Respiratory virus endpoints

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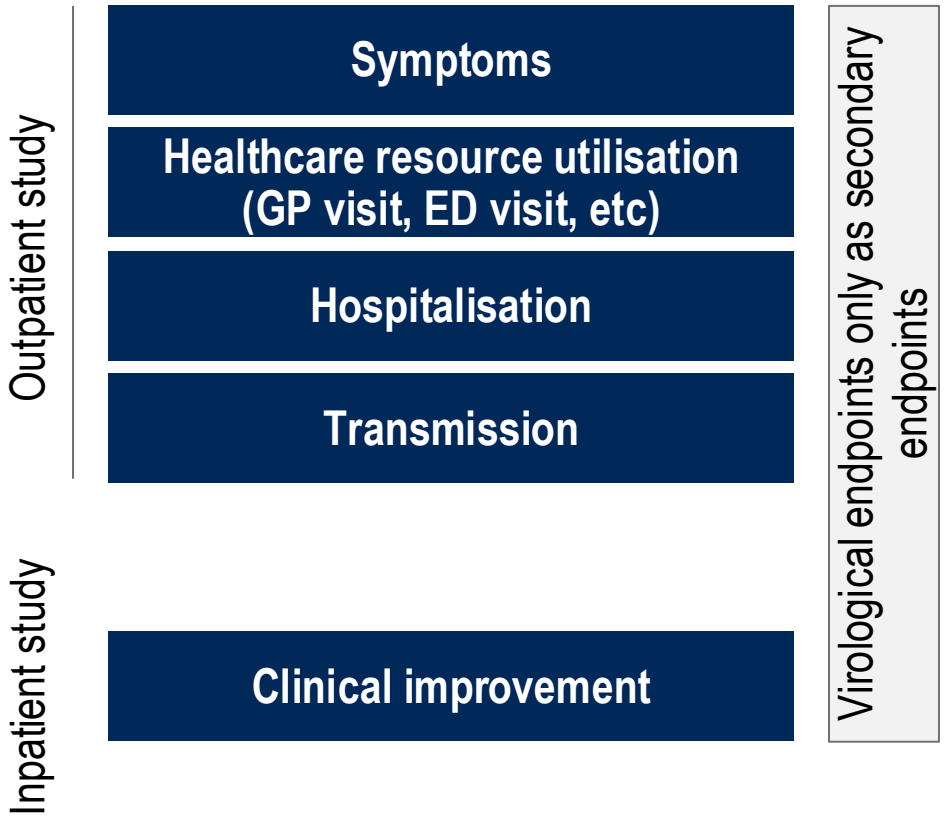
Dealing with uncertainty

- Changes/uncertainty in natural history of COVID-19 – endpoint selection problematic and regulatory approaches lacked flexibility
- Development of influenza and COVID-19 therapeutics using a symptom-based endpoint gave variable results and not reflective of antiviral potency and potential benefits beyond symptom recovery
- Hospitalization endpoints – short window during pandemic
- non-inferiority – impossible to define sample size if treatment effect unknown, access to comparators if Emergency Use Only, complication of double dummy design and over-encapsulating

Primary endpoints in Ph3 **treatment** studies used to evaluate respiratory virus antivirals



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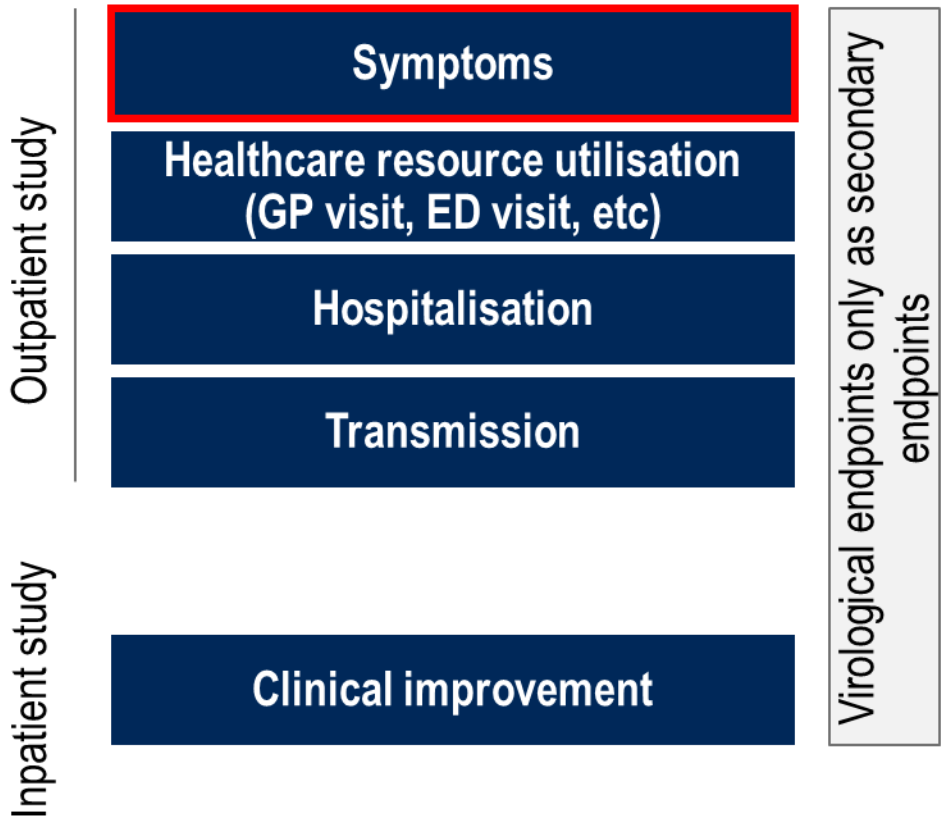


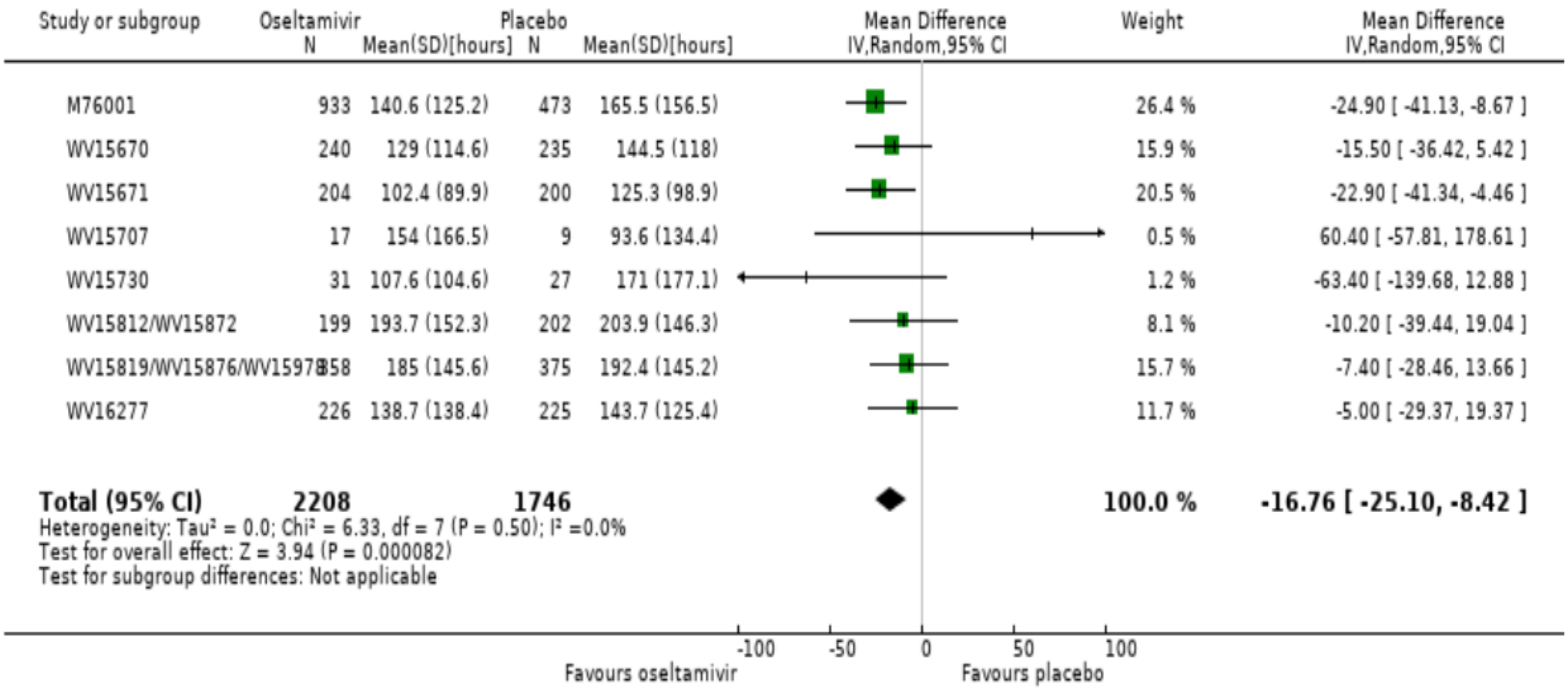
Historical/current examples: Influenza antivirals, COVID antivirals after rates of hospitalisation dropped, RSV antiviral

Pros: recruitable

Cons: Poor sensitivity, variable baseline for newly emerged viruses, may not be considered sufficiently important

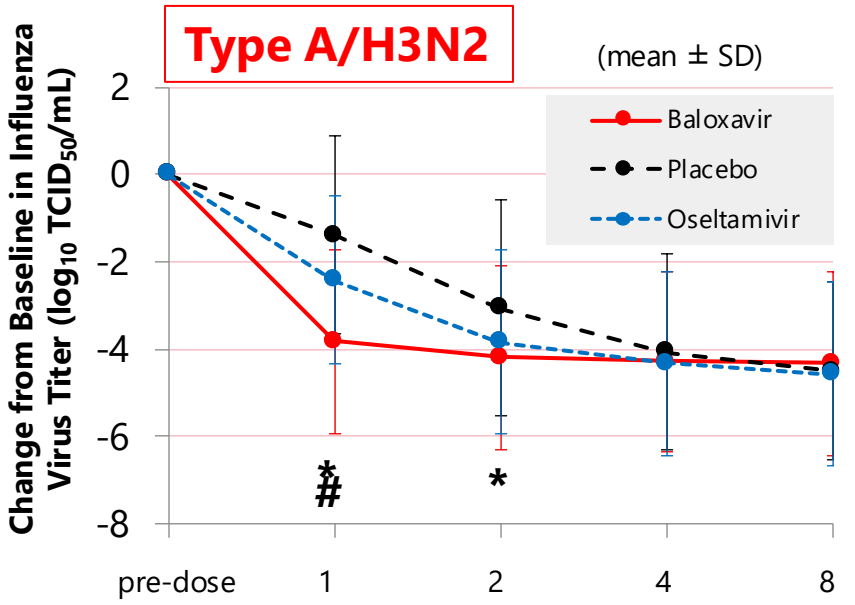
Future approaches: passive data collection (e.g. smart watches/rings), patient relevant measurements

Review: Neuraminidase inhibitors for preventing and treating influenza in adults and children
Comparison: 1 Oseltamivir versus placebo for treatment
Outcome: 1 Time to first alleviation of symptoms in adult treatment (ITT population)

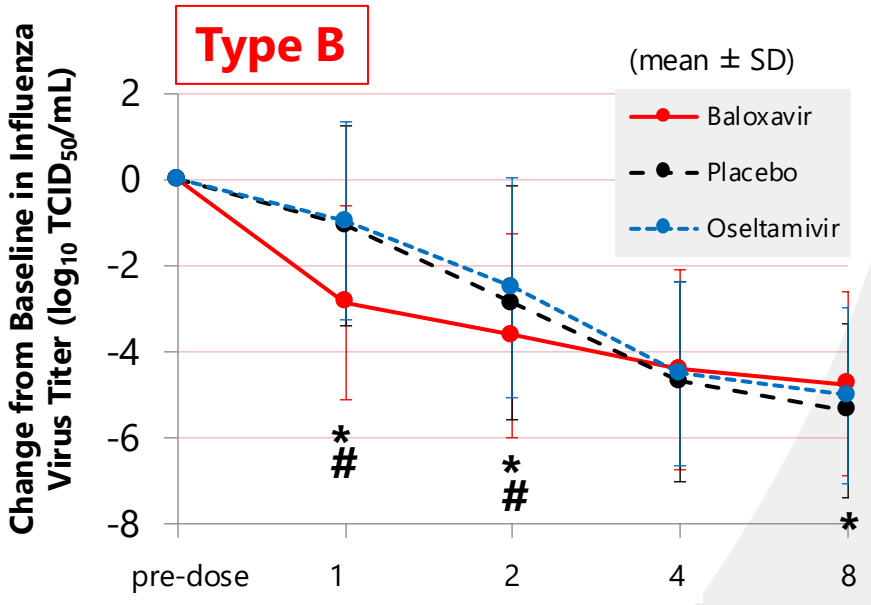


https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008965.pub4/full

Baloxavir Viral Titer Reduction: CAPSTONE-2



	pre-dose	1	2	4	8
Baloxavir (n)	170	154	158	150	152
Placebo (n)	169	165	162	152	153
Oseltamivir (n)	180	170	168	168	161



	pre-dose	1	2	4	8
Baloxavir (n)	153	150	148	145	145
Placebo (n)	159	154	150	145	145
Oseltamivir (n)	139	133	131	126	123

Day 1: Baseline, Pre-treatment
*p< 0.05 vs placebo, #p<0.05 vs Oseltamivir, ITTI population
Test: van Elteren test; Stratification factors: region, composite symptom scores at baseline and preexisting and worsened symptom.

Baloxavir significantly reduced viral titer compared with placebo and oseltamivir in High Risk patients

Ison et al. Lancet Infect Dis 2020

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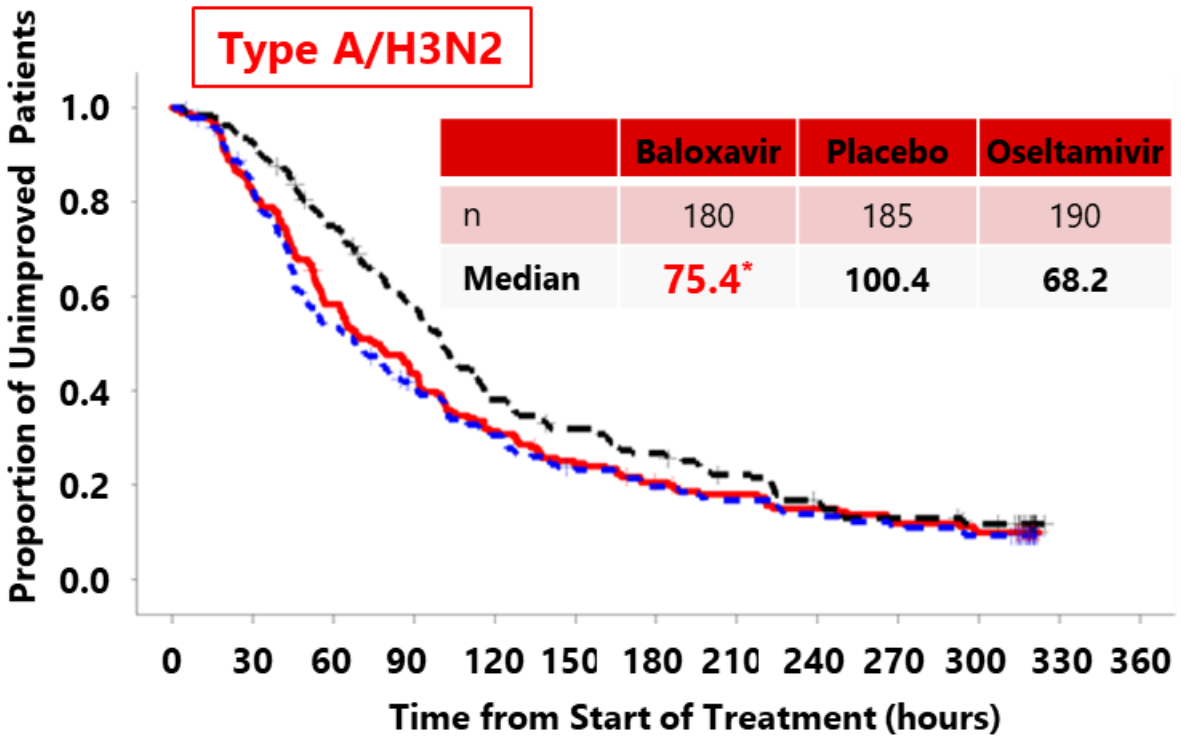
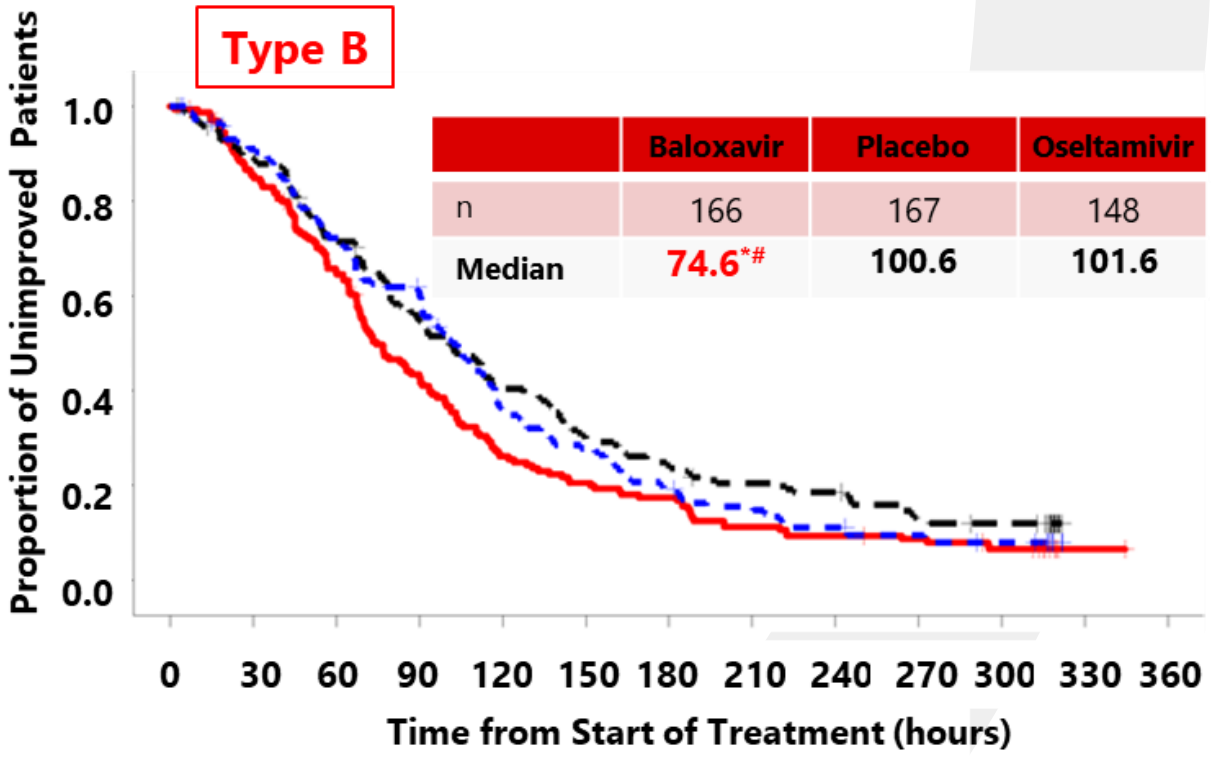
Baloxavir Time to Symptom Improvement: CAPSTONE-2



	Baloxavir	Placebo	Oseltamivir
n	180	185	190
Median	75.4*	100.4	68.2



	Baloxavir	Placebo	Oseltamivir
n	166	167	148
Median	74.6*#	100.6	101.6

Baloxavir Placebo Oseltamivir Censor

Unit of Median: hours, *p< 0.05 vs placebo, #p< 0.05 vs Oseltamivir, ITTI population

Baloxavir was superior to placebo in time to symptom improvement in High Risk patients
Baloxavir significantly reduced the time to symptom improvement compared with oseltamivir in influenza B infected High Risk patients

Ison et al. Lancet Infect Dis 2020

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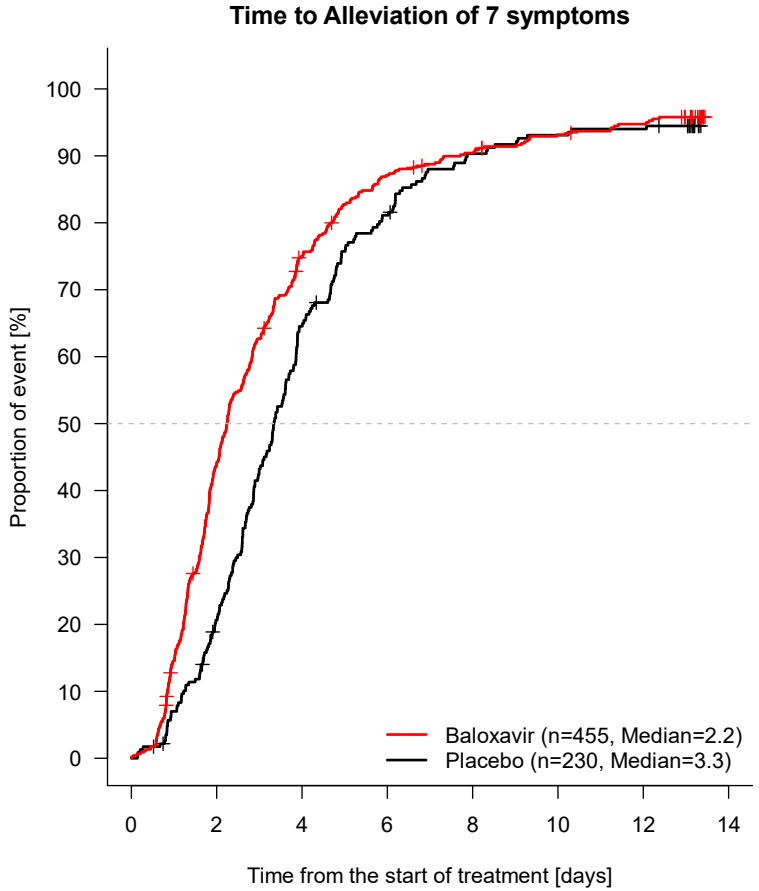
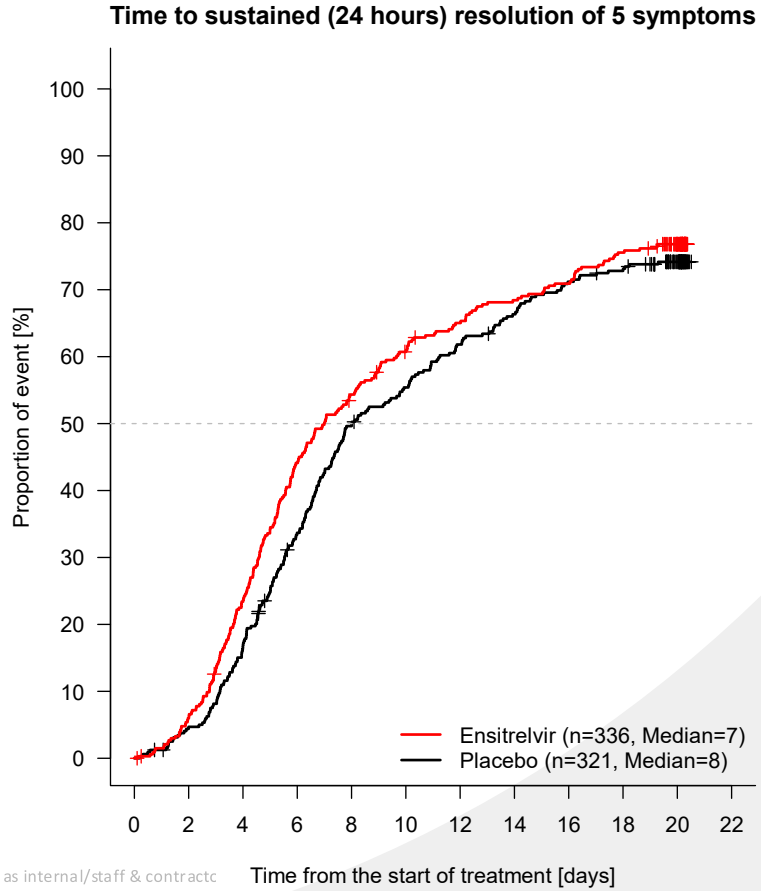
Symptoms are resolved naturally even under no treatment in both Influenza and SARS-Cov-2 viruses

- **Early treatment effect is clinically meaningful in efficacy evaluated via time to symptom resolution/alleviation**
- **Difference between the anti-virus agent and placebo was observed during the early treatment period in Kaplan-Meier plot for both Influenza and SARS-Cov-2 viruses**

Baloxavir OwH study for Influenza virus



Ensitrelvir SCORPIO-SR study for SARS-Cov-2 virus



Compared to influenza trials, COVID-19 trials had a higher rate of persistent symptoms.
→ Apparently, the median difference is shorter
→ It is necessary to specify a clinically meaningful evaluation period to evaluate early effects

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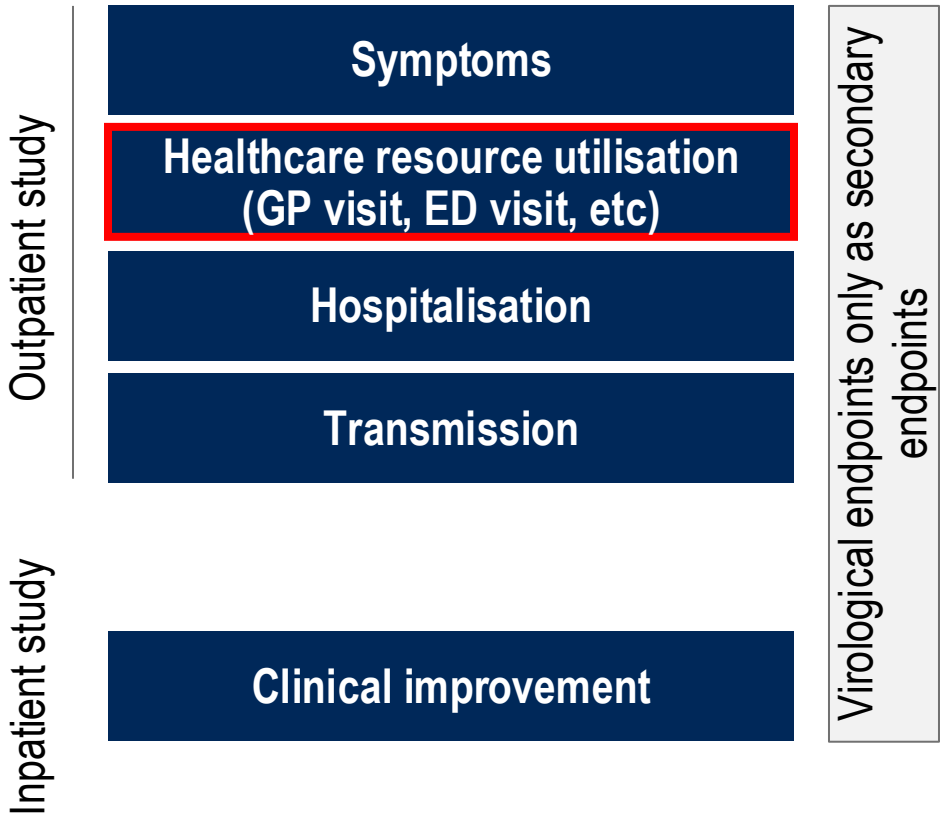

Historical/current examples: New COVID trials for ibuzatrelvir, etc

Pros: some relevance to payers, more recruitable than hospitalisation endpoints

Cons: variability between locations based on access to healthcare resources; new primary EP in this area so not yet proven

Future approaches: ?

What is the study measuring?

Primary Outcome Measures

Outcome Measure	Measure Description	Time Frame
Proportion of participants with COVID-19 related emergency department visits, all cause hospitalization and all cause mortality	The difference in proportions of patients requiring COVID 19 related emergency department visits with administration of supplemental oxygen, COVID-19 antiviral or IV treatment (eg hydration, antibiotics, or corticosteroids), all-cause hospitalization, or all-cause death through Day 28 between ibuzatrelvir and placebo, among patients who were treated ≤5 days after COVID-19 symptom onset and who were not receiving background SoC treatment for their COVID-19 infection at baseline.	Day 1 through Day 28

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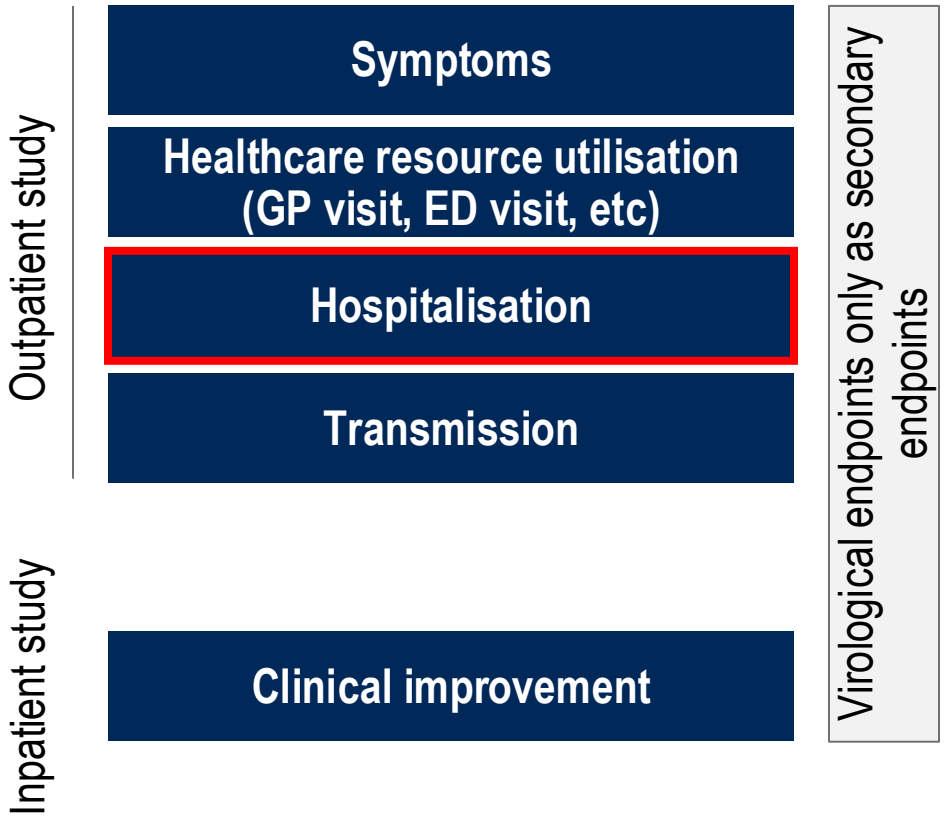

Historical/current examples: Achievable COVID endpoint during period of high rates of hospitalisation.

Pros: highly relevant endpoint for patients, HCPs and payers

Cons: requires very large numbers of patients

Future approaches: lean platform trials that enable very large number of patients to be recruited

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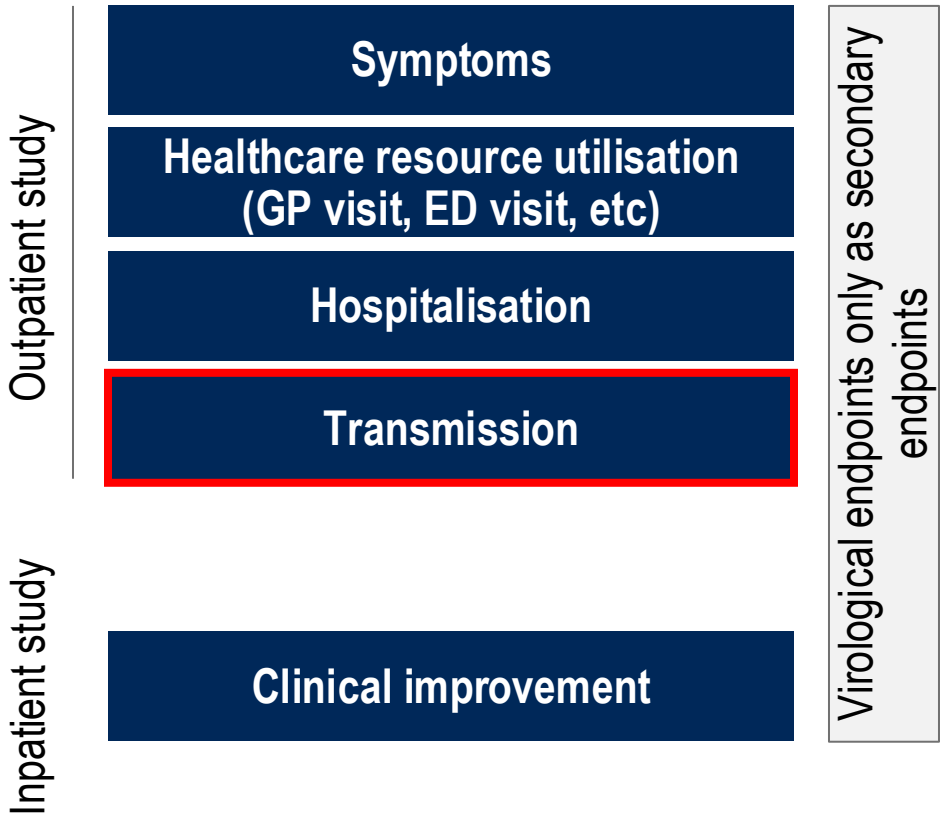

Historical/current examples: Household study evaluating baloxavir for influenza.

Pros: reflects virological potency of the antiviral, relevant for public health (particularly during a pandemic)

Cons: complex studies to conduct, traditional payer assessments do not evaluate public health benefits,

Future approaches: ?

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Wednesday, Sep 18, 2024

Positive Phase III Results Show Xofluza Significantly Reduces the Transmission of Influenza Viruses

Data from the CENTERSTONE study shows single-dose Xofluza reduces transmission of influenza from an infected person to household members

This is the first time that any antiviral used in the treatment of a respiratory viral illness has demonstrated a transmission reduction benefit in a global Phase III study

Reducing the spread of infection in the household could help limit transmission within communities and societies, easing the burden of both seasonal and pandemic influenza on healthcare systems

South San Francisco, CA -- September 18, 2024 --

Genentech, a member of the Roche Group (SIX: RO, ROG; OTCQX: RHHBY), announced today positive topline results of the Phase III CENTERSTONE study of Xofluza® (baloxavir

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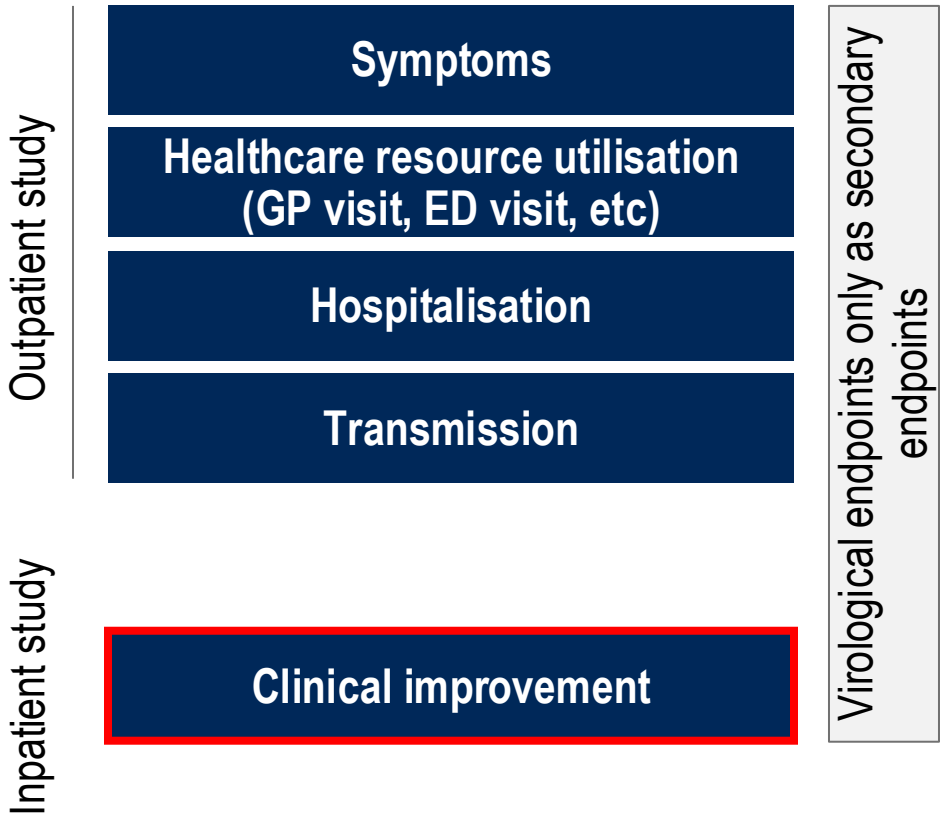

Historical/current examples: Remdesivir in COVID, Baloxavir/oseltamivir combination in influenza

Pros: highly relevant endpoint for patients, HCPs and payers

Cons: complex patient conditions, slow recruitment, evaluation vs standard of care (which can be variable)

Future approaches: Platform trials (RECOVERY, REMAP-CAP, STRIVE)

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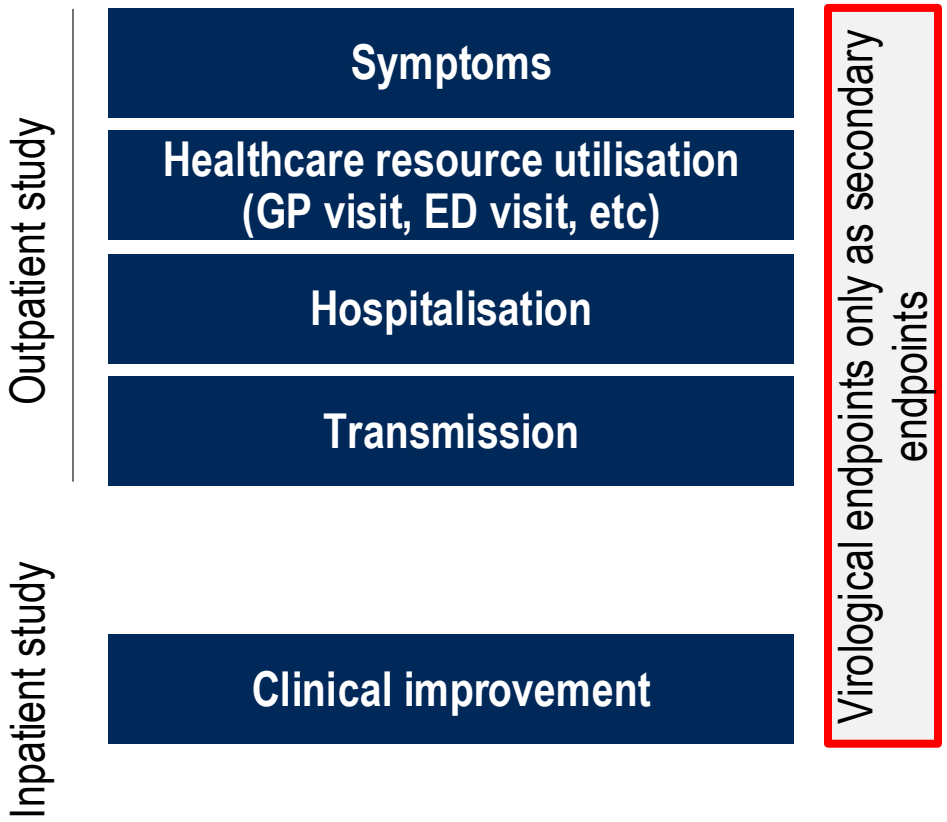

Arguments for the use of virological endpoints as the primary

Pros: direct measurement of antiviral effect,

Cons: requires confidence regarding the correlation between virological effect and clinical outcomes

Future approaches: approaches similar to antibiotic Ph3 endpoints, virological/clinical composite endpoints, platform trials (PLAT CoV)

Viral clearance as a surrogate of clinical efficacy for COVID-19 therapies in outpatients: a systematic review and meta-analysis

Karen M Elias, Shanchita R Khan, Eva Stadler, Timothy E Schlub, Deborah Cromer, Mark N Polizzotto, Stephen J Kent, Tari Turner, Miles P Davenport, David S Khoury

Summary

Background Surrogates of antiviral efficacy are needed for COVID-19. We aimed to investigate the relationship between the virological effect of treatment and clinical efficacy as measured by progression to severe disease in outpatients treated for mild-to-moderate COVID-19.

Methods In this systematic review and meta-analysis, we searched PubMed, Scopus, and medRxiv from database inception to Aug 16, 2023, for randomised placebo-controlled trials that tested virus-directed treatments (ie, any monoclonal antibodies, convalescent plasma, or antivirals) in non-hospitalised individuals with COVID-19. We only included studies that reported both clinical outcomes (ie, rate of disease progression to hospitalisation or death) and virological outcomes (ie, viral load within the first 7 days of treatment). We extracted summary data from eligible reports, with discrepancies resolved through discussion. We used an established meta-regression model with random effects to assess the association between clinical efficacy and virological treatment effect, and calculated I^2 to quantify residual study heterogeneity.

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Viral clearance as a surrogate of clinical efficacy for COVID-19 therapies in outpatients: a systematic review and meta-analysis

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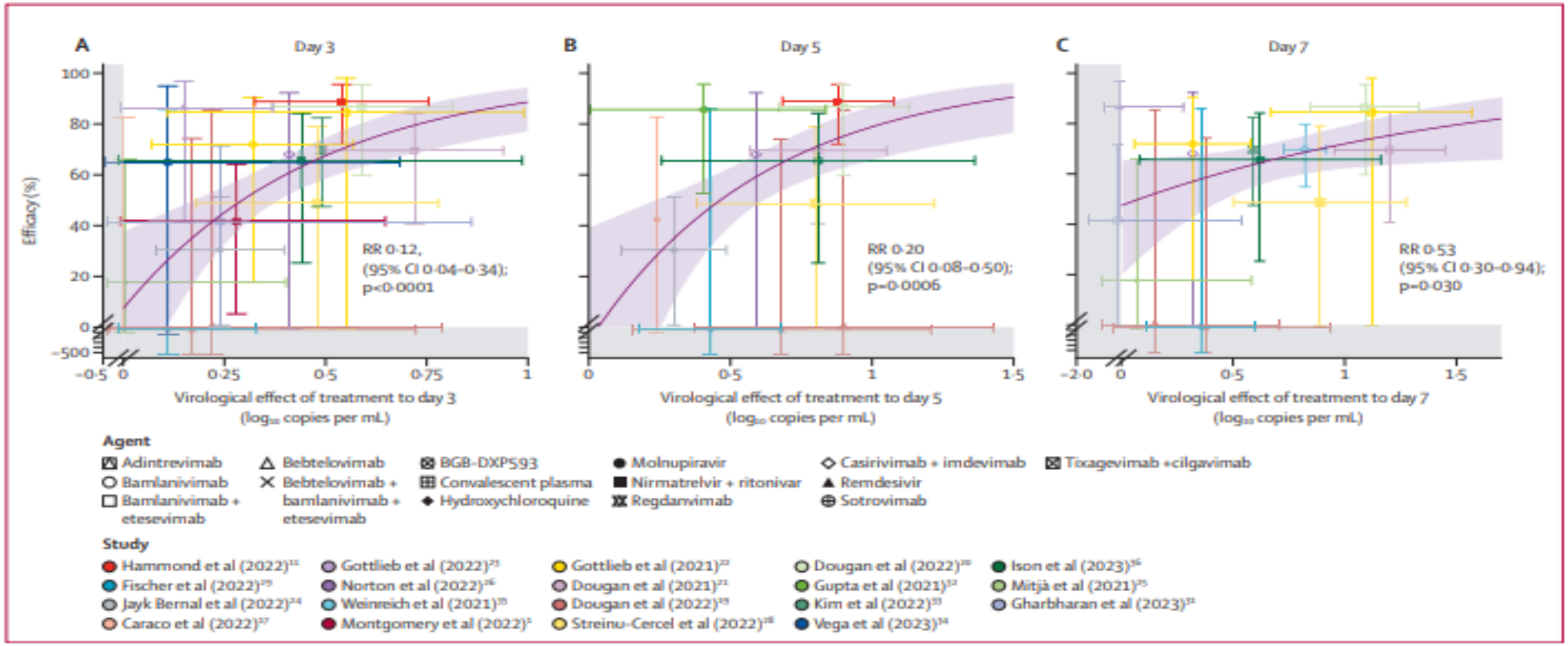

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Suggestions

- Reliance on a single endpoint? Should not ignore totality of evidence
  - Evidence from other agents in same class
  - Surrogacy data
  - Real World Evidence

- Potential for primary virologic endpoint – with directional secondary clinical endpoints
  - Symptoms change but some are more relevant for patients i.e fatigue
  - Composite endpoints or flexible endpoints

- Other endpoints demonstrate effective mechanism of action
  - Post-exposure prophylaxis
  - Transmission

Thank you

- With thanks to Aeron Hurt, Takeki Uehara, Takahiro Hasegawa, Stuart Lacey