**Supplementary Table 1**: Medical conditions defining high-risk status for influenza-associated complications

| Condition                                                                                     |
|-----------------------------------------------------------------------------------------------|
| • **Asthma** (of any severity)                                                                |
| • **Neurological and Neurodevelopmental Conditions**, including: Brain disorders; Spinal cord  |
|   disorders / injury; Peripheral nerve disorders; Muscle disorders (e.g. cerebral palsy); Stroke; |
|   Intellectual disability; Developmental delay (moderate to severe); Muscular dystrophy        |
| • **Chronic Lung Diseases**, including: Chronic obstructive pulmonary disease; Cystic fibrosis;  |
|   Chronic lung disease secondary to prematurity                                               |
| • **Heart Diseases**, including: Congenital heart disease; Congestive heart failure; Coronary   |
|   artery disease                                                                             |
| • **Blood Disorders**, including: Sickle cell disease                                         |
| • **Endocrine Disorders**, including: Non-insulin dependent (Type 2) diabetes mellitus          |
| • **Kidney Disorders**                                                                        |
| • **Liver Disorders**                                                                         |
| • **Metabolic Disorders**, including: Inherited metabolic disorders; Mitochondrial disorders    |
| • **Immune System Disorders**, including: HIV; AIDS; Immunosuppression (due to either disease or |
|   medication); Cancer; Steroid treatment (chronic)                                             |
| • **Aspirin** therapy (long-term)                                                             |
| • **Morbid Obesity**                                                                         |
| **Inclusion Criteria** |
|---------------------------------------------------------------|
| ▪ Children (males and females, healthy or at high risk of complications from influenza) between ≥ 6 to < 72 months of age |
| ▪ Documented consent provided by the subject’s parent(s) / legal guardian(s) according to local regulatory requirements (after the nature of the study had been explained in full) |
| ▪ Subject’s and / or subject’s parent(s) / legal guardian(s) able to comply with all study procedures, and available for all scheduled clinic visits, and telephone, email, and / or text message (SMS) contacts |
| ▪ Subject’s parent(s) / legal guardian(s) willing to allow serum samples to be stored beyond the defined study period, for potential additional future testing to further characterize immune responses to vaccination |

| **Exclusion Criteria** |
|---------------------------------------------------------------|
| ▪ Children whose parent(s) / legal guardian(s) were not able to comprehend and to follow all required study procedures for the entire period of the study |
| ▪ History of Guillain-Barré syndrome, epilepsy, or convulsions (excluding febrile convulsions) |
| ▪ Children with any fatal prognosis of an underlying medical condition (< 12 months life expectancy) |
| ▪ Children who had any medical condition defined as an Adverse Event of Special Interest (for the purposes of this study) |
| ▪ Children hospitalized at the time of enrollment |
| ▪ History of any anaphylaxis, serious reactions to vaccine, or hypersensitivity to any vaccine component, eggs, ovalbumin, chicken protein, or latex |
| ▪ Children of research staff directly involved with the clinical study or who were otherwise related to research staff or had household members who were research staff. Research staff with direct or indirect contact with study subjects. Study site personnel who had access to any study documents containing subject information (including receptionists, persons scheduling appointments or making screening calls, regulatory specialists, laboratory technicians, etc.) |
| ▪ Fever (i.e. body temperature ≥ 38°C [≥ 100.4°F]), preferably measured orally. Note, this was not an absolute exclusion criterion; the individual could have been enrolled / vaccinated once he or she was free of fever for at least three days |
| ▪ Children who had received vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrollment. Depending upon the duration of enrollment, children with this exclusion criterion could have been eligible for enrollment into the study once either 14 days (for inactivated vaccine administration) or 28 days (for live vaccine administration) had passed |
| ▪ Children who had received antipyretic medication within 24 hours prior to vaccination (subjects could return for vaccination after a period of 24 hours since antipyretic administration) |
| ▪ Receipt of another investigational agent within 30 days prior to enrollment or before completion of the safety follow-up period in this or another study, or unwillingness to refuse to participate in another clinical trial occurring at the same time as this study |
| ▪ Children who had been immunized with any influenza vaccine (licensed or investigational), or children with laboratory-confirmed influenza disease occurring within 6 months prior to enrollment |
| ▪ Children’s parent(s) / guardian(s) who were unwilling to be contacted by phone for safety phone calls, or by phone, email, or text message (SMS) for the active influenza surveillance |
| ▪ Individuals who had been diagnosed with any growth disorders, such as failure to thrive or short stature |
| ▪ Subjects who had previously participated in this study (NCT01964989) |
Supplementary Table 3: Immunogenicity results in high-risk and healthy subjects. Antibody responses against strains heterologous to vaccine antigens, assessed by HI assay three weeks after administration of last vaccine dose (FAS - Immunogenicity data)

|                      | High-Risk allIV4 | High-Risk Comparator | High-Risk GMTr (95% CI) | Healthy allIV4 | Healthy Comparator | Healthy GMTr (95% CI) |
|----------------------|------------------|-----------------------|-------------------------|----------------|--------------------|-----------------------|
| **A/H1N1**           |                  |                       |                         |                |                    |                       |
| GMT: Day 1           | 5.5 (n = 55)     | 6.2 (n = 44)          | –                       | 5.8 (n = 242) | 5.5 (n = 251)      | –                     |
| GMT: Day 22/50       | 7.6 (n = 55)     | 6.9 (n = 44)          | 1.1 (0.8 – 1.5)         | 7.2 (n = 240) | 6.1 (n = 247)      | 1.2 (1.0 – 1.3)       |
| GMR: (Day 22/50) / Day 1 | 1.4 (n = 55) | 1.1 (n = 44)          | –                       | 1.3 (n = 240) | 1.1 (n = 247)      | –                     |
| **A/H3N2**           |                  |                       |                         |                |                    |                       |
| GMT: Day 1           | 43 (n = 55)      | 30 (n = 44)           | –                       | 23 (n = 242)  | 26 (n = 251)       | –                     |
| GMT: Day 22/50       | 622 (n = 53)     | 375 (n = 44)          | 1.7 (1.0 – 2.8)         | 476 (n = 239) | 244 (n = 246)      | 2.0 (1.5 – 2.5)       |
| GMR: (Day 22/50) / Day 1 | 16 (n = 53) | 12 (n = 44)           | –                       | 21 (n = 239) | 9.3 (n = 246)      | –                     |
| **B/Yamagata**       |                  |                       |                         |                |                    |                       |
| GMT: Day 1           | 11 (n = 55)      | 12 (n = 44)           | –                       | 8.0 (n = 242) | 8.4 (n = 251)      | –                     |
| GMT: Day 22/50       | 153 (n = 55)     | 82 (n = 44)           | 1.9 (1.1 – 3.1)         | 115 (n = 240) | 55 (n = 248)       | 2.1 (1.7 – 2.7)       |
| GMR: (Day 22/50) / Day 1 | 14 (n = 55) | 6.9 (n = 44)           | –                       | 14 (n = 240) | 6.5 (n = 248)      | –                     |
| **B/Victoria**       |                  |                       |                         |                |                    |                       |
| GMT: Day 1           | 11 (n = 55)      | 9.7 (n = 28)          | –                       | 8.8 (n = 242) | 9.1 (n = 130)      | –                     |
| GMT: Day 22/50       | 188 (n = 55)     | 102 (n = 28)          | –                       | 190 (n = 240) | 85 (n = 129)       | –                     |
| GMR: (Day 22/50) / Day 1 | 17 (n = 55) | 11 (n = 28)           | –                       | 22 (n = 240) | 9.4 (n = 129)      | –                     |

GMTr, geometric mean titer ratio; GMT, geometric mean titer; GMR, geometric mean ratio; HI analyses three weeks after last dose occurred on Day 22 for non-vaccine naïve subjects (vaccinated on Day 1); HI analyses three weeks after last dose occurred on Day 50 for vaccine naïve subjects (vaccinated on Days 1 and 29); *B/Victoria data from seasons one and two (aIIV4), and season two alone (comparator) are presented (no comparison analyses were performed for season two data / no GMTr values are presented)