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Short Communication

Epidemiology Section

COVID-19: An Epidemiological Puzzle

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ABSTRACT

A cluster of pneumonia cases of unknown aetiology was reported from Wuhan, Hubei province of China on 31st December, 2019. The World Health Organisation (WHO) declared the outbreak a Public Health Emergency of International Concern (PHEIC) on 30th January, 2020. Thereafter, it has spread through China and reached the level of a pandemic expanding to 210 countries with 77.9M confirmed cases and 1.71M deaths as per Corona virus Disease (COVID-19) situation report issued by WHO based on data received upto 23rd December, 2020. A number of questions remain unanswered regarding pathogen-associated variables for amplification dynamics, host environment and agent interaction. This short communication makes an effort to compile the information gathered from published articles of renowned journals and newsletters to explore the epidemiological characteristics of COVID-19. Hereby in this article, authors have tried to assemble the epidemiological lacunae created by the novel characteristics of the SARS-CoV-2 (Severe Acute Respiratory Syndrome-Corona Virus-2) which presently pose a rather puzzling transmission dynamics of COVID-19 that still remain unanswered.

Keywords: Challenges, Corona virus disease-19, Epidemiology, Queries, Transmission dynamics

INTRODUCTION

There is a greek myth in which gods had given Pandora, a locked box and advised never to open. However, driven by human weakness she nevertheless opened it, releasing the world's misfortune. Such is the scenario with COVID-19 [1]. A cluster of pneumonia cases of unknown aetiology was reported from Wuhan, Hubei province of China on 31st December, 2019. The WHO declared the outbreak a PHEIC on 30th January, 2020 [2]. Thereafter, it was spread throughout China, expanding to 210 countries and reached the level of a pandemic. On 11th February, 2020 a name was announced for this novel coronavirus disease: COVID-19 [3]. Established public health measures, such as contact tracing, quarantining, testing and treatment, supported by social distancing and wearing facemasks are the gold standards for tackling this global pandemic. To this effect, on 24th March, 2020, the Government of India ordered a nationwide lockdown for 21 days, at a point when the number of confirmed cases was approximately 500 in the country [4]. Currently India has witnessed cases related to both local and community transmission in almost all the states. Community transmission has been confirmed nationally. However, a statewise difference of opinion regarding the same still persists at some levels . Historically, if we look back, there were multiple viral outbreaks globally. Coronavirus (CoV) has been responsible for previous epidemics, such as the Severe Acute Respiratory Syndrome (SARS) of 2003 and Middle East Respiratory Syndrome (MERS) of 2012. However, SARS-CoV-2 emergence has taken a different trajectory. Despite the fact that all three viruses (SARS-CoV-1, MERS-CoV, SARS-CoV-2) apparently originated from bats [1], multiple questions remain unanswered regarding pathogen associated variables for amplification dynamics, host environment, agent interaction. With this present analysis of different documentations, we have tried to understand the different variables pertaining to the COVID-19 transmission dynamics.

The present study was done to perform a descriptive analysis of COVID-19 epidemiological characteristics based on different published articles. The information was analysed and gathered from published articles of renowned journals and newsletters to explore the epidemiological characteristics of COVID-19.

DISCUSSION

A pooled analysis of confirmed COVID-19 cases reported in China estimated the median incubation period to be 5.8 days, almost similar to SARS. However, the symptoms appeared in 97.5% subjects within 11.5 days [5]. This infection has led in a multitude of knowledge gaps that has resulted in random spread and initiation of a pandemic of global proportions. A brief compilation of the major lacunae perplexing researchers worldwide is presented below:

Transmission dynamics: Any infectious disease outbreak can be characterised by its reproductive number Ro. If Ro>1, cases are statistically capable of secondary transmission. For COVID-19 outbreak in China, Ro ranged from 2.5-2.9 [6,7] in contrast to the 1918-19 Spanish Flu Pandemic that killed 50-100 million people worldwide with estimated Ro being 1.8. For SARS (2003) and MERS (2012) outbreaks, the Ro was <2 [8]. So, the current pattern of COVID-19 transmission presents a shorter doubling time, which is a cause for concern. Unlike the SARS (2003) and MERS (2012) outbreaks, where almost all onward transmission occurred after symptom onset, COVID-19 transmission can occur prior to that. Based on this fact 'contacts' have been defined as "those who have been in close contact since two days before onset of symptoms of suspected and confirmed cases, or two days prior to asymptomatic cases". This reflects that secondary transmission of COVID-19 virus is possible in minimum of two days prior to symptom onset [9]. Studies have also shown evidence of transmission by asymptomatic subjects who were later tested positive for SARS-CoV-2. This is an indication to the latent period extending from the point when it first enters the body to when symptoms begin to appear [10,11]. The complete SARS of COVID-19 is manifested by only 5-10% of the total infected persons [12]. Whilst respiratory droplets and fomites have been advocated to be the major modes of transmission, studies have shown airborne transmission might be the cause of the extraordinary attack rate [13,14]. Apart from oral swabs and Bronchoalveolar Lavage Fluid (BALF), the virus has also been detected in anal swabs and blood [15,16]. This connotes the possibility of viral shedding through faeco-oral and body-fluid routes, providing a lead for further interventions. Although the human CoV does not replicate outside a living cell, it remains viable on contaminated surfaces for varied durations, subject to humidity and temperature [17,18]. A high stability was found at 4°C in vitro but when the temperature was raised to 70°C, the inactivation time reduced to five minutes [19,20]. Hence, delving into new factors and new temperature determinants can shed light on the combination effect of temperature and humidity on the half-life of the virus. Droplet

inoculation on different surfaces showed that the virus did not persist post three-hours incubation on printing/tissue papers and two-days incubation on wood. The viability was higher on smooth surfaces and recovery ceased on day four from glass and banknotes and day seven on stainless steel and plastic. Persistence was observed on the outer layer of surgical mask even on day seven [1]. Hence, the survival of the virus varies on different surfaces and gives an idea how the safety and utility guidelines should be formulated, which can prove vital in breaking the transmission chain via inanimate objects in community settings.

Morbidity and mortality: Mean duration from onset of symptoms to death was found to be 17.8 days (95% CI 16.9-19.2) and to hospital discharge 24.7 days (95% CI 22.9-28) [20]. Estimated fatality may vary between countries owing to difference in prevention, control and implemented policy utilisation. Severity of a disease is usually measured by the fatality ratio i.e., the reported Case Fatality Rate (CFR). Verity R et al., reported from a model-based analysis, accounting for censoring and ascertainment bias, crude CFR of 3.67%. Best estimate from China reported, after adjustment of demography and ascertainment of CFR, to be 1.38% [20]. Even if the CFR of COVID-19 is lower as compared to 14-15% for SARS outbreak [21] and approximately 35% for MERS outbreak [22], rapid progression and evidence of multiple human-to-human transmission modes suggest SARS-CoV-2 to be more dangerous [10,23-25]. A preliminary study conducted in the Hubei province found that almost four or fifth of the affected population were aged 30-69 years, indicating a major impact on the global workforce. The ≥80 years of age group has the highest CFR [6]. A new question is cropping up regarding whether ethnicity is linked to incidence or outcome of COVID-19 [26]. A higher incidence and severity has been observed among ethnic minorities. Moreover, the first 10 doctors in the United Kingdom to succumb to COVID-19 have been identified to be from the ethnic section [27]. This could be due to socio-cultural, lifestyle, genetic predisposition, or pathophysiological differences in susceptibility to infection. A higher mortality was observed in presence of co-morbidities [10] and hence, ethnic groups with higher rates of diabetes, hypertension and other co-existing conditions are at exemplified risk [28-30]. Countries like India with a diverse geographic and demographic spectrum calls for further detailed studies. Even though data suggests no significant gender disproportion with 56% males being affected [28] but a higher COVID-19 related mortality among males maybe the result of immunological or habitual differences such as smoking [31,32]. However, it is too early to make any assumptions. Children of all age groups are sensitive to COVID-19 with neonates being the most vulnerable [33]. Disease severity and CFR is less as compared to adults [6,34]. This is puzzling, as children are often considered at higher risk of viral respiratory diseases owing to limited immune experience and incomplete airway development [35]. It indicates a knowledge gap that must be filled fast, as children can be important transmission facilitators for COVID-19. As for pregnancy, no obstetric or neonatal complications related to COVID-19 have been reported so far [36]. But data being insufficient, the medical and social risks cannot be ruled out. Very recently, a nonpeer-reviewed article by Miller A et al., reported a correlation between universal Bacillus Calmette Guerrin (BCG) vaccination and reduced impact of COVID-19. Five countries without universal BCG vaccination policy had 264.90±134.88 cases per million and 55 countries having a current policy had 59.54±23.29 cases per million inhabitants. A plausible explanation maybe the broad-spectrum protection against viral infection and sepsis conferred by the BCG vaccine [37], but this report was refuted as an ecological fallacy [38]. Reports of countries with high burden of leprosy being less vulnerable are also present [39]. Nevertheless, this does not rule out the possibility of a higher proportion of asymptomatic cases in comparison to clinical cases.

Diagnostics: The detection of SARS-CoV-2 is conducted by Real-Time Polymerase Chain Reaction (RT-PCR) method and screened via serological tests. Although the former is confirmatory, it can only detect the virus during the acute stage of viral shedding which is uncertain in case of COVID-19, plus the sensitivity and specificity of the COVID-19 RT-PCR test is not 100% [40]. The seroconversion kinetics show a gap between end of convalescent phase and period of antibody response. Therefore, the conversion of a potential carrier of SARS-CoV-2 to seronegative state is one of significance in preventing/controlling community transmission. This might give serological testing an upper hand with respect to public health in the detection of asymptomatic/subclinical cases [41].

Thus, from the analysis of different reports, a few-month-old disease appeared with total puzzling epidemiological characteristics, initiating a global pandemic. Multidimensional issues regarding the epidemiological spectrum came forward but could not be resolved. Animal-to-human viral transmission has also been under study by the global medical fraternity, although differences of opinion might keep cropping up [42]. Positive samples have been derived from pet dogs as well as cats. Also, outbreak incidence among tigers in a Malayan Zoo and in a mink farm indicates presence of animal-related transmission [43]. Regarding ethnicity, reports from developed countries are having perplexing implications. The reason isn't clear as to why minority origin countries are reporting lesser case incidences and symptomatic patients. Clinical manifestation is in line with airborne respiratory infections but gastrointestinal complications are now also emerging [31]. Although preferential selectivity of lungs is observed during the infection, recent studies have shown predisposition to myocarditis, acute myocardial infarction, exacerbation of heart failure and acute kidney injury due to COVID-19 [44]. The global diversity in mortality rates with significant numbers are being reported from developed countries is difficult to reason. Regarding diagnosis and treatment, the prevailing dilemma regarding the most suitable test is unresolved by administrators with no fixed drug therapy in pipeline at the moment except convalescent plasma showing some hope is perturbing. However, it is worth mentioning here that patients treated with a triple drug combination comprising of Human Immunodeficiency Virus (HIV) medicine lopinavir-ritonavir, hepatitis drug ribavirin, and multiple sclerosis therapy interferon-beta were observed to have tested negative five days earlier as compared to those treated with lopinavir-ritonavir alone after a duration of seven days and 12 days, respectively [45].

CONCLUSION(S)

The above analysis brings to the fore the puzzling epidemiological characteristics of the COVID-19 pandemic, including identification of the animal reservoir, determination of infective period, transmission dynamics, effective treatment and prevention methods including further test development, drug development and vaccine development which still remains under vigorous research, with final answers eagerly awaited. It is an attempt to briefly highlight the research gaps that still persist as limitations to the disease management strategies worldwide. In-depth and rigorous research is necessary to understand the puzzling epidemiological characteristics of COVID-19 disease. Though we tried to analyse different epidemiological studies, there are certain limitations of information collection and availability. Nevertheless, this study will hopefully help to identify epidemiological lacunae and aid in directing the development of solid evidences.

REFERENCES

[1] Morens DM, Daszak P, Taubenberger JK. Escaping Pandora's box- another novel coronavirus. N Engl J Med. 2020;382:1293-95. doi:10.1056/NEJMp2002106.
[2] World Health Organisation. Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV). Jan 30, 2020. https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov). (accessed Sep 9, 2020).
[3] World Health Organisation. Rolling updates on coronavirus disease (COVID-19). Updated 31st March 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen (accessed Apr 2, 2020).

[4] Gettleman J, Schultz K. Modi orders 3-week total lockdown for all 1.3 billion Indians. The New York Times. 24 March, 2020. https://www.nytimes.com/2020/03/24/world/asia/india-coronavirus-lockdown.html. (accessed Sep 9, 2020).

[5] Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: Estimation and application. Ann Intern Med. 2020;172(9):577-82. doi:10.7326/M20-0504.

[6] The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. Vital surveillances: The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19)-China 2020. China CDC Weekly. 2020;2(8):113-22. http://weekly.chinacdc.cn/en/article/id/e53946e2-c6c4-41e9-9a9b-fea8db1a8f51 (accessed Sep 9, 2020).

[7] Wu JT, Leung K, Leung GM. Now casting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: A modeling study. Lancet. 2020;395:689-97. doi:10.1016/S0140-6736(20):30260-9.

[8] Kwok KO, Tang A, Wei WI, Park WH, Yeoh EK, Riley S. Epidemic models of contact tracing: Systematic review of transmission studies of severe acute respiratory syndrome and Middle East respiratory syndrome. Comput Struct Biotechnol J. 2019;17:186-94.

[9] World Health Organisation. WHO Director-General's opening remarks at the media briefing on COVID-19. March 16, 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019?gclid=CjwKCAjwnef6BRAgEiwAgv8mQcVlieBAe4m49OzuosevSrnNnSQwXz2klQJMgxytONn5DqWW2HFT7BoCjfYQAvD_BwE.(accessed on 09/10/20).

[10] Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: A study of a family cluster. Lancet. 2020;395:514-23. [PMID: 31986261] doi:10.1016/S0140-6736(20)30154-9.

[11] Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, et al. Transmission of 2019 nCoV infection from an asymptomatic contact in Germany [Letter]. N Engl J Med. 2020;382:970-71. [PMID: 32003551] doi:10.1056/NEJMc2001468.

[12] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. Lancet Respir Med. 2020;pii:S2213-2600(20)300795. DOI: 10.1016/S2213-2600(20)30079-5. [Epub ahead of print].

[13] Yu IT, Li Y, Wong TW, Tam W, Chan AT, Lee JH, et al. Evidence of airborne transmission of the severe acute respiratory syndrome virus. N Engl J Med. 2004;350(17):1731-39.

[14] Shen Y, Li C, Martinez L, Chen Z. Airborne transmission of COVID-19: Epidemiologic evidence from two outbreak investigations. Preprint, 2020; 10.13140/RG.2.2.36685.38881.(accessed on 09/10/20).

[15] Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang B, et al. Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin. Nature. 2020;579:270-73. https://doi.org/10.1038/s41586-020-2012-7.

[16] Zhang W, Du RH, Li B, Zheng XS, Yang XL, Hu B, et al. Molecular and serological investigation of 2019-nCoV infected patients: Implication of multiple shedding routes. Emerg Microbes Infect. 2020;9(1):386-89. doi: 10.1080/22221751.2020.1729071.

[17] Ijaz MK, Brunner AH, Sattar SA. Survival characteristics of airborne human coronavirus 229E. J Gen Virol. 1985;66(12):2743-48.

[18] Warnes SL, Little ZR, Keevil CW. Human coronavirus 229E remains infectious on common touch surface materials. mBio. 2015;6(6):e01697-15.

[19] Chin AW, Chu JT, Perera MR, Hui KP, Yen H, Chan MC, et al. Stability of SARS-CoV-2 in different environmental conditions. The Lancet Microbe. 2020;5247(20)30003-03. https://doi.org/10.1016/S2666.

[20] Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, et al. Estimates of the severity of coronavirus disease 2019: A model-based analysis. Lancet. 2020;20(6):699-77. https://doi.org/10.1016/S1473-3099(20)30243-7.

[21] World Health Organisation. Update 49- SARS case fatality ratio, incubation period. May 7, 2003. https://www.who.int/csr/sars/archive/2003_05_07a/en/.

[22] World Health Organisation. Middle East respiratory syndrome coronavirus (MERS-CoV): Key facts. March 11, 2019. https://www.who.int/news-room/fact-sheets/detail/middle-east-respiratory-syndrome-coronavirus-(mers-cov). (accessed on 09/10/20).

[23] Paules CI, Marston HD, Fauci AS. Coronavirus infection-more than just the common cold. JAMA. 2020;323(8):707-08. http://dx.doi.org/10.1001/jama.2020. 075.

[24] Munster VJ, Koopmans M, van Doremalen N, van Riel D, de Wit E. A novel coronavirus emerging in China- Key questions for impact assessment. N Engl J Med. 2020;382:692-94. http://dx.doi.org/10.1056/NEJMp2000929.

[25] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506. http://dx.doi.org/10.1016/S0140-6736(20)30183-5.

[26] Khunti K, Singh AK, Pareek M, Hanif W. Is ethnicity linked to incidence or outcomes of COVID-19? BMJ. 2020;369:m1548. doi:10.1136/bmj.m1548.

[27] Siddique H. UK government urged to investigate coronavirus deaths of BAME doctors. The Guardian 2020 Apr 10. https://www.theguardian.com/society/2020/apr/10/uk-coronavirus-deaths-bame-doctors-bma.(accessed on 09/10/20).

[28] Go AS, Mozaffarian D, Roger VL. Executive summary: Heart disease and stroke statistics-2014 update: A report from the American Heart Association. Circulation. 2014;129:399-410.

[29] Fauci AS, Lane HC, Redfield RR. Covid-19- Navigating the uncharted. N Engl J Med. 2020;382:1268-69.

[30] Unnikrishnan R, Gupta PK, Mohan V. Diabetes in South Asians: Phenotype, clinical presentation and natural history. Curr Diab Rep. 2018;18:30.

[31] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet. 2020;395:507-13.

[32] Liu S, Zhang M, Yang L, Li Y, Wang L, Huang Z, et al. Prevalence and patterns of tobacco smoking among Chinese adult men and women: Findings of the 2010 national smoking survey. J Epidemiol Community Health. 2017;71:154-61.

[33] Dong Y, Mo X, Hu Y, Li Y, Wang L, Huang Z, et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. Pediatrics. 2020;71(2):154-61. doi: 10.1542/peds.2020-0702.

[34] Guan WJ, Ni ZY, Hu Y, Liang W, Ow C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708-20. doi: 10.1056/NEJMoa2002032.

[35] Tregoning JS, Schwarze J. Respiratory viral infections in infants: Causes, clinical symptoms, virology, and immunology. Clin Microbiol Rev. 2010;23:74-98.

[36] Buekens P, Alger J, Breart G, Cafferata ML, Harville E, Tomasso G. A call for action for COVID-19 surveillance and research during pregnancy. Lancet. 2020;8(7):e877-88. DOI:https://doi.org/10.1016/S2214-109X(20)30206-0.

[37] Miller A, Reandelar MJ, Fasciglione K, Roumenova V, Li Y, Otazu GH. Correlation between universal BCG vaccination policy and reduced mortality for COVID-19. medRxiv preprint doi: https://doi.org/10.1101/2020.03.24.20042937.

[38] MacLean E. Universal BCG vaccination and protection against COVID-19: Critique of an ecological study. Journal Club, Coronaviruses: Past, present and future. April 1, 2020. https://naturemicrobiologycommunity.nature.com/posts/64892-universal-bcg-vaccination-and-protection-against-covid-19-critique-of-an-ecological-study.

[39] Dharmshaktu NS. An exploratory review of magnitude of COVID-19 cases in non-leprosy affected countries to leprosy endemic countries. Epidemiol Int. 2020;5(2):01-09. doi:https://doi.org/10.24321/2455.7048.202010.

[40] Vetter P, Eckerle I, Kaiser L. Covid-19: A puzzle with many missing pieces. BMJ. 2020;368:m627.

[41] Yong SF, Anderson DE, Wei WE, Pang J, Chia WN, Tan CW, et al. Connecting clusters of COVID-19: An epidemiological and serological investigation. Lancet. April 21, 2020 https://doi.org/10.1016/ S1473-3099(20)30273-5.

[42] Lari N, Rindi L, Bonanni D, Tortoli E, Garzelli C. Animal-to-human SARS-associated coronavirus transmission? Emerg Infect Dis. 2014;10(5):959.

[43] Akhmetzhanov AR, Linton NM, Nishiura H. Rising evidence of COVID-19 transmission potential to and between animals: Do we need to be concerned? medRxiv. 2020.05.21.20109041; doi: https://doi.org/10.1101/2020.05.21.20109041.

[44] Apetrii M, Enache S, Siriopol D, Burlacu A, Kanbay A, Kanbay M, et al. A brand-new cardiorenal syndrome in the COVID-19 setting. Clinical Kidney Journal. 2020;13(3):291-96. https://doi.org/10.1093/ckj/sfaa082.

[45] Clinical Trials. Triple drug combination shows promise in Covid-19 treatment. 11th May 2020 (Last Updated May 11th, 2020 11:55).

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