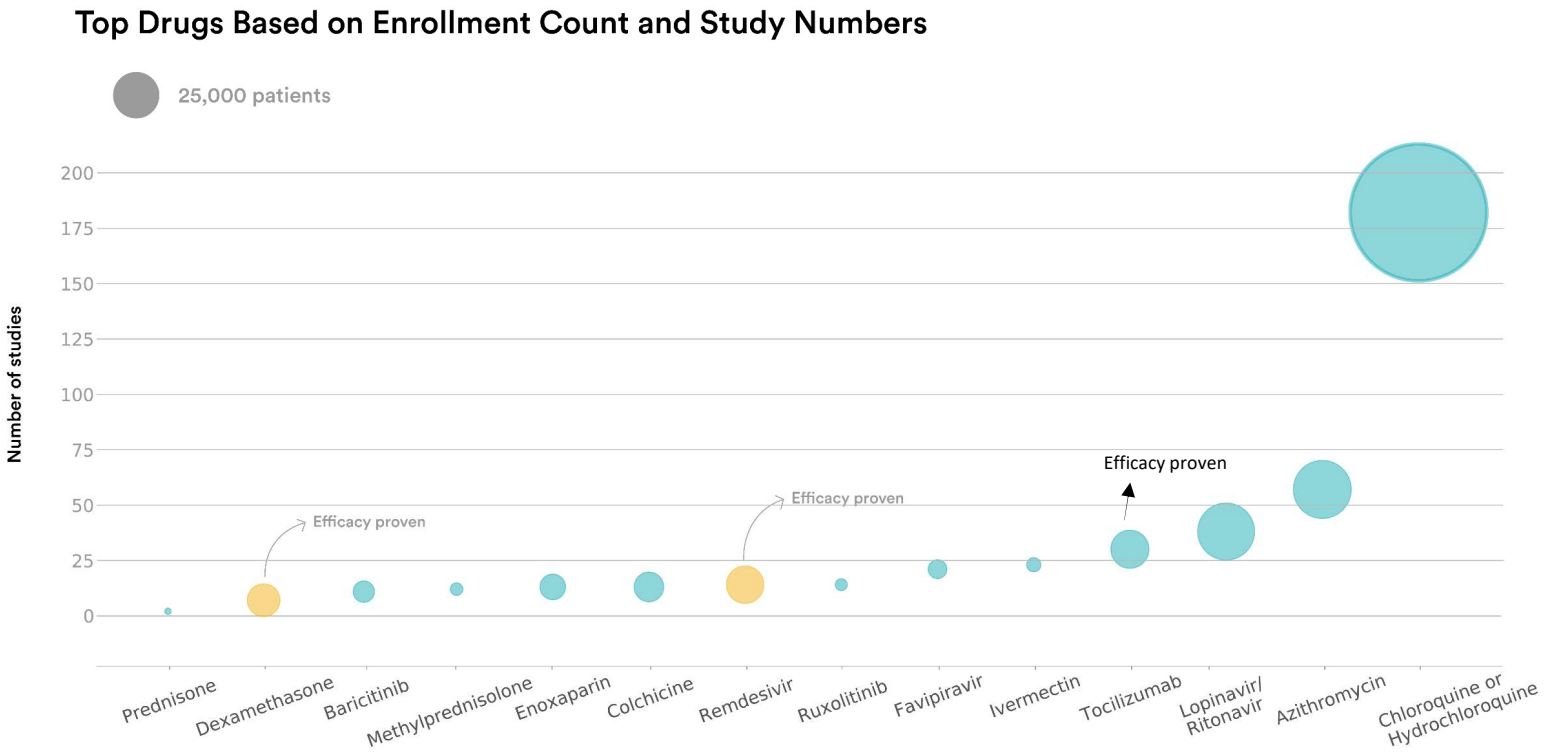
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101015736

The EU-RESPONSE trials

EU workshop on broad-spectrum antivirals

Marius Trøseid, on behalf of EU RESPONSE

How to avoid the research chaos of 2020?

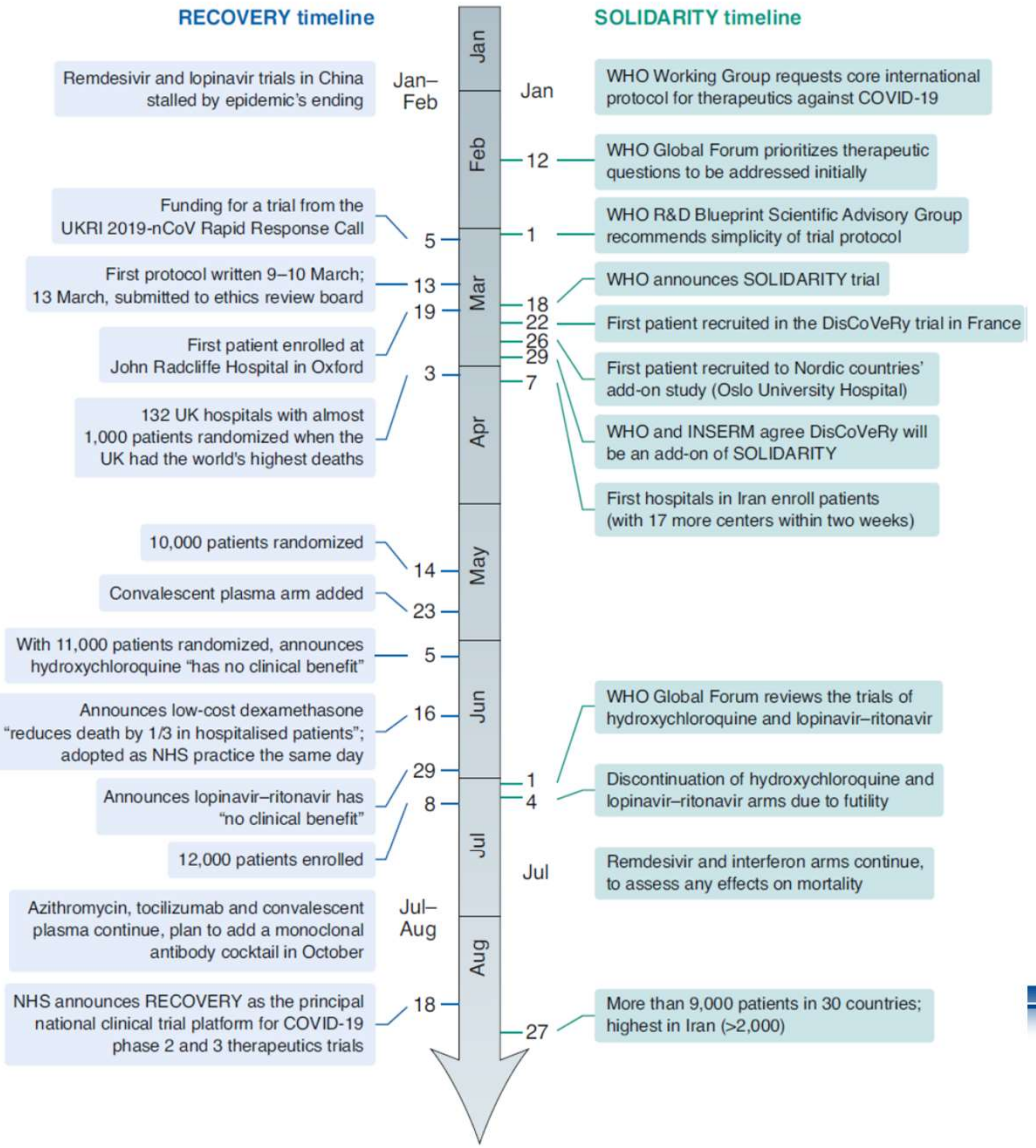


If we had access to broad spectrum antivirals from the start…

- How to test efficacy of drugs fast enough?
- How to test safety of drugs detailed enough?

- How to test the right drug for the right population?

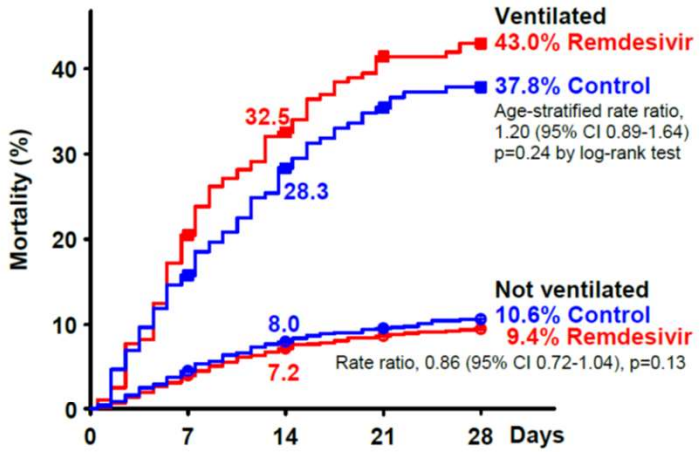
- How to update knowledge when the virus and patient population evolve during the pandemic?



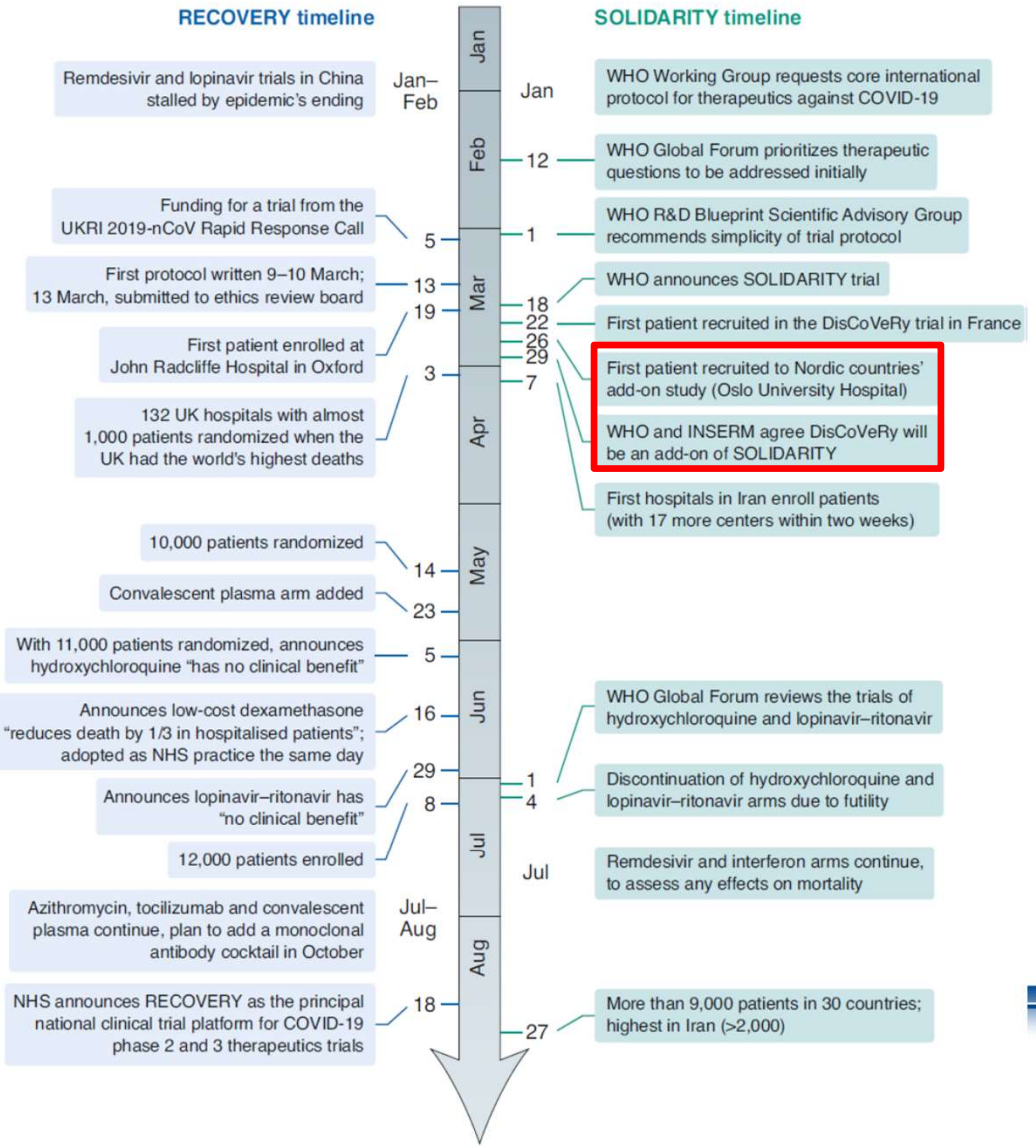
COVID-19 clinical trials: learning from exceptions in the research chaos

Of the >2,000 planned drug studies examining COVID-19 treatments (https://www.covid-trials.org), most have delivered little or no directly useful information[1].

NATURE MEDICINE | www.nature.com/naturemedicine



Solidarity, N Engl J Med 2020



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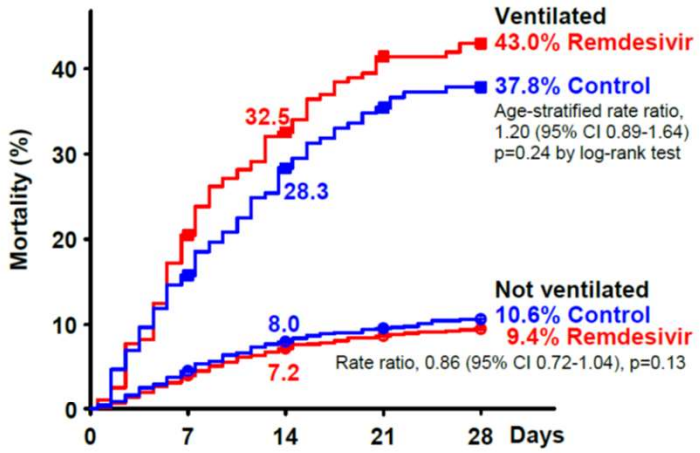


Solidarity, N Engl J Med 2020

EU RESPONSE

21 Partners

16 Countries

WP	Title	Lead
1	Extending **Discovery** in Europe	**Inserm** Université Libre de Bruxelles Centro Hospitalar Sao Joao
2	**EU-SolidAct**	**Oslo University Hospital** Inserm Universita degli Studi di Verona
3	Coordination of the European COVID-19 Adaptive Platform trials	ECRIN Norwegian Institute of Public Health
4	Project management, coordination, communication and dissemination	Inserm Inserm Transfert

DISCOVERY

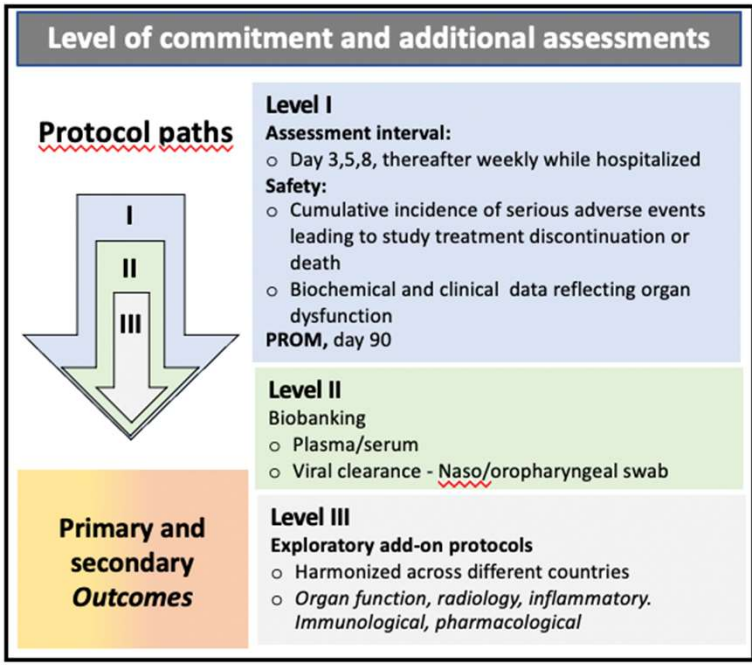
EU SOLIDACT Part of EU-RESPONSE

Oslo University Hospital

EU SOLIDACT Part of EU-RESPONSE

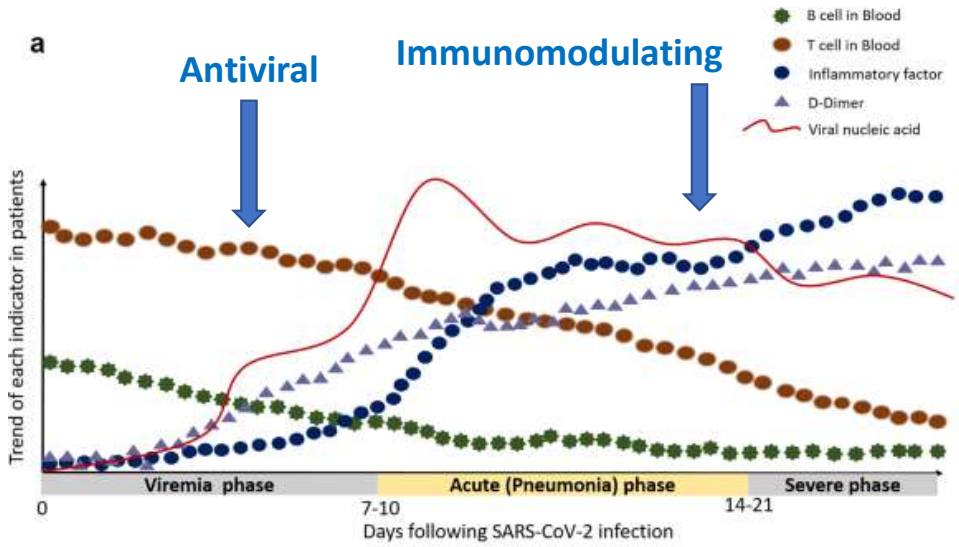
Creating a platform trial for future pandemics

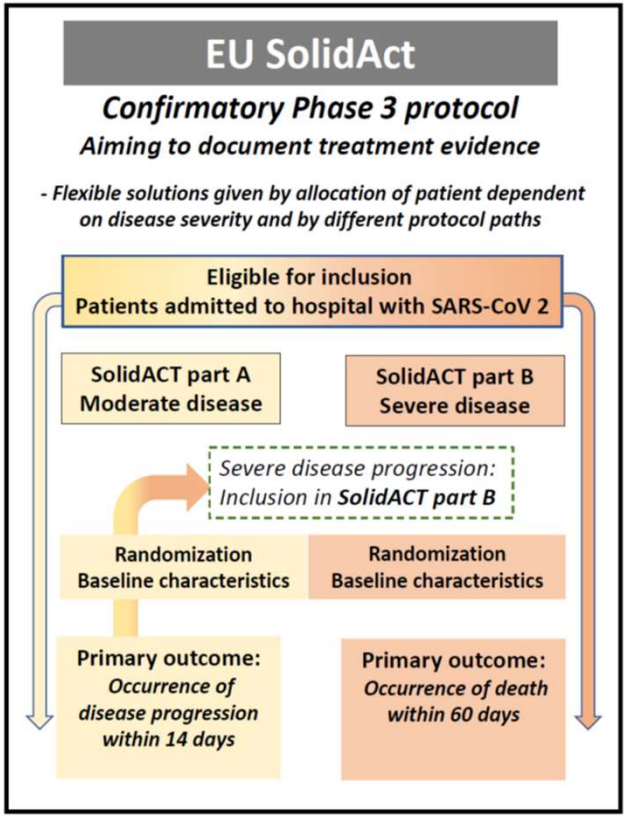
- Pragmatic enough to enable patient inclusion across Europe
- Granular safety data for EMA approval
- Flexible data capture related to local resources
  - Biobanking in sites with capacity and experience
- Remote follow-up after discharge



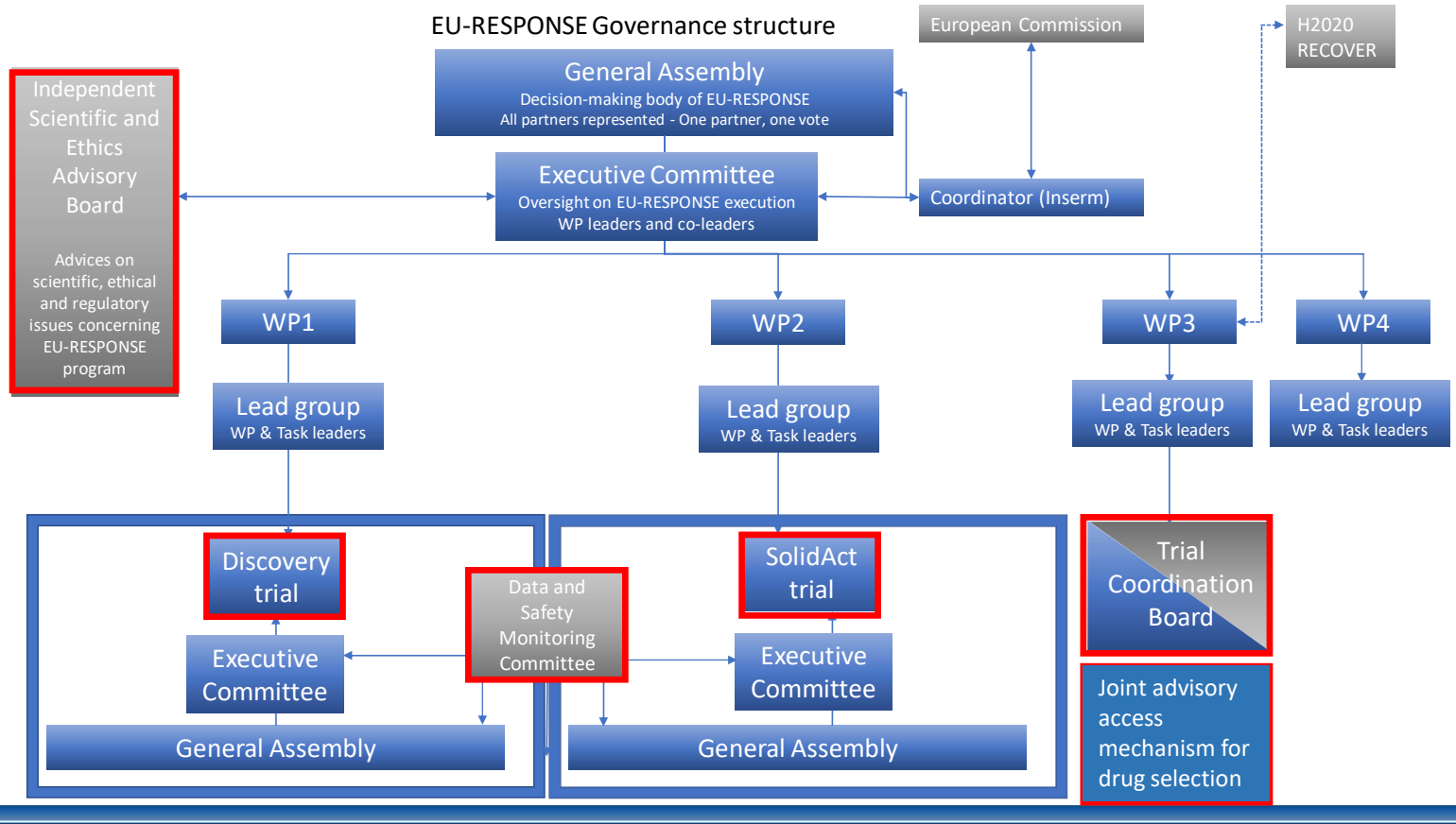
Creating a platform trial for future pandemics

- Testing different drugs for different disease states





Trial coordination and shared resources



Completed and ongoing* trials

	Population	Intervention	Main outcome
NOR-Solidarity	Moderate, severe	Remdesivir	Viral clearance
DicCoVeRy I	Moderate, severe	Remdesivir	Clinical status day 15
DicCoVeRy II	Moderate	Evusheld	Clinical status Day 15
Bari-SolidAct	Severe, critical	Baricitinib	Mortality Day 60
AXL-SolidAct*	Moderate	Bemcentinib	Disease state Day 8

DISCOVERY

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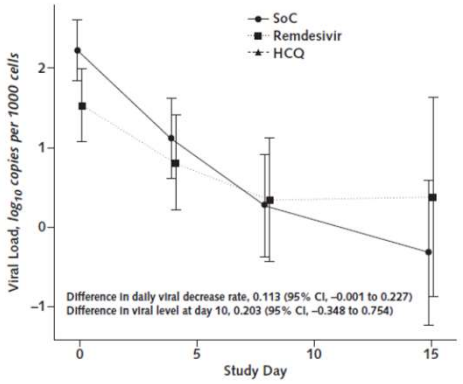
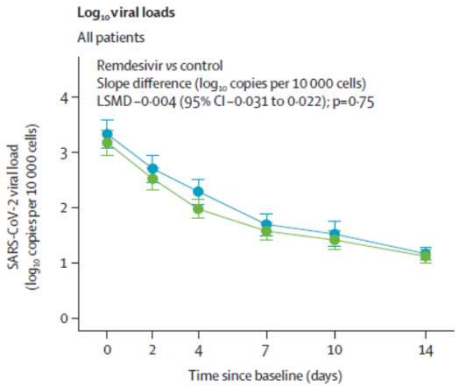
EU RESPONSE trials and remdesivir



Barratt-Due et al, Ann Int Med 2021

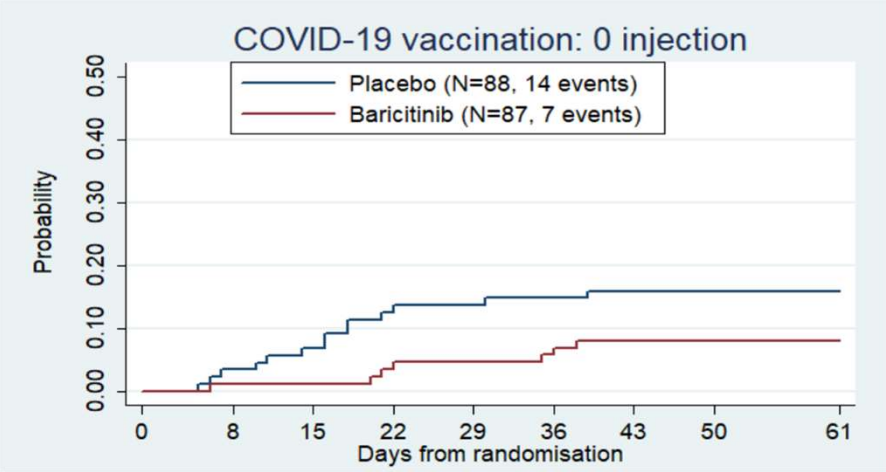


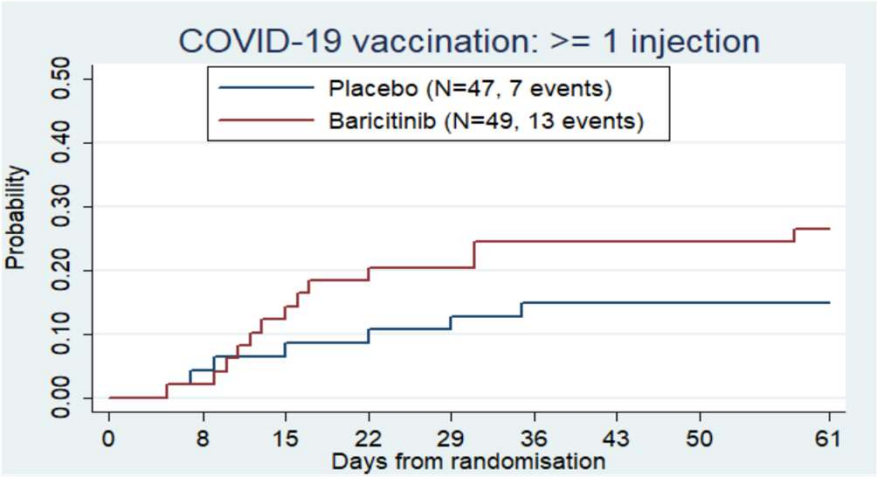
Ader F et al, Lancet Inf Dis 2021

- Antiviral drug, but no documented effect on viral load in nasopharynx
- Other modes of action?
- Need for individual level meta analysis (paper submitted)

Trøseid et al, Lancet Inf Dis 2021

Baricitinib: Different safety profile in vaccinated?





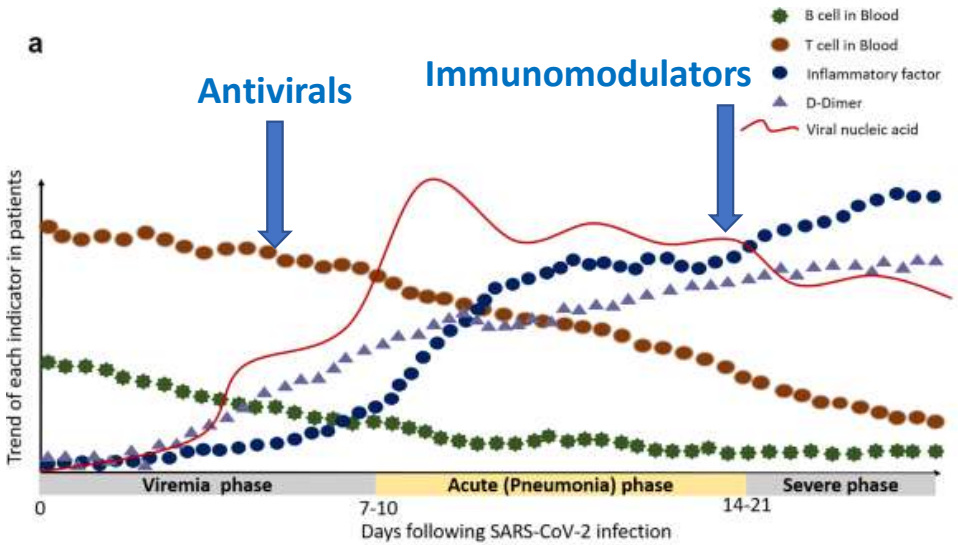
Significant interaction between vaccination and serious adverse events

Vaccinated were older with more comorbidities and less inflammation: inadequate immune response to vaccines?

EU SolidAct, Critical Care 2022

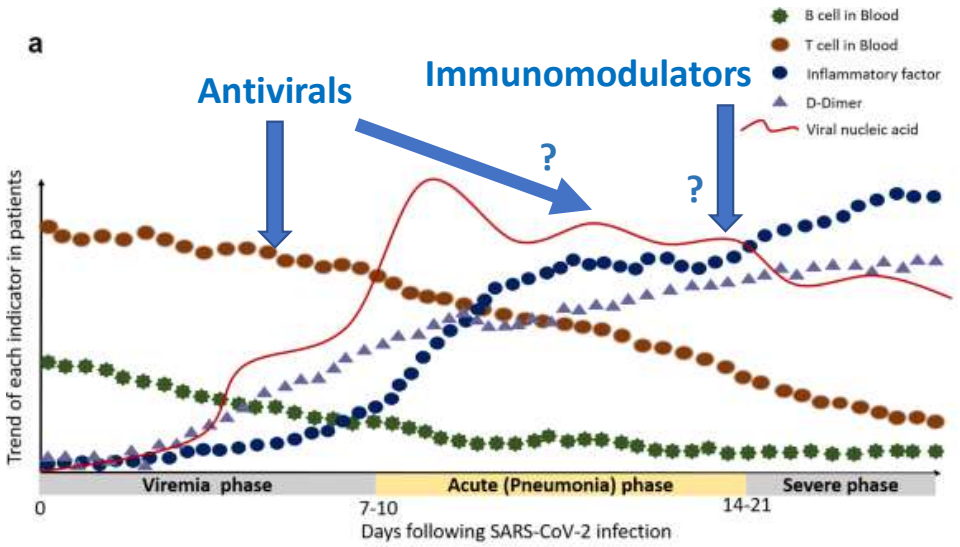
Are data from immunologically naive patients pre-Omicron still relevant?

- Pre-omicron/unvaccinated



Are data from immunologically naive patients pre-Omicron still relevant?

- Omicron/vaccinated/immunocompromised



Are data from immunologically naive patients pre-Omicron still relevant?

Immunocompromised patients have been neglected in COVID-19 trials: a call for action

Marius Trøseid [1,*], Maxime Hentzien [2], Florence Ader [3], Sandra Wagner Cardoso [4], Jose R. Arribas [5], Jean-Michel Molina [6], Nicolas Mueller [7], Maya Hites [8], Fabrice Bonnet [9], Oriol Manuel [10], Dominique Costagliola [11], Beatriz Grinsztejn [4], Inge Christoffer Olsen [12], Yazdan Yazdapanah [13], Alexandra Calmy [2], On behalf of EU RESPONSE, COMBINE

Table 1
Proportion of immunocompromised participants in registration trials of antiviral drugs

Drug	Remdesivir	Nirmatrelvir/ritonavir	Sotrovimab
Primary end point	Hospitalization or death within 28 days	Hospitalization or death within 28 days	Hospitalization or death within 29 days
Population	Symptoms <7 days, at least one risk factor	Symptoms <5 days, high risk patients	Symptoms <5 days, at least one risk factor
Immuno-compromized, %	5	<1	Excluded
Efficacy data, *n* (%)	2/279 (0.7) (remdesivir); 15/283 (5.3) (placebo); p = 0.008; RRR = 87%	3/389 (0.8) (nirmatrelvir); 27/385 (7.0) (placebo); p < 0.0001; RRR = 89%	3/291 (1) (sotrovimab); 21/292 (7) (placebo); p = 0.002; RRR = 85%
Publication	Gottlieb et al. [4]	Hammond et al. [5]	Gupta et al. [6]

RRR, relative risk reduction.

Plans ahead

- Use biobanked material to improve knowledge on safety profile, mode of action of drugs and interaction with host immunity
- Use the network and infrastructure for other emerging infectious diseases, collaboration with other networks on Monkeypox
- Keep the network alive in «peacetime»

If we had access to broad spectrum antivirals we would still need…

- to test drugs in relevant populations
- platform trials that allow rapid inclusion, yet detailed enough regarding safety data
- to include fragile groups of patients from the start
- trial coordination rather than trial competition

Acknowledgements

- Patients
- Site staff
- Investigators
- International Sponsor team
- EMA and regulators
- EU RESPONSE partners
- European Commission

The EU-RESPONSE project has received funding from the European Union's Horizon 2020 Research and Innovation programme, under the Grant Agreement number 101015736