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Letter to the Editor

Efficacy and safety of respiratory syncytial virus prefusion F protein vaccines in adults

Dear Editor,

Respiratory syncytial virus (RSV) discovered in 1956 is the most common cause of acute lower respiratory tract infection (ALRTI) worldwide in children under 5 years old and adults at 65 years or above.[1,2] Efficacy and safety are essential in the development, testing, and evaluation of vaccines to ensure their effectiveness in preventing diseases while minimizing the potential risks to vaccinated individuals. Here, we performed a systematic review to synthesize data from those published studies estimating the efficacy and safety for RSV prefusion F (pre-F) protein vaccines, which is the only vaccine type that received the FDA approval as of October 2023.

The goal of vaccination is to establish immunity in the individual, therefore to prevent disease upon exposure to the infectious pathogen, and provide indirect protection to those unvaccinated. However, RSV vaccine development has faced many challenges including the complex immune response, safety, and viral diversity. One instance of vaccine failure is the use of a formalin-inactivated alum-formulated vaccine for respiratory syncytial virus (FI-RSV) during the 1960s, leading to a syndrome of vaccine-enhanced illness upon subsequent natural RSV infection in the following season.[3] The availability of structural information for viral surface proteins has revolutionized vaccine antigen design in recent years. The development of RSV vaccines has been greatly accelerated by a study of the structure-based design of a fusion glycoprotein vaccine published in 2013 [4] that led to the two vaccines, as of July 2023, Arexvy from GSK and Abrysvo from Pfizer, and both have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to protect older adults against severe RSV infection. One month later, FDA further approved Abrysvo for use in pregnant women to protect infants from RSV.

We identified 59 published articles by searching PubMed, and retrieved 57 related clinical trials of adults, excluding maternal vaccination, from ClinicalTrials.gov on 21 Nov, 2023. After removing 14 duplicates, we identified 102 distinct studies for screening. Of 22 studies meeting the inclusion requirements for this review, 6 reported efficacy results, and 22 reported safety results, as shown in Fig. S1. The efficacy and safety results for four types of RSV pre-F vaccines were included: RSVpreF (MEDI8897), RSVpreF3 OA (GSK3844766A), and Ad26. RSV.preF. Table 1 summarized the efficacy values and the associated RSV infection/illness.

The efficacy results of phase 3 clinical trials for the vaccines of RSVPreF for older adults [OA] and RSVpreF show that a range of RSV-associated illnesses were significantly reduced in the vaccine group for all younger, middle-aged and older adults (Table 1). For example, RSVPreF OA in older adults has the vaccine efficacy 82.6% (95% CI: 57.9%, 94.1%) against RSV-related lower respiratory tract disease (RSV LRTD).[5] RSVPreF would prevent 86.7% (95% CI: 53.8, 96.5) symptomatic infection in old adults, and 85.7 (96.66% CI: 32.0, 98.7) RSV-associated lower respiratory tract illness (RSV-LRTI) in young and middle-aged adults.[6]

The safety results suggest that the incidence of adverse events (AE) was similar across treatment groups and the control groups (either placebo or vaccines with long-term usage and well-proven safety) in adults (Table S2). For example, in the solicited safety population of older adults, the incidence of unsolicited AEs within 30 days after RSVPreF3 OA injection was similar between the two groups, with rates of 14.9% in the vaccine group and 14.6% in the placebo group.[5] In contrast, the RSVpreF vaccine resulted in a non-significant 1% higher risk of systemic AEs in the treatment group than in the placebo group among older adults (aged 60 or older), with 27% experiencing such events,[7] and a 5.8% incidence rate of AEs in the vaccination group of young and middle-aged adults aged 18–49 years, slightly 0.3% lower than the placebo group.[8] These results from the included studies demonstrated encouraging efficacy and acceptable safety of the two study RSV vaccines.

The ideal RSV vaccine would induce a strong and long-lasting immune response without causing significant side effects. It would also need to be effective against different strains of RSV, as the virus can evolve and mutate over time. Although GSK and Pfizer's vaccines have gained significant success, concerns about RSV vaccines still have been raised. The immune response to the virus can be complex and not fully understood. In the past, some vaccine candidates have actually worsened the disease or led to enhanced respiratory disease in animal studies. This is a phenomenon known as vaccine-associated enhanced respiratory disease (VAERD). There is still a need for long-term follow-up to examine the safety of the approved RSV vaccines.

In conclusion, the development of RSV pre-F protein vaccines has been a result of decades of research and has led to significant advancements in preventing RSV-related illnesses, especially in vulnerable populations. The systematic review of published studies and clinical trials presented in this article demonstrates encouraging efficacy and acceptable safety of the two study RSV vaccines, Arexvy from GSK and Abrysvo from Pfizer. Accurate estimates of vaccine

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Table 1
Summary of the efficacy results for the pre-F protein vaccines in development (More details in Table S1, Table S3).

Vaccine	Phase as of 30 August 2023	Outcome	Population		Efficacy Period
			Young and middle-aged adults[a]	Older adults[b]	
GSK's RSVPreF3 OA	Approved for older adults	LRTD [c]		82.6 (57.9, 94.1)[5,i]	Follow-up of 6.7 months on average
Pfizer's RSVpreF	Approved for older adults and maternal vaccination	LRTI [d]		85.7 (32.0, 98.7)[7,j]	Follow-up of 11 months from day 15 after vaccination until the end of season 1
		Symptomatic infection[e]	86.7 (53.8, 96.5)[6]		Follow-up of 12 days after challenge
		Infection [f]	47.06 (2.18, 71.35)[9]		Follow-up of 12 days after challenge
Janssen's Ad26.RSV.preF	Phase 2	LRTD [g]		80.0 (52.2, 92.9)[10,h]	Follow-up of 21 months from 1 Sep 2019 to 6 June 2022

Note, the values and 95% confidence interval for the efficacy of RSV vaccines against RSV infection/illness were summarized in this table.
[a] Young and middle-aged adults aged 18–50.
[b] Older adults, could be aged 60 or older or 65 or older in different studies.
[c] RSV-related lower respiratory tract disease (RSV LRTD) was identified by the adjudication committee.
[d] RSV-associated lower respiratory tract illness (RSV-LRTI) is an ARI with 3 or more of the lower respiratory signs/symptoms lasting more than 1 day during the same illness, plus RT-PCR-confirmed RSV infection within 7 days of ARI symptom onset.
[e] qRT-PCR–confirmed symptomatic RSV infection (Variant 1). Any 2 detectable (quantifiable OR detectable and < LLOQ) qRT-PCR results from nasal swabs obtained on ≥2 consecutive days from Day 2 to Day 12 AND symptoms from 2 different categories (URT, LRT, systemic) or any grade 2 symptom (bothersome but not interfering with daily activity)
[f] Liberal RSV infection is defined as ≥2 quantifiable rt-PCR measurements above the LLOQ plus any clinical symptom of any severity.
[g] RSV LRTD definition is ≥3 symptoms of lower respiratory tract infection (LRTI).
[h] The confidence interval of the efficacy results is 94.2%.
[i] The confidence interval of the efficacy results is 96.5%.
[j] The confidence interval of the efficacy results is 96.66%.

efficacy and effectiveness are crucial to fully understand the potential impact of RSV pre-F vaccination in populations.

Code availability

Code used for data analysis is freely available upon request.

Author contributions

ZD, SW, RC, SS, and YB: conceived the study, designed statistical and modellingmethods, conducted analyses, interpreted results, wrote and revised themanuscript; LW, EL, PW and BJC: interpreted results and revised the manuscript.

Data availability

All data are collected from open source with detailed description in Section Method.

Declaration of Competing Interest

BJC reports honoraria from AstraZeneca, Sanofi Pasteur, GSK, Moderna and Roche. The authors report no other potential conflicts of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106211.

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