For better response to clinical trials under public health emergency: a descriptive analysis COVID-19, SARS, MERS and Ebola intervention clinical trials registration

Yuxia Xiang  
Central South University Third Xiangya Hospital

Zeyu Zhang  
Central South University Third Xiangya Hospital

Chan Zeng  
Central South University Third Xiangya Hospital

Zhanqing Hu  
Central South University Third Xiangya Hospital

Yaxin Liu  
Central South University Third Xiangya Hospital

Wenjing Chen  
Central South University Third Xiangya Hospital

Zhijun Huang  
Central South University Third Xiangya Hospital

Xiaomin Wang  
Central South University Third Xiangya Hospital

Guoping Yang  
Central South University Third Xiangya Hospital

Keywords: Public health emergency, COVID-19, SARS, MERS, Ebola, Clinical trial

Posted Date: May 12th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-25169/v1

License: © This work is licensed under a Creative Commons Attribution 4.0 International License.  Read Full License
Abstract

Background

COVID-19 is a novel and highly virulent virus, which caused a rapid and massive onset of clinical trials in a short period of time. With the aim to obtain suggestions in the guidance on performing public health emergency clinical trials, and control this virus in China and other countries and for the prevention of the onset of other infectious viruses in the future.

Methods

COVID-19, SARS, MERS and Ebola clinical trials registered in the Chinese clinical trial registry and clinical trials.gov were collected and analyzed and intervention protocols were descriptively analyzed, focusing on the analysis and comparison of the drug used. The search period ended on February 24, 2020.

Results

The number of the registered COVID-19 clinical trials was 295. Among 203 intervention trials, 78.3% (159) were drug clinical trials.

The 159 COVID-19 trials were designed and analyzed with the highest proportion of random, open control study [66.0% (105)], and blind randomized trials [13.8% (22)]. The drug mostly used was Lopinavir/Ritonavir (15.1%). The sample size median 100, IQR (interquartile range) 140. The number of the registered SARS was 6, MERS 15, and Ebola 97. Among 3 MERS and 19 Ebola drug intervention clinical trials, MERS and Ebola were randomized, blind, and placebo-controlled drug clinical trials accounting for 100% (3) and 31.6% (6), respectively, while SARS were vaccine trials, without drug intervention clinical trials registered.

Conclusions

Some of the COVID-19 clinical trials and drug selection performed are somewhat disordered, requiring greater attention to the needs, science assumptions, ethics and quality management of the clinical research. Thus, during the epidemic period, the country should deliver guidance on how to perform appropriate emergency clinical trials, design a scientifically based clinical trial program and focus on researching drugs or vaccines that have great potential.

Introduction

An outbreak of pneumonia occurred in Wuhan, China, on Dec 2019. A novel coronavirus isolated from the bronchoalveolar lavage fluid of a patient was identified as the cause of the outbreak [1]. On Jan 30, 2020, the WHO (World Health Organization) declared the Corona Virus Disease 2019 (COVID–19) epidemic as a Public Health Emergency of International Concern [2] and now it became a global pandemic. As of March 23, 2020, WHO reported 294,110 confirmed cases worldwide, including 12,944 deaths in 187 countries, areas or territories, and assessed the risk of COVID–19 at a very high level [3]. COVID–19 is the cause of a sudden outbreak, has a high transmission rate, is an infectious disease with a high mortality rate, and so far, no therapeutic drugs are available [4]. Severe Acute Respiratory Syndrome (SARS) suddenly appeared in 2002 in the Guangdong province, China. By July 2003 and after a total of 8,096 reported cases, including 774 deaths in 27 countries, the death rate was 9.6% [5]. Middle East Respiratory Syndrome (MERS) was found in patients in Saudi Arabia in September 2012, and caused severe respiratory diseases and kidney failure [6]. As of November 2020, WHO reported 2494 confirmed cases of MERS and up to 858 (34.4%) deaths [7]. Ebola first occurred in Africa, with an average mortality rate of 50% in previous outbreaks [8].

The above data show that these viruses have a high transmission capacity and mortality, which raised global concern and seriously affected public health safety. However, the treatment methods are often unknown and lagging, thus, it is necessary to urgently launch clinical trials to explore effective treatment protocols. Under the emergency, a large number of COVID–19
clinical trials have been registered. Therefore, the clinical trial data of three viruses with similar emergency background, such as SARS, MERS, and Ebola, were systematically analyzed and compared with COVID–19 clinical trials, with the aim to obtain suggestions on performing appropriate emergency clinical trials to control this virus and prevent the onset of other infectious viruses in the future.

**Methods**

COVID–19, SARS, MERS and Ebola clinical trials registered in the Chinese clinical trials registry and clinical trials.gov were collected until February 24, 2020. Only one copy of the duplicate projects present in the two websites was considered. The research type, research distribution, research design, and intervention program were analyzed. All interventional clinical trial of the four virus were included, which were divided into several intervention programs such as vaccine, chemical drugs and biological products, cell therapy, plasma therapy and medical devices. The protocol design methods and sample size used in drug clinical research of the four viruses was analyzed. There are four design methods included open-lable, single-arm study, nonrandom, open control study, random, open control study, random, open control study. The data of this paper are mainly analyzed by description.

**Results**

1. **Total number and research type**

As of Feb 24, 2020, Only one copy of the three duplicate projects present of COVID–19 in both the two registration sites was excluded. 2 duplicate studies of SARS and MERS, which were mainly observational studies on a variety of respiratory viruses were excluded. Thus, the total number of the registered clinical trials considered was 295 COVID–19, 6 SARS, 15 MERS and 97 Ebola. Among them, interventional clinical trials and durg clinical trial in Figure 1. The time span are 1 month (23 Jan 2020 – 24 Feb 2020), 174 month (6 Aug 2003 – 22 Feb 2018), 64 month (15 Jul 2014 - 20 Nov 2019), 195 month (5 Nov 2003–13 Feb 2020).

2. **Regional distribution**

Of the 295 COVID–19 clinical trials, 1 was registered in US NIAID, 2 in France Institut National DE la Sante Et DE la Recherche Medicale, France, and the other 292 were registered in China (including 1 in Hong Kong). Four of the 6 clinical trials of SARS were performed in the United States, 1 in Beijing and 1 in Taiwan. Fifteen MERS clinical trials were distributed in four regions, 4 in Saudi Arabia, 3 in the United States, 3 in South Korea, 2 in Germany and 2 in Russia, and 1 in the United Kingdom. Ninety seven Ebola clinical trials were distributed in 10 countries, with the top represented by the United States accounting for 57.7% (56). The top sponsor was the National Institute of Allergy and Infectious Diseases (NIAID) accounting for 24.7% (24).

3. **Clinical trial intervention types**

According to the intervention classification of COVID–19, SARS, MERS and Ebola, the interventional studies regarding COVID–19 were mainly drug clinical trials accounting for 78.3%. Two SARS intervention studies were all about vaccines. The majority of the interventional clinical trials regarding MERS and Ebola were also about vaccines, accounting for 61.5% and 72.9%, respectively, followed by drug trials accounting for 23.1% and 22.4%, respectively. COVID–19, MERS and Ebola carried out a small number of clinical studies about plasma therapy. Cell therapy was only applied in COVID–19, accounting for 8.9%. (Table 1)
Table 1
Intervention type used in SARS-CoV, MERS-CoV, Ebola virus and COVID-19 clinical trials

| Intervention type      | COVID-19 (N=159) | SARS-CoV (N=2) | MERS-CoV (N=3) | Ebola virus (N=19) |
|------------------------|-------------------|----------------|----------------|-------------------|
| Vaccine, %             | 0.5 (N=1)         | 100 (N=2)      | 61.5 (N=8)     | 72.9 (N=62)       |
| Drug therapy, %        | 78.3 (N=94)       | 0 (N=0)        | 23.1 (N=3)     | 22.4 (N=19)       |
| Cell therapy, %        | 8.9 (N=18)        | 0 (N=0)        | 0 (N=0)        | 0 (N=0)           |
| Plasma therapy, %      | 3.4 (N=7)         | 0 (N=0)        | 7.7 (N=1)      | 3.5 (N=3)         |
| Medical devices, %     | 2.5 (N=5)         | 0 (N=0)        | 7.7 (N=1)      | 0 (N=0)           |
| a others, %            | 6.4 (N=13)        | 0 (N=0)        | 0 (N=0)        | 1.2 (N=1)         |
| total                  | N=203             | N=2            | N=13           | N=85              |

a Mainly behavioral interventions and psychological interventions.

4. Drug clinical trial design

Of the 159 COVID–19 clinical trials analyzed, 79.9% (127) were designed using randomized controlled trials, which included 66.0% (105 open control) and 13.8% (22 blind control). But the most commonly used was negative control accounting for 45.9% (73) (both the experimental group and the control group were subjected to standard treatments or the same drug treatment as the basis). Among 3 MERS and 19 Ebola drug intervention clinical trials, MERS and Ebola were randomized, blind, and placebo-controlled drug clinical trials accounting for 100% (3) and 31.6% (6). 42.1% Ebola drug clinical trials were open-lable, single-arm study because 84.2% (16) were in phase I or II. Table 2.

Table 2
Study design used in drug clinical trials of COVID-19, MERS, Ebola

| Study design                  | COVID-19 (N=159) | MERS (N=3) | Ebola (N=19) |
|-------------------------------|------------------|------------|--------------|
| open-lable, single-arm study, %| 8.8 (N=14)       | 0          | 42.1 (N=8)   |
| nonrandom, open control study, %| 11.3 (N=18)     | 0          | 0 (N=0)      |
| random, open control study, %  | 66.0 (N=105)     | 0          | 26.3 (N=5)   |
| random, blind control study, % | 13.8 (N=22)     | 100 (N=3)  | 31.6 (N=6)   |

26146 subjects were involved in the 159 COVID–19 drug intervention trials. The sample size median 100, IQR (interquartile range) 140. 52.8% sample size between 10 and 100. The sample size of MERS and Ebola drug clinical trials were showed individual description in Table 3 as small number and most of them were in phase I or II. 8 of the 19 Ebola drug clinical trials were interrupted or withdrawn, accounting for 42.1%. 

Page 4/12
| **NCT**      | **test group**                                      | **control group** | **study design**                  | **sample size** | **phase** | **results/status**                                                                 |
|-------------|---------------------------------------------------|-------------------|-----------------------------------|-----------------|-----------|-----------------------------------------------------------------------------------|
| NCT02845843 | Combination of Lopinavir/Ritonavir and Interferon Beta-1b | Placebo           | Double-blind randomized controlled trial | 194             | II/III   | Recruiting [9]                                                                    |
| MERS        | NCT03301090 REGN3048 and REGN3051                  | Placebo           | Double-blind randomized controlled trial | 48              | I        | Completed but the results were not released                                       |
|             | NCT02788188 SAB-301                                | Placebo           | Double-blind randomized controlled trial | 38              | I        | Single infusions of SAB-301 up to 50 mg/kg appear to be safe and well tolerated in healthy participants [11] |
| Ebola       | NCT02818582 Remdesivir                             | Placebo           | Double-blind randomized controlled trial | 38              | II       | Completed but the results were not released                                       |
|             | NCT02319772 BCX4430                                | Placebo           | Double-blind randomized controlled trial | 94              | I        | Completed but the results were not released                                       |
|             | NCT02662855 Favipiravir Plus WHO-recommended therapies | WHO-recommended therapies | Open-label randomized controlled trial | 77              | II       | Completed but the results were not released                                       |
|             | NCT02329054 Favipiravir plus standardized care      | Single Group Assignment |                              | 126             | II       | 111 were analyzed and sixty participants died. RNA viral load values and mortality were not significantly different between adults Starting favipiravir within <72 h of symptoms compared to others [12] |
|             | NCT03478891 MAb114                                | Open Label Dose-Escalation Study |                              | 19              | I        | MAb114 was well tolerated, showed linear pharmacokinetics [13]                  |
NCT03428347 GamEMab Open Label Dose-Escalation Study I 25 Completed but the results were not released

NCT02363322 ZMAPP Plus Current Standard of Care Current Standard of Care Alone Open-label randomized controlled trial I&II 72 Although the estimated effect of ZMapp appeared to be beneficial, the result did not meet the pre-specified statistical threshold for efficacy [14]

\[^a\]NCT03719586 REGN-EB3 Remdesivir MAb114 Zmapp Open-label randomized controlled trial II&III 1500 Both MAb114 and REGN-EB3 were superior to ZMapp in reducing mortality from Ebola Virus Disease[15]

\[^a\]All patients received standard care and were randomly assigned in a 1:1:1:1 ratio to REGN-EB3, Remdesivir, MAb114, and Zmapp

5. Major drugs used

The 159 COVID–19 clinical trials with drug intervention were analyzed. A total of 50 types of chemical and biological agents and nearly 30 types of TCM (Traditional Chinese Medicine) were used. Most of the chemical drugs and biological preparations are on the market except for the unlisted drugs such as Remdesivir, Azvudine tablets, ASC09/ritonavir tablets, and GD31. The top three used chemical drugs were anti-HIV drugs, antimalarial drugs, and anti-influenza drugs, and among them Lopinavir/Ritonavir, Hydroxychloroquine, Hloroquine, and Abidor were used on 15.1% (24), 13.8% (22) and 5.0% (8), respectively. The biological products used were mainly interferon, with a frequency of 8.2%. Other monoclonal drugs such as Carrillizumab, Adamumab, Meplazumab, and Bevacizumab were also used.

Only 3 MERS drug clinical trials were registered. One protocol was a patient-based evaluation of Lopinavir/Ritonavir and interferon phase III, the first patients of this trial was enrolled in November 2016. Although only 194 patients were plan to be recruited, the recruitment process progressed slowly and they are still in the recruitment phase [9]. The other two were phase I clinical trials. One of these was the first human trial using two monoclonal antibodies, REGN3048 and REGN3051 [10]. The other, a fully human polyclonal IgG antibody (sab–301) [11]. Six specific chemicals were tested in the Ebola clinical trials, including Remdesivir, Favipiravir, Brincidofovir, Avi–7537, TKM and BCX4430, and four antibodies, including REGN-EB3, MAb114, ZMAPP, and GamEMab (Table 3).

Discussion

A total of 292 COVID–19 clinical trials were registered in China in one month. The current awareness and capability of the clinical trials in China significantly improved compared with those related to the SARS period in 2003. However, there are several problems that need to be analyzed and summarized, including an appropriate scientific design of the study and clinical trials management.
The types of intervention protocols were analyzed. Currently, COVID–19 clinical trials were mainly registered with the use of marketed drugs. In a period of sudden outbreak, it is necessary to select the most suitable marketed products to control the spread of the virus as soon as possible and provide timely treatments to patients. But there is no evidence to support an effective treatment. The most represented clinical trial registrations regarding SARS, MERS and Ebola used vaccines. The results of the safety and immunogenicity tests of MERS GLS - 5300 coronavirus vaccine clinical trials were completed to support the next step of the efficacy study[16]. After nearly 16 years of work, the Ebola vaccine has been a milestone success. One VSVΔG - ZEBOV- GP of Ebola vaccine efficiency reached the 97.5%, and it was successively approved on the market by the European Medicines Agency (EMA), World Health Organization (WHO) and four countries in the African region [17–21]. As of April 8, 2020, there are 115 candidate vaccine research projects targeting COVID–19 worldwide, 5 of which have entered the clinical phase. The successful experience of the Ebola vaccine is a useful example to learn from [22].

Van Griensven J et al reported that 84 subjects received plasma from Ebola survivors with an unknown neutralizing antibody levels, and no serious adverse reactions were observed, but the survival rate of the experimental group was not significantly improved [23]. This may be related to the lack of moderate antibody levels, and further research is needed to evaluate the effectiveness of antibodies at a high level [24]. The use of plasma may be an option for critically ill patients, but there are many problems and risks, including epidemiological, virological, immunological, and ethical ones [25]. COVID–19 registered 7 clinical trials regarding plasma therapy and 18 clinical trials regarding cell therapy and also focused on carrying psychological intervention studies for medical staff and patients [26–27]. TCM and integrated Chinese and western medicine also accounted for a large proportion of the treatment plan, making a huge contribution during the SARS period [28]. In terms of intervention methods, COVID–19 used more types of interventions, but to establish which one it is effective or not requires the support of more data.

We focused our analysis on the interventional drug clinical trial design, since COVID–19 is mainly an exploratory trial of marketed drugs, with the purpose of obtaining effective data. Most of the trials registered to solve MERS and Ebola were designed using drugs for drug development, requiring phase validation of safety and efficacy. In the absence of a clear and effective treatment regimen for COVID–19, the negative control group, which was consistent with the clinical trial design of MERS and Ebola [9,14]. The proportion of COVID–19 blind controlled trials (13.8%) was lower than that of MERS (100%) and Ebola (31.6%). Although the cumulative sample size of COVID–19 was large, it is mainly distributed in the range of 10 to 100, which is still small, thus resulting in a waste of research resource (for example human subjects) and in a failure to achieve the expected results and meet the statistical requirements. Nature reported that if China's COVID–19 trials are not designed with strict standards on study parameters, such as control groups, randomization and the measures of clinical outcomes, the efforts will be in vain [29].

The drugs used in 159 COVID–19 drug clinical trials were analyzed, and showed that a wide variety of drugs were used. Many trials, such as the ones using Lopinavir/Ritonavir, Hydroxychloroquine, Chloroquine, and Abidor, were repeated and resulting in a waste of resources. A retrospective study reported by Chen jun et al. did not find that Lopinavir/Ritonavir and Abidor had the ability of improving symptoms or shortening the time of negative transformation of the respiratory virus nucleic acid [30]. A recently RCT open-label study showed that in hospitalized adult patients with severe COVID–19, no benefit was observed using the Lopinavir–Ritonavir treatment beyond the standard care. Future trials in patients with severe illness may help to confirm or exclude the possibility of a treatment benefit [31]. Currently, Chloroquine, Remdesivir, Famivir and Abidol resulted effective against COVID–19 in vitro [32–33]. Many other drugs may be used directly on patients without in vitro experiments, with a consequent risk for many patients to receive ineffective or even adverse treatments. A total of 42.1% of the 19 clinical trials on Ebola drugs were concluded or withdrawn, and so far no drugs have been approved for the market. Thus, it is foreseeable that a large proportion of clinical trials on COVID–19 may not produce satisfactory results.

Gilead's Remdesivir nucleoside analog received the highest level of attention in ongoing clinical trials. Remdesivir is a broad spectrum antiviral drug, Remdesivir proved on SARS - CoV, and MERS - CoV showed an inhibiting effect in vitro and in animal models [5]. Compared with the effect of biological antibody drugs in the other two groups (MAb114 is 35.1% 33.5%, REGN EB3) [15], tentative analyzes revealed that the 28-day mortality of the Remdesivir group was 53.1%, which did not show any
advantage, nor significantly reduced the average mortality rate of Ebola disease (about 50%) [8]. However, in N Engl J Med, Michelle I. et al. reported that the first confirmed COVID–19 patient’s symptoms were improved after 1 day of using Remdesivir under emergency conditions, and no drug-related adverse reactions were found [34]. The Remdesivir protocol in the United States is designed with an adaptive approach and a data safety oversight board. This flexible trial design and data management is important for subject protection and risk management and has been used in several trial designs for the Ebola and MERS. Many of the Ebola and MERS trials were conducted by national research institutions such as the NIAID or by large pharmaceutical companies, which can pool resources and maintain uniform standards. Therefore, China should learn from these good designs and management experiences in conducting clinical trials on COVID–19.

The ethics of clinical trials and the quality of research during outbreaks are also representing a concern. The spread of the virus created panic in some subjects, and the review of the ethics committee and the subject’s knowledge raise sufficient concern in these trials. Some procedures can be simplified to initiate clinical trials during specific periods of virus outbreaks, but the standards of clinical trial ethics and research quality cannot be lowered because of the outbreak [35]. The research team of the joint prevention and control mechanism of new coronavirus pneumonia under the state council of China issued “the notice on standardizing medical institutions to carry out clinical research on drug treatment of new coronavirus pneumonia” [36]. WHO also evaluated many COVID–19 clinical trials, and suggested that experts from other countries together with Chinese experts draft the COVID–19 clinical trial protocols [29], to regulate COVID–19 clinical trials in an appropriate manner.

Conclusions

The clinical trials on COVID–19 demonstrated the improvement in the awareness and capability of clinical research in China. However, COVID–19 clinical trials are somewhat disordered, with lack of unified standard, study design, drug screening, sufficient pre-clinical or clinical data, repetition of a large number of intervention methods in clinical trials, and scattered resources. Therefore, it is necessary to pay attention on the needs, scientific assumptions, ethics and quality management of the clinical research. The clinical trials on COVID–19 should summarize the research and management experience of SARS, MERS and Ebola. It is of utmost importance to carry out clinical trials efficiently through a international or national protocol design and screening of potential drugs. Therefore, during the epidemic period, the country should deliver a guidance on emergency clinical trials, design a scientifically based clinical trial program and focus on researching drugs or vaccines that have great potential. In addition, when the COVID–19 pandemic is over, all the case information should be collected to perform a big data analysis, to summarize the experience and lessons, and to analyze and compare the benefits and risks of various treatment schemes. However, the retrieval time is up to February 24, 2020, the subsequent updated registration data are not present in the article. In addition, there are only 2 databases we could use in the world, which may not be complete.

Abbreviations

MERS: Middle East Respiratory Syndrome; SARS: Severe Acute Respiratory Syndrome; WHO: World Health Organization; TCM: Traditional Chinese Medicine; NIAID: National Institute of Allergy and Infectious Diseases; RCTs: Randomized Clinical Trials; NMPA: National Medical Products Administration

Declarations

Acknowledgements

Not applicable.

Authors’ contributions

(There is no need to polish this section)
GY, XW contributed to the study concept and design. YX was responsible for the search design, literature search, data analysis, interpretation of data, and preparation of the first draft of the manuscript, figures, and tables. ZZ, HZ and HZ were responsible for the literature review. ZC and LY, CW were responsible for the data extraction and acquisition of data. YG and WX substantively revised the manuscript for significant content and provided translation and editing for English language. All authors critically revised the manuscript for relevant intellectual content. All authors read and approved the final manuscript.

**Funding**

This work was partially supported by the National Major New Drug Creation Project of China (No. 2020ZX09201–010), The Emergency Project of Prevention and Control for COVID–19 of Central South University (502701001).

**Availability of data and materials**

The data sets generated and/or analyzed during the current study are available in Chinese clinical trial registry and clinical trials.gov.

**Ethics approval and consent to participate**

All data were publicly available, no patient contact was established, no patient identification was necessary and no individual identifiers were required. Therefore, ethical approval for this study was not required.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**References**

[1] Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: the mystery and the miracle. J Med Virol 2020;92:401–402.

[https://doi.org/10.1002/jmv.25678](https://doi.org/10.1002/jmv.25678)

[2] Sohrabi C, Alsafi Z, O’Neill N, Khan M, Kerwan A, Al-Jabir A. et al. World Health Organization declares Global Emergency: A review of the 2019 Novel Coronavirus (COVID–19). Int J Surg. Int J Surg. 2020;76:71–76.

[https://doi.org/10.1016/j.ijsu.2020.02.034](https://doi.org/10.1016/j.ijsu.2020.02.034)

[3] World Health Organization. WHO Director-General’s opening remarks at the media briefing on COVID–19 - 13 March2020.

[https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-mission-briefing-on-covid–19---13-march---2020](https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-mission-briefing-on-covid–19---13-march---2020). Accessed 13 March 2020.

[4] Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet. 2020;395(10223):473–475. [https://doi.org/10.1016/S0140–6736(20)30317–2](https://doi.org/10.1016/S0140–6736(20)30317–2)
[5] de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol. 2016;14(8):523–34. https://doi.org/10.1038/nrmicro.2016.81

[6] Wong G, Liu W, Liu Y, Zhou B, Bi Y, Gao G, et al. MERS, SARS, and Ebola: The Role of Super-Spreaders in Infectious Disease. Cell Host Microbe. 2015;18(4):398–401. https://doi.org/10.1016/j.chom.2015.09.013

[7] World Health Organization. MERS monthly summary, November 2019. https://www.who.int/emergencies/mers-cov/en/. Accessed 31 November 2019.

[8] World Health Organization. Ebola virus disease. https://www.who.int/health-topics/ebola#tab = tab

[9] Arabi YM, Asiri AY, Assiri AM, Jokhdar HAA, Alothman A, Balkhy HH, et al. Treatment of Middle East respiratory syndrome with a combination of lopinavir/ritonavir and interferon-β1b (MIRACLE trial): statistical analysis plan for a recursive two-stage group sequential randomized controlled trial. Trials. 2020;21(1):8. https://doi.org/10.1186/s13063–019–3846-x

[10] De Wit E, Feldmann F, Okumura A, Horne E, Haddock E, Saturday G, et al. Prophylactic and therapeutic efficacy of mAb treatment against MERS-CoV in common marmosets. Antiviral Res. 2018;156:64–71. https://doi.org/10.1016/j.antiviral.2018.06.006

[11] Beigel JH, Voell J, Kumar P, Raviprakash K, Wu H, Jiao J, et al. Safety and tolerability of a novel, polyclonal human anti-MERS coronavirus antibody produced from transchromosomic cattle: a phase 1 randomised, double-blind, single-dose-escalation study. Lancet Infect Dis. 2018;18(4):410–418. https://doi.org/10.1016/S1473–3099(18)30002–1

[12] Siisoko D, Laouenan C, Folkesson E, M’Lebing AB, Beavogui AH, Baize S, et al. Experimental Treatment with Favipiravir for Ebola Virus Disease (the JIKI Trial): A Historically Controlled, Single-Arm Proof-of-Concept Trial in Guinea. PLoS Med. 2016;13(3):e1001967. https://doi.org/10.1371/journal.pmed.1001967

[13] Gaudinski MR, Coates EE, Novik L, Widge A, Houser KV, Burch E, et al. Safety, tolerability, pharmacokinetics, and immunogenicity of the therapeutic monoclonal antibody mAb114 targeting Ebola virus glycoprotein (VRC 608): an open-label phase 1 study. Lancet. 2019;393(10174):889–898. https://doi.org/10.1016/S0140–6736(19)30036–4

[14] PREVAIL II Writing Group, Multi-National PREVAIL II Study Team, Davey RT Jr, Dodd L, Proschan MA, Neaton J, et al. A Randomized, Controlled Trial of ZMapp for Ebola Virus Infection. N Engl J Med. 2016;375(15):1448–1456. https://doi.org/10.1056/NEJMoa1604330

[15] Mulangu S, Dodd LE, Davey RT, Mbaya OT, Proschan M, MUkadi D, et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. N Engl J Med. 2019;381(24):2293–2303. https://doi.org/10.1056/NEJMoa1910993

[16] Modjarrad K, Roberts CC, Mills KT, Castellano AR, Paolino K, Muthumani K, et al. Safety and immunogenicity of an anti-Middle East respiratory syndrome coronavirus DNA vaccine: a phase 1, open-label, single-arm, dose-escalation trial. Lancet Infect Dis. 2019;19(9):1013–1022. https://doi.org/10.1016/S1473–3099(19)30266-X

[17] Samai M, Seward JF, Goldstein ST, Mahon BE, Lisk DR, Widdowson MA, et al. The Sierra Leone Trial to Introduce a Vaccine Against Ebola: An Evaluation of rVSVΔG-ZEBOV-GP Vaccine Tolerability and Safety During the West Africa Ebola Outbreak. J Infect Dis. 2018;217(suppl_1):S6-S15. https://doi.org/10.1093/infdis/jiy020

[18] Halperin SA, Arribas JR, Rupp R, Andrews CP, Chu L, Das R, et al. Six-Month Safety Data of Recombinant Vesicular Stomatitis Virus-Zaire Ebola Virus Envelope Glycoprotein Vaccine in a Phase 3 Double-Blind, Placebo-Controlled Randomized Study in Healthy Adults. J Infect Dis. 2017;215(12):1789–1798. https://doi.org/10.1093/infdis/jix189

[19] Halperin SA, Das R, Onorato MT, Liu K, Martin J, GK RJ, et al. Immunogenicity, Lot Consistency, and Extended Safety of rVSVΔG-ZEBOV-GP Vaccine: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study in Healthy Adults. J Infect Dis.
[20] Regules JA, Beigel JH, Paolino KM, Voell J, Castellano A, Hu Z, et al. A Recombinant Vesicular Stomatitis Virus Ebola Vaccine. N Engl J Med. 2017;376(4):330–341. https://doi.org/10.1056/NEJMoia1414216

[21] World Health Organization. Four countries in the African region license vaccine in milestone for Ebola prevention. https://www.who.int/news-room/detail/14–02–2020-four-countries-in-the-african-region-license-vaccine-in-milestone-for-ebola-prevention. Accessed 14 February 2020.

[22] Tung Thanh Le, Andreadakis Z, Kumar A, Gómez Román R, Tollefsen S, Saville M, et al. The COVID–19 vaccine development landscape. Nature Review Drug Discovery. Nat Rev Drug Discov. 2020 Apr 9. doi: 10.1038/d41573–020–00073–5.

[23] van Griensven J, Edwards T, de Lamballerie X, Semple MG, Gallian P, Baize S, et al. Evaluation of Convalescent Plasma for Ebola Virus Disease in Guinea. N Engl J Med. 2016;374(1):33–42. https://doi.org/10.1056/NEJMoia1511812

[24] van Griensven J, Edwards T, Baize S, Consortium E. Efficacy of Convalescent Plasma in Relation to Dose of Ebola Virus Antibodies. N Engl J Med. 2016;375(23):2307–2309. https://doi.org/10.1056/NEJMc1609116

[25] Garraud O. Use of convalescent plasma in Ebola virus infection. Transfus Apher Sci. 2017;56(1):31–34. https://doi.org/10.1016/j.transci.2016.12.014

[26] Yang Y, Li W, Zhang Q, Zhang L, Cheung T, Xiang Y. Mental health services for older adults in China during the COVID–19 outbreak. Lancet Psychiatry. 2020;S2215–0366(20)30079–1. https://doi.org/10.1016/S2215–0366(20)30079–1

[27] Chen Q, Liang M, Li Y, Guo J, Fei D, Wang L, et al. Mental health care for medical staff in China during the COVID–19 outbreak. Lancet Psychiatry. 2020;S2215–0366(20)30078-X. https://doi.org/10.1016/S2215–0366(20)30078-X

[28] Liu X, Zhang M, He L, Li Y. Chinese herbs combined with Western medicine for severe acute respiratory syndrome (SARS). Cochrane Database Syst Rev. 2012;10(10):CD004882. https://doi.org/10.1002/14651858.CD004882.pub3

[29] More than 80 clinical trials launch to test coronavirus treatments. Nature. 2020. https://www.nature.com/articles/d41586–020–00444–3. Accessed 15 February 2020.

[30] Chen J, Ling Y, Xi X, Liu P, Li F, Li T, et al. Efficacies of lopinavir/ritonavir and abidol in the treatment of novel coronavirus pneumonia. Chinese Journal of Infectious Diseases, 2020, 38(00): E008-E008. https://doi.org/10.3760/cma.j.cn311365–20200210–00050.

[31] B. Cao, Y. Wang, D. Wen, W. Liu, Jingli Wang, G. Fan, et al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid–19. The New England Journal of Medicine. 2020. March 18, https://www.nejm.org/doi/pdf/10.1056/NEJMoa2001282?articleTools = true

[32] Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269–271. https://doi.org/10.1038/s41422–020–0282–0.

[33] Wang H, Wang Q. Advances in research of novel coronavirus (COVID–19) related drugs and biological products. Acta Pharmaceutica Sinica. 2020;2020–03–17:1–13. http://kns.cnki.net/kcms/detail/11.2163.R.20200226.1702.007.html.

[34] Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce J, et al. First Case of 2019 Novel Coronavirus in the United States. N Engl J Med. 2020;382(10):929–936. https://doi.org/10.1056/NEJMoa2001191

[35] Xiang Y, ZENG C, HUANG Z, Wang X, Zhang Z, Yang G. Analysis of clinical trial registration information of COVID–19 in China. Chin J Clin Pharmacol Ther. 2020;2020–03–17:1–6.
[36] Ministry of science and technology of the People’s Republic of China. The research team of the joint prevention and control mechanism of new coronavirus pneumonia under the state council of China issued “the notice on standardizing medical institutions to carry out clinical research on drug treatment of new coronavirus pneumonia”

http://www.most.gov.cn/tztg/202002/t20200225_151897.htm. Accessed 25 February 2020.

**Figures**

Figure 1

number of COVID-19, SARS, MERS and Ebola searched from two website

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- SPIRITChecklistdownload8Jan13.doc