Medicines Adverse Reactions Committee

Meeting date	12/06/2025	Agenda item	3.2.2
Title	**Arexvy and Guillain-Barré syndrome (GBS)**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Product name Arexvy	**Active ingredient** recombinant respiratory syncytial virus (RSV) pre-fusion F protein		**Sponsor** GlaxoSmithKline
Pharmac funding	Not funded		
Previous MARC meetings	Not previously discussed. The Arexvy EU RMP version 1.0 was reviewed by the MARC at the Jun 2024 meeting		
International action	US FDA drug safety communication (7 Jan 2025) on adding warning in their RSV vaccine data sheets		
Prescriber Update	None		
Classification	Prescription medicine that can be administered by pharmacists		
Usage data	Approximately 1,600 people have been vaccinated with Arexvy		

Advice sought	**The Committee is asked to advise on the following:**
	• The strength of the evidence for an association between Arexvy and GBS, based on:
	  ○ FDA's postmarket study for observed vs. expected rates and self-controlled case series (SCCS) analyses.
	  ○ CDC's rapid cycle analysis (RCA).
	  ○ Please comment on the methods, results, strengths and limitations of the above FDA and CDC analyses.
	[redacted]
	• If the Arexvy NZ data sheet requires updating to include information on GBS.
	  ○ If so, what information should be included and in which sections (eg, warnings and precautions, undesirable effects etc.)
	• If any other regulatory action is needed (eg, safety communication on the Medsafe website, article in *Prescriber Update* etc.).		

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1 PURPOSE

In January 2025, the United States Food and Drug Administration (US FDA) published a safety communication informing that a new warning on Guillain-Barré syndrome (GBS) has been added to the US data sheets for the respiratory syncytial virus (RSV) vaccines Abrysvo and Arexvy. Based on FDA's evaluation of data from clinical trials, reports to the Vaccine Adverse Event Reporting System (VAERS), and a postmarketing study conducted by them, FDA has determined that the overall body of evidence suggests increased risks of GBS with Abrysvo and Arexvy, but that available evidence is insufficient to establish a causal relationship.

Data from the FDA's postmarket study is provided in this report along with other relevant information, including information in the published scientific literature, the sponsor's review, and worldwide spontaneous case reports.

Currently, Arexvy is the only RSV vaccine approved for use in New Zealand. Therefore, information in this paper focuses on Arexvy, but data on other RSV vaccines is included where appropriate.

2 BACKGROUND

2.1 Guillain-Barré syndrome (GBS)

Guillain-Barré syndrome (GBS) is characterised by various degrees of weakness, sensory abnormalities, and autonomic dysfunction due to damage to peripheral nerves and nerve roots. The underlying aetiology and pathophysiology are not completely understood but it is thought that immune stimulation plays a central role in its pathogenesis. GBS is considered to be an immune-mediated disorder resulting from generation of autoimmune antibodies and/or inflammatory cells which cross-react with epitopes on peripheral nerves and roots, leading to demyelination, axonal damage or both [1].

The Brighton Collaboration's work on Guillain Barré syndrome is most often cited in reviews investigating its association with vaccines. The publication in *Vaccine* by Sejvar et al [1], the companion guide, and the algorithm are all publicly available.

2.1.1 Epidemiology

The incidence of GBS has been estimated at between 0.4 and 4.0 cases per 100,000 population per year. Most well-designed prospective studies in developed countries suggest an incidence of 1-2 per 100,000 population per year. In North America and Europe, GBS is more common in adults and steadily increases with age. Many studies suggest men are more likely to be affected than women [1].

Most cases are sporadic and there does not appear to be a seasonal pattern, with some exceptions [1]. A 2015 systematic review and meta-analysis [2] looking at the seasonality in incidence of GBS globally found there was a greater incidence of GBS in winter in Western countries (IRR 1.28), the Far East (IRR 1.20) and Middle East (IRR 1.12), with a lower incidence in the Indian subcontinent (IRR 0.86) and Latin America (IRR 0.75). Based on the 42 studies with significant heterogeneity between studies, there was a 14% increased risk of GBS in winter versus summer (IRR 1.14, 95% CI 1.02, 1.27).

Compared with many other countries, the rate of GBS in New Zealand was considered high until poultry handling processes were improved to reduce contamination with Campylobacter species from 2006 [3]. See section 2.1.6 of this paper for more recent NZ-specific background rates for GBS.

2.1.2 Signs and symptoms [1]

Clinically, GBS is characterised by the acute or subacute onset of varying degrees of weakness in limbs or cranial nerve-innervated muscles, associated with hypo- or areflexia, and a characteristic profile in the cerebrospinal fluid (CSF).

Patients typically experience progressive limb weakness, most often beginning in the legs and progressing to the arms and bulbar muscles. The weakness is associated with decreased or absent deep tendon reflexes, and tends to be relatively symmetric. Paraesthesias and subjective numbness or tingling may be an early feature and tends to affect the distal extremities.

The weakness progresses in an acute to subacute fashion, reaching its clinical nadir of weakness within 2-4 weeks, although in some cases rapidly progressive weakness reaching nadir within several hours could occur.

Cranial nerve palsies including involvement of the facial nerve resulting in facial weakness or extraocular motor nerve involvement or bulbar palsy may be seen. Autonomic dysfunction may occur and can result in signs including postural hypotension, ileus, and labile heart rate.

The CSF is characterised by cytoalbuminologic dissociation, with protein elevation but no increase of white blood cell count. However, in a small percentage of cases particularly if CSF is obtained early in the course of illness, CSF protein may be normal.

2.1.3 Prognosis [1]

Overall, the outcome is eventually favourable with most patients experiencing clinical improvement over weeks to months. Elderly patients have a worse prognosis. Requirement of mechanical ventilation, severe weakness at nadir, and rapid onset of weakness have been identified as poor prognostic features.

About 5-15% of patients die, and continued disability after 1 year has been estimated in about 20% of patients. Complete recovery is common in the remainder, although persistent mild weakness, numbness, pain, and fatigue may be reported.

2.1.4 Causes

As an immune-mediated disorder, auto-antibodies may form in response to a variety of antigenic stimuli, such as bacterial or viral infection. About two-thirds of people report an antecedent infectious illness, most commonly a diarrhoeal or respiratory illness, in the days or weeks preceding neurologic signs. One of the strongest associations is with *Campylobacter jejuni*. While immunologic evidence is strongest for antecedent *C. jejuni* infection, other infectious agents have been temporally associated with subsequent GBS and have included influenza viruses, *Mycoplasma pneumoniae*, human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus, and possibly others [1].

GBS has been associated temporally with some vaccines, but this temporal association requires differentiation from causality. It should be emphasised that GBS, or any other adverse event, which follows administration of an inactivated component or live vaccine may be associated with, but is not necessarily the result of administration of a vaccine [1].

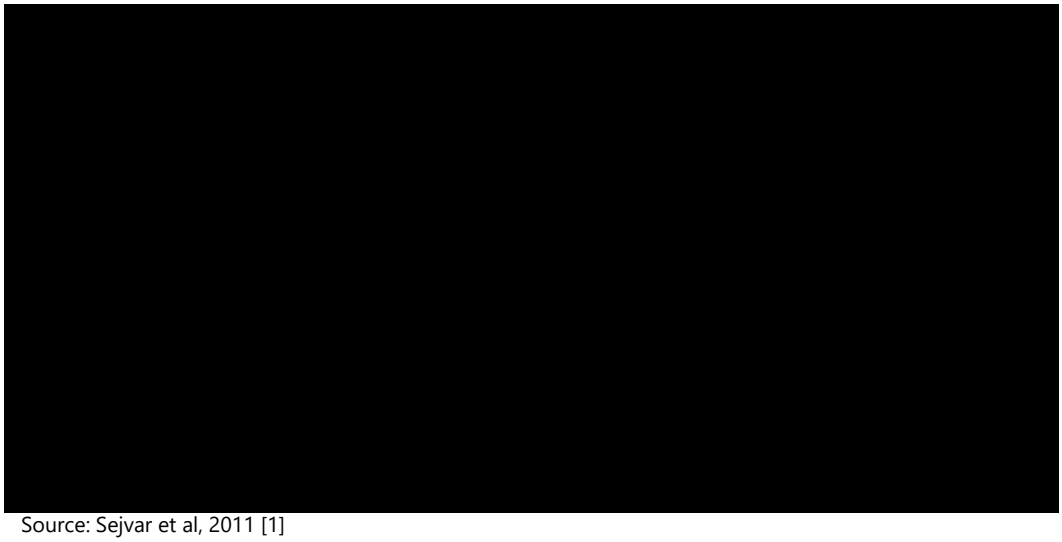
The CDC estimates there is a small increased risk of GBS following influenza vaccination at about one to two additional GBS cases per million doses of influenza vaccine administered.

2.1.5 Brighton Collaboration (BC) criteria [1]

The Brighton Collaboration criteria for GBS includes 3 levels of diagnostic certainty, with level 3 being the lowest level of certainty. The criteria for these 3 GBS levels are summarised in Figure 1. There is also a decision tree algorithm that can be used.

Level 4 is used for persons reported to have GBS for which no alternative diagnosis is apparent, but the case lacks sufficient documentation to fulfil minimal case criteria.

Figure 1: Clinical case definitions for GBS



Source: Sejvar et al, 2011 [1]

2.1.6 New Zealand background rates

The Qlik app on background rates for vaccination associated conditions was used to obtain background rates of GBS in NZ. This app uses data from the National Minimum Dataset (NMDS) and contained data on publicly funded hospital discharges between 01 Jul 2015 and 14 Apr 2025 at the time of extraction (1 May 2025). During this time period, there were a total of 1,111 people hospitalised with GBS.

Figure 2 shows the number of people hospitalised with GBS by season and year. No seasonality trend was observed, although winter and/or spring tend to have a higher number of cases in most years. There was a drop in the number of cases during 2020 (n=102) compared with more recent years (n=170 in 2023, n=123 in 2024).

Source: National Minimum Dataset (data extracted via Qlik background rates for vaccination associated conditions app 1 May 2025)
Notes: Spring = Sep to Nov, summer = Dec to Feb, autumn = Mar to May, winter = Jun to Aug

Figure 3 shows the number of people hospitalised with GBS by age group at discharge. The 55- to 69-year age groups have the greatest number of people hospitalised with GBS (total of 350 people).

Figure 4 shows the number of people hospitalised by prioritised ethnicity (level 1) and year of discharge. Most cases are reported in the European or other group, followed by Māori, Asian, and Pacific Peoples.

Source: National Minimum Dataset (data extracted via Qlik background rates for vaccination associated conditions app 1 May 2025)

Source: National Minimum Dataset (data extracted via Qlik background rates for vaccination associated conditions app 1 May 2025)
Notes: MELAA = Middle Eastern/Latin American/African

2.2 Arexvy

Arexvy is the only RSV vaccine approved for use in New Zealand. Abrysvo (Pfizer) and mResvia (Moderna) are approved in other countries.

Arexvy is an adjuvanted recombinant protein vaccine. Arexvy contains RSV glycoprotein F stabilised in the pre-fusion conformation (RSVPreF3) produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells. The adjuvant used is $AS01_E$ [4].

2.2.1 Indications and dose

Arexvy is indicated for active immunisation for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus RSV-A and RSV-B subtypes in adults 60 years of age and older [4]. The indication was recently expanded to adults 50 to 59 years of age who are at increased risk for RSV disease.

It is administered as a single dose of 0.5 mL.

Comments:

Other RSV vaccines and indications

Abrysvo (Pfizer) which is approved in other countries has an additional indication for pregnant women (32-36 weeks gestational age) to provide protection to infants from birth through 6 months of age.

The FDA has also approved Arexvy for individuals 50 to 59 years of age at increased risk for LRTD caused by RSV, and Abrysvo for adults aged 18 to 59 years at increased risk for LRTD caused by RSV.

There are differences in the composition of Arexvy and Abrysvo. Arexvy is an adjuvanted, monovalent vaccine whereas Abrysvo doesn't contain an adjuvant but it is bivalent.

Data on long-term efficacy

Arexvy is a relatively new vaccine first approved in the US on 3 May 2023 (approved in NZ on 4 Apr 2024). Therefore, long-term efficacy data is lacking. In October 2024, GSK announced new data from the AReSVi-006 phase III trial evaluating the efficacy of a single dose of Arexvy against LRTD caused by RSV in adults aged 60 years and older. The study showed that after a single dose of Arexvy, cumulative efficacy over three full RSV seasons was clinically meaningful at 62.9% against RSV-caused LRTD and 67.4% against severe disease when compared with placebo. In the third season, the vaccine's efficacy was 48% against RSV-LRTD.

Risk management plan

The EU RMP version 1.0 was reviewed by the MARC at the Jun 2024 meeting. The committee was satisfied with the RMP. This RMP does not contain any important identified risks, important potential risks or missing information.

The EU RMP has since been updated to version 2.0. The summary of safety concerns in this updated version remains unchanged (no important identified risks, important potential risks or missing information).

2.2.2 Usage

Since approval in Apr 2024 up to 5 May 2025, [redacted], mostly people aged ≥60 years (Figure 5). There appears to be a seasonal trend with higher numbers of vaccinated people during the colder months (Figure 6).

[redacted]

Comments:

The Qlik app provides a rough measure of how many people have been vaccinated whereas [redacted] from Apr to Nov 2024, respectively). The number of people vaccinated is a better estimate for usage but we have noted inaccuracies with Qlik data before, which may also explain the numbers of people vaccinated in the lower age groups.

Source: Aotearoa Immunisation Register ImmSOT database (data extracted via Qlik immunisations app 5 May 2025)

Source: Aotearoa Immunisation Register ImmSOT database (data extracted via Qlik immunisations app 5 May 2025)

2.3 Data sheets

Information on GBS in Arexvy data sheets (NZ and overseas) is summarised in Table 1 with more detail outlined in Table 2.

Table 1: Summary of information on GBS in Arexvy data sheets, by country

	Warning	Clinical trial AE	Postmarket AE
NZ			
Europe			
UK			
Australia			
US			
Canada			

Notes: green = information included; red = no information; AE = adverse effect

Table 2: Information on GBS in Arexvy data sheets, by country

Country	Section 4.4 Warnings and precautions	Section 4.8 Undesirable effects
NZ	-	-
Europe	-	-
UK (updated Feb 2025)	Guillain-Barré Syndrome Guillain-Barré syndrome has been reported very rarely following vaccination with Arexvy (see section 4.8). Healthcare professionals should be attentive to signs and symptoms of Guillain-Barré syndrome in Arexvy recipients to ensure correct diagnosis, initiate adequate supportive care and treatment, and rule out other causes.	Tabulated list of adverse reactions Nervous system disorders: Guillain-Barré syndrome (very rare) Description of selected adverse events In an open label, phase 3, multi-country study in individuals 60 years of age and older, one case of Guillain-Barré syndrome was reported in a participant enrolled in a study site in Japan with an onset of 9 days after receiving Arexvy and assessed by the investigator as possibly related to the administered vaccine. In a US post-marketing observational study in individuals aged 65 years or older, an increased risk of Guillain-Barré syndrome (estimated 7 excess cases per million doses administered) was observed during the 42 days following vaccination with Arexvy.
Australia (warning and postmarket AE info added Mar 2025)	Guillain-Barré Syndrome Guillain-Barré Syndrome has been reported very rarely following vaccination with AREXVY in individuals ≥ 60 years (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Healthcare professionals should closely monitor signs and symptoms of Guillain-Barré Syndrome in all AREXVY recipients to ensure correct diagnosis and to rule out other causes. If Guillain-Barré Syndrome is diagnosed, prompt management with adequate supportive care and treatment is recommended.	Serious adverse events reported from other studies Study RSV OA=ADJ-004 (NCT04732871): One case of Guillain-Barré syndrome beginning 9 days after AREXVY vaccination was reported in a participant enrolled in a study site in Japan. Post-marketing experience Nervous system disorders: Guillain-Barré syndrome (very rare) Description of selected adverse events The results of a post-marketing observational study over 1 RSV season in patients 65 years or older suggest an increased risk of Guillain-Barré Syndrome (estimated 7 excess cases per million doses administered) during the 42 days following vaccination with AREXVY. However, available evidence is insufficient to establish a causal relationship.

US (warning added Jan 2025)	Guillain-Barré Syndrome The results of a postmarketing observational study suggest an increased risk of Guillain-Barré syndrome during the 42 days following vaccination with AREXVY [see Adverse Reactions (6.2)].	Serious adverse events reported from other studies Study 2: Guillain-Barré syndrome beginning 9 days after AREXVY vaccination was reported in a participant enrolled in a study site in Japan. Post-marketing experience Nervous system disorders: Guillain-Barré syndrome Postmarketing observational study The association between vaccination with AREXVY and Guillain-Barré syndrome (GBS) was evaluated among Medicare beneficiaries 65 years of age and older. Using Medicare claims data, between May 2023 through July 2024, vaccinations with AREXVY were identified through Current Procedural Terminology (CPT)/Healthcare Common Procedure Coding System (HCPCS) codes and National Drug Codes, and potential cases of hospitalized GBS among recipients of AREXVY were identified through International Classification of Diseases (ICD) codes. GBS diagnoses in claims data were confirmed by medical record review when available. The risk of GBS following vaccination with AREXVY was assessed in self-controlled case series analyses using a risk window of 1 to 42 days post-vaccination and a control window of 43 to 90 days post-vaccination. The analyses of all GBS cases based on claims data suggest an increased risk of GBS during the 42 days following vaccination with AREXVY, with an incidence rate ratio (GBS cases in the risk window/control window) of 2.46 (95% CI 1.19, 5.08) and an estimated 7 excess cases of GBS per million doses administered to individuals 65 years of age and older. The background risk of GBS in a study population influences the excess GBS case estimate and may differ between studies, precluding direct comparison to excess GBS case estimates from other vaccine studies or populations. The analyses of GBS diagnoses in claims data were supported by analyses of GBS cases confirmed by medical record review and by analyses of GBS cases in individuals who received AREXVY alone, without other concomitantly administered vaccines. While the results of this observational study suggest an increased risk of GBS with AREXVY, available evidence is insufficient to establish a causal relationship.
Canada		Serious adverse events reported from other studies Study RSV OA=ADJ-004 (NCT04732871): One case of Guillain-Barré syndrome (GBS) beginning 9 days after AREXVY vaccination was reported in an adult enrolled in a study site in Japan.

3 SCIENTIFIC INFORMATION

3.1 Published literature

A PubMed search of (((arexvy) OR (rsv) OR (syncytial)) AND ((guillain) OR (gbs))) on 7 May 2025 yielded 39 results. Abstracts were manually reviewed. Relevant articles are summarised below. Some of these articles discussed other relevant information in the literature which are also included in this section.

3.1.1 GBS following RSV vaccines

3.1.1.1 Huynh et al (2024) – Exploring the "two-hit" phenomenon of Guillain-Barré syndrome following respiratory syncytial virus and influenza vaccinations [5]

The authors present a case of a 60-year-old Caucasian male with a medical history of peripheral artery disease, hyperlipidaemia, hypertension, and trigeminal neuralgia. The patient presented to the emergency department with a chief compliant of progressive tingling that developed into numbness. Two weeks prior to the presentation, he experienced new-onset tingling in both legs accompanied by nausea, vomiting, constipation, metallic taste, body aches and lower back pain. At that time, he was diagnosed in ED with exacerbation of sciatica and discharged. Five days later, the tingling in lower extremities transformed into numbness causing stumbling and difficulty walking. The symptoms then ascended to his hands and mouth prompting his second ED visit and subsequent admission.

About 3 weeks before the symptoms appeared, the patient received Pfizer's COVID-19 vaccine booster, followed by his first ever administration of both Flucelvax Quadrivalent influenza vaccine and Abrysvo five days later.

The patient's clinical presentation and CSF findings with elevated protein levels were consistent with a diagnosis of GBS. The patient was treated with immunoglobulin (IVIg).

Comments:

The authors note that the CDC states there is no minimum waiting period between influenza, RSV and COVID-19 vaccines. More studies are needed to further evaluate the incidence of GBS following coadministration of these vaccines.

It is impossible to know which vaccine is most associated with the onset of GBS in this patient as they were all given around the same time. The RSV vaccine administered to the patient was Abrysvo (not Arexvy).

3.1.1.2 Mikhail et al (2024) – Acute demyelinating polyradiculoneuropathy after the novel RSV vaccination: A case report and literature review [6]

An 81-year-old male patient presented to the emergency department with generalised weakness which began 2 weeks after receiving the Arexvy vaccine. His weakness was painless, symmetrical and ascending in nature. Physical exam revealed symmetric quadriparesis worse in the lower extremities compared to upper extremities with associated areflexia. There were no upper respiratory or gastrointestinal symptoms. CT scan of the head showed no acute intracranial process. Lumbar puncture revealed cytoalbuminologic dissociation. CT scan of the cervical spine showed chronic degenerative changes most significant at C5-C6 and C6-C7. MRI of the cervical spine showed spondylolytic changes with minimal spinal canal stenosis at C5-C6 and C6-C7 with central spinal cord impingement. However, no core signal change was found. Intravenous immunoglobulin was initiated. The patient experienced improvement in his symptoms and was transferred to an inpatient rehabilitation facility upon discharge.

Comments:

[redacted] Acute demyelinating polyradiculoneuropathy is thought to be the most common form of GBS in North America and Europe (approximately 90% of cases) [7].

3.1.2 GBS following RSV infection

3.1.2.1 Helgeson et al (2018) – First reported case of respiratory syncytial virus infection causing Guillain-Barré syndrome [8]

The authors report a case of an elderly woman with RSV infection who developed GBS.

An 81-year-old female was admitted with a 7-day history of cough, runny nose and sore throat. Her medical history included multiple myeloma currently treated with dexamethasone and zoledronic acid, breast cancer treated 5 years prior, hypertension, and hypothyroidism. The patient was also tachypneic. Computed tomography chest showed left lower and right lower lobe small airway disease. RSV polymerase chain reaction from a nasopharyngeal swab was positive.

On the 2nd day of admission, her oxygen requirements increased and ribavirin was started. The patient was eventually transferred to the intensive care unit and intubated on day-5 for respiratory distress. She was extubated 4 days later but bilateral lower extremity weakness and absent lower extremity deep tendon reflexes were noted on physical examination. The patient also had paraesthesias of her feet. This weakness progressed and her upper extremities became involved over the course of 24 hours. Electromyography showed low amplitude motor responses consistent with axonal sensorimotor peripheral neuropathy. Care was eventually withdrawn.

The authors note this case highlights the importance of physicians being aware of the clinical presentation of GBS because more common infections are starting to be reported as causing GBS.

3.1.2.2 Jayakumar et al (2021) – RSV-induced Guillain-Barré syndrome: A case report [9]

A 44-year-old man presented to the emergency department with a one-month history of intermittent fever, cough and congestion. He was prescribed an antibiotic, steroid and bronchodilator but these were ineffective. He felt worse, experiencing fatigue, malaise, headache and gait imbalance. Blurry vision emerged in his right eye and a binocular diplopia was documented.

Over the next two days, his condition worsened with slurred speech, numbness in the face and extremities and difficulty voiding. He was hospitalised and exhibited several neurologic deficits including orbicularis oculi and oris weakness, bilateral intrinsic hand muscle weakness, dyscoordination, and diminished sensation in the hands and feet.

Testing for RSV was positive. Re-imaging confirmed the left maxillary sinusitis. MRI of the thoracic spine revealed leptomeningeal enhancement and degenerative changes in the lumbar region.

The patient was initially diagnosed with meningitis which was deemed unlikely by brain MRI. A diagnosis of Guillain-Barré syndrome secondary to RSV was then made. He was treated with intravenous immunoglobulin. The definitive diagnosis was GD1a antibody-associated RSV-induced Guillain-Barré syndrome with post-infectious acute disseminated encephalomyelitis.

3.1.2.3 Ueshima et al 2024 – A pediatric suspected case of Guillain-Barré syndrome following respiratory syncytial virus RSV infection [10]

A 3-year-old boy was brought to the clinic after 4 days of progressive difficulty with gait. Three weeks earlier he had become ill with a fever and cough that lasted for a week. Respiratory syncytial virus infections had been reported in the nursery school he was attending. Neurologic examination revealed normal consciousness and normal cranial nerve function. His gait was wide with poor dorsiflexion of both ankle joints and he

sometimes fell. He could grab toys with either hand and weakly moved his legs against gravity bilaterally. His reflexes in the upper and lower extremities were diminished.

A nasopharyngeal rapid RSV antigen test was negative but a nasopharyngeal mPCR for RSV was positive. Contrast MRI of the spine showed gadolinium enhancement of the anterior and posterior roots of the cauda equina. A nerve conduction study showed decreased nerve conduction velocity and compound muscle action potentials of the upper and lower extremities without reduction in sensory conduction velocity or in sensory nerve action potentials. These abnormalities are compatible with the neuropathy of GBS.

Pure-motor GBS was diagnosed. The patient received intravenous immunoglobulin. His muscle strength improved and his gait became stable a few days after admission. He was discharged 2 weeks after admission with continued follow up and physical therapy.

3.1.2.4 Gupta et al (2023) – A case of pediatric Guillain-Barré syndrome after respiratory syncytial virus infection [11]

A 2-year-old girl presented with abdominal pain, fever and upper respiratory tract symptoms which started 10 days prior. Abdominal pain and decreased oral intake prompted evaluation. There were no vaccinations within 42 days of presentation. She was diagnosed with otitis media initially but within 24 hours, she stopped walking and was only able to crawl. The following day she developed diarrhoea, generalised weakness and bilateral leg pain with a refusal to move her legs, walk or crawl.

On examination, she had diffuse bilateral lower extremity tenderness to palpation and was only able to stand independently briefly without significant pain and discomfort. She was areflexic in the lower extremities bilaterally and could only generate antigravity movements in the bilateral lower extremities up to the hip flexors. Her respiratory viral panel returned positive for RSV.

Both CSF and neuroimaging were indicative of GBS. Intravenous immunoglobulin was initiated. Her weakness continued to improve daily but eventually plateaued. She required 2 months of hospitalisation including 3 weeks of inpatient rehabilitation.

According to the authors, this case was considered to meet level 2 of the Brighton Collaboration diagnostic criteria for GBS given that electrodiagnostic testing was not done due to lack of tolerance in a young patient, with a sensitivity of 84% to 96%.

The authors discuss that molecular mimicry is the leading pathogenic mechanism hypothesised in postinfectious GBS. After exposure of the immune system to an antigen, fragments of these proteins are expressed to T cells via antigen-presenting cells, triggering subsequent plasma cell generation of antibodies. These antibodies then cross-react with autoantigens found on the axolemma resulting in injury to axons. These autoantibodies such as to gangliosides and related glycolipids are detected in many patients with axonal GBS variants and Miller-Fisher syndrome. Of note, peripheral nerve cross-reactive epitopes have been found in microbes isolated from patients, especially *C. jejuni*, that are capable of carrying ganglioside-like moieties. Similar findings have been reported in influenza A, but it is still unknown whether GBS after influenza infection is generally associated with consistent generation of ganglioside antibodies.

Comments:

GBS can be triggered by various infections, most commonly a gastrointestinal or respiratory infection. These four case reports suggest that RSV infection is a potential trigger for GBS. The rate of GBS following RSV infection is unknown but is likely to be higher than the rate of GBS following RSV vaccination [12].

3.1.3 General safety of RSV vaccines

There are other general published articles on RSV vaccines that mention GBS.

Laemmle-Ruff & Crawford (2024) [13] summarised safety data on RSV prevention products focusing on those approved by the TGA in Australia. The authors note the one case of GBS reported in Arexvy clinical trials and postmarket data from the US vaccine adverse event reporting system (VAERS) reporting the equivalent of 4.4 and 1.8 cases per million doses of Abrysvo and Arexvy, respectively, which exceeded expected background rates.

Anastassopoulou et al (2025) [14] conducted a comparative overview of the safety and efficacy of RSV vaccines in adults 60 years of age and older. This article also notes postmarket data from VAERS indicating that the incidence of GBS following vaccination with Arexvy and Abrysvo may be higher than estimated expected background rates in the vaccinated population.

Kelleher et al (2025) [15] summarised information on recent advances in RSV vaccine research. They also note the one case of GBS reported in an Arexvy clinical trial and postmarket cases reported to VAERS.

Comments:

For Arexvy, all three articles mention the same clinical trial case of GBS and a VAERS reporting rate of 1.8 GBS cases per million doses.

3.2 FDA's review

On 7 Jan 2025, the FDA issued a safety communication about their requirement for a warning on GBS in the data sheets for Abrysvo and Arexvy. The FDA conducted a postmarketing observational study that assessed the risk of GBS following vaccination with Abrysvo and Arexvy. Based on FDA's evaluation of data from clinical trials, reports to the Vaccine Adverse Event Reporting System (VAERS) and the postmarketing study, the FDA determined that the overall body of evidence suggests increased risks of GBS with Abrysvo and Arexvy, but the available evidence is insufficient to establish a causal relationship.

3.2.1 Clinical trial data

As part of the FDA's review to support the approval of Arexvy, FDA evaluated safety data from clinical trials in which ~16,000 individuals received Arexvy and ~13,000 individuals received placebo. One participant developed GBS 9 days after receiving Arexvy. FDA has required the manufacturer to conduct a study to evaluate the risk of GBS among 1.9 million adults 50 years of age and older vaccinated with Arexvy in the US.

As part of the FDA's review to support the approval of Abrysvo, FDA evaluated safety data from clinical trials in which ~22,000 individuals received Abrysvo and ~22,000 individuals received placebo. Among study participants 60 years of age and older, one participant developed GBS 7 days following vaccination and one participant developed Miller-Fisher syndrome (a variant of GBS) 8 days following vaccination. The initial approval included a requirement by FDA for the manufacturer to conduct a study to evaluate the risk of GBS among ~1.5 million older adults vaccinated with Abrysvo in the US. The approval of Abrysvo in individuals 18 to 59 years of age who are at increased risk of LRTD caused by RSV included an FDA requirement for the manufacturer to conduct a study to evaluate GBS in this population. FDA has also required the manufacturer to conduct a study to assess the serious risk of GBS following administration of Abrysvo in pregnant individuals.

Comments:

The study required by the FDA for Arexvy has an expected study completion date of 30 June 2030 and a final report submission due 31 Dec 2031 (see section 3.5.5 of this report).

3.2.2 FDA's postmarket study (BEST initiative)

The risks of GBS following vaccination with Abrysvo and Arexvy, using Medicare claims data, were assessed in self-controlled case series (SCCS) analyses using risk windows of 1 to 42 days post vaccination and control windows of 43 to 90 days post vaccination. The analyses of all GBS cases suggest an increased risk of GBS during the 42 days following vaccination, with an estimated 9 excess cases of GBS per million doses of Abrysvo and an estimated 7 excess cases of GBS per million doses of Arexvy administered to individuals 65 years of age and older.

The results from the FDA's study are publicly available:

- Early-season results: FDA presentation at the June 2024 meeting of the Advisory Committee on Immunization Practices (ACIP).
- End-of season results: FDA presentation at the October 2024 meeting of ACIP and preprint version of the manuscript.

Description

The FDA conducted 3 separate post-market analyses to assess the risk of GBS following Arexvy and Abrysvo among Medicare beneficiaries aged 65 years and older:

1. A preliminary observed vs. expected (O/E) analysis to compare the rates of GBS following either vaccine to historical control (expected) rates (see section 3.5.4 of this report for results from this analysis).
2. An early-season self-controlled case series (SCCS) included beneficiaries vaccinated between May 2023 and Oct 2023 to support early detection of GBS risk shortly after approval of these vaccines.
3. The end-of-season SCCS included beneficiaries vaccinated between May 2023 and Jan 2024 and used medical record review (MRR) to provide more precise estimates of GBS risk following RSV vaccination.

The vaccines included in the study were:

- RSVPreF3+AS01 (Arexvy, GSK)
- RSVPreF (Abrysvo, Pfizer).

Moderna's mResvia vaccine was not included because it was approved after the analyses were conducted.

Methods

Figure 7 shows the SCCS design which compares the incidence of GBS during periods of hypothesised excess risk due to vaccine administration (risk interval) to the incidence in the rest of the observation period (control interval). A risk window of 1 to 42 days post vaccination and control window of 43 to 90 days post vaccination were used. A summary of the study methods is shown in Table 3.

Figure 7: Self-controlled case series (SCCS) design

Source: FDA presentation to ACIP, Oct 2024 (https://www.cdc.gov/acip/downloads/slides-2024-10-23-24/05-RSV-Adult-Lloyd-508.pdf)

Table 3: Summary of study methods

Source: FDA presentation to ACIP, Oct 2024 (https://www.cdc.gov/acip/downloads/slides-2024-10-23-24/05-RSV-Adult-Lloyd-508.pdf)

Medical record review (MRR)

MRR was conducted for GBS cases identified through SCCS analyses to validate the claims-based outcome definition. Each case was independently adjudicated by 2 neurologists using Brighton Collaboration's case definition for GBS. Those classified as levels 1, 2 or 3 were classified as 'chart-confirmed' GBS cases. Positive predictive values (PPVs) with corresponding 95% confidence intervals (CIs) were calculated as the percentage of received records classified as chart-confirmed. Results from this MRR were used to conduct inferential analyses.

Inferential analyses

The end-of-season SCCS analysis was conducted on accumulation of a sufficient number of GBS cases to detect an incidence rate ratio (IRR) of at least 3 at 80% power with a two-sided alpha of 0.05.

For the primary analyses, a conditional Poisson regression was used to estimate IRRs and 95% CIs comparing GBS rates in risk and control intervals for each RSV vaccine. Attributable risk (AR) estimates and 95% CIs were

calculated as the number of excess cases per 100,000 vaccine doses and per 100,000 person-years. Primary analyses included adjustments for outcome-dependent observation time (ie, censoring of the observation period due to death or disenrollment; referred to as the Farrington adjustment), seasonality adjustment using incidence rates of GBS estimated from the Medicare FFS population aged 65 years and older from corresponding calendar months in 2022-2023 used as baseline incidence of GBS in risk and control intervals, and positive predictive value (PPV)-based imputation adjustment to account for potential misclassification of GBS cases in administrative claims data.

Secondary analyses stratifying by concomitant vaccination status were conducted for each vaccine product with a statistically significant elevation of IRR in the primary analyses to evaluate the potential effect of same-day concomitant vaccination.

Sensitivity analyses were conducted that (i) incorporated a 14-day washout interval between risk and control intervals to evaluate potential bias associated with carryover effects from RSV vaccination contributing to the risk in control intervals, and (ii) included an individuals' full observation period length for persons that died or disenrolled to evaluate potential bias from a violation of the SCCS assumption that observation length is independent of outcomes.

Results

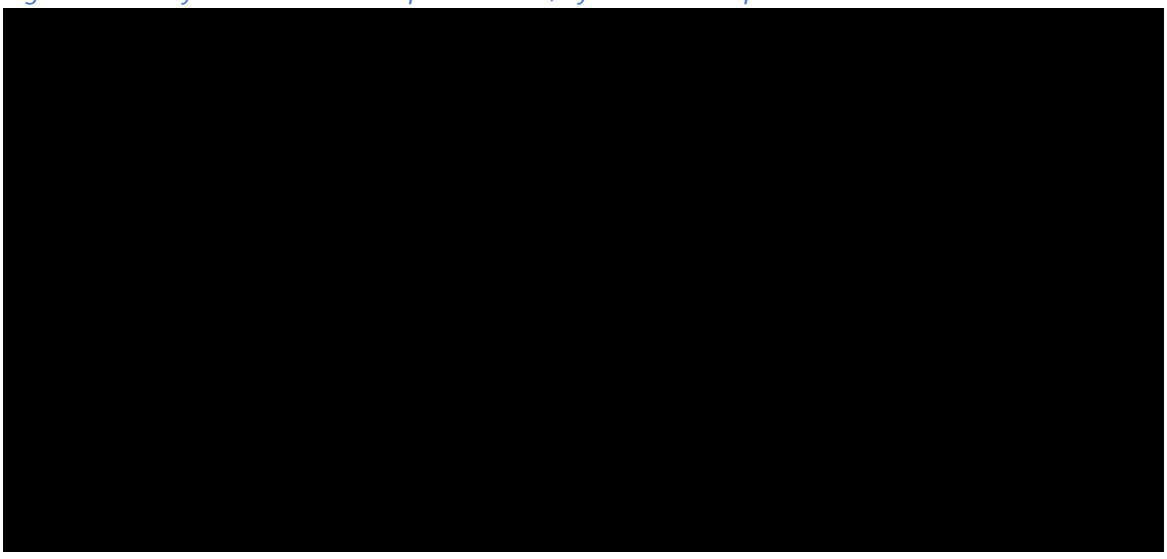
There were 3,226,689 Medicare beneficiaries aged 65 years and older who received RSV vaccination before 28 Jan 2024. Of these, 2,202,247 (68.25%) received Arexvy and 1,024,442 received Abrysvo (Table 4). Population characteristics were largely consistent by RSV vaccine products. Weekly vaccination uptake trends by RSV vaccine products are presented in Figure 8. A summary of GBS cases following RSV vaccination is shown in Table 5.

Table 4: Summary of early-season and end-of-season SCCS analyses

[redacted]

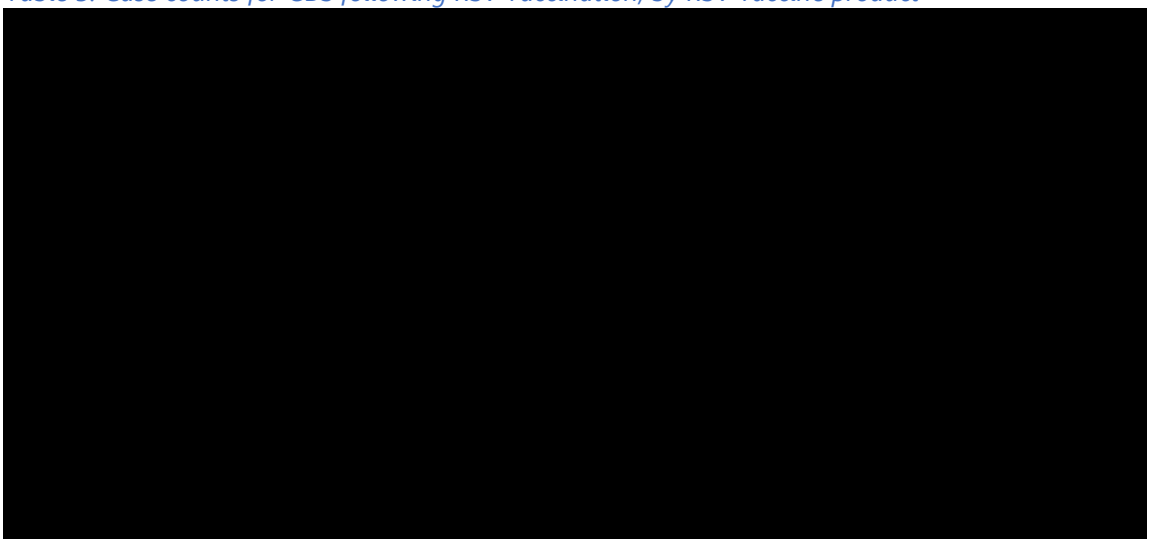
Source: FDA presentation to ACIP, Oct 2024 (https://www.cdc.gov/acip/downloads/slides-2024-10-23-24/05-RSV-Adult-Lloyd-508.pdf)

Figure 8: Weekly RSV vaccination uptake trends, by RSV vaccine product



Source: FDA presentation to ACIP, Oct 2024 (https://www.cdc.gov/acip/downloads/slides-2024-10-23-24/05-RSV-Adult-Lloyd-508.pdf)

Table 5: Case counts for GBS following RSV vaccination, by RSV vaccine product



Source: FDA presentation to ACIP, Oct 2024 (https://www.cdc.gov/acip/downloads/slides-2024-10-23-24/05-RSV-Adult-Lloyd-508.pdf)

Early-season: Inferential results

A summary of the number of GBS cases and the number of vaccine doses administered are shown in Table 6. The incidence rate ratio (IRR) and attributable risk (AR) of GBS adjusted for positive predictive value (PPV), seasonality and outcome-dependent observation time are shown in Table 7.

Table 6: Case counts for GBS following RSV vaccination, by vaccine type (early season)

Source: FDA presentation to ACIP, Jun 2024 (https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/06-RSV-Adult-Lloyd-508.pdf)

Table 7: IRRs and ARs of GBS adjusted for PPV, seasonality and outcome-dependent observation time (early season)

/slides-2024-06-26-28/06-RSV-Adult-Lloyd-508.pdf)

End-of-season: Medical record review (MRR) results

From the end-of-season SCCS analysis dataset, 95 records of incident GBS cases were requested (see Table 8) and 75 were received and reviewed. Table 8 summarises the medical records status, case classifications derived after adjudication of records, and positive predictive values (PPVs) of GBS following RSV vaccination. The overall PPV of claims-based GBS definition in the primary diagnosis position on hospital inpatient claims following RSV vaccination was slightly lower (PPV 68%, 95% CI 56.79, 77.46) compared to a prior MRR of GBS following influenza vaccination (PPV 71.21%, 95% CI 63.49, 78.94). PPVs of GBS following RSV vaccination were higher for the control interval (PPV 81.82%, 95% CI 61.48, 92.69) compared to the risk interval (PPV 62.26%, 95% CI 48.81, 74.06) (Table 8).

Table 8: Summary of GBS medical record review (MRR) results and positive predictive values (PPVs)

Source: Table 2 of FDA preprint version of manuscript (https://www.medrxiv.org/content/10.1101/2024.12.27.24319702v1)

Comments:

Positive predictive values (PPVs) are a measure of how accurately a positive result identifies individuals who actually have the disease/condition being tested for. PPVs quantify the proportion of positive test results that are genuine positives. The PPV of GBS following RSV vaccination during the risk interval was 62.26% (95% CI 48.81, 74.06) which is lower than the PPVs for GBS during the control interval and for GBS with influenza vaccine.

End-of-season: Inferential results

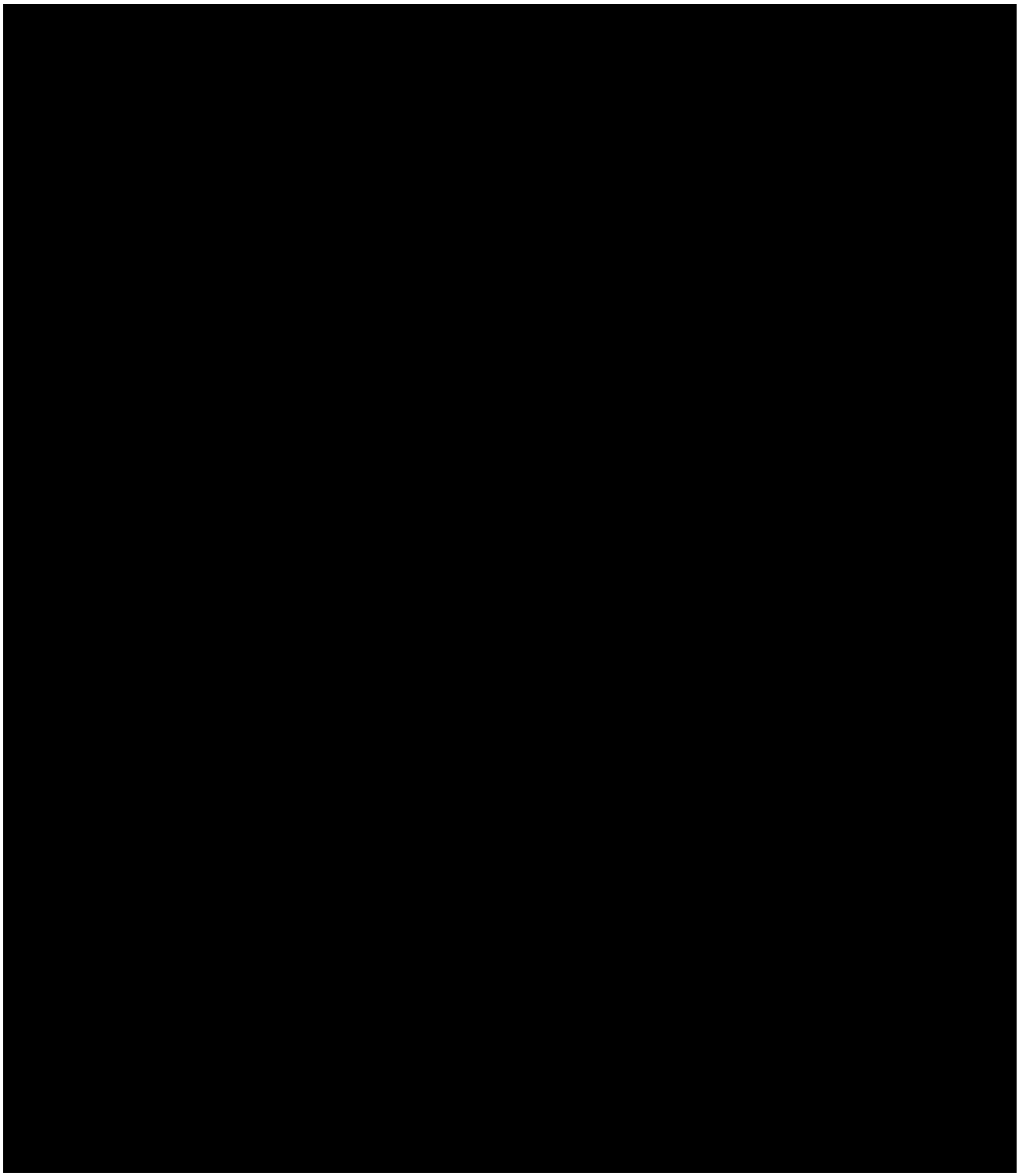
For the primary analyses, a total of 95 incident cases were identified (56 with Arexvy, 39 with Abrysvo). Table 9 summarises the IRR and AR estimates from primary analyses of GBS following RSV vaccination for (i) PPV-based imputation analyses cases (n=71), (ii) chart-confirmed cases (n=51), and (iii) all claims-identified cases (n=95).

A statistically significant elevation in risk was observed following Arexvy (**IRR 2.46, 95% CI 1.19, 5.08**) in seasonality, Farrington, and PPV-based imputation adjustment analysis that included chart-confirmed and non-returned cases (Table 9). This elevation in GBS risk following Arexvy remained statistically significant for PPV-based imputation analyses, chart-confirmed cases, and all claims-identified cases (Table 9).

Although a statistically significant elevation in risk was observed following Abrysvo for all claims-identified cases, subsequent analyses showed an elevated yet non-statistically significant result (Table 9). A non-statistically significant elevation in risk was observed following Abrysvo (IRR 2.02, 95% CI 0.93, 4.40) for PPV-based imputation analyses cases in seasonality, Farrington and PPV-based imputation adjustment analysis that used separate risk and control interval PPVs on unreturned cases (Table 9). This result remained consistent for PPV-based imputation analyses and chart-confirmed cases (Table 9).

The AR per 100,000 doses following Arexvy and Abrysvo were similar in magnitude (AR 0.65, 95% CI 0.18, 1.12 and AR 0.90, 95% CI -0.02, 1.81, respectively) in the most-adjusted analysis (ie, seasonality, Farrington and PPV-based imputation adjustment) that used separate risk and control interval PPVs on unreturned cases (Table 9). Figure 9 summarises primary SCCS analyses results of GBS.

Table 9: Primary analyses: IRR and AR of GBS following RSV vaccination for PPV-based imputation analyses, chart-confirmed and all claims-identified GBS cases



Source: Table 3 of FDA preprint version of manuscript (https://www.medrxiv.org/content/10.1101/2024.12.27.24319702v1)

Figure 9: Primary analyses: IRR of GBS following RSV vaccination for PPV-based imputation analyses, chart-confirmed and all claims-identified GBS cases

Source: Figure 2 of FDA preprint version of manuscript (https://www.medrxiv.org/content/10.1101/2024.12.27.24319702v1)

In the secondary analyses, 20 (35.71%) and 19 (48.71%) GBS cases were observed to have a concomitant vaccination with Arexvy and Abrysvo vaccines, respectively. Figure 10 and Table 10 summarise the IRR and AR estimates of GBS following RSV vaccination by concomitant vaccination status for all claims-identified cases. A statistically significant elevation in risk was observed following Arexvy (IRR 3.47, 95% CI 1.61, 7.46) and Abrysvo (IRR 4.48, 95% CI 1.50, 13.42) without concomitant vaccination. A non-statistically significant elevation in risk was observed following both RSV vaccines with concomitant vaccination in seasonality and Farrington-adjusted analyses (Arexvy IRR 2.19, 95% CI 0.87, 5.49; Abrysvo IRR 2.26, 95% CI 0.89, 5.73) (Table 10). In summary, there was no evidence of difference in GBS risk among persons with and without same day concomitant vaccination with RSV vaccines.

Figure 10: Secondary analyses: IRR of GBS following RSV vaccination for seasonality and Farrington adjusted analysis (all cases)

Source: FDA presentation to ACIP, Oct 2024 (https://www.cdc.gov/acip/downloads/slides-2024-10-23-24/05-RSV-Adult-Lloyd-508.pdf)

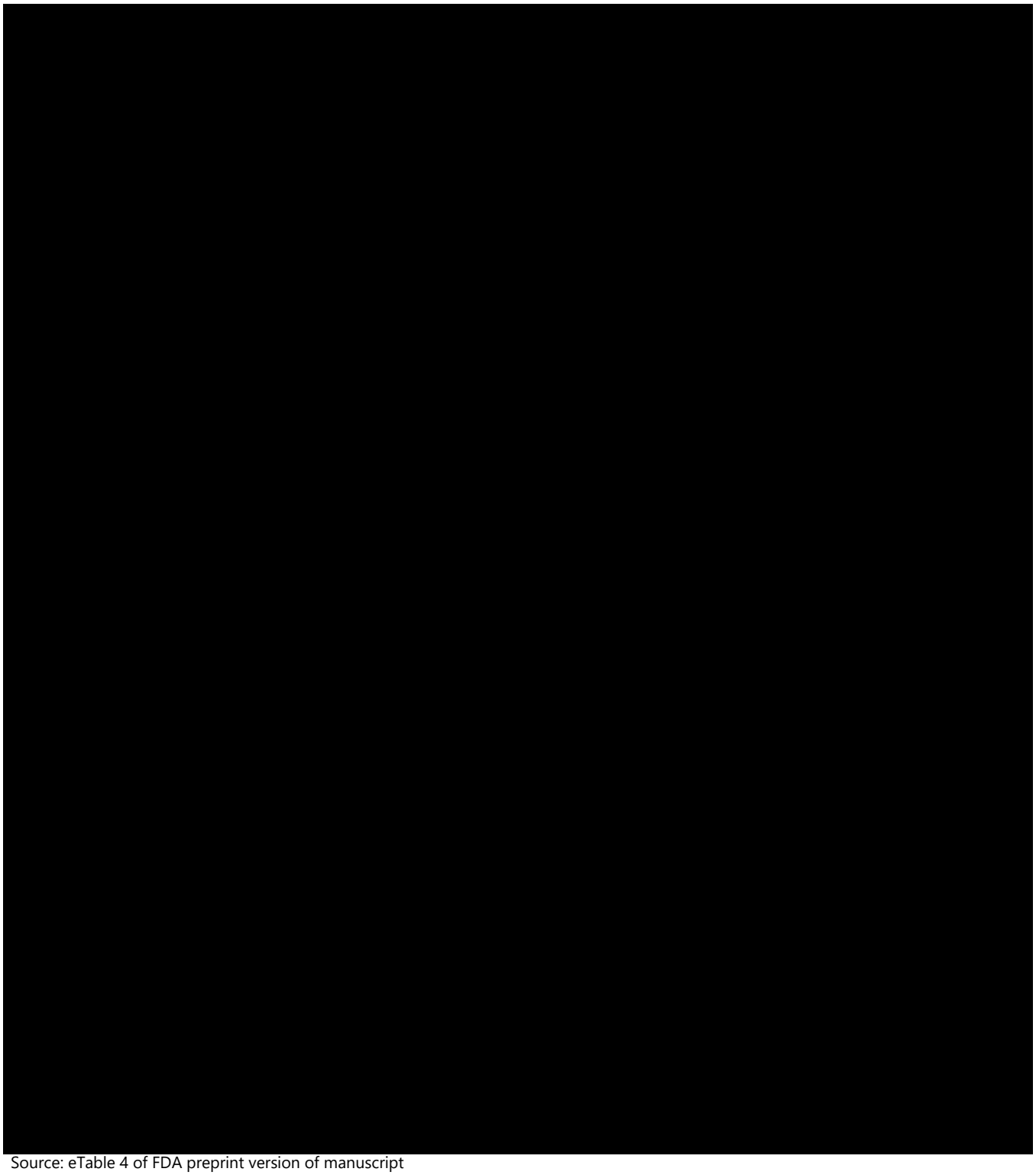
Comments:
The Arexvy NZ data sheet states that it can be given concomitantly with inactivated seasonal influenza vaccines. Data are currently not available for concomitant vaccination with other vaccines.

Table 10: Secondary analyses: IRR and AR of GBS following RSV vaccination for all claims-identified GBS cases

(https://www.medrxiv.org/content/10.1101/2024.12.27.24319702v1.supplementary-material)

Sensitivity analyses results are presented in Table 11. In an assessment of the washout interval of PPV-based imputation analyses cases, a non-statistically significant elevation in risk was observed following both RSV vaccines in the most-adjusted analysis (Arexvy IRR 2.03, 95% CI 0.93, 4.42; Abrysvo IRR 1.54, 95% CI 0.69, 3.44). In the full-planned observation time analysis of PPV-based imputation analyses cases, a statistically significant elevation in risk was observed following Arexvy (IRR 2.40, 95% CI 1.16, 4.95) and risk was elevated yet not statistically significant following Abrysvo (IRR 2.02, 95% CI 0.93, 4.39) in the most adjusted analysis (Table 11).

Table 11: Sensitivity analyses: IRR and AR of GBS following RSV vaccination for PPV-based imputation analyses, chart-confirmed and all claims-identified GBS cases



Source: eTable 4 of FDA preprint version of manuscript (https://www.medrxiv.org/content/10.1101/2024.12.27.24319702v1.supplementary-material)

Early vs. end of season results

The early vs. end of season results are summarised in Figure 11 for Arexvy and Figure 12 for Abrysvo. For Arexvy, a statistically significant elevation in GBS risk was observed with seasonality, Farrington, PPV adjusted analysis that included chart-confirmed and non-returned cases (**IRR 2.46, 95% CI 1.19, 5.08**). For Abrysvo, an elevated but non-statistically significant IRR was observed for GBS with seasonality, Farrington and PPV adjusted analysis that included chart-confirmed and non-returned cases (IRR 2.02, 95% CI 0.93, 4.40).

Figure 11: Comparison of early vs. end of season results for Arexvy

Figure 12: Comparison of early vs. end of season results for Abrysvo

3.3 CDC rapid cycle analysis (RCA)

The interim report of the CDC's rapid cycle analysis (RCA) of RSV vaccines was presented to the ACIP at their June 2024 meeting.

Objectives

To monitor RSV vaccine uptake and occurrence of pre-specified outcomes following RSV vaccination, and conduct near real-time surveillance of pre-specified outcomes using RCA methods.

Data source

The study used data from the Vaccine Safety Datalink (VSD) which is a collaborative project between CDC and 13 integrated healthcare organisations containing data on approximately 13.5 million persons per year (Figure 13). Rapid cycle analyses with VSD-data permits rapid assessment of vaccine safety by providing near real-time data for weekly, biweekly or monthly analyses. The outcome incidence in vaccinated persons can be compared to outcome incidence in a comparator group.

Figure 13: Vaccine safety datalink, 2024

Source: Presentation to ACIP, Jun 2024 (https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/05-RSV-Adult-Donahue-508.pdf)

Study design and population

Near real-time surveillance was conducted among a prospective cohort of people aged ≥60 years who received an RSV vaccine. Eligible participants were members of a participating VSD site. Data was extracted every week and analyses conducted biweekly.

The surveillance period is from 1 Aug 2023 to 31 May 2025. Sequential analyses started in Mar 2024 and the project ends in Sep 2025.

Sequential analysis methods

The biweekly analyses include a sequential test of the one-sided null hypothesis that the vaccine does not increase the risk in the risk interval. A statistical signal occurs when the analysis produces a one-sided P value that is less than a pre-specified threshold. These statistical signals are interpreted as potential associations. The signal threshold is determined from an alpha-spending plan that keeps the overall chance of a type 1 error <0.05 during the surveillance period. Formal sequential analysis stops after a signal, but surveillance continues.

The design and analysis are similar to that used in the VSD RCA of COVID-19 vaccines (Klein et al, 2021) [16].

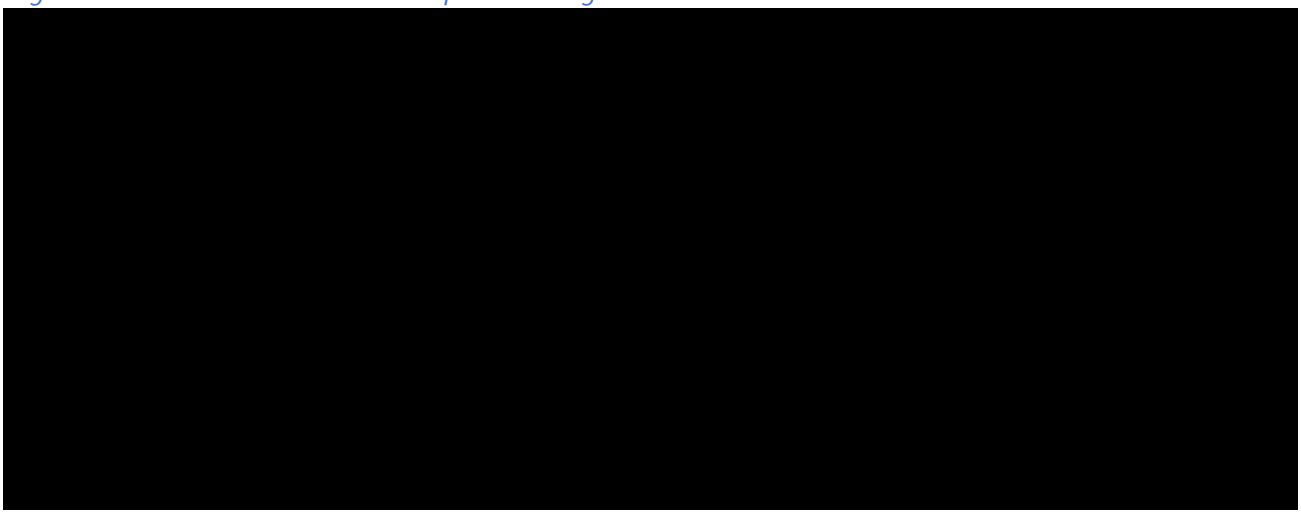
Risk and comparison intervals

The primary risk interval for all outcomes was defined as 1-21 days following RSV vaccination, except for anaphylaxis and chronic inflammatory demyelinating polyneuropathy (CIDP). The primary comparison interval of 43-63 days was used and a secondary comparison interval of 22-42 days.

The secondary risk interval was defined as 1-42 days following RSV vaccination. A comparison interval of 43-84 days was used.

Comparators were RSV vaccinees who were in the same stratum (eg, age, sex, race/ethnicity, VSD site) on the same day as the exposed case in a risk interval, but in a comparison interval (Figure 14). Outcome incidence was calculated during the risk interval and compared with the incidence in the comparison interval, adjusted for calendar day, age group, sex, race/ethnicity, and VSD site. Relative risk estimates were computed with 95% confidence intervals.

Figure 14: Vaccinated concurrent comparator design



Source: Presentation to ACIP, Jun 2024 (https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/05-RSV-Adult-Donahue-508.pdf)

Exposures and outcomes

There were 4 exposure groups:

- Arexvy with simultaneous vaccination of another vaccine
- Arexvy without simultaneous vaccination
- Abrysvo with simultaneous vaccination of another vaccine
- Abrysvo without simultaneous vaccination.

Non-RSV vaccines typically include routine vaccines in this age group (eg, COVID-19, influenza, shingles, pneumococcal, Tdap).

There were 14 pre-specified outcomes, including Guillain-Barré syndrome (Table 12). RSV vaccines administered in VSD from 1 Aug 2023 to 25 May 2024 are shown in Table 13, and Figure 15 shows weekly administration of Arexvy and Abrysvo.

Table 12: Pre-specified outcomes and primary risk intervals used (n=14)

Outcome	Primary risk interval (days)[1]
Acute disseminated encephalomyelitis (ADEM)[2]	1-21
Acute myocardial infarction (AMI)	1-21
Anaphylaxis[2]	0-1
Atrial fibrillation	1-21
Bell's palsy	1-21
Chronic inflammatory demyelinating polyneuropathy (CIDP)[2]	1-84
Deep vein thrombosis (DVT)	1-21
Encephalitis / myelitis / encephalomyelitis (not ADEM or TM)	1-21
Guillain-Barré syndrome (GBS)[2]	1-21
Immune thrombocytopenia (ITP)	1-21
Myocarditis / pericarditis	1-21
Pulmonary embolism (PE)	1-21
Stroke	1-21
Transverse myelitis (TM)[2]	1-21

Source: Adapted from presentation to ACIP, Jun 2024 (https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/05-RSV-Adult-Donahue-508.pdf)

Notes:
[1]All outcomes also have a secondary risk interval of 1-42 days after vaccination, except anaphylaxis and CIDP.
[2]Chart review regardless of whether there is a statistical signal; sequential analyses will use only chart-confirmed cases (ADEM, GBS, TM).

Table 13: RSV vaccines administered in VSD (1 Aug 2023 to 25 May 2024)

Arexvy		Abrysvo		Unspecified		Total
N	%	N	%	N	%	
338,290	87.7	47,287	12.3	152	0.0	385,729

Source: Adapted from presentation to ACIP, Jun 2024 (https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/05-RSV-Adult-Donahue-508.pdf)

All subsequent analyses and information exclude RSV vaccines in the 'unspecified' category.

Figure 15: Weekly RSV vaccinations

Source: Presentation to ACIP, Jun 2024 (https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/05-RSV-Adult-Donahue-508.pdf)

Results of sequential analysis for Guillain-Barré syndrome (GBS)

There was a total of six runs of data through to 25 May 2024.

No statistical signal was found for GBS following RSV vaccination. GBS cases were identified electronically, received medical record review, and presumptive cases were adjudicated by two reviewers. Cases were defined using Brighton Collaboration (BC) criteria.

There were 7 cases of GBS (BC levels 1-3) following any RSV vaccination:

- 5 following Arexvy: onset days 6, 10, 31, 54, 76
- 2 following Abrysvo: onset days 9, 46

There were a further 2 BC level 4 cases following Arexvy.

The concurrent comparator sequential analysis signal assessment for GBS is shown in Table 14 and crude incidence rates are shown in Table 15.

Table 14: Concurrent comparator sequential analysis signal assessment for GBS (1 Aug 2023 to 25 May 2024, run #6, week #1846)

Source: Presentation to ACIP, Jun 2024 (https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/05-RSV-Adult-Donahue-508.pdf)

Table 15: Crude incidence rates for GBS after RSV vaccination[1]

Risk interval estimates

Source: Presentation to ACIP, Jun 2024 (https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/05-RSV-Adult-Donahue-508.pdf)

Comments:

From the CDC's analysis, there was no statistical signal for GBS with RSV vaccines (Arexvy and Abrysvo). The 95% confidence intervals for the ARRs all included one and were very wide which reflects the low number of GBS cases seen.

3.4 Summary of FDA and CDC results

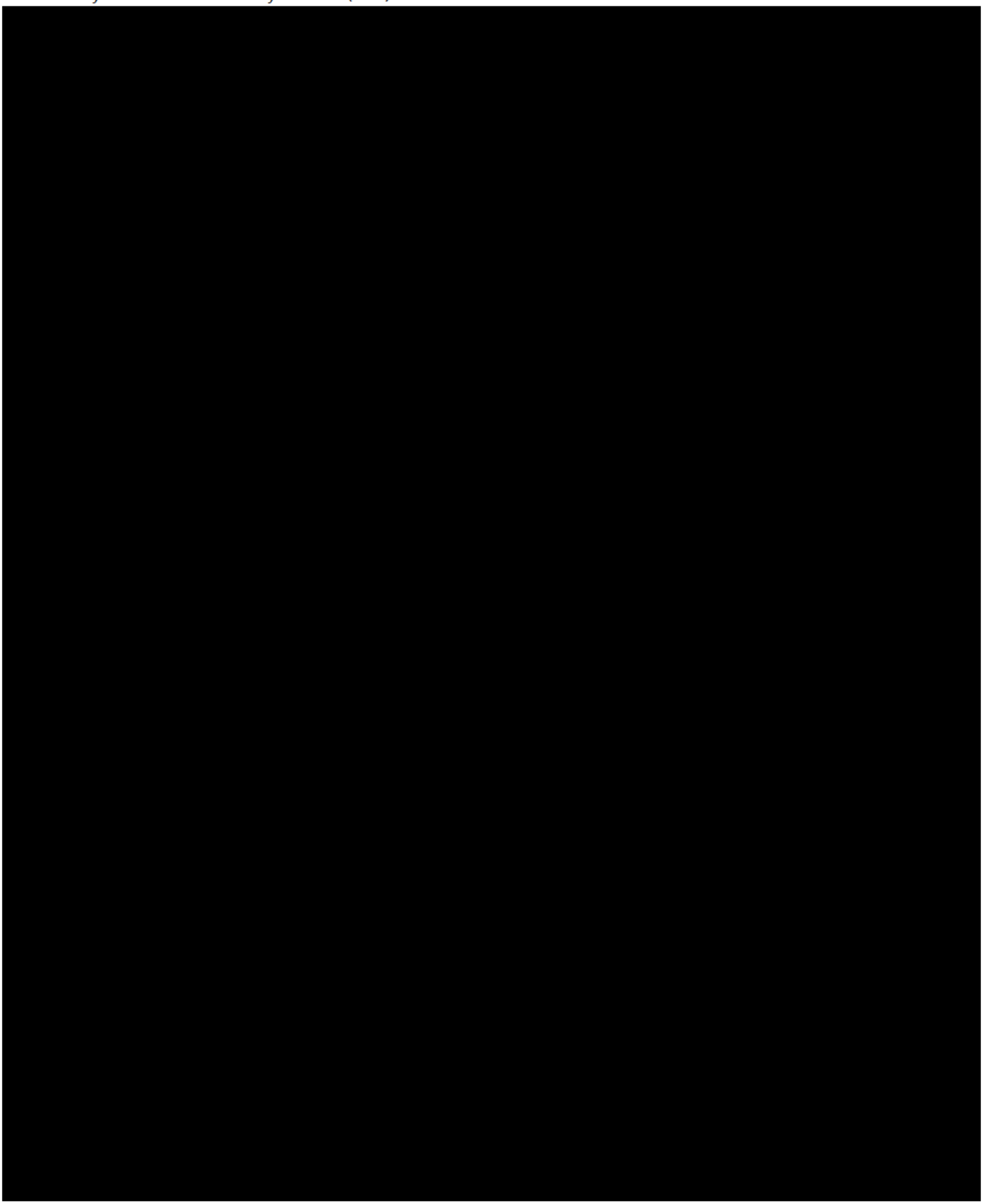
Results from the FDA and CDC analyses are summarised in Table 16.

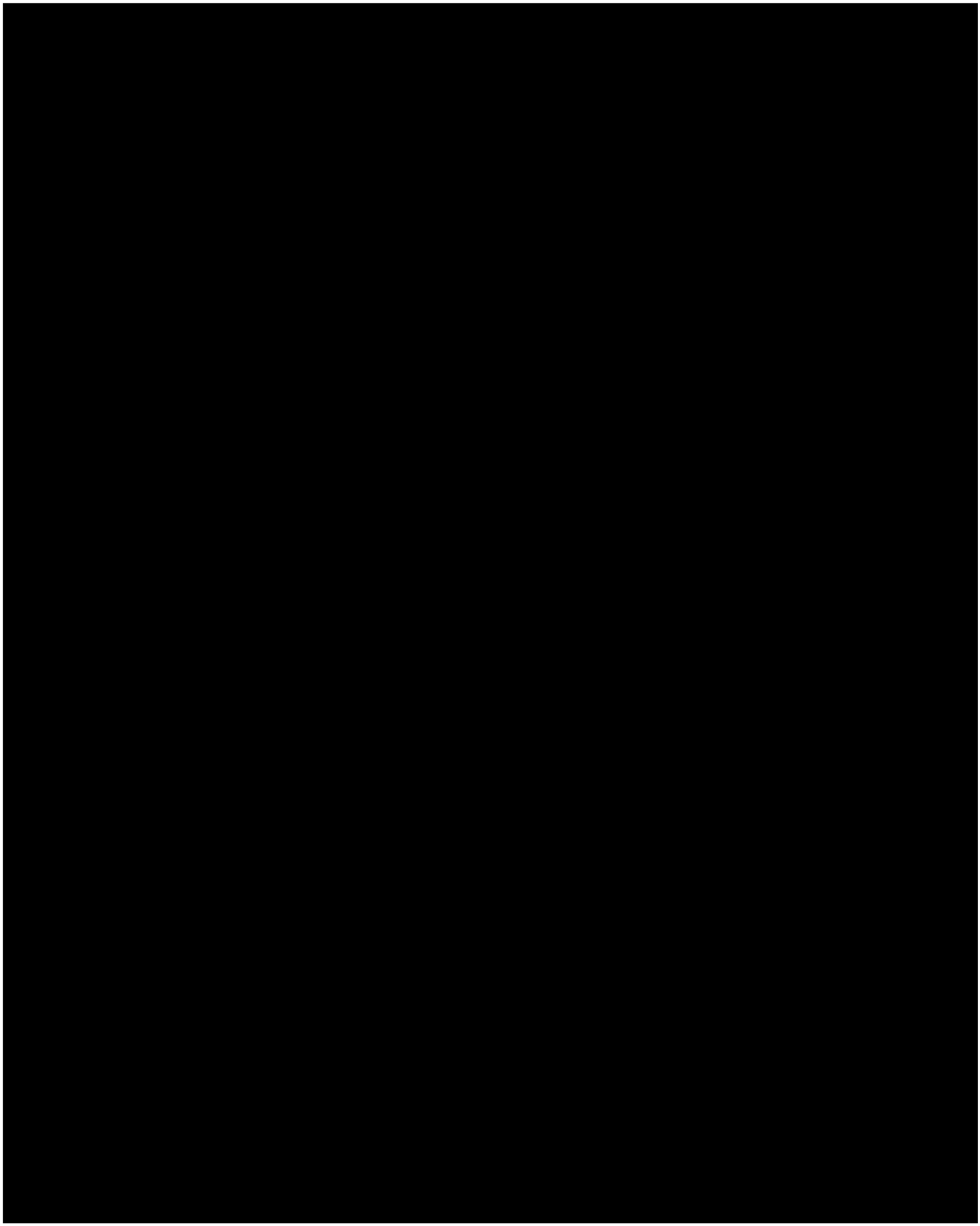
Table 16: Summary of results from the FDA and CDC analyses

	FDA O/E	FDA SCCS (early-season)	FDA SCCS (end-of-season)	CDC RCA
Time period	May 2023 to Dec 2023	May 2023 to Oct 2023	May 2023 to Jan 2024	Aug 2023 to May 2024
No. of Arexvy doses	1,379,335	872,068	2,202,247	338,290
No. of GBS cases	<11	11	56	7
Main results (95% CI)	IRR 2.76 (1.32, 5.07)	IRR 2.30 (0.39, 13.72) AR 2.81 cases per 100,000 PY (-2.64, 8.26)	IRR 2.46 (1.19, 5.08) AR 5.71 cases per 100,000 PY (1.61, 9.80)	ARR 2.33 (0.10, 93.95)

Abbreviations:
AR = Attributable risk, ARR = Adjusted rate ratio, CDC = Centers for Disease Control and Prevention, CI = Confidence interval, FDA = United States Food and Drug Administration, IRR = Incidence rate ratio, O/E = Observed vs. expected analysis, RCA = Rapid cycle analysis, SCCS = Self-controlled case series

[redacted]





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3.6 Spontaneous adverse reaction data

3.6.1 New Zealand

There are 2 reports in the NZ pharmacovigilance database with Arexvy as the suspect medicine. These are summarised in Table 19. None of the cases report Guillain-Barré syndrome, but one of them reports muscle weakness.

Table 19: Summary of reports with Arexvy as suspect medicine (n=2)

Report ID	Date	Age	Sex	Medicine(s)	Reactions(s) #
158125	Aug 2024	72	F	Arexvy*, quinapril, amlodipine, aspirin, bendroflumethiazide, colecalciferol, omeprazole, Seebri inhaler, Symbicort inhaler, amoxicillin, benralizumab injection	vomiting, diarrhoea, abdominal cramp
158886	Sep 2024	76	M	Arexvy*, paracetamol, atorvastatin, zopiclone, ibuprofen, quetiapine, Flixonase	muscle weakness, fatigue

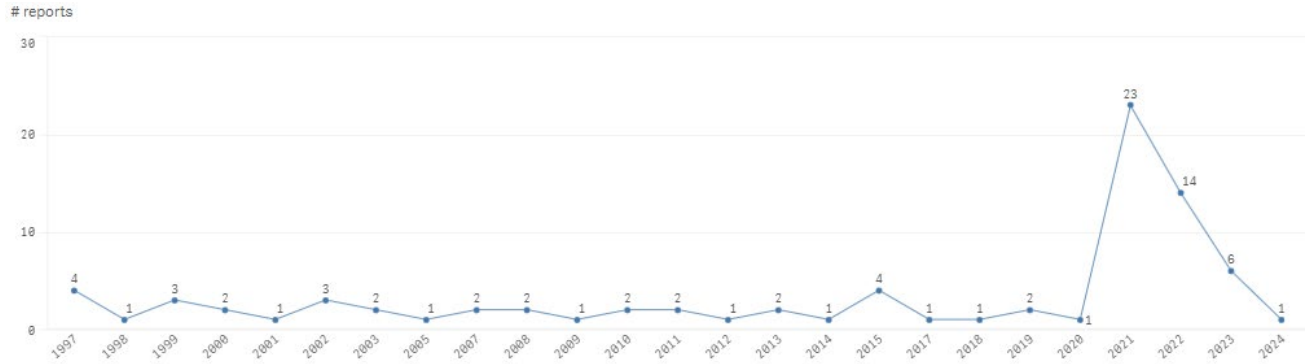
[redacted]

Source: NZ pharmacovigilance database (data extracted 7 May 2025)
* = suspect medicine as reported by the reporter
# = reaction as coded in database

There are 83 reports of Guillain-Barré syndrome in the NZ pharmacovigilance database. Reports received over time are shown in Figure 18. There was a peak of reports in 2021 (n=23) followed by a tapering down to pre-2021 levels (n=1 in 2024).

The 83 cases of Guillain-Barré syndrome are summarised in Table 20. Of the 83 cases, 77 report a vaccine as the suspect medicine. Reports by age are roughly consistent with NZ background rates of Guillain-Barré syndrome (see section 2.1.6 of this report). The median time to onset was 13 days which is within the risk window of 1 to 42 days used by the FDA in their end-of-season analysis of their postmarket study, and a risk window of 1 to 21 days used elsewhere.

Figure 18: Number of Guillain-Barré syndrome cases in the NZ pharmacovigilance database, by year



Source: NZ pharmacovigilance database (data extracted via Qlik suspected adverse reactions to medicines app 7 May 2025)

[redacted]

[redacted]

4 DISCUSSION AND CONCLUSIONS

Guillain Barré syndrome (GBS) is a rare disorder with an incidence estimated at between 0.4 and 4.0 cases per 100,000 persons per year. Most well-designed prospective studies conducted in developed countries suggest an incidence of 1-2 per 100,000 persons per year. It is thought that cases are generally sporadic with no seasonal pattern, but there is some data to suggest that the incidence of GBS is slightly higher in winter in Western countries.

One case of GBS has been reported from an Arexvy clinical trial, concerning a participant enrolled in a study site in Japan. Data sheets in the UK, Australia, US and Canada all include this case in the undesirable effects section, but the NZ one does not. There is also one case report of GBS with Arexvy reported in the literature by Mikhail et al.

The FDA and CDC have conducted postmarket analyses to investigate the risk of GBS following RSV vaccination. Their findings are summarised in Table 16 of this report and the incidence rate ratios (IRR) range from 2.30 to 2.76, some with very wide confidence intervals.

[redacted] the FDA's analyses, including whether data on a single season is sufficient to investigate the risk of GBS which has seasonal fluctuations, whether the data and findings for people aged ≥65 years can be applied to younger age groups (ie, those aged 50 to 64 years), potential confounders that weren't controlled for, and whether a risk window of 1-42 days was appropriate.

5 ADVICE SOUGHT

The Committee is asked to advise on the following:

- The strength of the evidence for an association between Arexvy and GBS, based on:
  - FDA's postmarket study for observed vs. expected rates and self-controlled case series (SCCS) analyses.
  - CDC's rapid cycle analysis (RCA).
  - Please comment on the methods, results, strengths and limitations of the above FDA and CDC analyses.

[redacted]

- If the Arexvy NZ data sheet requires updating to include information on GBS.
  - If so, what information should be included and in which sections (eg, warnings and precautions, undesirable effects etc.)
- If any other regulatory action is needed (eg, safety communication on the Medsafe website, article in *Prescriber Update* etc.).

[redacted]

7 REFERENCES

1. Sejvar, J.J., et al., *Guillain–Barré syndrome and Fisher syndrome: Case definitions and guidelines for collection, analysis, and presentation of immunization safety data.* Vaccine, 2011. **29**(3): p. 599-612.
2. Webb, A.J.S., et al., *Seasonal variation in Guillain-Barré syndrome: a systematic review, meta-analysis and Oxfordshire cohort study.* Journal of Neurology, Neurosurgery & Psychiatry, 2015. **86**(11): p. 1196-1201.
3. Immunisation Advisory Centre. *Guillain-Barré Syndrome (GBS) and vaccines*. 2025 [accessed 19 May 2025]; Available from: https://www.immune.org.nz/factsheets/guillain-barre-syndrome-gbs-and-vaccines.
4. GlaxoSmithKline NZ Limited. *Arexvy New Zealand Data Sheet*. 2025 4 February 2025 [accessed 19 May 2025]; Available from: https://www.medsafe.govt.nz/profs/Datasheet/a/Arexvyinj.pdf.
5. Huynh, K., et al., *Exploring the "Two-Hit" Phenomenon of Guillain-Barré Syndrome Following Respiratory Syncytial Virus and Influenza Vaccinations.* Cureus, 2024. **16**(9): p. e68899.
6. Mikhail, E., et al., *ACUTE DEMYELINATING POLYRADICULONEUROPATHY AFTER THE NOVEL RSV VACCINATION: A CASE REPORT AND LITERATURE REVIEW.* CHEST, 2024. **166**(4, Supplement): p. A2791-A2792.
7. Medscape. *Acute Inflammatory Demyelinating Polyradiculoneuropathy* 2021 [accessed 12 May 2025]; Available from: https://emedicine.medscape.com/article/1169959-overview.
8. Helgeson, S.A., A.J. Heckman, and D.M. Harris, *First Reported Case of Respiratory Syncytial Virus Infection Causing Guillain-Barré Syndrome.* Indian J Crit Care Med, 2018. **22**(4): p. 309-310.
9. Jayakumar, P., et al., *RSV-induced Guillain-Barré Syndrome: A Case Report.* 2023.
10. Ueshima, M., et al., *A pediatric suspected case of Guillain-Barré syndrome following respiratory syncytial virus RSV infection.* Pediatr Int, 2024. **66**(1): p. e15733.
11. Gupta, M., et al., *A Case of Pediatric Guillain-Barré Syndrome After Respiratory Syncytial Virus Infection.* Pediatr Neurol, 2023. **146**: p. 129-131.
12. Immunisations UK. *RSV Vaccine and the rare Guillain-Barré Syndrome (GBS) side effect: Understanding Prevalence and Risks*. 2025 [accessed 12 May 2025]; Available from: https://immunisationsuk.co.uk/rsv-vaccine-and-the-rare-guillain-barre-syndrome-gbs-side-effect-understanding-prevalence-and-risks/.
13. Laemmle-Ruff, I. and N.W. Crawford, *Respiratory syncytial virus prevention is finally here: An overview of safety.* Aust J Gen Pract, 2024. **53**(10): p. 704-708.
14. Anastassopoulou, C., et al., *Development, Current Status, and Remaining Challenges for Respiratory Syncytial Virus Vaccines.* Vaccines (Basel), 2025. **13**(2).
15. Kelleher, K., N. Subramaniam, and S.B. Drysdale, *The recent landscape of RSV vaccine research.* Ther Adv Vaccines Immunother, 2025. **13**: p. 25151355241310601.
16. Klein, N.P., et al., *Surveillance for Adverse Events After COVID-19 mRNA Vaccination.* Jama, 2021. **326**(14): p. 1390-1399.
17. Moll, K., et al., *Background rates of adverse events of special interest for COVID-19 vaccine safety monitoring in the United States, 2019-2020.* Vaccine, 2023. **41**(2): p. 333-353.
18. Li, X., et al., *Characterising the background incidence rates of adverse events of special interest for covid-19 vaccines in eight countries: multinational network cohort study.* Bmj, 2021. **373**: p. n1435