



















SYSTEMATIC REVIEW

The fragmented COVID-19 therapeutics research landscape: a living systematic review of clinical trial registrations evaluating priority pharmacological interventions. [version 1; peer review: 1 approved]

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Abstract

Background: Many available medicines have been evaluated as potential repurposed treatments for coronavirus disease 2019 (COVID-19). We summarise the registered study landscape for 32 priority pharmacological treatments identified following consultation

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view

with external experts of the COVID-19 Clinical Research Coalition.


Methods: All eligible trial registry records identified by systematic searches of the World Health Organisation International Clinical Trials Registry Platform as of 26th May 2021 were reviewed and extracted. A descriptive summary of study characteristics was performed.

Results: We identified 1,314 registered studies that included at least one of the 32 priority pharmacological interventions. The majority (1,043, 79%) were randomised controlled trials (RCTs). The sample size of the RCTs identified was typically small (median (25th, 75th percentile) sample size = 140 patients (70, 383)), i.e. individually powered only to show very large effects. The most extensively evaluated medicine was hydroxychloroquine (418 registered studies). Other widely studied interventions were convalescent plasma (n=208), ritonavir (n=189) usually combined with lopinavir (n=181), and azithromycin (n=147). Very few RCTs planned to recruit participants in low-income countries (n=14; 1.3%). A minority of studies (348, 26%) indicated a willingness to share individual participant data. The living systematic review data are available at <https://iddo.cognitive.city>

Conclusions: There are many registered studies planning to evaluate available medicines as potential repurposed treatments of COVID-19. Most of these planned studies are small, and therefore substantially underpowered for most relevant endpoints. Very few are large enough to have any chance of providing enough convincing evidence to change policies and practices. The sharing of individual participant data (IPD) from these studies would allow pooled IPD meta-analyses which could generate definitive conclusions, but most registered studies did not indicate that they were willing to share their data.

Keywords

COVID-19, SARS2-CoV2, coronavirus, clinical trials, emerging infections, trial registries, Living systematic review

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Any reports and responses or comments on the article can be found at the end of the article.

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Introduction

The 2019 novel coronavirus (SARS-CoV2) was first reported in December 2019¹. Over a year and half later, it has resulted in at least 270 million reported infections and over 5 million reported deaths ([World Health Organization \[WHO\]](#)). In response to the urgent need to understand the biology and epidemiology of coronavirus disease 2019 (COVID-19) and identify effective interventions, the scientific community has conducted a very large number of studies in a short period of time. As a consequence, a large number of studies have been registered in trial registries around the world. WHO compiles data from 21 trial registries in the International Clinical Trials Registry Platform (ICTRP). The ICTRP reported 9,990 COVID-19 related studies between January 2020 and May 2021 ([WHO](#)). In the same period of time, over 133,500 peer-reviewed articles on COVID-19 were indexed by the US National Library of Medicine PubMed alone². In comparison, PubMed has recorded approximately 98,000 malaria articles since 1950, and 10,000 Ebola articles.

It is notable that the only trials which have changed therapeutics policies and practices are very large -typically enrolling thousands per treatment arm. The large quantity of ongoing research makes it difficult to evaluate and assimilate the scope of work being done. This can be addressed by the development of tools and public databases to provide an overview of the COVID-19 research landscape, showcase the most relevant trials and identify knowledge gaps to explore in future studies. As highlighted in our earlier analysis, conducted in April 2020³, these tools are key to preventing unnecessary duplication of independent research efforts. This is particularly important for areas where collaboration would enable consolidation of finite resources to help provide sufficient evidence to inform clinical practice. It is critical to identify ongoing research, which may not yet be published but could contribute data to aggregated meta-analyses, as well as clinical studies which indicate an intent to share Individual Patient Data (IPD), as these could contribute data towards IPD meta-analyses.

An increasingly popular approach, which provides up-to-date evidence syntheses, is the “living systematic review” (LSR)⁴. This is suited to distilling the extensive and diverse COVID-19 research landscape as trial registries continue to expand and navigation becomes increasingly difficult. Towards the end of the second year of the pandemic, there are still no proven small molecule treatments or chemoprophylactics for COVID-19 so the ability to review studies registered in clinical trial registries using standardised data on patient populations, study designs, and interventions is of increasing importance. We created a LSR of COVID-19 clinical trial registrations in April 2020^{3,5}. In its current form, the ICTRP database compiles data from heterogeneous trial registries using different standards and terminologies. The results presented here are the product of a large standardisation effort and focus on a subset of the registrations in the LSR database. The relevant studies were selected if they included one of 32 repurposed drugs prioritised through consultation with external experts of the COVID-19 Clinical Research Coalition (COVID19-CRC)⁶. These priority drugs are

primarily repurposed drugs likely to be affordable and available rapidly in LMICs if they prove to be effective. In this paper, we have summarised the characteristics of all studies, which included at least one of the 32 priority pharmacological interventions as identified by systematic searches as of the 26th May 2021.

Methods

For the scope of this systematic review, we systematically identified relevant drug therapeutic trials within the Infectious Diseases Data Observatory (IDDO) COVID-19 LSR REDCap database. A list of priority pharmacological interventions was identified by a group of experts from [COVID19CRC](#). The drugs were chosen from the total list of pharmaceutical interventions registered as of November 2020 and drugs were selected based on the following criteria: they were therapeutic interventions, they were repurposed drugs, and more than one registered study included them.

The 32 priority therapeutic interventions identified were acetaminophen; amodiaquine; artemisinin derivatives; azithromycin; betamethasone; inhaled budesonide; chloroquine; colchicine; convalescent plasma; daclatasvir; dexamethasone; favipiravir; hydrocortisone; hydroxychloroquine; imatinib; any immunoglobulin; interferons; interleukin-2; ivermectin; lopinavir; mefloquine; methylprednisolone; niclosamide; nitazoxanide; prednisolone; prednisone; remdesivir; ritonavir; sofosbuvir; telmisartan; tocilizumab; tofacitinib. This review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines⁷. All data used in this study are openly available at [IDDO's website](#).

Registration and protocol

A protocol for the Living Systematic Review of COVID-19 clinical trials was designed prospectively and published on the 2nd of April 2020⁵. Several deviations from the protocol have taken place. It was originally stated that the WHO ICTRP would be searched every week; this was revised to every three months, due to human resource constraints. The protocol also stated that grey literature searches would be conducted, but this was not done due to resource constraints and the comprehensiveness of the the WHO ICTRP database. The protocol states that we would capture planned outcome measures, but due to the unexpectedly large heterogeneity in the reporting of the outcome measures we were unable to proceed with reliable extraction of these measures. The prioritisation system in the protocol has not been implemented. The risk of bias of individual studies is no longer assessed using the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence, as this was not an adequate tool for the broad set of studies identified by the review. Preliminary baseline results have already been reported³.

Search strategy

Formal searches for clinical trial registrations were conducted as detailed in the protocol publication⁵ up until 23 March 2020. Due to heavy traffic on the WHO ICTRP database which aggregates records from 21 country and regional trial registries, on 24 March 2020 this central information source was

no longer accessible to anyone outside of the WHO. A download of all COVID-19 trials from the ICTRP database, derived using the search terms ((COVID-19) OR (novel coronavirus) OR (2019-ncov)), was made available on the WHO ICTRP website, and used for subsequent updates (last downloaded on the 26th May 2021). Results from ICTRP were imported into a REDCap database for eligibility screening, de-duplication, and data extraction. The source registry records which supplemented all included studies identified through the WHO ICTRP, were accessed live on the dates of data extraction for each record and not from an archived version.

Eligibility criteria

Experimental and observational studies registered in a clinical trial registry that provides its data to the ICTRP planning to enrol human participants were eligible for inclusion in the overall living systematic review. Populations of interest included patients diagnosed with COVID-19 (as defined by the investigators) and studies enrolling healthy volunteers, healthcare workers, or other groups at risk of exposure or suspected infection where COVID-19 related outcomes were to be assessed⁵. For this review we only included registered studies which listed any of the 32 priority pharmacological interventions as a component of the study. All registered studies were included, regardless of study design or whether the intervention was intended as prophylaxis or treatment. Studies were not excluded on the basis of language, as all clinical trial registries from which studies were obtained were either only in English or included an English language translation.

Study identification and selection

A search of the active pharmacological ingredients and proprietary names of the priority pharmacological interventions of interest was conducted in the LSR REDCap database by one author (SR). Any trial record that did not fit the eligibility criteria was highlighted by the data extractor to a member of the core LSR team to obtain consensus. If this was not obtained, then a third member was consulted to make a decision.

Data extraction and variable dictionary

A REDCap database was designed for data extraction, for which the database and variable dictionaries are available⁸. Information on study characteristics, geographic distribution, interventions, outcomes, and data sharing, were captured by one data extractor. For quality control, a second extractor cross-checked all variables. Any discrepancies were resolved through a discussion with another author (SR) or another member of the LSR research group if necessary.

De-duplication

A duplicate is defined as an additional clinical trial registration for the same study (e.g. with the same scientific title, sponsor, sample size, etc.). De-duplication was conducted alongside data extraction. Extractors were asked to search the internet for the scientific title and acronym of each study they extracted. Additionally, extractors checked for information on additional registrations in the clinical trial registration record, and conducted a final check for duplicates using the [CEBM database's](#) 'cross-registration' variable as a supplementary source, for records

registered up to November 2020. If duplicate registrations were identified, the duplicate would be flagged for review by a second extractor, and subsequently merged. The trial ID and other relevant information reported in the duplicate source registration were extracted with a primary registration selected for the study.

Risk of bias

This review of registered studies involving priority pharmacological interventions is descriptive and there is no specific estimand or effect measure of interest, therefore, no risk of bias assessment or certainty assessment was carried out on the study registrations.

Descriptive analyses

As this is a descriptive analysis of study registrations, not an analysis of the results of the studies, there was no effect measure of interest and, accordingly, no sensitivity analysis. Descriptive statistics were used to present the extracted data. Categorical variables were summarised with proportions and frequencies; continuous variables were summarised with totals, means, quartiles, minimums and maximums. For the presentation of sample size at the study arm level, where sample size at the study arm level was unknown we assumed equal allocation across study arms. Summary statistics and figures were produced using Stata 17.0 (StataCorp, College Station, TX, USA) and R software (version 3.6.3, The R Foundation for Statistical Computing, Vienna, Austria). The map was generated using the 'tmap' and 'tmaptools' packages in R⁹.

Future plans

The living systematic review database will be updated on a Bi-annual basis, with data freely available through <https://iddo.cognitive.city>. We will extend the list of priority pharmacological interventions based on the recommendations of an expert group of the COVID-19 clinical research coalition. The LSR's effort will continue until the end of 2022, with interim analyses being conducted when substantial outcomes are reached. The LSR work will be extended pending sufficient outputs and funding.

Results

A total of 10,074 records were screened in the REDCap database, after de-duplication. Following a review of the study records, a total of 8,760 were excluded. Most (n=8,316) records were excluded because the study did not administer any priority pharmacological intervention. Thus, 1,314 study registrations were included in the systematic review ([Figure 1](#))¹⁰.

Study design of registered studies

Most registered studies investigating priority pharmacological interventions were of a randomised control trial (RCT) design (n=1,043, (79%) [Figure 2](#)). There were 194 non-randomised (interventional) studies; 38 cohort studies; twelve case-control studies; seven case series; seven quasi-randomised; four cross-sectional; one prognostic study; and eight classified as "other". Of the three most frequent study design types, RCT design studies tended to have the largest study sample sizes (median sample size (25th, 75th percentile) = 140 (70, 382)), followed by cohort studies (112.5 (40, 229)) and non-randomised (interventional) studies (60 (30, 120)).

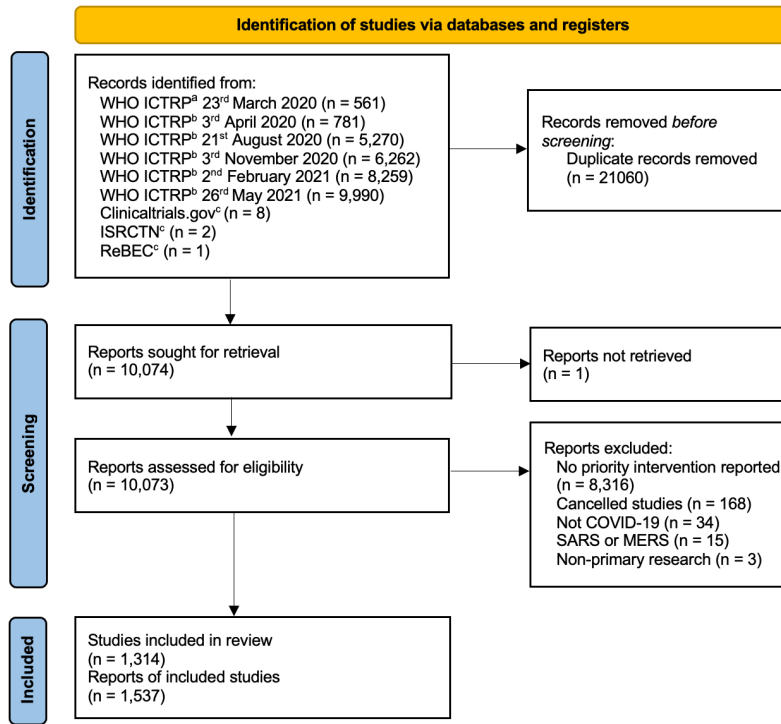


Figure 1. PRISMA flow diagram. **a** Per protocol search terms of ((COVID-19) OR (coronav*) OR (*CoV-2) OR (nCoV*)). **b** Search terms as per only publicly available WHO ICTRP registry export of COVID-19 trials, compiled by WHO ICTRP using the terms ((COVID-19) OR (novel coronavirus) OR (2019-ncov)). **c** Records identified via manual searches and other sources last searched as per protocol up to 31st March 2020. Abbreviations: WHO ICTRP, World Health Organization International Clinical Trials Registry Platform; ReBEC, Brazilian Clinical Trials Registry

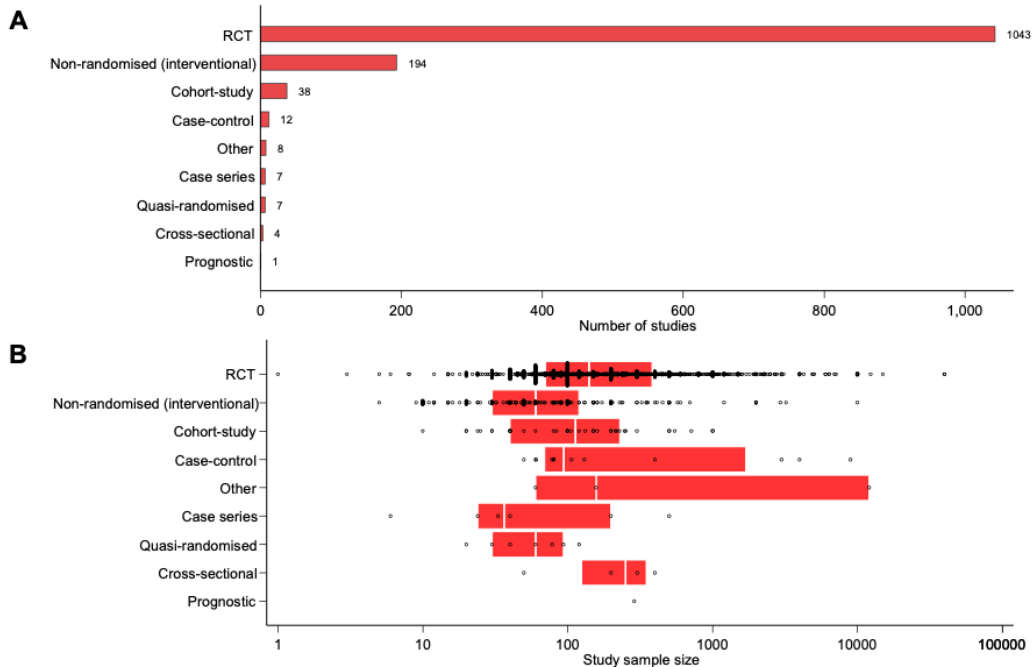


Figure 2. (A) Number of studies and **(B)** planned study sample size by design type. Note that these are study sample sizes, thus the number of patients enrolled per arm in comparative studies is equal or less than half the total study sample size. Each black circle denotes one trial; red box denotes the range between 25th and 75th percentiles; vertical white line indicates the median.

Study sample size in all studies

The number of studies that included each priority pharmacological intervention are displayed in Figure 3A. Interventions

that were more frequently administered within registered studies were hydroxychloroquine (n=418 studies, 351,550 planned participants); convalescent plasma (n=208, 49,209 planned

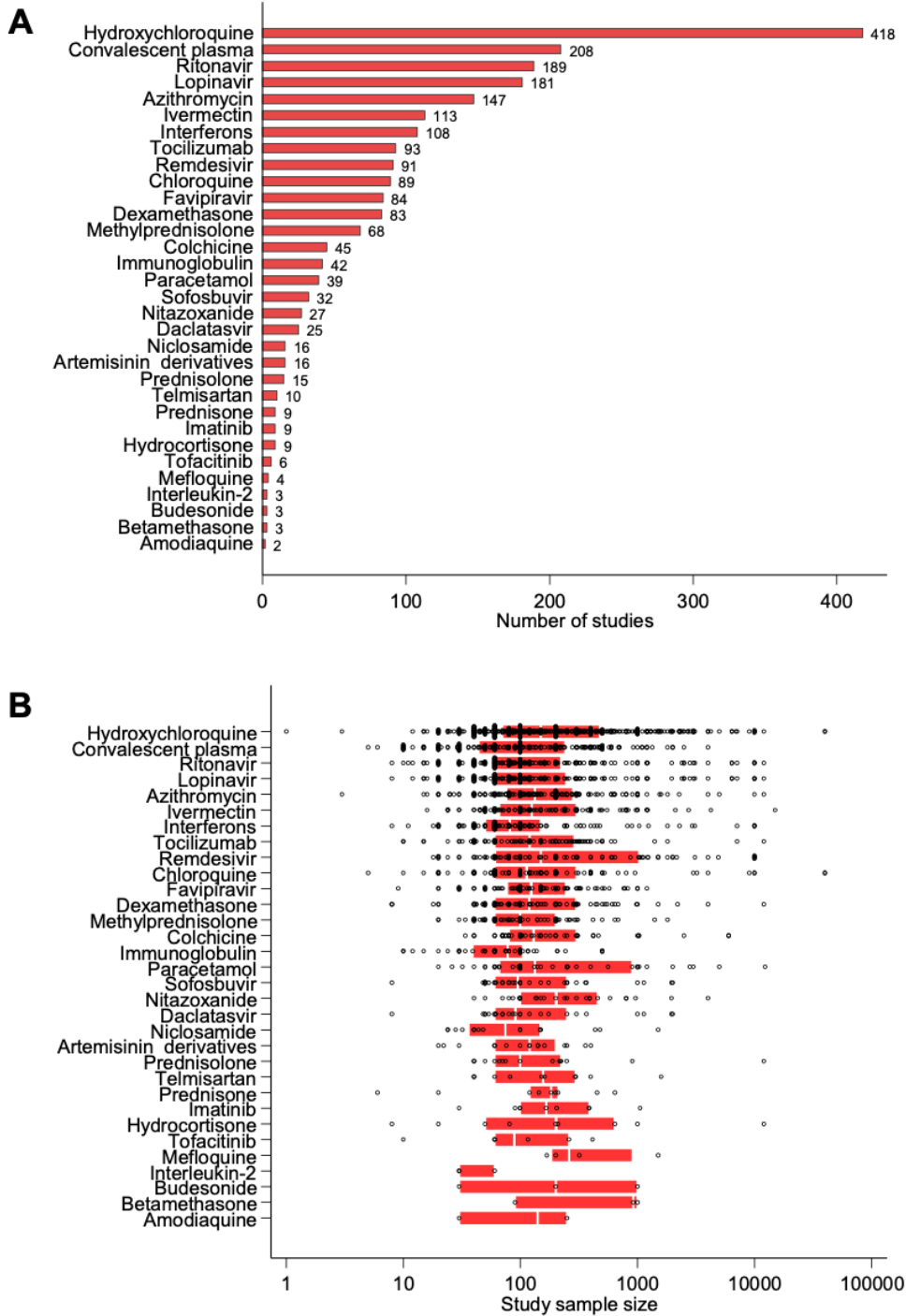


Figure 3. (A) Number of studies and (B) planned study sample size by priority pharmacological intervention. Each black circle denotes one study; red box denotes the range between 25th and 75th percentiles; vertical white line indicates the median.

participants); ritonavir (n=189, 112,921 planned participants); lopinavir (n=181, 112,740 planned participants) and azithromycin (n=147, 67,729 planned participants). Conversely, there were very few studies that investigated patients receiving mefloquine (n=4, 2,188 planned participants); interleukin-2 (n=3, 120 planned participants); inhaled budesonide (n=3, 1,230 planned participants); betamethasone (n=3, 2,010 planned participants); and amodiaquine (n=2, 280 planned participants). The distribution of sample sizes of studies investigating each priority

intervention are displayed in [Figure 3B](#). Some of the registered studies indicated that the priority pharmacological interventions could be given to some participants in an arm or cohort, for example at the discretion of the physician as part of standard of care, but were not necessarily intended to be administered to all participants in an arm. The number of studies and sample sizes where the priority pharmacological interventions were intended for all participants in an arm or cohort are shown in [Figure 4](#).

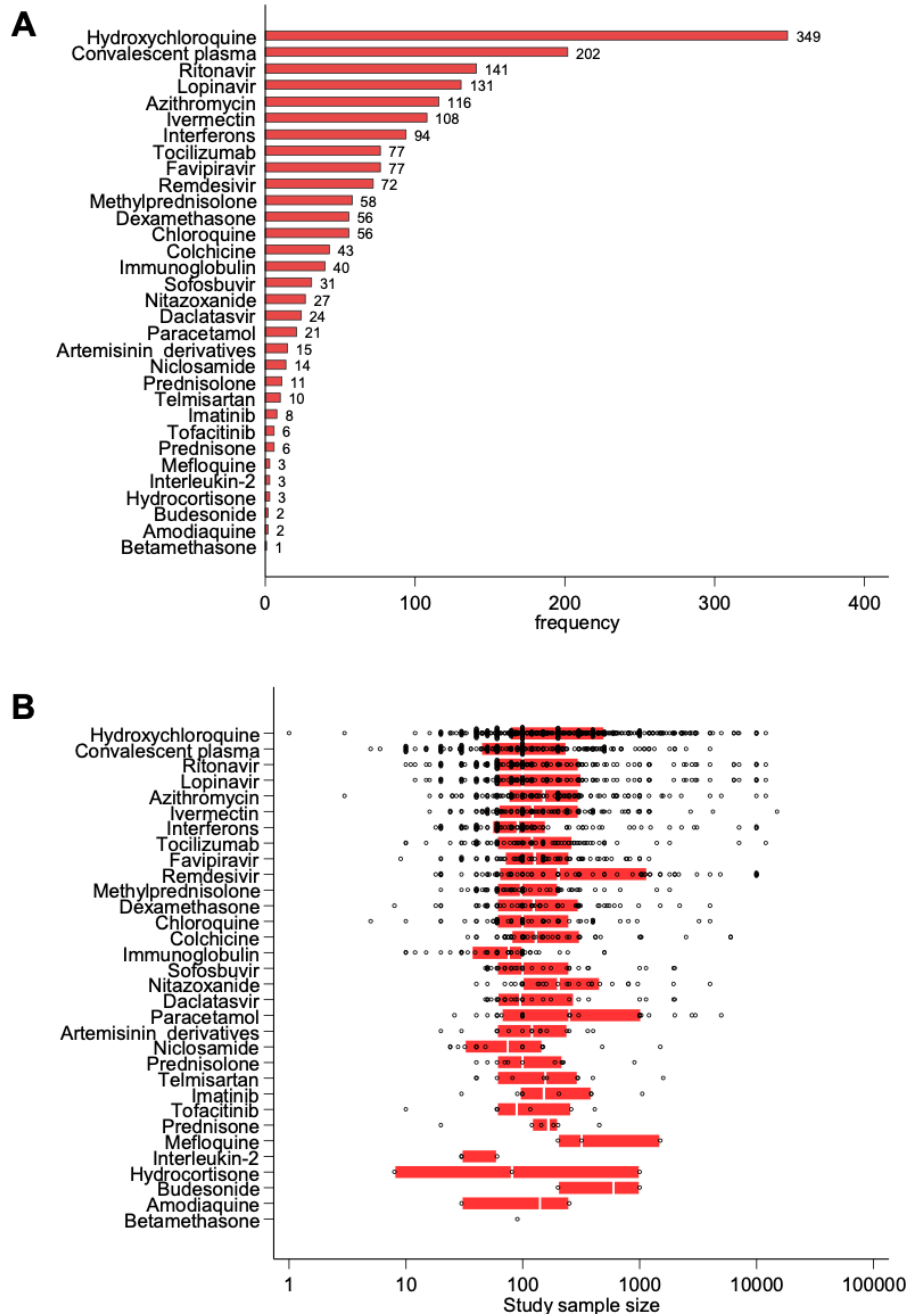


Figure 4. (A) Number of studies and (B) planned study sample size by priority pharmacological intervention when intended to be administered to all participants. Each black circle denotes one study; red box denotes the range between 25th and 75th percentiles; vertical white line indicates the median.

RCT study arms and sample size

The sample size and number of study arms in phase I or II RCTs with per-protocol administration of each priority pharmacological intervention are displayed in [Figure 5A and B](#) with phase III or IV RCTs shown in [Figure 5C and D](#). Among phase III or IV, RCTs there were 277 arms featuring hydroxychloroquine; 91 arms featuring ritonavir; 84 arms featuring lopinavir; 63 arms featuring azithromycin; 48 arms featuring remdesivir; 63 arms featuring azithromycin; 48 arms featuring remdesivir; and 48 arms featuring interferons. There was only a single phase 3 or 4 RCT study arm featuring each of niclosamide, mefloquine, hydrocortisone, budesonide and interleukin-2.

Location of studies

As of the 26th May 2021 there were still very few (16/1,315, 1%) registered studies that planned to include participants from

low-income countries ([Figure 6](#)). The largest number of studies planned in any low-income country was four (Burkina Faso; Uganda) and only nine lower-income countries were represented in at least one registered study. The largest number of studies planned in any lower middle-income country was 110 in India and 23 lower-middle income countries were represented in at least one of the studies identified. By contrast, the countries most frequently represented in registered studies were Iran (n=225); United States of America (n=188); India (n=110); China (n=109) and Spain (n=82) ([Figure 7](#)). Similarly, there are few registered RCTs planning to include participants from low-income countries. The countries most frequently represented in registered RCTs were Iran (n=187); United States of America (n=140); India (n=93); China (n=78) and Spain (n=76) ([Figure 8](#)).

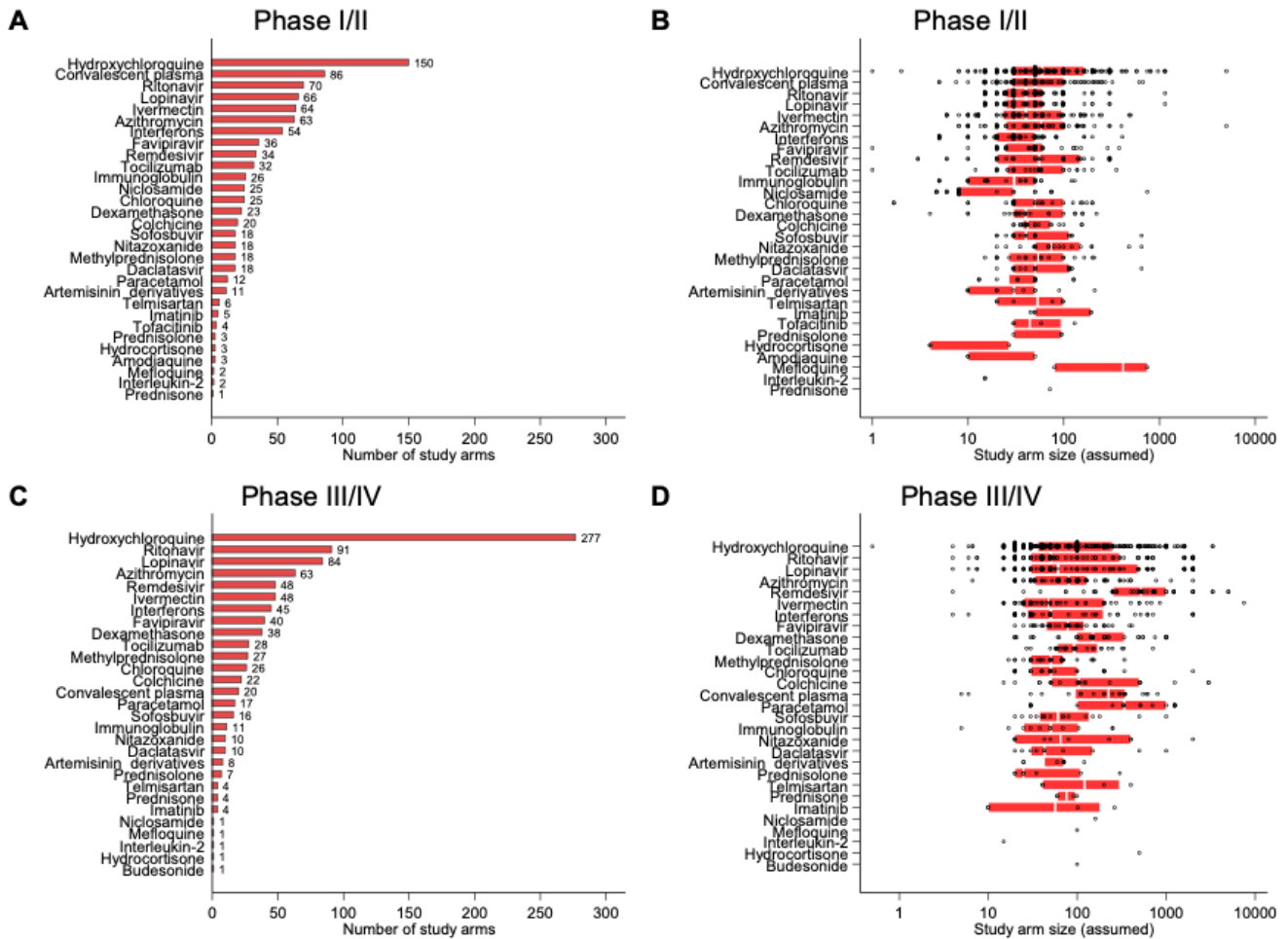


Figure 5. (A) Number of study arms and (B) assumed arm sample size in RCT study designs with per-protocol administration of each priority pharmacological intervention in phase 1 or phase 2 RCTs. (C) Number of study arms and (D) arm sample sizes in RCT study designs with per-protocol administration of each priority pharmacological intervention in phase 3 or phase 4 RCTs. (B) and (D) Each black circle denotes one study; red box denotes the range between 25th and 75th percentiles; vertical white line indicates the median. Where details of a sample size were not provided for each study arm (for example only a total study sample size was provided) we have assumed an equal distribution of study participants across the arms. Note that phase 2/3 studies are displayed in A and B but not C and D.

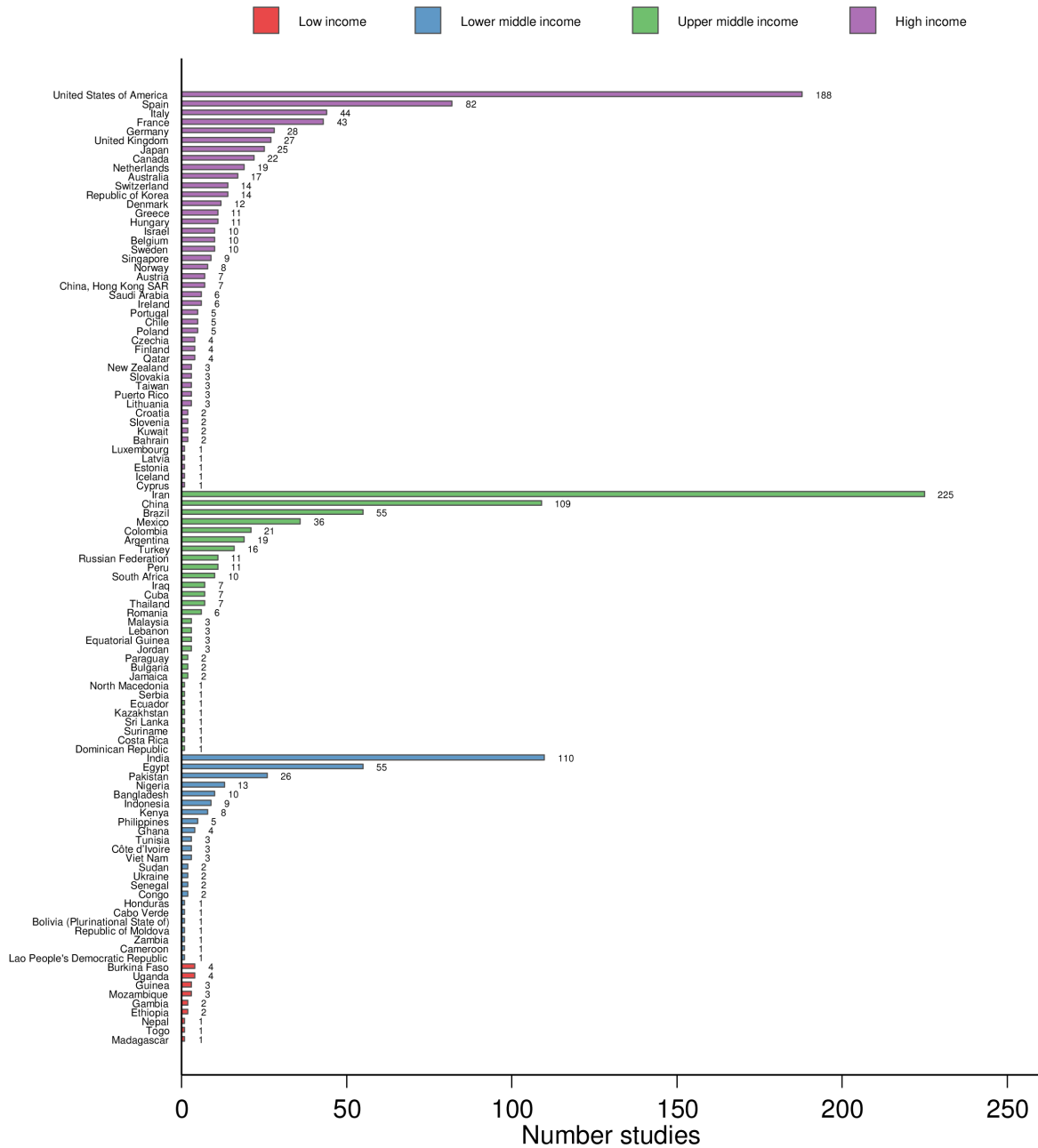


Figure 6. Number of registered studies planning to recruit participants in each country. Countries are grouped by their World Bank income group classification.

Statement of intention to share Individual Participant Data (IPD)

Overall, 767 (58%) studies out of 1,314 clearly reported whether they intended to share Individual Participant Data (IPD) while 192 (15%) were undecided and 355 (27%) did not provide any information. Among those reporting their intentions about half (348/767, 45%) indicated they planned to share IPD. No registered study involving budesonide (n=3), imatinib (n=9), interleukin-2 (n=3) or mefloquine (n=4) reported an intention

to share IPD (Figure 9). Other interventions with a small proportion of registered studies that stated an intention to share IPD included niclosamide (1/16, 6%), colchicine (5/45, 11%), hydrocortisone (1/9, 11%) and prednisone (1/9, 11%).

A low proportion of studies conducted in high income and lower middle-income settings indicated they intended to share IPD (15% and 17% respectively, Figure 10 and Figure 11). Studies conducted in upper middle-income countries were more

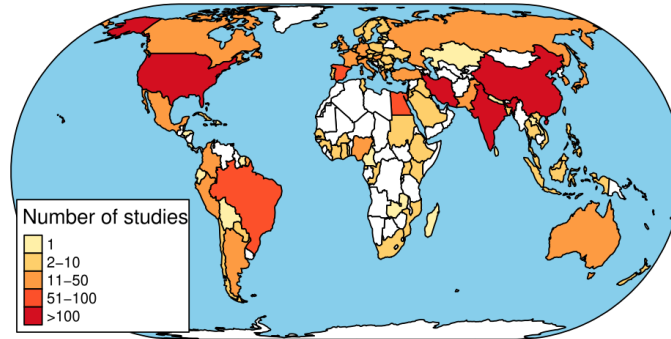


Figure 7. Map of countries with registered studies.

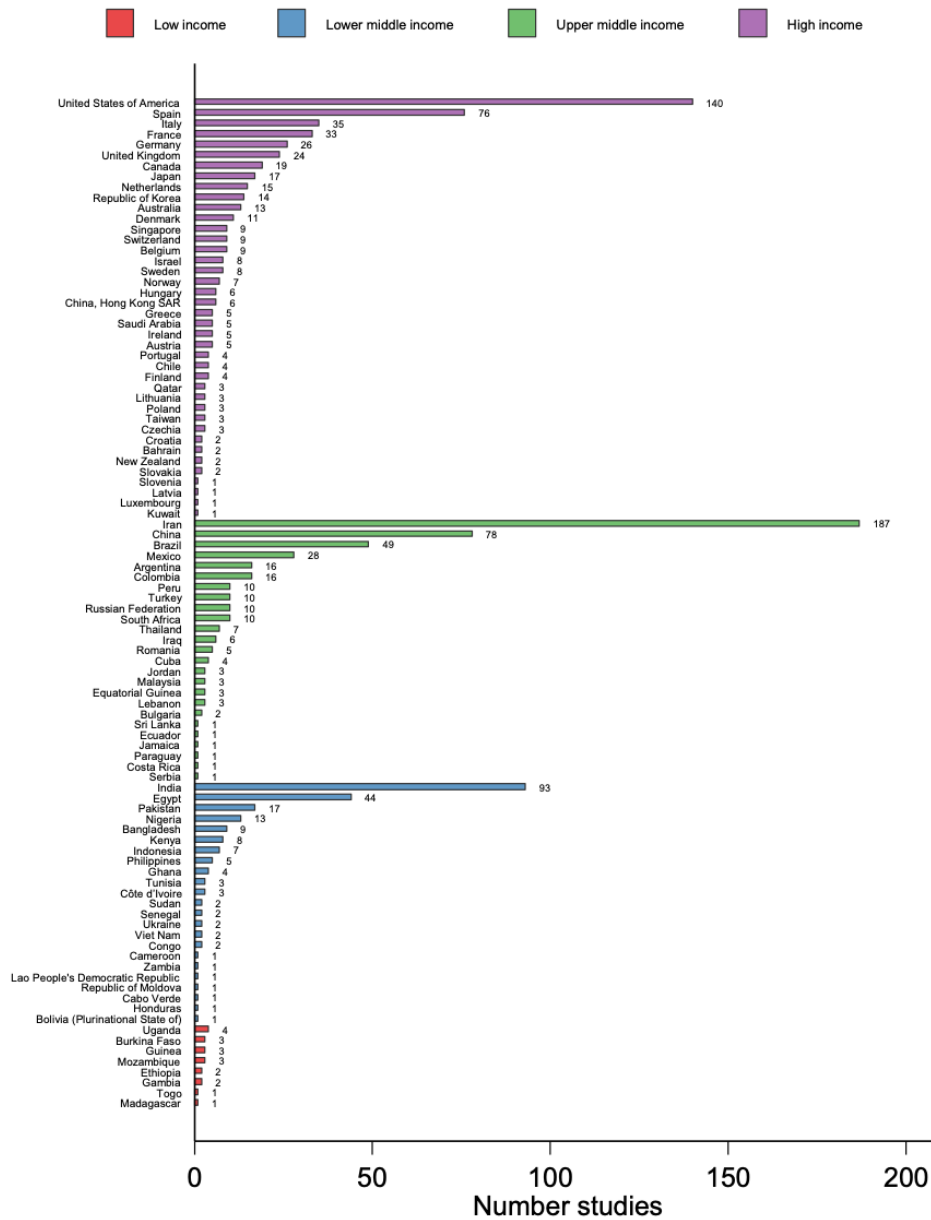


Figure 8. Number of registered RCTs planning to recruit participants in each country. Countries are grouped by their World Bank income group classification.

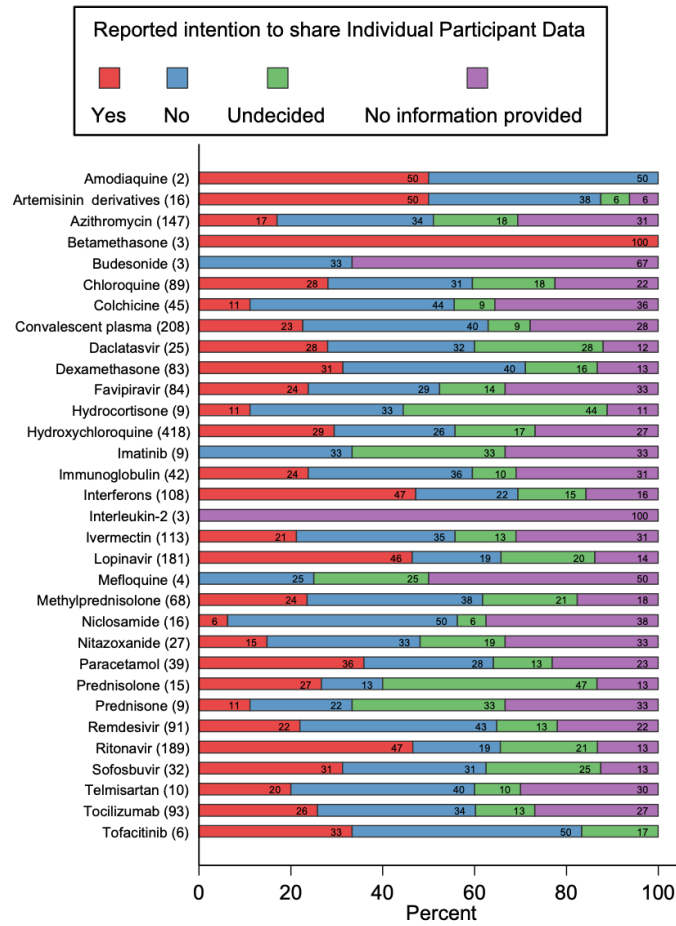


Figure 9. Reported intention to share Individual Participant Data (IPD) by priority intervention.

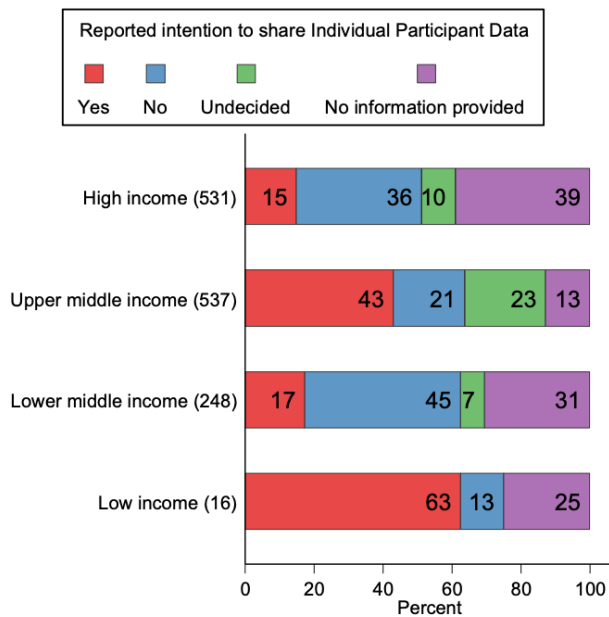


Figure 10. Reported intention to share Individual Participant Data (IPD) by country income group.

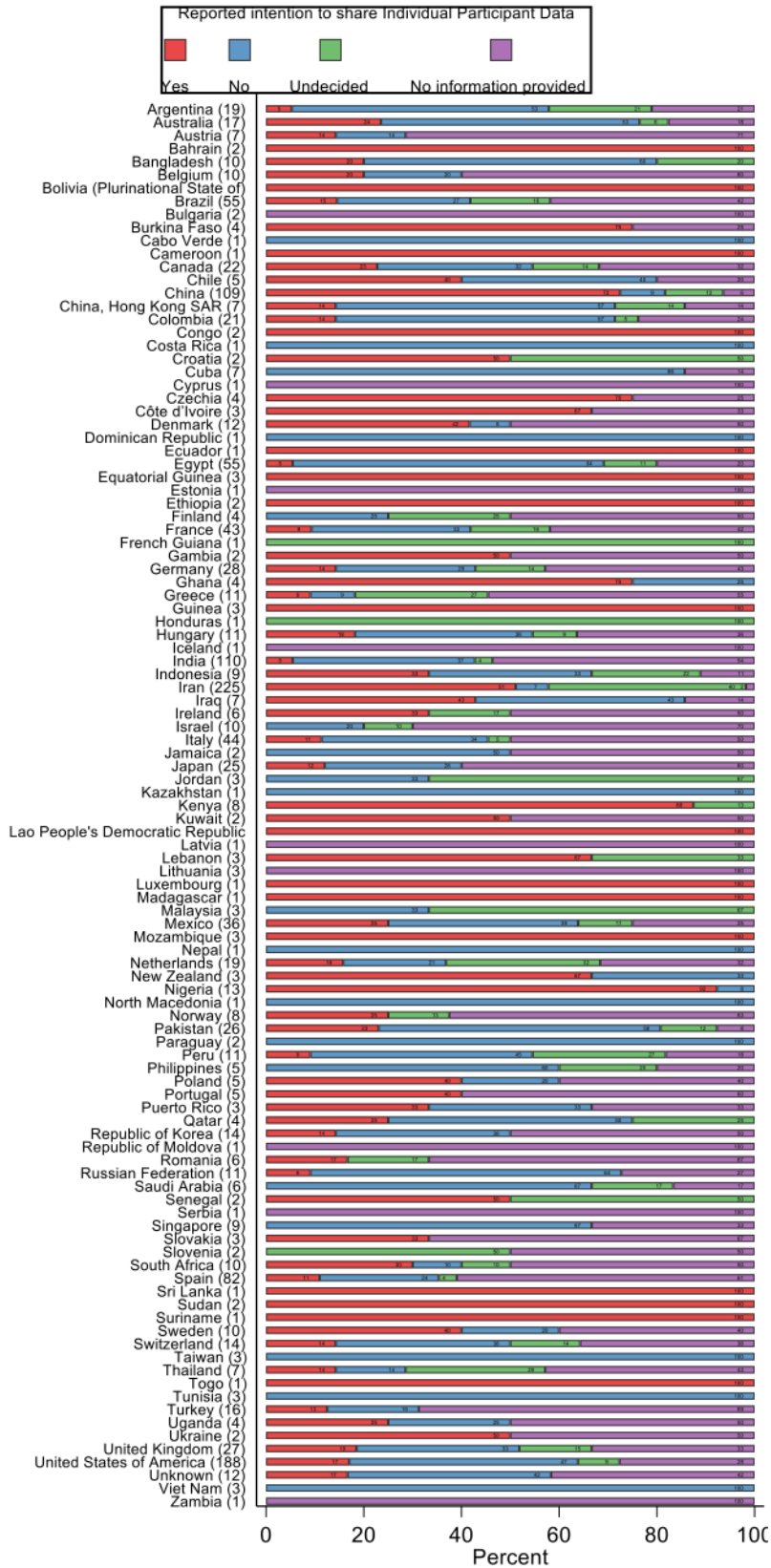


Figure 11. Reported intention to share Individual Participant Data (IPD) by country.

likely to indicate that they intended to share IPD (43%), largely driven by studies in China and Iran (72% and 51% respectively). Of the sixteen studies that are planning to include participants in low-income countries, roughly two thirds (10/16) stated their intent to share IPD.

Discussion

Of over 10,000 unique COVID-19 related studies registered in clinical trial registries, 1,314 studies assessed one or more of the 32 priority pharmacological interventions. Most of these were RCTs (n=1,037 studies). A large number of registered studies involved hydroxychloroquine (n=418 studies, 351,550 planned participants); convalescent plasma (n=208, 49,209 planned participants); ritonavir (n=189, 112,921 planned participants); lopinavir (n=181, 112,740 planned participants) and azithromycin (n=147, 67,729 planned participants). In total these are large numbers, but they have yet to provide clear answers in prevention and early treatment. Most RCTs had small planned sample sizes (median = 140 i.e. <70 per treatment arm). These small sample sizes will only be able to reliably identify very large and generally implausible benefits for most relevant endpoints. To put this sample size in perspective, if the primary endpoint of the study was prevention of hospitalisation and the percentage of individuals in the placebo arm requiring admission to hospital was 5% (a relatively high figure globally), then in a trial with 140 patients (70 patients in each arm) one would expect 3 or 4 hospitalisations in the placebo group, so this trial alone would be unable to demonstrate significant benefits. Even if the incidence of the primary endpoint was 20% then a trial of this size would only have approximately 80% power to detect a risk ratio of <0.25 with 95% confidence, i.e. approximately a 75% reduction in the primary endpoint. This is comparable to the remarkable benefits observed in early treatment with monoclonal antibodies. The recent randomised trial of casirivimab and imdevimab recruited over 1,400 patients to demonstrate a difference of 1.0% vs 3.2% (70.4% reduction (95% CI: 31.6%, 87.1%)) in hospitalisation and death for the 1200mg regimen¹¹. It seems very unlikely that a repurposed small molecule drug would be able to achieve anything close to this effect. A trial which could identify a 20% benefit in the previous scenario (prevention of hospital admission with a placebo rate of 5%) would need to enrol over 13,000 patients. However, the many small trials could contribute to the identification of small and more plausible benefits if their data were pooled together. But just over half (n=767) of all studies gave a clear indication of whether they intended to share Individual Participant Data (IPD), with just under half of those (n=348) stating their intention was to share IPD.

The aim of this living systematic review is to provide an overview of the landscape of COVID-19 related studies listed in clinical trial registries. The decision was made to prioritise records for extraction that likely contained information about “priority pharmacological interventions”, i.e. repurposed drugs likely to be affordable and available rapidly in LMICs if they proved to be effective. New chemical entities have been developed but are likely to be less affordable and available than repurposed drugs. Our goal for future extraction and updates of the review database is to include the entire landscape of COVID-19 related studies listed in clinical trial registries. A

limitation to our approach is that we are only capturing studies that have been registered in clinical trial registries, which likely constitutes the majority of RCTs, and the minority of all observational studies.

The use of trial registry records comes with challenges. There can be major discrepancies between the clinical trial registry records and the final publication^{12,13}. Often the trial experiences difficulties in recruitment and may not reach the intended sample size. Furthermore, study records are time-varying documents; any changes made by investigators or sponsors after the extraction/cross-checking of data :any record in a trial registry that has been updated since the date of extraction/cross-checking will not be in this report. The high degree of variability in the study designs, interventions and the different registry structures make it difficult to define standardised variables to extract from the study registration. For example, there is insufficient information contained in the majority of study registrations to identify if the population of COVID-19 patients in the study are considered to be of mild, moderate, severe or critical disease severity.

Among the RCTs identified the five most frequently administered drugs to all participants in a study arm were hydroxychloroquine (427 arms), ritonavir (161 arms), lopinavir (150 arms), azithromycin (126 arms) or convalescent plasma (106 arms). All five of these drugs were found to have no clinical benefit in hospitalised patients in the largest ongoing randomised controlled platform trial (the RECOVERY trial). These conclusions were made with between 1,000 and 6,000 patients enrolled in the intervention arms (hydroxychloroquine¹⁴ = 1,561 patients; lopinavir/ritonavir¹⁵ = 1,616 patients; azithromycin¹⁶ = 2,582 patients; convalescent plasma¹⁷ = 5,795 patients). The effects of hydroxychloroquine, ritonavir, lopinavir, along with remdesivir and interferon-β1 on COVID-19 hospitalised patients were also evaluated by the WHO SOLIDARITY Trial¹⁸, an international platform RCT conducted in over 30 countries, 500 sites and 10,000 patients. This trial, with between 600 and 3,000 patients enrolled per intervention arm (hydroxychloroquine = 954 patients; remdesivir = 2,750 patients; lopinavir/ritonavir = 1,411 patients; Interferon with lopinavir = 651 patients; interferon = 1,412 patients), also found no significant benefit for any of these interventions.

In this review of registered trials, the planned sample sizes (median sample size for RCTs = 148) mean that most studies would only be powered to detect benefits of an implausible magnitude. Although not all RCTs had the same research question, it seems likely that more coordination and data sharing would have provided definitive answers much earlier in the pandemic. This continued uncertainty contributes to the remarkable diversity in guidelines and national treatment recommendations across the world. Underpowered trials have maintained confusion around the potential benefits and risks of interventions, duplicated efforts and sometimes wasted resources. A more coordinated response with data sharing across trials would presumably have enabled clinicians to stop unnecessary treatments with ineffective drugs earlier and enabled research to pivot towards other candidate drugs. Although there is substantial evidence for the clinical futility of many

interventions in hospitalised patients, there are few data available on the efficacy of these drugs in outpatients experiencing mild symptoms¹⁹, and a small number of pre-exposure and post-exposure prophylaxis studies. Drugs with antiviral activity are likely to be more effective when administered early in the course of illness when viral burdens are highest, but to date most of the good quality evidence on drug efficacy has come from large platform trials conducted in hospitalised patients.

Only one in four studies stated an intention to share IPD. Although this is a low proportion, it is not unusually low. A review observed that only 5% of trials registered in Clinicaltrials.gov in early 2018 committed to sharing IPD²⁰. Given that the International Committee of Medical Journal Editors (ICMJE) mandates that anyone wishing to publish a trial that began enrolment after 2018 in an ICMJE journal must include a data sharing statement in the trial registration, it is surprising that almost half (42%) of all registered studies in this review did not state whether they intended to share IPD or not. The lack of plans to share IPD is not readily explained by limited capacity or resources. Studies which included patients in high-income countries were among the least likely to state an intention to share IPD. Funders supporting small clinical trials should insist that the data are shared subsequently for pooled individual patient data analyses. The COVID-19 Clinical Research Coalition has emphasised the importance of transparency and data sharing. The Coalition, in collaboration with IDDO, intend to provide an equitable data sharing platform to assemble, standardise and facilitate IPD meta-analyses to improve the strength of evidence generated by the research community.

As further search updates are conducted, we will continue to update our database, link trial registrations with published results as they become available and report their data sharing status. The database can be explored and downloaded from the [IDDO website](#). Standardisation and harmonisation of disparate information in the clinical trial registries will make it easier for researchers, funders and policy makers to assess the COVID-19 research landscape.

Data availability

Underlying data

Harvard Dataverse: All associated data including underlying and extended data and supplementary materials for the

publication: McLean *et al.* The fragmented COVID-19 therapeutics research landscape: a living systematic review of clinical trial registrations evaluating priority pharmacological <https://doi.org/10.7910/DVN/D0ZXJ5>¹⁰.

This project contains the following underlying data:

- Copy of COVID_LSR_PriorityDrugPaper_Consolidation_20210819.xlsx (list of ICTRP protocols)

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

All data used in this study are also openly available at <https://iddo.cognitive.city>.

Extended data

Harvard Dataverse: All associated data including underlying and extended data and supplementary materials for the publication: McLean *et al.* The fragmented COVID-19 therapeutics research landscape: a living systematic review of clinical trial registrations evaluating priority pharmacological interventions. Wellcome Open Research, 2021. <https://doi.org/10.7910/DVN/D0ZXJ5>¹⁰.

This project contains the following extended data:

- Priority_Drug_IDDO_Variable_Dictionary.xlsx (data key)

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

Reporting guidelines

Harvard Dataverse: PRISMA checklist and flow diagram for “Associated data for IDDO living systematic review of COVID-19 clinical trial registrations evaluating priority pharmacological interventions”. <https://doi.org/10.7910/DVN/D0ZXJ5>

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Early diagnosis of infected people and their treatment through long known and affordable medicine is an effective public health strategy for controlling an epidemic. Finding such a new drug or new use of an existing drug (repurposing) through urgent clinical research is, therefore, crucial for tackling a new epidemic. The current paper examines the efforts towards the above through systematic searches of more than 10000 registration from the World Health Organisation International Clinical Trials Registry Platform as of 26th May 2021 and analysing nearly 1300 records.

This article is timely and relevant in the current context of the global COVID response which has often not been driven by evidence. Policy and practices (for treatment and prevention) have been heterogeneous between and within countries. This paper provides an important insight behind such fracturation and makes a case that in spite of unprecedented volume and speed of research on COVID the clinical practice and policy responses, in the main, not been guided by these research efforts due to: a) lack of large sample size in majority studies b) lack of ownership and conduct of the study in the countries of the Global South c) lack of optimal investment within and outside World Health Organization to synthesize updates through research coordination, ensuring the quality of design, rigor and homogeneity in implementation and their (lack of) use in shaping policy.

As a solution, it makes a strong case for living systematic research and review (this paper itself is being one such example), and ability to pool individual data form individual studies and creation of enabling factors (one example being ensuring that journal articles record willingness for sharing data by the authors).

While this work needs to be published as soon as possible to potentially stimulate an important stream of work in the middle of the current epidemic, it needs to be strengthened by better highlighting some of the limitations of the study as well as the proposed solutions as below.

1. The rationale for the selection of repurposed drugs (vis a vis all drugs) needs to be better justified. While affordability is a plausible reason, current practices by the regulatory bodies and pharma companies do not necessarily lead to lower prices of the repurposed drugs. A

big example is HIV where repurposed drugs for HIV (AZT) were unaffordable for most patients for many years.

I guess that simplicity and manageability of analysis have been one of the main rationale behind the selection of the repurposed drugs in this study it could be mentioned in the paper (provided the authors agree).

2. Under the result section easily available additional information could have been presented. For example, how many studies were designed for prophylaxis, how many were for treatment could have been shared? Also, the percentage of studies sponsored by the pharma companies could be useful information. If this information is not readily available, it could be mentioned in the results or discussion as a limitation of the paper. Some measurement of heterogeneity in the existing studies could also have been important (provided these are already analyzed or available). At a minimum, some references could be added on these.

I suggest not to delay the publication If the above are not readily available or further analyses are required.

3. Under the discussion:

1. The main solution mentions individual patient data pooling, it does not discuss poor uptake of this approach as is seen for some time in the case of NTDs initiated by some of the authors of this paper. In this context, some solutions need to be offered to make it a viable approach. This calls for drawing attention to the need for dedicated funding both within and outside WHO (as the current WHO situation described in the paper shows)

2. Possible enablers and problems of pooled IPD need to be mentioned as well. For example, lack of robust design, common scientific end points, quality of research are important issues that need to be addressed for successful pooling of the data. Several enablers may also be in place to encourage or enforce pooling. One mention in the paper of enabler is mention of the willingness of sharing of data by the researchers in the published journals. Another could be the requirement by the regulators to ensure the updated status of trials in the registry. On many occasions, these trials are not updated in the registry even after a successful study.

4. Overall, I congratulate the authors for this excellent work with a sound design and good writing. I suggest that the paper can be quickly revised as suggested above and published without delay,

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious disease, policy , evidence based practices, global health

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
