# Supplemental Digital Content 3: Methods

## Ethics approval

The study was funded by GlaxoSmithKine Biologicals SA and registered with ClinicalTrials.gov (NCT01439360). It was approved by independent ethics committees or institutional review boards, conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines, and regulatory requirements of participating countries. Parents or legally acceptable representatives provided written informed consent.

## Study locations and timings

The study was conducted in northern hemisphere countries (Belgium, the Czech Republic, Lebanon, Poland, Spain, Turkey, and the UK) and subtropical countries (Bangladesh, the Dominican Republic, Honduras, India, the Philippines, and Thailand). Each study cohort was conducted during a different influenza season: October 2011 to July 2012 (northern hemisphere); April 2012 to December 2012 (subtropical countries); October 2012 to July 2013 (northern hemisphere); March 2013 to December 2013 (subtropical countries); and March 2014 to December 2014 (subtropical countries).

## Study vaccines

The IIV4 was manufactured by GSK, Dresden, Germany and contained 15 µg hemagglutinin antigen per strain per 0.5 mL dose, with strain composition according to WHO seasonal recommendations. Vaccine-primed children received a single intramuscular dose on Day 0; vaccine-unprimed children received two doses on Days 0 and 28. Most (99%) were unprimed for influenza vaccination i.e. they had not previously received at least two doses of seasonal influenza vaccine separated by at least 28 days.

Three possible control vaccines were used in the study: hepatitis A vaccine, varicella vaccine or pneumococcal conjugate vaccine (PCV), based on age and vaccine-priming status.

## Recording of symptoms and healthcare utilization

For ILI and LRI, parents recorded temperature and symptoms of cough, runny nose/nasal congestion, vomiting and feeling unwell; symptom severity was rated as none, minor, moderate or major. For AOM, parents recorded temperature and symptoms of ear tugging or holding ear, increased crying, fussiness, disturbed sleep, decreased play and eating less; symptom severity was rated as none, a little or a lot using the AOM-severity of symptoms scale. Parents were asked to complete the information in full without missing any questions.

Healthcare utilization was recorded by study staff at the end of the episode as: general practitioner or pediatrician visit; medical specialist visit; emergency room visit; hospitalization, including intensive care unit admissions; use of supplementary oxygen therapy). Absenteeism was recorded as the number of missed day-care days for the child and missed days of paid work for the parents if applicable.

## Statistical methods

### Severity score

A severity score for clinical symptoms was calculated post hoc based on the symptom diary for children in whom ILI or LRI was the primary event triggering the nasal swab. For each daily ILI/LRI symptom recorded, severity was scored as minor=1, moderate=2, major=3; fever was scored as ≥38−39°C =1, >39−40°C =2, >40°C=3. A symptom profile for each case was determined by adding together the scores across the time period under consideration (days 0−3 and days 0−13). Missing entries for a recorded symptom were ignored and treated as missing completely at random. A symptom score for AOM was not calculated.

### Vaccine probe analysis

Several tools are available to apply in randomized clinical trials to assess the public health impact of the vaccine.[[1]](#footnote-1) These include the estimation of etiologic fraction (AF) of ILE caused by RT-PCR-confirmed influenza, the vaccine prevention disease index (VPDI) and the estimated number of vaccinees needed to prevent one new case of influenza (NNV). The AF estimates the proportion of a clinical syndrome (i.e. ILI, clinical pneumonia, diarrhea) caused by a specific pathogen, and was defined as the VE against ILE divided by the VE against RT-PCR-confirmed influenza. The VPDI is a combined measure of the disease burden and the vaccine's ability to prevent that disease,1 and was defined as the incidence of RT-PCR-confirmed influenza in the control group minus the incidence of RT-PCR-confirmed influenza in the IIV4 group (this is mathematically equivalent to the product of VE and incidence in the control population). The CI for the VPDI was computed using the Wald normal approximation method for calculating the CI for the difference between two proportions. The NNV represents the number of individuals who need to be vaccinated to prevent one case of vaccine-preventable disease,1 and was calculated as 1 divided by the annual incidence of events in the control group multiplied by VE (or 1 divided by the VPDI). This is equivalent to the reciprocal of the annual absolute risk reduction, since the VE estimate measures the relative risk reduction.

1. Feikin DR, Scott JA, Gessner BD. Use of vaccines as probes to define disease burden. *Lancet* 2014; **383**: 1762−1770. [↑](#footnote-ref-1)