COVID-19 Update
February 16, 2023

Jorge Mera, MD, FACP

The average number of new cases in the United States fell to **38,926** yesterday, a **2 percent decrease** from the day before.

Maps for the United States

	ON FEB. 13	DAILY AVG.	PER 100,000	14-DAY CHANGE	TOTAL REPORTED
Cases	24,468	38,926	12	–7%	102,598,932
Deaths	213	452	<1	–8%	1,120,904
Hospitalized	27,484	28,716	9	–12%	
Test positivity		10%			

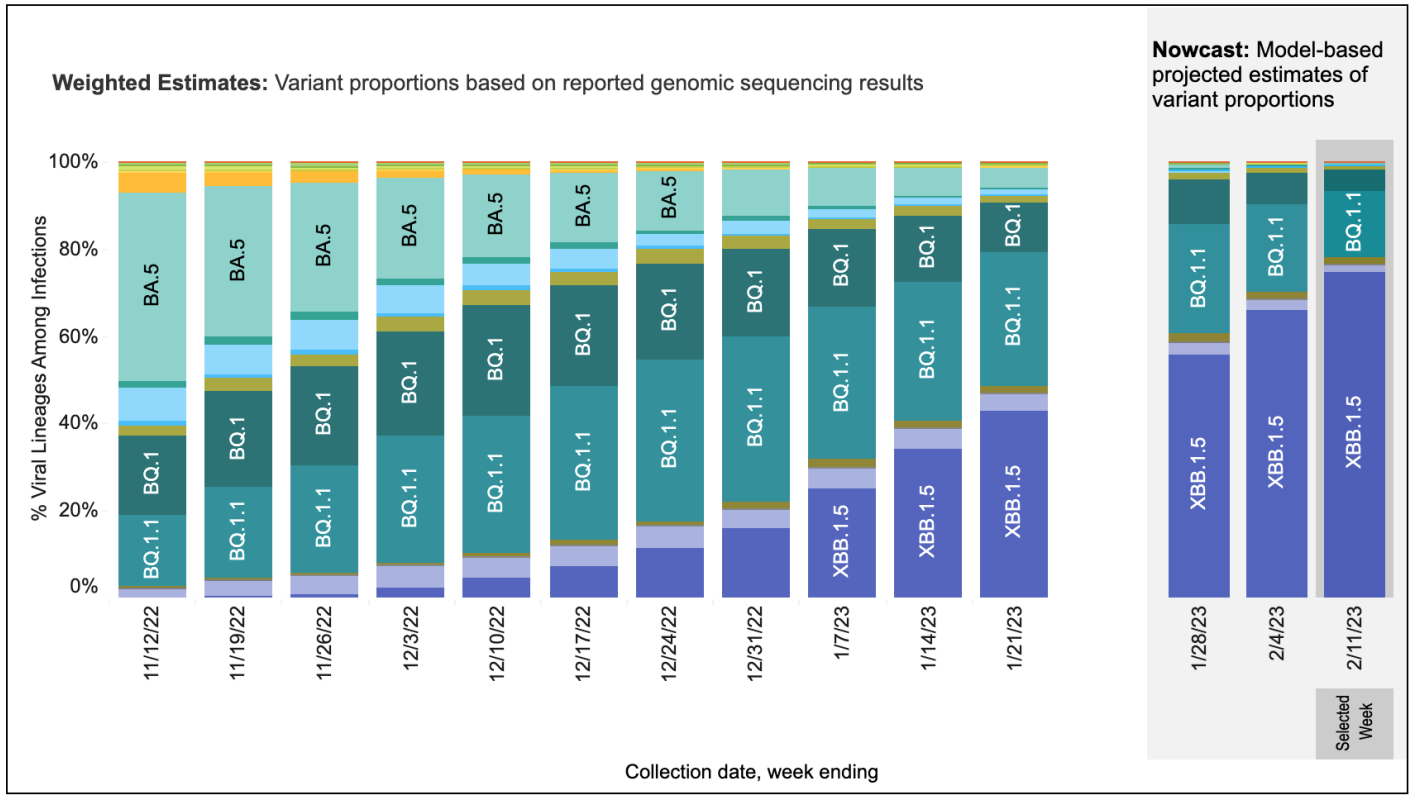
Vaccination rate for the U.S.

Source: Centers for Disease Control and Prevention. Percentages are the share of a population that is fully vaccinated.

This shows weighted and Nowcast estimates for the United States. The table and map show estimates for the week ending in 2/11/2023 (Nowcast).

Weighted and Nowcast Estimates in United States for Weeks of 11/6/2022 – 2/11/2023

Hover over (or tap in mobile) any lineage of interest to see the amount of uncertainty in that lineage's estimate.



Nowcast Estimates in United States for 2/5/2023 – 2/11/2023

USA

WHO label	Lineage #	US Class	%Total	95%PI
Omicron	XBB.1.5	VOC	74.7%	67.0-81.2%
	BQ.1.1	VOC	15.3%	11.4-20.2%
	BQ.1	VOC	5.1%	3.7-6.8%
	XBB	VOC	1.9%	1.4-2.5%
	CH.1.1	VOC	1.3%	0.9-1.9%
	BN.1	VOC	0.8%	0.5-1.1%
	BA.5	VOC	0.3%	0.2-0.5%
	BF.7	VOC	0.3%	0.2-0.4%
	BA.5.2.6	VOC	0.1%	0.1-0.2%
	BA.2	VOC	0.1%	0.0-0.1%
	BF.11	VOC	0.0%	0.0-0.1%
	BA.2.75	VOC	0.0%	0.0-0.0%
	BA.2.75.2	VOC	0.0%	0.0-0.0%
	BA.4.6	VOC	0.0%	0.0-0.0%
	B.1.1.529	VOC	0.0%	0.0-0.0%
	BA.2.12.1	VOC	0.0%	0.0-0.0%
	BA.4	VOC	0.0%	0.0-0.0%
	BA.1.1	VOC	0.0%	0.0-0.0%
Delta	B.1.617.2	VBM	0.0%	0.0-0.0%
Other	Other*		0.1%	0.0-0.1%

* Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during all weeks displayed.
\# BA.1, BA.3 and their sublineages (except BA.1.1 and its sublineages) are aggregated with B.1.1.529. Except BA.2.12.1, BA.2.75, XBB and their sublineages, BA.2 sublineages are aggregated with BA.2. Except BA.2.75.2, CH.1.1 and BN.1, BA.2.75 sublineages are aggregated with BA.2.75. Except BA.4.6, sublineages of BA.4 are aggregated to BA.4. Except BF.7, BF.11, BA.5.2.6, BQ.1 and BQ.1.1, sublineages of BA.5 are aggregated to BA.5. Except XBB.1.5, sublineages of XBB are aggregated to XBB. For all the other lineages listed, their sublineages are aggregated to the listed parental lineages respectively. Previously, CH.1.1 was aggregated to BA.2.75. Lineages BA.2.75.2, XBB, XBB.1.5, BN.1, BA.4.6, BF.7, BF.11, BA.5.2.6 and BQ.1.1 contain the spike substitution R346T.

In Vitro Efficacy of Therapeutic Monoclonal Antibodies and Antiviral Drugs against Omicron Subvariants.

BA.2 and BA.5 variants have been shown to have less sensitivity to certain monoclonal antibodies than previously circulating variants of concern.

- **BQ.1.1 and XBB carry additional substitutions in RBD of the spike protein** as compared with BA.5 and BA.2

This study assessed the efficacy of monoclonal antibodies and antivirals against omicron BQ.1.1 and XBB, isolated from patients.

- The BQ.1.1 isolate had three more substitutions in its RBD than a BA.5 isolate
- The XBB isolate had nine more changes in its RBD than the BA.2 isolate.

in vitro neutralizing activity of the monoclonal antibodies was performed by using a live-virus neutralization assay.

- **Imdevimab–casirivimab, tixagevimab–cilgavimab, sotrovimab, and bebtelovimab may not be effective against BQ.1.1 or XBB in the clinical setting.**

Imai et al. N Engl J Med 2023;388:89-91.

In Vitro Efficacy of Therapeutic Monoclonal Antibodies and Antiviral Drugs against Omicron Subvariants

Remdesivir (an inhibitor of the RdRp], molnupiravir (an RdRp inhibitor) and nirmatrelvir (a protease inhibitor) were tested

- BQ.1.1 and XBB isolates encode the P3395H substitution in their main protease
- The BQ.1.1 and XBB isolates also have 2 and 3 substitutions in their RdRp, respectively.

The susceptibilities of BQ.1.1 and XBB to the three compounds were like those of the ancestral strain

- **Remdesivir, molnupiravir, and nirmatrelvir are efficacious against both BQ.1.1 and XBB**

The continued evolution of omicron variants reinforces the need for new therapeutic monoclonal antibodies for Covid-19.

Imai et al. N Engl J Med 2023;388:89-91.

NIH Treatment Guidelines Update

January 30, 2023:

- The prevalence of SARS-CoV-2 Omicron subvariants that are not susceptible to tixagevimab plus cilgavimab (Evusheld) has been rapidly increasing in the United States.
- Because the overall prevalence of non-susceptible subvariants is now **>97%**, tixagevimab plus cilgavimab ***is not authorized*** for use as pre-exposure prophylaxis (PrEP) of COVID-19 in the United States.
- The Panel now **recommends against** the use of **tixagevimab plus cilgavimab** as PrEP of COVID-19 **(AIII)**.

January 26, 2023

- **On November 9, 2022, the FDA issued an EUA for the use of anakinra in certain hospitalized adults with COVID-19.**
  - *Indicated for patients with moderate or severe COVID-19 pneumonia and plasma levels of soluble urokinase plasminogen activator receptor (suPAR) ≥6 ng/mL.*
  - *Because the assays that measure suPAR levels are not available in the United States, the FDA developed a scoring system that uses common clinical and laboratory factors to identify patients who are likely to have suPAR levels ≥6 ng/mL.*
  - *The EUA allows for the use of anakinra in patients who meet ≥3 of these criteria.*
- **The Panel continues to note that there is insufficient evidence to recommend either for or against the use of anakinra**

Last Updated: December 28, 2022

Patient Disposition	Panel's Recommendations
All Patients	• All patients should be offered symptom management **(AIII)**. • The Panel **recommends against** the use of **dexamethasone**[a] or **other systemic corticosteroids** in the absence of another indication **(AIIb)**.
Patients Who Are at High Risk of Progressing to Severe COVID-19[b]	*Preferred therapies. Listed in order of preference:* • **Ritonavir-boosted nirmatrelvir (Paxlovid)**[c,d] **(AIIa)** • **Remdesivir**[d,e] **(BIIa)** *Alternative therapy. For use when the preferred therapies are not available, feasible to use, or clinically appropriate:* • **Molnupiravir**[d,f,g] **(CIIa)**
Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.	

Therapeutic Management of Nonhospitalized Adults With COVID-19

- [a] There is currently a lack of safety and efficacy data on the use of dexamethasone in outpatients with COVID-19. Using systemic glucocorticoids in outpatients with COVID-19 may cause harm.
- [b] For a list of risk factors, see the CDC webpage Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19. When deciding whether to prescribe antiviral treatment to a patient who has been vaccinated, clinicians should be aware of the conditions associated with a high risk of disease progression. These conditions include older age, a prolonged amount of time since the most recent vaccine dose (e.g., >6 months), and a decreased likelihood of an adequate immune response to vaccination due to a moderate to severe immunocompromising condition or the receipt of immunosuppressive medications. The number and severity of risk factors also affects the level of risk.
- [c] Ritonavir-boosted nirmatrelvir has significant drug-drug interactions. Clinicians should carefully review a patient's concomitant medications and evaluate potential drug-drug interactions. See Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications for more information.
- [d] If a patient requires hospitalization after starting treatment, the full treatment course can be completed at the health care provider's discretion.
- [e] Administration of remdesivir requires an IV infusion once daily for 3 days.
- [f] Molnupiravir appears to have lower efficacy than the other options recommended by the Panel. Therefore, it should be considered when the other options are not available, feasible to use, or clinically appropriate.
- [g] The Panel **recommends against** the use of **molnupiravir** for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated **(AIII)**.

https://www.covid19treatmentguidelines.nih.gov/tables/management-of-hospitalized-adults-summary/

Therapeutic Management of Adults Hospitalized for COVID-19 Based on Disease Severity

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy		Recommendations for Anticoagulant Therapy
	Clinical Scenario	Recommendation	
Hospitalized for Reasons Other Than COVID-19	Patients with mild to moderate COVID-19 who are at high risk of progressing to severe COVID-19[a,b]	See Therapeutic Management of Nonhospitalized Adults With COVID-19.	For patients without an indication for therapeutic anticoagulation: • **Prophylactic dose of heparin**, unless contraindicated (**AI**); (**BIII**) for pregnant patients
Hospitalized but Does Not Require Oxygen Supplementation	All patients	The Panel **recommends against** the use of **dexamethasone** (**AIIa**) or **other systemic corticosteroids** (**AIII**) for the treatment of COVID-19.[c]	
	Patients who are at high risk of progressing to severe COVID-19[a,b]	**Remdesivir**[d] (**BIII**)	
Hospitalized and Requires Conventional Oxygen[e]	Patients who require minimal conventional oxygen	**Remdesivir**[f] (**BIIa**)	For nonpregnant patients with D-dimer levels above the ULN who do not have an increased bleeding risk: • **Therapeutic dose of heparin**[h] (**CIIa**) For other patients: • **Prophylactic dose of heparin**, unless contraindicated (**AI**); (**BIII**) for pregnant patients
	Most patients	Use **dexamethasone plus remdesivir**[f] (**BIIa**). If remdesivir cannot be obtained, use **dexamethasone** (**BI**).	
	Patients who are receiving dexamethasone and who have rapidly increasing oxygen needs and systemic inflammation	Add **PO baricitinib**[g] or **IV tocilizumab**[g] to 1 of the options above (**BIIa**).	
Hospitalized and Requires HFNC Oxygen or NIV	Most patients	Promptly start 1 of the following, if not already initiated: • **Dexamethasone plus PO baricitinib**[g] (**AI**) • **Dexamethasone plus IV tocilizumab**[g] (**BIIa**) If **baricitinib, tofacitinib, tocilizumab,** or **sarilumab** cannot be obtained: • **Dexamethasone**[i] (**AI**) Add **remdesivir** to 1 of the options above in certain patients (**CIIa**).[j]	For patients without an indication for therapeutic anticoagulation: • **Prophylactic dose of heparin**, unless contraindicated (**AI**); (**BIII**) for pregnant patients For patients who are started on a therapeutic dose of heparin in a non-ICU setting and then transferred to the ICU, the Panel recommends switching to a **prophylactic dose of heparin**, unless there is another indication for therapeutic anticoagulation (**BIII**).
Hospitalized and Requires MV or ECMO	Most patients	Promptly start 1 of the following, if not already initiated: • **Dexamethasone plus PO baricitinib**[g] (**BIIa**) • **Dexamethasone plus IV tocilizumab**[g] (**BIIa**) If **baricitinib, tofacitinib, tocilizumab,** or **sarilumab** cannot be obtained: • **Dexamethasone**[i] (**AI**)	

https://www.covid19treatmentguidelines.nih.gov/tables/management-of-hospitalized-adults-summary/

Hypothesis of how delayed but exaggerated type I IFN responses are involved in hyperinflammation and contribute to the severe progression of COVID-19.

After respiratory epithelial cells are infected

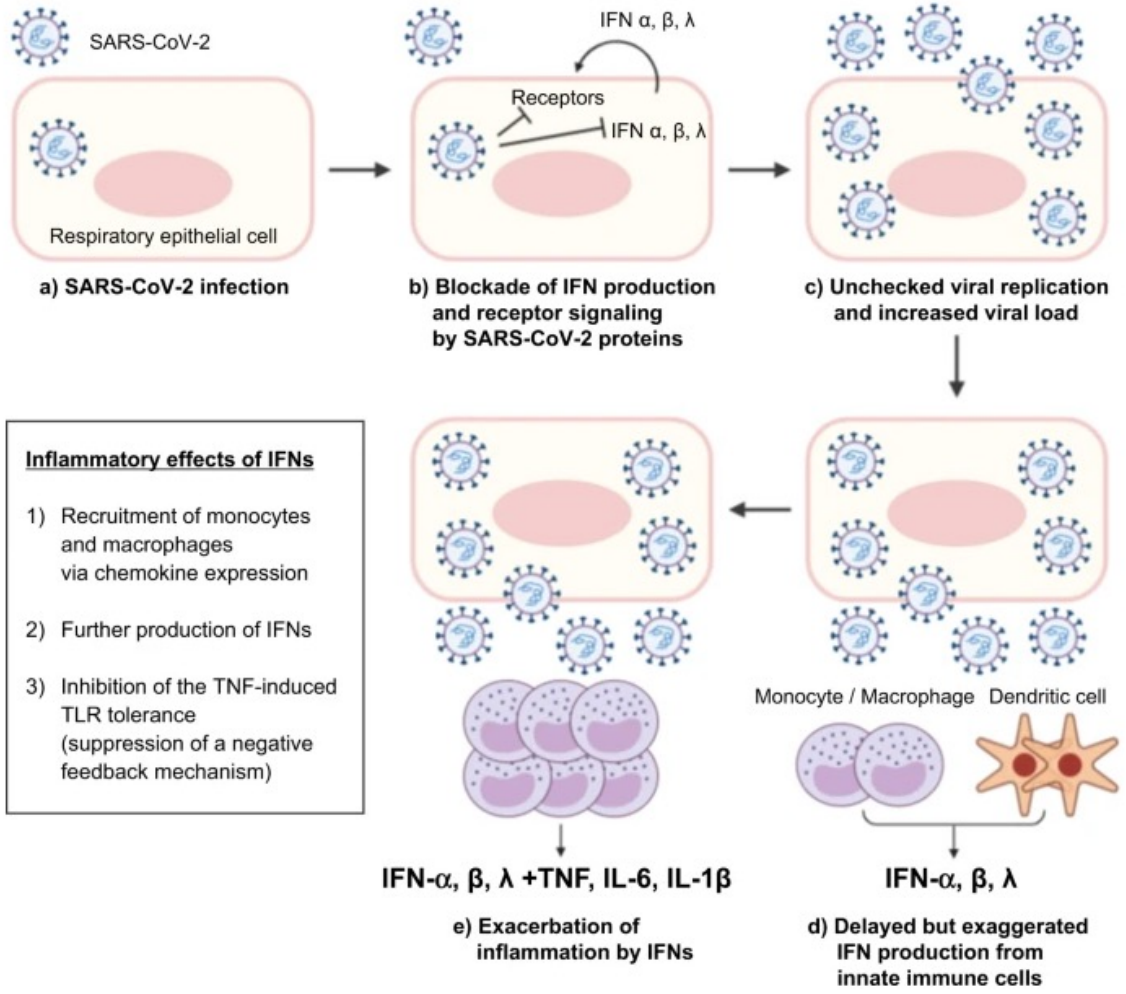
(**a**) SARS-CoV-2 proteins block type I and III interferon (IFN) responses

(**b**) The viral load increases

(**c**) Uninfected innate immune cells, such as monocytes, macrophages, and dendritic cells, are stimulated by viral components via Toll-like receptors and produce type I and III IFNs

(**d**) Type I and III IFNs further induce the accumulation and activation of monocytes and macrophages, leading to the production of large amounts of IFNs and proinflammatory cytokines

(**e**) Type I IFNs also enhance TNF-mediated inflammation by disrupting TNF-induced tolerance to TLR stimulation in monocytes and macrophages.



Originally identified as secretory factors that inhibit viral infections, IFNs are classified into three groups: types I, II, and III. Type I IFNs consist of multiple subtypes of IFN-α and a single type of IFN-β, in addition to the less well-characterized IFN-δ, -ε, -κ, -τ, -ω, and -ζ. In contrast, the type II IFN group has only a single member, IFN-γ, which is secreted by natural killer and T cells but not directly by virus-infected cells, and is therefore not described further in this review. Type III IFNs are structurally related to IL-10 family cytokines and consist of IFN-λ1 (IL-29), -λ2 (IL-28A), -λ3 (IL-28B), and -λ4[7,8,9]. IFN-β and IFN-λs can be secreted by any type of cell upon viral infection, whereas IFN-αs are generally produced by immune cells, particularly monocytes and dendritic cells (DCs).

Kim, YM., Shin, EC. Type I and III interferon responses in SARS-CoV-2 infection. *Exp Mol Med* **53**, 750–760 (2021)

Treatment Update

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Early Treatment with Pegylated Interferon Lambda for Covid-19

Reis G et al. DOI: 10.1056/NEJMoa2209760

CLINICAL PROBLEM

Convenient, widely available, and effective therapies to treat Covid-19 in outpatients are needed. SARS-CoV-2 infection induces weak expression of naturally produced type III interferons — an early line of defense against respiratory viruses — in infected cells. Whether an exogenous source of interferons, such as pegylated interferon lambda, can treat early SARS-CoV-2 infection is unknown.

CLINICAL TRIAL

Design: A phase 3, adaptive platform, randomized, placebo-controlled trial assessed the efficacy and safety of pegylated interferon lambda in adult outpatients in Brazil and Canada who were at high risk for severe illness soon after they received a diagnosis of Covid-19.

Intervention: 1949 adults presenting within 7 days after symptom onset with a positive rapid test for SARS-CoV-2 and with at least one high-risk criterion (e.g., age ≥50 years, diabetes mellitus, and hypertension leading to the use of medication) were assigned to receive a single subcutaneous injection of pegylated interferon lambda (180 μg) or placebo. Most patients had received at least one dose of Covid-19 vaccine. The primary outcome was a composite of Covid-19–related hospitalization (or referral to a tertiary hospital) or admission to an emergency department (ED) (observation for >6 hours) within 28 days after randomization.

RESULTS

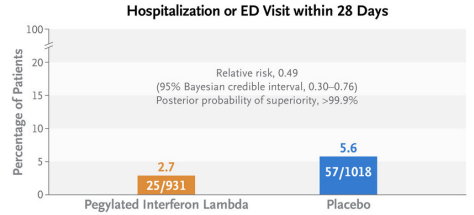
Efficacy: The risk of Covid-19–related hospitalization or an ED visit was approximately 50% lower in the interferon group than in the placebo group. Results were consistent regardless of vaccination status.

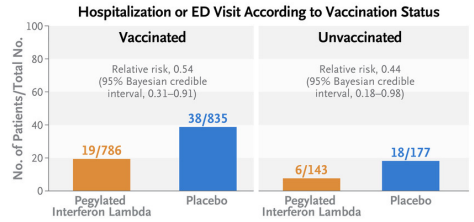
Safety: The incidence of adverse events was similar in the two groups.

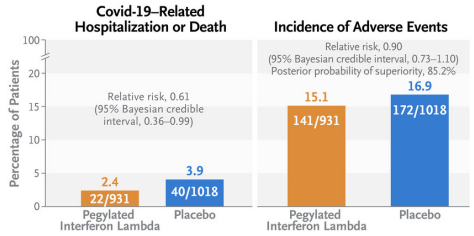
REMAINING QUESTIONS

- Since the completion of the trial, a polymorphism in the innate antiviral response gene *OAS1* has been linked to clearance of SARS-CoV-2, and a common haplotype could indicate a greater likelihood of response to pegylated interferon lambda and other interferons.

Links: Full Article | NEJM Quick Take



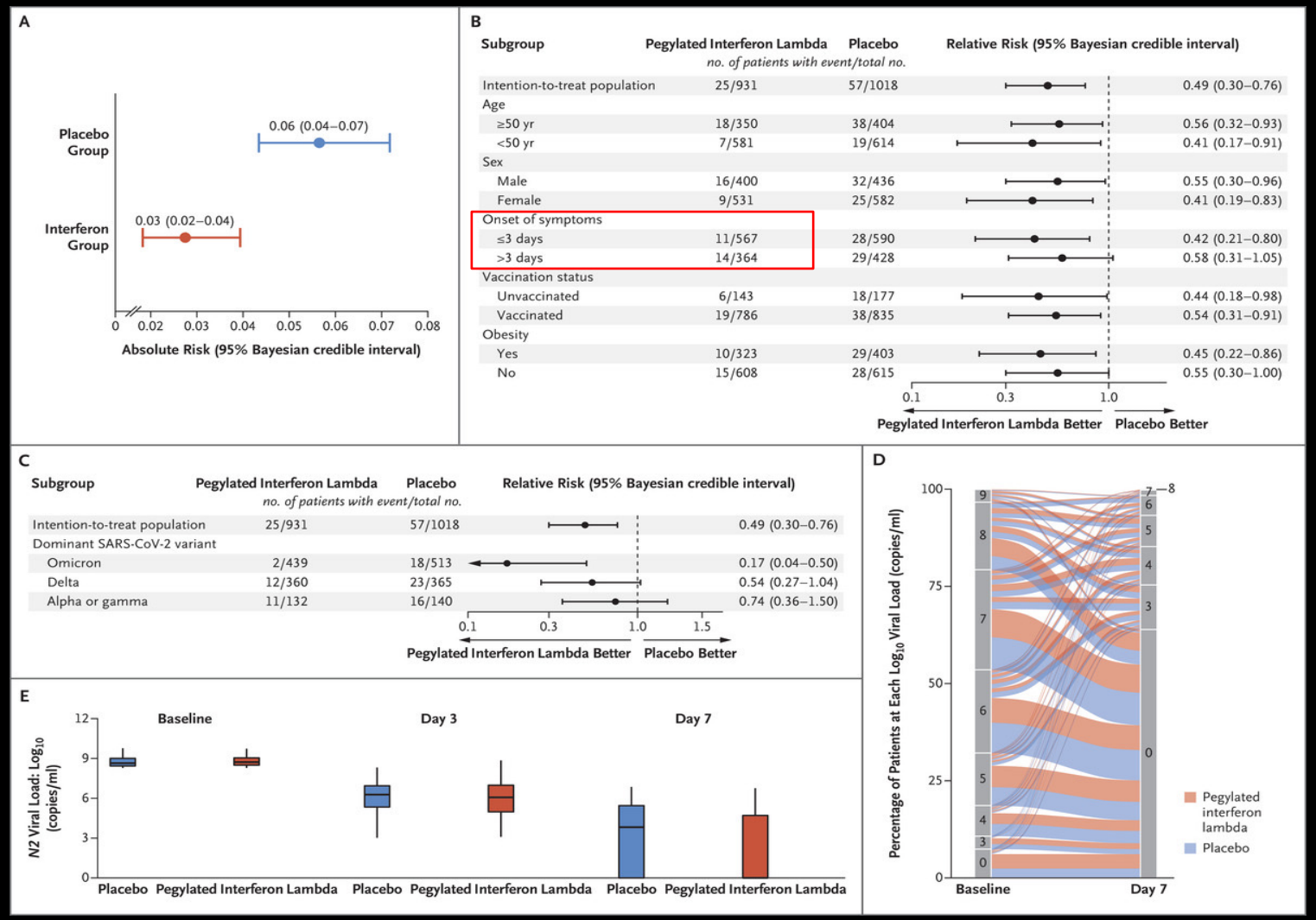




CONCLUSIONS

Among high-risk, symptomatic, largely vaccinated outpatients with a recent diagnosis of Covid-19, those who received a single subcutaneous injection of pegylated interferon lambda had a lower risk of Covid-19–related hospitalization or an ED visit within 28 days than those who received placebo.

Subgroup Analyses.



G Reis et al. N Engl J Med 2023;388:518-528.

The NEW ENGLAND JOURNAL of MEDICINE

Maternal mRNA covid-19 vaccination during pregnancy and delta or omicron infection or hospital admission in infants: test negative design study

Objective

- To estimate the effectiveness of maternal mRNA covid-19 vaccination during pregnancy against delta and omicron severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection and hospital admission in infants.

Design

- Test negative design study.

Setting

- Community and hospital testing in Ontario, Canada.
- Participants Infants younger than six months of age, born between 7 May 2021 and 31 March 2022, who were tested for SARS-CoV-2 between 7 May 2021 and 5 September 2022.

Intervention

- Maternal mRNA covid-19 vaccination during pregnancy.

Main outcome measures:

- Laboratory confirmed delta or omicron infection or hospital admission of the infant. Multivariable logistic regression estimated vaccine effectiveness, with adjustments for clinical and sociodemographic characteristics associated with vaccination and infection.

BMJ 2023;380:e074035 | doi: 10.1136/bmj-2022-074035

Maternal mRNA covid-19 vaccination during pregnancy and delta or omicron infection or hospital admission in infants: test negative design study

8809 infants met eligibility criteria, including 99 delta cases (4365 controls) and 1501 omicron cases (4847 controls).

Infant vaccine effectiveness from two maternal doses for Delta virus was:

- **95%** against infection and **97% against infant hospital admission**

Infant vaccine effectiveness from two maternal doses for Omicron virus was:

- **45%** against infection and **53% against hospital admission**
- Effectiveness for infant infection was highest with the second dose in the **third trimester 53%** compared with the **first 47%** or **second 37%** trimesters
- Effectiveness against infant omicron infection decreased from **57%** between birth and eight weeks to **40%** after 16 weeks of age.

Infant vaccine effectiveness against omicron for three doses was:

- **73%** against omicron infection and **80%** against hospital admission due to omicron.

Additionally, receipt of only the first vaccine dose during pregnancy offered less protection than completion of the two or three dose series.

BMJ 2023;380:e074035 | doi: 10.1136/bmj-2022-074035

COVID-19 Update Take Home Points

Omicron subvariant XBB.1.5 is the predominant variant followed by BQ1.1

- Remdesivir, molnupiravir, and nirmatrelvir are efficacious against both BQ.1.1 and XBB in vitro.
- **Imdevimab–casirivimab, tixagevimab–cilgavimab, sotrovimab, and bebtelovimab may not be effective against BQ.1.1 or XBB in the clinical setting**

COVID-19 cases, hospitalizations and deaths are decreasing

- **But the daily death average is 452**

Among predominantly vaccinated outpatients with Covid-19

- The incidence of hospitalization or an emergency department visit **was significantly lower among those who received a single dose of pegylated interferon lambda** than among those who received placebo

Maternal covid-19 vaccination with a second dose during pregnancy

- Was highly effective against delta and moderately effective against omicron infection and hospital admission in infants during the first six months of life.
- Effectiveness highest with maternal vaccination in the third trimester, and decreased in infants beyond eight weeks of age
- A third covid-19 vaccine dose during pregnancy increased protection against omicron.