

Review Article

COVID-19 Disease Pandemic in the 21st Century: As Africa Braces up for the Disease What Needs to be known

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ABSTRACT

It was on 7th of January 2020 that China announced an outbreak of a form of strange pneumonia among her people in Wuhan Hubei province and little did the global community anticipate that the announcement would turn out to be a global nightmare within 60 days; COVID-19 pandemic caused by SARS-COV-2 a beta-Coronavirus. This study was therefore set up to review the present impact of COVID-19 pandemic in presentations and drug management along with clinical presentations and suggest best approach for Africa. Study was carried out based on available information, data, records and published scientific works from electronic and print media, social media and communications, newsletters and broadcasts. Data and information was obtained from 1st January 2020 to 31st March 2020 and relevant information such as evolution of Coronaviruses, clinical presentation of SARS-COV-2 infections, laboratory diagnosis, drugs on therapeutic trial for COVID-19 and control models from different endemic countries were compiled. Data obtained was analysed using simple quantitative and qualitative methods. Coronaviruses were first discovered to be human pathogens in 1965 and the first strain to cause disease was CoV-NL-63 that caused only mild respiratory symptoms and SARS-COV-2 SARS-COV-2 is a long term evolutionary mutant of a mild CoV-NL-63 and has no relationship with 5G radiations in the present COVID-19 pandemic. Fever, difficulty in breathing, tiredness and dizziness accounted for 97.3% (n=2,713), 88.6% (n=2,470), 66.2% (n=1,846), 62.7% (n=1,748), and 32.5% (n=906) respectively of the clinical presentation, and gastrointestinal features ranged from 11% to 22%. Rate of specimen positivity from infected individuals showed that bronchoalveolar lavage fluid, sputum, nasal swabs and fibrobronchoscope brush biopsy specimens would give 93%, 72%, 63% and 46% positivity respectively. Drugs on therapeutic trials for SARS-CoV-2 infections across the globe include: chloroquine, Hydroxychloroquine plus azithromycin, remdesivir, actemra, kevsara, convalescent plasma, avigan, TAK-888, and antibody treatment among others all with mixed degrees of success in different parts of the world. We therefore recommend an Afrocentric control model with the following components: wearing of face mask, proper hand washing with soap and water, sanitizers, avoid reflex hand touch on the face, eyes or picking nose, avoid unhealthy cultural practices like handshakes, observe social distancing, regular habit of removing cloaks or outer wears outside the house, regular steam inhalation and drinking of hot fluids. Hydroxychloroquine + azithromycin should be readily available for mass treatment..

Keywords: Clinical Features, Control, Coronaviruses, COVID-19, SARS-COV-2

INTRODUCTION

It all started in Wuhan city, Hubei province in China where doctors noticed a strange severe form of pneumonia in late 2019 following a similar pattern in some patients in the hospital in Wuhan¹⁻². The alarm raised by Dr Li Wenliang, a 34 year old ophthalmologist led to the discovery of a hitherto an unknown form of a virus-associated pneumonia among humans called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus which belongs the family Coronaviridae, a single stranded RNA virus which is predominantly zoonotic causing diseases in other animals both wild and domestic. The virus is now known to cause Coronavirus Disease 2019 (COVID-19) among humans presenting with severe pneumonias with high fatalities and within two months has spread from Wuhan to all continents and most countries of the world³⁻⁵.

As at 6th of April 2020 COVID-19 had afflicted about 1.3 Million people worldwide with 70, 590 deaths; Spain recording 135,032 infections and 13,055 deaths while Italy has so far recorded 128,948 infections with 15, 887 deaths and USA, 337,797 infections with 9,670 deaths. In China where it all started the virus has infected at least 81,708 people with 3,331 deaths and in Nigeria it has infected 322 people with 5 deaths. While the disease has been substantially contained in China where it all started, the spread to other parts of the world is still on the increase with proportionate death tolls. As at today Africa appear to be the only continent yet to experience the monumental havoc the disease has wrecked in other continents of the world. It is therefore difficult to tell whether the disease is on its way heading to Africa or Africa is going to experience less impact from it⁶⁻⁸.

As researches are ongoing across the world to find a lasting cure and also to produce a potent vaccine to contain the disease, it apparently appears not all about the physicochemical, clinical, epidemiological, human kinetic, and pathologic properties of the disease are fully understood. This may explain the different approaches in the control, treatment and prevention of the disease from

different parts of the world and different management outcomes from countries with similar standards of healthcare services recording discordant fatalities. The conspiracy theories about the 5G and religious theories surrounding the illness have all contributed to confusing both the teaming public and health professionals inclusive the world over. As the global struggle to combat the disease continues where Africa stands in this pandemic at present is not precisely known in terms of the likely impact on the continent. A regular and periodic review of the various presentations of the disease from the worst hit parts of the world with far more advanced health settings will serve as a viable source of information for Africa and Africans⁹⁻¹¹.

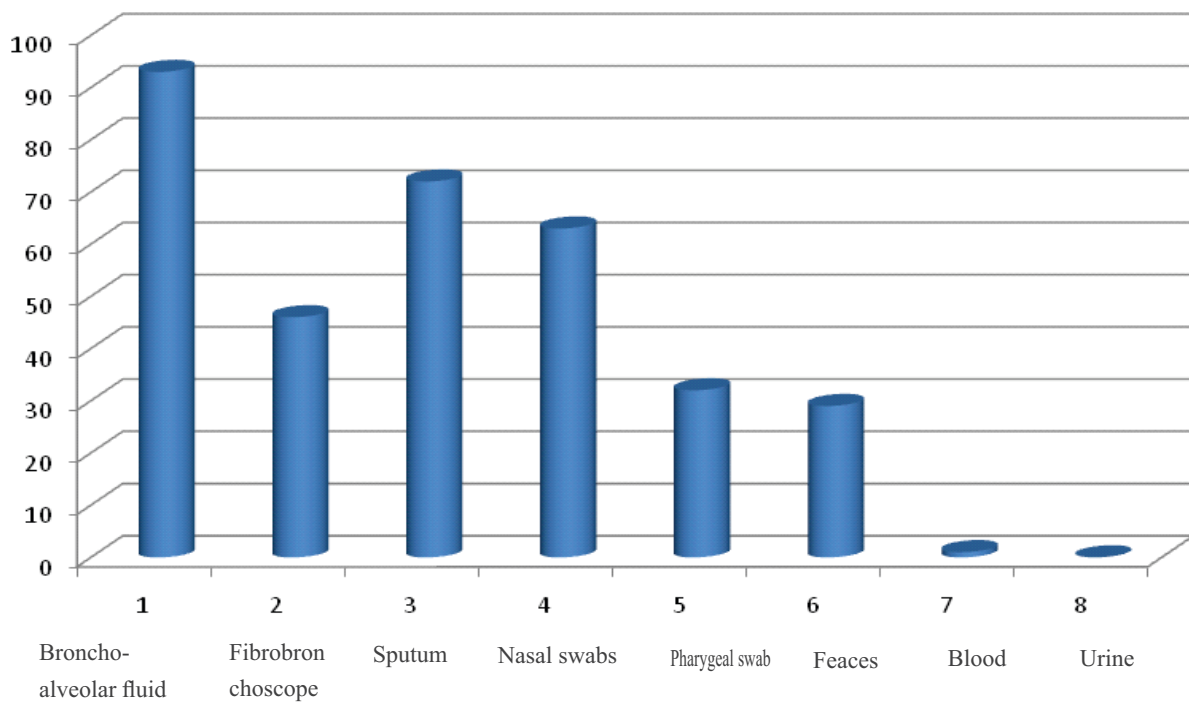
With her poor health facilities, African countries including Nigeria with inadequate facilities for laboratory diagnosis of COVID-19, reliance on clinical picture may be the only process that health professionals and indeed all healthcare givers may rely upon to make early index of suspicion for the disease. This study was therefore set up to review the various clinical presentations and features associated with the disease from the most affected countries of the world and other related discussions¹²⁻¹⁴.

MATERIALS AND METHODS

The study was based on literature searches on reports and documentations on the clinical presentations and management protocols of SARS-CoV-2 infections among the most afflicted countries and regions of the world from January 1st 2020 to 31st March 2020. This includes clinical presentations; drugs used in the management, likely modes of spread and associated threats in continuous spread of the disease as captured in scientific write-ups, electronic and print media and social media groups. Information was gathered from China, Italy, Spain, France, Germany, USA, Iran, United Kingdom, South Korea as well as other less heavily infected countries. Data was analysed using simple quantitative descriptive and qualitative methods.

Table 1 : Human Coronaviruses associated with clinical diseases

| Virus | Genus | Disease | Year of Discovery |
|------------|-------|---|-------------------|
| CoV-NL-63 | Alpha | Mild Respiratory Tract Infection | 1965 |
| Cov-229E | Alpha | Mild Respiratory Tract Infection | 1967 |
| SARS-CoV | Beta | Human Severe Acute Respiratory Syndrome, 10% Mortality rate | 2003 |
| CoV-OC43 | Beta | Mild Respiratory Tract Infection | 2004 |
| CoV-HKU-1 | Beta | Mild Respiratory Tract Infection, Pneumonia | 2005 |
| MERS-CoV | Beta | Human Severe Acute Respiratory Syndrome, 37% Mortality rate | 2012 |
| SARS-CoV-2 | Beta | Severe Acute Respiratory Infections, <2% Mortality rate | 2019 |



Specimens processed for SARS-COV-2 Isolation in China

Figure 1: Percentage Positivity in Laboratory Diagnosis of SARS-CoV-2 Infections using PCR from different human samples¹⁶.

Table 2: Associated Clinical Features of SARS-CoV-2 Infections across the globe (N=2,788)

| Clinical Presentation | Frequency (%) |
|-------------------------------------|---------------|
| Fever | 2,713(97.3) |
| Difficulty Breathing (Severe Cases) | 2,470(88.6) |
| Tiredness | 1,846(66.2) |
| Cough (Dry usually) | 1,748 (62.7) |
| Headache | 906 (32.5) |
| Diarrhoea | 622(22.3) |
| Nausea | 496 (17.8) |
| Dizziness | 388(13.9) |
| Vomiting | 326(11.7) |
| Anosmia | 268(9.6) |
| Loss of appetite | 165(59.1) |
| Abdominal pain | 153(5.5) |
| CNS disease | 13(0.5) |
| Sickle cell Crisis | 1(0.04) |
| Tiger | 1(0.04) |

Table 3: Drugs presently on therapeutic trials for SARS-CoV-2 Infections across the globe

| |
|--|
| Chloroquine, Hydroxychloroquine + Azithromycin |
| Remdesivir- An anti-Ebola drug |
| Actemra- Rheumatoid arthritis drug |
| Kaletra (Lopinavir + Ritonavir) Antiretroviral drug |
| Kevzara |
| Convalescent Plasma |
| Avigan |
| TAK-888 from Japan |
| Antibody Treatment |
| Tocilizumab |
| Sarilumab |
| Losartan an ACE Inhibiting Antihypertensive |
| Favipiravir (Avigon) an Anti-Flu drug in Japan |
| ELDD-2801- Anti-viral genetic mutations, on trial in USA |

RESULTS

A total of 2,788 documented records of SARS-CoV-2 infections across the globe were considered. The Coronaviruses that have caused human infections in the past include: CoV- 229E and CoV-NL-63 discovered in 1967 and 1965 respectively up to SARS-CoV-2 which was discovered in 2019. Other Coronavirus species include CoV-HKU-1, CoV-OC43, SARS-CoV and MERS-CoV discovered at different intervals in between but all of them causing varying degrees of respiratory illnesses (Table 1). Analyses of the various clinical presentations of SARS-CoV-2 infections from the available reports show that: fever, difficulty in breathing, tiredness and dizziness accounted for 97.3% (n=2,713), 88.6% (n=2,470), 66.2% (n=1,846), 62.7% (n=1,748), and 32.5% (n=906) respectively. Gastrointestinal clinical features such as diarrhea, nausea and vomiting were not uncommon with 22.3% (n=622), 17.8% (n=496), and 11.7% (n=326) respectively. Central nervous system involvement was reported in 0.5% (n=13) while a clinical case in a caged tiger was reported 0.04% (n=1) (Table 2).

Findings on the clinical samples for isolation of SARS-CoV-2 virus isolation showed that: bronchoalveolar lavage fluid, sputum, nasal swabs and fibrobronchoscope brush biopsy specimens would give 93%, 72%, 63% and 46% positivity respectively. The rate of positivity to SARS-CoV-2 infection from other clinical specimens include: pharyngeal swabs 32%, faeces 29%, blood 1% and urine 0% (Figure 1).

Drugs on therapeutic trials for SARS-CoV-2 infections across the globe include: chloroquine, Hydroxychloroquine plus azithromycin, remdesivir, actemra, kevzara, convalescent plasma, avigan, TAK-888, and antibody treatment. Other drugs include tocilizumab, sarilumab, losartan, favipiravir and ELDD-2801 (Table 3).

DISCUSSION

Research findings have shown that Coronaviruses have been in existence much earlier than the last five decades

when it was first discovered in 1967. From the outset this group of viruses was not associated with severe infections in humans as they often caused asymptomatic to mild and transient respiratory tract infections requiring no hospitalization and no aggressive medical intervention^{17,18}. The very severe and life threatening diseases associated with Coronaviruses began to emerge in 2003 with the emergence of SARS-CoV strain and was followed in 2012 by MERS-CoV, and then the present SARS-CoV-2 strain. The last strain has caused the COVID-19 disease pandemic which is presently ongoing and has claimed lives approaching 100,000 across the globe as at April 11th 2020. This progressive increase in virulence with aggressive worsening clinical picture of Coronaviruses generally can be attributed to the evolutionary trend of the members of the Coronaviridae family. The evolutionary process going on among the viral group has given them increasing adaptations and capabilities to live and survive more comfortably in human tissues and systems with additional ability to cause more damage to the human host.¹⁹⁻²¹

These evolutionary trends as earlier propounded by Charles Darwin in 1859 in his book titled: “*On the Origin of Species*” are purely accidental and a game of chance in the process of selection of preferred species. Viruses evolve through mutations while horizontal gene transfer between viruses, bacteria and eukaryotes can occur via transduction, conjugation, transformation, meiosis and mitosis depending on the cellular complexity.^{22,23}

Noah Whiteman of Integrative Biology research of University of California once remarked:

“*How does something that has been out of a lineage for hundreds of millions of years potentially get incorporated into a foreign lineage that it has no experience with? It's an absolutely fascinating question*” This evolutionary process has not stopped and is still ongoing and is bound to give rise to more virulent infectious agents with potentially more catastrophic impacts on humans. It is interesting to note than microorganisms when they evolved about 4 billion years ago were harmless and were referred to as extremophiles and in the course of evolution

over 95% of these organisms went extinct from natural selection and survival of the fittest. This has given birth to the few that have survived the course of evolution and a few now cause disease in man^{24,25}.

There is therefore a pressing need to be more vigilant in critical patient examination and management to detect early onset of these hitherto unknown infections. Also there should be preparedness in the area of vaccines and appropriate drugs against the likely zoonotic and reemerging viruses with high propensity to higher human virulence and as well higher disease burden.

SARS-CoV-2 Infections and 5G Network

The present theories trying to establish a link between 5G radiations and SARS-CoV-2 infections with the global deaths toll associated with COVID-19 disease lack sufficient scientific basis. COVID-19 is caused by a virus which has been detected and isolated from infected individuals and the evolution of 5G network appear to be a mere coincidence at this time of COVID-19 pandemic. The pulling down of 5G masts in London and Wuhan due to its perceived association with COVID-19 disease clearly shows how limited knowledge the general public have about Corona viruses generally. This could influence the level of acceptability of the control and preventive measures available by the people to break the chain of transmission of the disease. Interestingly, these viruses have been undergoing adaptation over the past century for human habitation in line with the normal evolutionary trends of microorganisms.²⁶

Clinical Presentations of SARS-CoV-2 Infections

Among the common clinical features of SARS-CoV-2 infections include fever, cough, difficulty in breathing, headache, diarrhea and nausea. Both health professionals and the general public should be on a lookout for individuals and groups presenting with these features in health settings and communities respectively to ensure prompt medical attention and arrest spread. More public enlightenment should be intensified in Nigeria and indeed Africa to dissuade the general public from the supernatural

and spiritual dimensions being given to the disease. The detection of the virus in a caged tiger in a zoo in New York brings to attention the possibility of animal reservoirs within the reach of humans as the virus could spread among the wild animals caged in zoos as well as domestic animals such as cats and dogs. The infected animals in zoos could serve as a formidable reservoir for a sustained community spread and re-infections as people continue to visit the parks for social, academic and other purposes. It becomes therefore necessary as the world battles to control COVID-19 pandemic all human visits to zoos in the country should also be highly restricted to break that chain of possible transmission as well. Also special attention should be paid to all domestic animals in settlements and homes where SARS-CoV-2 has had a foothold. These should be equally screened to ensure that there is no animal reservoirs in homes and communities which would have rendered all control measures targeted at humans now ineffective²⁷⁻³⁰.

The activities of cattle, goats and sheep pastoralists in Nigeria and many parts of Africa should be properly designed and ordered to limit their free movements in communities and the countryside. Also mass screening for SARS-CoV-2 infection among livestock should be carried out on regular basis especially in high risk areas.

Laboratory Diagnosis of SARS-CoV-2 infections

From the available reports the three most common samples to yield appreciable positive results in SARS-CoV-2 infected individuals include bronchoalveolar lavage fluid, sputum, and nasal swabs with 93%, 72%, and 63% positivity respectively. This underscores the need for extra vigilance in the prevention of COVID-19 disease as no sample guarantees 100% accuracy and the chances of getting a false negative report is also a possible occurrence. The lack of available confirmatory tests in most health centres across Nigeria and indeed all over Africa makes it mandatory that all health personnel should adopt strict adherence to universal protection protocol in the hospitals while attending to all patients especially during this time of outbreak. This will largely mitigate the

risk of transmission from both carriers and patients in incubation period^{16,31-33}

Drug Treatment of SARS-CoV-2 Infections

It is on record that since the commencement of SARS-CoV-2 infection late last year to date there has been no specific drug for its management and several drugs are on trial on the severely infected patients. These include chloroquine, hydroxychloroquine + azithromycin which was first tried in Wuhan China but with mixed management outcomes and is presently on trial in New York USA also with mixed recovery rate outcomes; remdesivir an anti-Ebola drug is also on trial in China, Italy, Spain and Thailand with varying treatment successes in each country. Also other drugs such as: acterna an anti-rheumatoid arthritis drug, kaletra an anti-retroviral drug, TAK-888 on use in Japan, and losartan an anti-hypertensive have all not agreed on level of uniform successes in different countries of use. The ELDD-2801, a drug that attacks viral genetic mutations is presently on trial in USA, and its success story will be known in due course³⁴⁻³⁶.

As efforts to obtain a lasting cure for SARS-CoV-2 infections continue, the various drugs in use for therapeutic trial should continue to be handy to physicians and other health personnel, and the choices depending on individual preferences and patients pre-morbid and associated clinical picture. Appropriate back up with oxygen and ventilators which are the last treatments of choice should always be handy whenever these drugs fail.

COVID-19 Control Models Across the globe

There are presently at least four main epidemiological approaches across the globe to combat the SARS-CoV-2 infections being implemented by different countries in different ways:

The Dutch model has adopted mass immunization of the entire population through a progressive containment of the entire population. Here only the very vulnerable and sick people are isolated and there is no mass screening. This would allow herd immunity to develop over time and the entire community

will eventually develop resistance to the disease as in the case of influenza disease³⁷.

The Chinese/French-Italian model has adopted a forced and generalized containment with the closure of all places prone to large gatherings such as: both private and public schools, airports and sea ports, metro stations, markets, restaurants and bars, religious gatherings, shopping malls and factories. There is restriction of movements and travels reserved to only essential services, and there is screening of only serious cases and not the general population³⁸.

The South Korean/German model has adopted the testing of all people as in South Korea, or testing of only suspected cases as in Germany. There is isolation of patients or suspects with or without specified places of confinement. In both countries there is closure of all public places such as: both private and public schools, airports and sea ports, religious gatherings, metro stations, markets, restaurants and bars, shopping malls and factories³⁹.

The Raoult model propounded by Professor Didier Raoult in Marseille adopts the policy of mass screening of the entire populace. All those who test positive will then immediately be placed hydroxychloroquine + azithromycin. This is inexpensive with potential impressive outcomes as it yielded over 99% full recovery rate on patients tried⁴⁰⁻⁴³.

Limitations to the Study

This study is limited due to the fact that some of the sources of the information cannot be sufficiently verified especially from social media and the possibility of biases in reportage about the disease from different media organizations. Also the influence of governments over the authenticity and type of information coming from different countries about the disease to suite particular political interests could affect the genuineness of some of the information obtained.

CONCLUSION

As COVID-19 pandemic heads towards Africa, health personnel on the continent should learn from the experiences and challenges of the most advanced countries where the disease has defiled all available control remedies. Important information on clinical presentation, laboratory diagnosis, drug management and various treatment models should be critically analysed in the context of affordability and cost versus benefit to arrive at an implementable and workable plan in the context of the economic and technological strengths of individual African nations. Therefore general containment, restriction of movement of persons, closure of all public places, mass testing of whole populations if adopted while those positive are placed immediately on hydroxychloroquine + azithromycin and promptly isolated would control the disease on the continent. Also adequate supplies of PPE, face masks, respirators, and adequate treatment and well furnished isolation centres would be necessary backup for efficient management of COVID-19.

Recommendations

For African countries that have sufficient resources and can afford we recommend a hybrid of Korean/German and Raoult models which is basically testing all the people, imposing restriction order to movements and banning all social gatherings, and prompt commencement of hydroxychloroquine + azithromycin on those who test positive. Other facilities such as respirators, PPEs, face masks, and adequate treatment and isolation centres should all be adequately provided to ensure that nothing is left to chance in the control of the disease.

Considering the level of poverty, heavy burden of other diseases, and a dysfunctional health system and maladministration, African countries may lack the capacity to implement the Korean/German and Raoult's model of COVID-19 control. This is coupled with the fact that in some African countries such as Nigeria which is experiencing large displacement of people presently in refugee camps, starvation and armed banditry, lockdown

will be more devastating than COVID-19 especially if prolonged. This is because many Nigerians feed daily from their daily outdoor activities and prolonged restriction of movement would lead to mass starvation in the land as the poor of the poor do not have bank accounts to access any social benefits.

We therefore recommend an Afro-centric model of COVID-19 control in Africa to avert grave consequences on national economies especially in the long run. We suggest that the message of infection control practices should be conveyed through every available medium. Even a lay man on the street should be thoroughly educated on infection control practices. This includes among others wearing of face mask, proper hand washing with soap and water, sanitizers, avoiding reflex hand touch on the face, eyes or picking nose, avoiding unhealthy cultural practices like handshakes, observing social distancing, regular habit of removing cloaks or outer wears outside the house and exposing them in the sun at least over 24 hours as one comes back to the house and bathing with soap and water before entering your house and many more.

Also regular steam inhalation and, drinking hot water and in addition to any of our herbs or fruits that are immune boosters, detoxifiers, Ph modifiers and antioxidants should be used. Hydroxychloroquine + azithromycin which are cheap drugs should be readily made available for treatment of symptomatic cases. Finally, provision should be made for adequate and well equipped treatment centres for management of severe cases.

REFERENCES

1. Lai CC, Wang CY, Wang YH, Hsueh SC, Ko WC, Hsueh PR Global epidemiology of coronavirus disease 2019 (COVID-19): disease incidence, daily cumulative index, mortality, and their association with country healthcare resources and economic status. *Int J Antimicrob Agents.* 2020; 19:105946. doi: 10.1016/j.ijantimicag.2020.105946.
2. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med.* 2020 Feb 28. doi: 10.1056/NEJMoa2002032.
3. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol.* 2020; 5(4):536-544. doi: 10.1038/s41564-020-0695-z.
4. Lai CC, Liu YH, Wang CY, Wang YH, Hsueh SC, Yen MY, Ko WC, Hsueh PR. Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): Facts and myths. *J Microbiol Immunol Infect.* 2020; 4: S1684-1182(20)30040-2. doi: 10.1016/j.jmii.2020.02.012.
5. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. *Int J Antimicrob Agents.* 2020; 55(3):105924. doi: 10.1016/j.ijantimicag.2020.105924.
6. World Health Organization (WHO). Coronavirus Disease (COVID-19) Situation reports. Situation Report 79, 8th April, 2020. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports>.
7. World Health Organization (WHO). Coronavirus Disease (COVID-19) Situation reports. Situation Report 78, 7th April, 2020. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports>.
8. Ashour HM, Elkhatib WF, Rahman MM, Elshabrawy HA. Insights into the Recent 2019 Novel Coronavirus (SARS-CoV-2) in Light of Past Human Coronavirus Outbreaks. *Pathogens.* 2020; 4; 9(3): E186. doi: 10.3390/pathogens9030186.
9. Shanmugaraj B, Siri wattananon K, Wangkanont K, Phoolcharoen W. Perspectives on monoclonal antibody therapy as potential therapeutic intervention for Coronavirus disease-19 (COVID-19). *Asian Pac J Allergy Immunol.* 2020; 38(1):10-18. doi: 10.12932/AP-200220-0773.
10. Yan Y, Shin WI, Pang YX, Meng Y, Lai J, You C, Zhao H, Lester E, Wu T, Pang CH. The First 75 Days of Novel Coronavirus (SARS-CoV-2) Outbreak: Recent Advances, Prevention, and Treatment. *Int J Environ Res Public Health.* 2020; 30;17(7): E2323. doi: 10.3390/ijerph17072323.
11. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med*

- Virology. 2020; 27e. doi: 10.1002/jmv.25728.
12. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? *Int J Antimicrob Agents*. 2020; 12:105938e. doi: 10.1016/j.ijantimicag.2020.105938.
 13. Contini C, Di Nuzzo M, Barp N, Bonazza A, De Giorgio R, Tognon M, Rubino S. The novel zoonotic COVID-19 pandemic: An expected global health concern. *J Infect Dev Ctries*. 2020; 31;14(3):254-264. doi: 10.3855/jidc.12671.
 14. Ahn DG, Shin HJ, Kim MH, Lee S, Kim HS, Myoung J, Kim BT, Kim SJ. Current Status of Epidemiology, Diagnosis, Therapeutics, and Vaccines for Novel Coronavirus Disease 2019 (COVID-19). *J Microbiol Biotechnol*. 2020; 28: 30(3):313-324. doi: 10.4014/jmb.2003.03011.
 15. Loeffelholz MJ, Tangb YW. Laboratory diagnosis of emerging human coronavirus infections – the state of the art. *Emerg Microbes & Infect*. 2020; 9:e. <https://doi.org/10.1080/22221751.2020.1745095>.
 16. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, Tan W. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA* 2020; 11: 203786e.
 17. Su S, Wong G, Shi W, et al. Epidemiology, genetic recombination, and Pathogenesis of coronaviruses. *Trends Microbiol* 2016;24(6):490–502. doi:10.1016/j.tim.2016.1003.1003.
 18. Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med*. 2003; 348(20):1953–1966. doi:1910.1056/NEJMoa030781.
 19. Bradburne AF, Somerset BA. Coronavirus antibody titres in sera of healthy adults and experimentally infected volunteers. *J Hyg (Lond)* 1972; 70(2): 235–244. doi: 10.1017/s0022172400022294.
 20. Kapikian AZ, Harvey D, James HD, Jr, Kelly SJ, Vaughn AL. Detection of Coronavirus Strain 692 by Immune Electron Microscopy. *Infect Immun*. 1973 ; 7(1): 111–116.
 21. Coria MF. Protective effect of an inactivated avian coronavirus vaccine administered by aerosol. *Arch Gesamte Virusforsch*. 1973; 41(1): 66–70. doi: 10.1007/BF01249930.
 22. Darwin C. Darwinism. *Ind Med Gaz*. 1872; 7(2):47. PMID: 28995415; PMCID: PMC5132969.
 23. Darwin C. Experiments. *Med Phys J*. 1800; 4(17):50-53. PMID: 30490902; PMCID: PMC5670582.
 24. Callier V. Core Concept: Gene transfers from bacteria and viruses may be shaping complex organisms. *PNAS*. 2019; 116 (28) 13714-13716; <https://doi.org/10.1073/pnas.1909030116>.
 25. R. Cordaux R, Gilbert C. Evolutionary significance of *Wolbachia*-to-animal horizontal gene transfer: Female sex determination and the *felement* in the isopod *Armadillidium vulgare*. *Genes (Basel)* 2017; 8: 186e.
 26. Koonin EV, Dolja VV, Krupovic M. Origins and evolution of viruses of eukaryotes: The ultimate modularity. *Virology*. 2015 May;479-480:2-25. doi: 10.1016/j.virol.2015.02.039. Epub 2015 Mar 12. PMID: 25771806; PMCID: PMC5898234.
 27. Liang WH, Guan WJ, Li CC, Li YM, Liang HR, Zhao Y, et al. Clinical characteristics and outcomes of hospitalised patients with COVID-19 treated in Hubei (epicenter) and outside Hubei (non-epicenter): A Nationwide Analysis of China. *Eur Respir J*. 2020; 8:2000562. doi: 10.1183/13993003.00562-2020. Epub ahead of print. PMID: 32269086; PMCID: PMC7144336.
 28. Meo SA, Al-Khlaiwi T, Usmani AM, Meo AS, Klonoff DC, Hoang TD. Biological and Epidemiological Trends in the Prevalence and Mortality due to Outbreaks of Novel Coronavirus COVID-19. *J King Saud Univ Sci*. 2020; 9:e doi: 10.1016/j.jksus.2020.04.004. Epub ahead of print. PMCID: PMC7144605.
 29. Zhang ZJ, Yu XJ, Fu T, Liu Y, Jiang Y, Yang BX, Bi Y. Novel Coronavirus Infection in Newborn Babies Under 28 Days in China. *Eur Respir J*. 2020; 8:2000697e. doi: 10.1183/13993003.00697-2020. Epub ahead of print. PMID: 32269087; PMCID: PMC7144267.
 30. Liang WH, Guan WJ, Li CC, Li YM, Liang HR, et al. Clinical characteristics and outcomes of hospitalised patients with COVID-19 treated in Hubei (epicenter) and outside Hubei (non-epicenter): A Nationwide Analysis of China. *Eur Respir J*. 2020; 8:2000562. doi: 10.1183/13993003.00562-2020. Epub ahead of print. PMID: 32269086; PMCID: PMC7144336.
 31. Alberici F, Delbarba E, Manenti C, Econimo L, Valerio F, Pola A, Maffei C, Possenti S, Zambetti N, Moscato M, Venturini M, Affatato S, Gaggiotti M, Bossini N, Scolari F. A single center observational study of the clinical characteristics and short-term

- outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia. *Kidney Int.* 2020; 9. doi: 10.1016/j.kint.2020.04.002. Epub ahead of print. PMID: PMC7142691.
32. Yan C, Cui J, Huang L, Du B, Chen L, Xue G, et al. Rapid and visual detection of 2019 novel coronavirus (SARS-CoV-2) by a reverse transcription loop-mediated isothermal amplification assay. *Clin Microbiol Infect.* 2020; 7:S1198-743X(20)30186-5. doi: 10.1016/j.cmi.2020.04.001. Epub ahead of print. PMID: 32276116; PMID: PMC7144850.
33. Colson P, Lagier JC, Baudoin JP, Bou Khalil J, La Scola B, Raoult D. Ultrarapid diagnosis, microscope imaging, genome sequencing, and culture isolation of SARS-CoV-2. *Eur J Clin Microbiol Infect Dis.* 2020; 8:1–3. doi: 10.1007/s10096-020-03869-w. Epub ahead of print. PMID: PMC7138953.
34. Zhang TY, Zhong B. Meeting the Potential Emergency Global Drug Supply Challenge of Hydroxychloroquine for COVID-19. *Medicine in Drug Discovery.* 2020; 9:100036. doi: 10.1016/j.medidd.2020.100036. Epub ahead of print. PMID: PMC7144509.
35. Lythgoe MP, Middleton P. Ongoing Clinical Trials for the Management of the COVID-19 Pandemic. *Trends Pharmacol Sci.* 2020; 9e. doi: 10.1016/j.tips.2020.03.006. Epub ahead of print. PMID: PMC7144665.
36. Tanja FS, Nancy P, Keller N, Claudia G. Conservative management of Covid-19 patients - emergency palliative care in action. *J Pain Symptom Manage.* 2020; 7:S0885-3924(20)30183-4. doi: 10.1016/j.jpainsymman.2020.03.030. Epub ahead of print. PMID: 32276101; PMID: PMC7144848.
37. Etkind SN, Bone AE, Lovell N, Cripps RL, Harding R, Higginson IJ, Sleeman KE. The role and response of palliative care and hospice services in epidemics and pandemics: a rapid review to inform practice during the COVID-19 pandemic. *J Pain Symptom Manage.* 2020; 8. doi: 10.1016/j.jpainsymman.2020.03.029. Epub ahead of print. PMID: PMC7141635.
38. Buonomo B. Effects of information-dependent vaccination behavior on coronavirus outbreak: insights from a SIRI model. *Ricerche di Matematica.* 2020; 9:1–17. doi: 10.1007/s11587-020-00506-8. Epub ahead of print. PMID: PMC7144546.
39. Li C, Romagnani P, von Brunn A, Anders HJ. SARS-CoV-2 and Europe: timing of containment measures for outbreak control. *Infection.* 2020; 9:1–4. doi: 10.1007/s15010-020-01420-9. Epub ahead of print. PMID: PMC7142270.
40. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19?. *Int J Antimicrob Agents.* 2020; 105938e. <https://doi.org/10.1016/j.ijantimicag.2020.105938>.
41. Deng XQ, Xu XJ, Wu SH, Li H, Cheng YJ. Association between resting painless ST-segment depression with sudden cardiac death in middle-aged population: A prospective cohort study. *Int J Cardiol.* 2020; 15;301:1-6. doi: 10.1016/j.ijcard.2019.11.148. Epub 2019 Nov 28. PMID: 31810811; PMID: PMC7141178.
42. Gabutti G, d'Anchera E, Sandri F, Savio M, Stefanati A. Coronavirus: Update Related to the Current Outbreak of COVID-19. *Infect Dis Ther.* 2020; 8:1–13. doi: 10.1007/s40121-020-00295-5. Epub ahead of print. PMID: PMC7139198.
43. Harapan H, Itoh N, Yufika A, Winardi W, Keam S, Te H, Megawati D, Hayati Z, Wagner AL, Mudatsir M. Coronavirus disease 2019 (COVID-19): A literature review. *J Infect Public Health.* 2020; 8. doi: 10.1016/j.jiph.2020.03.019. Epub ahead of print. PMID: PMC7142680.