | --- | --- | --- |
| Virus type | Auckland hospital assay |  | Counties Manukau hospital assay |
| Sensitivity (95% CI) | Specificity (95% CI) |  | Sensitivity (95% CI) | Specificity (95% CI) |
| Flu | 96.49 (94.74-97.67) | 99.75 (99.52-99.87) |  | 97.82 (96.43-98.67) | 99.50 (99.29-99.65) |
| RSV | 95.74 (93.84-97.08) | 99.61 (99.32-99.78) |  | 91.38 (88.95-93.32) | 98.18 (97.47-98.69) |
| RV | 94.79 (92.48-96.42) | 99.86 (99.58-99.95) |  | ------------------------ | 85.71 (60.06-95.99) |
| ADV | 87.87 (83.45-91.23) | 99.65 (99.39-99.80) |  | 69.87 (64.56-74.70) | 97.89 (97.14-98.44) |

**Supplementary Text S2: Acute lower respiratory tract infections discharge diagnosis - ICD-10 codes.**

J09 - Influenza due to certain identified influenza viruses

J10 - Influenza due to other identified influenza virus

J11 - Influenza due to unidentified influenza virus

J12 - Viral pneumonia, not elsewhere classified

J13 - Pneumonia due to Streptococcus pneumoniae

J14 - Pneumonia due to Hemophilus influenzae

J15 - Bacterial pneumonia, not elsewhere classified

J16 - Pneumonia due to other infectious organisms, not elsewhere classified

J17 - Pneumonia in diseases classified elsewhere

J18 - Pneumonia, unspecified organism

J20 - Acute bronchitis

J21 - Acute bronchiolitis

J22 - Unspecified acute lower respiratory infection

**Supplementary Table S2: Comparison of demographics and clinical outcomes among children tested for influenza, RSV, RV, ADV and non-tested children aged <2 years hospitalised with acute lower respiratory infections in Auckland, New Zealand 2012-2015**

|  |  |  |
| --- | --- | --- |
|   | Tested ALRI hospitalisations | Non-tested ALRI hospitalisations |
| n |  (column %) | n | (column %) |
| **Total** | 1780 | (100.0) | 469 | (100.0) |
| **Age**  |   |   |   |   |
| 0 - 2 months | 352 | (19.8) | 111 | (23.7) |
| 3 - 5 months | 368 | (20.7) | 98 | (20.9) |
| 6 - 11 months | 601 | (33.8) | 164 | (35.0) |
| 12 - 23 months | 459 | (25.8) | 96 | (20.5) |
| **Ethnicity** |   |   |   |   |
| Maori | 513 | (28.8) | 132 | (28.1) |
| Pacific | 896 | (50.3) | 230 | (49.0) |
| European, Asian, and Other | 371 | (20.8) | 107 | (22.8) |
| **Sex** |   |   |   |   |
| Male | 1082 | (60.8) | 263 | (56.1) |
| **Household deprivation** |   |   |   |   |
| NZ dep 1-6 (Least deprived) | 359 | (20.2) | 102 | (21.8) |
| NZ dep 7-8 | 282 | (15.8) | 50 | (10.7) |
| NZ dep 9-10 (Most deprived) | 1139 | (63.9) | 317 | (67.6) |
| **ICU Admission** | 228 | (12.8) | 74 | (15.8) |
| **Hospital length of stay – mean (range)** | 3 | (1-27) | 3 | (1-29) |

**Supplementary Table S3: Sources and definitions of covariates used in models**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Definition** | **Source** | **Completeness** |
| Age | Age in months at time of hospital event - calculated from date of birth and date of event | SHIVERS case report form (CRF), New Zealand (NZ) Ministry of Health (MoH) National Hospitalization (NMDS) data collections.a | All patients |
| Sex | Male or Female | SHIVERS CRF, NZ MoH National Hospitalization (NMDS) data collections  | All patients |
| Ethnicity | Prioritized ethnicity - Maori, Pacific, Asian, European, and Other. (European and Other ethnicity combined for the current analysis).  | SHIVERS case report form (CRF), National Hospitalization (NMDS) data collections  | All patients |
| Neighborhood socio-economic status (NZ Deprivation score)b | NZ Deprivation 2013 (NZDep) Index of Deprivation - combines census data relating to income, home ownership, employment, qualifications, family structure, housing, access to transport and communications to create a deprivation score for each meshblock in New Zealand. Meshblocks are the smallest geographical area defined by Statistics New Zealand, with a population of around 60–110 people.NZDep2013 groups deprivation scores into deciles, where 1 represents the areas with the least deprived scores and 10 the areas with the most deprived scores. A value of 10 therefore indicates that a meshblock is in the most deprived 10% of areas in New Zealand.Deciles (1-10) are converted to an NZDep2013 score (1-5) which were used for the current analysis.  | NZ MoH National Hospitalization (NMDS) data collections  | All patients |
| Current influenza vaccination | Had an influenza vaccination in the last 12 months | Self-report SHIVERS CRF, NZ MoH National Immunization Register c | All consented patients. 9% of hospitalizations with unknown/missing vaccination record.  |
| Pre-term birth | <37 weeks of gestational age - determined from gestational age at birth | SHIVERS CRF, NZ MoH National Maternity collections d  | All patients |
| Low birth weight | <2500 grams - determined from birth weight | SHIVERS CRF, NZ MoH National Maternity collections d | All patients |
| Asthma | Does the patient have asthma (based on medical report) | SHIVERS CRF – hospital medical records | All consented patients |
| Other lung condition | Does the patient have another lung condition (based on medical report) | SHIVERS CRF – hospital medical records | All consented patients |
| Prior respiratory hospitalization beyond last 14 days | Flag patients with primary respiratory discharge diagnoses (J ICD-codes) before the 14 days preceding the hospitalization. Data from 2004-2016. For children aged <2 years, only applicable from 2009/2010). Emergency visits and non-admitted cases excluded.  | NZ MoH National Hospitalization (NMDS) data collections  | All patients |
| Congenital heart conditions | Does the patient have a congenital heart condition (based on medical report) | SHIVERS CRF – hospital medical records | All consented patients |
| Immunodeficiency | Does the patient have any immune condition (based on medical report) | SHIVERS CRF – hospital medical records | All consented patients |
| Renal or hepatic disease | Does the patient have any renal or hepatic condition (based on medical report) | SHIVERS CRF – hospital medical records | All consented patients |

a New Zealand Ministry of Health. National collections and surveys. Available at: <http://www.health.govt.nz/nz-health-statistics/national-collections-and-surveys/collections>.

b Salmond C, Crampton P, King P, Waldegrave C. NZiDep: a New Zealand index of socioeconomic deprivation for individuals. Social science & medicine **2006**; 62:1474-85.

c New Zealand Ministry of Health. National Immunication Register. Availabe at: <http://www.health.govt.nz/our-work/preventative-health-wellness/immunisation/national-immunisation-register>.

d. New Zealand Ministry of Health. National Maternity collections. Available at: <http://www.health.govt.nz/nz-health-statistics/national-collections-and-surveys/collections/national-maternity-collection>.

**Supplementary Table S4: Association of intensive care unit admission and prolonged hospital stay with age and virus among children aged <2 years hospitalized with acute lower respiratory infection in Auckland, New Zealand 2012-2015– *including influenza vaccination***

|  |  |  |  |
| --- | --- | --- | --- |
|  | **ICU Admission** |  | **Prolonged hospital stay** |
|  | **RR** | **(95% CI)** | **P-value** | **RR** | **(95% CI)** | **P-value** |
| **Main effects** |   |   |   |   |   |   |   |
| **Demographics** |   |   |   |   |   |   |   |
| Age in months | 0.95 | (0.92-0.99) | 0.016 |   | 0.96 | (0.96-0.97 | 0.000 |
| European/ Asian/ Other | ref  |   |   |   |   |   |   |
| Maori  | 1.41 | (0.98-2.04) | 0.063 |   | 1.06 | (0.95-1.18 | 0.317 |
| Pacific | 1.07 | (0.73-1.57) | 0.745 |   | 1.01 | (0.90-1.13 | 0.894 |
| Nz dep 1-6 (High socio-economic area) a | 0.87 | (0.59-1.27) | 0.459 |   | 1.06 | (0.93-1.20 | 0.382 |
| Nz dep 7-8 | ref  |   |   |   |   |   |   |
| Nz dep 9-10 (Low socio-economic area) | 0.50 | (0.36-0.70) | 0.000 |   | 0.96 | (0.86-1.06 | 0.402 |
| Current influenza vaccine | 1.46 | (0.80-2.68) | 0.220 |   | 1.30 | (1.03-1.64 | 0.029 |
| **Underlying conditions** |   |   |   |   |   |   |   |
| Premature birth and/or low birth weight b | 1.84 | (1.40-2.42) | 0.000 |   | 1.15 | (1.04-1.26 | 0.004 |
| Chronic respiratory (asthma, other lung disease, and/or prior respiratory hospitalization) | 1.58 | (1.21-2.07) | 0.001 |   | 1.17 | (1.08-1.27 | 0.000 |
| Other underlying condition (Congenital cardiovascular, immune, renal, hepatic) | 2.08 | (1.34-3.23) | 0.001 |   | 1.70 | (1.38-2.09 | 0.000 |
| **Viral Infection** |   |   |   |   |   |   |   |
| Influenza  | 0.42 | (0.15-1.13) | 0.084 |   | 0.76 | (0.62-0.94 | 0.011 |
| RSV  | 1.47 | (0.93-2.32) | 0.101 |   | 1.01 | (0.93-1.10 | 0.846 |
| Rhinovirus  | 0.88 | (0.66-1.18) | 0.394 |   | 0.83 | (0.76-0.91 | 0.000 |
| Adenovirus  | 1.50 | (1.09-2.07) | 0.012 |   | 0.99 | (0.79-1.24 | 0.937 |
| **Interactive effects** |   |   |   |   |   |   |   |
| Influenza and age in months (multiplicative) | 1.07 | (0.98-1.16) | 0.137 |   | 1.04 | (1.02-1.06 | 0.000 |
| Influenza and age in months (additive [RERI]) | 0.05 | (0.01-0.10) | 0.014 |   |   |   |   |
| RSV and age in months (multiplicative) | 0.92 | (0.86-0.97) | 0.005 |   |   |   |   |
| RSV and age in months (additive [RERI]) | -0.14 | (-0.28-0.01) | 0.063 |   |   |   |   |
| Adenovirus and age in months (multiplicative) |   |   |   |   | 1.02 | (1.00-1.04 | 0.041 |
| Adenovirus and age in months (additive [RERI]) |   |   |   |   |   |   |   |

Abbreviations: ICU = Intensive care unit; RR =risk ratio; RERI =relative excess risk owing to interaction; RSV = respiratory syncytial virus

**a** Socio-economic status ascertained from New Zealand Deprivation score (2013).

**b** Preterm birth defined as <37 weeks of gestational age. Low birth weight defined as birth weight <2500 grams.

**Supplementary Figure S1: Proportion of ICU by hospital length of stay in days among children <2 years with an acute lower respiratory tract infection (ALRI), 2012-2015 winter seasons, Auckland, New Zealand**

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**Supplementary Table S5. *Unadjusted* association of Intensive care unit admission and prolonged hospital stay with age and virus among children aged <2 years hospitalized with acute lower respiratory infection in Auckland, New Zealand 2012-2015**

|  |  |  |  |
| --- | --- | --- | --- |
|   | **ICU Admission** |  | **Prolonged hospital stay** |
|  | **RR** | **(95% CI)** | **P-value** | **RR** | **(95% CI)** | **P-value** |
| **Main effects** |   |   |   |   |   |   |   |
| **Demographics** |  |  |  |   |  |   |  |
| Age in months | 0.96 | (0.93-0.98) | 0.0008 |   | 0.99 | (0.97-0.99) | 0.0000 |
| Male | 1.15 | (0.89-1.48) | 0.2891 |   | 1.00 | (0.93-1.09) | 0.9073 |
| European/ Asian /Other |  ref |   |   |   |  ref |   |   |
| Maori  | 1.13 | (0.81-1.56) | 0.4720 |   | 1.02 | (0.91-1.14) | 0.7500 |
| Pacific | 0.76 | (0.55-1.04) | 0.0840 |   | 0.95 | (0.86-1.05) | 0.3230 |
| Nz dep 1-6 (High socio-economic area) a | 0.96 | (0.68-1.36) | 0.8120 |   | 1.10 | (0.96-1.25) | 0.1650 |
| Nz dep 7-8 |   |   |   |   |   |   |   |
| Nz dep 9-10 (Low socio-economic area) | 0.60 | (0.44-0.82) | 0.0010 |   | 0.98 | (0.89-1.09) | 0.7290 |
| **Underlying conditions** |  |  |  |   |  |   |  |
| Premature birth and/or low birth weight b | 1.91 | (1.48-2.47) | 0.0000 |   | 1.21 | (1.11-1.33) | 0.0000 |
| Chronic respiratory (asthma, other lung disease, and/or prior respiratory hospitalization) | 1.69 | (1.32-2.15) | 0.0000 |   | 1.18 | (1.09-1.27) | 0.0000 |
| Other underlying condition (Congenital cardiovascular, immune, renal, hepatic) | 2.26 | (1.58-3.22) | 0.0000 |   | 1.70 | (1.42-2.20) | 0.0000 |
| **Viral Infection** |  |  |  |   |  |   |  |
| Influenza  | 0.61 | (0.39-0.96) | 0.0322 |   | 0.99 | (0.87-1.13) | 0.8593 |
| RSV | 0.88 | (0.68-1.12) | 0.2960 |   | 1.04 | (0.97-1.12) | 0.2779 |
| Rhinovirus  | 1.02 | (0.77-1.34) | 0.9107 |   | 0.88 | (0.81-0.95) | 0.0021 |
| Adenovirus  | 1.28 | (0.95-1.72) | 0.1106 |   | 1.15 | (1.03-1.29) | 0.0122 |
| Multiple viruses | 0.96 | (0.70-1.32) | 0.7832 |   | 1.04 | (0.94-1.14) | 0.4510 |
| **Interactive effects** |  |  |  |   |  |   |  |
| Influenza and age in months (multiplicative) | 1.08 | (1.00-1.17) | 0.0380 |   | 1.03 | (1.01-1.05) | 0.0030 |
| Influenza and age in months (additive [RERI]) | 0.06 | (0.03-0.09) | 0.0000 |   |   |   |   |
| RSV and age in months (multiplicative) | 0.92 | (0.87-0.97) | 0.0040 |   | 0.99 | (0.97-1.00) | 0.0510 |
| RSV and age in months (additive [RERI]) | -0.12 | (-0.24-0.00) | 0.0430 |   |   |   |   |
| RV and age in months (multiplicative) | 1.00 | (0.94-1.07) | 0.9470 |   | 0.99 | (0.98-1.01) | 0.4130 |
| RV and age in months (additive [RERI]) | 0.00 | (-0.08-0.08) | 0.9330 |   |   |   |   |
| Adenovirus and age in months (multiplicative) | 1.03 | (0.96-1.10) | 0.4180 |   | 1.02 | (0.99-1.04) | 0.1520 |
| Adenovirus and age in months (additive [RERI]) | 0.02 | (-0.07-0.11) | 0.6150 |   |   |   |   |

Abbreviations: ICU = Intensive care unit; RR =risk ratio; RERI =relative excess risk owing to interaction; RSV = respiratory syncytial virus

**Supplementary Figure S2: Percentage (%) RSV positive in ICU by age in months among hospitalizations in children <2 years with an acute lower respiratory tract infection (ALRI), 2012-2015 winter seasons, Auckland, New Zealand**

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**Supplementary Figure S3: Percentage (%) influenza positive in ICU by age in months among hospitalizations in children <2 years with an acute lower respiratory tract infection (ALRI), 2012-2015 winter seasons, Auckland, New Zealand**

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