The Medical Journal of Australia – **Pre-print – 30 June 2020**

An evaluation of the quality and impact of the global research response to the COVID-19 pandemic.

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The initial months of the coronavirus disease 2019 (COVID-19) pandemic have led to an unprecedented response from the global medical research community[1]. Simultaneously, concerns have been raised about the rapid publication of misleading, biased studies[2]. We provide a systematic evaluation of the early global research response to COVID-19 by characterizing the methodological quality of registered COVID-19 studies. We also compare the research response with previous respiratory viral epidemics- Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and the Influenza H1N109 pandemic.

We reviewed COVID-19 studies registered from 01/01/2020 to 06/05/2020 in five international clinical trial registries (Clinicaltrials.gov[3], International Clinical Trial Registration Platform[4], European Union Clinical Trials Register[5], International Standardised Randomised Controlled Trial Number[6] and Australia New Zealand Clinical Trials Register[7]). The available registries were searched for studies of SARS, MERS and H1N109 registered within six months beginning from the month after these epidemics were first detected.

We identified 1694 registered COVID-19 studies, of which 698(41%) were randomised controlled trials (RCT) (Supplement). The growth in number of registered studies has paralleled the rise in confirmed global cases (Figure 1). Of the registered studies, 785(46%) are currently recruiting participants, 842(50%) have not commenced recruitment, 10(0.6%) were completed studies and 53(3%) withdrawn or suspended.

Most RCTs evaluated interventions for infected subjects 661(94%), whilst 37(5%) prophylactic therapies. 423 (61%) evaluated drugs, including hydroxychloroquine 122(17%), lopinavir/ritonavir 36(5%) and chloroquine 31(4%). Non-standard drug therapies included traditional Chinese medicines 84(12%), biological agents 60(9%) and vaccines 14(2%).

Among RCTs, 144(21%) clearly reported the use of allocation concealment and 253(36%) clearly reported blinding of either- patient, investigator, clinician, or outcome assessor. Placebo-control was used in 184(26%) of RCTs, while 514(73%) used standard care or active control arms. The presence of a data safety monitoring committee (DSMC) was reported by the majority (427, 62%) of RCTs. Only 35(5%) of RCTs reported both measures of internal validity - allocation concealment and blinding.

Six months after the declaration of the SARS and MERS epidemics, there were no registered studies. Comparatively, there were 99 registered studies, out of which 71 were RCTs, in the six months after the onset of the 2009 H1N1 pandemic.

The global research response to COVID-19 has been substantially larger than that observed with previous epidemics and pandemics. The potential drivers of this include the absence of proven therapies,[8] preparedness lessons from past outbreaks, improved healthcare information technology integration, ease of transmissibility of COVID-19[9], rapidity of global spread, and high hospitalization and mortality rate[10]. Concerningly, only a minority of trials adhered to established markers of internal validity such as blinding, allocation concealment, placebo where applicable and DSMC presence.

The high discontinuation rate of trials within five months into the pandemic could be due to data from case series and observational studies indicating lack of benefit or even harm with the interventions being tested in RCTs, loss of equipoise or control of the pandemic resulting in fewer eligible patients for enrolment.

The trade-off for the rapid expansion of COVID-19 research has been the suspension of non-COVID-19 research in several jurisdictions and a substantive shift by granting bodies to prioritise COVID-19 research funding away from non-COVID-19 research applications.[11,12]

While the global research response to COVID-19 has been rapid and substantial, many studies of interventions may not lead to high-quality evidence to guide treatment of COVID-19, due to methodological insufficiencies. There was significant duplication with multiple trials of several interventions. The impact on non-COVID-19 research has been substantial.

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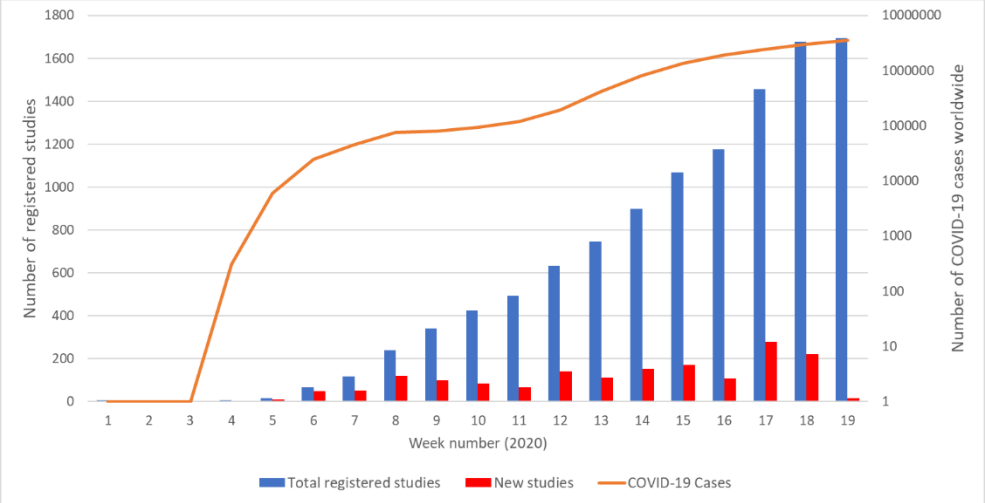
1800
1600
1400
1200
1000
800
600
400
200
0
Number of registered studies
10000000
1000000
100000
10000
1000
100
10
1
Number of COVID-19 cases worldwide
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
Week number (2020)
Total registered studies
New studies
COVID-19 Cases

Supplement Table 1: Characteristics of 1694 registered studies			
Characteristic	Non-RCT (N=966)	RCT (N=698)	Total (N=1694)
Registry - no. (%)			
ANZCTR	17 (2%)	14 (2%)	31 (2%)
CLINICALTRIALS.GOV	489 (49%)	366 (52%)	855 (50%)
CTREU	8 (1%)	67 (10%)	75 (4%)
ISRCTN	9 (1%)	7 (1%)	16 (1%)
WHO ICTRP	473 (47%)	244 (35%)	717 (42%)
Continent - no. (%)			
Africa	8 (1%)	15 (2%)	23 (1%)
Asia	515 (52%)	323 (46%)	838 (49%)
Europe	322 (32%)	202 (29%)	524 (31%)
North America	121 (12%)	130 (19%)	251 (15%)
Oceania	20 (2%)	19 (3%)	39 (2%)
South America	10 (1%)	9 (1%)	19 (1%)
Funding - no. (%)			
University/Government/Charitable organization	926 (93%)	603 (86%)	1529 (90%)
Industry	41 (4%)	65 (9%)	106 (6%)
Industry + Other	19 (2%)	18 (3%)	37 (2%)
Unclear	10 (1%)	12 (2%)	22 (1%)
Study status - no. (%)			
Completed	9 (1%)	1 (0.001%)	10 (1%)
Not yet recruiting	475 (48%)	367 (53%)	842 (50%)
Recruiting	485 (49%)	300 (43%)	785 (46%)
Withdrawn	25 (3%)	28 (4%)	53 (3%)
Not available	2 (0.003%)	2 (0.002%)	4 (0.002%)
Interventions - no. (%)			
Drug	134 (13%)	423 (61%)	557 (33%)
Biological agent	51 (5%)	60 (9%)	111 (7%)
Vaccine	6 (1%)	14 (2%)	20 (1%)

Device	47 (5%)	30 (4%)	77 (5%)
Non-pharmacological interventions	52 (5%)	42 (6%)	94 (6%)
Complementary medicine	61 (6%)	84 (12%)	145 (9%)
Dietary supplements	8 (1%)	21 (3%)	29 (2%)
Other interventions	0 (0%)	24 (3%)	24 (1%)
Non- interventional	637 (64%)	0 (0%)	637 (38%)
Sample size categories - no. (%)			
<=20	114 (11%)	23 (3%)	137 (8%)
21-50	128 (13%)	82 (12%)	210 (12%)
51-100	180 (18%)	169 (24%)	349 (21%)
101-500	333 (33%)	298 (43%)	631 (37%)
501-5000	189 (19%)	109 (16%)	298 (18%)
>5000	52 (5%)	17 (2%)	69 (4%)
Median sample size (IQR)	158 (60-500)	150 (72-400)	150 (60-498)
Quality markers - no. (%)			
Allocation concealment		144 (21%)	
Blinding		253 (36%)	
Placebo-controlled		184 (26%)	
Data safety monitoring committee		427 (62%)	
Special RCT design features - no. (%)			
Adaptive randomization		11 (2%)	
Cluster randomization		7 (1%)	
Factorial design		6 (0.9%)	
Crossover design		4 (0.6%)	

Table Legend

1- RCT- randomized controlled trial

2- WHO ICTRP- World Health Organization International Clinical Trials Registration Platform

3- CTREU- European Union Clinical Trials Register

4- ANZCTR- Australia New Zealand Clinical Trials Registry

5- ISRCTN- International Standardised Randomized Controlled Trial Number

6- IQR- interquartile range