

Global Research and Clinical Trials in COVID-19

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Introduction

The study attempts to capture the influential research and insights of ongoing clinical trials surrounding COVID-19. It attempts to address the following research questions:

- To capture the key research papers and their characterisation?
- To draw insights from ongoing clinical trials?

The intended goal of this study is to help the research community and policy makers to keep track of highly relevant research and drug development (as seen through the lens of clinical trials) in COVID-19.

Method

- The data for this study was drawn from Dimensions database (www.dimensions.ai), an integrated linked database that provides data of funding agencies (grant), research publications, patents, clinical trials and key policy documents. The database captures clinical trials database from a number of international clinical trials registry and contains 557322 clinical trials data.
- The COVID-19 research papers and clinical trials were extracted from Dimensions database using the search string "Covid-19" Or "SARS-CoV-2" Or "SARS-CoV2" Or "2019-nCoV" on 20th May, 2020 from this database in the full text. Altmetrics or article level metrics was chosen as the popularity qualifier. Data for twitter, news, facebook and blog mentions was collected from altmetrics.com. Audience and country where the paper is most popular was based on the type of tweeter (public, scientists, practitioners)
- Co-occurrence map of research condition and disease categorisation (RCDC) and interventions of these clinical trials was constructed using text analytics software VOSviewer and Pajek. The co-occurrence calculates the number of times two or more words (concepts/topics) occur together. The paper has used the co-occurrence map to analyse the relationship between various RCDC categories and interventions.

Highlights of the Study

- A very intensive research activity and clinical trials can be observed surrounding COVID-19. There were 32,250 research papers (26999 published articles and 5251 preprints), and 2234 clinical trials covering various aspects of this disease as on May 20, 2020.
- The ten most influential papers identified based on their altmetric score show that they have actively been covered in news and policy documents. Another common characteristic of these papers are they have been published in *highly reputed journal* which plausibly was also a factor in attracting high online influence. Further indications behind their influence can be observed from content analysis. Other indicators highlight the dissemination of these papers in the diverse community from public, practitioners to scientists. This type of fast and diverse dissemination of research papers underscore the importance of this research for academics, practitioners and society.
- Content analysis of these ten influential papers draw attention to the importance of this papers in identifying virus characteristic, drug treatment/treatment protocols, disease

contamination, epidemic model, etc. Examining cited policy documents and clinical studies shows their wide reaching impact.

- Clinical studies demonstrate the importance of repositioning as a key strategy undertaken for addressing this disease. Randomised clinical trials with placebo

Table Highlighting Key Characteristics of the Ten Influential Papers

Author(s)	Paper	Fields of Research/RCDC	Popularity Breakup	Audience and Country (% of tweeters)
Andersen, G.K., Rambaut, A., Lipkin, W.I., Holmes, E.C., & Garry, R.F.	Proximal Origins of SARS-CoV-2. <i>Nature Medicine</i> , https://doi.org/10.1038/s41591-020-0820-9	Medical and Health Sciences	<u>Altmetrics Score- 34352</u> Twitter- 84244 tweets from 74080 users News- 1186 news stories from 586 outlets Facebook- 128 public wall posts from 123 users Blog- 103 posts from 73 blogs	Public (91) Scientists (6) Practitioners (2) Spain (8) USA (6) Brazil (5)
van Doremalen, N., Bushmaker, T., Morris, D.H., Holbrook, M.G., Amandine Gamble, A., <i>et al.</i>	Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. <i>New England Journal of Medicine</i> , doi: 10.1056/NEJMc2004973	Medical and Health Sciences	<u>Altmetrics Score-23996</u> Twitter- 26019 tweets from 22268 users News-2239 news stories from 826 outlets Facebook- 84 public wall posts from 79 users Blog- 144 posts from 91 blogs 6 Policy Documents	Public (85) Scientists (8) Practitioners (5) USA (13) Spain (4) UK (4)
Bendavid, E., Mulaney, B., Sood, N., Shah, S., Ling, E., Bromley-Dulfano, R., <i>et al.</i>	COVID-19 Antibody Seroprevalence in Santa Clara County, California. doi: 10.1101/2020.04.14.20062463	Biodefense Emerging Infectious Diseases Prevention Vaccine Related	<u>Altmetrics Score-21251</u> Twitter- 41773 tweets from 30456 users News- 598 news stories from 416 outlets Facebook- 23 public wall posts from 20 users Blog- 59 posts from 43 blogs	Public (91) Scientists (5) Practitioners (2) USA (33) Japan (3) UK (2)
Kissler, S. M., Tedijanto, C., Goldstein, E., Grad, Y. H., & Lipsitch, M.	Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. <i>Science</i> . doi: 10.1126/science.abb5793	Lung Biodefense Emerging Infectious Diseases Infectious Diseases Pneumonia & Influenza Prevention Vaccine Related	<u>Altmetrics Score-19940</u> Twitter- 31290 tweets from 27711 users News- 907 news stories from 548 outlets Facebook- 25 public wall posts from 23 users Blog- 76 posts from 47 blogs 1 Policy Document	Public (88) Scientists (7) Practitioners (2) USA (12) Brazil (7) Japan (7)
Li, R., Pei, S., Chen, B., Song, Y., Zhang, T., Yang, W., & Shaman, J.	Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV2). <i>Science</i> , doi: 10.1126/science.abb3221	Lung Pneumonia Biodefense Clinical Research Emerging Infectious Diseases Infectious Diseases Pneumonia & Influenza	<u>Altmetrics Score-17120</u> Twitter- 24793 tweets from 21266 users News- 638 news stories from 361 outlets Facebook- 31 public wall posts from 29 users Blog- 69 posts from 52 blogs 6 Policy Documents	Public (83) Scientists (11) Practitioners (4) USA (15) Brazil (5) Spain (5)

Author(s)	Paper	Fields of Research/RCDC	Popularity Breakup	Audience and Country (% of tweeters)
		Prevention Vaccine Related		
Leung, N. H. L., Chu, D. K. W., Shiu, E. Y. C., Chan, K.-H., Mcdevitt, J. J., Hau, B. J. P. <i>et al.</i>	Respiratory virus shedding in exhaled breath and efficacy of face masks. <i>Nature Medicine</i> . doi: 10.1038/s41591-020-0843-2	Influenza Lung Biodefense Emerging Infectious Diseases Infectious Diseases Pneumonia & Influenza Prevention Vaccine Related	<u>Altmetrics Score-16754</u> Twitter- 36534 tweets from 30856 users News- 296 news stories from 185 outlets Facebook- 47 public wall posts from 44 users Blog- 71 posts from 41 blogs	Public (84) Scientists (9) Practitioners (4) USA (15) Germany (7) Japan (4)
Shen, C., Wang, Z., Zhao, F., Yang, Y., Li, J., Yuan, J.	Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. <i>Jama</i> . doi: 10.1001/jama.2020.4783	Acute Respiratory Distress Syndrome Lung Pneumonia Clinical Research Clinical Trials and Supportive Activities Emerging Infectious Diseases Infectious Diseases Pneumonia & Influenza Rare Diseases	<u>Altmetrics Score-15117</u> Twitter- 43921 tweets from 40089 users News- 254 news stories from 188 outlets Facebook- 26 public wall posts from 25 users Blog- 25 posts from 19 blogs 1 Policy Document	Public (91) Scientists (4) Practitioners (4) USA (14) India (8) France (4)
Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, <i>et al.</i>	Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. <i>The Lancet</i> , 395(10223), 497–506. doi: 10.1016/s0140-6736(20)30183-5	Cardiovascular Lung Pneumonia Clinical Research Infectious Diseases Pneumonia & Influenza Rare Diseases	<u>Altmetrics Score-14461</u> Twitter- 19602 tweets from 15703 users News- 1259 news stories from 507 outlets Facebook- 59 public wall posts from 50 users Blog- 107 posts from 70 blogs 21 Policy Documents	Public (91) Scientists (4) Practitioners (3) Japan (12) USA (9) UK (5)
Kampf, G., Todt, D., Pfaender, S., & Steinmann, E.	Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. <i>Journal of Hospital Infection</i> , 104(3), 246–251. doi: 10.1016/j.jhin.2020.01.022	Lung Pneumonia Emerging Infectious Diseases Infectious Diseases Pneumonia & Influenza Prevention	<u>Altmetrics Score-12639</u> Twitter- 14562 tweets from 12091 users News- 756 news stories from 408 outlets Facebook- 60 public wall posts from 54 users Blog-30 posts from 21 blogs 8 Policy Documents	Public (91) Scientists (5) Practitioners (3) USA (10) Spain (5) Japan (4)
Caly, L., Druce, J. D., Catton, M. G., Jans, D. A., & Wagstaff, K. M.	The FDA-approved Drug Ivermectin inhibits the replication of SARS-CoV-2 in vitro. <i>Antiviral Research</i> , 104787. doi: 10.1016/j.antiviral.2020.104787	Lung Pneumonia Biodefense Clinical Research	<u>Altmetrics Score-12463</u> Twitter- 19057 tweets from 15691 users News- 305 news stories from 257 outlets	Public (93) Scientists (4) Practitioners (3) Japan (11) USA (8) Brazil (2)

Author(s)	Paper	Fields of Research/RCDC	Popularity Breakup	Audience and Country (% of tweeters)
		Emerging Infectious Diseases Infectious Diseases Pneumonia & Influenza Prevention Vaccine Related	Facebook- 45 public wall posts from 42 users Blog- 15 posts from 15 blogs	

Note: If RCDC is not available for a paper then fields of research (FOR) is taken for that paper.

Content Analysis of the above Ten Papers

- Anderson *et al.* (2020), the study most popular on social media platforms (number of tweets more than three times the next popular paper) showed that “SARS-COV-2” is the seventh coronavirus to infect humans”. It further claimed that this virus is not a product of purposeful manipulation, most likely the result of natural selection of human or human-like ACE2 receptor. It also found that SARS-COV-2 spike protein has high affinity to bind to human ACE2 receptor. *The different aspects covered by this disease can be seen highly important and thus contributed to its online impact.*
- van Doremelen *et al.* (2020) analysed the “aerosol and surface stability of SARS-COV-2 and compared it with SARS-COV-1. The study highlighted the need to protect from five environmental conditions: aerosols, plastic, stainless steel, copper and cardboard. Further it showed that SARS-COV-2 remains viable in aerosols for 3 hours, on plastic and stainless steel for 3 days, 4 hours on copper and on cardboard for 24 hours. The study found that the stability of SARS-COV-1 is similar on plastic, stainless steel and aerosols to SARS-COV-2 and different to SARS-COV-2 on cardboard (8 hours) and copper (8 hours). *The implications of this study can be clearly seen in the preventive measures of COVID-19. This study was also cited in policy documents.*
- Leung *et al.* (2020) explored “the importance of respiratory droplet and aerosol route of transmission” by quantifying the “amount of respiratory virus in exhaled breath of participants” that have acute respiratory virus illness (ARI). The 246 participants were divided in two groups, one wearing surgical face mask and other not wearing face mask. The study found that surgical face masks can efficaciously reduce the respiratory droplet emission of influenza virus particles but not in aerosols. They also found that surgical face masks can be used by ill patients of COVID-19 to reduce “onward transmission”. Face mask is getting increasing attention and now being incorporated as essential guideline in health policies of different countries. *The paper provided a good empirical support to this i.e. face masks.*
- Li *et al.* (2020) estimated that 86% of COVID-19 cases went undocumented in China prior to their travel restrictions. The study also estimated that the undocumented cases contagiousness or transmission rate was 55% of documented infections, yet 79% of documented infection cases were due to these undocumented infections. The suggestion of this study that undocumented infections “isolation and identification is necessary to fully control the virus” is very important and the spread of this virus may be seen as a consequence of this. This study also was cited in policy documents.
- Caly *et al.* (2020) tested Ivermectin’s (an FDA approved drug) antiviral activity towards SARS-COV-2. The study found that a single dose of Ivermectin was “able to control viral replication within 24-48 hours” in the system provided by them. Doctors are struggling to control this dangerous disease. *A study like this which gives some hope is quickly tracked which is indicated by its high altmetrics score.*

- Shen *et al.* (2020) study examined coalescent plasma transfusion benefit in treatment of critically ill COVID-19 patients. The clinical trial was conducted on 5 critically ill patients with COVID-19 and acute respiratory distress syndrome (ARDS) along with certain other conditions. The study found decline in viral load, clinical conditions of patients improved as “indicated by body temperature reduction, improved PAO_2/FIO_2 and chest imaging”. This treatment is now being incorporated in many countries.
- Bendavid *et al.* reported a new dimension to address epidemic models, projections and public policies on COVID-19 on the basis of measurement of seroprevalence of antibodies to SARS-CoV-2 in Santa Clara County. Using lateral flow immunoassay, a World Health Organization protocol for COVID-19 antibody testing, serological testing was conducted for SARS-CoV-2 antibodies in a sample of 3300 people selected on the basis of three data elements: zip code of residence, sex and ethnicity/race. On the basis of seroprevalence data of antibodies to SARS-CoV-2 (between 2.49% to 4.16%) among the population, they estimated that the number of infections is much higher of the order of 50-85 fold in Santa Clara than indicated by the number of confirmed cases and the fatality rate is 0.12-0.2% which is much lower than the reported average increase of 6% daily as of April 10, 2020. This well-measured data on population prevalence estimates provided important understanding to calibrate epidemic stage, calculate fatality rates and frame public policy decisions. The paper is attracting attention of several research groups worldwide who are testing population samples for SARS-CoV-2 antibodies and citing this paper frequently.
- Kampf *et al.* provided a comprehensive review on the persistence of human and veterinary coronaviruses on different type of inanimate surfaces as well as their inactivation strategies with biocidal agents used in surface disinfectants. The data showed that human coronaviruses such as Severe Acute Respiratory Syndrome (SARS-CoV), Middle East Respiratory Syndrome (MERS-CoV) and endemic Human coronavirus strain (HCoV-229E) can remain infectious on inanimate surfaces like steel, aluminium, metal, wood, paper, glass, plastic, PVC, silicon rubber, latex, disposable gown, ceramic and Teflon for from 2 hours to 9 days. It also captured the effect of temperature, humidity and concentration of inoculum (viral titer) on the persistence of coronavirus. Inactivation of these coronaviruses by a variety of commonly used biocidal agents namely ethanol (78-95%), 2-propanol (70-100%), combination of 1-and 2-propanols (45% and 30%), glutardialdehyde (0.5-2.5%), benzalkonium chloride (0.05-0.2%), chlorohexidine digluconate (0.02%), sodium hypochlorite (0.001-0.21%), hydrogen peroxide (0.5%), formaldehyde (0.009-1%) and povidone Iodine (0.23-4%) has also been compiled. The study indicated that the most efficient disinfectants to inactivate these viruses on the surfaces within 1 minute are 62-71% ethanol, 0.5% hydrogen peroxide or 0.1% sodium hypochlorite and are also expected to disinfect SARS Cov-2 similarly. As no antiviral treatment for SARS-CoV-2 has been proven to be effective till date, contamination and prevention of further spread is the key strategy to stop the ongoing outbreak. This review article gained popularity as it provided inputs about the best disinfectants to be used to ensure disinfection of frequently touched surfaces, hand hygiene in healthcare set ups and for public usages at large to combat the spread of pandemic.
- Huang *et al.* reported the epidemiological, clinical, laboratory and radiological features of patients infected with 2019 novel coronavirus in Wuhan, China. Data of 41 laboratory-confirmed patients for the period Dec.16, 2019 to Jan.2,2020, collected from clinical charts, nursing records, laboratory findings and chest x-rays revealed similarities of clinical features between 2019-nCoV and previous betacoronaviruses such as SARS-CoV and MERS-CoV. Some of the important features highlighted in this article about the illness were: most of the infected patients were men (73%) with less than half having co-morbidities like diabetes, hypertension, cardiovascular disease; 66% patients had direct exposure to Huanan seafood market; most patients suffered with fever, dry cough, dyspnoea, fatigue and bilateral ground-glass opacities on chest CT scans and only a few with haemoptysis and diarrhoea. The pathophysiological studies of patients infected with 2019-nCoV indicated that amount of proinflammatory cytokines IL1B, IFN γ , IP10 and MCP1 and TNF α , responsible for pulmonary inflammation and extensive lung damage, were increased in serum. Patients with higher

concentrations of GCSF, IP10, MCP1, MIP1A and TNF α required ICU admission suggesting that cytokine storm was associated with disease severity. This article gained significance as it was one of the earliest reports to provide evidence based information on common complications associated with infection with COVID 19 and the line of treatment adopted by the doctors in Wuhan.

- Kissler *et al.* projected SARS-CoV-2 transmission model for the pandemic period using time series data from the USA for betacoronaviruses namely OC43 and HKU1. The assessments were based on role of seasonal variation, duration of immunity and cross immunity on the transmissibility of these two viruses. Through model simulations they predicted some patterns of outbreaks: substantial outbreaks in autumn/winter than winter/spring; annual outbreaks if SARS-CoV-2 establishes short-term immunity on the order of 40 weeks while biennial for long term immunity of two years; seasonal variation in SARS-CoV-2 differ between geographical locations as for influenza; decline or elimination of incidences of betacoronaviruses if SARS-CoV-2 induces 70% cross immunity against HCoV-43 and HCoV-HKU1; elimination of transmission for upto three years if low level of cross immunity (30%) is induced after the initial, most severe pandemic wave. Complimentary interventions such as expanding critical care demand and effective therapeutics along with success of social distancing would hasten the acquisition of herd immunity. The study emphasized the urgency of longitudinal serological studies to be undertaken to determine the extent and duration of immunity of SARS-CoV-2 and epidemiological surveillance to be maintained in the coming years to anticipate the possibility of resurgence. The study is important as it gives valuable inputs for the prediction of outbreaks so that world is better prepared in terms of healthcare, therapeutics and economic front to deal with it effectively.

Clinical Trials

As on 20th May, 2020 there are 2897 clinical trials. The present analysis is based on 2234 clinical trials as on 4th May, 2020. During this period there were 1114 intervention based clinical trials and 917 observational clinical trials, 116 retrospective studies, 6 new treatment measure clinical study, and 81 clinical trials with no Phase data given. Drug repositioning is the key strategy of the clinical trials as can be distinguished from the map. Hydroxychloroquine, Azithromycin, Remdesivir, Tozilizumab as some of the key target drugs now been actively involved in clinical trials to see their possible effectiveness in the treatment of COVID-19. Strong linkage of these drug trials to Placebo underscores that trials are not 'open labels' wherein participants know the treatment they are getting. The variation in placebo types may indicate the different drug delivery route as placebo can't be different from that.

Solidarity trials undertaken by the WHO is also a repositioning drug strategy conducted on four drugs Remdesivir, Lopinavir/Ritonavir, Interferon beta-1a and Chloroquine and Hydroxychloroquine. These are large scale trials of these drugs in which various countries are participating. Three of the 4 drugs (Remdesivir, Lopinavir/Ritonavir, Chloroquine and Hydroxychloroquine) included in the WHO solidarity trials can be seen in this map. Each of the terms present in the map and their co-occurrence highlight the different aspects of the clinical trials. For example, Umbilical Cord Mesenchymal Stem Cells (UC MSC) is also now used to reduce mortality and morbidity among severe COVID-19 patients.¹ Keeping in view the plausible adverse impact of the repurpose drugs, they are being administered along with

¹ <https://pubmed.ncbi.nlm.nih.gov/32214286/>

following standard of care (standard care) protocol. This explains the occurrence of standard care in this map. The map thus speaks to a large audience.

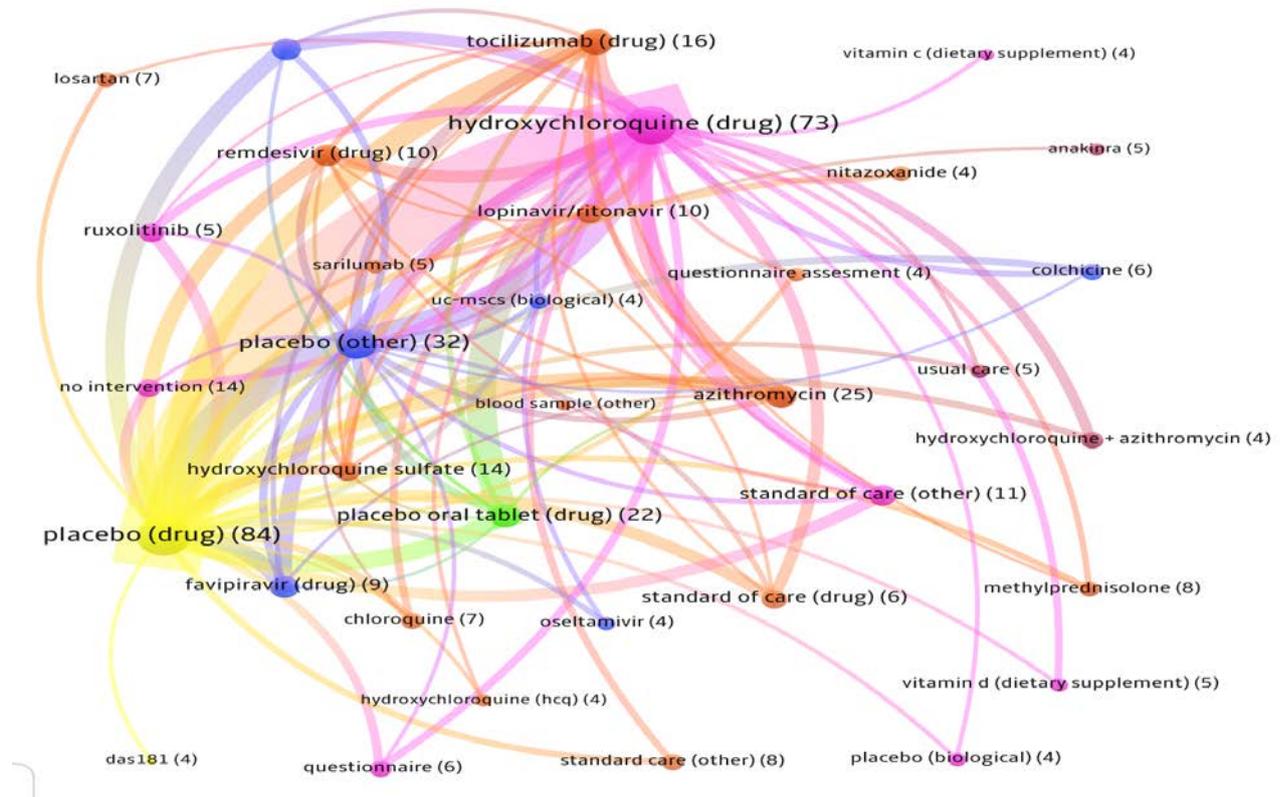


Figure 1: Co-occurrence map of Interventions in Global Clinical Trials

Note: The values in brackets shows the frequency of these interventions.