

*"This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses."*

# Clinical presentation of influenza in children 6 to 35 months of age: findings from a randomized clinical trial of inactivated quadrivalent influenza vaccine

Danier J<sup>1</sup>, MD; Rivera L<sup>\*2</sup>, MD; Claeys C<sup>3</sup>, MD; Dbaibo G<sup>4</sup>, MD; Jain VK<sup>5</sup>, MD;  
Kosalaraksa P<sup>6</sup>, MD; Woo W<sup>1</sup>, ALM; Yanni E<sup>1</sup>, MD; Zaman K<sup>7</sup>, PhD; Acosta B<sup>8</sup>, MD;  
Amanullah A<sup>1</sup>, PhD; Ariza M<sup>9</sup>, MD; Arroba Basanta ML<sup>10</sup>, MD; Bavdekar A<sup>11</sup>, MD;  
Carmona A<sup>12</sup>, MD; Cousin L<sup>13</sup>, MD; Diaz A<sup>14</sup>, MD; Diez-Domingo J<sup>15</sup>, MD; Dinleyici  
EC<sup>16</sup>, MD; Faust SN<sup>17</sup>, FRCPCH PhD; Garcia-Sicilia J<sup>18</sup>, MD; Gomez-Go GD<sup>19</sup>, MD;  
Gonzales MLA<sup>20</sup>, MS; Hacimustafaoglu M<sup>21</sup>, MD; Hughes SM<sup>22</sup>, PhD; Izu A<sup>1</sup>, MS;  
Jackowska T<sup>23</sup>, MD; Kant S<sup>24</sup>, MD; Lucero M<sup>25</sup>, MD; Mares Bermudez J<sup>26</sup>, MD;  
Martinón-Torres F<sup>27</sup>, PhD; Montellano M<sup>19</sup>, MD; Prymula R<sup>28</sup>, MD; Puthanakit T<sup>29</sup>,  
MD; Ruzkova R<sup>30</sup>, MD; Sadowska-Krawczenko I<sup>31</sup>, PhD; Soni J<sup>32</sup>, MA; Szymanski  
H<sup>33</sup>, MD; Ulied A<sup>34</sup>, MD; Schuind A<sup>\*\*1</sup>, MD; Innis BL<sup>35</sup>, MD; for the Flu4VEC Study  
Group

\*co-lead

\*\*co-last

*"This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses."*

## **Affiliations**

<sup>1</sup>GSK, Rockville, MD, United States; <sup>2</sup>National Autonomous University of Santo Domingo, Santo Domingo, Dominican Republic; <sup>3</sup>GSK, Wavre, Belgium; <sup>4</sup>American University of Beirut, Beirut, Lebanon; <sup>5</sup>GSK, King of Prussia, PA, United States (current affiliation: Bill & Melinda Gates Foundation, Seattle, WA, United States); <sup>6</sup>Khon Kaen University, Khon Kaen, Thailand; <sup>7</sup>icddr,b, Dhaka, Bangladesh; <sup>8</sup>Dr Castroviejo Primary Health Care Center, Madrid, Spain; <sup>9</sup>Centro Médico Dominicano, Santo Domingo, Dominican Republic; <sup>10</sup>Complutense University of Madrid, Madrid, Spain; <sup>11</sup>KEM Hospital Research Centre, Pune, India; <sup>12</sup>Instituto Hispalense de Pediatría, Sevilla, Spain; <sup>13</sup>Tecnología en Investigación, San Pedro Sula, Honduras; <sup>14</sup>National Autonomous University of Honduras, Tegucigalpa, Honduras; <sup>15</sup>FISABIO-Public Health, Valencia, Spain; <sup>16</sup>Eskisehir Osmangazi University, Eskisehir, Turkey; <sup>17</sup>NIHR Southampton Clinical Research Facility and NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom; <sup>18</sup>Hospital Infantil Universitario La Paz, Madrid, Spain; <sup>19</sup>Mary Chiles General Hospital, Manila, Philippines; <sup>20</sup>University of the Philippines – Philippine General Hospital, Manila, Philippines; <sup>21</sup>Uludag University, Bursa, Turkey; <sup>22</sup>NIHR Manchester Clinical Research Facility, Royal Manchester Children's Hospital, Manchester, United Kingdom; <sup>23</sup>Center of Postgraduate Medical Education, Warsaw, Poland; <sup>24</sup>Centre for Community Medicine, All India Institute of Medical Sciences, New Delhi, India; <sup>25</sup>Research Institute for Tropical Medicine, Manila, Philippines; <sup>26</sup>Paediatric Institute Mares-Riera, Blanes, Spain; <sup>27</sup>Hospital Clínico Universitario de Santiago, Santiago,

*"This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses."*

Spain; <sup>28</sup>University of Hradec Kralove, Hradec Kralove, Czech Republic; <sup>29</sup>Center for Excellence in Pediatric Infectious Diseases and Vaccines, Chulalongkorn University, Bangkok, Thailand; <sup>30</sup>Medicentrum 6 s.r.o., Prague, Czech Republic; <sup>31</sup>Nicolaus Copernicus University in Torun, Collegium Medicum, Bydgoszcz, Poland; University Hospital No 2, Bydgoszcz, Poland; <sup>32</sup>GSK, Bangalore, India; <sup>33</sup>St. Hedwig of Silesia Hospital, Trzebnica, Poland; <sup>34</sup>EBA Centelles, Barcelona, Spain; <sup>35</sup>GSK, King of Prussia, PA, United States (current affiliation: PATH, Washington, DC, United States)

#### **Co-authors email addresses**

Danier J: [jasur.x.danier@gsk.com](mailto:jasur.x.danier@gsk.com); Rivera L: [lrp@claro.net.do](mailto:lrp@claro.net.do); Claeys C: [CARINE.X.CLAEYS@GSK.COM](mailto:CARINE.X.CLAEYS@GSK.COM); Dbaibo G: [gdbaibo@aub.edu.lb](mailto:gdbaibo@aub.edu.lb); Jain VK: [varshakjain@gmail.com](mailto:varshakjain@gmail.com); Kosalaraksa P: [pkosalaraksa@yahoo.com](mailto:pkosalaraksa@yahoo.com); Woo W: [wayne.f.woo@gsk.com](mailto:wayne.f.woo@gsk.com); Yanni E: [emad.a.yanni@gsk.com](mailto:emad.a.yanni@gsk.com); Zaman K: [kzaman@icddrb.org](mailto:kzaman@icddrb.org); Acosta B: [beatrizan25@yahoo.es](mailto:beatrizan25@yahoo.es); Amanullah A: [Arshad.A.Amanullah@gsk.com](mailto:Arshad.A.Amanullah@gsk.com); Ariza M: [arizamd19@gmail.com](mailto:arizamd19@gmail.com); Arroba Basanta ML: [mlarroba@pap.es](mailto:mlarroba@pap.es); Bavdekar A: [bavdekar@vsnl.com](mailto:bavdekar@vsnl.com); Carmona A: [alfonsocarmona@ihppediatrics.com](mailto:alfonsocarmona@ihppediatrics.com); Cousin L: [luis cousin@gmail.com](mailto:luis cousin@gmail.com); Diaz A: [adolfmart@hotmail.com](mailto:adolfmart@hotmail.com); Diez-Domingo J: [diez\\_jav@gva.es](mailto:diez_jav@gva.es); Dinleyici EC: [enercagri@gmail.com](mailto:enercagri@gmail.com); Faust SN: [s.faust@soton.ac.uk](mailto:s.faust@soton.ac.uk); Garcia-Sicilia J: [josegarciasicilia@gmail.com](mailto:josegarciasicilia@gmail.com); Gomez-Go GD: [docpedia3g@yahoo.com.ph](mailto:docpedia3g@yahoo.com.ph); Gonzales LA: [lizmgonzales@yahoo.com](mailto:lizmgonzales@yahoo.com); Hacimustafaoglu M: [mkemal@uludag.edu.tr](mailto:mkemal@uludag.edu.tr); Hughes SM: [stephen.hughes@mft.nhs.uk](mailto:stephen.hughes@mft.nhs.uk); Izu A: [allenizu@gmail.com](mailto:allenizu@gmail.com); Jackowska T: [tjackowska@cmkp.edu.pl](mailto:tjackowska@cmkp.edu.pl); Kant S: [skant76@gmail.com](mailto:skant76@gmail.com); Lucero M:

*“This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses.”*

[marilla.lucero@gmail.com](mailto:marilla.lucero@gmail.com); Mares Bermudez J: [jmares@acmcb.es](mailto:jmares@acmcb.es); Martinon-Torres

F: [federico.martinon.torres@sergas.es](mailto:federico.martinon.torres@sergas.es); Montellano M: [maymd16@gmail.com](mailto:maymd16@gmail.com);

Prymula R: [Prymula@seznam.cz](mailto:Prymula@seznam.cz); Puthanakit T: [Thanyawee.P@chula.ac.th](mailto:Thanyawee.P@chula.ac.th);

Ruzkova R: [drruzkova@email.cz](mailto:drruzkova@email.cz); Sadowska-Krawczenko I:

[sadowskakrawczenko@gmail.com](mailto:sadowskakrawczenko@gmail.com); Soni J: [jyoti.7.kumari@gsk.com](mailto:jyoti.7.kumari@gsk.com); Szymanski H:

[henryktomasz@poczta.onet.pl](mailto:henryktomasz@poczta.onet.pl); Ulied A: [aulier@ebacentelles.cat](mailto:aulier@ebacentelles.cat); Schuind A:

[Anne.E.Schuind@gsk.com](mailto:Anne.E.Schuind@gsk.com); Innis BL: [innisb00@gmail.com](mailto:innisb00@gmail.com)

**Corresponding author:** Jasur Danier; 14200 Shady Grove Rd, Rockville, MD 20850, USA; phone number: +12028160312; email: [jasur.x.danier@gsk.com](mailto:jasur.x.danier@gsk.com)

## **Acknowledgements**

The authors are indebted to the participating study volunteers and their parents, clinicians, nurses and laboratory technicians at the study sites. The authors also thank the sponsor’s project staff for their support and contributions throughout the study, in particular Ilse Vastiau, Pascale Dieryck and Frans Corthals. Finally, the authors thank Mary L Greenacre (An Sgriobhadair, UK, on behalf of GSK) for providing medical writing services, and Business & Decision Life Sciences platform (on behalf of GSK) for editorial assistance, manuscript coordination and design support for the audio slides/animation related to this publication. Bruno Dumont coordinated the manuscript development and editorial support, and Valerie Lafontaine provided design support.

*"This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses."*

## **Conflicts of Interest and Source of Funding**

Danier J is employed by the GSK group of companies and hold shares in the GSK group of companies. Rivera L has nothing to disclose. Claeys C is employed by the GSK group of companies and hold shares in the GSK group of companies. Dbaiho G reports grants from American University of Beirut, during the conduct of the study. Jain VK reports she was employed by the GSK group of companies and hold shares in the GSK group of companies. Kosalaraksa P reports payments to his institution from the GSK group of companies for the conduct of this study. Woo W is employed by the GSK group of companies and holds shares in the GSK group of companies. Yanni E is employed by the GSK group of companies and holds shares in the GSK group of companies. Zaman K has nothing to disclose. Acosta B has nothing to disclose. Amanullah A is employed by the GSK group of companies and hold shares in the GSK group of companies. Ariza M has nothing to disclose. Arroba Basanta ML has nothing to disclose. Bavdekar A has nothing to disclose. Carmona A has nothing to disclose. Cousin L has nothing to disclose. Diaz A has nothing to disclose. Diez-Domingo J reports payments from the GSK group of companies, MSD and SPMSD to his institution, participation in clinical trials sponsored by the GSK group of companies, Abbot, MSD, Sanofi without receiving any fee, and personal fees for participation as independent monitoring committee for clinical trials with the GSK group of companies, Seqirus and Janssen. Dinleyici EC reports payments from the GSK group of companies for the conduct of this study and from Pfizer, Sanofi Pasteur outside this submitted work. Faust SN reports his institution received payments from the GSK group of companies for the conduct of this study, and from

*"This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses."*

Pfizer, Astra Zeneca, Cubist, Merck, Pfizer, Sanofi Pasteur, Sequerius, the GSK group of companies, Alios, J&J, Janssen and Medimmune for speakers or advisory board or clinical trials on behalf of his institution (no personal payments were made). Garcia-Sicilia J reports payments to his institution from the GSK group of companies for the conduct of this study and outside this submitted work. Gomez-Go GD reports payments from the GSK group of companies for the conduct of the study. Gonzales MLA reports payments from the GSK group of companies for the conduct of the study. Hacimustafaoglu M has nothing to disclose. Hughes SM reports payments from the GSK group of companies outside the submitted work. Izu A is employed by the GSK group of companies and hold shares in the GSK group of companies. Jackowska T reports payments from the GSK group of companies for the conduct of this study. Kant S has nothing to disclose. Lucero M has nothing to disclose. Mares Bermudez J reports payments from the GSK group of companies for the conduct of this study and payments from the GSK group of companies, Sanofi Pasteur, MSD-Merck, Pfizer, AstraZeneca, and Sequirus for speakers or advisory board or clinical trials on behalf of his institution. Martinon-Torres F reports payments from the GSK group of companies for the conduct of this study to his institution and payments from the GSK group of companies, Ablynx, Jansen, Regeneron, Medimmune, Pfizer, MSD, Sanofi Pasteur, Novavax, AstraZeneca and Novartis outside the submitted work. Montellano M reports payment from the GSK group of company for the conduct of this study and payment from Sanofi Pasteur, Serum Staten Institute, SK Chemicals, MSD and Unilab for lectures and clinical trials, outside the submitted work. Prymula R reports payments from the GSK group of companies for the conduct of this study and payments from the GSK group of companies, Novartis and

*“This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses.”*

Sanofi Pasteur outside the submitted work. Puthanakit T reports payments to her institution from the GSK group of companies for the conduct of this study. Ruzkova R has nothing to disclose. Sadowska-Krawczenko I reports payments from the GSK group of companies for the conduct of this study. Soni J is employed by the GSK group of companies. Szymanski H reports payments to his institution from the GSK group of companies for the conduct of this study, and from Ablynx, Sanofi Pasteur, Novartis and Pfizer outside this submitted work. Ulied A reports payments to her institution from the GSK group of companies for the conduct of this study, and from MSD, Novartis and Pfizer outside this submitted work. Schuind A is employed by the GSK group of companies and hold shares in the GSK group of companies. Innis BL reports he was employed by the GSK group of companies at the time of the study.

GlaxoSmithKline Biologicals SA funded this study and was involved in all stages of study conduct, including analysis of the data. GlaxoSmithKline Biologicals SA also took in charge all costs associated with the development and publication of this manuscript.

### **Contributorship**

All authors participated in the design or implementation or analysis, and interpretation of the study; and the development of this manuscript. All authors had full access to the data and gave final approval before submission. The Flu4VEC study group is shown in Supplemental Digital Content 1.

### **Data sharing statement**

*“This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses.”*

Anonymized individual participant data from this study plus the annotated case report form, protocol, reporting and analysis plan, data set specifications, raw dataset, analysis-ready dataset, and clinical study report are available for research proposals approved by an independent review committee. Proposals should be submitted to [www.clinicalstudydatarequest.com](http://www.clinicalstudydatarequest.com). A data access agreement will be required.

**Keywords:** influenza, symptoms, quadrivalent influenza vaccine, healthcare utilization

**Abbreviated title:** Clinical presentation of influenza in a vaccine trial (53 characters [max 55])

**Running title:** Influenza symptoms in a vaccine trial (37 characters [max 44])

**Type of publication:** Vaccine report

**Word count:** 3198 words (limit 3000 words; limit to 5 tables/figures)



*“This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses.”*

## **Abstract**

**Background:** In an exploratory analysis of an inactivated quadrivalent influenza vaccine (IIV4) trial in children 6–35 months without risk factors for influenza, we evaluated clinical presentation of influenza illness and vaccine impact on health outcomes.

**Methods:** This phase III trial was conducted in 13 geographically diverse countries across five influenza seasons (2011–2014). Children were randomized 1:1 to IIV4 or control. Active surveillance was performed for influenza-like episodes (ILE); influenza was confirmed by reverse transcription polymerase chain reaction (RT-PCR). The total vaccinated cohort was evaluated (N=12,018).

**Results:** 5702 children experienced  $\geq 1$  ILE; 356 (IIV4 group) and 693 (control group) children had RT-PCR-confirmed influenza. Prevalence of ILE was similar in RT-PCR-positive and RT-PCR-negative cases regardless of vaccination. Breakthrough influenza illness was attenuated in children vaccinated with IIV4; moderate-to-severe illness was 41% less likely to be reported in the IIV4 group than the control group (crude odds ratio: 0.59 [95% CI: 0.44–0.77]). Furthermore, fever  $>39^{\circ}\text{C}$  was 46% less frequent following vaccination with IIV4 than with control (crude odds ratio: 0.54 [95% CI: 0.39–0.75]) in children with breakthrough illness. Health outcome analysis showed that, each year, IIV4 would prevent 54 influenza cases/1000 children and 19 children would need to be vaccinated to prevent one new influenza case.

*"This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses."*

**Conclusion:** In addition to preventing influenza in 50% of participants, IIV4 attenuated illness severity and disease burden in children who had a breakthrough influenza episode despite vaccination.

ClinicalTrials.gov number: NCT01439360

**Word count:** 232 (max 250)

CONFIDENTIAL

*"This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses."*

## **Focus on patient**

### **What is the context?**

Morbidity and mortality caused by influenza are important global public health concerns. Children less than 5 years of age are highly susceptible to influenza disease leading to hospitalization and other healthcare resource use. Accurate clinical diagnosis of influenza is particularly difficult in young children because symptoms vary in severity and may overlap with symptoms caused by other respiratory pathogens. Timely diagnosis of influenza utilizing available diagnostic tests is particularly important for appropriate management of patients.

### **What is new?**

In this paper, clinical presentation and impact of influenza vaccination on disease severity were evaluated in healthy children 6 to 35 months of age. Regardless of vaccination status, we confirmed that symptoms associated with influenza disease were similar to those associated with the other respiratory pathogens. However, we observed that children vaccinated against influenza were less susceptible to experience more severe disease. Most notably, prevalence of high fever was lower in vaccinated children.

### **What is the impact?**

We aimed to characterize influenza disease and estimate the impact of influenza vaccination in young children. The severity of influenza illness is attenuated in

*"This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses."*

children who acquired infection despite vaccination, confirming the value of  
vaccinating children against influenza.

CONFIDENTIAL

*“This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses.”*

## Introduction

In children, influenza attack rates are high<sup>1</sup> and influenza illness is associated with substantial hospitalization and other healthcare resource use.<sup>2-5</sup> Vaccination of children against influenza is now recommended in many countries. Although its main goal is prevention of influenza, there is some evidence that breakthrough illness is attenuated in people who acquire influenza despite vaccination. Studies in both adults and children have shown that vaccinated individuals with laboratory-confirmed influenza had lower death rates, fewer admissions to an intensive care unit, shorter hospital stay and less severe symptoms compared with non-vaccinated individuals.<sup>6-</sup>

9

The lack of specificity in influenza symptoms means that a differential diagnosis from other illnesses associated with respiratory viruses remains a significant challenge, particularly in young children.<sup>10-13</sup> The increasing availability of technologies to detect and identify viruses has revealed that many cases of influenza-like illness (ILI) are in fact caused by viruses other than influenza.<sup>14-16</sup>

Between 2011 and 2014, we conducted a multinational, randomized, controlled clinical trial in healthy children 6 to 35 months of age to determine the efficacy of an inactivated quadrivalent influenza vaccine (IIV4) against reverse transcription polymerase chain reaction (RT-PCR)-confirmed influenza.<sup>17</sup> Vaccine efficacy (VE) was 63% against moderate-to-severe influenza illness and 50% against all influenza illness.<sup>17</sup> In this article, we present an exploratory analysis of the trial to evaluate the clinical presentation of influenza and influenza-like episodes (ILE) and to assess the

*"This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses."*

vaccine's impact on outcomes relevant to public health using a vaccine probe

approach (see video, Supplemental Digital Content 2).

CONFIDENTIAL

*"This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses."*

## **Materials and Methods**

Detailed methods of this randomized, controlled, observer-blind phase III trial have been presented previously.<sup>17</sup> The study was funded by GlaxoSmithKline Biologicals SA and registered with ClinicalTrials.gov (NCT01439360) and received appropriate ethics approval (see Supplemental Digital Content 3).

### **Study design and participants**

The study was conducted in 13 northern hemisphere and subtropical countries (see Supplemental Digital Content 3). Healthy children (6–35 months of age) without risk factors for complications of influenza illness were recruited in five independent cohorts and each study cohort was conducted during a different influenza season (see Supplemental Digital Content 3). Children were randomized 1:1 to IIV4 or non-influenza control vaccines (see Supplemental Digital Content 3).

### **Surveillance for illness and recording of symptoms**

Influenza surveillance began for each individual child from 14 days after final vaccination and lasted until the end of the influenza season. The surveillance period covered the peak of the influenza season in each country.<sup>17-19</sup> Nasal swabs were collected according to the study protocol within 7 days (preferably within 24 hours) of the onset of an ILE that included influenza-like illness (ILI, which was defined as temperature  $\geq 38^{\circ}\text{C}$  in combination with one or more of the following: cough, runny nose, nasal congestion or breathing difficulty), physician-diagnosed acute otitis media (AOM) or lower respiratory infection (LRI).

*"This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses."*

Influenza A or B was confirmed by RT-PCR. Further antigenic characterization was performed for influenza A subtype or B lineage as described previously.<sup>17</sup> Parents recorded temperature, symptoms (specified separately for ILI/LRI and AOM), and any medication used daily using an internet-based system or paper booklet (see Supplemental Digital Content 3). Symptoms were recorded until they resolved or a maximum of 13 days after onset. Study staff made a follow-up contact at the end of the episode at which they recorded its outcome; final physician diagnosis; medications; healthcare utilization; and absenteeism (see Supplemental Digital Content 3).

### **Study objectives**

The primary objectives of the study (efficacy of IIV4 against the first occurrence of RT-PCR-confirmed influenza of any severity [all influenza] and moderate-to-severe influenza) have been previously reported.<sup>17</sup> Moderate-to-severe influenza was defined as any of the following: fever  $>39^{\circ}\text{C}$ ; physician-diagnosed AOM; physician-diagnosed LRI; physician-diagnosed serious extra-pulmonary complication (e.g. myositis, encephalitis, seizure, myocarditis/pericarditis or other serious medical condition); hospitalization in the intensive care unit (ICU); or supplemental oxygen for  $>8$  hours. The latter three criteria defined severe influenza illness.

The objectives of the present analyses were (1) to describe the clinical characteristics of ILE in influenza-positive compared with influenza-negative (confirmed by RT-PCR) children, regardless of influenza vaccination status; (2) to compare the symptoms and symptom severity of RT-PCR-confirmed influenza in



*"This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses."*

children in the IIV4 group who experienced breakthrough illness versus children in the control group; (3) to evaluate the public health impact of the IIV4 using a vaccine probe approach (see figure, Supplemental Digital Content 4).

## **Statistical methods**

All analyses conducted for this paper were exploratory and were conducted in the total vaccinated cohort (TVC), which included all vaccinated children with available data. VE was defined as the hazard ratio of cases of influenza A and/or B disease in children receiving IIV4 in contrast with children receiving non-influenza vaccine control, subtracted from 1. The Cox proportional hazard regression model included treatment group as the explanatory variable, age category as a covariate, and cohort as a stratification variable in the analysis. Full details on the regression modelling have been previously described.<sup>17</sup>

The crude odds ratio (OR) was calculated along with 95% confidence intervals (CI) to measure the association between children with RT-PCR-confirmed influenza experiencing moderate-to-severe versus mild illness for IIV4 versus control: (no. moderate-to-severe cases IIV4/no. moderate-to-severe cases control)/(no. mild cases IIV4/no. mild cases control). The crude OR for the proportion of children with RT-PCR-confirmed influenza with ILI or LRI as the primary event experiencing fever >39°C was calculated in the same way.

In an analysis attempting to further assess disease severity (in addition to categorization of influenza as mild and moderate-to-severe), a severity score for clinical symptoms was calculated based on the symptom diary for children in whom

*“This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses.”*

ILI or LRI was the primary event triggering the nasal swab (see Supplemental Digital Content 3). A symptom score for AOM was not calculated because few children with RT-PCR-confirmed influenza experienced AOM as the event triggering the nasal swab.

Using established methods as described in Supplemental Digital Content 3,<sup>20</sup> we estimated the etiologic fraction (AF) of ILE caused by a pathogen, the vaccine prevention disease index (VPDI) and the number of vaccinees needed to prevent one new case of disease (NNV).

CONFIDENTIAL

*“This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses.”*

## **Results**

A total of 12,018 children were included in the TVC; median age was 22 months, with approximately equal numbers of boys and girls. Most children were of South East Asian, White European, Central/South Asian or Hispanic ancestry. A total of 2,747 children in the IIV4 group experienced 4153 ILE episodes and 2955 children in the control group experienced 4411 ILE episodes (Figure 1). In the TVC, most (77.4%) events presented as ILI, 16.3% presented as LRI, and 6.3% presented as AOM.

### **Prevalence of symptoms defining ILI: influenza-positive versus influenza-negative episodes regardless of vaccination status**

In total, 6625 ILI episodes were identified; 987 were RT-PCR-positive, 5464 were RT-PCR-negative, and 174 had a missing RT-PCR result (Figure 1). The frequency of episodes of any non-specific (before RT-PCR confirmation of influenza) ILI, LRI and AOM in the IIV4 group was similar to the control group. The prevalence of symptoms defining ILI was similar in RT-PCR-positive and RT-PCR-negative episodes (see figure, Supplemental Digital Content 5). All ILI cases were associated with fever, as this was part of the definition of ILI. Symptoms of at least fever, cough and runny nose were present in 73.4% and 74.9% of RT-PCR-positive and RT-PCR-negative cases, respectively (see figure, Supplemental Digital Content 5).

*“This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses.”*

## **Comparison of RT-PCR-confirmed influenza symptoms in vaccinated and unvaccinated children**

A total of 356 (IIV4) and 693 children (control) had RT-PCR-confirmed influenza (Figure 1).

### ***Clinical symptoms in RT-PCR-confirmed influenza***

Among children with RT-PCR-confirmed influenza who received IIV4, the event triggering the nasal swab was ILI in 92.3%, LRI in 6.3% and AOM in 1.4% (Figure 1). Corresponding values in the control group were 91.3%, 6.3% and 2.4%.

In children with ILI or LRI associated with RT-PCR-confirmed influenza, the frequency of symptoms and symptom duration were similar in both study groups (Table 1). Normal activities (parental absence from paid work or child absence from day-care) were disrupted in 78–79% of children with influenza-positive ILI or LRI in both study groups (Table 1). However, a lower prevalence of fever  $>39^{\circ}\text{C}$  was observed in children in the IIV4 group than in the control group (17.7% [95% CI: 13.8, 22.1] vs 28.30% [25.0, 31.9]; crude OR: 0.54 (95% CI: 0.39, 0.75); Figure 2). Among children with AOM, the frequency of all symptoms was similar in both groups (data not shown).

### ***Symptom severity and hospitalization in RT-PCR-confirmed influenza***

Of children in the IIV4 group with RT-PCR-confirmed influenza, 25.8% experienced moderate-to-severe illness and 74.2% experienced mild illness; corresponding values in the control group were 37.2% and 62.8%. The crude OR (0.59 [95% CI:

*“This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses.”*

0.44, 0.77]) demonstrated that breakthrough influenza illness was attenuated in children vaccinated with IIV4, with moderate-to-severe illness being 41% less likely to be reported in the IIV4 group versus the control group. However, the calculated severity scores for ILI and LRI showed little difference between the study groups (see table, Supplemental Digital Content 6).

Three children out of 356 (0.8%) with RT-PCR-confirmed influenza in the IIV4 group were hospitalized compared with nine out of 693 (1.3%) in the control group (see table, Supplemental Digital Content 7). Children remained in hospital for between 1 and 7 days, except for one child in the IIV4 group who was hospitalized for 19 days associated with pneumonia and sepsis. Two cases meeting the definition of severe influenza were reported in the IIV4 group (associated with sepsis and febrile convulsion) and three in the control group (two associated with febrile convulsion and one with febrile convulsion and typhoid fever).

At the time of hospitalization, children had concurrent symptoms of ILE, but it was unknown at admission whether they were RT-PCR-positive or -negative for influenza. The recorded diagnoses were based on clinical data, and the clinical presentation of each case was consistent with an episode of influenza. Further evaluation of each case identified a variety of medical conditions, including other infectious etiologies (RSV, roseola, typhoid fever and rotavirus), pneumonia (unknown etiology), febrile convulsion, and other respiratory conditions (see table, Supplemental Digital Content 7). Among those hospitalized with pneumonia (two in the IIV4 group and four in the control group), the events seemed consistent with secondary infections. Four cases of febrile convulsion prompting hospitalization were

*"This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses."*

recorded in children with confirmed influenza, one in the IIV4 group child and three in the control group. The case in the vaccinated child occurred after the child developed an upper respiratory tract infection. The cases in the control group occurred in conjunction with typhoid fever, pneumonia and upper respiratory tract infection. Thus, although these 12 hospitalized children presented with influenza-like symptoms and had influenza virus detected by RT-PCR, clinical tests performed during the hospital stay indicated that the hospitalization was associated with a medical condition in addition to influenza.

#### **Public health impact of the IIV4 (vaccine probe analysis)**

For RT-PCR-confirmed influenza of any severity, AF was 14.0%, VPDI was 5.4 per 100 children per year (i.e. IIV4 would prevent 54 influenza cases per 1000 children each year), and NNV was 19.0 (i.e. 19 children would need to be vaccinated to prevent one new influenza case each year). Other values are shown in Table 2.

*“This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses.”*

## Discussion

Our study recruited healthy young children without medical conditions that could place them at higher risk for influenza disease or complications, and excluded children with such conditions. These population characteristics should be borne in mind when interpreting the study results. We found that clinical symptoms did not distinguish between confirmed influenza cases (RT-PCR-positive) and cases unlikely to be influenza-related (RT-PCR-negative), providing further evidence of the difficulty of accurate clinical diagnosis of influenza in young children without the aid of diagnostic tests.<sup>10-13</sup> This likely results in underdiagnosis of influenza in children in real world settings, which in turn might lead to an underestimation of the impact of childhood influenza and the importance of vaccination.<sup>21,22</sup> The analysis of symptoms indicative of influenza was limited by the fact that only pre-specified symptoms were collected and therefore the whole clinical picture was not necessarily captured. A further limitation is that nasal swabs could be collected up to 7 days after symptom onset, which could decrease the positivity rate. However, parents were asked to report ILI symptoms as soon as they occurred, and every effort was made to collect swabs within 1 day of symptom onset. In fact, approximately 70% were collected within 0–1 days and approximately 90% within 3 days of symptoms onset.

Nevertheless, the symptoms observed in our study were consistent with those seen in other studies.<sup>23,24</sup> In a trial of live attenuated influenza vaccine (LAIV) among children 24–59 months of age, fever, cough or runny nose were reported in approximately 70% of children with confirmed influenza; fever was reported more frequently in children with confirmed influenza than those who were influenza-

*“This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses.”*

negative.<sup>23</sup> A longitudinal active surveillance study in pre-school children found that children with febrile or respiratory illnesses testing positive for influenza were more likely to experience fever, headache, myalgia, runny nose, and loss of appetite than children testing negative for influenza.<sup>24</sup>

The control group of our study provides a global picture of influenza illness experienced in diverse locations over five influenza seasons in healthy young children. A study in Germany of unvaccinated children less than 5 years of age with laboratory-confirmed influenza reported a duration of 4 days for fever and 10–11 days for cough and runny nose.<sup>25</sup> This was longer than the median 2 days for fever, 6 days for cough and 7 days for runny nose observed in our study’s control group. This difference might be due to differences in methodology. For example, our study excluded children at risk of influenza complications and included active follow-up for ILE, whilst the German study included all children presenting at outpatient pediatric practices with febrile acute respiratory infection.<sup>25</sup> Furthermore, the children enrolled in our study were younger than those enrolled in the German study (mean age of 22 months versus 43 months).

Higher VE against moderate-to-severe influenza versus influenza of any severity has been previously reported for this study.<sup>17</sup> Our analysis suggests that disease attenuation may occur in breakthrough cases. In children with RT-PCR-confirmed influenza, those vaccinated with IIV4 were 41% less likely to develop moderate-to-severe illness and 46% less likely to develop fever >39°C compared with unvaccinated children. Furthermore, there were fewer influenza-associated medically attended and emergency room visits among children who received IIV4. Several



*“This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses.”*

other studies have reported attenuation of influenza severity following vaccination.<sup>6-9,26,27</sup> Another study of IIV4 in children 3–8 years of age reported higher vaccine efficacy against moderate-to-severe influenza (74%) than against influenza of any severity (59%).<sup>26</sup> A case-cohort study of children with confirmed influenza who died reported that 74% of deaths occurred among unvaccinated children.<sup>6</sup> Similarly, a trial of LAIV reported that vaccinated children missed substantially less day-care than unvaccinated children.<sup>27</sup> The latter has also been previously reported for the present study.<sup>17</sup>

The above findings emphasize the importance of selecting appropriate endpoints for the evaluation of influenza vaccine efficacy in clinical trials. The moderate-to-severe endpoint reflects clinical outcomes of LRI, ear infection, other serious non-pulmonary complications and high fever that are most likely to result in medical consultations.<sup>28</sup> Failure to distinguish moderate-to-severe influenza from mild influenza might mask the vaccine’s ability to attenuate illness, and therefore its true benefit to individuals may be undervalued. The value of the moderate-to-severe endpoint has been confirmed using real-life data from community-based studies.<sup>25,29,30</sup> Perceived severity of disease influences the decision to vaccinate,<sup>31</sup> and thus raising awareness of the overall impact of influenza may help to improve vaccination rates. Furthermore, in low-resource settings with competing health priorities, an awareness of the impact of moderate-to-severe influenza and the benefits of vaccination may be required for prioritization of influenza among other vaccine-preventable diseases in young healthy children. We attempted to explore disease attenuation in the vaccine group by calculating a symptom severity score, but found that the score was not able

*"This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses."*

to differentiate between vaccinated and unvaccinated children. This might suggest that the symptoms collected in this study are unable to quantify or adequately describe the degree of illness severity experienced. Alternatively, the lack of difference in the score between study groups may be explained by methodology issues such as incomplete diaries, masking of the severity of influenza symptoms by co-infections, or recruitment of a population without pre-existing conditions putting them at risk for influenza. We concluded that the score as developed was not fit for the purpose of scoring influenza symptom severity.

Data from vaccine clinical trials can be used to assess the public health impact of vaccination by characterizing the disease burden and quantifying the reduction in disease outcomes through vaccination.<sup>32</sup> However, such analyses are limited to assessment of the direct impact of vaccination and are unable to evaluate any indirect effects. Thus, the true impact of vaccination is likely to be underestimated. We found that confirmed influenza contributed to 14% of all ILE episodes, indicating that 86% of episodes might result from other respiratory pathogens in this population of young children. Thus, the study suggests that IIV4 decreases the burden of RT-PCR confirmed influenza in young children, but has a limited net impact against non-specific ILE. However, evaluation of net impact was not the focus of the study, and the results should be interpreted with caution. The proportion of ILE associated with confirmed influenza depends upon the virulence of the circulating influenza strains, period of data collection since influenza is a seasonal disease, vaccine uptake, and, importantly, the susceptibility of the population against circulating influenza viruses.

*“This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses.”*

The study showed that vaccination with IIV4 of 1000 children averted annually 54 influenza cases of any severity and 22 incidents of fever  $>39^{\circ}\text{C}$  associated with influenza. The study findings are within the range of VPDI estimates by other studies and reflect the role of influenza vaccination in reducing the burden of influenza in children and preventing circulation of the virus in the community. In a review of studies in children, the VPDI ranged from 0 to 380 per 1000, with a mean value of 128/1000 children based on 17 studies or sub-studies.<sup>33</sup>

With regard to healthcare utilization, we estimated that, from our study population, 21 children would need to be vaccinated to prevent one new medically-attended visit and 36 to prevent one new event of antibiotic use (the NNV). A previous study has estimated that, assuming 50% VE based on data from previously published studies in a variety of settings and populations, 12–42 children 6–59 months of age would need to be vaccinated to prevent one outpatient visit, depending on the severity of the influenza season.<sup>34</sup> The NNV results from our study need to be taken in context because the estimates depend on several study-related factors such as location (multiple study centers in 13 countries in northern hemisphere and subtropical countries), disease prevalence over five seasons with three mostly mismatched seasons, demographic and clinical characteristics of the study population, and healthcare systems (westernized versus non-westernized countries). In addition, it is important to note that influenza disease in young children was indistinguishable from other respiratory infectious diseases and cannot be conclusively identified without the use of specific diagnostic tests. Without such tests, which are not readily

*"This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses."*

available in most settings, the burden of influenza-associated healthcare utilization cannot be reliably estimated.

In conclusion, our analysis showed that influenza is common and drives substantial use of healthcare resource even in healthy children without risk factors for influenza and influenza-related complications. The incidence of breakthrough illness was reduced, and disease was attenuated in breakthrough cases in vaccinated children. The public health impact assessment using a vaccine probe approach demonstrated that the IIV4 can help to reduce the burden of influenza in children and confirmed at the individual level the value of vaccinating children against influenza.

CONFIDENTIAL

"This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses."

## References

1. Tokars JI, Olsen SJ, Reed C. Seasonal incidence of symptomatic influenza in the United States. *Clin Infect Dis* 2018;66:1511–1518.
2. O'Brien MA, Uyeki TM, Shay DK, et al. Incidence of outpatient visits and hospitalizations related to influenza in infants and young children. *Pediatrics* 2004;113:585–593.
3. Molinari NA, Ortega-Sanchez IR, Messonnier ML, et al. The annual impact of seasonal influenza in the US: measuring disease burden and costs. *Vaccine* 2007;25:5086–5096.
4. Izurieta HS, Thompson WW, Kramarz P, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. *N Engl J Med* 2000;342:232–239.
5. Bourgeois FT, Valim C, Wei JC, et al. Influenza and other respiratory virus-related emergency department visits among young children. *Pediatrics* 2006;118:e1–8.
6. Flannery B, Reynolds SB, Blanton L, et al. Influenza vaccine effectiveness against pediatric deaths: 2010-2014. *Pediatrics* 2017;139:e20164244.
7. Arriola C, Garg S, Anderson EJ, et al. Influenza vaccination modifies disease severity among community-dwelling adults hospitalized with influenza. *Clin Infect Dis* 2017;65:1289–1297.

"This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses."

8. Deiss RG, Arnold JC, Chen WJ, et al. Vaccine-associated reduction in symptom severity among patients with influenza A/H3N2 disease. *Vaccine* 2015;33:7160–167.
9. Castilla J, Godoy P, Dominguez A, et al. Influenza vaccine effectiveness in preventing outpatient, inpatient, and severe cases of laboratory-confirmed influenza. *Clin Infect Dis* 2013;57:167–175.
10. Fitzner J, Qasmieh S, Mounts AW, et al. Revision of clinical case definitions: influenza-like illness and severe acute respiratory infection. *Bull World Health Organ* 2018;96:122–128.
11. Casalegno JS, Eibach D, Valette M, et al. Performance of influenza case definitions for influenza community surveillance: based on the French influenza surveillance network GROG, 2009-2014. *Euro Surveill* 2017;22:30504.
12. Peltola V, Reunanen T, Ziegler T, et al. Accuracy of clinical diagnosis of influenza in outpatient children. *Clin Infect Dis* 2005;41:1198–1200.
13. Dwyer DE, Smith DW, Catton MG, et al. Laboratory diagnosis of human seasonal and pandemic influenza virus infection. *Med J Aus* 2006;185(10 Suppl):S48–53.
14. Pavia AT. Viral infections of the lower respiratory tract: old viruses, new viruses, and the role of diagnosis. *Clin Infect Dis* 2011;52(Suppl 4):S284–289.

"This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses."

15. Debiaggi M, Canducci F, Ceresola ER, et al. The role of infections and coinfections with newly identified and emerging respiratory viruses in children. *Virology* 2012;9:247.
16. Taylor S, Lopez P, Weckx L, et al. Respiratory viruses and influenza-like illness: Epidemiology and outcomes in children aged 6 months to 10 years in a multi-country population sample. *J Infect* 2017;74:29–41.
17. Claeys C, Zaman K, Dbaibo G, et al. Prevention of vaccine-matched and mismatched influenza in children aged 6-35 months: a multinational randomised trial across five influenza seasons. *Lancet Child Adolesc Health* 2018;2:338–349.
18. World Health Organization. FluNet. Available from: [http://www.who.int/influenza/gisrs\\_laboratory/flunet/en/](http://www.who.int/influenza/gisrs_laboratory/flunet/en/). Accessed July 2017.
19. European Centre for Disease Control and Prevention. Seasonal influenza 2011-2012 in Europe (EU/EEA countries). 2012. Available from: <https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/120312-TER-Seasonal-influenza-risk-assessment.pdf>. Accessed September 2017.
20. Feikin DR, Scott JA, Gessner BD. Use of vaccines as probes to define disease burden. *Lancet* 2014;383:1762–1770.
21. Poehling KA, Edwards KM, Griffin MR, et al. The burden of influenza in young children, 2004–2009. *Pediatrics* 2013;131:207–16.

"This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses."

22. Poehling KA, Edwards KM, Weinberg GA, et al. New Vaccine Surveillance Network. The underrecognized burden of influenza in young children. *N Engl J Med* 2006;355:31-40.
23. Rotrosen E, Zaman K, Feser J, et al. Influenza among young children in Bangladesh: clinical characteristics and outcomes from a randomized clinical trial. *Clin Infect Dis* 2017;65:1914–1920.
24. Brooks WA, Goswami D, Rahman M, et al. Influenza is a major contributor to childhood pneumonia in a tropical developing country. *Pediatr Infect Dis J* 2010;29:216–221.
25. Streng A, Prifert C, Weissbrich B, et al. Subtype-specific clinical presentation, medical treatment and family impact of influenza in children one to five years of age treated in outpatient practices in Germany during three post-pandemic years, 2013-2015. *Pediatr Infect Dis J* 2018;37:861–867.
26. Jain VK, Rivera L, Zaman K, et al. Vaccine for prevention of mild and moderate-to-severe influenza in children. *N Engl J Med* 2013;369:2481–2491.
27. Ambrose CS, Antonova EN. The healthcare and societal burden associated with influenza in vaccinated and unvaccinated European and Israeli children. *Eur J Clin Microbiol Infect Dis* 2014;33:569–575.
28. Saunders NR, Tennis O, Jacobson S, et al. Parents' responses to symptoms of respiratory tract infection in their children. *CMAJ* 2003;168:25–30.



"This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses."

29. Heikkinen T, Silvennoinen H, Heinonen S, et al. Clinical and socioeconomic impact of moderate-to-severe versus mild influenza in children. *Eur J Clin Microbiol Infect Dis* 2016;35:1107–1113.
30. Hsiao A, Buck P, Yee A, et al. Health outcomes associated with mild versus moderate-to-severe laboratory-confirmed influenza in 6- to 36-month old children. IDWeek 2017. Available from: <https://idsa.confex.com/idsa/2017/webprogram/Paper65344.html>. Accessed April 2018.
31. Omer SB, Amin AB, Limaye RJ. Communicating about vaccines in a fact-resistant world. *JAMA Pediatr* 2017;171:929–930.
32. Kostova D, Reed C, Finelli L, et al. Influenza illness and hospitalizations averted by influenza vaccination in the United States, 2005-2011. *PLoS One* 2013;8:e66312.
33. Arnoux S, Weinberger C, Gessner BD. Vaccine-preventable influenza disease burden from clinical trials of Vaxigrip - an inactivated split virion influenza vaccine - supports wider vaccine use. *Vaccine* 2007;25:7720–7731.
34. Lewis EN, Griffin MR, Szilagyi PG, et al. Childhood influenza: number needed to vaccinate to prevent 1 hospitalization or outpatient visit. *Pediatrics* 2007;120:467–472.

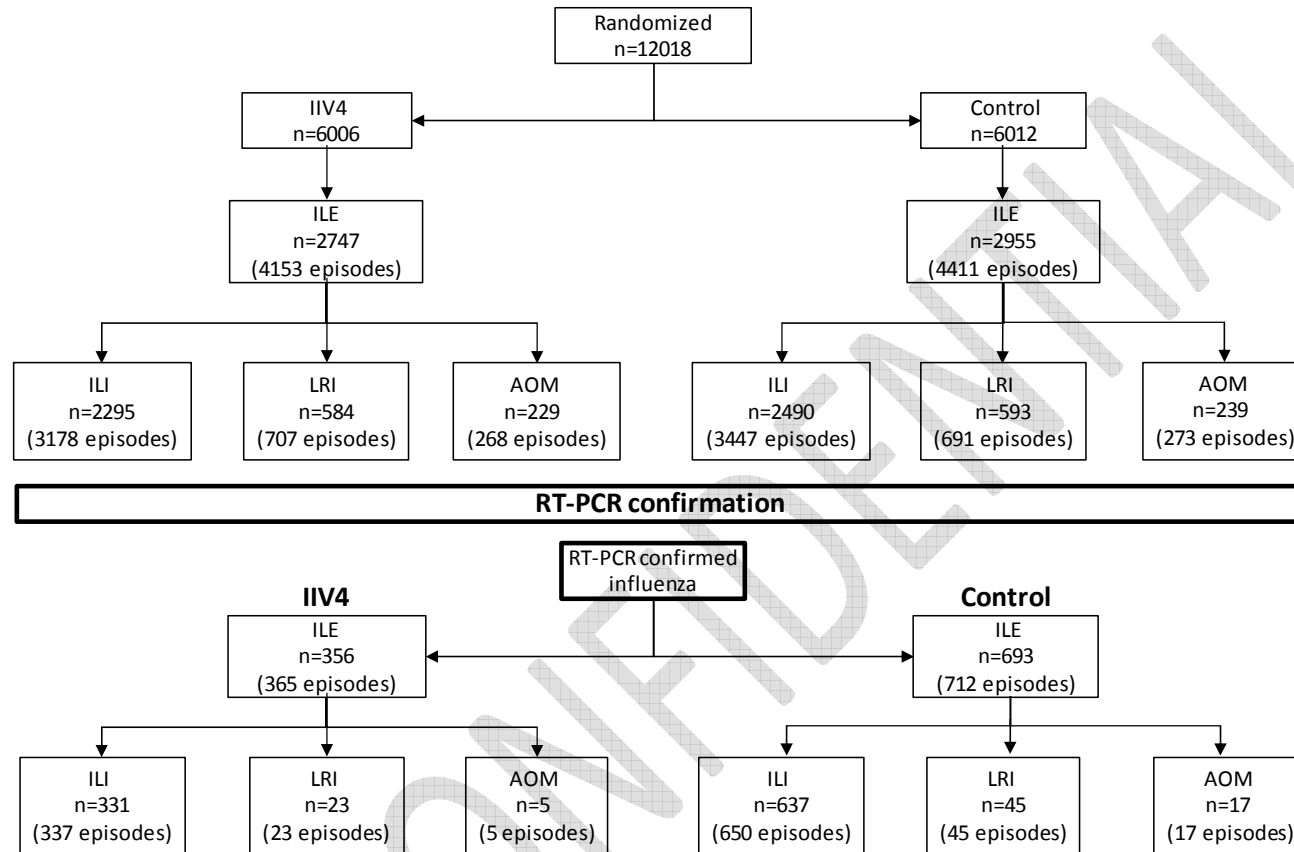
*“This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses.”*

## **Figures**

**Figure 1. Disposition of influenza-like episodes**

CONFIDENTIAL

*“This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses.”*



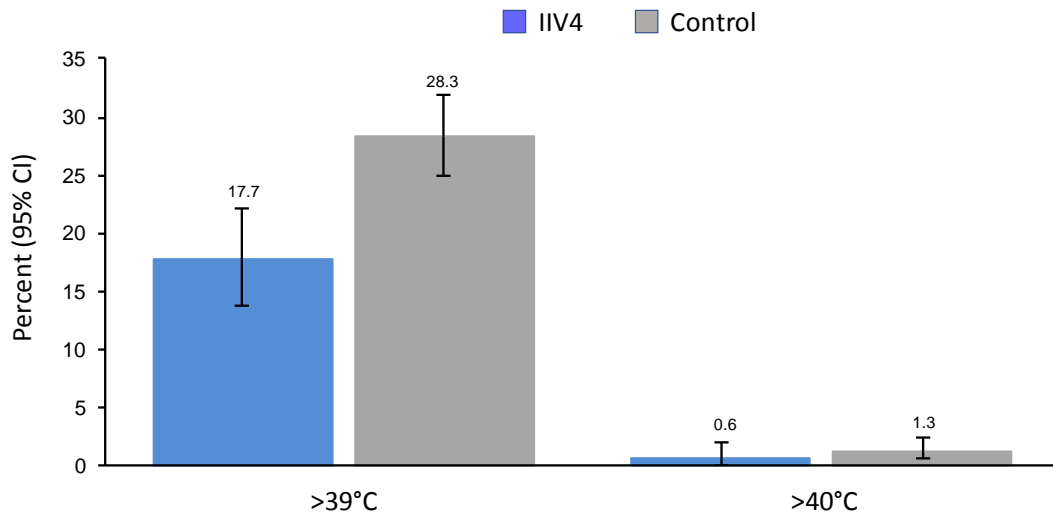
Three children in the IIV4 group and six children in the control group had two RT-PCR-confirmed infections that fell into different diagnostic categories (ILI, LRI and AOM) and are therefore counted twice in Figure 1. In the IIV4 group, all three children had one episode categorized as ILI and one episode categorized as LRI. In the control group, four children had one episode categorized as ILI and one episode categorized as LRI, and two children had one episode categorized as ILI and one episode categorized as AOM.

RT-PCR result missing (number of cases): ILI, n=94 and 80 for IIV4 and control, respectively; LRI, n=30 and 36 for IIV4 and control, respectively; AOM, n=27 and 24 for IIV4 and control, respectively.

AOM: acute otitis media; ILI: influenza-like illness; LRI: lower respiratory illness; RT-PCR: reverse transcription polymerase chain reaction

*"This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses."*

**Figure 2. Fever >39°C and >40°C associated with ILI/LRI in children with RT-PCR-confirmed influenza**



CI: confidence interval; ILI: influenza-like illness; LRI: lower respiratory illness; RT-PCR: reverse transcription polymerase chain reaction

*“This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses.”*

**Table 1. Clinical presentation of RT-PCR-confirmed influenza associated with ILI or LRI (day 0 to day 13 of episode)**

Symptom <sup>1</sup>	IIV4 N=351			Control N=678		
	n	% (95% CI)	Median duration (range), days	n	% (95% CI)	Median duration (range), days
Fever ≥38°C	325	92.6 (89.3, 95.1)	2.0 (1–14)	614	90.6 (88.1, 92.7)	2.0 (1–8)
Cough	303	86.3 (82.3, 89.7)	6.0 (1–14)	608	89.7 (87.1, 91.9)	6.0 (1–14)
Runny nose or nasal congestion	340	96.9 (94.5, 98.4)	7.0 (1–14)	641	94.5 (92.6, 96.1)	7.0 (1–14)
Vomiting	71	20.2 (16.1, 24.8)	2.0 (1–8)	125	18.4 (15.6, 21.6)	2.0 (1–13)
Feeling unwell	322	91.7 (88.3, 94.4)	4.0 (1–14)	621	91.6 (89.2, 93.6)	4.0 (1–14)
Normal activities disrupted <sup>2</sup>	278	79.2 (74.6, 83.3)	3.0 (1–14)	531	78.3 (75.0, 81.4)	3.0 (1–14)

<sup>1</sup>Specified symptoms recorded by parents daily using an internet-based system or paper booklet

<sup>2</sup>The end of the period of disruption to normal activities was the last day (inclusive) on which a 'no' response was recorded for the question 'Return to normal activity'

Data for the first episode of infection are shown in the Table

N: number of children with RT-PCR-confirmed influenza and a diagnosis of ILI or LRI; n: number of children with specified symptom

CI: confidence interval; ILI: influenza-like illness; LRI: lower respiratory illness; RT-PCR: reverse transcription polymerase chain reaction

*"This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses."*

CONFIDENTIAL

*“This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses.”*

**Table 2. Public health impact of the IIV4: vaccine probe analysis**

	Attack rate, IIV4, %	Attack rate, control, %	Vaccine efficacy, %	Etiological fraction, % <sup>1</sup>	VPDI, % (95% CI) <sup>2</sup>	NNV <sup>3</sup>
<b>Impact on manifestations of RT-PCR-confirmed influenza</b>						
All influenza	5.88	11.24	49.5	14.0	5.4 (4.4, 6.4)	19
Moderate-to-severe influenza	1.52	4.14	63.9	10.9	2.6 (2.0, 3.2)	38
Mild influenza	4.45	7.25	39.9	17.4	2.8 (2.0, 3.6)	36
Severe influenza	0.03	0.05	34.0	20.4	0.02 (-0.06, 0.09)	6024
Influenza associated with AOM <sup>4</sup>	0.20	0.47	56.7	12.3	0.27 (0.06, 0.47)	376
Influenza associated with LRI <sup>4</sup>	0.47	1.03	54.9	12.7	0.57 (0.26, 0.87)	177
Fever >39°C	1.03	3.19	-	-	2.2 (1.6, 2.7)	46
<b>Impact on healthcare resource associated with RT-PCR-confirmed influenza (any severity)</b>						
Any medical care	5.2	10.0	-	-	4.8 (3.8, 5.7)	21
Visit to GP or pediatrician	5.2	9.7	-	-	4.5 (3.6, 5.5)	22
Visit to medical specialist	0.1	0.2	-	-	0.15 (0.02, 0.28)	668

*“This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses.”*

ER visit	0.1	0.5	-	-	0.43 (0.23, 0.64)	231
Hospitalization	0.0	0.1	-	-	0.07 (-0.04, 0.17)	1504
Antibiotic use	2.9	5.7	-	-	2.8 (2.1, 3.5)	36
Antipyretic use	5.6	10.4	-	-	4.8 (3.8, 5.8)	21
Days of paid work missed by parents	0.4	0.9	-	-	0.5 (0.2-0.7)	215
Days of day care or school missed by child	0.8	1.8	-	-	1.0 (0.6-1.4)	102

<sup>1</sup>AF: VE against ILE divided by VE against RT-PCR-confirmed influenza

Calculation of VE against ILE: 1 minus the relative risk of ILE in vaccinated group versus unvaccinated group (1 minus [2747/6006]/[2955/6012])

AR against first ILE in IIV4 group: 2747/6006 = 45.7%

AR against first ILE in control group: 2955/6012 = 49.8%

VE against ILE: 1-(45.7/49.1) = 6.95% (95% CI: 3.4, 10.4)

<sup>2</sup>VPDI: incidence of RT-PCR-confirmed influenza in control group minus incidence of RT-PCR-confirmed influenza in IIV4 population (mathematically equivalent to the product of VE and incidence in the control population)

<sup>3</sup>NNV: 1 divided by VPDI

<sup>4</sup>Based on the clinical diagnosis of AOM or LRI rather than the documented reason for the initial swab taken on report of an ILE

AF: etiological fraction; AOM: acute otitis media; AR: attack rate; CI: confidence interval; ER: emergency room; GP: general practitioner; ILE: influenza-like episode; LRI: lower respiratory



*“This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses.”*

infection; NA: not applicable; NNV: number needed to vaccinate; RT-PCR: reverse transcription polymerase chain reaction; VE: vaccine efficacy; VPDI: vaccine-preventable disease incidence

CONFIDENTIAL

*"This is confidential information. This document is the submitted version of the publication on which you are an author. The content of this document can differ from the published version according to feedback from the peer-reviewers and should therefore not be used as a reference. This document is for your personal use only and should not be used for other purposes nor shared further in any circumstances (this could generate a violation of journal copyright). Premature disclosure of unpublished or unrepresented material can result in refusal of publications by journals and congresses."*

## **Supplemental Digital Content**

Supplemental Digital Content 1. Text

Supplemental Digital Content 2. Video

Supplemental Digital Content 3. Text

Supplemental Digital Content 4. Figure

Supplemental Digital Content 5. Figure

Supplemental Digital Content 6. Table

Supplemental Digital Content 7. Table