What Should Pathogen X Antiviral TPP Look Like? A clinician's perspective

WHO Meeting: Scientific strategies from recent outbreaks to help us prepare for Pathogen X
August 29-30, 2022

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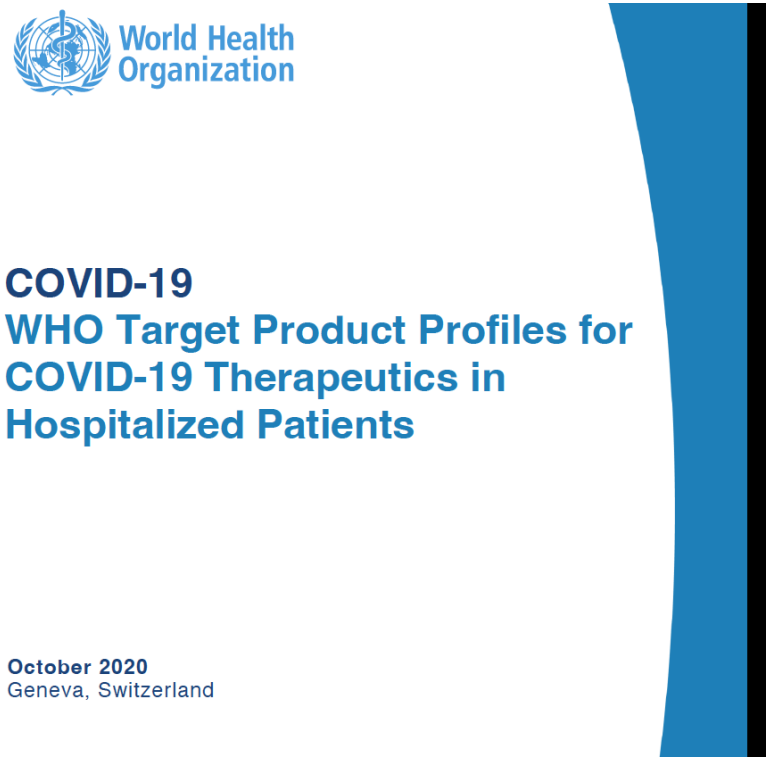
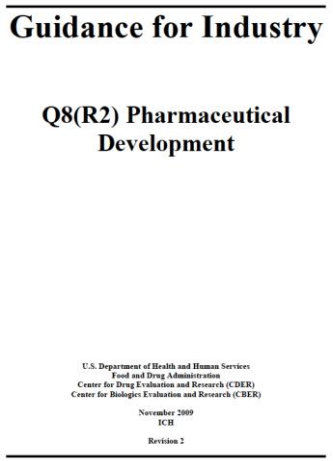
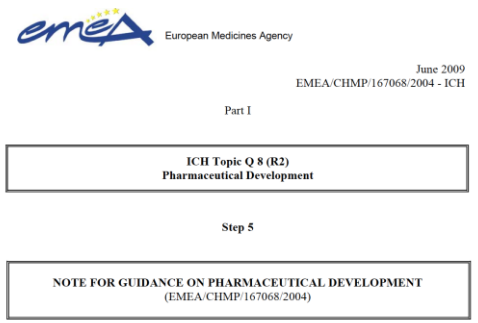
Typical Target Product Profile (TPP) Considerations

1. Indication for use
2. Target population
3. Safety/tolerability
4. Efficacy
5. Treatment regimen
6. Route of administration
7. Product stability and storage
8. Interactions
9. Formulation
10. Accessibility
11. Registration and prequalification







Pathogen X: Draw on Recent Challenges

- Ebola
  - Contact, significant symptomatic rate, high mortality
- Zika
  - Vector born, teratogenicity
- SARS-CoV-2
  - Droplet, asymptomatic, 90+% do well, increased mortality in sub-groups
  - Non-infectious consequences – immune dysregulation, thrombosis
- Monkeypox
  - Contact, low mortality

- How novel is pathogen X?
  - Do we have experience and knowledge for the pathogen's family?

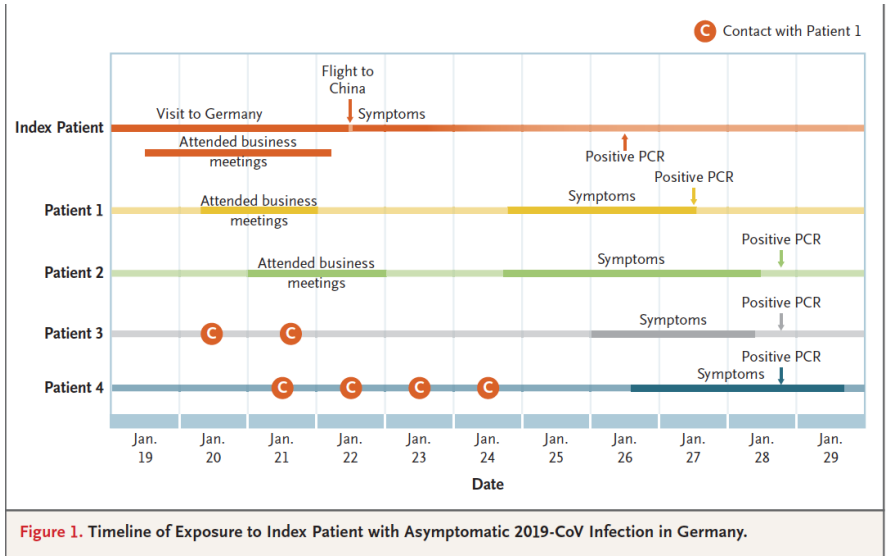


Figure 1. Timeline of Exposure to Index Patient with Asymptomatic 2019-CoV Infection in Germany.

Rothe C et al., *NEJM* 30Jan 2020

Defining Illness Pattern

When in Illness will an intervention have impact and on what?

Pre-exposure Post-exposure Early Treatment Treatment →

- Prophylaxis
  - Pre-exposure prophylaxis (PrEP)
- Pre-emptive
  - Post-exposure prophylaxis (PEP)
- Empiric
- Treatment
  - Early
  - Late

- *Transmission*

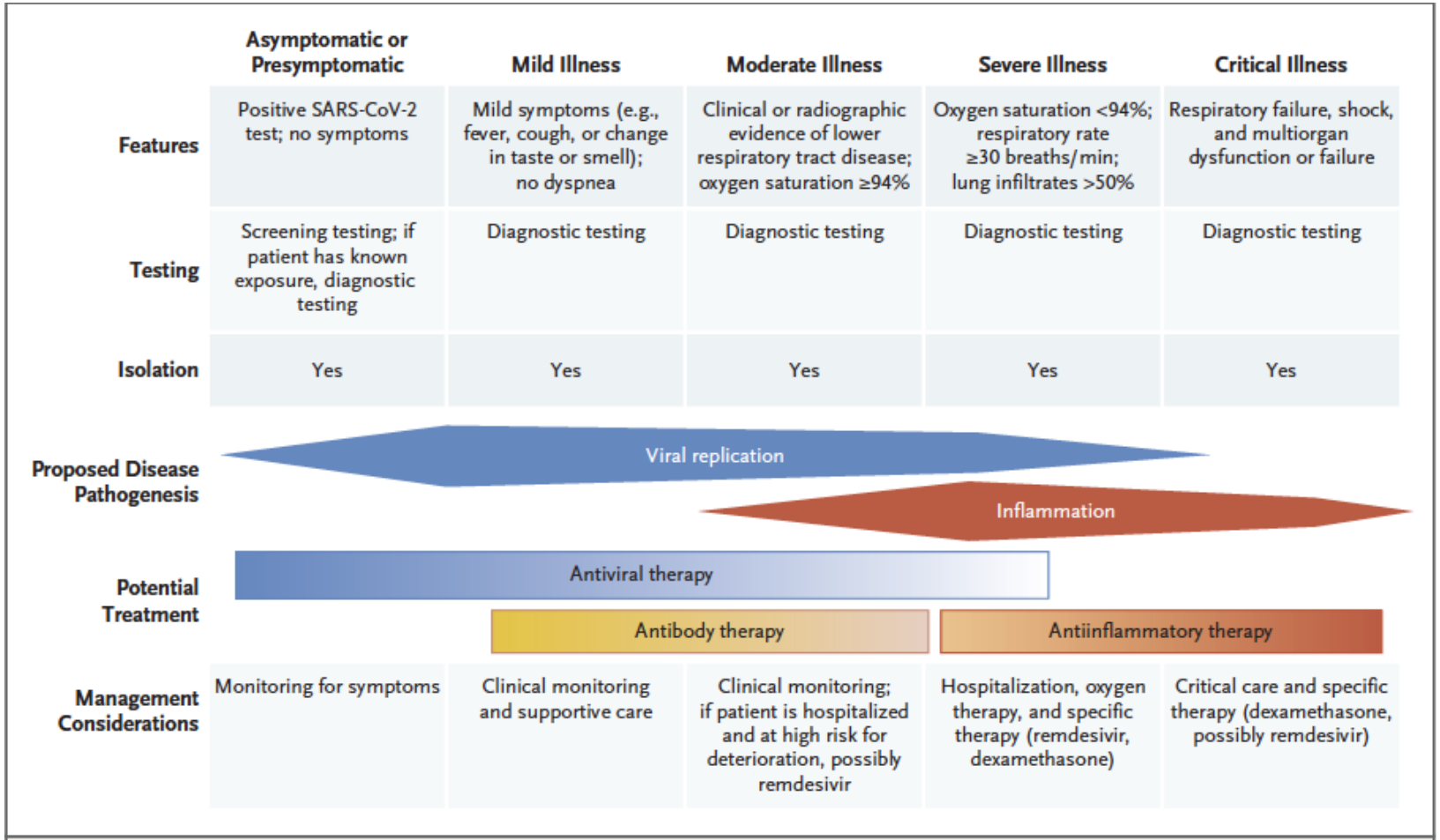


Figure 1. Characteristics, Diagnosis, and Management of Covid-19 According to Disease Stage or Severity.

Gandhi RT *NEJM* 24Apr 2020

Properties of the Therapeutic Product

Examples from SARS-CoV-2

- Prevention
  - Vaccines
- Treatments
  - Antivirals
    - Monoclonal antibodies
    - Small molecules
- Host modifiers

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

Peter Chen, M.D., Ajay Nirula, M.D., Ph.D., Barry Heller, M.D., Robert L. Gottlieb, M.D., Ph.D., Joseph Boscia, M.D., Jason Morris, M.D., Gregory Huhn, M.D., M.P.H.T.M., Jose Cardona, M.D., Bharat Mocherla, M.D., Valentina Stosor, M.D., Imad Shawa, M.D., Andrew C. Adams, Ph.D., Jacob Van Naarden, B.S., Kenneth L. Custer, Ph.D., Lei Shen, Ph.D., Michael Durante, M.S., Gerard Oakley, M.D., Andrew E. Schade, M.D., Ph.D., Janelle Sabo, Pharm.D., Dipak R. Patel, M.D., Ph.D., Paul Klekotka, M.D., Ph.D., and Daniel M. Skovronsky, M.D., Ph.D., for the BLAZE-1 Investigators*

NEJM 20Oct20

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19

ACTIV-3/TICO LY-CoV555 Study Group*

NEJM 22Dec20

Forecasting mAb Utility

Integrate Several Lines of Evidence

- Pathogen and Variant of Concern (VOC)
- *in vitro* activity of mAb
- PK/PD of mAb
- Clinical safety data
- Clinical efficacy data
  - In general vs against the specific VOC
  - Tempo of availability

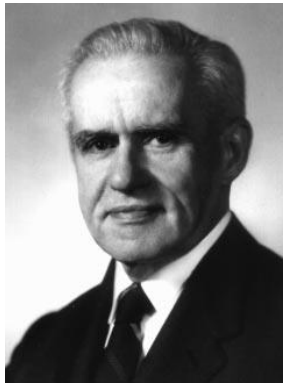
NATIONAL ACADEMY OF SCIENCES

MAXWELL FINLAND

1902—1987

A Biographical Memoir by

FREDERICK C. ROBBINS



In 1929 Finland was asked by Dr. Nye to join his laboratory at the Thorndike. Thus began one of the most remarkable careers in the field of infectious diseases. The first studies conducted by Max and his associates dealt with pneumonia. At that time the only treatment for pneumococcal pneumonia was administration of type-specific antiserum. The process of treating patients was cumbersome, to say the least. A naso-pharyngeal swab was taken and placed in a tube containing culture medium. After a few hours of incubation when enough bacteria had proliferated, material from the culture was exposed to type-specific antisera. If there was a match between the antiserum and the chemical composition of the polysaccharide on the surface of the bacterium, the capsule would swell and it could be seen with an ordinary light microscope (known as the Quellung reaction). If Quellung occurred, the corresponding antiserum (horse or rabbit) was administered to the patient. The patients usually survived the infection, but they invariably suffered from serum sickness, which could be most unpleasant. Finland and his fellows did a series of studies on the treatment of pneumococcal infection conducted with meticulous care, a hallmark of Finland's research throughout. When sulfonamides became available

Remdesivir

- Gilead: **Compassionate** use – NEJM 10Apr20
  - N=61, open label, hospitalized, hypoxemic. LD200/100mg for 9days
- NIAID-ACTT-1 – NEJM 22May (prelim) and 5Nov20
  - N=1062, RCT-pbo, LD200/100mg 9days, hospitalized
  - **Time to recovery** –median 10 vs 15 days
- Gilead: 5 or 10 days, **Severe** Covid -- NEJM 27May2020
  - N=397, Randomized, **open-label**, hospitalized no IMV
  - Clinical status improvement d14 – 64% in 5D vs 54% in 10D
- Gilead: 5 vs 10 days vs pbo, **Moderate** Covid – JAMA 21Aug2020
  - N=596, RCT-pbo, hospitalized, O2>94%, LD200/100 for 5 or 10d (median 6d)
  - Clinical status d11 – 5d>pbo, 10d~pbo
- WHO-Solidarity: Inpatient – NEJM 11Feb2021, Lancet 02May2022
  - N= 2750 remdesivir (10d)+2708 SOC, RCT-SOC, hospitalized, moderate Covid
  - **Mortality** – 11.0% (14.5%) vs 11.1% (15.6%)
- PineTree: **Outpatient** – NEJM 27Jan2022
  - N=562, RCT, LD200/100 2days. Outpatients
  - Hospitalization/death – 0.7% vs 5.3%

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ESTABLISHED IN 1812 FEBRUARY 10, 2022 VOL. 386 NO. 6

Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients

A. Jayk Bernal, M.M. Gomes da Silva, D.B. Musungaie, E. Kovalchuk, A. Gonzalez, V. Delos Reyes, A. Martín-Quirós, Y. Caraco, A. Williams-Diaz, M.L. Brown, J. Du, A. Pedley, C. Assaid, J. Strizki, J.A. Grobler, H.H. Shamsuddin, R. Tipping, H. Wan, A. Paschke, J.R. Butterton, M.G. Johnson, and C. De Anda, for the MOVe-OUT Study Group*

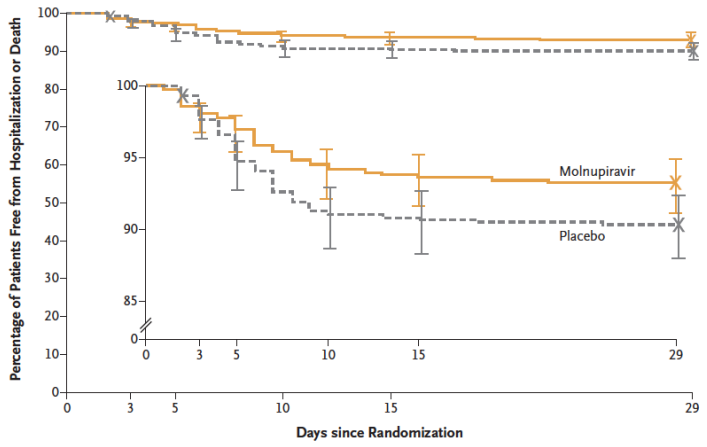


Figure 2. Time-to-Event Analysis of Hospitalization or Death through Day 29 in the Modified Intention-to-Treat Population.

Figure 13 Incidence of Hospitalization or Death Through Day 29 MITT Population (P002 Phase 3 IA)

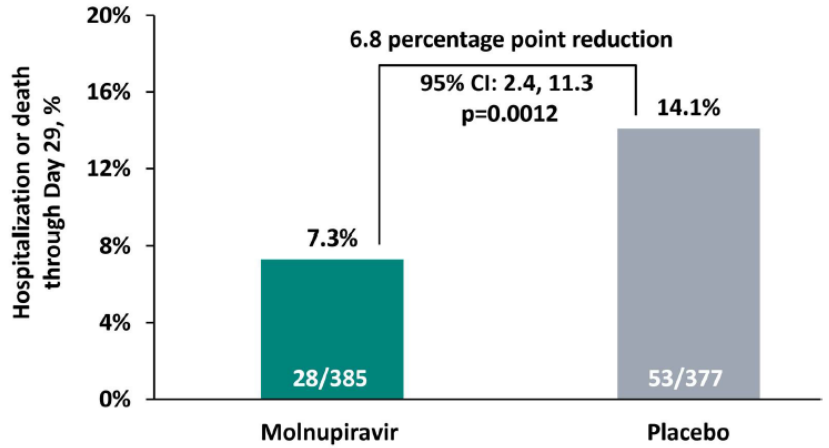


Table 1

Efficacy Results in Non-Hospitalized Adults with COVID-19 (Protocol 002 – Full Population)

	Molnupiravir (N=709) n (%)	Placebo (N=699) n (%)	Risk Difference* (95% CI)	p-value†
All-cause hospitalization or death through Day 29	48 (6.8)	68 (9.7)	-3.0 (-5.9, -0.1)	0.0218
Hospitalization‡	48 (6.8)	67 (9.6)		
Death	1 (0.1)	9 (1.3)		
Unknown§	0 (0.0)	1 (0.1)		

Figure 1

Incidence of Hospitalization or Death Through Day 29 by Subgroup (Protocol 002 – Full Population)

Baseline Antibody Status					
Positive	5/136	2/146	2.3	-1.7	7.1
Negative	39/541	64/520	-5.1	-8.8	-1.6

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 14, 2022 VOL. 386 NO. 15

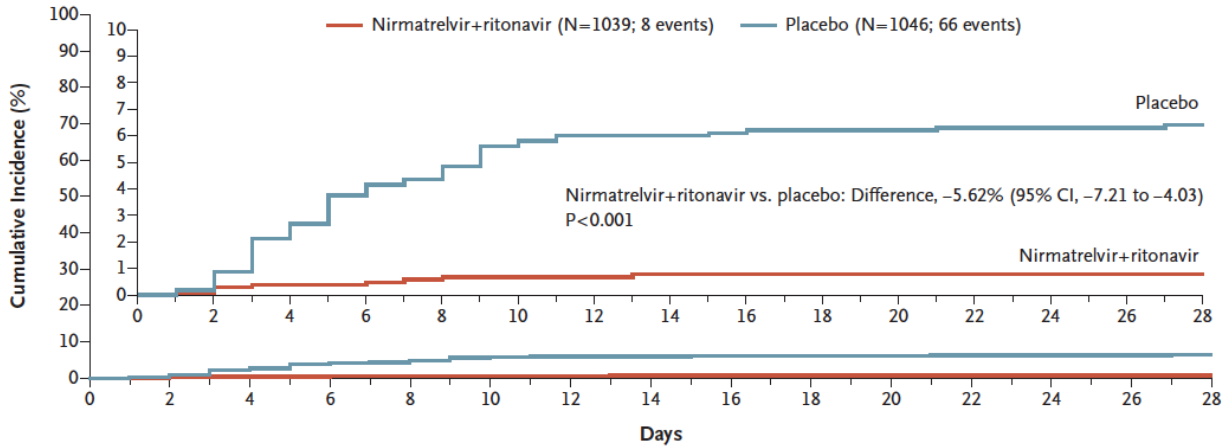
Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

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*

A Outcomes According to Time Since Onset of Covid-19 Symptoms

	Treated ≤3 Days after Onset of Symptoms (modified intention-to-treat population)		Treated ≤5 Days after Onset of Symptoms	
	Nirmatrelvir+ritonavir (N=697)	Placebo (N=682)	Nirmatrelvir+ritonavir (N=1039)	Placebo (N=1046)
Patients with event — no. (%)	5 (0.72)	44 (6.45)	8 (0.77)	66 (6.31)
Hospitalization for Covid-19	5 (0.72)	44 (6.45)	8 (0.77)	65 (6.21)
Death from any cause	0	9 (1.32)	0	12 (1.15)
Average time at risk for event — days	27.29	26.19	27.05	25.97
Average follow-up — days	27.45	27.25	27.20	27.05
Estimated percentage with event (95% CI) — %	0.72 (0.30 to 1.73)	6.53 (4.90 to 8.68)	0.78 (0.39 to 1.56)	6.40 (5.06 to 8.08)
Difference (±SE) from placebo — percentage points	−5.81±1.01		−5.62±0.81	
95% CI of difference	−7.78 to −3.84		−7.21 to −4.03	
P value	<0.001		<0.001	

B Covid-19–Related Hospitalization or Death from Any Cause through Day 28 among Patients Treated ≤5 Days after Symptom Onset

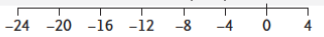


No. at Risk

NMV-r	1039	1034	1023	1013	1007	1004	1002	1000	997	995	993	993	993	993	992
Placebo	1046	1042	1015	990	977	963	959	959	955	953	951	948	948	948	945

C Subgroup Analysis

Subgroup	Nirmatrelvir+Ritonavir (no. of events/total no.)	Placebo (no. of events/total no.)	Difference from Placebo (95% CI) (percentage points)
Overall	8/1039	66/1046	−5.62 (−7.21 to −4.03)
Time since symptom onset			
≤3 days	5/697	44/682	−5.81 (−7.78 to −3.84)
>3 days	3/342	22/364	−5.23 (−7.91 to −2.55)
Age			
<65 yr	7/908	46/909	−4.35 (−5.91 to −2.79)
≥65 yr	1/131	20/137	−13.93 (−20.07 to −7.80)
Sex			
Male	4/520	41/540	−6.93 (−9.32 to −4.53)
Female	4/519	25/506	−4.23 (−6.29 to −2.17)
Body-mass index			
<25	1/209	9/207	−3.88 (−6.83 to −0.94)
25 to <30	3/458	28/466	−5.44 (−7.75 to −3.13)
≥30	4/371	29/373	−6.85 (−9.82 to −3.87)
Diabetes mellitus			
Yes	2/125	9/127	−5.51 (−10.51 to −0.52)
No	6/913	57/919	−5.63 (−7.30 to −3.96)
Baseline SARS-CoV-2 serology status			
Negative	7/487	58/505	−10.25 (−13.28 to −7.21)
Positive	1/540	8/528	−1.34 (−2.45 to −0.23)
Received or expected to receive Covid-19 monoclonal antibody treatment			
Yes	1/70	2/69	−1.51 (−6.40 to 3.37)
No	8/1039	66/1046	−5.62 (−7.21 to −4.03)



Reflections

- *Determine risk/benefit ratio of the novel therapy in different clinical settings*
- Must rapidly define key aspects of the biology of pathogen X to determine prevention/treatment opportunities
- Need to carefully consider what we want the intervention to do
  - Preventing mortality, overwhelming of healthcare system - important
  - Impact on illness and transmission - worthy
- Must (re-)define efficacy as epidemic parameters change over time
- Leverage emerging biotechnological advances
  - Diagnostics, mAbs, pre-clinical models
- Understand scalability
  - In a timeframe relevant to the speed of the pathogen
- Develop a global regulatory framework
- Must be globally deployable
  - Develop local capacity