Supplemental Tables: Upper respiratory tract co-detection of human endemic coronaviruses and high-density pneumococcus associated with increased severity among HIV-uninfected children under 5 years old in the PERCH study

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## 1. Distribution of human endemic coronavirus (CoV) and high-density pneumococcus (HDSpn) co-detection category by PERCH case-control status and sex

|  |  |
| --- | --- |
| **Case / Control** | **Co-detection Category** |
| **A. CoV+ / HDSpn+** | **B. CoV+ / HDSpn-** | **C. CoV- / HDSpn+** | **D. CoV- and HDSpn -** |
| **n=90** | **n=701** | **n=781** | **n=7292** |
| **Male** |  |  |  |  |
|  **Case** n = 2248 row% col% | 22 | 158 | 242 | 1826 |
| 1.0 | 7.0 | 10.8 | 81.2 |
| 46.8 | 41.3 | 61.1 | 46.5 |
|  **Control** n = 2505 row% col% | 25 | 225 | 154 | 2101 |
| 1.0 | 9.0 | 6.2 | 83.9 |
| 53.2 | 58.8 | 38.9 | 53.5 |
| **Female** |   |   |   |   |
|  **Case** n=1640 row% col% | 21 | 89 | 207 | 1323 |
| 1.3 | 5.4 | 12.6 | 80.7 |
| 48.8 | 28.1 | 53.8 | 39.3 |
|  **Control** n=2470 row% col% | 22 | 228 | 178 | 2042 |
| 0.9 | 9.2 | 7.2 | 82.7 |
| 51.2 | 71.9 | 46.2 | 60.7 |

## 2. Distribution of human endemic coronavirus (CoV) and high-density pneumococcus (HDSpn) co-detection category by PERCH case-control status and age

|  |  |
| --- | --- |
| **Case / Control** | **Co-detection Category** |
| **A. CoV+ / HDSpn+** | **B. CoV+ / HDSpn-** | **C. CoV- / HDSpn+** | **D. CoV- and HDSpn -** |
| **n=90** | **n=701** | **n=781** | **n=7292** |
| **Case** |  |  |  |  |
|  **1-5m (n=1581)** | 17 | 116 | 177 | 1271 |
|  Row % | 1.1 | 7.3 | 11.2 | 80.4 |
|  Col % | 39.5 | 47.0 | 39.4 | 40.4 |
|  **6-11m (n=884)** | 10 | 58 | 107 | 709 |
|  Row % | 1.1 | 6.6 | 12.1 | 80.2 |
|  Col % | 23.3 | 23.5 | 23.8 | 22.5 |
|  **12-23m (n=883)** | 8 | 45 | 119 | 711 |
|  Row % | 0.9 | 5.1 | 13.5 | 80.5 |
|  Col % | 18.6 | 18.2 | 26.5 | 22.6 |
|  **24-59m (n=540)** | 8 | 28 | 46 | 458 |
|  Row % | 1.5 | 5.2 | 8.5 | 84.8 |
|  Col % | 18.6 | 11.3 | 10.2 | 14.5 |
| **Control** |   |   |   |   |
|  **1-5m (n=1552)** | 17 | 143 | 117 | 1275 |
|  Row % | 1.1 | 9.2 | 7.5 | 82.2 |
|  Col % | 36.2 | 31.5 | 35.2 | 30.8 |
|  **6-11m (n=1182)** | 10 | 116 | 74 | 982 |
|  Row % | 0.9 | 9.8 | 6.3 | 83.1 |
|  Col % | 21.3 | 25.6 | 22.3 | 23.7 |
|  **12-23m (n=1232)** | 14 | 106 | 70 | 1042 |
|  Row % | 1.1 | 8.6 | 5.7 | 84.6 |
|  Col % | 29.8 | 23.4 | 21.1 | 25.2 |
|  **24-59m (n=1010)** | 6 | 89 | 71 | 844 |
|  Row % | 0.6 | 8.8 | 7.0 | 83.6 |
|  Col % | 12.8 | 19.6 | 21.4 | 20.4 |

Chi-square p-value for difference among cases p=0.077, among controls p=0.540

## 3. Clinical Characteristics of Children Hospitalized with Severe or Very Severe Pneumonia by NP/OP Co-detection Status of Endemic Coronavirus (CoV-NL63, CoV-229E, CoV-OC43 or CoV-HKU1) and High-density S. pneumoniaea, by sex.

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristics** | **No. (% with available information)** |  | **Adjusted p-valuea** |
| **A. CoV+ / HDSpn+****n=43** | **B. CoV+ / HDSpn-****n=247** | **C. CoV- / HDSpn+****n=449** | **D. CoV- or HDSpn -****n=3149** | **Overall** | **A vs B** | **A vs C** | **A vs D** |
| **Very severe pneumonia (2005 WHO definition)** | 23 | 81 | 174 | 969 | **<0.001** | **0.013** | 0.084 | **0.004** |
| (53.5) | (32.8) | (38.8) | (30.8) |  |
|  Male | 13/22  | 46/158 | 84/242 | 539/1826 | **0.039** | **0.021** | 0.092 | **0.015** |
| (59.1) | (29.1) | (34.7) | (29.5) |  |
|  Female | 10/21 | 35/89 | 90/207 | 430/1323 | **0.009** | 0.324 | 0.623 | 0.131 |
| (47.6) | (39.3) | (43.5) | (32.5) |  |
| **Hypoxemia at admission** | 17 | 90 | 183 | 1098 | 0.061 | 0.631 | 0.853 | 0.503 |
| (39.5) | (36.6) | (40.9) | (35.0) |  |
|  Male | 8 | 49 | 91 | 592 | 0.182 | 0.735 | 0.740 | 0.716 |
| (36.4) | (31.0) | (37.6) | (32.5) |  |
|  Female | 9 | 41 | 92 | 506 | 0.265 | 0.900 | 0.796 | 0.644 |
| (42.9) | (46.6) | (44.7) | (38.3) |  |
| **WHO defined very severe or hypoxemia** | 30 | 130 | 254 | 1601 | **0.002** | **0.026** | 0.070 | **0.008** |
| (69.8) | (52.9) | (56.6) | (50.9) |  |
|  Male | 16 | 74 | 125 | 885 | 0.094 | **0.042** | 0.103 | **0.033** |
| (72.7) | (46.8) | (51.7) | (48.5) |  |
|  Female | 14 | 56 | 129 | 716 | **0.015** | 0.400 | 0.371 | 0.125 |
| (66.7) | (63.6) | (62.3) | (54.2) |  |
| **Supplemental oxygen (ever)b,c** | 13/36 | 48/192 | 99/367 | 687/2475 | **0.001** | **0.030** | 0.179 | **0.013** |
| (36.11) | (25.0) | (27.0) | (27.8) |  |
|  Male | 9/20 | 26/126 | 59/206 | 373/1460 | **<0.001** | **0.010** | 0.331 | **0.012** |
| (45.0) | (20.6) | (28.6) | (25.5) |  |
|  Female | 4/16 | 22/66 | 40/161 | 314/1015 | 0.584 | 0.834 | 0.348 | 0.397 |
| (25.0) | (33.3) | (24.8) | (30.9) |  |
| **Tachypneac** | 38 | 199 | 398 | 2546 | **0.044** | 0.528 | 0.858 | 0.479 |
| (88.4) | (81.2) | (88.6) | (81.5) |  |
|  Male | 17 | 122 | 220 | 1479 | **0.009** | 0.900 | **0.085** | 0.418 |
| (77.3) | (77.2) | (90.9) | (81.5) |  |
|  Female | 21 | 77 | 178 | 1067 | 0.423 | 0.948 | 0.864 | 0.910 |
| (100.0) | (88.5) | (86.0) | (81.5) |  |
| **Fever** | 37 | 193 | 400 | 2533 | **0.001** | 0.311 | 0.389 | 0.593 |
| (86.1) | (78.1) | (89.1) | (80.4) |  |
|  Male | 20 | 121 | 212 | 1462 | **0.025** | 0.200 | 0.892 | 0.367 |
| (90.9) | (76.6) | (87.6) | (80.1) |  |
|  Female | 17 | 72 | 188 | 1071 | **0.017** | 0.855 | 0.199 | 0.871 |
| (81.0) | (80.9) | (90.8) | (81.0) |  |
| **Observed cough** | 22 | 168 | 302 | 2215 | 0.175 | 0.174 | 0.078 | **0.030** |
| (51.2) | (68.0) | (67.4) | (70.6) |  |
|  Male | 10 | 110 | 167 | 1310 | 0.204 | 0.193 | 0.089 | **0.031** |
| (45.5) | (69.6) | (69.0) | (71.9) |  |
|  Female | 12 | 58 | 135 | 905 | 0.720 | 0.681 | 0.354 | 0.395 |
| (57.1) | (65.2) | (65.5) | (68.7) |  |
| **Vomiting** | 12 | 49 | 104 | 643 | 0.382 | 0.404 | 0.560 | 0.252 |
| (28.6) | (19.8) | (23.2) | (20.4) |  |
|  Male | 9 | 28 | 52 | 358 | 0.133 | **0.040** | 0.076 | **0.029** |
|  | (40.9) | (17.7) | (21.5) | (19.6) |  |
|  Female | 3 | 21 | 52 | 285 | 0.726 | 0.254 | 0.318 | 0.448 |
|   | (15.0) | (23.6) | (25.1) | (21.5) |  |
| **Diarrhea** | 9 | 38 | 86 | 439 | 0.062 | 0.219 | 0.975 | 0.313 |
| (20.9) | (15.4) | (19.2) | (13.9) |  |
|  Male | 5 | 27 | 53 | 248 | **0.004** | 0.481 | 0.605 | 0.326 |
|  | (22.7) | (17.1) | (22.0) | (13.6) |  |
|  Female | 4 | 11 | 33 | 191 | 0.816 | 0.283 | 0.760 | 0.637 |
|  | (19.1) | (12.4) | (16.0) | (14.4) |  |
| **Abnormal chest X-ray c**  | 15/31 | 110/213 | 220/377 | 1381/2706 | 0.077 | 0.834 | 0.294 | 0.930 |
| (48.4) | (51.6) | (58.4) | (51.0) |  |
|  Male | 11/17 | 60/137 | 119/205 | 783/1585 | **0.030** | 0.081 | 0.664 | 0.215 |
| (64.7) | (43.8) | (58.1) | 49.4) |  |
|  Female | 4/14 | 50/76 | 101/172 | 598/1121 | **0.030** | **0.025** | **0.023** | 0.127 |
| (28.6) | (65.8) | (58.7) | (53.4) |  |
| **Weight-for-height Z-score < -3 SDs** | 5 | 25 | 73 | 338 | 0.118 | 0.904 | 0.282 | 0.852 |
| (11.9) | (10.6) | (16.6) | (11.1) |  |
|  Male | 4 | 19 | 43 | 184 | 0.052 | 0.852 | 0.901 | 0.333 |
| (19.1) | (12.3) | (18.1) | (10.4) |  |
|  Female | 1 | 6 | 30 | 154 | 0.247 | 0.771 | 0.177 | 0.249 |
| (4.8) | (7.3) | (14.9) | (12.1) |  |
| **Weight-for-age Z-score < -3 SDs c** | 7 | 31 | 84 | 491 | 0.216 | 0.575 | 0.677 | 0.874 |
| (16.7) | (12.7) | (18.7) | (15.7) |  |
|  Male | 6 | 18 | 54 | 280 | **0.014** | **0.046** | 0.705 | 0.126 |
| (28.6) | (11.5) | (22.3) | (15.4) |  |
|  Female | 1 | 13 | 30 | 212 | 0.604 | 0.173 | 0.348 | 0.203 |
| (4.8) | (14.8) | (14.5) | (16.1) |  |
| **Arm circumference for age Z-score < -3 SDsd**  | 4 | 6 | 34 | 120 | 0.172 | 0.237 | 0.930 | 0.528 |
| (15.4) | (4.6) | (12.8) | (6.5) |  |
|  Male | 3 | 2 | 21 | 67 | **0.005** | **0.043** | 0.546 | 0.121 |
|  | (21.4) | (2.6) | (14.6) | (6.4) |  |
|  Female | 1 | 4 | 13 | 53 | 0.828 | 0.447 | 0.577 | 0.429 |
|  | (8.3) | (7.4) | (10.7) | (6.8) |  |
| **Severe acute malnutritione** | 7 | 43 | 97 | 556 | 0.635 | 0.714 | 0.257 | 0.473 |
| (16.3) | (17.7) | (21.8) | (17.8) |  |
|  Male | 6 | 26 | 55 | 295 | 0.298 | 0.480 | 0.928 | 0.308 |
| (27.3) | (16.6) | (22.9) | (16.3) |  |
|  Female | 1 | 17 | 42 | 261 | 0.308 | 0.149 | 0.095 | 0.075 |
| (4.8) | (19.8) | (20.5) | (20.0) |  |
| **Height-for-age Z-score < -3 SDs** | 8 | 29 | 67 | 522 | 0.192 | 0.062 | 0.421 | 0.268 |
| (21.1) | (14.2) | (18.1) | (19.8) |  |
|  Male | 6 | 21 | 37 | 329 | 0.234 | 0.053 | 0.305 | 0.160 |
| (30.0) | (15.7) | (18.9) | (21.5) |  |
|  Female | 2 | 8 | 30 | 193 | 0.427 | 0.491 | 0.952 | 0.972 |
| (11.1) | (11.4) | (17.1) | (17.4) |  |
| **Leukocytosis** | 22 | 114 | 176 | 1273 | **0.004** | 0.517 | 0.098 | **0.018** |
| (55.0) | (49.1) | (42.6) | (42.9) |  |
|  Male | 9 | 69 | 96 | 723 | 0.129 | 0.606 | 0.930 | 0.730 |
| (40.9) | (47.9) | (43.1) | (42.5) |  |
|  Female | 13 | 45 | 80 | 550 | **0.010** | 0.165 | **0.011** | **0.003** |
| (72.2) | (51.1) | (42.1) | (43.4) |  |
| **Lymphopenia**f | 14 | 62 | 138 | 796 | 0.086 | 0.228 | 0.944 | 0.370 |
| (32.6) | (25.1) | (30.7) | (25.3) |  |
|  Male | 6 | 42 | 71 | 453 | 0.425 | 0.856 | 0.705 | 0.935 |
| (27.3) | (26.6) | (29.3) | (24.8) |  |
|  Female | 8 | 20 | 67 | 343 | 0.146 | 0.065 | 0.611 | 0.230 |
| (38.1) | (22.5) | (32.4) | (25.9) |  |
| **C-reactive protein (mg/L), median, [IQR]** | 44.3 [8.1 - 176.4] | 14.8 [3.4 - 44.9] | 27.8[7.2 - 95.7] | 12.9[3.3 - 39.0] | **<0.001** | **<0.001** | 0.094 | **<0.001** |
|  Male | 44.3[7.8 - 176.4] | 14.6[4.5 - 39.5] | 22.6[5.2 - 82.9] | 12.5[3.0 - 37.8] | **<0.001** | **<0.001** | **0.015** | **<0.001** |
|  Female | 43.5[8.5 - 130.7] | 15.7[2.4 - 53.6] | 34.4[11.9 - 107.6] | 13.1[3.6 - 41.3] | **<0.001** | **0.029** | 0.967 | **0.004** |
| **Underlying condition**g | 9 | 61 | 129 | 803 | 0.637 | 0.371 | 0.294 | 0.214 |
| (20.9) | (24.7) | (28.7) | (25.5) |  |
|  Male | 7 | 35 | 65 | 429 | 0.713 | 0.968 | 0.806 | 0.620 |
| (31.8) | (22.2) | (26.9) | (23.5) |  |
|  Female | 2 | 26 | 64 | 374 | 0.988 | 0.221 | 0.212 | 0.209 |
| (9.5) | (29.2) | (30.9) | (28.3) |  |

WHO, World Health Organization; SD, Standard deviation; IQR, Inter-quartile range; CoV, Coronavirus; HDSpn, High-density *Streptococcus pneumoniae*; NP/OP, Nasopharyngeal/oropharyngeal.

a. P-values for pairwise comparisons of categorical variables obtained from logistic regression model adjusted for age and site (where applicable). P-values comparing co-detection groups are presented for males and females together, followed by sex-stratified p-values listed below the grouped p-values.

b. Excludes South Africa due to near uniformity of receiving oxygen at the South Africa PERCH site.

c. Significant effect modification by sex, as indicated by interaction term p<0.05 adjusted for site and age.

d. Restricted to children aged 6 months or older.

e. Severe acute malnutrition: weight-for-height Z-score <-3 SD or middle arm circumference Z-score <-3 SDs or diagnosis of acute severe malnutrition.

f. Below 3,000 cells per microliter of blood (3 × 109 per liter)

g. Underlying conditions: cerebral palsy, congenital heart disease/defect, congenital abnormalities, developmental delay, severe malnutrition, prematurity in an infant <6 months old. f. The number of days with cough, fever, difficulty breathing, wheeze, or runny nose, whichever symptom is longest.

## 4. C-Reactive protein levels by human endemic coronavirus (CoV) and high-density pneumococcus (HDSpn) NP/OP co-detection status and sex



Kruskal-Wallis test p < 0.001 for differences in log CRP among males and also among females. Median values indicated by horizontal line. Mean values indicated by circles. Quartile 1 and quartile 3 indicated by the bottom and top of box, respectively.

## 5. Overall mortality by sex among PERCH cases

|  |  |  |  |
| --- | --- | --- | --- |
| **Sex of Child** | **Died** | **aOR****(95% CI)** | **p-value** |
| **Yes** | **No** |
| **n = 292** | **n = 3343** |
| Malen=2105 | 1567.4% | 196993.5% | 0.640(0.497-0.822) | 0.001 |
| Femalen=1530 | 1368.9% | 137489.8% | Ref |  |

## 6. Mortality by age and sex category by human endemic coronavirus (CoV) and high-density pneumococcus (HDSpn) NP/OP co-detection category

|  |  |  |  |
| --- | --- | --- | --- |
| **Mortality a** | **No. (% with available information)** |  | **Adjusted p-valuea** |
| **A. CoV+ / HDSpn+****n=43** | **B. CoV+ / HDSpn-****n=247** | **C. CoV- / HDSpn+****n=449** | **D. CoV- or HDSpn -****n=3149** | **Overall** | **A vs B** | **A vs C** | **A vs D** |
| **Overall** | 9 / 40 | 19 / 235 | 41 / 422 | 205 / 2864 | 0.053 | **0.006** | **0.035** | **0.006** |
| (22.5) | (8.1) | (9.7) | (7.2) |  |
| **By Sex** |  |  |  |  |  |  |  |  |
|  Male | 7 / 20 | 8 / 150 | 16 / 227 | 95 / 1670 | **0.004** | **<0.001** | **0.002** | **<0.001** |
| (35.0) | (5.3) | (7.1) | (5.7) |  |
|  Female | 2 / 20 | 11 / 85 | 25 / 195 | 110 / 1194 | 0.694 | 0.739 | 0.762 | 0.992 |
| (10.0) | (12.9) | (12.8) | (9.2) |  |
| **By Age Category** |  |  |  |  |  |  |  |  |
|  28 days – 11 months | 5 / 25 | 15 / 164 | 24 / 262 | 158 / 1765 | 0.304 | 0.100 | 0.089 | 0.057 |
| (20.0) | (9.2) | (9.2) | (9.0) |  |
|  12 – 59 months | 4 / 15 | 4 / 71 | 17 / 160 | 47 / 1099 | **<0.001** | **0.011** | 0.068 | **<0.001** |
| (26.7) | (5.6) | (10.6) | (4.3) |  |

a. Death within 30 days of admission. Data missing for 3/43 in CoV+/Spn+ group.

## 7. Adjusted Odds Ratios for Morbidity and Mortality for Nasopharyngeal/Oropharyngeal Co-Detection with Human Endemic Coronavirus (Cov) and High-Density *S. Pneumoniae* (HDSpn) among Children Hospitalized with Severe or Very Severe Pneumonia, Adjusted for Age, Site Region, and Malnutrition.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **CoV+/HDSpn+ vs. CoV+/HDSpn-** |  | **CoV+/HDSpn+ vs. CoV-/HDSpn+** |  | **CoV+/HDSpn+ vs. CoV-/HDSpn-** |
| **aORa** **(95% CI)** | **p-value** |  | **aORa** **(95% CI)** | **p-value** |  | **aORa** **(95% CI)** | **p-value** |
| **Deathb** |   |  |  |   |  |  |   |  |
|  Male | 11.65(3.05-44.43) | **<0.001** |  | 5.92(1.72 – 20.32) | **0.005** |  | 8.61(3.06 – 24.23) | **<0.001** |
|  Female | 0.40(0.06 - 2.88) | 0.365 |  | 0.85(0.16 – 4.40) | 0.842 |  | 1.23(0.27 – 5.72) | 0.788 |
| **Very severe pneumonia** |  |  |  |  |  |  |  |  |
|  Male | 5.01(1.74 – 14.47) | **0.003** |  | 2.06(0.70 – 6.06) | 0.187 |  | 3.71(1.46 – 9.43) | **0.006** |
|  Female | 1.55(0.50 – 4.80) | 0.445 |  | 1.51(0.54 – 4.18) | 0.432 |  | 2.14(0.83 – 5.51) | 0.116 |
| **Very severe pneumonia or hypoxemia** |  |  |  |  |  |  |  |  |
|  Male | 6.05(1.83 – 20.06) | **0.003** |  | 2.63(0.77 – 8.95) | 0.123 |  | 4.14(1.44 – 11.91) | **0.008** |
|  Female | 1.54(0.47 – 5.08) | 0.477 |  | 2.02(0.65 – 6.23) | 0.223 |  | 2.35(0.85 – 6.52) | 0.101 |
| **Supplemental oxygen (ever)c** |  |  |  |  |  |  |  |  |
|  Male | 4.12(1.30 – 13.10) | **0.016** |  | 1.55(0.52 – 4.65) | 0.433 |  | 3.25(1.21 – 8.69) | **0.019** |
|  Female | 0.87(0.19 – 4.13) | 0.864 |  | 1.27(0.31 – 5.21) | 0.740 |  | 1.14(0.31 – 4.23) | 0.845 |

CoV, Coronavirus; HDSpn, High-density *Streptococcus pneumoniae*; OR, Odds ratio; CI, Confidence interval

a. Adjusted for age, site region (Asia, West Africa, Southern Africa, and East Africa), and severe malnutrition by Z-score <-3 standard deviations.

b. Death within 30 days of admission.

c. Excludes South Africa due to near uniformity of receiving oxygen at the South Africa PERCH site.

## 8a. Case fatality ratio by NP/OP co-detection of any density *S. pneumoniae* (Spn) with human endemic coronavirus (CoV)

|  |  |
| --- | --- |
|  | **Co-detection Category** |
| **A. CoV+ / Spn+** | **B. CoV+ / Spn-** | **C. CoV- / Spn+** | **D. CoV- / Spn -** |
| **n=196** | **n=79** | **n=2369** | **n=917** |
| **Death** | 19(9.7) | 9(11.4) | 163(6.9) | 83(9.1) |
|  Male n=2067 | 10(8.3) | 5(10.2) | 72(5.3) | 39(7.4) |
|  Female n=1494 | 9(12.0) | 4(13.3) | 91(9.1) | 44(11.4) |

## 8b. Case fatality ratio by NP/OP co-detection of high (HDSpn) or low (LDSpn) density *S. pneumoniae* with coronavirus (CoV)

|  |  |
| --- | --- |
|  | **Mortalitya** |
| **CoV+ (n=275)** | **Cov- (n=3287)** |
| ***S. pneumoniae* carriage** | **Spn-** | **LDSpn**b | **HDSpn** | **Spn-** | **LDSpn** | **HDSpn** |
| **Total** | 9/7911.4% | 10/1566.4% | 9/4022.5% | 83/9179.1% | 122/19486.3% | 41/4229.7% |
| **Males** | 5/4910.2% | 3/1013.0% | 7/2035.0% | 39/5307.4% | 56/11404.9% | 16/2277.0% |
| **Females** | 4/3013.3% | 7/5512.7% | 2/2010.0% | 44/38711.4% | 66/8088.2% | 25/19512.8% |

1. Died within 30 days of hospital admission
2. Low density carriage defined as *S. pneumoniae* PCR detection <6.9 log10 copies/mL

## 9. Coronavirus (CoV) density (log10 copies/mL) by sex, mortality, and *S. pneumoniae* (Spn) co-detection status

|  |  |  |
| --- | --- | --- |
| **CoV group** | **N** | **CoV Median Viral Load (log10 copies/mL)** |
| **Median**  | **Lower Quartile** | **Upper Quartile** | **Wilcoxon p-value** |
| **Overall CoV+** | 290 | 5.23 | 3.73 | 6.41 |  |
|  Male | 180 | 5.21 | 3.76 | 6.32 | 0.127 |
|  Female | 110 | 5.29 | 3.62 | 6.56 |
| **Co-detection with high-density Spn** | 43 | 5.78 | 3.74 | 7.15 |  |
|  Male | 22 | 6.19 | 3.68 | 7.15 | 0.474 |
|  Female | 21 | 5.72 | 4.22 | 6.56 |
| **Mortality** |  |  |  |  |  |
|  Alive | 247 | 5.15 | 3.58 | 6.29 | 0.092 |
|  Dieda | 28 | 5.74 | 4.11 | 7.37 |
| **Mortality among co-detection with high-density Spn** |  |  |  |  |  |
|  Alive | 31 | 5.58 | 3.74 | 6.19 | **0.025** |
|  Dieda | 9 | 7.15 | 6.27 | 7.87 |
| **Spn Density Category** |  |  |  |  |  |
|  Non-carriers | 82 | 4.91 | 3.73 | 6.28 | 0.360 |
|  Low-density carriage | 165 | 5.34 | 3.65 | 6.37 |
|  High-density carriage (≥6.9 log10 copies/mL) | 43 | 5.78 | 3.74 | 7.15 |

a. Died within 30 days of admission

## 10. Coronavirus (CoV) viral load by high-density *S. pneumoniae* (HDSpn) co-detection status and sex



No statistically significant differences in log CoV density between groups. Median values indicated by horizontal line. Mean values indicated by circles. Quartile 1 and quartile 3 indicated by the bottom and top of box, respectively.

## 11. Clinical and etiologic findings among cases who died with human endemic coronavirus (CoV) in NP/OP

## 11a. With high-density *S. pneumoniae* (HDSpn) NP/OP co-detection

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Site** | **Sex** | **Age (mo.)** | **Days Ill Prior to Admission (days)** | **Severitya** | **Clinical history and presentationb** | **C-reactive protein (normal: <40)** | **Chest X-ray conclusion (at admission)** | **Malnutritionc** | **Other comorbidities** | **Immediate and secondary cause of death from medical record** | **Pleural fluid culture** | **Blood culture** | **NP/OP PCR** | **Induced Sputume PCR** |
| **S.pn log10 copies/mL** | **S.pn serotype** | **CoV log10 copies/mL** | **High density *H. influenzaed*** | **Other Organisms Detected** | ***S.pn*** **log10 copies/mL** | **CoV log10 copies/mL** |
| G | F | 6 | 2 | Very Severe  | Cough, Fever, Hypoxia, Lethargy | 193.6 | Consolidation | Normal | 0 | 1. Hypoxia2. Pneumonia | *S. aureus* | Negative | 7.6 | 6A | 7.9 | Yes | CMV, *C. pneumoniae,* *M. catarrhalis* | NAf | NA |
| M | F | 27 | 4 | Very Severe  | Cough, Diarrhea, Lethargy, Lymphopenia | Missing | Missing | WFA, WFH, HFA | 0 | 1. Shock / dehydration2. Metabolic acidosis |  | S.pn | 8.0 | 19F | 6.6 | Yes | CMV | NA | NA |
| K | M | 12 | 14 | Very Severe  |  Cough, Fever, Vomiting, Diarrhea, Lethargy | 18.4 | Normal | MUAC <115, HFA | 0 | 1. Malnutrition2. Gastroenteritis |  | Negative | 7.5 | 19F | 3.6 | Yes | Adenovirus, CMV, Human bocavirus, *M. catarrhalis*, Rhinovirus, RSV | 6.29 | 0 |
| M | M | 3 | 6 | Severe  | Cough, Fever, Vomiting, Diarrhea, Hypoxia, Meningitis | 3.4 | Normal | WFH, HFA | 0 | 1. Pneumonia |  | Negative | 8.5 | 6B | 8.2 | Yes | *M. catarrhalis* | NA | NA |
| M | M | 12 | 5 | Severe | Cough, Fever, Vomiting, Hypoxia | 384.4 | Consolidation with other infiltrate | WFA, WFH, HFA | 0 | 1. Shock / dehydration2. Pneumonia |  | Negative | 7.2 | 6A | 6.3 | Yes | CMV, *M. catarrhalis*, PV/EV | 0 | 5.43 |
| M | M | 10 | 3 | Very Severe  | Cough, Fever, Vomiting, Hypoxia | 105.0 | Missing | WFA, HFA | 0 | 1. Metabolic acidosis2. Pneumonia, malnutrition |  | Pseudomonas aeruginosa | 7.2 | NA | 7.2 | 0 | *M. catarrhalis*, rhinovirus | NA | NA |
| M | M | 6 | 7 | Very Severe  | Cough, Fever, Vomiting, Diarrhea | 24.5 | Consolidation | Normal | 0 | 1. Pneumonia |  | Negative | 7.6 | 19A | 8.1 | 0 | Adenovirus, CMV, *M. catarrhalis*, PIV 2, Rhinovirus | NA | NA |
| M | M | 14 | 1 | Very Severe  | Fever, Hypoxia | 1.9 | Missing | WFA, WFH | HIV admission diagnosis (HIV test status unknown) | 1. Pneumonia |  | Negative | 6.9 | 23F | 7.7 | 0 | CMV, *M. catarrhalis* | NA | NA |
| Z | M | 5 | 2 | Very Severe  | Cough, Fever, Lethargy, Lymphopenia | 2.7 | Uninterpretable | Normal | 0 | 1. Pneumonia2. Meningitis, sepsis, paralytic ileus |  | Negative | 7.6 | 23B | 3.7 | 0 | CMV, *M. catarrhalis* | NA | NA |

## 11b. Without high-density *S. pneumoniae* (HDSpn) NP/OP co-detection

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Site** | **Sex** | **Age (mo.)** | **Days Ill Prior to Admission (days)** | **Severitya** | **Clinical history and presentationb** | **C-reactive protein (normal: <40)** | **Chest X-ray conclusion (at admission)** | **Malnutritionc** | **Immediate and secondary cause of death from medical record** | **Pleural fluid culture** | **Blood culture** | **NP/OP PCR** | **Induced Sputume PCR** |
| **S.pn log10 copies/mL** | **CoV log10 copies/mL** | **High density *H. influenzaed*** | **Other Organisms Detected** | ***S.pn*** **log10 copies/mL** | **CoV log10 copies/mL** |
| K | F | 43 | **7** | Very Severe | Fever, Lethargy | 382.6 | Consolidation |  | 1. Malaria |  | Negative | 5.4 | 7.5 |  | *M. catarrhalis* | NA | NA |
| K | F | 1 | 14 | Very Severe | Cough, Fever, Hypoxia | . | Consolidation | HFA, WFA | 1. Heart disease |  | Negative | 0 | 5.1 |  | PCP, Rhinovirus, RSV, Salmonella, *S. aureus* | 0 | 4.4 |
| G | F | 6 | 3 | Severe | Cough, Fever, Hypoxia | 20.7 | Normal | MUAC<115 | 1. Pneumonia |  | Negative | 3.6 | 6.2 |  | CMV, *M. catarrhalis* | 0 | 4.7 |
| G | F | 16 | 8 | Very Severe | Cough, Fever, Lethargy | 87.4 | Consolidation | HFA, WFA | 1. Pneumonia |  | E.coli | 0 | 6.0 |  | *S. aureus* | 0 | 6.5 |
| G | F | 3 | 3 | Severe | Cough, Fever | 41 | Consolidation |  | 1. Pneumonia |  | Negative | 4.5 | 3.5 |  | CMV, *M. catarrhalis,* RSV | 4.6 | 0 |
| M | F | 6 | **7** | Very Severe | Cough, Fever, Hypoxia | 100.4 | Missing |  | 1. Pneumonia |  | Negative | 5.5 | 4.4 |  | CMV, *M. catarrhalis* | NA | NA |
| M | F | 2 | 3 | Very Severe | Cough, Fever, Vomiting | 27.3 | Missing |  | 1. Pneumonia |  | Negative | 4.3 | 2.2 |  | Human bocavirus, *M. catarrhalis,* PCP | NA | NA |
| M | F | 3 | 6 | Severe | Cough, Fever, Hypoxia, Lymphopenia, Vomiting | 3 | Uninterpretable | MUAC<115, WFA, WFH | 1. Pneumonia |  | Negative | 4.0 | 3.8 |  | CMV, PCP | 4.2 | 5.4 |
| M | F | 3 | 14 | Very Severe | Cough, Fever, Hypoxia, Vomiting, Meningitis | 0.8 | Consolidation |  | 1. Pneumonia, 2. Heart disease, Anemia |  | Negative | 0 | 3.1 |  | CMV, PCP | NA | NA |
| M | F | 8 | 3 | Severe | Cough, Fever, Vomiting,  | 3.4 | Uninterpretable | MUAC<115, WFA, WFH | 1. Pneumonia, Heart disease |  | Negative | 0 | 7.2 |  | CMV, Human bocavirus, *M. catarrhalis*, PCP, *S. aureus* | NA | NA |
| S | F | 6 | **4** | Severe | Cough, Diarrhea, Fever, Hypoxia, Vomiting | 1.8 | Consolidation |  | 1. Cardiac shock |  | Negative | 6.7 | 4.7 | Yes | *M. catarrhalis*, PCP | NA | NA |
| K | M | 0 | 1 | Severe | Hypoxia | 0.2 | Uninterpretable |  | 1. Pneumonia |  | Negative | 0 | 5.3 |  | PV/EV, *S. aureus* | NA | NA |
| M | M | 6 | 4 | Very Severe | Cough, Fever, Hypoxia, Vomiting | 47 | Normal | MUAC<115, WFA, WFH | 1. Heart disease |  | Negative | 0 | 4.7 |  |  | NA | NA |
| M | M | 28 | 3 | Very Severe | Meningitis | 23.9 | Normal | HFA, WFA, WFH | Tetanus |  | Negative | 0 | 1.5 |  | Adenovirus, CMV, *M. catarrhalis* | NA | NA |
| M | M | 12 | 4 | Very Severe | Fever, Lethargy, Meningitis | 4.9 | Normal | WFH | 1. Malaria, Meningitis |  | Negative | 4.4 | 6.0 |  | CMV, *S. aureus* | 0 | 4.2 |
| Z | M | 7 | **5** | Severe | Cough, Diarrhea, Fever, Lymphopenia | 86.2 | Normal |  | 1. Pneumonia |  | Negative | 6.8 | 8.1 | Yes | CMV, *M. catarrhalis*, PCP | NA | NA |
| Z | M | 4 | 5 | Very Severe | Cough, Fever, Hypoxia, Lethargy | 16.8 | Uninterpretable |  | 1. Pneumonia, Septicaemia |  | Negative | 3.6 | 5.5 |  |  | NA | NA |
| S | M | 0 | 3 | Very Severe | Cough, Fever, Hypoxia, Lethargy | 70.9 | Consolidation |  | 1. Pneumonia |  | Negative | 0 | 4.5 |  | Rhinovirus, RSV | NA | NA |
| T | M | 2 | 7 | Severe | Cough, Fever, Vomiting | 2.6 | Normal |  | 1. Pneumonia |  | Negative | 0 | 7.5 | Yes | CMV, Human bocavirus, *M. catarrhalis*, PV/EV | 0 | 7.4 |

1. Severe vs. very severe pneumonia defined using pre-2013 WHO classification. Severe pneumonia was defined as having cough or difficulty breathing and lower chest wall indrawing; very severe pneumonia was defined as cough or difficulty breathing and at least one of the following: central cyanosis, difficulty breastfeeding/drinking, vomiting everything, convulsions, lethargy, unconsciousness or head nodding.
2. Including cough, fever, vomiting, diarrhea, lethargy, hypoxia, lymphopenia, and meningitis.
3. Malnutrition listed if patients are severe (<-3 Z score).
4. High density *H. influenzae* > 5.9 log10 copies/mL.
5. Mycobacterium tuberculosis was tested for using induced sputum culture and was not detected among the listed patients.
6. Induced sputum not collected because patient died or was deemed to be too severe to undergo sampling procedure.

Abbreviations: site: G=Gambia, K=Kenya, M=Mali, S=South Africa, T=Thailand, Z=Zambia; sex: F=female, M=male; NA = not available; organisms: CoV=coronavirus, CMV=cytomegalovirus, PCP=pneumocystis jirovecii, PIV=parainfluenza virus, PV/EV= parechovirus/enterovirus, RSV=respiratory syncytial virus, S.pn = S. pneumoniae; malnutrition: MUAC=middle upper arm circumference, HFA=height for age, WFA=weight for age, WFH=weight for height.

## 12. High-density pneumococcus (HDSpn) detection and pneumococcal load in clinical samples by co-detection category with human endemic coronavirus (CoV)

|  |  |
| --- | --- |
| **Cases** | **No. with available information (col %)** |
| **Co-detection Category** |
| **A. CoV+ / HDSpn+** | **B. CoV+ / HDSpn-** | **C. CoV- / HDSpn+** | **D. CoV- / HDSpn -** |
| **n=43** | **n=247** | **n=449** | **n=3149** |
| **Invasive pneumococcal diseasea** | 4 | 3 | 23 | 14 |
|  | (9.5) | (1.2) | (5.2) | (0.5) |
|  Lung aspirate PCR | 1 / 1 | 0 / 0 | 3 / 8 | 1 / 17 |
|   | (100.0) | . | (37.5) | (5.9) |
|  Lung aspirate culture | 0 / 2 | 0 / 2 | 3 / 11 | 1 / 27 |
|  | - | - | (27.3) | (3.7) |
|  Pleural fluid PCR | 0/0 | 1 / 1 | 0 / 2 | 4 / 13 |
|  | - | (100) | - | (30.8) |
|  Pleural fluid culture | 0 / 1 | 1 / 1 | 0 / 4 | 0 / 15 |
|  | - | (100) | - | - |
|  Blood culture | 3 | 3 | 19 | 8 |
|   | (7.1) | (1.2) | (4.3) | (0.3) |
| **Blood lytA PCR** | 3 | 15 | 56 | 174 |
|  | (7.7) | (6.4) | (13.0) | (5.9) |
| **Blood lytA PCR > 2.2 log copies/mL** | 3 | 13 | 45 | 111 |
|  | (7.7) | (5.5) | (10.4) | (3.7) |
| **Induced sputum culture** | 14 | 63 | 192 | 772 |
|  | (41.2) | (28.8) | (49.2) | (27.0) |
| **Induced sputum PCR** | 28 | 132 | 368 | 1849 |
|  | (93.3) | (62.9) | (96.1) | (65.3) |
| **Nasopharyngeal culture** | 37 | 117 | 400 | 1510 |
|   | (88.1) | (48.0) | (90.5) | (48.4) |
| ***S. pneumoniae* (median log10 copies/mL)** | 7.24 | 4.50 | 7.23 | 4.67 |
|  IQR | 7.14-7.54 | 0-5.96 | 7.08-7.52 | 0-5.95 |

a. *Streptococcus pneumoniae* detected on blood culture, lung aspirate PCR, lung aspirate culture, pleural fluid culture, or pleural fluid PCR

## 13. Median number of pathogens positive on NP/OP PCR by human endemic coronavirus (CoV) and high-density pneumococcus (HDSpn) co-detection category, among cases

|  |  |  |
| --- | --- | --- |
| **Cases** | **Co-detection Category** |  |
| **A. CoV+ / HDSpn+** | **B. CoV+ / HDSpn-** | **C. CoV- / HDSpn+** | **D. CoV- and HDSpn -** | **p-value** |
| **n=43** | **n=247** | **n=449** | **n=3149** |
| **Number of pathogens** | 5.0 | 4.0 | 4.0 | 2.0 | <0.001 |
|  Male | 5.0 | 4.0 | 4.0 | 2.0 |  |
|  Female | 5.0 | 3.0 | 4.0 | 2.0 |  |

## 14. Sensitivity analyses evaluating association of clinical outcomes by co-detection group including additional CoV and Spn cases

## 14a. Adding microbiologically confirmed pneumococcal pneumoniaa to high density *S. pneumoniae* (HDSpn) and adding human endemic CoV detected in induced sputum to cases with CoV detected in NP/OP

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Co-detection Category** | **Adjusted Odds Ratiob** | **p-valueb** |
| **A. CoV+ / HDSpn+** | **B. CoV+ / HDSpn-** | **C. CoV- / HDSpn+** | **D. CoV- and HDSpn -** | **A v B** | **A v C** | **A v D** | **Overall** | **AvB** | **AvC** | **AvD** |
| **n=53** | **n=337** | **n=388** | **n=2730** |
| **Very severe pneumonia (WHO Definition)** | 2547.2 | 10631.5 | 13334.3 | 76528.0 |  |  |  |  |  |  |  |
|  Male | 1451.9 | 6630.0 | 6731.5 | 43827.4 | 2.81.1-7.0 | 2.30.9-6.0 | 2.81.2-6.7 | **0.038** | **0.032** | 0.092 | **0.017** |
|  Female | 1142.3 | 4034.2 | 6637.7 | 32728.8 | 1.40.5-3.7 | 1.50.6-3.8 | 1.90.8-4.3 | **0.032** | 0.526 | 0.394 | 0.148 |
| **WHO Defined Very Severe or Hypoxic** | 3362.3 | 17050.6 | 20853.6 | 130848.0 |  |  |  |  |  |  |  |
|  Male | 1763.0 | 10648.2 | 10448.8 | 73145.9 | 2.20.8-6.0 | 2.10.7-5.8 | 2.51.0-6.4 | **0.010** | 0.118 | 0.178 | 0.055 |
|  Female | 1661.5 | 6455.2 | 10459.4 | 57750.9 | 1.60.6-4.4 | 1.80.6-5.0 | 2.20.9-5.5 | **0.039** | 0.379 | 0.274 | 0.100 |
| **Supplemental oxygen (ever)b** | 1532.6 | 6624.8 | 7624.2 | 51724.3 |  |  |  |  |  |  |  |
|  Male | 1040.0 | 3720.9 | 4525.0 | 28922.9 | 4.11.4-12.0 | 1.90.7-5.3 | 3.41.3-8.6 | **0.001** | **0.009** | 0.240 | **0.010** |
|  Female | 523.8 | 2932.6 | 3123.1 | 22826.4 | 0.90.3-2.8 | 2.10.7-7.0 | 2.60.8-7.7 | 0.153 | 0.809 | 0.210 | 0.095 |
| **Observed Cough** | 2547.2 | 23670.5 | 27671.3 | 197672.6 |  |  |  |  |  |  |  |
|  Male | 1140.7 | 15771.7 | 15472.3 | 116473.1 | 3.01.2-7.5 | 0.30.1-0.7 | 3.61.6-8.3 | **0.038** | **0.017** | **0.007** | **0.003** |
|  Female | 1453.9 | 7968.1 | 12270.1 | 81271.9 | 1.60.6-4.5 | 2.00.8-5.0 | 2.00.9-4.6 | 0.328 | 0.346 | 0.144 | 0.111 |
| **Abnormal Chest X-ray\*** | 2052.6 | 14449.2 | 20560.7 | 119250.1 |  |  |  |  |  |  |  |
|  Male | 1470.0 | 8443.3 | 10959.6 | 69049.2 | 3.61.2-9.9 | 1.40.5-4.1 | 2.30.9-6.0 | **0.002** | **0.015** | 0.483 | 0.094 |
|  Female | 633.3 | 6060.6 | 9661.9 | 50251.4 | 0.30.1-1.0 | 0.30.1-0.8 | 0.50.2-1.4 | **0.002** | 0.061 | **0.021** | 0.186 |
| **Severe Acute Malnutritiond** | 917.0 | 5616.9 | 7419.3 | 43616.1 |  |  |  |  |  |  |  |
|  Male | 725.9 | 3415.5 | 4119.4 | 23114.6 | 1.80.7-5.0 | 1.40.5-3.7 | 1.80.7-4.4 | 0.348 | 0.257 | 0.514 | 0.186 |
|  Female | 27.7 | 2219.5 | 3319.1 | 20518.3 | 0.40.1-1.8 | 0.30.1-1.5 | 0.30.1-1.5 | 0.557 | 0.229 | 0.143 | 0.159 |
| **Height-for-Age Z-Score < -3 SDs** | 1021.3 | 4616.3 | 5216.6 | 43018.7 |  |  |  |  |  |  |  |
|  Male | 728.0 | 3418.1 | 2514.8 | 27320.3 | 2.10.7-6.0 | 2.70.8-8.6 | 2.30.9-5.9 | 0.327 | 0.171 | 0.095 | 0.098 |
|  Female | 313.6 | 1212.8 | 2718.6 | 15716.4 | 1.60.3-7.8 | 1.10.3-4.6 | 1.40.4-5.1 | 0.162 | 0.585 | 0.898 | 0.575 |
| **C-Reactive Protein (mg/L) (median, IQR)** | 43.7(8.0 – 185.9) | 13.5(3.9 – 41.0) | 26.7(7.0 – 96.7) | 12.6(3.4 – 37.8) |  |  |  |  |  |  |  |
|  Male | 43.7(7.8 – 258.5) | 13.2(4.6 – 38.6) | 22.0(5.9 – 84.9) | 12.6(3.0 – 37.6) |  |  |  | **<0.001** | **<0.001** | 0.053 | **<0.001** |
|  Female | 43.5(8.1 – 178.2) | 15.7(3.3 – 48.9) | 30.4(11.1 – 110.1) | 12.8(3.8 – 38.1) |  |  |  | **<0.001** | 0.261 | 0.809 | **0.031** |
| **Underlying Conditione** | 59.4 | 4112.2 | 4010.3 | 31211.4 |  |  |  |  |  |  |  |
|  Male | 414.8 | 2410.9 | 157.0 | 16810.5 | 1.90.6-6.5 | 2.00.6-7.3 | 2.00.7-6.1 | 0.457 | 0.305 | 0.286 | 0.206 |
|  Female | 13.9 | 1714.5 | 2514.3 | 14412.7 | 0.020.0-2.0 | 0.30.0-2.4 | 0.40.1-3.3 | 0.353 | 0.179 | 0.246 | 0.420 |
| **Deathf** | 9/5018.0 | 23/3197.2 | 15/3644.1 | 71/24782.9 |  |  |  |  |  |  |  |
|  Male | 7/2528.0 | 11/2075.3 | 5/1992.5 | 31/14592.1 | 8.42.3-30.7 | 15.34.4-53.6 | 15.85.6-44.9 | **<0.001** | **0.001** | **<0.001** | **<0.001** |
|  Female | 2/258.0 | 12/11210.7 | 10/1656.1 | 40/10193.9 | 0.50.1-2.7 | 1.40.3-7.1 | 2.60.6-11.9 | **0.048** | 0.443 | 0.649 | 0.226 |

## 14b. Lowering the threshold to >6.6 log10 copies/mL to define high density *S. pneumoniae* (HDSpn)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Co-detection Category** | **Adjusted Odds Ratiob** | **p-valueb** |
| **A. CoV+ / HDSpn+** | **B. CoV+ / HDSpn-** | **C. CoV- / HDSpn+** | **D. CoV- and HDSpn -** | **A v B** | **A v C** | **A v D** | **Overall** | **AvB** | **AvC** | **AvD** |
| **n=64** | **n=226** | **n=697** | **n=2902** |
| **Deathf** |  |  |  |  |  |  |  |  |  |  |  |
|  Male | 8/3423.5 | 7/1365.2 | 22/3516.3 | 89/15465.8 | 5.71.5-21.4 | 4.71.9-11.6 | 3.81.5-9.3 | **<0.001** | **0.009** | **0.001** | **0.004** |
|  Female | 3/2611.5 | 10/7912.7 | 33/29611.2 | 102/10949.3 | 0.60.1-2.5 | 1.10.3-4.2 | 1.10.3-4.2 | **0.033** | 0.465 | 0.870 | 0.842 |

a. Pneumococcus detected from a normally sterile site

b. P-values for pairwise comparisons of categorical variables obtained from logistic regression model adjusted for age and site (only age adjusted for A vs C comparison on death due to sample size limitations). Overall p-value obtained from multinomial logistic regression adjusted for age and site (where applicable).

c. Excludes South Africa due to near uniformity of receiving oxygen at the South Africa PERCH site.

d. Severe acute malnutrition

e. Underlying conditions: cerebral palsy, congenital heart disease/defect, congenital abnormalities, developmental delay, severe malnutrition, prematurity in an infant <6 months old. f. The number of days with cough, fever, difficulty breathing, wheeze, or runny nose, whichever symptom is longest.

f. Death within 30 days of admission

## 15. Case fatality risk by NP/OP co-detection of other pathogen combinations, by sex

## 15a. High-density *H. influenzae* (HDHinf) and any coronavirus (CoV)

|  |  |  |
| --- | --- | --- |
|  | **Co-detection Category** |  |
| **CoV+ / HDHinf+** | **CoV+ / HDHinf-** | **CoV- / HDHinf+** | **CoV- and HDHinf -** | **p-value** |
| **n=84** | **n=191** | **n=896** | **n=2390** |  |
| **Death** | 8(9.5) | 20(10.5) | 60(6.7) | 186(7.8) | 0.290 |
|  Male n=2067 | 5/55(9.1) | 10/115(8.7) | 27/512(5.3) | 84/1385(6.1) | 0.419 |
|  Female n=1494 | 3/29(10.3) | 10/76(13.2) | 33/384(8.6) | 102/1005(10.2) | 0.634 |

## 15b. *S. aureus* (Saur) and any coronavirus (CoV)

|  |  |  |
| --- | --- | --- |
|  | **Co-detection Category** |  |
| **CoV+ / Saur+** | **CoV+ / Saur-** | **CoV- / Saur+** | **CoV- and Saur -** | **p-value** |
| **n=45** | **n=230** | **n=523** | **n=2763** |  |
| **Death** | 5(11.1) | 23(10.0) | 71(13.6) | 175(6.3) | **<0.001** |
|  Male n=2067 | 2/29(6.9) | 13/141(9.2) | 36/299(12.0) | 75/1598(4.7) | **<0.001** |
|  Female n=1494 | 3/16(18.8) | 10/89(11.2) | 35/224(15.6) | 100/1165(8.6) | **0.007** |

## 15c. High-density *S. pneumoniae* (HDSpn) and any influenza A, B or C (Flu)

|  |  |  |
| --- | --- | --- |
|  | **Co-detection Category** |  |
| **Flu+ / HDSpn+** | **Flu+ / HDSpn-** | **Flu- / HDSpn+** | **Flu- and HDSpn -** | **p-value** |
| **n=22** | **n=144** | **n=440** | **n=2972** |  |
| **Death** | 0- | 117.6 | 5011.4 | 2147.2 | **0.011** |
|  Male n=2075 | 0/10- | 7/858.2 | 23/2379.7 | 96/17435.5 | 0.050 |
|  Female n=1503 | 0/12- | 4/596.8 | 27/20313.3 | 118/12299.6 | 0.194 |

## 15d. High-density *S. pneumoniae* (HDSpn) and HMPV

|  |  |  |
| --- | --- | --- |
|  | **Co-detection Category** |  |
| **HMPV+ / HDSpn+** | **HMPV+ / HDSpn-** | **HMPV- / HDSpn+** | **HMPV- and HDSpn -** | **p-value** |
| **n=35** | **n=203** | **n=427** | **n=2895** |  |
| **Death** | 25.7 | 83.9 | 4811.2 | 2167.5 | **0.007** |
|  Male n=2066 | 1/175.9 | 3/1172.6 | 22/2309.6 | 100/17025.9 | 0.057 |
|  Female n=1494 | 1/185.6 | 5/865.8 | 26/19713.2 | 116/11939.7 | 0.218 |

## 15e. High-density *S.pneumoniae* (HDSpn) and RSV A/B

|  |  |  |
| --- | --- | --- |
|  | **Co-detection Category** |  |
| **RSV+ / HDSpn+** | **RSV+ / HDSpn-** | **RSV- / HDSpn+** | **RSV- and HDSpn -** | **p-value** |
| **n=130** | **n=810** | **n=332** | **n=2289** |  |
| **Death** | 43.1 | 202.5 | 4613.9 | 1048.9 | **<0.001** |
|  Male n=2067 | 2/692.9 | 9/4881.8 | 21/17811.8 | 94/13327.1 | **<0.001** |
|  Female n=1494 | 2/613.3 | 11/3223.4 | 25/15416.2 | 110/95711.5 | **<0.001** |

## 15f. High-density *S.pneumoniae* (HDSpn) and Parainfluenza 1 or 3 (Para1/3)

|  |  |  |
| --- | --- | --- |
|  | **Co-detection Category** |  |
| **Para1/3+ / HDSpn+** | **Para1/3+ / HDSpn-** | **Para1/3- / HDSpn+** | **Para1/3- and HDSpn -** | **p-value** |
| **n=41** | **n=258** | **n=421** | **n=2841** |  |
| **Death** | 7 | 12 | 43 | 212 | **0.006** |
|  | 17.1 | 4.7 | 10.2 | 7.5 |  |
|  Male n=2067 | 2/25 | 4/152 | 21/222 | 99/1668 | 0.050 |
|  | 8.0 | 2.6 | 9.5 | 5.9 |  |
|  Female n=1494 | 5/16 | 8/106 | 22/199 | 113/1173 | **0.027** |
|  | 31.3 | 7.6 | 11.1 | 9.6 |  |

## 16. Mortality by coronavirus species and gender by human endemic coronavirus (CoV) and high-density pneumococcus (HDSpn) NP/OP co-detection category

|  |  |  |  |
| --- | --- | --- | --- |
| **CoV Species** |  | **Case Fatality Risk by Co-detection Category** | **p-value** |
|  | **CoV+ / HDSpn+** | **CoV- and HDSpn -** |  |
| CoV OC43 | **Overall** | 5 / 19(26.3) | 217 / 3012(7.2) | **0.001** |
|  Male | 3 / 9(33.3) | 100(5.7) | **<0.001** |
|  Female | 2 / 10(20.0) | 117(9.4) | 0.254 |
| CoV HKU1 | **Overall** | 2 / 8(25.0) | 219 / 3012(7.2) | 0.052 |
|  Male | 2 / 6(33.3) | 101(5.7) | **0.004** |
|  Female | 0 / 2- | 118(9.4) | 0.650 |
| CoV 229E | **Overall** | 0- | 220 / 3060(7.2) | 0.578 |
|  Male | 0 / 1- | 102(5.7) | 0.806 |
|  Female | 0 / 3- | 118(9.3) | 0.579 |
| CoV NL63 | **Overall** | 2 / 9(22.2) | 220 / 3031(7.3) | 0.085 |
|  Male | 2 / 4(50.0) | 101(5.7) | **<0.001** |
|  Female | 0 / 5- | 119(9.5) | 0.469 |