kinarus

Clinical Update Covid-19

Webcasting event

August 24, 2022

Disclaimer

This presentation is not and under no circumstances to be construed as a solicitation, offer, or recommendation, to buy or sell securities issued by Kinarus Therapeutics Holding AG. Kinarus Therapeutics Holding AG makes no representation (either express or implied) that information and opinions expressed in this presentation are accurate, complete or up to date. Kinarus Therapeutics Holdings AG disclaims, without limitation, all liability for any loss or damage of any kind, including any direct, indirect or consequential damages, which might be incurred in connection with the information contained in this presentation.

This presentation expressly or implicitly contains certain forward-looking statements concerning Kinarus Therapeutics Holdings AG and its business. Certain of these forward-looking statements can be identified by the use of forward-looking terminology or by discussions of strategy, plans or intentions. Such statements involve certain known and unknown risks, uncertainties and other factors, which could cause the actual results, financial condition, performance or achievements of Kinarus Therapeutics Holdings AG to be materially different from any expected results, performance or achievements expressed or implied by such forward-looking statements. There can be no guarantee that any of the research and/or development projects described will succeed or that any news products or indications will be brought to market. Similarly, there can be no guarantee that Kinarus Therapeutics Holdings or any future product or indication will achieve any particular level of revenue. In particular, management's expectations could be affected by, among other things, uncertainties involved in the development of new pharmaceutical products, including unexpected preclinical and clinical trial results; unexpected regulatory actions or delays or government regulation generally; the Kinarus Therapeutics Holding AG's ability to obtain or maintain patent or other proprietary intellectual property protection; competition in general; government, industry, and general public pricing and other political pressures. Kinarus Therapeutics Holding AG is providing the information in this presentation as of the date of the publication and does not undertake any obligation to update any forward-looking statements contained herein as a result of new information, future events or otherwise.

Agenda

- Introduce Kinarus
- Recent evolution of COVID-19 pandemic
- What does this mean for developing drugs to treat COVID-19?
- Overview of *KINETIC* and *KINFAST* clinical trials
- Q&A

Experienced Leadership
We are drug developers

Dr. Alexander Bausch
Chief Executive Officer

Roche

strekin

Dr. Matthew Wright
Chief Operations Officer
Head of Research

Roche

strekin

Dr. Thierry Fumeaux
Chief Medical Officer

SWISS NATIONAL COVID-19 SCIENCE TASK FORCE

G H O L

Claudia Berger
Chief Clinical Dev. Officer

NOVARTIS

ImmunOs THERAPEUTICS

strekin

Subhasis Roy
Interim CFO

NOVAREMED

Sirius Healthcare Partners

Kepler Cheuvreux

HSBC

UBS

Dresdner Kleinwort

- Direct know-how and in-depth expertise with Kinarus' therapeutic targets and disease indications
- Established relationships with leading experts in clinical development

Business strategy
Aligned with competencies

- In-license drug-candidates with a history of safety and activity in human clinical testing
  - Right drug, wrong indication
  - Limitations we can fix through innovation
- Leverage new knowledge
  - Findings specific to disease indication(s)
  - Findings specific to the molecule's mechanism of action
- Kinarus develops to clinical proof of concept, creates value & exits
  - License out
  - Trade sale
- Proven business model with many examples in biotech space

Pamapimod – Exemplifies Kinarus Strategy

Clinical-stage p38 MAPK inhibitor in-licensed from Roche

The Asset

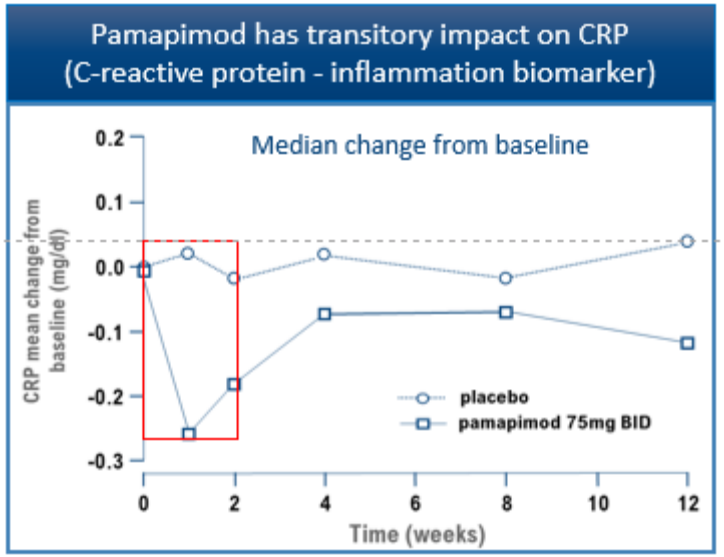
- p38 MAPK inhibitors were intensely studied by big pharma between 2005-2010 to treat inflammatory diseases (e.g. Rheumatoid Arthritis)
- Pamapimod was initially discovered and developed by Roche
  - ✓ Shown to be safe in preclinical and clinical testing
  - ✓ Engages with target and showed acute efficacy

The Problem

- Relatively short-lived efficacy (see graph)
  - Body has compensatory mechanisms that neutralize pamapimod
  - Clinical efficacy muted after 2 weeks
- Roche discontinued pamapimod development 2007

The Kinarus Solution

- Pamapimod + pioglitazone = KIN001
  - ✓ Pioglitazone neutralizes compensatory mechanisms
  - ✓ Prolonged pamapimod's efficacy without compromising safety
  - ✓ Novel intellectual property
- KIN001 is Phase 2-ready patent protected innovative drug that can capture the value promised by the original p38 MAPK inhibitors

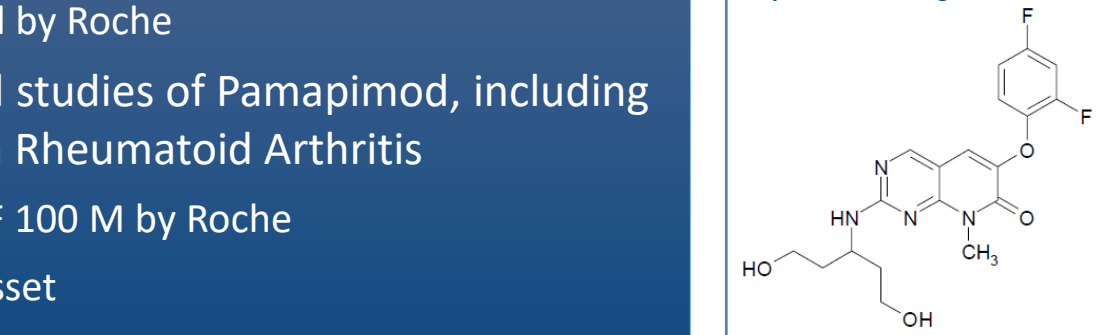


Diamond in the Rough

- Pamapimod is a high quality p38 MAPK inhibitor
  - Discovered and optimized by Roche
- Roche completed 10 clinical studies of Pamapimod, including two large Phase 2 studies in Rheumatoid Arthritis
  - Investment of approx. CHF 100 M by Roche
  - High quality big pharma asset
  - Excellent safety data package
- Kinarus obtained
  - Exclusive license and global rights
  - Phase 3 GMP supply of 500 kg API
  - Exclusive use of all clinical, CMC, preclinical data and regulatory documents
- Roche is eligible for
  - Low-to-mid single digit royalty
  - Low-to-mid double digit milestone payments
  - Right of first negotiation after first Phase 2 data

Pamapimod

Optimized through structure-based design



- **Blocks the catalytic site**
- **Highly potent and selective against p38 MAPKα**

p38 Isoform selectivity of pamapimod

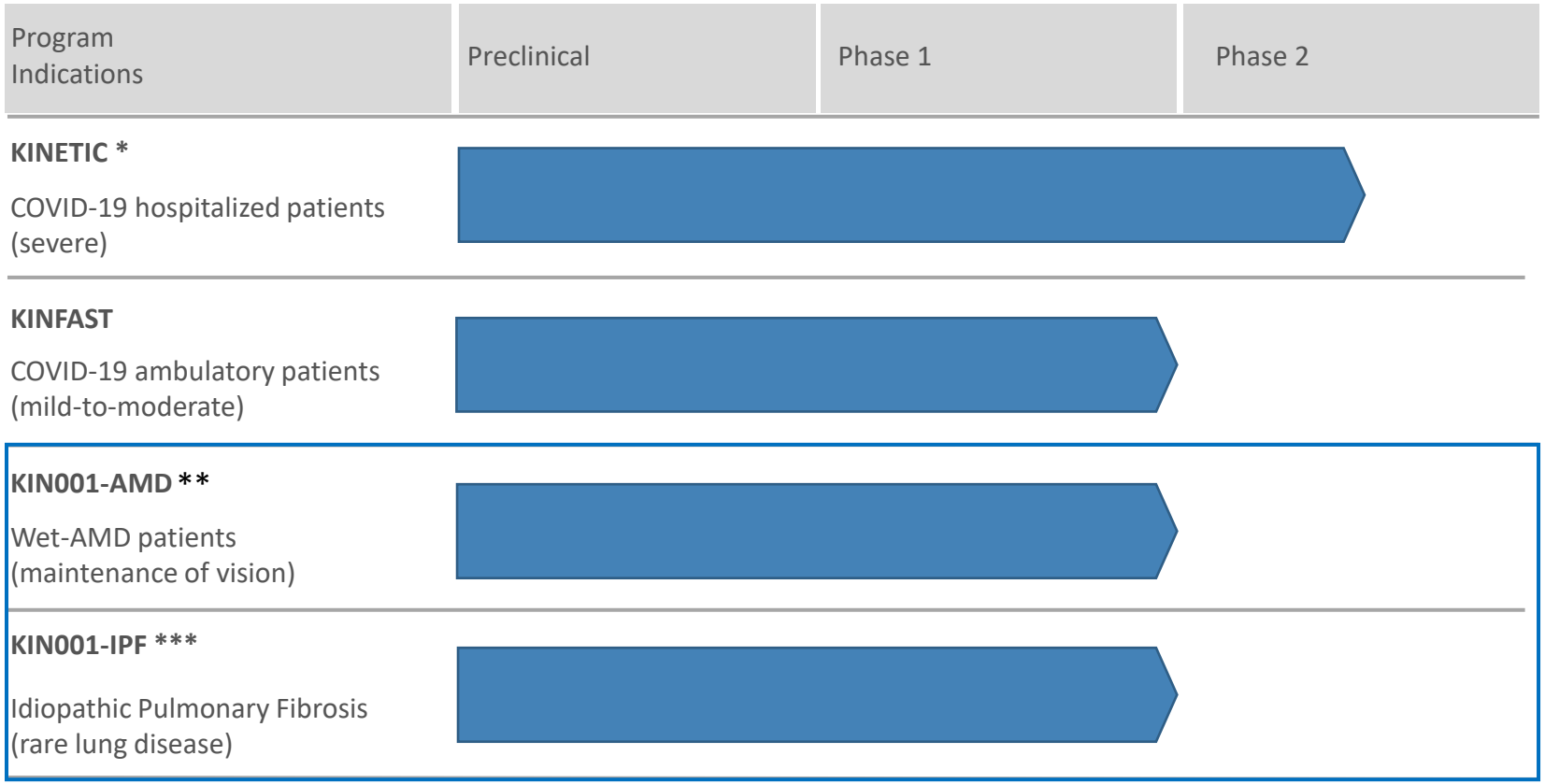
Preactivated recombinant p38 isoforms were assayed for activity by ^{33}P incorporation into myelin basic protein substrate in the presence of varying concentrations of pamapimod as described.

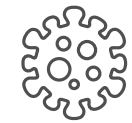
	IC_{50}*	IC_{75}*
	μM	
p38α	0.014 ± 0.002	0.098 ± 0.014
p38β	0.48 ± 0.04	3.32 ± 2.0
p38γ	>100	>100
p38δ	>100	>100

* IC_{50} and IC_{75} values are expressed ± S.E.M.

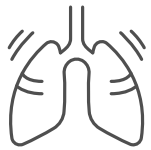
Hill RJ et al. JPET 2008 Pamapimod, a Novel p38 Mitogen-Activated Protein Kinase Inhibitor: Preclinical Analysis of Efficacy and Selectivity

KIN001 Has Broad Potential
Our focus: *wAMD & IPF*




COVID-19


Wet AMD


IPF

* Independent Drug Safety Monitoring Board (DSMB) recommended to continue trial after interim safety assessment
** Trial initiation contingent upon financing
*** Trial initiation contingent upon interim results of KINETIC Covid-19 trial

Roche's preclinical and clinical development enables direct start of Phase 2 in Kinarus indications

non-confidential

kinarus

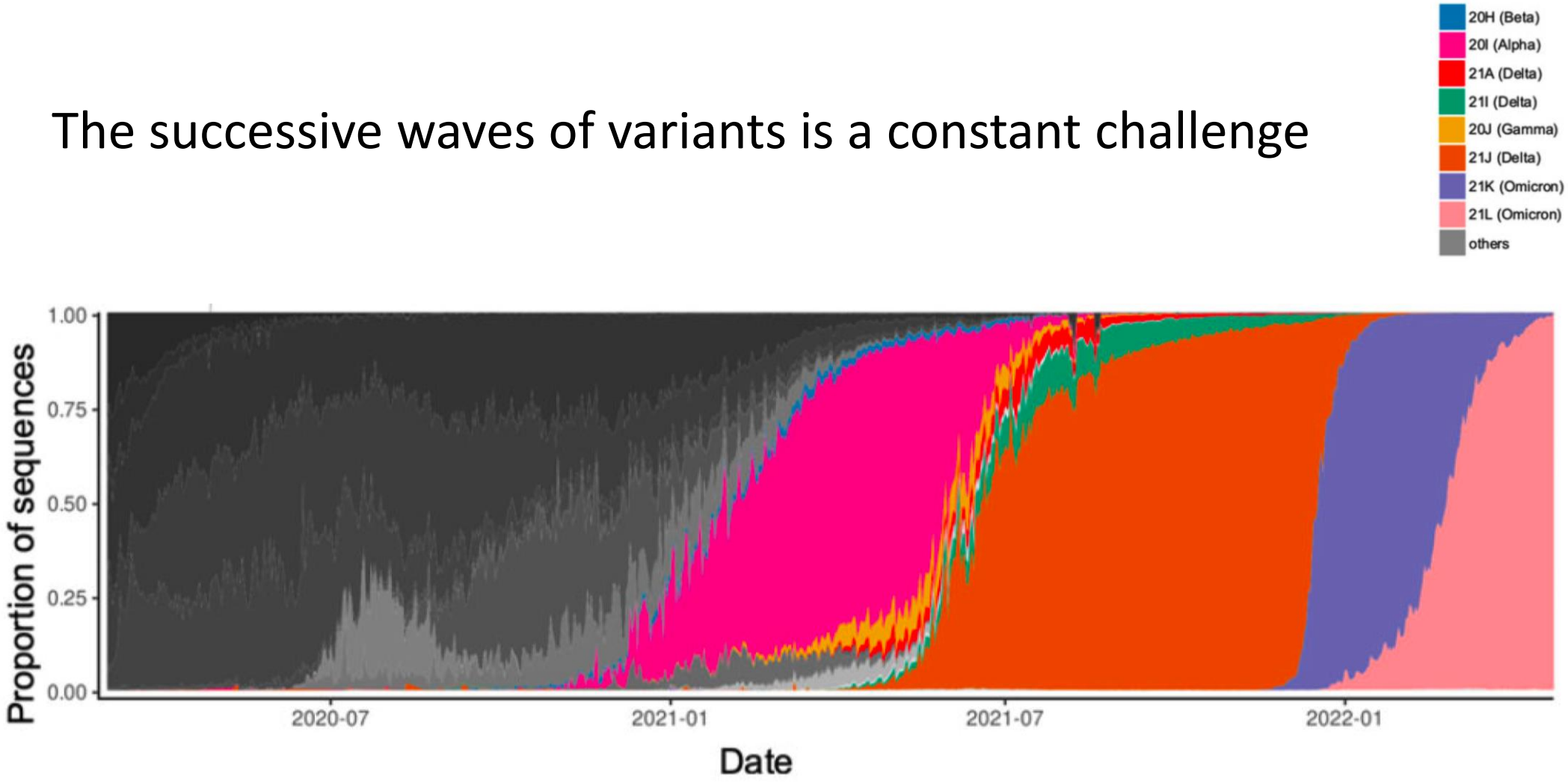
Clinical Update Covid-19

The evolution of the pandemic

Thierry Fumeaux, MD, EMBA, Kinarus CMO

The pandemic is not over yet

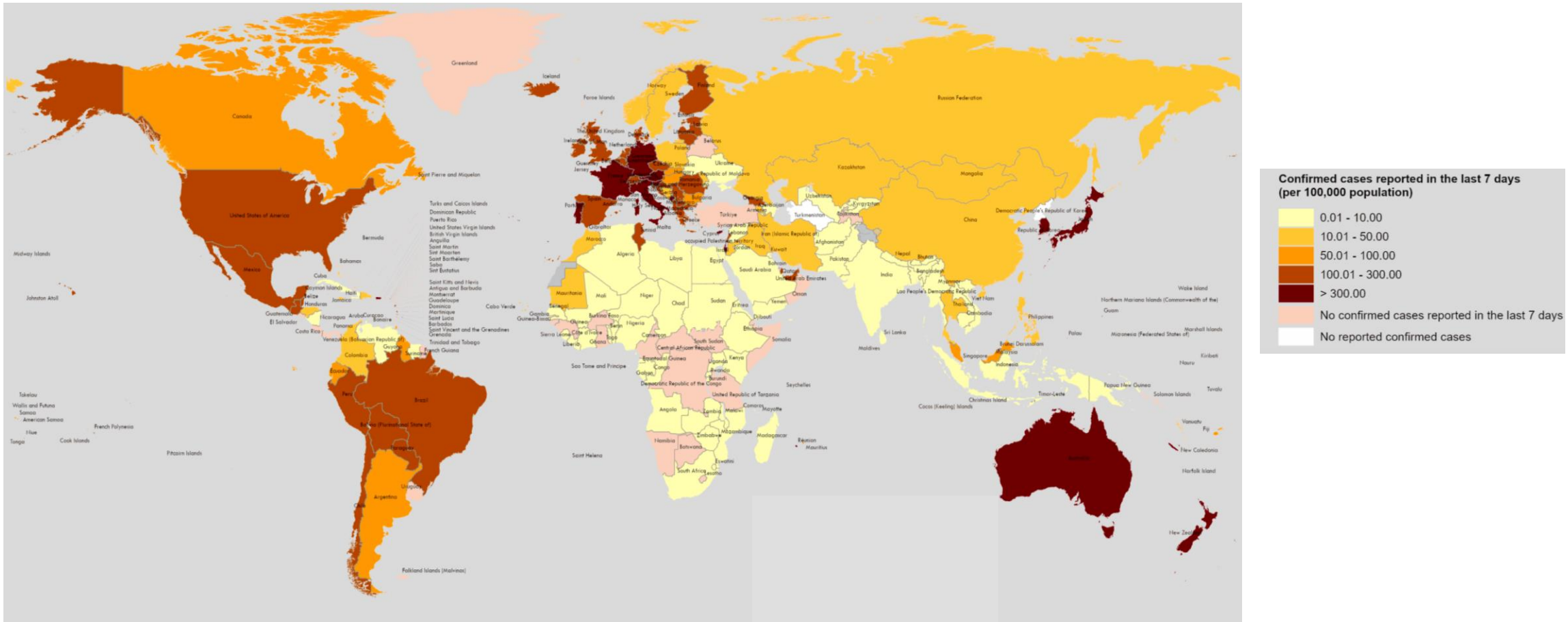
The successive waves of variants is a constant challenge



Balloux Oxf Open Immunol 2022

The pandemic is not over yet

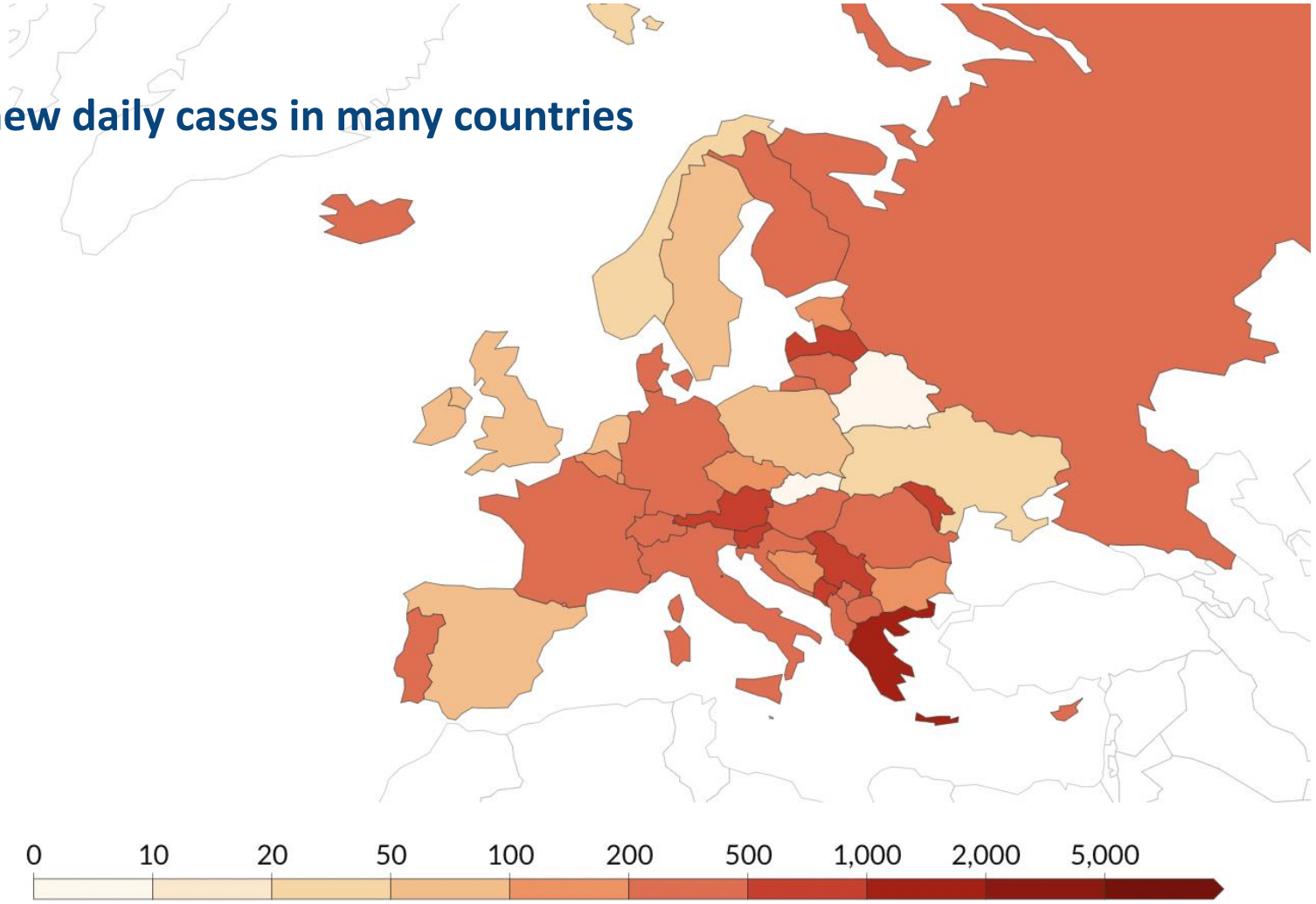
- The number of cases is still high (higher than in 2021)



WHO Weekly Epidemiological Report 101 July 2022

Daily new confirmed COVID-19 cases per million people

> 200 new daily cases in many countries



Our World in Data

ourworldindata.org

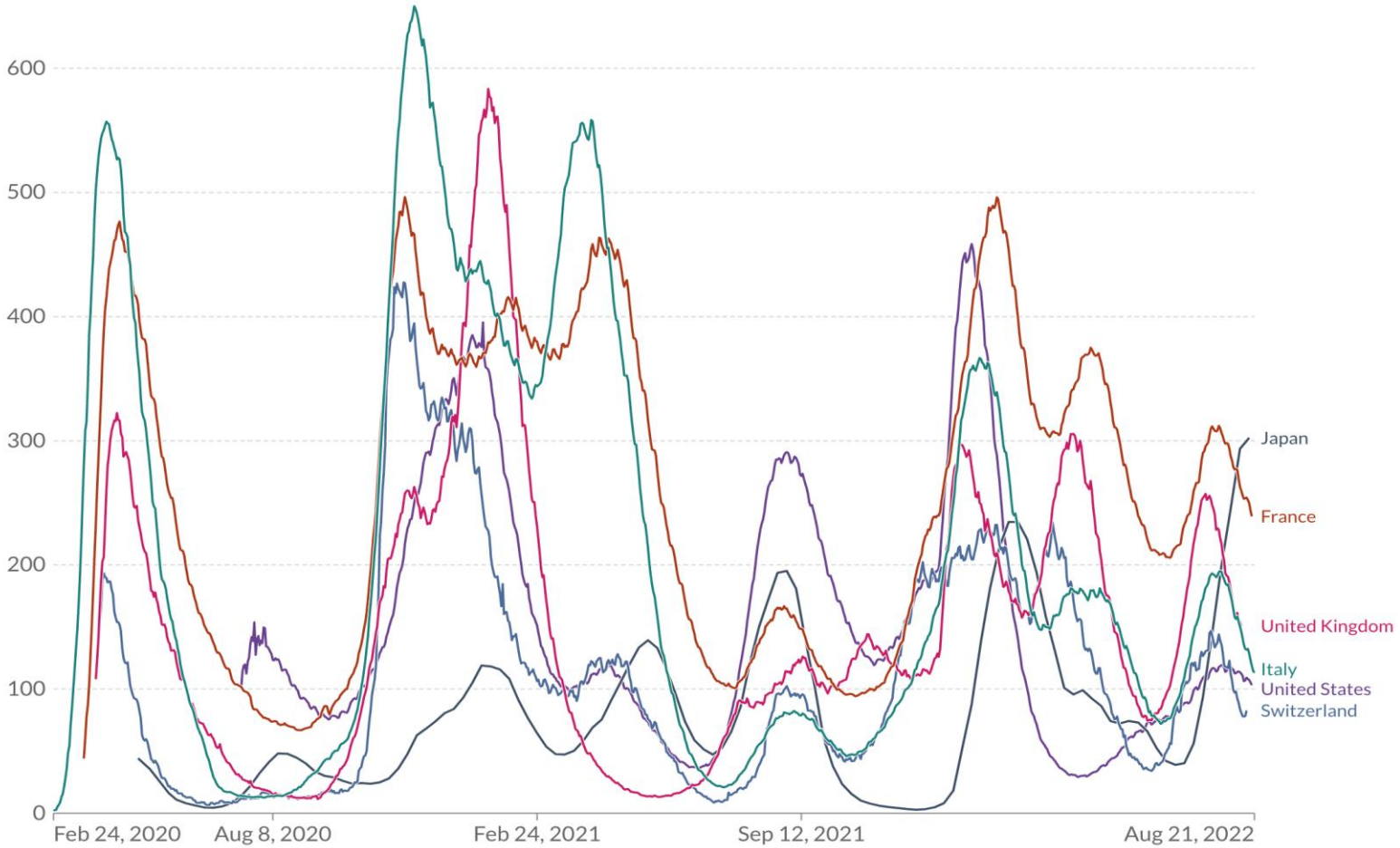
The pandemic is not over yet

- The number of cases is still high (higher than in 2021)

- Hospital and ICU admission rates are decreasing but still high

Our World in Data

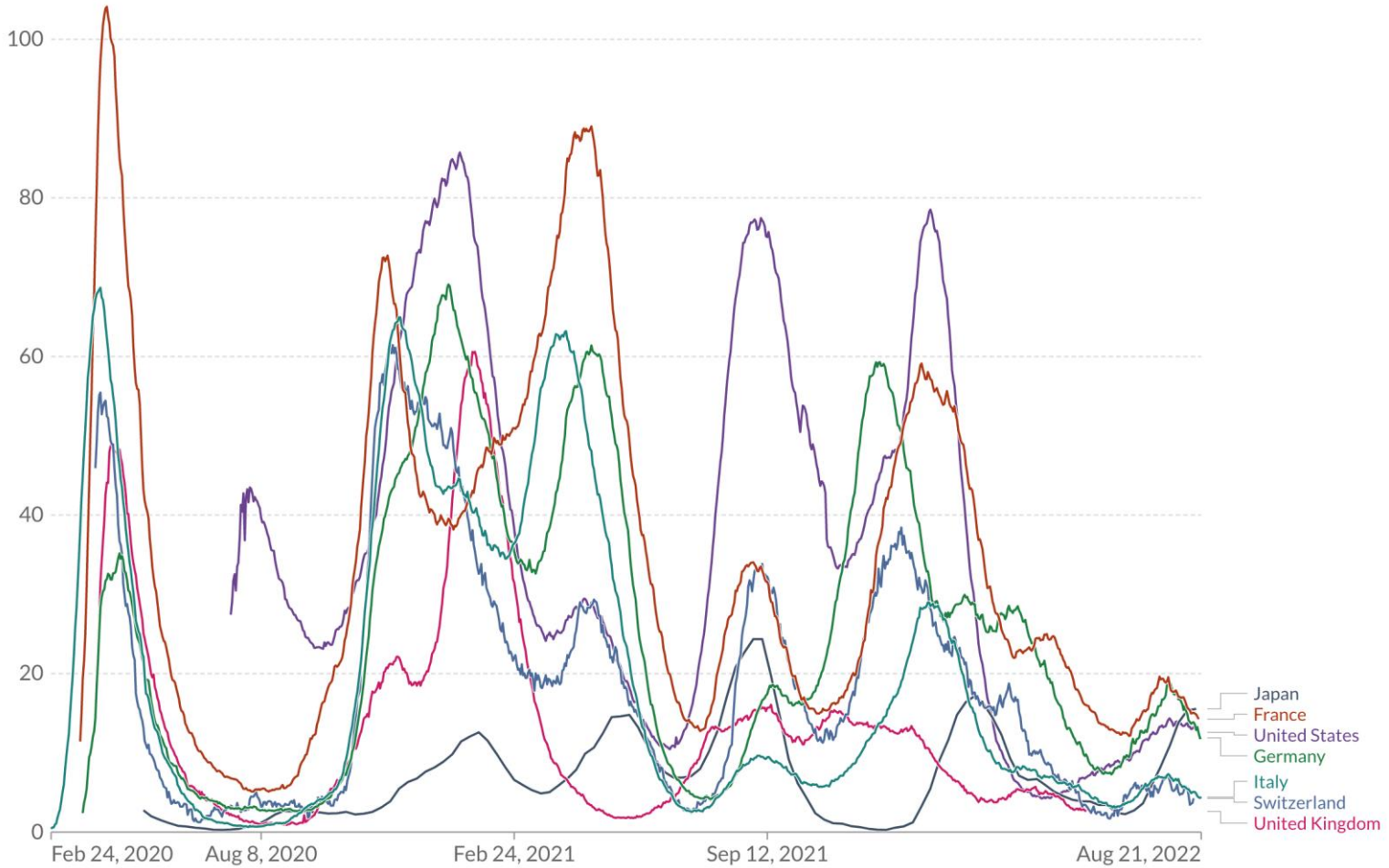
Number of COVID-19 patients in hospital per million



Aug 10, 2022	
Japan	293.61
France	262.96
United Kingdom	153.82
Italy	150.46
United States	113.54
Switzerland	83.99

ourworldindata.org

Number of COVID-19 patients in ICU per million



Aug 15, 2022

France	15.05
Germany	13.85
United States	13.26
Italy	5.08
Switzerland	4.26

ourworldindata.org

The pandemic is not over yet

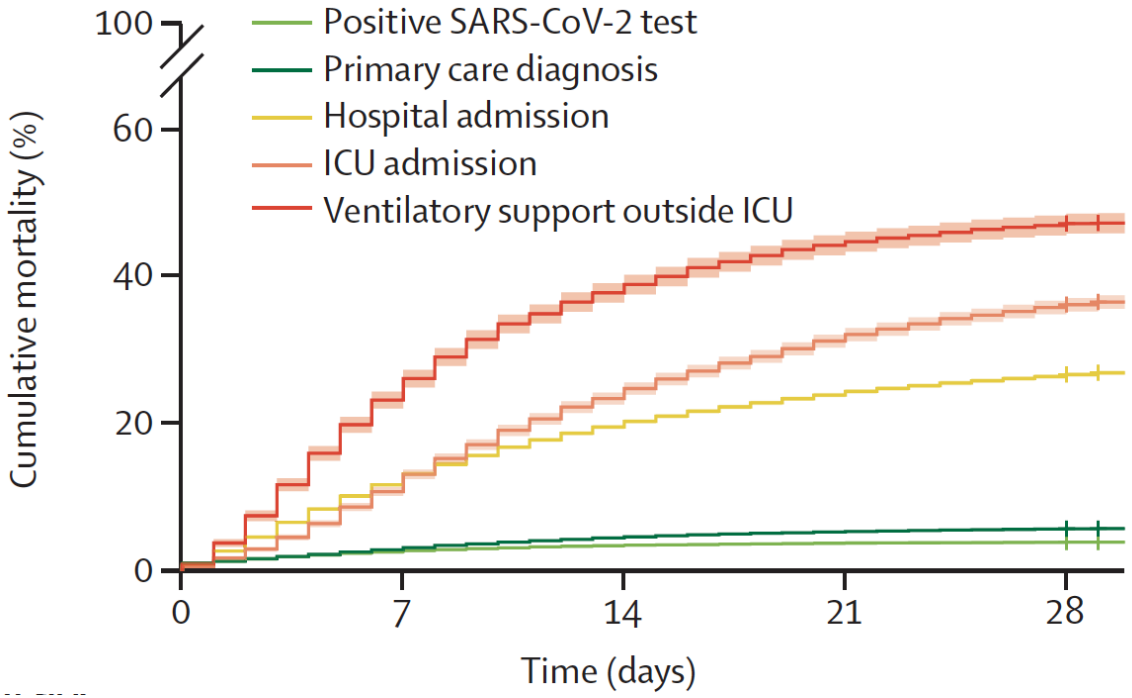
- The number of cases is still high (higher than in 2021)

- Hospital and ICU admission rates are decreasing but still high

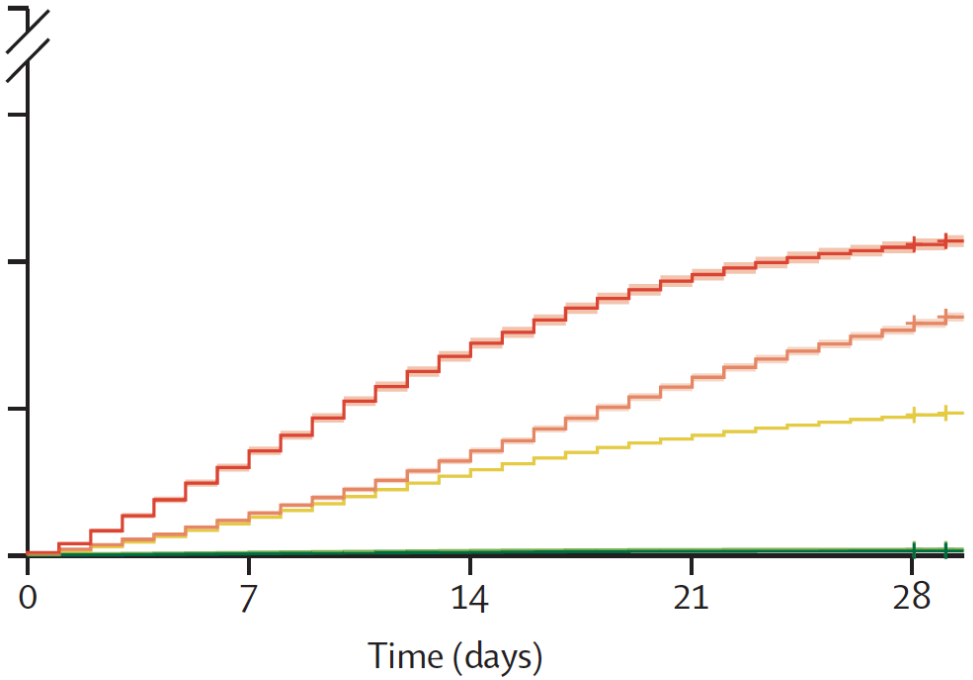
- The mortality is decreasing but still significant

Mortality rate: successive waves

1st wave

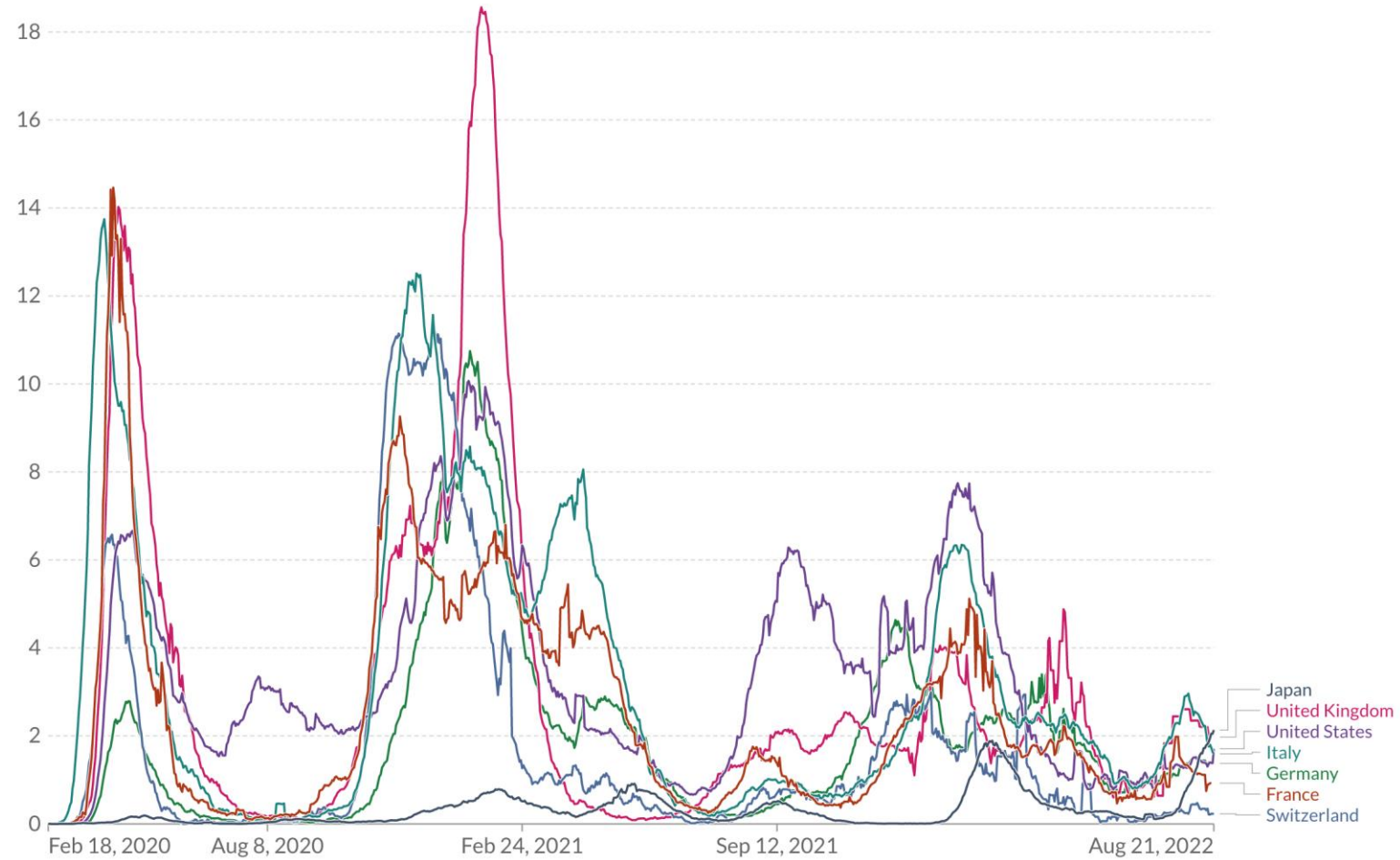


2nd wave



Thygesen Lancet Digit Health 2022

Daily new confirmed COVID-19 deaths per million people



Aug 12, 2022

Italy	2.29
United Kingdom	2.20
Germany	1.44
United States	1.40
Europe	1.21
France	1.12
Switzerland	0.34
India	0.04

The pandemic is not over yet

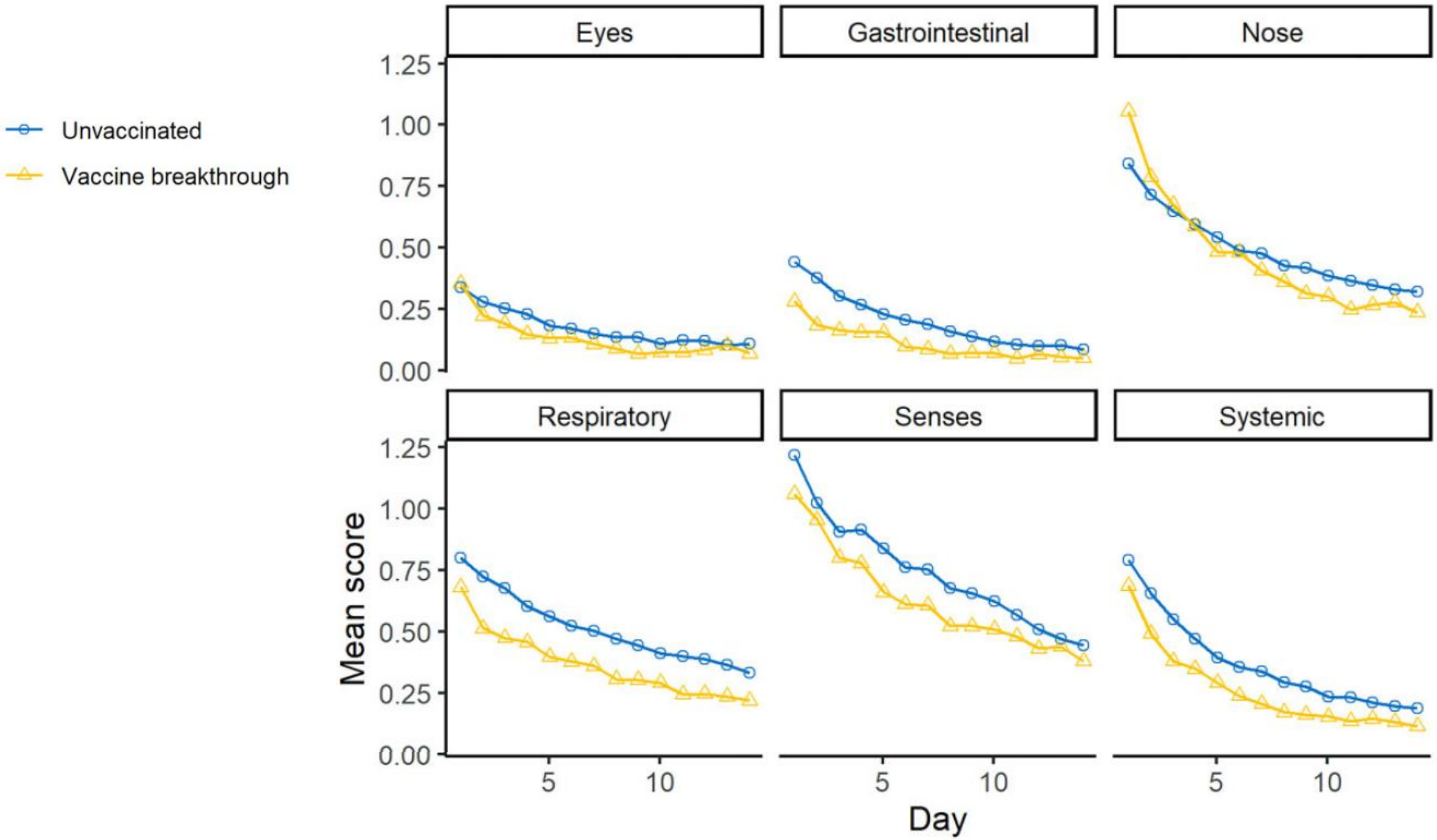
- The number of cases is still high (higher than in 2021)

- Hospital and ICU admission rates are decreasing but still high

- The mortality is decreasing but still significant

- Symptoms are evolving, but may last over 7 days

Covid-19 is associated with lasting symptoms



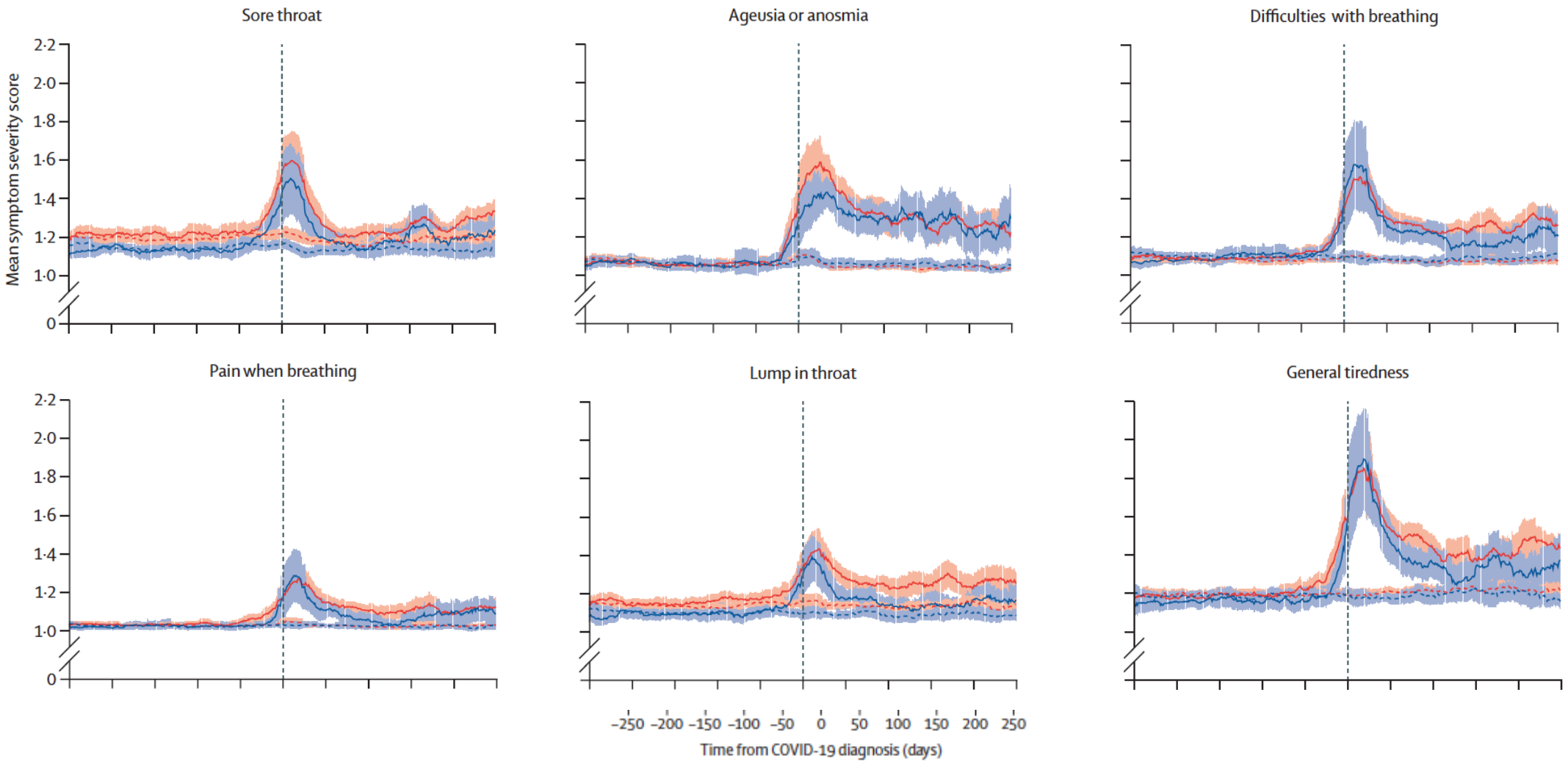
Delta

Richard Op Forum Infect Dis 2022

The pandemic is not over yet

- The number of cases is still high (higher than in 2021)
- Hospital and ICU admission rates are decreasing but still high
- The mortality is decreasing but still significant
- Symptoms are evolving, but may last over 7 days
- Post-acute sequelae of Covid (PASC – Long-Covid) are frequent

Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study



Ballering Lancet 2022

The pandemic is not over yet

- The number of cases is still high (higher than in 2021)
- Hospital and ICU admission rates are decreasing but still high
- The mortality is decreasing but still significant
- Symptoms are evolving, but may last over 7 days
- Post-acute sequelae of Covid (PASC – Long-Covid) are frequent

→ **less severe but significant symptoms and long-term consequences**

Covid-19: Patient trajectories

	All COVID-19 cases (n=7 244 925)
Hospital admission	460 737 (6·4%)
Ventilatory support	76 607 (1·1%)
ICU admission	48 847 (0·7%)
Non-invasive ventilation	69 090 (1·0%)
Invasive ventilation	25 928 (0·4%)
Extracorporeal membrane oxygenation	696 (0·0%)

EVOLUTION:

Less use of invasive ventilation and extracorporeal membrane oxygenation (ECMO)

More use of non-invasive ventilatory support, particularly outside of ICU

Adapted from Thygesen Lancet Digit Health 2022

Evolution of the Covid-19 pandemic

Conclusions:

- **Mortality** and **mechanical ventilation** remain relevant outcomes
- Their **declining incidence** results from vaccination, improved care, and emerging variants
- This has an impact on the **conduct of clinical studies**
- Larger **sample size are** needed to show differences

→ Other **relevant outcomes** have emerged:

- *Resources use (ICU days, advanced ventilatory support)*
- *Symptom burden*
- *Long-term sequelae*

kinarus

Clinical Update Covid-19

Therapeutic approach

Thierry Fumeaux, MD, EMBA, Kinarus CMO

Therapeutic approach: principle

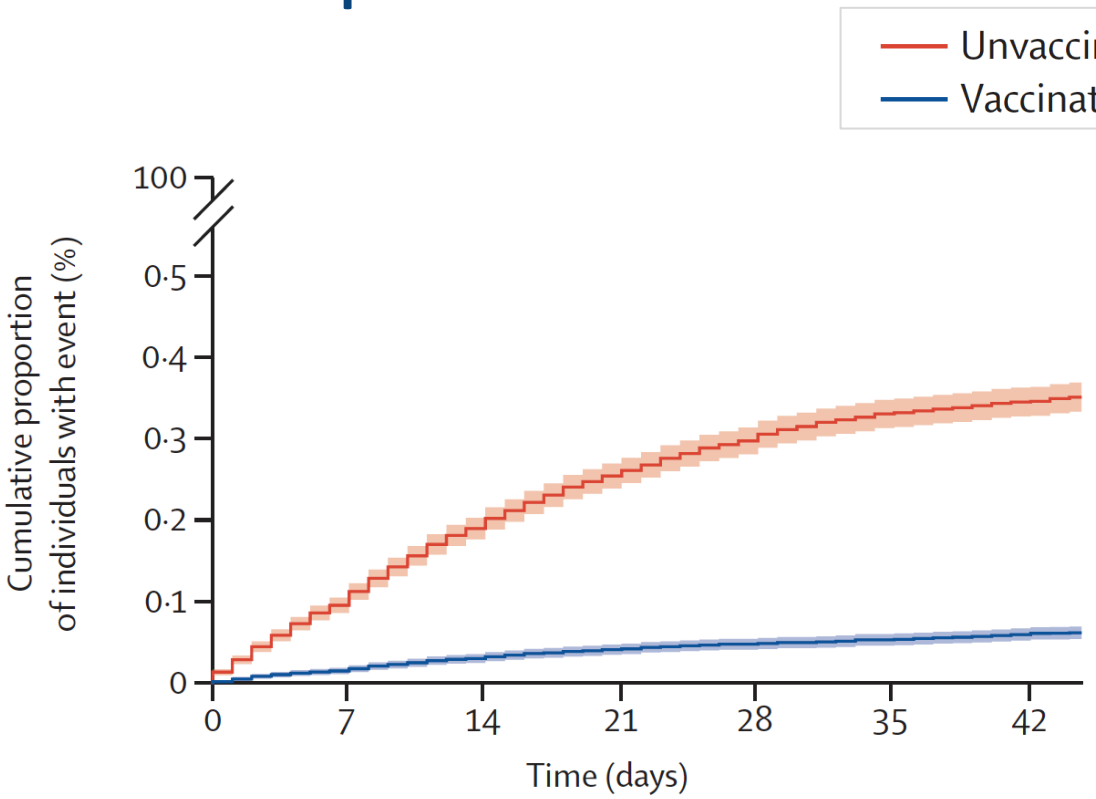
As such, whether SARS-CoV-2 will in time become a fifth 'common cold HCoV', or exert a more significant burden on human health comparable to, or even higher than, seasonal influenza will largely depend on the intrinsic virulence of future viral lineages. We have essentially no control over the global evolution of the virus and the trajectory in terms of virulence of future SARS-CoV-2 variants is unknown, if not unknowable. However, what we have considerable control over is the morbidity and mortality associated with endemic SARS-CoV-2 in the future.

Vaccines and therapies can decrease mortality and morbidity

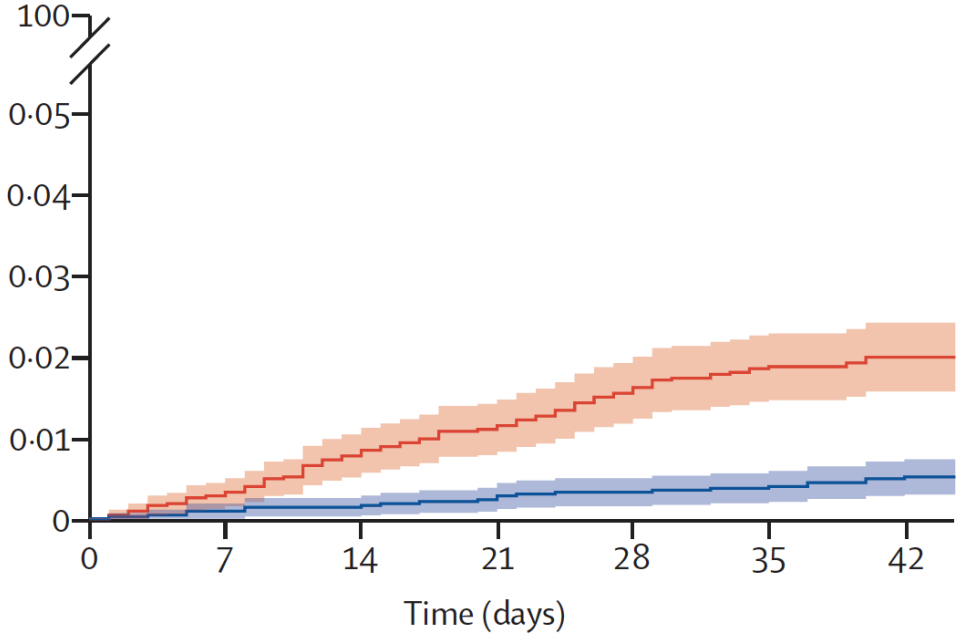
Balloux Oxf Open Immunol 2022

The effect of mass vaccination

Hospitalization rate



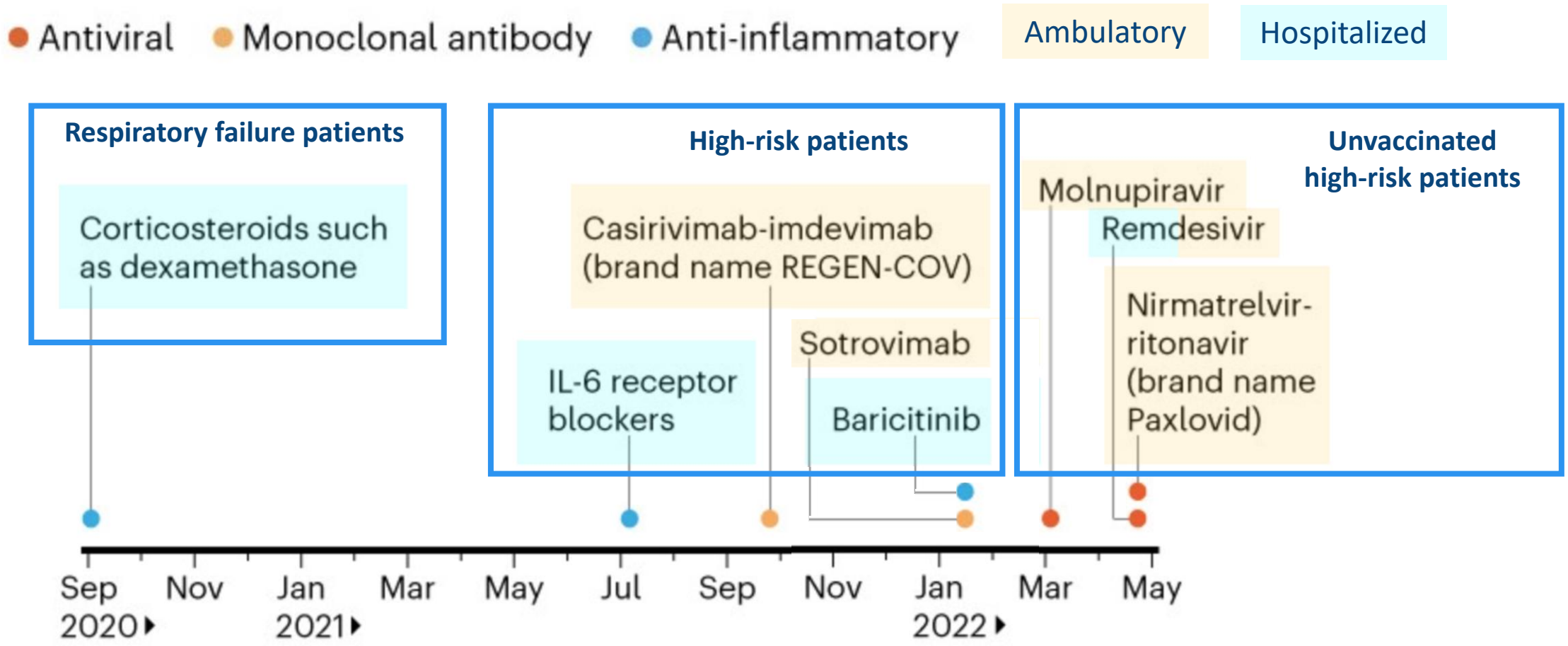
Ventilatory support rate



Vaccination has a profound impact on the severity of clinical evolution

Thygesen Lancet Digit Health 2022

WHO recommended therapies



BUT: *current therapies* are indicated only in selected patient populations

Adapted from Sidik Nature 2022

The example of recent antiviral drugs

Antiviral drug treatment for nonsevere COVID-19: a systematic review and network meta-analysis

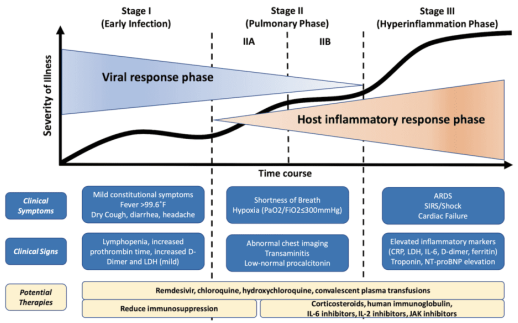
Interpretation: Molnupiravir and nirmatrelvir–ritonavir probably reduce risk of hospital admissions and death among patients with nonsevere COVID-19. Nirmatrelvir–ritonavir is probably more effective than molnupiravir for reducing risk of hospital admissions. Most trials were conducted with unvaccinated patients, before the emergence of the Omicron variant; the effectiveness of these drugs must thus be tested among vaccinated patients and against newer variants.

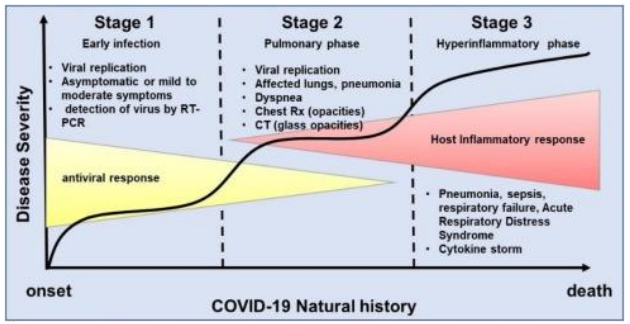
Pitre CMAJ 2022

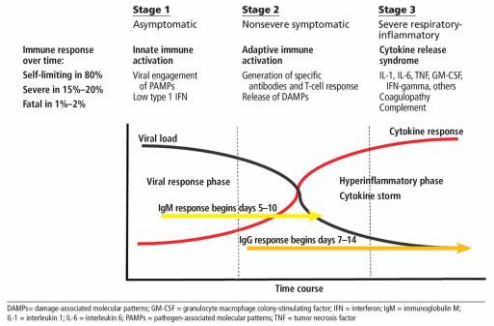
There is a ***clear need*** for more therapies to add to the currently available drugs, in order to cover all the spectrum of SARS-CoV-2-associated morbidity

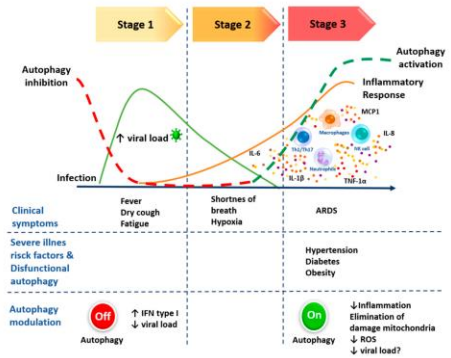
Covid-19 therapy: what have we learned?

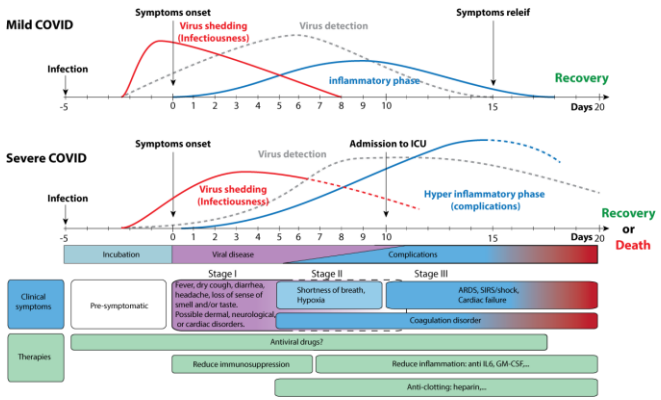
The **clinical stages** of Covid-19 are a continuum, and not clear-cut phases!

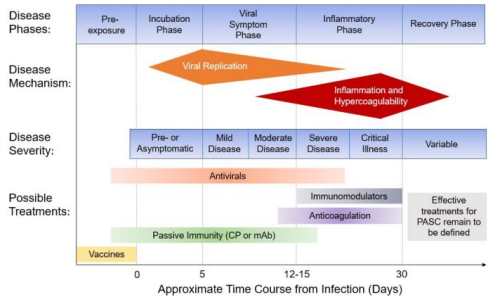






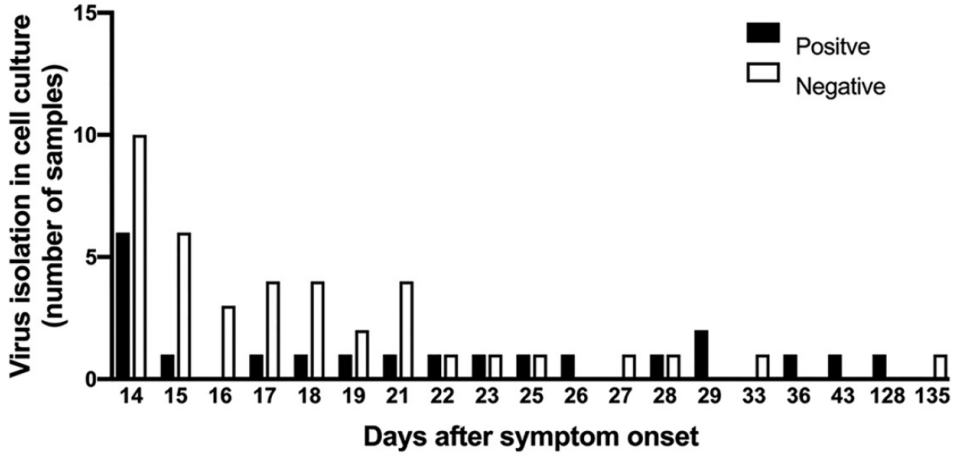


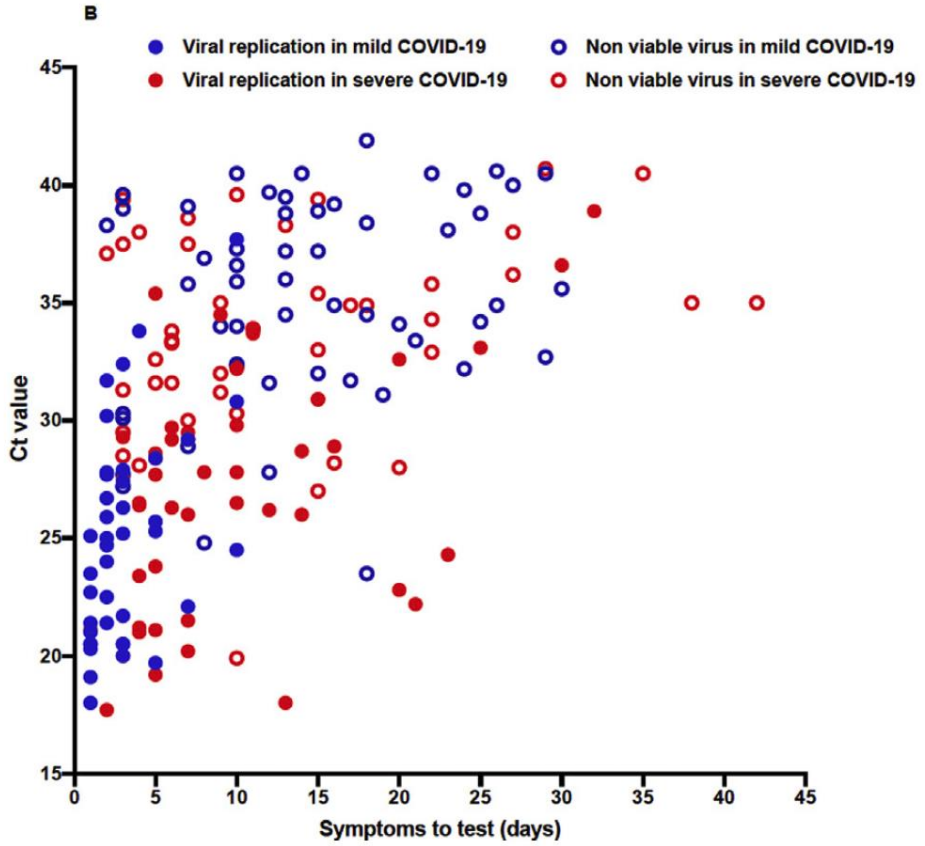




Covid-19 therapy: what have we learned?

Viral replication can be a lasting process, even in mild disease

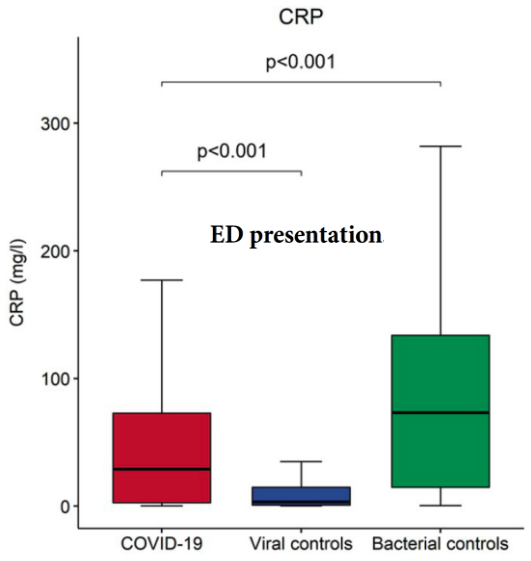


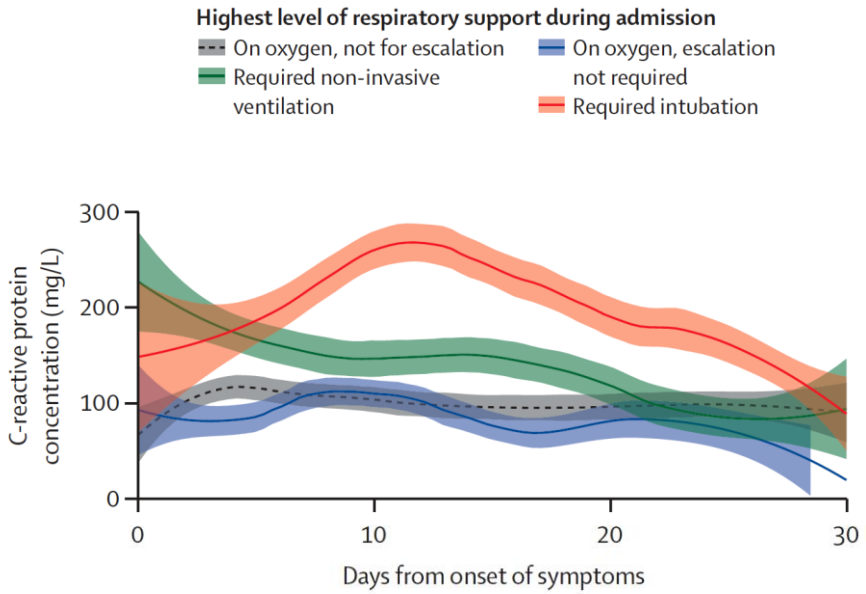


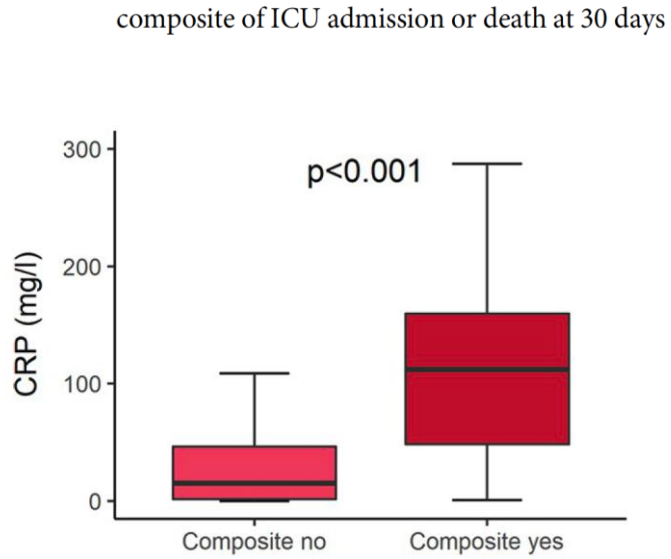
Leitao Microbiol Spectr 2021 - Folgueira, Clin Microbiol Infect 2021

Covid-19 therapy: what have we learned?

Inflammatory response starts early, lasts for long, and is related to prognosis







Early start

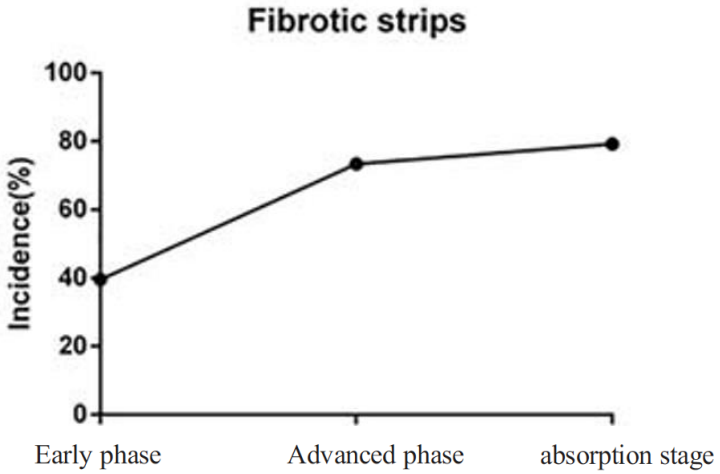
Long duration

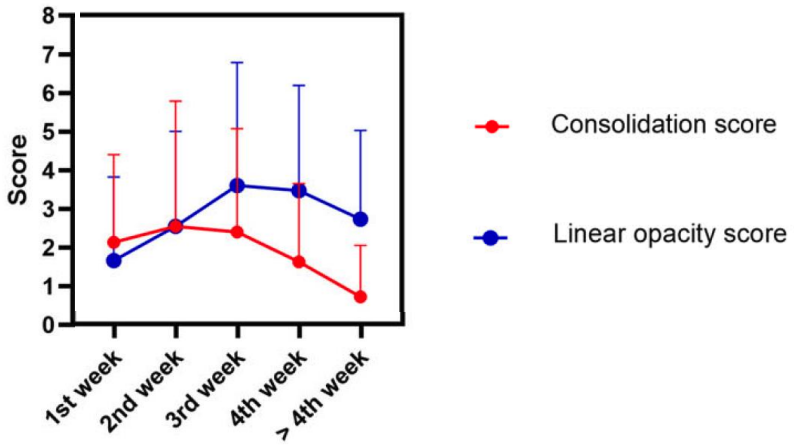
Predictive

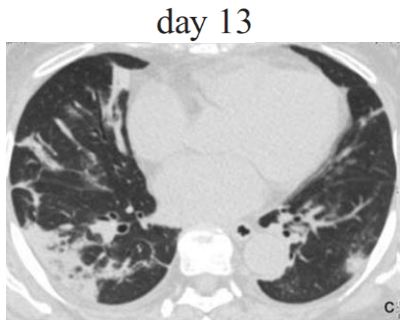
Lampart PLOS One 2022 – Manson Lancet Rheumatol 2020

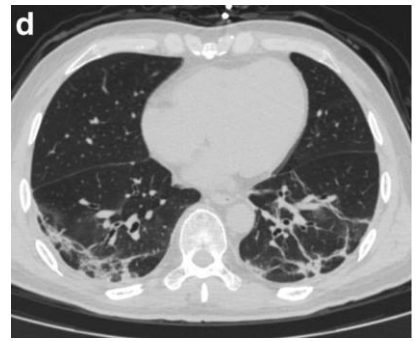
Covid-19 therapy: what have we learned?

Lung fibrosis can be detected early on CT-scan, also in mild cases









Zhou Eur Radiol 2020 – adapted from Liu Infect Dis Ther 2020

Covid-19 Clinical Studies KIN001

Update

Dr Thierry Fumeaux, MD, EMBA, Kinarus CMO

The challenge of Covid-19 clinical studies

NEWS | 13 June 2022

New COVID drugs face delays as trials grow more difficult

nature

Another type of hesitancy

Scientists also worry that even those people who do qualify for trials are more reluctant to take part than they would have been at the beginning of the pandemic.

Nature 2022

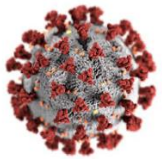
KIN001: Covid-19 studies

Kinarus is conducting two phase 2 randomised clinical trials with KIN001

- **KINETIC** (in hospitalized patients):
  - KIN001 vs placebo for 4 weeks
  - Primary endpoint: combined mortality and invasive ventilation rate at 8 weeks
  - Key secondary enpoint: number of days alive and free of advanced ventilatory support
- **KINFAST** (in outpatients):
  - KIN001 vs placebo for 2 weeks
  - Primary endpoint: patient reported time to recovery from symptoms
  - Key secondary endpoint: number of days alive and with resolution of symptoms

KIN001: rationale of use in Covid-19

With its **triple mode of action** KIN001 might be active at all clinical stages



Anti Viral

- KIN001 possesses anti-viral activity against Sars-CoV-2
- The combination is synergistic at concentrations lower than IC_{50} for individual drugs
- Pamapimod is active against emerging variants

Anti Inflammatory

- KIN001 represses multiple inflammatory cytokines in preclinical models, potentially addressing the Covid-19 “cytokine storm”
- Pamapimod dose selection derived from Roche Phase 2 RA studies based on CRP reduction

Anti Fibrotic

- KIN001 is predicted to possess several antifibrotic mechanisms
- KIN001 robustly reduces fibrosis in the bleomycin model of lung fibrosis in mice
- KIN001 may address the pulmonary and cardiovascular effects of Covid-19

KIN001: rationale of use in Covid-19

The **clinical stages** of Covid-19 are a continuum, and not clear-cut phases!

Large therapeutic window of KIN001

Viral replication can be a lasting process, even in mild disease

Antiviral effect of KIN001

Inflammatory response starts early, lasts for long, and is prognostic

Anti-inflammatory effect of KIN001

Lung fibrosis can be detected early on CT-scan, also in mild cases

Anti-fibrotic effect of KIN001

KINETIC trial: update

- First **safety review** after treatment of 40 patients was passed in April 2022
- KIN001 was **well tolerated** in 131 patients (blinded data)
- First **interim analysis** based on data from 131 patients will be available in

  September 2022

KINETIC trial: update

The **evolving incidence** of usual primary endpoints has to be considered

- The **decreased** indicence of the primary endpoint decrease the power and may require a higher sample size
- The **clinical relevance** of small statistical differences might become questionable
- A **pharmaco-economic approach**, focusing on resources use (advanced ventilatory support) is relevant
- The **key secondary outcome** was selected by Kinarus for this reason

KINETIC: the key secondary outcome

Oxygen-Free Days as an Outcome Measure in Clinical Trials of Therapies for COVID-19 and Other Causes of New-Onset Hypoxemia

Severity	OFDs (d)	Interpretation
More severe	−1	Patient died before the end of day 28.
↕	0	Patient survived through day 28 and received oxygen on days 1 and 28.
	1	Patient survived through day 28 and was free of oxygen use for 1 d in the first 28 d after randomization.
	10	Patient survived through day 28 and was free of oxygen use for 10 d in the first 28 d after randomization.
	25	Patient survived through day 28 and was free of oxygen use for 25 d in the first 28 d after randomization.
Less severe	28	Patient survived through day 28 and was free of oxygen use on every calendar day from days 1 to 28.

Moskowitz Chest 2022, in press

KINFAST: rationale to treat outpatients

nature

NEWS | 18 July 2022

Not just a luxury

The hunt for drugs for mild COVID: scientists seek to treat those at lower risk

People who are unlikely to develop severe COVID-19 have no widely approved medications to ease the illness.

A shift is afoot in the search for COVID-19 therapies: some researchers are turning their attention towards drugs that could be used to treat mild illness, even in people who are not at high risk of severe disease.

Such drugs could fill a yawning gap, says infectious-disease expert Oriol Mitjà at Germans Trias i Pujol University Hospital in Barcelona, Spain. High-risk people have treatment options, he says, but moderate-risk people who don't quite qualify for existing treatments are left fearing for their safety. "There is a need there," he says. Such treatments could reduce the disruption that even mild cases can inflict on people's jobs and family lives.

Nature 2022

KINFAST: patients and endpoints selection

- **Patients**: unselected patients (indep. of vaccination status or other therapies)

- **Primary** endpoint: time to recovery from mild and severe symptoms
  - Patient Reported Outcome Measure (PROM) proposed by the FDA
  - May currently be more relevant than hospitalization rate
  - Time to recovery drives the economic consequences of Covid 19

- **Key secondary** endpoint: number of days alive and with resolution of symptoms

- **Other secondary** endpoint: rate of hospitalization and mortality

Conclusions

The evolution of the Covid-19 pandemic has impacted the conduct of clinical trials

KINARUS is taking this evolution into consideration to adapt the plan and conduct of the clinical studies KINFAST and KINETIC

Due to its combined triple mode of action, KIN001 has the potential to improve multiple significant outcomes at all stages of the diseases

KINETIC and **KINFAST** are designed to demonstrate this benefit

KIN001

Other clinical indications

Dr Thierry Fumeaux, MD, EMBA, Kinarus CMO

KIN001- A platform for additional indications

- P38 inhibitors have a potential positive effect in other clinical indications
- With KIN001, Kinarus can overcome the issue of transient efficacy that led to the discontiuation of the clinical development of p38 inhibitors in the past
  - KIN001 has got a composition of matter claim in the US, Europe, and China
  - Kinarus is ready to start a one-year phase 2 study in wet Age-related Macular Degeneration with KIN001 based on strong efficacy data generated in monkeys
  - Kinarus can start a one-year phase 2 study in Idiopatic Pulmonary Fibrosis based on strong preclinical data. First results in the KINETIC study could guide this development
  - Kinarus will preclinically assess additional potential indications to maximize the value of the platform

KIN001- The COVID studies will support subsequent programs

- Safety/Tolerability
  - Pamapimod has documented favorable tolerability in a complete phase 1 program and two phase 2 studies performed by Roche, Pioglitazone has shown to be very safe at the dose used
  - Long term tox studies with Pamapimod and a 3 month combination tox study completed with no unexpected findings
  - In 131 patients in the KINETIC study KIN001 has shown to be well tolerated which reducees the risk of failure in subsequent phase 2 studies
- Mechanism of effect
  - KINETIC and KINFAST will allow Kinarus to learn about the the anti-inflammatory and anti fibrotic effect of KIN001 in human
  - Inflammation and fibrosis are key drivers in several indications including wet AMD and IPF

kinarus

Questions?