Study Protocol
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eTrack study number and Abbreviated Title	205049 (EPI-FLU-052 BOD PA DB)
Date of protocol	Final Version 1: 29 March 2016
Title	Prevalence, strain circulation and disease burden of seasonal Influenza A and B in Panama, selected countries of Central America and the Caribbean from the Year 2010 to 2015.
Detailed Title	An observational, retrospective, database study of the burden of seasonal Influenza A and B in Panama, selected countries of Central America and the Caribbean from the Year 2010 to 2015.
Co-ordinating author	PPD, Scientific Writer
Contributing authors	• PPD Regional Epidemiology Manager, LATAM • PPD, Global Epidemiologist • PPD, Director Epidemiology, LATAM • PPD, Study Delivery Lead • PPD, Lead Statistician • PPD, Project Statistician • PPD, Local Delivery Lead • PPD, Study Data Manager • PPD, Cluster Medical Lead Andina-Caricam • PPD, Medical Affairs Manager, Caricam • PPD, Senior Manager, Clinical Data Management

GSK Biologicals' protocol template for database studies based on the Protocol Document Standard version 14.1.1

Protocol Sponsor Signatory Approval

eTrack study number and Abbreviated Title	205049 (EPI-FLU-052 BOD PA DB)
Date of protocol	Final Version 1: 29 March 2016
Detailed Title	An observational, retrospective, database study of the burden of seasonal Influenza A and B in Panama, selected countries of Central America and the Caribbean from the Year 2010 to 2015.
Sponsor signatory	Eduardo Ortega-Barria Vice President and Head of Clinical R&D and Medical Affairs, Latin America GlaxoSmithKline Biologicals
Signature	_____
Date	_____

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Protocol Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, with the terms of the study agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- To assume responsibility for the proper conduct of the study.
- That I am aware of, and will comply with applicable guidelines and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about study-related duties and functions as described in the protocol.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study number and Abbreviated Title	205049 (EPI-FLU-052 BOD PA DB)
Date of protocol	Final Version 1: 29 March 2016
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Investigator name	_____
Signature	_____
Date	_____

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Sponsor Information

1. Sponsor

GlaxoSmithKline Biologicals
GlaxoSmithKline Export Panamá, S. A, Clayton City of Knowledge, Bldg 230
P.O. Box 0819-08530
Panama, Rep. Of Panama

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

SYNOPSIS

Detailed Title	An observational, retrospective, database study of the burden of seasonal Influenza A and B in Panama, selected countries of Central America and the Caribbean from the Year 2010 to 2015
Rationale for the study	Evidence is needed to assess prevalence and incidence of seasonal influenza A and B, assess the potential mismatch and identify clinical features of seasonal Influenza A and B by country. Thus, this study aims to raise awareness to the public health stakeholders the need for quadrivalent influenza vaccine (QIV) and support its recommendation by: • Generating burden of disease data that highlights the contribution of influenza to hospitalization, mortality, cardiovascular disease and other complications. • Providing evidence, documenting the mismatch between circulating B strains and those included in the recommended seasonal vaccine and co-circulation of influenza across different seasons. • Understanding the burden of disease of influenza B strains and the added value of a QIV. The data from this study, • May support the implementation and expansion of existing universal mass vaccination (UMV) strategies for influenza. – the current recommendation is to vaccinate the elderly, health care workers, children (in some countries vaccination is limited to children with chronic diseases), adults with chronic diseases. Some countries in the study region also recommend influenza vaccination in pregnant women [TAG recommendations for influenza vaccination, 2014] • Can provide robust and reliable data to develop future health economics (HE) model adaptations in the selected study regions. • May provide evidence of the added value of deploying QIVs and thus further support the need and recommendation for QIVs for different age groups.
Description of the	The Gorgas Memorial Institute for Health Studies (ICGES) is a public health institution established in Panama dedicated to

database

health research and disease prevention. It has been performing virological isolations of influenza and is a part of the World Health Organisation (WHO) Global Influenza Surveillance and Response System (GISRS) and a direct collaborator of the CDC.

From 2010 a sentinel surveillance program is being conducted in Panama within the ICGES to collect data on influenza and other respiratory viruses using CDC guidance for Respiratory Disease Surveillance.:

Respiratory samples from 18 sentinel sites scattered around the country are sent to ICGES and tested for 16 respiratory viruses, including influenza, using real-time PCR.

In addition to ICGES role in Panama, the ICGES will serve as a coordinating center for compiling influenza surveillance data from National Influenza Surveillance Programs from 3 other countries within the region as well as conducting strain typing of influenza B isolates, a procedure not routinely done in these countries

The seasonal influenza A and/or B cases reported in the study region are recorded in country specific national influenza surveillance program databases. The data recorded in these databases is individual level data and anonymised with unique ID and key.

Samples of seasonal influenza A and/or B positive cases identified in the country specific databases are transferred to ICGES with unique ID and key. At ICGES, the specimen/samples are processed and tested. The results are cleaned and collated in the ICGES database.

This multi-country study aims to utilize this data recorded via National Influenza Surveillance Program at ICGES for analyzing the burden of influenza in Panama and selected countries of Central America and the Caribbean.

Objectives

Primary

- To describe seasonal influenza A and/or B cases by age and virus subtype (AH1N1/A H3N2) and B-strain lineage (Victoria and Yamagata) using data reported via National Surveillance Program in Panama, selected countries of Central America and the Caribbean from January 2010 to December 2015.

Secondary

From the January 2010 to December 2015, in each selected country:

- To describe clinical features and outcomes (clinical manifestations, duration of illness, complications) of seasonal Influenza A cases and B cases (overall and by subtypes or lineages) in different seasons.
- To describe the temporal and geographical distribution of seasonal influenza A and/or B (overall and by subtypes or lineages) cases within different seasons.
- To estimate the percentage of co-circulation of influenza B lineages (yamagata and Victoria lineages) among the study population, by age (<1, 1-4, 5-9, 10-14, 15-19, 20-24, 25-44, 45-49, 50-59, 60-64 and ≥ 65 years) or age groups and by region.
- To describe the mismatch between the B-strain included in the Trivalent Influenza Vaccines (TIV) and the circulating B strains in different seasons.

Study design

- Type of study: Self contained.
- Type of design: Epidemiological, non-interventional, observational, retrospective, database study.
- Study population: All subjects who have laboratory confirmed diagnosis of influenza (laboratory confirmed case) and reported in the national influenza surveillance system in selected countries from the Year 2010-2015.
- General study aspects: All seasonal influenza A and/or B cases reported in the ICGES database will be screened. Demographic data, date of onset of the first symptom and data on A-virus subtype and B-strain lineage, geographic region where the virus was isolated, clinical features and outcomes (clinical symptoms, duration of illness, complications) experienced by all influenza positive subjects (subjects with a laboratory confirmed influenza diagnosis) will be validated, extracted and transferred from the ICGES database to the sponsor or to the site of analysis, as applicable.
- Period of data collection: The study will include data on all the subjects with a laboratory confirmed influenza diagnosis, reported in the ICGES database of Panama, from January 2010 to December 2015. For all eligible subjects, individual level anonymised and key coded data

will be collected from the database.

- Epoch 001: Retrospective data collection.

Synopsis Table 1 Study group and epoch foreseen in the study

Study Group	Epoch
	Epoch 001
Retrospective	x

Number of subjects

The study will encompass all subjects reported in the ICGES database of Panama from January 2010 to December 2015 who meet the inclusion criteria.

Endpoints

Primary

- Occurrence of seasonal influenza A and/or B cases by age, virus subtype and strain lineage from January 2010 to December 2015, in Panama, selected countries of Central America and the Caribbean (using the data reported via National Influenza Surveillance Program).

Secondary

- Occurrence of clinical features and outcomes (clinical symptoms, duration of illness, complications) experienced by subjects who have laboratory confirmed diagnosis of seasonal influenza A and/or B, in different seasons from 2010 to 2015.
- Frequency of seasonal influenza A and/or B cases reported in different temporal and geographical locations within different seasons from 2010 to 2015.
- Occurrence of influenza caused by B-strain and presented by B lineages among the study population, by age (<1, 1-4, 5-9, 10-14, 15-19, 20-24, 25-44, 45-49, 50-59, 60-64 and ≥ 65 years) and by region.
- Compare the characteristics of the influenza B-infection as observed in the database and the B-strain included in the trivalent influenza vaccine.

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LIST OF ABBREVIATIONS

CI:	Confidence Interval
DB:	Database
GSK:	GlaxoSmithKline
ICH:	International Conference on Harmonisation
ICGES:	Instituto Conmemorativo Gorgas de Estudios de la Salud
IEC:	Independent Ethics Committee
IRB:	Institutional Review Board
ISPE:	International Society for Pharmacoepidemiology
LL:	Lower Limit
UL:	Upper Limit
UMV:	Universal Mass Vaccination

GLOSSARY OF TERMS

Anonymised data:	Information about an individual that GSK or a third party cannot reasonably attribute to the individual, or could only attribute to the individual by expending a disproportionate amount of time, effort or expense (e.g. de-identified or aggregated information). For the purpose of this template, Key-Coded personally identifiable information (PII) shall not be considered Anonymised Information.
Database:	A database is a set of pre-existing tables and views containing data. The term "pre-existing" implies that the analysis will be done on retrospective data and the term "views" implies that the data can be made readily available in an electronic format through a straightforward extract, without re-encoding and manual manipulation (like a transpose, a translation, split of a field into several fields, etc).
Database study:	A study involving the use of pre-existing data maintained in an electronic format; this will not include collection of new data that requires (re-) encoding via CRF/eCRF and retesting of human biological samples.
Eligible:	Qualified for enrolment into the study based upon the inclusion/exclusion criteria.
Epidemiology study:	An observational study or an interventional study without administration of medicinal product(s) as described in a research protocol.
Epoch:	An epoch is a self-contained set of consecutive timepoints or a single timepoint from a single protocol. Self-contained means that data collected for all subjects at all timepoints within that epoch allows to draw a complete conclusion. A typical example of epoch is retrospective data collection.
eTrack:	GSK's tracking tool for clinical/epidemiology studies.
Evaluable:	Meeting all eligibility criteria, and, therefore, included in the analysis (see Section 5.3 for details on criteria for evaluability).
Key coded information:	Refers to encoded or otherwise pseudoanonymised PII from which direct identifiers have been removed and replace by a unique identifier or random code. Key coded

	PII shall not be considered anonymised information.
Non-interventional (observational) Human Subject Research:	Studies where medicinal products, should they be administered, are prescribed in normal (routine) medical practice. No medical care or medical/scientific procedures as required in a research protocol are administered to participants except as part of routine medical care.
Personally Identifiable Information:	Refers to information, regardless of the medium in which such information is held or expressed, that identifies or that reasonably could be used to identify an individual.
Retrospective study:	A study that looks backward in time (e.g. at events that occurred in the past; outcomes and exposure can no longer be influenced), usually using medical records, databases or interviews in order to address one or more study endpoints.
Self-contained study:	Study with objectives not linked to the data of another study.
Study population:	Sample of population of interest.
Subject:	Term used throughout the protocol to denote a person about whom some medical information has been recorded in a database.

1. INTRODUCTION

1.1. Background

Influenza A and B viruses are important human respiratory pathogens which are transmitted mainly by droplets and aerosols originating from the respiratory secretions of infected people. Both influenza A and influenza B viruses cause seasonal influenza epidemics and out-of season sporadic cases and outbreaks. Influenza occurs globally with an annual attack rate estimated at 5%-10% in adults and 20%-30% in children [WHO, 2012]. The annual mortality rate due to influenza is as high as 300,000–500,000 deaths worldwide [WHO, 2008].

In temperate climates, seasonal epidemics are experienced mainly during the winter while in tropical regions, influenza may occur throughout the year, causing outbreaks more irregularly [WHO, 2012]. In tropical areas, seasonal patterns appear to be less pronounced, with year-round isolation of virus [WHO, 2008].

Annual incidence and dominance of seasonal influenza A and/or B vary geographically. In addition environmental factors such as viral coexistence and Latitudinal Gradients have at least some impact on the geographic spread of seasonal influenza A and/or B, either through effects on transmission or host susceptibility [Finkelman, 2007]. In addition, influenza pandemics occur due to the emergence of new influenza A virus subtype s. These pandemics spread globally due to lack of existing or limited immunity against these new subtypes [Hampson, 2006]. In the region of Latin America and the Caribbean (LA&C), due to underreporting, scarce information on influenza mortality and morbidity is available. It is therefore difficult to estimate the burden of disease due to poor quality and heterogeneity of the accessible data. The actual amplitude of influenza infections in LA&C is often unclear by the lack of usage of specific diagnostic methods by physicians to confirm etiology, as most reported data come from clinical diagnoses of influenza-like illnesses (ILI) [Savy, 2012].

Most of the current seasonal influenza vaccines include two influenza A strains and one influenza B strain and are registered as Trivalent Influenza Vaccines (TIVs) [WHO, 2012]. The reported efficacy/effectiveness of influenza vaccines varies substantially with factors such as the case definition (e.g. laboratory-confirmed influenza disease or the less specific ILI), and with the level match/ mismatch between the vaccine strains and prevailing influenza strains. When the vaccine strains closely match the circulating influenza viruses, vaccine efficacy rates in individuals younger than 65 years of age typically range from 70% to 90% [WHO, 2012]. Hence, surveillance platforms for seasonal influenza are critical for monitoring and communicating the observed impact of introducing seasonal influenza vaccination in a given population [WHO, 2012].

1.2. Description of the database

The Gorgas Memorial Institute for Health Studies (ICGES) is a public health institution established in Panama dedicated to health research and disease prevention. It has been performing virological isolations of influenza and is a part of the World Health

Organisation (WHO) Global Influenza Surveillance and Response System (GISRS) and a direct collaborator of the CDC.

From 2010 a sentinel surveillance program is being conducted in Panama within the ICGES to collect data on influenza and other respiratory viruses using CDC guidance for Respiratory Disease Surveillance.

Respiratory samples from 18 sentinel sites scattered around the country are sent to ICGES and tested for 16 respiratory viruses (such as Adenovirus, parainfluenza, RSV/VSR, Bocavirus, Coronavirus, Metapneumovirus, Rhinovirus, other viruses, etc), including influenza, using multiplex PCR.

In addition to ICGES role in Panama, the ICGES will serve as a coordinating center for compiling influenza surveillance data from National Influenza Surveillance Programs from 3 other countries within the region as well as conducting strain typing of influenza B isolates, a procedure not routinely done in these countries

The seasonal influenza A and/or B cases reported in the study centers are recorded in country specific national influenza surveillance program databases. The data in these databases is individual level data and anonymised with unique ID and key.

Samples of seasonal influenza A and/or B positive cases identified in the country specific databases are transferred to ICGES with unique ID and key. At ICGES, the specimen/samples are processed. The results are cleaned and collated in the ICGES database.

This multi-country study aims to utilize this data recorded via National Influenza Surveillance Program at ICGES for analyzing the burden of influenza in Panama and selected countries of Central America and the Caribbean (potential countries may include Guatemala, El Salvador and Jamaica).

1.3. Rationale for the study

Evidence is needed to assess prevalence and incidence of seasonal influenza A & B, assess the potential mismatch and identify clinical features of seasonal Influenza A and B by country and in this region. Thus, this study aims to raise awareness to the public health stakeholders the need for quadrivalent influenza vaccine (QIV) and support its recommendation by:

- Generating burden of disease data that highlights the contribution of influenza to hospitalization, mortality, cardiovascular disease and other complications.
- Providing evidence and documenting the mismatch between circulating B strains and those included in the recommended trivalent seasonal vaccines and B-lineage co-circulation of influenza across different seasons.
- Understanding the burden of disease caused by influenza B strains and the added value of a QIV.

The data from this study,

- may support the implementation and expansion of existing universal mass vaccination (UMV) strategies for influenza.
  - the current recommendation is to vaccinate the elderly, health care workers, children (in some countries vaccination is limited to children with chronic diseases), adults with chronic diseases. Some countries in the study region also recommend influenza vaccination in pregnant women [TAG recommendations for influenza vaccination, 2014]
- can provide robust and reliable data to develop future HE model adaptations in the selected study regions.
- may provide evidence of the added value of deploying QIVs and thus further support the need and recommendation for QIVs for different age groups.

2. OBJECTIVES

2.1. Primary objective

- To describe seasonal influenza A and/or B cases by age and virus subtype (AH1N1/A H3N2) and B-strain lineage (Victoria and Yamagata) using data reported via National Surveillance Program in Panama, selected countries of Central America and the Caribbean from January 2010 to December 2015.

Refer to Section 5.1.1 for the definition of the primary endpoint.

2.2. Secondary objectives

From January 2010 to December 2015, in each selected country:

- To describe clinical features and outcomes (clinical manifestations, duration of illness, complications) of seasonal Influenza A and B cases in (overall and by subtypes or lineages) different seasons.
- To describe the temporal and geographical distribution of seasonal influenza A and/or B (overall and by subtypes or lineages) cases within different seasons.
- To estimate the percentage of co-circulation of influenza B lineages (yamagata and Victoria lineages) among the study population, by age (<1, 1-4, 5-9, 10-14, 15-19, 20-24, 25-44, 45-49, 50-59, 60-64 and ≥ 65 years) or age group and by region.
- To describe the mismatch between the B-strain included in the Trivalent Influenza Vaccines (TIV) and the circulating B strains in different seasons.

Refer to Section 5.1.2 for the definition of the secondary endpoints.

3. STUDY DESIGN

3.1. Feasibility assessment

Since 2010, Panama has implemented a sentinel surveillance program to collect data on influenza and other respiratory viruses. This national passive surveillance program collects, integrates and analyzes epidemiological information from select hospitals and health centers across the country (10 hospitals and 12 health centers). The ICGES plays an integral part of this surveillance system by serving as the National Reference Laboratory. Its technical capacity and expertise includes immunofluorescence, multiplex reverse transcription polymerase chain reaction (RT-PCR) and viral isolation. The average samples processed per year for this surveillance program is approximately 1,872 samples.

Due to the robust reputation of ICGES in influenza surveillance within the region for being excellent reference laboratory for influenza, collaboration with Influenza surveillance program in other countries will be possible for this study.

The ICGES laboratory works closely with CDC and is one of the National Influenza Center (NIC) laboratories as well as part of the WHO Influenza External Quality Assessment Project (EQAP) Working Team. Since 2008, the ICGES laboratory has obtained the highest score in quality control.

ICGES has also played a strong role in the region by serving as a sub-regional center of reference during the influenza pre-pandemic and pandemic period and got strong support of the US HHS (United States Health and Human Services).

3.2. Study limitations

This study has a few limitations listed below:

- Since ICGES is a secondary database underreporting may be expected.

3.3. Study design overview

- Type of study: Self contained.
- Type of design: Epidemiological, non-interventional, observational, retrospective, database study.
- General study aspects: All seasonal influenza A and/or B cases reported in the ICGES database will be screened. Demographic data, date of onset of the first symptom and data on A-virus subtype and B-strain lineage, geographic region where the virus was isolated, clinical features and outcomes (clinical symptoms, duration of illness, complications) experienced by all influenza positive subjects will be validated, extracted and transferred from the ICGES database to the sponsor or to the site of analysis, as applicable. The data will then be analysed and the results will be presented.

- Period of data collection: The study will include data of all subjects with a laboratory confirmed influenza diagnosis, reported in the ICGES database of Panama, from January 2010 to December 2015. For all eligible subjects, individual level anonymised and key coded data will be collected from the database.
  - Epoch 001: Retrospective data collection.

Table 1 Study group and epoch foreseen in the study

Study Group	Epoch
	Epoch 001
Retrospective	x

4. STUDY POPULATION

4.1. Number of subjects

The study will encompass all subjects reported in the ICGES database of Panama from the January 2010 to December 2015.

4.2. Inclusion criterion

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study or regulatory acceptability. Therefore, adherence to the criteria as specified in the protocol is essential.

All subjects must satisfy the following criterion at study entry:

- All subjects diagnosed with seasonal influenza A and/or B, reported in the ICGES database of Panama, from January 2010 to December 2015.

4.3. Exclusion criteria

Not applicable.

5. STATISTICAL METHODS

5.1. Endpoints

5.1.1. Primary endpoint

- Occurrence of seasonal influenza A and/or B cases by age, virus subtype and strain lineage from the January 2010 to December 2015, in Panama, selected countries of Central America and the Caribbean (using the data reported via National Influenza Surveillance Program).

5.1.2. Secondary endpoints

- Occurrence of clinical features and outcomes (clinical symptoms, duration of illness, complications) experienced by subjects who have laboratory confirmed diagnosis seasonal influenza A and/or B, in different seasons from 2010 to 2015.
- Frequency of seasonal influenza A and/or B cases reported in different temporal and geographical locations within different seasons from 2010 to 2015.
- Occurrence of influenza caused by B-strain and presented by B lineages among the study population, by age (<1, 1-4, 5-9, 10-14, 15-19, 20-24, 25-44, 45-49, 50-59, 60-64 and ≥ 65 years) and by region.
- Compare the characteristics of the influenza B-infection as observed in the database and the B-strain included in the trivalent influenza vaccine.

5.2. Sample size consideration

Since this is a retrospective database study, all cases of seasonal influenza A and/or B, reported in the ICGES database of Panama, from January 2010 to December 2015 will be included in the study. The total specimen samples of influenza cases per year ranged from 47 to 276 (refer to Table 2).

Table 2 Number of specimen samples of influenza cases per year from January 2010 to December 2014

Year	Total specimen samples received (N)	Influenza (A+B) positive	Influenza B positive
		N	N
2010	1665	207	14
2011	1413	47	0
2012	2236	276	178
2013	2115	190	0
2014	1725	140	55

5.3. Study cohort/ data sets to be analysed

5.3.1. Total cohort

The Total cohort will comprise of all eligible subjects included in the study.

5.4. Derived and transformed data

- Influenza is defined as any positive laboratory test from one or more of the clinical specimens [Guidelines for the epidemiological surveillance of influenza, 2012].

5.5. Statistical methods

5.5.1. Analysis of demographics/baseline characteristics

Demographic characteristics (age and gender) will be summarised by group using descriptive statistics:

- Frequency tables will be generated for categorical variable such as gender.
- Mean, median and standard deviation will be provided for continuous data such as age.
- The distribution of influenza cases by month and year will also be tabulated.

5.5.2. Analysis of primary objective

The proportion of subjects with influenza caused by seasonal influenza A and/or B among all influenza cases reported with exact 95% confidence interval (CI) by age, A-virus subtype and B-strain lineage and overall will be calculated.

5.5.3. Analysis of secondary objectives

Seasonal influenza A and/or B cases will be described using frequency and percentages by temporal (calendar weeks/months) and geographical distributions (by country and by region within the country [if data is available])within different influenza seasons (2010-2011, 2011-2012, 2012-2013, 2013-2014 and 2014-2015).Frequency and percentage for clinical features and outcomes (clinical manifestations, duration of illness, complications) experienced by influenza positive subjects will be tabulated by type of influenza (seasonal influenza A and/or B) in different seasons from 2010-2015. Frequency and percentage for influenza B lineages by age (<1, 1-4, 5-9, 10-14, 15-19, 20-24, 25-44, 45-49, 50-59, 60-64 and ≥ 65 years) and region will also be provided.

The characteristics of the influenza B-infection as observed in the database and the B strain included in the trivalent influenza vaccine will be assessed using frequency and percentage for each year. The proportion of matched B-strains and mis-matched B-strains will be estimated along with 95% CI.

5.6. Interpretation of analyses

All the analyses with respect to the primary and secondary endpoints will be descriptive. These descriptive analyses will not be interpreted, except describing the study results.

5.7. Conduct of analyses

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

5.7.1. Sequence of analyses

The final analysis will be performed when all required data for the study have been extracted from the ICGES database and transferred to the sponsor or to the site of analysis, as applicable.

5.7.2. Statistical considerations for interim analyses

All analyses will be conducted using the final data and no statistical adjustment will be required as no interim analysis is planned for this study.

6. CONDUCT OF THE STUDY

6.1. Regulatory and ethical considerations

The study will be conducted in accordance with all applicable regulatory requirements, including all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

GlaxoSmithKline Biologicals (GSK Biologicals) will seek favourable opinion/approval to conduct the study prior to data extraction or will document that neither a favourable opinion nor an approval to conduct the study is needed.

Conduct of the study includes, but is not limited to, the following:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Investigator reporting requirements as stated in the protocol.

GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both

6.2. Informed consent

Prior to the data processing and analysis, all data will be anonymised. GSK Biologicals personnel and delegates will not be able to make a link between the data and specific individuals. Therefore no patient consent is needed. For further details see Section 6.3.

6.3. Data privacy

Data privacy is protected by using anonymised data (see glossary of terms).

The ICGES database is fully coded. No GSK Biologicals personnel will have the ability to link data to an identifiable individual.

6.4. Outline of data extraction procedures

Table 3 presents the list of data extraction procedures.

Table 3 List of data extraction procedures

Epoch: Retrospective data collection
Identification of eligible study cases in ICGES influenza national surveillance program database
Identification and anonymisation of eligible subjects
Extraction of individual data
Dataset check and transfer from ICGES to GSK
Handling of incomplete data, missing data and discrepancies

6.5. Detailed description of data extraction and handling procedures

6.5.1. Identification of eligible study cases in ICGES influenza national surveillance program database

The ICGES database of Panama will be checked for all seasonal influenza A and/or B positive cases reported via influenza surveillance programs from 2010 to 2015.

6.5.2. Identification and anonymisation of eligible subjects

All subjects with a laboratory diagnosis of seasonal influenza A and/or B, will be identified from this database. The data present in ICGES database is already anonymised, therefore subject identification number allocation is not required.

6.5.3. Extraction of individual data

All seasonal influenza A and/or B cases reported in the ICGES database will be validated and extracted in the required file format e.g. Statistical Analysis System (SAS) datasets. The following data will be collected for seasonal influenza A and/or B positive subjects:

- Demographic data such as age and gender.
- Data on A-virus subtype and B-strain lineage (when available), geographic region, clinical features and outcomes (clinical manifestations, duration of illness, complications) etc.

6.5.4. Database check and transfer from ICGES to GSK

ICGES will transfer the data files extracted for the study on GSK SAS Drug Development (SDD) secured web platform (SDD) as SAS data sets (if data cannot be provided by ICGES in SAS format, GSK can alternatively accept Excel spreadsheets).

Additionally to the data sets, ICGES will provide a description of each data set, including a description of each column and its attributes (data type, length and as applicable, decodes if codes are used, and coding dictionary reference for codes and terms related to a specific coding and terminology system like ICD-10, SNOMED, WHOART, MedDRA, …).

6.5.4.1. Check of data set content and format

Prior to starting the programming of the analyses, the GSK person responsible for the analyses will check if the data files content and format meet the requirements for the statistical analyses. This will include (but will not be limited to) checks on the subject/case identifiers consistency, checks on the presence of the analyses variables, checks on list of values and/or codes and checks on the numeric and date formats. Any finding will be feedback to ICGES database owner and require a new transfer, until content and format are appropriate for the statistical analyses.

6.5.4.2. Check of data completeness and consistency

Any data deficiency such as incomplete data, missing data and data discrepancies that would be detected by GSK statistician or epidemiologist and that are critical for the analyses will be feedback to ICGES database owner. Depending on the possibility of the database owner to correct data, corrected data will be retransferred or not to GSK.

6.5.5. Handling of incomplete data, missing data and discrepancies

As applicable, the rules taken for handling incomplete data, missing data and data discrepancies in statistical analyses will be documented in the SAP (e.g.: handling missing data and codes such as ‘UNK’, ‘N/A’, ‘ND’; calculation of a duration from partial dates; censoring of discrepant data …)

7. ADMINISTRATIVE MATTERS

To comply with regulatory requirements and GSK standards, administrative obligations relating to protocol amendments, protocol administrative changes and termination of the study must be fulfilled.

7.1. Record retention

The datasets sent by the database owner will be loaded and archived at GSK as per the applicable requirements and the retention policies.

The minimum retention time will meet the strictest standard applicable for the study, as dictated by the applicable guidelines or applicable laws or regulations, or GSK standards/procedures; otherwise, the minimum retention period will default to 30 years.

7.2. Quality assurance

To ensure compliance with Good Clinical Practice (GCP) or other applicable guidelines and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections could occur at any time during or after completion of the study. If an audit or inspection occurs, the database owner and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

7.3. Posting of information on publicly available clinical trial registers and publication policy

Database studies that do not evaluate vaccines/products are progressed for publication in the scientific literature when the results provide important scientific or medical knowledge.

7.4. Provision of study results to investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

8. COUNTRY SPECIFIC REQUIREMENTS

IRB approval for epidemiological observational studies.

9. REFERENCES

Brian S. Finkelman, Ce´cile Viboud, Katia Koelle, Matthew J. Ferrari, Nita Bharti, Bryan T. Grenfell. Global Patterns in Seasonal Activity of Influenza A/H3N2, A/H1N1, and B from 1997 to 2005: Viral Coexistence and Latitudinal Gradients. PLoS ONE 2007; 2(12): e1296.

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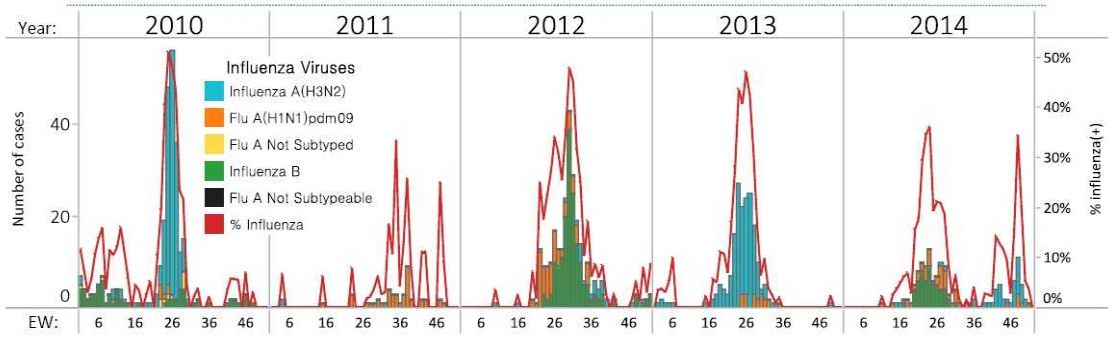
World Health Organisation (WHO). Influenza. 25 January 2008. http://www.who.int/immunisation/topics/influenza/en/index.html

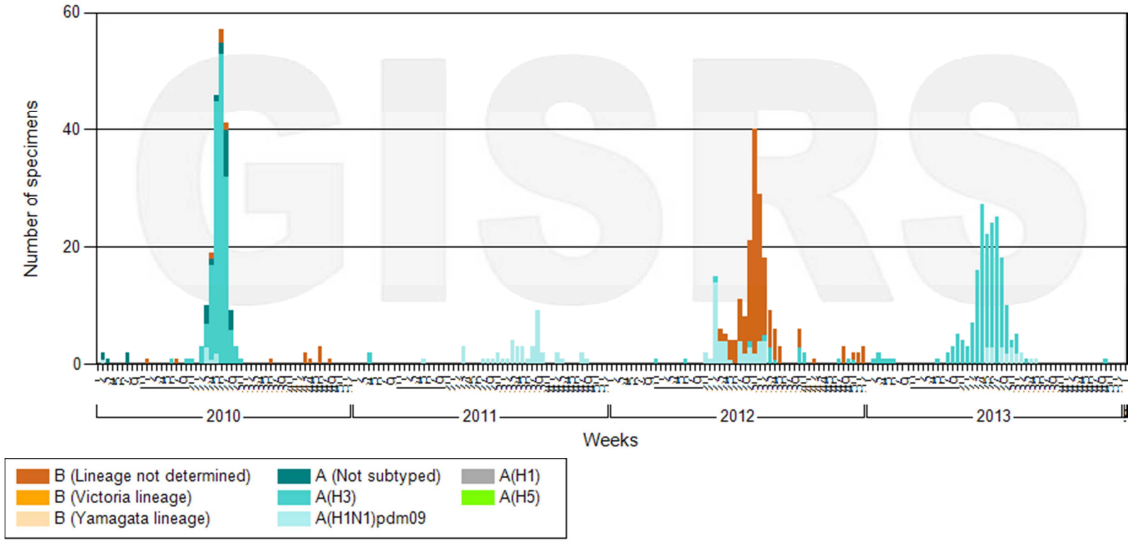
World Health Organisation (WHO) - Weekly epidemiological record. 23 November 2012, 87th year. No. 47, 2012, 87, 461–476. http://www.who.int/wer.

APPENDIX A CURRENT DATABASE STATISTICS FOR PANAMA

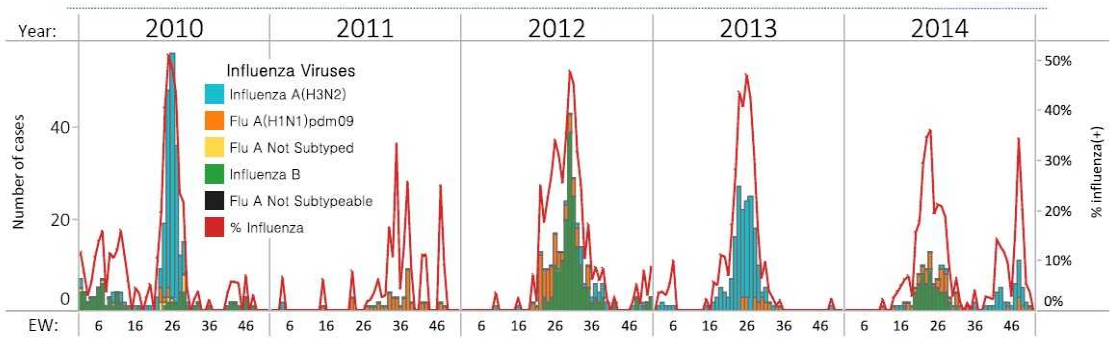
Circulation of Influenza Viruses 2010-2014[3]



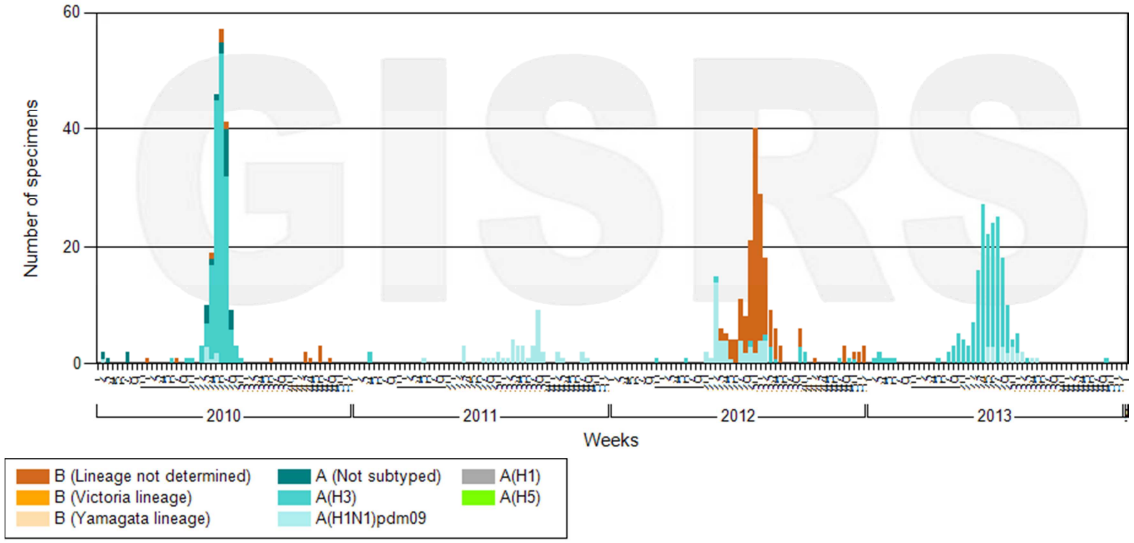
Number of specimens positive for influenza by subtype



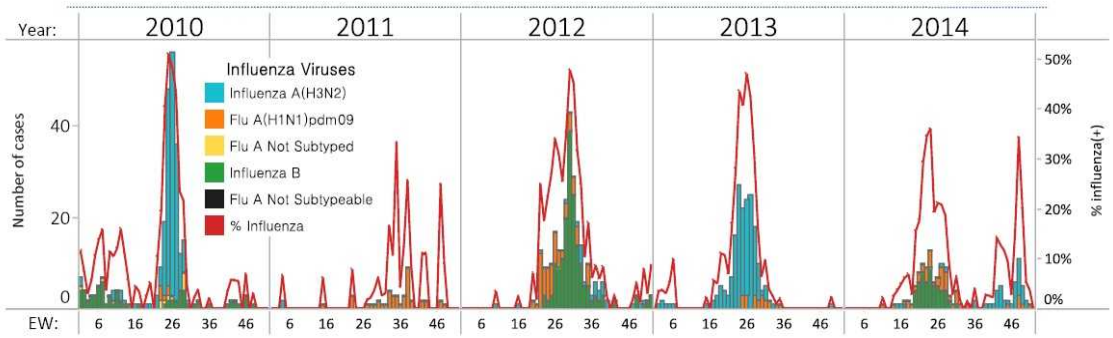
Circulation of Influenza Viruses 2010-2014[3]



Number of specimens positive for influenza by subtype



Circulation of Influenza Viruses 2010-2014[3]



Number of specimens positive for influenza by subtype