



**Superior
Health Council**

**VACCINATION AGAINST RSV
(ADULTS)**

**SEPTEMBER 2023
SHC № 9725**



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Federal Public Service Health, Food Chain Safety
and Environment

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**ADVISORY REPORT OF THE SUPERIOR HEALTH COUNCIL no.
9725**

Vaccination against RSV (adults)

In this scientific advisory report, which offers guidance to public health policy-makers, the Superior Health Council of Belgium provides recommendations on vaccination against RSV (adults).

This version was validated by the Board on
Wednesday 6th of September 2023¹

I INTRODUCTION AND ISSUE

Respiratory syncytial virus (RSV) is a highly contagious human pathogen that causes respiratory tract infections in people of all ages.

RSV is usually spread through direct contact with the virus, such as droplets from another person's cough or sneeze contacting your eyes, nose, or mouth. It can also be spread by touching a surface that has the virus on it, like a doorknob, and then touching your face before washing your hands.

RSV infection does not confer long-term immunity; therefore, re-infection with RSV occurs throughout life and is common in all age groups. Usually, re-infections manifest as common acute upper respiratory tract infections. However, in more vulnerable individuals (e.g., immunocompromised persons or older adults), reinfections can also lead to more severe diseases, involving the lower respiratory tract and lower respiratory tract disease (LTRD).

In adults, the highest burden of disease is in older people and those with comorbidities such as lung or heart disease and diabetes. In these patient populations, RSV can exacerbate conditions like chronic obstructive pulmonary disease (COPD), asthma, chronic heart failure leading to severe outcomes such as acute respiratory failure, pneumonia, hospitalisation, and death.

Treatment for RSV in older adults is limited to supportive care consisting of supplemental oxygen, intravenous fluids and bronchodilators. In addition, inhaled and systemic corticosteroids are often prescribed in patients with asthma or COPD. Antibiotic prescription, appropriate or not, is frequent among patients hospitalized with RSV infection. Until recently there was no vaccine to prevent RSV for older adults on the market.

¹ The Council reserves the right to make minor typographical amendments to this document at any time. On the other hand, amendments that alter its content are automatically included in an erratum. In this case, a new version of the advisory report is issued.

There are currently 3 RSV vaccines that have gone through phase III trials, Arexvy® (GSK), Abrysvo® (Pfizer) and the Moderna RSV vaccine, with potential licensure timelines for 2023 or early 2024.

In June 2023, the EC granted market authorisation for Arexvy® (GSK). Arexvy® is on the Belgian market since mid-August 2023.

https://www.ema.europa.eu/en/documents/assessment-report/arexvy-epar-public-assessment-report_.pdf

In August 2023, the EC granted marketing authorisation for Abrysvo® (Pfizer), this vaccine is expected to be on the Belgian market mid December 2023.

Arexvy® is a vaccine authorised for adults 60 years of age and older to protect them against lower respiratory tract disease (LRTD; diseases of the lungs such as bronchitis or pneumonia) caused by RSV.

This advisory report aims to provide recommendations on risk groups to be vaccinated against RSV.

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III CONCLUSIONS AND RECOMMENDATIONS

Arexvy® (GSK), is on the Belgian market since mid-august 2023. Two more vaccines will become available in the coming months (Pfizer and Moderna).

Arexvy® has shown efficacy in the prevention of RSV associated lower-respiratory tract infection although data on the efficacy on the prevention of severe disease (i.e. hospitalisation, need for oxygen) is very limited but more data will be available in the coming months. Data on the efficacy amongst very frail or immunosuppressed patients is also lacking.

At this moment, there is no head-to-head comparison between the vaccines against RSV coming to the market.

Risk factors for severe RSV disease include:

- Chronic Respiratory Diseases (COPD, asthma, bronchiectasis, interstitial lung diseases, chronic respiratory failure)
- Chronic Heart Failure
- Chronic Kidney Disease
- Diabetes
- Obesity
- Immunodeficiency, including patients with solid cancer or haematologic malignancy, use of immunosuppressive medications, solid organ transplantation, allogenic HCT
- Institutionalized Patients

Considering the high morbidity and mortality associated with RSV infection among patients with known risk factors, the lack of effective anti-viral therapy but also the limited data on vaccine efficacy (VE) on severe outcome especially in frail patients, the Superior Health Council concludes that RSV vaccination can be offered on an individual basis to high risk patients over 60 years old with at least one risk factor of severe RSV disease.

The recommended dose is one single injection IM.

Considering the pre-COVID seasonality of RSV, September/October are the preferred months to be vaccinated.

Recent data from the 2nd season analysis (Arexvy®) showed that VE remains durable over 2 seasons (after receiving only one dose) in adults with underlying comorbidities and across advancing ages (from presentation GSK, hearing 29/06/2023).

Therefore, the optimal timing for a revaccination/booster still needs to be determined.

The SHC would like to emphasise on the need of increased surveillance to help to follow the clinical impact on RSV infection and the vaccine effectiveness especially in frail and/or immunosuppressed patients.

This advisory report will be revised as soon as new important data will become available or when new vaccines enter the market.

Keywords

| Keywords | Sleutelwoorden | Mots clés | Schlüsselwörter |
|-----------------------------|-------------------------------------|-------------------------------------|--|
| Respiratory Syncytial Virus | <i>Respiratoir Syncytieel Virus</i> | <i>Virus respiratoire syncytial</i> | <i>Respiratorisches Synzytialvirus</i> |
| Human | <i>Mens</i> | <i>Humain</i> | <i>Mensch</i> |
| Vaccination | <i>Vaccinatie</i> | <i>Vaccination</i> | <i>Impfung</i> |
| Elderly | <i>Ouderen</i> | <i>Personnes âgées</i> | <i>Ältere Menschen</i> |
| Risk Factors | <i>Risicofactoren</i> | <i>Facteurs de risque</i> | <i>Risikofaktoren</i> |

IV METHODOLOGY

After analysing the request, the Board and the co-presidents of the NITAG identified the necessary fields of expertise. An *ad hoc* working group was set up which included experts in microbiology, epidemiology, infectiology, immunology, intensive care, general medicine, geriatrics and pneumology.

The experts of this working group provided a general and an *ad hoc* declaration of interests and the Committee on Deontology assessed the potential risk of conflicts of interest.

This advisory report is based on a review of the scientific literature published in both scientific journals and reports from national and international organisations competent in this field (peer-reviewed), as well as on the opinion of the experts.

Once the advisory report was endorsed by the working group and by the NITAG, it was ultimately validated by the Board.

V ELABORATION AND ARGUMENTATION

List of abbreviations used

| | |
|-------|--|
| CFP | Case Fatality Proportion |
| CFR | Case Fatality Ratio |
| COPD | Chronic Obstructive Pulmonary Disease |
| ER | Emergency Room |
| GBD | Global Burden of Diseases |
| GP | General Practitioner |
| ICU | Intensive Care Unit |
| IgA | Immunoglobuline A |
| IgG | Immunoglobuline G |
| LRTD | Lower Respiratory Tract Disease |
| NITAG | National Immunization Technical Advisory Group |
| NK | Natural Killer |
| NPI | Non-Pharmaceutical Interventions |
| RSV | Respiratory Syncytial Virus |
| SARI | Severe Cute Respiratory Infection |
| SHC | Superior Health Council |
| SPC | Summary of Product Characteristics |
| VE | Vaccine Effectiveness |

1 RSV

1.1 Epidemiology

1.1.1 *Worldwide*

Lower respiratory tract infections were the sixth leading cause of total disability-adjusted life years worldwide in 2019, according to the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) among persons aged 75 years and older. Among persons aged 50 - 74 years, it was the 13th leading cause [1]. In 2016, the number of episodes of acute lower respiratory tract infections in people aged 70 years and older was estimated at 63 million episodes worldwide and 6.1 million episodes in Western Europe. The number of deaths due to acute lower respiratory tract infections was estimated at 1 080 958 deaths worldwide and 125 000 deaths in Western Europe [2, 3]

As for older persons, due to the often scarce data on aetiology, there is wide variation in estimating the annual number of episodes and deaths that could be specifically attributed to RSV in the years before COVID-19. Estimates range between 1.5 million symptomatic episodes in persons aged 50 years and older in industrialised countries to 2.5 million episodes in persons aged 70 years and older worldwide. The number of deaths due to RSV infections was estimated at 76 600 worldwide, including 22 000 deaths in persons aged 70 years and older [2, 4].

In 2022 systematic review on the burden of RSV disease in older and high-risk adults in developed countries, RSV was found to account for 4.66 % (95 % CI: 3.34 - 6.48 %) of symptomatic respiratory tract infections in annual studies and 7.80 % (95 % CI: 5.77 - 10.45 %) in seasonal studies. The RSV-related case fatality ratio (CFR) was estimated to be 8.18 % (95 % CI 5.54 - 11.94 %). Among high-risk (i.e. patients with lung and heart diseases, diabetes, chronic kidney disease, immunosuppression, dementia, functional impairment or institutionalized) adults, 7.03 % (95 % CI: 5.18 - 9.48 %) of symptomatic respiratory tract infections in annual studies and 7.69 % (95 % CI: 6.23 - 9.46 %) in seasonal studies were attributed to RSV. The RSV-related case fatality ratio in this high-risk group was estimated to be 9.88 % (95 % CI: 6.66 - 14.43 %) [5].

The Global Burden of Diseases, Injuries, and Risk Factors Study found that, unlike in young children, the number of disability-adjusted life years and of deaths from lower respiratory tract infections caused by RSV in persons aged 70 years and older has hardly changed since 1990. The sharp decrease in deaths from RSV infections in young children is not seen in persons aged 70 years and older, where death rates for pneumonia caused by RSV infection have barely decreased since 1990 [3]. Due to the ageing of the population, the absolute annual number of deaths attributed to RSV has increased in the last three decades.

Data on severe complications and healthcare utilisation among older adults are very scarce. The few available data show that overall, an estimated 27 % of older RSV patients develop pneumonia. Respectively 24 % of older adults with RSV infection and 33 % of high-risk RSV-positive patients require hospitalisation and in 5 % require admission to intensive care (in both patient groups) [5].

Until spring 2020, RSV showed a strong seasonal and highly predictable circulation: epidemics from November to April in the northern hemisphere, between August and December in equatorial regions, and from April to August in the southern hemisphere. During the first phase of the COVID-19 pandemic in the autumn of 2020 and the first months of 2021, a sharp reduction in RSV infections was initially observed in many countries, most likely due to the implementation of non-pharmaceutical interventions (NPIs) such as increased hand hygiene, mask wearing, physical distance, closure of schools and day care centers. As the pandemic

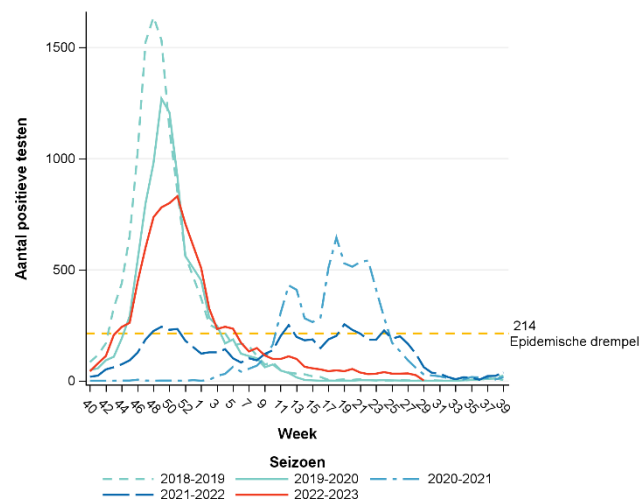
progressed, atypical peaks of RSV disease occurred outside the normal season [6]. In 2022, increased levels of RSV transmission were again seen during normal peak times, as well as outside of the typical seasons.

1.1.2 Belgium

In Belgium, the public health institute Sciensano monitors the transmissibility, severity and impact of RSV mainly through sentinel surveillance networks of laboratories, general practitioners and hospitals. Some of these surveillances collect clinical data as well as nasopharyngeal swabs.

Before COVID-19, high numbers of confirmed RSV diagnoses were reported by the sentinel laboratories every autumn, from mid-October to the end of January. The weeks with the highest incidences usually fell from early to mid-December. More than 80 % of the positive RSV tests were seen in children aged 0 - 2 years. Prior to 2016, fewer than 5 % of the positive test results pertained to individuals aged 64 years and above. Since 2016, the proportion of positive RSV tests in people aged 65 and over has increased. It is difficult to discern whether this is a result of changed testing practices (because of the growing understanding of the importance of RSV infections in the elderly and the increased use of multiplex panels) or a real increase in the relative number of infections in this age group.

As in other countries, in Belgium, in the first phase of the COVID-19 pandemic in 2020, almost no RSV infections were reported and, for the first time since the starting of surveillance in 1996, there was no autumn peak of RSV infections in Belgium. In 2021, exceptionally, an elevation in the number of RSV infections was seen in the period March - May, even exceeding the epidemic threshold. This peak was longer in duration than the pre-COVID-19 peaks. A spike of RSV infections was seen in autumn 2021, at the same time as the pre-COVID-19 peaks, but with a much lower intensity.



There were also multiple RSV epidemics in Belgium in 2022. As in 2021, March and April of 2022 saw a peak of RSV infections that exceeded the epidemic threshold. The number of infections decreased thereafter, but remained above baseline until a second epidemic in June 2022. After a decline in the number of infections in summer, a third epidemic of RSV infections was seen from the second week of November until the end of January 2023. This epidemic was of similar intensity as in the pre-COVID-19 years, but lasted one month longer and affected relatively more old persons (22 % of positive tests in persons aged 65 years and over). The fact that this peak coincided with simultaneous elevations of COVID-19, influenza and human metapneumovirus resulted in a very heavy burden on the healthcare system.

Surveillance by GP and hospital sentinel networks give an idea about the relative proportion of RSV infections among patients with flu-like symptoms and other signs of acute respiratory tract infections. In 2022, 17.1 % (95 % CI: 6.5 % - 33.6 %) of patients aged 65 years and over who consulted the GP because of flu-like symptoms or other signs of acute respiratory tract infection were affected by a confirmed RSV infection. Likewise, in the sentinel network of hospitals in 2022, 4.6 % (CI: 3.4 % - 6.1 %) of the patients aged 65 years and over who were admitted for a severe acute respiratory infection had a positive RSV PRC test at admission.

Pooled over all the seasons before 2021, in the SARI surveillance 7.3 % (CI: 6.5 % - 8.1 %) of the patients aged 65 years and over who were admitted for a severe acute respiratory infection had a positive RSV PRC test at admission, in line with the international cohorts [5]. The RSV-related case fatality ratio (CFR) in this age group was estimated to be 11.3 % (95 % CI: 7.6 - 16.0 %). Among the admitted RSV patients aged 65 years and over 14.2 % (95 % CI: 10.0 - 19.3 %) required transfer to ICU and pneumonia occurred in 25.1 % of the cases (95 % CI: 19.7 - 31.1 %)

The SARI surveillance yields an approximate minimum count of admissions. This is largely due to the stringent case definition that includes fever, even though RSV-infected patients are known to manifest fever less often compared to those infected with influenza. These estimates pertain to severe acute respiratory infection cases that have a confirmed RSV lab test at the point of admission. In the winter of 2022 - 2023, it was estimated that at least 1 100 patients aged 65 years and over were admitted to hospital for a confirmed RSV infection in Belgium (Incidence = 0.48/1 000). These estimates coincide with those published in a study by the European consortium, RESCEU. It was estimated that 3 340 patients (2 704 – 3 975) over 65 are hospitalized annually on average in Belgium (Incidence = 1.44/1 000). When considering all patients hospitalized in Europe for RSV every year, 92 % are over 65 years [7].

1.2 Physiopathology of severe RSV disease

Severe clinical manifestations of RSV infection are the results of lung immunopathology. It is recognized that severe manifestations are the results of different factors: lack of control of viral replication and viral clearance and subsequent inappropriate immune responses, leading to inflammation and tissue damage [8].

Viral entry and infection of the upper respiratory epithelium is blocked by specific mucosal antibodies (IgA), mucus, surfactant proteins and antimicrobial peptides such as cathelicidin. Different arms of the innate immune system allow an early control of the viral replication, including type I interferon, alveolar macrophages and NK cells.

Adaptive immune responses including systemic and lower respiratory tract IgG, cellular CD4+ and CD8+ T cells contribute both to clearance of the virus from the respiratory tract and immunopathology. The balance between the protection and immunopathology seems to depend on the polarization of CD4+ T cells. Th2 and Th17 CD4+ cells are associated with neutrophilic and eosinophilic inflammation while Th1 responses are not [9].

1.3 Symptoms/clinical aspects

A seminal study published in 2005 in the NEJM assessed the burden of RSV among healthy elderly patients and high-risk adults with chronic heart or lung disease. The study was prospective, during 4 consecutive winters in New York City. RSV was associated with a high proportion of calls and visits to physicians in the ambulatory settings. Emergency Room (ER) visits and hospitalization were restricted to high-risk adults with chronic lung or heart disease [10]. Moreover, in these at-risk patients, RSV infections may be associated with severe disease and complications at rates comparable to those of influenza infection.

Most frequently identified clinical symptoms among older adults were cough (86 %), weakness/malaise (86.7 %), shortness of breath (72.3 %), sputum (56,1 %) and fever

(53.3 %). It was estimated that among older adults, the rate of pneumonia was 27.44 %, hospitalization 24.48 %, and ICU admission 5.01 %. The overall case fatality proportion was 8.18 % (95 % CI: 5.54 - 11.94 %). Of note, a high proportion of older adults were treated with antibiotics (76.95 - 77.91 %). The seasonal incidence among high-risk adults was the highest among immunodeficient patients (260.89 (95 % CI 82.33 – 826.65) RSV cases per 1 000 person - years) followed by cardiopulmonary disease (19.15 (95 % CI 6.06 – 60.49) RSV cases per 1 000 person - years.) and institutionalized older adults (9.78 (95 % CI 3.18 – 20.04) RSV cases per 1 000 person - years). In the case of high-risk adults, 32.82 % required hospitalization, and ICU admission was necessary for 26.74 %. The RSV-related case fatality proportion (CFP) was 9.88 % (95 % CI 6.66 - 14.43) [5].

Unpublished findings of the aforementioned Belgian SARI surveillance data facilitated the profiling of RSV-positive patients who were admitted with SARI over the course of four influenza seasons. Median age was comparable to influenza patients (71.8 years). There was a similar proportion of patients with diabetes (14.9 %), obesity (11.5 %) and immunosuppression (18.2 %). Compared to influenza, there was a significantly higher proportion of patients with heart disease (39.9 % vs 31.5 %, $p = 0.04$). Meanwhile, the proportion of patients with lung diseases was roughly equivalent (31.1 % vs 27.4 %). Similar proportions of pneumonia on x-ray (25 %), ARDS (3.5 %), ICU admission (9.5 %) and mortality (7.4 %) were found in RSV patients as compared to influenza patients. Of note, RSV patients had 1 day longer length of stay (12.7 vs 11.6 days, $p = 0.04$) [11]. Findings from a tertiary center in Wallonia revealed a higher incidence of ICU admissions among RSV patients compared to those with influenza, even though the mortality rate was comparable between the two groups. [22].

A recent Belgian-French multicentric study analyses of 309 cases of RSV-infected patients admitted to ICU between 2011 and 2018 found high mortality after ICU admission (23.9 %), comparable to patients with influenza infection (25.6 %). The study highlighted several prominent risk factors. Among these, the most common was underlying respiratory conditions, which accounted for 60.2 % of cases. This category included conditions such as COPD (38.8 %), asthma (12.6 %), interstitial lung diseases, and bronchiectasis. Immunodeficiency was found in 35 % of patients, including conditions like solid organ transplantation, solid cancer or hematological malignancy, and the use of immunosuppressive therapy. Chronic heart failure was reported as a risk factor in 17.2 % of cases. Chronic kidney disease was identified in 12.9 % of cases. Diabetes was present in 22.3 % of the cases studied. Lastly, obesity was noted as a risk factor in 16.6 % of the patients. Mean age was 67.2 years, comparable to influenza patients (65.3). ARDS was reported in 14.2 % of the patients with 36.6 % of the patients requiring invasive ventilation. Bacterial respiratory co infection were present in 27,2 % of the case, similar to influenza infected patients [12].

1.4 Immune response after RSV infection

It is considered that RSV infection universally occurs in childhood and that 100 % of the population has been infected. Infection-induced immunity is not sufficient to prevent re-infection but experimental models of RSV infection indicate that mucosal IgA plays an important role in symptom intensity [14].

The increase of severity of RSV disease in elderly adults is likely multifactorial and involves a decrease in both the quality and quantity of immune responses. Notably, decreased frequency of RSV-specific CD4+ and CD8+ T cells, are reported in elderly. There is also a shift toward Th2-biased responses, associated with higher immunopathology. Lower levels of RSV-specific neutralizing antibodies are associated with increased risk of RSV infection and RSV severe disease [9]. Following RSV infection, high titers of neutralizing antibody are induced, indicating that elderly are able to produce RSV-specific antibodies. Cross neutralisation is reported between the two subtype, RSV A and RSV B.

1.5 History of RSV Vaccines

The first RSV vaccine developed in the 1960 (formalin inactivated RSV) was associated with a higher rate of hospitalization and more severe respiratory disease upon exposure to natural RSV infection among vaccinated children. Post-mortem studies also showed that the lungs of vaccinated children had more severe inflammation than unvaccinated children who died from RSV infection. The mechanisms of vaccine-induced disease enhancement include induction of non-neutralizing antibodies leading to antibody-dependent enhancement, i.e. antibody binding to the virus and promoting its entry into the immune cells, leading to uncontrolled viral replication and exaggerated immune response. The formalin inactivated vaccine was also associated with TH2-biased immune response in animal models, which could also explain the more severe immunopathology among vaccine recipients [9].

A breakthrough in the understanding of protective immune responses toward RSV occurred in 2015 when it was discovered that the neutralizing activity was restricted to an antigen expressed in the prefusion form of the F glycoprotein, located on the virus. The antigenic site II is a relatively small region on the surface of the F protein that is exposed when the protein undergoes a conformational change during the fusion process. Antibodies that recognize and bind to this region can block the interaction between the F protein and its receptor on host cells, thereby preventing viral entry and infection.

Accordingly, vaccines based on the post-fusion conformation of the F protein have failed in clinical trials [15].

1.6 RSV Vaccines

1.6.1 *Arexvy® (GSK) on the Belgian market mid-august 2023*

GSK has engineered an RSV preF vaccine, Arexvy®, combined with the AS01 adjuvant for increasing RSV-specific CD4+ T-cell frequencies [20]. In pre-clinical trials formulations with AS01E were less reactogenic than those with AS01B (which contains twice the dose of immunostimulants). Therefore, an AS01E-adjuvanted formulation was selected for further development.

GSK vaccine include 120 µg of RSV PreF3 recombinant antigen derived from the RSV fusion surface glycoprotein of an RSV-A strain and is adjuvanted with the AS01 adjuvant, already in use in the malaria and zoster vaccines. The adjuvant is known to increase the recruitment of antigen presenting cells at the level of injection and is associated with strong neutralising antibody and polyfunctional T cells responses [16, 17].

Vaccine efficacy Arexvy® (from KCE Report - in preparation)

The vaccine efficacy was assessed in a large phase III trial (AReSVi-006) that included 24,966 participants randomized to Arexvy® or placebo [20]. **Vaccine efficacy was 82.6 %** (96.9 % CI: 57.9; 94.1) **for LRTI² and 94.1 %** (96.9 % CI: 62.4; 99.9) **for severe LRTI³**. Incidence of LRTI was low (5.8 per 1 000 person - years overall; 2.5 % for severe LRTI). Absolute rate reduction was modest (4.8 per 1 000 PY for LRTI, and 2.4 per 1 000 PY for severe LRTI). Efficacy against LRTI was similar across groups with or without baseline coexisting conditions, with wide confidence intervals. For severe LRTI, no stratified results were provided [20].

² With at least two lower respiratory symptoms or signs (including at least one lower respiratory sign) or at least three lower respiratory symptoms lasting for at least 24 hours. Lower respiratory signs were new or increased wheezing; new or increased crackles/ronchi based on chest auscultation; respiratory rate ≥ 20 respirations/min; low or decreased oxygen saturation (= O₂ saturation $< 95\%$ or $\leq 90\%$ if pre-season baseline is $< 95\%$); or need for oxygen supplementation.

³ Severe LRTI was a secondary end point. It was defined either on the basis of clinical signs (at least 2 lower respiratory signs) or investigator assessment or on the basis of receipt of supportive therapy.

The GRADE framework was used to evaluate evidence quality. There was no data for most of the primary efficacy outcomes, i.e. no data on mortality rate, hospitalisation rate, hospitalisation LOS. For rate of severe LRTI, some results were provided in the AReSVi-006 trial (GSK) (see table below). Evidence was downgraded by one level due to indirectness of results, as the trial population included a minority of individuals at high risk for a severe RSV infection and thus it is not representative of the target population. Notably, patients with immunosuppression and unstable co-morbidities were excluded. Indeed trial participants were relatively young, with the majority being younger than 70 years (55.9 % were aged 60 - 69 years), and approximately 70 % of the participants in each group had no coexisting conditions at baseline. Downgrading by one more level could be justified as critical outcomes such as mortality rate or hospitalisation rate are not documented. Additionally, the results presented are from the interim analysis of one unique trial, and it has been demonstrated that such analysis can yield more positive results than observed in subsequent trials or in real world data. Downgrading further the evidence by one level could be considered. The overall certainty of evidence is considered moderate to low.

Note: The GRADE table must be completed for the few other outcomes. But we already know that evidence can be at best moderate to low as this is the level for the only documented crucial outcome.

Table: GRADE

| Certainty assessment | | | | | | | Summary of findings | | | | |
|--|--------------|---------------|--------------|-------------|---------|-------------------------------|---|--------------|---------------------------|-------------------------------------|--------------------------|
| Total number of person - years (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Remarks | Overall certainty of evidence | Number of events per 1 000 person - years | | Relative effect (95 % CI) | Anticipated absolute effects | |
| | | | | | | | With placebo or no vaccination | With vaccine | | Rate with placebo or no vaccination | Rate difference with RZV |

Severe LRTI in AreSVi-006 trial:

| | | | | | | | | | | | |
|--------------------------------------|-------------|----|----------|-------------|------------------|-----------------|----|---|----------------------------------|---------------------|---|
| 24 966 (1 RCT) FU: 6.7 m (median) | not serious | NA | Indirect | Not serious | Interim analysis | Moderate to low | 17 | 1 | RR 0.06 (0.01 to 0.38) | 2.5 per 1 000 PY | 2.4 fewer per 1 000 PY (from 1.1 fewer to 3.5 fewer) |
|--------------------------------------|-------------|----|----------|-------------|------------------|-----------------|----|---|----------------------------------|---------------------|---|

Adverse events Arexvy® (from SPC)

https://www.ema.europa.eu/en/documents/product-information/arexvy-epar-product-information_en.pdf

There was no difference in the rate of serious adverse events between vaccine and placebo recipient.

The safety profile for **Arexvy®** is based on a placebo-controlled Phase III clinical study (conducted in Europe, North America, Asia and Southern hemisphere) in adults ≥ 60 years of age in which more than 12 000 adults received one dose of Arexvy® and more than 12 000 received placebo. In study participants 60 years of age and older, the most commonly reported adverse reactions were injection site pain (61 %), fatigue (34 %), myalgia (29 %), headache (28 %), and arthralgia (18 %). These adverse reactions were usually mild or moderate in intensity and resolved within a few days after vaccination.

Most other adverse reactions were uncommon and similarly reported between the study groups.

Of interest is 1 case of Guillain-Barré syndrome occurring 9 days after vaccination which was assessed as related to the vaccine by the investigator.

Coadministration Arexvy® (from SPC)

https://www.ema.europa.eu/en/documents/product-information/arexvy-epar-product-information_en.pdf

Arexvy® may be administered concomitantly with seasonal influenza vaccine (quadrivalent, standard dose, unadjuvanted, inactivated). In a randomised study in adults 60 years of age and older, the criteria for non-inferiority of the immune responses in the co-administration versus the separate administration group were met. However, numerically lower RSV A and B neutralizing titres and numerically lower influenza A and B haemagglutination inhibition titres were observed when Arexvy® and inactivated seasonal influenza vaccine were co-administered than when they were administered separately. The clinical relevance of this finding is unknown. There are no data on co-administration with high dose or adjuvanted seasonal influenza vaccines.

If Arexvy® is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites.

Concomitant administration of Arexvy® with other vaccines such as COVID-19 and pneumococcal vaccines has not been studied.

1.6.2 *Abrysvo® (Pfizer, expected to be on the Belgian market by end 2023)*

The active substances of Abrysvo® are two recombinant stabilised RSV prefusion F antigens representing the subgroups RSV-A and RSV-B. Abrysvo® induces the production of specific antibodies against the prefusion F protein, which inhibits RSV infection and thereby protects against RSV-associated LRT disease.

Pfizer vaccine include 60 µg of RSV preF from both RSV A and RSV B strains.

The vaccine is currently being tested in pivotal phase 3 trial, the RSV Vaccine Efficacy Study in Older Adults Immunized against RSV Disease (RENOIR), involving adults who were at least 60 years of age. A second trial, the Maternal Immunization Study for Safety and Efficacy (MATISSE) evaluates the efficacy and safety of maternal RSVpreF vaccination in preventing RSV-associated lower respiratory tract illness in infants [21].

Vaccine efficacy Abrysvo®

Vaccine efficacy in older adults was 66.7 % (96.66 % CI: 28.8; 85.8) and **85.7 %** (96.66 % CI: 32.0; 98.7) in patients with **RSV-associated LRTI with at least 2 signs or symptoms⁴ and 3 signs**, respectively [19]. Confidence intervals were wide. Efficacy against severe LRTI was not reported because the number of events was too low. The incidence of LRTI was low (3.68 per 1 000 person - years), possibly reflecting altered epidemiologic characteristics of RSV because of the Covid-19 pandemic. Absolute risk differences were thus modest (2.39 per 1 000 PY for LRTI, 1.30 per 1 000 PY for severe LRTI). Subgroup analyses of the primary end points according to participant age group (60 to 69 years, 70 to 79 years, or ≥ 80 years) and risk status (no prespecified high-risk conditions or ≥ 1 prespecified high-risk condition) indicated similar vaccine efficacy across subgroups, with wide confidence intervals reflecting small subgroup sizes.

⁴ Cough, wheezing, sputum production, shortness of breath, or tachypnea, lasting at least 24h.

Adverse events Abrysvo®

Vaccine recipients had more local reactions than by placebo recipients (12 % vs. 7 %); the incidence of systemic events was similar in the two groups (27 % and 26 %, respectively). These events were generally self-limiting and mild to moderate in severity.

The incidence of serious adverse events was comparable in both groups at 2.3 %. Out of these, investigators deemed three serious adverse events as potentially linked to the trial intervention. The first was a delayed allergic reaction occurring seven hours post-injection of the RSV preF vaccine, with the patient fully recovering on the same day. The second event was a diagnosis of Miller–Fisher syndrome, a variant of Guillain–Barré syndrome characterized by ophthalmoplegia, ataxia, and areflexia. The final event was the identification of acute inflammatory demyelinating polyradiculoneuropathy, consistent with Guillain–Barré syndrome, that manifested seven days post-injection.

1.6.3 Moderna Vaccine (expected to be on the Belgian market Q1 2024)

First data presented by Moderna (Study 301) amongst adults ≥ 60 years showed a VE of **83.7 %** (66.0 % - 92.2 %) against LRTD with at least 2 symptoms and **82.4 % (34.8 % - 95.3 %)** against LRTD with at least 3 symptoms.

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VII COMPOSITION OF THE WORKING GROUP

The composition of the Committee and that of the Board as well as the list of experts appointed by Royal Decree are available on the following website: [About us](#).

All experts joined the working group *in a private capacity*. Their general declarations of interests as well as those of the members of the Committee and the Board can be viewed on the SHC website (site: [conflicts of interest](#)).

The following experts were involved in drawing up and endorsing this advisory report. The working group was chaired by **Nicolas DAUBY**; the scientific secretary were Veerle MERTENS and Fabrice PETERS.

| | | |
|-------------------------------------|--|-----------------------------|
| ANDRE Emmanuel | Medical Microbiology | <i>CU Saint-Luc, KUL</i> |
| BOSSUYT Nathalie | Epidemiology | <i>Sciensano</i> |
| CALLENS Steven | Infectiology, internal medicine | <i>UZ Gent</i> |
| DAUBY Nicolas | Infectiology, medical immunology | <i>CHU Saint-Pierre/ULB</i> |
| DE SCHEERDER Marie-Angélique | Internal Medicine, infectious diseases, travel medicine, HIV | <i>UZ Gent</i> |
| DELAERE Bénédicte | Infectiology | <i>UCL Mont-Godinne</i> |
| DERDELINCKX Inge | Infectiology | <i>UZ Leuven</i> |
| GRIMALDI David | Intensive Care | <i>Erasme</i> |
| REYNDERS Marijke | Medical Microbiologist | <i>AZ Sint-Jan</i> |
| ROBERFROID Dominique | Epidemiology | <i>KCE, UNamur</i> |
| SCHOEVAERDTS Didier | Geriatrics | <i>CHU UCL Namur</i> |
| SPODEN Julie | General Medicine | <i>SSMG</i> |
| VAN BRAECKEL Eva | Pneumology, ID physician | <i>UZ Gent</i> |
| VAN LAETHEM Yves | Infectiology, vaccinology, travel clinic | <i>CHU Saint-Pierre</i> |

The standing working group Vaccination (NITAG) has endorsed the advisory report. The following experts send their approval by mail by August 28 2023. The standing working group was chaired by **David TUERLINCKX and Steven CALLENS**; the scientific secretary were Veerle MERTENS and Fabrice PETERS.

| | | |
|-------------------------------------|--|---------------------|
| BLUMENTAL Sophie | Pediatric Infectious Disease | <i>ULB - HUDERF</i> |
| BOIY Tine | Pediatrics | <i>UZA</i> |
| CALLENS Steven | Internal Medicine, infectiology | <i>UZ Gent</i> |
| CORNELISSEN Laura | Epidemiology, obstetrics, gynaecology | <i>Sciensano</i> |
| DE LOOF Geert | General Medicine | <i>BCFI</i> |
| DE SCHEERDER Marie-Angélique | Internal Medicine, infectiology, travel clinic, HIV | <i>UZ Gent</i> |
| MICHIELS Barbara | General Medicine | <i>UAntwerpen</i> |
| PELEMAN Renaat | Infectiology and vaccinology | <i>UZ Gent</i> |
| ROBERFROID Dominique | Epidemiology | <i>KCE, UNamur</i> |
| SOENTJENS Patrick | Internal Medicine, tropical infectious diseases, vaccinology | <i>ITM</i> |

| | | |
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| VAN LAETHEM Yves | Infectiology, vaccinology and travel medicine | <i>ex-CHU Saint-Pierre, ULB</i> |
| VERHAEGEN Jan | Microbiology, bacteriology | <i>UZ Leuven</i> |

The following administrations and/or ministerial cabinets were heard:

| | | |
|---------------|-------------------|---------------|
| DAEMS Joël | Directorate Drugs | RIZIV - INAMI |
| THEETEN Heidi | Vaccinology | VAZG |

About the Superior Health Council (SHC)

The Superior Health Council is a federal advisory body. Its secretariat is provided by the Federal Public Service Health, Food Chain Safety and Environment. It was founded in 1849 and provides scientific advisory reports on public health issues to the Ministers of Public Health and the Environment, their administration, and a few agencies. These advisory reports are drawn up on request or on the SHC's own initiative. The SHC aims at giving guidance to political decision-makers on public health matters. It does this on the basis of the most recent scientific knowledge.

Apart from its 25-member internal secretariat, the Council draws upon a vast network of over 500 experts (university professors, staff members of scientific institutions, stakeholders in the field, etc.), 300 of whom are appointed experts of the Council by Royal Decree. These experts meet in multidisciplinary working groups in order to write the advisory reports.

As an official body, the Superior Health Council takes the view that it is of key importance to guarantee that the scientific advisory reports it issues are neutral and impartial. In order to do so, it has provided itself with a structure, rules and procedures with which these requirements can be met efficiently at each stage of the coming into being of the advisory reports. The key stages in the latter process are: 1) the preliminary analysis of the request, 2) the appointing of the experts within the working groups, 3) the implementation of the procedures for managing potential conflicts of interest (based on the declaration of interest, the analysis of possible conflicts of interest, and a Committee on Professional Conduct) as well as the final endorsement of the advisory reports by the Board (ultimate decision-making body of the SHC, which consists of 30 members from the pool of appointed experts). This coherent set of procedures aims at allowing the SHC to issue advisory reports that are based on the highest level of scientific expertise available whilst maintaining all possible impartiality.

Once they have been endorsed by the Board, the advisory reports are sent to those who requested them as well as to the Minister of Public Health and are subsequently published on the SHC website (www.hgr-css.be). Some of them are also communicated to the press and to specific target groups (healthcare professionals, universities, politicians, consumer organisations, etc.).

In order to receive notification about the activities and publications of the SHC, please contact: info.hgr-css@health.belgium.be.

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