

S4 Table: MMRM model 1 for WURSS-11 mean daily total score (without imputation)

| Effect                         | Symptom Day | LS-Means | 95% CI         | p-value |
|--------------------------------|-------------|----------|----------------|---------|
| Age                            | .           | .        |                | 0.6922  |
| Baseline WURSS Score           | .           | .        |                | <.0001  |
| Previous influenza vaccination | .           | .        |                | 0.1608  |
| Sex                            | .           | .        |                | 0.1530  |
| Stratum <= 12 hours            | 1           | 27.92    | [26.40, 29.43] |         |
|                                | 2           | 25.11    | [23.45, 26.76] |         |
|                                | 3           | 20.74    | [18.90, 22.59] |         |
|                                | 4           | 17.03    | [15.06, 18.99] |         |
|                                | 5           | 13.67    | [11.68, 15.67] |         |
|                                | 6           | 10.72    | [8.69, 12.74]  |         |
|                                | 7           | 8.24     | [6.18, 10.30]  |         |
|                                | 8           | 6.37     | [4.36, 8.37]   |         |
|                                | 9           | 4.65     | [2.77, 6.54]   |         |
|                                | 10          | 3.85     | [2.07, 5.63]   |         |
|                                | 11          | 2.99     | [1.40, 4.58]   |         |
|                                | 12          | 1.84     | [0.44, 3.23]   |         |
|                                | 13          | 1.29     | [0.00, 2.60]   |         |
|                                | 14          | 0.84     | [0.00, 2.01]   |         |
|                                | 15          | 0.50     | [0.00, 1.61]   |         |
|                                | 16          | 0.22     | [0.00, 1.23]   |         |
|                                | 17          | 0.22     | [0.00, 1.21]   |         |
| Stratum 12-24 hours            | 1           | 28.94    | [27.16, 30.71] |         |
|                                | 2           | 28.68    | [26.74, 30.62] |         |
|                                | 3           | 26.43    | [24.27, 28.59] |         |
|                                | 4           | 23.27    | [20.97, 25.57] |         |
|                                | 5           | 19.42    | [17.09, 21.76] |         |
|                                | 6           | 15.42    | [13.05, 17.79] |         |
|                                | 7           | 11.89    | [9.47, 14.31]  |         |
|                                | 8           | 9.49     | [7.14, 11.84]  |         |
|                                | 9           | 6.97     | [4.76, 9.17]   |         |
|                                | 10          | 5.45     | [3.37, 7.53]   |         |
|                                | 11          | 3.33     | [1.48, 5.18]   |         |
|                                | 12          | 2.20     | [0.57, 3.82]   |         |
|                                | 13          | 1.59     | [0.07, 3.10]   |         |
|                                | 14          | 0.90     | [0.00, 2.25]   |         |
|                                | 15          | 0.25     | [0.00, 1.52]   |         |
|                                | 16          | 0.00     | [0.00, 1.03]   |         |
|                                | 17          | 0.00     | [0.00, 0.93]   |         |

| Effect                                       | Symptom Day | LS-Means | 95% CI          | p-value  |
|--|-------------|----------|-----------------|----------|
| Stratum >24 hours                            | 1           | 28.90    | [27.20, 30.60]  |          |
|  | 2           | 30.82    | [28.96, 32.67]  |          |
|  | 3           | 30.01    | [27.95, 32.07]  |          |
|  | 4           | 28.06    | [25.86, 30.25]  |          |
|  | 5           | 25.12    | [22.89, 27.35]  |          |
|  | 6           | 21.23    | [18.97, 23.49]  |          |
|  | 7           | 18.42    | [16.11, 20.72]  |          |
|  | 8           | 14.68    | [12.44, 16.91]  |          |
|  | 9           | 11.59    | [9.49, 13.70]   |          |
|  | 10          | 9.41     | [7.43, 11.40]   |          |
|  | 11          | 7.74     | [5.97, 9.50]    |          |
|  | 12          | 5.79     | [4.24, 7.35]    |          |
|  | 13          | 4.86     | [3.40, 6.31]    |          |
|  | 14          | 3.37     | [2.08, 4.66]    |          |
|  | 15          | 2.42     | [1.20, 3.65]    |          |
|  | 16          | 1.67     | [0.55, 2.79]    |          |
|  | 17          | 1.55     | [0.46, 2.65]    |          |
| Stratum <= 12 hours -<br>Stratum 12-24 hours | 1           | -1.02    | [-3.31, 1.27]   | 0.3803   |
|  | 2           | -3.58    | [-6.09, -1.07]  | 0.0054 * |
|  | 3           | -5.69    | [-8.49, -2.88]  | <.0001 * |
|  | 4           | -6.24    | [-9.24, -3.25]  | <.0001 * |
|  | 5           | -5.75    | [-8.79, -2.71]  | 0.0002 * |
|  | 6           | -4.70    | [-7.79, -1.62]  | 0.0029 * |
|  | 7           | -3.65    | [-6.80, -0.50]  | 0.0233 * |
|  | 8           | -3.12    | [-6.17, -0.07]  | 0.0451 * |
|  | 9           | -2.31    | [-5.18, 0.55]   | 0.1133   |
|  | 10          | -1.60    | [-4.30, 1.10]   | 0.2456   |
|  | 11          | -0.34    | [-2.74, 2.05]   | 0.7787   |
|  | 12          | -0.36    | [-2.46, 1.74]   | 0.7363   |
|  | 13          | -0.30    | [-2.25, 1.66]   | 0.7664   |
|  | 14          | -0.06    | [-1.78, 1.66]   | 0.9449   |
|  | 15          | 0.25     | [-1.37, 1.87]   | 0.7624   |
|  | 16          | 0.35     | [-1.12, 1.83]   | 0.6367   |
|  | 17          | 0.42     | [-1.02, 1.86]   | 0.5671   |
| Stratum <= 12 hours -<br>Stratum >24 hours   | 1           | -0.98    | [-3.21, 1.24]   | 0.3840   |
|  | 2           | -5.71    | [-8.15, -3.27]  | <.0001 * |
|  | 3           | -9.27    | [-11.99, -6.55] | <.0001 * |
|  | 4           | -11.03   | [-13.93, -8.13] | <.0001 * |
|  | 5           | -11.45   | [-14.40, -8.50] | <.0001 * |
|  | 6           | -10.51   | [-13.50, -7.52] | <.0001 * |
|  | 7           | -10.18   | [-13.23, -7.12] | <.0001 * |
|  | 8           | -8.31    | [-11.27, -5.34] | <.0001 * |
|  | 9           | -6.94    | [-9.72, -4.16]  | <.0001 * |
|  | 10          | -5.56    | [-8.18, -2.94]  | <.0001 * |
|  | 11          | -4.75    | [-7.07, -2.42]  | <.0001 * |
|  | 12          | -3.96    | [-5.99, -1.92]  | 0.0002 * |
|  | 13          | -3.57    | [-5.46, -1.67]  | 0.0003 * |
|  | 14          | -2.53    | [-4.20, -0.85]  | 0.0032 * |
|  | 15          | -1.92    | [-3.50, -0.35]  | 0.0170 * |
|  | 16          | -1.45    | [-2.88, -0.02]  | 0.0472 * |
|  | 17          | -1.34    | [-2.74, 0.06]   | 0.0606   |

| Effect                                     | Symptom Day | LS-Means | 95% CI         | p-value  |
|--|-------------|----------|----------------|----------|
| Stratum 12-24 hours -<br>Stratum >24 hours | 1           | 0.04     | [-2.37, 2.45]  | 0.9759   |
|  | 2           | -2.14    | [-4.77, 0.50]  | 0.1120   |
|  | 3           | -3.58    | [-6.52, -0.64] | 0.0172 * |
|  | 4           | -4.79    | [-7.93, -1.64] | 0.0029 * |
|  | 5           | -5.70    | [-8.89, -2.51] | 0.0005 * |
|  | 6           | -5.81    | [-9.05, -2.57] | 0.0005 * |
|  | 7           | -6.53    | [-9.83, -3.22] | 0.0001 * |
|  | 8           | -5.19    | [-8.39, -1.98] | 0.0016 * |
|  | 9           | -4.63    | [-7.63, -1.62] | 0.0027 * |
|  | 10          | -3.96    | [-6.80, -1.13] | 0.0062 * |
|  | 11          | -4.40    | [-6.92, -1.89] | 0.0006 * |
|  | 12          | -3.60    | [-5.79, -1.40] | 0.0014 * |
|  | 13          | -3.27    | [-5.32, -1.23] | 0.0018 * |
|  | 14          | -2.47    | [-4.26, -0.67] | 0.0074 * |
|  | 15          | -2.17    | [-3.86, -0.48] | 0.0122 * |
|  | 16          | -1.80    | [-3.34, -0.26] | 0.0219 * |
|  | 17          | -1.76    | [-3.26, -0.25] | 0.0222 * |

<sup>a</sup> If lower limit of 95% confidence interval of LSMEANS is below 0 then this value is set to 0. \* = significant difference between LSMEANS.