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Impact of twelve immunization-preventable infectious diseases on population health using disability-adjusted life years (DALYs) in Spain

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Abstract

Background The objective of this study is to estimate the burden of selected immunization-preventable infectious diseases in Spain using the Burden of Communicable Diseases in Europe (BCoDE) methodology, as well as focusing on the national immunization programme and potential new inclusions.

Methods The BCoDE methodology relies on an incidence and pathogen-based approach to calculate disease burden via disability-adjusted life year (DALY) estimates. It considers short and long-term sequelae associated to an infection via outcome trees. The BCoDE toolkit was used to populate those trees with Spanish-specific incidence estimates, and *de novo* outcome trees were developed for four infections (herpes zoster, rotavirus, respiratory syncytial virus [RSV], and varicella) not covered by the toolkit. Age/sex specific incidences were estimated based on data from the Spanish Network of Epidemiological Surveillance; hospitalisation and mortality rates were collected from the Minimum Basic Data Set. A literature review was performed to design the *de novo* models and obtain the rest of the parameters. The methodology, assumptions, data inputs and results were validated by a group of experts in epidemiology and disease modelling, immunization and public health policy.

Results The total burden of disease amounted to 163.54 annual DALYs/100,000 population. Among the selected twelve diseases, respiratory infections represented around 90% of the total burden. Influenza exhibited the highest burden, with 110.00 DALYs/100,000 population, followed by invasive pneumococcal disease and RSV, with 25.20 and 10.57 DALYs/100,000 population, respectively. Herpes zoster, invasive meningococcal disease, invasive *Haemophilus influenza* infection and hepatitis B virus infection ranked lower with fewer than 10 DALYs/100,000 population each, while the rest of the infections had a limited burden (< 1 DALY/100,000 population). A higher burden of disease was observed in the elderly (≥ 60 years) and children < 5 years, with influenza being the main cause. In infants < 1 year, RSV represented the greatest burden.

Conclusions Aligned with the BCoDE study, the results of this analysis show a persisting high burden of immunization-preventable respiratory infections in Spain and, for the first time, highlight a high number of DALYs due

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to RSV. These estimates provide a basis to guide prevention strategies and make public health decisions to prioritise interventions and allocate healthcare resources in Spain.

Keywords Burden, DALY, Infectious diseases, Immunization, Vaccines

Background

Infectious diseases represent a challenge for healthcare systems worldwide. Nonetheless, the continuous emergence of effective immunization strategies, followed by the implementation of national immunization programmes (NIP) coupled with surveillance systems, have proven to be an efficient approach to control them [1–4]. According to the Global Burden of Disease study conducted by the Institute for Health Metrics and Evaluation (IHME), the global burden of infectious diseases decreased from 821.8 M to 420.4 M disability-adjusted life years (DALYs) (-49%) from 1990 to 2019 and from 20.7 M to12.0 M DALYs (-42%) in the European Union (EU) (calculated from [5]).

Similar to global and European trends, a reduction in the burden of infectious diseases was observed in Spain between 1990 and 2019, although it was lower (from 0.4 M to 0.3 M DALYs; -23%) (calculated from [5]). In a study that assessed the burden of 31 communicable infectious diseases in Europe, regardless of vaccination and/or surveillance systems in place, immunization-preventable infections were ranked among the highest-burden diseases, with influenza exhibiting the greatest burden (29.8% of the total) [6]. This aligns with IHME data from 2019, which show that respiratory infections accounted for 63% of the total burden of infectious diseases (calculated from [5]) in Spain.

Studies estimating the burden of disease using composite health measures are conducted to provide relevant information about its impact and support public health decisions [6–8]. In 2006, the European Centre for Disease Prevention and Control (ECDC) began the Burden of Communicable Diseases in Europe (BCoDE) project to develop a methodology to assess the impact of infectious diseases on population health in EU/EEA countries, and ultimately provide a tool for the planning and prioritisation of infectious disease prevention, preparedness, and control measures [6, 9–11]. This methodology uses a composite health measure, the DALY [12], to express the disease burden of an infectious disease. DALYs not only reflect the impact of a clinical condition on life expectancy, but also on quality of life. The BCoDE work estimated a total of 275 DALYs per 100,000 population/year were lost due to community-associated infectious diseases in Europe before 2013 [6].

The objective of this study is to estimate the burden of selected immunization-preventable infectious diseases in Spain using the BCoDE methodology, focusing on the current NIP and potential future inclusions.

Methods

Selection of infectious diseases

The following diseases were included in the analysis: hepatitis A virus (HAV) infection, hepatitis B virus (HBV) infection, herpes zoster, influenza, invasive *Haemophilus influenzae* infection, invasive meningococcal disease, invasive pneumococcal disease, measles, mumps, rotavirus, respiratory syncytial virus (RSV) and varicella zoster. These twelve diseases were selected based on the current Spanish immunization calendar (2023) [13, 14], excluding infections that are currently classified as no or low incidence in Spain, as well as human papilloma virus (HPV) while adding rotavirus as a potential immunization target (Supplementary Table 1).

DALY estimates

The BCoDE methodology relies on an incidence and pathogen-based approach to calculate disease burden via DALY estimates [6, 9, 10]. DALYs are taken from the sum of two variables: years of life lived with disability (YLD) following a disease and years of life lost due to premature mortality (YLL). This approach considers short- and long-term sequelae associated to an infection via outcome trees [9, 10]. For the Spanish adaptation, we used the outcome trees, as well as the mortality probabilities and disability weights data, available in the BCoDE toolkit and populated the model with national age- and sex-specific incidence and socio-demographic data [15]. Additionally, we generated *de novo* outcome trees for four infections (herpes zoster, rotavirus, RSV and varicella) that were not included in the toolkit at the time of our analysis [16] (see De novo models methodology section).

Incidence and mortality

Age- and sex-specific incidence for each infection was approximated based on estimates from the Spanish National Epidemiological Surveillance Network (RENAVE) [17] (data on file; Table 1). The annual number of cases corresponds to primary and secondary diagnoses for 2018, which is the latest available data prior to the SARS-COV-2 pandemic to avoid any bias in incidence due to this healthcare situation. The age-specific incidence of influenza obtained from the annual RENAVE report [17] was adjusted for underestimation for age groups between 15 and 64 years according to a previous study from the UK [18] (Supplementary Table 2); however, no sex-specific estimates were found for influenza in Spain. While no pre- or post-pandemic data were available in the RENAVE reports for RSV at the time of this analysis, the Acute Respiratory Infection Surveillance System

Table 1 Annual incidence of selected infectious diseases

Infectious disease	Annual number of cases	
	Female	Male
HAV infection	537	1,179
HBV infection	101	291
Herpes Zoster	37,562	26,834
Influenza[a]	1,839,426	1,839,426
Invasive *Haemophilus influenzae* infection	161	192
Invasive meningococcal disease	197	154
Invasive pneumococcal disease	1,830	2,588
Measles	98	91
Mumps	3,822	5,116
RSV[b]	73,543	77,105
Rotavirus	2,122	2,443
Varicella zoster	27,652	29,618

HAV: hepatitis A virus; HBV: hepatitis B virus; RSV: respiratory syncytial virus

[a]Under-estimation factors were considered at 17.85% for the age groups between 14 and 44 years and at 14.43% for age groups corresponding to 45–64 years based on the Flu Watch study [18]

[b]Annual number of cases correspond to primary care data for 2019 from the Catalonian surveillance system for infections (SIVIC)

(*Sistema de Vigilancia de las Infecciones Respiratorias Agudas*, SIVIRA) weekly-reported incidence rates did not allow the estimation of the total annual cases in Spain due to low transparency in the estimation method [19]. Hence, reported cases of RSV in primary care during 2019 were collected from the Infection Surveillance System of Catalonia (*Sistema d'Informació per a la Vigilància d'Infeccions a Catalunya*, SIVIC) [20], which has a broader and more consistent experience in monitoring this infection, as well as a higher degree of detail regarding age and sex (Supplementary Table 3). Since there were no available RSV data for all the age groups defined in the model, especially for groups older than 5 years, we used age distribution among hospitalised patients due to RSV as a proxy measure [20].

Annual mortality rates were obtained from the BCoDE for the previously modelled infections, assuming mortality to be disease- and age-specific. Regarding the four *de novo* models, the annual age- and sex-specific mortality data for primary and secondary diagnoses were collected from the Minimum Basic Data Set (MBDS) published by the Spanish Ministry of Health for the 2016–2019 period [21], employing the ICD-10-CM codes listed in Supplementary Table 4.

De novo models methodology

New outcome trees were generated for four infections: herpes zoster, rotavirus, RSV, and varicella zoster (Fig. 1). For this purpose, an analysis of previously published literature was conducted to define the course of each disease, as well as their associated health conditions. The parameters for each model were characterized based on publicly available data and are listed in Table 2. The parameters assigned to the different infections previously

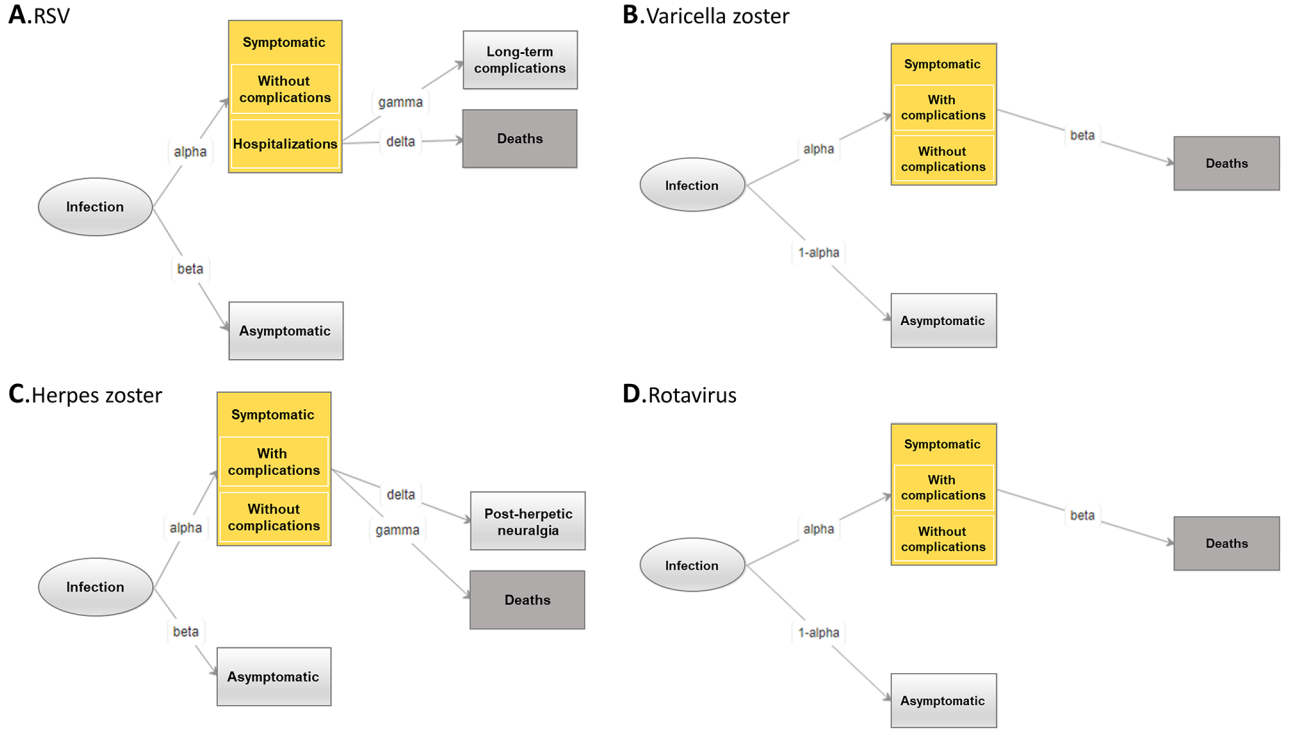

Fig. 1 Outcome trees designed for the de novo models. The diagrams correspond to the following infections: respiratory syncytial virus (RSV) (**A**), varicella zoster (**B**), herpes zoster (**C**) and rotavirus (**D**)

Table 2 Proportion, duration and disability weight of health conditions associated to the infectious diseases modelled *de novo*

Infectious disease	Clinical state	Proportion	Disability weight (UI)	Duration
RSV	Symptomatic infection complicated	0.98-1[8]	0.133[9] (0.008–0.19)	5.3 days[3]
	Symptomatic infection uncomplicated	0-0.02[8]	0.051[9] (0.032–0.074)	5.11 days[4b]
	Symptomatic infection: long-term complications	0.28[9]	0.015[10]	5 years[5]
	Symptomatic infection: fatal	0.012[3]	n/a	n/a
Varicella zoster	Symptomatic infection complicated	0.078[1]	0.131[2]	7 days[3]
	Symptomatic infection uncomplicated	0.922[1]	0.051[4e,6] (0.039–0.06)	14 days[11]
	Symptomatic infection: fatal	0.0032[3]	n/a	n/a
Herpes zoster	Symptomatic infection complicated	0.06–0.09[1]	0.131[2]	8.7 days[3]
	Symptomatic infection uncomplicated	0.91–0.94[1]	0.051[4,6] (0.039–0.06)	28 days[5]
	Symptomatic infection: postherpetic neuralgia	0.1[2]	0.068[6]	9 months[7]
	Symptomatic infection: fatal	0.06–0.07[3]	n/a	n/a
Rotavirus	Symptomatic infection complicated	0.063[1]	0.239[4c,6] (0.202–0.285)	3.38 days[3]
	Symptomatic infection uncomplicated	0.933[1]	0.073[4d,6] (0.061–0.092)	5.48 days[4d]
	Symptomatic infection: fatal	0.0032[3]	n/a	n/a

MBDS: Minimum Basic Data Set; n/a: not applicable; RENAVE: Spanish Network of Epidemiological Surveillance; RSV: respiratory syncytial virus; SIVIC: Catalonian surveillance system for infections; UI: uncertainty intervals

[1]MBDS/RENAVE

[2]Matthews et al. [33]

[3]MBDS

[4]BCoDE: [a]Disability weight from BCoDE for uncomplicated symptomatic measles applied. [b]Duration from BCoDE for uncomplicated influenza applied. [c]Disability weight from BCoDE for severe diarrhoea due to salmonellosis infection applied. [d]Disability weight and duration from BCoDE for mild diarrhoea due to salmonellosis infection applied. [e]For individuals older than 15 years, disability weight from BCoDE for uncomplicated symptomatic measles applied. No burden of disease was considered for children under 15 years based on expert's opinion

[5]Expert opinion

[6]Haagsma et al. [42]

[7]Lopez-Belmonte et al. [37]

[8]MBDS/SIVIC

[9]Villamil et al. [23]

[10]Emerson et al. [28] (controlled asthma)

[11]Patil et al. [34]

defined in the BCoDE model are described in Supplementary Table 5.

The proportion of complicated and uncomplicated cases were estimated integrating incidence data from RENAVE (SIVIC for RSV) [17, 20] and hospitalisation ratios for primary and secondary diagnoses from the MBDS [21] registered during the 2016–2019 period. In particular, the number of complicated cases was assumed as the number of hospitalisations, while the duration of complicated infections was approximated as the length of hospital stay.

RSV

RSV is one of the main causes of acute respiratory tract infections and can lead to long-term complications [22–24]. At the time of this analysis, the monoclonal antibody nirsevimab had been approved for the prevention of RSV lower respiratory tract disease in neonates and infants during their first RSV season in Spain, although no population-wide immunization strategy had been implemented [25].

In this analysis, two health conditions were defined for the outcome tree of RSV: hospitalisation and uncomplicated infection (Fig. 1A). For the hospitalised patients, we extracted incidence, in-hospital mortality, and duration of hospitalisation data from the MBDS [21]. To minimize incidence variations, a conservative strategy was followed, so that (1) uncomplicated cases were calculated assuming that all hospitalisations were previously reported in primary care, on the basis of the BARI study [26, 27]; and (2) only those cases corresponding to RSV-specific ICD-10-CM codes were included, following a study by Heppe-Montero et al [28]. Moreover, hospitalised patients could develop long-term complications, out of which asthma would be the most serious [29, 30]. Therefore, in our model, some patients (28%)

progressed to a third health state, namely asthma [29, 30]. According to expert opinion, a mean duration of 5 years was assumed for asthma. Uncomplicated RSV was associated with a reduction in quality of life only for the duration of the infection (assumed to be 5.11 days similar to uncomplicated influenza) (Table 2). Disability weights for both uncomplicated and complicated (hospitalising) disease were obtained from a previous study in children under 2 years [23], while the disability weight for asthma was taken from the Tufts Medical Center database [31] (Table 2). In the absence of publicly available data to estimate the percentage of individuals that develop asthma as a consequence of RSV, the probability of progressing to recurrent wheezing reported in a previous pharmacoeconomic analysis was used, while the disutility value associated to controlled asthma for 5 years was considered a conservative approach for this health state [26, 27].

Varicella zoster

The classic symptom of varicella infection is a rash throughout the body, which can lead to severe complications, such as meningitis, that require hospitalisation and can even be fatal [32]. In Spain, vaccination against varicella in children was firstly introduced in 2006 [33].

The outcome tree for this infection comprised two health states: complicated and uncomplicated (Fig. 1B). To describe the outcomes of complicated infection we used hospitalisation data from MBDS [21] and extracted the disability weight of varicella from the Matthews et al. analysis [34] (Table 2). Uncomplicated disease was assumed to last 14 days, following the study from Patil et al. [35], with a disability comparable to uncomplicated measles (Table 2). However, based on expert opinion, no burden of the uncomplicated disease was considered for children under 15 years, given the increasing rates of varicella vaccination in Spain and subsequent reduction in hospital burden according to MBDS data [21].

Herpes zoster

Herpes zoster appears upon reactivation of varicella zoster, which can remain latent after a primary infection [36, 37].

Two health conditions were included in the outcome tree for herpes zoster: complicated and uncomplicated infection (Fig. 1C). Similar to RSV and varicella, complicated herpes zoster outcomes were extracted from the MBDS database [21]. Postherpetic neuralgia, characterized by intense pain, was considered the main long-term sequela of this disease [35, 36]. A proportion of 10% of herpes zoster patients were assumed to progress to postherpetic neuralgia [34], with a mean duration of 9 months [38] (Table 2). The disability weight for this health condition was obtained from a study by Kwong et al [39]. (Table 2). Based on the duration of symptoms and expert opinion, a 28-day duration of uncomplicated disease was assumed [40]. The disability weight for the uncomplicated state was assumed as the value for uncomplicated measles from the BCoDE model, since skin rash is the main clinical manifestation in both cases [40].

Rotavirus

Gastroenteritis is the primary symptom associated to rotavirus infection, which can worsen and lead to hospitalisation [41]. Vaccination against this virus was first recommended for newborns in Spain in 2019 [42].

Based on previous literature, the outcome tree for rotavirus was divided into two categories: complicated and uncomplicated infection (Fig. 1D). Again, complicated disease was modelled through hospitalisation data from MBDS [21]. In the absence of specific values for rotavirus, we assumed a clinical behaviour similar to mild and severe diarrhoea due to salmonellosis, for which disability values and duration were available in the BCoDE model (Table 2).

Uncertainty

Uncertainty intervals were used for parameters with elevated uncertainty levels in the BCoDE toolkit, as described in Cassini et al [6]. (Supplementary Table 5). The ones used in the *de novo* models are shown in Table 2. Intervals were incorporated in the models as uniform distributions (containing two values) or as Project Evaluation and Review Techniques distributions (PERT; containing three values). No public data for the confidence intervals were available for the incidence estimates in Spain; therefore, we varied incidence using a PERT distribution with a minimum and maximum value representing +/- 20% values. Similar to Cassini et al. [6], we used the BCoDE toolkit to run the models at 10,000 iterations of the Monte Carlo simulations, without time discounting and age-weighting. All model outputs report the median and the 95% uncertainty intervals (UIs).

Experts in epidemiology, immunization, health economics and public health policy participated in all phases of the analysis, which included the study design and selection of the diseases to be evaluated, *de novo* model design, appropriateness of data sources, inputs and assumptions made to tackle uncertainty or in the absence of suitable public information, and validation of the results. All consultations were carried out via email and a virtual meeting served as a point of discussion and agreement.

Alternative scenarios

We also performed alternative scenarios to assess the impact of distinct assumptions on the study results. First, the burden of influenza was estimated using direct

incidence data reported by RENAVE, considering no underestimation factors.

The base case scenario included the most recently published disability weights available in the literature for the four infections with *de novo* models. In an alternative scenario, the effect of applying disability weight values from an early study by the European disability weight project [43] was explored (Supplementary Table 6).

For RSV, disability associated with partially controlled and uncontrolled asthma (0.036 and 0.133 disability values, respectively) was also evaluated, since these values are higher than the ones assumed for recurrent wheezing [31].

Results

The selected infectious diseases accounted for an incidence and mortality of 8,550.49 and 10.43 cases per 100,000 population/year in Spain, respectively (Table 3). The disease burden for each infection, which is expressed as the median values of different DALY measures, are shown in Table 3. The total burden of these diseases amounted to 163.54 annual DALYs per 100,000 population. Respiratory infections, which include any communicable infection affecting the respiratory tract, represented around 90% of the total burden of the selected infections in the Spanish population. Influenza exhibited the highest burden, with 110.00 DALYs per 100,000 population/year, followed by invasive pneumococcal disease and RSV, with 25.20 and 10.57 DALYs per 100,000 population/year, respectively (Table 3; Fig. 2). Interestingly, the burden of influenza at the individual level was relatively low (0.01 DALYs per case) compared to other infections, which highlights the high incidence of this disease.

Herpes zoster, invasive meningococcal disease, invasive *Haemophilus influenza* infection and HBV infection ranked lower with a burden below 10 annual DALYs per 100,000 population each. Nonetheless, invasive meningococcal disease exhibited the highest individual burden by far (4.5 DALYs per case) due to the severity of this infection. The rest of the selected infections had a limited burden of less than 1 annual DALY per 100,000 population, with measles and mumps being the least burdensome at the population level.

Table 3 Ranking of selected infectious diseases according to their burden measured as annual DALYs per 100,000 population

Infectious disease	Median 95% UI						
	Incidence per 100,000	Mortality per 100,000	DALYs per case	YLD per 100,000	YLL per 100,000	DALYs per 100,000	% of total DALYs
Influenza	7,921.2 (7,688.1-8,153)	7.92 (7.7–8.2)	0.01 (0.01–0.01)	7.32 (6.36–8.31)	102.67 (99.68-105.69)	110.00 (106.65–113.30)	67.26
Invasive pneumococcal disease	9.51 (9.22–9.80)	1.03 (0.99–1.06)	2.65 (2.61–2.69)	2.15 (1.94–2.37)	23.04 (22.39–23.68)	25.20 (24.47–25.93)	15.41
RSV	324.36 (300.41-348.23)	0.58 (0.55–0.61)	0.03 (0.03–0.03)	1.19 (1.11–1.28)	9.37 (9.07–9.67)	10.57 (10.21–10.97)	6.46
Herpes zoster	138.64 (134.67-142.64)	0.66 (0.62–0.69)	0.06 (0.06–0.07)	1.23 (1.19–1.26)	7.75 (7.45–8.03)	8.97 (8.66–9.29)	5.49
Invasive meningococcal disease	0.76 (0.73–0.78)	0.08 (0.08–0.08)	4.50 (4.42–4.58)	0.35 (0.31–0.39)	3.06 (2.95–3.17)	3.40 (3.28–3.53)	2.08
Invasive *Haemophilus influenzae* infection	0.76 (0.74–0.78)	0.09 (0.08–0.09)	3.23 (3.13–3.33)	0.14 (0.12–0.15)	2.32 (2.22–2.41)	2.46 (2.36–2.55)	1.50
HBV infection	0.84 (0.81–0.87)	0.02 (0.02–0.02)	1.24 (0.89–1.67)	0.08 (0.06–0.10)	0.97 (0.66–1.34)	1.05 (0.75–1.41)	0.64
Rotavirus	9.83 (9.30-10.35)	0.02 (0.02–0.02)	0.09 (0.09–0.10)	0.02 (0.02–0.02)	0.90 (0.86–0.95)	0.92 (0.88–0.97)	0.56
Varicella zoster	123.29 (116.23-130.33)	0.03 (0.03–0.03)	< 0.01	0.03 (0.03–0.03)	0.58 (0.55–0.60)	0.61 (0.58–0.64)	0.37
HAV infection	3.69 (3.57–3.82)	0.01 (0.01–0.01)	0.07 (0.07–0.08)	0.06 (0.05–0.08)	0.21 (0.18–0.24)	0.27 (0.24–0.31)	0.17
Mumps	19.24 (18.55–19.94)	< 0.01	< 0.01	0.05 (0.05–0.06)	0.02 (0.02–0.02)	0.07 (0.06–0.07)	0.04
Measles	0.41 (0.39–0.42)	< 0.01	0.06 (0.06–0.06)	0.01 (0.01–0.01)	0.02 (0.02–0.02)	0.02 (0.02–0.03)	0.01
Total	**8,550.49**	**10.43**	**11.98**	**12.63**	**150.91**	**163.54**	**100**

DALY: disability-adjusted life year; HAV: hepatitis A virus; HBV: hepatitis B virus; n/a: not applicable; RSV: respiratory syncytial virus; UI: uncertainty intervals; YLD: years lived with disability; YLL: years of life lost

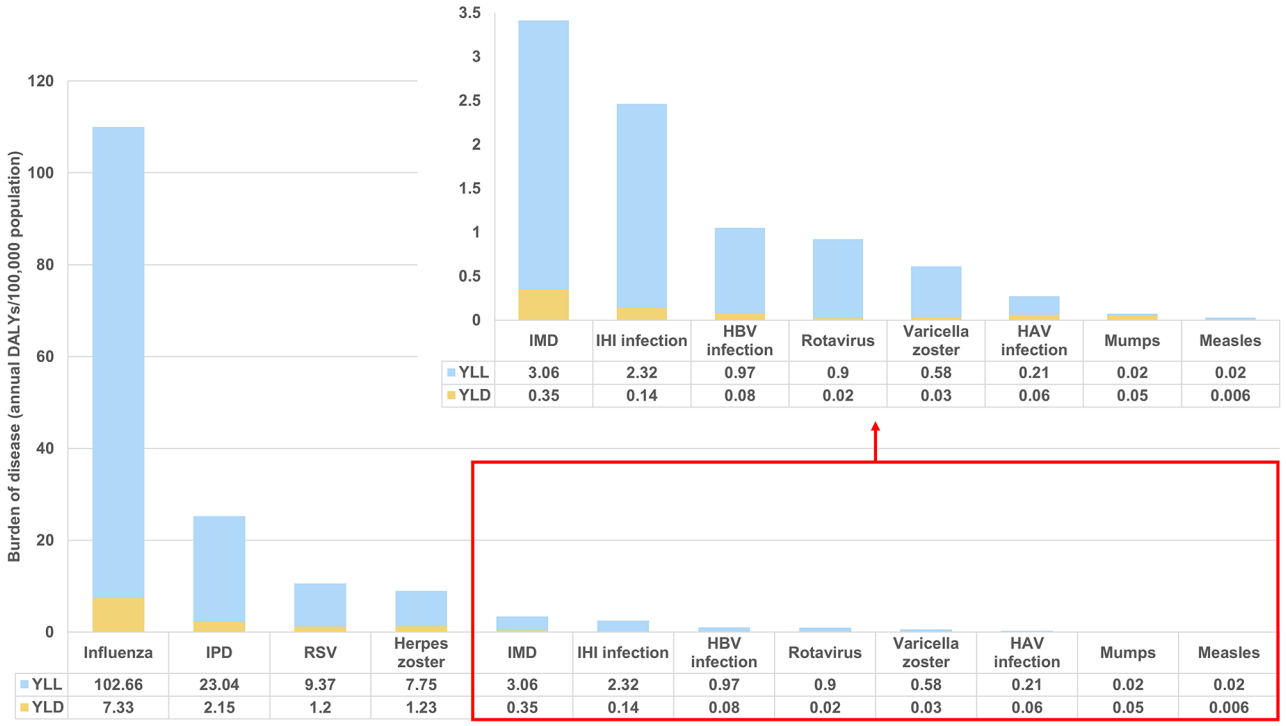

Fig. 2 Burden of selected infectious diseases represented as annual DALYs per 100,000 population. The bars depict the median annual years lived with disability (YLD) and years of life lost (YLL) per 100,000 population for each infection in Spain. DALY: disability adjusted life year; HAV: hepatitis A virus; HBV: hepatitis B virus; IHI: invasive *Haemophilus influenzae*; IMD: invasive meningococcal disease; IPD: invasive pneumococcal disease; RSV: respiratory syncytial virus

The burden of the selected infectious diseases mainly derived from YLL (mortality), which reached 92% of the total (Fig. 3). Morbidity showed a major impact in mumps, with YLD representing 76% of the total annual DALY per 100,000 population, although its burden was modest in the Spanish population (0.07 DALYs per 100,000 population/year).

Influenza had the greatest incidence and mortality among the infections analysed, which was in line with the large burden of the infection (Fig. 4). Similarly, RSV and herpes zoster classified as high incidence/high mortality infections. Invasive pneumococcal disease, while second in terms of total burden of disease, fell into the high mortality, but low incidence group. Varicella zoster had considerable incidence, but low mortality, resulting in a minor disease burden (0.61 DALYS per 100,000 population/year; Table 3), although still higher than the rest of the low mortality diseases. The remaining infections showed discreet incidence and mortality numbers and, thus, a minor disease burden. Altogether, respiratory infections, especially influenza and RSV, which combined both high mortality and high incidence, are relevant infectious diseases in the Spanish population.

Burden of disease by age groups

Stratification of DALY estimates by age brought to light that there is a substantial increase in disease burden among individuals of 60 years or older (55% of annual DALYs per 100,000 over the total population), with the highest overall burden identified for the population over 85 years (Fig. 5). Children under 5 years also accounted for a significant proportion of DALYs (11% of annual DALYs per 100,000 over the total population) compared to other age groups. In general, the burden of the selected infections calculated for the various age groups was mainly driven by premature mortality (Supplementary Fig. 1). Similar disease burden was found between male and female groups (Fig. 5).

A deeper analysis of the individual burden in the elderly population (60 years or over) revealed that influenza remains the infectious disease with the greatest burden among those analysed here, closely followed by invasive pneumococcal disease (Fig. 6A). In line with these results, respiratory infections had a large burden in children (Fig. 6B, C). In children under 5 years, influenza, RSV, and invasive pneumococcal disease were the infections with the highest burden, whereas RSV placed first for infants under 1 year, followed by influenza and invasive pneumococcal disease. In general, mumps and measles remained as low-burden infections across all

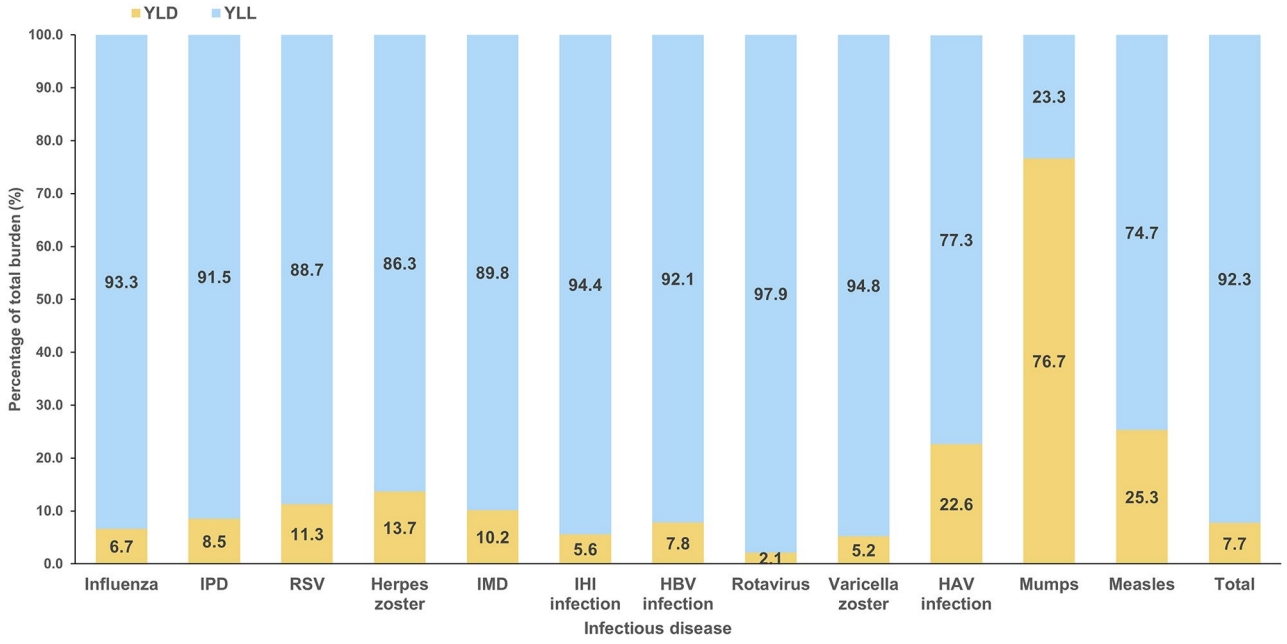

Fig. 3 Contribution of YLD and YLL to the total burden for each infectious disease. Total years lived with disability (YLD) and years of life lost (YLL) values were normalized as a percentage of the total annual DALYs per 100,000 population for each infectious disease. HAV: hepatitis A virus; HBV: hepatitis B virus; IHI: invasive *Haemophilus influenzae*; IMD: invasive meningococcal disease; IPD: invasive pneumococcal disease; RSV: respiratory syncytial virus

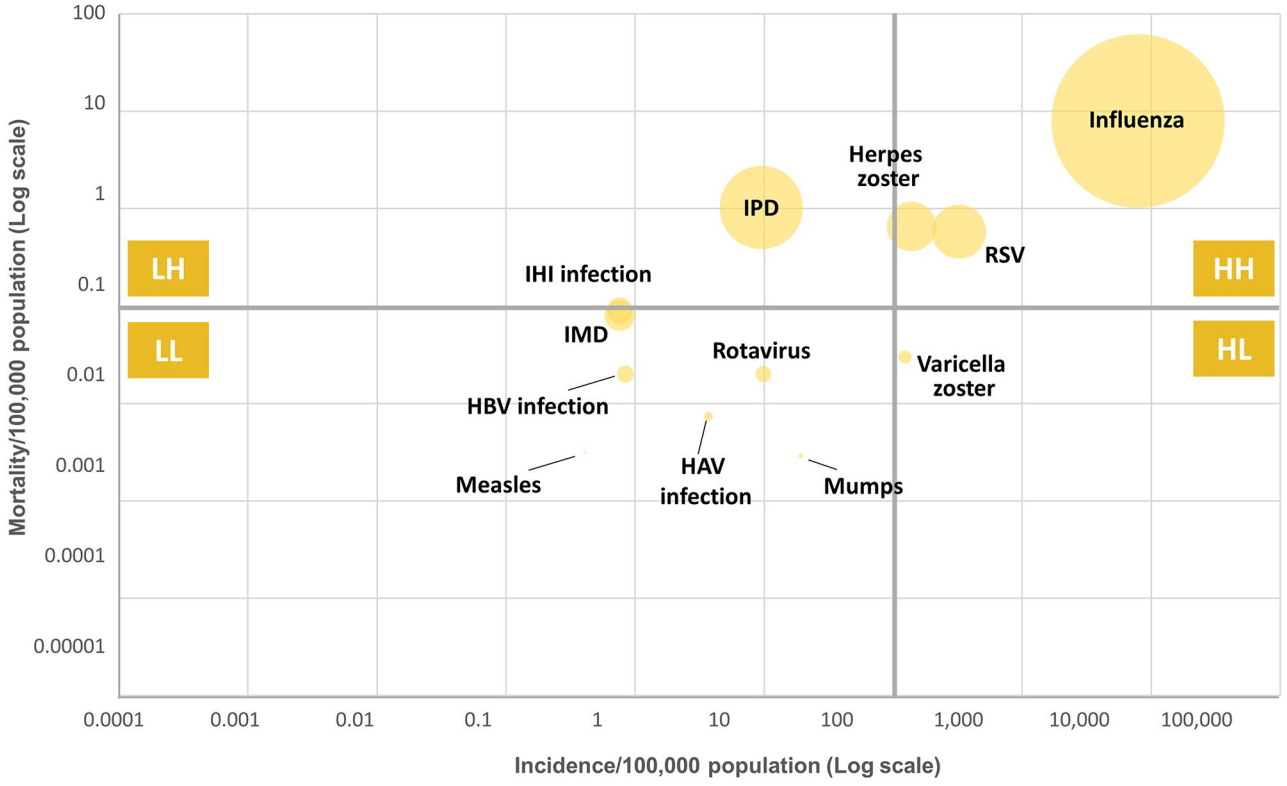

Fig. 4 Burden of selected infectious diseases classified by incidence and mortality rates per 100,000 population. Divisions are established following the work by Cassini et al. [6] and delineate four distinct subgroups of infections: high incidence/high mortality (HH), high incidence/low mortality (HL), low incidence/high mortality (LH), and low incidence/low mortality (LL). Bubble area corresponds to the number of DALYs per 100,000 population/year for each infection. HAV: hepatitis A virus; HBV: hepatitis B virus; IHI: invasive *Haemophilus influenzae*; IMD: invasive meningococcal disease; IPD: invasive pneumococcal disease; RSV: respiratory syncytial virus

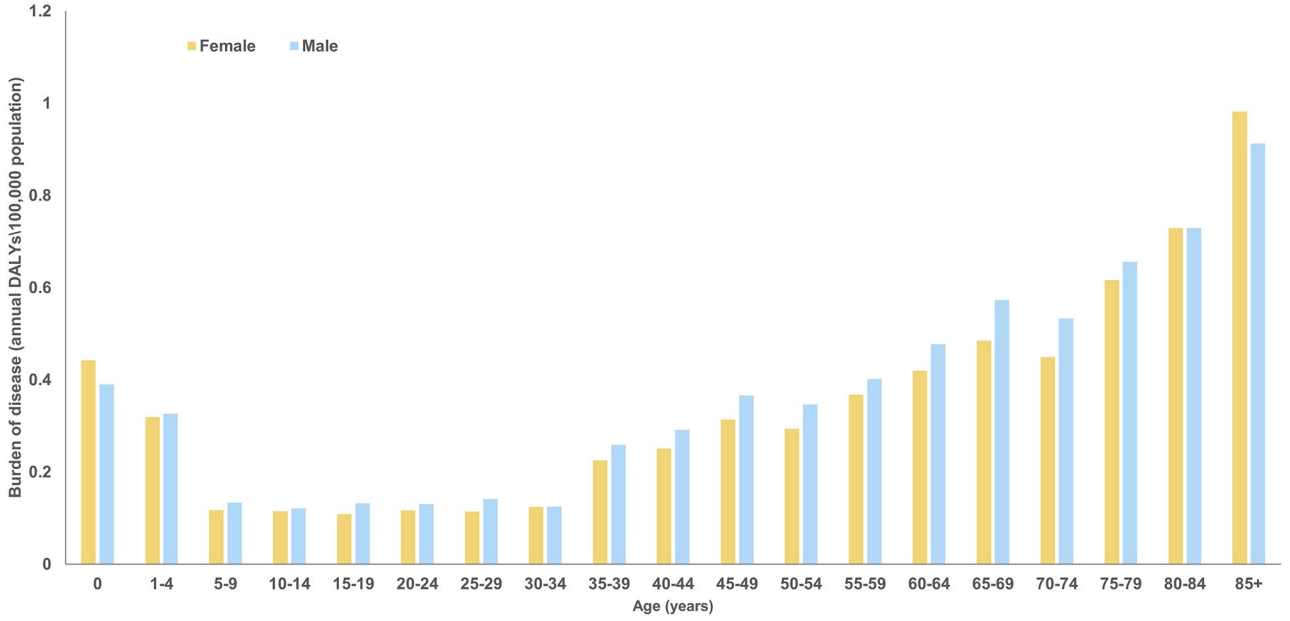

Fig. 5 Annual burden of selected infectious diseases stratified by sex and age groups. The bars represent the total DALYs per 100,000 population/year for all the infections evaluated. DALY: disability adjusted life year

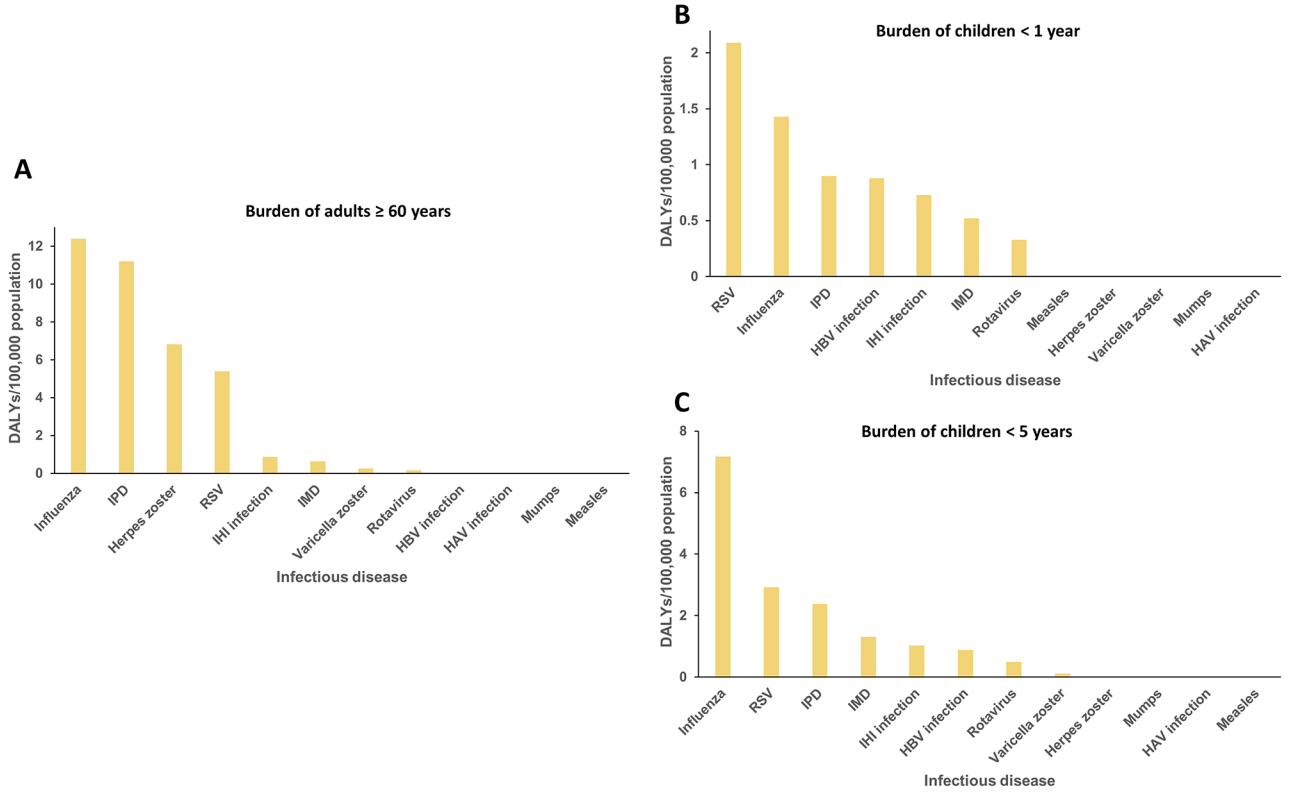

Fig. 6 Total burden of disease by age groups. The graphs depict the total DALYs per 100,000 population/year for each selected infectious disease. The age groups represented are ≥ 60 years (**A**), < 1 year (**B**) and < 5 years (**C**). DALY: disability adjusted life year; HAV: hepatitis A virus; HBV: hepatitis B virus; IHI: invasive *Haemophilus influenzae*; IMD: invasive meningococcal disease; IPD: invasive pneumococcal disease; RSV: respiratory syncytial virus

age groups. It is worth mentioning that herpes zoster appeared in third place for older adults, exhibiting a certain burden for this age group (6.82 DALYs per 100,000 population/year), whereas it had little impact in children, with an estimated burden under 0.01 annual DALYs per 100,000 population.

Alternative scenarios

If no underestimation of incidence were considered, influenza would remain the most burdensome disease of the infections selected in the study, with a total of 31.45 annual DALYs/100,000 population (data not shown).

The use of alternative disability weights in the *de novo* models had a minor impact on the results (+0.30 DALYs for herpes zoster, +0.01 DALYs for RSV and neglectable for varicella; data not shown).

For RSV, the inclusion of partially controlled and uncontrolled asthma disabilities in the model would have increased the number of annual DALYs per 100,000 associated with this infection to 11.84 and 17.71, respectively.

Discussion

Previous studies have brought to attention the high burden of immunization-preventable diseases in Spain in terms of epidemiology and costs [28, 44–48]. Here, we provide an updated estimation of disease burden employing the BCoDE methodology, considering a holistic DALY approach.

Our analysis showed that, despite immunization efforts, the burden of disease for certain immunization-preventable infections remains high in Spain. Respiratory infections exhibited the highest burden among the infectious diseases analysed, with 110.00, 25.20 and 10.57 annual DALYs per 100,000 population estimated for influenza, invasive pneumococcal disease, and RSV, respectively. In general, disease burden derived from YLLs for most infections, in line with previously published results at a European level [6].

Our study revealed a great variability in the burden across the different infections evaluated, in agreement with a previous study in the EU/EEA countries [6], but also across distinct countries. This may be linked to many factors, such as different moments of analysis or data availability, but also to the immunization strategies in place and their effectiveness. For instance, the burden of HBV infection is calculated at 1.05 DALYs per 100,000/year in Spain, compared to 10.6 as reported in a German study [49] or the European average of 7.86 [6]. Furthermore, measles incidence is estimated at 0.41 cases per 100,000, as opposed to the median of 7.46 calculated for Europe [6].

Influenza ranked highest across all the infections studied herein and had the greatest annual burden of disease in Europe, with 81.8 annual DALYs per 100,000 population, being primarily associated to mortality as well [6]. These findings are further supported by BCoDE studies from individual European countries. Influenza and invasive pneumococcal disease were among the highest burden communicable diseases among the 32 analysed in the Netherlands [50]. In Germany, influenza reported the highest burden (40.2 DALYs/100,000 population) among the four communicable diseases evaluated [49].

In Spanish older adults aged 60 or above, influenza imposed the greatest burden in our analysis, potentially due to a consistently low vaccination coverage rates (VCR), reaching only about 53.5% of those over 64 in the 2019–2020 vaccination campaign, a percentage that has barely changed since 2010 [51, 52]. Although high compared to other European countries [53], the Spanish coverage rates for influenza vaccination (Supplementary Table 7) fall far from the EU goal of 75% [54, 55], which highlights the need to maximise immunization especially in adults over 60 years. While an increase in influenza VCR was observed post COVID-19 pandemic [21], Spanish experts propose several measures for continued improvement and steps are already being taken. Based on evidence on the improved efficacy in reducing the influenza viral load and severe complications, such as pneumonia and cardiorespiratory events, and consequent hospitalisations in the elderly [56–59], the Spanish Society of Geriatrics and Gerontology recommends universal vaccination to all adults ≥60 years of age with the high-dose (HD) influenza vaccine as a first option, the second choice being the adjuvant alternative. It also advocates for progressively extending the benefits of vaccination to individuals over 50 years [60]. And while the Spanish Ministry of Health recommends vaccination for individuals ≥65 years, some regions are already lowering the threshold to 60 years.

In our study, DALY estimates for invasive pneumococcal disease and RSV followed that of influenza, uncovering these respiratory infections as important healthcare problems in Spain, as previously described in literature [26, 27, 47, 61–64]. The burden of invasive pneumococcal disease increased with age, being significantly higher in older adults (60 years or over), in coherence with general observations in Europe [6]. Similarly, in the European estimation [6], invasive pneumococcal disease was found among the greatest burden communicable diseases researched, while it ranked highest in the Netherlands [50, 65]. The authors of the latter mention that, at the time of the analysis, pneumococcal vaccination was not routinely offered to people over 60 years of age, as was the case for influenza [65], and highlighted a decrease of the VCR between 2007 and 2011 and an increase of non-vaccine type disease due to serotype replacement, on the other [50].

RSV was associated with a significant burden in children under 5 years, with 2.92 DALYs per 100,000 population/year, driven by high infectivity and incidence coupled with high mortality [66, 67], as indicated by a vast number of studies that highlight the burden of hospitalisations due to bronchiolitis and RSV in children in Spain [28, 47, 68–71]. Moreover, findings from a recently published longitudinal study that followed 51,292 Spanish children < 5 years suggest that hospitalisation data alone underestimate the RSV infections requiring medical care and describe a larger clinical and economic burden in both primary care and hospital settings [26, 27]. Given the significant burden of RSV, especially in children under 1 year, the Spanish Association of Pediatrics recommends immunization of neonates and infants under 6 months at the beginning of their first RSV season, as well as pregnant women [72]. At the time of this study, the only efficient preventive strategy in Spain was the single-dose monoclonal antibody nirsevimab, approved to prevent RSV in neonates and infants during their first RSV season [25]. The Spanish Ministry of Health has recently published the first national RSV immunization recommendations, with nirsevimab addressing high-risk children under 24 months as well as infants under 6 months [13]. Immunization with this long-acting antibody reduces the risk of infections requiring medical attention and hospitalisations in term and preterm neonates [73], highlighting the potential of this approach to reduce the burden of RSV in infants. Incidence estimates after the introduction of immunization programmes are already available in some regions [74, 75] and, as VCR increases, further epidemiologic numbers are expected to confirm the impact of RSV immunization in the coming seasons.

On the contrary, infections with high VCRs registered in Spain, such as HBV, *Haemophilus influenza*, meningococcus, measles, mumps and varicella (Supplementary Table 7), resulted in a substantially lower disease burden, mainly due to lower reported incidence. This highlights the importance of effective public health measures. Therefore, immunization, coupled with efforts to improve coverage rates to maintain current results and avoid potential outbreaks can reduce the incidence of some infections to a minimum, as is the case with poliomyelitis, rubella, diphtheria, and tetanus in Spain (Supplementary Table 1). It also emphasises the role of programmatic decision-making and prioritisation of prevention strategies, with immunization being one of the most successful public health interventions in history [76]. These estimates provide a basis to guide prevention strategies, prioritise interventions and make public health decisions in the field of infectious diseases in Spain. In this regard, it is noteworthy that, in 2019, the Spanish public spending in vaccines for influenza prevention was lower than that of invasive pneumococcal disease, HBV and meningococcal disease [77], despite having the highest disease burden. Since then, the emergence of the COVID-19 pandemic and the subsequent in-hospital burden, potentially influenced priority setting. By 2022, public spending investment in prevention increased by 36.5% and preventing influenza became top priority together with invasive pneumococcal disease [77], highlighting the importance of prioritising and increasing investment in public health measures aimed at reducing the burden of diseases with a major impact on population health and healthcare resources.

The major strength of this study is that it uses the BCoDE toolkit, which employs a thoroughly validated methodology already used in previous European studies [6, 49, 50, 65], allowing for consistent comparisons between infectious diseases and geographies. In addition, our study covers most of the diseases included in the Spanish vaccination calendar that are not labelled as no or low incidence, representing a reasonably accurate approach to infectious disease burden estimation in Spain [78]. Compared to previously published BCoDE analysis, it also incorporates four infections (herpes zoster, rotavirus, RSV, and varicella zoster) as *de novo* models.

While a thorough literature review and step by step expert validation process was performed for each parameter of the model, these publicly available data have limitations. Furthermore, mortality rates were collected from the MBDS [21], and correspond to in-hospital fatality across the reported cases for a particular infection, whether the infectious agent was the ultimate cause of death or not. Thus, mortality probabilities might be over or underestimated. This was minimized by including mean mortality rates associated to main and secondary diagnosis hospitalisations, an approach used in previously published studies assessing mortality estimates in Spain [28, 47, 70, 79]. Besides, probabilities of developing complications and disability weights for the *de novo* models came from the limited information accessible in the literature, except for some cases where it was collected from healthcare databases (e.g., MBDS). Age-specific risk of developing certain sequelae is not generally available, so the impact of complications that worsen in the aging population could not be considered. As a conservative approach, long-term clinical conditions were simplified, and outcome trees were built considering only severe complications (asthma for RSV [29, 30] and postherpetic neuralgia for herpes zoster [34]), given that other sequelae account for a low burden in these infections.

In this work, annual case numbers were collected from reliable nationwide sentinel systems [19, 79] with the limitation that in such systems not all reported cases are tested for the virus [6, 51]. Furthermore, as unveiled by a study in the UK, routine surveillance systems fail

to capture a large proportion of subclinical and clinical cases of influenza, since not all cases seek medical consultation [18], which we attempted to address by adjusting the data for underestimation. While this may also be the case for other infectious diseases included in this analysis, experts commented that this would be of a much lesser impact that in the case of influenza. Therefore, in the absence of any data regarding the potential underestimation, underreporting or underascertainment of the RENAVE estimates and considering the variation of the incidence data with +/-20% in the sensitivity analysis, no further adjustment was performed for any of the other infectious diseases.

Lastly, similarly to Cassini et al. [6], while included in the Spanish national vaccination calendar [78], HPV infection was not included in the analysis due to the complexity of modelling it with the BCoDE tool in the absence of incidence data from the Spanish surveillance system [17] and due to the variety of long-term diseases associated with it, including different types of cancers and genital warts. However, we expect a low burden of this disease in the long term since high VCRs (+85%) are being registered in Spain since 2017 [52]. In 2019, the Global Burden of Disease study reported a burden of cervical cancer of 118 DALYs for 100,000 women in Spain (<60 DALYs/100,000 population), which was lower than the European rate of 189 [5]. Furthermore, at the time of our analysis, SARS-CoV-2 immunization was not included in the Spanish national vaccination calendar [14] and recommendations have varied immensely over the past three years, with no clear immunization recommendations defined. Similarly to influenza, SARS-CoV-2 cases may be underestimated [80], mainly due to diverse symptomatology and social consequences linked to positive diagnosis. Hence, it was agreed to not include SARS-CoV-2 in this analysis.

Taking all of the above into account, we believe that the estimated burden of the selected infectious diseases presented herein is based on a robust and reproducible methodology and is a fair reflection of the Spanish context, which can contribute to the evaluation of the impact of current vaccination strategies and future programmes.

Conclusions

The results of this analysis highlight a persisting high burden of disease due to the respiratory infections analysed, despite the availability of some effective vaccines and immunization recommendations in the NIP (e.g., influenza, invasive pneumococcal disease), and point towards the necessity for increasing VCRs.

In addition to increasing vaccination and close monitoring of infections in high-burden diseases, the introduction of novel and more effective immunization strategies, such as HD influenza vaccines for routine vaccination of the elderly or the recently approved long-acting antibody for RSV prevention in children, could further reduce this burden [57, 73, 81]. At the same time, maintaining the VCR of low burden diseases over time is essential to prevent outbreaks and keep these diseases under control, as illustrated by the limited overall burden of infections such as measles, varicella or rotavirus.

Abbreviations

BCoDE	Burden of Communicable Diseases in Europe
DALY	Disability-adjusted life year
EU	European Union
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HD	High-dose
IHME	Institute for Health Metrics and Evaluation
MBDS	Minimum Basic Data Set
NIP	National immunization programme
RENAVE	Spanish National Epidemiological Surveillance Network
RSV	Respiratory syncytial virus
SIMC	Infection Surveillance System of Catalonia
SIVIRA	Acute Respiratory Infection Surveillance System
VCR	Vaccination coverage rates
WHO	World Health Organization
YLL	Years of life lost
YLD	Years lived with disability

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-024-09637-x.

Supplementary Material 1

Author contributions

APR and JMF participated in the review and interpretation of the model methodology, inputs and results, as well as in the manuscript review process. JLLB participated in the project conceptualization. AD participated in the project administration, supervision and manuscript drafting. CC participated in the conceptualization of the study, methodology, analysis and manuscript drafting. SLH participated in the analysis and manuscript drafting. All authors reviewed the manuscript. All authors agree to be accountable for all aspects of the work and give their consent to publish this study.

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Data availability

The data sets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

AD and JLLB are employees of Sanofi and may hold shares and/or stock options in the company. SLH and CC are consultants of Axentiva Solutions, which received consultancy fees from Sanofi, Spain and, during the conduct of this study, from other pharmaceutical companies in unrelated projects. JMF reports having received a consulting fee from Axentiva Solutions for collaboration in this study and, during the conduct of this study, from other Sanofi funded projects related to RSV. AP reports having received funding

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References

1. Baker RE, Mahmud AS, Miller IF et al. Infectious disease in an era of global change. *Nature Reviews Microbiology 2021 20:4*. 2021;20(4):193–205. https://doi.org/10.1038/s41579-021-00639-z.
2. Alwan A, MacLean DR, Riley LM, et al. Monitoring and surveillance of chronic non-communicable diseases: Progress and capacity in high-burden countries. Lancet. 2010;376(9755):1861–8. https://doi.org/10.1016/S0140-6736(10)61853-3.
3. Ellwanger JH, da Veiga ABG, Kaminski VdeL, Valverde-Villegas JM, de Freitas AWQ, Chies JAB. Control and prevention of infectious diseases from a one health perspective. Genet Mol Biol. 2021;44(1 Suppl 1):1–23. https://doi.org/10.1590/1678-4685-GMB-2020-0256.
4. Lo SW, Jamrozy D. Genomics and epidemiological surveillance. Nature Reviews Microbiology 2020 18:9. 2020;18(9):478–478. https://doi.org/10.1038/s41579-020-0421-0.
5. Roser M, Ritchie H, Spooner F. Burden of Disease. OurWorldInData.org. Published online 2021. Accessed March 3, 2023. https://ourworldindata.org/burden-of-disease.
6. Cassini A, Colzani E, Pini A, et al. Impact of infectious diseases on population health using incidence-based disability-adjusted life years (DALYs): results from the burden of communicable diseases in Europe study, European Union and European economic countries, 2009 to 2013. Euro-surveillance. 2018;23(16):17–00454. https://doi.org/10.2807/1560-7917.ES.2018.23.16.17-00454/CITE/PLAINTEXT.
7. Kuchenmüller T, Hird S, Stein C, Kramarz P, Nanda A, Havelaar AH. Estimating the global burden of foodborne diseases–a collaborative effort. Euro Surveill. 2009;14(18). https://doi.org/10.2807/ESE.14.18.19195-EN.
8. Abbafati C, Abbas KM, Abbasi-Kangevari M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of Disease Study 2019. Lancet. 2020;396(10258):1204–22. https://doi.org/10.1016/S0140-6736(20)30925-9.
9. Kretzschmar M, Mangen MJJ, Pinheiro P, et al. New Methodology for estimating the Burden of Infectious diseases in Europe. PLoS Med. 2012;9(4):e1001205. https://doi.org/10.1371/JOURNAL.PMED.1001205.
10. Mangen MJJ, Plass D, Havelaar AH, et al. The Pathogen- and incidence-based DALY Approach: an appropriated methodology for estimating the Burden of Infectious diseases. PLoS ONE. 2013;8(11). https://doi.org/10.1371/JOURNAL.PONE.0079740.
11. Colzani E, Cassini A, Lewandowski D, et al. A Software Tool for Estimation of Burden of Infectious diseases in Europe using incidence-based disability adjusted Life Years. PLoS ONE. 2017;12(1). https://doi.org/10.1371/JOURNAL.PONE.0170662.
12. Murray CJL, Lopez AD. Global mortality, disability, and the contribution of risk factors: global burden of Disease Study. Lancet. 1997;349(9063):1436–42. https://doi.org/10.1016/S0140-6736(96)07495-8.
13. Comisión de Salud Pública del Consejo Interterritorial del Sistema Nacional de Salud. Ministerio de Sanidad. Recomendaciones de Utilización de Nirsevimab Frente a Infección Por Virus Respiratorio Sincitial de la Ponencia de Programa y Registro de Vacunaciones. 2023. Accessed March 3, 2023. https://www.sanidad.gob.es/areas/promocionPrevencion/vacunaciones/comoTrabajamos/docs/Nirsevimab.pdf.
14. Consejo, Interterritorial. Sistema Nacional de Salud. Calendario Común de Vacunación a Lo Largo de Toda La Vida. Calendario Recomendado Año 2023.; 2023. Accessed February 14, 2023. https://www.sanidad.gob.es/areas/promocionPrevencion/vacunaciones/calendario-y-coberturas/docs/CalendarioVacunacion_Todalavida.pdf.
15. Spanish Statistical Office. Accessed February 1. 2023. https://www.ine.es/en/.
16. Burden of Disease toolkit - Application to calculate DALYs. Accessed February 1. 2023. https://www.ecdc.europa.eu/en/publications-data/toolkit-application-calculate-dalys.
17. Red Nacional de Vigilancia Epidemiológica. Resultados de la Vigilancia Epidemiológica de las enfermedades transmisibles. Informe anual. Años 2017–2018. Published online 2018.
18. Hayward AC, Fragaszy EB, Bermingham A, et al. Comparative community burden and severity of seasonal and pandemic influenza: results of the Flu Watch cohort study. Lancet Respir Med. 2014;2(6):445–54. https://doi.org/10.1016/S2213-2600(14)70034-7.
19. Sistema de Vigilancia de Infección Respiratoria Aguda. Vigilancia Centinela de Infección Respiratoria Aguda En Atención Primaria (IRAs) y En Hospitales (IRAG) Gripe, COVID-19 y Otros Virus Respiratorios.; 2023.
20. Sistema d'Informació per a la Vigilància d'Infeccions a Catalunya. Accessed February 1. 2023. https://sivic.salut.gencat.cat/.
21. Portal estadístico CMBD. Accessed February 1. 2023. https://pestadistico.inteligenciadegestion.sanidad.gob.es/publicoSNS/.
22. Russell CD, Unger SA, Walton M, Schwarze J. The human Immune response to respiratory syncytial virus infection. Clin Microbiol Rev. 2017;30(2):481–502. https://doi.org/10.1128/CMR.00090-16.
23. Villamil JPS, Polack FP, Buendía JA. Disability-adjusted life years for respiratory syncytial virus in children under 2 years. BMC Public Health. 2020;20(1):1–5. https://doi.org/10.1186/S12889-020-09796-X/FIGURES/2.
24. Nam HH, Ison MG. Respiratory syncytial virus infection in adults. BMJ. 2019;366. https://doi.org/10.1136/BMJ.L5021.
25. Agencia Española de Medicamentos y Productos Sanitarios. Reunión del Comité de Medicamentos de Uso Humano (CHMP) de septiembre 2022. Published 2022. Accessed March 3. 2023. https://www.aemps.gob.es/informa/reunion-del-comite-de-medicamentos-de-uso-humano-chmp-de-septiembre-2022/.
26. Martinón-Torres F, Carmo M, Platero L, et al. Clinical and economic burden of respiratory syncytial virus in Spanish children: the BARI study. BMC Infect Dis. 2022;22(1). https://doi.org/10.1186/S12879-022-07745-0.
27. Martinón-Torres F, Carmo M, Platero L, et al. Clinical and economic hospital burden of acute respiratory infection (BARI) due to respiratory syncytial virus in Spanish children, 2015–2018. BMC Infect Dis. 2023;23(1). https://doi.org/10.1186/S12879-023-08358-X.
28. Heppe-Montero M, Gil-Prieto R, del Diego Salas J, Hernández-Barrera V, Gil-de-Miguel Á. Impact of respiratory syncytial virus and influenza virus infection in the Adult Population in Spain between 2012 and 2020. Int J Environ Res Public Health. 2022;19(22). https://doi.org/10.3390/IJERPH192214680.
29. Mejias A, Wu B, Tandon N, et al. Risk of childhood wheeze and asthma after respiratory syncytial virus infection in full-term infants. Pediatr Allergy Immunol. 2020;31(1):47–56. https://doi.org/10.1111/PAI.13131.
30. Shi T, Ooi Y, Zaw EM, et al. Association between Respiratory Syncytial Virus-Associated Acute Lower respiratory infection in early life and recurrent wheeze and asthma in later childhood. J Infect Dis. 2020;222(Supplement7):S628–33. https://doi.org/10.1093/INFDIS/JIZ311.
31. Emerson J, Kim DD. DALY Calculator.; 2018. Accessed February 1, 2024. https://cevr.shinyapps.io/DALYcalculation/.
32. Dooling K, Marin M, Gershon AA. Clinical manifestations of Varicella: disease is largely forgotten, but it's not gone. J Infect Dis. 2022;226(Supplement4):S380–4. https://doi.org/10.1093/INFDIS/JIAC390.
33. Comité Asesor de Vacunas (CAV-AEP). Manual de Inmunizaciones en línea de la AEP. Sección II. Capítulo 7. Calendarios de inmunización en España. https://doi.org/10.1016/J.ANPEDI.2022.10.002.
34. Matthews S, De Maria A, Passamonti M, et al. The Economic Burden and Impact on Quality of life of herpes zoster and Postherpetic Neuralgia in individuals aged 50 years or older in Italy. Open Forum Infect Dis. 2019;6(2). https://doi.org/10.1093/OFID/OFZ007.
35. Patil A, Goldust M, Wollina U. Herpes zoster: a review of clinical manifestations and management. Viruses. 2022;14(2). https://doi.org/10.3390/V14020192.
36. Redondo Fernández M, Costillo Rodríguez J, Jiménez Rodríguez M. Terapéutica en Atención Primaria: Abordaje de la neuralgia postherpética en Atención Primaria: situación actual del tratamiento farmacológico. *Semergen: revista española de medicina de familia, ISSN 1138–3593, No 2*, 2007, págs 80–85. 2007;(2):80–85.
37. Red Nacional de Vigilancia Epidemiológica. Informe Epidemiológico Sobre La Situación de Herpes Zóster En España, 1998–2018.; 2020.

38. Lopez-Belmonte JL, Cisterna R, Demiguel A, Guilmet C, Biani F, Uhart M. The use of Zostavax in Spain: the economic case for vaccination of individuals aged 50 years and older. J Med Econ. 2016;19(6):576–86. https://doi.org/10.3111/13696998.2016.1146726.
39. Kwong JC, Ratnasingham S, Campitelli MA, et al. The impact of infection on population health: results of the Ontario burden of infectious diseases study. PLoS ONE. 2012;7(9). https://doi.org/10.1371/JOURNAL.PONE.0044103.
40. Clinical Overview of Herpes Zoster (Shingles) | CDC. Accessed February 21. 2023. https://www.cdc.gov/shingles/hcp/clinical-overview.html.
41. Dennehy PH. Rotavirus infection: an update on management and prevention. Adv Pediatr. 2012;59(1):47–74. https://doi.org/10.1016/J.YAPD.2012.04.002.
42. Comisión de Salud Pública del Consejo Interterritorial del Sistema Nacional de Salud. Ministerio de Sanidad Consumo y Bienestar Social. Grupo de Trabajo Vacunación En Prematuros de La Ponencia de Programa y Registro de Vacunaciones. Vacunación En. 2019. Accessed June 2, 2023. https://www.sanidad.gob.es/areas/promocionPrevencion/vacunaciones/enfermedades/docs/Vacunacion_Prematuros.pdf.
43. Haagsma JA, de Noordhout CM, Polinder S, et al. Assessing disability weights based on the responses of 30,660 people from four European countries. Popul Health Metr. 2015;13(1):1–15. https://doi.org/10.1186/S12963-015-0042-4/TABLES/3.
44. Rejas J, Sicras-Mainar A, Sicras-Navarro A, Lwoff N, Méndez C. All-cause community acquired pneumonia cost by age and risk in real-world conditions of care in Spain. Expert Rev Pharmacoecon Outcomes Res. 2022;22(5):853–67. https://doi.org/10.1080/14737167.2022.2020649.
45. Soriano JB, Rojas-Rueda D, Alonso J, et al. The burden of disease in Spain: results from the global burden of Disease 2016. Med Clínica (English Edition). 2018;151(5):171–90. https://doi.org/10.1016/J.MEDCLE.2018.05.043.
46. Leache L, Gutiérrez-Valencia M, Saiz LC, Erviti J. Morbi-mortality of lower respiratory tract infections in Spain, 1997–2018. Sist Sanit Navar. 2021;44(3):385–96. https://doi.org/10.23938/ASSN.0962.
47. Gil-Prieto R, Allouch N, Jimeno I, Hernández-Barrera V, Arguedas-Sanz R, Gil-de-Miguel Á. Burden of hospitalizations related to pneumococcal infection in Spain (2016–2020). Antibiot (Basel). 2023;12(1):172. https://doi.org/10.3390/ANTIBIOTICS12010172.
48. de Gil Á, Martinón-Torres F, Díez-Domingo J, et al. Clinical and economic burden of physician-diagnosed influenza in adults during the 2017/2018 epidemic season in Spain. BMC Public Health. 2022;22(1). https://doi.org/10.1186/S12889-022-14732-2.
49. Plass D, Mangen MJJ, Kraemer A, et al. The disease burden of hepatitis B, influenza, measles and salmonellosis in Germany: first results of the Burden of Communicable diseases in Europe Study. Epidemiol Infect. 2014;142(10):2024–35. https://doi.org/10.1017/S0950268813003312.
50. Van Lier A, McDonald SA, Bouwknegt M, et al. Disease Burden of 32 infectious diseases in the Netherlands, 2007–2011. PLoS ONE. 2016;11(4):e0153106. https://doi.org/10.1371/JOURNAL.PONE.0153106.
51. Centro Nacional de Epidemiología, Instituto de Salud Carlos III. Informe de Vigilancia de La Gripe En España. Temporada 2019–2020. 2020. Accessed February 15, 2023. http://vgripe.isciii.es/.
52. Ministerio de Sanidad. Sistema de Información de Vacunaciones (SIVAMIN). Portal estadístico. Área de Inteligencia de Gestión. Accessed February 15. 2023. https://pestadistico.inteligenciadegestion.sanidad.gob.es/publicoSNS/S/sivamin.
53. European Centre for Disease Prevention and Control. Seasonal Influenza Vaccination Recommendations and Coverage Rates in EU/EEA Member States. 2023. https://doi.org/10.2900/335933.
54. Council of the European Union. Council recommendation of 7 December 2018 on strengthened cooperation against vaccine-preventable diseases (2018/C 466/01). Oficial Journal of the European Union. Published online 2018.
55. European Centre for Disease Prevention and Control. Seasonal Influenza Vaccination and Antiviral Use in EU/EEA Member States. 2018. Accessed February 15, 2023. https://www.ecdc.europa.eu/en/publications-data/seasonal-influenza-vaccination-antiviral-use-eu-eea-member-states.
56. DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. N Engl J Med. 2014;371(7):635–45. https://doi.org/10.1056/NEJMOA1315727.
57. Lee JKH, Lam GKL, Shin T, Samson SI, Greenberg DP, Chit A. Efficacy and effectiveness of high-dose influenza vaccine in older adults by circulating strain and antigenic match: an updated systematic review and meta-analysis. Vaccine. 2021;39(Suppl 1):A24–35. https://doi.org/10.1016/J.VACCINE.2020.09.004.
58. Chang LJ, Meng Y, Janosczyk H, Landolfi V, Talbot HK. Safety and immunogenicity of high-dose quadrivalent influenza vaccine in adults ≥ 65 years of age: a phase 3 randomized clinical trial. Vaccine. 2019;37(39):5825–34. https://doi.org/10.1016/J.VACCINE.2019.08.016.
59. de Miguel ÁG, Marguello ER, Domingo JD, de Lejarazu RO, Torres FM. [High-dose trivalent influenza vaccine. Efficacy and effectiveness]. Rev Esp Quimioter. 2020;33(4):226–39. https://doi.org/10.37201/REQ/043.2020.
60. Sociedad Española de Geriatría y Gerontología. Recomendaciones de Vacunación Para Adultos y Mayores 2022–2023. 2022. Accessed June 29, 2023. https://www.segg.es/media/descargas/Recomendaciones-de-vacunacion-2022-2023.pdf.
61. Heppe Montero M, Gil-Prieto R, Walter S, Aleixandre Blanquer F, De Gil Á. Burden of severe bronchiolitis in children up to 2 years of age in Spain from 2012 to 2017. Hum Vaccin Immunother. 2022;18(1). https://doi.org/10.1080/21645515.2021.1883379.
62. Gea-Izquierdo E, Gil-Prieto R, Hernández-Barrera V, Gil-de-Miguel Á. Respiratory syncytial virus-associated hospitalization in children aged < 2 years in Spain from 2018 to 2021. Hum Vaccin Immunother. 2023;19(2). https://doi.org/10.1080/21645515.2023.2231818.
63. Mao Z, Li X, Dacosta-Urbieta A, et al. Economic burden and health-related quality-of-life among infants with respiratory syncytial virus infection: a multi-country prospective cohort study in Europe. Vaccine. 2023;41(16):2707–15. https://doi.org/10.1016/J.VACCINE.2023.03.024.
64. de Gil Á, Eiros Bouza JM, Martínez Alcorta LI, et al. Direct Medical costs of four vaccine-preventable infectious diseases in older adults in Spain. Pharmacoecon Open. 2022;6(4):509. https://doi.org/10.1007/S41669-022-00329-3.
65. Kristensen M, Van Lier A, Eilers R, et al. Burden of four vaccine preventable diseases in older adults. Vaccine. 2016;34(7):942–9. https://doi.org/10.1016/J.VACCINE.2015.12.052.
66. Li Y, Wang X, Blau DM, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. Lancet. 2022;399(10340):2047–64. https://doi.org/10.1016/S0140-6736(22)00478-0.
67. Bont L, Checchia PA, Fauroux B, et al. Defining the epidemiology and burden of severe respiratory syncytial virus infection among infants and children in Western Countries. Infect Dis Ther. 2016;5(3):271–98. https://doi.org/10.1007/S40121-016-0123-0.
68. Mira-Iglesias A, Demont C, López-Labrador FX, et al. Role of age and birth month in infants hospitalized with RSV-confirmed disease in the Valencia Region, Spain. Influenza Other Respir Viruses. 2022;16(2):328–39. https://doi.org/10.1111/IRV.12937.
69. Muñoz-Quiles C, López-Lacort M, Úbeda-Sansano I, et al. Population-based Analysis of Bronchiolitis Epidemiology in Valencia, Spain. Pediatr Infect Dis J. 2016;35(3):275–80. https://doi.org/10.1097/INF.0000000000000993.
70. Viguria N, Martínez-Baz I, Moreno-Galarraga L, Sierrasesúmaga L, Salcedo B, Castilla J. Respiratory syncytial virus hospitalization in children in northern Spain. PLoS ONE. 2018;13(11). https://doi.org/10.1371/JOURNAL.PONE.0206474.
71. Servia-Dopazo M, Purriños-Hermida MJ, Pérez S, et al. [Usefulness of the microbiological surveillance of respiratory syncytial virus in Galicia (Spain): 2008–2017]. Gac Sanit. 2020;34(5):474–9. https://doi.org/10.1016/J.GACETA.2018.11.009.
72. Álvarez García FJ, Cilleruelo Ortega MJ, Álvarez Aldeán J, et al. Calendario De inmunizaciones de la Asociación Española De Pediatría: recomendaciones 2023. Pediatr (Engl Ed). 2023;98(1):58e. 1-58.e10.
73. Simões EAF, Madhi SA, Muller WJ, et al. Efficacy of nirsevimab against respiratory syncytial virus lower respiratory tract infections in preterm and term infants, and pharmacokinetic extrapolation to infants with congenital heart disease and chronic lung disease: a pooled analysis of randomised controlled trials. Lancet Child Adolesc Health. 2023;7(3):180–9. https://doi.org/10.1016/S2352-4642(22)00321-2.
74. SIVIC - VRS, Accessed. January 19, 2023. https://sivic.salut.gencat.cat/vrs?ftemporada=13.
75. Virus Sincitial Respiratorio - Consellería de Sanidade - Servizo Galego de Saúde. Accessed March 19. 2023. https://www.sergas.es/Saude-publica/Virus-Sincitial-Respiratorio?idioma=es.
76. den Boon S, Ahmed S, Sarker AR. Economic evaluations of immunization programs as an indispensable tool for policymakers. BMC Health Serv Res. 2023;23(1):1–3. https://doi.org/10.1186/S12913-023-10071-Z/METRICS.
77. Plataforma de Contratación del Sector Público. Accessed February 20. 2023. https://contrataciondelestado.es/wps/portal/plataforma.

78. Sistema Nacional de Salud. Calendario Común de Vacunación a Lo Largo de Toda La Vida. 2022. https://www.sanidad.gob.es/areas/promocionPrevencion/vacunaciones/calendario-y-coberturas/calendario/docs/CalendarioVacunacion_Todalavida_2022.pdf.
79. Pumarola T, Díez-Domingo J, Martinón-Torres F, et al. Excess hospitalizations and mortality associated with seasonal influenza in Spain, 2008–2018. BMC Infect Dis. 2023;23(1):86. https://doi.org/10.1186/S12879-023-08015-3.
80. Vallée A. Underestimation of the number of COVID-19 cases, an epidemiological threat. Epidemiol Infect. 2022;150. https://doi.org/10.1017/S0950268822001728.
81. Duong D. What RSV interventions are in the research pipeline? CMAJ. 2023;195(1):E19–20. https://doi.org/10.1503/CMAJ.1096031.

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