ÉCOLE DES HAUTES ÉTUDES EN SANTÉ PUBLIQUE

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Development of an ecological approach to measure the hospital burden associated with the RSV in the elderly (people over 65 years old), in France from 2010 to 2018.

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Acknowledgements page

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1 Table of content

1.1 List of figures and tables

1.2 List of abbreviation

PMSI	Programme de médicalisation des systèmes d'information
RSV	Respiratory Syncytial Virus
RNA	Ribonucleic acid
SNIIRAM	Système national d’information inter-régimes de l'assurance maladie
MCO	Medicine, Surgery and Obstetrics
HAD	Hospitalisation à Domicile
SSR	Soin de suite et réadaptation
ILI	influenza-like illness
WHO	World Health Organization
SURSAUD	Surveillance Sanitaire des urgences et des décès
CépiDC	Centre d'épidémiologie sur les causes médicales de Décès
CNSA	Caisse nationale de solidarité pour l'autonomie
ATIH	Agence technique de l'information sur l'hospitalisation
CNAM	Caisse National Assurance Maladie
INSEE	Institut national de la statistique et des études économiques
ICD 10	International Classification of Diseases
SNDS	Système National des Données de Santé

1.3 Abstract

Background: Infectious diseases such as influenza, respiratory syncytal virus (RSV) infections and pneumonia are caused by the transmission of a virus or a bacterium. Most people infected by them have a mild form of the disease and require no medical intervention. But the people over 65-year-old can present severe complications due to their physical condition. Thus, these respiratory infections represent a heavy hospital burden in France. In addition, it is very difficult to diagnose and differentiate influenza and RSV complications and therefore to identify all affected patients during epidemic seasons. This is due to the common characteristics of the two viruses, the lack of systematic diagnosis of respiratory secretions and to the latency between infections and the onset of symptoms and complications. The hospital burden directly associated with influenza and RSV is therefore underestimated because it is based solely on hospitalizations or deaths for which influenza or RSV diagnoses are identified.

Objective: Our objective was to develop an ecological approach to measure the hospital burden associated with the RSV infection in the elderly (people over 65 years old), in France from 2010 to 2018.

Method: Firstly, we presented descriptive statistics of influenza and RSV. Then we used a statistical model to measure the hospital burden of RSV regarding two categories of hospitalizations. On the one hand a category regrouping the majority of respiratory infections, on the other hand a category called extended RSV, including pneumonia and respiratory infections being consequences of RSV. In our model, we took into account the circulation of influenza, using data from the Sentinelles database. We used the Santé Publique France database for the RSV circulation, and the SNDS database for the hospitalizations.

Results: Our results show a high incidence of RSV in people over 65 years old. The estimated RSV-associated hospitalizations for respiratory cause was equal to 261 321 and to 186 272 for the extended RSV category from 2010 to 2018. Moreover, our results show an increasing number of hospitalizations due to RSV over the study period in people older than 65 years old with a peak in 2017. Rsv-related hospitalizations also tend to increase with age.

Conclusion: These results reflect the impact of RSV in the elderly and the need to set up a specific surveillance system to accurately assess the circulation of this virus in this population, and the development of a vaccine to prevent this disease being a real public health issue, especially as the population is ageing.

Keywords: Influenza, RSV, Respiratory infection, Ecological approach, Poisson model

2 Introduction

According to WHO, respiratory diseases are a main cause of death and disability worldwide which makes it an important public health issue (WHO, The Global Impact of Respiratory Disease – Second Edition, 2017). We focus our study on respiratory infectious diseases, more specifically on influenza and the respiratory syncytial virus which have common characteristics. In order to dissociate them and to be able to evaluate the hospital burden attributable to RSV it is important to detail their characteristics and their temporality.

2.1 Influenza

Respiratory infectious diseases, are caused by the transmission of a bacterium, virus, fungus or parasite. The transmission of respiratory viruses happens through direct or indirect contact (via fomites), and droplets containing respiratory secretions (Fumihiro Kodama, 2017).

One of the main respiratory infectious disease is influenza, a viral infection caused by RNA viruses divided in three types; type A which circulates in humans and animals, type B which has only been described in humans, and type C which currently does not circulate significantly in humans. According to their antigenic properties, the viruses are classified into subtypes. Only the A/H1N1, A/H2N2 and A/H3N2 subtypes are associated with human epidemics; the most common circulating viruses are A/H1N1, A/H3N2 and type B for which no subtype has been identified (CDC, 2019).

Influenza can manifest itself by one or more symptoms: fever, cough, rhinorrhea, headaches, aches, sore throat and sometimes nausea. The diagnostic of influenza is mostly clinical. Molecular diagnosis (RT-PCR) could be used for biological diagnosis but this test is expensive and cannot be carried out outside a medical biology laboratory (Pasteur, 2020).

According to WHO, every year, influenza is responsible for 1 billion cases, 3-5 million severe cases, and 290 000-650 000 influenza-related respiratory deaths worldwide (WHO, 2018). In France, an IQVIA study called Fardogrip, calculated the numbers of all hospitalizations for main, related or associated diagnosis with influenza thanks to the Programme de médicalisation des systèmes d'information (PMSI) database. This database references reimbursement data for hospital stays in private and public hospitals in France. Between July 2009 and June 2018, the total number of patients hospitalized for influenza was 165,141. In the study period, the number of patients hospitalized for influenza per season varied according to the season, from 8,311 (2013/14 season characterized by the circulation of A(H1N1) and A/H3N2 viruses) to 40,887 (2017/18 season characterized by the circulation of A/H1N1 and B viruses).

Table 1: Number and proportion of patients hospitalized for influenza per epidemic season and per age group, in France over the period 2009-2018, PMSI data base

Season	Virus	65-74 years old		75-84 years old		85 years old and older		Number Total of hospitalization in France
		Numbers of hospitalisation	**%**	**Numbers of hospitalisation**	**%**	**Numbers of hospitalisation**	**%**	
2009/2010	h1	887	4%	772	4%	395	2%	21 022
2010/2011	h1/b	504	5%	495	5%	325	3%	9 619
2011/2012	h3	686	8%	1 136	13%	1 036	12%	8 532
2012/2013	h3 mixte	1 026	8%	1 267	10%	1 000	8%	12 960
2013/2014	h3 mixte	739	9%	829	10%	519	6%	8 311
2014/2015	h3 mixte	2 208	11%	3 536	17%	3 461	17%	20 274
2015/2016	h1/b	1 794	10%	1 658	10%	1 085	6%	17 161
2016/2017	h3	3 378	13%	6 116	23%	7 728	29%	26 375
2017/2018	h1/b	5 588	14%	7 661	19%	7 766	19%	40 887
	Total	16810	10%	23470	14%	23315	14%	165141

Table 1 represents the number and proportion of hospitalization for people older than 65 years old. They are divided into three age groups, 65-74 years old, 75-84 years old and 85 years old and older. They were compared with the total number of hospitalizations including people from 0 to 85 years old and older for each season of reference.

The people over 65 years old are particularly affected by the influenza virus. They suffered in particular during the 2017/2018 period which was the most severe epidemic period with a total number of 40 887 hospitalizations in France. There were 5 588 hospitalizations for the people between 65-74 years old, representing 14% of the annual hospitalizations, 7 661 for the 75-84 years old representing 19% of the total annual hospitalizations and 7 766 for the 85 years old and older also representing 19% of the total hospitalizations. Over the period 2009 to 2018 it appears that the people aged 75-84 years old are the most affected by the influenza virus.

2.2 Respiratory Syncytial Virus

Another main respiratory infectious disease is the RSV. Discovered in 1956, it is the leading cause of acute lower respiratory infections in young children and the main cause of hospitalizations in this population. Member of the Paramyxovirus family, RSV is a single-stranded, negative-polarity RNA virus with two antigenic groups (types A and B) (Falsey & Walsh, 2005). The symptoms are a runny nose, decrease in appetite, coughing, sneezing, fever and wheezing. The RSV diagnosis is usually based on symptoms, however RSV infection is difficult to diagnose because of its similar symptoms with other respiratory infection (Walsh A. R., 2005). A virological diagnosis via respiratory secretions by immunocytodiagnosis can be carried out in severe forms, notably during hospitalization. To date, there is no real treatment for RSV disease, only the management of the symptoms.

Moreover, RSV is responsible for respiratory infections such as bronchiolitis, an acute contagious viral infection (Ann R. Falsey, 2005) which affects the bronchioles (small airways). The symptoms are coughing, rapid breathing and wheezing. It is recognized as the leading cause of hospitalization in infants aged < 1 year old worldwide (Marika K. Iwane, 2013). A study on the burden of RSV infection also estimates that 33.8 million children under 5 years of age were infected with RSV in 2015 worldwide, with 3.2 million being hospitalized and 59,600 deaths (S.Graham, 2008) (Ting Shi D. A., 2017). In France, a study estimated that 30% of children under the age of two are infected with the respiratory syncytial virus (RSV) which causes severe respiratory infections (N. Petrica, 2020). Also in France, a retrospective study estimated the incidence of RSV hospital admissions at 14.5 per 1000 births in the first year of life (Kramer, Duclos, Lina, & Casalegno, 2018) (Che, Nicolau, Bergounioux, Perez, & Bitar, 2012).

An IQVIA study called Bronchiopic on the impact of the RSV among children referenced the number of hospitalizations due to RSV in children younger than 5 years old from 2010 to 2018. Over the study period, there were 407 025 hospitalizations and 84% of them were in children younger than 2-year-old. The results of this study show an increasing number of hospitalization attributable to RSV over the study period with 43 715 hospitalizations in 2010/2011 and 54 616 hospitalizations in 2017/2018.

Table 2: Number of patients hospitalized for RSV per epidemic season from 0 to 5 years old, in France over the period 2010-2018, PMSI database

Seasons	Number of hospitalizations stay for RSV	Number of patients younger than 2-year-old
2010/2011	43,715	84%
2011/2012	47,973	84%
2012/2013	50,949	84%
2013/2014	50,373	84%
2014/2015	50,728	81%
2015/2016	54,585	84%
2016/2017	54,086	84%
2017/2018	54,616	84%

In adults the RSV disease is usually mild and can be treated as a cold. However, for the elderly (over 65 years of age) (L.Ailhaud, 2020), immunocompromised people or high-risk adults, especially with underlying chronic cardiopulmonary disease are at risk of severe infection due to RSV, including pneumonia (Scott F. Dowell, 1996) (Ann R. Falsey, 2005). Ting Shi et al. estimated the global disease burden of respiratory syncytial virus associated with acute respiratory infections in older adults ≥65 years in 2015 worldwide. The global number of hospital admissions for RSV in older adults was estimated at 336,000 (Ting Shi A. D., 2019). Age-related characteristics like frailty and immunosenescence could explain respiratory infections in elderly people (Arielle Childs, 2019).

In France, there is surveillance of bronchiolitis cases in children but there is no surveillance and therefore little data on RSV in vulnerable adults such as people aged 65 or older. However, the timing of the RSV presents a similar activity in children and elderly people (Zambon, Stockton, Clewley, & Fleming, 2001). This is why, in order to study the circulation of RSV in 65 years old people and older, we based ourselves on data from the SOS Médecins network monitoring the circulation of bronchiolitis in children, assuming that the virus circulates in the same way in older people.

2.3 Temporality of RSV and influenza epidemics

In addition to the similarity of their symptoms, RSV and influenza tend to circulate during the same period, in winter, being associated with a cold and dry climate (Nicklas Sundella, 2016). It makes them difficult to dissociate (Liang Chen, 2020). Even tough, compare to the influenza outbreaks, the epidemic curve for RSV is fairly constant (Walsh A. R., 2005).

Furthermore, according to an IQVIA study called Bronchiopic, RSV is responsible for seasonal epidemics which happen most frequently before the influenza season, the two epidemics being rarely concomitant. It has been noted that RSV circulation generally predates that of the influenza virus by 6–8 weeks in western countries (Pablo Obando-Pacheco, 2018). It occurs between October and March in Northern Europe, mostly in young children who are nearly all infected by 2 years of age (Hall C. B., et al., 2009) (Jepsen , et al., 2018).

In France, the influenza epidemic occurs every year, generally between November and April. It lasts on average 10 to 11 weeks (Santé Publique France, 2019).

There is little concrete data available to indicate why influenza virus infections peak in the wintertime (Anice C. Lowen, 2007). Hypotheses have been made suggesting factors that might explain the seasonality of influenza. They include antigenic drift and shift in influenza viruses, host immune response and social behavior changes (Nicklas Sundella, 2016) . Anice C. et al, demonstrated that the seasonality is also dependent on environmental factors, including temperature. According to their study, transmission efficiency is dependent on relative humidity and also that transmission efficiency is inversely correlated with temperature (Anice C. Lowen, 2007). In fact, low relative humidity and cold temperature have been shown to contribute to the transmission and survival of influenza virus (Nicklas Sundella, 2016). In addition to the virus stability in such dry and cold weather, some researchers assume that inhalation of cold air causes cooling of the nasal epithelium, and that it would be sufficient to inhibit respiratory defences against infection. (ECCLES, 2002)

2.4 Objective

Because the symptoms of RSV and influenza are similar, the hospital burden of RSV is difficult to differentiate and therefore underestimated, particularly in the elderly. Currently in France there is no surveillance system that allows to really assess the impact of RSV on the general population. Therefore, it is necessary to set up a specific analysis method to calculate the hospital burden related to RSV.

Since we cannot directly estimate the hospital burden of RSV because of a lack of diagnostic, we need to develop an indirect approach which consists in estimating the excess hospitalization attributable to RSV, using national data on viruses' surveillance. In recent years, ecological studies using time series regression have become popular to estimate excess morbidity and mortality burden indirectly attributable to respiratory pathogens, in particular for influenza virus, in an IQVIA's study called Fardogrip and in other studies (Muscatello, Newall, Dwyer, & MacIntyre, 2013) (Jackson, et al., 2015) (Pitman, et al., 2007) (Simonsen, et al., 2011). Such models have been applied to estimate RSV- indirectly attributable hospital excess burden in the UK (Taylor, et al., 2016) (Reeves, et al., 2017) (Fleming, et al., 2015) but never in France for the elderly. However, a similar method has been used in an IQVIA study called Bronchiopic to estimate the indirect burden of RSV hospitalizations among children under 5 years old in France between 2010 and 2018.

The present study aimed to estimate the excess hospitalization rates indirectly due to RSV in people aged 65 years and older in France from 2010 to 2018.

3 Methods

This study was conducted using different databases.

3.1 Databases

3.1.1 Sentinelles network database

The Sentinelles Network database is a research and monitoring network in primary care (general medicine and paediatrics) in metropolitan France accessible in open data through the Sentinelles Network website. Its objectives are to build up databases in general medicine and paediatrics for health monitoring and research purposes, to develop tools for detecting and forecasting epidemics and to set up clinical and epidemiological studies. This surveillance network relies on volunteer general practitioners (1% of all general practitioners), who have been reporting medical consultations for ILI and other infections since 1984 (Réseau Sentinelles, s.d.) (Costagliola, et al., 1991 Jan). The Sentinelles Network data available for the study are weekly aggregated data and concern the incidence of influenza-like illness (ILI) in people older than 65 years old, per 100 000 inhabitants.

3.1.2 « SOS Médecins » Network from Santé Publique France

The SOS Médecins Network is one of the four sources of the syndromic surveillance system SurSaUD (Surveillance Sanitaire des Urgences et des Décès). This system was set up to detect unexpected health events or a predefined health events, such as a seasonal epidemic, and to measure the impact of these events of environmental, infectious or societal origins on the population. The data from the SOS Médecins Network are collected from the Geodes website and are aggregated data by week. The indicator used in this study represents the weekly proportion of medical acts with a diagnosis of bronchiolitis made by the doctors of the SOS Médecins associations. This proportion is expressed per 10,000 consultations and concerns only children under the age of 2.

3.1.3 SNDS : Système National des Données de Santé

Created in April 2017, the National Health Data System (SNDS) brings together the main existing public health databases in France. Unique in Europe, the SNDS brings together for nearly 66 million individuals:

- Health insurance reimbursement data (SNIIRAM database)
- Hospital activity data (PMSI database)
- Data on medical causes of death (CepiDC database)
- Data relating to disability (CNSA)
- Eventually, a sample of data from complementary organizations

Since 2017, access to SNDS data has been extended to private and public companies, in order to carry out studies of public interest.

The “Programme de médicalisation des systèmes d'information”, or PMSI, is an exhaustive national database that lists all hospital stays in all French public and private healthcare establishments, the information provided is focused on reimbursements, not on the prescriptions. It is managed by the “Agence Technique de l'Information sur hospitalization” (ATIH). The PMSI is made up of several databases: short-term hospitalizations recorded in the Medicine, Surgery and Obstetrics (MCO) database, then hospitalizations at home recorded in the “Hospitalisation à Domicile” (HAD) database, followed by the “Soin de suite et réadaptation” recorded in the SSR database and finally the medicalized information for psychiatry encoded in the PMSI RIM-P database.

The data used in this study from the SNDS database were weekly aggregated data transmitted by the CNAM (Caisse Nationale d'Assurance Maladie) including information on hospitalizations for the respiratory cause category and the extended RSV category, in France between 2010 and 2018.

3.1.4 INSEE data

The National Institute of Statistics and Economic Studies (INSEE) produces, analyses and disseminates official statistics in France. It is a public body responsible for the analysis and publication of official statistics of the French state. We have used INSEE opened data to calculate the proportions of the French population by age group and to standardize the number of hospitalizations by the data of the reference population of 2018.

3.1.5 Météo France

Météo France is the French national meteorological service. The files used for this study are exported in free access from Météo France website. We used them to calculate the average temperature per season in France from 2010 to 2018. These data are added to the statistical model to calculate the excess of hospitalization related to RSV.

4 Statistical Analysis

In this part we will explain the different variables of our statistical model, the explanatory variables, as well as our outcomes of interest and the statistical method used to calculate the excess of hospitalizations attributable to RSV.

4.1 Explanatory variables

Our explanatory variables for the statistical model come from different sources. Firstly, we added the weekly aggregated data regarding the incidence of influenza-like illness (ILI) in people over 65 years old using data from the Sentinelles Network from 2010 to 2018. Influenza virus' activity was considered in the model to avoid attributing to RSV the potential excess due to ILI.

Then, we added the bronchiolitis rates from SOS Médecins Network for children aged 0-2 years representing the circulation of the RSV from 2010 to 2018 representing the circulation of RSV in the population.

Since we observed a periodicity in the evolution of the number of hospitalizations from 2010 to 2018, we included trigonometrical terms in our equation representing the periodicity of the data as well as trend terms to take into account the tendency of the changes over the season.

Finally, we added the meteorological data from Météo France which are the average temperatures per season from 2010 to 2018.

4.2 Outcomes

Thanks to the statistical model we tried to explain two outcomes which are number of hospitalizations that could be linked to RSV. The first one is the number of hospitalizations due to a category that we called extended RSV, which includes a number of hospital admissions due to possible potential complications of RSV. The strict definition of RSV is not representative enough of the impact of RSV on the elderly due to a lack of testing and diagnostic of this population. We have therefore created this category which includes RSV complications such as acute upper respiratory tract infections, pneumonia/pneumonitis, acute bronchitis, acute bronchiolitis, acute lower respiratory tract infections, bronchitis (not specified as acute or chronic), asthma and wheezing (see appendix for the ICD 10 codes).

The second outcome of our model is the number of hospitalizations due to respiratory causes. The respiratory infections studied in this section concern all respiratory diseases including all cases of influenza, pneumonia, bronchitis, bronchiolitis, respiratory distress, and respiratory tract infections (see appendix for the ICD 10 codes).

4.3 Introduction to the model

We used an ecological approach to estimate excess hospital stays associated with RSV infections in people aged over 65 years. This approach was based on modelling the data against weekly indicators of RSV, influenza activity, meteorological data trend and seasonality terms.

In order to calculate the number of hospitalizations attributable to RSV infections we therefore estimated the number of hospitalizations in the absence of RSV circulation, we called it the “baseline”. Then, by subtracting the total number of hospitalizations from the baseline, we get the number of hospitalizations due to RSV per age class and per cause.

In this way, several log-linked Poisson cyclical models (time series) were constructed (by age class and cause) incorporating SOS Médecins rates for bronchiolitis (RSV), influenza incidence, meteorological data, trend and seasonality parameters. The model equation is detailed below:

$$\boldsymbol{log\left(\frac{H_t^{(c,a)}}{Pop}\right) = \alpha_0 + \alpha_1 t + \alpha_2 t^2 + \sum_{i=1}^{12}[\beta_i cos\left(\frac{it\pi}{52,14}\right) + \gamma_i sin\left(\frac{it\pi}{52,14}\right)] + \delta ILI_t + \phi Temp + \theta RSV_t + \varepsilon_t}$$

Where $\boldsymbol{H_t^{(c,a)}}$ is the weekly number of hospitals stays for cause **c** in an age class $\boldsymbol{a}$, ***Pop*** is the corresponding population at offset (standardisation to the exposed population). $\boldsymbol{t}$ and $\boldsymbol{t^2}$ is the linear and quadratic trend terms, cos and sin the terms representing seasonality. $\boldsymbol{RSV_t}$ corresponds to the weekly rate of SOS Médecins visits for bronchiolitis (RSV activity) and $\boldsymbol{ILI_t}$ the weekly incidence of influenza (indicator of influenza activity). ***Temp*** is the average temperature by season given by Météo France. Parameters α, β, γ, δ, ϕ and θ were estimated using a likelihood method (see appendix tables 13 to 18).

In a first step, we tested for $\boldsymbol{H_t^{(c,a)}}$ the weekly number of hospital stays for extended RSV cause with data from Météo France, from the SNDS for $\boldsymbol{ILI_t}$ the weekly rate of consultations for an influenza-like illness with data from the Sentinelles Network and for RSV the weekly rate of SOS Médecins visits for RSV cause with data from Santé Publique France.

In a second step, we tested for $\boldsymbol{H_t^{(c,a)}}$ the weekly number of hospital stays for respiratory causes with data from Météo France, from the SNDS for $\boldsymbol{ILI_t}$ the weekly rate of consultations for influenza-like illness with data from the Sentinelles data source and for RSV the weekly rate SOS Médecins visits for RSV with data from Santé Publique France.

4.4 The variables

The dependent variable represents the numbers of hospitalizations. It is the variable of interest. They were tested in crude form and as a moving average (t-1, t, t+1) in an attempt to limit the impact of fluctuations in hospitalisations on the model estimates.

The independent variables were indicators for RSV_t and for ILI_t [indicator by season, moving average (t-1, t, t+1), moving average by season]. They were tested in order to take into account the difference in the evolution between seasons.

Thus, height models were created for each cause and age group:

- RSV_t and ILI_t
- RSV_t and ILI_t by season
- RSV_t by season and ILI_t
- RSV_t by season and ILI_t by season
- Moving average RSV_t and moving average ILI_t
- Moving average RSV_t and moving average ILI_t by season
- Moving average RSV_t by season and moving average ILI_t
- Moving average RSV_t by season and moving average ILI_t by season

The selection of the best indicators was made based on the AIC (Akaike Information Criterion) and the correlation between the observed values and the values predicted by the model (number of hospital stays). The model including the moving average RSV_t by season and the moving average ILI_t by season was the most suitable.

4.5 Selection of variables

For people over 65 years of age, we decided to study three age groups to see if there is a change in the number of hospitalisations with age: 65-74 years, 75-84 years and over 85 years. For each age class and cause, a Poisson model integrating the variables with the form selected in the previous step was performed. A backward variable selection method was used on each model to identify trend and seasonality effects that have a significant impact on the number of hospital stays. In addition, during the variable selection process, the RSV and influenza indicators were fixed in the models.

4.6 Estimation of RSV related excesses in the over-65s

Excess hospitalizations related to RSV in people over 65 years of age were estimated as the difference between the model predicted values and the "base" number of hospitalizations. The number of 'baseline' hospitalizations was calculated from the Poisson model when the parameter $\boldsymbol{RSV_t}$ is set to 0.

5 Descriptive statistics

This section aims to present descriptive statistics of influenza, RSV, and the two categories of hospitalizations of interest: extended RSV and respiratory cause.

5.1 Influenza

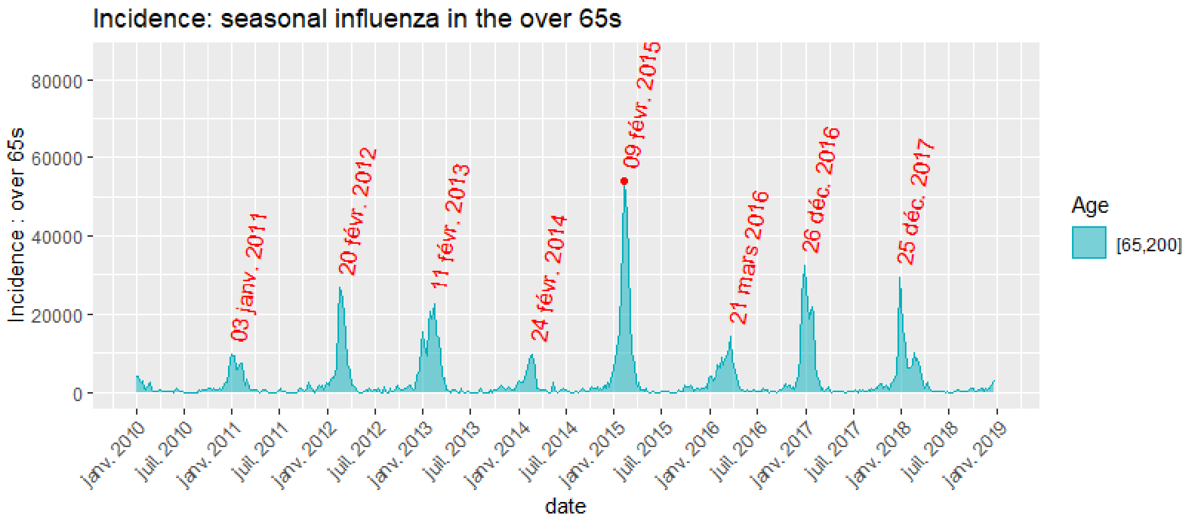

Figure 1 : Incidence rate of patients hospitalized with influenza in France, for people older than 65 years old, Sentinelles Database

This graph represents the circulation of influenza in France from 2010 to 2018 from Sentinelles Database. In line with what has been described in the literature, the influenza epidemic always tends to start in December with a peak in activity between late December and March. The most important epidemic period for people over 65 years of age according to this graph is the year 2015 which is due to the circulation of the H3N2 virus.

5.2 RSV circulation

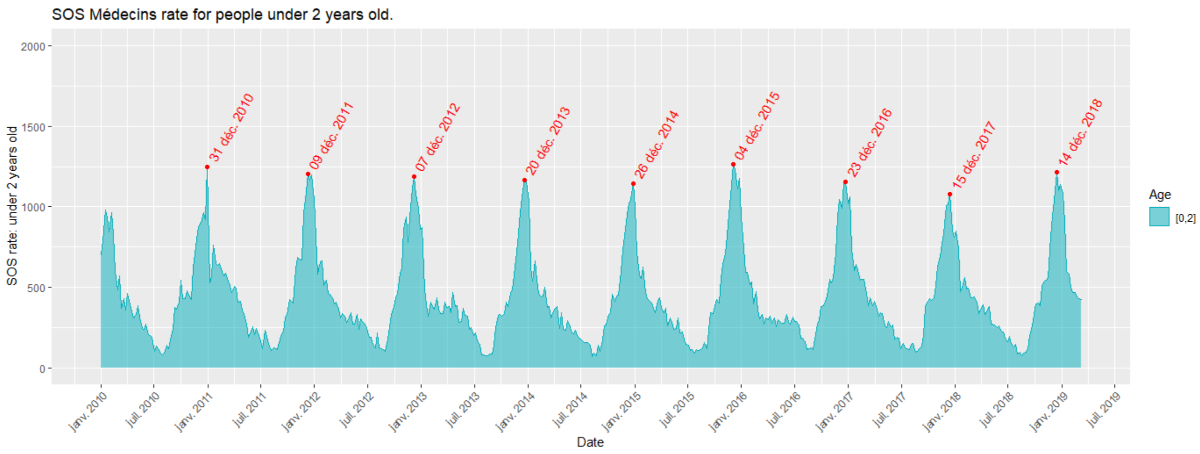

Figure 2: SOS Médecins rate for children under 2 years old

This graph (Figure 2) represents the circulation of RSV according to the rates of bronchiolitis from the SOS doctor database in children under 2 years old in France. According to these results, RSV appears to circulate throughout the year with a peak of activity in winter around December every year.

Table 3: Epidemic peak of influenza and RSV

Epidemic peaks			
Season	**Influenza**	**RSV**	**Time difference in days**
2010-2011	**03/01/2011**	**31/12/2010**	**3**
2011-2012	20/02/2012	09/12/2011	73
2012-2013	11/02/2013	07/12/2012	66
2013-2014	24/02/2014	20/12/2013	66
2014-2015	09/02/2015	26/12/2014	45
2015-2016	21/03/2016	04/12/2015	108
2016-2017	**26/12/2016**	**23/12/2016**	**3**
2017-2018	**25/12/2017**	**15/12/2017**	**10**

This table (Table 3) shows a summary of the dates of the epidemic peaks for influenza and RSV. We observe that the epidemic peaks occur almost at the same time in the epidemic seasons 2010/2011, 2016/2017 and in 2017/2018.

5.3 Extended RSV

The ICD 10 codes included in this category were defined by a scientific committee of experts in the framework of the IQVIA Bronchiopic study.

The extended RSV category includes RSV complications such as acute upper respiratory tract infections, pneumonia/pneumonitis, acute bronchitis, acute bronchiolitis, acute lower respiratory tract infections, bronchitis (not specified as acute or chronic), asthma and wheezing (see Appendix Table 12).

The following figure shows the total number of hospitalizations for people over 65 years old per epidemic season (from July of the previous year to June of the following year).

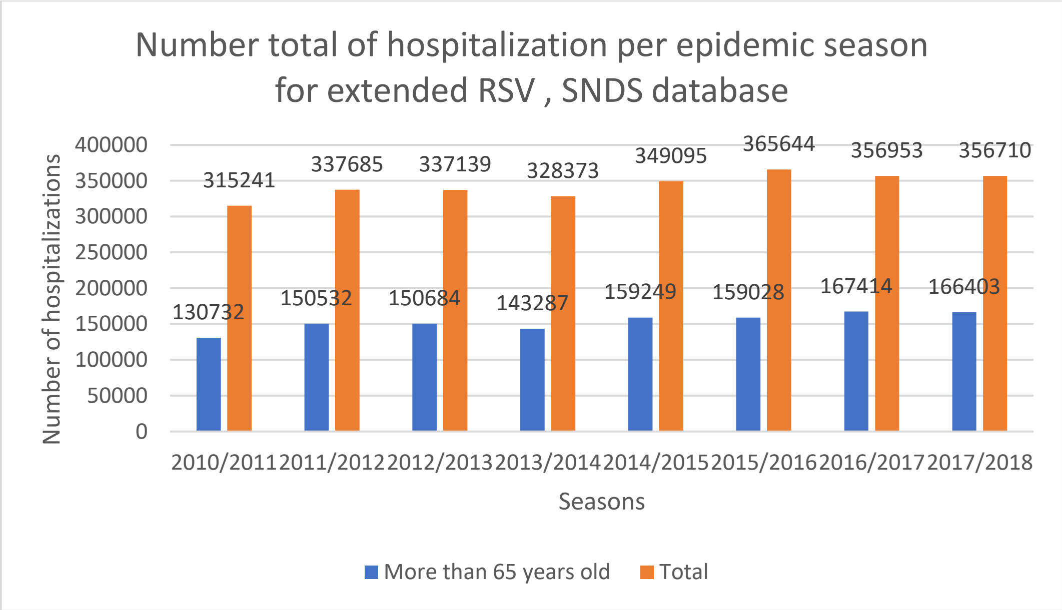

Figure 3: Number total of hospitalization per epidemic season for extended RSV, SNDS database

This figure shows the number of hospitalizations for the population total in France and for the people older than 65 years old. From 2010 to 2018 the proportion of hospitalization for extended RSV category in people older than 65 years old is relatively stable and varies around 45% of the total hospitalizations. As the extended RSV category includes bronchiolitis, we can assume that the most affected part of the population are children under 5 years old (see Table 2) since, based on the IQVIA study called Bronchiopic, almost 50 000 hospitalizations are due to RSV for this age group.

The total number of hospitalizations per epidemic season is relatively stable with a small variation due to pneumonia which is included in the definition of extended RSV and affects particularly 65-year old people and older.

RSV is an important cause of pneumonia (Zambon, Stockton, Clewley, & Fleming, 2001) which is why we included it in the extended RSV category. The severity of pneumonia epidemics is measured by the total number of hospital admissions (SNDS-PMSI data).

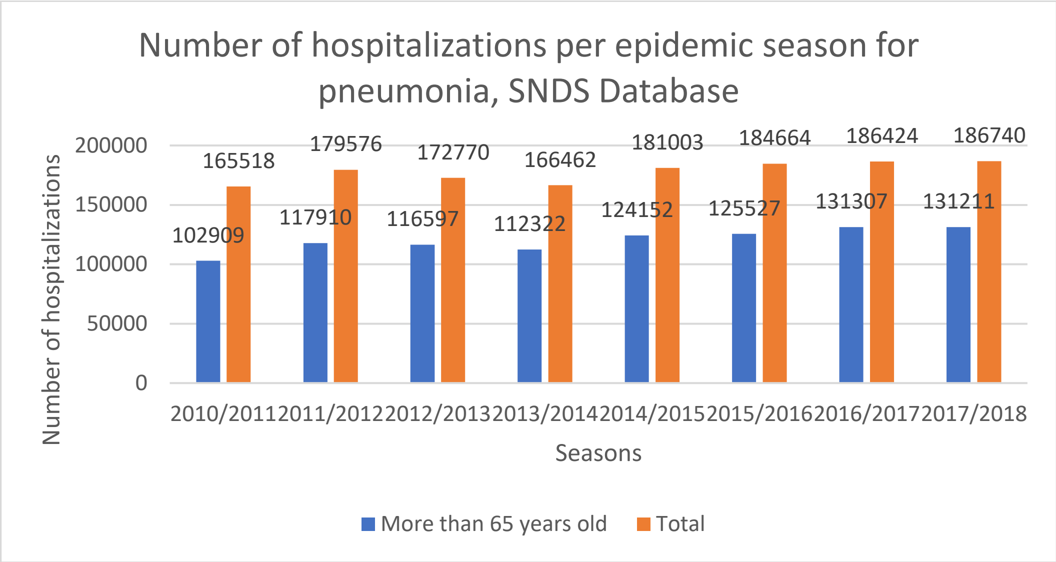

Figure 4: Number of hospitalizations per epidemic season for pneumonia, SNDS Database

The total number of hospitalizations for pneumonia ranged from 165,518 to 186,740 over the entire season from 2010 to 2018 of which 62-70% are attributable to people over 65. The season most affected by the pneumonia epidemic was the 2017/2018 season with a total of 186, 740 hospitalizations, of which 131,211 in people over 65 years old which represents 70% of the total hospitalizations.

It should be recalled that this same epidemic season (2017/18) was the most severe for the influenza epidemic with a total of 40 887 hospitalizations, including 21 015 in people aged over 65 years old which represented 51% of the national cases.

The first four epidemic seasons studied in 2010/2014 for pneumonia were marked by lower numbers than the last four seasons in 2014/2018. There is an increase in the total number of hospital admissions per epidemic season for pneumonia in people aged over 65 years.

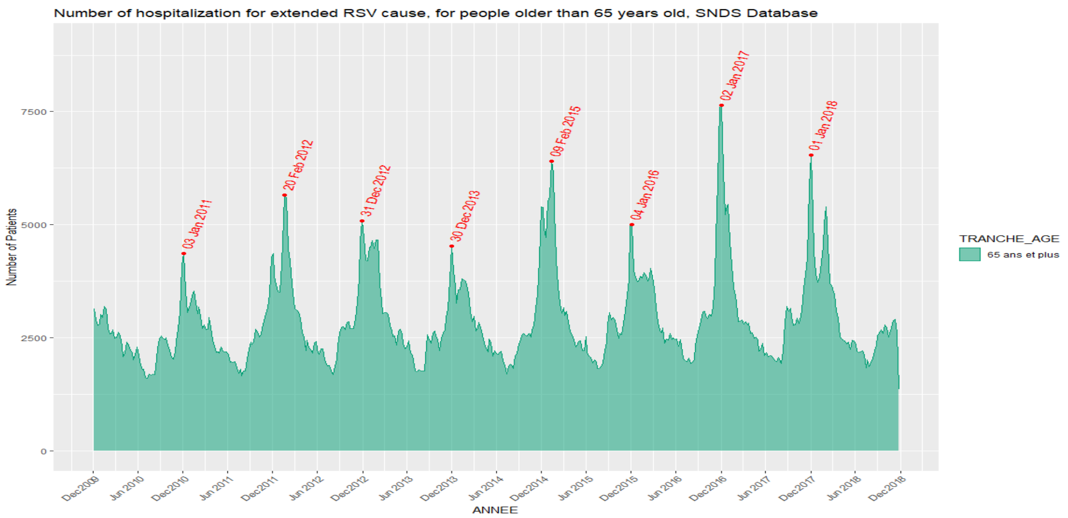

Figure 5: Weekly number of hospitalizations for extended RSV per epidemic season, in France for 65 years old people and older over the period 2010-2018, SNDS data

This graph (Figure 5) shows the number of hospitalizations for extended RSV per epidemic season, in France for 65 years old people and older from 2010 to 2018. The most important epidemic peak is observed at the beginning of January 2017.

Compared to the number of hospitalizations due to the extended RSV category, the number of hospitalizations among people over 65 years old is in fact the highest during the period 2016 to 2017 with a total of 167,414 hospitalizations.

5.4 Respiratory causes

The respiratory infections studied in this section concern all respiratory diseases including all cases of influenza, pneumonia, bronchitis, bronchiolitis, respiratory distress, and respiratory tract infections (see Appendix Table 13). This category is intended to include a very broad range of respiratory diseases that must include complications of RSV.

The severity of respiratory infections is measured by the total number of hospitalizations per epidemic season. The following figure shows the total number of hospitalizations for people over 65 years old.

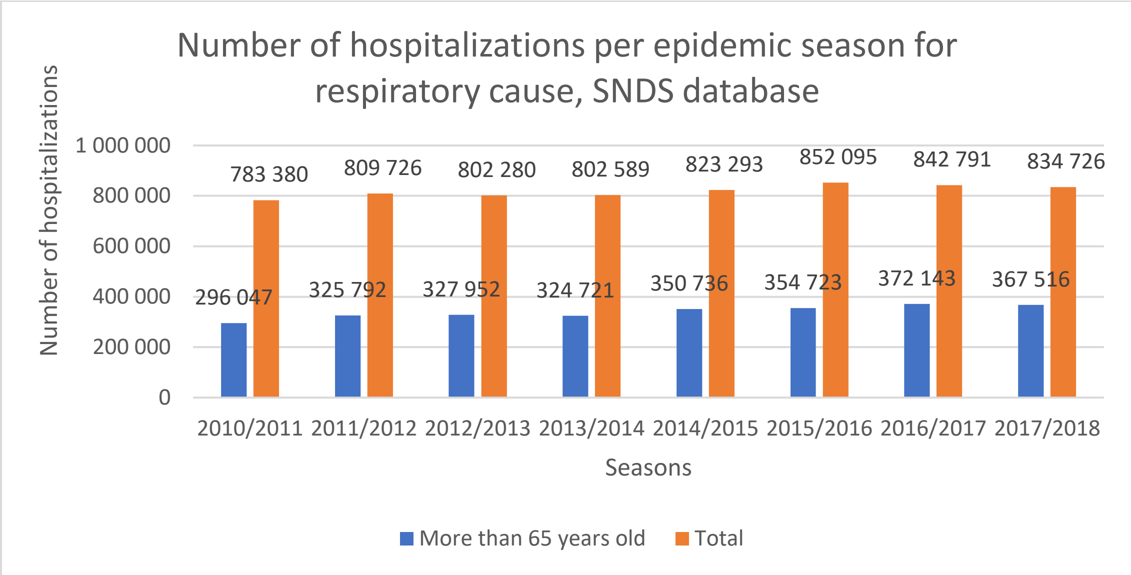

Figure 6: Total number of hospital admissions for respiratory causes per epidemic season, in France over the period 2010-2018, SNDS data

Over the whole period studied between 2010 and 2018, the total number of hospital admissions for respiratory infection varied slightly between 783,380 and 852,095 with a variation between 296,047 and 372,143 in people over 65 years of age representing 37 to 44% of the total hospitalizations. The most severe epidemic season was the 2015/2016 season with 852,095 hospitalizations for respiratory infection, of which 354,723 were in people aged over 65 years old corresponding to 41% of the hospitalizations.

Regarding only the elderly people, 65 years old and older, the worst period was 2016/2017 with a total of 372,143 hospitalizations or 44% of the total hospitalizations.

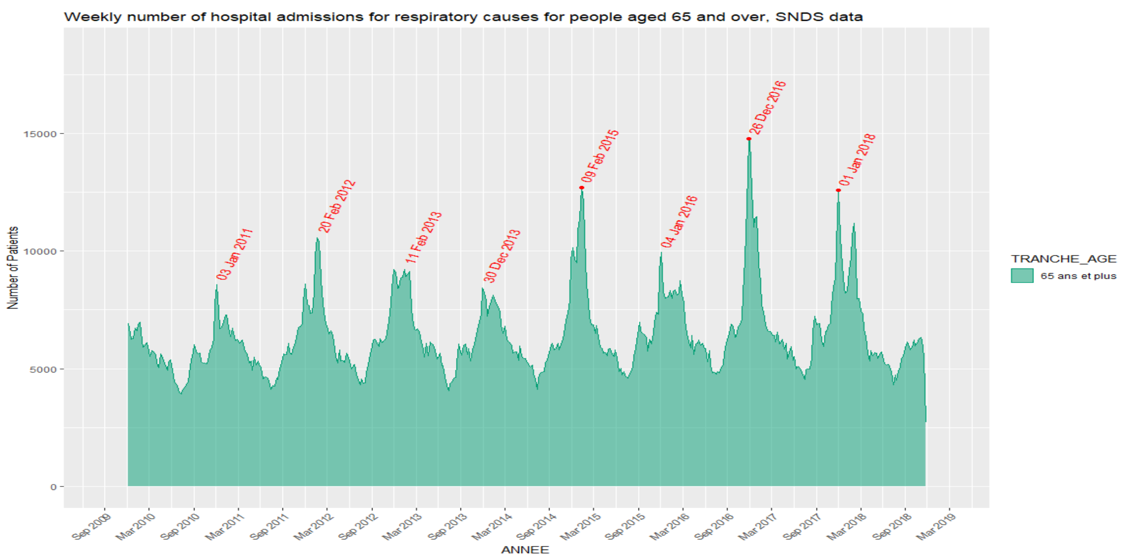

Figure 7: Weekly number of hospitalizations for respiratory causes by epidemic season in France over the period 2010-2018 for 65 years old people and older, SNDS data

Epidemic peaks for respiratory infection are observed between December and February. The dates of the peaks vary from year to year. This graph is consistent with the numbers of hospital admissions described earlier, showing a larger peak in the period 2016 to 2017 for people aged over 65 on the 26th of December 2016.

6 Model results

In this part we will present the number of hospitalizations observed per season, age class and category, thanks to the SNDS database, and the excesses of these hospitalizations attributable to the RSV calculated by the model.

6.1 Impact of RSV infections on hospitalization for Extended RSV category

6.1.1 Number of hospitalizations for Extended RSV category

Between July 2010 and June 2018, the number of hospitalizations for extended RSV category in people over 65 years old is increasing. Among people aged 65 to 74, the number of hospitalizations ranges from 27 738 in 2011 to 37 911 in 2018 (Table 5). The excess attributed to the RSV among these hospitalizations varies from 4 058 in 2014 to 7 610 in 2018, thus also showing a strong increase over the whole period. The percentage of hospitalization for extended RSV cause represented by these excesses ranges from 13% in 2014 to 21% in 2017.

Table 4: Estimated excess hospitalizations for extended RSV category, due to RSV, in people between 65-74 years old in France, from 2010 to 2018

65-74 years old	Excess	Number of hospitalization	% of excess
2011	4 654	27 738	17%
2012	5 331	29 526	18%
2013	4 938	30 034	16%
2014	4 058	30 146	13%
2015	5 691	32 707	17%
2016	5 326	34 577	15%
2017	7 584	36 100	21%
2018	7 610	37 911	20%
MEAN	**5 649**	**32 342**	**17 %**

Among people aged 75 to 84, the number of hospitalizations for extended RSV cause increases irregularly with a minimum in 2011 of 51 759 hospitalization and a maximum of 58 205 in 2012, with an average value of 55 201 over the period. The excess attributable to the RSV increases from 2011 to 2018 ranging from 5 290 to 9 655 in 2018 representing a percentage of 10% and 18% respectively of the number of hospitalizations for extended RSV cause.

Table 5: Estimated excess hospitalizations due to RSV, for extended RSV category, in people between 75-84 years old in France, from 2010 to 2018

75-84 years old	Excess	Number of hospitalization	% of excess
2011	5 290	51 759	10%
2012	9 364	58 205	16%
2013	7 772	56 307	14%
2014	5 968	52 886	11%
2015	8 106	57 173	14%
2016	7 529	54 958	14%
2017	9 856	55 812	18%
2018	9 655	54 509	18%
MEAN	**7 942**	**55 201**	**14 %**

For people aged 85 and over there is a significant increase in the number of hospitalizations for extended RSV cause, from 51 235 in 2011 to 75 502 in 2017. The excess attributable to the RSV also increases considerably ranging from 3 905 in 2011 to 13 469 in 2017. There was a significant decrease in the number of hospitalizations between 2017 and 2018 although the percentage of excess attributable to the RSV was the highest that year, being equal to 24%.

Table 6: Estimated excess hospitalizations due to RSV, for extended RSV category, in people being 85 years old and older in France, from 2010 to 2018

85+ years old	Excess	Number of hospitalization	% of excess
2011	3 905	51 235	8%
2012	9 300	62 801	15%
2013	10 021	56 307	18%
2014	6 794	60 255	11%
2015	10 381	69 369	15%
2016	10 332	69 493	15%
2017	13 469	75 502	18%
2018	13 338	54 509	24%
MEAN	**9 692**	**62 434**	**15%**

Regarding the impact of RSV on all elderly people over 65 years old, we observe an increasing number of hospitalizations between 2010 and 2018. The results also show that the impact of the RSV was greater in 2017 and 2018 than in previous years. In those years, the RSV and the flu circulated almost at the same time and the flu epidemic was particularly deadly. We could assume a link between the two epidemics.

Table 7: Impact of RSV on people over 65 years old, on hospitalization for extended RSV cause, in France from 2010 to 2018.

65+ years old	Excess	Number of hospitalization	% of excess
2011	13 849	130 732	11%
2012	23 995	150 532	16%
2013	22 731	142 648	16%
2014	16 820	143287	12%
2015	24 178	159 249	15%
2016	23 187	159 028	15%
2017	30 910	167 414	18%
2018	30 603	146 929	21%
Total	**186 272**	**1 199 819**	**16%**

6.1.2 Temporality

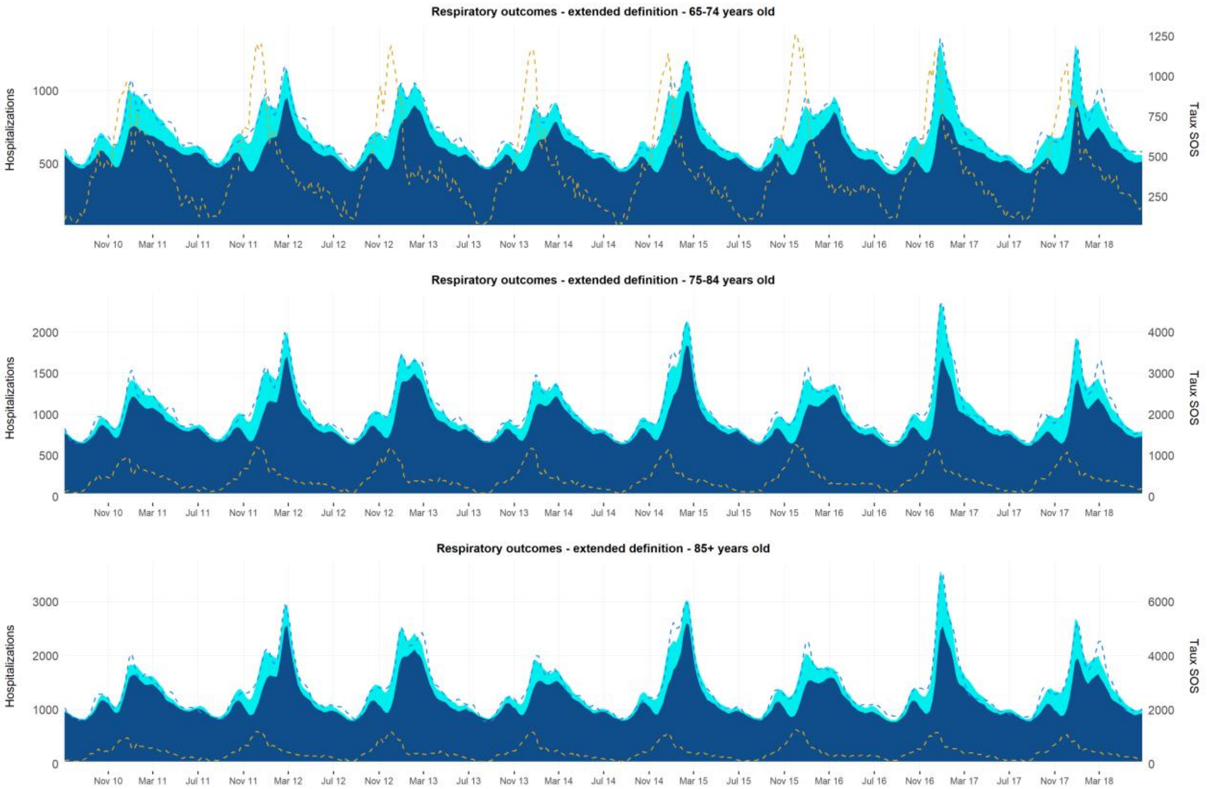

Figure 8 : Cyclic regression model for Extended RSV cause in France from 2010 to 2018

This graph represents the results of our cyclic regression model for estimating the excesses hospitalizations due to RSV regarding the extended RSV category. The dark blue area corresponds to the number of hospitalizations at the "baseline", i.e. estimated by the model in the absence of an RSV epidemic, the blue dotted line represents the actual number of hospitalizations for extended RSV cause. The light blue part represents excess hospitalizations due to RSV and the yellow dotted line corresponds to the SOS Médecins rate for RSV.

We observe that the highest number of excesses is usually measured in December, which corresponds to the epidemic peak of RSV. Higher peaks happen in 2017 when influenza and RSV viruses circulate at the same time.

6.2 Impact of RSV infections on hospitalization for respiratory cause

6.2.1 Number of hospitalizations for respiratory cause

Between July 2010 and June 2018, the number of hospitalizations for respiratory cause in people over 65 years old is increasing significantly. For people aged 65 to 74, the number of hospitalizations for respiratory cause varies from 79 667 in 2011 to 139 883 in 2018. The excess attributable to RSV is also increasing with a minimum of 5 477 hospitalizations in 2011 and 10 055 in 2018. The percentage of excess due to RSV varies only slightly with an average of 7% over the whole period, the highest percentage, equal to 9%, was observed in 2017.

Table 8: Estimated excess hospitalizations due to RSV, for respiratory cause, in people aged 65 to 74 years old in France, from 2010 to 2018

65-74 years old	Excess	Number of hospitalization	% of excess
2011	5 477	79 667	7%
2012	6 099	83 034	7%
2013	5 678	85 588	7%
2014	4 107	88 760	5%
2015	5 774	93 968	6%
2016	6 921	100 692	7%
2017	9 743	104 046	9%
2018	10 055	139 883	7%
MEAN	**6 732**	**96 955**	**7%**

For people aged 75 to 84, the number of hospitalizations varies from 121 550 in 2011 to 129 556 in 2015 with an average of 126 278 over the whole period. The excess attributable to RSV ranges from 8 991 in 2011 to 15 182 in 2017 representing a percentage of 7 to 12% of the number of hospitalizations for respiratory cause.

Table 9: Estimated excess hospitalizations due to RSV, for respiratory cause, in people aged 75 to 84 years old in France, from 2010 to 2018

75-84 years old	Excess	Number of hospitalization	% of excess
2011	8 991	121 550	7%
2012	14 949	130 083	11%
2013	12 543	127 147	10%
2014	10 266	123 580	8%
2015	12 874	129 556	10%
2016	12 578	126 044	10%
2017	15 182	128 214	12%
2018	15 116	124 049	12%
MEAN	**12 812**	**126 278**	**10%**

Among people aged 85 years old and over, the number of hospitalizations for respiratory cause varies from 94 830 in 2011 to 139 883 in 2017. The excess attributable to

RSV also increases over the whole period with a maximum number of 17 005 hospitalization in 2017 representing 12% of the number of hospitalizations for respiratory cause.

Table 10: Estimated excess hospitalizations due to RSV, for respiratory cause, in people being 85 years old and older, in France, from 2010 to 2018

85+ years old	Excess	Number of hospitalization	% of excess
2011	5 909	94 830	6%
2012	13 398	112 675	12%
2013	13 685	115 217	12%
2014	10 320	112 381	9%
2015	14 482	127 212	11%
2016	14 571	127 987	11%
2017	17 005	139 883	12%
2018	15 598	136 039	11%
MEAN	**13 121**	**120 778**	**11%**

From an overall point of view, among all people aged over 65, there was an increase in the number of hospitalizations due to RSV between 2010 and 2018. We observe that there were more hospitalizations in 2017 and 2018. In the same way as for the extended RSV category, we can assume a link with the flu epidemic.

Table 12: Impact of RSV on people over 65 years old, on hospitalization for respiratory cause, in France from 2010 to 2018.

65+ years old	Excess	Number of hospitalization	% of excess
2011	20 377	296 047	7%
2012	34 446	325 792	11%
2013	31 907	327 952	10%
2014	24 693	324 721	8%
2015	33 130	350 736	9%
2016	34 070	354 723	10%
2017	41 929	372 143	11%
2018	40 770	399 971	10%
Total	**261 321**	**2 752 085**	**9%**

6.2.2 Temporality

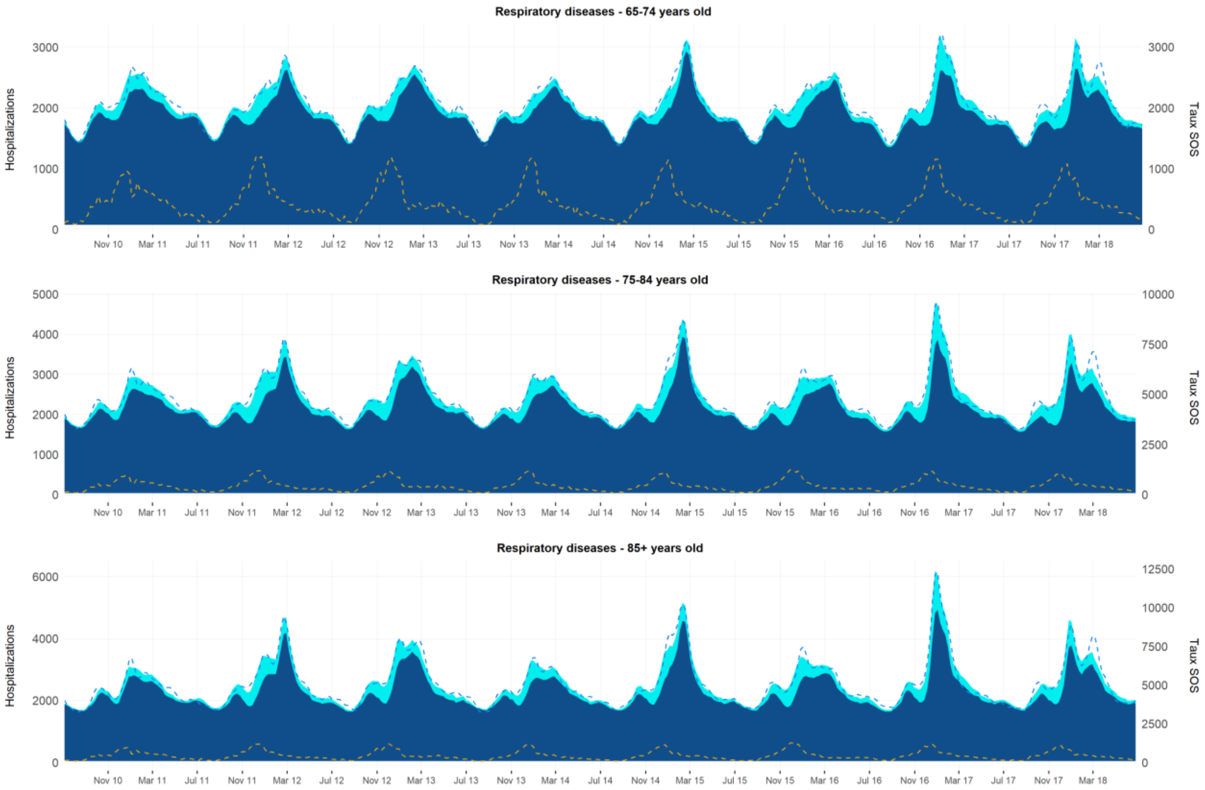

Figure 9: Cyclic regression model for respiratory cause in France from 2010 to 2018

This graph represents the results of our cyclic regression model for estimating the excesses hospitalizations due to RSV regarding the extended RSV category. The dark blue area corresponds to the number of hospitalizations at the "baseline", i.e. estimated by the model in the absence of an RSV epidemic, the blue dotted line represents the actual number of hospitalizations for extended RSV cause. The light blue part represents excess hospitalizations due to RSV and the yellow dotted line corresponds to the SOS Médecins rate for RSV. We observe that each year there is an epidemic peak around December with an overall higher peak in 2017.

Table 13: Averages of the model results

	Extended RSV			Respiratory Cause		
	Mean Excess	Mean Number of hospitalization	Mean % of excess	Mean Excess	Mean Number of hospitalization	Mean % of excess
65-74 years old	5 649	32 342	17%	6 732	96 955	7%
75-84 years old	7 942	55 201	14%	12 812	126 278	10%
85 + years old	9 692	62 434	15%	13 121	120 778	11%

7 Discussion

This study aimed to estimate the excess rates of RSV-associated hospital admissions in people older than 65 years old in France from 2010 to 2018. This approach was conducted from the modelling of the excess hospitalization associated with RSV regarding two outcomes, the extended RSV category and the respiratory cause category.

Regarding the extended RSV category, the number of hospital admissions tend to increase with age. On average, there is an increase of 71% of hospitalization between the people aged 65 to 74 and the people aged 75 to 84 with a 41 % increase in excess due to RSV. Between people aged 75 to 84 and the 85 years old and over people, there is an increase of 13% of the hospitalizations and 22% of the excess due to RSV. This is in line with many recent studies which showed that the incidence of RSV increases with age (A.R. Falsey, 2014) (K. Widmer, 2014) (M.E. Sundaram, 2014) (D.L. McClure, 2014). We can assume that this increase is only partially related to the ageing of the population and could also be due to many parameters such as other comorbidities.

Our results also showed that the impact of the RSV for the extended RSV category was the most important in 2017/2018 which is consistent with the peak of hospitalizations observed on the 2nd of January 2017 for people older than 65 years old, with 167 414 hospitalizations. We could assume a link between this epidemic peak of RSV and the low temperature peak observed on the 1st of January 2017 (see appendix Figure 10). In fact, Yusuf et al. demonstrated that RSV activity is correlated with lower temperatures in temperate climate (S. Yusuf, 2007).

Compared to the extended RSV, there is a higher number of hospitalizations in the respiratory cause category since this category encompasses more respiratory diseases than the extended RSV. The most affected age group seems to be the people aged 75 to 84, however the excess attributable to the RSV is higher in the older age group, 85 years old and over.

Overall, our results show a high incidence of RSV-related hospitalizations, in France, in the over-65s with a total number of 261 321 hospitalizations for respiratory cause and 186 272 hospitalizations for the extended RSV category from 2010 to 2018. Our results show a significant increase in the number of hospitalizations due to RSV over the studied period. This is consistent with the results of another study conducted in the United States which demonstrated that respiratory syncytial virus hospitalizations in adults are increasing. According to their study it is likely due to increasing recognition and diagnosis of the disease more than an increase in incidence (Susan T. Pastula, 2017).

Our study has advantages, including the fact that it allowed us to calculate the indirect hospital burden of RSV in people over 65, which has not been done in France, using a statistical method that has already been validated by other studies (Taylor, et al., 2016) (Reeves, et al., 2017) (Fleming, et al., 2015). Also, our model showed a good fit between the estimated values of hospitalizations and the actual values, allowing us to believe that the estimates we calculated for the excess of hospitalizations due to RSV are reliable.

However, our study had some limitations which must be taken into account when interpreting the results. First, we used clinical bronchiolitis as a unique indicator of RSV infection whereas other pathogens with similar temporal patterns cocirculate with RSV and can present the same clinical characteristics (such as Rhinovirus, parainfluenza, adenovirus or bacterial agents) (Müller-Pebody, Edmunds, Zambon, Gay, & Crowcroft, 2002) (Van Rostenberghe, Kew, & Hanifah, 2006) (Smyth & Openshaw, 2006). Consequently, even though RSV is responsible for bronchiolitis in most cases (Hall C. B., et al., 2009) (Henrickson, 2004), our results are likely to be an over estimation of the true RSV- associated hospitalization excess.

It is also possible that the co-circulation of influenza and RSV in 2010/2011, 2016/2017 and 2017/2018 distorts the calculation of excess hospitalization due to RSV. In 2010/2011 there is no significant impact given that the influenza epidemic is low. However, in 2016/2017 and especially in 2017/2018 there was a large number of excesses attributed to RSV and these were seasons when the impact of influenza was also very high. We could assume that our model has difficulty in accurately calculating the burden of RSV in seasons when influenza is also high and circulates at the same time. It has already been demonstrated that the overlapping seasonality of influenza and the RSV and the similarity of their symptoms makes them difficult to distinguish (Liang Chen, 2020).

Another limitation was that the circulation of RSV in our model has been calculated assuming that this virus affects children and the elderly in the same way. This decision was taken on the basis of studies that showed that RSV presents a similar activity in children and elderly people (Zambon, Stockton, Clewley, & Fleming, 2001) (Walsh, Falsey, & Edward, 2005). Indeed, if we look at the results of excess hospitalization due to RSV for the over-65s as a whole, we observe a relative stability which may be due to the fact that the evolution of RSV in children is itself relatively stable rather than being a true estimate of the burden in the elderly. For more precision it would be necessary to have access to surveillance data on RSV in the elderly.

Also, we did not take into account other complicated RSV infections such as non-respiratory complications of RSV (cardiac disease for example) in our analysis. Although these have been shown to be possible complications of RSV (Linda L. Han, 1999), leading to a possible underestimation of the burden of RSV in our results (Van Rostenberghe, Kew, & Hanifah, 2006).

8 Conclusion

In conclusion, the analysis conducted in this study provided an approximation of the actual number of hospitalizations due to RSV and confirms that this number is underestimated. It showed that RSV is a significant cause of hospital admission in elderly aged 65 years and older, especially the 85 years old and older, showing that the number of hospitalizations increases with age. Also, our study demonstrated that the number of hospitalizations due to RSV increases significantly between 2010 and 2018 with a higher epidemic peak in 2017. Thus, RSV remains a major public health problem; surveillance of these epidemics must remain a priority and prevention and action plans need to be strengthened.

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Appendix

List of appendix

Appendix 1: ICD 10 codes regarding hospitalizations for extended RSV category and the respiratory cause category from SNDS Database

Table 11: ICD 10 code, hospitalization for extended RSV, SNDS Database

Code ICD10	Text
J00 to J06	Acute upper respiratory tract infections
J12 to J18	Pneumonia / pneumopathy
J20	Acute bronchitis
J21	Acute bronchiolitis
J22	Acute lower respiratory tract infections, unspecified
J40	Bronchitis, not specified as acute or chronic
J45	Asthma
R062	Wheezing

Table 12: ICD 10 code, hospitalization for respiratory cause, SNDS Database

Code ICD10	Text
J00-J06	Acute upper respiratory tract disorders
J09-J18	Influenza and pneumonia
J20-J22	Other acute lower respiratory tract conditions
J30-J39	Other upper respiratory tract diseases
J40-J47	Chronic lower respiratory diseases
J60-J70	Lung diseases caused by external agents
J80-J84	Other respiratory diseases mainly affecting interstitial tissue
J85-J86	Suppurative and necrotic diseases of the lower respiratory tract
J90-J94	Other conditions of the pleura
J95-J99	Other diseases of the respiratory system

Appendix 2: Average temperature in France from 2010 to 2020

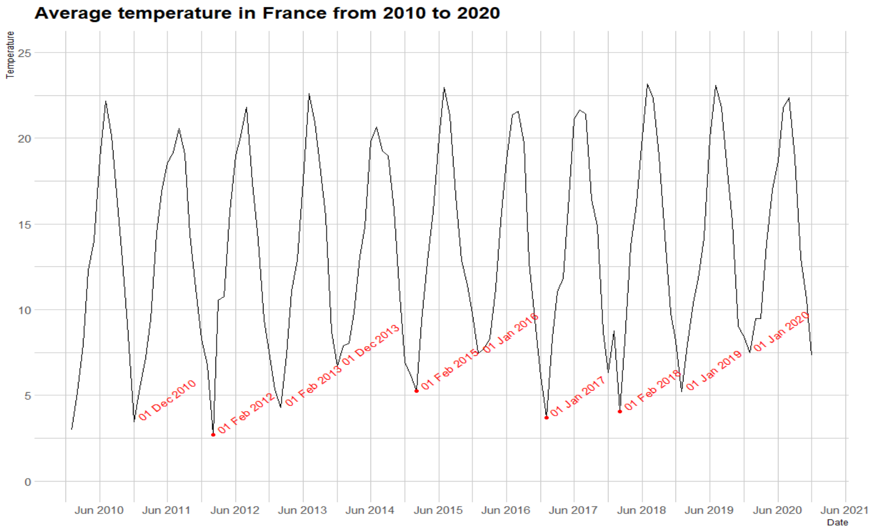

Figure 10: Average temperature in France from 2010 to 2020

Appendix 3: Analysis of maximum likelihood parameter estimates per age group and cause

Table 13 : Analysis of maximum likelihood parameter estimates for people aged 65 to 74 years old, for the respiratory cause category

Parameter	Estimation	Pr > khi-2
Intercept	-8.1311	<.0001
Mean Temperature	-0.0052	<.0001
cos10	-0.0057	0.0124
cos12	-0.0057	0.0118
cos2	0.0489	<.0001
cos3	-0.0068	0.0080
cos4	-0.0136	<.0001
cos6	-0.0304	<.0001
cos8	0.0451	<.0001
RSV 2011	0.0002	<.0001
RSV 2012	0.0002	<.0001
RSV 2013	0.0001	<.0001
RSV 2014	0.0001	<.0001
RSV 2015	0.0001	<.0001
RSV 2016	0.0002	<.0001
RSV 2017	0.0002	<.0001
RSV 2018	0.0002	<.0001
ILI 2011	0.0013	<.0001
ILI 2012	0.0009	<.0001
ILI 2013	0.0010	<.0001
ILI 2014	0.0017	<.0001
ILI 2015	0.0009	<.0001
ILI 2016	0.0019	<.0001
ILI 2017	0.0013	<.0001
ILI 2018	0.0020	<.0001
T^2	-0.0000	<.0001
sin10	-0.0053	0.0300
sin12	0.0062	0.0072
sin2	0.0965	<.0001
sin3	0.0095	0.0007
sin6	0.0487	<.0001
sin8	0.0066	0.0071

Table 14: Analysis of maximum likelihood parameter estimates for people aged 75 to 84 years old, for the respiratory cause category

Parameter	Estimation	Pr > khi-2
Intercept	-7.4633	<.0001
Mean Temperature	-0.0065	<.0001
cos10	0.0149	<.0001
cos12	0.0084	0.0020
cos2	0.0486	0.0005
cos4	-0.0087	0.0374
cos6	-0.0242	<.0001
cos8	0.0469	<.0001
RSV 2011	0.0002	<.0001
RSV 2012	0.0003	<.0001
RSV 2013	0.0002	<.0001
RSV 2014	0.0002	<.0001
RSV 2015	0.0002	<.0001
RSV 2016	0.0002	<.0001
RSV 2017	0.0003	<.0001
RSV 2018	0.0003	<.0001
ILI 2011	0.0008	0.0086
ILI 2012	0.0013	<.0001
ILI 2013	0.0015	<.0001
ILI 2014	0.0013	<.0001
ILI 2015	0.0013	<.0001
ILI 2016	0.0015	<.0001
ILI 2017	0.0023	<.0001
ILI 2018	0.0020	<.0001
T^2	-0.0000	<.0001
sin2	0.1065	<.0001
sin3	0.0183	<.0001
sin4	0.0267	<.0001
sin6	0.0460	<.0001
sin8	0.0203	<.0001

Table 15: Analysis of maximum likelihood parameter estimates for people aged 85 years old and older, for the respiratory cause category

Parameter	Estimation	Pr > khi-2
Intercept	-6.7653	<.0001
Mean Temperature	-0.0097	<.0001
cos10	0.0331	<.0001
cos12	0.0204	<.0001
cos2	0.0792	<.0001
cos3	-0.0092	0.0240
cos6	-0.0265	<.0001
cos8	0.0476	<.0001
RSV 2011	0.0001	0.0003
RSV 2012	0.0003	<.0001
RSV 2013	0.0003	<.0001
RSV 2014	0.0002	<.0001
RSV 2015	0.0003	<.0001
RSV 2016	0.0003	<.0001
RSV 2017	0.0003	<.0001
RSV 2018	0.0003	<.0001
ILI 2011	0.0001	0.7708
ILI 2012	0.0019	<.0001
ILI 2013	0.0016	<.0001
ILI 2014	0.0006	0.1302
ILI 2015	0.0015	<.0001
ILI 2016	0.0010	0.0001
ILI 2017	0.0026	<.0001
ILI 2018	0.0020	<.0001
sin2	0.1035	<.0001
sin3	0.0127	0.0032
sin4	0.0465	<.0001
sin6	0.0477	<.0001
sin8	0.0380	<.0001

Table 16: Analysis of maximum likelihood parameter estimates for people aged 65 to 74 years old, for the extended RSV category

Parameter	Estimation	Pr > khi-2
Intercept	-9.2708	<.0001
Mean Temperature	-0.0067	<.0001
cos10	0.0239	<.0001
cos12	0.0182	<.0001
cos3	-0.0157	<.0001
cos4	-0.0181	<.0001
cos6	-0.0195	<.0001
cos8	0.0490	<.0001
RSV 2011	0.0004	<.0001
RSV 2012	0.0004	<.0001
RSV 2013	0.0004	<.0001
RSV 2014	0.0003	<.0001
RSV 2015	0.0004	<.0001
RSV 2016	0.0004	<.0001
RSV 2017	0.0005	<.0001
RSV 2018	0.0005	<.0001
ILI 2011	0.0014	<.0001
ILI 2012	0.0015	<.0001
ILI 2013	0.0018	<.0001
ILI 2014	0.0027	<.0001
ILI 2015	0.0012	<.0001
ILI 2016	0.0030	<.0001
ILI 2017	0.0014	<.0001
ILI 2018	0.0024	<.0001
T	-0.0003	<.0001
sin2	0.1302	<.0001
sin3	0.0083	0.0401
sin4	0.0369	<.0001
sin6	0.0520	<.0001
sin8	0.0420	<.0001

Table 17: Analysis of maximum likelihood parameter estimates for people aged 75 to 84 years old, for the extended RSV category

Parameter	Estimation	Pr > khi-2
Intercept	-8.3390	<.0001
Mean Temperature	-0.0077	<.0001
cos10	0.0356	<.0001
cos12	0.0252	<.0001
cos2	0.0694	<.0001
cos3	-0.0122	0.0045
cos6	-0.0189	<.0001
cos8	0.0613	<.0001
RSV 2011	0.0002	<.0001
RSV 2012	0.0004	<.0001
RSV 2013	0.0003	<.0001
RSV 2014	0.0003	<.0001
RSV 2015	0.0003	<.0001
RSV 2016	0.0003	<.0001
RSV 2017	0.0004	<.0001
RSV 2018	0.0004	<.0001
ILI 2011	0.0008	0.0406
ILI 2012	0.0019	<.0001
ILI 2013	0.0020	<.0001
ILI 2014	0.0018	<.0001
ILI 2015	0.0016	<.0001
ILI 2016	0.0018	<.0001
ILI 2017	0.0020	<.0001
ILI 2018	0.0019	<.0001
T^2	-0.0000	<.0001
sin2	0.1483	<.0001
sin3	0.0188	<.0001
sin4	0.0430	<.0001
sin6	0.0473	<.0001
sin8	0.0434	<.0001

Table 18: Analysis of maximum likelihood parameter estimates for people aged 85 years old and older, for the extended RSV category

Parameter	Estimation	Pr > khi-2
Intercept	-7.4136	<.0001
Mean Temperature	-0.0094	<.0001
cos10	0.0459	<.0001
cos12	0.0303	<.0001
cos2	0.1185	<.0001
cos3	-0.0144	0.0041
cos6	-0.0287	<.0001
cos8	0.0605	<.0001
RSV 2011	0.0002	0.0006
RSV 2012	0.0003	<.0001
RSV 2013	0.0003	<.0001
RSV 2014	0.0003	<.0001
RSV 2015	0.0004	<.0001
RSV 2016	0.0004	<.0001
RSV 2017	0.0004	<.0001
RSV 2018	0.0004	<.0001
ILI 2011	0.0004	0.3899
ILI 2012	0.0023	<.0001
ILI 2013	0.0020	<.0001
ILI 2014	0.0007	0.1622
ILI 2015	0.0016	<.0001
ILI 2016	0.0013	<.0001
ILI 2017	0.0023	<.0001
ILI 2018	0.0017	<.0001
T^2	-0.0000	0.0118
sin2	0.1531	<.0001
sin3	0.0125	0.0180
sin4	0.0563	<.0001
sin6	0.0544	<.0001
sin8	0.0578	<.0001

Résumé

Développement d'une approche écologique pour mesurer le fardeau hospitalier lié au VRS chez les personnes âgées (personnes de plus de 65 ans), en France de 2010 à 2018.

Contexte : Les maladies infectieuses telles que la grippe, les infections dues au virus respiratoire syncytial (VRS) et à la pneumonie sont causées par la transmission d'un virus ou d'une bactérie. La plupart des personnes infectées par ces maladies présentent une forme légère de la maladie et ne nécessitent aucune intervention médicale. Cependant, les personnes de plus de 65 ans peuvent présenter des complications sévères en raison de l'amoindrissement de leur condition physique notamment lié à l'âge. Ainsi, ces infections respiratoires représentent un fardeau hospitalier important en France. De plus, il est très difficile de diagnostiquer et de différencier les complications liées au virus de la grippe et du VRS et, par conséquent, d'identifier tous les patients touchés au cours des différentes saisons épidémiques. D'une part en raison des caractéristiques communes de ces deux virus et au manque de diagnostique systématique des sécrétions respiratoires, d'autre part en raison de la latence qu'il existe entre l'infection et la survenue des symptômes et des complications. Le fardeau hospitalier directement associé à la grippe et au VRS reste donc sous-estimé car est basé uniquement sur les hospitalisations ou les décès pour lesquels les diagnostiques de la grippe ou du VRS sont identifiés.

Objectif : Dans cette étude, notre objectif était de développer une approche écologique pour mesurer le fardeau hospitalier associé au VRS chez les personnes âgées (personnes de plus de 65 ans), en France de 2010 à 2018.

Méthode : Dans un premier temps, nous avons présenté les caractéristiques de la grippe et du VRS. Puis nous avons utilisé un modèle statistique pour mesurer le fardeau hospitalier du VRS sur deux catégories d'hospitalisations. D'une part une catégorie regroupant la majorité des infections respiratoires, d'autre part une catégorie appelée VRS élargie, incluant la pneumonie et les infections respiratoires étant des conséquences principalement du VRS. Dans notre modèle, nous avons pris en compte la circulation de la grippe en utilisant les données du réseau Sentinelles. Nous avons utilisé la base de données de Santé Publique France pour la circulation du VRS, et le SNDS pour les données des hospitalisations.

Résultats : Nos résultats montrent une incidence élevée du VRS chez les personnes âgées de plus de 65 ans. L'estimation des hospitalisations associées au VRS pour la catégorie des causes respiratoires était égale à 261 321 et à 186 272 pour la catégorie VRS élargie, de 2010 à 2018. De plus, nos résultats montrent un nombre croissant d'hospitalisations dues au VRS au cours de la période d'étude chez les personnes âgées de plus de 65 ans avec un pic en

2017. En outre, les hospitalisations liées au VRS semblent également avoir tendance à augmenter avec l'âge.

Conclusion : Ces résultats traduisent l'impact du VRS chez les personnes âgées. Ils mettent en exergue la nécessité de mettre en place non seulement un système de surveillance spécifique pour évaluer précisément la circulation de ce virus dans cette population, mais aussi l’importance du développement d'un vaccin afin de palier à ce réel problème de santé publique, d'autant plus que la population française est vieillissante.

Mots-clés : Grippe, VRS, Infection respiratoire, Approche écologique, Modèle de Poisson