Respiratory syncytial virus (RSV) vaccine effectiveness and antibody correlates of protection among older adults in the Community Vaccine Effectiveness (CoVE) observational study

Elie-Tino Godonou,[a,*] Amy P. Callear,[a] Casey L. Juntila-Raymond,[a] Dolapo Raji,[a] Matthew Smith,[a] Kalee E. Rumfelt,[a] Claire M. Midgley,[b] Leora R. Feldstein,[b] Jefferson M. Jones,[b] Melissa Briggs Hagen,[b] Marisa C. Eisenberg,[a] Adam S. Lauring,[c] Arnold S. Monto,[a] Abram L. Wagner,[a] and Emily T. Martin[a]

[a]Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, MI, 48109, USA
[b]Coronavirus and Other Respiratory Viruses Division, National Center for Immunisation and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, 30333, USA
[c]Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI, 48109, USA

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Summary

Background The first RSV vaccines for adults 60 years and older were approved prior to the 2023–2024 respiratory virus season. This study aims to evaluate RSV vaccine effectiveness (VE) in preventing RSV infections among older adults, and to examine antibody correlates of protection.

Methods This study used data from adults 60 years and older, enrolled into the Community Vaccine Effectiveness (CoVE) prospective cohort study, in Michigan, U.S.A. A Cox regression model was used to compare incidence of symptomatic/all RSV infections in those vaccinated versus unvaccinated. RSV-specific (preF) binding antibodies were measured in serum specimens and assessed longitudinally. A correlates of protection analysis was conducted using logistic regression.

Findings Of the 281 participants (n = 117 vaccinated) enrolled (August 1, 2023, to March 1, 2024), 14 tested positive for RSV. Adjusted RSV VE against any RSV infection was 50.8% (95% CI: −79.1% to 86.5%), and 59.8% (95% CI: −105.2% to 92.1%) against symptomatic RSV. There were 61.2 (95% CI: 16.9, 163.2) RSV infections per 1000 person-years among participants who were vaccinated compared to 165.8 infections (95% CI: 88.0, 287.0) per 1000 person-years among those unvaccinated. A 31% decrease in odds (OR: 0.69, 95% CI: 0.44–1.07) of RSV infection per 2–fold increase in antibody concentration was observed.

Interpretation Our findings suggest that higher antibody levels may be associated with a reduced risk of RSV infection, but further research is needed to confirm this relationship. RSV incidence appeared to be lowest among adults who were vaccinated, though the difference was not statistically significant. Low number of RSV events and limited availability of serology data limit the precision of the estimates. Continued monitoring of reduction of RSV infection in years following vaccination is warranted.

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Keywords: Respiratory syncytial virus; Vaccine effectiveness; Correlates of protection; Antibody waning; Cohort study; Older adults

*Corresponding author. Department of Epidemiology, University of Michigan School of Public Health, 1415 Washington Hts, Ann Arbor, MI, 48109, USA.
E-mail address: elietino@umich.edu (E.-T. Godonou).

Research in context

Evidence before this study

Respiratory syncytial virus (RSV) can cause severe disease in older adults. The first RSV vaccines for adults 60 years and older were approved, in the U.S.A., prior to the 2023–2024 respiratory virus season. Clinical trials have demonstrated the efficacy of RSV vaccines (62.1% for ABRYSVO and 71.7% for AREXVY) against RSV-related acute respiratory illness in this population and vaccine effectiveness studies in clinical populations are underway. There have yet to be prospective, longitudinal community-based evaluations of the impact of RSV vaccine in older adults in preventing infection leading to a range of diseases from asymptomatic to mild to severe. While correlates of protection against RSV infection have been explored in various contexts or groups, the role of baseline antibody concentrations in older adults and the durability of vaccine-induced protection needs to be further examined in an observational setting. We searched PubMed for published articles, using the terms "RSV vaccine effectiveness older adults", "RSV correlates of protection older adults", and "RSV antibody waning older adults". The search identified a few relevant studies on RSV vaccine efficacy and VE from clinical trials and medical record data but little to no observational data on prevention of infection across a range of outcomes, including asymptomatic infection, or data on infection antibody kinetics or the duration of protection following vaccination in older adults following the initiation of community-wide vaccine campaigns.

Added value of this study

This observational study assesses RSV VE in adults aged 60 years and older using real-world prospectively collected cohort data. The study also investigates potential correlates of protection by examining baseline antibody concentrations, established prior to infection, and their association with RSV infection risk. Additionally, it characterises antibody kinetics, including estimates of decay rates and antibody half-life. Our study suggested a slower waning of antibody concentration among vaccinated versus unvaccinated, and RSV infection risk appeared lower among those with higher antibody levels. By integrating these elements, our study offers essential understanding of how pre-existing immunity and vaccine-induced responses influence protection against RSV in older adults. The interpretation of these findings must consider the study's limitations, particularly the relatively low number of RSV cases in the vaccinated group during the study period.

Implications of all the available evidence

This study contributes valuable real-world insights on RSV VE in older adults, complementing findings from clinical trials and electronic health record studies. Understanding post-vaccination antibody waning and half-life estimation will be essential for informing whether a second dose recommendation is warranted and other efforts to ensure prolonged protection against RSV in this population.

Introduction

Considerable evidence has accumulated regarding the significant burden of RSV disease in adults, especially older adults and those with underlying conditions.[1] A recent U.S.-wide multicentre study of adults hospitalised for acute respiratory illness found that the severity of illness due to RSV was comparable to illness in individuals who were unvaccinated and hospitalised with influenza or COVID.[2,3] Prevention of RSV infection stands to directly benefit older adults who are at increased risk of severe disease. Simulations suggest that a reduction of infection in this group could lead to indirect reductions in other non-vaccinated groups as well,[4,5] although this has not been confirmed epidemiologically.

Two protein subunit vaccines for RSV were approved in the U.S. prior to the 2023–2024 respiratory virus season: an adjuvanted vaccine containing recombinant stabilised prefusion RSV-A F protein (AREXVY) and an unadjuvanted vaccine containing recombinant stabilised prefusion RSV-A and RSV-B F proteins combined into a single bivalent product (ABRYSVO). For the first year of implementation, which coincided with our study period, ACIP recommendations for the administration of a single dose of one of the two protein subunit vaccines were for administration to adults 60 and older, based on shared decision making between provider and patient.[6]

Vaccine efficacy estimates from the randomised clinical trials for these vaccines was 62.1% (ABRYSVO)[7] and (AREXVY) 71.7%,[8] for adults 60 and older against RSV-related acute respiratory illness (defined broadly as at least one[7] or two[8] new or worsening ARI symptom with RT-PCR-confirmed RSV infection). Test-negative evaluations in the U.S. following use in the 2023–2024 season indicated that the real-world vaccine effectiveness against RSV hospitalisation in adults 60 and older was 75% (95% CI, 50%–87%).[9] Broader vaccine effectiveness estimates against less severe outcomes have been limited by the slow uptake of RSV vaccines nationwide.[10]

We sought to evaluate the potential overall benefit of RSV vaccine in older adults during this initial season in a prospective, observational study in a population with high vaccine uptake enrolled across the state of Michigan, The Community Vaccine Evaluation (CoVE) study.[11] We analysed RSV symptomatic and asymptomatic infection in vaccinated and unvaccinated cohort participants 60 years of age and older during the

2023–2024 respiratory virus season. Further, we evaluated vaccine immunogenicity, the correlation between antibody levels and RSV infection, and antibody waning in vaccinated and unvaccinated groups.

Methods

Study population and data collection

The analysis population included all participating adults in the CoVE cohort who were 60 years of age and over as of their enrolment date, and enrolled at any point during the surveillance period (August 1, 2023, to March 1, 2024). Participant follow-up time was included through the approximate end of RSV circulation in Michigan, March 1, 2024. Individuals were recruited from social media, the University of Michigan research registry, targeted mailing, and an existing household cohort (Household Influenza Vaccine Evaluation Study [HIVE], methods previously described[12,13]). In anticipation of RSV vaccine availability, targeted social media recruitment was used beginning 6/20/2023 to increase enrolment of participants aged 60 and above throughout the state. Adults provided written informed consent. A sample size calculation was not conducted for the CoVE study. The plan was to maintain a cohort of approximately 1350 participants (~540 adults and 810 children) for the CoVE study. The study was designed to maximise enrolment, meaning that recruitment would continue as needed to maintain the cohort size and replace participants lost to follow-up. This study was reviewed and approved by the University of Michigan Institutional Review Board, and was conducted consistent with applicable federal law and CDC policy (See 45 C.F.R. part 46.114; 21 C.F.R. part 56.114).

Participant and household characteristics, health history, and vaccination history were collected at enrolment. Sex, race, and ethnicity were self-reported by participants at enrolment. Self-reported data were used to document the presence of high-risk health conditions (a binary yes/no variable). The following conditions were considered to define "high-risk" status: respiratory conditions, including asthma, chronic obstructive pulmonary disease (COPD), chronic bronchitis, and emphysema; cardiovascular conditions, such as heart disease; renal conditions, including chronic kidney disease or loss of kidney function; liver conditions, such as chronic liver disease including hepatitis; haematologic conditions, including bleeding disorders and blood diseases such as sickle cell anaemia; a weakened immune system, due to immunosuppressive treatment or other conditions; and neurologic or neuromuscular conditions, such as cerebral palsy, multiple sclerosis, and myasthenia gravis. RSV vaccination, including date of vaccination and product, was documented (Vaccine Administered—CVX codes: 305, 303) using the Michigan Care Improvement Registry (a statewide immunisation information system),[14] at the conclusion of the study period.

Participants self-collected mid-turbinate swabs weekly, returned them to the study site by mail, and completed weekly surveys on illnesses and individual symptoms (cough, chills, fever, sore throat, nasal congestion, body aches, headache, trouble breathing, wheezing, fatigue). An additional swab was collected upon onset of eligible symptoms meeting the study illness case definition (two or more of: fever, chills, cough, nasal congestion, body aches, headache, sore throat) with symptoms recorded at illness report. A blood sample was requested upon enrolment, with optional additional collections semi-annually and following COVID-19 vaccination. Samples were secondarily used to study RSV vaccination if timed appropriately (see inclusion criteria below). Blood samples were self-collected using an at-home capillary collection kit (TASSO + SST, Tasso, Inc. Seattle, WA) or collected by study staff or clinical phlebotomist via venous draw. The median time from collection to receipt in the laboratory was 2 days for venous samples (n = 112; centrifuged day of collection) and 3 days for home-collected samples (n = 400). Home-collected samples were returned via mail; samples were discarded if serum failed to appropriately separate after centrifugation. Haemolysed serum was not excluded from analysis.

Laboratory testing

Dry nasal swabs received from participants were transferred into 2 ml stabilising solution (DNA/RNA Shield, Zymo Research Corporation, Irvine, CA) upon receipt in the study laboratory. All respiratory specimens were tested by real-time reverse-transcription polymerase chain reaction (RT-PCR) for detection of RSV virus using a multiplex assay for RSV, SARS-CoV-2, and influenza (Taqman SARS-CoV-2, Flu A/B, RSV Multiplex Assay, AppliedBiosystems, Waltham, MA) as previously described.[11]

Available serum specimens were tested for IgG antibody against the RSV Pre-Fusion F protein using a quantitative electrochemoluminescence assay (V-PLEX Respiratory Panel 1 (IgG), Mesoscale Discovery, Rockville, MD). Specimens were tested in duplicate using a 1:5000 dilution with retesting at 1:50,000 if the first test was above the upper limit of quantitation. Absolute antibody quantity was determined using a standard curve, in arbitrary units per mL (AU/mL).

RSV antibody kinetics

The kinetics of RSV preF IgG levels in the vaccinated and unvaccinated groups were characterised using multiple models, based on blood specimens collected between August 1, 2023, and July 15, 2024.

Among participants who were vaccinated, individuals with at least two post-vaccination samples

collected at least 14 days after RSV vaccination were selected. If any participants became infected (PCR-confirmed RSV, regardless of symptoms) after vaccination, antibody levels measured after infection were excluded from the waning analysis.[15]

Among participants who were not vaccinated, individuals with at least two samples collected at different time points after August 1, 2023, were selected. The same method described above (i.e., with exclusion of post-infection samples) was applied if any participants were infected (PCR-confirmed RSV, regardless of symptoms). Post-infection antibody kinetics were not assessed due to fewer PCR-confirmed RSV cases with associated samples.

Statistical analysis

A descriptive analysis was performed to characterise participants who received RSV vaccination during the study period and those who did not, including demographic characteristics, RSV infections (any positive swab, inclusive of symptomatic *and* asymptomatic detections), and symptomatic RSV illness (a positive test and illness symptoms meeting the case definition above; henceforth referred to as "symptomatic RSV"). Symptom frequency and intensity were described among participants with symptomatic RSV. Symptomatic RSV infection was defined as a positive RT-PCR test and the presence of at least two respiratory symptoms reported within seven days before or after the specimen collection date. Repeated RSV positives observed in the same participant within 14 days were considered a continuation of the prior RSV infection. Asymptomatic cases were defined as those that did not meet the symptomatic RSV case definition, and may have included individuals with other non-qualifying symptom combinations. Participants contributed time under observation to the vaccinated group if they were vaccinated at least 14 days prior to either any RSV infection, or the end of the study period.

A Cox regression model with time-varying covariate, and a robust sandwich estimate for the covariance matrix, was used to evaluate vaccine effectiveness in reducing the hazard rate of RSV infections (symptomatic infections only and all cases of RSV infection) over time, adjusted for sex, race, ethnicity, and presence of high-risk health conditions.[2,11,16–19] Vaccination status was a time-varying covariate and time to infection was measured from August 1, 2023, or participant enrolment date if later. The Efron approximation method was used for ties in event times. Vaccine effectiveness (VE) was estimated as (1 − Hazard ratio) × 100. Unadjusted incidence rates per 1000 person-years, with 95% confidence intervals (CIs),[20] were calculated separately for RSV infection and symptomatic RSV overall and stratified by vaccination status. Person-years were calculated up to the occurrence of the first event, loss to follow up, or the end of the study period.

We also fit an unadjusted logistic regression model to evaluate continuous levels of RSV antibody on the log scale as a correlate of protection (CoP) in our study population. This model estimated the change in the odds of RSV infection associated with each 2-fold rise in baseline titres. This CoP analysis included both participants who were vaccinated and those who were not (Supplemental Materials). Additionally, CoP analysis was stratified by vaccination status and conducted using Firth's penalised logistic regression.

For the immunogenicity assessment, Geometric Mean Fold Rise (GMFR) with a 95% confidence interval (CI) was calculated for participants with both pre- and post-vaccination titre results.

We modelled RSV preF IgG waning from 14 to 302 days after vaccination among individuals who were vaccinated, and from 1 to 349 days after the start of the study period among unvaccinated, based on the timeframe of available specimens within one year of vaccination. RSV preF IgG waning predicted trajectories were estimated using exponential decay (ED), power-law (PL), and natural cubic splines (NCS) mixed models, starting from day 14 post-vaccination for the vaccinated group and from day one after the start of the study period for the unvaccinated group. The mixed models included time as the predictor variable. The outcome of interest was the log-transformed antibody concentration. The time variable was treated differently depending on the model (see Supplemental Materials). These mixed models were not adjusted for covariates; model assumptions (i.e., normality of residuals, constant variance or homoscedasticity, posterior predictive checks) were evaluated and reasonably satisfied. All waning models were implemented using the lme4 package in R,[21] and 95% confidence intervals of the fixed effects from ED and PL mixed models are calculated by computing a likelihood profile and finding the appropriate cutoffs based on the likelihood ratio test.[21] A description of these three models is provided in the Supplemental Materials.

Antibody half-life ($t_{1/2}$), representing the number of days required to halve RSV preF IgG antibody levels, was estimated for both vaccinated and unvaccinated groups for each model (Supplemental Materials). The confidence intervals for the estimated half-lives were computed using a nonparametric bootstrap method as implemented in the boot package in R.[22,23] All analyses were conducted using SAS software (version 9.4; SAS Institute, Cary, NC) and R software (version 4.3.0; R Core Team).

Role of funders

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Results

A total of 281 participants aged 60 years and older participated in the study between August 1, 2023, to March 1, 2024, and contributed 5733 respiratory specimens (weekly and illness swabs) and 115.38 person-years of person-time to the analyses. Overall, participants were predominantly female (71.2%, n = 200) and White (93.6%, n = 263) with a median age of 67 years (range, 60–87); a large proportion (90.7%, n = 255) of participants belonged to the age category 60–74 years. One third of participants (33.1%, n = 93) had at least one high-risk health condition, and 5% (n = 14) had a PCR-confirmed RSV infection (Table 1).

Among the 14 participants with RSV infection, ten had the RSV-B antigenic subtype, three had the RSV-A subtype, and one sample was unsubtypeable. Among symptomatic RSV cases (3.6%, n = 10), all participants experienced cough and nasal congestion, while nine also reported a sore throat (Table 2); only one (unvaccinated) participant missed work, due to the illness, for two days. No symptomatic RSV cases required hospitalisation or visits to an emergency department or urgent care. Only one participant had an outpatient healthcare visit (Table 2). Of the 14 participants with RSV infection, three (21.4%) were vaccinated; of these three individuals, two were symptomatic, and none

	All	Vaccinated[a]	Unvaccinated
Participants enrolled (age 60+), n	281	117	164
Age, years, mean (median, range)	67.34 (67, 60–87)	67.86 (68, 60–83)	66.97 (66, 60–87)
Age group, years			
60–74	255 (90.7%)	107 (91.4%)	148 (90.2%)
75+	26 (9.3%)	10 (8.6%)	16 (9.8%)
Sex			
Male	80 (28.5%)	32 (27.4%)	48 (29.3%)
Female	200 (71.2%)	85 (72.6%)	115 (70.1%)
Missing	1 (<1%)	–	1 (<1%)
Ethnicity			
Not Hispanic or Latino	267 (95.0%)	109 (93.2%)	158 (96.3%)
Hispanic or Latino	8 (2.9%)	4 (3.4%)	4 (2.5%)
Missing	6 (2.1%)	4 (3.4%)	2 (1.2%)
Race			
White	263 (93.6%)	108 (92.3%)	155 (94.5%)
Black/African American	5 (1.8%)	2 (1.7%)	3 (1.8%)
Asian	3 (1.1%)	1 (<1%)	2 (1.2%)
More than 1 Race	4 (1.4%)	2 (1.7%)	2 (1.2%)
Middle Eastern/North African	1 (<1%)	–	1 (<1%)
Unknown/Missing	5 (1.8%)	4 (3.4%)	1 (<1%)
Any (≥1) high-risk health conditions, n	93 (33.1%)	45 (38.5%)	48 (29.3%)
Product-specific vaccination			
Bivalent (ABRYSVO) vaccine	–	31.6% (37)	–
Monovalent (AREXVY) vaccine	–	67.5% (79)	–
Unspecified/Unknown	–	<1% (1)	–
PCR-Confirmed RSV	14 (5%)	3 (2.6%)	11 (6.7%)
RSV-A	3	2	1
RSV-B	10	1	9
Unsubtyped	1	0	1

High-risk health conditions: At least one of the following conditions: asthma, chronic obstructive pulmonary disease including chronic bronchitis and emphysema, heart disease, diabetes, chronic kidney disease or loss of kidney function, chronic liver disease such as hepatitis, a bleeding disorder or a blood disease such as sickle cell anaemia, weakened immune system, and a neurologic or neuromuscular disorder such as cerebral palsy, multiple sclerosis, or myasthenia gravis). %: column percentages. RSV: Respiratory Syncytial Virus. PCR: Real-Time Polymerase Chain Reaction. [a]Participants were vaccinated at least 14 days prior either to infection or the end of the surveillance period (if not infected). This includes both RSV vaccine products.

Table 1: **Characteristics (age, sex, race, high-risk health conditions) of participants aged 60 and older, PCR-Confirmed RSV infections, and RSV subtypes, grouped by RSV vaccination status.**

	All	Vaccinated[a]	Unvaccinated
Symptomatic RSV, n	10	2	8
Symptoms			
Cough	10 (100%)	2 (100%)	8 (100%)
Chills	4 (40%)	0	4 (50%)
Fever	3 (30%)	0	3 (37.5%)
Sore Throat	9 (90%)	1 (50%)	8 (100%)
Nasal Congestion	10 (100%)	2 (100%)	8 (100%)
Body Aches	5 (50%)	0	5 (62.5%)
Headache	8 (80%)	2 (100%)	6 (75%)
Trouble Breathing	1 (10%)	1 (50%)	0
Wheezing	4 (40%)	1 (50%)	3 (37.5%)
Fatigue	8 (80%)	1 (50%)	7 (87.5%)
Outpatient Healthcare Visit	1	0	1
Emergency Department or Urgent Care Visit	0	0	0
Hospitalisation (overnight)	0	0	0

%: column percentages. [a]Participants were vaccinated at least 14 days prior either to infection or the end of the surveillance period (if not infected). This includes both RSV vaccine products.

Table 2: **Frequency of symptoms, outpatient healthcare visits, emergency department or urgent care visits, and hospitalisations in participants aged 60 and older with symptomatic RSV infection grouped by vaccination status.**

sought medical care. In the two vaccinated cases with symptomatic infection, illness onset occurred 80 and 145 days following vaccination. In the third individual, asymptomatic RSV detection occurred by RT-PCR in a weekly swab 68 days following vaccination.

A total of 41.6% (n = 117) of included participants received an RSV vaccine, and 91.4% (n = 107) of those vaccinated were in the 60–74 age category. Importantly, vaccine uptake coincided with circulation of RSV in the broader cohort (Fig. 1). Regarding product-specific vaccination, 67.5% received GlaxoSmithKline's monovalent (AREXVY) vaccine, while 31.6% received the Pfizer's bivalent (ABRYSVO) vaccine among those vaccinated (Table 1). All RSV infections in the vaccinated group were observed among those who received the monovalent (AREXVY) vaccine.

The unadjusted incidence rate (IR) of all RSV infections, inclusive of symptomatic and asymptomatic cases, was 121.3 (95% CI: 69.5, 198.1) per 1000 person-years. For RSV cases that did not meet the symptomatic case definition, IR was 34.7 (95% CI: 11.6, 82.4) per 1000 person-years, which was lower than that for

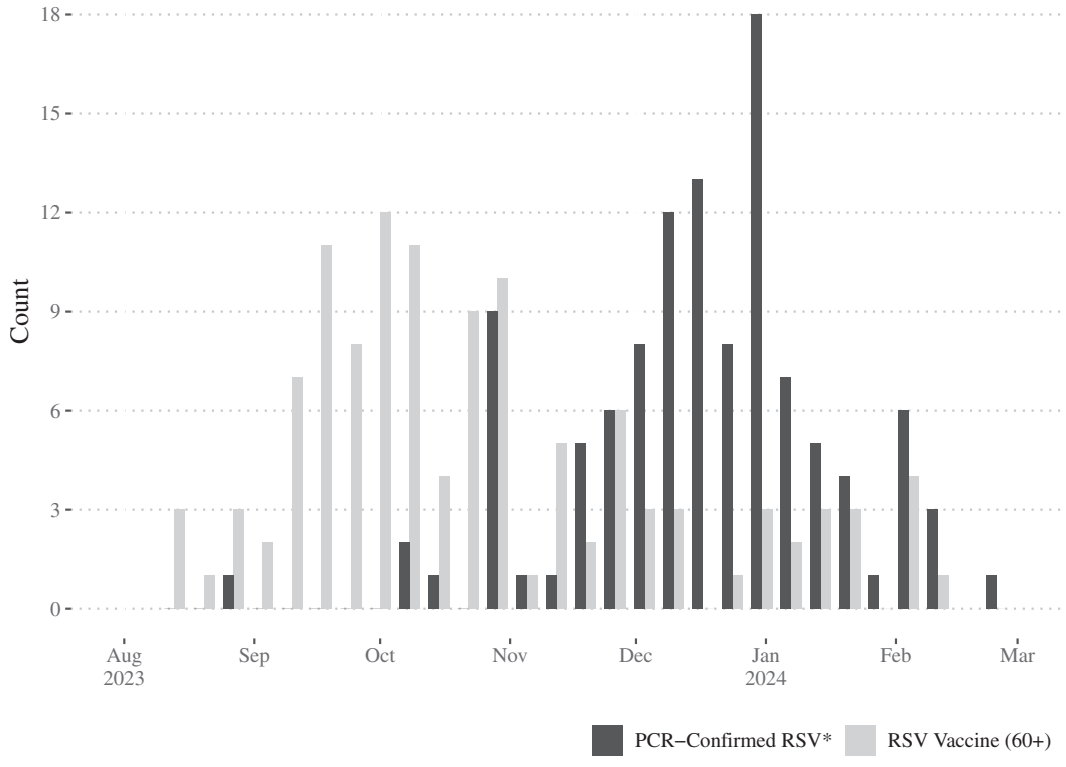

Fig. 1: COVE RSV vaccinations (light grey) in adults 60 years of age and older, included in the analysis. All RT-PCR-confirmed RSV infections (dark grey) in all CoVE participants of any age during the 2023–2024 season are noted in green. *RSV among 994 participants enrolled in COVE. 112 RSV infections among 108 people (4 people with 2 infections). Median age 13.6 years (1–83). RSV: Respiratory Syncytial Virus. RT-PCR: Real-Time Polymerase Chain Reaction.

	N	PCR-confirmed RSV				Symptomatic RSV			
		No. of cases	Unadjusted incidence rate per 1000 person-years (95% CI)	RSV vaccine effectiveness (95% CI)		No. of cases	Unadjusted incidence rate per 1000 person-years (95% CI)	RSV vaccine effectiveness (95% CI)	
				Unadjusted	Adjusted[b]			Unadjusted	Adjusted[b]
Group									
Unvaccinated	164	11	165.8 (88.0–287.0)	[Reference]	[Reference]	8	120.6 (56.9–227.6)	[Reference]	[Reference]
Vaccinated[a]	117	3	61.2 (16.9–163.2)	45.3 (−92.2 to 84.5)	50.8 (−79.1 to 86.5)	2	40.8 (8.1–130.7)	49.7 (−135.6 to 89.3)	59.8 (−105.2 to 92.1)

RSV: Respiratory Syncytial Virus. PCR: Real-Time Polymerase Chain Reaction. [a]Participants were vaccinated at least 14 days prior either to infection or the end of the surveillance period (if not infected). This includes both RSV vaccine products. [b]Adjusting for covariates: sex, race, ethnicity, and presence of high-risk health conditions.

Table 3: **RSV vaccine effectiveness against PCR-Confirmed or symptomatic RSV infection among older adults.**

symptomatic RSV cases (86.7; 95% CI: 44.5, 153.7); this difference was not statistically significant. IR among unvaccinated was higher than participants who were vaccinated, however the difference was not statistically significant. Overall, there were 61.2 (95% CI: 16.9, 163.2) RSV infections per 1000 person-years among participants who were vaccinated, compared to 165.8 infections (95% CI: 88.0, 287.0) per 1000 person-years among those unvaccinated (Table 3); the incidence of symptomatic RSV among unvaccinated was 120.6 infections (95% CI: 56.9, 227.6) per 1000 person-years compared to 40.8 infections (95% CI: 8.1, 130.7) per 1000 person-years among participants who were vaccinated. The adjusted RSV VE against any RSV (Hazard Ratio: 0.492, 95% CI: 0.135–1.791) infection was 50.8% (95% CI: –79.1%–86.5%) and 59.8% (95% CI: –105.2% to 92.1%) against symptomatic RSV (HR: 0.402, 95% CI: 0.079–2.052) (Table 3).

Geometric mean fold rise (GMFR) for antibody titres against RSV was 14.03 (95% CI: 10.1–19.5) among 35 participants who had blood specimens collected before and after their vaccination; 32 participants had at least a 4-fold rise (range, 4.0–126.8) in antibody titre. Overall, risk of RSV infection decreased as the titre of IgG antibody against RSV pre-fusion F increased (Fig. 2), this analysis included both vaccinated and unvaccinated groups. In total, 13 participants with infection and 81 without infection were included in the CoP analysis, after baseline sample selection. A 31% decrease in odds (OR: 0.69, 95% CI: 0.44–1.07) of RSV infection per 2-fold increase in baseline titres was observed but was not statistically significant. A 53% decrease in odds, not significant, was observed (OR: 0.47, 95% CI: 0.19–1.15) per 4-fold increase in baseline titres. CoP analysis was stratified by vaccination status, yielding an odds ratio (OR) of 0.48 (95% CI: 0.24–0.97; statistically significant) among unvaccinated and 0.52 (95% CI: 0.14–1.96) among vaccinated.

Overall, 54 individuals were included from the vaccinated group and 95 from the unvaccinated group, for the analysis of longitudinal changes in RSV preF IgG levels on a $\log_{10}$ scale over time since vaccination among the vaccinated (14 days+) and time since the start of the study period for the unvaccinated (Fig. 3). The decay rates (with 95% CI), AICc and BIC criteria from ED and PL mixed models are reported in Table 4. NCS mixed models' AICc criteria for the vaccinated and unvaccinated groups were 80.3 (with BIC = 96.5) and 337.5 (with BIC = 357.7) respectively (Table 4). Based on these criteria, the best fit for the vaccinated group was the NCS mixed model, with an AICc value of 80.3, compared to 126 and 139.2 for the ED and PL mixed models, respectively. Likewise, the NCS mixed model was the best fit for the unvaccinated group (Table 4). We explored the pattern of RSV preF IgG waning over time using the three models described above. We compared the predicted trajectories of RSV preF IgG levels on a $\log_{10}$ scale over time based on the three models above (Fig. 4). According to the NCS mixed model, the number of days required to halve RSV preF IgG antibody levels, compared to the levels on the 14th day after vaccination, was 37.8 days (95% CI: 23.3, 145.5). In the ED (i.e., steady decay rate over time) and PL (i.e., decay rates decrease over time) mixed models, this was 72.7 days (95% CI: 61.1, 90.2), and 17.5 days (95% CI: 14.5, 26.2), respectively (Table 4).

Discussion

We present an early look at RSV infection and symptomatic illness among vaccine-eligible, community-dwelling adults during the 2023–2024 respiratory season. Vaccine uptake in the cohort was high (42%) compared to 17% reported nationally,[10] serologic antibody responses to vaccine administration were uniformly strong, and RSV infection risk appeared to be lower among those with higher antibody titres. The observed lower incidence of RSV among individuals, who were vaccinated, did not reach statistical significance, indicating that more data are needed to determine the vaccine's impact. Three individuals who were vaccinated had subsequent RSV infection in our study. Little is currently known about mechanisms that might lead to RSV infection following vaccination, and

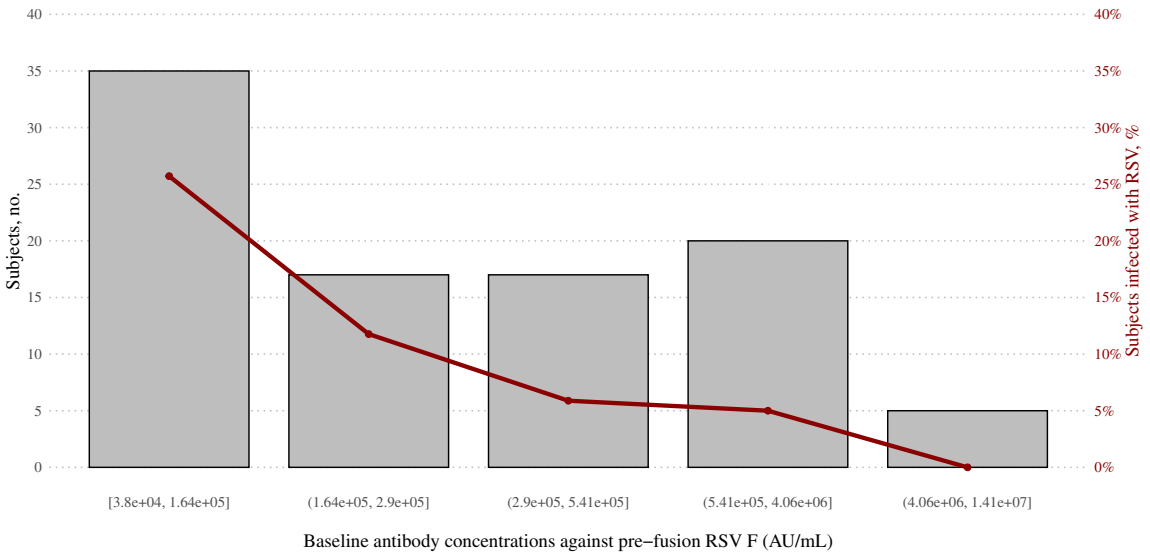

Fig. 2: Relationship between measured antibody concentrations against pre-fusion RSV F protein and RSV infection risk. The number of subjects within each interval is plotted on the left y-axis, and the proportion of subjects who were infected with RSV is plotted on the right y-axis, with the red line denoting the proportion infected. RSV: Respiratory Syncytial Virus. AU/ml: Arbitrary Units per ml.

prospective studies such as this have valuable baseline samples and participant information that can shed light on this question.

The RSV illnesses observed in this study were mild, rarely requiring medical care, and sometimes asymptomatic. The importance of asymptomatic infection in RSV transmission is unknown. To that effect, the degree to which RSV vaccination of older adults may confer indirect protection to other vulnerable individuals is an important consideration for public

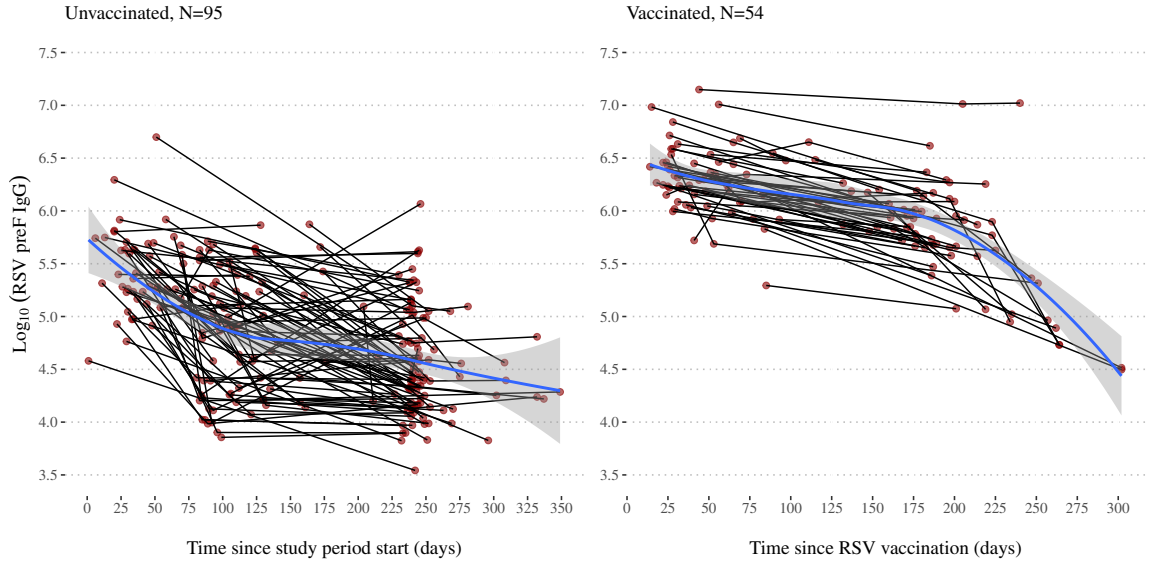

Fig. 3: Spaghetti plots of longitudinal changes in RSV preF IgG concentrations over time. The time scale on the left panel (unvaccinated group) corresponds to the time since the start of the study period (derived from the timing between August 1, 2023, and sample collection date). The time scale on the right panel (vaccinated group) is time since RSV vaccination (derived from the timing between RSV vaccination date and sample collection date). A loess curve was added to each panel to examine the overall trend. N = number of individuals. RSV: Respiratory Syncytial Virus.

	N	Mixed Models	Decay rate (95% CI)	Half-Life (95% CI)	AICc	BIC
Group						
Vaccinated	54	Exponential decay	−0.00416 (−0.00484, −0.00347)	72.7 (61.1, 90.2)	126	137
		Power-Law	−0.819 (−0.990, −0.646)	17.5 (14.5, 26.2)	139.2	150.1
		NCS	–	37.8 (23.3, 145.5)	80.3	96.5
Unvaccinated	95	Exponential decay	−0.00340 (−0.00407, −0.00273)	87.9 (73.8, 109.0)	356.9	370.4
		Power-Law	−0.847 (−1.007, −0.683)	3.5 (0, 3.6)	345.2	358.8
		NCS	–	31.6 (21.1, 42.2)	337.5	357.7

Decay rate: The rate at which the RSV preF IgG antibody levels decrease over time, along with the associated 95% confidence interval (CI). RSV: Respiratory Syncytial Virus. Half-Life: Number of days required to halve RSV preF IgG antibody levels, compared to the levels on the 1st day after the start of the study period for the unvaccinated group, or the levels on the 1st day after the vaccination for the vaccinated group. NCS: Natural Cubic Splines. AICc: Akaike's information Criterion (AIC) with a small sample correction. BIC: Bayesian Information Criterion.

Table 4: **Time (Days) Required to Halve RSV preF IgG Antibody Levels: Estimates from Exponential Decay, Power-Law, and Natural Cubic Splines Mixed Models.**

health. Overall, the mild nature of illnesses in this study was unsurprising given the weekly participation that may be too intensive for someone with a high level of multimorbidity and functional limitations, both risk factors for more severe RSV illness.[24]

In June 2024, the ACIP updated their recommendation for RSV vaccine use in older adults.[25] The revised guidance recommended RSV vaccine for all adults 75 years of age or older, and adults 60–74 with risk factors for severe disease. The age distribution of our study population is on the younger end of the age range from the original 2023 guidance[6] and, on average, younger than recent epidemiologic analyses of severe RSV illnesses.[9] The importance of understanding RSV epidemiology, and potential prevention strategies in this age group, is twofold. First, the vaccine recommendation for those 60–74 years of age is for those at high risk of severe RSV disease. Our group and others have described over many years the potential burden of disease and severe outcomes of RSV that can occur for adults with chronic conditions even if they are in their 50's and 60's. One-third of our study population reported at least one high-risk health condition. Second, adults 60 to 74 are frequently still in the workforce as well as providing direct care for their children or grandchildren. Other studies have shown that RSV can lead to missed days of work in over a third of infections in adults,[26] and the economic impact of mild illnesses can still be substantial even when medical care is not required.

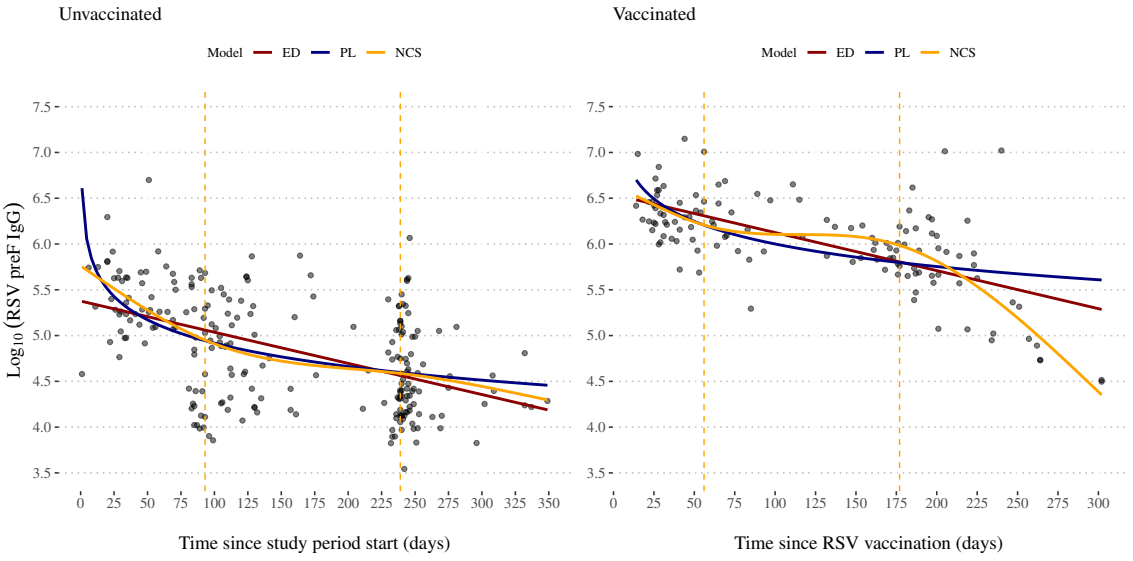

Fig. 4: Predicted trajectories of RSV preF IgG levels over time using ED (Exponential Decay), PL (Power-Law), and NCS (Natural Cubic Splines) mixed models. Dots on both panels represent the original data points on a log10 scale. The vertical dashed lines represent the location of the two inner knots from the NCS mixed models. RSV: Respiratory Syncytial Virus.

The CDC currently only recommends one dose of RSV vaccine for eligible adults, without a recommendation for repeating doses in subsequent RSV seasons.[6] It is too early to know whether this durability over multiple years will hold true in real-world settings outside the context of a clinical trial, highlighting a need for continued assessment. In addition, future efforts will need to account for the fact that additional products have been approved prior to the 2024–2025 season. Thus, continued monitoring of real-world RSV vaccine effectiveness and immunologic waning in the coming years will be critical to inform future recommendations. Although the current recommendation is to administer the vaccine in the fall or winter prior to the beginning of the RSV season, 2023–2024 vaccine administration in our cohort occurred concurrently with RSV circulation in the community, and our analysis was adjusted accordingly. It is likely that this delayed roll out after the beginning of the season reduced the total potential averted burden due to RSV vaccine last season. More so, later-vaccinated individuals received their single vaccine 10 months or more before their next likely exposure to RSV, fall of 2024. This group of vaccinees will be a valuable source of information on vaccine durability in the 2024–2025 season.

Our study is limited in its generalisability to the broader US population as evident in our higher immunisation rate and relatively low rate of high-risk health conditions. Our low event rate, which is not uncommon in prospective cohort studies, precluded a fully adjusted evaluation of vaccine effectiveness and only a subset of participants had serology collected at times relevant to our analysis. The study sample size and small number of symptomatic and all RSV events limit the precision of our estimates, or constrain the statistical power of the analyses. As a result, the VE and CoP estimates presented should be interpreted with caution. The wide confidence intervals further reflect the uncertainty around the VE estimates, and show that larger studies are needed to better confirm these results. However, this data still provides important, preliminary observational data during the first year of vaccine implementation, and the longitudinal nature of this cohort presents the opportunity to revisit these questions in future years. The dropout rate among older participants was very low; only one participant withdrew during the study period. This is unlikely to affect the findings. Although the average number of missing swabs during the study period was low (mean = 4.6, median = 3), specimen non-return or non-collection may have impacted the detection of asymptomatic RSV infections. It could have potentially led to an underestimation of the total number of RSV cases in this cohort. Over two-thirds (71.2%) of the study population were female. While this is unlikely to have materially affected the primary findings (i.e., VE estimates), particularly as the analysis was adjusted for sex, it may limit the generalisability of these findings.

This study did not assess VE against severe RSV outcomes, such as hospitalisation or death; only one participant with symptomatic RSV sought medical care (outpatient visit), and no hospitalisations occurred. Therefore, our findings cannot address vaccine performance against these clinically significant outcomes, which remains an important area for future research in CoVE study. Although it was not assessed in this study, there could also be a relationship between RSV exposure and vaccine uptake, especially considering the overlap in timing of RSV circulation versus vaccine uptake in the cohort. The characteristics of participants vaccinated earlier versus later in the season might differ; older adults at a higher risk (i.e., with comorbidities or chronic conditions) of severe RSV disease, might be more likely to seek early RSV vaccination. A potential relationship between RSV exposure and vaccine uptake raises the possibility of bias due to possible differences between early and late vaccine recipients. Additionally, for the study period, data on potential exposure intensity such as household composition (e.g., living with school-age children or residing in elder-only households), were not available. These unmeasured factors could influence infection risk. Not adjusting for potential differences in exposure risk between vaccinated and unvaccinated might introduce unmeasured confounding. Although these factors could not be accounted for in the current analysis, they are being captured in the ongoing CoVE study through new survey questions, allowing for better assessments in future work.

Antibody against pre-fusion RSV F is expected to have sufficient cross protection between the RSV-A and the RSV-B subgroups. To date, no major differences between the bivalent and monovalent RSV vaccine have emerged. A subgroup analysis by vaccine product was not conducted in this study due to the lower number of RSV events in the vaccinated group, with only 3 RSV events (n = 0 for ABRYSVO, and n = 3 for AREXVY). RSV-B was the most common infecting subtype in our study, and most participants (67.5%) received the GlaxoSmithKline's monovalent (AREXVY) vaccine, which is constructed from an RSV-A virus.[27] Continuing genomic surveillance of RSV is key to ensuring that RSV vaccine effectiveness monitoring is robust going forward, allowing public health to respond to new strains of the virus if they emerge.

The 2023–2024 RSV vaccine program in the United States is the culmination of decades of vaccine development, and an additional vaccine has been approved as of June 2024. Over the next year, focused attention is warranted regarding the durability of vaccine-elicited immunity and the future potential for direct and indirect reduction of illness burden in all adults over 60.

Contributors

E.T.M., A.P.C., E.T.G., D.R., and M.S. planned the analysis of the study, and have accessed and verified the underlying data reported in the manuscript. E.T.G. and M.S. performed the statistical analysis. E.T.G interpreted the results, draughted and revised the article. M.C.E provided intellectual guidance, validated the statistical analysis, and revised the article. A.P.C. coordinated the CoVE study, performed data curation, draughted and revised the article. C.L.J-R. performed the CoVE specimen laboratory testing. K.E.R. provided statistical guidance and revised the article. C.M.M., L.R.F, J.M.J, M.B.H., A.S.M., and A.L.W. provided intellectual guidance and revised the article. A.S.L. oversaw all aspects of the CoVE specimen laboratory testing. E.T.M. conceptualised and oversaw all aspects of the project and revised the article. All authors read and approved the final version of the manuscript.

Data sharing statement

The data used in this study can be made available upon request. Due to Institutional Review Board (IRB) regulations, data access is controlled. Per the guidelines of the Centers for Excellence in Influenza Research and Response (CEIRR) Network, individuals seeking access must complete a data and specimen collaboration form. Requests received will be reviewed by the study investigators. For enquiries, please contact covestudy@umich.edu. Requests will generally receive an initial response within 3–5 business days.

Declaration of interests

ASL received consulting fees from Roche related to the baloxavir clinical trial. All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2025.105961.

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