Needs for future pharmacoeconomic analysis of RSV vaccines: Assessing the burden of paediatric RSV disease and QALYs lost (Phase II: retrospective part)

AIV_VRS_2020_11_QALY_RETRO_AOS

Principal Investigator	Alejandro Orrico-Sánchez
Co-Investigators	Carla Gómez-Álvarez, Mónica López-Lacort, Ainara Mira-Iglesias, Javier Diez-Domingo.
Inputs	María Díaz-López
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List of abbreviations

ACS: Acute Coronary Syndrome

ALRI: Acute Lower respiratory tract infections

BoD: Burden of Disease

COPD: Chronic Obstructive Pulmonary Disease

CUA: Cost-Utility Analysis

DRG: Diagnosis Related Groups

ECMO: Extracorporeal membrane oxygenation

ED: Emergency Departments

GP: General Practitioner

MBDS: Minimum Basic Data Set at Hospital Discharge

NICE: National Institute for Health and Clinical Excellence

QALY: Quality-Adjusted Life Year

RedMIVA: Red de Vigilancia Microbiológica de la Comunitat Valenciana (Microbiological Surveillance Network)

RESCEU: Respiratory Syncitial Virus Consortium in Europe

RSV: Respiratory Syncitial virus

SIA: Ambulatory Information System

SIP: Population Information System

SIRS: Systemic Inflammatory Response Syndrome

VHS: Valencia Health System

VID: Valencia Health System Integrated Database

VIS: Vaccine Information System

VR: Valencia Region

Table of contents

1. Introduction

Respiratory syncytial virus (RSV) is the leading cause of severe acute lower respiratory tract infections (ALRI), in infants worldwide (1). Over 95% of all children in the world have been infected with RSV by 2 years of age (1, 2). RSV bronchiolitis is one of the leading causes of hospital admission of infants under 2 years of age worldwide and contributes greatly to the mortality rate in those infants (2, 3). Moreover, annual winter seasonal RSV-epidemics overlap in time with other infections outbreak, such as influenza or rotavirus collapsing emergency departments (ED) and hospital wards. Furthermore, severe RSV infection early in life might be linked to later development of chronic respiratory conditions such as recurrent wheezing or asthma (4, 5). Such problematic situation has led to an investment of 29 million euros in the Respiratory Syncytial Virus Consortium in Europe (RESCEU) project by the European Union (6), in which the AIV-FISABIO participates and would be able to obtain valuable data for the project. At present, Palivizumab is the only prophylactic therapy available for RSV. This is a costly humanized monoclonal RSV-specific antibody that is given to infants of high-risk groups (premature babies, and infants with Congenital Heart Disease or Congenital Lung Disease) (7-9). However, there are now 60 RSV vaccine candidates in development targeting paediatric as well as elderly populations, and 16 candidates are in Phase 1-3 Trials (10). The AIV-FISABIO participates in one of these Trials. Therefore, an RSV vaccine could possibly be licensed over the next 5–10 years (11, 12). Before the licensure of these vaccines, decision makers will need to understand their potential health and economic benefits.

Health burden of RSV is considered challenging because 1) multiple viral agents have been identified as causative of acute bronchiolitis (and other ALRI) and most of the cases (50%–80%), but not all, are estimated to be caused by RSV (13-15), 2) the size of RSV-epidemics varies across seasons and 3) most people with ALRI are not routinely tested for RSV, especially in outpatients where the majority of cases are treated. In a previous publication of the AIV-FISABIO we estimated that the incidence rate of bronchiolitis in the Valencia Region of Spain was 16.4 cases/100 children <2 years per year, which means approximately 13,000-15,000 cases per year only in this region (13). Of them, 13% were admitted to hospital and the average length of stay (LOS) was 5 days (13). The RSV-related costs in this Region could reach more than €10Mill considering indirect costs (16). However, these studies presented some variability and their results might be underestimated because: 1) 40% of all hospitalizations for bronchiolitis diagnosed as RSV-negative in The Valencia Region did not have a confirmation test and 7% had an error of encoding (13, 17), and 2) 87% of cases of bronchiolitis in children under 2 years were managed as outpatients (13), where confirmation

test are not usually used, since the results do not modify the management of the disease. Hence primary care or hospital databases are not on their own a reliable estimate of RSV disease incidence. Therefore, the estimation of the percentage of the RSV-related bronchiolitis, pneumonias and other ALRI in outpatients and inpatients is required to estimate the real BoD. In a parallel prospective study started one year ago, we are assessing the percentage of RSV-confirmed ALRI and the direct and indirect-related costs. The inference of the prospective study in the Real-World Data analysis will allow extrapolating the overall burden of RSV disease to the general population, and thus, being able to assess the incidence of ALRI due to RSV and the overall BoD in very young children. These data are a cornerstone for the future estimation of the overall cost-utility of the different vaccination strategies (infant or pregnant women) against RSV, expressed in euros per quality-adjusted life year (QALY) gained.

2. Objectives

The overall objective is to assess the burden of RSV-associated acute lower respiratory infections (ALRI) in children less than 2 years old in the Valencia Region.

2.1. Primary objectives

Estimate RSV and ALRI rates among children less than 2 years of age in the Valencia Region using Real World Data.

2.2. Secondary objectives

Estimate RSV related healthcare resource consumption and their costs among children less than 2 years old age.

Estimate the proportion of outpatient ALRI episodes potentially caused by the RSV.

Assess the RSV subgroup-specific (RSV A and RSV B) epidemiology and burden in hospitalized children less than 2 years old.

Estimate the burden potentially attributable to RSV extrapolating the percentage of RSV-confirmed ALRI obtained in the prospective study.

2.3. Exploratory objectives

Asses QALY scores in RSV-ALRI cases using the Q-Twist as a method for collecting quality of life data.

Assess the effectiveness of the pneumococcal vaccine on ALRI and pneumonia-related hospitalizations.

3. Methods

3.1. Study design

A population-based, retrospective cohort study will be performed using real world data from health care databases.

3.2. Real World Data

The Valencia Health System Integrated Database (VID) is a set of multiple, public, population-wide electronic databases for the Valencia Region described elsewhere. The VID provides exhaustive longitudinal information including socio-demographic and administrative data, clinical, pharmaceutical and healthcare utilization data from hospital care, emergency departments, specialized care, primary care and other public health services. All the information in the VID databases can be linked at the individual level through a single personal identification code.

Potentially useful databases for the study are described below:

- Population Information System (SIP)

SIP is a region-wide database that provides basic information on VHS coverage (dates and causes of VHS entitlement or disentitlement, insurance modality, pharmaceutical copayment status, assigned Healthcare Department, Primary Healthcare District and primary care doctor, etc…), and also some socio-demographic (as sex, date of birth, nationality, country of origin, risk of social exclusion, geographic location, address, etc…). The SIP database includes the date of death captured from the Mortality Registry. Also, is paramount to the VID as it is the source of the individual, exclusive and permanent identifier number associated to each individual (the SIP number) that is then used throughout the rest of the databases, allowing data linkage across the multiple databases in the network.

- Minimum Basic Data Set at Hospital Discharge (MBDS)

The MBDS is a synopsis of clinical and administrative information on all hospital admissions and major ambulatory surgery in the Valencia Health System (VHS) hospitals, including public-private partnership hospitals (around 450.000 admissions per year in the region). The MBDS includes admission and discharge dates, age, sex, geographical area and zone of

residence, main diagnosis at discharge, up to 30 secondary diagnoses (comorbidities or complications), clinical procedures performed during the hospital episode and the Diagnosis Related Groups (DRG; a system to classify hospital cases into one of approximately 500 groups, expected to have similar hospital resource use) assigned at discharge.

The MBDS used the ICD9CM system for coding until December 2015 and the ICD10ES (a Spanish translation of the ICD10CM) since then.

- Microbiological Surveillance Network (RedMIVA)

RedMIVA contains the results of the microbiological analyses performed in the VHS. Data is transferred from the laboratories to the RedMIVA database on a daily basis, providing real-time detection of circulating microorganisms and resistance patterns, and enabling microbiological surveillance. Importantly, RedMIVA gathers not only positive but also negative determinations. This database has been available since 2008.

- Ambulatory Information System (SIA)

The SIA include paediatric and adult primary care, mental health care, prenatal care and specialist outpatient services, as well as providing information about dates, visits, procedures, lab test results, diagnoses, clinical and lifestyle information. It also includes information on several health programmes (healthy children, vaccines, pregnancy, notifiable diseases, etc.), the primary care nurse clinical record and the health-related social assistance record. The SIA module uses the International Classification of Diseases revision Clinical Modification (ICD-CM 9, ICD-CM 10) for coding diagnoses.

- VAHNSI Network

VAHNSI (the Valencia Hospital Surveillance Network for the Study of Influenza and other Respiratory Viruses). Set up in 2009, it has been conducting a prospective active-surveillance hospital-based study on respiratory infections in different hospitals in the Valencia Region of Spain. The network is coordinated by the AIV. Depending on the season, VAHNSI includes from 4 to 10 hospitals, covering from 22% to 46% of the total population from the Valencia Region (around 5,000,000 inhabitants). Fulltime dedicated nurses (one at each hospital) screen consecutive hospitalized patients discharged from the Emergency Department with complaints possibly related to a respiratory infection. Patients fulfilling the inclusion criteria are included in the study and a sample of nasopharyngeal exudate is taken with a swab, after written informed consent. All swabs are sent to a centralized laboratory in FISABIO-Public Health and are analyzed by real-time RT-PCR for 8 different viruses: coronavirus, influenza, RSV, rhinovirus/enterovirus, bocavirus, adenovirus,

metapneumovirus, and parainfluenza. Coronavirus, influenza, RSV, rhinovirus/enterovirus and parainfluenza are subtyped *a posteriori*.

3.3. Study population, study period and follow up

All children under 2 years of age and covered by the Public Health System (PHS) from 1st January 2010 and 31st December 2018. Start of follow-up will be the latest of: start of the study (01/01/2010), first date of registration in the database. End of follow-up will be the earliest of: end of the study (31/12/2018), 2 years birthdate, or end of registration in the database.

3.4. Case definitions

The main outcome will be any episode of ALRI coded in outpatient visits or hospitalization in the cohort children under 2 years of age that could be due to RSV disease. The International Classification of Disease, 9th and 10th edition (ICD- 9 and ICD-10) diagnostic codes and RSV detection-test results from RedMIVA will be used to identify the different case definitions:

- Severe RSV-ALRI: all RSV-related hospitalizations (Table 1.1) in any diagnostic position or other ALRI-related hospitalizations (Table 1.2) in any diagnostic position with RSV-confirmed result from RedMIVA (Table 1).

- Severe non-RSV-ALRI: all other ALRI-related hospitalizations (Table 1.2) in any diagnostic position with negative or missing RSV-result from RedMIVA.

- Severe miscellaneous ARLI: all ALRI-related hospitalizations (table 1.2), excluding RSV-related codes, without laboratory test associated.

- Outpatient ALRI: All Primary Care visits with RSV-ALRI and other ALRI related ICD-codes (table 1).

- Non-ALRI case: A child from the cohort that had no registers of ALRI-related diagnostic codes.

RSV sub-types:

- RSV A: All ALRI hospitalizations (table 1) from VANHSI network with a type A RSV laboratory confirmed result.
- RSV B: All ALRI hospitalizations (table 1) from VANHSI network with a type B RSV laboratory confirmed result.

Every primary care visit coded as ALRI (Table 1) followed by a hospitalization in the next 30 days will be assumed to be the same case and it will be considered a hospitalization case. A laboratory result will be considered associated to the admission if available 5 days before or 10 days after the discharge date. We will consider different episodes if time between two diagnoses are longer than 30 days.

Table 1

DESCRIPTION	ICD-9	ICD-10	DESCRIPTION
1.1 RSV-ALRI:			
RSV infection	079.6	B97.4	RSV infection
Acute RSV bronchiolitis	466.11	J21.0	Acute RSV bronchiolitis
Pneumonia due to RSV	480.1	J12.1	Pneumonia due to RSV
1.2 Other ALRI:			
Acute bronchitis and bronchiolitis	466	J21	Acute bronchiolitis
Acute bronchitis	466.0	J20	Acute bronchitis
		J20.9	Not-specified acute bronchitis
Acute bronchiolitis	466.1		
Acute bronchiolitis caused by other infectious organism	466.19	J21.8, J21.9	Unspecified acute bronchiolitis
Non-specified pneumonia	486	J189.9	Non-specified pneumonia

Wheeze	786.07	R0.62	Wheeze
Acute bronchospasm	519.11	J98.1	Acute bronchospasm
Other non-specified ALRI	519.8	J22	Other non-specified ALRI

3.5. Healthcare resource consumption

Healthcare resources consumption due to ALRI within the 30 days following episode diagnosis will be measured. The assessment of resources will include: AED visits, specialist visits, general practitioner, hospitalizations, admission to the intensive care unit (ICU), and length of hospitalizations stay and readmission (any admission for the same cause within 1 month after diagnosis).

3.6. Covariates

Variables that are relevant to the diseases will be considered for the analysis: Birth date, age, sex, urban/rural residence, social exclusion risk, calendar year, month of birth, health department, zip code, municipality, health care district, having received any vaccination by a private provider, anti-pneumococcal vaccination, antibiotic consumption in the first year of life (ATC-code: J01). High-risk preterm babies (defined as infants who require hospitalization for prematurity) will be identified through the ICD-codes 765.XX or P07.XX (shortened gestation and low-birth-weight-related disorders) in MBDS.

	Categories/units
Birth date	YYYY-mm-dd
Age	0-2 months 3-6 6-11 ≥12
Sex	Male Female
Preterm	No Yes
Rural residence	No Yes

Social exclusion risk	No Yes
Nationality	Spanish Other
Calendar year	2010:2018
Seasonality	Month
Health department	24
Health care districts	241
Municipality	542

3 Provinces **24 Health departments** **241 Health care districtis** **542 Municipalities**

Pneumococcal Vaccination	No Yes
Private vaccination	No Yes
VAHNSI Covariates	
Birth date	YYYY-mm-dd
Age at admission	0-23 months
Sex	Male Female
Date of admission	YYYY-mm-dd

Reason for admission: ARI	No Yes
Reason for admission: bronquiolitis	No Yes
Reason for admission: pneumonia	No Yes
Reason for admission: COPD	No Yes
Reason for admission: asthma	No Yes
Reason for admission: dyspnea	No Yes
Reason for admission: tachypnea	No Yes
Reason for admission: cough	No Yes
Reason for admission: apnea	No Yes
Reason for admission: myalgia	No Yes
Reason for admission: ACS	No Yes
Reason for admission: heart failure	No Yes
Reason for admission: metabolic failure	No Yes
Reason for admission: multiorgan failure	No Yes
Reason for admission: convulsions/confusion	No Yes
Reasons for admission: sepsis/SIRS	No Yes
Date of symptoms onset	YYYY-mm-dd
Oxygen saturation at admission	%
Birth weight	Grams (or do not remember)

Gestational week at birth	Week (or do not remember)
Breastfeeding	No Yes Do not remember
Duration of breastfeeding	1-2 months 3-5 months ≥6 months
Comorbidity: heart disease	No Yes
Comorbidity: cerebrovascular disease	No Yes
Comorbidity: asthma	No Yes
Comorbidity: bronchitis	No Yes
Comorbidity: diabetes	No Yes
Comorbidity: endocrine disease (no diabetes)	No Yes
Comorbidity: anemia	No Yes
Comorbidity: chronic hepatic disease	No Yes
Comorbidity: chronic renal disease	No Yes
Comorbidity: immunodeficiency	No Yes
Comorbidity: neuromuscular disorder	No Yes
Comorbidity: neoplasia	No Yes
Comorbidity: autoimmune disease	No Yes
Comorbidity: dementia	No Yes

Treatments: antihypertensives	No Yes
Treatments: anticoagulants	No Yes
Treatments: antiplatelet aggregants	No Yes
Treatments: hypolipemiants	No Yes
Treatments: insulin	No Yes
Treatments: oral hypoglycaemics	No Yes
Treatments: immunosuppressant	No Yes
Treatments: corticosteroids	No Yes
Weight	In kg
Height	In cm
Tobacco exposure: smokers at home	No Yes
Tobacco exposure: directly exposed	No Yes
Kids contact: Contact with other children	No Yes
Kids contact: School or nursery attendance	No Yes
Kids contact: Siblings at school or nursery	No Yes
GP consultations in the last 3 months	0 1 2 3 >3 Do not remember
Hospitalization in the previous year	No

	Yes Do not remember
Number of hospitalizations in the previous year	Number
Social class (parents' occupation)	Professional managerial Managerial and technical occupations Skilled (not manual) Skilled (manual) Partially skilled Unskilled Unclassifiable
VIS: Seasonal influenza vaccine	No Yes Not registered in VIS
VIS: Pneumococcal vaccine	No Yes Not registered in VIS
Antivirals treatment before hospitalization	No Yes
Antivirals treatment during hospitalization	No Yes
Days of antiviral treatment	Number
Date of discharge	YYYY-mm-dd
ICU admission	No Yes
Mechanical ventilation	No Yes
ECMO	No Yes
In-hospital death	No Yes
Main discharge diagnosis	ICD9/10 code
Secondary discharge diagnosis (complication)	ICD9/10 code
Base disease	ICD9/10 code

RSV type	A B
Coinfection	No Yes

3.7. Data collection

Data privacy will be protected by using anonymized data. The following variables will be requested to the different databases for the period from 1 January 2010 until 31 December 2018 from children aged < 2 years old from the Valencia Region.

Data to be extracted from SIP:

- Identification block including SIP number, sex, date of birth and other geographical of birth, place and date of registration (excluding identifying data as surnames, ID card number, phone numbers, etc.).

Variables: N_Sip, Sexo, Fecha_Nacimiento, Pais_Nacimiento(Cod:Desc), Prov_Nacimiento(Cod:Desc), Loc_Nac(Cod:Desc), Nacionalidad Española, Sit_Empadronamiento, Fecha_Alta.

- Regular location block that includes complete address, health map information as health department and census information among others (excluding exact data that allows the exact residence location of the subjects).

Variables: Provincia_Hab(Cod:Desc), Localidad_Hab(Cod:Desc), Nucleo_Hab(Cod:Desc), Cp_Hab, Dpto_Hab(Cod:Desc), Zona_Hab(Cod:Desc), Distrito_Hab, Seccion_Hab, Subseccion_Hab, Unidad Residencia.

- Assignation block, excluding (excluding identifying data as surnames, medical doctor ID, etc.)

Variables: Centro (Cod:Desc), Dpto_Centro (Cod:Desc), Zona_Centro (Cod:Desc), Hospital De Referencia.

- Cessation block including cessation cause and description, cessation date and date of death (when applicable).

Variables: Causa De Baja (Cod:Desc), Fecha De Baja, Indicador Baja Por Exitus, Fecha Defuncion.

- APSI codes corresponding with 2010, 2014, 2018

Data to be extracted from MBDS:

- Anonymized Personal Identification Number (SIP)
- Health department
- Health care district
- Date of hospital admission
- Date of hospital discharge
- Diagnoses at discharge (main and secondary diagnoses)
- Procedures during the hospitalization
- Discharge destination (destination on discharge)
- ICU

For any diagnosis code ICD-9-CM or ICD-10-CM related with ALRI (Table 1).

Data to be requested from SIA-GAIA:

SIP number

Morbidity database

Date of diagnosis activation (diagnosis of interest)

Date of diagnosis deactivation (diagnosis of interest)

Diagnosis description (diagnosis of interest)

ICD-code (diagnosis of interest)

Outpatient visits database

Date of the visit

Diagnosis description

ICD-code

Specialist visits database

Date of the visit

Diagnosis description

ICD-code

Professional attendance (GP/Specialist)

Specialties Service

Prescription

Medical prescription number

Dosage

Number of units prescribed

Treatment number

Active ingredient code

Active ingredient description

ATC code

ATC description

Pharmaceutical form

Date of prescription (dd/mm/yyyy)

ICD-code or procedure

Treatment

Treatment number

Starting date of the treatment

Closing date of the treatment

Active ingredient code

Active ingredient description

ATC code

ATC description

ICD-code or procedure

Dispensation

Dispensation id

Number of units dispensed

Active ingredient code

Active ingredient description

ATC code

ATC description

ICD-code or prodedure

Date of dispensation

For any diagnosis code ICD-9-CM or ICD-10-CM related to ALRI (table1)

Data to be extracted from RedMIVA:

All results for RSV detection in children younger than 2 years during the study period.

SIP number

Date of laboratory test (dd/mm/yyyy)

Microorganism/antigen

Date of test result (dd/mm/yyyy)

Sample type

Laboratory test

Result

Data from VAHNSI network:

All ALRI-related hospitalizations in children younger than 2 years during the seasons 2014/15 to 2018/19 and the variables gathered in the study.

4. Regulatory and ethical considerations

The study will be conducted in accordance with all applicable regulatory requirements, including all applicable subject privacy requirements, the Declaration of Helsinki, and the International Ethical Guidelines for Epidemiological Investigations.

The study will be submitted for approval to the institutional review board. **The Spanish Agency of Medicines and Medical Devices** (AEMPS) will be informed of the performance of the study, so it can be classified (as 'Estudio no post-autorización, NO EPA') according to the existing legislation (Orden SAS/3470/2009). The Pharmacy Agency of the Valencia Government will also be informed about the study according to the existing legislation [Resolución de 16 de junio de 2009, de la Conselleria de Sanitat].

5. Sample size and considerations

Considering that annual birth cohort in the Valencia Region is about 48.000 infants we might expect approximately 0.5 million infants less than 2 years to be followed (2010-2018).

6. Statistical Analysis

Demographic characteristics of the study population will be summarized using descriptive tables including proportions, frequencies, ranges, standard deviations and mean/median (depending on variable type).

For all case definitions, we will estimate RSV and other ALRI rates (number of events per-X persons-year) globally and stratified by sex, age groups, prematurity and calendar year. Their respective 95% confidence intervals will be calculated by the exact method of Poisson. The person-time-at-risk contributed to the study rates starts at the date of follow-up up and ends at the date of loss to follow-up. Persons-time will be estimated as the sum of total time contributed by all subjects divided by 365.25. RSV and other ALRI monthly rates will be also calculated as the number of episodes per-X persons globally and by sex and age groups.

Healthcare resource consumption the following 30 days after RSV or ALRI episode will be studied. A descriptive analysis of the healthcare utilization (see section XX) will be developed overall and stratified by age, sex and prematurity. Health care resource consumption will be compared among age groups, sex and prematurity by different regression analyses using Generalized Linear Model (GLM). Variables mentioned in the covariates section (xxx) will be considered for the adjustment. Healthcare resource consumption-related costs will be calculated assuming the Diagnosis Related Groups (DRG) assigned at discharge for the overall in-hospital costs and the official estimated costs for the other resources. Descriptive analysis of cost will be developed by age, sex, prematurity and calendar year. The consumption of resources will be corrected by the real RSV-confirmed ALRI (%) estimated in the prospective study

RSV and ALRI rates will be modelled by a Bayesian model. In the same model, to estimate the burden potentially attributable to RSV potential outpatient's RSV episodes (primary care ALRI without lab-confirmation) will be estimated using multiple imputation technics. For each potential case in outpatients, N simulated values will be obtained incorporating the uncertainty of the true value to be imputed. Subjective data collected from the prospective study (% RSV cases in outpatients found in the prospective study (AIV_VRS_2019_10_QALY_AOS) will be included in the imputation model.

RSV hospitalizations severity (ICU vs. no ICU) will be compare among RSV A and RSV B sub-types by a logistic regression. Socio-demographic and clinical characteristics will be compared between A and B sub-types by a logistic regression when the response variable will be (RSV A =0; RSV B=1). A and B sub-types features also will be compared among negative VRS cases by a logistic regression model, all variables above-mentioned and their interactions will be contemplated in in the model.

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