Effective antiviral regimens to reduce COVID-19 hospitalizations: a systematic comparison of randomized controlled trials.

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Abstract

Background. Antiviral therapy has a greater impact when provided early in the disease to outpatients, potentially preventing hospitalization and subsequent deaths, while reducing healthcare system pressure. Controversies persist about the best treatment option for COVID-19 outpatients at risk of disease progression to hospital. No head-to-head RCT has been conducted to compare the three major modalities in current use-oral/intravenous antivirals, monoclonal antibodies and COVID-19 convalescent plasma (CCP).

Methods. We assembled data from March 2020 to April 2022 from published outpatient RCTs examining authorized COVID-19 therapies with hospitalization as the major endpoint, and that also assessed mortality, symptom resolution, underlying risk factors for progression, timing and dose of the intervention in relationship to evolving variants of concern (VOC).

Findings. CCP, monoclonal antibodies and oral antivirals each had comparable efficacy converging to 80% hospital risk reduction dependent on the dose and the timing of the intervention. Most RCTs targeted populations with at least one risk factor for severe COVID-19. Control group hospitalizations were less than 10% in 16 of 20 RCTs. Amongst the effective two CCP trials, monoclonals and three antiviral small molecules, deaths were reduced by 90% from 44 total in combined control arm to 4 in intervention arms. The overall risk of bias was deemed low for nine studies and some concerns for eight. The I^2 statistic heterogeneity amongst the outpatient trials with endpoint hospitalization is 72% ($p- < 0.01$).

Interpretation. The emerging resistance of Omicron BA.2 and related sublineages (XE, BA.2.12.1, BA.4, and BA.5) to monoclonal antibodies suggests a pressing need to reevaluate CCP (nowadays largely available from vaccinees with high neutralizing antibody levels) for COVID19 outpatients at risk of disease progression, especially in settings with constrained medical resources.

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Research in context

Evidence before this study. To date no head-to-head randomized controlled trial (RCT) has ever compared treatment options for COVID-19 outpatients, making comparisons and treatment choices difficult. We assembled RCTs with hospitalization as the primary endpoint. A literature search of MEDLINE (through PubMed), medRxiv and bioRxiv databases was carried out inclusive of RCTs published from March 2020 to April 2022 inclusive, using the search terms ("COVID-19" OR "SARS-CoV-2" OR "coronavirus disease 2019") AND ("treatment" OR "therapy") AND ("outpatient" OR "hospitalization"). The risk of bias obtained at COVID-19-Network Meta-Analysis (NMA), was low in half of the studies with some concerns for the remaining.

Added value of this study. This systematic review compared outcomes among RCTs of outpatient therapy for COVID-19, taking into account time between onset of symptoms and treatment administration. We found that small-chemical antivirals, convalescent plasma and anti-Spike monoclonal antibodies had comparable efficacy. Trials of monoclonals were performed prior to the recognition that they had become ineffective against the Omicron sublineages.

Implications of all the available evidence. Monoclonal antibodies and small chemical antivirals each have drawbacks. Both take time to be developed and are expensive. Monoclonals can lose efficacy with viral mutation, and chemical antivirals have contraindications and adverse events. Convalescent plasma retains its potency and is likely to be the only accessible therapeutic option for low-and-middle income countries.

Introduction

By late April 2022 the world had recorded over half a billion cases and more than 6 million deaths from COVID-19, while the USA had recorded more than 80 million cases with nearly 1 million deaths. Death rates in the USA and the rest of the world are similar at just above 1%. Hospitalization rates, not reported worldwide, are about 6% in the US, where from August 2020 to April 2022, nearly 5 million individuals were hospitalized for COVID-19. A pronounced spike in hospitalizations for COVID-19 in the US took place in the first two months of 2022 with the introduction of the Omicron variant of concern (VOC). Vaccination boosts have largely reduced the risk of hospitalization and death, but patients at risk still require early treatment to avoid disease progression.

The risk of hospitalization can be reduced by antivirals of different classes. Randomized controlled trials (RCTs) have tested therapeutic agents against placebo or standard of care, but no RCT has been conducted comparing the main classes of outpatient treatment – small chemical antivirals, monoclonal antibodies and convalescent plasma. COVID-19 convalescent plasma (CCP) was first administered to hospitalized patients across the world in March 2020, a few weeks after the pandemic began[1], but was not initially used in outpatients.

The first outpatient treatments for COVID-19 authorized by the FDA were two monoclonal antibody cocktails, bamlanivimab plus etesevimab[2] and casirivimab plus imdevimab[3], approvals that preceded the introduction of mRNA vaccines by two months [4,5]. While many small chemicals were repurposed as antivirals during the early stages of the pandemic, oral antivirals developed against SARS-CoV-2 for outpatients were not available until December 2021, when nirmatrelvir/ritonavir[6] and molnupiravir[7] were approved. The following month, intravenous remdesivir was also approved for out-patient use[8]. On December 2021, nearly two years after the first use of CCP, the FDA approved its outpatient use, but only for immunosuppressed patients[9]. [10].

Given that no direct (head-to-head) RCT comparison between outpatient treatments have ever been conducted, we here compare the efficacy of CCP, monoclonal antibodies and small chemical antivirals as reported in published outpatient RCTs, with hospitalization as the predefined endpoint.

Methods

Literature search

We assembled outpatient COVID-19 RCTs with hospitalization as the primary outcome, by searching MEDLINE (through PubMed), medRxiv and bioRxiv databases for the period of March 2020, to April 2022 inclusive, with English language as the only restriction. The Medical Subject Heading (MeSH) and key words used were: ("COVID-19" OR "SARS-CoV-2" OR "coronavirus disease 2019") AND ("treatment" OR "therapy") AND ("outpatient" OR "hospitalization"). In PubMed, the filter "Randomized Controlled Trial" was applied. We also screened the reference list of reviewed articles for additional studies not captured in our initial literature search. We included only RCTs dealing with antiviral agents (either intentional or repurposed), and excluded supportive treatments (e.g.: antihypertensive, anticoagulants, anti-inflammatory drugs). We also excluded case reports, case series, non-randomized trials, review articles, meta-analyses and original research articles reporting only aggregate data. Articles underwent a blind evaluation for inclusion by two assessors (D.S. and D.F.) and disagreements were resolved by a third senior assessor (A.C.). A risk of bias assessment of each selected trial was performed by COVID-19- Network Meta-Analysis (NMA)[11,12]. Figure 1 shows a PRISMA flowchart of the literature reviewing process. The following parameters were extracted from studies: time from onset of symptoms to treatment, study dates, recruiting countries, gender, age (including the fraction of participants over age 50, 60 and 65), ethnicity, risk factors for COVID-19 progression (systemic arterial hypertension, diabetes mellitus, and obesity),

sample size, dosage type of control, hospitalizations and deaths in each arm, baseline SARS-CoV-2 serology status and time to symptom resolution.

Statistical methods

Descriptive analysis included time-to-treatment, geography (country) of the study, age, sex, race (white and black), ethnicity, and medical high-risk conditions (e.g., diabetes, hypertension, and obesity or BMI > 30).

Absolute risk reduction (arithmetic difference in hospitalization between the 2 groups) and relative risk reduction (percent reduction in risk) were used to represent the efficacy of treatment. Odds ratios (the odds of hospitalization for the treatment group over the odds of hospitalization for the control group) and 95% confidence intervals (95% CI) were used to show the direction of effect and its significance in comparing treatment group and control groups.

The forest plot and the enrolment figure were used for visualization and comparison of the odds ratio among studies. The enrolment progress (duration and calendar months) of each study is shown as a Gantt plot. The statistical tests were two-tailed, and the significance level was 0.05. The figures were created in Prism software. All the data manipulation and the analyses were performed in Excel and MedCalc (Version 20.106, MedCalc Software Ltd., Ostend, Belgium).

Role of the funding source

The study sponsors did not contribute to the study design; the collection, analysis, and interpretation of data; manuscript preparation, and the decision to submit the paper for publication.

Results

Five large-scale outpatient RCTs investigating CCP have been published. A RCT from Argentina [13] was followed by a RCT halted after the data safety monitoring board (DSMB) determined "futility" before completion [14]. The third RCT involved methylene blue-treated CCP[15], and the fourth was a large RCT in the USA (CSSC-004) [10]. A fifth RCT was run in The Netherlands[16], published as combined analysis with the Spanish RCT[16]. Five monoclonal antibody RCTs (bamlanivimab[2], bamlanivimab/ etesevimab[17], casirivimab/ imdevimab[18], sotrovimab[19,20], and bebtelovimab[21]) led to initial FDA emergency use authorizations with regdanvimab[22] approved in Europe. Three outpatient RCTs of small chemical antivirals - oral molnupiravir[7], oral nirmatrelvir/ritonavir[6] and intravenous remdesivir[23] led to emergency authorization. Additionally, several repurposed drugs were tested in large outpatient RCTs were included in our analysis for context: fluvoxamine[24], nitazoxanide[25], ivermectin[26], colchicine[27], hydroxychloroquine[28], and peginterferon lambda[29]. Some small RCTs of repurposed drugs were excluded for being underpowered to detect effects (niclosamide[30], sofosbuvir/daclatasvir[31], fluvoxamine[32], hydroxychloroquine[33-35] and peginterferon lambda[36,37]).

Trial populations

We reviewed in detail 20 outpatient RCTs, conducted from March 2020 to December 2021 (5 of CCP, 6 of monoclonal antibodies, 9 of small chemical antivirals). Enrollment in these trials was from March 2020 to December 2021 and ranged in duration between 3 and 16 months, averaging 9, 4, and 6 months for the CCP, monoclonal antibodies, and small chemical antivirals, respectively (Figure 1). All RCTs used hospitalization as the primary endpoint, excepting the Argentinean RCT, which used severe respiratory distress as a proxy for hospitalization. These RCTs enrolled a total of 22,565 participants (11,224 control/11,341 intervention - Figure 1 and Table 1). The overall risk of bias was deemed low for 9 studies with some concerns for 10, with the peginterferon lambda trial yet to be reviewed.

Age and Ethnicity

Among CCP RCTs, participants in the CSSC-004 CCP were aged 18-85, with only 35% of participants over age 50[10] and COV-early had 86% over 50[16]. Both the ConV-ert[15] and C3PO[14] was restricted to participants over age 50. The Argentinean RCT enrolled exclusively over age 65. In most monoclonal antibody RCTs (sotrovimab[20], bamlanivimab/ etesevimab and casirivimab/ imdevimab) the median age was over 50, while in the bamlanivimab and bebtelovimab[21] RCTs median age was 45 and 34 years respectively. The three small chemical antiviral RCTs which led to FDA EUAs had younger median ages (43, 46 and 50) than did enrollees in the antibody-based therapy RCTs. The small chemical antiviral RCTs had a more even balance of female/male, while the antibody-based RCTs were weighted towards more females. Ethnicity in most RCTs except those in Latin countries was predominately Caucasian, with the monoclonal antibody and small chemical antivirals RCTs having single digit percentages of blacks (Table 1). Some RCTs (i.e., ConV-ert[15] and Argentinean CCP[15]) did not include all ethnicities.

Risk factors for COVID19 progression

The RCTs differed in the percentage of participants with risk factors for progression to severe COVID-19. All RCTs except bebtelovimab[21] and CSSC-004[10] had more than 60% of participants at high-risk of COVID-19 progression, with the small chemical antiviral RCTs having nearly 100% high-risk participants. Diabetes mellitus was represented in 10 to 20% of most RCTs. CCP RCTs had fewer obese participants than the monoclonal and small chemical antivirals RCTs (Table 1).

Geography and time period

Four of the five CCP RCTs (COV-early[16], CONV-ert[15], Argentina[13] and C3PO[14]), four of the five monoclonal antibody RCTs (except bebtelovimab[21]) and the colchicine[27] and hydroxychloroquine[28] RCTs took place in the setting of the D614G variant and the Alpha VOC. By contrast, most of the molnupiravir and nirmatrelvir/ritonavir[6] RCTs were conducted in the setting of the Delta VOC. The ivermectin[26] and fluvoxamine[24] RCTs ended as the Delta VOC wave began in August 2021. The remdesivir RCT spanned D614G, Alpha and Beta VOC but missed Delta. The CSSC-004 RCT of CCP was the longest RCT reviewed, spanning periods characterized by D614G to Delta VOC infections[10]. The CCP RCTs were conducted in the USA, Argentina, Netherlands and Spain (Table 1). The monoclonal antibody trials all had a USA component but were largely centered in the Americas with the exception of the sotrovimab RCT which took place in Spain[20].

Seropositivity, comorbidity and timing from symptom onset

Seven studies reported SARS-CoV-2 seropositivity at enrolment, ranging from 10 to 20%, which did not significantly influence hospitalization rates in subgroup analysis (Table 2). The exception was the nirmatrelvir/ritonavir RCT, in which 50% of participants were anti-Spike antibody positive at baseline enrolment, which did not change from overall results in subgroup analysis[6]. Among the approximately 500 people in each arm who were antibody positive, 8 in the control arm were hospitalized while only one in the intervention arm was hospitalized[6]. Reduction in hospitalizations was more sustained amongst diabetes mellitus, systemic arterial hypertension and obesity groups. In the majority of the successful RCTs, the median time to intervention from illness onset was 3 days, with CSSC-004 and remdesivir being the exception at 6 and 5 days (Figure 3). All the RCTs enrolled within 8 days except colchicine[27].

Efficacy endpoints

Efficacy at preventing hospitalization

Control hospitalization rates varied across the RCTs. Notably, 3 CCP RCTs had hospitalization rates of 11, 20 and 31% in their control populations, much higher than all other antiviral RCTs, including the fourth RCT of CCP, CSSC-004, where it was 6.3%[10] (Table 2 and Figure 2). The four monoclonal antibody RCTs

other than of bebtelovimab[21] had a hospitalization rate in controls (6%) similar to CSSC-004[10]. The bebtelovimab RCT was restricted to low-risk individuals and had a very low hospitalization rate of 1.6% (2/125) [21]. Hospitalization rates in the 3 small chemical antiviral RCTs averaged 7%, and for the 4 RCTs of repurposed drugs it was 8%. Thus, CCP trials, on average, treated sicker outpatients than either the chemical antiviral or convalescent antibody trials.

CCP efficacy in preventing hospitalization or progression was about 50% in both the Argentine and in CSSC-004 RCTs[10] and 36% and 31% in COV-early[16] and C3PO[14]. But risk reduction was 73% risk reduction in recipients of higher dose or higher antibody CCP in Argentina, [13] and was 80% in participants treated within 5 days of symptoms in CSSC-004 [10] (Figure 2). With the exception of the bebtelovimab trial, which had a null finding with just two hospitalizations in each study arm, monoclonal RCTs reduced the risk of hospitalization from 69% to 80% (average 75%). Two of the three small molecule antiviral drugs (remdesivir and nirmatrelvir/ritonavir[6]) showed very high levels of risk reduction - 86% and 88% respectively - but molnupiravir reduced risk of hospitalization by only 30%, and the combination of lopinavir/ritonavir was associated with a non-significant increase in risk of hospitalization[6].

Among RCTs of repurposed drugs, all showed small and non-significant reductions in risk - 11% for ivermectin[26], 20% for colchicine[27]o, 21% for fluvoxamine[24] and 24% for hydroxychlorochine[28]. The RCT of nitazoxanide[25] found one hospitalization among 184 treated participants compared to five hospitalizations among 195 controls, far too few events to achieve significance.

The heterogeneity amongst the outpatient trials with hospitalization as an endpoint measured by the I^2 statistic is 72%, with p-value < 0.01.

Efficacy at reducing mortality

Cumulatively, the two effective CCP RCTs (Argentine[13] and CSSC-004[10]) recorded 7 deaths in controls and 2 in the treatment arm. The monoclonal RCTs had 15 deaths among controls and 1 in the intervention arm (Table 2). The three small chemical antiviral RCTs experienced 22 deaths in the control groups and 1 in the intervention groups. Total deaths in the RCTs of the three drug classes of effective outpatient therapy numbered 44 in the control arms (n=6351) or 0.7% and 4 in the intervention arms (n=6528) or 0.06%. Thus, overall approved outpatient therapies reduced mortality by more than 90%. The repurposed drugs RCTs recorded 59 deaths in the control groups and 43 in the intervention groups, for a reduction in mortality of 26%.

Efficacy at symptom resolution

The two effective CCP RCTs (Argentine[13] and CSSC-004[10]) did not report comparison of time to symptom resolution, while the COV-early[16] and ConV-ert[15] RCTs reported no difference in the median time of symptom resolution in the two groups, but also had no efficacy in hospital outcome[15] (Table 2). The monoclonal antibodies noted statistical faster resolution by 1, 2 or 4 days for bamlanivimab/ etesevimab, bebtelovimab and casirivimab/imdevimab, respectively. The bamlanivimab-only smaller RCT did not show a difference. Of the three small chemical antivirals, molnupiravir detected no difference in symptom resolution, while the 3-day outpatient remdesivir noted a rate ratio difference of 1.92 (95% CI 1.26 to 2.94) for alleviations of symptoms by day 14. The three RCTs largely performed in Brazil for fluvoxamine, ivermectin[26] and hydroxychloroquine[28] noted no differences in symptom resolution. The nirmatrelvir/ritonavir RCT did not report an analysis of symptom resolution.

Costs and resiliency against variants of concern

The monoclonals and intravenous remdesivir schedules cost about 1000 to 2000 Euros per patient, respectively, while the oral drugs are less than 1000 Euros per patient. The cost of CCP approximates 200

Euros. The single and paired monoclonals successively lost efficacy against Delta and Omicron such that only bebtelovimab remains effective so far. Tixagevimab and cilgavimab were approved for pre-exposure prophylaxis, not COVID-19 treatment, and only cilgavimab retains anti-omicron activity *in vitro* so far. Small chemical antivirals retain *in vitro* efficacy against omicron, but concerns remain regarding both, with molnupiravir having very low efficacy *in vivo*[7] and mutagenicity *in vitro*[38]. Early clinical relapses are being described for nirmatrelvir in immunocompetent patients[39]. CCP from unvaccinated donors does not inhibit omicron but any CCP from donors having any sequence of vaccination and COVID-19 or having had three mRNA inoculations retains omicron neutralizing activity (Table 3).

Discussion

SARS-CoV-2 specific antibodies and small chemical antivirals all showed effectiveness in reducing COVID-19 hospitalizations, although their mechanisms of action (MOA) are not identical, and dosages, time from symptom onset to treatment, and the VOCs circulating during study enrolment all differed across RCTs. Despite these major limitations, the assembly of these effective, yet molecularly disparate RCT outpatient studies shows the consistent importance of early outpatient treatment for patients at risk of progression [40]. Treatment within 5 days of illness onset is more effective than later treatment, as would be expected for an antiviral. Importantly, for CCP, increasing the dose in the Argentina RCT and shortening the intervention interval to within five days of illness onset produces a risk reduction for hospitalization close to 80%, comparable to (or superior) to the findings of trials with monoclonal antibodies and small chemical antivirals. Overall, a reduction in mortality is suggested with these outpatient therapies, but the individual RCTs are underpowered to investigate death as an individual outcome.

Outpatient RCTs are more difficult for non-industrial institutions to perform during an infectious disease pandemic, requiring separate spaces within clinics or other healthcare structures. By contrast, the pharmaceutical industry has established mechanisms in place for outpatient trials. The relative ease of conducting inpatient trials may have led most CCP trials – all conducted by academic institutions - to have been conducted in hospitals. However most antiviral/antimicrobial therapies are more effective when given before hospital admission. SARS-CoV-2 antibodies, whether elicited by vaccines, or provided as polyclonal (CCP) or monoclonal antibodies, have all been demonstrated to substantially prevent progression of COVID-19 to hospitalization. Either vaccination of immunocompetent subjects and therapeutic administration of monoclonals generate high serum levels of neutralizing antibodies (albeit of different subclasses and at different times): dose concerns, as well as risk of immune escape under selective pressure[41] still exist for monoclonals (e.g., tixagevimab-cilgavimab[42]).

Our comparison shows a minimal effect of these agents on time to symptom resolution, but a more amplified effect of 50 to 80% reduction in rates of hospitalization, which might be further amplified for a more than 90% reduction in deaths when the same therapeutic intervention is given early in the course of disease rather than later.

Both vaccine-elicited antibodies and those found in CCP are polyclonal, which in turn means that they include various isotypes to provide functional diversity and target numerous epitopes making variant escape much more difficult. Hence polyclonal antibody preparations are more resilient to the relentless evolution of variants. This is in marked contrast to monoclonal antibodies, which target single epitopes of SARS-CoV-2. This exquisite specificity renders them susceptible to becoming ineffective with single amino acid changes. It has been shown that both adding boosters to the vaccine regimen and producing vaccine-boosted CCP provide high amounts of neutralizing antibodies which can be effective against practically any existing VOC, including Omicron[43] (thanks to the well-known phenomenon of “epitope spreading”).

The clinical armamentarium has been reduced since most single and double ("cocktail") monoclonals have lost effectiveness against new VOCs. Bebtelovimab is the only remaining effective monoclonal antibody approved for therapy. These antibodies bind to the everchanging receptor-binding domain of the SARS-CoV-2 Spike protein and have an ongoing risk of losing efficacy with any potential future VOC.

Another consider is cost. As shown in Table 3, the market cost of monoclonals is generally about 10 times higher than that for manufacturing CCP (at the same level of engagement), making CCP the only antiviral affordably available to LMIC. In this light, there is an urgent need to revise the current WHO guidelines, based for CCP on RCTs up to Summer 2021, which recommend against CCP in outpatients.

The three most important infectious disease threats to public health (tuberculosis, HIV and malaria) have all had well-documented histories of developing resistance to single molecule interventions. Polyclonal CCP (itself a multiple agent entity) and the use of multiple drugs together are the best approach to preventing single molecule resistance in these diseases, and the same seems to be true in fighting SARS-CoV-2. High-dose treatment early in disease with multiple molecules is the ideal strategy for infectious diseases.

Declaration of interests

DS, DFH, AC were investigators in the CSSC-004 study; D.F. and M.F. were investigators in the TSUNAMI RCT of CCP. DJS reports AliquantumRx Founder and Board member with stock options (macrolide for malaria), Hemex Health malaria diagnostics consulting and royalties for malaria diagnostic test control standards to Alere- all outside of submitted work. AC reports being part of the scientific advisory board of SabTherapeutics and has received personal fees from Ortho Diagnostics, outside of the submitted work. All other authors report no relevant disclosures.

Contributors

DS wrote the first draft. DF curated Figures 4 and 5 and revised the text. JO, DS performed statistical analyses. AC, NP, MF and DH critically revised the manuscript. DS and DF directly accessed and verified the underlying data reported here.

Data Sharing

Datasets used for this systematic review are publicly available in PubMed, medRxiv and bioRxiv.

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Figure Legends

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Figure 2

Duration and calendar months of the RCT in context of dominant variants of concern. Study start and end for enrollments with approximate time periods for variants of concern.

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Comparison of mean interval from symptom onset to enrollment as well as per protocol interval for all participants.

Figure 5

Venn diagram of mAb efficacy against Omicron sublineages**.** *In vitro* activity of currently approved mAbs against Omicron sublineages circulating as of May 2022 (BA.1, BA.2, BA.4, BA.5, and the BA.1-BA.2 recombinant XE). Specific Omicron Spike amino acid mutation causing baseline ≥ 4-fold-reduction in neutralization against mAbs are reported. Mutations for which the majority of studies are concordant are reported: the different fold-reductions for each mAb are identified across concordant studies as color coded numbers defining the mean median values of specific reduction in each study. Sourced from https://covdb.stanford.edu/page/susceptibility-data/.

[#] approved for prophylaxis only;

* L452R occurs in all BA.4/BA.5 lineages, but only in BA.2.12.1;

[!] no baseline resistance mutation found in Omicron sublineages for bebtelovimab so far.

Table 1

Demographic and clinical characteristics of recruits in the RCTs analyzed in this review.

	Geography	Enrolled	mITT	median age (range)	total female n (%)	White n (%)	Black n (%)	*LatinX n (%)	age over 65 n (%)	age over 60 n (%)	age over 50 n (%)	1 or more medical high risk conditons for COVID-19 progression (%)	diabetes n (%)	hypertension n (%)	obesity or BMI >30 n (%)
CONV-ert CCP	Spain		376	56	173 (46)	0	0	376 (100)			376 (100)	278 (74)	49 (13)	not reported	96 (26)
COV-early CCP	Netherlands		406	58	187 (46)	406 (100)	0	0			351 (86)	278 (68)	not reported	not reported	not reported
C3PO CCP	USA	511	511	54	274 (54)	237 (46)	103 (20)	156 (31)			511 (100)	511 (100)	142 (28)	216 (42)	302 (59)
Argentine CCP	Argentina	160	160	77 (65-90+)	100 (62)	0	0	160 (100)	160 (100)			131 (82)	36 (23)	114 (71)	12 (8)
CSSC-004 CCP	USA	1225	1181	43 (18-85)	675 (57)	934 (79)	163 (14)	170 (14)	80 (7)		410 (35)	470 (40)	99 (8)	276 (23)	444 (38)
Bamlanivimab	USA	467	452	45 (18-86)	249 (55)	389 (86)	29 (6)	198 (44)	53 (12)			310 (69)		not reported	201 (44)
Sotrovimab	United States, Canada, Brazil, and Spain	1057	1057	53(17-96)	571 (54)	919 (87)	42 (4)	687 (65)	211(20)			1055 (99.9)	233 (23)	not reported	665 (63)
Bamlanivimab/ etesevimab	USA	1035	1035	54 (12-77+)	538 (52)	896 (87)	83 (8)	304 (29)	323 (31)			983 (95)	285 (28)	not reported	median 34 bmi
casirivimab/ imdevimab	USA Mexico	2696	2696	50 (iqr 39-50)	1407 (52)	2297 (85)	143 (5)	935 (35)	358 (13)			2696 (100)	412 (15)	993 (37)	1559 (58)
bebtelovimab	USA	253	253	34	135 (53)	187 (74)	48 (19)	91 (36)	1 (<1)			0 (0)	not reported	not reported	
regdanvimab	South Korea,	327	307	51 (iqr40-60)	166 (51)	286 (87)	0	27 (8)		85 (26)		226 (69)	29 (9)	not reported	52 (16)

	Romania, Spain, USA														
molnupiravir	worldwide	1433	1408	43 (18-90)	735 (51.3)	813 (56)	75 (5)	711 (49)		246 (17)		1424 (99.4)	228 (15.9)	not reported	1056(73)
nirmatrelvir/ ritonavir	worldwide	2246	2085	46 (18-88)	1098 (49)	1607 (72)	110 (4.9)	1010 (45)	287(12.8)			2085 (100)	252 (11)	739 (33)	744 (36)
remdesivir	USA, Spain, Denmark UK	562	562	50 (12-77+)	269 (48)	452 (80)	42 (7.5)	235 (41)		170 (30)		562 (100)	346 (62)	268 (48)	310 (55)
fluvoxamine	Brazil	1497	1497		862 (58)	6 (1)	5 (1)	1486 (99)			655 (44)	1497 (100)	243 (16)	194 (13)	751 (50)
nitazoxanide	USA Peurto rico	379	379	40 (12-83)	214 (57)	233 (61)	8 (2)	130 (34)				238 (63)			
ivermectin	Brazil	1358	1349	49	791 (58)	12 (1)	12 (1)	1310 (98)				1349 (100)	180 (13)	114 (8)	675 (50)
colchicine	Brazil, Canada, Greece, South Africa, Spain, and the USA	4488	4488	54 (iqr 47-61)	2421 (54)	4182 (93)	233 (5)	<10%		1122 (25)		4488 (100)	894 (20)	1629 (36)	2052 (46)
hydroxychloroquine	Brazil	441	427	53 (18-81)	243 (55)	12 (3)	7 (1)	422 (96)			262 (59)	441 (100)	89 (20)	210 (48)	177 (40)
peginteferon lamda	Brazil	1936	1936	Not done	Not done	Not done	Not done	Not done	Not done	Not done	Not done	xx (100)	Not done	Not done	Not done

Table 2

Deaths, hospital rates and odd ratios, antibody status and symptom resolution

	Deaths control n (%)	Deaths intervention n(%)	Control hospita-lizations %	Intervention hospitaliza-tions %	Absolute Risk Reduction	Relative Risk Reduction	Odds ratio	95 CI low	95 CI high	z statistic	signifi-cance (p)	Antibody positive at Baseline n(%)	Symptom resolution: Intervention to control in days
CONV-ert CCP	2 (1.1)	0	11.2	11.7	-0.5	-4.8	1.05	0.56	1.99	0.16	0.8700	43 (11)	NO difference
COV-early CCP	0	1 (0.5)	9.3	5.9	3.4	36.0	0.62	0.29	1.30	1.27	0.2042	51 (13)	NO difference
C3PO CCP	1 (0.4)	5 (1.9)	22.0	20.2	1.8	8.2	0.90	0.59	1.37	0.50	0.6157		
C3PO CCP mod per protocol	1 (0.4)	5 (2.1)	20.2	13.9	6.3	31.2	0.64	0.39	1.03	1.84	0.0666		
Argentine CCP	4 (5)	2 (2.5)	31.3	16.3	15.0	48.0	0.56	0.20	0.91	2.19	0.0280		
High titer Argentine CCP			31.3	8.3	22.9	73.4	0.20	0.06	0.71	2.48	0.0132		
CSSC-004 CCP	3 (0.5)	0	6.3	2.9	3.4	54.3	0.44	0.25	0.79	2.73	0.0060		
CSSC-004 CCP <=5d	3 (1.2)	0	9.7	1.9	7.7	79.9	0.19	0.07	0.49	3.38	0.0007		
bamlanivimab	0	0	6.3	1.6	4.7	74.3	0.24	0.08	0.74	2.48	0.0130		NO difference
sotrovimab	2 (0.4)	0	5.7	1.1	4.5	80.0	0.19	0.08	0.46	3.66	0.0002		
bamlanivimab/etesevimab	10 (1.9)	0	7.0	2.1	4.8	69.5	0.29	0.15	0.58	3.53	0.0004		YES- 8d vs 9d p=(.007)
casirivimab/imdevimab	3 (0.2)	1 (0.1)	4.6	1.3	3.3	71.3	0.27	0.16	0.46	4.84	0.0001	620 (23)	YES- 10 d vs 14 p=(.0001)
bebtelovimab	0	0	1.6	1.6	0.0	-2.4	1.02	0.14	7.39	0.02	0.9800	27 (11)	YES- 6d to 8d p=(.003)
regdanvimab	0	0	8.7	4.4	4.3	49.0	0.49	0.19	1.27	1.464	0.1432	9 (3)	yes 6 d vs 9 d p=(.01)

molnupiravir	9 (1.3)	1 (0.1)	9.7	6.8	3.0	30.4	0.67	0.40	0.86	2.73	0.0060	284 (19.8)	NO difference
nirmatrelvir/ritonavir	12 (1.1)	0	6.3	0.8	5.5	87.8	0.12	0.06	0.24	5.73	0.0001	1149 (51)	
remdesivir	1 (0.4)	0	5.3	0.7	4.6	86.5	0.13	0.03	0.57	2.70	0.0069		YES- Alleviation of symptoms by day 14 (rate ratio, 1.92; 95% CI, 1.26 to 2.94)
fluvoxamine	25 (3.3)	17 (2.3)	12.8	10.1	2.7	21.1	0.77	0.56	1.05	1.64	0.1010		NO difference- 40% resolved by day 14
nitazoxanide	0	0	2.6	0.5	2.0	78.8	0.21	0.02	1.79	1.43	0.1531	38 (10)	Yes mild illness, but NO for moderate illness
ivermectin	24 (3.6)	21 (3.1)	15.9	14.1	1.8	11.1	0.87	0.65	1.17	0.90	0.3661		NO difference- 40% resolved by day 14
colchicine	9 (0.4)	5 (0.5)	5.8	4.7	1.2	20.0	0.79	0.61	1.03	1.74	0.0814		
hydroxychloroquine	1 (0.5)	0	5.0	3.9	1.1	22.7	0.76	0.30	1.94	0.57	0.5707		NO difference by Cox proportional HR
peginterferon lamda	1 (0.1)	4 (0.3)	5.6	2.7	2.9	51.8	0.47	0.29	0.77	3.06	0.0023		

Table 3

Summary of historical efficacy of different therapeutics against SARS-CoV-2 VOCs. White = drug not available at that time; red : not effective; green = effective; orange = partially effective. Restriction reported refer to initial restrictions by FDA. rRR : relative risk reduction in hospitalization n registration RCTs allocated according to leading VOC.

	approximate cost per patient (€)	efficacy against VOC Alpha	efficacy against VOC Delta	efficacy against VOC BA.1	efficacy against VOC BA.2 and VOI XE
bamlanivimab+etesesevimab (Eli Lilly)	2000		restricted 04/2021		
casirivimab+imdevimab - Ronapreve® (Regeneron/Roche)	2000			restricted 01/2022	
sotrovimab - Xevudy® (GSK)	1000				restricted 03/2022
tixagevimab+cilgavimab - Evusheld® (AstraZeneca)	1000				approved for prophylaxis only
regdanvimab – Regkirona® (Celltrion)	300	rRR 71%			
nirmatrelvir - Paxlovid® (Pfizer)	635 (5 days)		rRR 87%		
molnupiravir - Lagevrio® (Merck)	635 (5 days))		rRR 30%		
remdesivir - Veklury® (Gilead)	1600 (3 days)		rRR 86%		
CCP	200 (600-ml)		rRR 80%		
Vax-CCP	200 (600-ml)				

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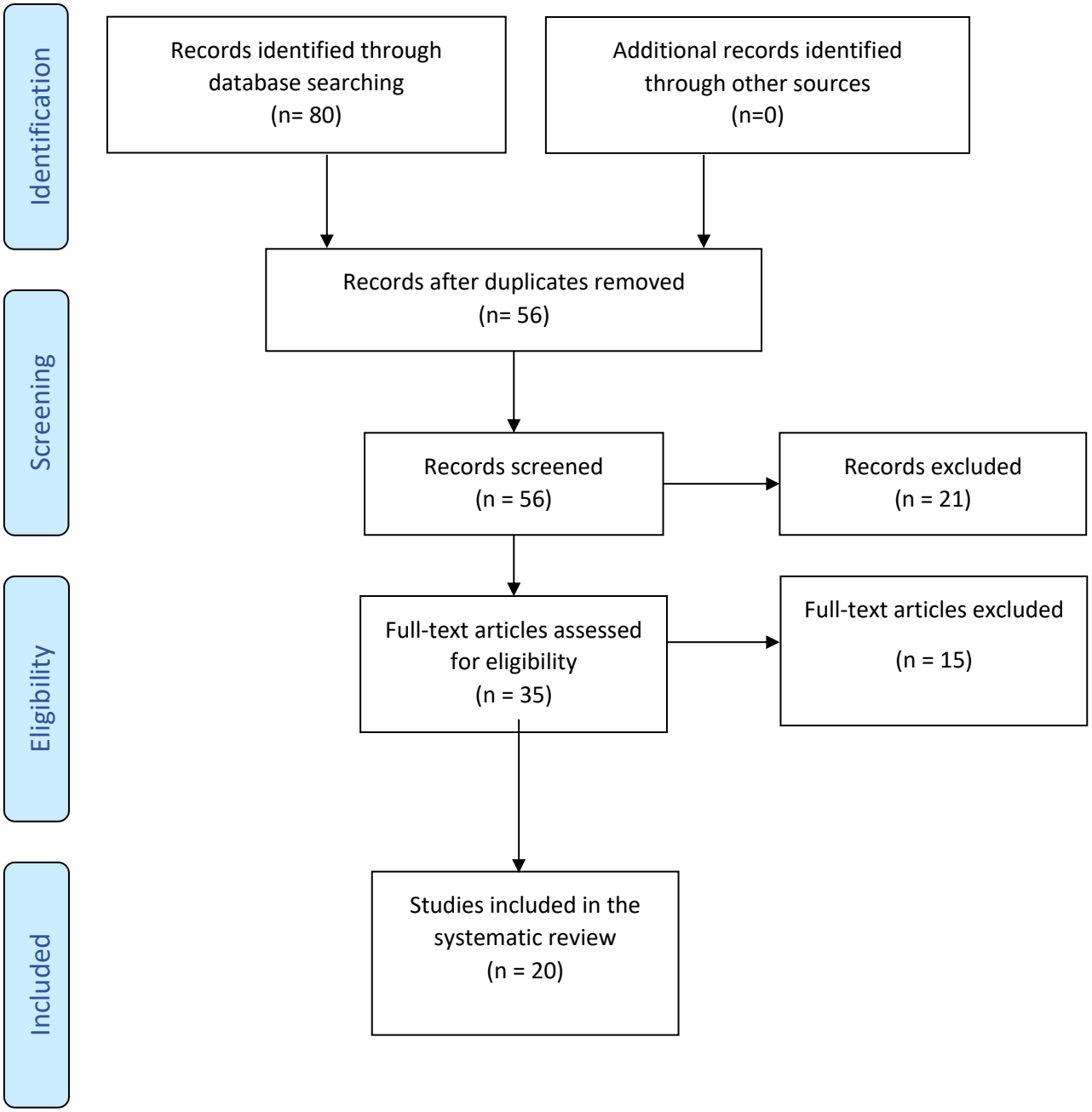

Figure 2

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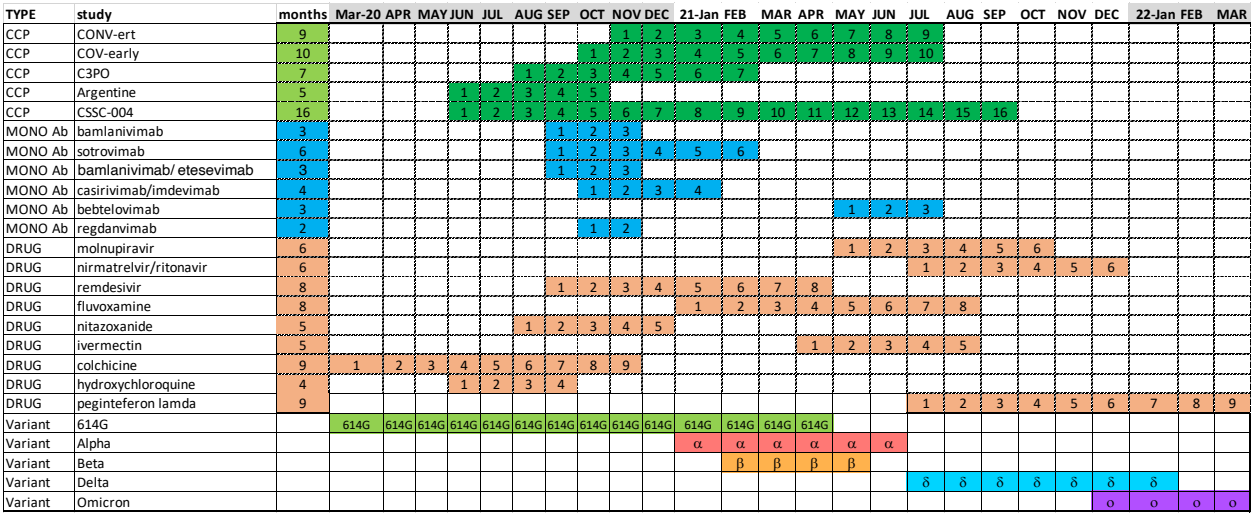

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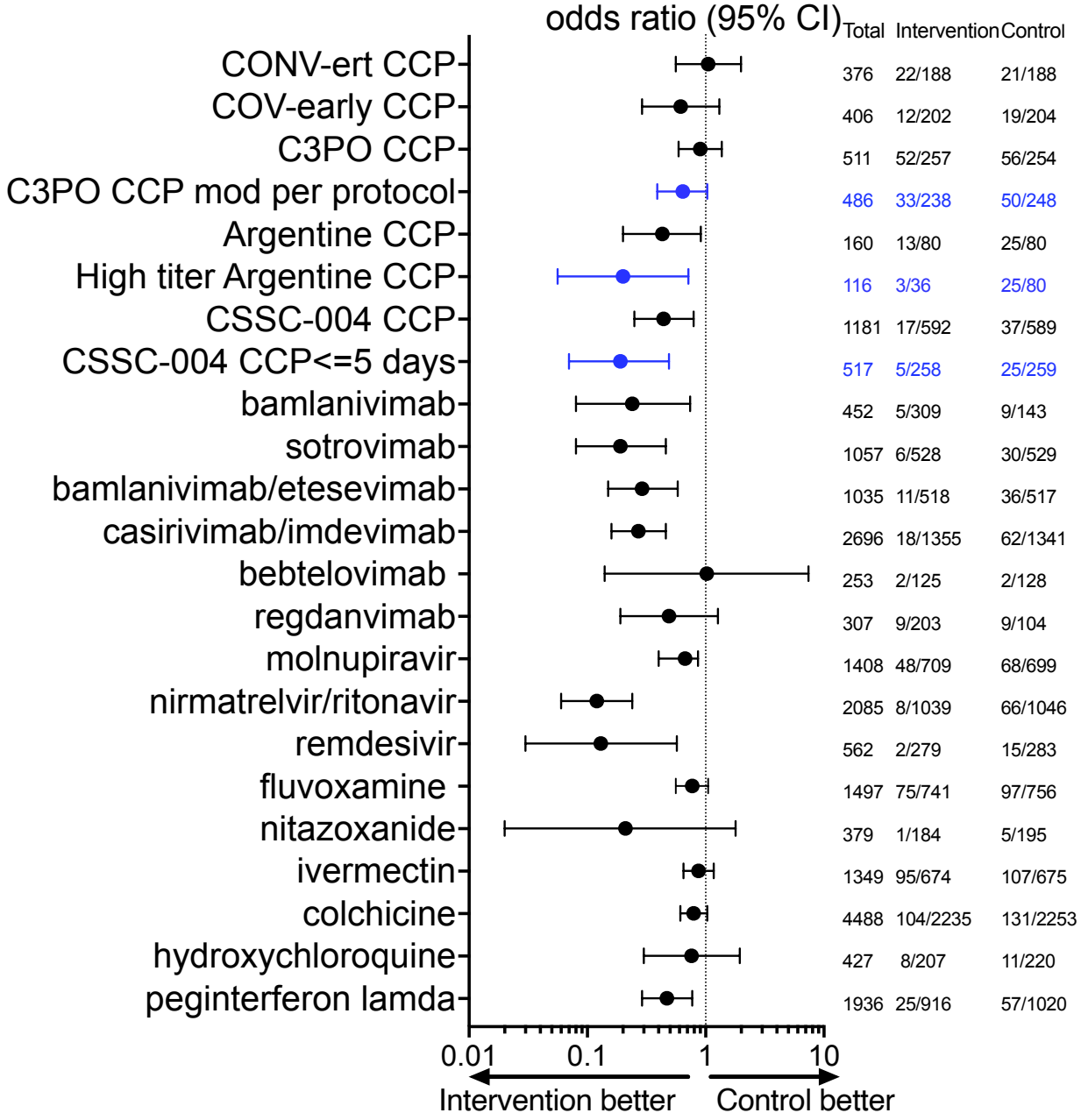

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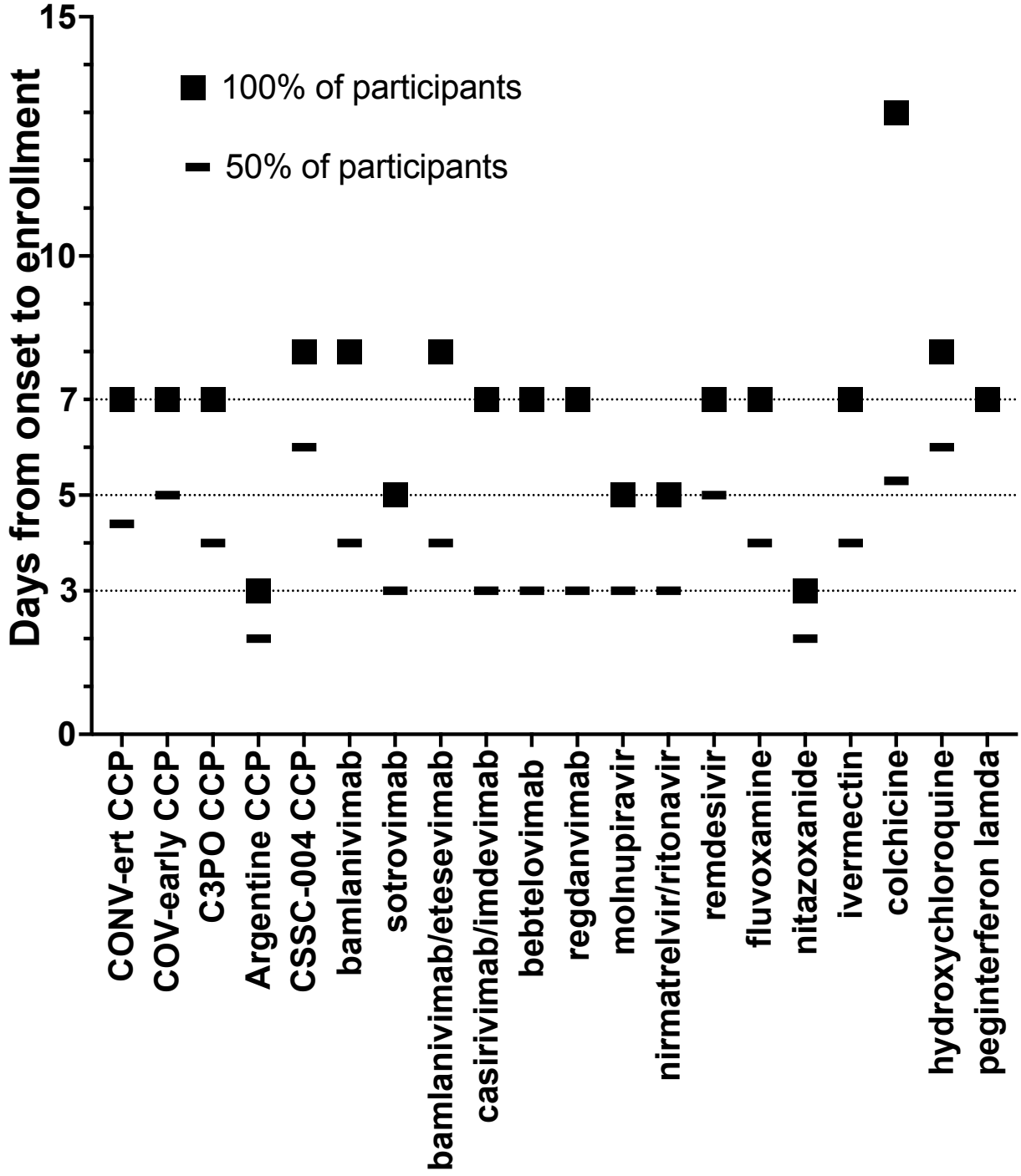

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