ORIGINAL ARTICLE

RSV Prefusion F Vaccine for Prevention of Hospitalization in Older Adults

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ABSTRACT

BACKGROUND

Respiratory syncytial virus (RSV) can cause serious illness in older adults. The bivalent RSV prefusion F protein–based vaccine (RSVpreF) has been shown to prevent RSV-associated respiratory illness, but data from randomized trials with regard to its effect on outcomes involving hospitalization are limited.

METHODS

In this pragmatic, open-label trial with individual randomization, participants who were 60 years of age or older were assigned in a 1:1 ratio to receive the RSVpreF vaccine (the RSVpreF group) or no vaccine (the control group) during the 2024–2025 winter season. Baseline and outcome data were collected with the use of national registries. The primary end point was hospitalization for RSV-related respiratory tract disease. Secondary end points included hospitalization for RSV-related lower respiratory tract disease and hospitalization for respiratory tract disease from any cause. The prespecified criterion for success for the primary end point and RSV-related secondary end points was a minimum vaccine effectiveness of greater than 20%.

RESULTS

Of 131,379 participants who underwent randomization, 131,276 were included in the intention-to-treat population. During follow-up, hospitalization for RSV-related respiratory tract disease occurred in 3 of 65,642 participants in the RSVpreF group and in 18 of 65,634 participants in the control group (0.11 events vs. 0.66 events per 1000 participant-years; vaccine effectiveness, 83.3%; 95% confidence interval [CI], 42.9 to 96.9; P=0.007 for minimum effectiveness of >20%). The RSVpreF group also had fewer hospitalizations for RSV-related lower respiratory tract disease than the control group (1 vs. 12; vaccine effectiveness, 91.7%; 95% CI, 43.7 to 99.8; P=0.009 for minimum effectiveness of >20%), as well as fewer hospitalizations for respiratory tract disease from any cause (284 vs. 335; vaccine effectiveness, 15.2%; 95% CI, 0.5 to 27.9; P=0.04 for vaccine effectiveness of >0%). The incidence of serious adverse events was similar in the two groups.

CONCLUSIONS

Among adults 60 years of age or older, the RSVpreF vaccine reduced the incidence of hospitalization for RSV-related respiratory tract disease as compared with no vaccine. (Funded by Pfizer; European Union Clinical Trials number, 2024-516600-42-00; DAN-RSV ClinicalTrials.gov number, NCT06684743.)

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Respiratory syncytial virus (RSV) is a common cause of respiratory tract disease in older adults[1,2] and a major cause of severe respiratory illness in both older adults and persons with underlying conditions. It is estimated that 5.2 million cases of severe RSV-related respiratory illness, 470,000 hospitalizations, and 33,000 deaths occur annually in industrialized countries.[3-7]

A bivalent RSV prefusion F protein–based vaccine (RSVpreF), which contains stabilized prefusion F glycoproteins from RSV, was recently developed for adults 60 years of age or older. Phase 3 trials of RSVpreF vaccines against RSV-related lower respiratory tract disease have shown vaccine efficacy levels of 88.9%, 82.6%, and 83.7% for nonadjuvanted, adjuvanted, and mRNA-based forms, respectively.[8-10] However, the trials were not designed or powered to evaluate severe outcomes such as hospitalization. Data from preliminary observational studies suggest that the RSVpreF vaccine has 73 to 90% real-world effectiveness against hospitalization for RSV-related respiratory illness, but such studies are limited by confounding factors.[11-13] In addition, the effects of RSVpreF vaccination on hospitalization for respiratory disease from any cause or for cardiorespiratory disease remain unclear.

To address this gap in evidence, we conducted DAN-RSV (A Pragmatic Randomized Trial to Evaluate Bivalent RSV Prefusion F Protein–based Vaccine Effectiveness for Preventing RSV Hospitalizations in Adults Aged 60 Years or Above) to compare the RSVpreF vaccine with no RSV vaccine in adults 60 years of age or older. The trial leveraged individual randomization, broad eligibility criteria, and an efficient, real-world data infrastructure, with the use of electronic health records and national administrative registries to support recruitment, follow-up, and ascertainment of outcomes. This approach enabled a rigorous evaluation of vaccine effectiveness against hospitalization for RSV-related respiratory tract disease, respiratory tract disease from any cause, or cardiorespiratory disease in a large population of older adults who were reasonably representative of the broader Danish adult population.

Methods

Trial Design and Oversight

We conducted this phase 4, investigator-initiated, pragmatic, open-label, parallel-group, individually randomized clinical trial in Denmark during the 2024–2025 winter season. The academic research group at the Center for Translational Cardiology and Pragmatic Randomized Trials (CTCPR) at the Department of Cardiology, Copenhagen University Hospital, Herlev and Gentofte, Copenhagen, oversaw the trial and assumed full responsibility for conducting the trial. The trial funder (Pfizer) participated in the trial design, development of the protocol (available with the full text of this article at NEJM.org), and development of the statistical methods but had no involvement in the conduct of the trial or in the collection or analysis of the data. The trial was carried out in collaboration with the private vaccination provider Danske Lægers Vaccinations Service, a member of the European LifeCare Group, which organized vaccination sessions at more than 40 locations, obtained informed consent, performed randomization, and administered the trial vaccine. CTCPR staff worked at the central trial site, oversaw the overall conduct of the trial, performed data linkage to the national health registries to obtain baseline and outcome data, and performed safety monitoring.

The rationale and design of the trial have been described in detail previously.[14] The trial protocol was approved by the Danish Medical Research Ethics Committees and the Danish Medicines Agency. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation guidelines for Good Clinical Practice. The Danish Health Data Authority granted access to nationwide registry data, which were used for the identification of eligible participants and for collection of baseline and outcome data. Four authors from academic institutions had access to the trial data and vouch for the accuracy and completeness of the data. All the authors agreed to submit the manuscript for publication and vouch for the fidelity of the trial to the protocol.

Trial Participants

Adults who were 60 years of age or older and had a Danish civil registration number were eligible to enroll in the trial. The trial had no formal exclusion criteria but required that vaccination follow routine clinical guidelines, with assessment for contraindications (hypersensitivity to the vaccine or its components or acute illness on the day of vaccination). Since the RSVpreF vaccine was approved as a one-time dose in Denmark at

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the time of enrollment, participants were asked at their vaccination appointment if they had previously received the vaccine, according to routine vaccination practices. All the participants provided written informed consent that authorized access to their electronic medical records and data linkage to the national health registries.

Participants were recruited primarily by means of electronic invitation letters delivered by the Danish governmental digital mail system, Digital Post.[15] All potentially eligible individuals in Denmark with access to Digital Post received an invitation (approximately 5.3% of the adult Danish population are exempt from Digital Post).[16]

RANDOMIZATION

Participants were randomly assigned in a 1:1 ratio to receive RSVpreF (the RSVpreF group) or no RSV vaccine (the control group) according to centralized computer-generated blocked randomization with varying blocks of 6, 8, and 10. Participants had the option to provide informed consent electronically before the trial visit; if this option was used, randomization occurred immediately after consent, the participant was immediately informed of the trial-group assignment, and those assigned to the control group were informed that they did not have to attend their scheduled trial visit. Only participants assigned to receive the RSVpreF vaccine were required to attend their scheduled visit. If participants provided informed consent in person at the trial visit, randomization was performed with the use of tablet computers linked to the centralized randomization system. The trial used an open-label design.

TRIAL PROCEDURES

The RSVpreF vaccine contained RSV subgroup A stabilized prefusion F antigen (60 μg) and RSV subgroup B stabilized prefusion F antigen (60 μg) and was administered as a single intramuscular injection. The control group did not receive any vaccine as part of the trial.

Identifying information, including the Danish civil registration number (a unique identification number assigned at birth or at the time of immigration to Denmark), signed informed consent, the date of the scheduled trial visit, and the assigned trial group, was automatically transferred to the central site once informed consent was obtained. Additional data collection at the vaccination clinic was limited to confirmation of trial participation and documentation of vaccine administration. Upload of all participants' civil registration numbers to the Danish Health Data Authority enabled linkage to the national administrative health registries, from which baseline and outcome data were collected. Access to electronic health records was available for confirmation of clinical outcomes. The registries are described in detail in the trial protocol.

International Classification of Diseases, 10th Revision (ICD-10), codes were used to define baseline conditions and outcomes, and Anatomical Therapeutic Chemical codes were used to define vaccination status. Clinical outcomes were ascertained with the use of prespecified registry-based definitions (provided in the protocol). We reviewed data from a period of 10 years before trial enrollment to identify baseline conditions. Participants were observed for clinical outcomes from 14 days after the initially scheduled trial visit date (regardless of any rescheduling of vaccination) until May 31, 2025. This 14-day window allowed for the vaccine to elicit a sufficient immune response.

END POINTS

The primary end point was hospitalization for RSV-related respiratory tract disease, defined as hospitalization with either a primary diagnosis code of RSV infection or a primary diagnosis code of respiratory tract disease combined with RSV infection that was confirmed by a specific ICD-10 code for RSV infection as the secondary diagnosis or a positive RSV test performed within 7 days before or 2 days after admission. Key secondary end points were hospitalization for RSV-related lower respiratory tract disease and hospitalization for respiratory tract disease from any cause. Additional secondary and exploratory end points included hospitalization for RSV-related cardiorespiratory disease, hospitalization for cardiorespiratory disease from any cause, hospitalization for lower respiratory tract disease from any cause, hospitalization for any cause, and death from any cause.

In a prespecified subgroup analysis of the primary end point, participants were stratified according to age group (60 to 74 years and ≥75 years), the presence or absence of immunosuppression, influenza vaccination in the same season (yes or no), previous pneumococcal vaccination (yes or no), and the presence or absence of any chronic disease, chronic lung disease, cardiovascular disease, cancer, or chronic kidney disease. A pre-

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specified analysis of secondary end points involving events from any cause was limited to data from the peak of the RSV season. Prespecified sensitivity analyses included end-point events that occurred during the 14-day window after the originally scheduled trial visit date. Serious adverse events, defined as deaths or hospitalizations that occurred within 6 weeks after vaccination in the RSVpreF group or within 6 weeks after the scheduled trial visit in the control group, were recorded.

STATISTICAL ANALYSIS

We estimated that in a sample of 83,990 participants, 72 primary end-point events would occur, which would provide the trial with approximately 90% power at a one-sided alpha level of 0.025 to reject the null hypothesis that vaccine effectiveness against hospitalization for RSV-related respiratory tract disease did not exceed 20%. In this calculation, we assumed a vaccine effectiveness of 65% and an incidence of hospitalization for RSV-related respiratory tract disease in the control group of 1.27 events per 1000 participants (on the basis of RSV data from the 2022–2023 winter season in Denmark). We estimated that 106,668 participants would be required to provide the trial with similar power for the first key secondary end point, assuming an incidence of hospitalization for RSV-related lower respiratory tract disease in the control group of 1.00 per 1000 participants. The final target sample size was increased to 130,000 to account for uncertainty in the severity of the RSV season and potential crossover between trial groups.

Participant characteristics at baseline were summarized according to trial group. All analyses were performed according to the intention-to-treat principle unless otherwise specified. In a key secondary analysis, the primary end point was assessed in the as-treated population with balanced follow-up times. In this analysis, participants who were assigned to the RSVpreF group were matched in a 1:1 ratio with participants assigned to the control group according to the randomization sequence. End-point events were then counted from 14 days after the actual vaccination date for those in the RSVpreF group, and controls were assigned an equivalent follow-up period to balance any time gained or lost through rescheduled vaccination visits (details are provided in the statistical analysis plan, included with the protocol). Because this analysis did not adhere to the intention-to-treat principle, it may be subject to potential bias. The as-treated approach with balanced follow-up times was also used for the prespecified sensitivity analyses of the additional secondary end points.

To calculate vaccine effectiveness, the incidence rate ratio for end-point events in the RSVpreF group as compared with the control group was subtracted from 1, and the difference was multiplied by 100 to obtain a percentage; 95% confidence intervals were constructed with the use of the exact Clopper–Pearson method.[17] Only the first end-point event to occur in a participant (for a given end point) was considered in the calculation of vaccine effectiveness. In the intention-to-treat analyses, time at risk was considered to begin 14 days after the originally scheduled trial visit and ended with the occurrence of an end-point event, death, emigration, or withdrawal of consent or on May 31, 2025, whichever occurred first.

The key secondary hypotheses were tested in a prespecified hierarchical order: analysis of the primary end point in the as-treated population with balanced follow-up times, followed by analysis of hospitalization for RSV-related lower respiratory tract disease and hospitalization for respiratory tract disease from any cause. The primary analysis of the primary end point (intention-to-treat approach), the analysis of the primary end point according to an as-treated approach with balanced follow-up times, and the analysis of hospitalization for RSV-related lower respiratory tract disease were performed with a two-sided alpha of 0.05 and a null hypothesis that vaccine effectiveness did not exceed 20% (the prespecified threshold for success of the vaccine); the reported P values were calculated on the basis of this null hypothesis. All other end points were analyzed at the same alpha level with a null hypothesis that vaccine effectiveness was 0%. P values were obtained from Poisson models, with exact models used for comparisons with few events. Testing of subsequent key secondary hypotheses would continue down the hierarchy with the same alpha until a null hypothesis could not be rejected, whereafter remaining end points were assessed descriptively.

Because the statistical analysis plan did not include a provision for correcting for multiplicity in tests for these additional secondary end points

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or in subgroups, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary end points other than the key secondary end points. The statistical analysis was performed with the use of SAS, version 9.4 (SAS Institute); Stata MP, version 19.5 (StataCorp); and R, version 4.3.3 (R Foundation for Statistical Computing). Additional information regarding the statistical analysis is provided in the protocol.

RESULTS

ENROLLMENT, RANDOMIZATION, AND FOLLOW-UP

From November 18, 2024, through December 28, 2024, a total of 1,399,220 potentially eligible adults were invited to enroll in the trial, and 131,379 adults (approximately 8.6% of the Danish population who were 60 years of age or older) underwent randomization: 131,276 were included in the intention-to-treat population: 65,642 in the RSVpreF group and 65,634 in the control group (Fig. 1). The as-treated analysis with balanced follow-up times included data from 124,927 participants: 62,469 in the RSVpreF group and 62,458 in the control group (Fig. S1 in the Supplementary Appendix, available at NEJM.org).

The baseline characteristics of the two groups were well balanced (Table 1); the representativeness of the trial population is shown in Table S1. Concordance between the assigned trial group and the intervention received was 95.9% in the RSVpreF group (2673 participants were never vaccinated) and more than 99.9% in the control group (30 participants received the RSVpreF vaccine at the trial visit despite being assigned to the control group). The median time from randomization to the initially scheduled trial visit was 13 days (interquartile range, 6 to 21). During follow-up, 786 participants in the control group (1.2%) received an RSV vaccine outside the trial. In the RSVpreF group, 5467 participants (8.3%) rescheduled to a later date (median delay, 13 days; interquartile range, 5 to 29) and 1264 (1.9%) rescheduled to an earlier date (median difference, 6 days; interquartile range, 2 to 14). Seventy-nine participants withdrew consent before registry linkage.

National RSV testing data were received on June 16, 2025, and the final trial database was assembled on June 29, 2025. During follow-up, a total of 2236 RSV tests were performed in 2175 participants (1.7%), including 1089 participants (1.7%) in the RSVpreF group and 1086 (1.7%) in the control group. In addition, 6660 influenza tests were performed. Of 619 participants who were hospitalized for any respiratory disease during follow-up, 141 (22.8%) underwent RSV testing — 65 of 284 participants (22.9%) in the RSVpreF group and 76 of 335 participants (22.7%) in the control group.

PRIMARY AND KEY SECONDARY END POINTS

In the intention-to-treat population, a primary end-point event occurred in 3 participants in the RSVpreF group (0.11 events per 1000 participant-years) and in 18 participants in the control group (0.66 events per 1000 participant-years; absolute rate reduction, 0.55 events per 1000 participant-years; vaccine effectiveness, 83.3%; 95% confidence interval [CI], 42.9 to 96.9; P=0.007). This result met the criterion for statistical success of the vaccine (minimum effectiveness of >20%) (Table 2 and Fig. 2). Similar results were found in the as-treated population with balanced follow-up times (3 vs. 17 events; absolute rate reduction, 0.54 per 1000 participant-years; vaccine effectiveness, 82.4%; 95% CI, 39.0 to 96.7; P=0.01) (Table 2). The effect of RSVpreF with respect to the primary end point was similar among prespecified subgroups (Fig. 3).

The incidence of hospitalization for RSV-related lower respiratory tract disease was lower in the RSVpreF group than in the control group (1 event vs. 12 events; absolute rate reduction, 0.40 events per 1000 participant-years; vaccine effectiveness, 91.7%; 95% CI, 43.7 to 99.8; P=0.009), as was the incidence of hospitalization for respiratory tract disease from any cause (284 events vs. 335 events; absolute rate reduction, 1.87 events per 1000 participant-years; vaccine effectiveness, 15.2%; 95% CI, 0.5 to 27.9; P=0.04).

Point estimates with 95% confidence intervals for the additional secondary and exploratory end points are listed in Table 2. Results of sensitivity analyses, the as-treated analysis, and the analysis of end points involving events from any cause during the peak of the RSV season are shown in the Supplementary Appendix (Tables S2 through S6).

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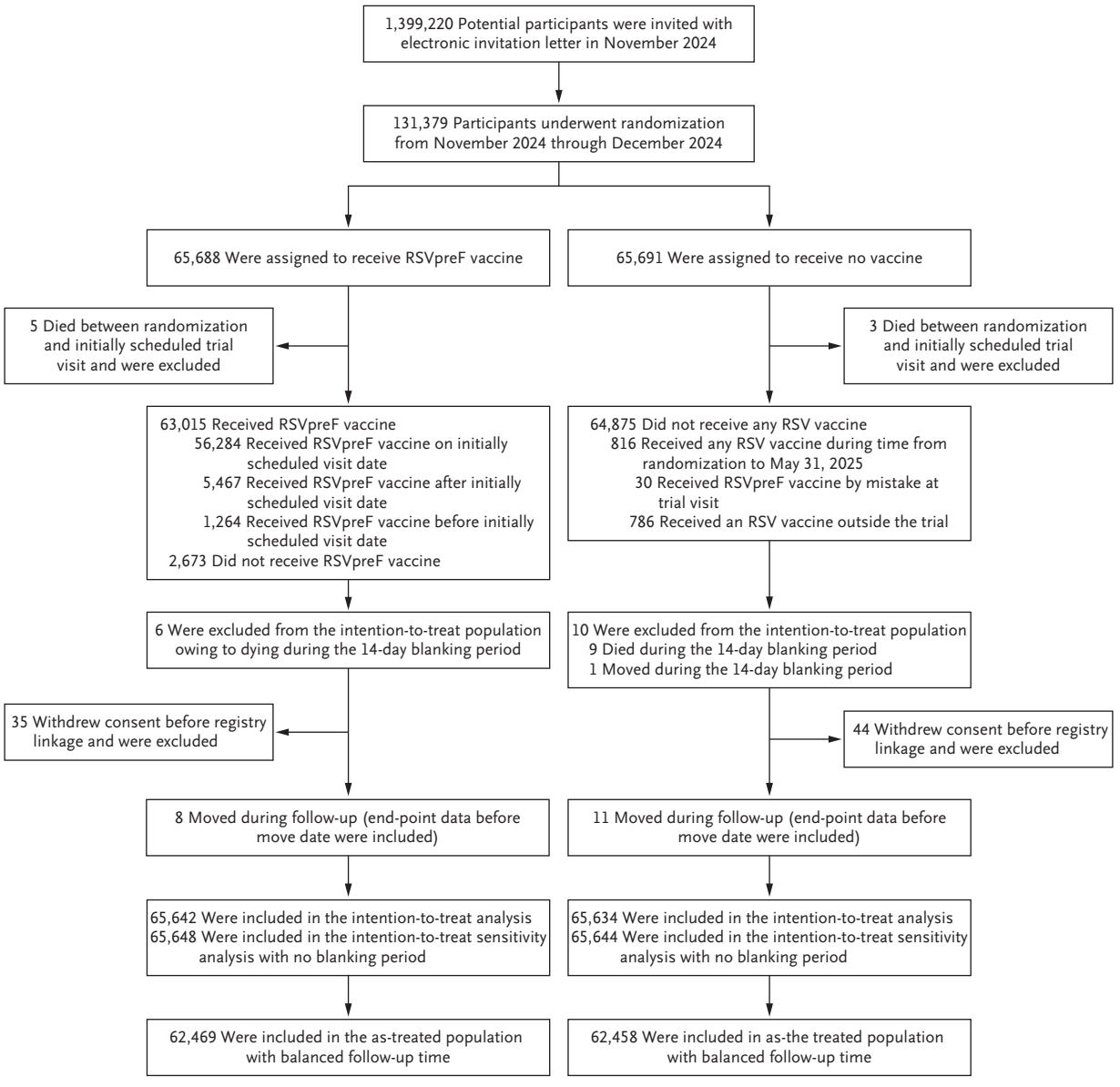

Figure 1. Enrollment, Randomization, and Follow-up.

All eligible adults in Denmark were sent an electronic invitation letter by means of the Danish governmental electronic letter system. Participants 60 years of age or older were assigned to receive the bivalent RSV prefusion F protein–based (RSVpreF) vaccine or no vaccine. The intention-to-treat population included all participants who had undergone randomization, regardless of crossover. The as-treated population was selected on the basis of a matching algorithm, in which participants in the RSVpreF group were matched with participants in the control group according to the randomization sequence. End-point events were then counted from 14 days after the actual vaccination date for those in the RSVpreF group, and controls were assigned an equivalent follow-up period to balance any time gained or lost through rescheduled vaccination visits (details are provided in the protocol).

SAFETY

During the 6-week safety surveillance window, at least one serious adverse event occurred in 3010 participants — 1341 participants in the RSVpreF group and 1669 in the control group (Table 3). Numbers of serious adverse events according to groups of organ systems were similar in the RSVpreF group and the control group (Table 3).

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Table 1. Characteristics of the Participants at Baseline.*

Characteristic	RSVpreF Group (N=65,642)	Control Group (N=65,634)
Age — yr	69.4±6.5	69.4±6.5
Age ≥75 yr — no. (%)	13,839 (21.1)	13,853 (21.1)
Male sex — no. (%)	32,931 (50.2)	33,082 (50.4)
Any chronic disease — no. (%)	27,562 (42.0)	27,554 (42.0)
Chronic lung disease — no. (%)	4,808 (7.3)	4,802 (7.3)
Chronic obstructive pulmonary disease — no. (%)	1,706 (2.6)	1,678 (2.6)
Diabetes — no. (%)	7,190 (11.0)	7,249 (11.0)
Cancer — no. (%)	7,549 (11.5)	7,547 (11.5)
Chronic cardiovascular disease — no. (%)	14,377 (21.9)	14,285 (21.8)
Ischemic heart disease — no. (%)	4,896 (7.5)	4,850 (7.4)
Heart failure — no. (%)	1,513 (2.3)	1,460 (2.2)
Atrial fibrillation — no. (%)	5,154 (7.9)	4,972 (7.6)
Cerebrovascular disease — no. (%)	2,287 (3.5)	2,386 (3.6)
Hypertension — no. (%)	9,818 (15.0)	9,904 (15.1)
Chronic kidney disease — no. (%)	6,660 (10.1)	6,704 (10.2)
Liver disease — no. (%)	960 (1.5)	1,051 (1.6)
Neurologic or neuromuscular disease — no. (%)	1,477 (2.3)	1,429 (2.2)
Rheumatic disease — no. (%)	1,511 (2.3)	1,475 (2.2)
Immunodeficiency — no. (%)	2,619 (4.0)	2,580 (3.9)
Influenza vaccination in previous season — no. (%)	52,552 (80.1)	52,381 (79.8)
Influenza vaccination in 2024–2025 season before randomization — no. (%)	53,008 (80.8)	52,818 (80.5)
Coadministration of influenza vaccine — no. (%)	113 (0.2)	0
Coadministration of Covid-19 vaccine — no. (%)	110 (0.2)	0
Previous pneumococcal vaccination — no. (%)	42,077 (64.1)	41,996 (64.0)
Previous RSV vaccination — no. (%)	61 (0.1)	66 (0.1)

* Data are shown for the participants included in the intention-to-treat population. Information with regard to characteristics at baseline was obtained from nationwide administrative health registries with the use of prespecified definitions. Covid-19 denotes coronavirus disease 2019, RSV respiratory syncytial virus, and RSVpreF RSV prefusion F protein–based vaccine.

A serious adverse event that was considered by the investigator to be related to the RSVpreF vaccine occurred in 5 participants. Of these serious adverse events, 2 were expected side effects (2 cases of headache or malaise) and 3 were unexpected (1 case of Bell's palsy, 1 case of abdominal pain with elevated liver enzymes, and 1 case of pericarditis). No cases of Guillain–Barré syndrome occurred within the 6-week safety period. A total of 50 fatal serious adverse events occurred during this period (17 in the RSVpreF group and 33 in the control group); none were considered by the investigator to be related to the vaccine. By the end of the first season of follow-up, 146 fatal events had occurred in the RSVpreF group and 120 had occurred in the control group; the between-group difference was not statistically significant.

DISCUSSION

Our randomized trial evaluated the real-world effectiveness of the RSVpreF vaccine against clinically severe outcomes involving hospitalization in adults 60 years of age or older. In this trial, the RSVpreF vaccine reduced the incidence of hospi-

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Table 2. Primary, Secondary, and Exploratory End Points.*

End Point	RSVpreF Group				Control Group				Absolute Rate Reduction†	Vaccine Effectiveness (95% CI)	P Value‡
	Participants	Events	Total Follow-up	Incidence Rate	Participants	Events	Total Follow-up	Incidence Rate			
	no.	*no.*	*participant-yr*	*events/1000 participant-yr*	*no.*	*no.*	*participant-yr*	*events/1000 participant-yr*	*events/1000 participant-yr*	%	
Primary end point											
Hospitalization for RSV-related respiratory tract disease											
ITT population	65,642	3	27,320	0.11	65,634	18	27,330	0.66	0.55	83.3 (42.9 to 96.9)	0.007§
Age group in ITT population											
60–74 years	51,803	1	21,670	0.05	51,781	10	21,668	0.46	0.41	90.0 (29.7 to 99.8)	
≥75 years	13,839	2	5,650	0.35	13,853	8	5,662	1.41	1.06	75.0 (−25.0 to 97.4)	
As-treated population with balanced follow-up times	62,469	3	25,639	0.12	62,458	17	25,630	0.66	0.54	82.4 (39.0 to 96.7)	0.01§
Key secondary end points											
Hospitalization for RSV-related lower respiratory tract disease	65,642	1	27,321	0.04	65,634	12	27,332	0.44	0.40	91.7 (43.7 to 99.8)	0.009§
Hospitalization for respiratory tract disease from any cause	65,642	284	27,257	10.42	65,634	335	27,268	12.29	1.87	15.2 (0.5 to 27.9)	0.04¶
Additional secondary end points											
RSV-related hospitalization‖	65,642	1	27,321	0.04	65,634	8	27,333	0.29	0.25	87.5 (6.8 to 99.7)**	
Hospitalization for RSV-related cardiorespiratory disease	65,642	3	27,320	0.11	65,634	19	27,330	0.70	0.59	84.2 (46.4 to 97.0)**	

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Hospitalization for cardiorespiratory disease from any cause	65,642	715	27,167	26.32	65,634	794	27,171	29.22	2.90	9.9 (0.3 to 18.7)**
Hospitalization for lower respiratory tract disease from any cause	65,642	236	27,269	8.65	65,634	298	27,278	10.92	2.27	20.8 (5.8 to 33.6)**
Hospitalization for any cause	65,642	3,526	26,581	132.7	65,634	3,598	26,583	135.4	2.70	2.0 (–2.7 to 6.5)**
Death from any cause	65,642	146	27,321	5.34	65,634	120	27,335	4.39	–0.95	–21.7 (–56.1 to 5.1)**
Prespecified exploratory RSV-related end points										
Laboratory-confirmed RSV infection (any health care setting)	65,642	19	27,316	0.70	65,634	67	27,316	2.45	1.75	71.6 (52.2 to 83.9)**
Hospitalization for any cause plus a positive RSV test	65,642	4	27,320	0.15	65,634	20	27,329	0.73	0.58	80.0 (40.3 to 95.0)**
Prespecified exploratory influenza-related end points										
Laboratory-confirmed influenza (any health-care setting)	65,642	251	27,257	9.21	65,634	217	27,280	7.95	–1.26	–15.8 (–39.3 to 4.0)**
Influenza-related hospitalization‖	65,642	48	27,309	1.76	65,634	37	27,325	1.35	–0.41	–29.8 (–104.8 to 17.3)**

* End-point events that occurred during the first RSV season in the winter of 2024–2025 are included. Analyses of primary and secondary end points were performed in the intention-to-treat (ITT) population unless otherwise specified. RSVpreF denotes RSV prefusion F protein–based vaccine.

† Absolute rate reductions were calculated by subtracting the incidence of events in the RSVpreF group from the incidence of events in the control group.

‡ P values are reported only for alpha-controlled end points (hospitalization for RSV-related respiratory tract disease in the ITT population, hospitalization for RSV-related respiratory tract disease in the as-treated population with balanced follow-up times, hospitalization for RSV-related lower respiratory tract disease, and hospitalization for respiratory tract disease from any cause) according to the prespecified hierarchical testing sequence.

§ The P value was obtained from a conditional exact model owing to the small number of events in RSVpreF group. The analysis was conducted at a two-sided alpha level of 0.05 with a null hypothesis that vaccine effectiveness would not exceed 20%, and the reported P value was calculated on the basis of this null hypothesis.

¶ The P value was obtained from a standard Poisson model. The analysis was conducted at a two-sided alpha level of 0.05 with a null hypothesis that vaccine effectiveness would be 0%, and the reported P value was calculated on the basis of this null hypothesis.

‖ RSV-related hospitalization and influenza-related hospitalization were defined according to *International Classification of Diseases, 10th Revision* (ICD-10), codes.

** The 95% confidence intervals have not been adjusted for multiplicity and should not be used to make inferences about effects.

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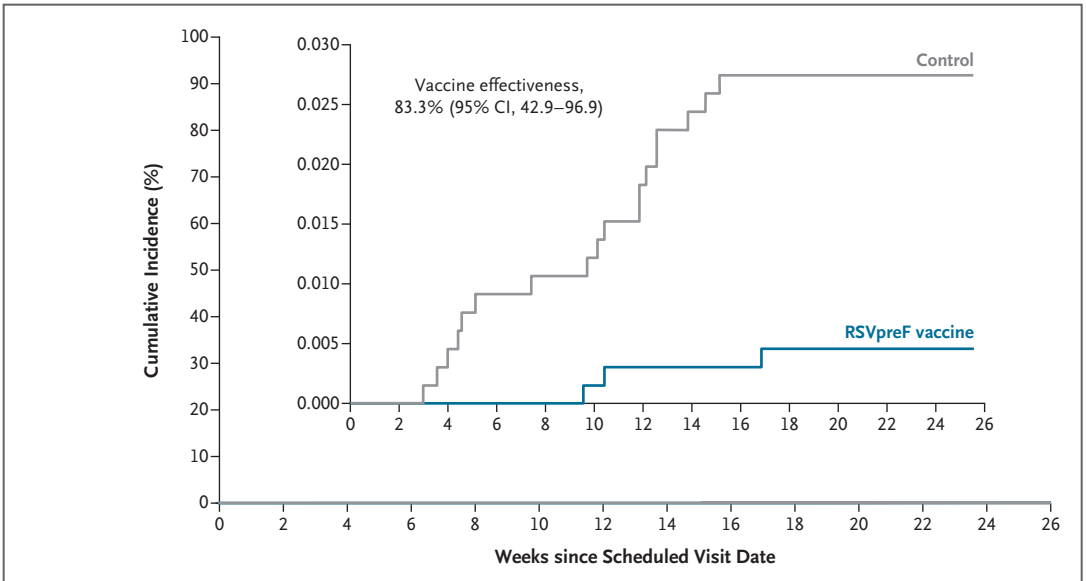

No. at Risk													
Control	65,634	65,624	65,611	65,598	65,579	65,568	65,558	65,541	65,518	60,626	51,431	37,329	4800	0
RSVpreF vaccine	65,642	65,633	65,625	65,613	65,607	65,590	65,573	65,548	65,528	60,548	51,392	37,169	4678	0

Figure 2. Hospitalization for RSV-Related Respiratory Tract Disease.

Time-to-event curves for the primary end point according to trial group are shown. Vaccine effectiveness was calculated by subtracting the incidence rate ratio for end-point events in the RSVpreF group as compared with the control group from 1 and multiplying by 100 to obtain a percentage. The inset displays the same data with an expanded y axis.

talization for RSV-related respiratory tract disease as compared with no vaccine. All RSV-related end-point events were less common in the RSVpreF group than in the control group. In addition, the RSVpreF vaccine reduced the incidence of hospitalization for respiratory tract disease from any cause and lower respiratory tract disease from any cause as compared with no vaccine, and the number of serious adverse events was similar in the two groups.

In the placebo-controlled RSV Vaccine Efficacy Study in Older Adults Immunized against RSV Disease (RENOIR), the RSVpreF vaccine effectively prevented RSV-associated lower respiratory tract illness and acute respiratory illness in adults 60 years of age or older.[8,18] Our trial builds on those findings by showing protection against severe RSV illness that leads to hospitalization. Because RSV is a major cause of hospitalization in older adults during the winter, vaccine effectiveness against hospitalization has relevance for public health.[1,2,19,20] An estimated 470,000 to 787,000 RSV-related hospitalizations occur annually among older adults in industrialized nations, and with the estimated vaccine effectiveness observed in this trial, approximately 416,500 to 655,500 of these events could be prevented with the RSVpreF vaccine if the vaccine effectiveness was identical in all populations.[7,21] Moreover, the true burden of RSV is probably underestimated, in part because of limited testing.[7,22,23] This lack of testing was reflected in our trial, in which fewer RSV-related events occurred than were expected. RSV testing declined as compared with the level of testing in previous post–coronavirus disease 2019 (Covid-19) pandemic seasons, and during the winter of 2024–2025, influenza tests were performed three times more often than RSV tests, which suggests substantial undertesting for RSV in routine care.[24] Absolute rate reductions in the incidence of hospitalization for respiratory tract disease from any cause and in the incidence of hospitalization for lower respiratory tract disease from any cause were higher than those observed for the corresponding RSV-related events, which indicates a substantial presence of undiagnosed RSV infection.

We also observed fewer hospitalizations for

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Subgroup	RSVpreF Vaccine	Control	Vaccine Effectiveness (95% CI)
	no. of events/total no. of participants		
Overall	3/65,642	18/65,634	83.3 (42.9 to 96.9)
Age			
60–74 yr	1/51,803	10/51,781	90.0 (29.7 to 99.8)
≥75 yr	2/13,839	8/13,853	75.0 (–25.0 to 97.4)
<Median	0/32,890	4/32,751	—
≥Median	3/32,752	14/32,883	78.5 (23.6 to 96.1)
Sex			
Male	2/32,931	9/33,082	77.7 (–6.8 to 97.7)
Female	1/32,711	9/32,552	88.9 (19.4 to 99.8)
Presence of at least 1 chronic disease			
No	0/38,080	5/38,080	—
Yes	3/27,562	13/27,554	76.9 (16.0 to 95.8)
Chronic lung disease			
No	3/60,834	13/60,832	76.9 (16.1 to 95.8)
Yes	0/4808	5/4802	—
Cardiovascular disease			
No	1/51,265	11/51,349	90.9 (37.6 to 99.8)
Yes	2/14,377	7/14,285	71.6 (–51.1 to 97.1)
Diabetes mellitus			
No	2/58,452	17/58,385	88.2 (50.4 to 98.7)
Yes	1/7190	1/7249	—
Cancer			
No	2/58,093	12/58,087	83.3 (25.2 to 98.2)
Yes	1/7549	6/7547	83.3 (–37.4 to 99.6)
Chronic kidney disease			
No	1/58,982	12/58,930	91.7 (43.7 to 99.8)
Yes	2/6660	6/6704	66.4 (–85.2 to 96.7)
Immunosuppression			
No	1/63,023	13/63,054	92.3 (48.8 to 99.8)
Yes	2/2619	5/2580	60.5 (–147.3 to 96.1)
Influenza vaccination in same season			
No	0/12,634	1/12,816	—
Yes	3/53,008	17/52,818	82.4 (38.8 to 96.7)
Previous pneumococcal vaccination			
No	0/23,565	3/23,638	—
Yes	3/42,077	15/41,996	80.0 (29.2 to 96.3)

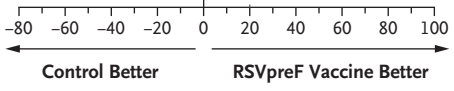

Figure 3. Primary End Point in Prespecified Subgroups.

For all subgroups, 95% confidence intervals have not been adjusted for multiplicity and should not be used to make inferences about effects. The vertical solid line represents a vaccine effectiveness of 0%, and the vertical dashed line represents a vaccine effectiveness of 20% (the minimum vaccine effectiveness used for the analysis of the primary end point). The presence of at least one chronic condition was defined as the presence of at least one of the following: chronic lung disease, cardiovascular disease, diabetes, cancer, chronic kidney disease, immunodeficiency, neurologic or neuromuscular disease, liver disease, or rheumatic disease. Diabetes was defined according to *International Classification of Diseases, 10th Revision* (ICD-10), codes and glycated hemoglobin levels. Chronic kidney disease was defined according to ICD-10 codes and laboratory measurements (the estimated glomerular filtration rate, albumin–creatinine ratio, and urine albumin level). Immunosuppression was defined according to ICD-10 codes and procedural codes. Detailed definitions of all subgroups are provided in the protocol.

cardiorespiratory disease in the RSVpreF group than in the control group, a finding that suggests that RSV may trigger both cardiovascular events and respiratory tract disease. The absolute rate reduction was greater for hospitalization for cardiorespiratory disease from any cause than for hospitalization for respiratory tract disease alone, which indicated that some cardiovascular events were averted in the RSVpreF group. This finding aligns with data from observational stud-

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Table 3. Serious Adverse Events during the 6-Week Safety Surveillance Period, According to Trial Group.*

Event	RSVpreF Group (N = 63,045)	Control Group (N = 68,326)
	no. of patients (%)	
Any serious adverse event	1341 (2.1)	1669 (2.4)
Any cardiovascular serious adverse event	224 (0.4)	286 (0.4)
Any respiratory serious adverse event	116 (0.2)	113 (0.2)
Any gastrointestinal serious adverse event	136 (0.2)	171 (0.3)
Any neurologic serious adverse event	41 (0.1)	40 (0.1)
Any cancer-related serious adverse event	61 (0.1)	85 (0.1)
Any infection-related serious adverse event	40 (0.1)	57 (0.1)
Any injury-related serious adverse event	156 (0.2)	205 (0.3)
Fatal serious adverse event	17 (<0.1)	33 (<0.1)
Any serious adverse reaction†	5 (<0.1)	NA
Bell's palsy	1 (<0.1)	3 (<0.1)
Pericarditis	2 (<0.1)	2 (<0.1)

* Serious adverse events were defined as deaths or hospitalizations that occurred within 6 weeks after vaccination in the RSVpreF group or within 6 weeks after the scheduled trial visit in the control group. A total of 1497 serious adverse events occurred in the RSVpreF group and 1937 in the control group. Events are grouped according to the organ system affected or the type of illness or event, except for clinically important safety events (Bell's palsy and pericarditis), which are listed individually. Bell's palsy, pericarditis, and Guillain–Barré syndrome have occurred in previous trials of vaccines against respiratory viruses. No cases of Guillain–Barré syndrome occurred during the 6-week safety period in our trial. For the analysis of serious adverse events, participants were grouped according to the intervention received at baseline (i.e., participants who were assigned to receive the vaccine but did not receive it were included in the control group, and participants who were assigned to the control group but received the RSVpreF vaccine at the trial visit were included in the RSVpreF group; participants who received an RSV vaccine outside the trial during follow-up were included in the control group for this analysis). The eight participants who died before the scheduled trial visit (five in the RSVpreF group and three in the control group) were not included in the analysis. For participants who withdrew consent, safety data until the date of consent withdrawal were included. NA denotes not applicable.

† A serious adverse reaction was defined as a serious adverse event related to the RSVpreF vaccine.

ies that have linked RSV to increased cardiovascular risk.[25-29] Vaccine evaluations should consider both indication-specific and broader effects. However, assessment of vaccine effects on severe events from any cause, such as hospitalization for cardiorespiratory disease from any cause, requires large trials. Pragmatic features in our trial, including the use of online consent forms and previsit disclosure of the trial-group assignment — which led to only those participants assigned to the RSVpreF group having to attend a trial visit — reduced the trial burden on participants and allowed for a control group in which participants received no treatment. This design allowed approximately 8.6% of the Danish population 60 years of age or older to undergo randomization, which enhanced the representativeness of the trial population.[30]

A limitation of our trial was the occurrence of fewer primary end-point events than expected. Absolute rate reductions were greater for end points involving events from any cause than for those involving RSV-related events, which suggests that many cases of RSV infection were undiagnosed. Because we used a pragmatic approach that relied on data from routine health care encounters, we were dependent on routine RSV testing in Denmark, which declined after the Covid-19 pandemic. Many hospitals reduced the use of combined polymerase-chain-reaction testing for influenza virus, RSV, and severe acute respiratory syndrome coronavirus 2 owing to cost and limited clinical utility in the absence of RSV-specific antiviral agents. Reduced testing, coupled with a milder RSV season, most likely contributed to the low number of events.[24] Nonetheless, our findings with respect to the primary end point (vaccine effectiveness of 83.3%) are consistent with those from RENOIR (in which vaccine effectiveness was 88.9%), pivotal trials of other RSV vaccines (which showed vaccine effectiveness that ranged from 82.6 to 83.7%), real-world estimates of RSVpreF vaccine effectiveness against RSV-related hospitalization (73 to 90%), and postlicensing test-negative case–control studies.[8-13,31,32] The RSVpreF vaccine also reduced the incidence of hospitalization for laboratory-confirmed RSV infection and the incidence of hospitalization for lower respiratory tract disease from any cause, which were higher than the incidence of hospitalization for RSV-related respiratory tract disease, a finding that supports the robustness of our results.

The trial had other limitations. We used an open-label design; however, this approach was expected to have limited effect on the severe outcomes represented in the trial end points. An additional limitation was that participants in the RSVpreF group could reschedule or miss the trial visit, unlike participants in the control group, a factor that could potentially bias the results toward the null hypothesis. Furthermore, data with respect to all end-point events were collected passively from the national registries with the use

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of prespecified definitions, and data on RSV testing during the 2024–2025 season were received only after the end of the follow-up period, which ensured that investigators were effectively unaware of the trial results. Participants in the control group could buy an RSV vaccine outside the trial if they wished, but only 1.2% of participants opted to do so. The use of electronic invitations as the primary recruitment strategy, along with the requirement for participants to provide informed consent independently, may have limited the inclusion of older persons at high risk for RSV-related disease. Despite broad eligibility criteria, the trial may have been subject to healthy volunteer bias. In addition, the trial was conducted in a single country. Although nearly 9% of the Danish population 60 years of age or older were enrolled, the participants may not fully represent global populations. Invitations were sent through a government electronic mail system, which Danish citizens can be exempted from, although approximately 86% of the total older Danish population was reached with this strategy.

In this large-scale, pragmatic, phase 4 trial, the RSVpreF vaccine as compared with no vaccine reduced the incidence of hospitalization for RSV-related respiratory tract disease, as well as the incidence of hospitalization for respiratory tract disease from any cause, among adults 60 years of age or older.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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REFERENCES

1. Wyffels V, Kariburyo F, Gavart S, Fleischhackl R, Yuce H. A real-world analysis of patient characteristics and predictors of hospitalization among US Medicare beneficiaries with respiratory syncytial virus infection. Adv Ther 2020;37:1203-17.
2. Prasad N, Walker TA, Waite B, et al. Respiratory syncytial virus-associated hospitalizations among adults with chronic medical conditions. Clin Infect Dis 2021;73(1):e158-e163.
3. Belongia EA, King JP, Kieke BA, et al. Clinical features, severity, and incidence of RSV illness during 12 consecutive seasons in a community cohort of adults ≥60 years old. Open Forum Infect Dis 2018;5:ofy316.
4. Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. N Engl J Med 2005;352:1749-59.
5. Lee N, Lui GCY, Wong KT, et al. High morbidity and mortality in adults hospitalized for respiratory syncytial virus infections. Clin Infect Dis 2013;57:1069-77.
6. Shi T, Denouel A, Tietjen AK, et al. Global disease burden estimates of respiratory syncytial virus-associated acute respiratory infection in older adults in 2015: a systematic review and meta-analysis. J Infect Dis 2020;222:Suppl 7:S577-S583.
7. Savic M, Penders Y, Shi T, Branche A, Pirçon J-Y. Respiratory syncytial virus disease burden in adults aged 60 years and older in high-income countries: a systematic literature review and meta-analysis. Influenza Other Respir Viruses 2023;17(1):e13031.
8. Walsh EE, Pérez Marc G, Zareba AM, et al. Efficacy and safety of a bivalent RSV prefusion F vaccine in older adults. N Engl J Med 2023;388:1465-77.
9. Papi A, Ison MG, Langley JM, et al. Respiratory syncytial virus prefusion F protein vaccine in older adults. N Engl J Med 2023;388:595-608.
10. Wilson E, Goswami J, Baqui AH, et al. Efficacy and safety of an mRNA-based RSV PreF vaccine in older adults. N Engl J Med 2023;389:2233-44.
11. Payne AB, Watts JA, Mitchell PK, et al. Respiratory syncytial virus (RSV) vaccine effectiveness against RSV-associated hospitalisations and emergency department encounters among adults aged 60 years and older in the USA, October, 2023, to March, 2024: a test-negative design analysis. Lancet 2024;404:1547-59.
12. Tartof SY, Aliabadi N, Goodwin G, et

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al. Estimated vaccine effectiveness for respiratory syncytial virus-related lower respiratory tract disease. JAMA Netw Open 2024;7(12):e2450832.
13. Symes R, Whitaker HJ, Ahmad S, et al. Vaccine effectiveness of a bivalent respiratory syncytial virus (RSV) pre-F vaccine against RSV-associated hospitalisation among adults aged 75-79 years in England. June 14, 2025 (https://www.medrxiv.org/content/10.1101/2025.06.13.25329583v1). preprint.
14. Lassen MCH, Christensen SH, Johansen ND, et al. A pragmatic individually randomized trial to evaluate bivalent RSV prefusion F protein-based vaccine effectiveness for preventing RSV hospitalizations in adults aged 60 years or above (DAN-RSV): rationale & trial design. Am Heart J 2025 July 28 (Epub ahead of print).
15. Agency for Digital Government. Digital post (https://en.digst.dk/systems/digital-post/).
16. Agency for Digital Government. Digital post user-data (https://en.digst.dk/systems/digital-post/digital-post-user-data/).
17. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med 1998;17:857-72.
18. Walsh EE, Pérez Marc G, Falsey AR, et al. RENOIR trial — RSVpreF vaccine efficacy over two seasons. N Engl J Med 2024;391:1459-60.
19. Kujawski SA, Whitaker M, Ritchey MD, et al. Rates of respiratory syncytial virus (RSV)-associated hospitalization among adults with congestive heart failure — United States, 2015-2017. PLoS One 2022;17(3):e0264890.
20. Havers FP, Whitaker M, Melgar M, et al. Characteristics and outcomes among adults aged ≥60 years hospitalized with laboratory-confirmed respiratory syncytial virus — RSV-NET, 12 states, July 2022-June 2023. MMWR Morb Mortal Wkly Rep 2023;72:1075-82.
21. Li Y, Kulkarni D, Begier E, et al. Adjusting for case under-ascertainment in estimating RSV hospitalisation burden of older adults in high-income countries: a systematic review and modelling study. Infect Dis Ther 2023;12:1137-49.
22. Rozenbaum MH, Begier E, Kurosky SK, et al. Incidence of respiratory syncytial virus infection in older adults: limitations of current data. Infect Dis Ther 2023;12:1487-504.
23. Begier E, Aliabadi N, Ramirez JA, et al. Detection by nasopharyngeal swabs alone underestimates respiratory syncytial virus-related hospitalization incidence in adults: the multispecimen study's final analysis. J Infect Dis 2025;232(1):e126-e136.
24. Statens Serum Institut. Integrated surveillance of respiratory infections in 2024/2025 — consolidated report. June 2025 (https://en.ssi.dk/surveillance-and-preparedness/surveillance-in-denmark/annual-reports-on-disease-incidence/i/integrated-surveillance-of-respiratory-infections-in-2024-25--consolidated-report).
25. Lassen MCH, Modin D, Johansen ND, et al. Respiratory syncytial virus and incidence of cardiovascular events: a nationwide self-controlled case series analysis. J Am Coll Cardiol 2025;85:1504-7.
26. Anderson NW, Binnicker MJ, Harris DM, et al. Morbidity and mortality among patients with respiratory syncytial virus infection: a 2-year retrospective review. Diagn Microbiol Infect Dis 2016;85:367-71.
27. Landi SN, Garofalo DC, Reimbaeva M, et al. Hospitalization following outpatient diagnosis of respiratory syncytial virus in adults. JAMA Netw Open 2024;7(11):e2446010.
28. Volling C, Hassan K, Mazzulli T, et al. Respiratory syncytial virus infection-associated hospitalization in adults: a retrospective cohort study. BMC Infect Dis 2014;14:665.
29. Wee LE, Lim JT, Ho RWL, Chiew CJ, Lye DCB, Tan KB. Cardiac events in adults hospitalized for respiratory syncytial virus vs COVID-19 or influenza. JAMA Netw Open 2025;8(5):e2511764.
30. Statistics Denmark. Population figures: population in Denmark, 6,002,420. July 2025 (https://www.dst.dk/en/Statistik/emner/borgere/befolkning/befolkningstal).
31. Surie D, Self WH, Zhu Y, et al. RSV vaccine effectiveness against hospitalization among US adults 60 years and older. JAMA 2024;332:1105-7.
32. Fry SE, Terebuh P, Kaelber DC, Xu R, Davis PB. Effectiveness and safety of respiratory syncytial virus vaccine for US adults aged 60 years or older. JAMA Netw Open 2025;8(5):e258322.

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