**Supplementary File 2**: Influenza A virus mutation rates

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|  | Mutation rate (mutations per nt per strand replicated)a | |
| Mutation class | A/Puerto Rico/8/1934 H1N1 | A/Hong Kong/4801/2014 H3N2 |
| A to C | 1.5 x 10-5 ± 0.9 x 10-5 | 3.4 x 10-5 ± 1.0 x 10-5 |
| A to G | 2.0 x 10-4 ± 1.1 x 10-4 | 3.0 x 10-4 ± 1.5 x 10-4 |
| A to U | 1.8 x 10-5 ± 1.8 x 10-5 | 1.3 x 10-5 ± 0.3 x 10-5 |
| C to A | 7.7 x 10-6 ± 4.4 x 10-6 | 1.7 x 10-5 ± 0.9 x 10-5 |
| C to G | 5.1 x 10-6 ± 2.3 x 10-6 | 9.7 x 10-6 ± 7.8 x 10-6 |
| C to U | 2.7 x 10-5 ± 0.7 x 10-5 | 4.6 x 10-5 ± 1.6 x 10-5 |
| G to A | 3.1 x 10-5 ± 0.2 x 10-5 | 7.2 x 10-5 ± 1.1 x 10-5 |
| G to C | 5.4 x 10-5 ± 2.4 x 10-5 | 2.8 x 10-5 ± 0.7 x 10-5 |
| G to U | 3.5 x 10-5 ± 0.9 x 10-5 | 6.0 x 10-5 ± 1.6 x 10-5 |
| U to A | 1.4 x 10-5 ± 0.7 x 10-5 | 4.5 x 10-6 ± 1.8 x 10-6 |
| U to C | 2.3 x 10-4 ± 0.5 x 10-4 | 3.1 x 10-4 ± 1.2 x 10-4 |
| U to G | 3.5 x 10-5 ± 2.3 x 10-5 | 3.6 x 10-5 ± 2.3 x 10-5 |
| Overallb | 1.8 x 10-4 | 2.5 x 10-4 |

a Arithmetic mean plus or minus the standard deviation calculated from at least three replicates.

b Overall mutation rates were determined as a weighted average of mutation rates, taking into account genomic base composition.