Study Report II

Follow-up Study

IBGP - Influenza B in General Practice

The burden of influenza B in Europe:
a prospective multi-country strain surveillance study
using community-based specimens

Seasons 2010-2011 to 2012-2013

May 2014

List of Contents

1 Glossary

ARI	Acute Respiratory Infection
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CRF	Case Report
CRO	Clinical Research Organization
ECDC	European Centre for Disease Prevention and Control
EISN	European Influenza surveillance Network
ES	Spain
EU	European Union
FR	France
GP	General Practitioner
GROG	Groupes Régionaux d'Observation de la Grippe (Regional groups for influenza surveillance)
IBGP	Influenza B in General Practice
ICF	Inform Consent Form
ID	Identification
ILI	Influenza-Like Illness
NIC	National Influenza Centre
RSV	Respiratory Syncytial Virus
RT-PCR	Real time-polymerase chain reaction
StC	Steering Committee
TR	Turkey
UK	United Kingdom
WHO	World Health Organization
Yo	year old

2 Introduction

2.1 Context

Seasonal influenza in humans is caused by influenza type A (H1N1 and H3N2), and influenza type B strains (lineage B/Victoria and B/Yamagata). It is known that several seasonal influenza epidemics are linked to a co-circulation of two or more of the influenza A sub-types and influenza B lineages [1].

The World Health Organization (WHO) estimates that during seasonal influenza epidemics, 5-15% of the population are affected with acute respiratory infections (ARI). These annual epidemics are thought to result in between three and five million cases of severe illness and between 250 000 and 500 000 deaths worldwide. Most deaths currently associated with influenza in industrialized countries occur among the elderly over 65 years of age. Influenza can cause serious public health and economic problems: high levels of worker absenteeism and productivity losses. While most people recover from this illness, there are large numbers of hospitalizations and death [2].

Influenza is in the spotlights for the last three decades, especially influenza A(H3N2) and, more recently, pandemic influenza A(H1N1), while influenza B is often regarded as the milder form of the disease.

Fewer studies have looked specifically at influenza B or comparisons between influenza B and A.

However, Centers for Disease Control and Prevention (CDC) seasonal influenza reports [3] show that seasonal influenza B incidence is regularly larger than that of H1N1, and sometimes larger than H3N2. Local B incidence could be significantly higher than national averages in a single year, and regions of high incidence vary between seasons.

Studies carried out in the United States showed that the burden of influenza differs by virus, with influenza A(H3N2) viruses having the highest impact, then Respiratory Syncytial Virus (RSV), then influenza B viruses and finally influenza A(H1N1) viruses. Data regarding the hospitalization had a similar pattern, but RSV was not included in this analysis [4, 5].

A community based study carried out in the United Kingdom (UK) found that total excesses of ILI (Influenza Like Illness) rates (over the baseline) were the highest for H3N2 viruses, then H1N1 and finally B (rough ratio of 3:2:1). Regarding excesses by age group, influenza B was highest in children aged 5-14, followed by children aged 0-4. These results suggest that influenza B is generally a milder illness than influenza H1, which is much milder than influenza H3 [6].

Another study conducted in UK found similar results: for General Practitioners (GP) consultations, hospital admissions and deaths, influenza A had a systematically higher burden than influenza B [7].

One study conducted during one single winter season (2002-2003) showed dominance of influenza B in parts of Western Europe (e.g. Portugal, Ireland and UK) [8].

In Wales, the early 2012-2013 influenza season saw the highest rate of influenza B (Yamagata lineage)-associated primary care consultations since 1994-1995 and considerable hospitalisations, mainly affecting younger adults. Admission to critical care was unexpectedly common [9].

Additionally, from the past few years, there are frequent oscillations between Yamagata and Victoria lineages (every 1.5–2 years) [10]. It is notable that the B lineage selected for the seasonal influenza vaccine and the dominant circulating B strain have matched only 5 times in the 10 seasons between 2001-2002 and 2010-2011 [11].

There is little community-based data in Europe regarding the differential burden of disease for influenza A and B viruses, specially the influenza B lineages (Victoria versus Yamagata).

Currently, in the European Union, national surveillance networks transmit to the ECDC various data on:

- Number of specimens collected and number of positive results for influenza A and B, without standardized data on lineage of B subtypes.
- Number of ILI/ARI cases reported by each network, stratified by standardized age groups (0-4 yo (years old); 5-14 yo; 15-64 yo; ≥65 yo).
- ILI/ARI attack rate estimated per country, not broken down by influenza type or lineage [12].

No studies have analyzed clinical presentation and complications of influenza B in all age classes during the same season. There is even less data regarding the differential burden of the influenza B lineages (Victoria versus Yamagata).

At the time where the launch of a quadrivalent vaccine, with both B lineages (Victoria and Yamagata) included, is being currently debated, further studies are required to fully ascertain influenza B burden across different countries and to provide useful data on epidemiology and burden of influenza B disease to estimate the public health impact and cost-effectiveness of alternative preventive interventions.

2.2 Rationale

Set up in 2010-2011, the Influenza B in General Practice (IBGP) project aimed to increase the understanding of the circulation of each B lineage in the same influenza season by:

- Describing the influenza circulation in European countries involved in the project, using routine surveillance practice data: **IBGP Surveillance Study**.
- Observing the differential burden of disease (ILI/ARI consultations, prescriptions, absenteeism) due to influenza B, including differences in age groups and lineages, compared to influenza A patients in some of these countries: **IBGP Follow-up Study**.

The study entire protocol is attached in Annex 1.

This report presents the IBGP Follow-up Study data collected during three seasons (2010-11, 2011-2012 and 2012-2013), in three countries (France, Spain, Turkey). This phase of the study is here called IBGP2b.

3 Background

During the 2010-2011 season, a first phase of the IBGP Follow-up Study was launched in France and Turkey.

The initial study protocol aimed at measuring the differential burden of disease (ILI/ARI consultations, prescriptions, absenteeism) due to influenza B, including differences in age groups and lineages, comparing to ILI/ARI influenza B negative patients in different countries.

Besides, a larger part of the project (IBGP Surveillance Study) enabled a preliminary virological understanding of the circulation of each B lineage in the same influenza season by country included in the study.

Since the subsequent winter 2011/2012, three main changes have been set up in the Follow-up Study:
- influenza B cases have to be matched with influenza A controls (prospectively and retrospectively for the 2010-2011 influenza B cases);
- the Influenza Surveillance Network of Castilla y León in Spain joined the IBGP Follow-up group;
- the first follow-up contact was changed from 7 days ± 2 days to 9 days ± 2 days.

Table 1: IBGP2b Follow-up Study participation by country and season

Countries	2010-2011 Season	2011-2012 Season	2012-2013 Season
France (all country)	X	X	X
Turkey (Istambul network)	X	X	X
Spain (Castilla y León autonomous community)		X	X

4 Objectives

4.1 Primary Objective

To describe influenza B cases by age groups and strain lineage in France, Spain and Turkey, using outpatient data collected from routine surveillance and follow-up questionnaires on demographic data, current flu vaccination status, anamneses (clinical symptoms, underlying conditions, hospitalization), duration of illness, drugs prescription and absenteeism (at work and school).

4.2 Secondary Objectives

- To compare the temporal and geographical distribution of influenza B cases within each season in the enrolled countries.
- To describe and compare the influenza B cases and influenza A controls, by age group and country, for clinical picture, duration of illness, current flu vaccination status, healthcare consumption (drugs prescription, subsequent medical visits and hospitalization) and absenteeism.
- To compare the influenza B Victoria and Yamagata cases (if enough cases), by age group and country, for clinical picture, duration of illness, current flu vaccination status, healthcare consumption (drugs prescription, subsequent medical visits and hospitalization) and absenteeism.

5 Methods

5.1 Study Design

The IBGP2b study is a multi-country observational descriptive study based on a case/control cohort design.

5.2 Study period

The IBGP2b study was conducted during three influenza seasons:
- 2010-2011,
- 2011-2012,
- 2012-2013.

The inclusions started from the beginning of the flu season, defined as “the time when the same influenza subtype virus is isolated in at least two samples during the same week”. The study was closed at the end of flu season defined as “two consecutive weeks during which no cases of influenza have been identified”.

5.3 Countries and sentinels networks participating in the study

Three influenza surveillance networks in three European countries (France, Spain and Turkey) were involved in the IBGP2b project.

General Practitioners (GP) and paediatricians participating in their national or local influenza surveillance networks are here called sentinels.

As part of routine surveillance of influenza, sentinels were responsible for completing the initial surveillance questionnaires.

A detailed description of each network is provided below in Table 2.

In France, sentinels practitioners were informed about the study and invited to participate. To confirm their participation, they were contacted by phone when a first possible case or control could be included in their practice. The presentation of the study was done by trained staff of the Grog network or Open Rome, clarifying critical points of the study:

- Brief background of IBGP study and funding.
- Remind of past patient swab and its result: influenza B or A positive.
- Patient follow-up principle.
- How to contact patient:
    - mainly by telephone, but no restrictions were made about personal contact or other ways of obtaining information;
    - need for an Inform Consent Form (ICF).
- How to fill in the Case Report Forms (CRF) and send it back to Grog network:
    - CRF could be completed manually or by computer, than sent by fax, e-mail or post.

If French sentinels agreed to participate in the study, they would receive by post an informative letter containing: the study contract, a copy of the protocol, a guide for the practical running of the study and the ICF to be signed for children's parents.

In Spain and Turkey, sentinels practitioners were informed about the study. Coordination trained staff directly recruited by phone patients matching inclusion criteria. If patients accepted to participate in the study, the staff applied the requested follow-up questionnaires.

Table 2: Sentinel Surveillance Networks participating in the IBGP2b Follow-up Study

Country	Influenza Network	Year the network started	Nb of sentinel physicians		Population covered (% national population)	Frequency of incidence reports	Information provided	ILI/ARI definition [13]	National influenza vaccine policy [14]
			GP	Paediat.					
France (FR)	Réseau des GROG [15]	1984	411	115	63.5 million	weekly in winter only (38-15)	ARI	Sudden onset of respiratory symptom(s) with infection context (fever, headaches...), in the absence of other diagnosis	People over 65 yo; medical conditions; pregnancy; household contacts
Spain (ES)	Red de vigilancia epidemiológica de Castilla y León [16, 17]	1998	45		38 500 (1.5% of the regional population)	weekly in winter only (40-15)	ILI	EU ILI case definition[1] Commission Decision of 28/IV/2008 [18]	People over 65 yo; medical conditions; pregnancy
Turkey (TR)	Istanbul Network [19]	2005	500	15	19 million (26% of 73.7 million)	weekly in winter only (40-15)	ILI	WHO definition[2] [20]	People over 65 yo; medical conditions

FR: France, ES: Spain, TR: Turkey, GROG: Groupes Régionaux d'Observation de la Grippe, GP: General Practitioners, Paediat.: Paediatricians, yo: years old

[1] Sudden onset of symptoms AND at least one of the following four systemic symptoms: (1) fever or feverishness, (2) malaise, (3) headache, (4) myalgia AND at least one of the following three respiratory symptoms: (1) cough, (2) sore throat, (3) shortness of breath.

[2] Sudden-onset fever (> 38 °C) with cough or sore throat, in the absence of other diagnoses.

5.4 Data collection

Study questionnaires

- Questionnaire of inclusion at day 0 – CRF D0
  - Standard Clinical Form routinely completed at the swabbing day.
  - Each enrolled country used its current clinical form (Annex 2).

- Questionnaire of follow-up at day D9 (± 2 days) after swabbing day – CRF D9
  - Case Report Form D9 filled by sentinels or coordination staff through a direct contact with the patient or his parents (phone call or consultation).
  - CRF D9 is common to all countries (Annex 3).

- Questionnaire of follow-up at day D28 (± 5 days) after swabbing day – CRF D28
  - Case Report Form D28 if needed filled by sentinels or coordination staff in the same way as CRF D9.
  - CRF D28 is common to all countries (Annex 4).
  - CRF D28 only completed when CRF D9 indicated that the patient has not returned to his "normal activities"[1] and/or has "still got any symptoms related to ILI swabbed"[2].
    CRF 28 was NOT applied if the patient had ONLY the following remaining symptoms at D9: persistent cough (with or without expectoration), nasal symptoms (rhinorrhea or nasal obstruction), headache or asthenia.

5.5 Study population

The target population of the study included all patients consulting a general practitioner or a paediatrician for ILI or ARI.

Although each country has its own ILI/ARI case definition adapted to local reality, this definition is based on the EU (2008) general concept [18], regarding clinical criteria:

Any person with at least one of the following clinical forms:

Sudden onset of symptoms
AND
At least one of the following four systemic symptoms:
1. Fever or feverishness
2. Malaise
3. Headache
4. Myalgia

AND
At least one of the following three respiratory symptoms:
1. Cough
2. Sore throat
3. Shortness of breath

[1] *"Normal activities": patient returned to his usual routine/occupation (work, school, homemade, day-to-day life...).*
[2] *"Symptoms" are here defined as Flu complications, for example: Fever, Throat symptoms (sore throat, pharyngitis), Otalgia/otitis, Sinusitis, Pneumonia, Low respiratory tract symptoms (asthma/COPD decompensation, bronchitis, bronchiolitis, shortness of breath, dyspnoea, thoracic pain...), Myalgia/myositis, Anorexia, Digestive symptoms, Vertigo, Adenopathy...*

The study population was triggered by laboratory results:

CASES: ILI/ARI patients lab-confirmed influenza B positive.

CONTROLS: ILI/ARI patients lab-confirmed influenza A positive.

5.5.1 Inclusion criteria

Two inclusion criteria were defined for the selection of **influenza B CASES**:

1- Patient diagnosed with influenza B through the sentinel network, all ages, both genders.

2- Informed consent according to national rules.

The **influenza A CONTROLS** were included according to CASES' characteristics, following the matching criteria:

1- Patient diagnosed with influenza A through the sentinel network, both genders.

2 - Same age group:

0 – 4 years old (if possible, subgroup of 0-2 and 3-4 years old);

5 – 14 years old;

15 – 64 years old (if possible, subgroup of 15-49 and 50-64 years old);

Over 64 years old.

3 - Same country, if possible the same interregion/region within the country and the same practitioner.

4 - If not recruited during the same season, CONTROLS can be selected in following seasons.

5.5.2 Exclusion criteria

Any subject :

- already included in the study with a first episode of ILI/ARI (each patient was included only once in the study);

- or who didn't accept to participate in the study;

- or for whom the virologic outcome comes back too late to fill the D9 questionnaire on time.

5.5.3 Subject identification

Patients selected to participate in the study received a specific identification (ID) for the IBGP study.

Firstly, the recognition of the country:

- France - FR
- Turkey - TR
- Spain - ES

Secondly, the virological test results:

- Influenza B positive lab confirmed – B
- Influenza A positive lab confirmed – A

Thirdly, the chronological order of inclusion, based on three digits – 301.

Example: in Turkey, the 45th patient positive for lab-confirmed influenza B was identified as **TRB045**. For matched control, the ID would be necessarily **TRA045**.

5.6 General study design

Table 3 summarize the procedures, including exams, undertaken during the study and clarify the intervals between the contact with the subject.

Table 3: List of IBGP2b Follow-up Study procedures

Time	D0	D9 (±2 days)	D28 (±5 days)
Visit/Observation/Contact	**Day of swabbing[1]**	**1st contact**	**2nd contact[2]**
ILI/ARI patient consulting and swabbed	x		
Complete initial routine surveillance questionnaire CRF D0	x		
Check inclusion/exclusion criteria		x	
Invite swabbed patients to participate		x	
Informed Consent Form		x	
Telephone interview and complete CRF		x	x
Document storage and related administrative tasks	x	x	x
Data validation and analysis of missing data	x	x	x
Local report of study results			x

[1] *Specimen collected (during routine influenza surveillance activity) and D0 form filled*
[2] *Only for subjects not recovered at D9*

5.7 Detailed description of study steps

5.7.1 CRF D0 application

The enrolled countries applied their own surveillance forms at D0 swabbing day (Annex 2).

The questions concern:

- Socio-demographic data (month and year of birth, gender)
- Current flu vaccination status (yes/no)
- Anamneses :
  - Dates of onset of symptoms and sample collection
  - Presence (yes/no) of defined symptoms
  - Presence of underlying condition/chronic disease
  - Antiviral treatment consumption before D0
- Prescription at D0 (request for hospitalization, prescription of antibiotics/antivirals).

5.7.2 Swabs management

Sentinels swab some of the ILI/ARI patients who they suspect having influenza.

- Nose or throat swab performance (at D0)
  Each sentinel uses the swabbing kit provided by the surveillance network and performs the swabs following national network protocol.

- Transportation of samples to the laboratory (National Influenza Centre (NIC) or affiliated lab)
  Specimens are mainly transported by post (together with the routine surveillance clinical form - CRF D0), with a triple packaging system following the international guideline for the transport of infectious substances (category B, classification UN 3373). In Spain, some specimen are sent from the health centre to the hospital using the blood transport official system.

Sampling are sent as soon as possible to the virology laboratory. While waiting for the post/delivery, the sample is kept in low temperature (4°C).

- Determination of sampling virological status, identification and typing is performed at the NIC or affiliated lab.

5.7.3 Virological laboratory management

All samples are sent to the NIC or affiliated lab. These referential laboratories determine the viral status of ILI/ARI patient and, if influenza positive, the type-subtype (A virus)-lineage (B virus) of influenza virus.

These results are recorded on an anonymized electronic file for transmission to the surveillance network (indicating the patient ID, date of receipt of the sample, date of analysis, results ...).

During the whole season, the labs mainly conduct RT-PCR (real time-polymerase chain reaction) tests to each specimen received.

5.7.4 CRF D9 application

If patient accepted to participate, only oral consent was required for adults in the three countries.

In France, for children, after parents oral consent, an ICF was sent to parents' signature and then sent back to the practitioner.

CRF D9 (Annex 3) was the same for all enrolled countries. It has to be completed between 7 to 11 days after the swabbing day with the following information:

- Date of contact
- Social status of the patient - remunerated job (yes/no)
- Healthcare consumption for the ILI/ARI episode:
  - Number of consultations with the sentinel (by phone call, in the medical office and/or at home)
  - Number of consultations with another doctor (by phone call, in the medical office and/or at home)
  - Use of Emergency Room or hospitalization (yes/no)
  - Hospitalization (yes/no)
  - Number of days of absenteeism (work or school). In case of a child, duration of parent's sick leave due to children's disease
  - Antiviral prescription (yes/no). Specification of antiviral (Tamiflu®/Relenza®). Delay between the onset of symptoms and the beginning of the medication (< 12h, 12h-24h, 24h-36h, 36h-48h, > 48h)
  - Name of drugs prescribed or taken on self-medication
  - Additional tests done and paramedical care used (yes/no). Specification of the test (open question)
- Patient returned to normal activities[3] (yes/no)?
  - Yes – date of return
- Remaining symptoms related to ILI/ARI (yes/no)
  - Yes – specify: persistent cough, headache, rhinorrhea/nasal obstruction, asthenia, others

[3] *"Normal activities": patient returned to his usual routine/occupation (work, school, homemade, day-to-day life...)*

- If “others”, specify (open question)
- Patient death (yes/no)
  - Yes - Cause of death.

5.7.5 CRF D28 application

CRF D28 (Annex 4) was applied only if CRF D9 indicated that the patient has not returned to his “normal activities” and/or presents “other symptoms”.

If he ONLY has the following remaining symptoms: persistent cough (with or without expectoration), nasal symptoms (rhinorrhea or nasal obstruction), headache or asthenia – CRF D28 was NOT applied.

D28 form was the same for all enrolled countries. It has to be completed between 23 to 33 days after the swabbing day with the following information:

- Date of contact
- Healthcare consumption for the ILI episode:
  - Number of consultations with the sentinel (by phone call, in the medical office and/or at home)
  - Number of consultations with another doctor (by phone call, in the medical office and/or at home)
  - Use of Emergency Room or hospitalization (yes/no)
  - Hospitalization (yes/no)
  - Number of days of absenteeism (work or school). In case of a child, duration of parent’s sick leave due to children’s disease
  - Name of drugs prescribed or self-medication
  - Additional tests done and paramedical care used (yes/no). Specification of the test (open question)
- Patient returned to normal activities (yes/no)?
  - Yes – date of return
- Remaining symptoms related to ILI (yes/no)
  - Yes – specify: persistent cough, headache, rhinorrhea/nasal obstruction, asthenia, others
  - If *others*, specify (open question)
- Patient death (yes/no)
  - Yes - Cause of death.

5.8 Data management

5.8.1 Centralized monitoring

A centralized monitoring of the study was organized at the Clinical Research Organization (CRO) named Open Rome. A specific and protected database has been developed for monitoring the follow-up of the study. Indicators of the proper conduct of the study (number of patients, age and sex of patients, number of samples taken, sampling results...) were input in real time in this database.

The quality control of data collected in the CRFs was performed by the surveillance network of each country. If necessary (missing data in the CRF), sentinels were contacted to complete the CRF or to give clarifications about free text provided.

Further validation of data sent by the surveillance networks was conducted by the European Coordination at the CRO.

Entry and treatment of data collected in the CRFs were performed according to a specific plan set by the European Coordination (according to the IBGP protocol). Only authorized people had access to the study data. A simple input in a database was conducted for all data. An exhaustive input verification was randomly done for 10% of questionnaires.

5.8.2 Size estimated for the study population

The final number of subjects will depend on the number of influenza B cases observed during each influenza season.

From 2004-2005 to 2009-2010, the number of reported B cases ranged, in France, from 6 to 550 by season, and in European Union, from 178 to 3114 by season.

Table 4: Number of Flu B cases in France and in the ECDC surveillance country members - 2004-2010

Season	France	ECDC surveillance country members (number of countries reporting)
2004-2005	100	754 (28)
2005-2006	550	2903 (30)
2006-2007	6	390 (33)
2007-2008	513	3114 (38)
2008-2009	241	2342 (45)
2009-2010	7	178 (52)

Incidence of Influenza B may vary from one season to another. In the first IBGP season (2010-2011), networks were able to enrol 356 cases of Flu B in France and Turkey. For the next seasons, we expected to enrol up to 750 CASES of Influenza B within the involved countries, and the same number of CONTROLS (Influenza A positive patients).

5.8.3 Definitions, derived data

- Age is calculated from the date of birth or the 15th day of the month of birth (if only month and year of birth are requested) to the date of D0 consultation. The age retained is the entire age obtained by subtracting the two dates.
- Influenza is defined as: an ILI/ARI patient with a laboratory test (mainly RT-PCR) positive. Patients for whom virological tests generate invalid results were not included in the analysis.
- Patients are considered as immunized against the current seasonal flu if they received at least one dose of seasonal vaccine in current season and:
  - or whose vaccination date is earlier at least 14 days to onset of symptoms,
  - or whose vaccination date is unknown.

5.8.4 Final analysis

- All analysis were descriptive.
- Data analysis was performed with STATA software (version 11).
- Demographic data of the subjects were presented in tables or graphs.
- Descriptive analysis of qualitative and ordinal variables included the number and frequency of each mode.
- N x 2 tables were built to evaluate clinical symptoms and healthcare consumption associated with influenza B Case or A Control.

- The mean number of days of work/school absenteeism among patients with influenza A and flu B and among patients with influenza B/Victoria and B/Yamagata was compared (Student test).
- The mean number of days of absenteeism of patients' caregivers during the study period was compared between patients with influenza A and B and among patients with influenza B/Victoria and B/Yamagata (Student test).
- The mean duration of illness was compared between patients with influenza A and B and among patients with influenza B/Victoria and B/Yamagata (Student test).
- The frequency of symptoms, drugs consumption linked with the influenza infection, number of medical contacts after D0 with patient's registered practitioner and number of recovered patients at D9 were compared between patients with influenza A and B and among patients with influenza B/Victoria and B/Yamagata (Chi 2 test).
- The seasonal distribution of influenza Cases and Controls was presented by epidemiological curves (histograms).
- No adjustment for multiple testing was done.
- No data imputation was done.

5.9 Scientific committee

The Influenza B in General Practice (IBGP) study was funded by GlaxoSmithKline Biologicals and managed by an European coordination located at a clinical research organization, Open Rome (Paris, France). This organization had the counselling of a steering committee (StC) composed by flu experts.

The steering committee of the IBGP study is composed as following:

Jean Marie Cohen *MD* - Director and founder of Open Rome CRO (Paris, France)
W. John Paget *PhD* - Senior Researcher, Netherlands Institute for Health Services Research - NIVEL (Utrecht, Netherlands)
Douglas M Fleming *MD* - Director of RCGP Research & Surveillance Centre - RSC (Birmingham, UK)

Permanent guests

Gonçalo Matias *DVM* - Senior Researcher, GlaxoSmithKline Biologicals (Brussels, Belgium)
Maria Laura Silva *PharmD, PhD student* - IBGP assistant, Open Rome CRO (Paris, France)

The study protocol and associated documents for collecting data have been validated under the auspices of the StC. This guarantees the ethics of surveillance monitoring techniques under the protocol: undertaking of a nasal swab does not pose a risk to patients agreeing to participate in this study. The role of this Committee is also to validate the statistical analysis plan and operating results. The committee is available for all situations that interfere with the investigation.

Many countries were invited to participate in this study. However, due to the industrial funding and to national ethic committee's delays, three countries have confirmed their participation in the Follow-up Study (France, Spain, Turkey).

A summary of meetings and teleconferences realized during the 3 IBGP seasons is given in Table 5.

Table 5: Summary of main IBGP meetings and telephone/video conferences

Event	Location	Date	Countries involved in Follow-up Study and participating
Face Meeting	Pullman Hotel CDG Airport Paris, France	21June 2011	France (2 presents) Spain (1 present) Turkey (1 present)
Videoconference	-	29 July 2011	France (1 present) Spain (1 present) Turkey (1 present)
Face Meeting	Pullman Hotel CDG Airport Paris, France	15 December 2011	France (1 present) Spain (1 present) Turkey (2 presents)
Conference Call	-	23 January 2013	France (1 present) Spain (1 present)
Face Meeting	Pullman Hotel CDG Airport Paris, France	19 April 2013	France (2 presents) Spain (2 presents) Turkey (2 presents)
Face Meeting	Terrass Hotel Paris, France	23 September 2013	France (2 presents) Spain (1 present)

The composition of the Follow-up teams is described below.

FRANCE – Grog network & Open Rome

Anne Mosnier (Coordination)

Françoise Barat, Marion Quesne, Elodie Nauleau (Data collection)

Isabelle Daviaud (Data management)

Tan Tai Bui (Informatics)

SPAIN - Castilla y León network

Tomas Vega (Coordination)

Maria Aranzazu Garcia Iglesias (Data management)

TURKEY – Istanbul Influenza Surveillance Network

Selim Badur and Meral Ciblak (Coordination)

Meral Ciblak (Data collection and validation)

5.10 Ethics and regulatory considerations

The study was conducted according to Good Clinical Practice (GCP), the Declaration of Helsinki, and local rules and regulations of each country participating.

In France, the IBGP protocol was approved by all pertinent ethics committees, related to the treatment of information, to human protection and liberty, and to physician's deontology (CPP – *Comité de Protection des Personnes;* CCTIRS – *Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé;* CNIL – *Commission nationale de l'informatique et des libertés;* CNOM – *Conseil National de l'Ordre des Médecins)* (Annex 5).

In Turkey and Spain, recommendations said that separate approval for this study was not necessary as its content was contained within the routine surveillance program and coordinating teams were agreed to perform such a follow-up.

5.11 Quality assurance procedures - audit

According to Good Epidemiological Practice, Open Rome accepts any sort of audit:

- from a representative of Quality Assurance of GlaxoSmithKline.
- from independent persons, designated by GlaxoSmithKline.
- from representatives of the national or international health authorities.

5.12 Data property

The results obtained in the course of the study were presented and discussed with the Steering Committee. StC members will also be part of abstracts sent to scientific congresses and articles submitted to scientific journals with referees.

The database will be accessible through Open Rome.

Electronic data from the study will be backed up and burned in a double set of CD-ROM and will be stored at Open Rome.

6 Protocol deviations

6.1 ARI/ILI definition

Influenza clinical case definition differs among countries (Table 2) [21].

In France, GROG network adopts the wider concept of ARI defined as sudden onset of respiratory symptom(s) with infection context (fever, headaches...), in the absence of other diagnosis.

In Spain, the Castilla y León influenza network uses the EU ILI case definition (Commission Decision of 28/IV/2008). The ILI patient must have sudden onset of symptoms and at least one of the following four systemic symptoms: fever or feverishness, malaise, headache, myalgia and at least one of the following three respiratory symptoms: cough, sore throat, shortness of breath.

In Turkey, the Ministry of Health adopts the World Health Organization (WHO) ILI case definition. The ILI patient must have sudden-onset fever (> 38 °C) with cough or sore throat, in the absence of other diagnoses.

6.2 Delay for swabbing

Practitioners are then encouraged to swab :

- ARI patients preferably with onset of symptoms < 2 days in France,

- ILI patients preferably with onset of symptoms < 4 days or 1 week if immunodeficiency in Spain,

- ILI patients preferably with onset of symptoms < 3 days in Turkey.

6.3 Clinical symptoms

Each country enrolled has its own surveillance form (CRF D0) requiring different clinical symptoms (Table 6).

In order to harmonize symptoms analysed with the IBGP Surveillance Study, the same rules defined by the Steering Committee are applied:

- group together symptoms with close physiopathology;
- select only clinical signs/groups of signs that are common to at least four of the IBGP Surveillance Study enrolled countries.

The nine symptoms selected are highlighted in bold on Table 6.

Table 6: Symptoms collected in swabbed patients in sentinel Surveillance Network participating in the IBGP Follow-up Study

SYMPTOMS	ES	FR	TR	Selected symptoms
Encoding	Box to tick if yes	Box to tick if yes	Box to tick if yes	
Adenopathies		X		
Asthenia		**X**		**Asthenia/Malaise/ Frissons/Chills**
Malaise				
Asthenia / Malaise	**X**			
Chills				
Frissons		**X**		
Frissons/Chills	**X**			
Bronchiolitis/bronchitis		X		
Conjunctivitis		X		
Burning eyes				
Runny nose			**X**	**Coryza/Rhinitis**
Coryza				
Coryza / Rhinitis		**X**		
Cough	**X**	**X**	**X**	**Cough**
Dyspnea	**X**			**Dyspnea/Polypnea**
Shortness of breath				
Dyspnea / Polypnea		**X**		
Difficulty in breathing			**X**	
Acute respiratory distress			**X**	
Fever	**X**	**X**	**X**	**Fever**
Fever >38°				
Temperature (°C)		**X**	**X**	
Gastrointestinal symptoms	X	X		
Headache	**X**	**X**	**X**	**Headache**
Myalgia		**X**	**X**	**Myalgia/ Joint Pain**
Joint pain			**X**	
Myalgia / General pain	**X**			
Myalgia/arthralgia				
Otalgia				
Otitis				
Otitis/Otalgia		X		
Rash		X		
Sore throat			**X**	**Sore throat/ Pharyngitis**
Pharyngitis		**X**		
Sore throat/nasal mucosa	**X**			
Hoarseness				
Pathologic pulm.				
Sputum		X		
Sudden onset of symptoms	**X**	**X**		**Sudden onset of symptoms**

6.4 Age groups

Four age groups are usually used for influenza surveillance in Europe : 0-4 yo; 5-14 yo; 15-64 yo; ≥65 yo

In order to balance the age groups analyzed in the IBGP Surveillance Study, the Steering Committee decided to extend the age stratification to 6 groups : 0-4 yo; 5-14 yo; 15-24 yo, 25-44 yo; 45-64 yo; ≥65 yo.

6.5 Employment situation

Due to the age stratification used in the analysis, employment situation was considered for only 2 age groups : 25-44 yo and 45-64 yo.

6.6 Underlying Conditions

Each country enrolled has its own surveillance form (CRF D0) requiring different information regarding underlying conditions (Table 7).

These conditions might appear as:

- An open general question about the presence of chronic conditions/comorbidities or flu vaccine indication.
- A box to tick if a specific condition is present or a "YES/NO" question.

In order to harmonize factors analysed on behalf of the IBGP study the Steering Committee selected the main conditions reported in each country: pregnancy, excessive weight and chronic diseases (at least one of the chronic diseases presented on Table 7).

Underlying conditions reported as an open question were considered for analysis. The variable was reconstructed in order to obtain the widest information as possible.

Pregnancy status was considered only in women 18-50 yo.

Table 7: Underlying conditions collected in sentinel Networks participating in the IBGP Follow-up Study

Underlying conditions	ES	FR	TR
Pregnancy	X	X	X
Excessive weight	BMI>40	BMI≥30 or 40[1]	BMI≥35
Chronic diseases			open
Cardiovascular disease	X	X	
Diabetes/endocrine disease	X	X	
Respiratory disease	X	X	
Cancer	X		
Immunodeficiency	X	X	X
Kidney disease	X		
Liver disease	X		
Stroke/ Neuromuscular disease			
Others	X	X	X

BMI = body mass index

[1] *In France, excessive weight was considered as flu vaccination indication if BMI≥30 for 2010-2011 and 2011-2012 vaccination campaign and ≥40 since 2012-2013*

6.7 Drugs

Due to differences in healthcare access and provision in France, Spain and Turkey, drugs were gathered in classes to enable same classification in each of the three countries. This classification was based on the general physiologic action of each drug.

Ten classes (+ other) were defined :

- analgesic/antipyretic
- antitussive/mucolytic
- drops/spray/wash
- drugs combination
- antihistaminic
- antibiotic
- oral corticosteroid
- antiasthmatic
- homeopathic medicine
- vitamins/trace element/dietary supplement
- other.

In France only, CRF D0 includes a question about antiviral use before D0 consultation and swabbing. StC decided to exclude from clinical symptoms analysis patients using antiviral before D0.

It was decided to keep all the others patients in the clinical symptoms, even if vaccinated against influenza.

6.8 Duration of illness and recovery

In order to measure the duration of the illness, a specific question is included in the CRF D9/D28.

For the first study season (2010-2011), it was asked how many days has been the "*duration of this (influenza) infection (including complications)* ". This appeared to be a hard question to sentinels and, for the following seasons, StC moved to a new question asking the "*date of return to the patient "normal activities", with "normal activities*" defined as "*patient returned to his usual routine/occupation (work, school, homemade, day-to-day life...)*".

The duration of illness was then calculated as the number of days between the date of symptoms' onset (available in the CRF D0) and the date of return to normal activities.

Recovery at D9 or D28 is defined as the fact that patient has returned to his normal activities.

If patient had recovered at D9, a CRF D28 could be applied if patients still presented "other symptoms".

Finally, the date of recovery seems to have been sometimes "qualitatively" defined, what as to be considered as a potential bias in the measure of the duration of illness.

6.9 Cases and Controls selection

6.9.1 Change of Controls definition

For the IBGP1 phase of the study (2010-2011 season), Controls were defined as "non Influenza B" ILI/ARI patients (with Influenza A or influenza negative virological result).

In order to permit a comparison of B and A influenza episodes, StC moved to a new definition for Controls in the IBGP2 Study. Due to the change of the Control definition between 2010-2011 (non Influenza B Controls) and 2011-2012 (only Influenza A Controls) seasons, negative Controls included in IBGP1 phase (2010-2011) had to be excluded and replaced by Influenza A Controls during the following seasons.

6.9.2 Change in the delay for the first follow-up questionnaire

Cases

Due to the change in the delay for the first follow-up questionnaire between 2010-2011 (7 days± 2 days) and 2011-2012 (9 days ± 2 days) seasons, some Influenza B Cases in IBGP1 phase (2010-2011) had to be excluded when their first follow-up contact occurred at D5 or D6.

Controls

Due to the change in the delay for the first follow-up questionnaire between 2010-2011 (7 days± 2 days) and 2011-2012 (9 days ± 2 days) seasons, some Influenza A Controls included in IBGP1 phase (2010-2011) had to be excluded when their first follow-up contact occurred at D5 or D6. In this situation, these controls had to be replaced by new Influenza A Controls during the following seasons.

6.9.3 Season of Control's recruitment

Due to potential differences between the epidemic curves of cases and controls, data collection was organized as following (see matching criteria in § 5.5.1): Influenza B Cases have preferably to be matched with an Influenza A Control during the same season. In case the surveillance system is unable to recruit Influenza A Control matching to each Influenza B Case enrolled in the same season, the inclusion will proceed in the following season.

6.9.4 Selection, inclusion and follow-up of Cases and Controls

France

Cases

GROG developed an electronic extraction of lab positive B Cases based on the virological results received by the NICs. This extraction segregated influenza B positives swabbed since more than 6 days and less than 10 days, according to the inclusion criteria and giving enough time (at least one day) to contact the practitioner. At this stage, many cases were lost because the results arrived too late at GROG coordination (>10 days). Anyway, it was decided that, if a few D9/D28 forms exceed the time allowed, they will not be excluded of the study.

A list of Cases and their respective sentinels was provided twice a week depending on the new databases received from NICs. Sentinels responsible for influenza B positives patients were then called as soon as possible. If sentinels accepted to participate in the study, GROG faxed or e-mailed the relevant documents: an IBGP abstract, the patient informed consent and the CRF D9 pre-filled with the available patient personal information (but anonymous).

Some Cases were lost because the patient had to be contacted in less than 24 hours, situation not accepted by sentinels, or patients were not reachable or didn't agree to participate. In addition, other lost happened when GROG staff did not succeed in contacting sentinels on time.

Sentinels participating in the study contacted patients, who generally, if available, accepted to provide information required in CRF D9. If these patients had not returned to their normal activities at the day of the contact, sentinels informed them about a future phone contact within a month on average. Then, at day 28 (±5 days) sentinels contacted patients again to obtain information required at CRF D28.

After recording information in the CRF D9, sentinels faxed or e-mailed it to GROG coordination. Trained staff was responsible for updating the monitoring database (if patient needed a CRF D28 or not) and validating the CRF D9 received. If patient needed a CRF D28, it was scheduled to be sent to the sentinel in the period when patient should be contacted again. Information recorded in the CRF was verified and in case of missing data, sentinels were asked by e-mail to complete the forms.

Controls

During winters of 2011/2012 and 2012/2013, Influenza A Controls were recruited for matching Influenza B Cases of the same or previous winter(s).

An extraction of the main database received from the NIC was established for selecting controls, (similar to that created for selecting cases) regarding inclusion criteria and matching cases in the following order:

1- Same age group

0 – 4 years old (if possible, subgroup of 0-2 and 3-4 years old)

5 – 14 years old

15 – 64 years old (if possible, subgroup of 15-49 and 50-64 years old)

Over 64 years old.

2 - Same country, if possible the same interregion/region within the country and the same doctor.

The same procedure for contacting sentinels and instructions for contacting patients were followed for controls.

Turkey

The CRF D0 were completed by sentinels GPs and paediatricians.

As the laboratory is located in the Turkish coordination of the IBGP study, coordination staff were able to immediately contact patients after the tests results.

Influenza B cases were matched with influenza A controls following established criteria.

Turkish staff called concomitantly cases and controls selected, who generally accepted to provide information required at CRF D9. If these patients had not returned to their normal activities and/or had presented other symptoms at the day of the call, Turkish staff contacted patients again to obtain information required at CRF D28.

Spain

The CRF D0 was completed by sentinels GPs and paediatricians.

CRF D9 were filled by Castilla y León Influenza Network staff through a phone call. If these patients had not returned to their normal activities and/or had presented other symptoms at the day of the call, Spanish staff informed them about a future phone contact within a month on average. Then, at day 28 (±5 days) Castilla y León staff called patients again to obtain information required at CRF D28.

All countries

It was decided that Cases or Controls contacted some days after eleven days for CRF D9 or some days before or after D28+/-5 for CRF D28 will be kept in the analysis.

7 Results

7.1 General descriptive analysis of the study

A total of 1 350 patients (Cases + Controls) have been included in the IBGP2b Follow-up Study.

7.1.1 Number of patients included by type of sentinels

Table 8: 3 seasons: Distribution of patients included by type of sentinel practitioners

Country	Patients recruited by paediatricians	Patients recruited by GP	Total patients recruited
ES	21	36	57
FR	314	605	919
TR	0	374	374
All	335	1015	1350

7.1.2 Number of patients included by flu type

Table 9: 3 seasons: Surveillance swabs, Cases and Controls recruited and total patients included in the Follow-up Study

	ES	FR	TR	All
Total Flu B swabbed (routine surveillance)	251	2423	366	3040
Cases responding to CRF9	44	486	216	746
Cases responding to CRF28	29	107	55	191
Total Flu B Cases included	44	486	216	746
Total Flu A swabbed (routine surveillance)	247	3648	631	4526
Controls responding to CRF9	13	433	158	604
Controls responding to CRF28	6	55	22	83
Total Flu A Controls included	13	433	158	604
TOTAL SUBJECTS INCLUDED	**57**	**919**	**374**	**1350**

Due to the change in the delay for the first follow-up questionnaire between 2010-2011 (7 days± 2 days) and 2011-2012 (9 days ± 2 days) seasons, 25 Influenza B Cases (22 in France and 3 in Turkey) and 13 Influenza A Controls (10 in France and 3 in Turkey) were excluded between IBGP1 and IBGP2.
Moreover, all 212 controls (114 in France and 98 in Turkey) negative for flu were also excluded and replaced by new Influenza A Controls searched during new seasons.

Table 10: Evolution of the number of Cases and Controls recruited in the study, by season and country

		Cases	Controls	All	Comments
France					
	2010-2011	179	32	211	included during IBGP1
	2011-2012	209	205	415	
	2012-2013	486	433	919	
Turkey					
	2010-2011	152	54	206	included during IBGP1
	2011-2012	210	150	360	
	2012-2013	216	158	374	
Spain					
	2010-2011	0	0	0	
	2011-2012	4	1	5	
	2012-2013	44	13	57	
TOTAL INCLUDED					
	2010-2011	**331**	**86**	**417**	**included during IBGP1**
	2011-2012	**423**	**356**	**779**	
	2012-2013	**746**	**604**	**1350**	

The results presented in the following sections are based on the analysis of the data of 1 350 Influenza patients, 746 Influenza B Cases and 604 Influenza A Controls, collected between December 2010 and April 2013.

7.1.3 Chronology of inclusions

Influenza circulation varied between the 3 study seasons:
- 2010-2011 was marked by the epidemic co-circulation of influenza A and B in France and Turkey.
- 2011-2012 was marked by a A(H3N2) epidemic in the three study countries; Influenza B was sporadic in France and Spain and circulated discreetly at the end on the season in Turkey.
- 2010-2011 was marked by the epidemic co-circulation of influenza A and B in France and Spain; Influenza B was sporadic in Turkey.

Due to this epidemiological situation, Influenza B Cases were mainly recruited:
- in 2010-2011 and 2012-2013 in France,
- in 2010-2011 and 2011-2012 in Turkey,
- in 2012-2013 in Spain.

Figure 1: Weekly distribution of sentinel flu A and B lab confirmations and Cases and Controls inclusions in FRANCE

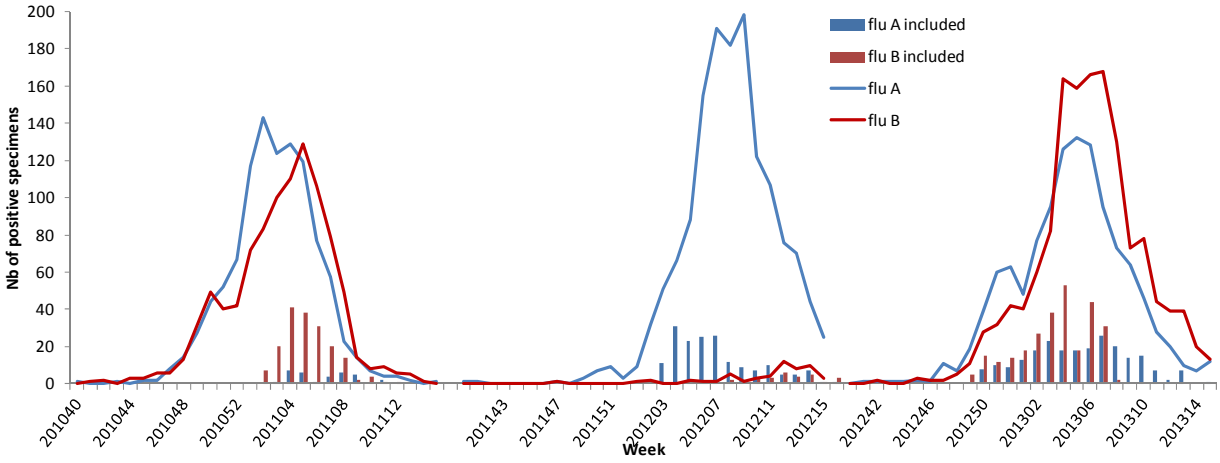


Figure 2: Weekly distribution of sentinel flu A and B lab confirmations and Cases and Controls inclusions in TURKEY

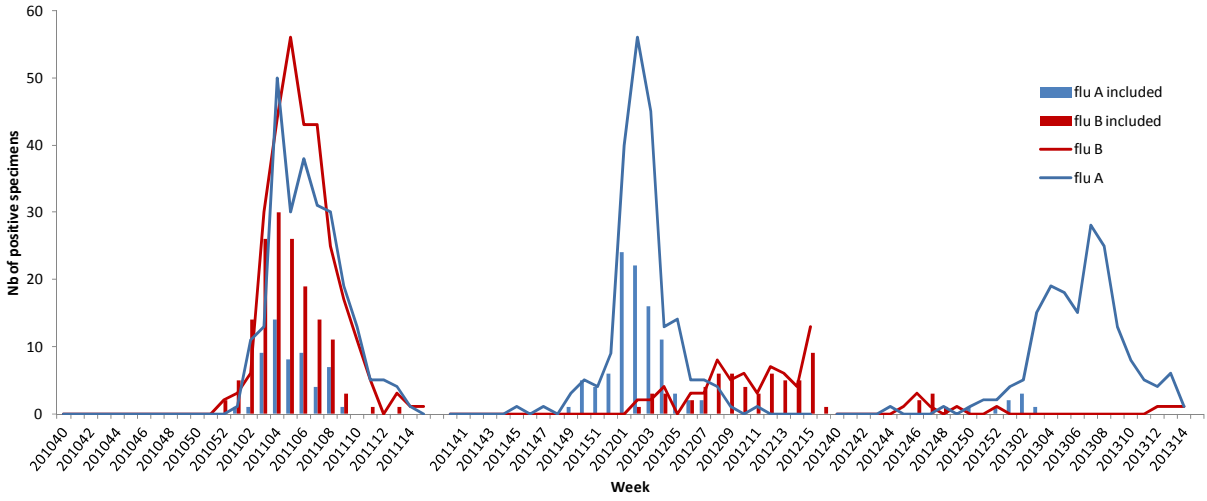
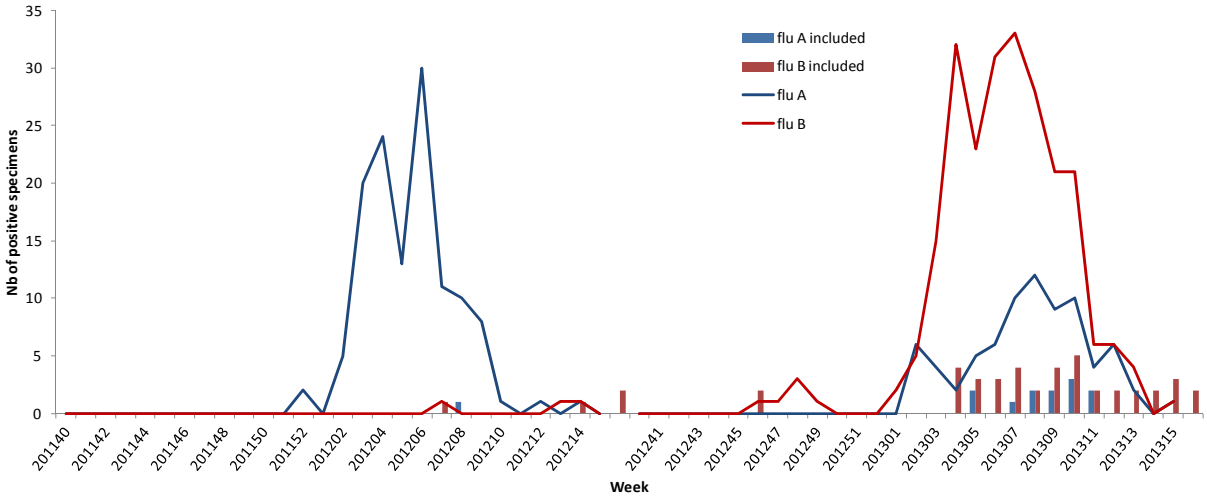


Figure 3: Weekly distribution of sentinel flu A and B lab confirmations and Cases and Controls inclusions in SPAIN



7.1.4 Virological characterization of Influenza Cases and Controls

Virological characterization is available for the largest part of the Cases and Controls included in the study:
- Lineage is available for 616 (82,6%) of the Influenza B Cases;
- Sub-type is available for 586 (97,0%) of the Influenza A Controls.

Table 11: 3 seasons: Virological characterization of Influenza Cases and Controls by country, type, subtype and lineage

	ES	FR	TR	All
Total Flu B (Cases)	**44**	**486**	**216**	**746**
B/Victoria	12	184	51	247
B/Yamagata	29	282	58	369
B/ not characterized	3	20	107	130
Total Flu A (Controls)	**13**	**433**	**158**	**604**
A/H1N1pdm09	10	167	46	223
A/H3N2	3	260	100	363
A/ not subtyped	0	6	12	18
TOTAL SUBJECTS INCLUDED	**57**	**919**	**374**	**1350**

7.2 General descriptive data of subjects included

Denominators used for percentage calculation only include data with no missing information for the item considered.

7.2.1 Socio-demographic data

7.2.1.1 Age

Age is available for the 1 350 cases as lack of birth date or age was a matching criteria.

Table 12: Distribution of the 1 350 Cases and Controls by age group, country and season

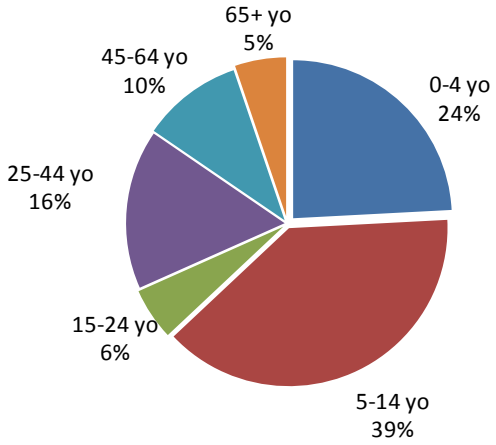
Age group	Season	France		Turkey		Spain	
		Flu B Cases	**Flu A Controls**	**Flu B Cases**	**Flu A Controls**	**Flu B Cases**	**Flu A Controls**
0-4 yo	2010-11	48	11	8	3	-	-
	2011-12	3	39	9	5	1	0
	2012-13	60	61	2	0	3	1
	Total	**111**	**111**	**19**	**8**	**4**	**1**
5-14 yo	2010-11	78	7	20	8	-	-
	2011-12	10	81	20	28	0	0
	2012-13	117	64	0	0	14	3
	Total	**205**	**152**	**40**	**36**	**14**	**3**
15-24 yo	2010-11	12	1	13	7	-	-
	2011-12	0	7	11	5	1	0
	2012-13	11	18	2	1	1	1
	Total	**23**	**26**	**26**	**13**	**2**	**1**
25-44 yo	2010-11	22	9	74	30	-	-
	2011-12	9	24	15	32	1	1
	2012-13	43	42	2	7	8	1
	Total	**74**	**75**	**91**	**69**	**9**	**2**
45-64 yo	2010-11	6	3	27	5	-	-
	2011-12	8	11	0	20	1	0
	2012-13	35	31	0	0	10	4
	Total	**49**	**45**	**27**	**25**	**11**	**4**
≥65 yo	2010-11	13	1	10	1	-	-
	2011-12	0	11	3	6	0	0
	2012-13	11	12	0	0	4	2
	Total	**24**	**24**	**13**	**7**	**4**	**2**
All age	2010-11	179	32	152	54	-	-
	2011-12	30	173	58	96	4	1
	2012-13	277	228	6	8	40	12
	Total	**486**	**433**	**216**	**158**	**44**	**13**

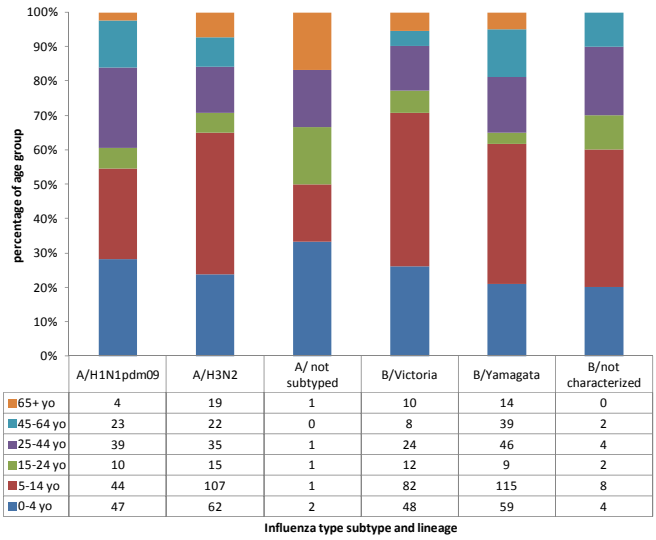
Figure 4 to 9 presents for each country the distribution of the included patients by age group, and the weight (%) of each age group among influenza A subtype and B lineage.

In France, subjects ranged from 0 to 87 years old, mean :19.7, median: 10, SD: 20.8.
Children (0-15 yo) represented the main part (63%) of the study population.

Figure 4: 3 seasons: Distribution of included patients by age group in FRANCE

Figure 5: 3 seasons: Weight (%) of each age group among influenza A subtype and B lineage in FRANCE



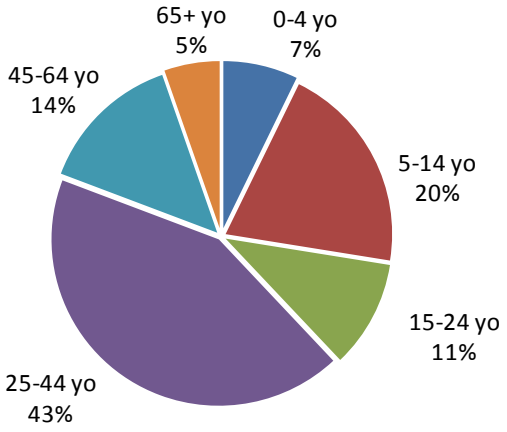


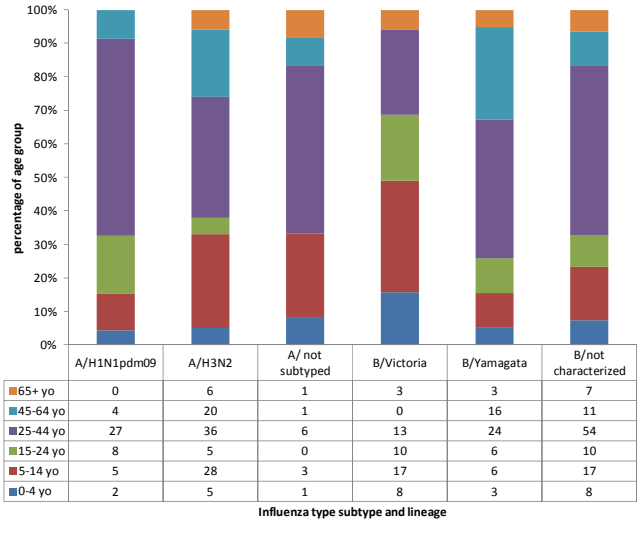
	A/H1N1pdm09	A/H3N2	A/ not subtyped	B/Victoria	B/Yamagata	B/not characterized
65+ yo	4	19	1	10	14	0
45-64 yo	23	22	0	8	39	2
25-44 yo	39	35	1	24	46	4
15-24 yo	10	15	1	12	9	2
5-14 yo	44	107	1	82	115	8
0-4 yo	47	62	2	48	59	4

In Turkey, subjects ranged from 0 to 100 years old, mean: 30.2, median: 30 , SD: 19.5.
Children (0-15 yo) represented a quarter (27%) of the study population.
Young adults (15-44 yo) represented the main part (54%) of the study population.

Figure 6: 3 seasons: Distribution of included patients by age group in TURKEY

Figure 7: 3 seasons: Weight (%) of each age group among influenza A subtype and B lineage in TURKEY



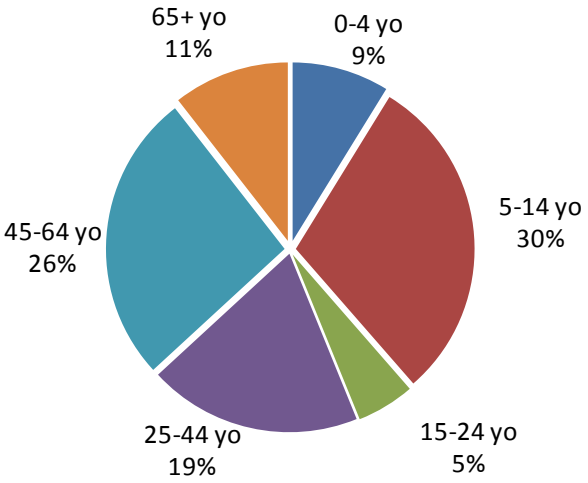


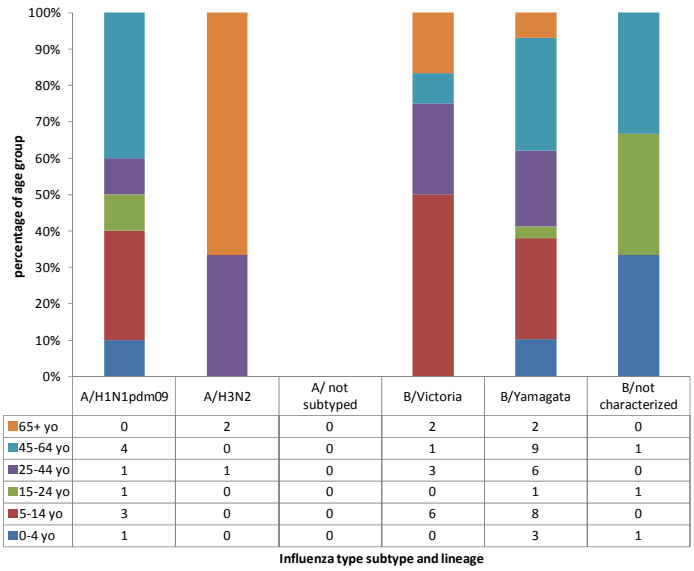
	A/H1N1pdm09	A/H3N2	A/ not subtyped	B/Victoria	B/Yamagata	B/not characterized
65+ yo	0	6	1	3	3	7
45-64 yo	4	20	1	0	16	11
25-44 yo	27	36	6	13	24	54
15-24 yo	8	5	0	10	6	10
5-14 yo	5	28	3	17	6	17
0-4 yo	2	5	1	8	3	8

In Spain, subjects ranged from 0 to 79 years old, mean: 31.5, median: 30 , SD: 23.5.
Children (0-15 yo) represented the main part (39%) of the study population.

Figure 8: 3 seasons: Distribution of included patients by age group in SPAIN

Figure 9: 3 seasons: Weight (%) of each age group among influenza A subtype and B lineage in SPAIN





7.2.1.2 Gender

Table 13: 3 seasons: Distribution by gender (male M and female F) and sex-ratio (S) of the 1 350 Cases and Controls by country and age group

Gender	France				Turkey				Spain			
	Flu B 485 Cases		**Flu A 433 Controls**		**Flu B 213 Cases**		**Flu A 158 Controls**		**Flu B 43 Cases**		**Flu A 13 Controls**	
Age group	M/F	S	M/F	S	M/F	S	M/F	S	M/F	S	M/F	S
0-4 yo	52 / 59	0.9	61 / 50	1.2	11 / 8	1.4	5 / 3	1.7	1 / 3	0.3	0 / 1	
5-14 yo	110 / 94	1.2	93 / 59	1.6	18 / 22	0.8	19 / 17	1.1	10 / 3	3.3	0 / 3	
15-24 yo	19 /4	4.8	15 / 11	1.4	13 / 13	1.0	4 / 9	0.4	2 / 0		0 / 1	
25-44 yo	26 / 48	0.5	39 / 36	1.1	40 / 51	0.8	34 / 35	1.0	7 / 2	3.5	1 / 1	1.0
45-64 yo	19 / 30	0.6	23 / 22	1.0	15 / 12	1.3	14 / 11	1.3	3 / 8	0.4	0 / 4	
≥65 yo	9 / 15	0.6	7 / 17	0.4	6 / 7	0.9	3 / 4	0.8	2 / 2	1.0	0 / 2	
All age	**235 / 250**	**0.9**	**238 / 195**	**1.2**	**103 / 113**	**0.9**	**79 / 79**	**1.0**	**25 / 18**	**1.4**	**1 / 12**	**0.1**

Table 14: 3 seasons: Distribution of the two B lineages by gender (male M and female F) and sex-ratio (S) by country and age group

Gender	France				Turkey				Spain			
	Flu B/V 183 Cases		Flu B/Y 282 Cases		Flu B/V 51 Cases		Flu B/Y 58 Cases		Flu B/V 12 Cases		Flu B/Y 28 Cases	
Age group	M/F	S	M/F	S	M/F	S	M/F	S	M/F	S	M/F	S
0-4 yo	23 / 25	0.9	27 / 32	0.8	4 / 4	1.0	1 / 2	0.5	0 / 0		1 / 2	0.5
5-14 yo	43 / 38	1.1	64 / 51	1.3	9 / 8	1.1	0 / 6		5 / 1	5.0	5 / 2	2.5
15-24 yo	10 / 2	5.0	7 / 2	3.5	3 / 7	0.4	3 / 3	1.0	0 / 0		1 / 0	
25-44 yo	8 / 16	0.5	18 / 28	0.6	3 / 10	0.3	10 / 14	0.7	2 / 1	2.0	5 / 1	5.0
45-64 yo	4 / 4	1.0	14 / 25	0.6	0 / 0		8 / 8	1.0	1 / 0		2 / 7	0.3
≥65 yo	4 / 6	0.7	5 / 9	0.6	0 / 3		1 / 2	0.5	1 / 1	1.0	1 / 1	1.0
All age	**92 / 91**	**1.0**	**135 / 147**	**0.9**	**19 / 32**	**0.6**	**23 / 35**	**0.7**	**9 / 3**	**3.0**	**15 / 13**	**1.2**

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

7.2.1.3 Employment situation

Overall, 72.1% of 25-64 years old patients are employed: 73.1% in Spain, 55.7% in Turkey, 86.4% in France.

Table 15: 3 seasons: Number and percentage of Cases and Controls with an employment by age group and country

Employment	France				Turkey				Spain			
	Flu B 123 Cases		Flu A 120 Controls		Flu B 118 Cases		Flu A 94 Controls		Flu B 20 Cases		Flu A 6 Controls	
Age group	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
25-44 yo	68	91.9	69	92.0	48	52.7	50	72.5	7	77.8	2	100
45-64 yo	37	75.5	36	80.0	10	37.0	10	40.0	7	63.6	3	75.0
Total 25-64 yo	**105**	**85.4**	**105**	**87.5**	**58**	**49.2**	**60**	**63.8**	**14**	**70.0**	**5**	**83.3**

Table 16: 3 seasons: Number and percentage of the Influenza B characterized Cases with an employment by age group and country

Employment	France				Turkey				Spain			
	Flu B/V 32 Cases		Flu B/Y 85 Cases		Flu B/V 13 Cases		Flu B/Y 40 Cases		Flu B/V 4 Cases		Flu B/Y 15 Cases	
Age group	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
25-44 yo	23	95.8	41	89.1	6	46.2	11	45.8	2	66.7	5	83.3
45-64 yo	6	75.0	30	76.9	0	0	5	31.3	0	0	7	77.8
Total 25-64 yo	**29**	**90.6**	**71**	**83.5**	**6**	**46.2**	**16**	**40**	**2**	**50.0**	**12**	**80.0**

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

7.2.2 Vaccination status

As vaccine status vary from one season to another, the vaccination status as to be analysed by season.

For the 2010-2011 season, data are only presented for France and Turkey, as Spain was not involved in the follow-up study during this season.

Globally :
- in 2010-2011, 4.8% of the study patients were vaccinated in France, 3.9% in Turkey;
- in 2011-2012, 5.4% of the study patients were vaccinated in France, 6.0% in Turkey; in Spain, only 4 influenza B Cases were recruited and only one lineage has been characterized, as B/Yamagata;
- in 2012-2013, 5.7% of the study patients were vaccinated in France, 5.8% in Spain; in Turkey, only 6 influenza B Cases were recruited and no lineage has been characterized.

As very few patients were vaccinated, statistical comparison of Cases and Controls was not done.

Table 17: 2010-2011 season: Number and percentage of Cases and Controls vaccinated by age group and country

Vaccination	France				Turkey*			
	Flu B 142 Cases		Flu A 25 Controls		Flu B 152 Cases		Flu A 54 Controls	
Age group	nb	%	nb	%	nb	%	nb	%
0-4 yo	2	5.1	0	0	0	0	1	33.3
5-14 yo	3	4.7	1	16.7	1	5.0	0	0
15-24 yo	0	0	0	0	0	0	0	0
25-44 yo	0	0	0	0	1	1.4	2	6.7
45-64 yo	1	20	0	0	2	7.4	0	0
≥65 yo	1	20	0	0	1	10.0	0	0
All age	**7**	**4.9**	**1**	**4.0**	**5**	**3.3**	**3**	**5.6**

**In Turkey, the date of vaccination is not available in 2010-2011 season. Above data are calculated without taken into account any date of vaccination.*

Table 18: 2010-2011 season: Number and percentage of Influenza B characterized Cases vaccinated by age group and country

Vaccination	France				Turkey			
	Flu B/V* 125 Cases		Flu B/Y 7 Cases		Flu B/V* 0 Case		Flu B/Y 55 Cases	
Age group	nb	%	nb	%	nb	%	nb	%
0-4 yo	1	2.9	0	0			0	0
5-14 yo	3	5.1	0	0			0	0
15-24 yo	0	0					0	0
25-44 yo	0	0	0	0			0	0
45-64 yo	1	20					0	0
I≥65 yo	0	0	1	100			0	0
All age	**5**	**4.0**	**1**	**14.3**			**0**	**0**

Flu B/V = Influenza B Case, Victoria lineage Flu B/Y = Influenza B Case, Yamagata lineage

** Influenza B lineage included in the vaccine for the 2010-2011 season*

Table 19: 2011-2012 season: Number and percentage of Cases and Controls vaccinated by age group and country

Vaccination	France				Turkey				Spain			
	Flu B 30 Cases		Flu A 173 Controls		Flu B 55 Cases		Flu A 96 Controls		Flu B 4 Cases		Flu A 1 Control	
Age group	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
0-4 yo	0	0	0	0	0	0	0	0	0	0		
5-14 yo	0	0	1	1.2	1	5.3	1	3.6				
15-24 yo			0	0	0	0	1	20.0	0	0		
25-44 yo	1	11.1	0	0	0	0	1	3.1	0	0	0	0
45-64 yo	2	25.0	0	0			2	10.0	0	0		
≥65 yo			7	63.6	1	33.3	2	33.3				
All age	**3**	**10.0**	**8**	**4.6**	**2**	**3.6**	**7**	**7.3**	**0**	**0**	**0**	**0**

Table 20: 2011-2012 season: Number and percentage of Influenza B characterized Cases vaccinated by age group and country

Vaccination	France				Turkey				Spain			
	Flu B/V* 15 Cases		Flu B/Y 14 Cases		Flu B/V* 48 Cases		Flu B/Y 0 Case		Flu B/V* 0 Case		Flu B/Y 1 Case	
Age group	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
0-4 yo			0	0	0	0						
5-14 yo	0	0	0	0	0	0						
15-24 yo					0	0						
25-44 yo	0	0	1	25.0	0	0					0	0
45-64 yo	0	0	1	20.0								
≥65 yo					1	33.3						
All age	**0**	**0**	**2**	**14.3**	**1**	**2.1**					**0**	**0**

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

** Influenza B lineage included in the vaccine for the 2011-2012 season*

Table 21: 2012-2013 season: Number and percentage of Cases and Controls vaccinated by age group and country

Vaccination	France				Turkey				Spain			
	Flu B 271 Cases		Flu A 222 Controls		Flu B 6 Cases		Flu A 8 Controls		Flu B 40 Cases		Flu A 12 Controls	
Age group	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
0-4 yo	1	1.7	1	1.7	0	0			0	0	0	0
5-14 yo	4	3.4	2	3.2					0	0	0	0
15-24 yo	0	0	0	0	0	0	0	0	0	0	0	0
25-44 yo	0	0	1	2.4	0	0	0	0	0	0	0	0
45-64 yo	4	12.9	5	16.7					1	10.0	0	0
≥65 yo	4	40.0	6	54.5					2	50.0	0	0
All age	**13**	**4.8**	**15**	**6.8**	**0**	**0**	**0**	**0**	**3**	**7.5**	**0**	**0**

Table 22: 2012-2013 season: Number and percentage of Influenza B characterized Cases vaccinated by age group and country

Vaccination	France				Turkey				Spain			
	Flu B/V 14 Cases		Flu B/Y* 252 Cases		Flu B/V 0 Case		Flu B/Y* 0 Case		Flu B/V 12 Cases		Flu B/Y* 28 Cases	
Age group	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
0-4 yo	0	0	1	1.8							0	0
5-14 yo	0	0	4	3.6					0	0	0	0
15-24 yo	0	0	0	0							0	0
25-44 yo	0	0	0	0					0	0	0	0
45-64 yo			4	13.3					0	0	1	11.1
≥65 yo			4	40.0					2	100	0	0
All age	**0**	**0**	**13**	**5.2**					**2**	**16.7**	**1**	**3.6**

Flu B/V = Influenza B Case, Victoria lineage Flu B/Y = Influenza B Case, Yamagata lineage
** Influenza B lineage included in the vaccine for the 2012-2013 season*

7.3 Underlying conditions

7.3.1 Pregnancy

Among the 18-50 years old women, only 15 women are pregnant in the population study: 8 (7.0%) in France, 7 (6.3%) in Turkey and none in Spain.

Table 23: 3 seasons: Number and percentage of pregnant women among the 234 female (18-50 years old) Cases and Controls by country

Pregnancy	France				Turkey				Spain			
	Flu B 62 Cases		Flu A 52 Controls		Flu B 65 Cases		Flu A 47 Controls		Flu B 4 Cases		Flu A 4 Controls	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
Women 18-50 yo	6	9.7	2	3.8	4	6.2	3	6.4	0	0.0	0	0.0

Table 24: 3 seasons: Number and percentage of pregnant women among the 95 female (18-50 years old) Influenza B characterized Cases by country

Pregnancy	France				Turkey				Spain			
	Flu B/V 17 Cases		Flu B/Y 41 Cases		Flu B/V 14 Cases		Flu B/Y 19 Cases		Flu B/V 1 Case		Flu B/Y 3 Cases	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
Women 18-50 yo	5	29.4	1	2.4	2	14.3	2	10.5	0	0.0	0	0.0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

7.3.2 Excessive weight

A very small part of the study population (0.6%) was concerned by an excessive weight.

Table 25: 3 seasons: Number and percentage of Cases and Controls with an excessive weight by age group and country

Excessive weight	France				Turkey				Spain			
	Flu B 456 Cases		Flu A 428 Controls		Flu B 216 Cases		Flu A 158 Controls		Flu B 44 Cases		Flu A 13 Controls	
Age group	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
0-4 yo	0	0	0	0	0	0	0	0	0	0	0	0
5-14 yo	1	0.5	0	0	0	0	0	0	0	0	0	0
15-24 yo	0	0	1	3.8	0	0	0	0	0	0	0	0
25-44 yo	0	0	1	1.4	0	0	0	0	0	0	0	0
45-64 yo	1	2.0	1	2.3	0	0	0	0	2	18.2	0	0
≥65 yo	0	0	1	4.2	0	0	0	0	0	0	0	0
All age	**2**	**0.4**	**4**	**0.9**	**0**	**0**	**0**	**0**	**2**	**4.5**	**0**	**0**

Table 26: 3 seasons: Number and percentage of Influenza B characterized Cases with an excessive weight by age group and country

Excessive weight	France				Turkey				Spain			
	Flu B/V 160 Cases		Flu B/Y 279 Cases		Flu B/V 51 Cases		Flu B/Y 58 Cases		Flu B/V 12 Cases		Flu B/Y 29 Cases	
Age group	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
0-4 yo	0	0	0	0	0	0	0	0			0	0
5-14 yo	1	1.4	0	0	0	0	0	0	0	0	0	0
15-24 yo	0	0	0	0	0	0	0	0			0	0
25-44 yo	0	0	0	0	0	0	0	0	0	0	0	0
45-64 yo	0	0	1	2.6			0	0	1	100	1	11.1
≥65 yo	0	0	0	0	0	0	0	0	0	0	0	0
All age	**1**	**0.6**	**1**	**0.4**	**0**	**0**	**0**	**0**	**1**	**8.3**	**1**	**3.4**

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

7.3.3 Chronic diseases

Globally, 9,5% of the study population was concerned by a listed chronic disease: 9.3% in France, 10.9% in Spain and 9.9% in Turkey.

Table 27: 3 seasons: Number and percentage of Cases and Controls with a chronic disease by age group and country

Chronic diseases	France				Turkey				Spain			
	Flu B 480 Cases		Flu A 411 Controls		Flu B 216 Cases		Flu A 158 Controls		Flu B 42 Cases		Flu A 13 Controls	
Age group	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
0-4 yo	6	5.5	4	3.8	3	15.8	1	12.5	0	0	0	0
5-14 yo	13	6.5	7	5.0	1	2.5	2	5.6	0	0	0	0
15-24 yo	1	4.3	2	7.7	1	3.8	0	0	0	0	0	0
25-44 yo	5	6.8	7	9.9	8	8.8	4	5.8	0	0	0	0
45-64 yo	7	14.3	9	20.9	6	22.2	6	24.0	2	20.0	1	25.0
≥65 yo	10	41.7	12	50.0	5	38.5	0	0	2	50.0	1	50.0
All age	**42**	**8.8**	**41**	**10.0**	**24**	**11.1**	**13**	**8.2**	**4**	**9.5**	**2**	**15.4**

Table 28: 3 seasons: Number and percentage of Influenza B characterized Cases with a chronic disease by age group and country

Chronic diseases	France				Turkey				Spain			
	Flu B/V 180 Cases		Flu B/Y 280 Cases		Flu B/V 51 Cases		Flu B/Y 58 Cases		Flu B/V 12 Cases		Flu B/Y 29 Cases	
Age group	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
0-4 yo	4	8.3	2	3.5	2	25.0	1	33.3			0	0
5-14 yo	3	3.8	9	7.8	0	0	1	16.7	0	0	0	0
15-24 yo	1	8.3	0	0	0	0	1	16.7			0	0
25-44 yo	3	12.5	2	4.3	1	7.7	3	12.5	0	0	0	0
45-64 yo	0	0	6	15.4			5	31.3	0	0	2	22.2
≥65 yo	4	40.0	6	42.9	1	33.3	1	33.3	2	100	0	0
All age	**15**	**8.3**	**25**	**8.9**	**4**	**7.8**	**12**	**20.7**	**2**	**16.7**	**2**	**6.9**

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

7.4 Antiviral treatment consumption before D0

Only one patient took an antiviral treatment before D0: a 47 years' old man, vaccinated against flu, in France, during 2012-2013 season, presenting with an influenza B/ Yamagata. This case is excluded from the clinical signs analysis.

7.5 Clinical picture of study population at D0

7.5.1 Delay between onset of symptoms and D0

Most of the included patients (81.1%) had consulted their practitioner within the two first days of symptoms.

Table 29: 0-4 years old patients, 3 seasons: Distribution (nb and %) of Cases and Controls by delay between onset of symptoms and swabbing and by country

Delay	France				Turkey				Spain			
	Flu B 111 Cases		Flu A 111 Controls		Flu B 19 Cases		Flu A 8 Controls		Flu B 4 Cases		Flu A 1 Control	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
≤ 1 day	62	55.9	79	71.2	6	31.6	5	62.5	3	75.0	1	100
2 days	34	30.6	22	19.8	8	42.1	1	12.5	1	25.0	0	0
3 days	10	9.0	4	3.6	3	15.8	1	12.5	0	0	0	0
4 days	2	1.8	2	1.8	0	0.0	1	12.5	0	0	0	0
≥ 5 days	3	2.7	4	3.6	2	10.5	0	0	0	0	0	0

Table 30: 0-4 years old patients, 3 seasons: Distribution (nb and %) of Influenza B characterized Cases by delay between onset of symptoms and swabbing and by country

Delay	France				Turkey				Spain			
	Flu B/V 48 Cases		Flu B/Y 59 Cases		Flu B/V 8 Cases		Flu B/Y 3 Cases		Flu B/V 0 Case		Flu B/Y 3 Cases	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
≤ 1 day	27	56.3	33	55.9	4	50.0	0	0			2	66.7
2 days	16	33.3	16	27.1	1	12.5	2	66.7			1	33.3
3 days	4	8.3	6	10.2	2	25.0	0	0			0	0
4 days	0	0	2	3.4	0	0	0	0			0	0
≥ 5 days	1	2.1	2	3.4	1	12.5	1	33.3			0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

Table 31: 5-14 years old patients, 3 seasons: Distribution (nb and %) of Cases and Controls by delay between onset of symptoms and swabbing and by country

Delay	France				Turkey				Spain			
	Flu B 201 Cases		Flu A 152 Controls		Flu B 40 Cases		Flu A 36 Controls		Flu B 14 Cases		Flu A 3 Controls	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
≤ 1 day	118	58.7	112	73.7	18	45.0	28	77.8	10	71.4	2	66.7
2 days	52	25.9	29	19.1	13	32.5	5	13.9	2	14.3	1	33.3
3 days	22	10.9	7	4.6	5	12.5	0	0	2	14.3	0	0
4 days	7	3.5	1	0.7	2	5.0	1	2.8	0	0	0	0
≥ 5 days	2	1.0	3	2.0	2	5.0	2	5.6	0	0	0	0

Table 32: 5-14 years old patients, 3 seasons: Distribution (nb and %) of Influenza B characterized Cases by delay between onset of symptoms and swabbing and by country

Delay	France				Turkey				Spain			
	Flu B/V 79 Cases		Flu B/Y 115 Cases		Flu B/V 17 Cases		Flu B/Y 6 Cases		Flu B/V 6 Cases		Flu B/Y 8 Cases	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
≤ 1 day	48	60.8	64	55.7	6	35.3	3	50.0	5	83.3	5	62.5
2 days	16	20.3	35	30.4	7	41.2	2	33.3	0	0	2	25.0
3 days	10	12.7	12	10.4	2	11.8	1	16.7	1	16.7	1	12.5
4 days	4	5.1	3	2.6	2	11.8	0	0	0	0	0	0
≥ 5 days	1	1.3	1	0.9	0	0	0	0	0	0	0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

Table 33: 15-24 years old patients, 3 seasons: Distribution (nb and %) of Cases and Controls by delay between onset of symptoms and swabbing and by country

Delay	France				Turkey				Spain			
	Flu B 23 Cases		Flu A 26 Controls		Flu B 26 Cases		Flu A 13 Controls		Flu B 2 Cases		Flu A 1 Control	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
≤ 1 day	14	60.9	16	61.5	6	23.1	5	38.5	2	100	1	100
2 days	8	34.8	6	23.1	8	30.8	4	30.8	0	0	0	0
3 days	1	4.3	3	11.5	5	19.2	1	7.7	0	0	0	0
4 days	0	0	1	3.8	2	7.7	2	15.4	0	0	0	0
≥ 5 days	0	0	0	0	5	19.2	1	7.7	0	0	0	0

Table 34: 15-24 years old patients, 3 seasons: Distribution (nb and %) of Influenza B characterized Cases by delay between onset of symptoms and swabbing and by country

Delay	France				Turkey				Spain			
	Flu B/V 12 Cases		Flu B/Y 9 Cases		Flu B/V 10 Cases		Flu B/Y 6 Cases		Flu B/V 0 Case		Flu B/Y 1 Case	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
≤ 1 day	7	58.3	5	55.6	3	30.0	0	0			1	100
2 days	4	33.3	4	44.4	2	20.0	2	33.3			0	0
3 days	1	8.3	0	0	2	20.0	3	50.0			0	0
4 days	0	0	0	0	2	20.0	0	0			0	0
≥ 5 days	0	0	0	0	1	10.0	1	16.7			0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

Table 35: 25-44 years old patients, 3 seasons: Distribution (nb and %) of Cases and Controls by delay between onset of symptoms and swabbing and by country

Delay	France				Turkey				Spain			
	Flu B 74 Cases		Flu A 74 Controls		Flu B 91 Cases		Flu A 68 Controls		Flu B 9 Cases		Flu A 2 Controls	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
≤ 1 day	33	44.6	49	66.2	31	34.1	33	48.5	5	55.6	2	100
2 days	26	35.1	17	23.0	20	22.0	16	23.5	2	22.2	0	0
3 days	10	13.5	6	8.1	18	19.8	13	19.1	1	11.1	0	0
4 days	4	5.4	2	2.7	7	7.7	3	4.4	1	11.1	0	0
≥ 5 days	1	1.4	0	0	15	16.5	3	4.4	0	0	0	0

Table 36: 25-44 years old patients, 3 seasons: Distribution (nb and %) of Influenza B characterized Cases by delay between onset of symptoms and swabbing and by country

Delay	France				Turkey				Spain			
	Flu B/V 24 Cases		Flu B/Y 46 Cases		Flu B/V 13 Cases		Flu B/Y 24 Cases		Flu B/V 3 Cases		Flu B/Y 6 Cases	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
≤ 1 day	9	37.5	22	47.8	7	53.8	6	25.0	2	66.7	3	50.0
2 days	7	29.2	18	39.1	4	30.8	6	25.0	0	0	2	33.3
3 days	6	25.0	4	8.7	1	7.7	3	12.5	1	33.3	0	0
4 days	2	8.3	1	2.2	1	7.7	1	4.2	0	0	1	16.7
≥ 5 days	0	0	1	2.2	0	0	8	33.3	0	0	0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

Table 37: 45-64 years old patients, 3 seasons: Distribution (nb and %) of Cases and Controls by delay between onset of symptoms and swabbing and by country

Delay	France				Turkey				Spain			
	Flu B 49 Cases		Flu A 45 Controls		Flu B 27 Cases		Flu A 25 Controls		Flu B 11 Cases		Flu A 4 Controls	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
≤ 1 day	22	44.9	21	46.7	6	22.2	13	52.0	7	63.6	1	25.0
2 days	20	40.8	14	31.1	5	18.5	8	32.0	3	27.3	3	75.0
3 days	6	12.2	8	17.8	7	25.9	3	12.0	1	9.1	0	0
4 days	1	2.0	2	4.4	4	14.8	0	0	0	0	0	0
≥ 5 days	0	0	0	0	5	18.5	1	4.0	0	0	0	0

Table 38: 45-64 years old patients, 3 seasons: Distribution (nb and %) of Influenza B characterized Cases by delay between onset of symptoms and swabbing and by country

Delay	France				Turkey				Spain			
	Flu B/V 8 Cases		Flu B/Y 39 Cases		Flu B/V 0 Case		Flu B/Y 16 Cases		Flu B/V 1 Case		Flu B/Y 9 Cases	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
≤ 1 day	2	25.0	19	48.7			4	25.0	0	0	6	66.7
2 days	4	50.0	15	38.5			3	18.8	1	100	2	22.2
3 days	2	25.0	4	10.3			4	25.0	0	0	1	11.1
4 days	0	0	1	2.6			2	12.5	0	0	0	0
≥ 5 days	0	0	0	0			3	18.8	0	0	0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

Table 39: ≥65 years old patients, 3 seasons: Distribution (nb and %) of Cases and Controls by delay between onset of symptoms and swabbing and by country

Delay	France				Turkey				Spain			
	Flu B 24 Cases		Flu A 24 Controls		Flu B 13 Cases		Flu A 7 Controls		Flu B 4 Cases		Flu A 2 Controls	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
≤ 1 day	10	41.7	12	50.0	5	38.5	2	28.6	1	25.0	0	0
2 days	7	29.2	8	33.3	1	7.7	3	42.9	1	25.0	1	50.0
3 days	7	29.2	2	8.3	4	30.8	2	28.6	1	25.0	0	0
4 days	0	0	2	8.3	0	0	0	0	0	0	1	50.0
≥ 5 days	0	0	0	0	3	23.1	0	0	1	25.0	0	0

Table 40: ≥65 years old patients, 3 seasons: Distribution (nb and %) of Influenza B characterized Cases by delay between onset of symptoms and swabbing and by country

Delay	France				Turkey				Spain			
	Flu B/V 10 Cases		Flu B/Y 14 Cases		Flu B/V 3 Cases		Flu B/Y 3 Cases		Flu B/V 2 Cases		Flu B/Y 2 Cases	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
≤ 1 day	4	40.0	6	42.9	1	33.3	1	33.3	0	0	1	50.0
2 days	3	30.0	4	28.6	1	33.3	0	0	1	50.0	0	0
3 days	3	30.0	4	28.6	1	33.3	2	66.7	0	0	1	50.0
4 days	0	0	0	0	0	0	0	0	0	0	0	0
≥ 5 days	0	0	0	0	0	0	0	0	1	50.0	0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

Table 41: All patients, 3 seasons: Distribution (nb and %) of Cases and Controls by delay between onset of symptoms and swabbing and by country

Delay	France				Turkey				Spain			
	Flu B 482 Cases		Flu A 432 Controls		Flu B 216 Cases		Flu A 157 Controls		Flu B 44 Cases		Flu A 13 Controls	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
≤ 1 day	259	53.7	289	66.9	72	33.3	86	54.8	28	63.6	7	53.8
2 days	147	30.5	96	22.2	55	25.5	37	23.6	9	20.5	5	38.5
3 days	56	11.6	30	6.9	42	19.4	20	12.7	5	11.4	0	0.0
4 days	14	2.9	10	2.3	15	6.9	7	4.5	1	2.3	1	7.7
≥ 5 days	6	1.2	7	1.6	32	14.8	7	4.5	1	2.3	0	0.0

Table 42: All patients, 3 seasons: Distribution (nb and %) of Influenza B characterized Cases by delay between onset of symptoms and swabbing and by country

Delay	France				Turkey				Spain			
	Flu B/V 181 Cases		Flu B/Y 282 Cases		Flu B/V 51 Cases		Flu B/Y 58 Cases		Flu B/V 12 Cases		Flu B/Y 29 Cases	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
≤ 1 day	97	53.6	149	52.8	21	41.2	14	24.1	7	58.3	18	62.1
2 days	50	27.6	92	32.6	15	29.4	15	25.9	2	16.7	7	24.1
3 days	26	14.4	30	10.6	8	15.7	13	22.4	2	16.7	3	10.3
4 days	6	3.3	7	2.5	5	9.8	3	5.2	0	0	1	3.4
≥ 5 days	2	1.1	4	1.4	2	3.9	13	22.4	1	8.3	0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

7.5.2 Clinical symptoms at D0

Clinical symptoms are presented below, for the nine selected symptoms (see Table 6) by age group (6 age groups) and by country.

Comparison of clinical symptoms between Influenza B Cases and Influenza A Controls is performed by Chi-square or Chi-square exact tests and given in the table :
- p value if significant,
- ns if non significant,
- empty if not applicable.

Comparison of clinical symptoms between Yamagata and Victoria Influenza B Cases is performed by Chi-square or Chi-square exact tests. Symptoms are highlighted in bold when significant p value; if significant, p value is given below the table.

Table 43: 0-4 years old patients, 3 seasons: Frequency (nb and %) of symptoms in Cases and Controls by country

clinical symptoms	France					Turkey					Spain				
	Flu B		Flu A		p	Flu B		Flu A		p	Flu B		Flu A		p
	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
Fever	111	100	111	100		16	84.2	7	87.5	ns	3	100	1	100	
Sudden onset	93	83.8	98	88.3	ns						2	66.7	1	100	ns
Asthenia	79	71.2	76	68.5	ns						1	33.3	1	100	ns
Myalgia	28	25.2	28	25.2	ns	7	36.8	4	57.1	ns	3	100	1	100	
Headache	29	26.1	26	23.4	ns	9	47.4	3	37.5	ns	1	33.3	1	100	ns
Dyspnea	2	1.8	2	1.8	ns	3	15.8	1	12.5	ns	0	0	0	0	
Cough	86	77.5	88	79.3	ns	18	94.7	7	87.5	ns	3	100	1	100	
Coryza	78	70.3	80	72.1	ns	16	84.2	8	100	ns	3	100	1	100	
Sore throat	45	40.5	66	59.5	<0.01	4	21.1	3	37.5	ns					

Table 44: 0-4 years old patients, 3 seasons: Frequency (nb and %) of symptoms in Influenza B characterized Cases by country

clinical symptoms	France				Turkey				Spain			
	Flu B/V		Flu B/Y		Flu B/V		Flu B/Y		Flu B/V		Flu B/Y	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
Fever	48	100	59	100	7	87.5	3	100			3	100
Sudden Onset	43	89.6	48	81.4							2	66.7
Asthenia	34	70.8	42	71.2							1	33.3
Myalgia	15	31.3	13	22.0	2	25.0	1	33.3			3	100
Headache	17	35.4	12	20.3	3	37.5	1	33.3			1	33.3
Dyspnea	0	0	1	1.7	1	12.5	1	33.3			0	0
Cough	38	79.2	44	74.6	7	87.5	3	100			3	100
Coryza	33	68.8	42	71.2	5	62.5	3	100			3	100
Sore throat	**12**	**25.0**	**33**	**55.9***	3	37.5	0	0				

Flu B/V = Influenza B Case, Victoria lineage Flu B/Y = Influenza B Case, Yamagata lineage

**p<0.001*

Table 45: 5-14 years old patients, 3 seasons: Frequency (nb and %) of symptoms in Cases and Controls by country

clinical symptoms	France					Turkey					Spain				
	Flu B		Flu A		p	Flu B		Flu A		p	Flu B		Flu A		p
	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
Fever	204	99.5	152	100	ns	36	94.7	35	97.2	ns	14	100	3	100	
Sudden Onset	180	88.2	133	87.5	ns						11	78.6	3	100	ns
Asthenia	185	90.7	137	90.1	ns						12	85.7	2	66.7	ns
Myalgia	121	59.3	81	53.3	ns	27	67.5	20	55.6	ns	11	78.6	3	100	ns
Headache	151	74.0	114	75.0	ns	25	62.5	24	66.7	ns	10	71.4	2	66.7	ns
Dyspnea	6	3.0	6	3.9	ns	2	5.1	1	2.8	ns	0	0	0	0	
Cough	178	86.8	131	86.2	ns	39	97.5	31	86.1	ns	13	92.9	2	66.7	ns
Coryza	146	71.2	109	71.7	ns	33	82.5	32	88.9	ns	12	100	2	100	
Sore throat	106	52.0	76	50.0	ns	22	55.0	19	52.8	ns					

Table 46: 5-14 years old patients, 3 seasons: Frequency (nb and %) of symptoms in Influenza B characterized Cases by country

clinical symptoms	France				Turkey				Spain			
	Flu B/V		Flu B/Y		Flu B/V		Flu B/Y		Flu B/V		Flu B/Y	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
Fever	82	100	114	99.1	15	88.2	6	100	6	100	8	100
Sudden Onset	70	86.4	102	88.7					6	100	5	62.5
Asthenia	71	87.7	106	92.2					4	66.7	8	100
Myalgia	52	64.2	64	55.7	8	47.1	5	83.3	4	66.7	7	87.5
Headache	61	75.3	85	73.9	9	52.9	4	66.7	4	66.7	6	75.0
Dyspnea	4	5.1	2	1.7	1	5.9	1	16.7	0	0	0	0
Cough	**76**	**92.7**	**94**	**81.7***	16	94.1	6	100	6	100	7	87.5
Coryza	61	74.4	80	69.6	14	82.4	5	83.3	4	100	8	100
Sore throat	45	55.6	58	50.4	10	58.8	1	16.7				

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

**p<0.05*

Table 47: 15-24 years old patients, 3 seasons: Frequency (nb and %) of symptoms in Cases and Controls by country

clinical symptoms	France					Turkey					Spain				
	Flu B		Flu A		p	Flu B		Flu A		p	Flu B		Flu A		p
	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
Fever	23	100	25	96.2	ns	24	96.0	10	83.3	ns	2	100	1	100	
Sudden onset	21	91.3	23	88.5	ns						2	100	1	100	
Asthenia	23	100	24	92.3	ns						2	100	1	100	
Myalgia	17	73.9	21	80.8	ns	18	69.2	9	69.2	ns	2	100	1	100	
Headache	18	78.3	22	84.6	ns	19	73.1	10	76.9	ns	2	100	1	100	
Dyspnea	1	4.3	1	3.8	ns	1	3.8	1	7.7	ns	0	0	0	0	
Cough	22	95.7	24	92.3	ns	26	100	11	84.6	<0.05	2	100	1	100	
Coryza	18	78.3	17	65.4	ns	26	100	12	92.3	ns	2	100	1	100	
Sore throat	18	78.3	18	69.2	ns	10	40.0	3	23.1	ns	1	100			

Table 48: 15-24 years old patients, 3 seasons: Frequency (nb and %) of symptoms in Influenza B characterized Cases by country

clinical symptoms	France				Turkey				Spain			
	Flu B/V		Flu B/Y		Flu B/V		Flu B/Y		Flu B/V		Flu B/Y	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
Fever	12	100	9	100	10	100	6	100			1	100
Sudden Onset	11	91.7	9	100							1	100
Asthenia	12	100	9	100							1	100
Myalgia	8	66.7	8	88.9	6	60.0	5	83.3			1	100
Headache	9	75.0	8	88.9	8	80.0	5	83.3			1	100
Dyspnea	0	0	1	11.1	0	0	0	0			0	0
Cough	12	100	8	88.9	10	100	6	100			1	100
Coryza	9	75.0	8	88.9	10	100	6	100			1	100
Sore throat	**7**	**58.3**	**9**	**100***	7	70.0	1	16.7				

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

**p<0.05*

Table 49: 25-44 years old patients, 3 seasons: Frequency (nb and %) of symptoms in Cases and Controls by country

clinical symptoms	France					Turkey					Spain				
	Flu B		Flu A		p	Flu B		Flu A		p	Flu B		Flu A		p
	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
Fever	73	98.6	72	96.0	ns	76	90.5	52	81.3	ns	9	100	2	100	
Sudden Onset	64	86.5	63	84.0	ns						8	88.9	2	100	ns
Asthenia	70	94.6	73	97.3	ns						9	100	2	100	
Myalgia	67	90.5	69	92.0	ns	81	89.0	60	87.0	ns	9	100	2	100	
Headache	63	85.1	60	80.0	ns	77	84.6	58	84.1	ns	7	77.8	2	100	ns
Dyspnea	8	10.8	7	9.3	ns	8	9.0	5	7.2	ns	1	11.1	0	0	ns
Cough	68	91.9	71	94.7	ns	83	91.2	64	92.8	ns	9	100	2	100	
Coryza	57	77.0	56	74.7	ns	73	80.2	59	85.5	ns	8	100	2	100	
Sore throat	43	58.1	41	54.7	ns	33	36.3	33	47.8	ns	0	0	1	100	ns

Table 50: 25-44 years old patients, 3 seasons: Frequency (nb and %) of symptoms in Influenza B characterized Cases by country

clinical symptoms	France				Turkey				Spain			
	Flu B/V		Flu B/Y		Flu B/V		Flu B/Y		Flu B/V		Flu B/Y	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
Fever	24	100	45	97.8	12	92.3	20	95.2	3	100	6	100
Sudden Onset	20	83.3	40	87.0					3	100	5	83.3
Asthenia	24	100	42	91.3					3	100	6	100
Myalgia	**19**	**79.2**	**44**	**95.7***	10	76.9	20	83.3	3	100	6	100
Headache	21	87.5	39	84.8	11	84.6	22	91.7	2	66.7	5	83.3
Dyspnea	4	16.7	4	8.7	0	0	2	8.3	0	0	1	16.7
Cough	22	91.7	42	91.3	11	84.6	23	95.8	3	100	6	100
Coryza	18	75.0	36	78.3	9	69.2	20	83.3	3	100	5	100
Sore throat	17	70.8	23	50.0	**8**	**61.5**	**5**	**20.8***			0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

**p<0.05*

Table 51: 45-64 years old patients, 3 seasons: Frequency (nb and %) of symptoms in Cases and Controls by country

clinical symptoms	France					Turkey					Spain				
	Flu B		Flu A		p	Flu B		Flu A		p	Flu B		Flu A		p
	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
Fever	48	100	44	97.8	ns	14	73.7	20	83.3	ns	10	100	4	100	
Sudden Onset	42	87.5	41	91.1	ns						9	90.0	3	75.0	ns
Asthenia	47	97.9	43	95.6	ns						10	100	3	75.0	ns
Myalgia	46	95.8	44	97.8	ns	25	92.6	24	96.0	ns	8	80.0	4	100.0	ns
Headache	39	81.3	33	73.3	ns	23	85.2	24	96.0	ns	8	80.0	3	75.0	ns
Dyspnea	4	8.3	4	8.9	ns	6	22.2	2	8.0	ns	2	20.0	0	0	ns
Cough	43	89.6	43	95.6	ns	27	100	24	96.0	ns	9	90.0	3	75.0	ns
Coryza	32	66.7	30	66.7	ns	20	74.1	20	80.0	ns	8	88.9	2	100	ns
Sore throat	32	66.7	26	57.8	ns	4	14.8	14	56.0	<0.01	1	100			

Table 52: 45-64 years old patients, 3 seasons: Frequency (nb and %) of symptoms in Influenza B characterized Cases by country

clinical symptoms	France				Turkey				Spain			
	Flu B/V		Flu B/Y		Flu B/V		Flu B/Y		Flu B/V		Flu B/Y	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
Fever	8	100	38	100			9	81.8	1	100	9	100
Sudden Onset	5	62.5	35	92.1					1	100	8	88.9
Asthenia	8	100	37	97.4					1	100	9	100
Myalgia	8	100	36	94.7			15	93.8	1	100	7	77.8
Headache	7	87.5	30	78.9			15	93.8	0	0	8	88.9
Dyspnea	0	0	3	7.9			4	25.0	1	100	1	11.1
Cough	8	100	33	86.8			16	100	1	100	8	88.9
Coryza	6	75.0	25	65.8			11	68.8	0	0	8	100
Sore throat	6	75.0	24	63.2			3	18.8	1	100		

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

Table 53: ≥65 years old patients, 3 seasons: Frequency (nb and %) of symptoms in Cases and Controls by country

clinical symptoms	France					Turkey					Spain				
	Flu B		Flu A		p	Flu B		Flu A		p	Flu B		Flu A		p
	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
Fever	21	87.5	22	91.7	ns	8	66.7	7	100	ns	3	75.0	2	100	ns
Sudden Onset	18	75.0	21	87.5	ns						4	100	2	100	
Asthenia	22	91.7	22	91.7	ns						4	100	2	100	
Myalgia	15	62.5	21	87.5	ns	10	76.9	7	100	ns	4	100	2	100	
Headache	11	45.8	15	62.5	ns	7	53.8	6	85.7	ns	3	75.0	1	50.0	ns
Dyspnea	5	20.8	4	16.7	ns	5	38.5	0	0	ns	0	0	1	50.0	ns
Cough	23	95.8	21	87.5	ns	13	100	6	85.7	ns	4	100	2	100	
Coryza	15	62.5	18	75.0	ns	7	53.8	7	100	ns	2	50.0	2	100	ns
Sore throat	9	37.5	13	54.2	ns	6	46.2	4	57.1	ns	0	0			

Table 54: ≥65 years old patients, 3 seasons: Frequency (nb and %) of symptoms in Influenza B characterized Cases by country

clinical symptoms	France				Turkey				Spain			
	Flu B/V		Flu B/Y		Flu B/V		Flu B/Y		Flu B/V		Flu B/Y	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
Fever	10	100	11	78.6	2	66.7	2	66.7	1	50.0	2	100
Sudden Onset	8	80.0	10	71.4					2	100	2	100
Asthenia	9	90.0	13	92.9					2	100	2	100
Myalgia	7	70.0	8	57.1	3	100	2	66.7	2	100	2	100
Headache	6	60.0	5	35.7	3	100	1	33.3	2	100	1	50.0
Dyspnea	2	20.0	3	21.4	3	100	0	0	0	0	0	0
Cough	10	100	13	92.9	3	100	3	100	2	100	2	100
Coryza	7	70.0	8	57.1	2	66.7	1	33.3	0	0	2	100
Sore throat	6	60.0	3	21.4	2	66.7	1	33.3	0	0		

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

Table 55: All patients, 3 seasons: Frequency (nb and %) of symptoms in Cases and Controls by country

clinical symptoms	France					Turkey					Spain				
	Flu B		Flu A		p	Flu B		Flu A		p	Flu B		Flu A		p
	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
Fever	480	99.0	426	98.4	ns	174	88.3	131	86.8	ns	41	97.6	13	100	ns
Sudden onset	418	86.4	379	87.5	ns						36	85.7	12	92.3	ns
Asthenia	426	88.0	375	86.6	ns						38	90.5	11	84.6	ns
Myalgia	294	60.7	264	61.0	ns	168	77.8	124	79.0	ns	37	88.1	13	100	ns
Headache	311	64.3	270	62.4	ns	160	74.1	125	79.1	ns	31	73.8	10	76.9	ns
Dyspnea	26	5.4	24	5.5	ns	25	11.7	10	6.3	ns	3	7.1	1	7.7	ns
Cough	420	86.6	378	87.3	ns	206	95.4	143	90.5	ns	40	95.2	11	84.6	ns
Coryza	346	71.3	310	71.6	ns	175	81.0	138	87.3	ns	35	92.1	10	100	ns
Sore throat	253	52.3	240	55.4	ns	79	36.7	76	48.1	<0.05	2	40.0	1	100	ns

Table 56: All patients, 3 seasons: Frequency (nb and %) of symptoms in Influenza B characterized Cases by country

clinical symptoms	France				Turkey				Spain			
	Flu B/V		Flu B/Y		Flu B/V		Flu B/Y		Flu B/V		Flu B/Y	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
Fever	184	100	276	98.2	46	90.2	46	92.0	11	91.7	29	100
Sudden Onset	157	85.8	244	86.8					12	100	23	79.3
Asthenia	158	86.3	249	88.6					10	83.3	27	93.1
Myalgia	109	59.6	173	61.6	**29**	**56.9**	**48**	**82.8[2]**	10	83.3	26	89.7
Headache	121	66.1	179	63.7	34	66.7	48	82.8	8	66.7	22	75.9
Dyspnea	10	5.5	14	5.0	5	9.8	8	13.8	1	8.3	2	6.9
Cough	**166**	**90.2**	**234**	**83.3[1]**	47	92.2	57	98.3	12	100	27	93.1
Coryza	134	72.8	199	70.8	40	78.4	46	79.3	**7**	**70.0**	**27**	**100[1]**
Sore throat	93	50.8	150	53.4	**30**	**58.8**	**11**	**19.0[3]**	1	33.3	0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

[1]p<0.05 [2]p<0.01 [3]p<0.001

7.6 Healthcare consumption at D0

Healthcare consumption at D0 is based on D0 form data. No item concerning medication and hospitalization were present in the 2010-2011 Turkish D0 form.

7.6.1 Request for Hospitalization

Table 57: 3 seasons: Number and percentage of hospitalization requested by the practitioner, by age group, flu type and country

Hospitalization	France				Turkey				Spain			
	Flu B 483 Cases		Flu A 427 Controls		Flu B 64 Cases		Flu A 104 Controls		Flu B 41 Cases		Flu A 11 Controls	
Age group	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
0-4 yo	0	0	0	0	2	18.2	0	0	0	0	0	0
5-14 yo	1	0.5	1	0.7	1	5.0	0	0	0	0	0	0
15-24 yo	0	0	0	0	1	7.7	0	0	0	0		
25-44 yo	0	0	0	0	2	11.8	2	5.1	0	0	0	0
45-64 yo	0	0	0	0			0	0	0	0	0	0
≥65 yo	2	8.3	0	0	3	100	0	0	0	0	0	0
All age	3	0.6	1	0.2	9	14.1	2	1.9	0	0	0	0

Fifteen hospitalization requests are reported in IBGP follow-up data base (hospitalization request rate of 1,3%).
A total of 12 influenza B with request of hospitalization are registered (hospitalization request rate of 2,0%):

- 3 in France, during 2012-2013 season, concerning:
  - a 5 years old child, non vaccinated against influenza,
  - 2 adults aged over 65 year (76 and 87 yo), both vaccinated against influenza,

  all presenting an influenza B/Yamagata (vaccine strain),
- 9 in Turkey during 2011-2012 season, concerning:
  - 3 children (0, 4 and 6 yo), non vaccinated against influenza,
  - 3 adults (22, 27 and 33 yo), one of them vaccinated against influenza,
  - 3 adults aged over 65 years (67, 90 and 99 yo),one of them vaccinated against influenza,

  all presenting an influenza B/Victoria (vaccine strain).

Only three influenza A with request of hospitalization are registered (hospitalization request rate of 0,6%):

- 1 in France, during 2011-2012 season, concerning a 6 years old child, non vaccinated against influenza, all presenting an influenza A(H3N2).
- -2 in Turkey concerning:
  - 1 adult (35 yo), during 2011-2012 season, presenting an influenza A(H3N2) and non vaccinated against influenza,
  - 1 adult (38 yo), during 2012-2013 season, presenting an influenza A(H3N2) and non vaccinated against influenza.

7.6.2 Antibiotics prescription

Table 58: 3 seasons: Number and percentage of antibiotics treatments prescribed by the practitioners by age group, flu type and country

Antibiotics	France					Turkey					Spain				
	Flu B 485 Cases		Flu A 433 Controls		p	Flu B 215 Cases		Flu A 158 Controls		p	Flu B 35 Cases		Flu A 13 Controls		p
Age group	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
0-4 yo	12	10.8	10	9.0	ns	10	52.6	4	50.0	ns	1	33.3	0	0	ns
5-14 yo	11	5.4	10	6.6	ns	20	50.0	11	30.6	ns	0	0	0	0	
15-24 yo	0	0	2	7.7	ns	9	36.0	3	23.1	ns	1	50.0	1	100	ns
25-44 yo	9	12.2	11	14.7	ns	42	46.2	17	24.6	<0.01	4	57.1	0	0	ns
45-64 yo	4	8.2	5	11.1	ns	15	55.6	9	36.0	ns	7	70.0	2	50.0	ns
≥65 yo	9	37.5	7	29.2	ns	10	76.9	4	57.1	ns	1	33.3	0	0	ns
All age	45	9.3	45	10.4	ns	106	49.3	48	30.4	<0.001	14	40.0	3	23.1	ns

Table 59: 3 seasons: Number and percentage of antibiotics treatments prescribed by the practitioners by age group, flu B lineage and country

Antibiotics	France				Turkey				Spain			
	Flu B/V 183 Cases		Flu B/Y 282 Cases		Flu B/V 51 Cases		Flu B/Y 58 Cases		Flu B/V 10 Cases		Flu B/Y 24 Cases	
Age group	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
0-4 yo	7	14.6	5	8.5	4	50.0	2	66.7			1	33.3
5-14 yo	7	8.6	4	3.5	6	35.3	3	50.0	0	0	0	0
15-24 yo	0	0	0	0	3	30.0	2	33.3			1	100
25-44 yo	5	20.8	4	8.7	4	30.8	15	62.5	2	66.7	2	50.0
45-64 yo	1	12.5	2	5.1			8	50.0	1	100	6	66.7
≥65 yo	2	20.0	7	50.0	3	100	3	100	0	0	1	100
All age	22	12.0	22	7.8	20	39.2	33	56.9	3	30.0	11	45.8

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

7.6.3 Antivirals prescription

Table 60: 3 seasons: Number and percentage of antiviral treatments prescribed by the practitioners by age group, flu type and country

Antivirals	France					Turkey					Spain				
	Flu B 484 Cases		Flu A 429 Controls		p	Flu B 63 Cases		Flu A 104 Controls		p	Flu B 38 Cases		Flu A 13 Controls		p
Age group	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
0-4 yo	12	10.8	5	4.6	ns	1	9.1	0	0	ns	0	0	0	0	
5-14 yo	14	6.9	13	8.6	ns	3	15.0	0	0	ns	0	0	0	0	
15-24 yo	3	13.0	9	34.6	ns	0	0	0	0		0	0	0	0	
25-44 yo	14	18.9	15	20.0	ns	5	29.4	5	12.8	ns	0	0	0	0	
45-64 yo	11	22.4	7	15.6	ns			2	10.0		0	0	0	0	
≥65 yo	3	12.5	4	17.4	ns	2	66.7	0	0	ns	0	0	0	0	
All age	57	11.8	53	12.4	ns	11	17.5	7	6.7	<0.05	0	0	0	0	

Table 61: 3 seasons: Number and percentage of antiviral treatments prescribed by the practitioners by age group, flu B lineage and country

Antivirals	France				Turkey				Spain			
	Flu B/V 182 Cases		Flu B/Y 282 Cases		Flu B/V 51 Cases		Flu B/Y 0 Case		Flu B/V 11 Cases		Flu B/Y 26 Cases	
Age group	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
0-4 yo	8	14.7	4	6.8	1	12.5					0	0
5-14 yo	7	8.8	5	4.3	2	11.8			0	0	0	0
15-24 yo	3	25.0	0	0	0	0					0	0
25-44 yo	**9**	**37.5**	**5**	**10.9[1]**	4	30.8			0	0	0	0
45-64 yo	4	50.0	6	15.4					0	0	0	0
≥65 yo	2	20.0	1	7.1	2	66.7			0	0	0	0
All age	**33**	**18.1**	**21**	**7.4[2]**	9	17.6			0	0	0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

[1]p<0.05 [2]p<0.001

7.7 Delay between swabbing day (D0) and D9 or D28

D9 contact: among the 1350 patients, 30 (2,2%) were followed after D11, mainly in Spain.

D28 contact: among the 274 patients monitored at D28, only 1 was contacted before D23 (D22, in France) and 20 (7,3%) were followed after D33.

Figure 10: Delay between D0 and D9 or D28. 3 seasons, by influenza type, in FRANCE

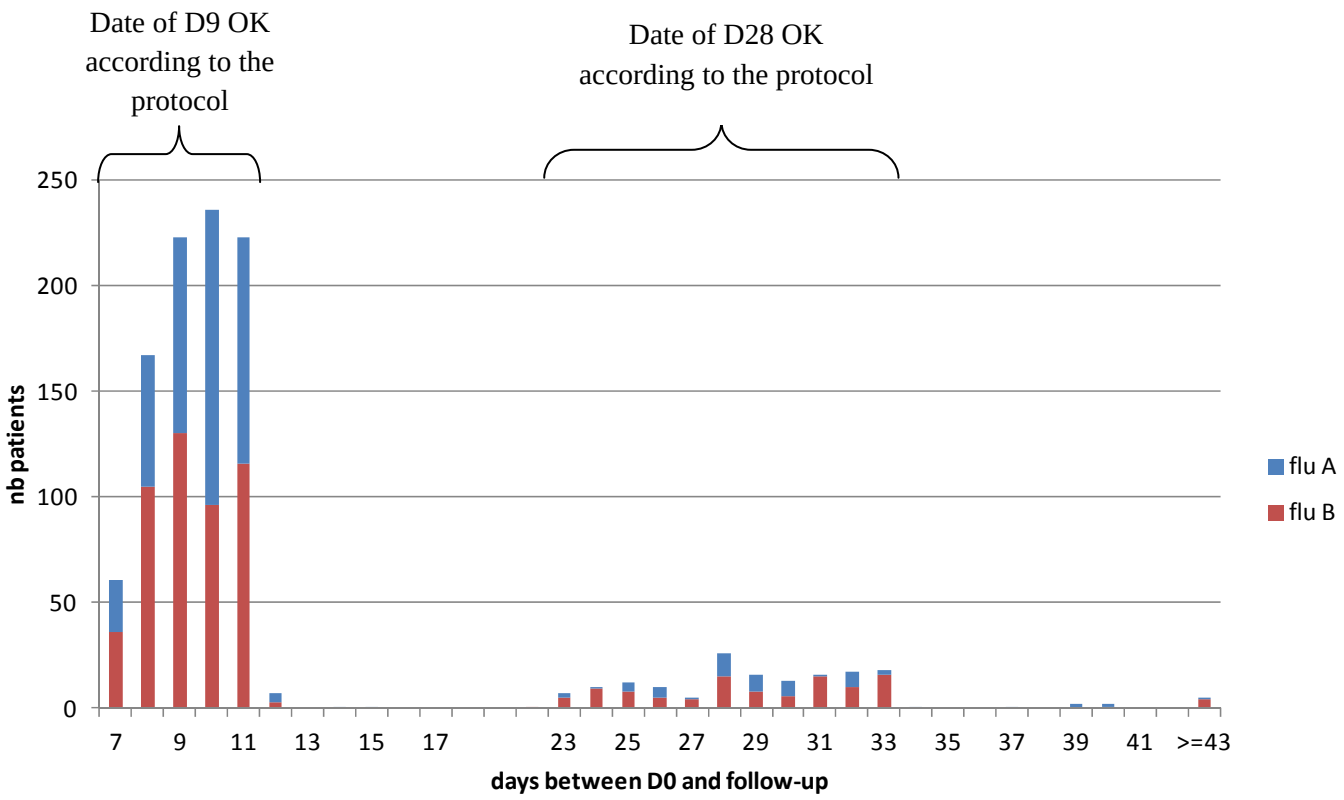


Figure 11: Delay between D0 and D9 or D28. 3 seasons, by influenza type, in TURKEY

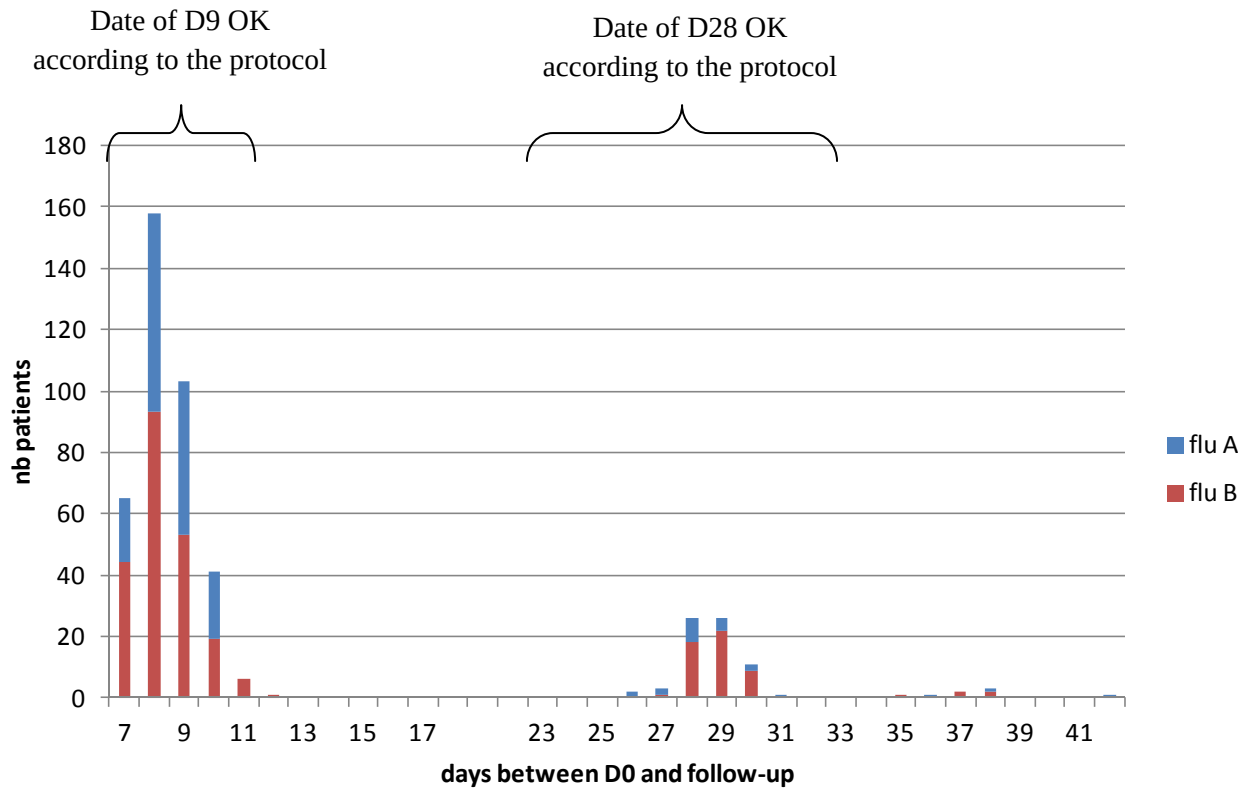
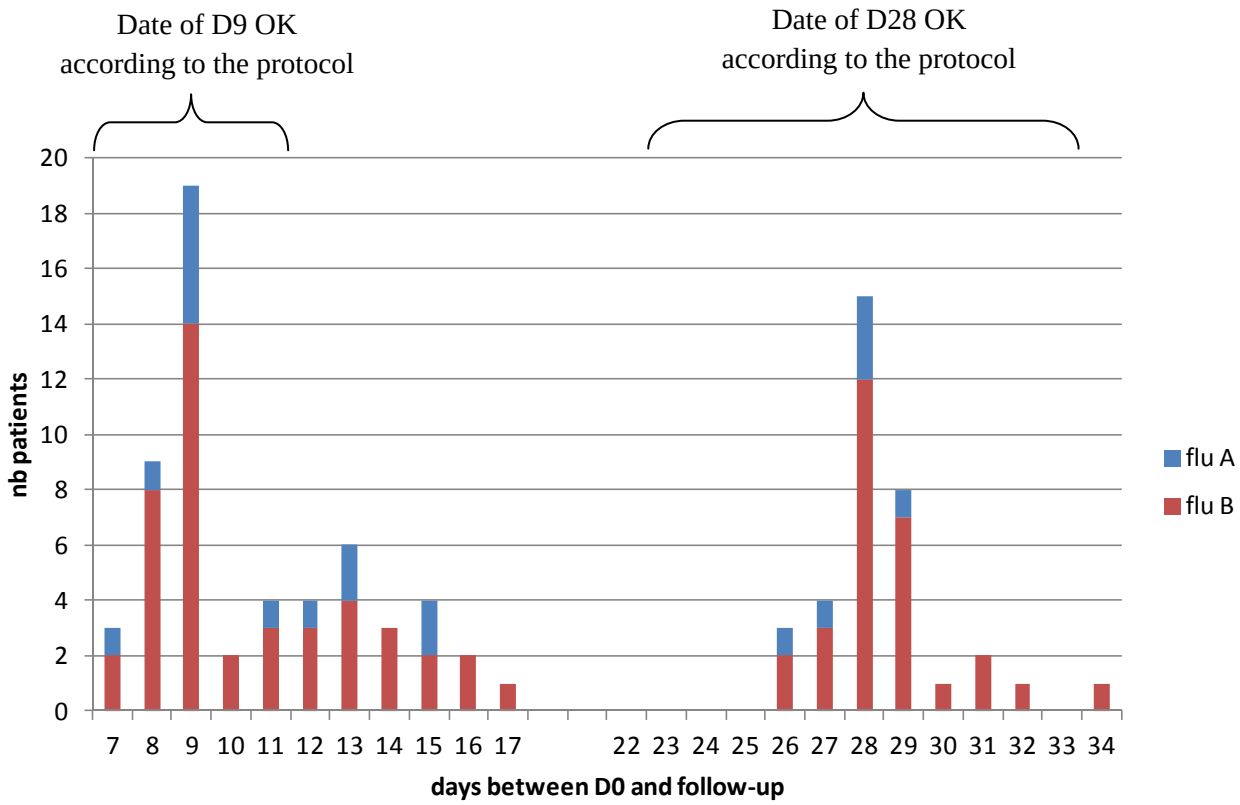


Figure 12: Delay between D0 and D9 or D28. 3 seasons, by influenza type, in SPAIN



7.8 Clinical situation at D9 and D28 and duration of illness

7.8.1 Patient recovered at D9

Recovery at D9 or D28 is defined as the fact that patient has returned to his normal activities.

Major part (1131/1350 - 83.8%) of the patients had recovered at D9.

In France and in Turkey, recovery at D9 was significantly more frequent for influenza A Controls than for influenza B Cases.

Table 62: 3 seasons: Number and percentage of patient recovered at D9 by age group, flu type and country

patient recovered at D9	France					Turkey					Spain				
	Flu B 486 Cases		Flu A 433 Controls		p	Flu B 216 Cases		Flu A 158 Controls		p	Flu B 44 Cases		Flu A 13 Controls		p
Age group	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
0-4 yo	99	89.2	105	94.6	ns	18	94.7	8	100	ns	3	75.0	1	100	ns
5-14 yo	165	80.5	144	94.7	<0.001	35	87.5	36	100	ns	14	100	3	100	ns
15-24 yo	14	60.9	25	96.2	<0.01	22	84.6	10	76.9	ns	2	100	0	0	ns
25-44 yo	58	78.4	66	88.0	ns	64	70.3	58	84.1	ns	9	100	1	50.0	ns
45-64 yo	38	77.6	34	75.6	ns	16	59.3	23	92.0	<0.01	7	63.6	4	100	ns
≥65 yo	15	62.5	15	62.5	ns	9	69.2	5	71.4	ns	3	75.0	2	100	ns
All age	389	80.0	389	89.8	<0.001	164	75.9	140	88.6	<0.01	38	86.4	11	84.6	ns

Table 63: 3 seasons: Number and percentage of patient recovered at D9 by age group, flu B lineage and country

patient recovered at D9	France				Turkey				Spain			
	Flu B/V 184 Cases		Flu B/Y 282 Cases		Flu B/V 51 Cases		Flu B/Y 58 Cases		Flu B/V 12 Cases		Flu B/Y 29 Cases	
Age group	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
0-4 yo	**37**	**77.1**	**59**	**100[1]**	8	100	3	100			3	100
5-14 yo	**52**	**63.4**	**107**	**93.0[1]**	16	94.1	6	100	6	100	8	100
15-24 yo	5	41.7	8	88.9	10	100	4	66.7			1	100
25-44 yo	17	70.8	38	82.6	**12**	**92.3**	**10**	**41.7[2]**	3	100	6	100
45-64 yo	4	50.0	32	82.1			9	56.3	0	0	7	77.8
≥65 yo	5	50.0	10	71.4	2	66.7	2	66.7	1	50.0	2	100
All age	**120**	**65.2**	**254**	**90.1[1]**	**48**	**94.1**	**34**	**58.6[1]**	10	83.3	27	93.1

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

[1]p<0.001 *[2]p<0.01*

7.8.2 Patient recovered at D28

If patient had recovered at D9, a CRF D28 could be applied if patients still presented "other symptoms".

A total of 274 patients had a D28 follow up; information about recovery is available for 272/274 patients.

At D28 follow-up, most of the patients (264/272, 97.1%) had recovered.

Table 64 give a description of the 8/272 (2,9%) patients who had still not recovered:
- 5 influenza B Cases (4 in France and 1 in Turkey),
- 3 influenza Controls in France.

Table 64: Description of patients not recovered at D28

Country	Flu	Age	Sex	vaccination	remaining symptoms
Turkey	B	100	F	No	
France	B	83	F	Yes	Bronchitis, asthma
France	B	12	M	-	cough
France	B	73	M	Yes	cough
France	B	61	F	No	headache, asthenia
France	A	64	F	No	cough
France	A	69	F	No	
France	A	40	M	Ni	cough

7.8.3 Duration of illness

Duration of illness was calculated as the number of days between the date of symptoms' onset and the date of return to normal activities. Median duration of illness was mainly 7 days.

No statistical difference was found between influenza B Cases and A Controls for the mean duration of illness.

Table 65: 3 seasons: Duration of illness (mean, median, SD and extreme) of patient by age group, flu type and country

Duration of illness / Age group	France			Turkey			Spain		
	Flu B 482 Cases	**Flu A 429 Controls**	**p**	**Flu B 212 Cases**	**Flu A 153 Controls**	**p**	**Flu B 41 Cases**	**Flu A 12 Controls**	**p**
0-4 yo									
av./median duration	7.45 / 7	7,47 / 7	ns	7.05 / 7	6.13 / 7	ns	8.33 / 9	35.00 (1 case)	ns
Sd	4.20	4,46		3.64	2.53		1.15		
min	2	1		3	2		7		
max	36	35		17	10		9		
5-14 yo									
av./median duration	7.74 / 7	7.37 / 9	ns	6.67 / 5	5.76 / 6	ns	7.00 / 7	6.33 / 7	ns
Sd	4.17	3.88		4.32	2.06		1.47	1.15	
min	2	2		3	3		4	5	
max	37	27		25	10		11	7	
15-24 yo									
av./median duration	9.04 / 8	7.08 / 7	ns	7.62 / 7	9.31 / 7	ns	7.00 (1case)	12.00 (1 case)	ns
Sd	5.01	2.58		4.51	6.41				
min	3	3		3	3				
max	26	14		21	21				
25-44 yo									
av./median duration	9.24 / 7.5	7.97 / 7.5	ns	8.72 / 7	7.97 / 7	ns	6.44 / 6	7.00 (1 case)	ns
Sd	5.55	4.53		5.68	4.24		1.74		
min	2	2		3	2		4		
max	30	31		25	22		9		
45-64 yo									
av./median duration	9.42 / 9	10.66 / 8.5	ns	9.07 / 7	7.21 / 7	ns	11.60 / 10	6.25 / 6.5	ns
Sd	4.76	7.50		5.93	3.22		5.60	0.96	
min	1	1		3	2		5	5	
max	30	39		25	15		21	7	
≥65 yo									
av./median duration	10.48 / 10	12.39 / 9	ns	8.18 / 6	10.86 / 7	ns	10.00 / 9	10.00 / 10	ns
Sd	5.72	8.74		3.68	9.39		5.29	1.41	
min	2	3		5	3		5	9	
max	25	30		15	30		17	11	
All age									
av./median duration	8.26 / 7	8.09 / 7	ns	8.08 / 6	7.52 / 7	ns	8.39 / 7	9.83 / 7	ns
Sd	4.65	5.09		5.13	4.37		3.87	8.21	
min	1	1		3	2		4	5	
max	37	39		25	30		21	35	

Table 66: 3 seasons: Duration of illness (mean, median, SD and extreme) of patient by age group, flu B lineage and country

Duration of illness / Age group	France		Turkey		Spain	
	Flu B/V 184 Cases	**Flu B/Y 278 Cases**	**Flu B/V 48 Cases**	**Flu B/Y 58 Cases**	**Flu B/V 12 Cases**	**Flu B/Y 29 Cases**
0-4 yo						
av./median duration	7.63 / 6.5	7.29 / 7	7.38 / 7	5.00 / 4		8.33 / 9
Sd	5.64	2.65	3.42	1.73		1.15
min	2	2	3	4		7
max	36	16	12	7		9
5-14 yo						
av./median duration	7.65 / 6	7.91 / 7	5.75 / 6	4.67 / 4.5	6.83 / 7	7.13 / 7
Sd	4.22	4.17	1.44	0.82	0.41	1.96
min	2	3	3	4	6	4
max	28	37	9	6	7	11
15-24 yo						
av. /median duration	9.25 / 10	8.67 / 6	7.40 / 6.5	8.83 / 5.5		7.00
Sd	4.05	6.76	2.84	7.49		(1 case)
min	3	4	4	3		
max	15	26	12	21		
25-44 yo						
av. /median duration	9.42 / 7	9.00 / 7	**6.75** / 7	**10.88**[1] / 10	6.33 / 6	6.50 / 6.5
Sd	5.84	5.63	1.91	5.89	2.52	1.52
min	4	2	3	3	4	5
max	29	30	9	20	9	9
45-64 yo						
av./median duration	11.25 / 9	9.16 / 9		9.81 / 7.5	12.00 / 12	11.56 / 9
Sd	7.76	4.04		6.63	(1 case)	5.96
min	6	1		3		5
max	30	24		25		21
≥65 yo						
av./median duration	11.00 / 9	10.08 / 10	9.50 / 9.5	8.67 / 6	12.00 / 12	8.00 / 8
Sd	7.38	4.33	0.71	5.51	7.07	4.24
min	2	4	9	5	7	5
max	25	19	10	15	17	11
All age						
av./median duration	8.32 / 7	8.25 / 8	**6.77** / 6.5	**9.31**[2] / 7	8.00 / 7	8.55 / 7
Sd	5.25	4.30	2.37	6.01	3.41	4.08
min	2	1	3	3	4	4
max	36	37	12	25	17	21

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

[1]p<0.05 [2]p<0.01

Figure 13: 3 seasons: Duration of illness of subjects with flu A by country

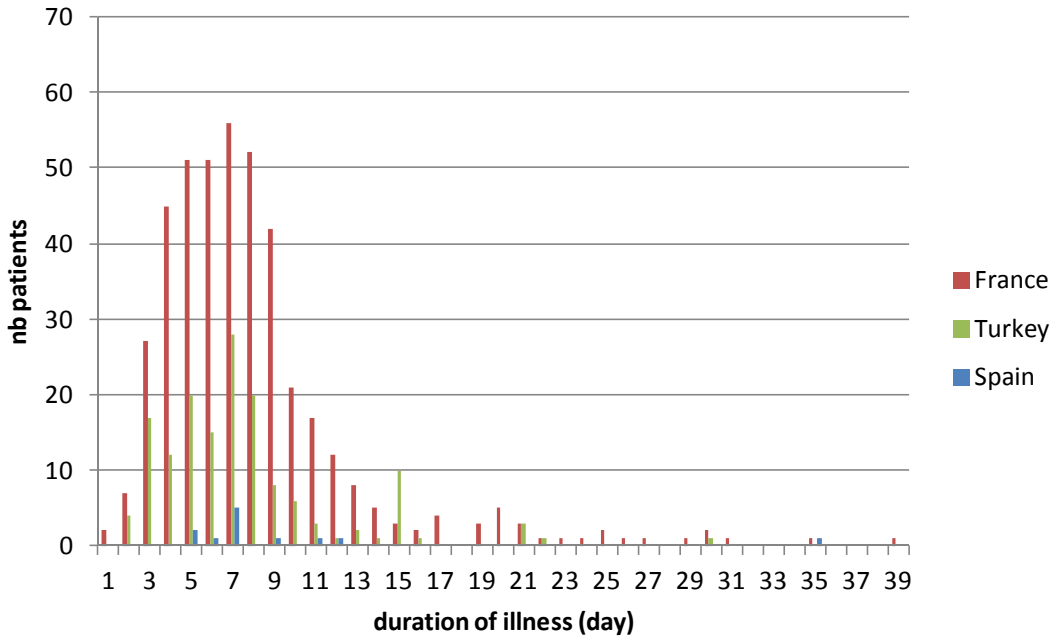
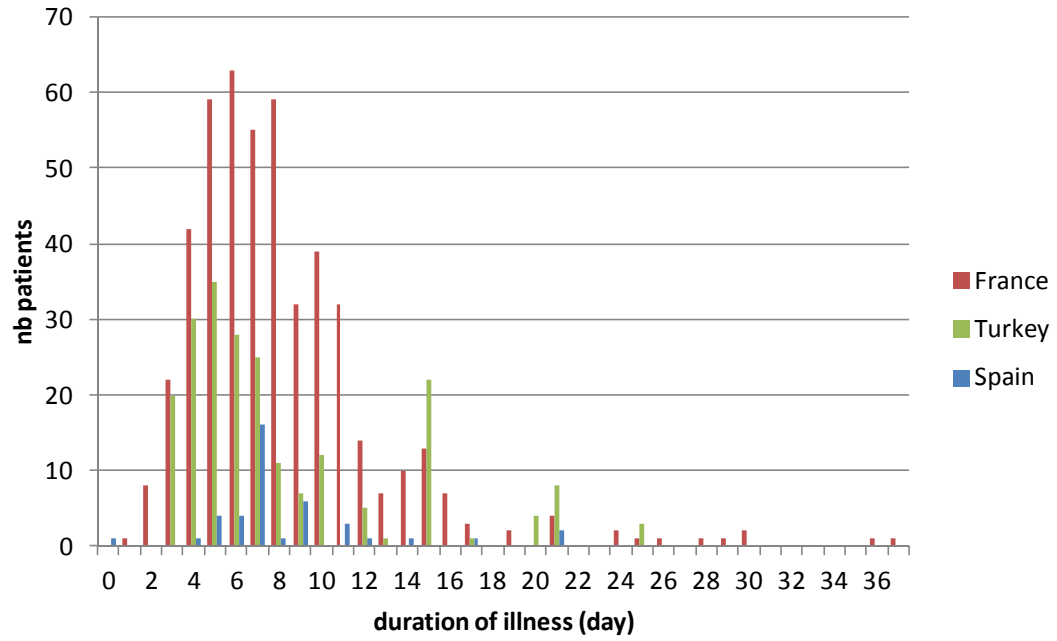


Figure 14: 3 seasons: Duration of illness of subjects with flu B by country



7.8.4 Remaining symptoms at D9

At D9, almost one patient in two (625/1350 - 46.3%) presented at least one remaining symptom, mainly cough and rhinitis, cough being more present in adults.

Table 67: 3 seasons: Number and percentage of remaining symptoms at D9 by age group, flu type and country

Remaining symptoms	France				Turkey				Spain			
	Flu B 484 Cases		Flu A 433 Controls		Flu B 216 Cases		Flu A 158 Controls		Flu B 44 Cases		Flu A 13 Controls	
Age group	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
0-4 yo												
At least one	36	32.7	56	50.5	2	10.5	1	12.5	3	75.0	0	0
cough	28	25.5	36	32.4	2	10.5	1	12.5	3	75.0	0	0
headache	0	0	0	0	0	0	0	0	0	0	0	0
rhinitis	17	15.5	36	32.4	1	5.3	1	12.5	2	50.0	0	0
asthenia	6	5.5	16	14.4	1	5.3	0	0	1	25.0	0	0
other	3	2.7	6	5.4	0	0	0	0	0	0	0	0
5-14 yo												
At least one	91	44.6	77	50.7	10	25.0	2	5.6	8	57.1	1	33.3
cough	64	31.4	65	42.8	10	25.0	2	5.6	5	35.7	0	0
headache	5	2.5	7	4.6	0	0	0	0	0	0	0	0
rhinitis	18	8.8	35	23.0	1	2.5	1	2.8	1	7.1	0	0
asthenia	40	19.6	32	21.1	0	0	0	0	2	14.3	1	33.3
other	17	8.3	4	2.6	0	0	0	0	0	0	0	0
15-24 yo												
At least one	17	73.9	19	73.1	6	23.1	2	15.4	0	0	1	100
cough	10	43.5	16	61.5	6	23.1	2	15.4	0	0	1	100
headache	0	0	3	11.5	0	0	0	0	0	0	0	0
rhinitis	4	17.4	8	30.8	0	0	0	0	0	0	0	0
asthenia	8	34.8	7	26.9	1	3.8	0	0	0	0	0	0
other	4	17.4	2	7.7	0	0	0	0	0	0	1	100
25-44 yo												
At least one	52	70.3	51	68	25	27.5	21	30.4	7	77.8	1	50.0
cough	41	55.4	38	50.7	23	25.3	15	21.7	4	44.4	0	0
headache	8	10.8	8	10.7	1	1.1	1	1.4	0	0	1	50.0
rhinitis	19	25.7	17	22.7	1	1.1	4	5.8	4	44.4	0	0
asthenia	33	44.6	21	28.0	9	9.9	2	2.9	0	0	0	0
other	9	12.2	6	8.0	1	1.1	5	7.2	1	11.1	0	0
45-64 yo												
At least one	36	73.5	34	75.6	8	29.6	5	20.0	10	90.9	2	50.0
cough	28	57.1	28	62.2	8	29.6	3	12.0	7	63.6	1	25.0
headache	1	2.0	8	17.8	0	0	2	8.0	1	9.1	0	0
rhinitis	5	10.2	11	24.4	0	0	1	4.0	7	63.6	0	0
asthenia	20	40.8	19	42.2	2	7.4	2	8.0	3	27.3	1	25.0
other	7	14.3	2	4.4	0	0	0	0	5	45.5	0	0
≥65 yo												
At least one	16	66.7	18	75	2	15.4	2	28.6	2	50.0	1	50.0

cough	11	45.8	15	62.5	2	15.4	1	14.3	2	50.0	1	50.0
headache	1	4.2	5	20.8	0	0	0	0	0	0	0	0
rhinitis	3	12.5	6	25.0	0	0	1	14.3	1	25.0	0	0
asthenia	7	29.2	14	58.3	0	0	2	28.6	2	50.0	1	50.0
other	4	16.7	3	12.5	0	0	0	0	0	0	0	0
All age												
At least one	248	51.2	255	58.9	53	24.5	33	20.9	30	68.2	6	46.2
cough	182	37.6	198	45.7	51	23.6	24	15.2	21	47.7	3	23.1
headache	15	3.1	31	7.2	1	0.5	3	1.9	1	2.3	1	7.7
rhinitis	66	13.6	113	26.1	3	1.4	8	5.1	15	34.1	0	0.0
asthenia	114	23.6	109	25.2	13	6.0	6	3.8	8	18.2	3	23.1
other	44	9.1	23	5.3	1	0.5	5	3.2	6	13.6	1	7.7

Table 68: 3 seasons: Number and percentage of remaining symptoms at D9 by age group, flu B lineage and country

Remaining symptoms	France				Turkey				Spain			
	Flu B/V 184 Cases		Flu B/Y 280 Cases		Flu B/V 51 Cases		Flu B/Y 58 Cases		Flu B/V 12 Cases		Flu B/Y 29 Cases	
Age group	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
0-4 yo												
At least one	12	25.0	22	37.9	0	0	0	0			2	66.7
cough	11	22.9	16	27.6	0	0	0	0			2	66.7
headache	0	0	0	0	0	0	0	0			0	0
rhinitis	5	10.4	12	20.7	0	0	0	0			1	33.3
asthenia	0	0	6	10.3	0	0	0	0			1	33.3
other	1	2.1	1	1.7	0	0	0	0			0	0
5-14 yo												
At least one	34	41.5	55	48.2	6	35.3	0	0	3	50.0	5	62.5
cough	27	32.9	35	30.7	6	35.3	0	0	1	16.7	4	50.0
headache	1	1.2	4	3.5	0	0	0	0	0	0	0	0
rhinitis	8	9.8	10	8.8	1	5.9	0	0	1	16.7	0	0
asthenia	13	15.9	27	23.7	0	0	0	0	1	16.7	1	12.5
other	7	8.5	9	7.9	0	0	0	0	0	0	0	0
15-24 yo												
At least one	8	66.7	7	77.8	1	10.0	2	33.3			0	0
cough	7	58.3	3	33.3	1	10.0	2	33.3			0	0
headache	0	0	0	0	0	0	0	0			0	0
rhinitis	1	8.3	3	33.3	0	0	0	0			0	0
asthenia	4	33.3	2	22.2	0	0	0	0			0	0
other	2	16.7	1	11.1	0	0	0	0			0	0
25-44 yo												
At least one	12	50.0	37	80.4	4	30.8	12	50.0	1	33.3	6	100.0
cough	9	37.5	29	63.0	4	30.8	12	50.0	1	33.3	3	50.0
headache	2	8.3	6	13.0	0	0	0	0	0	0	0	0
rhinitis	4	16.7	13	28.3	1	7.7	0	0	0	0	4	66.7
asthenia	7	29.2	24	52.2	0	0	3	12.5	0	0	0	0
other	4	16.7	5	10.9	0	0	0	0	0	0	1	16.7

45-64 yo												
At least one	5	62.5	30	76.9			5	31.3	1	100	8	88.9
cough	4	50.0	24	61.5			5	31.3	1	100	5	55.6
headache	0	0	1	2.6			0	0	0	0	1	11.1
rhinitis	0	0	5	12.8			0	0	0	0	6	66.7
asthenia	2	25.0	17	43.6			2	12.5	0	0	3	33.3
other	1	12.5	6	15.4			0	0	1	100	4	44.4
≥65 yo												
At least one	5	50.0	11	78.6	1	33.3	1	33.3	2	100	0	0
cough	4	40.0	7	50.0	1	33.3	1	33.3	2	100	0	0
headache	0	0	1	7.1	0	0	0	0	0	0	0	0
rhinitis	0	0	3	21.4	0	0	0	0	1	50.0	0	0
asthenia	0	0	7	50.0	0	0	0	0	2	100	0	0
other	3	30.0	1	7.1	0	0	0	0	0	0	0	0
All age												
At least one	76	41.3	162	57.9	12	23.5	20	34.5	7	58.3	21	72.4
cough	62	33.7	114	40.7	12	23.5	20	34.5	5	41.7	14	48.3
headache	3	1.6	12	4.3	0	0	0	0	0	0	1	3.4
rhinitis	18	9.8	46	16.4	2	3.9	0	0	2	16.7	11	37.9
asthenia	26	14.1	83	29.6	0	0	5	8.6	3	25.0	5	17.2
other	18	9.8	23	8.2	0	0	0	0	1	8.3	5	17.2

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

At D9, other remaining symptoms were declared in 80 patients:

- respiratory symptoms (asthma, dyspnoea, haemoptysis, bronchitis, bronchiolitis, expectoration or pneumonia...) for 19 patients,
- otitis and/or sinusitis for 15 patients,
- abdominal/digestive symptoms (pain, nausea, diarrhea...) for 12 patients,
- anorexia for 11 patients,
- throat symptoms (sore throat...) for 8 patients,
- chest/joint pain, myalgia for 7 patients,
- malaise, dizziness, pallor for 7 patients,
- fever for 6 patients,
- others (herpes, hearing loss, skin rash, teeth pain) for 4 patients.

7.8.5 Remaining symptoms at D28

At D28, 38 (13.9%) of 274 patients presented at least one remaining symptom:

- 31 (19.1%) in France: 15 B (4 B/Victoria, 11 B/Yamagata) and 16 A,
- 7 (20.0%) in Spain: 5 B (2 B/Victoria, 3 B/Yamagata) and 2 A.

These remaining symptoms were:

- asthenia for 19 patients,
- cough for 20 patients,
- rhinitis for 11 patients,
- headache for 3 patients,
- other symptoms such as joint pain, lack of appetite, otitis, broken voice, cold, dyspnea, sinusitis, …for 10 patients.

7.9 Medical care during follow-up

7.9.1 Medical contacts after D0 with patient's registered practitioner

Among the 1350 Cases/Controls included, information about further medical contact is available for 1349 patients, with 414 (30.7%) having requested a further medical contact (consultation, home visit or phone call) due to influenza symptoms, with their registered practitioner (practitioner performing the initial swab) during the follow-up:
- 303/919 (33.0%) in France,
- 91/373 (24.4%) in Turkey,
- 20/57 (35.1%) in Spain.

The total number of further contacts (1 to 10) is available for only 339 patients having requested at least one further medical contact:
- 231/339 patients with one further contact,
- 72/339 patients with one further contact,
- 36/339 patients with one further contact.

Table 69: 0-4 years old patients, 3 seasons: Number and percentage of patient consulting after D0 by flu type and country

Contacts after D0 with patient's registered practitioner	France					Turkey					Spain				
	Flu B 111 Cases		Flu A 111 Controls		p	Flu B 16 Cases		Flu A 8 Controls		p	Flu B 4 Cases		Flu A 1 Control		p
	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
All type of contacts															
none	82	73.9	82	73.9		15	93.8	7	87.5		3	75.0	0	0	
once	19	17.1	21	18.9	ns	0	0	1	12.5	ns	1	25.0	1	100	ns
twice	8	7.2	7	6.3		1	6.3	0	0		0	0	0	0	
3 times +	2	1.8	1	0.9		0	0	0	0		0	0	0	0	
Consultation															
none	89	80.2	92	82.9		15	93.8	7	87.5		3	75.0	0	0	
once	19	17.1	14	12.6	ns	0	0	1	12.5	ns	1	25.0	1	100	ns
twice	3	2.7	5	4.5		1	6.2	0	0		0	0	0	0	
3 times +	0	0	0	0		0	0	0	0		0	0	0	0	
Home visit															
none	111	100	110	99.1		16	100	8	100		4	100	1	100	
once	0	0	1	0.9	ns	0	0	0	0		0	0	0	0	
twice	0	0	0	0		0	0	0	0		0	0	0	0	
3 times +	0	0	0	0		0	0	0	0		0	0	0	0	
Phone contact															
none	95	85.6	98	88.3		16	100	8	100		4	100	1	100	
once	14	12.6	13	11.7	ns	0	0	0	0		0	0	0	0	
twice	0	0	0	0		0	0	0	0		0	0	0	0	
3 times +	2	1.8	0	0		0	0	0	0		0	0	0	0	

Table 70: 0-4 years old patients, 3 seasons: Number and percentage of patient consulting after D0 by flu B lineage and country

Contacts after D0 with patient's registered practitioner	France				Turkey				Spain			
	Flu B/V 48 Cases		Flu B/Y 59 Cases		Flu B/V 8 Cases		Flu B/Y 2 Cases		Flu B/V 0 Case		Flu B/Y 3 Cases	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
All type of contacts												
none	39	81.3	40	67.8	8	100	2	100			2	66.7
once	6	12.5	12	20.3	0	0	0	0			1	33.3
twice	2	4.2	6	10.2	0	0	0	0			0	0
3 times +	1	2.1	1	1.7	0	0	0	0			0	0
Consultation												
none	42	87.5	44	74.6	8	100	2	100			2	66.7
once	4	8.3	14	23.7	0	0	0	0			1	33.3
twice	2	4.2	1	1.7	0	0	0	0			0	0
3 times +	0	0	0	0	0	0	0	0			0	0
Home visit												
none	48	100	59	100	8	100	2	100			3	100
once	0	0	0	0	0	0	0	0			0	0
twice	0	0	0	0	0	0	0	0			0	0
3 times +	0	0	0	0	0	0	0	0			0	0
Phone contact												
none	43	89.6	48	81.4	8	100	2	100			3	100
once	4	8.3	10	16.9	0	0	0	0			0	0
twice	0	0	0	0	0	0	0	0			0	0
3 times +	1	2.1	1	1.7	0	0	0	0			0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

Table 71: 5-14 years old patients, 3 seasons: Number and percentage of patient consulting after D0 by flu type and country

Contacts after D0 with patient's registered practitioner	France					Turkey					Spain				
	Flu B 205 Cases		Flu A 152 Controls		p	Flu B 33 Cases		Flu A 34 Controls		p	Flu B 14 Cases		Flu A 3 Controls		p
	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
All type of contacts															
none	151	73.7	115	75.7	ns	31	93.9	31	91.2	ns	11	78.6	3	100	ns
once	34	16.6	27	17.8		2	6.1	3	8.8		3	21.4	0	0	
twice	15	7.3	6	3.9		0	0	0	0		0	0	0	0	
3 times +	5	2.4	4	2.6		0	0	0	0		0	0	0	0	
Consultation															
none	163	79.5	121	79.6	ns	31	93.9	31	91.2	ns	11	78.6	3	100	ns
once	32	15.6	27	17.8		2	6.1	3	8.8		3	21.4	0	0	
twice	8	3.9	2	1.3		0	0	0	0		0	0	0	0	
3 times +	2	1	2	1.3		0	0	0	0		0	0	0	0	
Home visit															
none	204	99.5	152	100	ns	33	100	34	100		14	100	3	100	
once	0	0	0	0		0	0	0	0		0	0	0	0	
twice	1	0.5	0	0		0	0	0	0		0	0	0	0	
3 times +	0	0	0	0		0	0	0	0		0	0	0	0	
Phone contact															
none	185	90.2	137	90.1	ns	33	100	34	100		14	100	3	100	
once	16	7.8	13	8.6		0	0	0	0		0	0	0	0	
twice	3	1.5	1	0.7		0	0	0	0		0	0	0	0	
3 times +	1	0.5	1	0.7		0	0	0	0		0	0	0	0	

Table 72: 5-14 years old patients, 3 seasons: Number and percentage of patient consulting after D0 by flu B lineage and country

Contacts after D0 with patient's registered practitioner	France				Turkey				Spain			
	Flu B/V 82 Cases		Flu B/Y 115 Cases		Flu B/V 17 Cases		Flu B/Y 5 Cases		Flu B/V 6 Cases		Flu B/Y 8 Cases	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
All type of contacts												
none	63	76.8	82	71.3	15	88.2	5	100	5	83.3	6	75.0
once	10	12.2	22	19.1	2	11.8	0	0	1	16.7	2	25.0
twice	5	6.1	10	8.7	0	0	0	0	0	0	0	0
3 times +	4	4.9	1	0.9	0	0	0	0	0	0	0	0
Consultation												
none	69	84.1	87	75.7	15	88.2	5	100	5	83.3	6	75.0
once	12	14.6	19	16.5	2	11.8	0	0	1	16.7	2	25.0
twice	0	0	8	7.0	0	0	0	0	0	0	0	0
3 times +	1	1.2	1	0.9	0	0	0	0	0	0	0	0
Home visit												
none	81	98.8	115	100	17	100	5	100	6	100	8	100
once	0	0	0	0	0	0	0	0	0	0	0	0
twice	1	1.2	0	0	0	0	0	0	0	0	0	0
3 times +	0	0	0	0	0	0	0	0	0	0	0	0
Phone contact												
none	71	86.6	107	93.0	17	100	5	100	6	100	8	100
once	7	8.5	8	7.0	0	0	0	0	0	0	0	0
twice	3	3.7	0	0	0	0	0	0	0	0	0	0
3 times +	1	1.2	0	0	0	0	0	0	0	0	0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

Table 73: 15-24 years old patients, 3 seasons: Number and percentage of patient consulting after D0 by flu type and country

Contacts after D0 with patient's registered practitioner	France					Turkey					Spain				
	Flu B 23 Cases		Flu A 26 Controls		p	Flu B 23 Cases		Flu A 10 Controls		p	Flu B 2 Cases		Flu A 1 Control		p
	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
All type of contacts															
none	16	69.6	16	61.5		22	95.7	10	100		1	50.0	0	0	
once	5	21.7	10	38.5	ns	1	4.3	0	0	ns	1	50.0	1	100	ns
twice	2	8.7	0	0		0	0	0	0		0	0	0	0	
3 times +	0	0	0	0		0	0	0	0		0	0	0	0	
Consultation															
none	18	78.3	18	69.2		22	95.7	10	100		1	50.0	0	0	
once	4	17.4	8	30.8	ns	1	4.3	0	0	ns	1	50.0	1	100	ns
twice	1	4.3	0	0		0	0	0	0		0	0	0	0	
3 times +	0	0	0	0		0	0	0	0		0	0	0	0	
Home visit															
none	23	100	25	96.2		23	100	10	100		2	100	1	100	
once	0	0	1	3.8	ns	0	0	0	0		0	0	0	0	
twice	0	0	0	0		0	0	0	0		0	0	0	0	
3 times +	0	0	0	0		0	0	0	0		0	0	0	0	
Phone contact															
none	20	87.0	25	96.2		23	100	10	100		2	100	1	100	
once	3	13.0	1	3.8	ns	0	0	0	0		0	0	0	0	
twice	0	0	0	0		0	0	0	0		0	0	0	0	
3 times +	0	0	0	0		0	0	0	0		0	0	0	0	

Table 74: 15-24 years old patients, 3 seasons: Number and percentage of patient consulting after D0 by flu B lineage and country

Contacts after D0 with patient's registered practitioner	France				Turkey				Spain			
	Flu B/V 12 Cases		Flu B/Y 9 Cases		Flu B/V 10 Cases		Flu B/Y 4 Cases		Flu B/V 0 Case		Flu B/Y 1 Case	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
All type of contacts												
none	7	58.3	8	88.9	10	100	4	100			1	100
once	3	25.0	1	11.1	0	0	0	0			0	0
twice	2	16.7	0	0	0	0	0	0			0	0
3 times +	0	0	0	0	0	0	0	0			0	0
Consultation												
none	8	66.7	8	88.9	10	100	4	100			1	100
once	3	25.0	1	11.1	0	0	0	0			0	0
twice	1	8.3	0	0	0	0	0	0			0	0
3 times +	0	0	0	0	0	0	0	0			0	0
Home visit												
none	12	100	9	100	10	100	4	100			1	100
once	0	0	0	0	0	0	0	0			0	0
twice	0	0	0	0	0	0	0	0			0	0
3 times +	0	0	0	0	0	0	0	0			0	0
Phone contact												
none	10	83.3	9	100	10	100	4	100			1	100
once	2	16.7	0	0	0	0	0	0			0	0
twice	0	0	0	0	0	0	0	0			0	0
3 times +	0	0	0	0	0	0	0	0			0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

Table 75: 25-44 years old patients, 3 seasons: Number and percentage of patient consulting after D0 by flu type and country

Contacts after D0 with patient's registered practitioner	France					Turkey					Spain				
	Flu B 74 Cases		Flu A 75 Controls		p	Flu B 65 Cases		Flu A 59 Controls		p	Flu B 9 Cases		Flu A 2 Controls		p
	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
All type of contacts															
none	41	55.4	43	57.3	ns	65	100	57	96.6	ns	7	77.8	2	100	ns
once	20	27.0	22	29.3		0	0	2	3.4		2	22.2	0	0	
twice	7	9.5	6	8.0		0	0	0	0		0	0	0	0	
3 times +	6	8.1	4	5.3		0	0	0	0		0	0	0	0	
Consultation															
none	51	68.9	49	65.3	ns	65	100	58	98.3	ns	7	77.8	2	100	ns
once	15	20.3	23	30.7		0	0	1	1.7		2	22.2	0	0	
twice	8	10.8	2	2.7		0	0	0	0		0	0	0	0	
3 times +	0	0	1	1.3		0	0	0	0		0	0	0	0	
Home visit															
none	73	98.6	74	98.7	ns	65	100	59	100		9	100	2	100	
once	1	1.4	1	1.3		0	0	0	0		0	0	0	0	
twice	0	0	0	0		0	0	0	0		0	0	0	0	
3 times +	0	0	0	0		0	0	0	0		0	0	0	0	
Phone contact															
none	56	75.7	62	82.7	ns	65	100	58	98.3	ns	9	100	2	100	
once	14	18.9	10	13.3		0	0	1	1.7		0	0	0	0	
twice	4	5.4	3	4.0		0	0	0	0		0	0	0	0	
3 times +	0	0	0	0		0	0	0	0		0	0	0	0	

Table 76: 25-44 years old patients, 3 seasons: Number and percentage of patient consulting after D0 by flu B lineage and country

Contacts after D0 with patient's registered practitioner	France				Turkey				Spain			
	Flu B/V 24 Cases		Flu B/Y 46 Cases		Flu B/V 13 Cases		Flu B/Y 11 Cases		Flu B/V 3 Cases		Flu B/Y 6 Cases	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
All type of contacts												
none	11	45.8	26	56.5	13	100	11	100	3	100	4	66.7
once	7	29.2	13	28.3	0	0	0	0	0	0	2	33.3
twice	2	8.3	5	10.9	0	0	0	0	0	0	0	0
3 times +	4	16.7	2	4.3	0	0	0	0	0	0	0	0
Consultation												
none	14	58.3	33	71.7	13	100	11	100	3	100	4	66.7
once	7	29.2	8	17.4	0	0	0	0	0	0	2	33.3
twice	3	12.5	5	10.9	0	0	0	0	0	0	0	0
3 times +	0	0	0	0	0	0	0	0	0	0	0	0
Home visit												
none	23	95.8	46	100	13	100	11	100	3	100	6	100
once	1	4.2	0	0	0	0	0	0	0	0	0	0
twice	0	0	0	0	0	0	0	0	0	0	0	0
3 times +	0	0	0	0	0	0	0	0	0	0	0	0
Phone contact												
none	16	66.7	36	78.3	13	100	11	100	3	100	6	100
once	6	25.0	8	17.4	0	0	0	0	0	0	0	0
twice	2	8.3	2	4.3	0	0	0	0	0	0	0	0
3 times +	0	0	0	0	0	0	0	0	0	0	0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

Table 77: 45-64 years old patients, 3 seasons: Number and percentage of patient consulting after D0 by flu type and country

Contacts after D0 with patient's registered practitioner	France					Turkey					Spain				
	Flu B 49 Cases		Flu A 45 Controls		p	Flu B 14 Cases		Flu A 24 Controls		p	Flu B 11 Cases		Flu A 4 Controls		p
	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
All type of contacts															
none	18	36.7	29	64.4		14	100	19	79.2		4	36.4	2	50.0	
once	17	34.7	12	26.7	<0.05	0	0	5	20.8	ns	2	18.2	1	25.0	ns
twice	8	16.3	2	4.4		0	0	0	0		1	9.1	1	25.0	
3 times +	6	12.2	2	4.4		0	0	0	0		4	36.4	0	0.0	
Consultation															
none	26	53.1	32	71.1		14	100	19	79.2		4	36.4	2	50.0	
once	13	26.5	10	22.2	ns	0	0	5	20.8	ns	2	18.2	1	25.0	ns
twice	10	20.4	3	6.7		0	0	0	0		1	9.1	1	25.0	
3 times +	0	0	0	0		0	0	0	0		4	36.4	0	0.0	
Home visit															
none	46	93.9	44	97.8		14	100	24	100		11	100	4	100	
once	1	2.0	1	2.2	ns	0	0	0	0		0	0	0	0	
twice	2	4.1	0	0		0	0	0	0		0	0	0	0	
3 times +	0	0	0	0		0	0	0	0		0	0	0	0	
Phone contact															
none	36	73.5	41	91.1		14	100	24	100		11	100	4	100	
once	12	24.5	2	4.4	<0.01	0	0	0	0		0	0	0	0	
twice	0	0	2	4.4		0	0	0	0		0	0	0	0	
3 times +	1	2.0	0	0		0	0	0	0		0	0	0	0	

Table 78: 45-64 years old patients, 3 seasons: Number and percentage of patient consulting after D0 by flu B lineage and country

Contacts after D0 with patient's registered practitioner	France				Turkey				Spain			
	Flu B/V 8 Cases		Flu B/Y 39 Cases		Flu B/V 0 Case		Flu B/Y 8 Cases		Flu B/V 1 Case		Flu B/Y 9 Cases	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
<u>All type of contacts</u>												
none	1	12.5	15	38.5			8	100	0	0	4	44.4
once	4	50.0	13	33.3			0	0	1	100	1	11.1
twice	1	12.5	7	17.9			0	0	0	0	1	11.1
3 times +	2	25.0	4	10.3			0	0	0	0	3	33.3
<u>Consultation</u>												
none	4	50.0	20	51.3			8	100	0	0	4	44.4
once	3	37.5	10	25.6			0	0	1	100	1	11.1
twice	1	12.5	9	23.1			0	0	0	0	1	11.1
3 times +	0	0	0	0			0	0	0	0	3	33.3
<u>Home visit</u>												
none	6	75.0	38	97.4			8	100	1	100	9	100
once	1	12.5	0	0			0	0	0	0	0	0
twice	1	12.5	1	2.6			0	0	0	0	0	0
3 times +	0	0	0	0			0	0	0	0	0	0
<u>Phone contact</u>												
none	4	50.0	30	76.9			8	100	1	100	9	100
once	3	37.5	9	23.1			0	0	0	0	0	0
twice	0	0	0	0			0	0	0	0	0	0
3 times +	1	12.5	0	0			0	0	0	0	0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

Table 79: ≥65 years old patients, 3 seasons: Number and percentage of patient consulting after D0 by flu type and country

Contacts after D0 with patient's registered practitioner	France					Turkey					Spain				
	Flu B 24 Cases		Flu A 24 Controls		p	Flu B 6 Cases		Flu A 6 Controls		p	Flu B 4 Cases		Flu A 2 Controls		p
	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
All type of contacts															
none	11	45.8	12	50		6	100	5	83.3		3	75.0	1	50.0	
once	8	33.3	8	33.3	ns	0	0	1	16.7	ns	1	25.0	0	0	ns
twice	3	12.5	4	16.7		0	0	0	0		0	0	1	50.0	
3 times +	2	8.3	0	0		0	0	0	0		0	0	0	0	
Consultation															
none	17	70.8	14	58.3		6	100	5	83.3		3	75.0	1	50.0	
once	4	16.7	8	33.3	ns	0	0	1	16.7	ns	1	25.0	1	50.0	ns
twice	3	12.5	2	8.3		0	0	0	0		0	0	0	0	
3 times +	0	0	0	0		0	0	0	0		0	0	0	0	
Home visit															
none	21	87.5	23	95.8		6	100	6	100		4	100	2	100	
once	2	8.3	0	0	ns	0	0	0	0		0	0	0	0	
twice	1	4.2	1	4.2		0	0	0	0		0	0	0	0	
3 times +	0	0	0	0		0	0	0	0		0	0	0	0	
Phone contact															
none	19	79.2	22	91.7		6	100	6	100		4	100	1	50.0	
once	4	16.7	2	8.3	ns	0	0	0	0		0	0	1	50.0	ns
twice	1	4.2	0	0		0	0	0	0		0	0	0	0	
3 times +	0	0	0	0		0	0	0	0		0	0	0	0	

Table 80: ≥65 years old patients, 3 seasons: Number and percentage of patient consulting after D0 by flu B lineage and country

Contacts after D0 with patient's registered practitioner	France				Turkey				Spain			
	Flu B/V 10 Cases		Flu B/Y 14 Cases		Flu B/V 3 Cases		Flu B/Y 1 Case		Flu B/V 2 Cases		Flu B/Y 2 Cases	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
All type of contacts												
none	**3**	**30.0**	**8**	**57.1***	3	100	1	100	1	50.0	2	100
once	**2**	**20.0**	**6**	**42.9**	0	0	0	0	1	50.0	0	0
twice	**3**	**30.0**	**0**	**0.0**	0	0	0	0	0	0	0	0
3 times +	**2**	**20.0**	**0**	**0.0**	0	0	0	0	0	0	0	0
Consultation												
none	6	60.0	11	78.6	3	100	1	100	1	50.0	2	100
once	1	10.0	3	21.4	0	0	0	0	1	50.0	0	0
twice	3	30.0	0	0	0	0	0	0	0	0	0	0
3 times +	0	0	0	0	0	0	0	0	0	0	0	0
Home visit												
none	9	90.0	12	85.7	3	100	1	100	2	100	2	100
once	0	0	2	14.3	0	0	0	0	0	0	0	0
twice	1	10.0	0	0	0	0	0	0	0	0	0	0
3 times +	0	0	0	0	0	0	0	0	0	0	0	0
Phone contact												
none	6	60.0	13	92.9	3	100	1	100	2	100	2	100
once	3	30.0	1	7.1	0	0	0	0	0	0	0	0
twice	1	10.0	0	0	0	0	0	0	0	0	0	0
3 times +	0	0	0	0	0	0	0	0	0	0	0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

**p<0.05*

Table 81: All patients, 3 seasons: Number and percentage of patient consulting after D0 by flu type and country

Contacts after D0 with patient's registered practitioner	France					Turkey					Spain				
	Flu B 486 cases		Flu A 433 Controls		p	Flu B 157 cases		Flu A 141 Controls		p	Flu B 44 cases		Flu A 13 Controls		p
	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
All type of contacts															
none	319	65.6	297	68.6	ns	153	97.5	129	91.5	<0.05	29	65.9	8	61.5	ns
once	103	21.2	100	23.1		3	1.9	12	8.5		10	22.7	3	23.1	
twice	43	8.8	25	5.8		1	0.6	0	0		1	2.3	2	15.4	
3 times +	21	4.3	11	2.5		0	0	0	0		4	9.1	0	0	
Consultation															
none	364	74.9	326	75.3	ns	153	97.5	130	92.2	<0.05	29	65.9	8	61.5	ns
once	87	17.9	90	20.8		3	1.9	11	7.8		10	22.7	4	30.8	
twice	33	6.8	14	3.2		1	0.6	0	0		1	2.3	1	7.7	
3 times +	2	0.4	3	0.7		0	0	0	0		4	9.1	0	0	
Home visit															
none	478	98.4	428	98.8	ns	157	100	141	100		44	100	13	100	
once	4	0.8	4	0.9		0	0	0	0		0	0	0	0	
twice	4	0.8	1	0.2		0	0	0	0		0	0	0	0	
3 times +	0	0	0	0		0	0	0	0		0	0	0	0	
Phone contact															
none	411	84.6	385	88.9	ns	157	100	140	99.3	ns	44	100	12	92.3	ns
once	63	13.0	41	9.5		0	0	1	0.7		0	0	1	7.7	
twice	8	1.6	6	1.4		0	0	0	0		0	0	0	0	
3 times +	4	0.8	1	0.2		0	0	0	0		0	0	0	0	

Table 82: All patients, 3 seasons: Number and percentage of patient consulting after D0 by flu B lineage and country

Contacts after D0 with patient's registered practitioner	France				Turkey				Spain			
	Flu B/V 184 Cases		Flu B/Y 282 Cases		Flu B/V 51 Cases		Flu B/Y 31 Cases		Flu B/V 12 Cases		Flu B/Y 29 Cases	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
All type of consultations												
none	124	67.4	179	63.5	49	96.1	31	100	9	75	19	65.5
once	32	17.4	67	23.8	2	3.9	0	0	3	25	6	20.7
twice	15	8.2	28	9.9	0	0	0	0	0	0	1	3.4
3 times +	13	7.1	8	2.8	0	0	0	0	0	0	3	10.3
Medical office												
none	143	77.7	203	72.0	49	96.1	31	100	9	75	19	65.5
once	30	16.3	55	19.5	2	3.9	0	0	3	25	6	20.7
twice	10	5.4	23	8.2	0	0	0	0	0	0	1	3.4
3 times +	1	0.5	1	0.4	0	0	0	0	0	0	3	10.3
Home visit												
none	179	97.3	279	98.9	51	100	31	100	12	100	29	100
once	2	1.1	2	0.7	0	0	0	0	0	0	0	0
twice	3	1.6	1	0.4	0	0	0	0	0	0	0	0
3 times +	0	0	0	0	0	0	0	0	0	0	0	0
Telephonic consultation												
none	150	81.5	243	86.2	51	100	31	100	12	100	29	100
once	25	13.6	36	12.8	0	0	0	0	0	0	0	0
twice	6	3.3	2	0.7	0	0	0	0	0	0	0	0
3 times +	3	1.6	1	0.4	0	0	0	0	0	0	0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

7.9.2 Medical contacts after D0 with another practitioner

Among the 1350 Cases/Controls included, information about further medical contact is available for 1343 patients, with 62 (4.6%) having requested a further medical contact (consultation, home visit or phone call) due to influenza symptoms, with another practitioner during the follow-up:
- 51/914 (5.6%) in France,
- 11/372 (2.9%) in Turkey,
- 0/57 (0.0%) in Spain.

The total number of further contacts (1 to 3) is available for only 58 patients having requested at least one further medical contact :
- 52/58 patients with one further contact,
- 4/58patients with one further contact,
- 2/58 patients with one further contact.

Due to the small number of patients concerned, these data have not been split by age group, neither for Cases and Controls (58 patients concerned, Table 83) nor for Yamagata/Victoria B Cases (27 patients concerned, Table 84).

Table 83: All patients, 3 seasons: Number and percentage of patient consulting after D0 by flu type and country

Contacts after D0 with another practitioner	France				Turkey				Spain			
	Flu B 484 Cases		Flu A 430 Controls		Flu B 210 Cases		Flu A 158 Controls		Flu B 44 Cases		Flu A 13 Controls	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
All type of contacts												
none	459	94.8	404	94	205	97.6	156	98.7	44	100	13	100
once	22	4.5	24	5.6	5	2.4	1	0.6	0	0	0	0
twice	2	0.4	1	0.2	0	0	1	0.6	0	0	0	0
3 times +	1	0.2	1	0.2	0	0	0	0	0	0	0	0
Consultation												
none	463	95.7	408	94.9	205	97.6	156	98.7	44	100	13	100
once	19	3.9	20	4.7	5	2.4	1	0.6	0	0	0	0
twice	2	0.4	1	0.2	0	0	1	0.6	0	0	0	0
3 times +	0	0	1	0.2	0	0	0	0	0	0	0	0
Home visit												
none	479	99	428	99.5	210	100	158	100	44	100	13	100
once	4	0.8	2	0.5	0	0	0	0	0	0	0	0
twice	1	0.2	0	0	0	0	0	0	0	0	0	0
3 times +	0	0	0	0	0	0	0	0	0	0	0	0
Phone contact												
none	475*	100	428*	99.5	210	100	158	100	44	100	13	100
once	0	0	2	0.5	0	0	0	0	0	0	0	0
twice	0	0	0	0	0	0	0	0	0	0	0	0
3 times +	0	0	0	0	0	0	0	0	0	0	0	0

** In France, the total cases is less than 914 because the item 'contact another gp by telephon' was not asked in 2010-2011 season.*

Table 84: All patients, 3 seasons: Number and percentage of patient consulting after D0 by flu B lineage and country

Contacts after D0 with another practitioner	France				Turkey				Spain			
	Flu B/V 184 Cases		Flu B/Y 280 Cases		Flu B/V 51 Cases		Flu B/Y 56 Cases		Flu B/V 12 Cases		Flu B/Y 29 Cases	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
All type of contacts												
none	176	95.7	264	94.3	48	94.1	56	100	12	100	29	100
once	8	4.3	14	5.0	3	5.9	0	0	0	0	0	0
twice	0	0	1	0.4	0	0	0	0	0	0	0	0
3 times +	0	0	1	0.4	0	0	0	0	0	0	0	0
Consultation												
none	177	96.2	267	95.4	48	94.1	56	100	12	100	29	100
once	7	3.8	12	4.3	3	5.9	0	0	0	0	0	0
twice	0	0	1	0.4	0	0	0	0	0	0	0	0
3 times +	0	0	0	0	0	0	0	0	0	0	0	0
Home visit												
none	183	99.5	276	98.6	51	100	56	100	12	100	29	100
once	1	0.5	3	1.1	0	0	0	0	0	0	0	0
twice	0	0	1	0.4	0	0	0	0	0	0	0	0
3 times +	0	0	0	0	0	0	0	0	0	0	0	0
Phone contact												
none	179	100	277	100	51	100	56	100	12	100	29	100
once	0	0	0	0	0	0	0	0	0	0	0	0
twice	0	0	0	0	0	0	0	0	0	0	0	0
3 times +	0	0	0	0	0	0	0	0	0	0	0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

7.9.3 Hospitalizations, Emergency Services & Paramedical Care request

Hospitalizations

A total of 40 patients (7 in France and 33 in Turkey) were hospitalized (3.0%). Most of them (38/40) were hospitalized between D0 and D9 and 2 between D9 and D28.

Due to the small number of patients concerned in each age group, no statistical comparison has been done.

Table 85: 3 seasons: Number and percentage of patient hospitalized after D0 by age group, flu type and country

Hospitalization after D0	France				Turkey				Spain			
	Flu B 485 Cases		Flu A 431 Controls		Flu B 216 Cases		Flu A 158 Controls		Flu B 44 Cases		Flu A 13 Controls	
Age group	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
0-4 yo	1	0.9	2	1.8	2	10.5	0	0	0	0	0	0
5-14 yo	1	0.5	1	0.7	3	7.5	1	2.8	0	0	0	0
15-24 yo	0	0	1	3.8	2	7.7	1	7.7	0	0	0	0
25-44 yo	0	0	0	0	6	6.6	4	5.8	0	0	0	0
45-64 yo	0	0	1	2.2	5	18.5	0	0	0	0	0	0
≥65 yo	0	0	0	0	9	69.2	0	0	0	0	0	0
All age	2	0.4	5	1.2	27	12.5	6	3.8	0	0	0	0

Table 86: 3 seasons: Number and percentage of patient hospitalized after D0 by age group, flu B lineage and country

Hospitalization after D0	France				Turkey				Spain			
	Flu B/V 183 Cases		Flu B/Y 282 Cases		Flu B/V 51 Cases		Flu B/Y 58 Cases		Flu B/V 12 Cases		Flu B/Y 29 Cases	
Age group	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
0-4 yo	1	2.1	0	0	2	25.0	0	0			0	0
5-14 yo	1	1.2	0	0	1	5.9	1	16.7	0	0	0	0
15-24 yo	0	0	0	0	1	10.0	0	0			0	0
25-44 yo	0	0	0	0	3	23.1	1	4.2	0	0	0	0
45-64 yo	0	0	0	0			4	25.0	0	0	0	0
≥65 yo	0	0	0	0	3	100	1	33.3	0	0	0	0
All age	2	1.1	0	0	10	19.6	7	12.1	0	0	0	0

Flu B/V = Influenza B Case, Victoria lineage Flu B/Y = Influenza B Case, Yamagata lineage

Emergency room consultations

The question about emergency room consultation was not asked during the 2010-2011 season.

For the two others seasons, 34 patients (13 in France, 17 in Turkey and 4 in Spain) consulted in an emergency room (2.5%), 32 between D0 and D9 and 2 between D9 and D28.

Table 87: 3 seasons: Number and percentage of patient consulting an emergency room by age group, flu type and country

Emergency room	France				Turkey				Spain			
	Flu B 485 Cases		Flu A 431 Controls		Flu B 216 Cases		Flu A 158 Controls		Flu B 44 Cases		Flu A 13 Controls	
Age group	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
0-4 yo	1	0.9	2	1.8	1	5.3	1	12.5	1	25.0	0	0
5-14 yo	4	2.0	1	0.7	2	5.0	1	2.8	3	21.4	0	0
15-24 yo	0	0	1	3.8	1	3.8	0	0	0	0	0	0
25-44 yo	0	0	1	1.3	2	2.2	2	2.9	0	0	0	0
45-64 yo	0	0	2	4.4	0	0	3	12.0	0	0	0	0
≥65 yo	1	4.2	0	0	3	23.1	1	14.3	0	0	0	0
All age	6	1.2	7	1.6	9	4.2	8	5.1	4	9.1	0	0

Table 88: 3 seasons: Number and percentage of patient consulting an emergency room by age group, flu B lineage and country

Emergency room	France				Turkey				Spain			
	Flu B/V 184 Cases		Flu B/Y 281 Cases		Flu B/V 51 Cases		Flu B/Y 58 Cases		Flu B/V 12 Cases		Flu B/Y 29 Cases	
Age group	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
0-4 yo	0	0	1	1.7	1	12.5	0	0			1	33.3
5-14 yo	2	2.4	2	1.8	1	5.9	0	0	2	33.3	1	12.5
15-24 yo	0	0	0	0	1	10.0	0	0			0	0
25-44 yo	0	0	0	0	0	0	1	4.2	0	0	0	0
45-64 yo	0	0	0	0			0	0	0	0	0	0
≥65 yo	0	0	1	7.1	3	100	0	0	0	0	0	0
All age	2	1.1	4	1.4	6	11.8	1	1.7	2	16.7	2	6.9

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

Paramedical Care request

Extra lab tests prescription

A total of 63 patients had extra lab tests prescription (63/1316, 4.8%).

In France, 51 patients have done at least one extra lab tests among:

- 7 urine tests,
- 24 blood tests,
- 29 X-ray (mainly chest X-ray and including 1 chest scanner and 1 hip ultrasound).

2 patients have done extra lab test at D9 and D28.

In Turkey, 8 patients have done extra lab tests which were described for 7:

- 4 blood tests,
- 3 chest X-ray,
- 1 X-ray .

In Spain, 4 patients have done extra lab tests which were all described:

- 3 chest X-ray,
- 1 blood test

Table 89: 3 seasons: Number and percentage of patient with extra lab tests by age group, flu type and country

Extra lab tests	France				Turkey				Spain			
	Flu B 468 Cases		Flu A 417 Controls		Flu B 216 Cases		Flu A 158 Controls		Flu B 44 Cases		Flu A 13 Controls	
Age group	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
0-4 yo	8	7.6	6	5.6	0	0	0	0	0	0	0	0
5-14 yo	6	3.0	8	5.5	0	0	0	0	0	0	0	0
15-24 yo	1	4.8	2	8.0	1	3.8	0	0	0	0	1	100
25-44 yo	6	8.6	5	7.0	0	0	1	1.4	1	11.1	0	0
45-64 yo	3	6.5	1	2.2	0	0	4	16.0	1	9.1	1	25.0
≥65 yo	3	12.5	2	8.7	1	7.7	1	14.3	0	0	0	0
All age	27	5.8	24	5.8	2	0.9	6	3.8	2	4.5	2	15.4

Table 90: 3 seasons: Number and percentage of patient with extra lab tests by age group, flu B lineage and country

Extra lab tests	France				Turkey				Spain			
	Flu B/V 184 Cases		Flu B/Y 264 Cases		Flu B/V 51 Cases		Flu B/Y 58 Cases		Flu B/V 12 Cases		Flu B/Y 29 Cases	
Age group	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
0-4 yo	4	8.3	4	7.5	0	0	0	0			0	0
5-14 yo	4	4.9	2	1.8	0	0	0	0	0	0	0	0
15-24 yo	1	8.3	0	0	0	0	0	0			0	0
25-44 yo	4	16.7	2	4.8	0	0	0	0	1	33.3	0	0
45-64 yo	1	12.5	2	5.6			0	0	0	0	0	0
≥65 yo	2	20.0	1	7.1	0	0	0	0	0	0	0	0
All age	16	8.7	11	4.2	0	0	0	0	1	8.3	0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

Paramedical care prescription

A total of 9 (0,7%) patients (8 in France and 1 in Spain) had paramedical care prescription after D0:

- 5 Influenza B Cases (4 B/Yam, 1 B/Vic),

- 4 Influenza A Controls (3 AH1, 1 AH3).

They were aged from <1 year to 87 years, 2 were vaccinated and another has been to hospital emergency room at D9.

Paramedical care are mainly nurse and physiotherapy.

Table 91: Description of patients with paramedical care prescription after D0

Country	Flu	Age	Sex	vaccination	ER	Paramed
Spain	B/Yam	11	F	No	No	D9 - ns
France	B/Yam	87	F	Yes	D9	D9: physiotherapy, D28: nurse (help for medication distribution)
France	B/Yam	76	M	Yes	No	D9: nurse
France	B/Yam	1	F	No	No	D9: physiotherapy
France	B/Vic	33	M	No	No	D28: blood sampling
France	AH1	<1 year	M	No	No	D9: physiotherapy
France	AH1	4	M	No	No	D9: respiratory physiotherapy
France	AH1	37	F	No	No	D28: osteopathy for cough
France	AH3	38	F	No	No	D9: nurse, injections against vomiting

Key: ER=Emergency Services, Paramed=Paramedical care, D9=condition reported at form D9, D28=condition reported at form D28

7.10 Drugs consumption linked with the influenza infection

Among the 1350 patients, 1335 (98.9%) have taken at least one drug, mean 3.1/patient (1 to 12 drugs).

7.10.1 All drugs (except for antiviral)

Among the 1350 patients, 1317 (97.6%) have taken a drug (other than antiviral).

Table 92: 0-4 years old patients, 3 seasons: For each drug class, total number (nb) of citation and average number per patient (/p) by flu type and country

Drug class	France				Turkey				Spain			
	Flu B 111 Cases		Flu A 111 Controls		Flu B 19 Cases		Flu A 8 Controls		Flu B 4 Cases		Flu A 1 Control	
	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p
analgesic/antipyretic	133	1.2	140	1.3	7	0.4	5	0.6	5	1.3	2	2.0
antitussive/mucolytic	27	0.2	33	0.3	3	0.2	4	0.5	1	0.3	0	0
drops/spray/wash	36	0.3	56	0.5	2	0.1	1	0.1	0	0	0	0
drugs combination	0	0	0	0	10	0.5	2	0.3	0	0	0	0
antihistaminic	3	0	1	0	0	0	0	0	0	0	0	0
antibiotic	30	0.3	42	0.4	24	1.3	8	1.0	2	0.5	0	0
oral corticosteroid	8	0.1	9	0.1	0	0	0	0	0	0	1	1.0
antiasthmatic	14	0.1	8	0.1	2	0.1	1	0.1	1	0.3	0	0
homeopathic medicine	29	0.3	6	0.1	0	0	0	0	0	0	0	0
vitamins/trace element/dietary supplement	1	0	6	0.1	4	0.2	0	0	0	0	0	0
other	13	0.1	25	0.2	0	0	0	0	0	0	0	0

Table 93: 0-4 years old patients, 3 seasons : For each drug class, total number (nb) of citation and average number per patient (/p) by flu B lineage and country

Drug class	France				Turkey				Spain			
	Flu B/V 48 Cases		Flu B/Y 59 Cases		Flu B/V 8 Cases		Flu B/Y 3 Cases		Flu B/V 0 Case		Flu B/Y 3 Cases	
	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p
analgesic/antipyretic	52	1.1	76	1.3	4	0.5	0	0			3	1.0
antitussive/mucolytic	8	0.2	17	0.3	2	0.3	0	0			1	0.3
drops/spray/wash	16	0.3	20	0.3	2	0.3	0	0			0	0
drugs combination	0	0	0	0	1	0.1	2	0.7			0	0
antihistaminic	3	0.1	0	0	0	0	0	0			0	0
antibiotic	16	0.3	13	0.2	14	1.8	2	0.7			2	0.7
oral corticosteroid	6	0.1	1	0	0	0	0	0			0	0
antiasthmatic	9	0.2	3	0.1	0	0	1	0.3			1	0.3
homeopathic medicine	18	0.4	11	0.2	0	0	0	0			0	0
vitamins/trace element/dietary supplement	1	0	0	0	3	0.4	0	0			0	0
other	6	0.1	7	0.1	0	0	0	0			0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

Table 94: 0-4 years old patients, 3 seasons: Number and percentage of patients with medication by drug class, flu type and country

Drug class	France					Turkey					Spain				
	Flu B 111 Cases		Flu A 111 Controls		p	Flu B 19 Cases		Flu A 8 Controls		p	Flu B 4 Cases		Flu A 1 Controls		p
	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
analgesic/antipyretic	98	88.3	100	90.1	ns	7	36.8	5	62.5	ns	4	100	1	100	
antitussive/mucolytic	26	23.4	30	27.0	ns	3	15.8	2	25.0	ns	1	25.0	0	0	ns
drops/spray/wash	33	29.7	48	43.2	<0.05	2	10.5	1	12.5	ns	0	0	0	0	
drugs combination	0	0	0	0		9	47.4	2	25.0	ns	0	0	0	0	
antihistaminic	3	2.7	1	0.9	ns	0	0	0	0		0	0	0	0	
antibiotic	22	19.8	32	28.8	ns	14	73.7	5	62.5	ns	1	25.0	0	0	ns
oral corticosteroid	7	6.3	9	8.1	ns	0	0	0	0		0	0	1	100	ns
antiasthmatic	10	9.0	6	5.4	ns	2	10.5	1	12.5	ns	1	25.0	0	0	ns
homeopathic medicine	12	10.8	4	3.6	<0.05	0	0	0	0		0	0	0	0	
vitamins/trace element/dietary supplement	1	0.9	6	5.4	ns	4	21.1	0	0	ns	0	0	0	0	
other	10	9.0	22	19.8	<0.05	0	0	0	0		0	0	0	0	

Table 95: 0-4 years old patients, 3 seasons: Number and percentage of patients with medication by drug class, flu B lineage and country

Drug class	France				Turkey				Spain			
	Flu B/V 48 Cases		Flu B/Y 59 Cases		Flu B/V 8 Cases		Flu B/Y 3 Cases		Flu B/V 0 Case		Flu B/Y 3 Cases	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
analgesic/antipyretic	40	83.3	54	91.5	4	50.0	0	0			3	100
antitussive/mucolytic	8	16.7	16	27.1	2	25.0	0	0			1	33.3
drops/spray/wash	15	31.3	18	30.5	2	25.0	0	0			0	0
drugs combination	0	0	0	0	1	12.5	2	66.7			0	0
antihistaminic	3	6.3	0	0	0	0	0	0			0	0
antibiotic	10	20.8	11	18.6	7	87.5	2	66.7			1	33.3
oral corticosteroid	5	10.4	1	1.7	0	0	0	0			0	0
antiasthmatic	5	10.4	3	5.1	0	0	1	33.3			1	33.3
homeopathic medicine	6	12.5	6	10.2	0	0	0	0			0	0
vitamins/trace element/dietary supplement	1	2.1	0	0	3	37.5	0	0			0	0
other	**5**	**10.4**	**5**	**8.5***	0	0	0	0			0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

**p<0.05*

Table 96: 5-14 years old patients, 3 seasons: For each drug class, total number (nb) of citation and average number per patient (/p) by flu type and country

Drug class	France				Turkey				Spain			
	Flu B 205 Cases		Flu A 152 Controls		Flu B 40 Cases		Flu A 36 Controls		Flu B 14 Cases		Flu A 3 Controls	
	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p
analgesic/antipyretic	281	1.4	215	1.4	23	0.6	23	0.6	17	1.2	4	1.3
antitussive/mucolytic	116	0.6	82	0.5	10	0.3	7	0.2	5	0.4	2	0.7
drops/spray/wash	111	0.5	79	0.5	8	0.2	12	0.3	0	0	0	0
drugs combination	2	0	0	0	20	0.5	19	0.5	0	0	0	0
antihistaminic	0	0	0	0	0	0	0	0	0	0	0	0
antibiotic	39	0.2	31	0.2	32	0.8	27	0.8	0	0	0	0
oral corticosteroid	5	0	5	0	1	0	1	0	0	0	0	0
antiasthmatic	11	0.1	9	0.1	3	0.1	0	0	0	0	0	0
homeopathic medicine	38	0.2	21	0.1	0	0	0	0	0	0	0	0
vitamins/trace element/dietary supplement	13	0.1	3	0	1	0	3	0.1	0	0	0	0
other	28	0.1	20	0.1	2	0.1	0	0	0	0	0	0

Table 97: 5-14 years old patients, 3 seasons: For each drug class, total number (nb) of citation and average number per patient (/p) by flu B lineage and country

Drug class	France				Turkey				Spain			
	Flu B/V 82 Cases		Flu B/Y 115 Cases		Flu B/V 17 Cases		Flu B/Y 6 Cases		Flu B/V 6 Cases		Flu B/Y 8 Cases	
	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p
analgesic/antipyretic	120	1.5	151	1.3	10	0.6	2	0.3	7	1.2	10	1.3
antitussive/mucolytic	53	0.6	55	0.5	2	0.1	0	0	1	0.2	4	0.5
drops/spray/wash	47	0.6	61	0.5	5	0.3	1	0.2	0	0	0	0
drugs combination	1	0	1	0	10	0.6	3	0.5	0	0	0	0
antihistaminic	0	0	0	0	0	0	0	0	0	0	0	0
antibiotic	16	0.2	22	0.2	16	0.9	3	0.5	0	0	0	0
oral corticosteroid	3	0	2	0	0	0	1	0.2	0	0	0	0
antiasthmatic	2	0	8	0.1	1	0.1	1	0.2	0	0	0	0
homeopathic medicine	15	0.2	23	0.2	0	0	0	0	0	0	0	0
vitamins/trace element/dietary supplement	4	0	9	0.1	0	0	0	0	0	0	0	0
other	6	0.1	22	0.2	0	0	0	0	0	0	0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

Table 98: 5-14 years old patients, 3 seasons: Number and percentage of patients with medication by drug class, flu type and country

Drug class	France					Turkey					Spain				
	Flu B 205 Cases		Flu A 152 Controls		p	Flu B 40 Cases		Flu A 36 Controls		p	Flu B 14 Cases		Flu A 3 Controls		p
	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
analgesic/antipyretic	189	92.2	146	96.1	ns	22	55.0	21	58.3	ns	14	100	3	100	
antitussive/mucolytic	104	50.7	74	48.7	ns	10	25.0	7	19.4	ns	5	35.7	2	66.7	ns
drops/spray/wash	93	45.4	74	48.7	ns	8	20.0	11	30.6	ns	0	0	0	0	
drugs combination	2	1.0	0	0	ns	19	47.5	19	52.8	ns	0	0	0	0	
antihistaminic	0	0	0	0		0	0	0	0		0	0	0	0	
antibiotic	31	15.1	22	14.5	ns	25	62.5	19	52.8	ns	0	0	0	0	
oral corticosteroid	4	2.0	5	3.3	ns	1	2.5	1	2.8	ns	0	0	0	0	
antiasthmatic	10	4.9	8	5.3	ns	3	7.5	0	0	ns	0	0	0	0	
homeopathic medicine	23	11.2	8	5.3	<0.05	0	0	0	0		0	0	0	0	
vitamins/trace element/dietary supplement	11	5.4	3	2.0	ns	1	2.5	3	8.3	ns	0	0	0	0	
other	23	11.2	18	11.8	ns	2	5.0	0	0		0	0	0	0	

Table 99: 5-14 years old patients, 3 seasons: Number and percentage of patients with medication by drug class, flu B lineage and country

Drug class	France				Turkey				Spain			
	Flu B/V 82 Cases		Flu B/Y 115 Cases		Flu B/V 17 Cases		Flu B/Y 6 Cases		Flu B/V 6 Cases		Flu B/Y 8 Cases	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
analgesic/antipyretic	77	93.9	106	92.2	10	58.8	2	33.3	6	100	8	100
antitussive/mucolytic	46	56.1	51	44.3	2	11.8	0	0	1	16.7	4	50.0
drops/spray/wash	41	50.0	49	42.6	5	29.4	1	16.7	0	0	0	0
drugs combination	1	1.2	1	0.9	9	52.9	3	50.0	0	0	0	0
antihistaminic	0	0	0	0	0	0	0	0	0	0	0	0
antibiotic	13	15.9	17	14.8	10	58.8	3	50.0	0	0	0	0
oral corticosteroid	3	3.7	1	0.9	0	0	1	16.7	0	0	0	0
antiasthmatic	2	2.4	7	6.1	1	5.9	1	16.7	0	0	0	0
homeopathic medicine	8	9.8	15	13.0	0	0	0	0	0	0	0	0
vitamins/trace element/dietary supplement	3	3.7	8	7.0	0	0	0	0	0	0	0	0
other	5	6.1	18	15.7	0	0	0	0	0	0	0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

Table 100: 15-24 years old patient, 3 seasons: For each drug class, total number (nb) of citation and average number per patient (/p) by flu type and country

Drug class	France				Turkey				Spain			
	Flu B 23 Cases		Flu A 26 Controls		Flu B 26 Cases		Flu A 13 Controls		Flu B 2 Cases		Flu A 1 Control	
	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p
analgesic/antipyretic	31	1.3	37	1.4	15	0.6	5	0.4	2	1.0	1	1.0
antitussive/mucolytic	16	0.7	16	0.6	8	0.3	4	0.3	1	0.5	1	1.0
drops/spray/wash	16	0.7	16	0.6	9	0.3	4	0.3	0	0	0	0
drugs combination	0	0	1	0	11	0.4	7	0.5	0	0	0	0
antihistaminic	0	0	1	0	0	0	0	0	0	0	0	0
antibiotic	4	0.2	7	0.3	21	0.8	7	0.5	2	1.0	2	2.0
oral corticosteroid	0	0	0	0	0	0	0	0	0	0	0	0
antiasthmatic	0	0	3	0.1	1	0	0	0	0	0	1	1
homeopathic medicine	0	0	2	0.1	0	0	0	0	0	0	0	0
vitamins/trace element/dietary supplement	4	0.2	4	0.2	3	0.1	1	0.1	0	0	0	0
other	2	0.1	7	0.3	0	0	0	0	0	0	0	0

Table 101: 15-24 years old patients, 3 seasons: For each drug class, total number (nb) of citation and average number per patient (/p) by flu B lineage and country

Drug class	France				Turkey				Spain			
	Flu B/V 12 Cases		Flu B/Y 9 Cases		Flu B/V 10 Cases		Flu B/Y 6 Cases		Flu B/V 0 Case		Flu B/Y 1 Case	
	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p
analgesic/antipyretic	12	1.0	15	1.7	5	0.5	3	0.5			1	1.0
antitussive/mucolytic	10	0.8	5	0.6	5	0.5	1	0.2			1	1.0
drops/spray/wash	8	0.7	6	0.7	7	0.7	1	0.2			0	0
drugs combination	0	0	0	0	3	0.3	3	0.5			0	0
antihistaminic	0	0	0	0	0	0	0	0			0	0
antibiotic	3	0.3	1	0.1	11	1.1	2	0.3			2	2.0
oral corticosteroid	0	0	0	0	0	0	0	0			0	0
antiasthmatic	0	0	0	0	0	0	0	0			0	0
homeopathic medicine	0	0	0	0	0	0	0	0			0	0
vitamins/trace element/dietary supplement	3	0.3	1	0.1	1	0.1	0	0			0	0
other	0	0	2	0.2	0	0	0	0			0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

Table 102: 15-24 years old patients, 3 seasons: Number and percentage of patients with medication by drug class, flu type and country

Drug class	France					Turkey					Spain				
	Flu B 23 Cases		Flu A 26 Controls		p	Flu B 26 Cases		Flu A 13 Controls		p	Flu B 2 Cases		Flu A 1 Control		p
	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
analgesic/antipyretic	21	91.3	26	100	ns	15	57.7	5	38.5	ns	2	100	1	100	
antitussive/mucolytic	14	60.9	14	53.8	ns	8	30.8	4	30.8	ns	1	50.0	1	100	ns
drops/spray/wash	12	52.2	12	46.2	ns	8	30.8	3	23.1	ns	0	0	0	0	
drugs combination	0	0	1	3.8	ns	11	42.3	6	46.2	ns	0	0	0	0	
antihistaminic	0	0	1	3.8	ns	0	0	0	0		0	0	0	0	
antibiotic	3	13.0	5	19.2	ns	16	61.5	6	46.2	ns	1	50.0	1	100	ns
oral corticosteroid	0	0	0	0		0	0	0	0		0	0	0	0	
antiasthmatic	0	0	2	7.7	ns	1	3.8	0	0	ns	0	0	1	100	ns
homeopathic medicine	0	0	2	7.7	ns	0	0	0	0		0	0	0	0	
vitamins/trace element/dietary supplement	3	13.0	4	15.4	ns	3	11.5	1	7.7	ns	0	0	0	0	
other	2	8.7	4	15.4	ns	0	0	0	0		0	0	0	0	

Table 103: 15-24 years old patients, 3 seasons: Number and percentage of patients with medication by drug class, flu B lineage and country

Drug class	France				Turkey				Spain			
	Flu B/V 12 Cases		Flu B/Y 9 Cases		Flu B/V 10 Cases		Flu B/Y 6 Cases		Flu B/V 0 Case		Flu B/Y 1 Case	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
analgesic/antipyretic	10	83.3	9	100	5	50.0	3	50.0			1	100
antitussive/mucolytic	8	66.7	5	55.6	5	50.0	1	16.7			1	100
drops/spray/wash	7	58.3	4	44.4	6	60.0	1	16.7			0	0
drugs combination	0	0	0	0	3	30.0	3	50.0			0	0
antihistaminic	0	0	0	0	0	0	0	0			0	0
antibiotic	2	16.7	1	11.1	8	80.0	2	33.3			1	100
oral corticosteroid	0	0	0	0	0	0	0	0			0	0
antiasthmatic	0	0	0	0	0	0	0	0			0	0
homeopathic medicine	0	0	0	0	0	0	0	0			0	0
vitamins/trace element/dietary supplement	2	16.7	1	11.1	1	10.0	0	0			0	0
other	0	0	2	22.2	0	0	0	0			0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

Table 104: 25-44 years old patients, 3 seasons: For each drug class, total number (nb) of citation and average number per patient (/p) by flu type and country

Drug class	France				Turkey				Spain			
	Flu B 74 Cases		Flu A 75 Controls		Flu B 91 Cases		Flu A 69 Controls		Flu B 9 Cases		Flu A 2 Controls	
	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p
analgesic/antipyretic	112	1.5	107	1.4	60	0.7	44	0.6	11	1.2	2	1.0
antitussive/mucolytic	42	0.6	61	0.8	30	0.3	27	0.4	5	0.6	0	0
drops/spray/wash	49	0.7	39	0.5	24	0.3	16	0.2	0	0	0	0
drugs combination	0	0	2	0	34	0.4	32	0.5	0	0	0	0
antihistaminic	0	0	0	0	4	0	3	0	1	0.1	0	0
antibiotic	29	0.4	33	0.4	52	0.6	44	0.6	8	0.9	1	0.5
oral corticosteroid	6	0.1	6	0.1	0	0	0	0	0	0	0	0
antiasthmatic	6	0.1	8	0.1	1	0	3	0	0	0	0	0
homeopathic medicine	5	0.1	0	0	0	0	0	0	0	0	0	0
vitamins/trace element/dietary supplement	7	0.1	6	0.1	2	0	2	0	0	0	0	0
other	3	0	3	0	1	0	0	0	0	0	0	0

Table 105: 25-44 years old patients, 3 seasons: For each drug class, total number (nb) of citation and average number per patient (/p) by flu B lineage and country

Drug class	France				Turkey				Spain			
	Flu B/V 24 Cases		Flu B/Y 46 Cases		Flu B/V 13 Cases		Flu B/Y 24 Cases		Flu B/V 3 Cases		Flu B/Y 6 Cases	
	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p
analgesic/antipyretic	32	1.3	75	1.6	8	0.6	18	0.8	3	1.0	8	1.3
antitussive/mucolytic	14	0.6	26	0.6	3	0.2	7	0.3	1	0.3	4	0.7
drops/spray/wash	17	0.7	30	0.7	9	0.7	3	0.1	0	0	0	0
drugs combination	0	0	0	0	5	0.4	6	0.3	0	0	0	0
antihistaminic	0	0	0	0	0	0	0	0	0	0	1	0.2
antibiotic	13	0.5	15	0.3	11	0.8	15	0.6	4	1.3	4	0.7
oral corticosteroid	1	0	4	0.1	0	0	0	0	0	0	0	0
antiasthmatic	2	0.1	4	0.1	0	0	0	0	0	0	0	0
homeopathic medicine	2	0.1	3	0.1	0	0	0	0	0	0	0	0
vitamins/trace element/dietary supplement	1	0	6	0.1	0	0	0	0	0	0	0	0
other	1	0	2	0	0	0	0	0	0	0	0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

Table 106: 25-44 years old patients, 3 seasons: Number and percentage of patients with medication by drug class, flu type and country

Drug class	France					Turkey					Spain				
	Flu B 74 Cases		Flu A 75 Controls		p	Flu B 91 Cases		Flu A 69 Controls		p	Flu B 9 Cases		Flu A 2 Controls		p
	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
analgesic/antipyretic	71	95.9	71	94.7	ns	60	65.9	38	55.1	ns	9	100	2	100	
antitussive/mucolytic	37	50.0	54	72.0	<0.01	29	31.9	25	36.2	ns	5	55.6	0	0	ns
drops/spray/wash	39	52.7	34	45.3	ns	21	23.1	16	23.2	ns	0	0	0	0	
drugs combination	0	0	2	2.7	ns	34	37.4	31	44.9	ns	0	0	0	0	
antihistaminic	0	0	0	0		4	4.4	3	4.3	ns	1	11.1	0	0	ns
antibiotic	21	28.4	20	26.7	ns	46	50.5	33	47.8	ns	4	44.4	1	50.0	ns
oral corticosteroid	6	8.1	5	6.7	ns	0	0	0	0		0	0	0	0	
antiasthmatic	6	8.1	7	9.3	ns	1	1.1	3	4.3	ns	0	0	0	0	
homeopathic medicine	3	4.1	0	0	ns	0	0	0	0		0	0	0	0	
vitamins/trace element/dietary supplement	6	8.1	6	8.0	ns	2	2.2	2	2.9	ns	0	0	0	0	
other	3	4.1	2	2.7	ns	1	1.1	0	0		0	0	0	0	

Table 107: 25-44 years old patients, 3 seasons: Number and percentage of patients with medication by drug class, flu B lineage and country

Drug class	France				Turkey				Spain			
	Flu B/V 24 Cases		Flu B/Y 46 Cases		Flu B/V 13 Cases		Flu B/Y 24 Cases		Flu B/V 3 Cases		Flu B/Y 6 Cases	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
analgesic/antipyretic	22	91.7	45	97.8	8	61.5	18	75.0	3	100	6	100
antitussive/mucolytic	**11**	**45.8**	**24**	**52.2***	3	23.1	7	29.2	1	33.3	4	66.7
drops/spray/wash	12	50.0	25	54.3	8	61.5	3	12.5	0	0	0	0
drugs combination	0	0	0	0	5	38.5	6	25.0	0	0	0	0
antihistaminic	0	0	0	0	0	0	0	0	0	0	1	16.7
antibiotic	9	37.5	11	23.9	7	53.8	15	62.5	2	66.7	2	33.3
oral corticosteroid	1	4.2	4	8.7	0	0	0	0	0	0	0	0
antiasthmatic	2	8.3	4	8.7	0	0	0	0	0	0	0	0
homeopathic medicine	1	4.2	2	4.3	0	0	0	0	0	0	0	0
vitamins/trace element/dietary supplement	1	4.2	5	10.9	0	0	0	0	0	0	0	0
other	1	4.2	2	4.3	0	0	0	0	0	0	0	0

Flu B/V = Influenza B Case, Victoria lineage Flu B/Y = Influenza B Case, Yamagata lineage

**p<0.01*

Table 108: 45-64 years old patients, 3 seasons: For each drug class, total number (nb) of citation and average number per patient (/p) by flu type and country

Drug class	France				Turkey				Spain			
	Flu B 49 Cases		Flu A 45 Controls		Flu B 27 Cases		Flu A 25 Controls		Flu B 11 Cases		Flu A 4 Controls	
	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p
analgesic/antipyretic	66	1.3	60	1.3	10	0.4	13	0.5	15	1.4	4	1.0
antitussive/mucolytic	35	0.7	29	0.6	6	0.2	15	0.6	10	0.9	2	0.5
drops/spray/wash	26	0.5	29	0.6	5	0.2	7	0.3	0	0	0	0
drugs combination	2	0	0	0	15	0.6	12	0.5	0	0	0	0
antihistaminic	1	0	0	0	0	0	0	0	1	0.1	0	0
antibiotic	17	0.3	17	0.4	15	0.6	22	0.9	16	1.5	4	1.0
oral corticosteroid	2	0	4	0.1	0	0	1	0	0	0	0	0
antiasthmatic	4	0.1	6	0.1	0	0	2	0.1	1	0.1	0	0
homeopathic medicine	6	0.1	13	0.3	0	0	0	0	0	0	0	0
vitamins/trace element/dietary supplement	6	0.1	4	0.1	2	0.1	1	0	0	0	0	0
other	4	0.1	4	0.1	0	0	3	0.1	0	0	0	0

Table 109: 45-64 years old patients, 3 seasons: For each drug class, total number (nb) of citation and average number per patient (/p) by flu B lineage and country

Drug class	France				Turkey				Spain			
	Flu B/V 8 Cases		Flu B/Y 39 Cases		Flu B/V 0 Case		Flu B/Y 16 Cases		Flu B/V 1 Case		Flu B/Y 9 Cases	
	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p
analgesic/antipyretic	11	1.4	53	1.4			5	0.3	2	2.0	11	1.2
antitussive/mucolytic	8	1.0	26	0.7			3	0.2	1	1.0	9	1.0
drops/spray/wash	5	0.6	20	0.5			2	0.1	0	0	0	0
drugs combination	0	0	2	0.1			9	0.6	0	0	0	0
antihistaminic	1	0.1	0	0			0	0	0	0	1	0.1
antibiotic	5	0.6	10	0.3			8	0.5	2	2.0	13	1.4
oral corticosteroid	0	0	2	0.1			0	0	0	0	0	0
antiasthmatic	1	0.1	3	0.1			0	0	0	0	1	0.1
homeopathic medicine	0	0	6	0.2			0	0	0	0	0	0
vitamins/trace element/dietary supplement	0	0	6	0.2			0	0	0	0	0	0
other	0	0	4	0.1			0	0	0	0	0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

Table 110: 45-64 years old patients, 3 seasons: Number and percentage of patients with medication by drug class, flu type and country

Drug class	France					Turkey					Spain				
	Flu B 49 cases		Flu A 45 Controls		p	Flu B 27 cases		Flu A 25 Controls		p	Flu B 11 cases		Flu A 4 Controls		p
	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
analgesic/antipyretic	48	98.0	44	97.8	ns	10	37.0	10	40.0	ns	11	100	4	100	
antitussive/mucolytic	29	59.2	27	60.0	ns	6	22.2	12	48.0	ns	9	81.8	2	50.0	ns
drops/spray/wash	22	44.9	23	51.1	ns	5	18.5	7	28.0	ns	0	0	0	0	
drugs combination	2	4.1	0	0	ns	15	55.6	12	48.0	ns	0	0	0	0	
antihistaminic	1	2.0	0	0	ns	0	0	0	0		1	9.1	0	0	ns
antibiotic	14	28.6	11	24.4	ns	15	55.6	14	56.0	ns	8	72.7	2	50.0	ns
oral corticosteroid	2	4.1	4	8.9	ns	0	0	1	4.0	ns	0	0	0	0	
antiasthmatic	4	8.2	4	8.9	ns	0	0	1	4.0	ns	1	9.1	0	0	ns
homeopathic medicine	6	12.2	6	13.3	ns	0	0	0	0		0	0	0	0	
vitamins/trace element/dietary supplement	6	12.2	3	6.7	ns	2	7.4	1	4.0	ns	0	0	0	0	
other	3	6.1	3	6.7	ns	0	0	3	12.0	ns	0	0	0	0	

Table 111: 45-64 years old patients, 3 seasons: Number and percentage of patients with medication by drug class, flu B lineage and country

Drug class	France				Turkey				Spain			
	Flu B/V 8 Cases		Flu B/Y 39 Cases		Flu B/V 0 Case		Flu B/Y 16 Cases		Flu B/V 1 Case		Flu B/Y 9 Cases	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
analgesic/antipyretic	8	100	38	97.4			5	31.3	1	100	9	100
antitussive/mucolytic	6	75.0	22	56.4			3	18.8	1	100	8	88.9
drops/spray/wash	5	62.5	16	41.0			2	12.5	0	0	0	0
drugs combination	0	0	2	5.1			9	56.3	0	0	0	0
antihistaminic	1	12.5	0	0			0	0	0	0	1	11.1
antibiotic	4	50.0	9	23.1			8	50.0	1	100	6	66.7
oral corticosteroid	0	0	2	5.1			0	0	0	0	0	0
antiasthmatic	1	12.5	3	7.7			0	0	0	0	1	11.1
homeopathic medicine	0	0	6	15.4			0	0	0	0	0	0
vitamins/trace element/dietary supplement	0	0	6	15.4			0	0	0	0	0	0
other	0	0	3	7.7			0	0	0	0	0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

Table 112: ≥65 years old patients, 3 seasons: For each drug class, total number (nb) of citation and average number per patient (/p) by flu type and country

Drug class	France				Turkey				Spain			
	Flu B 24 Cases		Flu A 24 Controls		Flu B 13 Cases		Flu A 7 Controls		Flu B 4 Cases		Flu A 2 Controls	
	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p
analgesic/antipyretic	25	1.0	27	1.1	3	0.2	2	0.3	3	0.8	2	1.0
antitussive/mucolytic	22	0.9	16	0.7	2	0.2	1	0.1	4	1.0	2	1.0
drops/spray/wash	12	0.5	7	0.3	3	0.2	4	0.6	0	0	0	0
drugs combination	1	0	1	0	3	0.2	2	0.3	0	0	0	0
antihistaminic	0	0	0	0	0	0	0	0	1	0.3	0	0
antibiotic	24	1.0	19	0.8	13	1	8	1.1	2	0.5	0	0
oral corticosteroid	2	0.1	1	0	0	0	0	0	0	0	0	0
antiasthmatic	1	0	2	0.1	0	0	0	0	0	0	0	0
homeopathic medicine	1	0	4	0.2	0	0	0	0	0	0	0	0
vitamins/trace element/dietary supplement	2	0.1	2	0.1	1	0.1	0	0	0	0	0	0
other	1	0	1	0	0	0	0	0	0	0	0	0

Table 113: ≥65 years old patients, 3 seasons: For each drug class, total number (nb) of citation and average number per patient (/p) by flu B lineage and country

Drug class	France				Turkey				Spain			
	Flu B/V 10 Cases		Flu B/Y 14 Cases		Flu B/V 3 Cases		Flu B/Y 3 Cases		Flu B/V 2 Cases		Flu B/Y 2 Cases	
	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p
analgesic/antipyretic	11	1.1	14	1.0	0	0	0	0	1	0.5	2	1.0
antitussive/mucolytic	10	1.0	12	0.9	0	0	0	0	4	2.0	0	0
drops/spray/wash	8	0.8	4	0.3	1	0.3	1	0.3	0	0	0	0
drugs combination	1	0.1	0	0	0	0	2	0.7	0	0	0	0
antihistaminic	0	0	0	0	0	0	0	0	0	0	1	0.5
antibiotic	8	0.8	16	1.1	6	2.0	3	1.0	0	0	2	1.0
oral corticosteroid	1	0.1	1	0.1	0	0	0	0	0	0	0	0
antiasthmatic	0	0	1	0.1	0	0	0	0	0	0	0	0
homeopathic medicine	1	0.1	0	0	0	0	0	0	0	0	0	0
vitamins/trace element/dietary supplement	1	0.1	1	0.1	0	0	0	0	0	0	0	0
other	0	0	1	0.1	0	0	0	0	0	0	0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

Table 114: ≥65 years old patients, 3 seasons: Number and percentage of patients with medication by drug class, flu type and country

Drug class	France					Turkey					Spain				
	Flu B 24 Cases		Flu A 24 Controls		p	Flu B 13 Cases		Flu A 7 Controls		p	Flu B 4 Cases		Flu A 2 Controls		p
	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
analgesic/antipyretic	21	87.5	22	91.7	ns	3	23.1	2	28.6	ns	3	75.0	2	100	ns
antitussive/mucolytic	19	79.2	15	62.5	ns	2	15.4	1	14.3	ns	2	50.0	2	100	ns
drops/spray/wash	10	41.7	6	25.0	ns	3	23.1	3	42.9	ns	0	0	0	0	
drugs combination	1	4.2	1	4.2	ns	3	23.1	2	28.6	ns	0	0	0	0	
antihistaminic	0	0	0	0		0	0	0	0		1	25.0	0	0	ns
antibiotic	15	62.5	11	45.8	ns	10	76.9	5	71.4	ns	1	25.0	0	0	ns
oral corticosteroid	2	8.3	1	4.2	ns	0	0	0	0		0	0	0	0	
antiasthmatic	1	4.2	2	8.3	ns	0	0	0	0		0	0	0	0	
homeopathic medicine	1	4.2	3	12.5	ns	0	0	0	0		0	0	0	0	
vitamins/trace element/dietary supplement	2	8.3	2	8.3	ns	1	7.7	0	0	ns	0	0	0	0	
other	1	4.2	1	4.2	ns	0	0	0	0		0	0	0	0	

Table 115: ≥65 years old patients, 3 seasons: Number and percentage of patients with medication by drug class, flu B lineage and country

Drug class	France				Turkey				Spain			
	Flu B/V 10 Cases		Flu B/Y 14 Cases		Flu B/V 3 Cases		Flu B/Y 3 Cases		Flu B/V 2 Cases		Flu B/Y 2 Cases	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
analgesic/antipyretic	9	90.0	12	85.7	0	0	0	0	1	50.0	2	100
antitussive/mucolytic	9	90.0	10	71.4	0	0	0	0	2	100	0	0
drops/spray/wash	6	60.0	4	28.6	1	33.3	1	33.3	0	0	0	0
drugs combination	1	10.0	0	0	0	0	2	66.7	0	0	0	0
antihistaminic	0	0	0	0	0	0	0	0	0	0	1	50.0
antibiotic	6	60.0	9	64.3	3	100	3	100	0	0	1	50.0
oral corticosteroid	1	10.0	1	7.1	0	0	0	0	0	0	0	0
antiasthmatic	0	0	1	7.1	0	0	0	0	0	0	0	0
homeopathic medicine	1	10.0	0	0	0	0	0	0	0	0	0	0
vitamins/trace element/dietary supplement	1	10.0	1	7.1	0	0	0	0	0	0	0	0
other	0	0	1	7.1	0	0	0	0	0	0	0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

Table 116: All patient, 3 seasons: For each drug class, total number (nb) of citation and average number per patient (/p) by flu type and country

Drug class	France				Turkey				Spain			
	Flu B 486 Cases		Flu A 433 Controls		Flu B 216 Cases		Flu A 158 Controls		Flu B 44 Cases		Flu A 13 Controls	
	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p
analgesic/antipyretic	648	1.3	586	1.4	118	0.5	92	0.6	53	1.2	15	1.2
antitussive/mucolytic	258	0.5	237	0.5	59	0.3	58	0.4	26	0.6	7	0.5
drops/spray/wash	250	0.5	226	0.5	51	0.2	44	0.3	0	0	0	0
drugs combination	5	0	4	0	93	0.4	74	0.5	0	0	0	0
antihistaminic	4	0	2	0	4	0	3	0	3	0.1	0	0
antibiotic	143	0.3	149	0.3	157	0.7	116	0.7	30	0.7	7	0.5
oral corticosteroid	23	0	25	0.1	1	0	2	0	0	0	1	0.1
antiasthmatic	36	0.1	36	0.1	7	0	6	0	2	0	1	0.1
homeopathic medicine	79	0.2	46	0.1	0	0	0	0	0	0	0	0
vitamins/trace element/dietary supplement	33	0.1	25	0.1	13	0.1	7	0	0	0	0	0
other	51	0.1	60	0.1	3	0	3	0	0	0	0	0

Table 117: All patient, 3 seasons: For each drug class, total number (nb) of citation and average number per patient (/p) by flu B lineage and country

Drug class	France				Turkey				Spain			
	Flu B/V 184 Cases		Flu B/Y 282 Cases		Flu B/V 51 Cases		Flu B/Y 58 Cases		Flu B/V 12 Cases		Flu B/Y 29 Cases	
	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p	nb	/p
analgesic/antipyretic	238	1.3	384	1.4	27	0.5	28	0.5	13	1.1	35	1.2
antitussive/mucolytic	103	0.6	141	0.5	12	0.2	11	0.2	7	0.6	19	0.7
drops/spray/wash	101	0.5	141	0.5	24	0.5	8	0.1	0	0	0	0
drugs combination	2	0	3	0	19	0.4	25	0.4	0	0	0	0
antihistaminic	4	0	0	0	0	0	0	0	0	0	3	0.1
antibiotic	61	0.3	77	0.3	58	1.1	33	0.6	6	0.5	23	0.8
oral corticosteroid	11	0.1	10	0	0	0	1	0	0	0	0	0
antiasthmatic	14	0.1	19	0.1	1	0	2	0	0	0	2	0.1
homeopathic medicine	36	0.2	43	0.2	0	0	0	0	0	0	0	0
vitamins/trace element/dietary supplement	10	0.1	23	0.1	4	0.1	0	0	0	0	0	0
other	13	0.1	38	0.1	0	0	0	0	0	0	0	0

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

Table 118: All patient, 3 seasons: Number and percentage of patients with medication by drug class, flu type and country

Drug class	France					Turkey					Spain				
	Flu B 486 Cases		Flu A 433 Controls		p	Flu B 216 Cases		Flu A 158 Controls		p	Flu B 44 Cases		Flu A 13 Controls		p
	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
analgesic/antipyretic	448	92.2	409	94.5	ns	117	54.2	81	51.3	ns	43	97.7	13	100	ns
antitussive/mucolytic	229	47.1	214	49.4	ns	58	26.9	51	32.3	ns	23	52.3	7	53.8	ns
drops/spray/wash	209	43.0	197	45.5	ns	47	21.8	41	25.9	ns	0	0	0	0	
drugs combination	5	1.0	4	0.9	ns	91	42.1	72	45.6	ns	0	0	0	0	
antihistaminic	4	0.8	2	0.5	ns	4	1.9	3	1.9	ns	3	6.8	0	0	ns
antibiotic	106	21.8	101	23.3	ns	126	58.3	82	51.9	ns	15	34.1	4	30.8	ns
oral corticosteroid	21	4.3	24	5.5	ns	1	0.5	2	1.3	ns	0	0	1	7.7	ns
antiasthmatic	31	6.4	29	6.7	ns	7	3.2	5	3.2	ns	2	4.5	1	7.7	ns
homeopathic medicine	45	9.3	23	5.3	<0.05	0	0	0	0		0	0	0	0	
vitamins/trace element/dietary supplement	29	6.0	24	5.5	ns	13	6.0	7	4.4	ns	0	0	0	0	
other	42	8.6	50	11.5	ns	3	1.4	3	1.9	ns	0	0	0	0	

Table 119: All patient, 3 seasons: Number and percentage of patients with medication by drug class, flu B lineage and country

Drug class	France				Turkey				Spain			
	Flu B/V 184 Cases		Flu B/Y 282 Cases		Flu B/V 51 Cases		Flu B/Y 58 Cases		Flu B/V 12 Cases		Flu B/Y 29 Cases	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
analgesic/antipyretic	166	90.2	264	93.6	27	52.9	28	48.3	11	91.7	29	100
antitussive/mucolytic	88	47.8	128	45.4	12	23.5	11	19.0	5	41.7	18	62.1
drops/spray/wash	86	46.7	116	41.1	22	43.1	8	13.8	0	0	0	0
drugs combination	2	1.1	3	1.1	18	35.3	25	43.1	0	0	0	0
antihistaminic	4	2.2	0	0	0	0	0	0	0	0	3	10.3
antibiotic	44	23.9	58	20.6	35	68.6	33	56.9	3	25.0	11	37.9
oral corticosteroid	10	5.4	9	3.2	0	0	1	1.7	0	0	0	0
antiasthmatic	10	5.4	18	6.4	1	2	2	3.4	0	0	2	6.9
homeopathic medicine	**16**	**8.7**	**29**	**10.3***	0	0	0	0	0	0	0	0
vitamins/trace element/dietary supplement	8	4.3	21	7.4	4	7.8	0	0	0	0	0	0
other	11	6	31	11	0	0	0	0	0	0	0	0

Flu B/V = Influenza B Case, Victoria lineage Flu B/Y = Influenza B Case, Yamagata lineage

**p<0.05*

7.10.2 Antivirals

A total of 217 (16.1%) patients took an antiviral at D0 or just after (reported on the D9 form):
- 128 (14,0%) in France, with 127/128 being Tamiflu®;
- 89 (23,8%) in Turkey, with 81/89 being Tamiflu®, 6 Relenza® and 2 not specified.
- 0 in Spain.

In France, among the 119 antiviral prescriptions with a known delay between onset of symptom and medication prescription, 110 (92.4%) took place within 48h after onset of symptoms, following the recommendations for antivirals use.

In Turkey, 53.9% of the patients have taken antiviral within 48h after onset of symptoms.

Table 120: 3 seasons: Number and percentage of patients with an antiviral prescription by age group, flu type and country

Antivirals	France					Turkey					Spain				
	Flu B 486 Cases		Flu A 433 Controls		p	Flu B 216 Cases		Flu A 158 Controls		p	Flu B 44 Cases		Flu A 13 Controls		p
Age group	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
0-4 yo	14	12.6	7	6.3	ns	1	5.3	1	12.5	ns	0	0	0	0	
5-14 yo	20	9.8	14	9.2	ns	8	20.0	1	2.8	<0.05	0	0	0	0	
15-24 yo	3	13.0	9	34.6	ns	4	15.4	1	7.7	ns	0	0	0	0	
25-44 yo	18	24.3	18	24.0	ns	30	33.0	16	23.2	ns	0	0	0	0	
45-64 yo	11	22.4	7	15.6	ns	11	40.7	4	16.0	ns	0	0	0	0	
≥65 yo	3	12.5	4	16.7	ns	11	84.6	1	14.3	<0.01	0	0	0	0	
All age	69	14.2	59	13.6	ns	65	30.1	24	15.2	<0.001	0	0	0	0	

Table 121: 3 seasons: Number and percentage of patients with an antiviral prescription by age group, flu B lineage and country

Antivirals	France				Turkey				Spain			
	Flu B/V 184 Cases		Flu B/Y 282 Cases		Flu B/V 51 Cases		Flu B/Y 58 Cases		Flu B/V 12 Cases		Flu B/Y 29 Cases	
Age group	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
0-4 yo	9	18.8	4	6.8	1	12.5	0	0			0	0
5-14 yo	9	11.0	9	7.8	2	11.8	2	33.3	0	0	0	0
15-24 yo	3	25.0	0	0.0	**0**	**0.0**	**3**	**50.0[1]**			0	0
25-44 yo	**10**	**41.7**	**8**	**17.4[1]**	4	30.8	7	29.2	0	0	0	0
45-64 yo	4	50.0	6	15.4			8	50.0	0	0	0	0
≥65 yo	2	20.0	1	7.1	3	100	2	66.7	0	0	0	0
All age	**37**	**20.1**	**28**	**9.9[2]**	10	19.6	22	37.9	0	0	0	0

Flu B/V = Influenza B Case, Victoria lineage Flu B/Y = Influenza B Case, Yamagata lineage
[1]p<0.05 [2]p<0.01

7.11 Absenteeism linked with the influenza infection

7.11.1 Work leave

Among 347 patients being 25-64 years old and having a remunerated job, 292 (84,1%) have had a work leave. The duration of the initial work leave ranged from 1 to 15 days, mean 4.7 days and median 4 days.

Nineteen patients (6.5%) had an extension of work leave at D28. The duration of this extension ranged from 3 to 24 days.

Finally, the total duration of work leave ranged from 1 to 34 days, mean 5.3 days and median 5 days.

Table 122: 3 seasons: Prescription of work leave (number, average, Standard Deviation (SD) and extreme duration) after D0 by age group, flu type and country

Work leave	France					Turkey					Spain				
	Flu B 105 Cases		Flu A 105 Controls		p	Flu B 58 Cases		Flu A 60 Controls		p	Flu B 14 Cases		Flu A 5 Controls		p
Age group	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
25-44 yo															
nb	54	79.4	59	85.5		44	91.7	45	90.0		7	100.0	1	50.0	
av./median duration	6.83 / 5		5.14 / 5		ns	4.36 / 4		3.58 / 3		ns	4.43 / 4		2.00 / 2		
SD	6.23		3.77			2.49		2.14			2.76		-		
min	1		1			1		1			2		2		
max	34		25			15		10			10		2		
45-64 yo															
nb	30	81.1	29	80.6		9	90.0	7	70.0		6	85.7	1	33.3	
av./median duration	5.83 / 5		6.66 / 5		ns	3.89 / 3		6.00 / 7		ns	4.83 / 5		5.00 / 5		
SD	2.76		5.81			2.42		2.52			3.25		-		
min	1		1			2		3			1		5		
max	13		31			10		10			9		5		
25-64 yo															
nb	84	80.0	88	83.8		53	91.4	52	86.7		13	92.9	2	40.0	
av./median duration	6.48 / 5		5.64 / 5		ns	4.28 / 3		3.90 / 3		ns	4.62 / 4		3.50 / 3.50		ns
SD	5.26		4.57			2.46		2.32			2.87		2.12		
min	1		1			1		1			1		2		
max	34		31			15		10			10		5		

Table 123: 3 seasons: Prescription of work leave (number, average, Standard Deviation (SD) and extreme duration) after D0 by age group, flu B lineage and country

Work leave	France				Turkey				Spain			
	Flu B/V 29 Cases		Flu B/Y 71 Cases		Flu B/V 6 Cases		Flu B/Y 16 Cases		Flu B/V 2 Cases		Flu B/Y 12 Cases	
Age group	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
25-44 yo												
nb	19	82.6	32	78.0	**4**	**66.7**	**11**	**100***	2	100	5	100
av./median duration	9.00 / 6		5.66 / 5		7.50 / 5		3.64 / 3		3.50 / 3.50		4.80 / 4	
SD	8.62		4.29		5.00		1.12		2.12		3.11	
min	1		1		5		2		2		2	
max	34		25		15		5		5		10	
45-64 yo												
nb	6	100	23	76.7			4	80			6	85.7
av./median duration	4.83 / 5		6.09 / 5		-		5.25 / 4		-		4.83 / 5	
SD	0.75		3.09		-		3.30		-		3.25	
min	4		1		-		3		-		1	
max	6		13		-		10		-		9	
25-64 yo												
nb	25	86.2	55	77.5	**4**	**66.7**	**15**	**93.8***	2	100	11	91.7
av./median duration	8.00 / 5		5.84 / 5		7.50 / 5		4.07 / 3		3.50 / 3.50		4.82 / 4	
SD	7.69		3.81		5.00		1.94		2.12		3.03	
min	1		1		5		2		2		1	
max	34		25		15		10		5		10	

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

**p<0.05*

7.11.2 School leave

Data analysis is provided for children between 3 and 16 years old (school age).

Among 632 patients aged from 3 to 16 years, 520 (82.3%) have had a school leave. The duration of the initial school leave ranged from 1 to 15 days, mean 4.6 days and median 4 days.

Thirty six (6.9%) patients have had an extension of school leave at D28, which ranged from 1 to 30 days.

Finally, the total duration of school leave ranged from 1 to 40 days, mean 5.1 days and median 4 days.

Table 124: 3 seasons: Prescription of school leave (number, average, Standard Deviation (SD) and extreme duration) after D0 by age group, flu type and country

School leave	France					Turkey					Spain				
	Flu B 280 Cases		Flu A 225 Controls		p	Flu B 61 Cases		Flu A 44 Controls		p	Flu B 18 Cases		Flu A 4 Controls		p
Age group	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
3-4 yo															
nb sch. leave	57	90.5	55	85.9		1	9.1	1	16.7		2	100	1	100	
av./median duration	5.18 / 5		4.73 / 4		ns	5.00 / 5		7.00 / 7			5.50 / 5.5		9.00 / 9		
Sd	2.41		2.78			(1 case)		(1 case)			1.12		(1 case)		
min	1		1								4				
max	12		15								7				
5-14 yo															
nb sch. leave	192	93.7	130	85.5		15	37.5	25	69.4		14	100	3	100	
av./median duration	5.60 / 5		5.25 / 4		ns	2.73 / 2		3.28 / 3		ns	5.21 / 5		2.00 / 2		<0.01
Sd	3.57		5.11			1.16		1.54			1.76		0.00		
min	1		1			1		1			2		2		
max	26		40			5		7			7		2		
15-16 yo															
nb sch. leave	11	91.7	6	66.7		4	40.0	2	100		1	50.0			
av./median duration	6.27 / 6		5.00 / 3.5		ns	2.25 / 2.5		2.50 / 2.5		ns	7.00 / 7		-		
Sd	3.38		3.69			0.96		0.71			(1 case)		-		
min	2		2			1		2					-		
max	13		12			3		3					-		
3-16 yo															
nb sch. leave	260	92.9	191	84.9		20	32.8	28	63.6		17	94.4	4	100	
av./median duration	5.53 / 5		5.09 / 4		ns	2.75 / 2.5		3.36 / 3		ns	5.35 / 5		3.75 / 2		ns
Sd	3.34		4.51			1.21		1.64			1.73		3.50		
min	1		1			1		1			2		2		
max	26		40			5		7			7		9		

Table 125: 3 seasons: Prescription of school leave (number, average, Standard Deviation (SD) and extreme duration) after D0 by age group, flu B lineage and country

School leave	France				Turkey				Spain			
	Flu B/V 117 Cases		Flu B/Y 151 Cases		Flu B/V 26 Cases		Flu B/Y 10 Cases		Flu B/V 6 Cases		Flu B/Y 11 Cases	
Age group	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
3-4 yo												
nb sch. leave	26	92.9	28	87.5	0	0	0	0			2	100
av./median duration	5.38 / 5		5.07 / 5		-		-		-		5.50 / 5.5	
Sd	2.70		2.24		-		-		-		2.12	
min	2		1		-		-		-		4	
max	12		10		-		-		-		7	
5-14 yo												
nb sch. leave	75	91.5	110	95.7	15	88.2	0	0	6	100	8	100
av./median duration	5.99 / 5		5.33 / 5		2.73 / 2		-		4.67 / 4.5		5.63 / 7	
Sd	3.97		3.27		1.16		-		1.37		2.00	
min	1		1		1		-		3		2	
max	26		22		5		-		7		7	
15-16 yo												
nb sch. leave	7	100	3	75.0	3	750	0	0			1	700
av./median duration	6.86 / 6		5.00 / 5		2.00 / 2		-		-		7.00 / 7	
Sd	4.06		2.00		1.00		-		-		(1 case)	
min	2		3		1		-		-			
max	13		7		3		-		-			
3-16 yo												
nb sch. leave	108	92.3	141	93.4	18	69.2	0	0	6	100	11	100
av./median duration	5.90 / 5		5.27 / 5		2.61 / 2		-		4.67 / 4.5		5.73 / 7	
Sd	3.70		3.06		1.14		-		1.37		1.85	
min	1		1		1		-		3		2	
max	26		22		5		-		7		7	

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

7.11.3 Caregiver leave

Data analysis are provided separately for caregiver of:
- children 0-2 years old, not going to school but possibly to day-care,
- children 3- 14 years old with or without a school leave.

Among 704 patients 0 to 14 years old, 255 (36.2%) needed a caregiver leave.
Caregiver leave occurred mainly in France (221/255 cases), where 38.1% (221/579) patients needed a caregiver leave.
In Turkey, a caregiver leave was needed for 32.0% (33/103) of the young patients.
Caregiver leave was needed only in one case in Spain.

The duration of caregiver leave at D9 ranged from 1 to 15 days, mean 3.2 days and median 3 days.
At D28, 14 (5.5%) patients had an extension of caregiver leave which ranged from 1 to 21 days.
Finally, the total duration of caregiver leave ranged from 1 to 29 days, mean 3.4 days and median 3 days.

Table 126: 3 seasons: Description of Caregiver leave (number, average and extreme duration, SD) after D0 by age group, flu type and country

Caregiver leave (C. leave)	France					Turkey					Spain				
	Flu B 316 Cases		Flu A 263 Controls		p	Flu B 59 Cases		Flu A 44 Controls		p	Flu B 18 Cases		Flu A 4 Controls		p
Age group	nb	%	nb	%		nb	%	nb	%		nb	%	nb	%	
0-2 yo															
nb C. leave	17	35.4	16	34.0		3	37.5	0	0		1	50.0	0	0	
av./median duration	2.41 / 2		3.06 / 2.5		ns	10.00 / 10					1.00 / 1				
Sd	1.00		1.95			5.00									
min	1		1			5									
max	5		8			15									
3-4 yo															
nb C. leave	35	55.6	30	46.9		3	27.3	2	33.3		0	0	0	0	
av./median duration	3.66 / 3		2.57 / 2		<0.05	5.00 / 5		7.00 / 7		ns					
Sd	2.45		1.59			2.00		4.24							
min	1		1			3		4							
max	12		7			7		10							
5-14 yo															
nb C. leave	73	35.6	50	32.9		17	42.5	8	22.2		0	0	0	0	
av./median duration	3.33 / 3		3.64 / 2		ns	3.59 / 3		3.88 / 3		ns					
Sd	2.35		4.33			1.54		2.64							
min	1		1			2		2							
max	12		29			7		10							
0-14 yo															
nb C. leave	125	39.6	96	36.5		23	39.0	10	22.7		1	5.6	0	0	
av./median duration	3.30 / 3		3.21 / 2		ns	4.61 / 3		4.50 / 3		ns	1.00 / 1				
Sd	2.26		3.36			3.03		3.03							
min	1		1			2		2							
max	12		29			15		10							

Table 127: 3 seasons: Description of Caregiver leave (number, average and extreme duration, SD) after D0 by age group, flu B lineage and country

Caregiver leave (C. leave) / Age group	France				Turkey				Spain			
	Flu B/V 130 Cases		Flu B/Y 174 Cases		Flu B/V 25 Cases		Flu B/Y 9 Cases		Flu B/V 6 Cases		Flu B/Y 11 Cases	
	nb	%	nb	%	nb	%	nb	%	nb	%	nb	%
0-2 yo												
nb C. leave	9	45.0	8	29.6	0	0	2	100			1	100
av./median duration	2.33 / 2		2.50 / 2.5				12.50 /12.5				1.00 / 1	
Sd	0.71		1.31				3.54					
min	1		1				10					
max	3		5				15					
3-4 yo												
nb C. leave	14	50.0	19	59.4	0	0	0	0			0	0
av./median duration	3.79 / 3.5		3.74 / 3		-		-				-	
Sd	2.83		2.28		-		-				-	
min	1		1		-		-				-	
max	12		10		-		-				-	
5-14 yo												
nb C. leave	30	36.6	41	35.7	0	0	5	83.3	0	0	0	0
av./median duration	3.67 / 3		3.07 / 2		-		4.20 / 3		-		-	
Sd	2.66		2.15		-		1.79		-		-	
min	1		1		-		3		-		-	
max	12		10		-		7		-		-	
0-14 yo												
nb C. leave	53	40.8	68	39.1	0	0	7	77.8	0	0	1	9.1
av./median duration	3.47 / 3		3.19 / 3		-		6.57 / 5		-		1.00 / 1	
Sd	2.51		2.12		-		4.54		-			
min	1		1		-		3		-			
max	12		10		-		15		-			

Flu B/V = Influenza B Case, Victoria lineage *Flu B/Y = Influenza B Case, Yamagata lineage*

7.12 Death

Among the 1350 patients followed during the 3 seasons, only 1 death is reported.

This death occurred in a flu B not characterized Case in Turkey during the 2010-2011 season and concerned a 100 years old woman not vaccinated against influenza.

At D0, she presented fever (38.5°C) with myalgia, cough and pneumonia and received an antibiotic treatment.

She was hospitalized between D0 and D9 and received oseltamivir between 24 and 36 hours after onset of symptoms.

8 Synthesis

IBGP Follow-up Study: an important European data base for influenza burden description and influenza A and B cases comparison

Influenza sentinel surveillance networks exist or are being developed in many countries.
The IBGP Follow-up Study shows how these networks realize an accurate framework to set up follow-up studies, helping to evaluate the influenza disease burden.

During the study period (2010-2013):
- influenza B circulated very actively during 2 of the 3 seasons (2010-2011 and 2012-2013),
- the two influenza A sub-types circulated: A/H1N1pdm09 dominant in 2010-2011, A/H3N2 dominant in 2011-2012, co-dominance of the 2 sub-types in 2012-2013.

Precise epidemiological description of influenza circulation during these 3 seasons has been previously given in the IBGP Surveillance Study report.

The 2010-2013 IBGP Follow-up Study gives access to medico-economic data from 1350 influenza patients (746 B Cases and 604 A Controls) of all ages, recruited in 3 countries : France, Spain and Turkey.

Influenza burden differs between countries, depending on influenza epidemiology

As described in the IBGP Surveillance Study report, impact of each influenza type/sub-type differs from one country to another, from one season to another and from one age group to another.

Therefore, demographic characteristics of the included patients differ by country.

For the same reasons, inclusion of age and country matched influenza A Controls has sometimes been difficult, mainly in youngest age groups.

Influenza burden differs between countries, depending on each country healthcare system

Access to care (population behaviour, reimbursement, need of sick leave…) may vary widely from one country to another.

Due to this situation, comparison between countries appeared not possible.

Study limitations

Our study has a number of limitations, mainly due to sentinel surveillance systems peculiarities.

Spain joined the Follow-up Study only for 2 seasons and got much few inclusions, as influenza B was specially active during the first (2011-2012) Study season.

Since in routine surveillance not every ILI/ARI patient is investigated, sampling bias in swabbing consenting patients may occur.

Differences in access to healthcare between countries and surveillance networks characteristics unbalanced the sample size between countries: much more ILI/ARI children consult GP/paediatricians in France than in Spain and Turkey, often to get access to a caregiver leave. Therefore, the French Influenza B Cases sample weighs a lot in the study (486/746 - 65.1%).

Differences in access to healthcare between countries also limits the use of pooled analyses and doesn't allow to compare data between countries. French Study population is younger than Turkish Study population, probably due to healthcare (and surveillance practitioner) access differing from one country to another.

These practical limitations are matters which need to be addressed in planning similar studies.

Age structure of included influenza B Cases doesn't differs between IBGP Surveillance and Follow-up Studies in the three countries.

As influenza impact by age vary between influenza type/sub-types, recruitment of age group matched influenza A Controls has not always been possible. At the end of the three seasons Study period, 142/746 (19%) of influenza A Controls have not been recruited, mainly in youngest age groups, specially hit by influenza B. However, sample size was often sufficient to allow comparison by age groups.

As vey few were vaccinated, our study doesn't permit to investigate possible milder symptomatology in vaccinated patients.

Definition of the date (day) the patient recovered from his influenza episode appeared to be difficult for the practitioners. The date of recovery seems to have been qualitatively defined, what as to be considered as a potential bias in the measure of the duration of illness.

→ Finally, the IBGP Follow-up Study gives access to national comparison of influenza B Cases and A Controls by age group.

Main lessons from IBGP Follow-up Study

- **Most of the included patients (81.1%) consult their practitioner within the two first days of symptoms**, with few differences between countries and age groups. This behaviour may be influenced by the need for a sick leave for working patients or parents and by the surveillance recommendations to preferably swab ILI/ARI patients seen within the very first days of symptoms.

- **Clinical picture at D0 vary very little with type of influenza**.
  - ❖ Global comparison, per country, of clinical symptoms between Influenza B Cases and Influenza A Controls shows that:
    - **no symptom is significantly different between Influenza B Cases and Influenza A Controls in each of the three countries;**
    - only sore throat is slightly more frequent during influenza A (significant in Turkey, trend in France and Spain).
  - ❖ Comparison, per country and age group, of clinical symptoms between Influenza B Cases and Influenza A Controls shows that:
    - sore throat is slightly more frequent during influenza A in 0-4 yo (significant in France, trend in Turkey, no case in Spain);
    - sore throat is significantly slightly more frequent during influenza A in 45-64 yo in Turkey (no trend in France, no case in Spain);
    - cough is slightly more frequent during influenza B in 15-24 yo (significant in Turkey, trend in France, no trend in Spain).

- **Clinical picture at D0 vary very little with lineage of influenza B.**
  - ❖ Global comparison, per country, of clinical symptoms between Victoria and Yamagata Influenza B Cases shows that:

- **no symptom is significantly different between Victoria and Yamagata Influenza B in each of the three countries;**

- sore throat is significantly slightly more frequent during Victoria influenza B (significant in Turkey, trend in Spain, no trend in France);

- myalgia are significantly slightly more frequent during Yamagata influenza B (significant in Turkey, trend in Spain and France);

- cough is significantly slightly more frequent during Victoria influenza B (significant in France, trend in Spain, no trend in Turkey);

- coryza is significantly slightly more frequent during Yamagata influenza B (significant in Spain, trend in Turkey, no trend in France).

❖ Comparison, per country and age group, of clinical symptoms between Victoria and Yamagata Influenza B Cases shows that:

- sore throat is slightly more frequent during Yamagata influenza B in 0-4 yo (significant in France, no trend in Turkey, no case in Spain);

- sore throat is slightly more frequent during Yamagata influenza B in 15-24 yo (significant in France, no trend in Turkey, no case in Spain);

- sore throat is slightly more frequent during Victoria influenza B in 25-44 yo (significant in Turkey, no trend in France, no case in Spain);

- cough is slightly more frequent during Victoria influenza B in 5-14 yo (significant in France, no trend in Turkey, trend in Spain);

- myalgia are slightly more frequent during Yamagata influenza B in 25-44 yo (significant in France, trend in Turkey, no trend in Spain).

Finally, IBGP Follow-up Study shows that a clinical diagnosis of influenza A/B type or influenza B Yamagata/Victoria lineage doesn't seem possible. This result is consistent with recent published data [22].

- **Healthcare consumption at D0 also vary from one country to another, mainly due to difference in healthcare system.**
  - ❖ **Rate of hospitalization request is very low (1.3%), either for influenza A and B.** As this data was not collected in Turkey in 2010-2011, this rate may be slightly overestimated.
    Most of the hospitalization requests occurred in Turkey, perhaps due to local characteristics of healthcare access.
  - ❖ Antibiotics prescription rate decreases from Turkey (41.3%) to Spain (29.2%) and France (9.8%). Antibiotics prescription was slightly more frequent during influenza B (significant in Turkey, trend in Spain, no trend in France) in the total population as in 25-44 yo patients.
    No significant difference was observed between lineage.
  - ❖ Antivirals prescription rate decreases from France (12.0%) to Turkey (10.8%), with no antiviral prescription in Spain.
  - ❖ Antivirals prescription was slightly more frequent during influenza B (significant in Turkey, no trend in France, no antiviral prescription in Spain).
    Antivirals prescription was slightly more frequent during influenza B Victoria globally and in 25-44 yo (significant in France, no case in Turkey, no antiviral prescription in Spain).

- Duration of influenza illness was estimated on two item at D9 and D28.
  ➔ Patient recovery at D9 or D28 is defined as the fact that patient has returned to his normal activities.
  Major part (1131/1350, 83.8%) of the patients had recovered at D9 and at D28 follow-up, most of the patients (264/272, 97.1%) had recovered.

- ❖ In France and in Turkey, recovery at D9 was significantly more frequent for influenza A Controls than for influenza B Cases (no trend in Spain).
  Same picture was observed in France in 5-14 yo B (trend in Turkey, no trend in Spain) and 15-24 yo (no trend in Turkey and Spain).
- ❖ In France, recovery at D9 was significantly more frequent for influenza B Yamagata lineage Cases than for influenza B Victoria lineage Cases, but, conversely in Turkey, recovery at D9 was significantly more frequent for influenza B Victoria lineage Cases than for influenza B Yamagata lineage Cases (no trend in Spain).
  In France, recovery at D9 was also significantly more frequent for influenza B Yamagata lineage Cases than for influenza B Victoria lineage Cases in 0-4 yo (no trend in Turkey and Spain) and 5-14 yo (trend in Turkey, no trend in Spain).
- ❖ Most of the 8 patients not recovered at D28 were in France (7/8) and aged over 64 yo (5/8). When available (6/8 patients), reason of non recovery was mainly mild symptoms (persistent cough/asthenia) and only one patient (France-83 yo) was still concerned by bronchitis symptoms at D28.

➔Duration of illness is calculated between date of symptoms onset and date of return to normal activities.

Median duration of illness was mainly 7 days in all countries.

- ❖ **No statistical difference was found between influenza B Cases and A Controls for the mean duration of illness.**
- ❖ In Turkey, mean duration of illness was significantly higher (+4 days) and median duration of illness was higher (+3 days) for influenza B Yamagata lineage Cases than for influenza B Victoria lineage Cases in 25-44 yo (trend in Spain, no trend in France).
  Same picture was situation in Turkey in the whole study population (0.5 days) (trend in France, no trend in Spain).

➔ **At D9, almost one patient in two (625/1350 - 46.3%) presented at least one remaining symptom, mainly cough and rhinitis**, cough being more present in adults.

- **Further medical contacts due to influenza mainly concerned the practitioner having performed the swab.**
  - ❖ Around **one third (30.7%) of the patients have requested a further medical contact** (consultation, home visit or phone call) due to influenza symptoms, with their registered practitioner (practitioner performing the initial swab), during the follow-up: 35.1% in Spain, 33.0% in France, 24.4% in Turkey.
  - ❖ Global comparison, per country, of need of further medical contact with the registered practitioner between Influenza B Cases and Influenza A Controls shows that:
    - this need is not significantly different between Influenza B Cases and Influenza A Controls in each of the three countries;
    - number of further contact(s) is only slightly more frequent during influenza A Controls than influenza B Cases in all ages in Turkey, for all types of contacts (trend in Spain, no trend in France) and for consultations (trend in Spain, no trend in France);
    - number of further contact(s) is only slightly more frequent in influenza B Cases than influenza A Controls in 45-64 yo in France, for all types of contacts (trend in Spain, no trend in Turkey) and for phone contacts (no trend in Spain and Turkey).
  - ❖ Global comparison, per country, of need of further medical contact with the registered practitioner between Influenza B Yamagata and Victoria Cases shows that:
    - this need is not significantly different between Influenza B Victoria and Yamagata Cases in each of the three countries;
    - number of further contact(s) is only slightly more frequent during influenza B Victoria than Yamagata in 64+ yo in France, for all types of contacts (too few in Spain and Turkey).
  - ❖ **Very few patients (4.6%) have requested a further medical contact** (consultation, home visit or phone call) due to influenza symptoms, **with another practitioner** during the follow-up.

- ❖ Very few patients (3.0%) have requested an hospitalization, mainly between D0 and D9, and mostly in Turkey (33/40).
- ❖ In the same way, only 34 (2.5%) patients (13 in France, 17 in Turkey and 4 in Spain) consulted in an emergency room, mainly between D0 and D9.
- ❖ Finally, only 63 patients (4.8%) had extra lab tests prescription, mainly chest X-ray (33/63).

- **Concerning drugs consumption, 1335 patients (98.9%) have taken at least one drug.**
  - ❖ Some minor differences are observed between type/lineage through the different age groups.
  - ❖ Globally, IBGP Follow-up Study shows that:
    - **most of the patients, whatever age group, took at least one drug for their influenza symptoms**;
    - **analgesic/antipyretic drug class is almost systematically prescribed or taken by the patient**;
    - **antibiotic prescription is still usual during influenza season in ARI/ILI patients**: 57.8% in Turkey, 33.3% in Spain and 22.5% in France. In France and Turkey where sample size is big enough, we can observe that antibiotic prescription is much more important in 0-4 yo (70.4%) and in 64+ yo (75.0%) in Turkey and in 64+ yo (54.2%) in France.
    - antiviral prescription (14,0% in France, 23,8% in Turkey), mainly took place within 48h after onset of symptoms, following the recommendations for antivirals use.

- **Concerning absenteeism linked with the influenza infection (work/school), at least 60.1% of the Study patients are concerned.**
  - **Among patients being 25-64 years old and having a remunerated job, 84,1% have had a work leave**. The total duration of work leave ranged from 1 to 34 days, mean 5.3 days and median 5 days: 5 days in France, 3 days in Turkey (too few data in Spain).
  - **Among patients being 3 to 16 years, 82.3% have had a school leave.** The total duration of school leave ranged from 1 to 40 days, mean 5.1 days and median 4 days: 5 days in France, 3 days in Turkey (too few data in Spain).
  - **Among patients being 0 to 14 years old, 36.2% needed a caregiver leave**: 38.1% in France, 32.0% in Turkey (too few data in Spain).The total duration of caregiver leave ranged from 1 to 29 days, mean 3.4 days and median 3 days: 2 days in France, 3 days in Turkey (too few data in Spain).

    Need of absenteeism leaves may be underestimated as influenza season often occur during school holidays when school/caregiver leaves and perhaps work leave are not useful.

- **Among the 1350 patients followed during the 3 seasons, only one death is reported.** This death occurred in a flu B not characterized Case in Turkey during the 2010-2011 season and concerned a 100 years old woman not vaccinated against influenza.

Planned further analysis

Analyses concerning compared medico-economics of influenza B Controls and A cases are still in process, using methodology developed in the first IBGP Follow-up data analysis published (Influenza B, French Data, 2010-2011 season) (Annex 6).

9 Annexes

9.1 Annex 1: IBGP Protocol

Open Rome
Organize and Promote Epidemiological Network
Réseau d'Observation des Maladies et des Epidémies

IBGP2

PROTOCOL

Detailed Title	The burden of influenza B in Europe: a prospective multi-country strain surveillance study using community-based specimens – Phase II
Study identifier	EPI-FLU 014 EU BOD CRT (115173)
Contributing Authors	Jean Marie Cohen, Anne Mosnier, Maria Laura Silva John Paget, Douglas Fleming, Gonçalo Matias
Version Date	Wednesday, 10 April 2013

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List of Abbreviations

ARI	Acute Respiratory Illness
ATP	According-to-Protocol
CI	Confidence Interval
CRF	Case Report Form
CSC	Central Study Coordinator
ECDC	European Centre for Disease Prevention and Control
EISS	European Influenza Surveillance Scheme
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
ICPC	International Classification of Primary Care
IEC	Independent Ethics Committee
ILI	Influenza like Illness
IRB	Institutional Review Board
NIC	National Influenza Center
PCR	Polymerase Chain Reaction
RAP	Reporting and Analysis Plan
SDV	Source Data Verification
WHO CC	World Health Organization Collaborating Centres

Glossary of Terms

Anonymisation	Information that identifies a specific individual (including, but not limited to name, address and national identification number such as social security number, date of birth) has been removed and no link to the donor, through a code number for example, is maintained.
Cohort study	An observational study used to analyse risk factors and following a group of people who do not have the disease, and using correlations to determine absolute risks. A cohort is a group of people who share a common characteristic or experience within a defined period.
Coded	Information is associated with a subject number i.e. a code number. Coded information can only be linked back to the individual via a key code i.e. a listing of the research participants and their code. Within the pharmaceutical industry coding data is the usual mechanism used for protecting an individual's research data. The key code is kept secure, usually by the investigator, and GSK researchers cannot identify the research individual other than in exceptional and controlled circumstances.
Complications	Defined as description of any "other symptom" [apart from persistent cough (with or without expectoration), nasal symptoms (rhinorrhea or nasal obstruction), headache or asthenia] or request of hospitalization. Examples of other symptoms: Fever, Throat symptoms (sore throat, pharyngitis), Otalgia/otitis, Sinusitis, Pneumonia, Low respiratory tract symptoms (asthma/COPD decompensation, bronchitis, bronchiolitis, shortness of breath, dyspnoea, thoracic pain...), Myalgia/myositis, Anorexia, Digestive symptoms, Vertigo, Adenopathy.
Eligible	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.

Epidemiology study	An observational study or an interventional study without administration of medicinal products as described in a research protocol.
Evaluable	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis (see Section 10.3.2 for details on criteria for evaluability).
Influenza case	An influenza case is defined as an ILI case with a respiratory sample positive for influenza during the study period.
Influenza season	Period from September to April during which seasonal influenza outbreaks usually occur.
Mismatch	Case of influenza due to a B strain from a lineage not antigenically related to vaccine reference strain
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.
Polymerase Chain Reaction	Polymerase Chain Reaction (PCR) is a molecular biological method for amplifying (creating multiple copies of) DNA. PCR is commonly used in medical and biological research labs for a variety of tasks, such as the detection of hereditary diseases, the identification of genetic fingerprints and the diagnosis of infectious diseases.
Open Rome	Clinical Research Organization
Research protocol	A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.

Study population	Sample of population of interest.
Subject	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical/ epidemiology study, or a person about whom some medical information has been recorded in a database.
Surveillance	Surveillance is defined as the ongoing systematic collection, collation, analysis, and interpretation of descriptive epidemiological health data on a specific disease. Surveillance can monitor incidence and/or prevalence, and/or inform about when and where health problems are occurring and who is affected.
VIRCASES database	Central influenza database developed and managed by Open Rome.

1. Steering Committee

Jean Marie Cohen M.D. Director and founder of Open Rome Clinical Research Organization

Jean Marie worked during twelve years in primary care as a general practitioner in France. In 1984 he participated in the creation of the Regional Groups for Flu Observation Network (GROG) and then founded a Research Organization (Open Rome) in order to develop GROG. Jean Marie has been a co-designer/responsible in France for the European Influenza Surveillance Scheme (EISS), the Mediterranean GROG and the European Vigilance Network for the Management of Antiviral Drugs Resistance (ViRgil). Since 2004 he is a counsellor of French Ministers of Health, participating in the pandemic planning development and in the steering committee of the national training program for caregivers in general practice and hospitals. He has been conducting trainings and lectures in various international meetings, especially in China CDC and in South African Institute of Public Health. Currently he also participates in European studies (EPIA, I-Move), EFG Senior, EFG Junior and boards in pharmaceutical companies.

W. John Paget, PhD, Senior Researcher, Netherlands Institute for Health Services Research

John is an expert in infectious diseases surveillance and epidemiology, with a particular specialization in influenza. Over the last 15 years he has developed novel tools for the surveillance of sexually transmitted diseases and mumps, measles and rubella while at the Swiss Federal Office of Public Health and for influenza while at the European Influenza Surveillance Scheme (EISS). He has also conducted research in the epidemiology and spread of influenza in Europe. Dr. Paget has shared his expertise with National Public Health Institutes across Europe and the European Centre for Disease Prevention and Control, and served as an expert advisor to WHO. He has published 40+ papers, book chapters and commentaries.

Douglas M Fleming M.D. Director of the RCGPs Research and Surveillance Centre
Douglas has been involved in community based influenza surveillance and in primary care epidemiology in the UK for 40 years. He has particular experience in interpreting epidemiological data from primary care. He was responsible for the initial integration of clinical observational data with routine virology which has become a fundamental part of influenza surveillance in England and which provided the first indication to WHO of influenza pandemic vaccine effectiveness. He has had a long collaboration with The Health Protection Agency and for several years was a Director of its forerunner 'The Public Health Laboratory Service'. He has been involved in estimating mortality attributable to influenza in seasonal epidemics. He has led a number of European projects and served on both national and European Commission advisory Committees.

2. Rationale for the study

Seasonal influenza in humans is caused by influenza type A strains H1N1 and H3N2, strains of influenza B lineage B/Victoria and B/Yamagata. It is known that in several seasonal influenza epidemics there is a co-circulation of both sub-types of influenza A and both lineages of influenza B.

Despite the little or no cross protection between influenza B lineages, the annual recommendation of WHO for a Trivalent Influenza Vaccine includes 2 influenza A strains, but only one strain of the influenza B virus. Thus, good protection against the circulating virus relies on correct prediction of influenza B lineage in each season. An evaluation of WHO recommendation for vaccine strains from 1990 to 2008 showed that the vaccine match for influenza B decreased from 100% to 33-54% following to the resurgence of Influenza B/Victoria in 1997 (Richard 2010).

Much attention has been paid to influenza in the last three decades, especially influenza A (H3N2) and, more recently, pandemic influenza A (H1N1). Fewer studies have looked specifically at influenza B or comparisons between the influenza B and A.

CDC Seasonal influenza' reports show that seasonal influenza B incidence is regularly larger than that of H1N1, and sometimes larger than H3N2. Local B incidence could be significantly higher than national averages in a single year, and regions of high incidence varied between seasons.

Two important studies carried out in the United States assessed the burden of disease associated with influenza by age group and type/subtype for hospitalisations and mortality These studies showed that the burden differed by virus, with influenza A(H3N2) viruses having the highest impact, then RSV, then influenza B viruses and finally influenza A(H1N1) viruses, similarly for mortality and hospitalisation (RSV was not included in the latter) [Thompson et al, 2003; Thompson et al, 2004].

A community based study carried out in England and Wales looked at the impact of each virus based on ILI (Influenza Like Illness) consultation rates and found that total excesses of ILI rates (over the baseline) were the highest for H3N2 viruses, then H1N1 and finally B (rough ratio of 3:2:1). Regarding excesses by age group, influenza B was highest in the children aged 5-14, followed by children aged 0-4. This suggests that influenza B is generally a milder illness than influenza H1, which is much milder than influenza H3 [Fleming et al, 2007]. Another study conducted in England and Wales also compared the burden of influenza A and B and found similar results, but for GP consultations, hospital admissions and deaths, influenza A had a systematically higher burden than influenza B [Pitman et al. 2007].

Only one study during one single winter season (2002-2003) showed that influenza B was dominant in parts of Western Europe (e.g. Portugal, Ireland and UK) [W Paget et al. 2003].

Furthermore, there is very little community-based data regarding the differential burden of disease for influenza B and A viruses in Europe. There is even less data regarding the differential burden of the influenza B lineages (Victoria versus Yamagata). No studies have look directly into clinical presentation and complications of Influenza B in all age groups during the same season.

Currently, in the EU, national warning systems transmit to ECDC various data on:

- Number of specimens collected and number of positive results for Influenza A and B, without standardized data on lineage of B subtypes.
- Number of ILI cases reported by each network, stratified by standardized age groups
- ILI attack rate estimated per country, not breakdown by influenza type or lineage

However, there is no data reported on:

- Influenza attack rate breakdown by influenza type or lineage or age groups
- Clinical description of influenza cases.

Further studies are required to fully ascertain influenza B burden across different countries and understand the medical need of a quadrivalent influenza vaccine with two B strains included in its formulation.

The study of the Influenza B in General Practice (IBGP) observed during the winter of 2010/2011 the differential burden of disease (ILI consultations, prescriptions, medical and socio-economic impact of influenza) due to influenza B, including differences in age groups and lineages, comparing to ILI influenza negative patients. We successfully collected detailed individual patient clinical and socio-economic data linked to strain specific influenza virology in 356 patients, as part of routine surveillance programs in France and Turkey.

We could observe a major difference between countries in circulating strain. B Brisbane was the selected virus strain for the 2010/11 seasonal vaccine and was well matched to B Victoria but not to B Yamagata. In France, as in most European countries, the majority of Flu B viruses belonged to the Victoria lineage; in marked contrast to Turkey, where almost all belonged to the Yamagata lineage

The criteria for continuing this first study according to the protocol were achieved, as a high percentage of influenza B cases detected. Also according to the protocol, an expansion of the first study aims to gather more data from other European countries, to enable a comparison between different geographical and temporal areas for estimate the circulation influenza B strains.

For the following season of 2011/2012, additional countries are going to participate: Spain, Italy, Portugal, Slovenia, Netherlands and Belgium. This study will be, as in the previous season, based on currently routine practice performed by the influenza surveillance network in each country included. However, in this season, influenza B cases included will be matched with influenza A controls.

3. Influenza Surveillance Network in Europe

WHO

The World Health Organization has the FluNet as a web-based data collection and a reporting tool of the Global Influenza Surveillance Network (GISN). FluNet includes virological influenza information since 1995 from countries worldwide, provided by National Influenza Centres (NIC) and other national influenza reference laboratories collaborating actively with GISN. Whereas data entry is restricted and data entry access password protected, data reports including tables, maps and graphs are available to all public users.

WHO/Europe analyses and presents epidemiological and virological data from the 53 Member States in the European Region that perform influenza surveillance and which report to the EuroFlu platform. The data is collected by clinicians' networks and laboratory networks, the latter consisting mainly of WHO-recognized National Influenza Centres (NIC).

This regional surveillance aims to help reduce influenza morbidity and mortality in the Region by collecting and exchanging timely information; contributing to the annual determination of vaccine content; providing relevant information to health professionals and the general public.

EISN

As of September 2008, the responsibility for the former activities of the European Influenza Surveillance Scheme (EISS) has been transferred to the European Centre for Disease Prevention and Control (ECDC).

The European Influenza Surveillance Network (EISN) took over from EISS which started in 1996 as a project funded by the national governments. Later it was funded by the European Commission (DG Sanco) - from 1999 until the end of September 2006. Since October 2006 until September 2008 when it took over the coordination, ECDC financed it through two consecutive grants. Participating in the network are all the 27 EU countries, Iceland and Norway.

Surveillance at the European level shall add value to Member States by directly strengthening and supporting the national surveillance systems and by coordinating the standardization of EU-wide surveillance activities to ensure better availability of more comparable data between countries. It shall strive to reduce the complexity of surveillance systems across Europe and enhance insight into communicable disease epidemiology in Europe.

The activities aim to contribute to reducing the burden of disease associated with influenza in

Europe and include collection and exchange of timely information on influenza activity, contribution to the annual determination of the influenza vaccine content, provision of relevant information about influenza to health professionals and the general public and contribution to European influenza pandemic preparedness activities.

3.1. Influenza surveillance network by country

The influenza surveillance in each European country follows the recommendations provided by WHO and EISN. Some information and numbers for the networks regarding the present project is following given.

3.1.1. France – GROG network

The establishment of the Regional Groups for Flu Observation Network – GROG – was based on the fact that doctors and primary caregivers were in the "front line" facing the influenza epidemic.

Founded in 1984, the GROG network, a network of early warning for influenza, has become a symbol of the participation of general practitioners into public health.

The GROG network participates as a correspondent in the National Health Service, since 2004, and covers 21 of the 22 metropolitan areas[1]. GROG sentinel practitioners are specifically trained by the national coordination and have the equipment which enables them to take samples in search of respiratory infectious agents. The specimens are collected in general population based on a weekly comparison of linked clinical and virological data compilation. Detection of influenza viruses is performed in rhinopharyngeal samples taken in community practices and mostly tested in laboratories. Recommendations are to swab within the first 2 days after onset of the symptoms, throughout nasal swabs or throat swabs.

The laboratories provide the kit for swabbing (ViroCult or UTM Copan). The specimens collected are sent to laboratories by post. All the virological samples sent to laboratories for analysis are accompanied with a clinical description.

A feedback is provided to these sentinel practitioners and it is a valuable tool for dissemination of warning signals to the clinicians and the public. Additionally, the regionalized structure helps maintain throughout France, a network proximity, request and adaptable when necessary.

[1] In Corsica, the GROG is not yet fully structured despite the presence of several GPs cooperating with this network.

GROG network in numbers

The total of sentinels for the season 2010/2011 are 525, being 410 GPs and 115 paediatricians.

Table 1 French network 2007/2008 – 2008/2009

Specimen 2007/2008			**Specimen 2008/2009**		
Flu negative	Influenza A	Influenza B	Flu negative	Influenza A	Influenza B
3709	893	482	3296	1336	228
5084			**4860**		

GROG network staff responsible for the study

- Anne Mosnier (network surveillance coordination)
- Isabelle Daviaud (data management)
- Tai Tan Bui (informatics)
- Sylvie Van der Werf (virological laboratory coordination – North France)
- Bruno Lina (virological laboratory coordination – South France)

3.1.2. Turkey – Istanbul Influenza Center

Before 2003, there was no information from Turkey regarding flu activity on FluNet from the WHO. In 2003-2004 season a small scale surveillance launched by Istanbul Faculty of Medicine generated the first available influenza information in Turkey.

Then in 2005-2006 season, sentinel influenza surveillance was launched by MoH which was to be conducted by Istanbul Faculty of Medicine Laboratory and by National Hygiene Center in Ankara. Currently, sentinel surveillance is conducted in 14 major provinces and National Influenza Reference Laboratory at Istanbul Faculty of Medicine in Istanbul receives samples from five major cities in the western part of the country; whereas, MoH receives samples from the rest of the 9 selected cities from the other parts of the country.

The laboratory visits the sentinels of each city they receive samples for analysis. These sentinels are then trained about the importance of the quality of the specimen collected (at the right time, from the right place and in adequate amount), its storage and transport. The recommendations are to swab within the first 3 days after onset of the symptoms, throughout nasal swabs or throat swabs. The laboratories provide the kit for swabbing (ViroCult) and Transportation (Cargo).

The sentinels are encouraged to complete a form which allows the laboratory to determine the percentage of ILI cases among weekly visitors of a polyclinic. The patient information form enables identifying whether the patient has underlying disease, vaccinated, given antivirals, etc. During an annual surveillance, there is approximately 600-1000 samples transported and analyzed. Samples are directly sent to the laboratories along with patient information forms

Istanbul Influenza Center in numbers

The total of sentinels for the season 2009/2010 were 515, being 500 GPs and 15 paediatricians.

Table 2 Turkish network 2007/2008 – 2008/2009

Specimen 2007/2008			**Specimen 2008/2009**		
Flu neg	Flu A	Flu B	Flu neg	Flu A	Flu B
361	111	52	518	31	31
524			**580**		

Istanbul network staff responsible for the study

- Meral Ciblak (coordination and data management)

3.1.3. Spain – Castilla y León sentinel Network and the National Influenza Center in Valladolid

Castilla y León is an autonomous community (region) located in the centre of Spain. It has a population of 2.5 millions people approximately in an extension of 100,000 km square (low population density).

The Health Sentinel Network was established by the regional government in 1988 with 125 GPs and 30 paediatricians working in primary care. Since then, more than 100 research studies have been carried out, covering infectious diseases, chronic conditions, risk factors and other public health problems.

In 1996 a sample of this sentinel doctors constituted the Influenza Sentinel Network, and the Integrated Program for the Influenza Surveillance was set up in collaboration with the National Influenza Center in Valladolid (one of the three NIC in Spain), which is attached to the University of Valladolid.

Nowadays, 45 GPs and Paediatricians participate in the seasonal surveillance of influenza, sending individualised clinical information of cases and taking swabs in approximately 200 patients each season. This weekly based information system is completed by a pre and post-vaccination study of antibody response to the vaccine strains and with the vaccination uptake in the covered population. The Influenza Network covers a population of 38,500 inhabitants (1.5% of the region population).

Castilla y Léon network in numbers

A total of 45 sentinels are contributing to Castilla y Léon network for the season 2011/2012.

Table 3 Castilla y Léon sentinel network 2007/2008 – 2008/2009

Specimen 2007/2008			**Specimen 2008/2009**		
Flu neg	Flu A	Flu B	Flu neg	Flu A	Flu B
38	22	29	79	24	7
89			**110**		

Castilla y Léon network staff responsible for the study

- Tomas Vega (network surveillance coordination)
- Carolina Rodriguez Gay (data management)
- Raul Ortiz de Lejarazu (virological laboratory coordination)

3.1.4. Italy – Lombardia Surveillance System

Influciri reporting system is dedicated to the surveillance of acute respiratory infections and is used for research in general practice. Since its foundation in 1991, from 400 to 550 GPs per year, paediatricians and internists, whose practice focuses on general practice, participate in the Influciri system. Through their voluntary statements, the reporting physicians testify the importance of primary care medicine, providing information on the health of the Italian population.

Influciri physicians are located in ten Italian regions: Abruzzo Calabria, Friuli, Venezia, Giulia Liguria, Lombardia, Marche, Puglia, Sicilia, Toscana, Umbria. To ensure optimal representation, special attention is paid to geographical distribution and socio-demographic group of physicians. The IBGP study Phase II, will have the participation of the Lombardia region, with physicians involved in Influrici surveillance System.

The epidemiological evaluation of seasonal influenza activity in Lombardia is based on weekly reports. Sentinel physicians take pharyngeal swabs from suspected influenza positive patients, and send the samples together with a clinical form to the Virology Institute of the University of Milano. Data are weekly transmitted to the National Institute for Public Health (ISS/NIC) in Roma. The ISS/NIC processes data which enable continuous monitoring of influenza viruses circulating in Italy. The NIC works with various partners in the WHO network.

Lombardia network in numbers

A total of 153 sentinels are contributing to Lombardia network for the season 2011/2012.

Table 4 Lombardia Influciri network 2007/2008 – 2008/2009

Specimen 2007/2008			**Specimen 2008/2009**		
Flu neg	Flu A	Flu B	Flu neg	Flu A	Flu B
463	126	111	629	339	22
700			**989**		

Lombardia network staff responsible for the study:

- Fabrizio Pregliasco (coordination)
- Giovanni Anselmi (data management)

3.1.5. Portugal – Portuguese Surveillance Network

The Portuguese surveillance network for influenza is a join collaboration of a GP's network "Médicos-Sentinela" (MS), coordinated by the Epidemiology Department of the National Institute for Health (INSA), and the National Influenza Reference Laboratory (also located at INSA).

Every season, the GP's network provides in a daily basis clinical data and biologic swabs for the virus characterization allowing a weekly estimative of incidence rates and identification and sub-typing of virus in circulation. Other sources of ILI cases, for the influenza network, are provided by some emergency services and specific research projects.

The MS operates since 1991 and it is constituted by approximately 150 voluntary GPs. The MS covers 2.5% of the Portuguese population and it is representative by sex and age. During the influenza surveillance season (from week 40 to week 20), and on a weekly basis, new ILI cases are notified to INSA (by paper or web-based application) which allows the estimate of ILI rates per 100,000 inhabitants, taking as denominator the sum of active GP's patient list. The ILI case definition follows the EU ILI definition since 2009/2010 season.

All the biological specimens are analysed at the National Influenza Reference Laboratory of INSA. On average the network yields about 10 samples per week for virological determination. The laboratory provides the kit for swabbing and nasal swabs or throat swabs are collected into a suitable transport medium. This procedure is conducted by the GP himself or by a nurse under his supervision. The swab collection is performed in ILI cases within seven days of symptom onset. The specimens are sent to the National Influenza Reference Laboratory by an express mail company within 24 hours.

Laboratory confirmation of influenza infection is done using cell-tissue culture for influenza viruses and a real-time multiplex RT-PCR. Isolates are characterized antigenically by haemagglutination inhibition tests (HAI), carried out using antisera and reference virus strains distributed by WHO Collaborating Center (Atlanta). Selected isolates are sent to the WHO Collaborating Center in London for further study. For influenza A subtyping the Real Time Ready Inf A/H1N1 detection (Roche) and ProFlu Influenza A subtyping (Prodesse) assays is used. For the influenza B lineage identification (Yamagata/88 and Victoria/87), a multiplex "in house" real-time RT-PCR is used.

Portuguese network in numbers

During the 2010/2011 influenza season a total of 144 sentinels contributed to the Portuguese network.

Table 5 Portuguese sentinel network 2007/2008 – 2008/2009

Specimen 2007/2008			**Specimen 2008/2009**		
Flu neg	Flu A	Flu B	Flu neg	Flu A	Flu B
174	53	68	336	316	6
295			**658**		

Portuguese network staff responsible for the study

- Carlos Dias (coordination)
- Ausenda Machado (data management)
- Baltazar Nunes (data management)

3.1.6. Slovenia – Slovenian Surveillance Network

Slovenian sentinel surveillance network for influenza-like illness (ILI) and other acute respiratory infections (ARI) was introduced in 1999. The network jointed The European Influenza Surveillance Scheme (EISS) a year later. The network includes approximately 40 primary care physicians (general practitioners, family doctors, school doctors and pediatricians) covering 4% of the population. The physicians report the weekly numbers of cases of the influenza like respiratory illnesses and other ARI, collect the patients' throat and nasal swabs (ILI specimens) and send them (together with short questionnaire) to National Influenza Center for testing. The network practices (public or private with concession) are located all over the country to provide geographical representativeness. The circulation of influenza virus is monitored through the whole year and becomes more intensive in October till May.

Each season plastic vials are distributed with transport medium, sterile swabs and padded envelopes together with clinical questionnaire to all network doctors (same ones that report ILI and ARI data). Specimens are sent to the National Influenza Center(NIC) laboratory by mail or brought by a courier. Transport time is from few hours to maximum of 3 days. Throat and nasal swabs from the same patient are merged and RNA extraction is mostly done on the day of specimen arrival to the laboratory.

NIC uses real time RT- PCR technique for detecting, typing and subtyping Influenza viruses (types A and B, subtypes A: H1, H1pdm, H3 and lineages B: Victoria, Yamagata). Isolation of virus is performed on the cell culture (MDCK). For isolates' subtyping micro-neutralisation is used. Selection of isolates is regularly sent to WHO CC. The data (epidemiological and virological) are available on the website of National Institute of Public Health and are reported regularly to ECDC and through ECDC to WHO.

Slovenian network in numbers

During the 2010/2011 influenza season a total of 44 sentinels contributed to the Slovenian network.

Table 6 Slovenian sentinel network 2007/2008 – 2008/2009

Specimen 2007/2008			Specimen 2008/2009		
Flu neg	Flu A	Flu B	Flu neg	Flu A	Flu B
1941	**253**	**17**	**3469**	**550**	**32**
2211			**4051**		

Slovenian network staff responsible for the study

- Maja Socan (coordination)
- Katarina Prosenc (data management)

3.1.7. Netherlands – Dutch Sentinel Stations

The Dutch sentinel stations started since Hong Kong flu (pandemic). Since 1970 they perform the registration of influenza and other diseases in general practice, for example: Pneumonia (SARI), Chickenpox, Whooping cough, STD and UTI.

The Dutch sentinel stations have about 45 general practices (now 42) who contribute to science independent of industry. They receive 1500€ per year + 0-300€ bonus per year depending on number of ILI swabs. An annual feedback report is produced with practice versus average performance in the network. In addition, an annual meeting is provided to discuss results, platform and practical instructions.

The GPs initially filled in the surveillance questionnaires by pencil and paper, but now they have an electronic tool for data collection. The swab collection is conducted for influenza, pneumonia and UTI, and a questionnaire goes together with disease symptoms and interventions (End-of-life care, Palliative sedation, Euthanasia requests, Suicide (attempts), Diabetes care, unwanted pregnancy) including virology of subsample.

ILI definition follows WHO Criteria: (1) acute onset (prodromal stage ≤ 4 days), (2) fever ≥38 degrees (rectal temperature), (3) one of the following symptoms: Cough, common cold, throatache, frontal headache, retrosternal pain, myalgia. ILI are only reported on week days and consultations by telephone meeting criteria are included.

An outbreak is considered when approaching the first 1000 cases. Facing this situation, each case is reported, antiviral protection of household members and each case is swabbed. In a routine situation of surveillance, GPs regularly report around 1% population, being swabbing of sample (2 per week per practice).

Dutch network in numbers

During the 2010/2011 influenza season a total of 42 sentinels contributed to the Dutch network.

Table 7 Dutch sentinel network 2007/2008 – 2008/2009

Specimen 2007/2008			Specimen 2008/2009		
Flu neg	Flu A	Flu B	Flu neg	Flu A	Flu B

Dutch network staff responsible for the study

- Ge Donker (network surveillance coordination)
- Adam Meijer (virological laboratory coordination)

3.1.8. Belgium – Belgian Surveillance System

In Belgium, a sentinel network specifically dedicated to influenza surveillance was initiated in 1985 and involved the participation of about 40 GPs. This network took part in various European influenza related projects over the years. From autumn 2007 on, the network became integrated into the network of the Sentinel General Practitioners (SGPs) existing since 1979 and being responsible for the surveillance of many other health problems. Since then, the SGPs have been continuously involved in the clinical and the virological influenza surveillance.

The SGPs are a nationwide sentinel surveillance network of about 160 voluntarily participating GPs homogeneously spread over the country. Besides the number of acute respiratory infections by age group, the GPs report weekly, on a standardized paper form, every patient with an influenza-like illness (ILI).

Physicians from the network are also invited to take pharyngeal swabs from influenza suspected patients. The two first patients of the week presenting at the GP consultation are tested systematically. Samples are sent together with a questionnaire form to the National Influenza Reference Centre (NIC) where they are analyzed.

Typing, subtyping of influenza A and determination of the lineage for influenza B are preformed by real time PCR. Further genetic characterization is also performed at the NIC by sequencing. A subset of samples is also sent to the WHO Collaborating Centre (London) for antigenic characterization. The results of the tests are communicated within 7 days to the sentinel practitioners. A weekly report is produced on the website http://influenza.wiv-isp.be and the data are encoded into the TESSy database.

Belgium network in numbers

During the 2010/2011 influenza season a total of 134 sentinels contributed to the Slovenian network.

Table 8 Belgium sentinel network 2007/2008 – 2008/2009

Specimen 2007/2008			Specimen 2008/2009		
Flu neg	Flu A	Flu B	Flu neg	Flu A	Flu B
473	335	134	483	477	33
942			**993**		

Belgian network staff responsible for the study

- Françoise Wuillaume (surveillance network coordination)
- Isabelle Thomas (virological laboratory coordination)

4. OBJECTIVES

4.1. Primary Objective

To describe influenza B cases by age and strain lineage, using outpatient data from routine surveillance and follow-up questionnaires in France, Turkey, Spain, Italy, Portugal, Netherlands, Belgium and Slovenia (five last countries contributing only with routine surveillance questionnaires) on clinical, duration of illness, drugs prescription, and absenteeism (work and school).

4.2. Secondary Objective(s)

- Compare the temporal and geographical distribution of influenza B cases within the season in the enrolled countries
- To describe, the incidence rate of influenza B, extrapolated to the whole population in each country
- To describe health care consumption (subsequent medical visits and hospitalization) among patients with influenza B by age group and country.
- To describe work absenteeism among patients and primary care givers of patients with influenza B.
- To estimate the percentage of co-circulation of B influenza lineages among the study population, by age and country.
- To compare the clinical features illness (clinical symptoms, duration of illness, complications[1], work absenteeism and drugs prescription) between cases-influenza B and controls-influenza A.
- To estimate the proportion of vaccine mismatch in the vaccinated patients by country.
- To evaluate the proportion of ILI due to influenza B by lineage during the influenza season in community based specimens of a selected population consulting general practitioners or paediatricians in the enrolled countries.

[1] 'Complications" are defined as description of any other symptom [apart from persistent cough (with or without expectoration), nasal symptoms (rhinorrhea or nasal obstruction), headache or asthenia] or request of hospitalization.

5. Methods

- Study design
  - Multi-country observational study
  - Case/control cohort design
- Data collection

  Questionnaire Survey
  - Questionnaire of inclusion – D0 – Time_0 day
    - All countries enrolled
    - Standard Clinical Form routinely completed at the swabbing day
    - Each enrolled country will use its current clinical form. A version of the clinical forms D0 of each enrolled country is attached on Appendix 1
    - A copy of D0 form of each patient included in the study must be sent to the European coordination
    - Every clinical form was analysed by the European coordination and main questions were retained for a common template (Appendix 2). Countries are going to entry data in this template available in the internet (http://openrome.org). Data security is insured by Open Rome.
  - Questionnaire of follow-up – D9 – Time_9 days (± 2 days)
    - Countries enrolled: France, Turkey and Spain
    - Case Report Form D9(±2) will be filled by sentinels or by surveillance network staff through a phone call (according to local ethical rules)
    - CRF D9 is common to all countries and is attached on Appendix 3.
    - Countries are going to entry data in a D9 template available in the internet (http://openrome.org). Data security is insured by Open Rome.
  - Questionnaire of follow-up – D28 – Time_28 days (± 5 days)
    - Countries enrolled: France, Turkey and Spain
    - Case Report Form D28(±5) will be also completed by sentinels or surveillance network staff in the same way as CRF D9 (according to local ethical rules)
    - CRF D28 is common to all countries and is attached on Appendix 4.
    - CRF D28 will be completed only if at CRF D9, the patient has *not returned to*

his "normal activities"[1] and/or presents "other symptoms"[2]

If s/he has ONLY the following remaining symptoms persistent cough (with or without expectoration), nasal symptoms (rhinorrhea or nasal obstruction), headache or asthenia – D28 is NOT required

- Countries are going to entry data in a D28 template available in the internet (http://openrome.org). Data security is insured by Open Rome.

- Duration of study
  - The study will be conducted during the influenza season of 2011/2012, approximately from week 36/2011 to week 15/2012.

  The inclusions will start from the beginning of the flu season, defined by GROG network as "the time when the same influenza subtype virus is isolated in two samples during the same week". It is expected that the study ends when the study population targeted size is reached or at the end of flu season, which is defined (GROG statement) as "two consecutive weeks during which no cases of influenza have been identified".

  - The duration of the study per subject is expected to be 7 to 33 days normal

- Sentinels participating in the study

  General Practitioners, paediatricians and other health professionals participating in the national or local influenza surveillance system in the enrolled countries are here called SENTINELS. They will be informed of the study and invited to participate:
  - to confirm their participation, they would be contacted by phone when a first possible case could be included.
  - the presentation of the study by phone contact would be done by trained staff, clarifying critical points of the study:
    - Briefly background of IBGP study and funding
    - Remind of past swab and its result: if influenza B positive or not
    - Patient follow up at day 9 and if necessary at day 28
    - How to contact patient
      - By telephone, but no restrictions were made about personal contact or other ways of obtaining information

[1] "Normal activities": patient returned to his usual routine/occupation (work, school, homemade, day-to-day life...)

[2] "Other symptoms" are defined as Flu complications, for example: Fever, Throat symptoms (sore throat, pharyngitis), Otalgia/otitis, Sinusitis, Pneumonia, Low respiratory tract symptoms (asthma/COPD decompensation, bronchitis, bronchiolitis, shortness of breath, dyspnoea, thoracic pain...), Myalgia/myositis, Anorexia, Digestive symptoms, Vertigo, Adenopathy

- Inform consent form

- How to fill in the Case Report Forms and (CRF) send it back
  - CRF could be completed manually or by computer, than sent back by fax, e-mail or post.

– if they agreed to participate in the study, they would receive an informative letter containing, the study contract, a copy of the protocol (in their native language), a guide for the practical running of the study and the patient Informed Consent Form - ICF - (Appendix 5).

5.1. Study population

- The target population of the study include all patients consulting in general practice for influenza like illness (ILI). Although each country has its own ILI case definition adapted to local reality, this definition is based on the EU (2009) general concept, regarding clinical criteria:

Any person with at least one of the following clinical forms: *Sudden onset of symptoms* *AND* *At least one of the following four systemic symptoms:* 1. *Fever or feverishness* 2. *Malaise* 3. *Headache* 4. *Myalgia* *AND* *At least one of the following three respiratory symptoms:* 1. *Cough* 2. *Sore throat* 3. *Shortness of breath*

The study population will be recruited by sentinels, who agreed to participate in the study and belonging to the Surveillance Network in the enrolled countries.

The number of subjects will depend on the number of cases of influenza B observed during the influenza season, through the surveillance network.

During the winter of 2011/2012, we are planning to recruit all Influenza B cases per country. Based on previous results of influenza seasons surveillance, we expect to enrol

up to 150 cases and the same number of patients will be enrolled for the cohort comparison group in each country. In other words, up to a total of 750 pairs of cases and controls within 5 countries.

- CASES: all ILI patients lab-confirmed influenza B positive
- CONTROLS: ILI patients lab-confirmed influenza A positive

Subtype or Lineage is not required to inclusion. However for entry data in the template at D0 it is mandatory to describe influenza B Cases lineage or influenza A Controls subtype.

Due to differences between the epidemic curves of cases and controls, their data collection will be done as following (see matching criteria in § 5.1.4): Influenza B Cases will be matched with an Influenza A Control during the same season. In case the surveillance system is unable to recruit flu A control matching to each flu B case enrolled, the inclusion will proceed in the following season.

For France and Turkey (countries participating in IBGP first phase) the controls flu A not enrolled in the last season (2010/11) will be included through the current IBGP second phase season (2011/12).

Controls influenza A positive included in IBGP1 must be verified: if they had at least 7 days of delay between the swabbing day and the phone contact (according to the current protocol IBGP2) they would be kept. If they have less than 7 days, s/he should be excluded, and another control influenza A of this season (2011/2012) should be selected).

5.1.1. Inclusion Criteria

IBGP 2 will include all Influenza B patients matched with influenza A patients selected by the networks even for those that were not enrolled for follow-up.

Any subject must meet the following inclusion criteria:

– Patients presenting ILI (as defined by each surveillance network)

AND

– Patient under all ages, who the sentinels believe s/he is able to comply with the conditions and requirements of this Protocol (e.g. be available for follow-up) may be included in the study.

– Patient agreed with the Informed Consent Form (Appendix 5). In case of a minor, ICF must be signed by a representative (where applicable).

5.1.2. Exclusion Criteria

Any subject already included in this study with a first episode of ILI (each patient may be included only once in the study).

5.1.3. Subject identification

Patients selected to participate in the study will receive a specific identification (ID) for the IBGP study. Firstly, the recognition of the country (internet code):

1. France - FR
2. Turkey - TR
3. Spain - ES
4. Italy - IT
5. Belgium - BE
6. Netherlands - NL
7. Portugal - PT
8. Slovenia - SI

Secondly, the virological test results:

- Influenza B positive lab confirmed – B
- Influenza A positive lab confirmed – A

Thirdly, the chronological order of inclusion, with three digits – 001.

Therefore, as an example, a sentinel in Spain has a patient who could possibly participate in the study, as he has a positive result for influenza B. This patient is the 45° case selected by the network. The CRF D9 for this patient will then be identified as ESB045. As controls should match cases, with same figure, his control would be necessarily ESA045.

5.1.4. Recruitment of subjects

The subjects' recruitment (cases and controls) is triggered by the laboratory results, within the routine surveillance (following standard ethical procedures). If they agree to participate, there will be a follow-up by their usual practitioner or other health professional at 9 ± 2 days after the swabbing day and if necessary, at day 28 ± 5.

- CASES: confirmed Influenza B patients will be included.
- CONTROLS: patients Influenza A (of any type) selected for a cohort comparison. They must match cases according to:
  - the same age group: 0-4 (0-2, 3-4), 5-14, 15-64 (15-49, 50-64), > 64;

– the same GP (if possible), same region, same country;

When the follow-up of patients is not possible, only D0 data for cases and controls will be provided. For example, Portugal, Slovenia, Belgium, Italy and Netherlands are going to contribute only with these data due to over workload and deficit of staff.

5.2. General outline of the study

The following Tables summarize the procedures, including exams, undertaken during the study and clarify the intervals between the contact with the subject.

Table 9 List of study procedures

Epoch	Epoch 001		
Time	D0	D9 (±2days)	D28 (±5days)
Visit/Observation/Contact	Day of swabbing[1]	1st phone contact[2]	2nd phone contact[3]
Invite patients swabbed to participate		x	
Check inclusion/exclusion criteria	x	x	
Informed Consent Form		x	
Complete initial routine surveillance questionnaire	x		
Document storage and related administrative tasks		x	x
Update questionnaire with influenza virology results		x	
Telephone interview and complete questionnaire		x	x
Data validation and analysis of missing data	x	x	x
Local report of study results			x

[1]Specimen collected during routine influenza surveillance activity

[2] D9 do not apply to countries participating in the study only with D0 data (Portugal)

[3]Only for subjects that declared remaining flu symptoms at D9

Table 10 Intervals between the swabbing day and the follow-up

Interval	Optimal length of interval[1]	Maximum interval allowed[2]
Day of swabbing - TC1	9 days	± 2 days
Day of swabbing - TC2	28 days	± 5 days

TC = Telephone Contact

[1] Whenever possible the investigator should arrange study visits/contacts within this interval

[2] Subjects will not be eligible for inclusion in the cohort for analysis if they make the study visit/contact outside this interval

5.2.1. Monitoring

Open Rome[1] will be responsible for monitoring patients' inclusion. An additional responsible in each surveillance network, belonging to the national surveillance network, will insure the recruitment and the follow-up of the patients:

Table 11 Name of staff responsible for IBGP2 management in the surveillance systems participating

#	Country	Staff
1	FRANCE	Anne Mosnier, Isabelle Daviaud, Tai Tan Bui
2	TURKEY	Selim Badur, Meral Ciblak
3	SPAIN	Tomas Vega, Carolina Rodriguez Gay, Raul Ortiz de Lejarazu
4	ITALY	Frabizio Pregliasco, Giovanni Anselmi
5	BELGIUM	Francoise Willaume, Isabelle Thomas
6	NETHERLANDS	Ge Donker, Adam Meijer
7	PORTUGAL	Carlos Dias, Ausenda Machado, Baltazar Nunes, Raquel Guiomar, Pedro Pechirra
8	SLOVENIA	Maja Socan, Katarina Prosenc

Every country coordinator is responsible for feeding the standard template created by Open Rome (an example of IBGP1 template is given in Appendix 6). This template has a MySQL platform that could be filled in through an internet provider. This template should be weekly updated to enable the production of reports showing the evolution of patients' inclusion on the study. Open Rome will insure sending this weekly report to all countries participating and to the steering committee.

The steering committee (composed by Jean Marie Cohen, John Paget, Douglas Fleming and Gonçalo Matias as an observer) will have frequent appointments to manage ethics issues, to do an overall quality control of the study, to validate monitoring procedures (rules for automatic or semi-automatic check of data entry), and the quality of data transmission to and from Vircases database.

[1] Open Rome is a clinical research organization located in Paris/France, which houses GROG network (the French influenza surveillance system). This organization routinely works with a database called Vircases. Data sent from the French regions (which make part of the surveillance system) are imported in the Vircases database in CSV format.

5.3. Laboratory assays

Laboratory testing will be carried by the Virology Lab of the National Influenza Centre (NIC) or hospitals labs involved in the surveillance networks enrolled in the study.

In regions where hospital labs serve the surveillance system as reference labs, only swabs sent by practitioners will be taken into account. Quality of virological results is controlled by NIC: in case of positive results for influenza, specimens are sent to NIC for controlling and subtyping.

NIC routinely use either PCR techniques or immune-fluorescence assay.

Influenza B virus are analyzed by antigenic characterizations by hemagglutination inhibition assay testing using ferret antisera. Ferret antisera used are prepared against the more recent vaccine reference strains of the two lineages Yamagata/Victoria.

5.4. Ethics and regulatory considerations

The study will be conducted according to Good Clinical Practice (GCP), the Declaration of Helsinki, and local rules and regulations of the country.

Submission of the protocol and any protocol amendments to regulatory agencies will occur in accordance with local regulatory requirements. For some countries, submission to the local regulatory authority may not be required. When submission to the local regulatory authority is required, the timing of the submission relative to Independent Ethics Committee/ Institutional Review Board (IEC/IRB) depends on local requirements. Further response and whether or not the authority will provide their approval or favourable opinion about the protocol or amendment before it can be implemented will also depend on local statements.

The study coordinator of each surveillance network will be accountable for the protocol submission to the local IEC/IRB, under the guidance of Open Rome.

6. Statistical Considerations

6.1. Endpoints

6.1.1. Primary endpoint(s)

- Number of laboratory confirmed influenza B (Victoria and Yamagata Lineages) in patients presenting ILI per age group and per country

6.1.2. Secondary endpoints

- Estimates of incidence rates for influenza A and B computed for each country and compared between countries.
- Number of days of illness since onset of illness.
- Number of days of absenteeism (school and work) since onset of illness
- Number of days of absenteeism of caregivers since patients onset of illness.
- Number of medical visits related to ILI in Influenza B positive patients since onset of illness.
- Use of medication (prescribed or non-prescribed drugs) during the follow-up period
- Hospitalisation since onset of illness.
- Vaccination against influenza during the current season.
- Occurrence of death.

6.2. Sample size estimation

The number of subjects will depend on the number of cases of influenza B observed during influenza season 2010/2011.

In France and in European Union, from 2004-2005 to 2010-2011, the number of documented cases of B strains ranged in France from 6 and 550 by season, and in European Union from 178 to 3114 by season.

Table 12 Flu B cases in France and in the- ECDC surveillance country members

Season	France	ECDC surveillance country members (nb of countries)
2004-2005	100	754 (28)
2005-2006	550	2903 (30)
2006-2007	6	390 (33)
2007-2008	513	3114 (38)
2008-2009	241	2342 (45)
2009-2010	7	178 (52)
2010-2011	952	?

Incidence of Influenza B may vary from one season to another. In the last season we were able to enrol 356 cases of Flu B in France and Turkey. For the next season, we expect to enrol up to 750 cases of Influenza B within 7 countries, and the same number of Influenza A positive patients for the comparison group, within the seven countries.

6.3. Study cohorts to be evaluated

6.3.1. Total Cohort

The total cohort will include all ILI subjects captured by the sentinel surveillance system of each country.

6.3.2. According-To-Protocol (ATP) cohort

The ATP cohort for analysis will include all evaluable subjects (i.e. those meeting all inclusion criteria and complying with the procedures defined in the protocol) for whom data concerning endpoint measures are available.

6.4. Conduct of analysis

6.4.1. Sequence of analyses

All analyses will be specified in the report and analysis plan.

Demographic characteristics (age, gender, centre distribution) of the total cohort and According to the Protocol cohort (ATP) will be tabulated.

All the following analyses will be performed on the ATP cohort:

- N by 2 tables will be constructed to assess **clinical features and health care consumption** in association with influenza B versus influenza A.
- N by 2 tables will be constructed to assess **clinical features** in association with influenza B and influenza A in non-vaccinated versus vaccinated patients. Comparison tests will be performed (Mann-Whitney's test for ordinal and continuous variables, respectively Fisher's exact test for categorical variables).
- The **number of days of absenteeism** among patients with influenza B versus influenza A will be compared using the Mann-Whitney's rank sum test.
- The **number of days of absenteeism** among caregivers will be compared among patients with influenza B versus influenza A (Mann-Whitney's test).
- N by 2 tables will be constructed to assess **clinical features and risk** (at D0) in association with influenza B versus Influenza A.

- The **seasonal distribution** of influenza cases will be tabulated by week, creating epidemiological curves (histograms) of the cases over time.
- Using data provided by sentinel network, the proportion of subjects with an ILI episode associated with an influenza B infection during the influenza season will be calculated with exact 95% CI in the total cohort.
- The **distribution** of influenza B and A by factors of interest will be computed from the total cohort (age group, gender).
- The proportion of **mismatch** between the circulating strains and the vaccine strains will be computed. For 2010/2011, strains antigenically related to vaccine reference strain (Victoria lineage) are considered as matching the vaccine formulation. Strains antigenically related to Yamagata lineage reference strain are considered as mismatching with the vaccine formulation.
- Some of the **point-estimates for the objectives** will be generated from a pooled data analysis and then break down by country, participating in the study, when comparable (a possible comparison could be done among risk groups, i.e. patients over 65 years old).
- Weekly **ILI incidence rate** will be estimated following EISN usual method. All networks involved in the study are used to follow this method, considered as a gold standard in WHO Euro area.
- Weekly **Influenza B incidence rate** will be estimated combining weekly ILI incidence rate and weekly percentage of influenza B among specimens of ILI, following usual method used in France by GROG Network (when possible).
    - The method for estimation uses the total cases of ILI by age group multiplied by the percentage of cases of Influenza B confirmed by laboratory. The percentage of Influenza B cases are calculated by the total randomized sample or by the total samples. Currently, randomized sample is only conducted by GPs of GROG network by demand of the National Coordination, during the epidemic period. Otherwise GROG GPs are encouraged to conduct non randomized sample when facing ILI patients, during the whole year, especially in the influenza season.
    - In other countries where GPs are not used to use a randomized sample of swabbed ILI patients, the weekly percentage of influenza B may be estimated by the total samples.
    - A sensitivity analysis will be done with French data, estimating the effect of using total sample (non randomized) instead of randomized sample.

6.4.2. Statistical considerations for interim analyses

A preliminary analysis will be performed at the end of the second influenza season (April-May 2012), using a provisional database and including the GO-NO GO criteria (see § 6.4.3), to expand the study to following influenza season and additional European countries.

6.4.3. GO-NO GO criteria

GO – Criteria for the continuation of the project:

- If a high percentage of influenza B cases detected by the sentinel networks are included in the study.
- Expansion of the project to achieve compatible data from similar studies in other European countries if:
    - It is necessary to pool data from more than the included countries to reach the primary objective.
    - If there are geographical and temporal differences in influenza B circulation between the countries analysed.

NO GO – Criteria regarding the cessation of the project:

- If there is high percentage of missing values between day 0 and the follow up.
- If less than 35% of influenza B cases detected by involved sentinel networks have been included in the study to reach all aims

7. Data Management

7.1. Data validation

Validations steps include:

- Systematic control centralized at Open Rome through the template for entry data;
- Consistency control and missing mandatory data

7.2. Missing data

Missing data will be described.

7.3. Consistency Control / Missing data

Missing or inconsistent data is stored in a specific table "validation" and recorded. Then, data are corrected and the entire history of these changes is kept. Records for which tests have been applied present a "v" for the variable "valid" at the standard table (ad hoc).

Status inconsistency is recorded as following:

- ‘C’ = corrected – the value of the laboratory is correct; the correction of the ad hoc table is realized
- ‘V’: validated = the value located at "clinic_10_11" is the right one
- ‘R’: correction request sent to current doctors
- ‘N’: new = to be handle
- ‘A’: waiting = value is not immediately correctable (e.g. it would require a return to the doctor for reanalyzing)

The technical description of Consistency Control is stored in a table ad hoc.

7.4. Automatic corrections before validation

- Some adjustments will be made on an automatic mode according to logical rules validated by the Steering Committee and National Coordinators.
- Controls of presence

A systematic check of data queries will be done at the central level (Open Rome) and communicated to the national coordinators for corrections.

8. Subject completion and withdrawal

8.1. Subject completion

A subject who is available for the concluding contact foreseen in the protocol is considered to have completed the study.

8.2. Subject withdrawal

From an analysis perspective, a ‘withdrawal’ from the study is any subject who was not available for the concluding contact foreseen in the protocol.

A subject is qualified as a ‘withdrawal’ from the study perspective when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

Sentinels will make an attempt to contact those subjects who do not return for scheduled visits or follow-ups.

Information related to the withdrawal will be documented on the Study Conclusion page of the CRF. The investigator will document which of the following possible reasons were responsible for the withdrawal:

- protocol violation (specify),
- consent withdrawal,
- lost to follow-up,
- other (specify).

Withdrawals will not be replaced.

References

ECDC Portal > English > Activities > Surveillance > EISN > Influenza case definitions:http://www.ecdc.europa.eu/en/activities/surveillance/EISN/Pages/AbouttheNetwork_Influienzacasedefinitions.aspx

Fleming DM, Elliot AJ. Differential presentation of clinical syndromes in relation to influenza virus type and subtype. Options for the Control of Influenza VI, Toronto, Ontario, Canada, June 17-23, 2007

Guarner J, Paddock CD, Shieh WJ, Packard MM, Patel M, et al. (2006) Histopathologic and immunohistochemical features of fatal influenza virus infection in children during the 2003-2004 season. Clin Infect Dis. 43(2): 132-140

McNeill KM, Vaughn BL, Brundage MB, Li Y, Poropatich RK, et al. (2005) Clinical presentations for influenza and influenza-like illness in young, immunized soldiers. Mil Med. 170(1): 94-97.

Pitman RJ, Melegaro A, Gelb D, Siddiqui MR, Gay NJ and Edmunds WJ. Assessing the burden of influenza and other respiratory infections in England and Wales. J Infect 2007; 6:530-538.

Stephanie A. Richard, Cecile Viboud, Mark A. Miller. Evaluation of Southern Hemisphere influenza vaccine recommendations. Vaccine 2010;

Thom DH, Grayston JT, Campbell LA, Kuo CC, Diwan VK, et al. (1994) Respiratory infection with Chlamydia pneumoniae in middle-aged and older adult outpatients. Eur J Clin Microbiol Infect Dis. 13(10): 785-792.

Thompson WW, Shay DK, Weintraub E, Brammer L, Bridges CB, Coz NJ, et al. Influenza-associated hospitalizations in the United States. JAMA 2004; 292 (11): 1333-40.

Thompson WW, Shay DK, Weintraub E, Brammer L, Coz NJ, Anderson LJ, et al. Mortality associated with infleunza and respiratory syncytial virus in the United States. JAMA 2003; 289 (2): 179-86.

Vilchez RA, McCurry K, Dauber J, Iacono A, Griffith B, et al. (2002) Influenza virus infection in adult solid organ transplant recipients. Am J Transplant. 2(3): 287-291.

Appendixes

Appendix 1 – Current Clinical Forms of influenza surveillance networks of enrolled countries – English version of CRF D0

Appendix 1.1 – French Clinical Form D0 – GROG network

Saison 2011-2012

PATIENT NOM

PRENOM

Suite à l'information donnée par le médecin, le patient s'est opposé ❑ ne s'est pas opposé ❑
à l'utilisation secondaire des données collectées et des échantillons pour des recherches sur les infections respiratoires.
(Cocher la case correspondant à la décision du patient)

Cachet du médecin	*Etiquette du laboratoire*	*Date d'arrivée au laboratoire*

Date de naissance _ _ _ _ _ _ _ _ (jj/mm/aaaa) Sexe ❑ F ❑ M Code postal de résidence _ _ _ _ _

Date de début de maladie _ _ _ _ _ _ _ _ (jj/mm/aaaa) Date de prélèvement _ _ _ _ _ _ _ _ (jj/mm/aaaa)

Vaccination antigrippale 2011-2012 ❑ Oui ❑ Non Si oui, date _ _ _ _ _ _ _ _ (jj/mm/aaaa)

❑ Agrippal ❑ Fluarix ❑ Immugrip ❑ Influvac ❑ Mutagrip ❑ Previgrip ❑ Vaxigrip ❑ Tetagrip

Vaccination antigrippale 2010-2011 ❑ Oui ❑ Non

Contexte

❑ Cas isolé ❑ Epidémie familiale ❑ Epidémie en collectivité (école, entreprise, EHPA…) Laquelle ……..

❑ Voyage récent (<15 jours) pays ……

Etat clinique

❑ Fièvre Température max …….	❑ Dyspnée / Polypnée	❑ Otite / Otalgie
❑ Début brutal	❑ Toux	❑ Troubles digestifs
❑ Asthénie	❑ Expectoration	❑ Conjonctivite
❑ Myalgies / Courbatures	❑ Bronchiolite / Bronchite	❑ Adénopathies
❑ Frissons	❑ Rhinite / Coryza	❑ Eruption
❑ Céphalées	❑ Pharyngite	❑ Autres signes ……

Adressé CE JOUR à l'hôpital ❑ Oui ❑ Non

Traitement prescrit CE JOUR ❑ Antibiotiques ❑ Antiviral lequel ……

Un antiviral a-t-il été consommé AUPARAVANT (au cours des 2 semaines précédant la consultation) **par :**

❑ Patient Date de début _ _ _ _ _ _ _ _ Dosage : ❑ curatif ❑ préventif Lequel ……
❑ Membre famille Date de début _ _ _ _ _ _ _ _ Dosage : ❑ curatif ❑ préventif Lequel ……

Nombre de consultations ou visites chez le médecin traitant **au cours des 12 derniers mois** ❑ 0-1 ❑ 2-4 ❑ 5 et+
Le patient est-il dépendant (besoin d'aide dans la vie quotidienne) ? ❑ Oui ❑ Non

Facteurs de risque, antécédents justifiant une vaccination antigrippale ❑ Oui ❑ Non
Précisez :

❑ Grossesse en cours ❑ IMC ≥ 30 ❑ Diabète ❑ Maladie cardio-vasculaire
❑ Maladie chronique pulmonaire ❑ Immunodépression ❑ Autre maladie chronique

Hospitalisation en lien avec la maladie chronique au cours des 12 derniers mois ❑ Oui ❑ Non

Commentaires

2011-2012

Appendix 1.2 – Turkish Clinical Form D0 – Istanbul Influenza Center

TURKISH MINISTRY of HEALTH

NATIONAL INFLUENZA REFERENCE LABORATORY INFLUENZA AND INFLUENZA -LIKE ILLNESS CASE REPORTING AND LABORATORY REQUEST INFORMATION FORM

☐ SENTİNEL SURVEİLLANCE — Date of reporting: ……/……/……..…
☐ OTHER (INDICATE,……...…… Date of symptoms onset: …../…../…….

SENDER/INSTITUTION INFORMATION	**HOSPITAL/HEALTH CARE CENTER INFORMATION**
	Name of the Institution
Name, Last Name	Has the patient been hospitalized? ☐No ☐Yes
İnstitution Name	Date of hospital visit: ……/……./……..…
City	Date of hospitalization: ……/……./……..…
Tel: ……	Date of discharge: ……../……../……
Speciality	Is the patient hospitalized due to ILI?
	☐Yes ☐No (Explain……
	Tel: …… Fax

PATIENT INFORMATION

Name, Last Name — DOB: :…../…../…….
İdentification Number
Residance Address:…… Cinsiyet: ☐Erkek
Street ☐Kadın
County:……..…City:……Occupation ……
Tel: (Home): ( )……GSM ( ) ……

CLINICAL SYMPTOMS

□ Fever (……°C) □ Headache □ Difficulty in breathing
□ Cough □ Joint pain □ Acut respiratory distress (requiring ventilation)
□ Miyalgia □ Sore throat □ Other symptoms (Explain……
□ Runny nose
Did you prescribe antivirals/ antibiotics due to these symptoms? □ No □ Yes (Explain, ……..)

PATIENT HISTORY

□ İmmunosuppression……..... □ Pregnant …. ….Months.…
□ Chronic diseases (Explain……...……. □ Morbid obesity (BKİ ≥ 35)
□ Comorbidity (Explain……..……..……)
□ Chronic use of medications (The purpose of use……)

VACCINATION STATUS

Has the patient been vaccinated for the current season? □ Yes □ No □ Doesn't know Date of vaccination: …./

EPIDEMIOLOGICAL INFORMATION

Route of Transmission

Are there others with the same symptoms? □ No □ Yes □ at work □ at school □at home

Travel History

□ Has the patient travelled from the place of residency within 2 weeks before the onset of the symptoms?
If yes, where/ when?……

□ Has the patient had contact with someone with travel history within 2 weeks before the onset of the symptoms?

SPECIMEN INFORMATION

Date sample was taken: …../…../……. Type of specimen:
☐Nasal Swab ☐Nasal +Throat Swab ☐Throat Swab ☐Nose/Throat Wash ☐Other ……..

LABORATORY CONTACT INFORMATION

Dr. Meral Akçay Ciblak 5379567545 ciblakm@yahoo.com

If this form is not completed properly the sample will not be tested

Appendix 1.3 – Spanish Clinical Form D0 – Castilla y Léon Network

Junta de Castilla y León
Consejería de Sanidad
Dirección General de Salud Pública e Investigación, Desarrollo e Innovación

CLINICAL AND LAB INFORMATION (SWABED CASES ONLY)

LABEL

IDENTIFICATION:

Nº Identification: |____|___|___|
(week,, sheet number, patient number)

Surname:_____ **Name:** _____ **Age:** ____ **Gender:**_____
Date of onset of symptoms: ____/____/_____ **Date swabbing:** ____/____/_____

Any contraindications against flu vaccination……. No • Yes • No data/Don´t know•	**Smoker:**……No • Yes • Used to •
	Chronic treatment with salicilates…… No • Yes • No data/Don´t know•
Flu vaccination: 2011/12 No • Yes • No data/Don´t know• Date of vaccination: ___/___ Type of vaccine (brand name): _____	**Paciente institucionalizado……** No • Yes • No data/Don´t know•
	Number of hospitalizations previous year for the chronic disease……..….._____
2010/11: No • Yes • No data/Don´t know•	**Number of GP consultatios previous year……._____**
	Requires assistance to walk No • Yes • No data/Don´t know•
Antibiotic treatment No • Yes • No data/Don´t know• **Antiviral treatment** No • Yes • No data/Don´t know•	**Requires assistance to bath** No • Yes • No data/Don´t know•

Date of swab dispatching: ____/____/_____
OBSERVATIONS:_____
_____

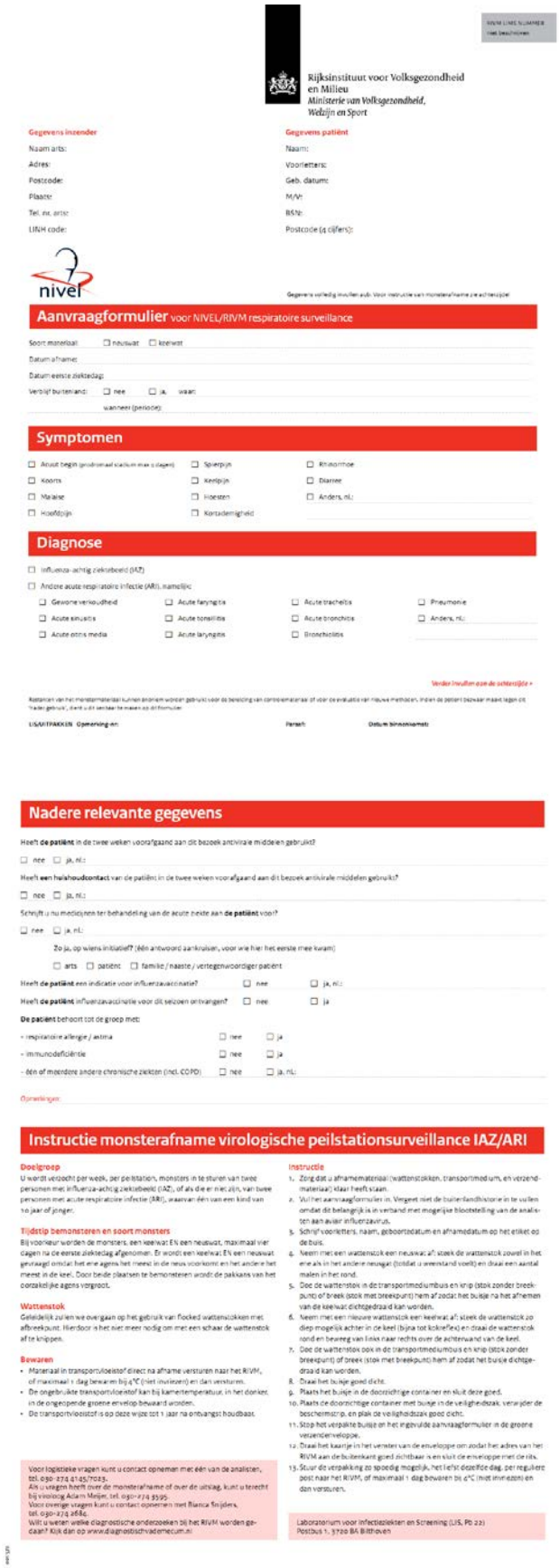
LABORATORY RESULTS

Date of reception: ___/___/_____ **Laboratory result** Negative• Positive• Date __/__/__
Detection: **Virus Type** Tipo: A• B•
Culture.. __ Date swabbing:___/___/____ **Subtype:**_____
PCR…. __ **Name:**_____
Others (specify) _____

Does the patient authorize telephone contact?
YES • Telephone number:……
No •

Guarde una copia de este anexo en la historia clínica del paciente

Appendix 1.4 – Dutch Clinical Form D0 – Dutch Surveillance Network



Rijksinstituut voor Volksgezondheid en Milieu
Ministerie van Volksgezondheid, Welzijn en Sport

Gegevens inzender
Naam arts:
Adres:
Postcode:
Plaats:
Tel. nr. arts:
LINH code:

Gegevens patiënt
Naam:
Voorletters:
Geb. datum:
M/V:
BSN:
Postcode (4 cijfers):

nivel

Gegevens volledig invullen a.u.b. Voor instructie van monsterafname zie achterzijde

Aanvraagformulier voor NIVEL/RIVM respiratoire surveillance

Soort materiaal: ☐ neuswat ☐ keelwat
Datum afname:
Datum eerste ziektedag:
Verblijf buitenland: ☐ nee ☐ ja, waar:
wanneer (periode):

Symptomen

☐ Acuut begin (prodromaal stadium max 5 dagen) ☐ Spierpijn ☐ Rhinorroe
☐ Koorts ☐ Keelpijn ☐ Diarree
☐ Malaise ☐ Hoesten ☐ Anders, nl.:
☐ Hoofdpijn ☐ Kortademigheid

Diagnose

☐ influenza-achtig ziektebeeld (IAZ)
☐ Andere acute respiratoire infectie (ARI), namelijk:
☐ Gewone verkoudheid ☐ Acute faryngitis ☐ Acute tracheitis ☐ Pneumonie
☐ Acute sinusitis ☐ Acute tonsillitis ☐ Acute bronchitis ☐ Anders, nl.:
☐ Acute otitis media ☐ Acute laryngitis ☐ Bronchiolitis

Verder invullen aan de achterzijde >

Restanten van het monstermateriaal kunnen anoniem worden gebruikt voor de bereiding van controlemateriaal of voor de evaluatie van nieuwe methoden. Indien de patiënt bezwaar maakt tegen dit (mede) gebruik, dient u dit aantekening te maken op dit formulier.

LIS/AFTAKKEN Opmerking en: Paraaf: Datum binnenkomst:

Nadere relevante gegevens

Heeft **de patiënt** in de twee weken voorafgaand aan dit bezoek antivirale middelen gebruikt?
☐ nee ☐ ja, nl.:

Heeft **een huishoudcontact** van de patiënt in de twee weken voorafgaand aan dit bezoek antivirale middelen gebruikt?
☐ nee ☐ ja, nl.:

Schrijft u nu medicijnen ter behandeling van de acute ziekte aan **de patiënt** voor?
☐ nee ☐ ja, nl.:

Zo ja, op wiens initiatief? (één antwoord aankruisen, voor wie het eerste mee kwam)
☐ arts ☐ patiënt ☐ familie / naaste / vertegenwoordiger patiënt

Heeft **de patiënt** een indicatie voor influenzavaccinatie? ☐ nee ☐ ja, nl.:
Heeft **de patiënt** influenzavaccinatie voor dit seizoen ontvangen? ☐ nee ☐ ja

De patiënt behoort tot de groep met:
- respiratoire allergie / astma ☐ nee ☐ ja
- immunodeficiëntie ☐ nee ☐ ja
- één of meerdere andere chronische ziekten (incl. COPD) ☐ nee ☐ ja, nl.:

Opmerkingen:

Instructie monsterafname virologische peilstationsurveillance IAZ/ARI

Doelgroep
U wordt verzocht per week, per peilstation, monsters in te sturen van twee personen met influenza-achtig ziektebeeld (IAZ), of als die er niet zijn, van twee personen met acute respiratoire infectie (ARI), waarvan één van een kind van 10 jaar of jonger.

Tijdstip bemonsteren en soort monsters
Bij voorkeur worden de monsters, een keelwat EN een neuswat, maximaal vier dagen na de eerste ziektedag afgenomen. Er wordt een keelwat EN een neuswat gevraagd omdat het ene agens het meest in de neus voorkomt en het andere het meest in de keel. Door beide plaatsen te bemonsteren wordt de pakkans van het oorzakelijke agens vergroot.

Wattenstok
Geleidelijk zullen we overgaan op het gebruik van flocked wattenstokken met afbreekpunt. Hierdoor is het niet meer nodig om met een schaar de wattenstok af te knippen.

Bewaren
- Materiaal in transportvloeistof direct na afname versturen naar het RIVM, of maximaal 1 dag bewaren bij 4°C (niet invriezen) en dan versturen.
- De ongebruikte transportvloeistof kan bij kamertemperatuur, in het donker, in de ongeopende groene envelop bewaard worden.
- De transportvloeistof is op deze wijze tot 1 jaar na ontvangst houdbaar.

Voor logistieke vragen kunt u contact opnemen met één van de analisten, tel. 030-274 91 65/7025.
Als u vragen heeft over de monsterafname of over de uitslag, kunt u terecht bij virologe Adam Meijer, tel. 030-274 3595.
Voor overige vragen kunt u contact opnemen met Bianca Snijders, tel. 030-274 2684.
Wilt u weten welke diagnostische onderzoeken bij het RIVM worden gedaan? Kijk dan op www.diagnostischvademecum.nl

Instructie
1. Zorg dat u afnamemateriaal (wattenstokken, transportmedium, en verzendmateriaal) klaar heeft staan.
2. Vul het aanvraagformulier in. Vergeet niet de buitenlandhistorie in te vullen omdat dit belangrijk is in verband met mogelijke blootstelling van de analisten aan aviair influenzavirus.
3. Schrijf voorletters, naam, geboortedatum en afnamedatum op het etiket op de buis.
4. Neem met een wattenstok een neuswat af; steek de wattenstok zowel in het ene als in het andere neusgat (totdat u weerstand voelt) en draai een aantal malen in het rond.
5. Doe de wattenstok in de transportmediumbuis en knip (stok zonder breekpunt) of breek (stok met breekpunt) hem af zodat het buisje na het afnemen van de keelwat dichtgedraaid kan worden.
6. Neem met een nieuwe wattenstok een keelwat af; steek de wattenstok zo diep mogelijk achter in de keel (bijna tot kokhalzen) en draai de wattenstok rond en heenweg van links naar rechts over de achterwand van de keel.
7. Doe de wattenstok ook in de transportmediumbuis en knip (stok zonder breekpunt) of breek (stok met breekpunt) hem af zodat het buisje dichtgedraaid kan worden.
8. Draai het buisje goed dicht.
9. Plaats het buisje in de doorzichtige container en sluit deze goed.
10. Plaats de doorzichtige container met buisje in de veiligheidszak, verwijder de beschermstrip, en plak de veiligheidszak goed dicht.
11. Stop het verpakte buisje en het ingevulde aanvraagformulier in de groene verzendenvelop.
12. Draai het kaartje in het venster van de enveloppe om zodat het adres van het RIVM aan de buitenkant goed zichtbaar is en sluit de enveloppe met de rits.
13. Stuur de verpakking zo spoedig mogelijk, het liefst dezelfde dag, per reguliere post naar het RIVM, of maximaal 1 dag bewaren bij 4°C (niet invriezen) en dan versturen.

Laboratorium voor Infectieziekten en Screening (LIS, Pb 22)
Postbus 1, 3720 BA Bilthoven

Appendix 1.5 – Belgian Clinical Form D0 –Surveillance Network

20110

9 1 1 3

Surveillance virologique de la Grippe
Centre national Influenza (O.M.S.)

Institut scientifique de Santé Publique (ISP)
14, Rue Juliette Wytsman – 1050 Bruxelles
Fax: 02/ 642 56 92

Dr. Thomas 02/642 50 74
Isabelle.Thomas@wiv-isp.be
Dr. Hombrouck: 02/642 55 96
Anneleen.Hombrouck@wiv-isp.be

Réf : H.R.O.

Date du prélèvement : 17/04/2011

Date de naissance : 26/08/1944

Sexe : ● Masc. ○ Fém.

Code postal : B E 5570

Dr GERARD Jean
Rue de Bouillon, 417
5570 BEAURAING

Symptomes

Date début des Symptômes 19/04/2011 Température > 38°C ● Oui ○ Non ○ Inconnu

○ Début brutal	● Toux	○ Dyspnée
● Frissons	● Expectorations	○ Râles, sibilences
● Asthénie, abattement	● Coryza, rhinorrhée	○ Troubles gastro-intestinaux
○ Céphalées	○ Symptômes oculaires	○ Confusion, désorientation
● Myalgies, courbatures	● Douleurs auriculaires	○ Vertiges
○ Manque d'appétit	○ Gorge rouge	○ Autre ----------

Groupes à risques

○ Maladie respiratoire chronique (hors asthme)	○ Troubles neuromusculaires
○ Maladie cardiaque chronique (hors hypertension)	○ Maladie cardiaque chronique (hors hypertension)
○ Insuffisance rénale modérée à sévère	○ Diabète type I ou II
○ Insuffisance hépatique modérée à sévère	○ Insuffisance hépatique modérée à sévère
○ Immunodépression (par maladie ou médicament)	○ Obésité (BMI > 30)
○ Grossesse	○ Inconnu
○ Asthme	○ Pas de groupe à risques
○ Autre ----------	

Questions supplémentaires

Hospitalisation : ○ Oui ● Non ○ Inconnu

Traitement antiviral : ○ Oseltamivir ○ Relenza ● Non ○ Inconnu

Vaccination contre la grippe saisonnière à partir du 1/10/2010 : ○ Oui ● Non ○ Inconnu

Si oui : Date de vaccination : ___/___/_____

Réservé pour le laboratoire de l'ISP

Date : 21/09/2011

201 G0926

Date du test 27/9/2011

Influenza A	Positif ○	Negatif ●	Indéterminé ○
Influenza B	Positif ○	Negatif ●	Indéterminé ○

Autres virus testés ○ Oui ● Non

RSV	Positif ○	Negatif ○	Indéterminé ○
HMPv	Positif ○	Negatif ○	Indéterminé ○
PIV (1,2,3)	Positif ○	Negatif ○	Indéterminé ○
Rhinovirus	Positif ○	Negatif ○	Indéterminé ○

Appendix 1.6 – Portuguese Clinical Form D0 – Portuguese Surveillance Network

Instituto Nacional de Saúde Doutor Ricardo Jorge

MS

Programa Nacional de Vigilância da Gripe 2010/2011

Clinical form

Health Center.....
GP number.....
Swab Date.....___/___/___

Swab Time .....|__|__|

To be filled in by INSA
Lab Nr: .....Req Nr.:.....

Date: ___/___/___ Sample Nr.....

Research for Influenza virus

Result: .....

Patient information

Gender.....|M|F| Age:....| _ | _ | years....| _ | _ | months

Influenza Like Illness
Case definition,EU criteria: A+1 symptom B +1 symptom C

Symptoms onset date.....__/__/__

A
- Sudden onset (<24h).....|Y|N|U|

B
- Fever ___,___ °C.....|Y|N|U|
- Malaise.....|Y|N|U|
- Headache.....|Y|N|U|
- Myalgia.....|Y|N|U|

C
- Cough.....|Y|N|U|
- Sorethroat .....|Y|N|U|
- Shortness of breath.....|Y|N|U|
- Chills.....|Y|N|U|
- Contact with patient with flu.....|Y|N|U|

Seasonal vaccine .....|Y|N|U|

Date __/__/__

Administration of antivirals in the last 14 days?

|_| No
|_| Yes, the patient
|_| Yes, one patient co-habitant

Name of the antiviral

.|_| Oseltamivir (Tamiflu)
|_| Zanamivir (Relenza)
|_|Other

Antiviral prescription? |Y|N|U|
Name of the antiviral
.....

Note: **M** – Male **F** – Female **Y** – Yes **N** – No **U** – Unknown

Appendix 1.7 – Slovenian Clinical Form D0 – Slovenian Surveillance Network

National programme of influenza like-illness and acute respiratory infections surveillance SLOVENIA

VIROLOGY ANALYSIS FORM

Health Centre: _____

Surname and first name:_____
Date of birth:_____
Address:_____

Date of onset :_____
Date of swab collection: _____

pharyngeal swab	yes	no
nose swab	yes	no

vaccinated against influenza	yes	no
Treatment with NI (oseltamivir, zanamivir)	yes	no

fever over 38.0°C	yes	no
chills	yes	no
headache	yes	no
myalgia/arthralgia	yes	no
malaise	yes	no
burning eyes	yes	no
coryza	yes	no
sore throat	yes	no
earache	yes	no
hoarseness	yes	no
cough	yes	no

conjuctivitis	yes	no
hyperemic throat	yes	no
signs of otitis media	yes	no
pathological pulmonary avscultation	yes	no
other	yes	no

MD:_____ Tel.:_____

Appendix 2 – Common data for D0 questionnaires of surveillance networks participating in the study

Open Rome

IBGP 2

D0 standard form
Common data for multi-country pooled analysis

Each country will have a login and password to access the template in the internet.
Bold characters: answer by default

questions	*Possible answers*	*Format IBGP2*
Sentinel or other	**Sentinel** Other	1=**sentinel** 2=other
Date of sample's arrival to the lab	dd/mm/yyyy	dd/mm/yyyy
Patient's profile		
Patient's identification	- country code automatic (ES, FR, TR, IT, BE, NL, PT, SI) - Flu type (B or A) - number of inclusion (###)	XX B/A ###
Date of birth (DOB) *OR* Age	- DOB : dd/mm/yyyy - Age : 3 digits	dd/mm/yyyy ###
Gender	Female Male	F M
Date of onset of symptoms	dd/mm/yyyy NA	dd/mm/yyyy
Date of swabbing	dd/mm/yyyy	dd/mm/yyyy
Current seasonal vaccination (2011-12)	yes / no /unknown date of vaccination	1/0/9 dd/mm/yyyy
Clinical symptoms		
Fever	yes / no /unknown	1/0/9
Sudden onset	yes / no /unknown	1/0/9
Malaise *(malaise, asthenia, frissons, chills)*	yes / no /unknown	1/0/9
Myalgia, joint pain	yes / no /unknown	1/0/9
Headache	yes / no /unknown	1/0/9
Shortness of breath, dyspnea, polypnea	yes / no /unknown	1/0/9
Cough	yes / no /unknown	1/0/9
Rhinitis, coryza, common cold	yes / no /unknown	1/0/9
Sore throat	yes / no /unknown	1/0/9
Other symptoms (several answers authorized)	yes / no /unknown Adenopathy Bronchitis/bronchiolitis Conjunctivitis Dizziness Gastrointestinal symptoms Laryngitis Otitis/Otalgia Pneumopathy Respiratory distress Rush Sinusitis Sputum Tonsillitis Tracheitis *others*	1/0/9 *Open-ended question (in English)*
Health care consumption		
Patient's use of antivirals within 2 weeks before onset of symptoms	yes / no /unknown	1/0/9
Antibiotics prescribed to patient	yes / no /unknown	1/0/9
Antivirals prescribed to patient	yes / no /unknown	1/0/9
Sent to hospital today	yes / no /unknown	1/0/9

Appendix 2 – Common data for D0 questionnaires of surveillance networks participating in the study (continuation)

Open Rome

IBGP 2

questions	*Possible answers*	*Format IBGP2*
	Underlying health problem / risk group	
Patient at risk	yes / no /unknown Pregnancy Excessive BMI Diabetes Heart diseases Pulmonary chronic disease Immunocompromised Other chronic disease Not specified	1/0/9
	Virological result	
Flu A	yes / no Flu A(H1N1) Flu A(H3N2) Flu A not subtyped Flu A new subtype	
Flu B	yes / no Flu B lineage Yamagata Flu B lineage Victoria Flu B lineage unknown	
Comments	-	*Open-ended question (in English)*

Appendix 3 – Case Report Form D9 – common to all influenza surveillance system participating in the study

IBGP2

Influenza B in General Practice

D 9 ± 2 days

Doctor's name: ***prefilled*** Patient ID code: ***prefilled***

Patient identification **Age:** *prefilled* **Gender**: *prefilled* **Date of swabbing:** *prefilled*

Does the patient have a remunerated job? YES ☐ NO ☐

Date of contact with the patient at D9 /___/___/___/ **no later than:** *prefilled*

⇨ SINCE THE DAY OF SWABBING (D0 included),

how many times did the patient consult you due to ILI swabbed (since the day of swabbing) ?
by phone call /__/ in your medical office /__/ at home /__/

did the patient see another doctor (since the day of swabbing)? YES ☐ NO ☐
if yes, how many times? by phone call /__/ in his medical office /__/ at home /__/

has he been to a hospital emergency room? YES ☐ NO ☐

has he been hospitalised? YES ☐ NO ☐
if NO, has he done additional tests? YES ☐ NO ☐
specify (ECG, blood test, RX…): _____
did he need paramedical care? YES ☐ NO ☐
specify (nurse, nutrition, physiotherapy...): _____

⇨ SINCE THE DAY OF SWABBING (D0 included),

how many days was he out of work? /__/__/ N/A ☐
children daycares *or* school? /__/__/ **Parent's sick leave due to children's disease?** /__/__/ **days**

A "curative" antiviral has been prescribed? YES ☐ NO ☐ **if YES,** specify Tamiflu® ☐ Relenza® ☐
how long was the delay between the onset of symptoms and the beginning of the medication?
less than 12h ☐ 12h-24h ☐ 24h-36h ☐ 36h-48h ☐ more than 48h ☐

⇨ **Drug treatment** SINCE THE DAY OF SWABBING (D0 included)

DRUG *(name)*	*Prescribed*	*Self-medication*
----------	☐	☐
----------	☐	☐
----------	☐	☐
----------	☐	☐
----------	☐	☐
----------	☐	☐
	☐	☐

⇨ WHAT IS THE CURRENT CLINICAL CONDITION OF THE PATIENT?

Has he returned to his "normal activities"[1] (school, work…)? YES ☐ NO ☐
if yes, specify (if not possible, estimate) the date of return /___/___/___/

Has he still got any symptoms related to ILI swabbed? YES ☐ NO ☐ **if YES,** specify:
/__/ persistent cough (with or without expectoration),
/__/ nasal symptoms (rhinorrhea or nasal obstruction),
/__/ headache, /__/asthenia, /__/ others symptoms[2]: _____

☐ **Death**

Comments:

Please, send this form to IBGP Coordination
☏ ✉ @

[1] "Normal activities": patient returned to his usual routine/occupation (work, school, homemade, day-to-day life...)
[2] "Other symptoms" are defined as Flu complications, for example: Fever, Throat symptoms (sore throat, pharyngitis), Otalgia/otitis, Sinusitis, Pneumonia, Low respiratory tract symptoms (asthma/COPD decompensation, bronchitis, bronchiolitis, shortness of breath, dyspnoea, thoracic pain...), Myalgia/myositis, Anorexia, Digestive symptoms, Vertigo, Adenopathy

Appendix 4 – Case Report Form D28 – common to all influenza surveillance system participating in the study

IBGP2

Influenza B in General Practice

D 28 ± 5 days

Doctor's name: ***prefilled*** Patient ID code: ***prefilled***

Patient identification **Age:** *prefilled* **Gender**: *prefilled* **Date of swabbing:** *prefilled*

Date of contact with the patient at D9 /___/___/___/ **no later than:** *prefilled*

⇨ SINCE THE FIRST PHONE CONTACT WITH THE PATIENT (D9±2 not included),

how many times did the patient consult you due to ILI swabbed (since the day of swabbing) ?

by phone call /__/ in your medical office /__/ at home /__/

did the patient see another doctor (since the day of swabbing)? YES ☐ NO ☐

if yes, how many times? by phone call /__/ in his medical office /__/ at home /__/

has he been to a hospital emergency room? YES ☐ NO ☐

has he been hospitalised? YES ☐ NO ☐

if NO, has he done additional tests? YES ☐ NO ☐

specify (ECG, blood test, RX…): _____

did he need paramedical care? YES ☐ NO ☐

specify (nurse, nutrition, physiotherapy...): _____

⇨ SINCE THE FIRST PHONE CONTACT WITH THE PATIENT (D9±2 not included),

how many days was he out of work? /__/__/ N/A ☐

children daycares *or* school? /__/__/ **Parent's sick leave due to children's disease?** /__/__/ **days**

⇨ **Drug treatment** SINCE THE FIRST PHONE CONTACT WITH THE PATIENT (D9±2 not included)

DRUG *(name)*	*Prescribed*	*Self-medication*
----------	☐	☐
----------	☐	☐
----------	☐	☐
----------	☐	☐
----------	☐	☐
----------	☐	☐
----------	☐	☐

⇨ WHAT IS THE CURRENT CLINICAL CONDITION OF THE PATIENT?

Has he returned to his "normal activities"[1] (school, work…)? YES ☐ NO ☐

if yes, specify (if not possible, estimate) the date of return /___/___/___/

Has he still got any symptoms related to ILI swabbed? YES ☐ NO ☐ **if YES,** specify:

/__/ persistent cough (with or without expectoration),

/__/ nasal symptoms (rhinorrhea or nasal obstruction),

/__/ headache, /__/asthenia, /__/ others symptoms[2]: _____

☐ **Death**

Comments:

Please, send this form to IBGP Coordination

☎ ✉ @

[1] "Normal activities": patient returned to his usual routine/occupation (work, school, homemade, day-to-day life...)

[2] "Other symptoms" are defined as Flu complications, for example: Fever, Throat symptoms (sore throat, pharyngitis), Otalgia/otitis, Sinusitis, Pneumonia, Low respiratory tract symptoms (asthma/COPD decompensation, bronchitis, bronchiolitis, shortness of breath, dyspnoea, thoracic pain...), Myalgia/myositis, Anorexia, Digestive symptoms, Vertigo, Adenopathy

Appendix 5 – Model of Informed Consent Form

Open Rome

IBGP

Influenza B in General Practice (IBGP)

Study Reference *EPI-FLU 014 EU BOD CRT (115173)*

Patient Information Leaflet

Following the consultation, of /__/__//__/__//__/__/__/__/ (dd/mm/yyyy)
at which a swabbing of the nose (or throat) was performed, you can participate, if you accept, in a study of acute respiratory infections, which your doctor coordinate locally.
The full title of the study is

« The burden of influenza B in Europe: a prospective multi-country strain surveillance study using community-based specimens. »

This is an observational study of patients with influenza like illness comparing the symptoms and the severity of illness experienced by patients whose infection is caused by influenza B or other respiratory viruses.

Background

Influenza is common and occurs in most winters. There are two main types of influenza virus which cause influenza likes illness in humans – influenza A and influenza B. When participating in this study is you will help us to find out more about the types B influenza, especially with regard to the severity and duration of illness. These data would aid on decisions on how best to manage flu and the development of new drugs and preventive vaccines.

Your role in this study

Apart from the swab, the study of the Influenza B involves answering some questions about your illness: the symptoms experienced, medicines taken and school/work absenteeism. It would be sensible to arrange suitable times for telephone or face to face contacts:

- 9 days after the nose/throat swab sample - we will phone to see how you are progressing. We will want to know how ill you have been, whether you are still having symptoms, what medicines or tablets you have taken and how long you have had to stay off school or off work as a career.
- 28 days after the nose/throat swab sample, we will telephone you again to ensure that you have had no complications and you have completely recovered and where appropriate, details of any hospital admission.

How Do I Take Part?

Your doctor will have handed you this leaflet because he/she thinks you are a suitable person to help with this study. You are free to decide weather to participate or not in this study. It is your choice to be involved and if you decide not to, it will not affect the way you are treated in any way. Any treatment offered to you is not related to whether you agree to take part or not.

Your participation in this study does not involve any additional treatment or vaccination beyond that currently required in the clinical picture. There is no risk to you to participate in this study.
If, after reading this information sheet and satisfying yourself about the answers to your questions provided by your doctor or practice nurse, you are willing to take part you will be asked to sign two copies of the

Influenza B in General Practice – IBGP – study Phase II 1/3

Appendix 5 – Model of Informed Consent Form (continuation)

Open Rome
IBGP

"Patient Consent Form" which is attached. The doctor will keep one copy and return the other copy for your own records.

Data Confidentiality

All information collected during the study will be kept by a computer system. The child's name will not appear at any time in the computer data in accordance with the law (*Article 40 of Law 78.17 of 6 January 1978*).
Article L1122-1 of the Code of Public Health.

Who is Responsible For This Study?

At the European level this study is led by a group of doctors working together under the overall leadership of the Open Rome medical research organisation in Paris. The steering group responsible for this study are JM Cohen, J Paget (the Netherlands), DM Fleming (England), who are all involved in routine influenza surveillance in their respective countries and G Matias (Belgium) who represents the sponsoring company (GlaxoSmithKline Pharmaceuticals) which has provided the funds for the study. These include the costs of the staff involvement in the medical practices and the clinical laboratories. The reimbursement of the practice and laboratory staff is in accordance with nationally approved guidelines for conducting medical research. In each country where this study takes place, a national co-ordinator has been appointed to supervise the conduct of the study, to oversee the collection of the records and to assist with the analysis of the material in that country.

Full Name,
address,
phone and e-mail contact of the responsible of IBGP study in each country

Appendix 5 – Model of Informed Consent Form (continuation)

Open Rome

IBGP

Influenza B in General Practice (IBGP)

Study Reference *EPI-FLU 014 EU BOD CRT (115173)*

Patient Consent Form

Name .....

Address .....

.....Telephone .....

1] I have received the patient information sheet entitled 'Influenza B in General Practice (IBGP)' study reference *EPI-FLU 014 EU BOD CRT (115173);* and I have had the opportunity to discuss this with

Dr ..... at the Medical Practice about my symptoms of Acute Respiratory Illness.

2] I am willing to help with this study recognising that I am free to withdraw at any time without offering any explanation and without it making any difference to my treatment.

3] I am willing for my doctor to use information in the medical records of my child for completing the research questions as outlined in the information leaflet. I have been assured that all information obtained in this study is stored in a medical report form which is anonymised and no named data are stored by the research team involved.

4] I acknowledge having had time for reflection that I needed to make my decision.

Signature (for persons over 16)

Individual Patient ..... date / /

Signature (Persons aged 12 to16),

Individual Patient ..... date / /

Plus Parent or Guardian ..... date / /

Signature (Persons aged less than 12years)

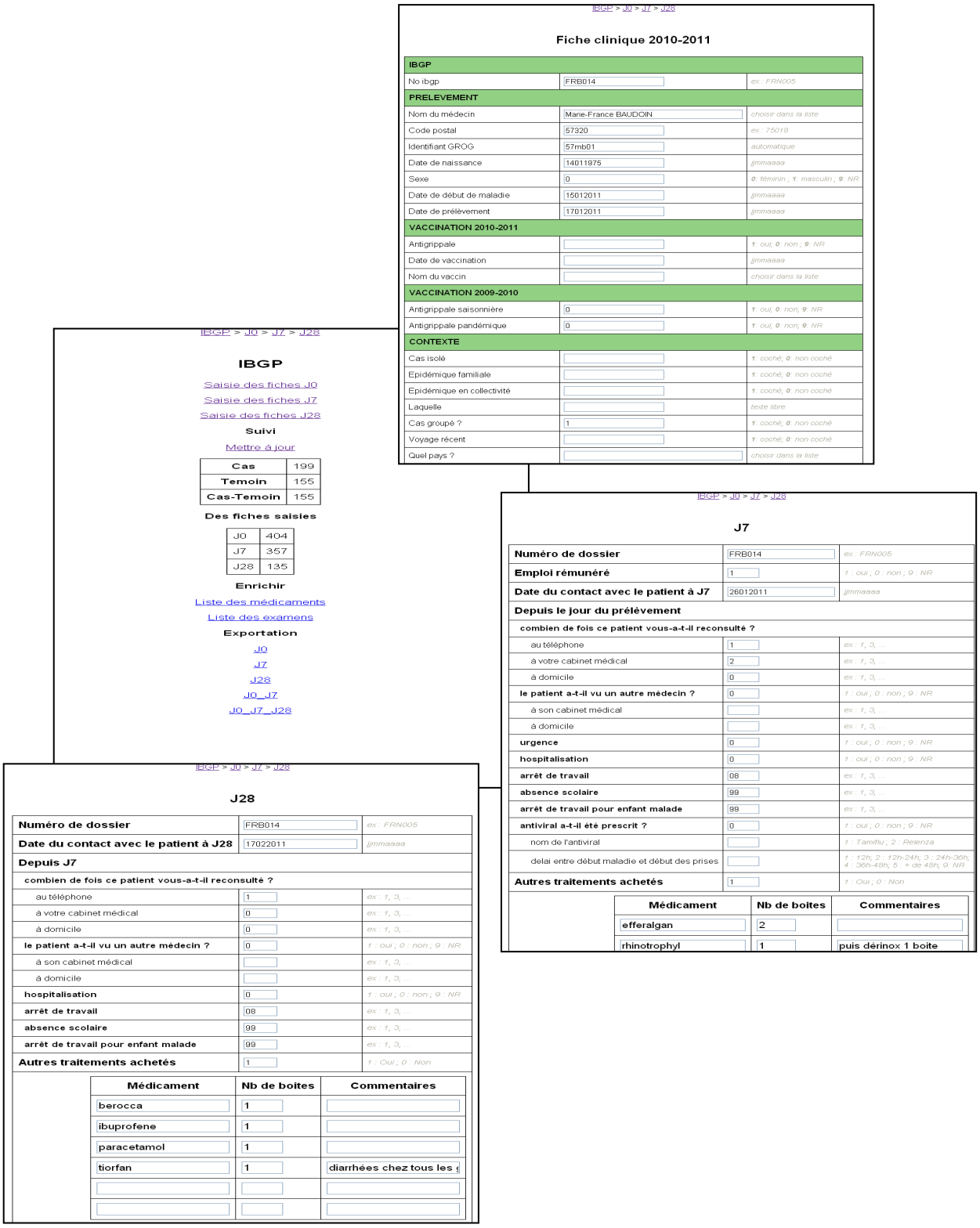
Parent or Guardian of patient ..... date / /

Signature witnessed by: Dr/Nurse .....

Signature ..... date / /

Influenza B in General Practice – IBGP – study Phase II 3/3

Appendix 6 – Template of clinical database of days 0, 7 and 28 (French version for IBGP 1st phase 2010-2011)



IBGP > J0 > J7 > J28

Fiche clinique 2010-2011

IBGP		
No ibgp	FRB014	ex : FRN005
PRELEVEMENT		
Nom du médecin	Marie-France BAUDOIN	choisir dans la liste
Code postal	57320	ex : 75018
Identifiant GROG	57mb01	automatique
Date de naissance	14011975	jjmmaaaa
Sexe	0	0: féminin ; 1: masculin ; 9: NR
Date de début de maladie	15012011	jjmmaaaa
Date de prélèvement	17012011	jjmmaaaa
VACCINATION 2010-2011		
Antigrippale		1: oui; 0: non ; 9: NR
Date de vaccination		jjmmaaaa
Nom du vaccin		choisir dans la liste
VACCINATION 2009-2010		
Antigrippale saisonnière	0	1: oui; 0: non; 9: NR
Antigrippale pandémique	0	1: oui; 0: non; 9: NR
CONTEXTE		
Cas isolé		1: coché; 0: non coché
Epidémique familiale		1: coché; 0: non coché
Epidémique en collectivité		1: coché; 0: non coché
Laquelle		texte libre
Cas groupé ?	1	1: coché; 0: non coché
Voyage récent		1: coché; 0: non coché
Quel pays ?		choisir dans la liste

IBGP > J0 > J7 > J28

IBGP

Saisie des fiches J0
Saisie des fiches J7
Saisie des fiches J28

Suivi

Mettre à jour

Cas	199
Temoin	155
Cas-Temoin	155

Des fiches saisies

J0	404
J7	357
J28	135

Enrichir

Liste des médicaments
Liste des examens

Exportation

J0
J7
J28
J0_J7
J0_J7_J28

IBGP > J0 > J7 > J28

J7

Numéro de dossier	FRB014	ex : FRN005
Emploi rémunéré	1	1 : oui ; 0 : non ; 9 : NR
Date du contact avec le patient à J7	26012011	jjmmaaaa
Depuis le jour du prélèvement		
combien de fois ce patient vous-a-t-il reconsulté ?		
au téléphone	1	ex : 1, 3, ...
à votre cabinet médical	2	ex : 1, 3, ...
à domicile	0	ex : 1, 3, ...
le patient a-t-il vu un autre médecin ?	0	1 : oui ; 0 : non ; 9 : NR
à son cabinet médical		ex : 1, 3, ...
à domicile		ex : 1, 3, ...
urgence	0	1 : oui ; 0 : non ; 9 : NR
hospitalisation	0	1 : oui ; 0 : non ; 9 : NR
arrêt de travail	08	ex : 1, 3, ...
absence scolaire	99	ex : 1, 3, ...
arrêt de travail pour enfant malade	99	ex : 1, 3, ...
antiviral a-t-il été prescrit ?	0	1 : oui ; 0 : non ; 9 : NR
nom de l'antiviral		1 : Tamiflu ; 2 : Relenza
delai entre début maladie et début des prises		1 : 12h; 2 : 12h-24h; 3 : 24h-36h; 4 : 36h-48h; 5 : + de 48h; 9: NR
Autres traitements achetés	1	1 : Oui ; 0 : Non

Médicament	Nb de boites	Commentaires
efferalgan	2	
rhinotrophyl	1	puis dérinox 1 boite

IBGP > J0 > J7 > J28

J28

Numéro de dossier	FRB014	ex : FRN005
Date du contact avec le patient à J28	17022011	jjmmaaaa
Depuis J7		
combien de fois ce patient vous-a-t-il reconsulté ?		
au téléphone	1	ex : 1, 3, ...
à votre cabinet médical	0	ex : 1, 3, ...
à domicile	0	ex : 1, 3, ...
le patient a-t-il vu un autre médecin ?	0	1 : oui ; 0 : non ; 9 : NR
à son cabinet médical		ex : 1, 3, ...
à domicile		ex : 1, 3, ...
hospitalisation	0	1 : oui ; 0 : non ; 9 : NR
arrêt de travail	08	ex : 1, 3, ...
absence scolaire	99	ex : 1, 3, ...
arrêt de travail pour enfant malade	99	ex : 1, 3, ...
Autres traitements achetés	1	1 : Oui ; 0 : Non

Médicament	Nb de boites	Commentaires
berocca	1	
ibuprofene	1	
paracetamol	1	
tiorfan	1	diarrhées chez tous les

9.2 Annex 2: Surveillance forms applied at the day of swab (D0)

9.2.1 Surveillance Form – FRANCE

Saison 2011-2012

GROG

PATIENT NOM

PRENOM

Suite à l'information donnée par le médecin, le patient s'est opposé ❑ ne s'est pas opposé ❑
à l'utilisation secondaire des données collectées et des échantillons pour des recherches sur les infections respiratoires.
(Cocher la case correspondant à la décision du patient)

Cachet du médecin	*Etiquette du laboratoire*	*Date d'arrivée au laboratoire*

Date de naissance _ _ _ _ _ _ _ _ (jj/mm/aaaa) Sexe ❑ F ❑ M Code postal de résidence _ _ _ _ _

Date de début de maladie _ _ _ _ _ _ _ _ (jj/mm/aaaa) Date de prélèvement _ _ _ _ _ _ _ _ (jj/mm/aaaa)

Vaccination antigrippale 2011-2012 ❑ Oui ❑ Non Si oui, date _ _ _ _ _ _ _ _ (jj/mm/aaaa)

❑ Agrippal ❑ Fluarix ❑ Immugrip ❑ Influvac ❑ Mutagrip ❑ Previgrip ❑ Vaxigrip ❑ Tetagrip

Vaccination antigrippale 2010-2011 ❑ Oui ❑ Non

Contexte

❑ Cas isolé ❑ Epidémie familiale ❑ Epidémie en collectivité (école, entreprise, EHPA...) Laquelle .....

❑ Voyage récent (<15 jours) pays .....

Etat clinique

❑ Fièvre Température max	❑ Dyspnée / Polypnée	❑ Otite / Otalgie
❑ Début brutal	❑ Toux	❑ Troubles digestifs
❑ Asthénie	❑ Expectoration	❑ Conjonctivite
❑ Myalgies / Courbatures	❑ Bronchiolite / Bronchite	❑ Adénopathies
❑ Frissons	❑ Rhinite / Coryza	❑ Eruption
❑ Céphalées	❑ Pharyngite	❑ Autres signes .....

Adressé CE JOUR à l'hôpital ❑ Oui ❑ Non

Traitement prescrit CE JOUR ❑ Antibiotiques ❑ Antiviral lequel .....

Un antiviral a-t-il été consommé AUPARAVANT (au cours des 2 semaines précédant la consultation) **par :**

❑ Patient Date de début _ _ _ _ _ _ _ Dosage : ❑ curatif ❑ préventif Lequel .....
❑ Membre famille Date de début _ _ _ _ _ _ _ Dosage : ❑ curatif ❑ préventif Lequel .....

Nombre de consultations ou visites chez le médecin traitant au cours des 12 derniers mois ❑ 0-1 ❑ 2-4 ❑ 5 et+
Le patient est-il dépendant (besoin d'aide dans la vie quotidienne) ? ❑ Oui ❑ Non

Facteurs de risque, antécédents justifiant une vaccination antigrippale ❑ Oui ❑ Non
Précisez :

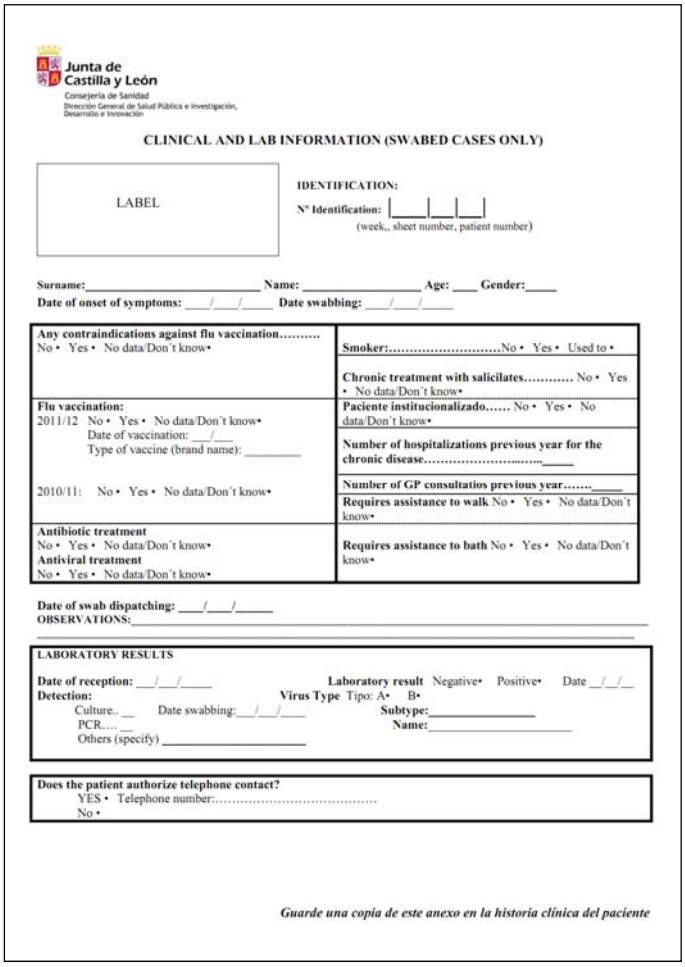
❑ Grossesse en cours ❑ IMC ≥ 30 ❑ Diabète ❑ Maladie cardio-vasculaire
❑ Maladie chronique pulmonaire ❑ Immunodépression ❑ Autre maladie chronique

Hospitalisation en lien avec la maladie chronique au cours des 12 derniers mois ❑ Oui ❑ Non

Commentaires

2011-2012

9.2.2 Surveillance Form – SPAIN



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Consejería de Sanidad
Dirección General de Salud Pública e Investigación, Desarrollo e Innovación

CLINICAL AND LAB INFORMATION (SWABED CASES ONLY)

LABEL

IDENTIFICATION:
Nº Identification: |___|___|___|
(week,, sheet number, patient number)

Surname:_____ **Name:** _____ **Age:** ___ **Gender:**_____
Date of onset of symptoms: ___/___/_____ **Date swabbing:** ___/___/_____

Any contraindications against flu vaccination…… No • Yes • No data/Don´t know•	**Smoker:**……No • Yes • Used to •
	Chronic treatment with salicilates…… No • Yes • No data/Don´t know•
Flu vaccination: 2011/12 No • Yes • No data/Don´t know• Date of vaccination: ___/___ Type of vaccine (brand name): _____	**Paciente institucionalizado**…… No • Yes • No data/Don´t know•
	Number of hospitalizations previous year for the chronic disease……..…..____
2010/11: No • Yes • No data/Don´t know•	**Number of GP consultatios previous year**……..____
	Requires assistance to walk No • Yes • No data/Don´t know•
Antibiotic treatment No • Yes • No data/Don´t know• **Antiviral treatment** No • Yes • No data/Don´t know•	**Requires assistance to bath** No • Yes • No data/Don´t know•

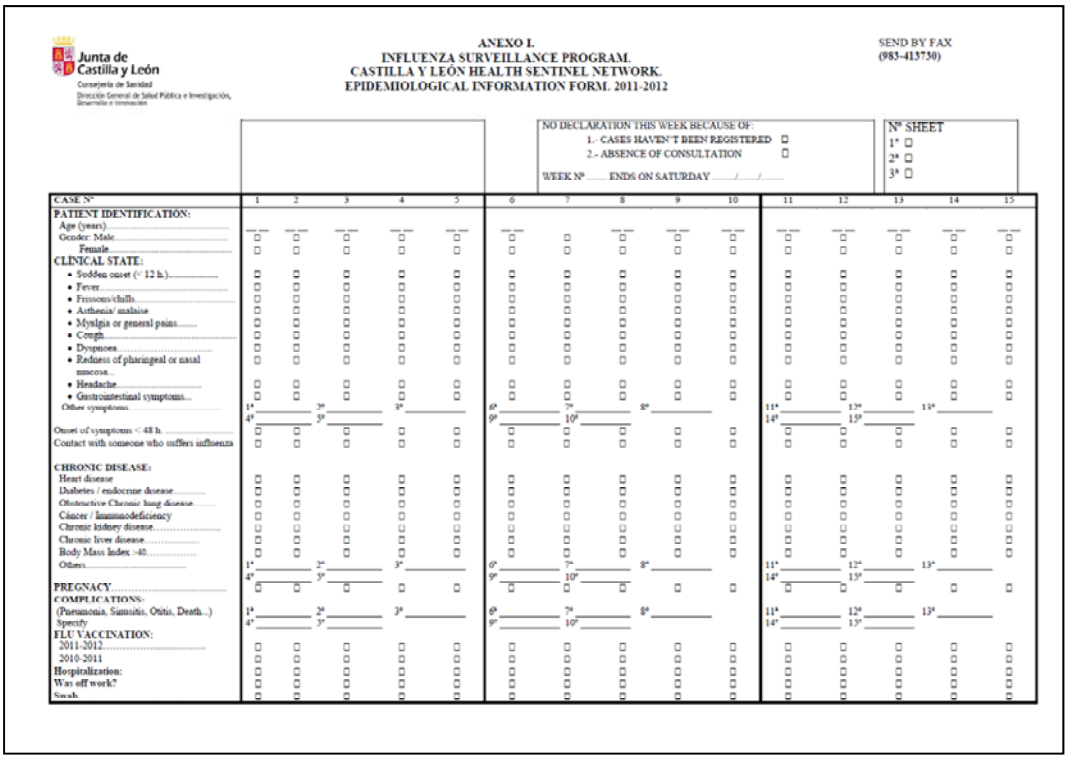
Date of swab dispatching: ___/___/_____
OBSERVATIONS:_____

LABORATORY RESULTS

Date of reception: __/__/____ **Laboratory result** Negative• Positive• Date __/__/__
Detection: **Virus Type** Tipo: A• B•
Culture.. __ Date swabbing:__/__/____ **Subtype:**_____
PCR…. __ **Name:**_____
Others (specify) _____

Does the patient authorize telephone contact?
YES • Telephone number:……
No •

Guarde una copia de este anexo en la historia clínica del paciente



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ANEXO I.
INFLUENZA SURVEILLANCE PROGRAM.
CASTILLA Y LEÓN HEALTH SENTINEL NETWORK.
EPIDEMIOLOGICAL INFORMATION FORM. 2011-2012

SEND BY FAX
(983-413730)

NO DECLARATION THIS WEEK BECAUSE OF:
1.- CASES HAVEN´T BEEN REGISTERED ☐
2.- ABSENCE OF CONSULTATION ☐
WEEK Nº ..... ENDS ON SATURDAY ...../...../.....

Nº SHEET
1ª ☐
2ª ☐
3ª ☐

CASE Nº	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
PATIENT IDENTIFICATION:															
Age (years)	__ __	__ __	__ __	__ __	__ __	__ __		__ __	__ __	__ __	__ __	__ __	__ __	__ __	__ __
Gender: Male	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Female	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
CLINICAL STATE:															
• Sudden onset (< 12 h.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
• Fever	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
• Frissons/chills	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
• Asthenia/ malaise	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
• Myalgia or general pains	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
• Cough	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
• Dyspnoea	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
• Redness of pharingeal or nasal mucosa	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
• Headache	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
• Gastrointestinal symptoms	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Other symptoms	1ª _____	2ª _____	3ª _____			6ª _____	7ª _____	8ª _____			11ª _____	12ª _____	13ª _____		
	4ª _____	5ª _____				9ª _____	10ª _____				14ª _____	15ª _____			
Onset of symptoms < 48 h.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Contact with someone who suffers influenza	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
CHRONIC DISEASE:															
Heart disease	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Diabetes / endocrine disease	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Obstructive Chronic lung disease	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Cáncer / Immunodeficiency	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Chronic kidney disease	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Chronic liver disease	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Body Mass Index >40	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Others	1ª _____	2ª _____	3ª _____			6ª _____	7ª _____	8ª _____			11ª _____	12ª _____	13ª _____		
	4ª _____	5ª _____				9ª _____	10ª _____				14ª _____	15ª _____			
PREGNACY	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
COMPLICATIONS:															
(Pneumonia, Sumsnhs, Otitis, Death...)	1ª _____	2ª _____	3ª _____			6ª _____	7ª _____	8ª _____			11ª _____	12ª _____	13ª _____		
Specify	4ª _____	5ª _____				9ª _____	10ª _____				14ª _____	15ª _____			
FLU VACCINATION:															
2011-2012	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
2010-2011	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Hospitalization:	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Was off work?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Swab	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

9.2.3 Surveillance Form – TURKEY

TURKISH MINISTRY of HEALTH

NATIONAL INFLUENZA REFERENCE LABORATORY INFLUENZA AND INFLUENZA -LIKE ILLNESS CASE REPORTING AND LABORATORY REQUEST INFORMATION FORM

☐ SENTİNEL SURVEİLLANCE — Date of reporting: ……/……/……..…

☐ OTHER (INDICATE,……...…… Date of symptoms onset: …../…../…….

SENDER/INSTITUTION INFORMATION	HOSPITAL/HEALTH CARE CENTER INFORMATION
	Name of the Institution
Name, Last Name	Has the patient been hospitalized? ☐No ☐Yes
İnstitution Name	Date of hospital visit: ……/……./……..…
City	Date of hospitalization: ……/……./……..…
Tel: ……	Date of discharge: ……../……../……
Speciality	Is the patient hospitalized due to ILI?
	☐Yes ☐No (Explain……
	Tel: …… Fax

PATIENT INFORMATION

Name, Last Name	DOB: :…../…../…….
İdentification Number	
Residance Address:……	Cinsiyet: ☐Erkek
Street	☐Kadın
County:……..…City:……	Occupation ……
Tel: (Home): ( )……	GSM ( ) ……

CLINICAL SYMPTOMS

□ Fever (……°C)	□ Headache	□ Difficulty in breathing
□ Cough	□ Joint pain	□ Acut respiratory distress (requiring ventilation)
□ Miyalgia	□ Sore throat	□ Other symptoms (Explain……
□ Runny nose		

Did you prescribe antivirals/ antibiotics due to these symptoms? □ No □ Yes (Explain, ……..)

PATIENT HISTORY

□ İmmunosuppression……..... □ Pregnant …. ….Months.…

□ Chronic diseases (Explain……..…… □ Morbid obesity (BKİ ≥ 35)

□ Comorbidity (Explain……..…….……)

□ Chronic use of medications (The purpose of use……)

VACCINATION STATUS

Has the patient been vaccinated for the current season? □ Yes □ No □ Doesn't know Date of vaccination: …./

EPIDEMIOLOGICAL INFORMATION

Route of Transmission

Are there others with the same symptoms? □ No □ Yes □ at work □ at school □at home

Travel History

□ Has the patient travelled from the place of residency within 2 weeks before the onset of the symptoms?

If yes, where/ when?……

□ Has the patient had contact with someone with travel history within 2 weeks before the onset of the symptoms?

SPECIMEN INFORMATION

Date sample was taken: …../…../……. Type of specimen:

☐Nasal Swab ☐Nasal +Throat Swab ☐Throat Swab ☐Nose/Throat Wash ☐Other ……..

LABORATORY CONTACT INFORMATION

Dr. Meral Akçay Ciblak 5379567545 ciblakm@yahoo.com

If this form is not completed properly the sample will not be tested

9.3 Annex 3: Case Report Form (CRF) at D9

IBGP
Influenza B in General Practice

D 9 ± 2 days

Doctor's name: **Patient ID code:**

Patient identification **Age:** **Gender:** **Date of swabbing:**

Does the patient have a remunerated job? yes☐ no☐

Date of contact with the patient at D9 /_____/_____/2012 **no later than** /_____/_____/**2012**

⇨ SINCE THE DAY OF SWABBING (D0 included),

*** how many days was he out of** work? /__/__/ days NA[1] ☐
children daycares *or* school? /__/__/ days NA ☐
work due to children's disease? /__/__/ days NA ☐

*** how many times did the patient consult you due to ILI swabbed?**
by phone call /__/ in your medical office /__/ at home visit /__/

*** did the patient see another doctor (since the day of swabbing)?** yes☐ no☐
if yes, how many times? by phone call /__/ in his medical office /__/ at home visit /__/

*** has he been to a hospital emergency room?** yes☐ no☐

*** has he been hospitalised'** yes☐ no☐
if NO, has he done additional tests? yes☐ no☐
specify (ECG, blood test, RX…): _____

did he need paramedical care? yes☐ no☐
specify (nurse, nutrition, physiotherapy...): _____

*** a "curative" antiviral has been prescribed?** yes☐ no☐
if YES, specify Tamiflu®☐ Relenza®☐
how long was the delay between the onset of symptoms and the beginning of the medication?
less than 12h☐ 12-24h☐ 25-36h☐ 37-48h☐ more than 48h☐

*** drug treatment for the ILI**

Drug	*Prescribed*	*Self-medication*
.....	☐	☐
.....	☐	☐
.....	☐	☐
.....	☐	☐
.....	☐	☐
.....	☐	☐
.....	☐	☐

⇨ WHAT IS THE CURRENT CLINICAL CONDITION OF THE PATIENT?

*** Has he returned to his "normal activities"[2] ?** yes☐ no☐
if yes, specify (if not possible, estimate) the date of return: /_____/_____/2012

*** Has he still got any symptoms related to ILI swabbed?** yes☐ no☐ if YES, specify:
☐ persistent cough (with or without expectoration) ☐headache
☐ rhinorrhea or nasal obstruction ☐asthenia
☐ others: _____

☐ **Patient is dead.** Cause of death: _____

⇨ COMMENTS: _____

Please, send this form to IBGP Coordination
☎ ✉ @

[1] NA : non applicable
[2] Normal activities": patient returned to his usual routine/occupation (work, school, homemade, day-to-day life...)

9.4 Annex 4: Case Report Form (CRF) at D28

IBGP

Influenza B in General Practice

D28 ± 2 days

Doctor's name: **Patient ID code:**

Patient identification **Age:** **Gender:** **Date of swabbing:**

Does the patient have a remunerated job? yes☐ no☐

Date of contact with the patient at D28 /_____/_____/2012 **no later than** /_____/_____/2012

➪ SINCE THE PHONE CONTACT AT D9 ± 2 AND STARTING THE DAY AFTER YOUR CALL,

*** how many days was he out of** work? /__/__/ days NA[1] ☐
children daycares *or* school? /__/__/ days NA ☐
work due to children's disease? /__/__/ days NA ☐

*** how many times did the patient consult you due to ILI swabbed?**
by phone call /__/ in your medical office /__/ at home visit /__/

*** did the patient see another doctor?** yes☐ no☐
if yes, how many times? by phone call /__/ in his medical office /__/ at home visit /__/

*** has he been to a hospital emergency room?** yes☐ no☐

*** has he been hospitalised'.** yes☐ no☐
if NO, has he done additional tests? yes☐ no☐
specify (ECG, blood test, RX…): _____

did he need paramedical care? yes☐ no☐
specify (nurse, nutrition, physiotherapy...): _____

*** drug treatment for the ILI**

Drug	*Prescribed*	*Self-medication*
.....	☐	☐
.....	☐	☐
.....	☐	☐
.....	☐	☐
.....	☐	☐
.....	☐	☐
.....	☐	☐
.....	☐	☐

➪ WHAT IS THE CURRENT CLINICAL CONDITION OF THE PATIENT?

*** Has he returned to his "normal activities"[2] ?** yes☐ no☐
if yes, specify (if not possible, estimate) the date of return: /_____/_____/2012

*** Has he still got any symptoms related to ILI swabbed?** yes☐ no☐ if YES, specify:
☐ persistent cough (with or without expectoration) ☐headache
☐ rhinorrhea or nasal obstruction ☐asthenia
☐ others: _____

☐ **Patient is dead.** Cause of death: _____

➪ COMMENTS: _____

Please, send this form to IBGP Coordination
☎ ✉ @

[1] NA : non applicable
[2] Normal activities": patient returned to his usual routine/occupation (work, school, homemade, day-to-day life...)

9.5 Annex 5: French ethical approvals

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RÉPUBLIQUE FRANÇAISE

MINISTÈRE
DE L'ENSEIGNEMENT SUPÉRIEUR
ET DE LA RECHERCHE

26 JAN. 2011

Direction générale
pour la recherche et l'innovation

Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé (CCTIRS)

Référence chrono : DGRI CCTIRS MG/CP°2011.018
Recommandé avec AR
Numéro de dossier à rappeler dans toute correspondance : 11.016

Téléphone : 01 55 55 87 82
Fax : 01 55 55 88 50

Mél. : michele.guillemot@recherche.gouv.fr

Paris, le 21 janvier 2011

Monsieur,

Conformément aux dispositions de la loi n° 94-548 du 1er juillet 1994, vous avez adressé au Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé, un projet de traitement automatisé de données nominatives relatif à une étude intitulée : «Impact de la grippe B en Europe : étude prospective internationale de cas virologiquement confirmés en médecine ambulatoire dans les réseaux du surveillance».

Après examen de votre dossier, le Comité consultatif a émis l'avis ci-joint.

Le Comité appelle par ailleurs votre attention sur le fait que toute modification ultérieure du projet que vous lui avez soumis doit être portée à sa connaissance.

Je vous prie d'agréer, Monsieur, l'expression de mes salutations les meilleures.

Michèle GUILLEMOT
Secrétaire générale du Comité

Monsieur Jean-Marie COHEN
OPEN ROME
Direction scientifique
67, rue du Poteau
75018 PARIS

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RÉPUBLIQUE FRANÇAISE

MINISTÈRE
DE L'ENSEIGNEMENT SUPÉRIEUR
ET DE LA RECHERCHE

DIRECTION GENERALE POUR LA RECHERCHE ET L'INNOVATION

Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé

Dossier n° 11.016

Intitulé de la demande : Impact de la grippe B en Europe : étude prospective internationale de cas virologiquement confirmés en médecine ambulatoire dans les réseaux du surveillance.

Responsable scientifique : Jean-Marie COHEN
OPEN ROME
Direction scientifique
67, rue du Poteau
75018 PARIS

Demandeur : Jean-Marie COHEN
OPEN ROME
-

Dossier reçu le : 8.12.10

Dossier examiné le : **13 janvier 2011**

Avis du Comité consultatif :

Avis favorable

Toutefois, les résultats des prélèvements ne devraient pas être communiqués au coordonnateur avant l'éligibilité : le numéro du prélèvement est déjà identifiant. Sauf s'il s'agit de la procédure habituelle de la surveillance de la grippe, il est probable que les cas de grippe comportent un numéro pour éviter les doublons. Dans la note d'information, la phrase « parce qu'il pense que vous êtes une personne compétente, capable de participer à l'étude » doit être supprimée.

Fait à Paris, le 21 janvier 2011

Le Président du Comité consultatif
Docteur Mahmoud ZUREIK

1, rue Descartes – 75231 Paris Cedex 05
http://ww.recherche.gouv.fr

CNIL

7 AVR. 2011

Le Vice-Président délégué

Monsieur Jean Marie COHEN
OPEN ROME
67, RUE DU POTEAU
75018 - PARIS

N/Réf. : EGY/FLR/AR112660

Paris. le - 5 AVR. 2011

Objet : NOTIFICATION D'AUTORISATION

Décision DR-2011-108 autorisant OPEN ROME à mettre en œuvre un traitement de données ayant pour finalité une étude internationale observationnelle et descriptive ayant pour but d'évaluer l'impact de la grippe B en Europe, à partir d'une étude de cas virologiquement confirmés en médecine ambulatoire dans les réseaux de surveillance (Étude IBGP) (Demande d'autorisation n° 911011)

Monsieur,

Vous avez saisi notre Commission d'une demande d'autorisation relative à un traitement de données à caractère personnel ayant pour finalité :

ÉTUDE INTERNATIONALE OBSERVATIONNELLE ET DESCRIPTIVE AYANT POUR BUT D'EVALUER L'IMPACT DE LA GRIPPE B EN EUROPE, A PARTIR D'UNE ETUDE DE CAS VIROLOGIQUEMENT CONFIRMES EN MEDECINE AMBULATOIRE DANS LES RÉSEAUX DE SURVEILLANCE

Ce traitement relève de la procédure des articles 54 et suivants de la loi du 6 janvier 1978 modifiée.

Les services de notre Commission ont étudié les conditions définies par le dossier de formalités préalables déposé à l'appui de cette demande et notamment celles relatives à l'exercice effectif des droits des participants à l'étude.

J'ai bien pris acte que la participation d'enfants mineurs sera subordonnée au recueil du consentement exprès de leurs représentants légaux.

J'ai pris acte également que l'identité des patients sera connue des seuls médecins qui effectuent les prélèvements, sont en contact direct avec les patients et seront également chargés d'assurer le suivi des patients à 7 et 28 jours.

Après avoir examiné les catégories de données traitées et les destinataires, je vous rappelle que conformément au 3ème alinéa de l'article 55, la présentation des résultats du traitement de données ne peut, en aucun cas, permettre l'identification directe ou indirecte les personnes concernées.

En application des articles 15 et 69 de la loi précitée et de la délibération n° 2009-674 du 26 novembre 2009 portant délégation d'attributions de la Commission nationale de l'informatique et des libertés à son président et à son vice-président délégué, j'autorise la mise en œuvre de ce traitement.

Je vous prie, Monsieur, d'agréer l'expression de mes salutations distinguées.

E. de Givry

Emmanuel de GIVRY

CPP - Ile-de-France VI

Groupe Hospitalier Pitié-Salpêtrière

24 DEC. 2010

A l'attention de :

Dr. Jean-Marie Cohen
Open Rome
67 rue du Poteau F
75018 Paris

Paris, le 16/12//2010

Objet : Cadre réglementaire d'un projet de recherche

Cher Collègue,

Le comité a examiné à la séance du 15 décembre 2010 votre étude intitulée « The burden of influenza B in Europe : a prospective multi-country strain surveillance study using community-based specimens». Dans la mesure où l'étude ne modifiera pas la prise en charge des patients, elle n'entre pas dans le cadre de la loi sur les recherches biomédicales. Le CPP ne voit donc pas d'obstacle à sa réalisation.

Je vous prie de recevoir, Cher Collègue, l'expression de mes sentiments les meilleurs.

Le président du CPP,
Dr. Laurent Capelle

4, Bâtiment de La Force -47, Boulevard de l'Hôpital 75651 Paris Cedex 13
Tél : 01 42 16 16 83 Fax : 01 42 16 27 15

9.6 Annex 6: BMC Public Health IBGP publication

Silva et al. BMC Public Health 2014, 14:56
http://www.biomedcentral.com/1471-2458/14/56

BMC Public Health

RESEARCH ARTICLE Open Access

Economic burden of seasonal influenza B in France during winter 2010-2011

Maria Laura Silva[1,2*], Lionel Perrier[1,3], Hans-Martin Späth[4], Isidore Grog[5], Anne Mosnier[2], Nathalie Havet[1], Jean Marie Cohen[2] and on behalf of the IBGP team

Abstract

Background: In France, 2–15% of the population is affected annually by influenza, which causes significant socioeconomic disruption. Nevertheless, despite its importance for policy makers, few published studies have evaluated the impact of influenza B. Therefore, we assessed the costs associated with influenza B during 2010–2011 in France.

Methods: Cases of lab-confirmed influenza B were analyzed as part of the Influenza B in General Practice Study. Cost calculations were based on micro-costing methods according to the French Health Insurance (FHI) perspective (in Euros, 2011). Costs were compared between age groups using the Kruskal–Wallis test, and when significant, by multiple comparisons based on rank. Moreover, uncertainties were assessed using one-way sensitivity and probabilistic analyses. Overall economic burden was estimated by multiplying cost per patient, flu attack rate, and the French population.

Results: A total of 201 patients were included in the study. We found that the mean cost associated with Influenza B was 72€ (SD: 205) per patient: 70€ (SD: 262) for younger children, 50€ (SD: 195) for older children, 126€ (SD: 180) for adults, and 42€ (SD: 18) for elderly. Thus, we observed significantly different costs between the distinct age groups ($p<0.0001$). Finally, the economic burden of influenza B for the FHI was estimated to be 145 million Euros (95% CI: 88–201).

Conclusions: Our findings highlight the important impact of influenza B and encourage further investigation on policy regarding vaccination strategies in France.

Keywords: Medical economics, Cost of illness, Influenza B, France, Health insurance reimbursement

Background

During seasonal influenza epidemics, it is estimated that 5–15% of the world population is affected by acute respiratory infections (ARIs) [1]. According to the World Health Organization (WHO) these annual epidemics result in 3–5 million cases of severe illness and 250–500 thousand deaths worldwide [1,2]. In France, during the 2010–2011 influenza season, the incidence of primary care medical consultations for lab confirmed flu was estimated to be 6.7% (6710/100,000; 95% CI: 4411–9009). This figure represented a typical attack rate in a medium intensity flu season when compared with data from recent years, which fluctuated between 2.5% (2007–2008) and 15% (2012–2013) [3,4].

Influenza viruses circulate during winter months (November–February in Europe), and epidemics last 8 weeks (on average) [4,5]. Generally, one circulating viral strain type or subtype is dominant during each season in a given location. However, in some seasons, there may be two or three different dominant viruses [6].

Patients with ARI induced by influenza, have the potential to develop a variety of complications, ranging from minor to life threatening [7]. Nevertheless, the majority of infected individuals experience only slight illness, which lasts less than two weeks and requires no medical intervention. In contrast, others may need medical consultations and/or work leave, but ultimately develop no complications [7]. However, influenza can be particularly

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Full list of author information is available at the end of the article

serious in young children, the elderly, and people with chronic diseases. Indeed, these individuals can display an increased risk of severe complications, including pneumonia and fatal illness [8]. Due to the widespread affects of influenza, the national costs associated with the illness are of vital importance, especially when considering sickness benefit payments due to work leave and hospital/emergency care [8].

Policy makers are typically interested in the socioeconomic impact of influenza in order to set priorities for interventions [9]. However, few studies have evaluated the costs associated with illness and influenza vaccination programs [10,11]. Additionally, previous studies were rarely specific to particular viral strains [12,13]. In fact, few studies have provided strict investigations of influenza B or comparisons between influenza B and other viruses [14]. Furthermore, there have been recent discussions about whether or not to include two influenza B lineages within the seasonal influenza vaccine [15,16]. Therefore, to bridge the gap in knowledge regarding influenza B, a study entitled "Influenza B in General Practice" (IBGP) was initiated during the influenza season of 2010–2011. Notably, the study was designed to cover France and Turkey in its first phase. The overall aim of the IBGP was to analyze the morbidity and differential burden of illness (i.e., influenza-like illness consultations, prescriptions, sick leave) due to influenza B, including differences in age groups and lineages.

In this paper, we used data collected from the IBGP study to assess the impact of influenza illness on the French economy. Despite the fact that flu B represents 11% (median rate) of the detected influenza cases over the past eight years, no previous study has assessed the costs associated with lab-confirmed influenza B in France [4]. Although some studies regarding influenza B have been conducted in other countries [17,18], they are very specific to local practices and health systems, potentially hindering their relevance to the French system. Indeed, universal healthcare in France is largely financed by the National Health Insurance [19,20]. Therefore, our objective was to describe the costs associated with seasonal influenza B during the 2010–2011 season for a population presenting with ARI, consulting in primary care, under the perspective of the French Health Insurance (*Assurance Maladie*).

Methods

Study design

IBGP was an observational, prospective study conducted within sentinel surveillance networks in Europe. In France, the study was approved by the National Ethics Committee (N°911011) and the National Committee for Protection of Personal Data (N°11.016). Moreover, the study was proposed to all practitioners participating in the GROG network (*Groupes Régionaux d'Observation de la Grippe*), which included 390 general practitioners (GPs) and 116 pediatricians (2010–2011 season). These physicians were well distributed throughout the country and were trained to collect swab specimens and clinical information. Swabbed patients represented individuals with an ARI, defined as individuals consulting the practitioner within seven days (preferably two days) of a sudden onset of symptoms, including at least one systemic symptom (e.g., fever, headache, or myalgia) and one respiratory symptom (e.g., cough, rhinitis, or sore throat). As part of the routine surveillance for influenza during the whole season, swabbed patients were ultimately selected based on ad-hoc sampling, whereas systematic random sampling was used to select those patients to be swabbed. In this regard, each practitioner was required to swab the first ARI patient of each week within his/her specific age group: 0–4 years (GPs and pediatricians), 5–14 years (GPs and pediatricians), 15–64 years (GPs) and 65 years or more (GPs) [21].

The swabs and specimen request forms were then sent to the collaborating National Influenza Center (NIC, North and South) [21]. Virological methods were used for influenza identification and lineage characterization following the WHO Collaborating Centers recommendations [22]. The laboratories entered the clinical data and swab identification results into an electronic database. An anonymized version of this database was sent to GROG coordination [21]. Thus, this routine swab monitoring technique was used to identify influenza B cases and recruit patients for follow-up.

Patients recruitment for follow-up

Following confirmation of an influenza B case, the study coordinator alerted the physician, who then made contact with the patient within 7 ± 2 days after the initial consultation. The patient was invited to participate in a follow-up assessment. For adults, oral consent was acceptable, whereas children required written parental agreement. For those patients who were not recovered at first follow-up contact, a further interview was arranged three weeks later. Thus, three study documents were used: the initial specimen request form (day 0; D0), the initial follow-up form (day 7 ± 2; D7), and the final follow-up form (day 28 ± 5; D28).

The D0 form included patient demographics, presence of similar cases in the household, vaccination status, presence of risk factors, and clinical symptoms [21]. The D7 and D28 follow-up forms were identical and were used to collect information regarding employment, ARI-related medical consults (e.g., telephone, medical office, or home visits), use of emergency services, hospitalization, additional tests, paramedical care, sick leave (work or school), drugs taken, duration of illness, and continuing symptoms [23].

Cost assessment

The overall use of resources was determined based on data from three study documents (D0, D7, D28). Illness duration was defined from the date of illness onset to the recovery date, and costs were assessed from the French Health Insurance (FHI) perspective. Cost calculations (in Euros) were based strictly on a micro-costing approach [24], which involved analysis of FHI reimbursed fees [25] and the GROG methodology [23] (Box 1, Additional file 1). The following items were considered:

- Initial office consultation for ARI (GPs or pediatricians) [26];
- Follow-up office consultations [26];
- Home visits and additional consultations at the patient's domicile [26];
- Telephone consultations (not cost allocated) [26];
- Emergency services (standard non-specific emergency care pack basis) [27];
- Hospitalizations (hospital care due to influenza complications) [28,29];
- Vaccine (cost of influenza vaccine, excluding administration) [30,31];
- Drugs taken (name and number of packs, assessed in three classes: antibiotics, antivirals, others [GROG methodology]). The lowest cost for each drug was used (age adjusted) [23,24,30,31];
- Additional tests costs (out of hospital) [32,33];
- Paramedical care costs (out of hospital) [26];
- Daily allowances (sick leave calculated per day after the fourth day of absence). The FHI calculates daily allowances based on patient's gross wage, and when sickness leaves are > 31 days, on the number of dependent children. Conditions vary depending on the number of hours previously worked (< or > 200 hours during the previous three months) and the duration of sickness leave (< or > 6 months). However, in the present study the number of dependent children was not considered because sickness leaves were < 31 days. Also, we made the assumption that patients worked > 200 hours during the three previous months (this variable was not recorded) and obtained a sickness leave period lower than six months (i.e., flu sick leaves did not extend six months). Within this framework, the daily allowance was equal to 50% of the daily wage. When gross monthly earnings exceeded the maximum paid by the FHI, patient's daily allowances were limited to the indemnity cap [34], which corresponded to 50% of the French mean daily wage (2830€ per month in 2011) [35].

The costs associated of influenza B per patient (the sum of reimbursements for each item) are summarized for four age groups: younger children (0–4 years), children (5–14 years), adults (15–64 years), and elderly (65 years or more).

A cost estimate for the whole French population [35] was obtained by applying this cost-related information to the national incidence estimate for influenza B as calculated by GROG [3,4,23] (Table 1).

Statistical analysis

Resource consumption and costs were summarized using descriptive statistics. Costs were compared between age groups using the Kruskal–Wallis test. Significant results were analyzed via multiple comparisons based on the rank. A significance value of 5% was retained, and one-way sensitivity analyses were conducted. Moreover, a variation of 20% was retained for each parameter value and illustrated graphically using a tornado diagram. The uncertainties surrounding the mean costs were assessed through probabilistic analyses using a non-parametric bootstrap method. A total of 1,000 simulated bootstrap samples were generated, and 95% confidence intervals were computed.

Results

Study population

Patient inclusion

During the 2010–2011 flu season in France we observed an outbreak of flu B/Victoria and A(H1N1)pdm09 viruses. These outbreaks peaked between week 51/2010 and week 08/2011. Overall, 153 sentinels participated in the study, recruiting patients between week 02/2011 and week 15/2011. A total of 460 swabs were confirmed as influenza B positive. Among these positive cases, 201 (44%) patients were successfully recruited: 115 were symptom free at D7, and 85 of the remaining 86 were followed at D28.

Furthermore, 56% of the lab-confirmed flu B swabs were not included (259), mainly due to the fact that the virology results were not available on time (nine days after swab) for the GROG coordination to invite physicians to recruit the patients (Figure 1).

Patients characteristics

The mean age of recruits was 17 years (extremes: 0–84). Seventy percent were children aged <15, 7% were elderly aged ≥ 65, and 23% were adults of working age, of whom 31 (over half) were employed with remuneration. Seven percent of the recruits were vaccinated against seasonal influenza, and 8% had a co-morbidity risk condition. Also, the M/F sex ratio was 1.25. Moreover, among the 20 women aged between 15 and 50, 3 were pregnant. A total of 115 patients (57%) recovered before day 9 (D9). The recovery rate before D9 was proportional: 63% of children, 43% of adults, and 13% of elderly (Table 2).

Table 1 Estimation by age group of the incidence of primary care medical consultations for lab confirmed influenza B (per 100,000 inhabitants) extrapolated for the whole French population (winter 2010–2011)

	Estimation of the incidence of consultations for influenza B	*French population*	*Estimation of influenza B patients in French population*
	[CI 95%]		
Younger children	6.6%	3 884 625	255 834
(0–4 yo)	[4.3 – 8.9%]		[166 534 – 345 149]
Older children	12.9%	7 733 990	993 998
(5–14 yo)	[10.6 – 15.2%]		[816 477 – 1 172 086]
Adults	1.5%	40 808 626	612 246
(15–64 yo)	[0.8 – 3.8%]		[326 061 – 1 550 320]
Elderly	1.5%	10 661 749	157 268
(≥65 yo)	[0.8 – 3.8%]		[87 853 – 402 374]
All ages	3.2%	63 088 990	2 019 346
	[0.9 – 5.5%]		[552 660 – 3 453 491]

Source: GROG[3,4,23], INSEE [35]; yo = years old.

Almost 20% of patients reconsulted their family physician, with children requiring these additional consultations less than adults and the elderly. Patients mostly returned to their medical office or made telephone consultations. Very few emergency services (n = 3) and hospitalizations (n = 2) were observed, and only in children.

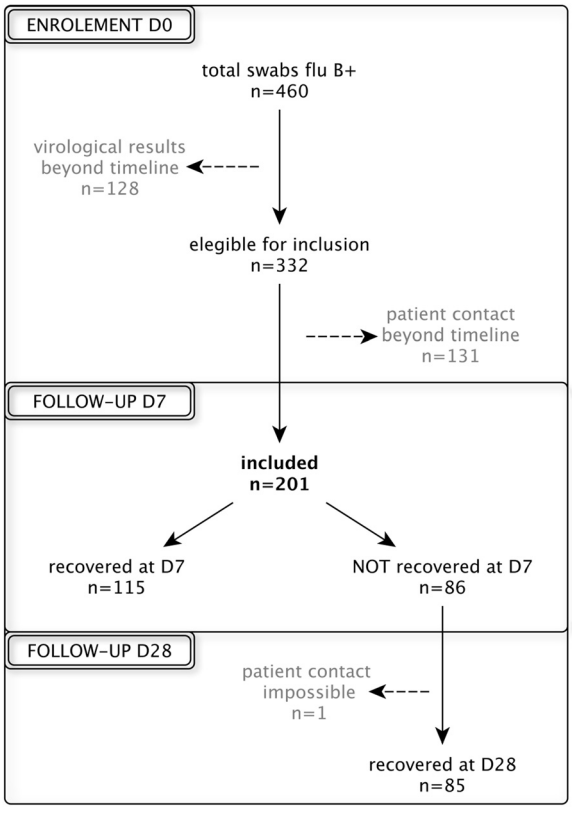

Figure 1 Flowchart for subjects included from D0 through the end of the follow-up period.

Drugs were taken by > 90% of patients, mainly for symptomatic relief. Overall, antibiotics were prescribed for 19% of the patients (all ages); but for the elderly 50%. Also, antivirals were prescribed in 20% of the cases.

Work leave was reported by 27 of 31 employed patients. These patients were out of work an average of 6.5 days (Box 2, Additional file 2).

Costs of influenza B

The estimated average cost of influenza B based on the FHI perspective was found to be 71.8€ (extremes: 16.1€ - 1876.6€) per patient. However, there were variations according to the distinct age groups (Table 3). In fact, costs were significantly different between age groups ($p<0.0001$). Costs related to antibiotic prescriptions were higher for those patients aged ≥ 65 years compared with the other age classes ($p = 0.02$).

Table 4 presents the mean drug-related costs for prescriptions containing at least one antibiotic. We observed that these costs were driven by antibiotic use in the entire population, with one antibiotic prescribed 46% of the time. However, when each age group was analyzed separately, antibiotics were also found to be cost drivers for children 0–4 years (47%) and adults (54%), but not for the remaining groups.

In the tornado diagram (Figure 2), the vertical lines represent the mean cost when all parameters are fixed at their base value of 71.8€. Using this analysis, we observed that the most sensitive parameter was the quantity of daily allowances, which was followed by hospitalizations. In fact, increasing the amount of daily allowances by 20% increased the mean cost from 71.8€ to 76.2€. Using a non-parametric bootstrap method, the 95% confidence interval related to influenza B mean costs was found to be 43.6€ – 100.0€.

Table 2 Characteristics of patients included in the study

Number of patients per age group and percentage of the total number	*Younger children* *0-4 yo*		*Older children* *5-14 yo*		*Adults* *15–64 yo*		*Elderly* *≥65 yo*		*All ages*	
	n	***%***	***n***	***%***	***n***	***%***	***n***	***%***	***n***	***%***
	50	**25%**	**91**	**45%**	**46**	**23%**	**14**	**7%**	**201**	**100%**
Age (yo) mean ± SD	2.6 ± 1.3		9.3 ± 2.8		31.5 ± 13.7		72.1 ± 5.7		17.1 ± 19.7	
Risk factors	2	4%	5	5%	5	11%	5	36%	17	8%
Pregnancy	*NA*		*NA*		*3*		*NA*		*3*	
BMI > 30	*0*		*1*		*0*		*0*		*1*	
Chronic disease	*2*		*4*		*2*		*5*		*13*	
Working age (>15 y)	-	-	-	-	40	87%	14	100%	54	27%
Employed	-	-	-	-	31	78%	0	-	31	57%
Recovering at day 7 ± 2	37	74%	52	57%	20	43%	6	*43%*	115	57%

NA = non applicable; yo = years old; BMI = body mass index.

Extrapolation to French population

An extrapolation to the national population was based on an incidence rate of 3.2% of French people (2 million persons) with influenza B consulting a physician [4]. An estimation of the costs associated with influenza B per person (by age group and for all ages) is presented in Table 5. Notably, we estimated that the overall cost of influenza B to the FHI in 2010–2011 was 145 million Euros (95% CI: 88–201 millions €).

Discussion

Our study has estimated that the total impact of influenza B in France during the 2010–2011 winter season was 145 million Euros based on the FHI perspective. This finding demonstrates the important economic burden associated with influenza B in France. We observed that the cost generated by infected children exceeds that of other age groups when only direct costs are considered. Indeed, although only two children were hospitalized, hospitalizations were found to have the highest impact on costs. On the other hand, in adults, costs were mainly affected by daily allowances due to work leave.

Limitations

Studies based on routine operational data can be exposed to potential biases, which might arise from the

Table 3 Mean costs per influenza B case per age group under the perspective of the French Health Insurance (in Euros, 2011)

	0-4 yo (n = 50)	*5-14 yo (n = 91)*	*15-64 yo (n = 46)*	*≥65 yo (n = 14)*	*All ages (n = 201)*	*p-value*
	Mean (SD)	***Mean (SD)***	***Mean (SD)***	***Mean (SD)***	***Mean (SD)***	
Direct costs (total)	70.0 (261.6)	50.0 (194.8)	33.4 (19.8)	41.8 (18.2)	50.6 (184.7)	<0.0003
Initial consultation at medical office (GP or pediatrician)	20.7 (1.7)	17.1 (1.6)	15.5 (1.0)	15.1 (0)	17.5 (2.4)	<0.0001
Vaccine	0.3 (1.3)	0.2 (1.1)	0.3 (1.3)	3.6 (3.2)	0.5 (1.7)	<0.0001
Follow-up consultations at medical office (GP)	3.3 (9.0)	3.5 (9.8)	7.0 (11.0)	11.9 (13.5)	4.9 (10.4)	0.0039
Follow-up at domicile (GP)	0.5 (3.6)	0.5 (4.8)	1.9 (7.8)	3.2 (11.8)	1.0 (6.1)	0.2718
Emergency services	0.0 (0)	1.2 (6.5)	0.0 (0)	0.0 (0)	0.5 (4.4)	0.3126
Hospitalization	36.0 (254.3)	19.8 (188.5)	0.0 (0)	0.0 (0)	17.9 (179.0)	0.7529
Drugs (total)	6.5 (10.3)	5.5 (8.8)	5.9 (5.5)	6.0 (6.2)	5.9 (8.4)	0.7705
Antibiotics	0.8 (2.2)	0.6 (1.8)	0.8 (2.0)	1.8 (2.9)	0.8 (2.0)	0.0214
Antivirals	0.7 (1.5)	0.8 (1.8)	2.3 (3.5)	1.1 (2.7)	1.1 (2.4)	0.0523
Other drugs	5.0 (9.2)	4.1 (8.5)	2.8 (3.3)	3.1 (3.9)	4.0 (7.6)	0.7518
Additional tests	2.8 (11.4)	2.2 (12.4)	2.8 (11.2)	2.1 (5.3)	2.5 (11.4)	0.5985
Daily allowances	0.0 (0)	0.0 (0)	92.7 (174.2)	0.0 (0)	21.2 (91.4)	<0.0001
TOTAL	*70.0 (261.6)*	*50.0 (194.8)*	*126.1 (179.6)*	*41.8 (18.2)*	*71.8 (205.1)*	*<0.0001*

yo = years old; GP = general practitioner.

Table 4 Mean drug-related costs for prescriptions containing at least one antibiotic prescribed per influenza B case per age group under the perspective of the French Health Insurance (in Euros, 2011)

	0-4 yo (n = 9)		*5-14 yo (n = 16)*		*15-64 yo (n = 10)*		*≥65 yo (n = 3)*		*All ages (n = 38)*	
	Mean	***%***	***€***	***%***	***€***	***%***	***€***	***%***	***€***	***%***
Drugs (total)	10.5		9.7		8.1		6.7		9.2	
Antibiotics	5.0	47%	4.3	44%	4.4	54%	1.2	19%	4.2	46%
Antivirals	2.5	24%	0.2	2%	1.5	19%	3.8	56%	1.4	15%
Others	3.0	29%	5.2	54%	2.2	27%	1.7	25%	3.6	39%

behavior of recruited subjects and/or selection by physicians. Recruitment to the study was initiated with a positive swab for influenza B. Thus, the extent to which the swabbing procedure might be selective is critical. Diagnoses were clinically based, and although guidance was given, strictly standard definitions are difficult due to the general symptoms of influenza.

Swab specimens were collected from consenting patients on an opportunistic basis. Therefore, these samples could have been influenced by several factors (e.g., the pressures of work and the time of the day). However, we are not aware of any bias that might have systematically prejudiced the incidence of laboratory-confirmed influenza positive samples. Moreover, GROG reports showed that ad-hoc and random selection of patients indicated good distribution based on age group [4].

Furthermore, limitations of the present study included possible selection bias for more susceptible patients (e.g., young infants and pregnant women) and reduced recruitments based on delays in the following processes: 1) transport of samples to the laboratory, 2) virological lab analysis, 3) transfer of lab results to the GROG, and 4) informing physicians of positive results (subsequently slowing patient contact).

Also, we have no further information, after the swab consultation, regarding the evolution of patients not included (259) in the study (e.g., if they had complications, if they were hospitalized). However, information collected (D0 form) on the swabbing day from patients not included in the study indicates that, in general, their characteristics were similar to our study population (Box 3, Additional file 3). Although the distribution of patients among age groups between the two populations was comparable, the proportion of adults was higher in the population not included. Moreover, the proportion of elderly was lower, but not significant. In addition, the proportion of males in the population not included was lower, with an insignificant M/F sex ratio of 1.02. There was also a significantly higher mean age for children (aged 5–14 years) included in the study ($p < 0.001$). Based on analysis of the population not included, it appears that no important differences in cost calculations or drivers were generated, except for perhaps the amount of overall costs.

Notably, our study only considered those patients consulting GROG physicians in general practice and pediatrics. Thus, patients directly admitted to hospitals or emergency departments (EDs) were not taken into account. According to the French Institute for Public Health Surveillance (InVS), during the influenza season studied, there were 17 019 ED visits for influenza-like illness and 919 hospitalizations observed within those services participating in the surveillance network. Overall, this represents 0.03% and 0.001% of the French population, respectively. Therefore, the weekly average proportion of

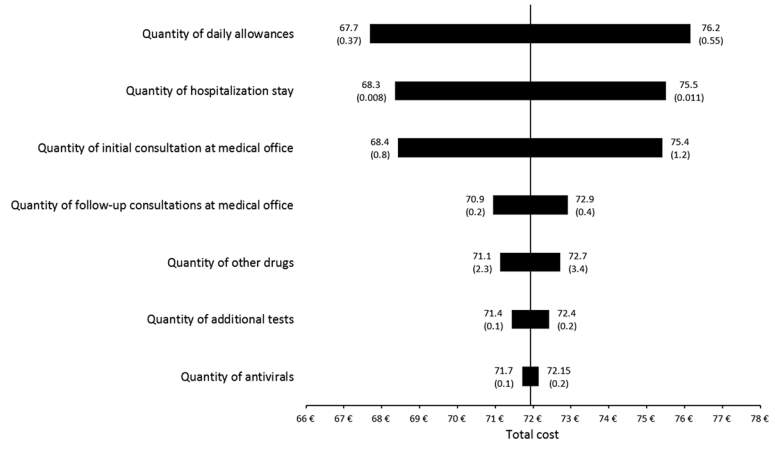

Figure 2 Sensitivity of the cost of influenza B in France (tornado diagrams are used to graphically illustrate the impact of ±20% variation of the value of each parameter). Legend: The length of the bar for each parameter represents the extent to which the mean of overall cost is sensitive to that particular variable. The graph presented so that the most influential parameter (the one with the longest bar) is on top. The vertical line represents the mean overall cost when all the parameters are at their base value.

Table 5 Estimation of the cost of influenza B per age group under the perspective of the French Health Insurance (in Euros, 2011)

	Population fluB + (IBGP)	Cost per patient (€) [CI 95%]	French population flu B + (estimation)	Costs for the FHI* (€) [CI 95%]
Younger children	50	70.0	255 834	17 908 380
(0–4 yo)		[0.4 – 139.6]		[102 333 – 35 714 426]
Older children	91	50.0	993 998	49 699 900
(5–14 yo)		[12.0 – 88.0]		[11 927 976 – 87 471 824]
Adults	46	126.1	612 246	77 204 220
(15–64 yo)		[74.9 – 177.3]		[45 857 225 – 108 551 215]
Elderly	14	41.8	157 268	6 573 802
(≥65 yo)		[32.9 – 50.7]		[5 174 117 – 7 973 488]
All ages	201	71.8	2 019 346	144 989 042
		[43.6 – 100.0]		[88 043 485 – 201 934 600]

*costs include direct costs plus daily allowances for adults (more than 3 days of sick leave) under the perspective of the French Health Insurance (FHI); yo = years old.

hospitalizations for influenza-like illness among all hospitalizations was 0.14% [36]. In the present study, we found that the proportion of hospitalizations following an ARI consultation in primary care was 0.3%. Based on this data, the direct access of patients to EDs and hospitals due to influenza is not very important when considering care following primary consultation. Therefore, although the exclusion of those expenses represented a possible limitation of our study, it was not likely have a critical influence on our final results.

According to the National Council of the College of Physicians, there were 96 669 active physicians (GPs and pediatricians) working regularly in France during the time of this investigation [37]. Members of the GROG network for the 2010–2011 winter season included 506 volunteer GPs and pediatricians, and 30% of these participated in our study. The two referenced laboratories partners of the GROG network provided 60% of the virological information [4]. Although our entire study population was made up of patients with lab-confirmed influenza B, they came from specific regions of France, representing 65% of the country (NIC North and South).

Patient characteristics, healthcare consumption and sick leave

A total of 6.7% of the French population was affected by influenza during our study period, and two influenza viruses were dominant: influenza B (3.2%) and influenza A(H1N1)pdm09 (3.5%). Notably, our investigation corresponded to a post-pandemic influenza season, which may have influenced the attitudes of patients and physicians (e.g., higher rate of antiviral prescriptions) [4]. Nevertheless, according to the GROG network, the number of consultations due to ARI was not higher than the usual rate observed during ordinary annual influenza outbreaks [4]. However, children were more likely to consult physicians than adults, which may have biased the average age of our study population. Consequently this may have influenced our results regarding higher costs for children.

Also, the small sample of elderly patients included may have resulted from a high vaccination coverage (54% in France 2011), which could have decreased influenza complications and consultations in this age group. In addition, elderly usually consult later than 48 h following the onset of symptoms. Indeed, this factor represents an important exclusion criterion for specimen collection in the GROG network [38].

Although the rate of employment in our working age population (67%) was rather high when compared to the French employment rate (58%), it was not statistically significant [35]. Notably, a lower employment rate (54%) was observed during a GROG study conducted during the 2005–2006 influenza season (also influenza B as dominant virus) [3], but the difference was also found to be insignificant when compared to the general French employment rate. We believe that our sample was representative of the general population; however, our costs may have possibly been overestimated.

From a societal perspective, each case of influenza in working people leads to between three and seven lost working days [39]. In Europe, influenza accounts for approximately 10% of sickness-related absences from work, while the cost of productivity lost in France and Germany has been estimated to be in the range of 9.3–14.1 billion USD per year [39]. Our results are comparable with these previous findings: adults with remunerated jobs displayed an average of 6.5 days of sick leave, which represented 13% of the population absent from work. In addition, we also calculated the work days lost by parents as a result of child illness. Although the FHI provides no daily allowances in these cases, it is important to state that

more than one in four parents (children < 14 years) were out of work for approximately 2.8 days under these circumstances. In fact, a recent socioeconomic study conducted in Hong Kong with hospitalized children reported an average of 5.3 ± 3.6 days of school leave for patients with lab-confirmed influenza B [40]. Indeed, our estimated school leave for treated children was similar (5.6 days).

The indemnity cap considered for daily allowances was critical for our obtained results. Since we were not allowed to collect personal information from the included patients, we considered French mean daily wage in 2011 [35]. Since the indemnity cap may not exceed the upper limit of daily allowances paid by the FHI, we applied the latter. We believe that careful considerations should be taken into account when extrapolating our results, due to possible over or underestimation of these cost calculations.

Cost of influenza B

The cost drivers for each age group varied. Our findings revealed that hospitalization was the major driver (51%) in younger children, whereas for older children costs were driven by hospitalization (40%) and initial consultation (34%). Daily allowances represented 73% of costs in adults. In contrast, for the elderly, the main driver was medical consultations (72%). Some authors have found similar drivers; however, others have also identified costs associated with vaccine administration, which was not assessed in our study [41,42].

Levy reported the only similar economic analysis of the burden of influenza illness in France for the seasons between 1985 and 1989. In the study by Levy, costs were estimated exclusively based on clinical incidence data related to influenza-like illness from the perspectives of both FHI and society [19]. Indeed, the results of our study are comparable with those presented by Levy. Both studies highlight to the economic importance of sick leave: first three days paid by the employer, followed by the FHI after the fourth day. According to Levy, FHI carried 70% of costs associated with influenza and the remaining 30% referred to the societal perspective (FHI excluded). This suggests that if we had measured the societal perspective in our study, the costs of influenza B might have increased by 43%. Thus, a further analysis of all indirect costs, including lost productive capacity and costs associated with the employment of substitute workers, will be needed in future studies. Additionally, different perspectives (e.g., patient, employer, private and mutual funds) could be considered.

Furthermore, Carrat et al. published an influenza burden of illness study that intended to obtain data for improving the cost-effectiveness of strategies against the disease, but no cost analyses were performed. Nevertheless, in the same study, the authors found that the mean number of sick leave for working adults was 4.0 ± 2.8 days [20]. In comparison, in our study, we found a higher duration (6.5 days) of sick leave among working age patients.

According to the French Ministry of Health, during the 2010–2011 influenza season, nearly 10 million people were targeted by the national influenza vaccination program, receiving an invitation from the French Health Insurance to obtain free vaccination. Among them, 51.8% were vaccinated [43]. Considering this vaccination coverage (approximately 5 million people), we estimate that the expenses related to vaccine cost and administration for the FHI would be around 110 million Euros. This amount is likely to be underestimated, as we did not consider expenses related to the national influenza program, institutional campaigns, postal services, and other indirect costs. Indeed, there is no public information available related to theses expenses. However, according to the estimates described above, we suggest that investments on vaccination strategies are still less expensive than the costs avoided with influenza care.

Conclusions

To our knowledge, this is the first cost study specifically related to influenza B in France. Our findings highlight avoidable costs related to influenza and are valuable in the context of evaluating healthcare interventions and public health strategies using economic models.

There is a lack of published literature about the costs associated with different viral strains of influenza. Thus, further knowledge is crucially required for policy makers to effectively decide on strategies regarding influenza (e.g., market access and reimbursement for new vaccines, implementation of vaccination programs in a pandemic situation). Therefore, we propose that refined studies targeting influenza economics should be developed in order to facilitate the work of policy-makers.

Furthermore, our results have the potential to influence decisions concerning seasonal influenza vaccine formulation. Currently, the most common available seasonal influenza vaccine contains only one lineage of influenza B (together with two flu A strains) [22]. Immunization against B virus strains of one lineage provides limited cross-protection against strains of the other lineage [18]. For this reason, and the difficulty of predicting which B virus lineage will predominate during a given season, vaccines containing two influenza B strains (together with two flu A strains) are recently receiving marketing authorization [15,18]. Therefore, policy-makers are evaluating the benefit of adopting those vaccines into their national influenza programs. Further investigations into the impact of such quadrivalent vaccines and vaccine effectiveness will be required.

Additional files

Additional file 1: Box 1. The unit costs of analyzed items [26–35] Legend: ATU: Reception and treatment of emergencies; CCAM: Classification commune des actes médicaux; FHI: French Health Insurance; GHM: Groupes Homogènes de Malades; GHS: Groupes Homogènes de Séjour; GP: General Practice[tioner]; GROG: Groupes Régionaux d'Observation de la Grippe; ICD: International Common Denomination; MCCO: activities of medicine, surgery, obstetrics and dentistry; MGE: supplement for children 2–6 years; MNO: supplement for children 0–2 years; NGAP: Nomenclature Générale des Actes Professionnels; sector 1: corresponds to the rate that is the basis for the reimbursement of health insurance; TNB: Table National de Biologie; yo: years old.

Additional file 2: Box 2. Healthcare consumption and sick leave per age group during the entire study period.

Additional file 3: Box 3. Characteristics of patients presenting with ARI consulting a GROG practitioner but NOT included in the study (259) in comparison with patients included in the study (201).

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
JMC and AM designed the IBGP study. IG, MLS, and AM acquired and analyzed clinical data. MLS, LP, and AM participated in cost data acquisition. MLS, LP, HMS, AM, NH, and JMC performed the statistical analysis and prepared the manuscript. All authors read and approved the final manuscript.

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References
1. WHO: *World Health Organization: Influenza (seasonal) fact sheet 211.* ; 2009. http://www.whoint/mediacentre/factsheets/fs211/en/2009 April 1Fact Sheet(211)Available from: URL:http://www.who.int/mediacentre/factsheets/fs211/en/.
2. ECDC. European Centre for Disease Prevention and Control: *Seasonal human influenza and vaccination - the facts*; 2007. http://ecdc.europa.eu/en/healthtopics/documents/0712_seasonal_human_influenza_vaccination.pdf.
3. GROG: *Estimation GROG du coût direct de l'épidemie de grippe 2005/2006.* Paris: Réseau des GROG - Groupes Régionaux d'Observation de la Grippe; 2007. Available on: http://openrome.org/documents/eco/2007_JNI_poster_ecogrippe.pdf.
4. GROG: *Situation de la grippe en France pour la semaine 2011/6.* Paris: Groupes Régionaux d'Observation de la Grippe; 2013. Available on http://www.grog.org/cgi-files/db.cgi?code=352&action=bulletin_grog.
5. Fleming DM, Zambon M, Bartelds AI, de Jong JC: **The duration and magnitude of influenza epidemics: a study of surveillance data from sentinel general practices in England, Wales and the Netherlands.** *Eur J Epidemiol* 1999, **15**(5):467–473.
6. Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K: **Systematic review and economic decision modelling for the prevention and treatment of influenza A and B.** *Health Technol Assess* 2003, **7**(35):1–170. iii–iv, xi–xiii.
7. Jefferson T, Demicheli V: **Socioeconomics of influenza.** In *Textbook of influenza.* Edited by Nicholson KG, Webster RG, Hay AJ. Malden, MA: Blackwell Science; 1998:541–547.
8. Ryan J, Zoellner Y, Gradl B, Palache B, Medema J: **Establishing the health and economic impact of influenza vaccination within the European Union 25 countries.** *Vaccine* 2006, **24**(47–48):6812–6822.
9. Molinari NA, Ortega-Sanchez IR, Messonnier ML, Thompson WW, Wortley PM, Weintraub E, *et al*: **The annual impact of seasonal influenza in the US: measuring disease burden and costs.** *Vaccine* 2007, **25**(27):5086–5096.
10. Cram P, Blitz SG, Monto A, Fendrick AM: **Influenza. Cost of illness and considerations in the economic evaluation of new and emerging therapies.** *Pharmacoeconomics* 2001, **19**(3):223–230.
11. Iskander M, Booy R, Lambert S: **The burden of influenza in children.** *Curr Opin Infect Dis* 2007, **20**(3):259–263.
12. Blanc P, Noel G, Dubus JC, Garnier JM, Chabrol B, Minodier P: **[Pediatric features of an influenza A seasonal outbreak and its burden in pediatric emergency rooms and pediatric departments].** *Arch Pediatr* 2006, **13**(1):11–16.
13. Narain JP, Kumar R, Bhatia R: **Pandemic (H1N1) 2009: epidemiological, clinical and prevention aspects.** *Natl Med J India* 2009, **22**(5):242–247.
14. Falchi A, Arena C, Andreoletti L, Jacques J, Leveque N, Blanchon T, *et al*: **Dual infections by influenza A/H3N2 and B viruses and by influenza A/H3N2 and A/H1N1 viruses during winter 2007, Corsica Island, France.** *J Clin Virol* 2008, **41**(2):148–151.
15. Ambrose CS, Levin MJ: **The rationale for quadrivalent influenza vaccines.** *Hum Vaccin Immunother* 2012, **1**:8(1).
16. Belshe RB: **The need for quadrivalent vaccine against seasonal influenza.** *Vaccine* 2010, **28**(Suppl 4):D45–D53.
17. Fitzner KA, Shortridge KF, McGhee SM, Hedley AJ: **Cost-effectiveness study on influenza prevention in Hong Kong.** *Health Policy* 2001, **56**(3):215–234.
18. Belshe RB, Coelingh K, Ambrose CS, Woo JC, Wu X: **Efficacy of live attenuated influenza vaccine in children against influenza B viruses by lineage and antigenic similarity.** *Vaccine* 2010, **28**(9):2149–2156.
19. Levy E: **French economic evaluations of influenza and influenza vaccination.** *Pharmacoeconomics* 1996, **9**(Suppl 3):62–66.
20. Carrat F, Sahler C, Rogez S, Leruez-Ville M, Freymuth F, le Gales C, *et al*: **Influenza burden of illness: estimates from a national prospective survey of household contacts in France.** *Arch Intern Med* 2002, **162**(16):1842–1848.
21. Mosnier A: **La surveillance nationale de la grippe en France: les groupes régionaux d'observation de la grippe (GROG).** *Arch Pediatr* 2000, **7**(Supplement 3):S472–S474.
22. World Health Organization, WHO Global Influenza Surveillance Network: *Manual for the laboratory diagnosis and virological surveillance of influenza.* Geneva: World Health Organization; 2011. http://xa.yimg.com/kq/groups/12239188/775439875/name/9789241548090_eng.pdf.
23. Open Rome. EFG Junior: *Etudes du Fardeau de la Grippe chez les enfants de moins de 15 ans consultant en médecine générale et pédiatrie pour infection respiratoire aiguë*; 2011. Sep. Report No. 2. Available on: http://www.openrome.org/documents/eco/Rapport_EFG%20Junior_2.pdf.
24. Drummond MF, Sulpher MJ, Torrance GW, O'Brien BG, Stoddart GL: *Methods for the economic evaluation of health care programmes.* 3rd edition. New York: Oxford University Press; 2005.
25. HAS: Choix méthodologiques pour l'évaluation économique à la HAS. Paris: Haute Autorité de santé; 2011. Available on http://www.has-sante.fr/portail/jcms/r_1499251/en/choix-methodologiques-pour-l-evaluation-economique-a-la-has.
26. Sécurité Sociale-Assurance Maladie: *Les consultations en métropole.* ; 2010. [consulted 2012 Nov 12]. Available from: http://www.ameli.fr/assures/soins-et-remboursements/combien-serez-vous-rembourse/consultations/

les-consultations-en-metropole/dans-le-cadre-du-parcours-de-soins-coordonnes.php.
27. Ministère des Affaires sociales et de la Santé: *Forfait Accueil et Traitement des Urgences « ATU » [Internet]*; 2010. [cited 2012 Dec 11]. Available from: http://www.sante.gouv.fr/forfait-accueil-et-traitement-des-urgences-atu.html.
28. Sécurité Sociale-Assurance Maladie: *Frais d'hospitalisation et remboursement*; 2010. [consulted 2012 Dec 11]. Available from: http://www.ameli.fr/assures/soins-et-remboursements/combien-serez-vous-rembourse/hospitalisation/frais-d-8217-hospitalisation-et-remboursement_rhone.php.
29. Ministère des Affaires sociales et de la Santé: *Règles de facturation des soins dispensées dans les établissements de santé.* Paris: Ministère des Affaires sociales et de la Santé; 2009. http://www.sante.gouv.fr/IMG/pdf/Guide_des_regles_de_facturation_des_soins_dispenses_dans_les_etablissements_de_sante_2009-2.pdf.
30. Vidal: *Le Dictionnaire VIDAL 2012.* 88th edition. Paris: du Vidal; 2012.
31. Thériaque: *Banque de données sur tous les médicaments disponibles en France*; 2012. http://www.theriaque.org/apps/recherche/rch_simple.php.
32. Sécurité Sociale-Assurance Maladie: *Présentation TNB [Internet]. Table Nationale de Codage de Biologie*; 2011. [cited 2012 Apr 3]. Available from: http://www.codage.ext.cnamts.fr/codif/nabm/index_presentation.php?p_site=AMELI.
33. Sécurité Sociale-Assurance Maladie: *CCAM en ligne. Classification commune des actes médicaux en France*; 2010. [consulted 2011 Dec 11]. Available from: http://www.ameli.fr/accueil-de-la-ccam/index.php.
34. Sécurité Sociale-Assurance Maladie: *Indemnité journalière salariés. Arrêt de travail pour maladie*; 2011. [consulted 2011 Dec 11] Available from: http://www.ameli.fr/assures/droits-et-demarches/par-situation-medicale/vous-etes-en-arret-de-travail-pour-maladie/salarie-vos-indemnites-journalieres.php.
35. INSEE: *National Institute of Statistics and Economic Studies - France*; 2011. [cited 2012 Jun 1]. Available from: http://www.insee.fr/en/default.asp.
36. INVS, I. de veille sanitaire: **Surveillance épidémiologique et virologique de la grippe en France, saison 2010–2011.** *Bull Épidémiologique Hebd* 2011, **37–38:**394–398.
37. Legmann M, Romestaing P, le Breton-Lerouvillois G: **Atlas de la Démographie Médicale en France.** *Conseil de l'Ordre des Médecins* 2011. [cited 2012 Apr 10]. Available from: http://www.conseil-national.medecin.fr/sites/default/files/Atlas2011.pdf.
38. Tuppin P, Choukroun S, Samson S, Weill A, Ricordeau P, Allemand H: **Vaccination contre la grippe saisonnière en France en 2010 et 2011: diminution des taux de couverture et facteurs associés.** *Presse Med* 2012, **41:**e568–e576.
39. Szucs TD: **Medical economics in the field of influenza–past, present and future.** *Virus Res* 2004, **103**(1–2):25–30.
40. Chiu SS, Chan K-H, So LY, Chen R, Chan ELY, Peiris JSM: **The population based socioeconomic burden of pediatric influenza-associated hospitalization in Hong Kong.** *Vaccine* 2012, **30**(10):1895–1900.
41. Lee BY, Bacon KM, Donohue JM, Wiringa AE, Bailey RR, Zimmerman RK: **From the patient perspective: the economic value of seasonal and H1N1 influenza vaccination.** *Vaccine* 2011, **29**(11):2149–2158.
42. Mercer NJ: **Cost analysis of public health influenza vaccine clinics in Ontario.** *Can J Public Health* 2009, **100**(5):340–343.
43. Sécurité Sociale-Assurance Maladie: *Vaccination contre la grippe saisonnière Lancement de la campagne 2011/2012 - Dossier de Presse.* Available on: http://www.sante.gouv.fr/IMG/pdf/Vaccination_contre_la_grippe_saisonniere_-_Lancement_de_la_campagne_2011-2012.pdf.

doi:10.1186/1471-2458-14-56
Cite this article as: Silva *et al.*: Economic burden of seasonal influenza B in France during winter 2010-2011. *BMC Public Health* 2014 **14**:56.

10 References

[1] European Centre for Disease prevention and Control influenza annual reports. http:/www.ecdc.europa.eu/en/publications/surveillance_reports/influenza/Pages/influenza.aspx

[2] Influenza (Seasonal). WHO Fact sheet N°211. April 2009. http://www.who.int/mediacentre/factsheets/2003/fs211/en/

[3] Centers for Disease Control and prevention influenza annual reports. http:/www.cdc.gov/flu/about/disease/index.htm

[4] Thompson et al. Mortality associated with influenza and respiratory syncytial virus in the US. JAMA 2003; 289:179-86.

[5] Thompson et al. Influenza associated hospitalizations in the US. JAMA 2004; 292:1333-40.

[6] Fleming DM et al. Lessons from 40 years' surveillance of influenza in England and Wales Epidemiol. Infect. 2008 July; 136(7): 866–875.

[7] Pitman RJ, Melegaro A, Gelb D, Siddiqui MR, Gay NJ, Edmunds WJ. Assessing the burden of influenza and other respiratory infections in England and Wales. J Infect. 2007 Jun;54(6):530-8.

[8] Paget WJ, Meerhoff TJ, Rebelo de Andrade H; EISS. Heterogeneous influenza activity across Europe during the winter of 2002-2003. Euro Surveill. 2003 Dec 1;8(12):230-9.

[9] Cottrell et al. Unusually high impact of influenza B during the early 2012–2013 influenza season in Wales – epidemiology and clinical analysis of the first 100 cases. Influenza and Other Respiratory Viruses. 2013 7(6), 1013–1016.

[10] Richard SA, Viboud C, Miller MA. Evaluation of Southern Hemisphere influenza vaccine recommendations. Vaccine. 2010 Mar 24;28(15):2693-9.

[11] Paul Glezen W, Schmier JK, Kuehn CM, Ryan KJ, Oxford J. The burden of influenza B: a structured literature review.Am J Public Health. 2013 Mar;103(3):e43-51. doi: 10.2105/AJPH.2012.301137. Epub 2013 Jan 17.

[12] European Influenza Surveillance Network data. http://ecdc.europa.eu/en/activities/surveillance/EISN/Pages/index.aspx

[13] EuroFlu website. Case definitions http:/www.euroflu.org/html/case_definitions.html

[14] Mereckiene J, Cotter S, D'Ancona F, Giambi C, Nicoll A, Levy-Bruhl D, et al. Differences in national influenza vaccination policies across the European Union, Norway and Iceland 2008-2009. Euro Surveill. 2010;15(44).

[15] Mosnier A. La surveillance nationale de la grippe en France: les groupes régionaux d'observation de la grippe (GROG). Archives de Pédiatrie. 2000;7, Supplement 3:S472 – S474.

[16] Agustín Tomás Vega Alonsoa et al. Guía de principios y métodos de las redes centinelas sanitarias en España. Gac Sanit. 2006;20(Supl 3):52-60.

[17] Red de vigilancia epidemiológica de Castilla y León http://www.saludcastillayleon.es/profesionales/es/informacion-epidemiologica/red-vigilancia-epidemiologica-castilla-leon

[18] EU case definitions for reporting communicable diseases. http://ec.europa.eu/health/ph_threats/com/docs/1589_2008_en.pdf

[19] Akçay Ciblak M, Kanturvardar Tütenyurd M, Asar S, Tulunoğlu M, Fındıkçı N, Badur S. Influenza surveillance in nine consecutive seasons, 2003-2012: results from National Influenza Reference Laboratory, Istanbul Faculty Of Medicine, Turkey. Mikrobiyol Bul. 2012 Oct;46(4):575-93.

[20] Commonly used World Health Organization (WHO) case definitions for influenza surveillance. http://www.who.int/bulletin/volumes/90/11/BLT-12-108837-table-T1.html

[21] Aguilera JF, Paget WJ, Mosnier A, Heijnen ML, Uphoff H, Van der Velden J, et al. Heterogeneous case definitions used for the surveillance of influenza in Europe. Eur. J. Epidemiol. 2003;18(8):751–754.

[22] Woolpert T et al. Determination of clinical and demographic predictors of laboratory-confirmed influneza with sub-type analysis. BMC Inf Dis 2012, 12:129