Η 1η εγκεκριμένη από τον EMA αντι-ιική θεραπεία από του στόματος για την COVID-19

Μεταλλίδης Συμεών

Καθηγητής Παθολογίας Λοιμωξιολογίας
Ιατρικό Τμήμα ΑΠΘ

Διευθυντής Α΄ Παθολογικής Κλινικής
ΠΓΝΘ ΑΧΕΠΑ

Σύγκρουση Συμφερόντων

- **Έχω λάβει τιμητικές αμοιβές και ερευνητικά χορηγίες από τις εταιρείες**
  - **Pfizer**
  - Astellas
  - Gilead
  - Janssen

«Η Pfizer έχει ελέγξει το περιεχόμενο ώστε να ανταποκρίνεται στις ειδικές προδιαγραφές της, αλλά δεν έχει επιβεβαιώσει ότι οι βιβλιογραφικές παραπομπές έχουν παρατεθεί ορθά”

Για όλα τα φαρμακευτικά προϊόντα που αναφέρονται παρακαλείστε να συμβουλεύεστε κυρίως τις εγκεκριμένες Περιλήψεις Χαρακτηριστικών των Προϊόντων

Κατανόηση του προβλήματος…

28 Ιανουαρίου 2020

Ορισμός Νοσοκομείου ΑΧΕΠΑ ως κέντρου Αναφοράς COVID-19

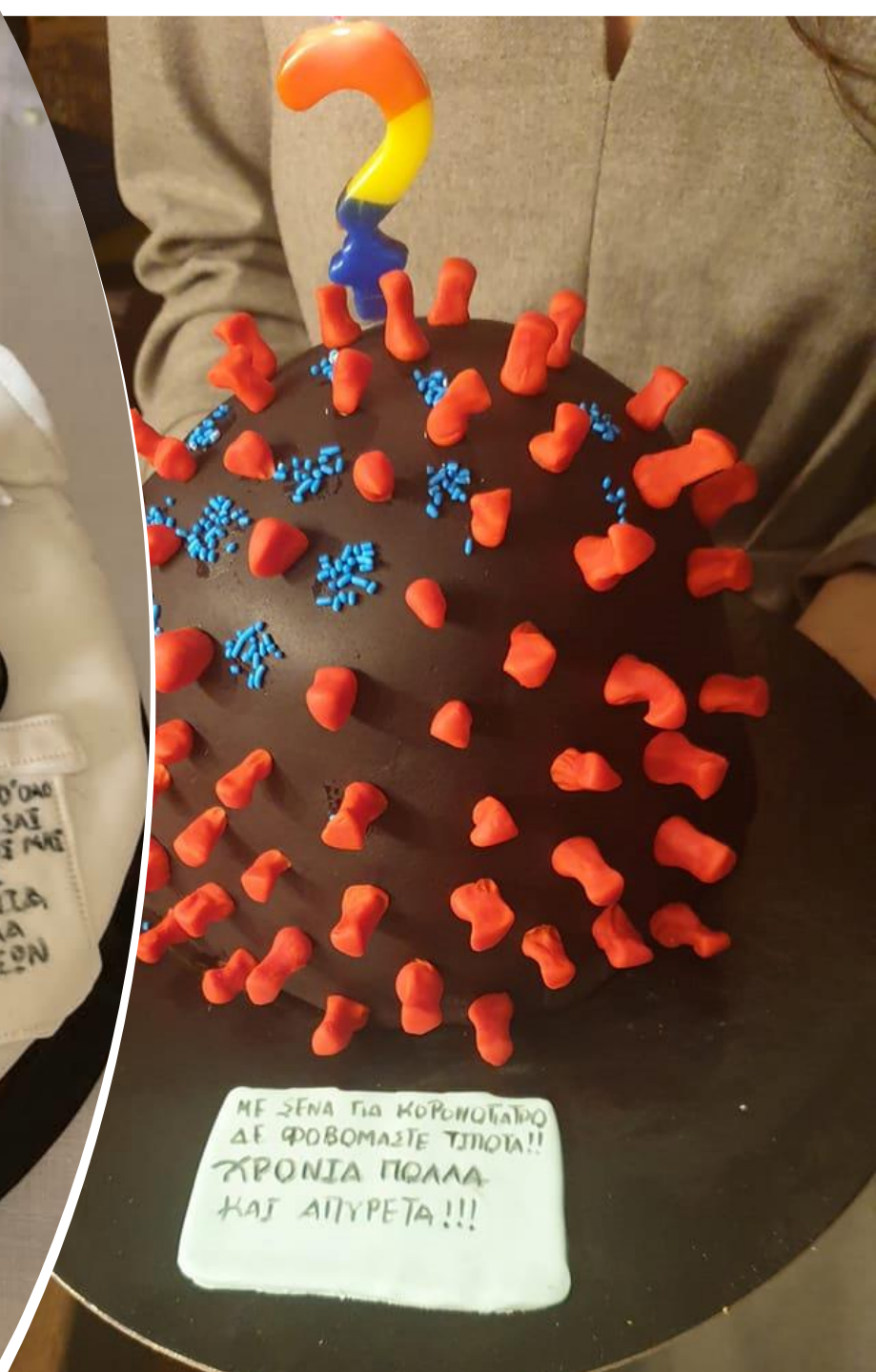
Παλεύοντας με έναν άγνωστο γνωστό εχθρό

Η ιστορία της πανδημίας …

29 Σεπτεμβρίου 2023

Ημέρα της σημερινής παρουσίασης

1340 ημέρες



1340 ημέρες COVID-19

Η νόσος COVID-19 παραμένει μια παγκόσμια απειλή για την δημόσια υγεία

Statement on the fifteenth meeting of the IHR (2005) Emergency Committee on the COVID-19 pandemic

5 May 2023 | Statement |Reading time: 7 min (1792 words)

World Health Organization

The WHO Director-General has the pleasure of transmitting the Report of the fifteenth meeting of the International Health Regulations (2005) (IHR) Emergency Committee regarding the coronavirus 2019 disease (COVID-19) pandemic, held on Thursday 4 May 2023, from 12:00 to 17:00 CET.

During the deliberative session, the Committee members highlighted the decreasing trend in COVID-19 deaths, the decline in COVID-19 related hospitalizations and intensive care unit admissions, and the high levels of population immunity to SARS-CoV-2. The Committee's position has been evolving over the last several months. While acknowledging the remaining uncertainties posted by potential evolution of SARS-CoV-2, they advised that it is time to transition to long-term management of the COVID-19 pandemic.

The WHO Director-General concurs with the advice offered by the Committee regarding the ongoing COVID-19 pandemic. He determines that COVID-19 is now an established and ongoing health issue which no longer constitutes a public health emergency of international concern (PHEIC).

Source: https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic , Accessed Sep 2023

Report of the Review Committee regarding standing recommendations for COVID-19

9 August 2023 | Meeting report

COVID-19 Strategic Preparedness and Response Plan APRIL 2023-APRIL 2025:

- *"**vaccination** in at **risk populations** to prevent severe disease and death*
- ***early diagnosis, treatment and clinical care**, especially in at-risk populations*
- *integration of COVID-19 vaccination and COVID-19 disease management into existing primary health services*
- *protecting health workers and other priority groups and*
- ***strong surveillance** and **monitoring of SARS-CoV-2 variants**, including strategic and geographically representative sequencing to track known and future variants, respiratory pathogens, and other pandemic threats."*

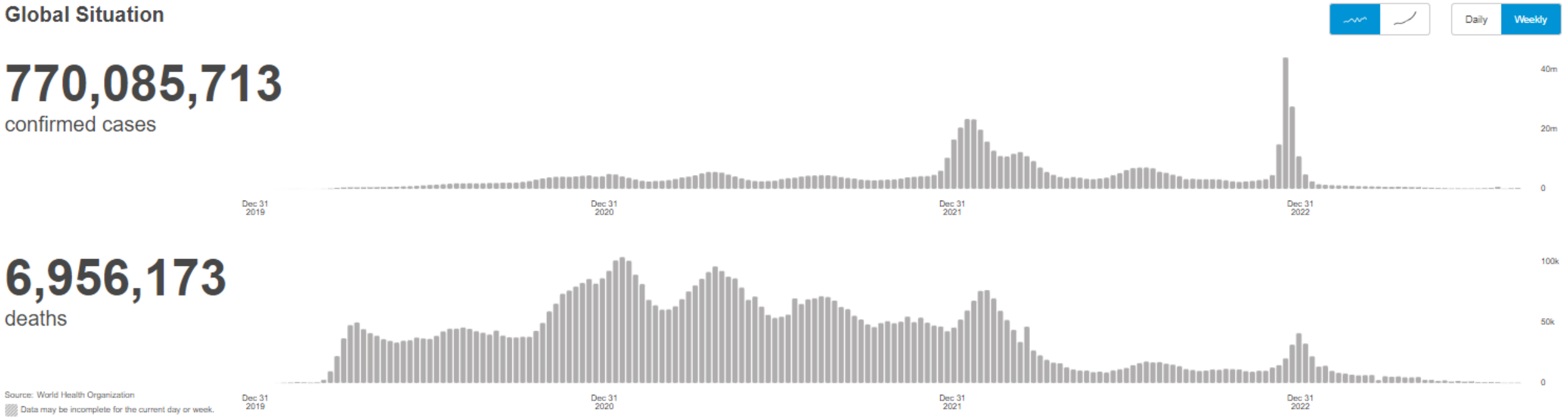
Source: Report of the Review Committee regarding standing recommendations for COVID-19 9 August 2023 | Meeting report: Report of the Review Committee regarding standing recommendations for COVID-19 (who.int), Accessed Sep 2023

6

Επιδημιολογία…

Παγκόσμια επιδημιολογικά δεδομένα της COVID-19 κατά ΠΟΥ

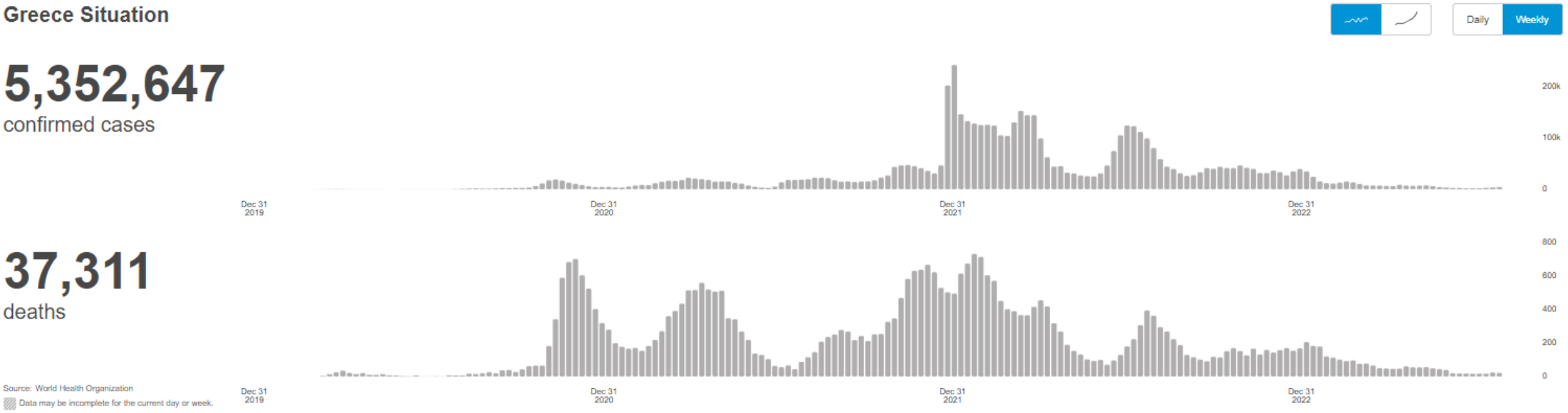
Globally, as of **12:20pm CEST, 30 August 2023**, there have been **770,085,713 confirmed cases** of COVID-19, including **6,956,173 deaths**, reported to WHO. As of **19 August 2023**, a total of **13,499,865,692 vaccine doses** have been administered.



Source: https://covid19.who.int/, Accessed 01 Sep 2023
ΠΟΥ: Παγκόσμιος Οργανισμός Υγείας

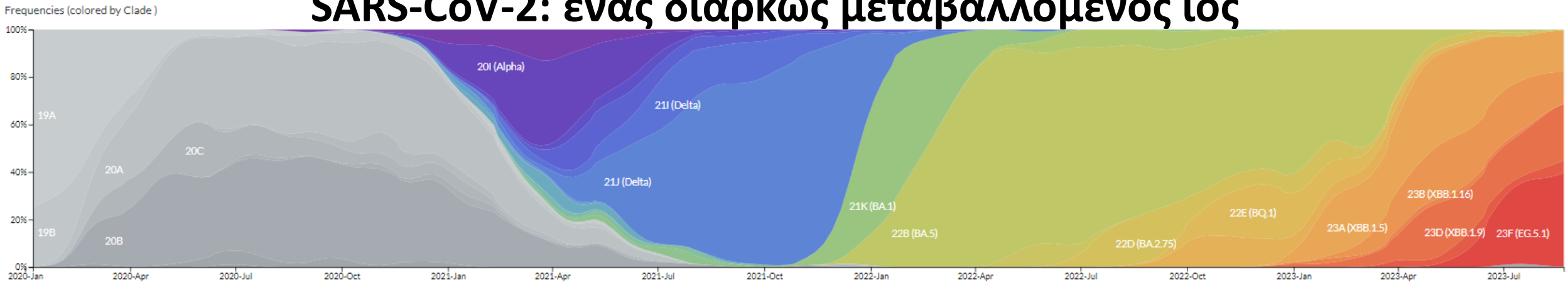
Ελλάδα: επιδημιολογικά δεδομένα COVID-19 κατά ΠΟΥ

In **Greece**, from **3 January 2020** to **12:20pm CEST, 30 August 2023**, there have been **5,352,647 confirmed cases** of COVID-19 with **37,311 deaths**, reported to WHO. As of **10 June 2023**, a total of **21,983,798 vaccine doses** have been administered.

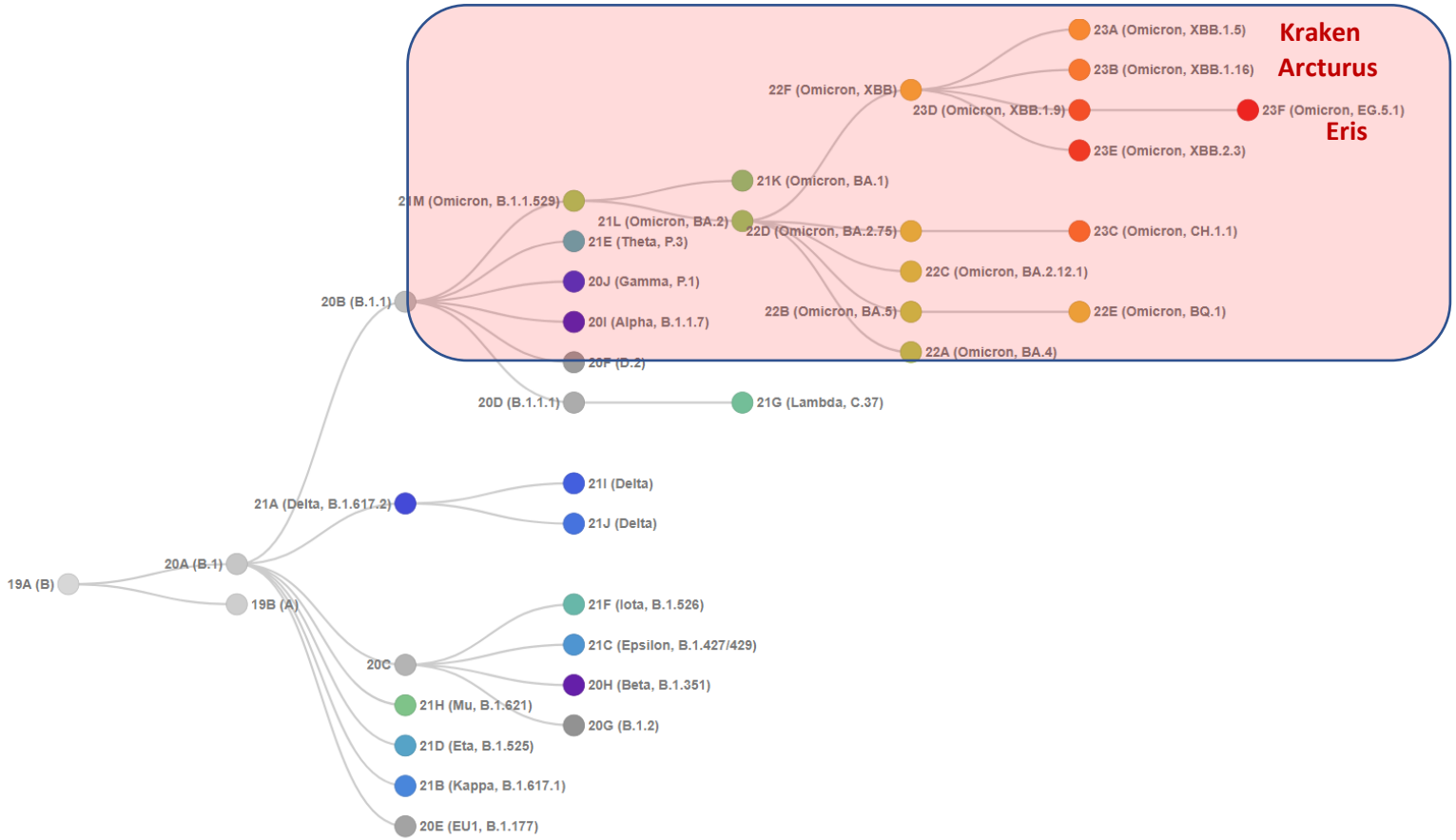


Source: https://covid19.who.int/region/euro/country/gr, Accessed 01 Sep 2023
ΠΟΥ: Παγκόσμιος Οργανισμός Υγείας

SARS-CoV-2: ένας διαρκώς μεταβαλλόμενος ιός



Source: https://nextstrain.org/ncov/gisaid/global/all-time?d=tree,frequencies&p=full

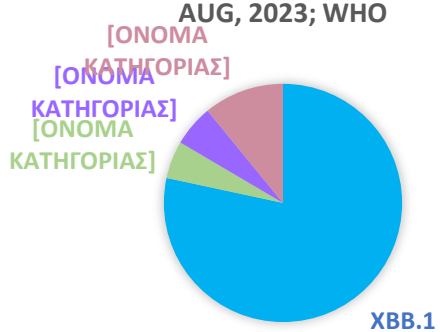


Source: GitHub - nextstrain/ncov-clades-schema: Renders SVG schema of SARS-CoV-2 clade as defined by Nextstrain, Accessed : 01 Sep 2023

WHO is currently tracking several SARS-CoV-2 variants, including:

- Three variants of interest (VOIs); XBB.1.5, XBB.1.16 and **EG.5**.
- Seven variants under monitoring (VUMs); BA.2.75, **BA.2.86**, CH.1.1, XBB, XBB.1.9.1, XBB.1.9.2 and XBB.2.3.

PREVELANCE OF VARIANTS OF INTEREST (VOIS) AND VARIANTS UNDER MONITORING (VUYMS) JULY 31 TO 6 AUG, 2023; WHO



XBB.1.5	10%
XBB.1.16	23,90%
XBB.1.9.1	10%
XBB.1.9.2	5,30%
EG.5	23,80%

Source: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---1-september-2023, Accessed : 01 Sep 2023

SARS CoV-2 Επιδημιολογικά Δεδομένα - Ελλάδα

Εβδομαδιαία Έκθεση
Επιδημιολογικής Επιτήρησης Αναπνευστικών Λοιμώξεων
Εβδομάδα 34/2023 (21 Αυγούστου 2023 – 27 Αυγούστου 2023)

Σύνοψη επιδημιολογικών δεδομένων – εβδομάδα 34/2023

***Συνοπτικά την εβδομάδα 34/2023*:**

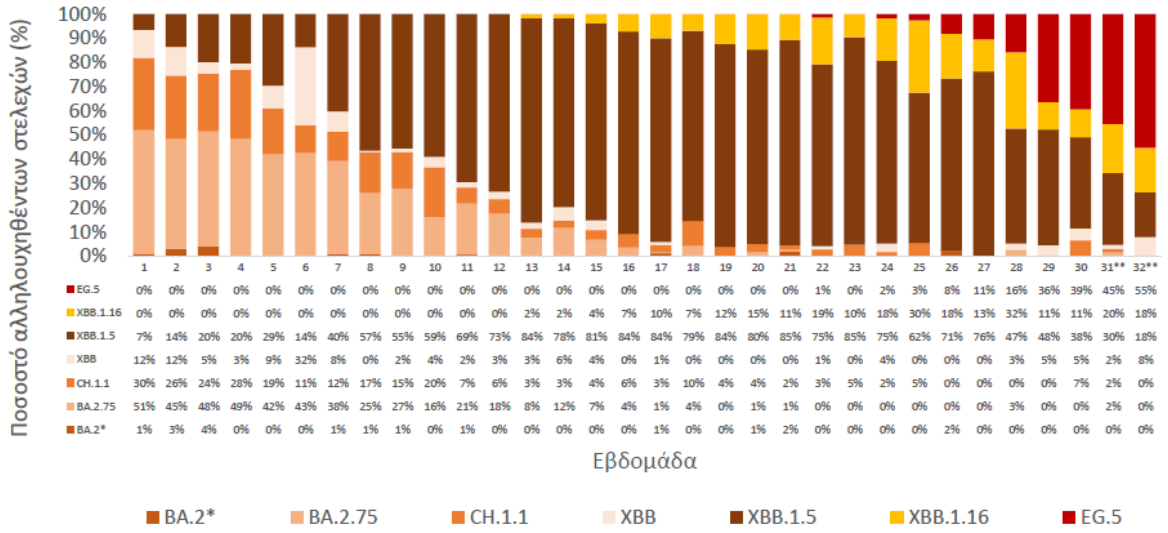
Γριπώδεις συνδρομές (ανεξαρτήτως παθογόνου)

- ✓ παραμένουν σε χαμηλά επίπεδα

Ιός SARS-CoV2 – λοίμωξη COVID-19

- ✓ η θετικότητα στο σύνολο των ελεγχθέντων δειγμάτων παρουσίασε μικρή μείωση σε σχέση με την προηγούμενη εβδομάδα
- ✓ ο αριθμός των εισαγωγών για COVID-19 (n=629) παρουσίασε μικρή μείωση σε σχέση με την προηγούμενη εβδομάδα και αύξηση 26% σε σχέση με τον μέσο εβδομαδιαίο αριθμό νέων εισαγωγών κατά τις προηγούμενες 4 εβδομάδες
- ✓ ο αριθμός των νέων διασωληνώσεων (n=19) παρουσίασε αύξηση σε σχέση με την προηγούμενη εβδομάδα και σε σχέση με τον μέσο εβδομαδιαίο αριθμό νέων διασωληνώσεων κατά τις προηγούμενες 4 εβδομάδες (n=8)
- ✓ ο αριθμός των ασθενών με λοίμωξη COVID-19 που νοσηλεύονται διασωληνωμένοι είναι 25
- ✓ καταγράφηκαν 40 θάνατοι με διάμεση ηλικία τα 87 έτη (εύρος 64-97 έτη)
- ✓ κατά τις τελευταίες εβδομάδες όλα τα αλληλουχηθέντα στελέχη ανήκαν στην υπο-παραλλαγή BA.2 της Όμικρον
- ✓ την εβδομάδα 30 η συχνότερη υπο-παραλλαγή της BA.2 ήταν η EG.5 (39%), ακολουθούμενη από την XBB.1.5 (38%)
- ✓ η επιτήρηση του ιικού φορτίου στα αστικά λύματα έδειξε αύξηση της κυκλοφορίας του ιού SARS-CoV-2 σε 4 από τις 10 περιοχές που ελέγχθηκαν

Διάγραμμα 17. Ποσοστό αλληλουχηθέντων δειγμάτων με απομονωθέν στέλεχος BA.2 ανά υπο-παραλλαγή επιδημιολογικού ενδιαφέροντος, ανά εβδομάδα, έως 11/08/2023



*Περιλαμβάνονται μόνο στελέχη BA.2 που δεν είναι BA.2.75 ή XBB ή XBB.1.5 ή CH.1.1 ή XBB.1.16 ή EG.5
**Προσωρινά δεδομένα

Πηγή: Εβδομαδιαία Έκθεση Επιδημιολογικής Επιτήρησης Αναπνευστικών Λοιμώξεων Εβδομάδα 34/2023 (21 Αυγούστου 2023 – 27 Αυγούστου 2023) . Available at: ekthesi-epitirisis-anapneustikon-ion-2023-34.pdf (eody.gov.gr), Accessed: 1 Sep 2023.

SARS CoV-2 Επιδημιολογικά Δεδομένα - Ελλάδα

Εβδομαδιαία Έκθεση
Επιδημιολογικής Επιτήρησης Αναπνευστικών Λοιμώξεων
Εβδομάδα 34/2023 (21 Αυγούστου 2023 – 27 Αυγούστου 2023)

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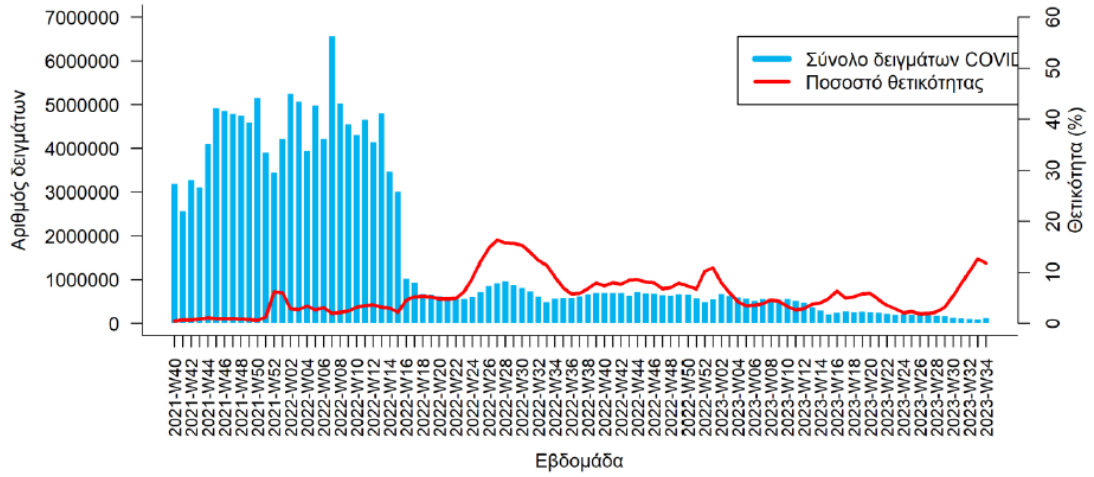
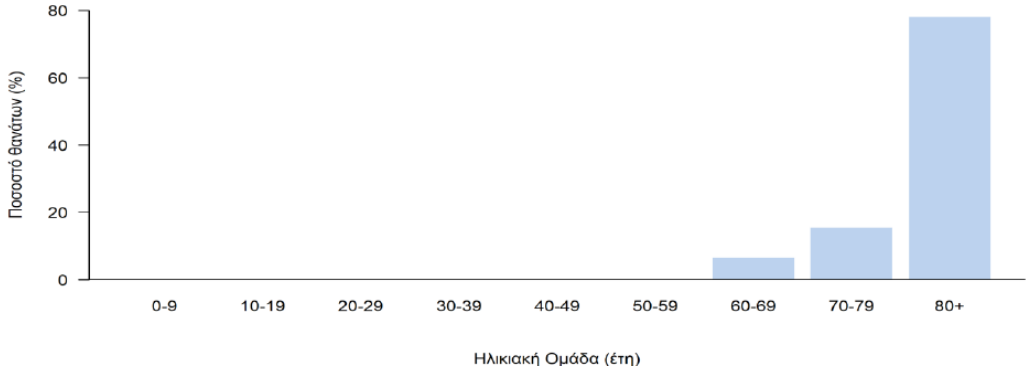
Διάγραμμα 7. Σύνολο δειγμάτων (Rapid-Ag/Rt-PCR) και ποσοστό θετικότητας με βάση το σύνολο των ελεγχθέντων δειγμάτων COVID-19, εβδομάδα 40/2021 - εβδομάδα 34/2023



Διάγραμμα 14. Ποσοστό θανάτων COVID-19 ανά ηλικιακή ομάδα, εβδομάδα 31/2023 – εβδομάδα 34/2023



Πηγή: Εβδομαδιαία Έκθεση Επιδημιολογικής Επιτήρησης Αναπνευστικών Λοιμώξεων Εβδομάδα 34/2023 (21 Αυγούστου 2023 – 27 Αυγούστου 2023) . Available at: ekthesi-epitirisis-anapneustikon-ion-2023-34.pdf (eody.gov.gr), Accessed: 1 Sep 2023.

COVID-19 disease course with the Omicron variant

26-34% asymptomatic[1,2]
~80% of infections are not severe[3]

~15% hospital admission[3]

~5% ICU admission[3]

Mechanical ventilation*:[4]
- 4% of patients overall
- 11% of patients with severe acute respiratory infection

In-hospital mortality*:[4]
- 5.5% of patients overall
- 15.7% of patients with severe acute respiratory infection

Long-term clinical sequelae with Omicron:[5]
- Fatigue
- Dyspnoea
- Hypomnesia
- Insomnia
- Chest tightness
- Muscle and joint pain
- Anxiety

*Overall Omicron population, n=1749; overall Omicron population with severe acute respiratory infection, n=535.
ICU, intensive care unit.
1. Yu W, et al. *J Med Virol* 2022;94(12):5790–801; 2. Shang W, et al. Vaccines 2022;10(7):1049; 3. Auwaerter P. John Hopkins ABX Guide, Coronavirus COVID-19 (SARS-CoV-2). Available at: https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540747/all/Coronavirus_COVID_19__SARS_CoV_2_. Accessed: Sep 2023; 4. Leiner J et al. *BMC Infect Dis* 2022;22:802; 5. Liao X, et al. *Glob Health & Med* 2022;4(6):322–6.

Mortality Risk Among Patients Hospitalized Primarily for COVID-19 During the Omicron and Delta Variant Pandemic Periods — United States, April 2020–June 2022

Weekly / September 16, 2022 / 71(37);1182–1189

Changing landscape
Omicron subvariants predominate
Most adults have received vaccine doses or have had infection with SARS-CoV-2

Summary

What is already known about this topic?

Risk for severe COVID-19 increases with age, disability, and underlying medical conditions. The SARS-CoV-2 Omicron variant is more infectious but has been associated with less severe disease.

What is added by this report?

In-hospital mortality among patients hospitalized primarily for COVID-19 decreased from 15.1% (Delta period) to 4.9% (later Omicron period; April–June 2022), despite high-risk patient groups representing a larger proportion of hospitalizations. During the later Omicron period, the majority of in-hospital deaths occurred among adults aged ≥65 years (81.9%) and persons with three or more underlying medical conditions (73.4%).

What are the implications for public health practice?

Vaccination, early treatment, and appropriate nonpharmaceutical interventions remain important public health priorities to prevent COVID-19 deaths, especially among persons most at risk.

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Adjei S, et al. MMWR Morb Mortal Wkly Rep. 2022 Sep 16;71(37):1182-1189. doi: 10.15585/mmwr.mm7137a4. PMID: 36107788; PMCID: PMC9484808.

Στρατηγική αντιμετώπισης…

Summary of considerations for treating people with COVID-19

Risk factors[1,2]

- Determine the risk of progression and eligibility for treatment
- Include age, race/ethnicity and certain comorbid conditions

Treatment options[2,3]

Based on:
- Marketing authorisation
- Treatment guidelines

Treatment factors[2]

- Use in special populations
- Concomitant medications:
  - DDIs
  - Contraindications
- Lean on specialist knowledge

Early intervention[4]

- Prevent hospitalisation and chronic sequelae
- Improve patient outcomes
- Help curb disease transmission

1. European Centre for Disease Prevention and Control. Risk factors and risk groups. Available at: https://www.ecdc.europa.eu/en/covid-19/latest-evidence/risk-factors-risk-groups. Accessed: Sep 2023; 2. Pfizer Limited. Summary of Product Characteristics: Paxlovid 150 mg +100 mg film-coated tablets. Available at: https://www.ema.europa.eu/en/documents/product-information/paxlovid-epar-product-information_en.pdf. Accessed: May 2023; 3. World Health Organization. Therapeutics and COVID-19: living guideline. Available at: https://app.magicapp.org/#/guideline/nBkO1E. Accessed: Sep 2023; 4. Kim P et al. *JAMA* 2020;324(21):2149–50.

Παράγοντες κινδύνου για εξέλιξη σε σοβαρή νόσο COVID-19

- Anyone can get COVID-19 and become seriously ill or die at any age[1]
- Certain risk factors elevate a person's risk of progression to severe COVID-19[1–3]

Age[1–3]

The strongest risk factor[2]

Risk

Risk of severe outcomes is increased in people who are ≥50 years; risk increases with age[2]

Age

Race & ethnicity[2]

People from racial and ethnic minority groups are more likely to experience severe COVID-19 at **younger ages**

***Barriers** to accessing healthcare support **are more common** in certain ethnic and racial minority groups*

Certain underlying conditions[1–3]

Risk

Death risk ratio increases with number of comorbid conditions[2]

Conditions

Male sex[3]

Male sex was associated with a higher risk of death, ARDS, admission to ICU, invasive ventilation, and cardiac abnormality in a meta-analysis of 61 studies[4]

Androgens may play a role in COVID-19 severity and progression[5]

Residents of LTCFs[3]

Residents of LTCFs are a vulnerable group associated with increased age and underlying health conditions

LTCFs are relatively closed and high-occupancy settings; COVID-19 outbreaks have spread rapidly, with high case fatality rates

Pregnancy and recent pregnancy[2]

Smoker (current or former)[2]

•ARDS, acute respiratory distress syndrome; ICU, intensive care unit; LTCF, long-term care facility.

1. World Health Organization. COVID-19 symptoms and severity. Available at: https://www.who.int/westernpacific/emergencies/covid-19/information/asymptomatic-covid-19 Accessed: Sep 2023; **2**. Centers for Disease Control and Prevention. Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html. Accessed: Sep 2023; **3**. European Centre for Disease Prevention and Control. Risk factors and risk groups. Available at: https://www.ecdc.europa.eu/en/covid-19/latest-evidence/risk-factors-risk-groups. Accessed: Sep 2023; **4**. Fang W, et al. Aging (Albany NY). 2020;12(13):12493–12503; **5**. Zong Z, et al. *Molecular Cancer*. 2021;20:76.

Παράγοντες κινδύνου για εξέλιξη σε σοβαρή νόσο COVID-19: Ηλικία

Age[1–3]

The strongest risk factor[2]

Risk

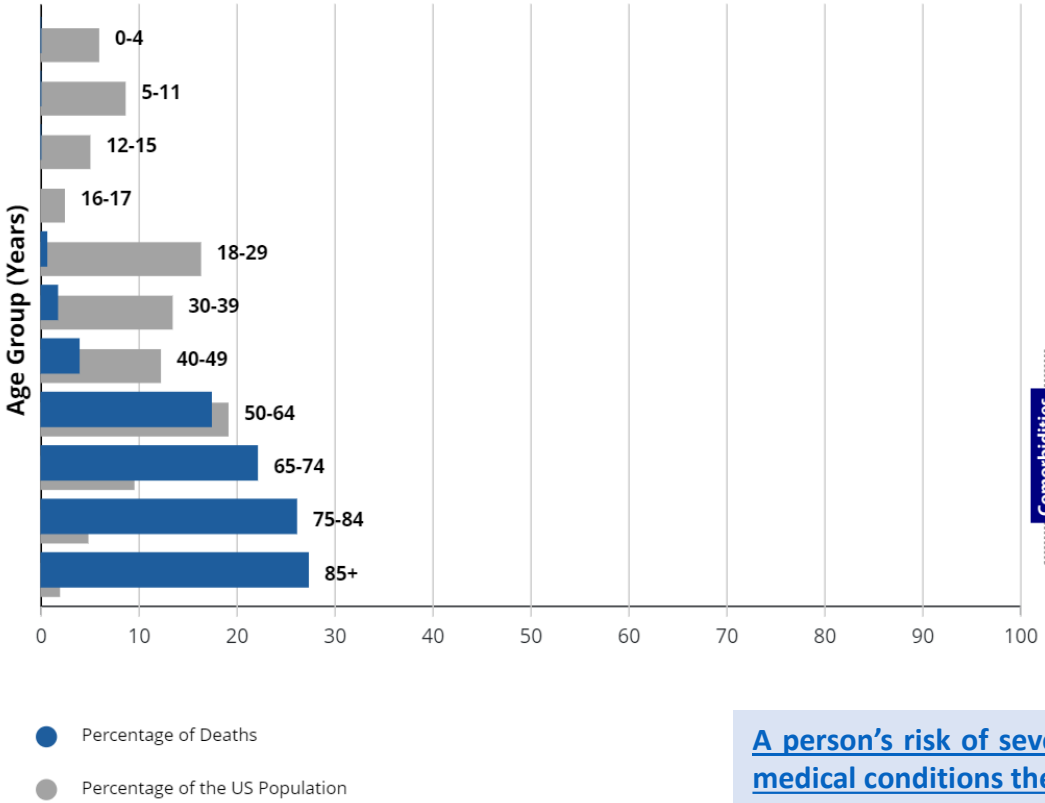
Risk of severe outcomes is increased in people who are ≥50 years; risk increases with age[2]

Age

>81% of COVID-19 deaths occur in over 65s[6]

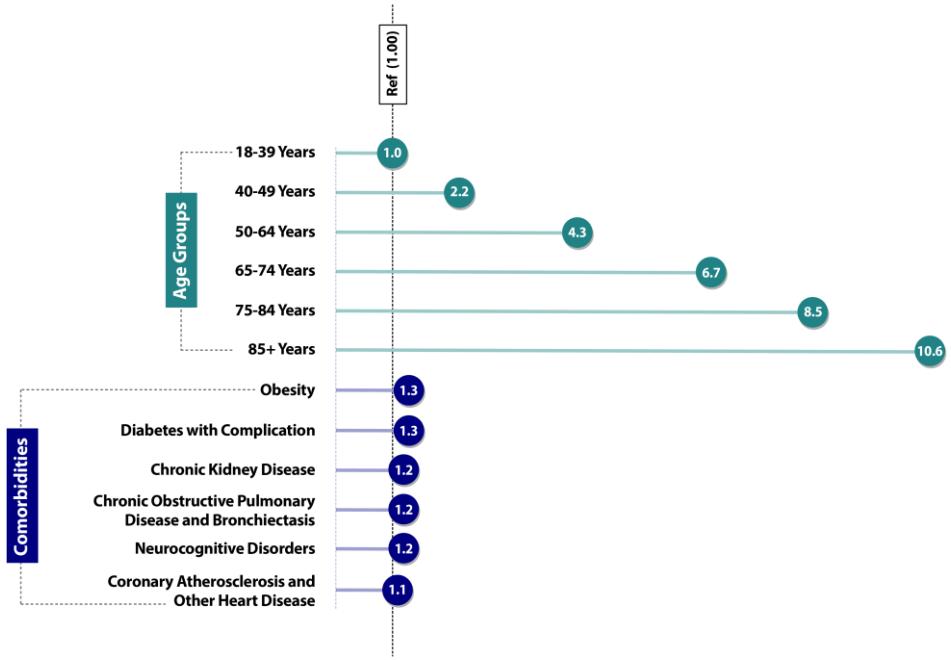
Deaths by Age Group:

Data from 998,513 deaths. Age group was available for 997,663 (99%) deaths.



Source. https://covid.cdc.gov/covid-data-tracker/#demographics, CDC | Data as of: August 20, 2023 ET. Posted: August 21, 2023 ET

COVID-19 Death Risk Ratio (RR) for Select Age Groups and Comorbid Conditions

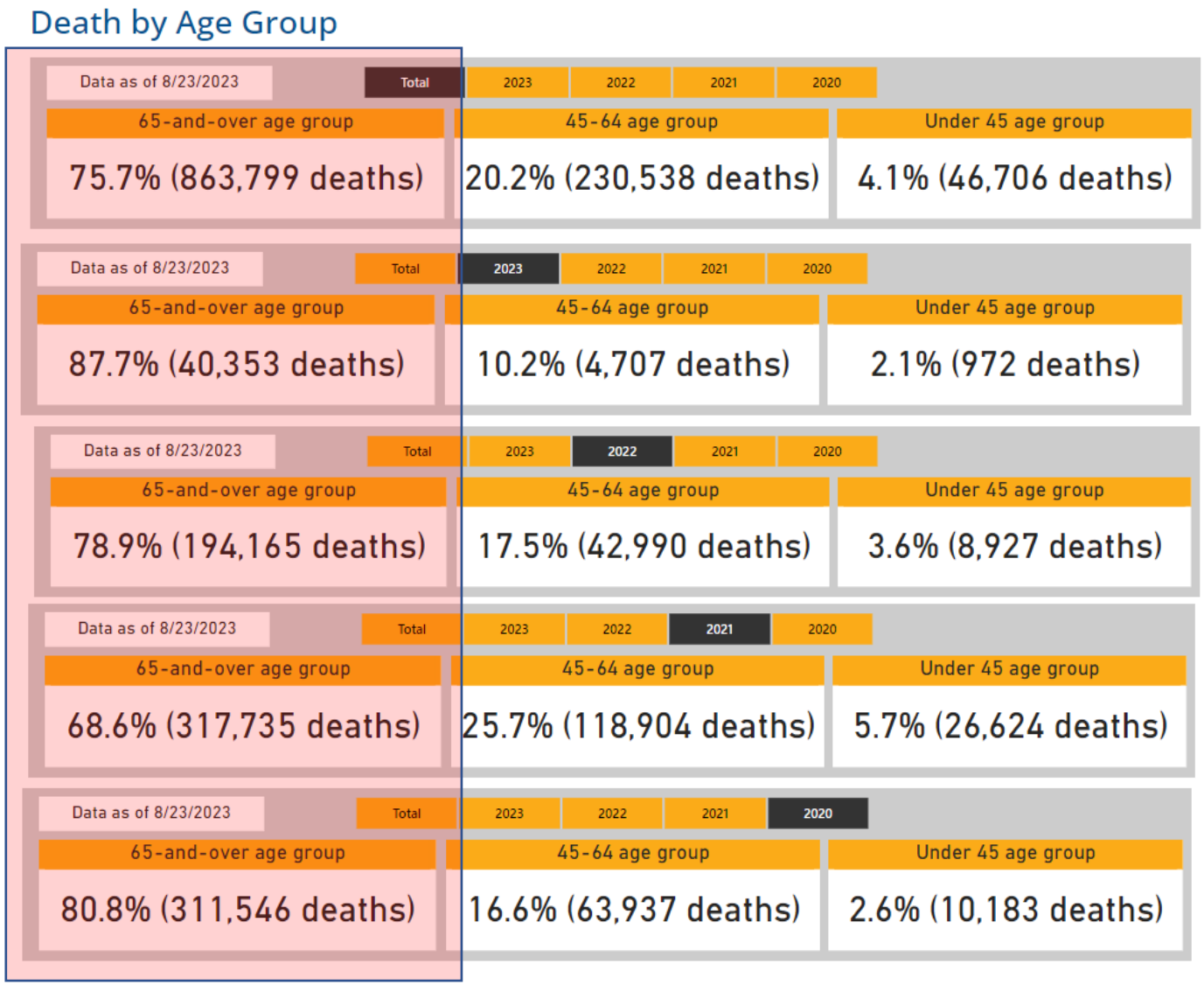


A person's risk of severe illness from COVID-19 increases as the number of underlying medical conditions they have increases.[4]

The number of deaths among people over age 65 is 97 times higher than the number of deaths among people ages 18-29 years.[5]

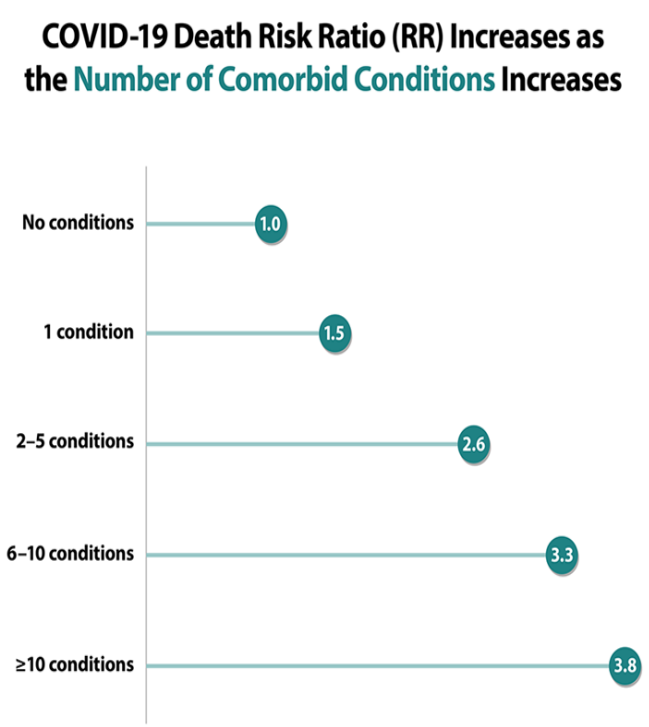
1. World Health Organization. COVID-19 symptoms and severity. Available at: https://www.who.int/westernpacific/emergencies/covid-19/information/asymptomatic-covid-19. Accessed: Sep 2023; 2. Centers for Disease Control and Prevention. Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html. Accessed: Sep 2023; 3. European Centre for Disease Prevention and Control. Risk factors and risk groups. Available at: https://www.ecdc.europa.eu/en/covid-19/latest-evidence/risk-factors-risk-groups. Accessed: Sep 2023; 4. Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals | CDC CDC *Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals.* Last Accessed Sep 2023. 5. CDC COVID-19 People with Certain Medical Conditions. Available at; People with Certain Medical Conditions | CDC, Accessed Sep 2023.6. People with Certain Medical Conditions | CDC, Accessed Sep 2023

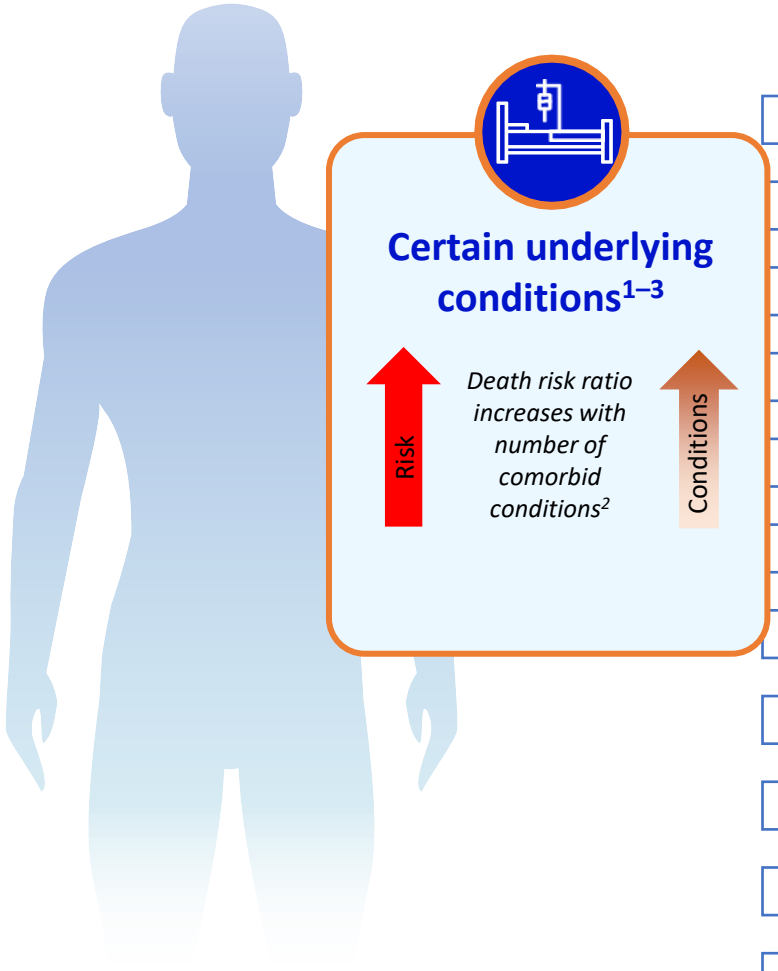
Επισκόπηση θνησιμότητας COVID-19 ανά ηλικιακή ομάδα



Source: NVSS - Provisional Death Counts for COVID-19 - Executive Summary (cdc.gov) . Accessed September 2023.

Παράγοντες κινδύνου για εξέλιξη σε σοβαρή νόσο COVID-19





Certain underlying conditions[1–3]

Risk

Death risk ratio increases with number of comorbid conditions[2]

Conditions

Certain medical conditions[2]

- Dementia or other neurological conditions[2]
- Chronic lung disease[2]
- Chronic liver disease[2]
- Chronic kidney disease[2]
- Cardiovascular Disease[2]
- Diabetes[2]
- Cancer[2]
- Immunocompromised condition or weakened immune system[2]
- Mental health conditions[2]
- Obesity, BMI ≥25 kg/m² [2]

1. People with Certain Medical Conditions | CDC, Accessed Sep 2023, **2.** CDC Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html, 01 Accessed Sep 2023,

Immunocompromised patients

- Individuals who are immunocompromised, either due to a medical condition or receipt of immunosuppressive treatment, are more likely to get ill with COVID-19 or to remain ill for a longer period
- Medical conditions or treatments that may result in moderate to severe immunocompromise include:

Active treatment for solid tumor and hematologic malignancies

Receipt of solid-organ transplant or an islet transplant and taking immunosuppressive therapy

Hematologic malignancies associated with poor responses to COVID-19 vaccines regardless of current treatment status
e.g., chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, acute leukemia

Receipt of CART therapy or hematopoietic stem cell transplant*

Moderate or severe primary immunodeficiency
e.g., common variable immunodeficiency disease, severe combined immunodeficiency, DiGeorge syndrome, Wiskott-Aldrich syndrome

Advanced or untreated HIV infection†

Active treatment with high-dose CS‡, alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, TNF-blockers, and other biologic agents that are immunosuppressive or immunomodulatory

This is not an exhaustive list.
*Within 2 years of transplantation or taking immunosuppressive therapy; †People with HIV and CD4 cell counts less than 200/mm^3, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV; ‡≥20 mg of prednisone or equivalent per day when administered for ≥2 weeks.
AIDS, acquired immune deficiency syndrome; CART, chimeric antigen receptor-T-cell; CDC, Centers for Disease Control; CS, corticosteroids; HIV, human immunodeficiency virus; TNF, tumor necrosis factor.
CDC. People who are Immunocompromised: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-who-are-immunocompromised.html (Accessed Sep 2023).

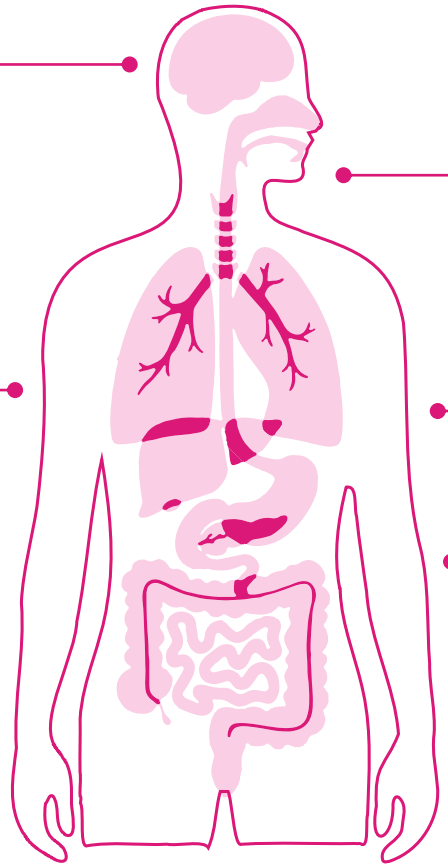
Potential mechanisms for the increased risk of progression to severe COVID-19 in immunocompromised people

Impaired immune response[1]

- Both underlying disease and treatment contribute to an **impaired immune response** to viral infection in immunocompromised patients
- They are at increased risk of **more severe infection** and **bacterial and fungal superinfection** compared with immunocompetent counterparts

Cancer-related[2,3]

- Compared with non oncology hosts, people that have active cancer exhibit:
  - Greater **susceptibility** and more **rapid progression** to pneumonia
  - Greater disease **severity**
  - **Prolonged** viral shedding



Overlap of existing comorbidities[4]

- Immunocompromised patients are **older**, making them more likely have **underlying conditions** known to be associated with severe COVID-19, including chronic lung disease, renal disease, and hypertension

Susceptibility to acute kidney injury[2]

- Factors that may contribute to COVID-19-related kidney injury include **hypoxia**, **CRS** and a **hypercoagulable state**

Vaccine effectiveness[4]

- Vaccine effectiveness is known to be lower in elderly and fragile subjects

CRS, cytokine release syndrome.

1. Fung M & Babek JM. *Clin Infect Dis* 2021;72(2):340–350; 2. Wang L, et al. *Aging (Albany NY)* 2020;12(23): 24462–24474; 3. Nakajima Y, et al. *J Infect Chemother* 2021;27(2):387–389; 4. Singson JRC, et al. *MMWR Morb Mortal Wkly Rep* 2022;71(27):878–884.

Απώτερες επιπλοκές…

Επιμονή των συμπτωμάτων και σύνδρομο Long-COVID

80%

των ενηλίκων ασθενών εξακολουθούν να έχουν τουλάχιστον ένα σύμπτωμα της νόσου COVID-19 εβδομάδες ή μήνες μετά από οξεία μόλυνση[1]

Πιο συνήθη συμπτώματα:[1]

Κόπωση 58%

Κεφαλαλγία 44%

Διαταραχή Συγκέντρωσης 27%

Τριχόπτωση 25%

Δύσπνοια 24%

≥65 εκατομμύρια άτομα παγκοσμίως έχουν διαγνωσθεί με long-COVID-19 (10% από >651 εκατομμύρια τεκμηριωμένες περιπτώσεις COVID-19)[4]

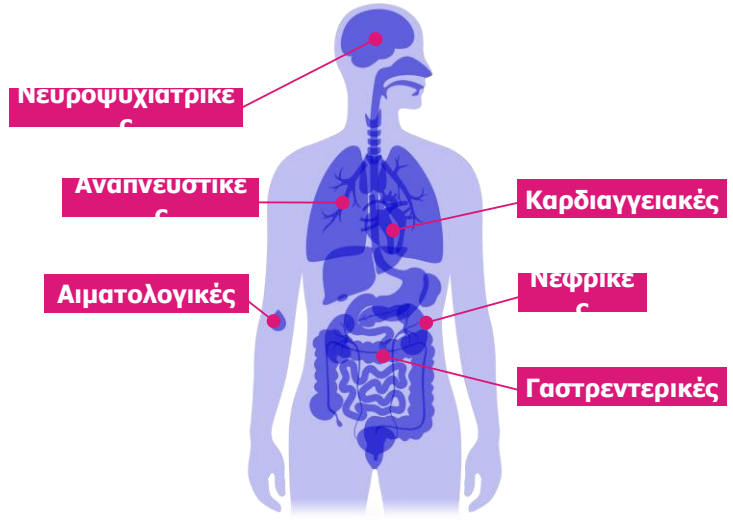
- **10%-30% των μη-νοσηλευόμενων** ασθενών
- **50%-70% των νοσηλευόμενών**
- **10%-12% των εμβολιασμένων**

WHO όρισμός[2]

"Σύνδρομο Long-Covid" εμφανίζεται σε άτομα με ιστορικό **πιθανής ή επιβεβαιωμένης λοίμωξης SARS-CoV-2**, συνήθως **3 μήνες από την έναρξη της** COVID-19 με **συμπτώματα που διαρκούν τουλάχιστον 2 μήνες** και δεν μπορούν να εξηγηθούν με εναλλακτική διάγνωση

Επιπλοκές[3]

Ευρύ φάσμα, συμπεριλαμβανομένων:



1. Lopez-Leon S, et al. *Sci Rep* 2021;11:16144; 2. WHO. https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-(covid-19)-post-covid-19-condition, Accessed 1 Sep 2023. 3. Nalbandian A, et al. *Nat Med* 2021;27:601–15. 4. Davis HE, et al. Nat Rev Microbiol. 2023 Mar;21(3):133-146. doi: 10.1038/s41579-022-00846-2

thebmj

Long term risk of death and readmission after hospital admission with covid-19 among older adults: retrospective cohort study

Andrew S Oseran,[1,2] Yang Song,[1] Jiaman Xu,[1] Issa J Dahabreh,[1,3] Rishi K Wadhera,[1,4] James A de Lemos,[5] Sandeep R Das,[5] Tianyu Sun,[1] Robert W Yeh,[1,4] Dhruv S Kazi[1,4]

BMJ 2023 ; 382 doi: https://doi.org/10.1136/bmj-2023-076222 (Published 09 August 2023)
Cite this as: *BMJ* 2023;382:e076222

PARTICIPANTS
883 394 Medicare fee-for-service beneficiaries age ≥65 years discharged alive after an index hospital admission with covid-19 between 1 March 2020 and 31 August 2022, compared with 56 409 historical controls discharged alive after a hospital admission with influenza between 1 March 2018 and 31 August 2019. Weighting methods were used to account for differences in observed characteristics.

MAIN OUTCOME MEASURES
All cause death within 180 days of discharge. Secondary outcomes included first all cause readmission and a composite of death or readmission within 180 days.

Results The covid-19 cohort compared with the influenza cohort was younger (77.9 *v* 78.9 years, standardized mean difference −0.12) and had a lower proportion of women (51.7% *v* 57.3%, −0.11). Both groups had a similar proportion of black beneficiaries (10.3% *v* 8.1%, 0.07) and beneficiaries with dual Medicaid-Medicare eligibility status (20.1% *v* 19.2%; 0.02). The covid-19 cohort had a lower comorbidity burden, including atrial fibrillation (24.3% *v* 29.5%, −0.12), heart failure (43.4% *v* 49.9%, −0.13), and chronic obstructive pulmonary disease (39.2% *v* 52.9%, −0.27). After weighting, the covid-19 cohort had a higher risk (ie, cumulative incidence) of all cause death at 30 days (10.9% *v* 3.9%; standardized risk difference 7.0%, 95% confidence interval 6.8% to 7.2%), 90 days (15.5% *v* 7.1%; 8.4%, 8.2% to 8.7%), and 180 days (19.1% *v* 10.5%; 8.6%, 8.3% to 8.9%) compared with the influenza cohort. The covid-19 cohort also experienced a higher risk of hospital readmission at 30 days (16.0% *v* 11.2%; 4.9%, 4.6% to 5.1%) and 90 days (24.1% *v* 21.3%; 2.8%, 2.5% to 3.2%) but a similar risk at 180 days (30.6% *v* 30.6%;−0.1%, −0.5% to 0.3%). Over the study period, the 30 day risk of death for patients discharged after a covid-19 admission decreased from 17.9% to 7.2%.

WHAT THIS STUDY ADDS

In this descriptive analysis, among people aged ≥ 65 years who were discharged alive after an index covid-19 related hospital admission, a high risk of death and readmission was found within 180 days after discharge

Compared with historical influenza controls, those who were discharged alive after covid-19 related hospital admission had higher risk of post-discharge death; this difference, however, was concentrated in the early post-discharge period

The risk of death after discharge from a covid-19 related hospital admission substantially declined during the pandemic

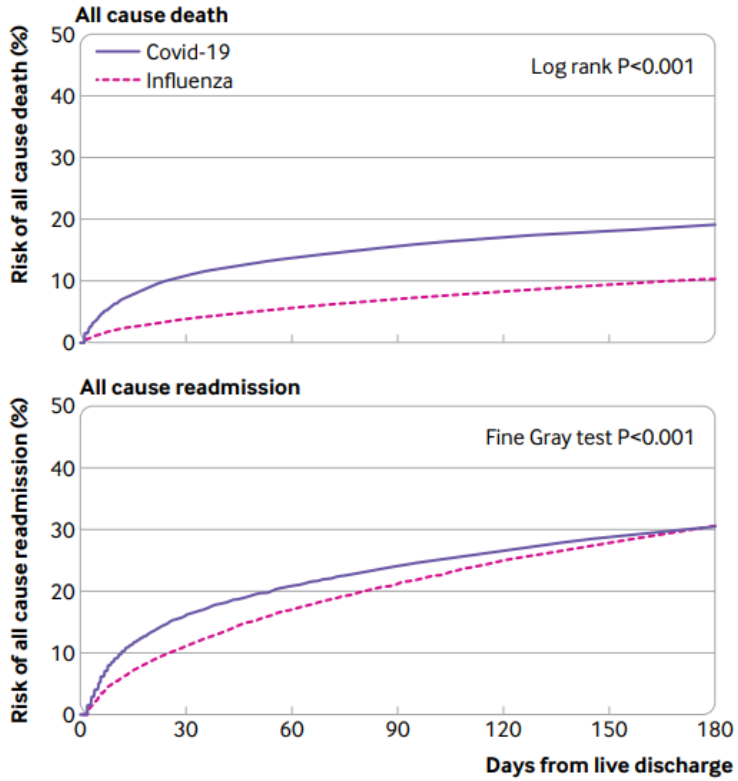
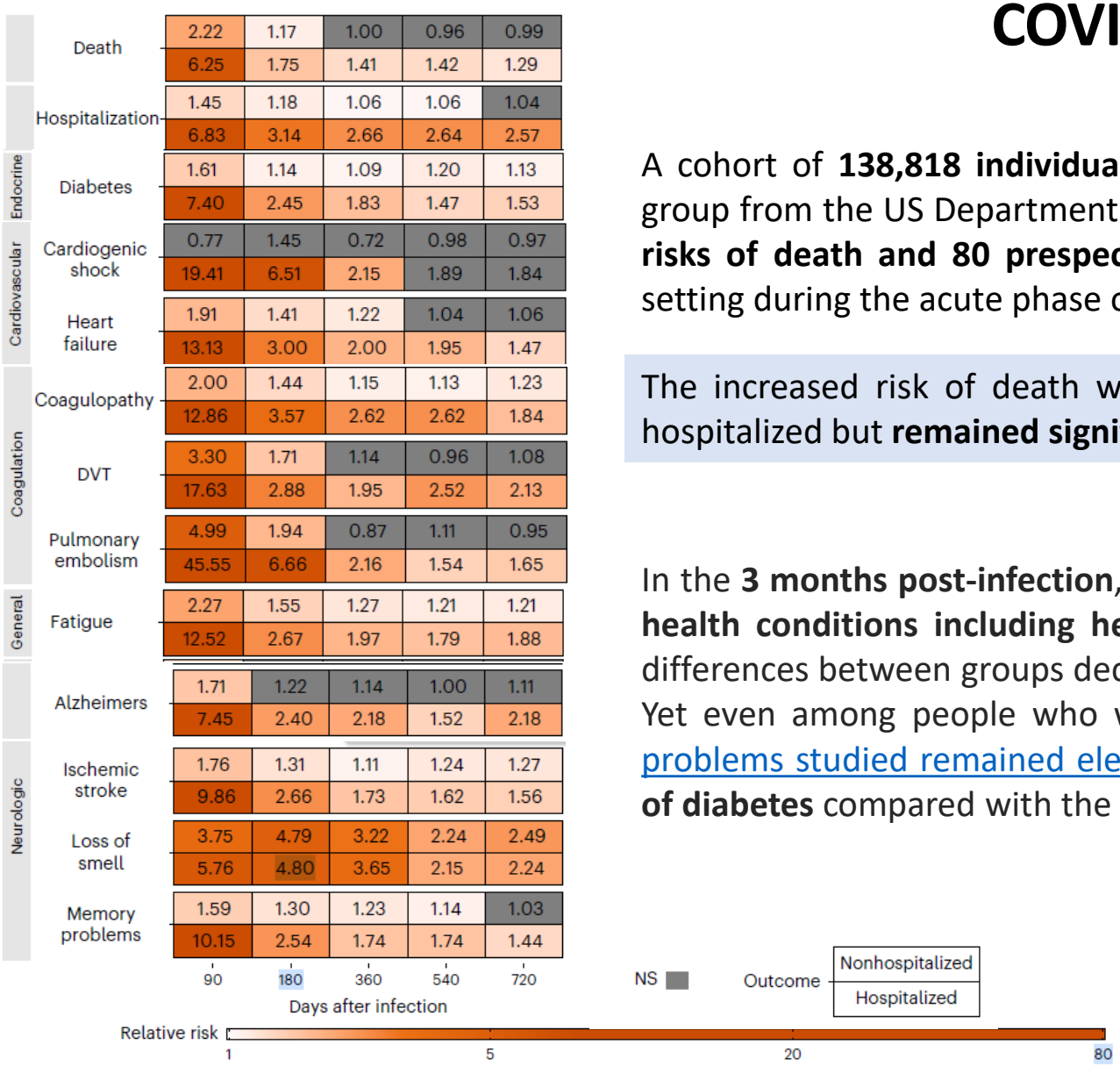


Fig 3 | Standardized risk of all cause death and readmission after live discharge from covid-19 related hospital admission compared with historical influenza controls

Oseran AS, et al. Long term risk of death and readmission after hospital admission with covid-19 among older adults: retrospective cohort study. BMJ. 2023 Aug 9;382:e076222. doi: 10.1136/bmj-2023-076222. PMID: 37558240.

Κίνδυνος προβλημάτων υγείας έως και 2 χρόνια μετά από την αρχική λοίμωξη COVID-19



A cohort of **138,818 individuals with SARS-CoV-2 infection** and 5,985,227 noninfected control group from the US Department of Veterans Affairs and **followed them for 2 years to estimate the risks of death and 80 prespecified postacute sequelae of COVID-19 (PASC)** according to care setting during the acute phase of infection

The increased risk of death was not significant beyond 6 months after infection among non-hospitalized but **remained significantly elevated through the 2 years in hospitalized individuals**.

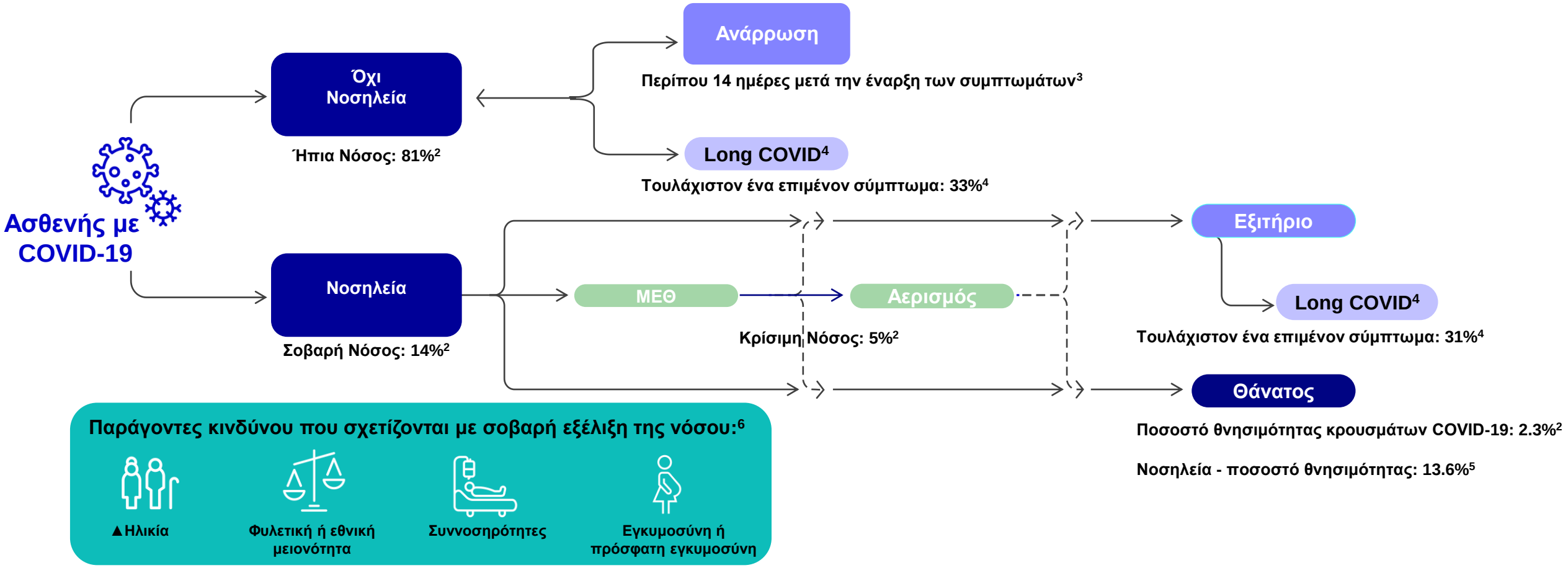
In the **3 months post-infection**, people who'd had COVID-19 had **higher rates of death and many health conditions including heart failure, diabetes, Alzheimer's disease, and depression**. The differences between groups declined over time.

Yet even among people who weren't hospitalized, the risks for about one-third of the health problems studied remained elevated 2 years later. These people had about a **13% increased risk of diabetes** compared with the no-infection group, for example.

Bowe, B., Xie, Y. & Al-Aly, Z. Postacute sequelae of COVID-19 at 2 years. *Nat Med* (2023). https://doi.org/10.1038/s41591-023-02521-2

Φυσική εξέλιξη της νόσου…

Πιθανότητες εξέλιξης της νόσου COVID-19[1]

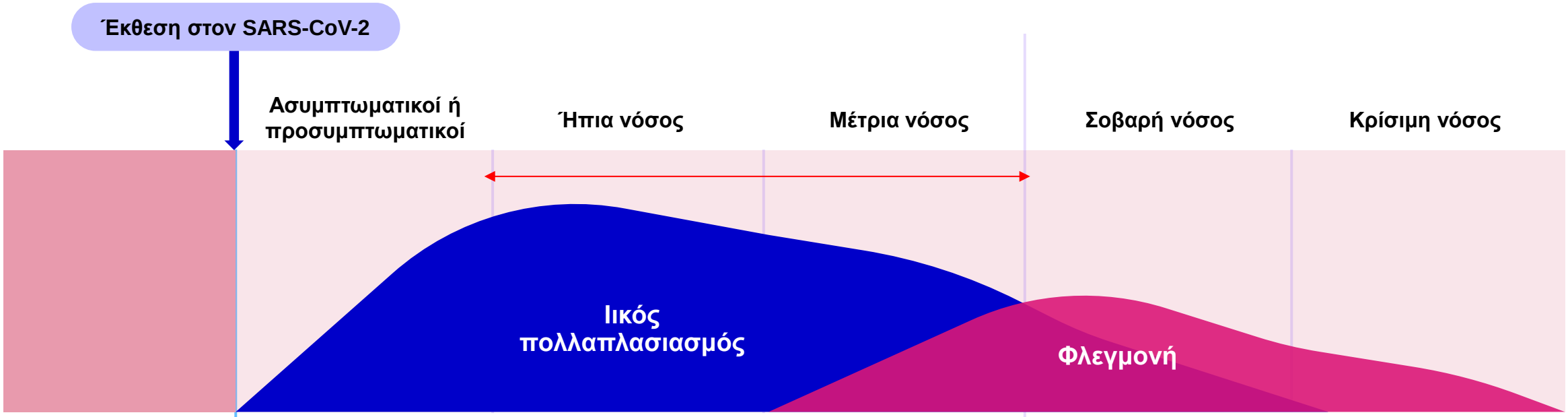


Created from: Estiri H, Strasser ZH, Murphy SN. *Sci Rep.* 2021;11(1):5322; and Di Fusco M, Shea KM, Lin J, Nguyen JL, Angulo FJ, Benigno M, et al. *J Med Econ.* 2021;24(1):308–17.

ICU, intensive care unit; **ΜΕΘ**, Μονάδα Εντατικής Θεραπείας

1. Estiri H, Strasser ZH, Murphy SN. *Sci Rep.* 2021;11(1):5322; 2. Wu Z, McGoogan JM. *JAMA.* 2020;323(13):1239–42; 3. WHO-China. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) 2020: www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf (Accessed August 2022); 4. Logue JK, Franko NM, McCulloch DJ, McDonald D, Magedson A, Wolf CR, et al. *JAMA Netw Open.* 2021;4(2):e210830; 5. Di Fusco M, Shea KM, Lin J, Nguyen JL, Angulo FJ, Benigno M, et al. *J Med Econ.* 2021;24(1):308–17; 6. CDC. People with Certain Medical Conditions: www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html (Accessed August 2022).

Θεραπευτική προσέγγιση της νόσου COVID-19



Για ασθενείς που διατρέχουν υψηλό κίνδυνο εξέλιξης σε σοβαρή νόσο COVID-19

- **Αντι-ιικά**
- **mAbs**

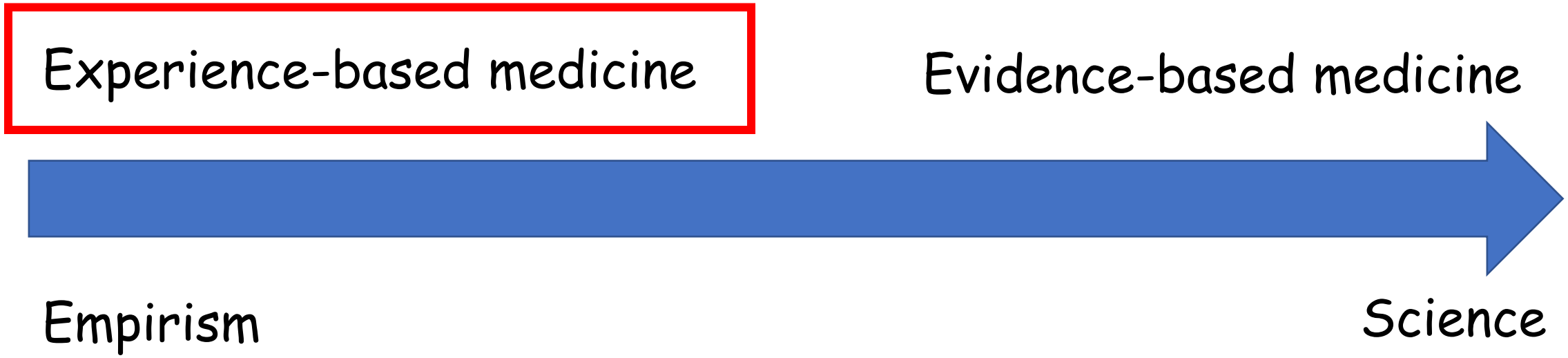
Πρώιμη θεραπεία

Η θεραπεία εξαρτάται από την ανάγκη του ασθενούς για συμπληρωματικό οξυγόνο, MV ή ECMO, αλλά μπορεί να περιλαμβάνει ένα ή συνδυασμό:*

- **Αναστολείς RNA πολυμεράσης**
- **Κορτικοστεροειδή**
- **Αναστολείς JAK**
- **mAbs**

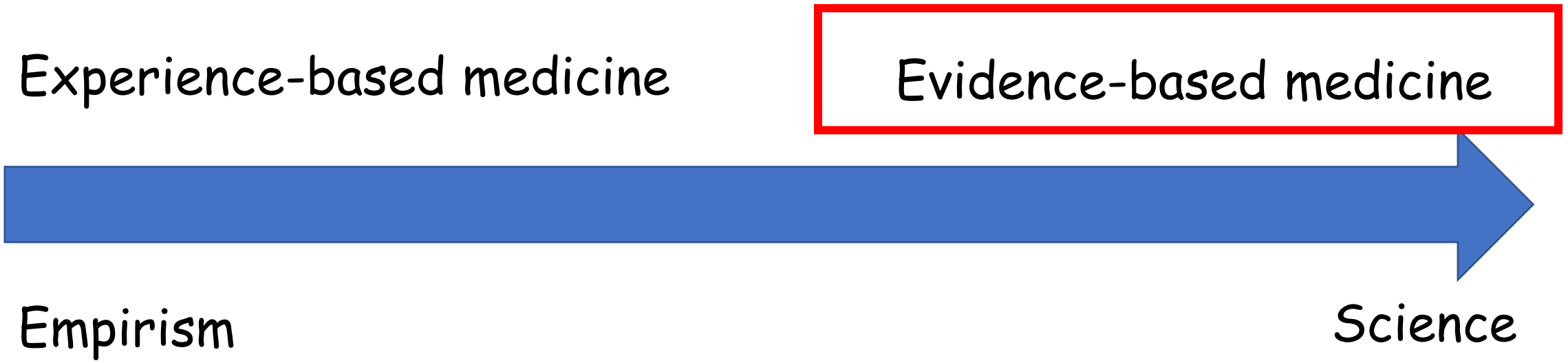
Information outside the scope of domestic approval is included here, please refer to the latest package insert for all treatments. *See guideline for full recommendations. **ECMO**, extracorporeal membrane oxygenation; **JAK**, Janus kinase; **mAb**, monoclonal antibody; **MV**, mechanical ventilation; **RNA**, ribonucleic acid. National Institutes of Health. COVID-19 treatment guidelines. Available at: https://www.covid19treatmentguidelines.nih.gov/. Accessed: Sep 2023.

Στην εποχή της evidence based medicine η εμφάνιση ενός νέου ιού χωρίς θεραπευτικές επιλογές αποτελεί πραγματικά μια πρόκληση …

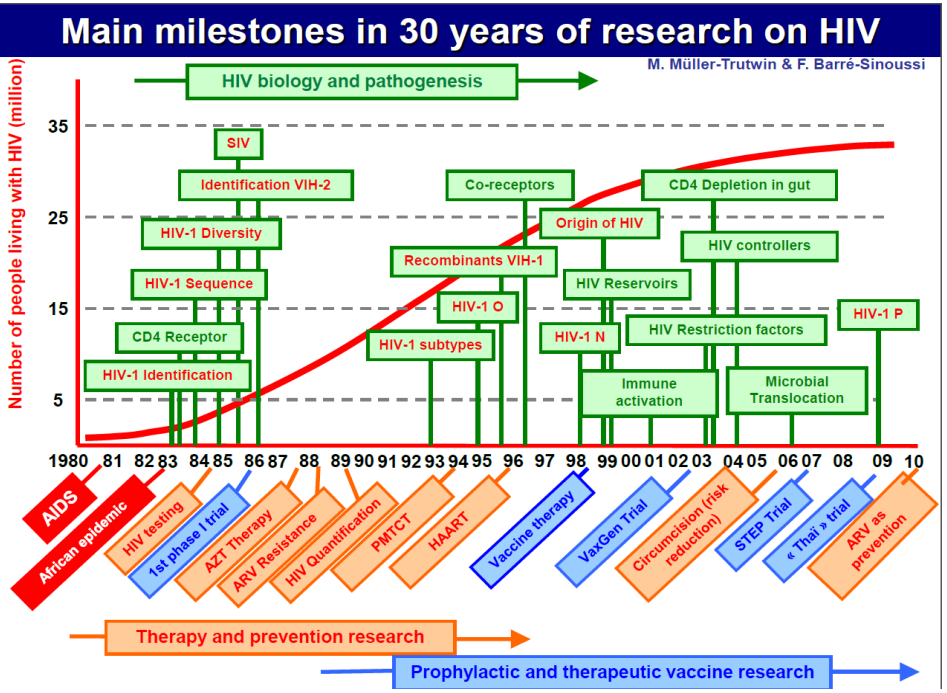


Η περίοδος της εμπειρικής θεραπείας…

Στην εποχή της evidence based medicine η εμφάνιση ενός νέου ιού χωρίς θεραπευτικές επιλογές αποτελεί πραγματικά μια πρόκληση …

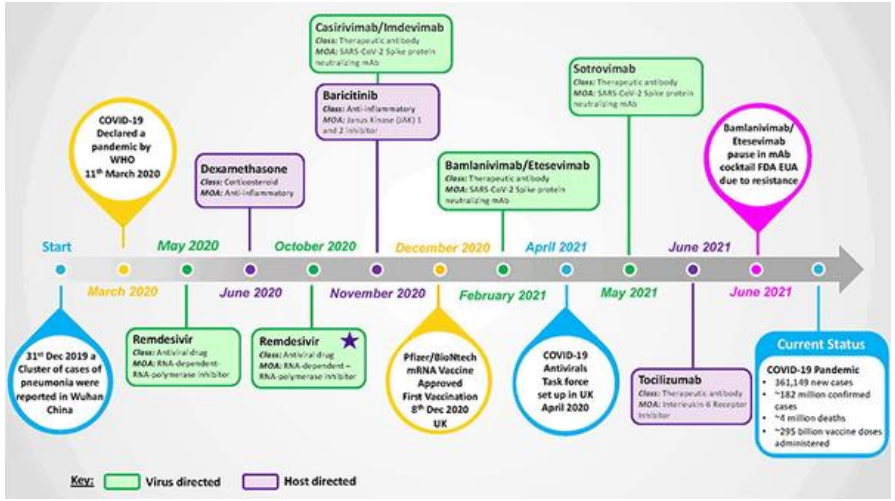


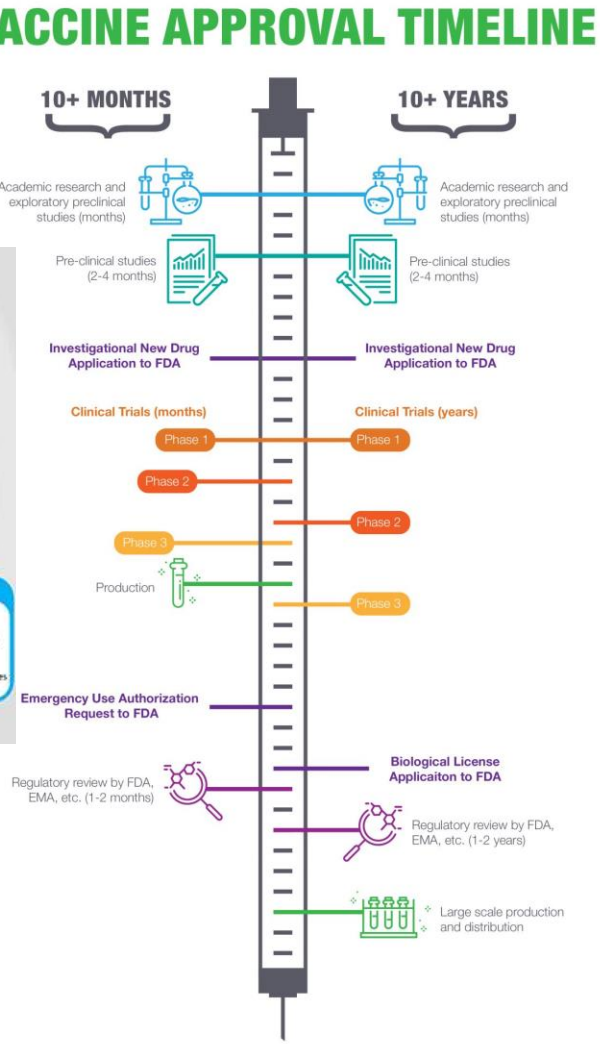
AIDS: the 21st Century Plague



40 χρόνια

COVID-19: the 21st Century Pandemic





2 χρόνια

Comparison of Treatment Options for High-Risk Nonhospitalized Patients With Mild to Moderate COVID-19

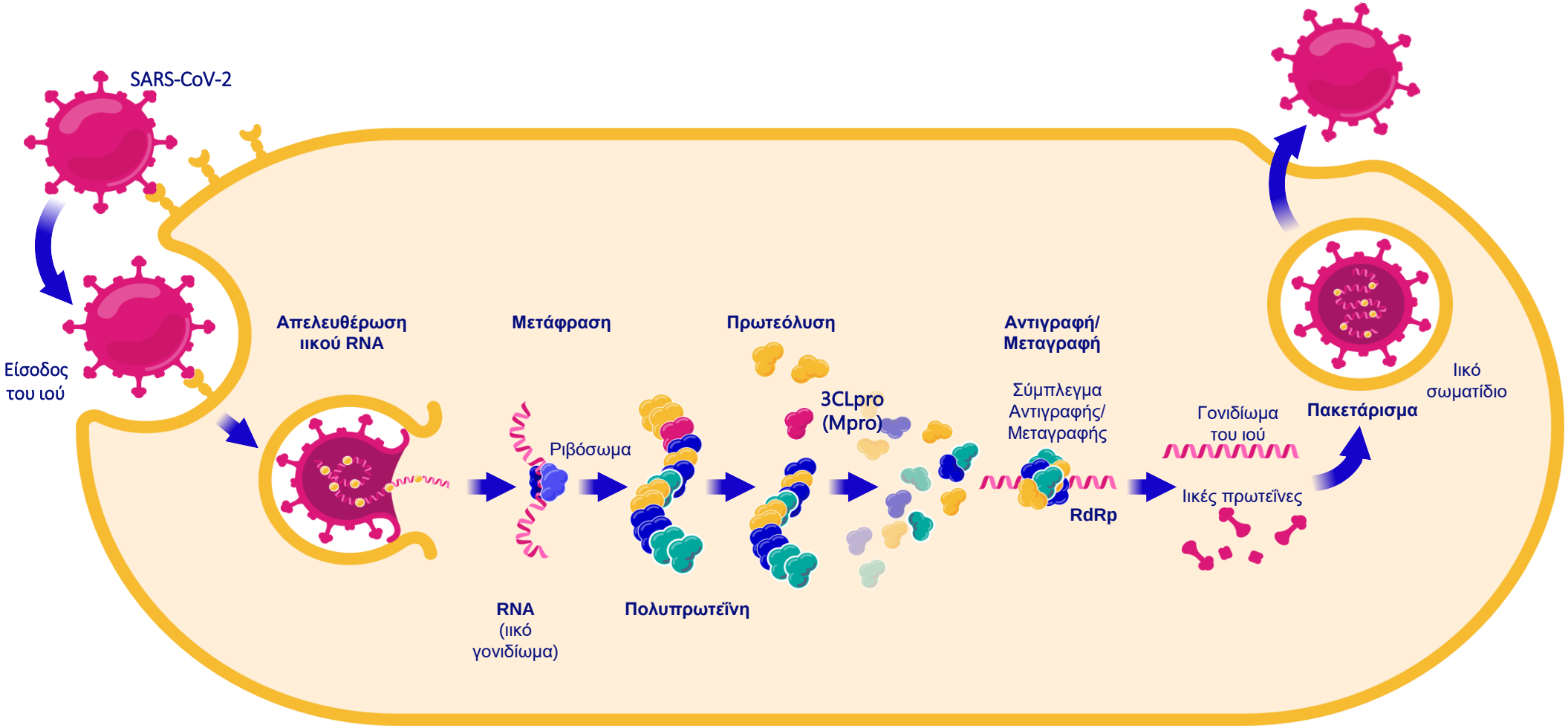
eTable 1. Comparison of Treatment Options for High-Risk Nonhospitalized Patients With Mild to Moderate COVID-19

	Nirmatrelvir-ritonavir[1]	Sotrovimab[2]	Remdesivir[3]	Molnupiravir[4]
Efficacy (prevention of hospitalization or death)	• Absolute risk reduction: 6.3%→0.8% • Relative risk reduction: 88% • NNT: 18	• Absolute risk reduction: 7%→1% • Relative risk reduction: 85% • NNT: 17	• Absolute risk reduction: 5.3%→0.7% • Relative risk reduction: 87% • NNT: 22	• Absolute risk reduction: 9.7%→6.8% • Relative risk reduction: 30% • NNT: 35
Advantages	• Highly efficacious • Oral regimen • Ritonavir studied (safe) in pregnancy	• Highly efficacious • Monoclonal antibodies typically safe in pregnancy • Few/no drug interactions	• Highly efficacious • Studied in pregnancy • Few/no drug interactions	• Oral regimen • Not anticipated to have drug interactions
Disadvantages	• Drug-drug interactions	• Requires IV infusion followed by 1-h observation	• Requires IV infusion on 3 consecutive days	• Low efficacy • Concern: mutagenicity • Not recommended in pregnancy/children

Abbreviations: IV, intravenous; NNT, number needed to treat.

1. Gandhi RT, Malani PN, del Rio C. COVID-19 therapeutics for nonhospitalized patients. JAMA. doi:10.1001/jama.2022.0335

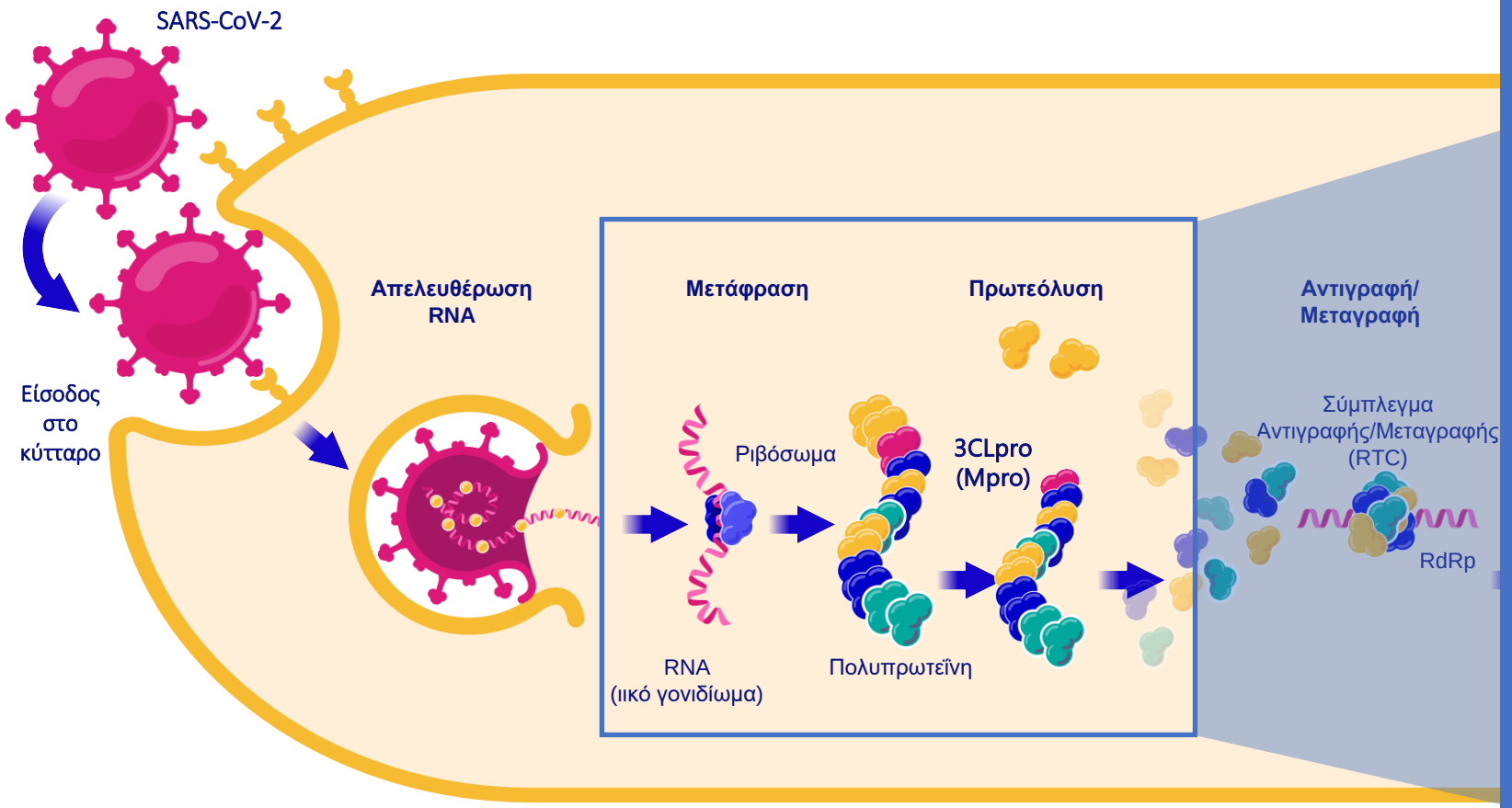
SARS-CoV-2: Κύκλος ζωής[1–2]



3CLpro, 3-chymotrypsin-like protease; Mpro, κύρια πρωτεάση; RdRp, RNA-dependent RNA polymerase; RNA, ribonucleic acid.

1. Pluskota-Karwatka D, et al. *J Pharm Anal* 2021;11(4):383-97; 2. V'Kovski P, et al. *Nat Rev Microbiol* 2021;19(3):155-70.

Σημασία της 3CLpro στον κύκλο ζωής του SARS-CoV-2[1–5]



PF-07321332

(Nirmatrelvir)

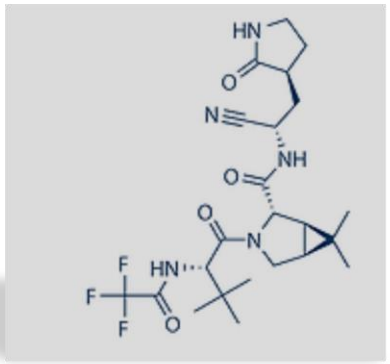
3CLpro, 3-chymotrypsin-like protease; Mpro, κύρια πρωτεάση; RdRp, RNA-dependent RNA polymerase; RNA, ribonucleic acid; RTC, replication and transcription complex.

1. Steinkühler C. Viral Proteases. In: Offermanns S, Rosenthal W (eds). *Encyclopedia of Molecular Pharmacology*. 2008, Springer, Berlin, Heidelberg. Available at: https://doi.org/10.1007/978-3-540-38918-7_146. Accessed: November 2021; 2. V'kovski P, et al. *Nat Rev Microbiol* 2021;19:155–70; 3. Owen DR, et al. *Science* 2021;374(6575):1586–93; 4. Mengist HM, et al. *Front Chem*. 2021 Mar 12;9:622898.

Paxlovid: PF-07321332 + Ριτοναβίρη

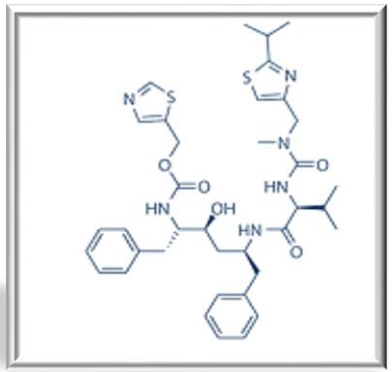
PF-07321332 *(Nirmatrelvir)*

- Αναστέλλει την κύρια πρωτεάση του SARS-CoV-2 (Mpro) [αναφέρεται επίσης ως 3C-like (3CLpro) ή nsp5 πρωτεάση]
- Ο **πρώτος μικρομοριακός** αντι-ιικός παράγοντας **σχεδιασμένος ειδικά να αναστέλλει τον SARS-CoV-2**



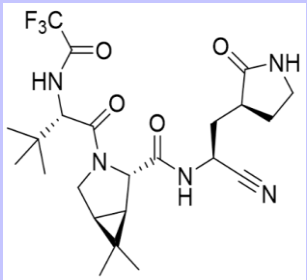
Ριτοναβίρη

- Αναστολέας πρωτεάσης του HIV-1 *Δεν είναι αποτελεσματική έναντι της Mpro του SARS-CoV-2*
- Φαρμακοκινητικός ενισχυτής (booster): *Σε χαμηλές δόσεις, παρέχει αυξημένες συγκεντρώσεις του PF-07321332 στο πλάσμα, αναστέλλοντας τον μεταβολισμό του μέσω του CYP3A*



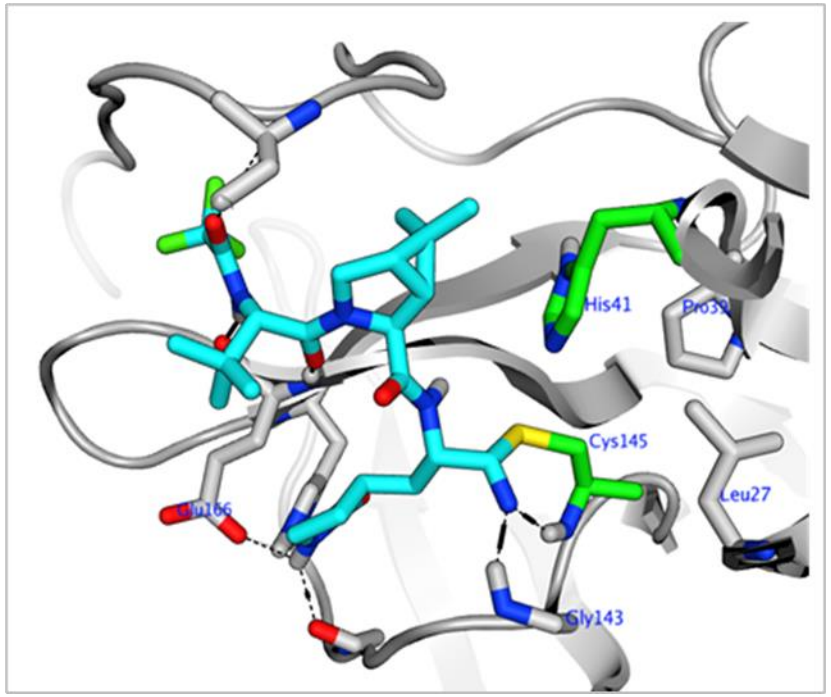
1.PAXLOVID Περίληψη Χαρακτηριστικών Προϊόντος 07/2022 2. EUA PAXLOVID Fact Sheet for Healthcare Providers, Aug 2022. 3. Rubin et al. N Engl J Med. 2022 Feb 16. doi: 10.1056/NEJMe2202160 4. Hammond J et al. N Engl J Med 2022. 386:1397-1408.

PF-07321332 (Nirmatrelvir)



➢ **Αναστολέας** της κύριας **πρωτεάσης** M^{pro}

Ο 1ος μικρομοριακός παράγοντας ειδικά σχεδιασμένος για δράση έναντι SARS-CoV2



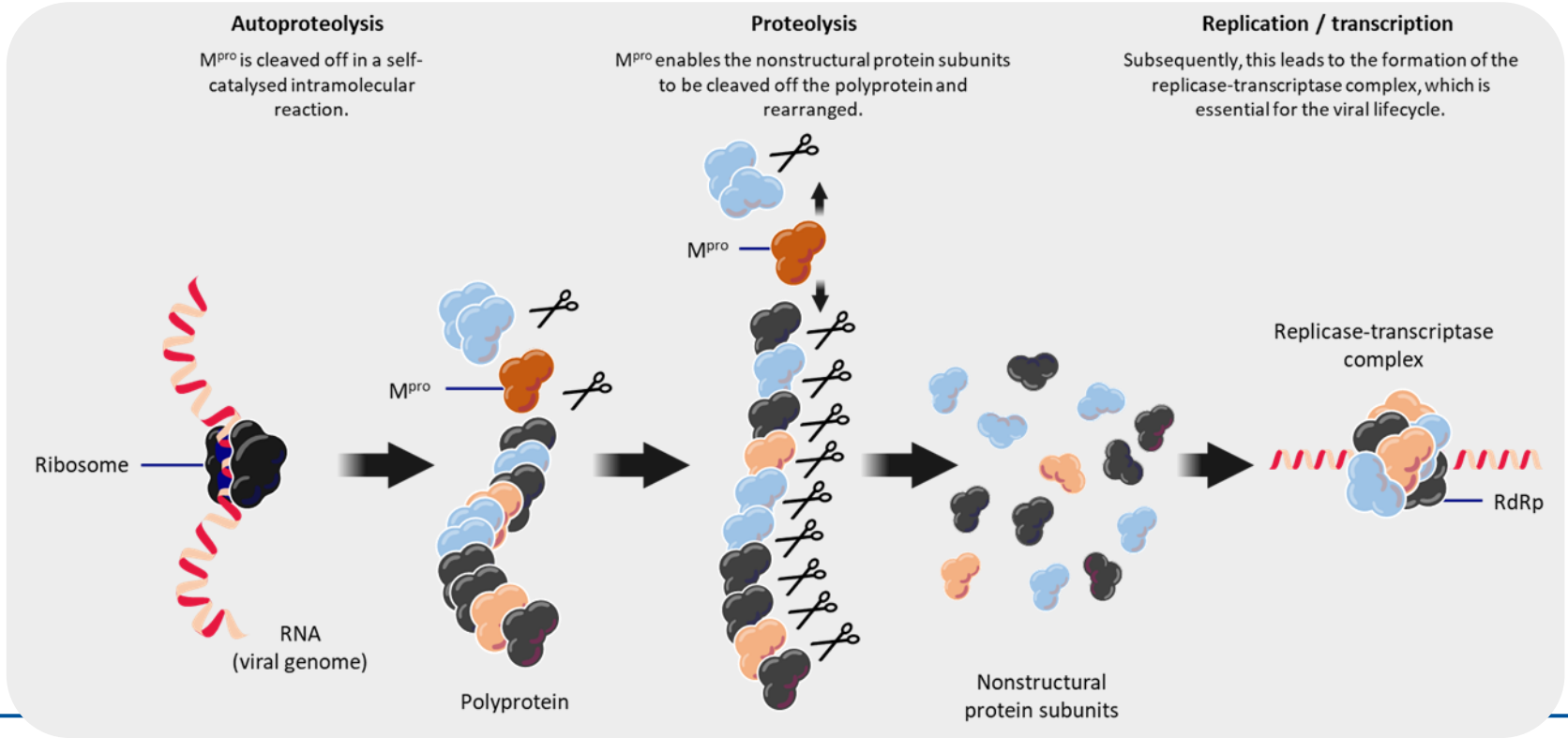
- ✓ Δεσμεύεται στο ενεργό κέντρο της M^{pro} πρωτεάσης
- ✓ Αναστέλλει τη δράση της M^{pro}
- ✓ Παρεμποδίζοντας τον πολλαπλασιασμό του ιού

Ο ρόλος της πρωτεάσης M^{pro} στον πολλαπλασιασμό του SARS-CoV-2

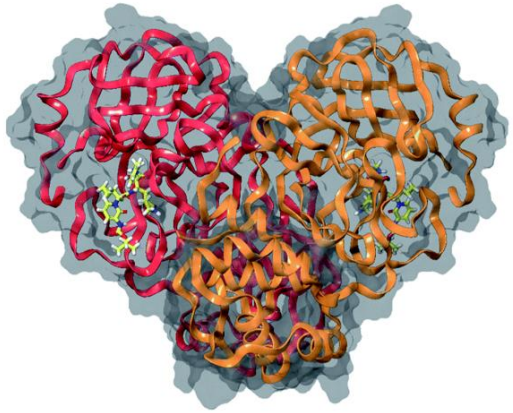
M^{pro} ή $3CL^{pro}$ (**3**-**C**hymotrypsin-**L**ike) protease

Παίζει πρωτεύοντα ρόλο στην **πρωτεόλυση**

- Διασπά τις πολυπρωτεΐνες του κορωνοϊού σε μικρότερες μη δομικές πρωτεΐνες (NSPs)
- Οι NSPs αναδιατάσσονται και τελικά σχηματίζουν το σύμπλεγμα αντιγραφής/μεταγραφής



3CL-M^{pro}: Ένας ελκυστικός θεραπευτικός στόχος



SARS-CoV-2 M^{pro}

1. Είναι **απαραίτητη για τον κύκλο πολλαπλασιασμού του ιού** (επεξεργασία των πρόδρομων πολυπρωτεϊνικών ενώσεων του ιού σε λειτουργικές μονάδες)

2. Έχει **χαμηλή πιθανότητα εκτός στόχου δραστικότητας**, λόγω απουσίας γνωστών ανθρώπινων αναλόγων

3. Είναι **καλά διατηρημένη πρωτεΐνη μέσα στην ομάδα των κορωνοϊών**

3CLpro, coronavirus 3-chymotrypsin-like-protease; Mpro, κύρια πρωτεάση. Image source: modified from Vladimir Frecer et al., RSC Adv., 2020, 10, 40244

1. Owen DR, et al. Science 2021;374(6575):1586–93; 2 Ahmad B, et al. Int J Mol Sci 2021;22(17):9124; 2. Yang H, et al. PLoS Biol 2005:3(10):e324; 3. Razali R, et al. Microorganisms 2021;9(12):2481. 4. Rubin et al. N Engl J Med. 2022 Feb 16. doi: 10.1056/NEJMe2202160 5. Hammond J et al. N Engl J Med 2022. 386:1397-1408.

Nirmatrelvir Retains Consistent, Potent in-vitro Anti-viral (AV) Activity Across SARS-CoV-2 Variants

Variant	M^{pro} Mutations	Variant Fold EC_{50} Relative to WT EC_{50} (n≥3)[a]
Washington	Wildtype	--
Alpha	N/A (same as WT)	~1
Beta B.1.351	K90R (99%)	~4
Delta	N/A (same as WT)	~0.5
Gamma	N/A (same as WT)	~1
Lambda	G15S (93%)	~0.6
Omicron BA.1	P132H (100%)	~0.5
Omicron variants: BA.2	P132H (100%)	~1
BA.2.12.1	P132H (100%)	~0.6
BA.4	P132H (100%)	~0.6
BA.5	P132H (100%)	~0.6
BF.7[b]	P132H (100%), P252L (31%), F294L (70%)	~1
BF.7[b]	P132H (100%), T243I (100%)	~0.8
BQ.1.11[b]	P132H (100%)	~0.9[c]
BQ.1[b]	P132H (100%)	~1
XBB.1.5[b]	P132H (100%)	~1

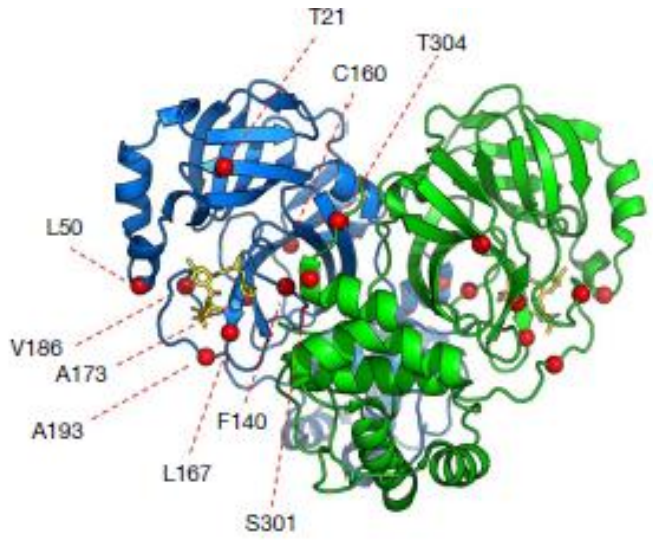
a. Cell type – Vero E6 P-gp KO or Vero E6 TMPRSS2; b. New data as of Feb. 27, 2023; c. n=2
Source: Pfizer Internal Data, Report #042713

CC-8

*Τα *in vitro* δεδομένα δεν συσχετίζονται απαραίτητα με κλινική αποτελεσματικότητα.

1. FOOD AND DRUG ADMINISTRATION (FDA) Center for Drug Evaluation and Research (CDER) Antimicrobial Drugs Advisory Committee (AMDAC) Antimicrobial Drugs Advisory Committee Meeting, 3/16/2023, Available at: March 16, 2023 Meeting of the Antimicrobial Drugs Advisory Committee Meeting (fda.gov) Accessed: Sep 2023

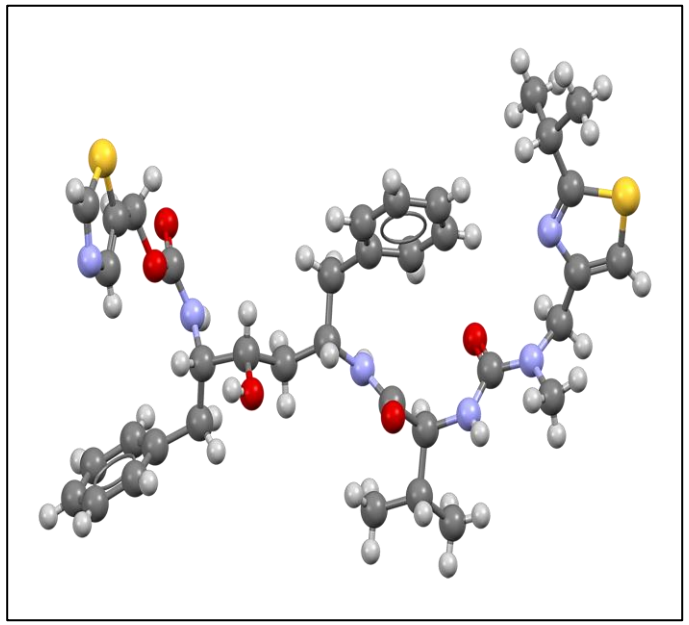
SARS-CoV 2 : Ένας διαρκώς μεταβαλλόμενος ιός- Ανάπτυξη αντοχής στη Νιρματρελβίρη;



- Προς το παρόν χωρίς εμφάνιση μεταλλάξεων σε κλινικά στελέχη που να προσδίδουν αντοχή
- Χωρίς συσχέτιση με εμφάνιση αντοχής το φαινόμενο Rebound
- Δυνατή η δημιουργία μεταλλάξεων αντοχής του ιού στο εργαστήριο (κάποιες έχουν παρατηρηθεί και σε φυσικά στελέχη χωρίς έκθεση σε νιρματρελβίρη)
- Αύξηση σε πρόσφατες επιδημιολογικές μελέτες της δυναμικής μεταλλάξεων του ιού

1. Iketani S et al. Nature 2022

Ριτοναβίρη



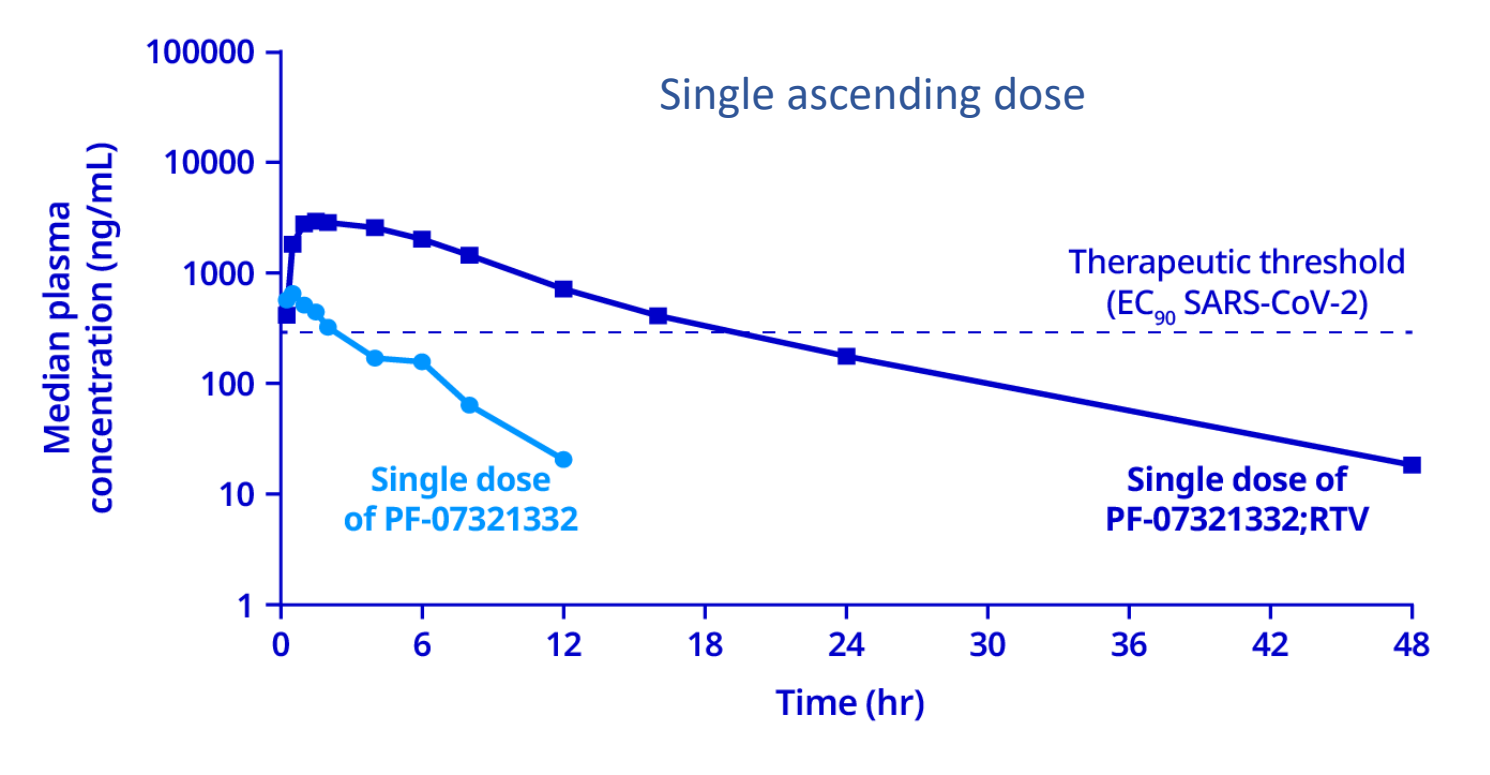
- Ενδείκνυται σε συνδυασμό με άλλους αντιρετροϊκούς παράγοντες για τη θεραπεία ασθενών που έχουν προσβληθεί από τον HIV-1 (ενήλικες και παιδιά ηλικίας 2 ετών και άνω)
- Χρησιμοποιείται ως φαρμακοκινητικός ενισχυτής σε συνδυασμό με άλλους HIV αναστολείς πρωτεάσης σε χαμηλότερη δόση (100mg/200mg μία έως δύο φορές ημερησίως ανάλογα με τον παράγοντα)
- Ισχυρός αναστολέας του CYP3A4 με γνωστό προφίλ ασφάλειας (οι περισσότερες ΑΕ παρατηρούνται σε υψηλότερες δόσεις : 600 mg δύο φορές ημερησίως)
- Δεν είναι δραστική έναντι του SARS-CoV-2

ΑΕ: Ανεπιθύμητες ενέργειες

1. Paxlovid Περίληψη Χαρακτηριστικών Προϊόντος 01/2022 2. Paxlovid-epar-public-assessmentreport 2022. Διαθέσιμο σε: https://www.ema.europa.eu/documents/assessment-report/paxlovid-epar-public-assessment-report_en.pdf, Τελευταία πρόσβαση 27 Μαρτίου 2022 3. Cooper, CL et al. Clin Infect Dis 2003 15;36(12):1585-92 4. Owen, D et al. Science. 2021 doi: 10.1126/science.abl4784 5.Norvir SmPC, Διαθέσιμο σε: http://www.emea.europa.eu/Τελευταία πρόσβαση 27 Μαρτίου 2022

Η Ριτοναβίρη ως φαρμακοκινητικός ενισχυτής του PF-07321332

Η Ριτοναβίρη αναστέλλει τον διαμεσολαβούμενο από το CYP3A μεταβολισμό του PF-07321332, παρέχοντας αυξημένες συγκεντρώσεις του PF-07321332 στο πλάσμα

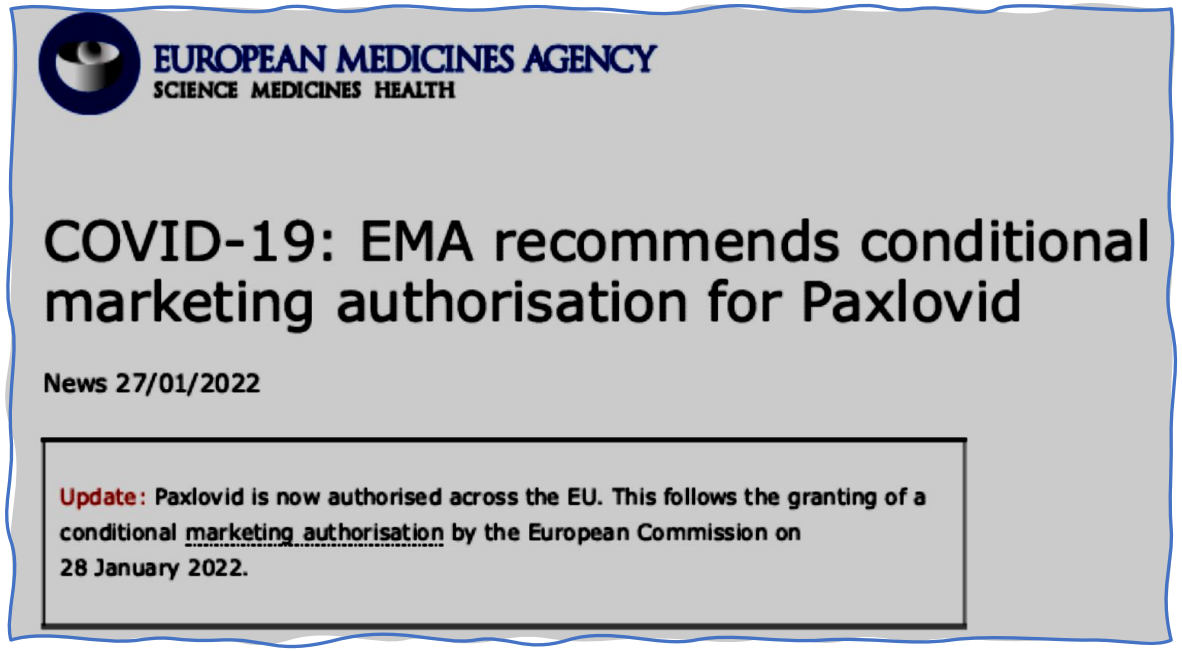


EC_{90}, 90% effective concentration

1. Owen, D et al. Science. 2021 doi: 10.1126/science.abl4784 2. Paxlovid Περίληψη Χαρακτηριστικών Προϊόντος, 01/2022.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

PF-0732133/Ριτοναβίρη
Το πρώτο αντιικό φάρμακο από του στόματος που εγκρίνεται στην Ε.Ε. για τη θεραπεία της COVID-19



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

COVID-19: EMA recommends conditional marketing authorisation for Paxlovid

News 27/01/2022

Update: Paxlovid is now authorised across the EU. This follows the granting of a conditional marketing authorisation by the European Commission on 28 January 2022.

Το PF-0732133/Ριτοναβίρη ενδείκνυται για τη **θεραπεία της νόσου του κορωνοϊού 2019** (**COVID-19**) σε **ενήλικες**

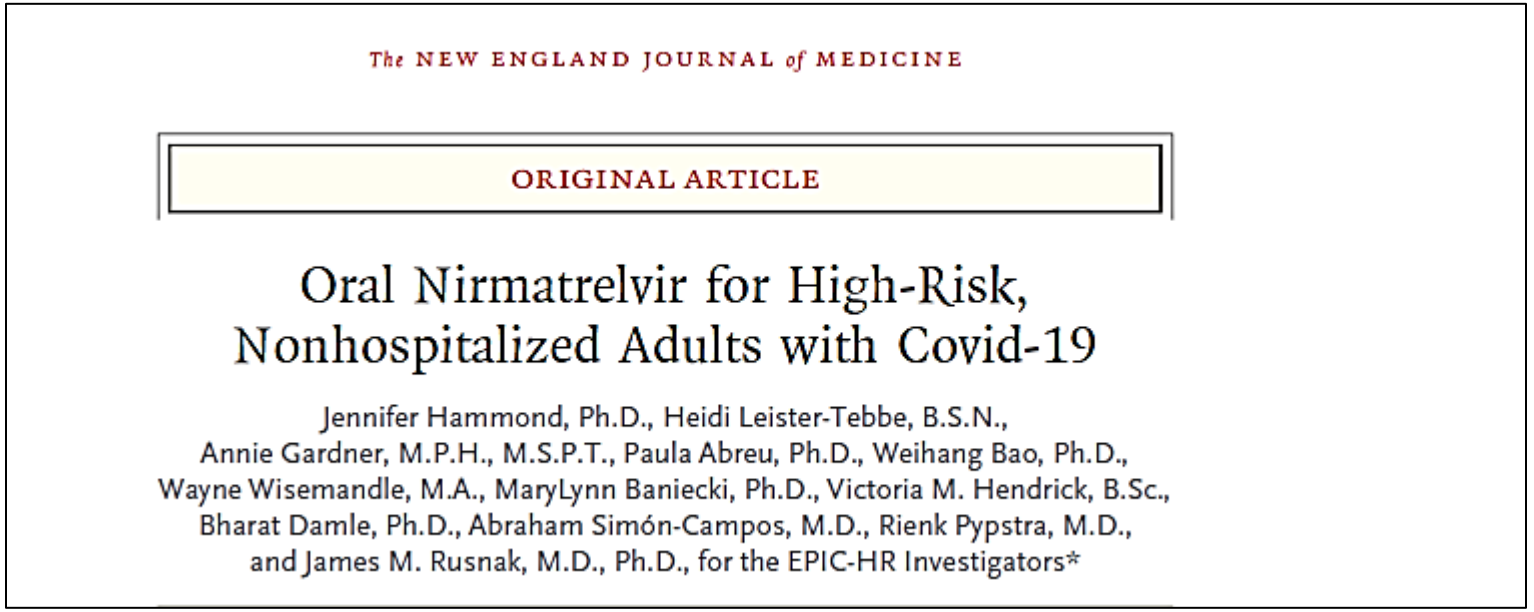
- ✓ για τους οποίους **δεν απαιτείται συμπληρωματική χορήγηση οξυγόνου**

ΚΑΙ

- ✓ οι οποίοι έχουν **αυξημένο κίνδυνο** εξέλιξης σε **σοβαρή νόσο COVID-19**

1. https://www.ema.europa.eu/en/news/covid-19-ema-recommends-conditional-marketing-authorisation-Paxlovid, Accessed: 02/06/2022
2. PAXLOVID Περίληψη Χαρακτηριστικών Προϊόντος 07/2022

Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR): Study of oral PF-07321332/ritonavir Compared with Placebo in Nonhospitalized High-Risk Adults with COVID-19



The NEW ENGLAND JOURNAL of MEDICINE

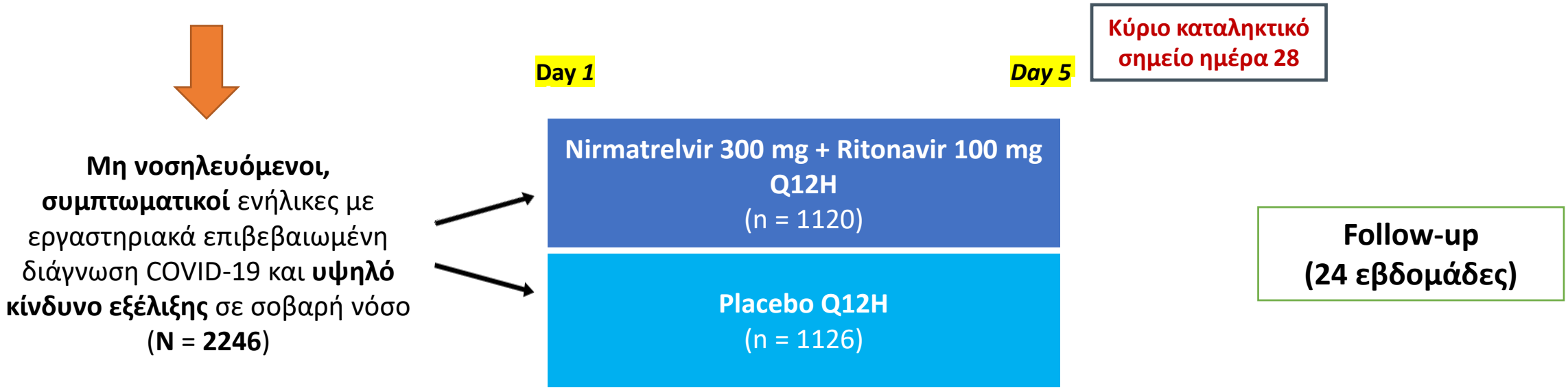
ORIGINAL ARTICLE

Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

Jennifer Hammond, Ph.D., Heidi Leister-Tebbe, B.S.N., Annie Gardner, M.P.H., M.S.P.T., Paula Abreu, Ph.D., Weihang Bao, Ph.D., Wayne Wisemandle, M.A., MaryLynn Baniecki, Ph.D., Victoria M. Hendrick, B.Sc., Bharat Damle, Ph.D., Abraham Simón-Campos, M.D., Rienk Pypstra, M.D., and James M. Rusnak, M.D., Ph.D., for the EPIC-HR Investigators*

EPIC-HR: Σχεδιασμός

Τυχαιοποιημένη (1:1), διπλά-τυφλή, ελεγχόμενη με εικονικό φάρμακο μελέτη φάσης II/III



Κύριο καταληκτικό σημείο: Ποσοστό **νοσηλειών** λόγω COVID-19 **ή/και θανάτων** από οποιαδήποτε αιτία έως την ημέρα 28

Hammond J, et al. N Engl J Med. 2022; 386:1397-1408.

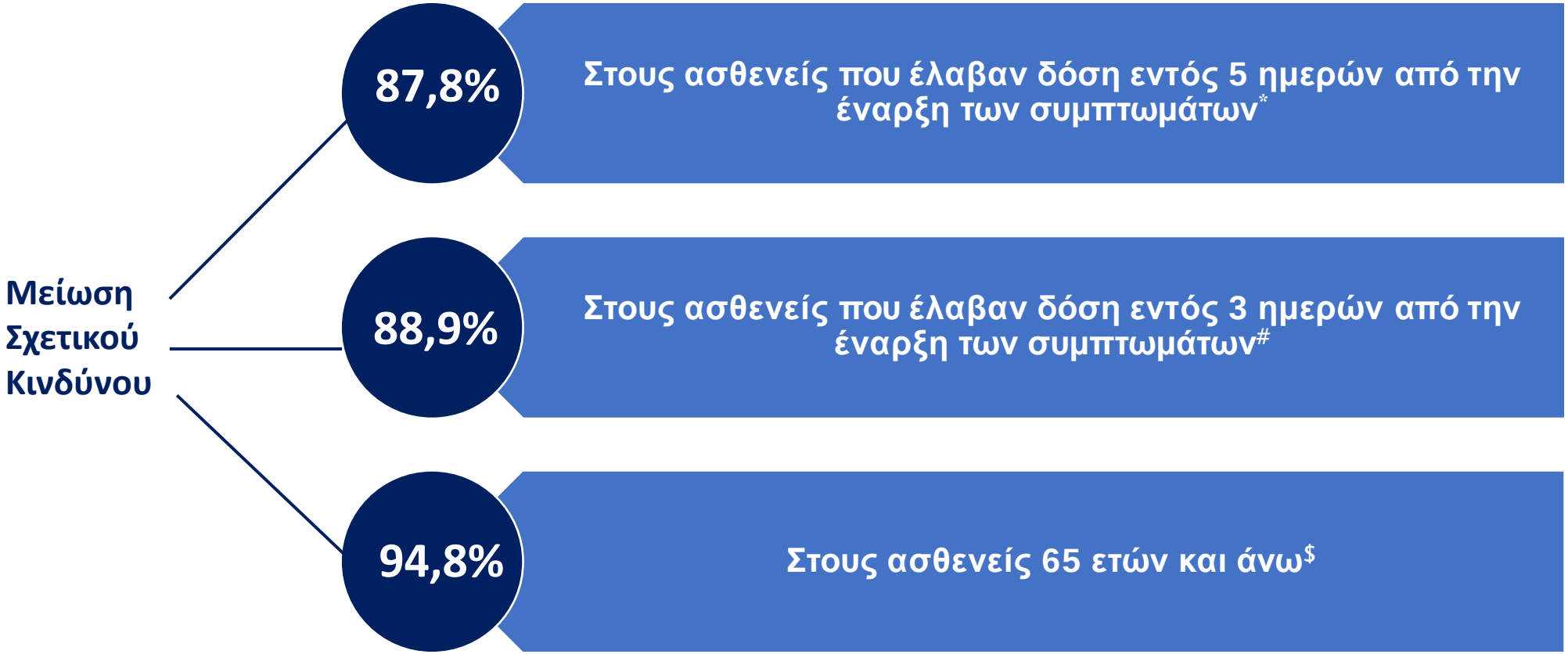
EPIC-HR: Κριτήρια ένταξης

Κριτήρια ένταξης	*Παράγοντες κινδύνου*
✓ **Ηλικία ≥18 ετών**	• Ηλικία ≥60 ετών
✓ **Επιβεβαιωμένη λοίμωξη από SARS-CoV-2 εντός 5 ημερών πριν την τυχαιοποίηση**	• BMI >25 kg/m²
✓ **Έναρξη των σημείων/συμπτωμάτων της COVID-19 εντός 5 ημερών πριν από την ημέρα της τυχαιοποίησης**	• Κάπνισμα • Ανοσοκατεσταλμένοι (συμπεριλαμβάνοντας λοίμωξη από HIV με CD4 <200 mm3 και ιικό φορτίο <400 αντίγραφα/mL) ή παρατεταμένη ιατρογενής ανοσοκαταστολή • Χρόνια πνευμονοπάθεια
✓ **≥1 σημείο/σύμπτωμα της COVID-19 παρόν την ημέρα της τυχαιοποίησης**	• Χρόνια καρδιαγγειακή νόσος • Χρόνια νεφρική νόσος • Δρεπανοκυτταρική νόσος • Υπέρταση • Διαβήτης
✓ **≥1 χαρακτηριστικό ή υποκείμενη ιατρική κατάσταση σχετιζόμενη με αυξημένο κίνδυνο εξέλιξης σε σοβαρή νόσο COVID-19**	• Καρκίνος • Νευροαναπτυξιακές διαταραχές ή άλλες σύνθετες ιατρικές καταστάσεις • Εξάρτηση από ιατρική τεχνολογία

1. Hammond J, et al. N Engl J Med. 2022; 386:1397-1408. 2. PAXLOVID Περίληψη Χαρακτηριστικών Προϊόντος 07/2022

Μελέτη EPIC-HR: Η Νιρματρελβίρη/ριτοναβίρη μείωσε σημαντικά τον κίνδυνο νοσηλείας ή θανάτου

Νιρματρελβίρη/ριτοναβίρη: Μείωση του σχετικού κινδύνου νοσηλείας που σχετίζεται με την COVID-19 ή θάνατο από οποιαδήποτε αιτία έως την Ημέρα 28 σε σχέση με το εικονικό φάρμακο σε μη νοσηλευόμενους συμπτωματικούς ενήλικες με νόσο COVID-19, οι οποίοι είχαν αυξημένο κίνδυνο εξέλιξης σε σοβαρή νόσο COVID-19 (πρωταρχικό τελικό σημείο).[1,2]

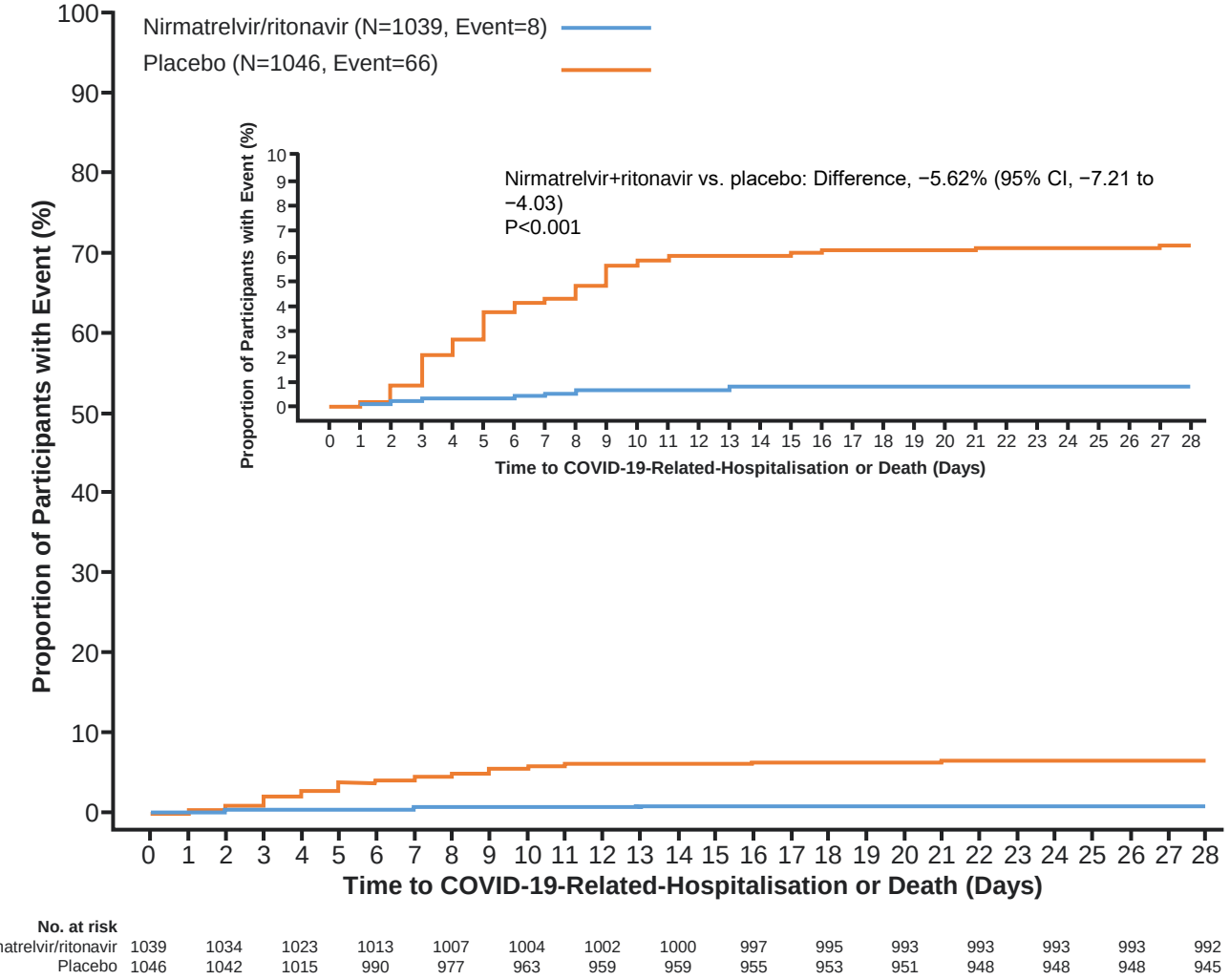


*Όλοι οι συμμετέχοντες που έλαβαν θεραπεία, με έναρξη συμπτωμάτων ≤ 5 ημέρες, οι οποίοι κατά την έναρξη δεν έλαβαν, ούτε αναμενόταν να λάβουν αγωγή με θεραπευτικό μονοκλωνικό αντίσωμα για την COVID-19 p<0,0001.
#Όλοι οι συμμετέχοντες που έλαβαν θεραπεία, με έναρξη συμπτωμάτων ≤ 3 ημέρες, οι οποίοι κατά την έναρξη δεν έλαβαν, ούτε αναμενόταν να λάβουν αγωγή με θεραπευτικό μονοκλωνικό αντίσωμα για την COVID-19, p<0,0001.
$p<0,0001 (μέσω x^2), Υπολογισμός μείωσης σχετικού κινδύνου (RRR):[3] Μείωση σχετικού κινδύνου (RRR) % = (Απόλυτος κίνδυνος συμβάντων στην ομάδα ελέγχου-Απόλυτος κίνδυνος συμβάντων στην ομάδα παρέμβασης)/ Απόλυτος κίνδυνος συμβάντων στην ομάδα ελέγχου x 100.
Μελέτη EPIC-HR: Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients.

1.Hammond et al. 2022. N Engl J Med. 386:1397-1408. 2. BMJ Best Practice https://bestpractice-bmj-com.eu1.proxy.openathens.net/info/toolkit/learn-ebm/how-to-calculate-risk/, Accessed: 1 Sep 2023

Key secondary efficacy endpoint: Analysis of primary endpoint in the full mITT1 population*

- **Endpoint:** Proportion of participants with **COVID-19-related hospitalisation or death** from any cause through Day 28
- **mITT1:** All subjects who received ≥1 dose of study intervention, with ≥1 post-baseline visit through Day 28, treated within **five days** of symptom onset, and who at baseline did not receive nor were expected to receive mAb treatment for COVID-19 (**N=2,085**)



*The cumulative percentage was estimated for each treatment group with use of the Kaplan–Meier method. The inset shows the same data on an expanded y axis.

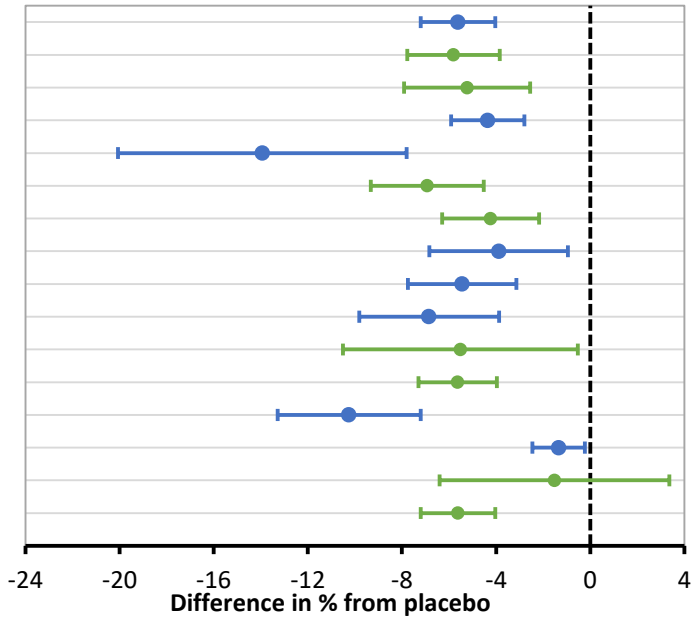
mAb, monoclonal antibody; mITT, modified intent-to-treat.

Hammond J, et al. *N Engl J Med* 2022;386(15):1397–408.

Key secondary efficacy endpoint: Subgroup analysis (mITT1 population)*

Consistent trend across secondary endpoints

- **Endpoint:** Proportion of participants with **COVID-19-related hospitalisation or death** from any cause through Day 28
- **mITT1:** All subjects who received ≥1 dose of study intervention, with ≥1 post-baseline visit through Day 28, treated within **five days** of symptom onset, and who at baseline did not receive nor were expected to receive mAb treatment for COVID-19 (**N=2,085**)



Category	Nirmatrelvir 300 mg; ritonavir 100 mg n/N	Placebo n/N	Difference in % (95% CI)
Overall (mITT1)	8/1,039	66/1,046	-5.62 (-7.21, -4.03)
Symptom onset duration: ≤3 days	5/697	44/682	-5.81 (-7.78, -3.84)
Symptom onset duration: >3 days	3/342	22/364	-5.23 (-7.91, -2.55)
Age: <65 years	7/908	46/909	-4.35 (-5.91, -2.79)
Age: ≥65 years	1/131	20/137	-13.93 (-20.07, -7.80)
Gender: Male	4/520	41/540	-6.93 (-9.32, -4.53)
Gender: Female	4/519	25/506	-4.23 (-6.29, -2.17)
BMI: <25 kg/m^2	1/209	9/207	-3.88 (-6.83, -0.94)
BMI: 25–<30 kg/m^2	3/458	28/466	-5.44 (-7.75, -3.13)
BMI: ≥30 kg/m^2	4/371	29/373	-6.85 (-9.82, -3.87)
Diabetes mellitus = Yes	2/125	9/127	-5.51 (-10.51, -0.52)
Diabetes mellitus = No	6/913	57/919	-5.63 (-7.30, -3.96)
Baseline SARS-CoV-2 serology status: Negative	7/487	58/505	-10.25 (-13.28, -7.21)
Baseline SARS-CoV-2 serology status: Positive	1/540	8/528	-1.34 (-2.45, -0.23)
Received/expected to receive COVID-19 mAbs treatment: Yes	1/70	2/69	-1.51 (-6.40, 3.37)
Received/expected to receive COVID-19 mAbs treatment: No	8/1,039	66/1,046	-5.62 (-7.21, -4.03)

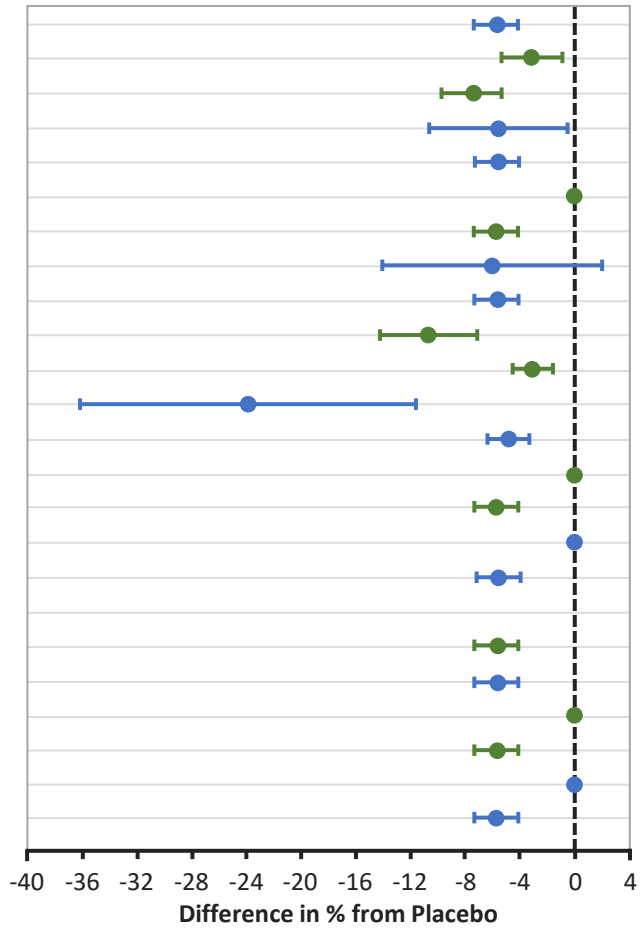
*Differences in the proportions (95% CIs) estimated for each treatment group using the Kaplan–Meier method.

BMI, body mass index; CI, confidence interval; mAb, monoclonal antibody; mITT, modified intent-to-treat; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Hammond J, et al. *N Engl J Med* 2022;386(15):1397–408.

Key secondary efficacy endpoint: Subgroup analysis (mITT1 population)*
Consistent trend across secondary endpoints

- **Endpoint:** Proportion of participants with **COVID-19-related hospitalisation or death** from any cause through Day 28
- **mITT1:** All subjects who received ≥1 dose of study intervention, with ≥1 post-baseline visit through Day 28, treated within **five days** of symptom onset, and who at baseline did not receive nor were expected to receive mAb treatment for COVID-19 (**N=2,085**)



Category	Nirmatrelvir 300 mg; ritonavir 100 mg n/N (%)	Placebo n/N (%)	Difference in % (95% CI)
Overall	8/1039 (0.770)	66/1046 (6.310)	-5.619 (-7.207, -4.031)
Cigarette smoker: Yes	4/405 (0.988)	17/424 (4.009)	-3.045 (-5.164, -0.926)
Cigarette smoker: No	4/632 (0.633)	49/622 (7.878)	-7.380 (-9.627, -5.134)
Diabetes mellitus: Yes	2/125 (1.600)	9/127 (7.087)	-5.512 (-10.510, -0.515)
Diabetes mellitus: No	6/913 (0.657)	57/919 (6.202)	-5.634 (-7.305, -3.963)
Immunosuppression: Yes	0/6	0/6	0.00 (0.000, 0.000)
Immunosuppression: No	8/1032 (0.775)	66/1040 (6.346)	-5.651 (-7.249, -4.053)
Chronic lung disease: Yes	0/58	2/34 (5.882)	-5.974 (-14.006, 2.057)
Chronic lung disease: No	8/980 (0.816)	64/1012 (6.324)	-5.585 (-7.209, -3.961)
Hypertension: Yes	5/338 (1.479)	42/351 (11.966)	-10.614 (-14.294, -6.935)
Hypertension: No	3/700 (0.429)	24/695 (3.453)	-3.066 (-4.526, -1.605)
Cardiovascular disorder: Yes	0/39	11/46 (23.913)	-23.913 (-36.240, -11.586)
Cardiovascular disorder: No	8/999 (0.801)	55/1000 (5.500)	-4.770 (-6.309, -3.231)
Chronic kidney disease: Yes	0/6	0/7	0.00 (0.000, 0.000)
Chronic kidney disease: No	8/1032 (0.775)	66/1039 (6.352)	-5.658 (-7.257, -4.059)
Device dependence: Yes	0/3	0/1	0.00 (0.000, 0.000)
Device dependence: No	8/1025 (0.780)	65/1037 (6.268)	-5.557 (-7.148, -3.966)
HIV infection: Yes	0/0	0/1	—
HIV infection: No	8/1038 (0.771)	66/1044 (6.322)	-5.631 (-7.222, -4.039)
Sickle cell disease: No	8/1038 (0.771)	66/1046 (6.310)	-5.618 (-7.207, -4.030)
Neurodevelopmental disorder: Yes	0/1	0/1	0.00 (0.00, 0.00)
Neurodevelopmental disorder: No	8/1037 (0.771)	66/1045 (6.316)	-5.624 (-7.214, -4.034)
Cancer: Yes	0/5	0/6	0.00 (0.000, 0.000)
Cancer: No	8/1033 (0.774)	66/1040 (6.346)	-5.652 (-7.250, -4.055)

*Differences in the proportions (95% CIs) estimated for each treatment group using the Kaplan–Meier method.

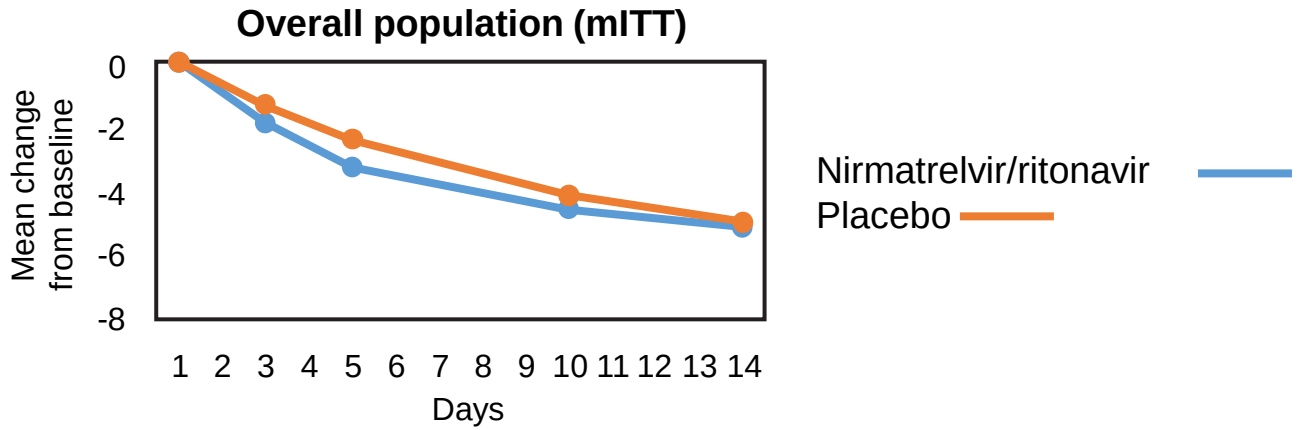
CI, confidence interval; HIV, human immunodeficiency virus; mAb, monoclonal antibody; mITT, modified intent-to-treat.

Hammond J, et al. *N Engl J Med* 2022;386(15):1397–408.

EPIC-HR: Δευτερεύον καταληκτικό σημείο
Μεταβολή του ιικού φορτίου (mITT πληθυσμός)

- **Συγκριτικά με το εικονικό φάρμακο, η θεραπεία με Νιρματρελβίρη/ριτοναβίρη συσχετίστηκε με περίπου 10 φορές μεγαλύτερη μείωση του ιικού φορτίου σε ρινοφαρυγγικά δείγματα έως τη μέρα 5**

Nirmatrelvir/ριτοναβίρη: Μειωμένο ιικό φορτίο την ημέρα 5 κατά επιπλέον 0.868±0.105 $\log_{10}$ αντίγραφα ανά ml (95% CI, –1.074 to –0.6615, P<0.001) σε σχέση με το εικονικό φάρμακο, όταν η θεραπεία ξεκίνησε εντός 3 ημερών από την εμφάνιση συμπτωμάτων*

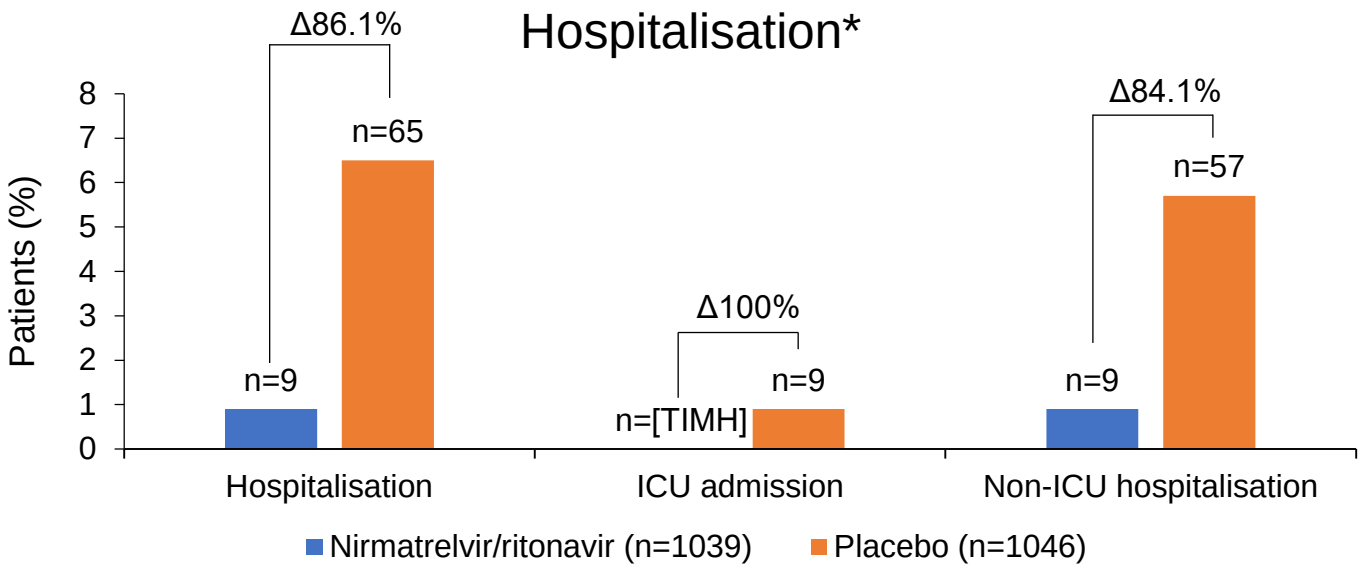


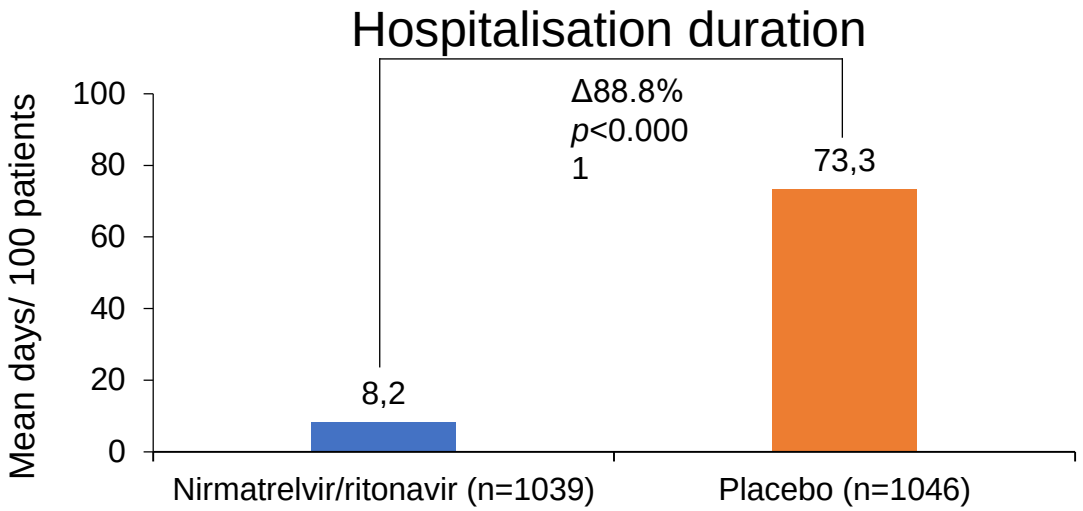
n	Baseline	Day 3	Day 5	Day 10	Day 14
Nirmatrelvir; ritonavir	552	529	508	502	507
Placebo	553	525	507	475	500
Mean (±SE) change from baseline vs placebo		–0.55 ±0.11	–0.8 ±0.10	–0.44 ±0.10	–0.16 ±0.08
P-value		<0.001	<0.001	<0.001	<0.045

Note: Geographic region, symptom onset duration, baseline SARS-CoV-2 serology status, baseline viral load and nasopharyngeal sample site were covariates along with participant as a random effect. mITT, modified intent-to-treat; SE, standard error of the mean.

Hammond J, et al. N Engl J Med. 2022; 386:1397-1408.

EPIC-HR
COVID-19–Related Hospitalisation (mITT1)

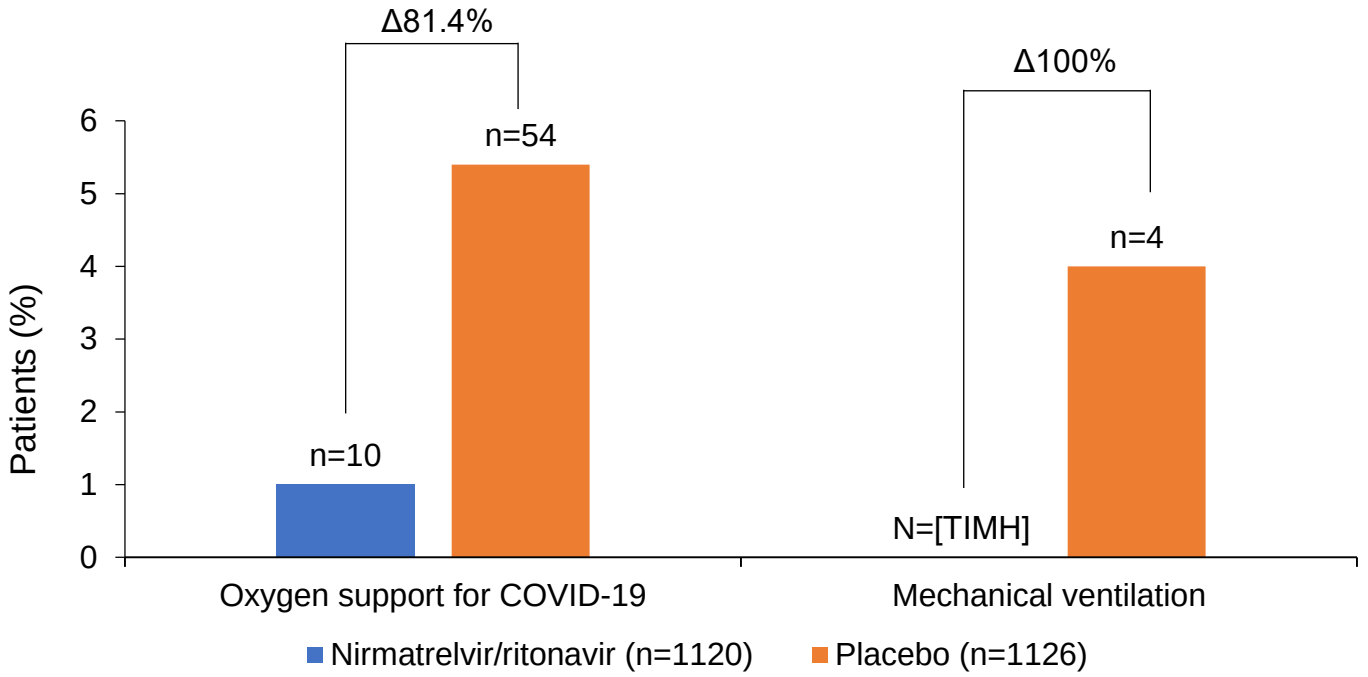




- Fewer hospitalisations were reported among those who received nirmatrelvir/ritonavir compared with placebo
  - No patients in the nirmatrelvir/ritonavir group and 9 patients in the placebo group were admitted to the ICU
  - Mean days of hospitalisation per 100 patients was significantly reduced among nirmatrelvir/ritonavir treated patients
- Among hospitalised participants with known discharge status, 100% of those who received nirmatrelvir/ritonavir were discharged to home self-care vs 52.9% of those receiving placebo

*Not limited through Day 28.
Δ, percentage reduction with nirmatrelvir/ritonavir compared with placebo.
ICU, intensive care unit; mITT1, modified intent-to-treat 1.
Hammond J, et al. Poster presented at IDWeek 2022. Poster 1156.

EPIC-HR
Patients who Received Oxygen Supplementation for COVID-19



- 81.5% RRR in requirement for oxygen support for COVID-19
- None of the patients in the nirmatrelvir/ritonavir group vs 4 patients in the placebo group received mechanical ventilation

Δ, percentage reduction with nirmatrelvir/ritonavir compared with placebo.
RRR, relative risk reduction.
Hammond J, et al. Poster presented at IDWeek 2022. Poster 1156.

EPIC-HR: Δεδομένα ασφάλειας*

Ανεπιθύμητες Ενέργειες (AE)	Νιρματρελβίρη/ριτοναβίρη (n=1115)	Εικονικό φάρμακο (n=1109)
Οποιαδήποτε AE	22,6 %	23,9%
Σοβαρές AE	1,6%	6,6%
AE που οδήγησε σε διακοπή της θεραπείας	2,1%	4,2%

- ✓ **Οι πιο συχνές AE που αναφέρθηκαν κατά τη διάρκεια της θεραπείας με Νιρματρελβίρη/ριτοναβίρη ήταν δυσγευσία (4,6%), διάρροια (3,0%), κεφαλαλγία (1,2%) και έμετος (1,2%)[1]**
- ✓ Οι ασθενείς που έλαβαν Νιρματρελβίρη/ριτοναβίρη εμφάνισαν λιγότερες σοβαρές AE σε σύγκριση με το εικονικό φάρμακο (1,6% έναντι 6,6%) και λιγότερες AE που οδήγησαν σε διακοπή της θεραπείας (2,1% έναντι 4,2%)[2]
- ✓ Έως την ημέρα 34 καμία σοβαρή AE δεν οδήγησε σε θάνατο μεταξύ των ασθενών που έλαβαν Νιρματρελβίρη/ριτοναβίρη, αλλά υπήρχαν 13 θάνατοι στην ομάδα του εικονικού φαρμάκου, οι οποίοι σχετίζονταν με την COVID-19[2]

* Βασικά δεδομένα από τον **πληθυσμό ασφάλειας:** όλοι οι ασθενείς που έλαβαν τουλάχιστον μία δόση του φαρμάκου ή του εικονικού φαρμάκου). Οι ερευνητές συνέλεξαν ενεργά δεδομένα ασφάλειας έως την ημέρα 34

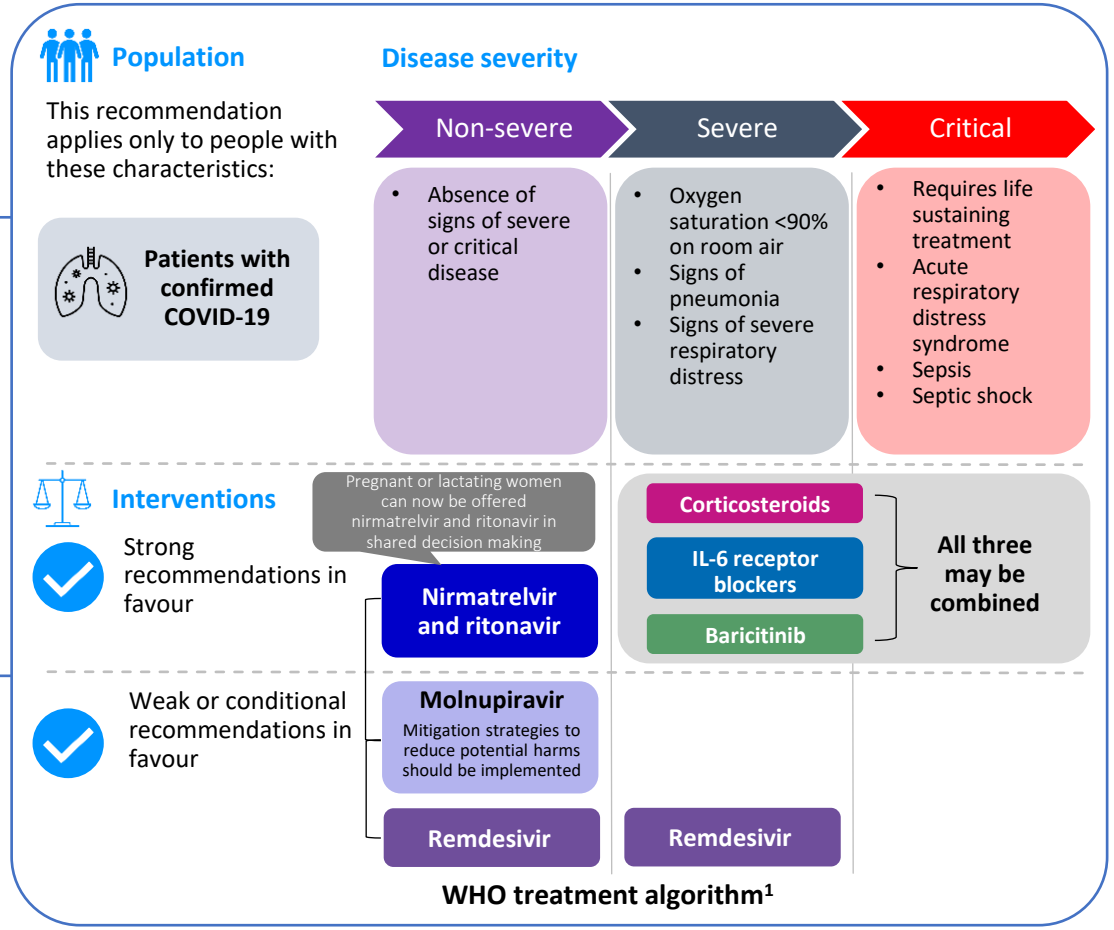
1.PAXLOVID Περίληψη Χαρακτηριστικών Προϊόντος 07/2023 2. Hammond J et al. N Engl J Med 2022. 386:1397-1408.

Treatment for COVID-19 outpatients that are at high risk of severe outcomes is available and recommended by treatment guidelines[1]

Therapies that directly target SARS-CoV-2 are anticipated to have the greatest effect early in the course of the disease[2]

WHO recommendations for patients with non-severe COVID-19 at highest risk of hospitalisation:[1]

- **A strong recommendation for nirmatrelvir / ritonavir**
  - Also an option for pregnant and breastfeeding women
- A *conditional* recommendation for molnupiravir
- A *conditional* recommendation for remdesivir



For non-severe COVID-19: strong recommendations against convalescent plasma, colchicine, hydroxychloroquine, lopinavir-ritonavir, casirivimab, imdevimab, and sotrovimab; weak or conditional recommendations against corticosteroids, ivermectin, and fluvoxamine.
For severe COVID-19: strong recommendations against hydroxychloroquine, lopinavir-ritonavir, casirivimab, imdevimab, and sotrovimab; weak or conditional recommendations against ruxolitinib, tofacitinib, ivermectin, and convalescent plasma.
For critical COVID-19: strong recommendations against hydroxychloroquine, lopinavir-ritonavir, casirivimab, imdevimab, and sotrovimab; weak or conditional recommendations against ruxolitinib, tofacitinib, ivermectin, convalescent plasma, and remdesivir.

WHO, World Health Organization.

1. World Health Organization. Therapeutics and COVID-19: living guideline: https://app.magicapp.org/#/guideline/nBkO1E (Accessed August 2023); 2. National Institutes of Health. Clinical Management of Adults Summary: https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-adults/clinical-management-of-adults-summary/ (Accessed August 2023).

Θεραπευτικός αλγόριθμος ενηλίκων ΜΗ νοσηλευόμενων ασθενών της Ελληνικής Εταιρείας Λοιμώξεων και της Ελληνικής Πνευμονολογικής Εταιρείας (Αναθεώρηση 17-10-2022)

Σειρά επιλογής	Αντι-ιικό φάρμακο	Αποτελεσματικότητα στην εγκριτική μελέτη	Έγκριση ΕΜΑ	Παρατηρήσεις
1.	**Νιρματρελβίρη / ριτοναβίρη**	**88%**	**ΝΑΙ**	Προσοχή στις φαρμακευτικές αλληλεπιδράσεις. Δεν χορηγείται σε ασθενείς με e-GFR<30 mL/min ή ηπατική ανεπάρκεια κατηγορίας C
2.	**Ρεμδεσιβίρη (τριήμερο σχήμα)**	**87%**	**ΝΑΙ**	Το Υπουργείο Υγείας δεν περιλαμβάνει ακόμη τη ρεμδεσιβίρη στα αντι-ιικά φάρμακα που χορηγούνται σε εξωνοσοκομειακούς ασθενείς
3.	**Tixagevimab/ cilgavimab**	**50%**	**ΝΑΙ**	Προσοχή στις αλλεργικές αντιδράσεις
4.	**Μολνουπιραβίρη**	**30%**	**ΟΧΙ**	Για χρήση μόνο εάν καμία από τις προηγούμενες θεραπείες δεν είναι διαθέσιμη, ή εάν η χορήγησή της δεν είναι εφικτή ή κλινικά κατάλληλη

Σημείωση: Εάν ένας ασθενής χρειαστεί **εισαγωγή στο νοσοκομείο** μετά την έναρξη της πρώιμης θεραπείας, ο θεράπων ιατρός μπορεί να επιλέξει την ολοκλήρωση του σχήματος με nirmatrelvir / ritonavir, ρεμδεσιβίρη ή μολνουπιραβίρη.

Source: Θεραπευτικός αλγόριθμος ενήλικων μη-νοσηλευόμενων ασθενών με COVID-19 **(Αναθεώρηση 17-10-2022**). Διαθέσιμο σε: https://www.loimoxeis.gr/. Τελευταία πρόσβαση: 09/2023.

Θεραπευτικός αλγόριθμος ενηλίκων ΝΟΣΗΛΕΥΟΜΕΝΩΝ ασθενών με COVID-19 της Ελληνικής Εταιρείας Λοιμώξεων και της Ελληνικής Πνευμονολογικής Εταιρείας (Αναθεώρηση 17-10-2022)

Σοβαρότητα Νόσου	Θεραπευτική παρέμβαση
Νοσηλευόμενος ασθενής με ήπια νόσο που δεν χρήζει παροχής συμπληρωματικού οξυγόνου	✓ Σε ασθενείς άνευ παραγόντων κινδύνου για επιδείνωση δεν χορηγείται ειδική φαρμακευτική αγωγή ✓ Σε ασθενείς με παράγοντες κινδύνου για επιδείνωση χορηγείται μέσα στο νοσοκομείο πρώιμη θεραπεία για την αποφυγή της προόδου σε σοβαρή νόσο ✓ Για τις θεραπευτικές επιλογές και την προτεραιοποίηση → Θεραπευτικός αλγόριθμος μη-νοσηλευόμενων ασθενών

Source: Θεραπευτικός αλγόριθμος ενήλικων μη-νοσηλευόμενων ασθενών με COVID-19 **(Αναθεώρηση 17-10-2022**). Διαθέσιμο σε: https://www.loimoxeis.gr/. Τελευταία πρόσβαση: 09/2023.

Νιρματρελβίρη/ριτοναβίρη: Δοσολογία

Εντός 5 ημερών από την έναρξη συμπτωμάτων

Δύο φορές ημερησίως για πέντε συνεχόμενες ημέρες

Πρωϊνή δόση

- **Δύο ροζ δισκία των 150 mg Νιρματρελβίρης**
- **Ένα λευκό δισκίο των 100mg ριτοναβίρης**

Βραδινή δόση

Δύο ροζ δισκία των 150 mg Νιρματρελβίρης

Ένα λευκό δισκίο των 100 mg ριτοναβίρης

- Η νιρματρελβίρη/ριτοναβίρη λαμβάνεται **με ή χωρίς τροφή**
- Τα δισκία θα πρέπει να καταπίνονται ολόκληρα, να μη μασώνται, να μη σπάζουν και να μη συνθλίβονται
- Να λαμβάνονται και τα 3 δισκία μαζί

Για το πλήρες κείμενο της δοσολογίας και του τρόπου χορήγησης συμβουλευτείτε την Περίληψη Χαρακτηριστικών του Προϊόντος. Paxlovid Περίληψη Χαρακτηριστικών Προϊόντος 07/2023

Νιρματρελβίρη/ριτοναβίρη: Η συμμόρφωση στη θεραπεία είναι σημαντική

Το PF-07321332/ριτοναβίρη θα πρέπει να χορηγείται όσο το δυνατόν συντομότερα μετά από τη διάγνωση της νόσου COVID-19 και εντός 5 ημερών από την έναρξη των συμπτωμάτων.

Συνιστάται η ολοκλήρωση του πλήρους κύκλου θεραπείας 5 ημερών, ακόμη και αν ο ασθενής χρειαστεί νοσηλεία λόγω σοβαρής ή κρίσιμης μορφής νόσου COVID-19 μετά την έναρξη της θεραπείας με PF-07321332/ριτοναβίρη.

Οδηγίες για παράλειψη δόσης

- Εάν ο ασθενής παραλείψει μια δόση **εντός 8 ωρών** από την ώρα που συνήθως λαμβάνεται, ο **ασθενής θα πρέπει να τη λάβει το συντομότερο δυνατό** και να **συνεχίσει το κανονικό πρόγραμμα χορήγησης** δόσεων

- Εάν ο ασθενής παραλείψει μια δόση για **περισσότερες από 8 ώρες**, ο ασθενής **δεν θα πρέπει να λάβει τη δόση** που παραλείφθηκε αλλά να **λάβει την επόμενη δόση κατά την κανονικά προγραμματισμένη ώρα**

- Ο ασθενής δεν θα πρέπει να πάρει διπλή δόση για να αναπληρώσει τη δόση που έχει παραλειφθεί

Για το πλήρες κείμενο της δοσολογίας και του τρόπου χορήγησης συμβουλευτείτε την Περίληψη Χαρακτηριστικών του Προϊόντος. Paxlovid Περίληψη Χαρακτηριστικών Προϊόντος 07/2023

Νιρματρελβίρη/ριτοναβίρη: Ειδικοί πληθυσμοί

Νεφρική δυσλειτουργία

- **Δεν χρειάζεται προσαρμογή της δόσης** σε ασθενείς με ήπια νεφρική δυσλειτουργία (eGFR 60-<90mL/min)
- Σε **μέτρια νεφρική δυσλειτουργία** (eGFR ≥30-<60 mL/min), η δόση θα πρέπει να μειώνεται σε **Νιρματρελβίρη** 150mg **& Ριτοναβίρη** 100 mg, κάθε 12 ώρες για 5 ημέρες
- **Δεν θα πρέπει να χρησιμοποιείται** σε ασθενείς με **σοβαρή νεφρική δυσλειτουργία** (eGFR <30mL/min, συμπεριλαμβανομένων των ασθενών υπό αιμοκάθαρση)

Πρωϊνή δόση +

- **Ένα ροζ δισκίο των 150mg Νιρματρελβίρης**
- **Ένα λευκό δισκίο των 100 mg ριτοναβίρης**

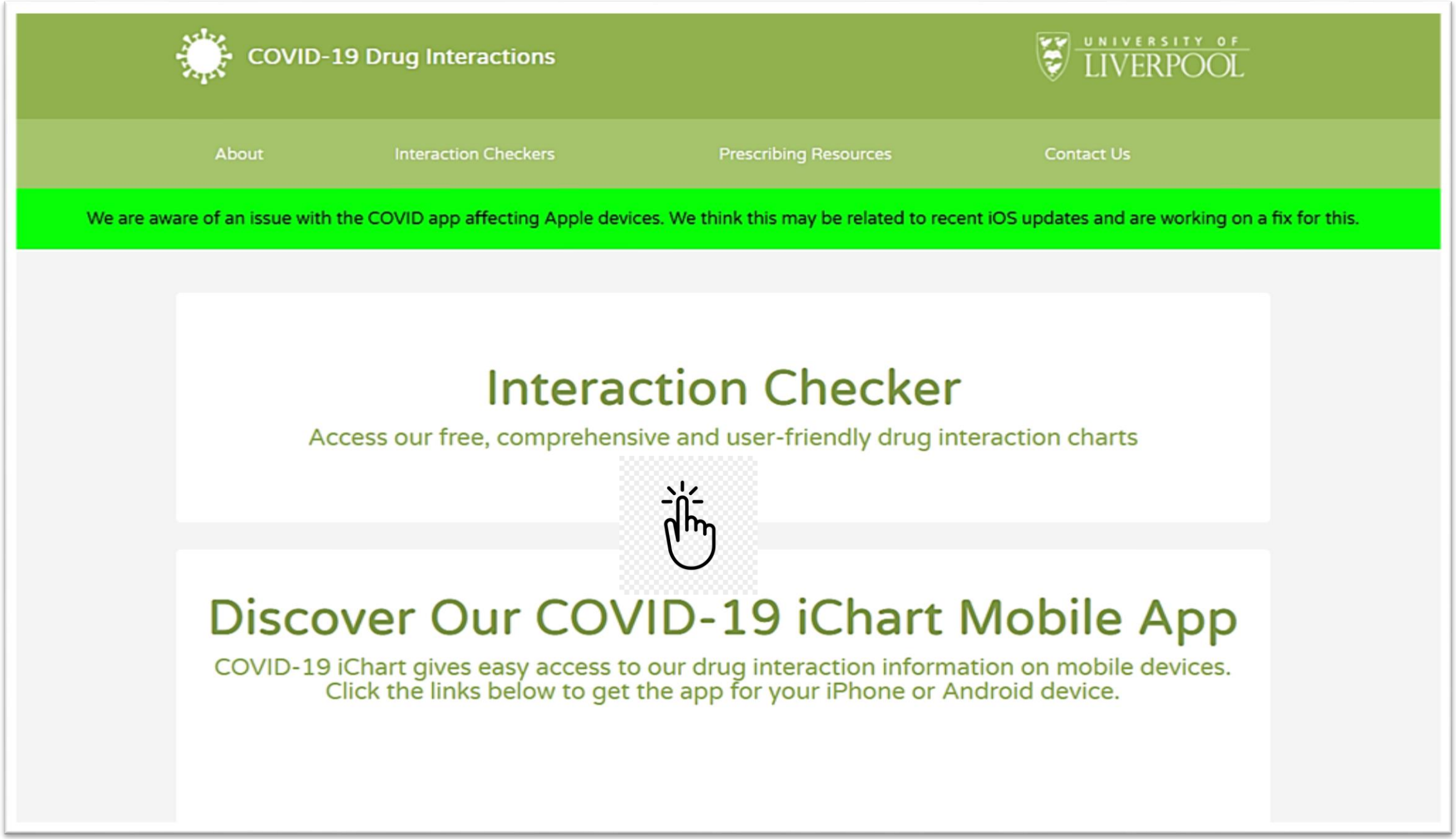
Οι ασθενείς θα πρέπει να λαμβάνουν και τα δύο δισκία μαζί

Βραδινή δόση +

- **Ένα ροζ δισκίο των 150mg Νιρματρελβίρης**
- **Ένα λευκό δισκίο των 100 mg ριτοναβίρης**

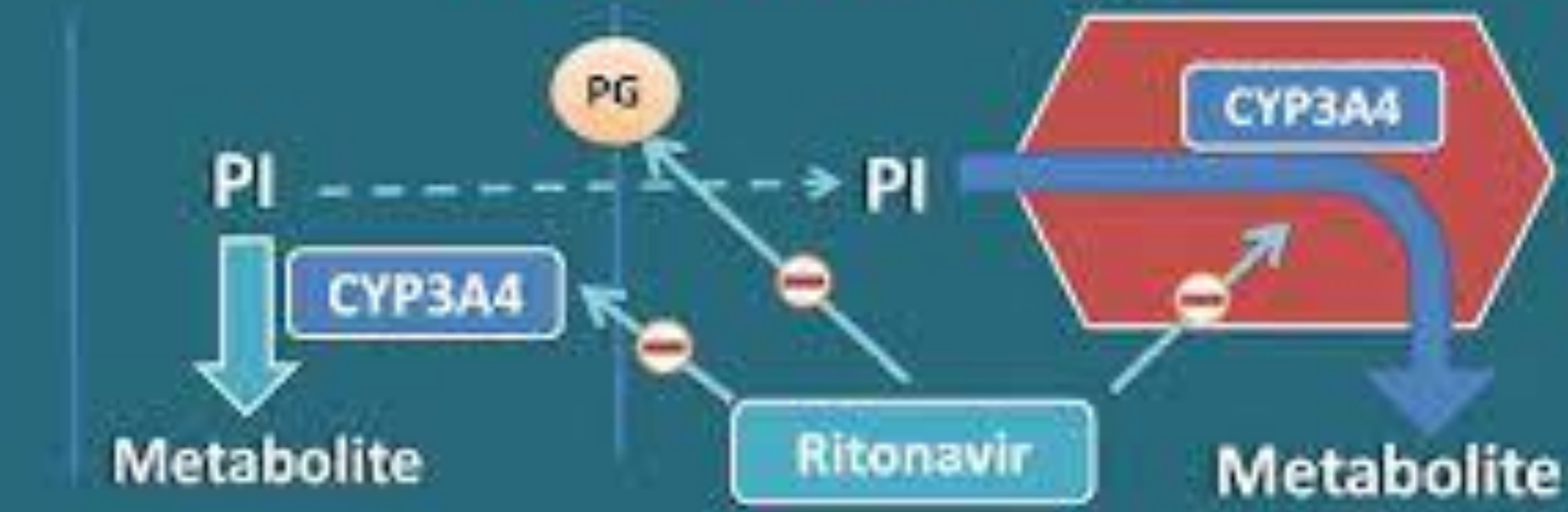
Οι ασθενείς θα πρέπει να λαμβάνουν και τα δύο δισκία μαζί

Για το πλήρες κείμενο της δοσολογίας και του τρόπου χορήγησης συμβουλευτείτε την Περίληψη Χαρακτηριστικών του Προϊόντος. Paxlovid Περίληψη Χαρακτηριστικών Προϊόντος 07/2023

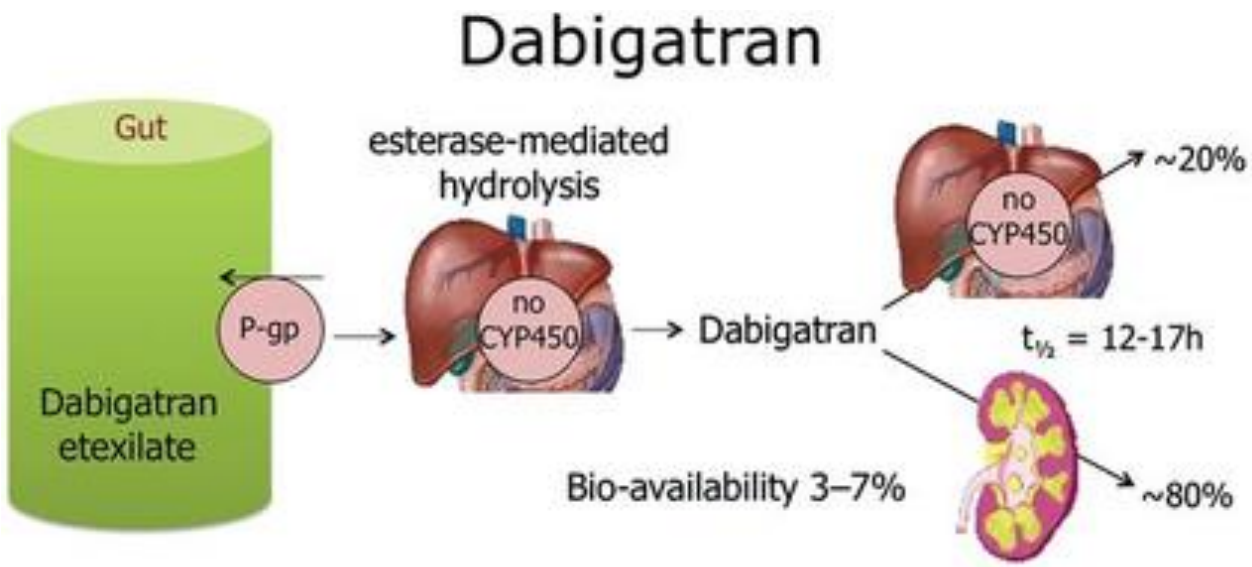


1. Liverpool COVID-19 Drug Interactions website. Available at: website https://www.covid19-druginteractions.org/ Accessed: 09/2023.

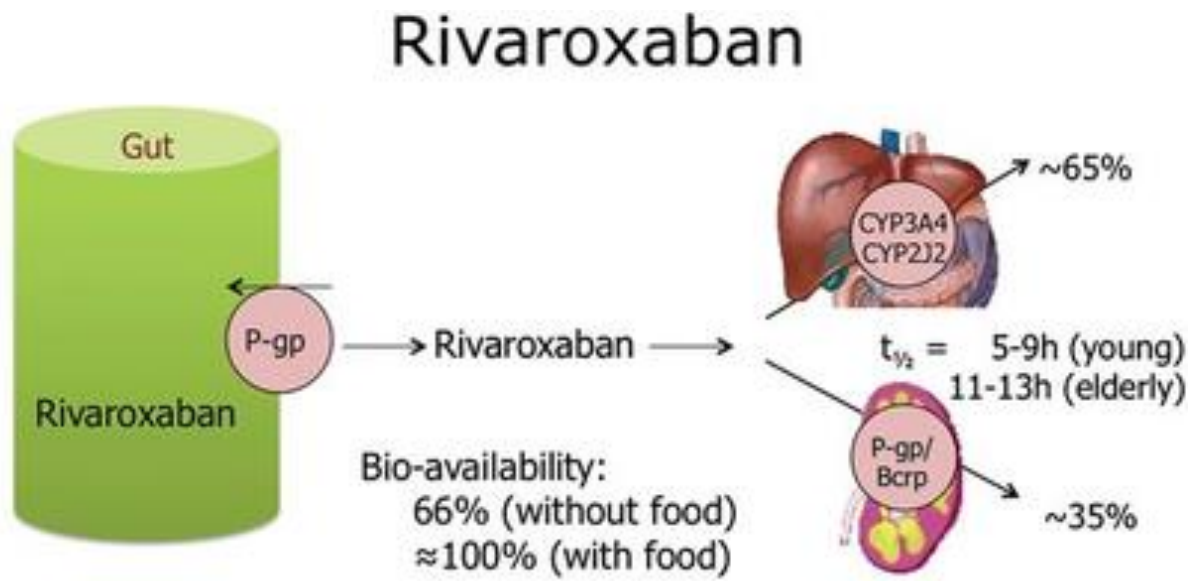
How Ritonavir acts as booster drug?



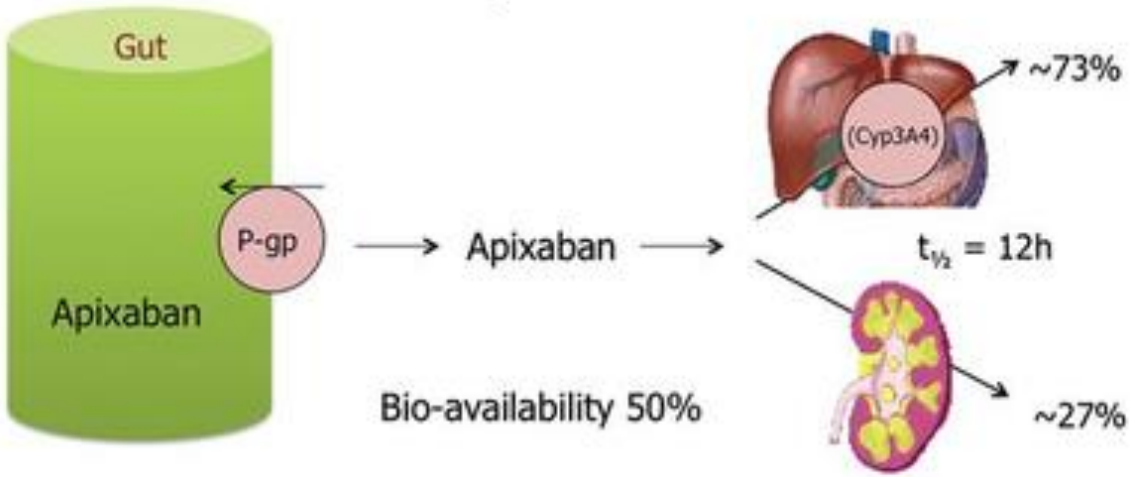
Pradaxa



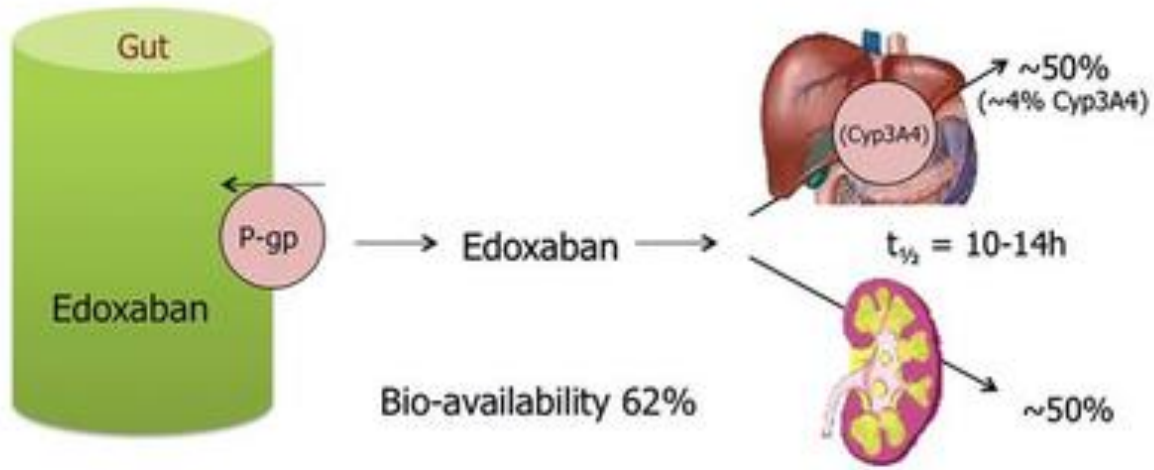
Xarelto



Eliquis



Lixiana



Παραδείγματα δυνητικών φαρμακευτικών αλληλεπιδράσεων του Paxlovid (1)

Anti-coagulant, Anti-platelet and Fibrinolytic

	Antivirals			*Corticosteroids*			*Host-directed*			*Anti-SARS-CoV-2 mABs*			
	MOL[1]	NMV/r[2]	RDV[3]	DEX	HC	MP	BAR	SAR	TCZ	B/E	C/I[4]	SOT[5]	T/C[6]
Acenocoumarol	↔	↓	↔	↔	↔	↔	↔	↓	↓	↔	↔	↔	↔
Apixaban	↔	↑	↔	↓	↔	↔	↔	↓	↓	↔	↔	↔	↔
Argatroban	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Aspirin (anti-platelet)	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Betrixaban	↔	↑	↔	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔
Clopidogrel	↔	↓	↔	↔	↔	↔	↔	↓	↓	↔	↔	↔	↔
Clopidogrel (recently stented patients)	↔	↓	↔	↔	↔	↔	↔	↓	↓	↔	↔	↔	↔
Dabigatran	↔	↔	↔	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔
Dalteparin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Dipyridamole	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Edoxaban	↔	↑	↔	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔
Enoxaparin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Fondaparinux	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Heparin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Phenprocoumon	↔	↑↓	↔	↔	↔	↔	↔	↓	↓	↔	↔	↔	↔
Prasugrel	↔	↔	↔	↔	↔	↔	↔	↓	↓	↔	↔	↔	↔
Rivaroxaban	↔	↑	↔	↓	↔	↔	↔	↓	↓	↔	↔	↔	↔
Streptokinase	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Ticagrelor	↔	↑	↔	↔	↔	↔	↔	↓	↓	↔	↔	↔	↔
Tinzaparin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Warfarin	↔	↓	↔	↔	↔	↔	↔	↓	↓	↔	↔	↔	↔

1 Lagevrio™
2 Paxlovid™
3 Veklury™
4 Ronapreve™, Regen-Cov™
5 Xevudy™
6 Evusheld™

Colour Legend

	These drugs should not be coadministered
	Potential interaction which may require a dose adjustment or close monitoring.
	Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment unlikely to be required.
	No clinically significant interaction expected

Text Legend

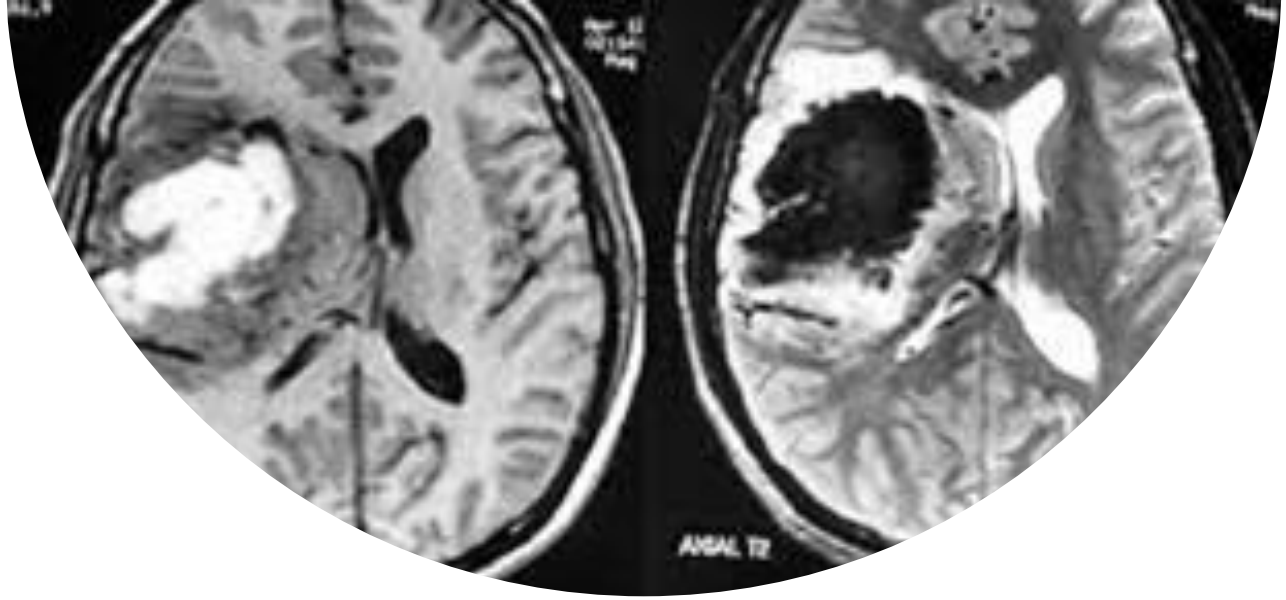
↑ Potential increased exposure of the comedication
↓ Potential decreased exposure of the comedication
⇑ Potential increased exposure of COVID drug
⇓ Potential decreased exposure of COVID drug
↔ No significant effect

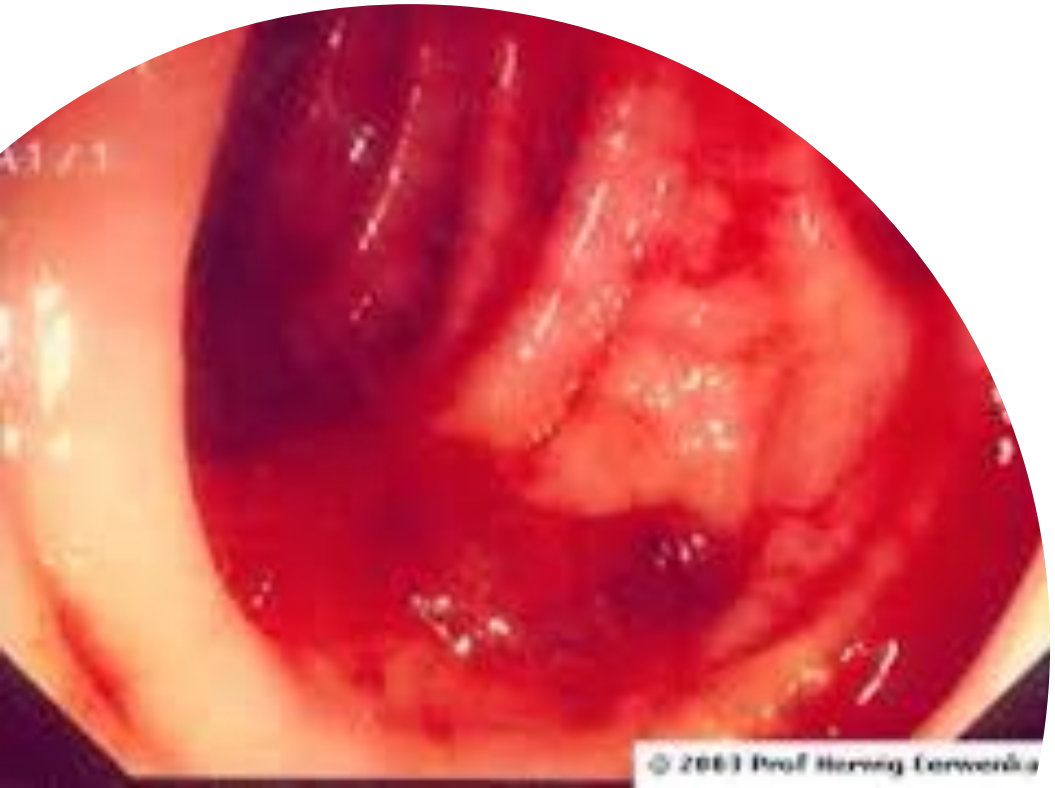
Numbers refer to increase/decrease in AUC as observed in drug-drug interaction studies.

♥ This interaction involves drugs identified by www.crediblemeds.org as having a known, possible or conditional risk of QT prolongation and/or TdP. Risk may be related to dose or concentration (due to DDIs) and/or additive if two or more such drugs are combined. Note, please check product labels for any additional cardiac warnings.

1. Liverpool COVID-19 Drug Interactions, Διαθέσιμο σε: https://covid19-druginteractions.org/checker, Τελευταία πρόσβαση 27 Μαρτίου 2022.

Για πλήρεις συνταγογραφικές πληροφορίες συμβουλευτείτε την Περίληψη Χαρακτηριστικών των Προϊόντων.


AXIAL T2



Anti-coagulant, Anti-platelet and Fibrinolytic

	Antivirals		
	MOL[1]	NMV/r[2]	RDV[3]
Acenocoumarol	↔	↓	↔
Apixaban	↔	↑	↔
Argatroban	↔	↔	↔
Aspirin (anti-platelet)	↔	↔	↔
Betrixaban	↔	↑	↔
Clopidogrel	↔	↓	↔
Clopidogrel (recently stented patients)	↔	↓	↔

a Reduced effectiveness of clopidogrel is likely. Do not coadminister clopidogrel in patients who are at a very high risk of thrombosis (e.g., those who are within 6 weeks of coronary stenting); consider prescribing an alternative antiplatelet (i.e., prasugrel) or an alternative COVID-19 therapy. For other indications, it may be acceptable to continue clopidogrel if the benefit of ritonavir-boosted nirmatrelvir treatment outweighs the risk of reduced clopidogrel effectiveness.

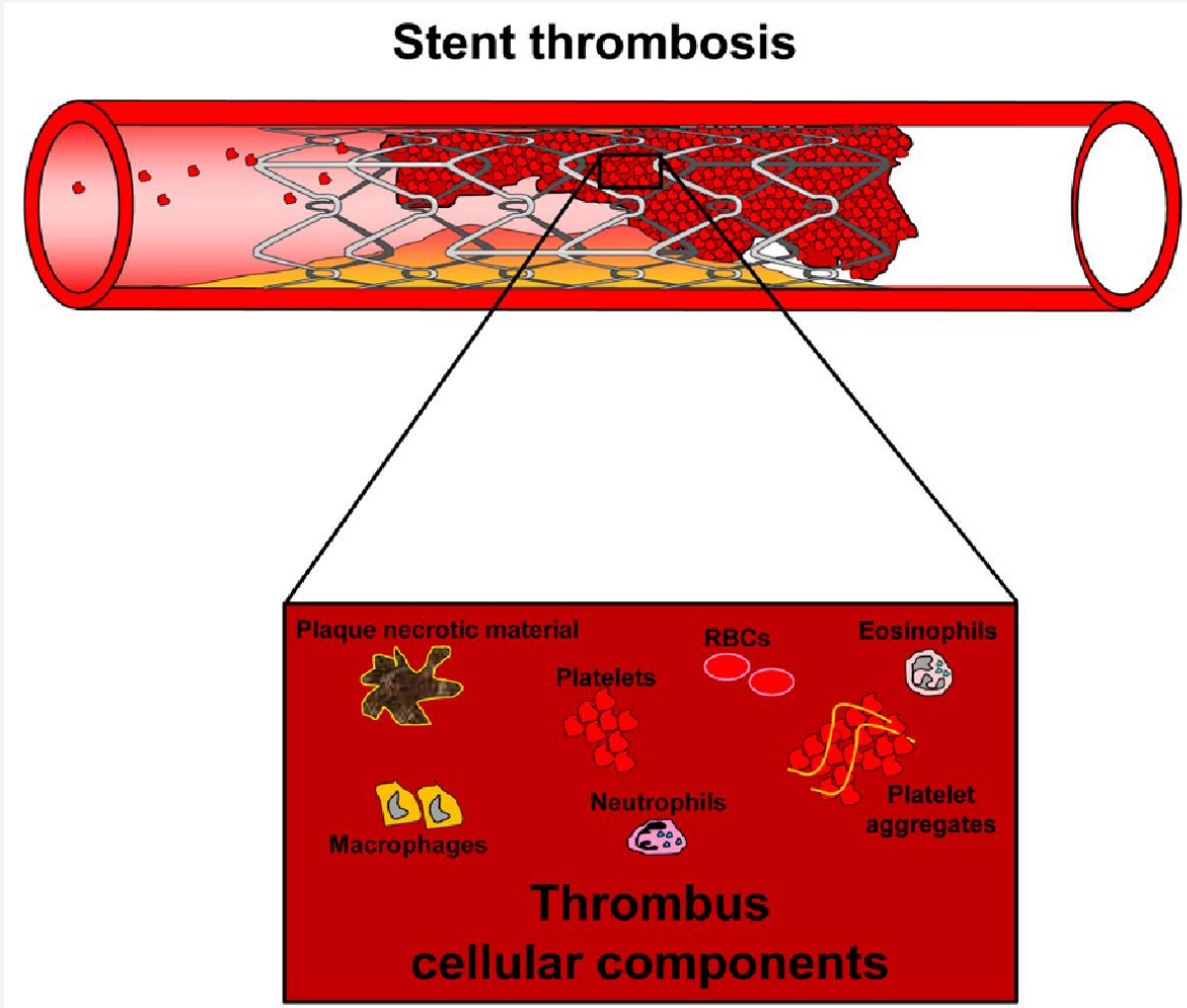


Figure 1

Observational evidence for the use of nirmatrelvir/ritonavir in immunocompromised people

Numerous observational studies support the effectiveness of nirmatrelvir/ritonavir in **immunocompromised people**, including:

- Patients with haematological malignancies[1–5]
- People with SARD[6–8]
- SOTR[8–11]
- Patients with solid tumours*[,8,13]
- Patients with virologically unsuppressed HIV[12,13]

Findings are supported by subgroup analyses of studies with broader populations[8,12–15]

*Evidence for this is limited.

HIV, human immunodeficiency virus; SARD, systemic autoimmune rheumatic diseases; SOTR, solid organ transplant recipients.

1. Salmanton-García J, et al. *eClinicalMedicine* 2023;58:101939; 2. Mikulska M, et al. *Br J Haematol* 2023;201(4):628–39; 3. Tadmor T, et al. *Blood* 2023;141(18):2239–44; 4. Bruno G, et al. *Recenti Prog Med* 2023;114:815–17; 5. Ford ES, et al. *Clin Infect Dis* 2023;76(5):926–9; 6. Gerolymatou N, et al. *J Rheumatol* 2022;jrheum.221014; 7. Qian G, et al. *Lancet Rheumatol* 2023;5:e139–e150; 8. Sun F, et al. *Lancet Infect Dis* 2022;22:1279; 9. Hedvat J, et al. *Am J Transplant* 2022;22:2682–8; 10. Salerno DM, et al. *Am J Transplant* 2022;22(8):2083–8; 11. Radcliffe C, et al. *Am J Transplant* 2022;22(10):2458–63; 12. Najjar-Debbiny R, et al. *Clin Infect Dis* 2023;76:e342–e349; 13. Al-Obaidi MM, et al. *Am J Med* 2023;136(6):577–584; 14. Martin-Blondel G, et al. *Clin Microbiol Infect* 2023;29:543.e5-543; 15. Aggarwal NR, et al. *Lancet Infect Dis* 2023;23(6):696–705.

Severe COVID-19 outcomes from observational studies of nirmatrelvir/ritonavir treatment in people with SARD

- The effectiveness of nirmatrelvir/ritonavir has also been demonstrated in real-world studies in patients with SARD
  - In patients with SARD and SARS-CoV-2 who were treated with either nirmatrelvir/ritonavir (65%) or molnupiravir (35%), majority of patients (n=72, 97.3%) recovered at home without COVID-19 related complications. Therapy had acceptable safety profile[1]
  - Administration of outpatient SARS-CoV-2 treatment, including nirmatrelvir/ritonavir, in patients with SARD and SARS-CoV-2 has been associated with lower odds of severe COVID-19 outcomes compared with no treatment[2]

Nirmatrelvir/ritonavir is an effective treatment option for people that are immunocompromised due to SARD[1,2]

SARD, systemic autoimmune rheumatic diseases.

1. Gerolymatou N, et al. *J Rheumatol* 2022;jrheum.221014; 2. Qian G, et al. *Lancet Rheumatol* 2023;5:e139–e150.

Summary of outcomes from studies of nirmatrelvir/ritonavir treatment: SOTR

Study	Hedvat et al, 2022[1]	Salerno et al, 2022[2]	Radcliffe et al, 2022[3]
Population	Outpatient SOTR with mild/moderate COVID-19	Adult SOTR on a CNI or mammalian target of rapamycin inhibitor who were prescribed nirmatrelvir/ritonavir	Adult outpatient SOTR diagnosed with COVID-19
N	154	25	122
Interventions	Nirmatrelvir/ritonavir (n=28) versus sotrovimab (n=51) versus no treatment (n=75)	Nirmatrelvir/ritonavir (n=25)	Nirmatrelvir/ritonavir (n=1), molunipiravir (n=49), sotrovimab (n=24) or no treatment (n=48)
Severe COVID-19 outcomes	**Hospitalisation or death from any cause through day 30** Nirmatrelvir/ritonavir: 14.3%; sotrovimab: 11.8%; no treatment: 33.3% Nirmatrelvir/ritonavir versus no treatment: P=0.083	**Hospital admission or mortality within 30 days of nirmatrelvir/ritonavir completion** 4 hospitalisations; 0 deaths	**Hospital admission ≤30 days after initiating therapy** Received treatment: 10 (14%); no treatment: 13 (27%); P=0.06 **Death ≤30 days after initiating therapy** Received treatment: 0; no treatment: 3 (6%); P=0.002
Viral elimination outcomes	NR	NR	NR

NR, not reported; SOTR, solid-organ transplant recipients.

1. Hedvat J, et al. *Am J Transplant* 2022;22:2682–8; 2. Salerno DM, et al. *Am J Transplant* 2022;22(8):2083–8; 3. Radcliffe C, et al. *Am J Transplant* 2022;22(10):2458–63.

Δεδομένα από τον πραγματικό κόσμο…

Summary of Nirmatrelvir/r RWE studies in Greece

Oral antiviral treatment in patients with systemic rheumatic disease at risk for development of severe COVID-19: a case series Fragoulis GE, et al. *Ann Rheum Dis* 2022;81:1477–9	• Three tertiary rheumatology centres • 15 February–30 April 2022	• Outpatients with systemic rheumatic disease and COVID-19 (N=31) • Nirmatrelvir/r (n=29) or molnupiravir (n=2) during the first 5 days after COVID-19 diagnosis • Mean age: 55.4 years; 94% fully vaccinated	**COVID-19 outcomes (cured, long COVID [>30 days], hospitalisation and death) and AEs from antivirals** • No patient required hospitalisation for COVID-19 after receiving antiviral therapy • Three patients reported mild AEs that could be also related to COVID-19 • In four cases, comedications had to be temporally discontinued due to potential interactions with Nirmatrelvir/r
Oral antiviral treatment for COVID-19 in patients with systemic autoimmune rheumatic diseases Gerolymatou N, et al. *J Rheumatol* 2022; doi: 10.3899/jrheum.221014 (Epub ahead of print)	• Two tertiary outpatient rheumatology clinics • February–August 2022	• Patients with systemic autoimmune rheumatic diseases (N=74) infected with SARS-CoV-2 • Treated with molnupiravir (n=26, 35.1%) or Nirmatrelvir/r (n=48, 64.9%) • Mean age: 50.8 years; 83.8% were vaccinated	**Safety and efficacy of molnupiravir and Nirmatrelvir/r in patients with systemic autoimmune rheumatic diseases** • AEs were reported by only four patients with Nirmatrelvir/r (metallic taste, GI upset, hypertension) • All but two patients (n=72, 97.3%) recovered at home without COVID-19 related complications • Two presumptive cases of COVID-19 rebound (1 in each treatment group) progressed to severe COVID-19 and were hospitalised • Both molnupiravir and Nirmatrelvir/r had favourable outcomes in this population
Use of Oral Antivirals Ritonavir-Nirmatrelvir and Molnupiravir in Patients with Multiple Myeloma Is Associated with Low Rates of Severe COVID-19: A Single-Center, Prospective Study Spiliopoulou Vassiliki, et al. *Viruses* 2023 Mar 8;15(3):704. doi: 10.3390/v15030704.	• Prospective single centre study February–October 2022	• Patients (N=169) with multiple myeloma infected with SARS-CoV-2 • Treated with Nirmatrelvir/r (n=138, 64.9%) or molnupiravir (n=30, 17.8%) • Mean age: 64.4 years; 96.4% were vaccinated	**COVID-19 outcomes and AEs from antivirals in patients with MM** • Patients with severe disease had lower neutralizing antibody levels before the COVID-19 infection compared to patients with mild disease (p = 0.04). • COVID-19 infection was resolved in all patients, except for three fatal cases • Five (3%) patients developed severe COVID-19 & required oxygen support • Antivirals were well tolerated and no major adverse events were noted

Summary of Nirmatrelvir/r RWE studies in Greece (continued)

The Antiviral Effect of Nirmatrelvir/ Ritonavir during COVID-19 Pandemic Real-World Data Petrakis V, et al. *Viruses*. 2023 Apr; 15(4): 976. doi: 10.3390/v15040976	• Routine care patient charts, Hospital of Alexandroupolis • March 2022- March 2023	• Non-hospitalised COVID-19 adults at high risk of progression to severe disease (N=400) • Nirmatrelvir/r recipients (n=200, study group) during the first 5 days after COVID-19 diagnosis or non-Nirmatrelvir/r recipients (n=200, control group) • Matched-pair design	**COVID-19 outcomes** • 3 patients from study group A (1.5%) and 111 (55.5%) from control group required hospitalization • The duration of hospitalization (3 days vs. 10 days, $p < 0.001$) & the total time needed for recovery (5 days vs. 9 days, $p < 0.001$) was shorter in the study group • Rebound of SARS-CoV-2 infection within 8–12 days after diagnosis was documented in 6.5% of patients in study group and 8% of patients in control group
Real-world Effectiveness of Molnupiravir and Nirmatrelvir/ Ritonavir as Treatments for COVID-19 in Patients at High Risk Paraskevis D, et al. *The Journal of Infectious Diseases*, 2023; jiad324, doi.org/10.1093/infdis/jiad324V	• COVID-19 national registry & SARS-CoV-2 surveillance data maintained by the National Public Health Organization in Greece • Matched retrospective cohort study • Nirmatrelvir/ritonavir: 26 March 2022 - 20 July 2022	• Outpatient COVID-19 non-hospitalized patients ≥ 65 y.o., at high risk of progression to severe disease, who received molnupiravir or Nirmatrelvir/r. Nirmatrelvir/ritonavir: • Patients: 13,462 patients, Control group: 12,728 • Data adjusted for age, previous SARS-CoV-2 infection, vaccination status, and time elapsed since the most recent vaccination	**Safety and efficacy of Nirmatrelvir/r in patients** • Nirmatrelvir/r resulted in significant reductions in the risk of hospitalization (OR 0.31, $p < 0.001$) and death (OR 0.28, $p < 0.00$). • Gastrointestinal effects, allergy, headache/dizziness, and other events were reported by 1.03%, 0.02%, 0.08%, and 0.20% of the population. • Complete adherence to the Nirmatrelvir/ritonavir regimen had a significantly lower risk of hospitalization (OR, 0.27; $P < .001$) or death (OR, 0.25 [$P = .01$]) • Nirmatrelvir/r recipients exhibited a lower risk of hospitalization & death when compared with those treated with molnupiravir; the differences observed were based largely on the lower incidence of death secondary to COVID-19 vs hospital admission.

Viruses. 2023 Apr 16;15(4):976. doi: 10.3390/v15040976.

The Antiviral Effect of Nirmatrelvir/Ritonavir during COVID-19 Pandemic Real-World Data

Vasilios Petrakis [1], Petros Rafailidis [1], Grigorios Trypsianis [2], Dimitrios Papazoglou [1], Periklis Panagopoulos [1]

Affiliations + expand

PMID: 37112956 PMCID: PMC10144059 DOI: 10.3390/v15040976

Baseline Characteristics

- Patients included in the study were at least 18 years old, had confirmed SARS-CoV-2 infection, experienced symptom onset no more than 5 days before drug administration and had at least one coexisting condition associated with a high risk of progression to severe COVID-19.

Group A (study group)	Group B (comparison group)
N=200	N=200
consisted of increased risk, non-hospitalized patients who received **nirmatrelvir/ritonavir** orally	consisted of non-hospitalized patients with SARS-CoV-2 infection during the same period of time/who did not receive oral antiviral agents due to unwillingness or drug interactions without available treatment modification for comorbidities or delayed clinical estimation after 5 days from symptoms onset. Patients of group B were treated based on the National Guidelines for hospitalized patients with COVID-19 pneumonia if hospitalization was needed

The dosing scheme was: 300 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days, or 150 mg nirmatrelvir and 100 mg ritonavir twice daily when the estimated glomerular filtration rate
was 30–59 mL/min per 1.73 m^2.

- Patients with anticipated hospitalization within 48 h, severe drug interactions with concomitant medications and/or those being treated with alternative antiviral agents **were excluded**.

Baseline Characteristics

- The median age (75.24 +/- 13.12 years in the study group and 76.91 +/- 14.02 years in the comparison group) and the proportion of males (59% vs. 60.5% respectively) were similar between the two groups

- A total of 6.5% of patients in group A and 10.5% in group B were unvaccinated against SARS-CoV-2

- The full vaccination scheme with two booster doses was completed in 10% of patients in group A and in 7% in group B, and 45% and 38% were vaccinated with one booster dose, respectively. Seven patients from group A (3.5%) and eight from group B (4%) received two vaccine doses within 6 months. More than 6 months after vaccination, 32.5% of group A and 38% of group B were reported to have received two doses.

- The percentage of individuals with previous SARS-CoV-2 infection was 8.5% in group A and 9% in group B.

Table 1. Demographic data, vaccination status, comorbidities and clinical characteristics of Group A (un-hospitalized patients treated with nirmatrelvir/ritonavir) and Group B (untreated patients with oral antivirals).

	Study Group Group A (n = 200)	Comparison Group Group B (n = 200)	*p* Value
Male gender, n (%)	118 (59.0)	121 (60.5)	0.654
Age	75.24 ± 13.12	76.91 ± 14.02	0.970
Vaccination status			
Single dose	5 (2.5)	5 (2.5)	0.547
2 doses (<6 months)	7 (3.5)	8 (4.0)	0.447
2 doses (>6 months)	65 (32.5)	76 (38.0)	0.867
1st booster dose	90 (45.0)	76 (38.0)	0.997
2nd booster dose	20 (10.0)	14 (7.0)	1.000
Unvaccinated	13 (6.5)	21 (10.5)	0.657
Previous SARS-CoV-2 infection	17 (8.5)	19 (9.5)	0.657
Comorbitidies			
BMI >30	59 (29.5)	61 (30.5)	0.758
Hypertension	129 (64.5)	137 (68.5)	0.987
Diabetes mellitus	74 (37)	79 (39.5)	0.765
Heart Failure	66 (33)	67 (33.5)	0.831
Atrial Fibrilation	29 (14.5)	32 (16.0)	0.867
Ischemic heart disease	31 (15.5)	33 (16.5)	0.826
Neoplastic disease or hematologic malignancy	44 (22)	42 (21.0)	0.631
Respiratory problems	18 (9)	16 (8.0)	0.727
Immunosuppresion	71 (35.5)	69 (34.5)	0.413

Petrakis V, Rafailidis P, Trypsianis G, Papazoglou D, Panagopoulos P. The Antiviral Effect of Nirmatrelvir/Ritonavir during COVID-19 Pandemic Real-World Data. Viruses. 2023 Apr 16;15(4):976.

Baseline Characteristics

The most frequent comorbidities for group A and B were:
hypertension (64.5% vs. 68.5%),
obesity (29.5% vs. 30.5%),
diabetes mellitus (37% vs. 39.5%),
heart failure (33% vs. 33.5%),
atrial fibrillation (14.5% vs. 16%),
malignancies (22% vs. 21%),
chronic respiratory disease (8% vs. 9%) and
immunosuppression (35.5% vs. 34.5%).

More than two comorbidities (multicomorbidities) were present in 68% of patients in group A and in 72% in group B with four coexisting comorbidities in 45% and 56%, respectively.

Table 1. Demographic data, vaccination status, comorbidities and clinical characteristics of Group A (un-hospitalized patients treated with nirmatrelvir/ritonavir) and Group B (untreated patients with oral antivirals).

	Study Group Group A (n = 200)	Comparison Group Group B (n = 200)	*p* Value
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Previous SARS-CoV-2 infection	17 (8.5)	19 (9.5)	0.657
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Petrakis V, Rafailidis P, Trypsianis G, Papazoglou D, Panagopoulos P. The Antiviral Effect of Nirmatrelvir/Ritonavir during COVID-19 Pandemic Real-World Data. Viruses. 2023 Apr 16;15(4):976.

Outcome: hospital admission or death within 30 days after a positive SARS-CoV-2 test

Table 1. Demographic data, vaccination status, comorbidities and clinical characteristics of Group A (un-hospitalized patients treated with nirmatrelvir/ritonavir) and Group B (untreated patients with oral antivirals).

	Study Group Group A (n = 200)	Comparison Group Group B (n = 200)	*p* Value
Days of symptoms onset	2 (1–4)	7 (4–13)	<0.001
Hospitalization	3 (1.5)	111 (55.5)	<0.001
Days of hospitalization	3 (2–5)	10 (5–42)	<0.001
Respiratory Failure	0 (0.0)	73 (36.5)	<0.001
Intubation	0 (0.0)	6 (3.0)	0.034
Death	0 (0.0)	9 (4.5)	0.052
Time for recovery (days)	5 (3–11)	9 (5–18)	**<0.001**
Rebound Infection			
Yes	13 (6.5)	16 (8.0)	**0.004**

- The number of days from symptom onset until treatment initiation was significantly lower in group A (2 days vs. 7 days in group B, $p < 0.001$).
- Three patients from group A required hospitalization (1.5%).
- None of the patients were intubated or died.
- In group B, one hundred eleven (55.5%) patients were hospitalized, seventy-three (36.5%) had respiratory failure, six (3.0%) were intubated and nine (4.5%) died.
- The duration of hospitalization (3 days vs. 10 days in group B, $p < 0.001$) and the total time needed for recovery (5 days vs. 9 days, $p < 0.001$) was shorter in the study group.
- Rebound of SARS-CoV-2 infection (within 8–12 days after diagnosis) was documented in 6.5% of group A and 8% of group B.

Petrakis V, Rafailidis P, Trypsianis G, Papazoglou D, Panagopoulos P. The Antiviral Effect of Nirmatrelvir/Ritonavir during COVID-19 Pandemic Real-World Data. Viruses. 2023 Apr 16;15(4):976.

Outcome: Multivariable logistic regression models for all patients (group A and B, n = 400)

- Treatment with **nirmatrelvir/ritonavir** and a **complete vaccination** scheme against SARS-CoV-2, were **significantly associated with a lower probability of severe clinical progress of COVID-19**
- **Increased age, male gender and comorbidities increase the risk for severe clinical outcome**
- **Malignancies and immunosuppression** were the major comorbidities leading to hospitalization, intubation and/or death

Table 4. Logistic Regression Analysis for Severe COVID-19 (Hospitalization, Intubation, Death) (n = 400, Group A and B).

Variable	OR (95% CI)	*p* Value
Nirmatrelvir/Ritonavir		
• Treated patients	0.34 (0.29–0.55)	<0.001
• Untreated patients	2.54 (2.23-2.75)	<0.001
COVID-19 vaccination		
• Complete scheme (2 booster doses)	0.24 (0.19–0.29)	<0.001
• Incomplete scheme	1.03 (0.97–1.23)	<0.001
• Unvaccianted	2.45 (2.36–2.88)	<0.001
Age (HR for each 10-year increase)	2.78 (2.65–2.85)	<0.001
Male sex	2.04 (1.95–2.29)	<0.001
Comorbidities		
• Diabetes	2.07 (1.85–2.23)	<0.001
• Cardiovascular disease	1.98 (1.63–2.19)	<0.001
• Chronic lung disease	2.33 (1.75–2.81)	<0.001
• Chronic kidney disease	2.56 (1.86–2.83)	<0.001
• Malignancies (hematologic, solid)	3.65 (1.54–3.0)	<0.001
• Immunosuppression	5.73 (4.84–7.14)	<0.001

Petrakis V, Rafailidis P, Trypsianis G, Papazoglou D, Panagopoulos P. The Antiviral Effect of Nirmatrelvir/Ritonavir during COVID-19 Pandemic Real-World Data. Viruses. 2023 Apr 16;15(4):976.

Outcome: adverse events

Adverse events had occurred in 23 (11.5%) patients in the study group and were mild and self-limited.

The most common were:

- stomachache (2.5%),
- nausea (4.5%),
- vomiting (2.5%) and
- dysgeusia (3.5%).

No serious adverse events were documented and no disruption of treatment was needed. No lab abnormalities associated with nirmatrelvir/ ritonavir were documented. Only two patients received treatment for adverse events, but no hospitalization or additional clinical visit was needed.

Table 2. Treatment adherence and adverse events in patients treated with nirmatrelvir/ritonavir (Group A, n = 200).

	Treated Patients (n = 200) n, (%)	*p* Value
Treatment Adherence		0.421
Partial (missing pills)	5 (2.5)	-
Total (no missing pills)	195 (97.5)	-
Adverse Events		
Any adverse reaction	23 (11.5)	0.257
Adverse reaction above Grade 3	0	-
Treatment for adverse reaction	2 (1)	-
Discontinuation of treatment	0	-
Need for extended hospitalization	0	-
Additional clinical visit	0	-
• Stomachache	5 (2.5)	-
• Nausea	9 (4.5)	-
• Vomiting	5 (2.5)	-
• Dysgeusia	7 (3.5)	-

The Journal of Infectious Diseases

MAJOR ARTICLE

Real-world Effectiveness of Molnupiravir and Nirmatrelvir/Ritonavir as Treatments for COVID-19 in Patients at High Risk

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Background. Using a retrospective cohort study design, we aimed to evaluate the effectiveness of molnupiravir and nirmatrelvir/ritonavir in patients with SARS-CoV-2 who were highly vulnerable.

Methods. The impact of each drug was determined via comparisons with age-matched control groups of patients positive for SARS-CoV-2 who did not receive oral antiviral therapy.

Results. Administration of molnupiravir significantly reduced the risk of hospitalization (odds ratio [OR], 0.40; $P < .001$) and death (OR, 0.31; $P < .001$) among these patients based on data adjusted for age, previous SARS-CoV-2 infection, vaccination status, and time elapsed since the most recent vaccination. The reductions in risk were most profound among elderly patients (≥75 years old) and among those with high levels of drug adherence. Administration of nirmatrelvir/ritonavir also resulted in significant reductions in the risk of hospitalization (OR, 0.31; $P < .001$) and death (OR, 0.28; $P < .001$). Similar to molnupiravir, the impact of nirmatrelvir/ritonavir was more substantial among elderly patients and in those with high levels of drug adherence.

Conclusions. Collectively, these real-world findings suggest that although the risks of hospitalization and death due to COVID-19 have been reduced, antivirals can provide additional benefits to members of highly vulnerable patient populations.

Keywords. antivirals; COVID-19; molnupiravir; nirmatrelvir/ritonavir; SARS-CoV-2.

Study design

Evidence before this study: While administration of oral antivirals in patients diagnosed with COVID-19 and at high risk for disease progression has resulted in a significant reduction in the risk of hospitalization and death in real-world studies, critical questions remain, especially in the era of emergence of Omicron variants.

Study design: Retrospective, nationwide, cohort study of patients from COVID-19 national registry, crossed checked with SARS-CoV-2 surveillance database maintained by the National Public Health Organization (NPHO).

Objective: Evaluate the effectiveness of molnupiravir and nirmatrelvir/ritonavir in patients with SARS-CoV-2 at high risk of progression to severe disease.

Population/ Period: Patients ≥ 65 y.o., non-hospitalized, with confirmed SARS-CoV-2 infection, at high risk of progression to severe disease, who received molnupiravir or Nirmatrelvir/r, following the national guidelines for SARS-CoV-2 antiviral treatment. Nirmatrelvir/r study period: 26 March 2022 - 20 July 2022.

Methods: Matched retrospective cohort study- Outpatient oral antiviral users and controls were matched for age, calendar week of SARS-CoV-2 diagnosis, vaccination status and vaccination recency – Main outcomes: hospital admission, death, composite (hospitalization, including ICU admission/intubation, or death) due to COVID-19.

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Characteristics of the Study Population

Nirmatrelvir/Ritonavir recipients

Most patients received SARS-CoV-2 vaccination (90.2%)

- ❖ 68.1% and 16.6% had received one and two booster doses, respectively
- ❖ These proportions are similar to those reported among the non-recipients

- 5198 (37.5%) were ≥80 years old

	Nirmatrelvir/Ritonavir			
	Recipients		Nonrecipients	
	No.	%	No.	%
Vaccination status				
Unvaccinated	1312	9.5	2074	15.0
Single dose	53	0.4	37	0.3
Two doses: before index SARS-CoV-2 infection				
≤6 mo	458	3.3	657	4.7
>6 mo	294	2.1	412	3.0
First booster: before index SARS-CoV-2 infection				
≤6 mo	3533	25.5	3745	27.0
>6 mo	5906	42.6	5681	41.0
Second booster	2305	16.6	1255	9.1
Gender				
Male	6671	48.1	6462	46.6
Female	7190	51.9	7399	53.4
Age, y				
65–69	2775	20.0	2775	20.0
70–74	2958	21.3	2958	21.3
75–79	2930	21.1	2930	21.1
≥80	5198	37.5	5198	37.5

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Characteristics of the Study Population (2)

Nirmatrelvir/Ritonavir recipients

Comorbidities
- Cardiovascular disease: 69.8%
- Diabetes mellitus: 27.6%
- ***Immunosuppression: 8.72***

Adherence
- Complete: 74.7%

	Nirmatrelvir/Ritonavir Recipients	
	No.	**%**
Comorbidity		
Obesity: BMI ≥35 kg/m²	2250	16.23
Cardiovascular disease	9668	69.75
Moderate-severe immunosuppression	1209	8.72
Type 2 diabetes mellitus	3827	27.61
Chronic disease		
Liver	51	0.37
Kidney	598	4.31
Lung	1046	7.55
Treatment adherence: No. of pills missed		
None	2626	19.0
0–5	308	2.2
>5 to 12	141	1.0
>12 but not all	117	0.8
All	309	2.2
Unknown	10 360	74.7

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Primary Outcomes

	Nirmatrelvir/Ritonavir			
	Recipients		Nonrecipients	
	No.	%	No.	%
Outcome				
No hospitalization, clinical deterioration, or COVID-19-associated deaths	13 462	**97.12**	12 728	91.83
Hospitalization without ICU admission, clinical deterioration, or death	297	**2.14**	857	6.18
ICU admission or clinical deterioration	14	**0.10**	17	0.12
COVID-19–associated death	88	**0.63**	259	1.87
Hospitalization, ICU admission, clinical deterioration, or death	399	**2.88**	1133	8.17

Safety

- 3274 Nirmatrelvir/Ritonavir recipients (5.4%) reported ≥1 adverse drug reactions
- Gastrointestinal effects, allergy, headache/dizziness, and other events were reported by 1.03%, 0.02%, 0.08%, and 0.20% of the population.

Multivariable Logistic Regression Analysis to Determine the Effectiveness of Nirmatrelvir/Ritonavir Treatment

Hospitalization without ICU admission, clinical deterioration, or death:
OR: 0,31 (95% CI: 0.27-0.36, P< 0.001)

Multivariable Logistic Regression Analysis to Determine the Effectiveness of Nirmatrelvir/Ritonavir Treatment

Death with or without ICU admission or clinical deterioration
OR: 0,28 (95% CI: 0.22-0.36, P< 0.001)

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Discussion

Hospitalization increased with number of comorbidities;

Patients reporting two or more comorbidities exhibited a higher risk of hospitalization compared to those with no comorbidities

Patients treated with nirmatrelvir/ritonavir had a lower relative risk for developing symptomatic disease (OR = 0.58, p < 0.001) or death (OR = 0.69, p = 0.09) compared to those treated with molnupiravir, adjusted for age, previous SARS-CoV-2 infection, vaccination status, and comorbidities

Reduced risk of hospital admission or death from COVID-19 among nirmatrelvir/r recipients as compared with nonrecipients → independent of vaccination status, time elapsed since last vaccination & previous SARS-CoV-2 infection. The impact of nirmatrelvir/r was also most significant in older groups, most notably those ≥70 years old.

The effectiveness of oral antivirals was higher among those with full adherence

Patients reporting complete adherence to the nirmatrelvir/r had a significantly lower risk of hospitalization (OR, 0.27; P < .001) as compared with those reporting poor or incomplete adherence. Similar results were identified for the risk of death (OR, 0.25, P = .01)

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