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SARS-CoV-2 Infected Cases with Untraceable Epidemic Origin: Its Values, Identification and TCM Treatment in Preventing Recurrence

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ABSTRACT

During the outbreak of coronavirus disease 2019 (COVID-19), the identification of a SARS-CoV-2 infected case with untraceable epidemic origin has three values: (1) the region has community transmission of the virus; (2) a certain portion of population in the community is getting immunized and more individuals have already been immunized; (3) an unpredictable future risk exists for regions where there are no infected cases with untraceable epidemic origin. Minimizing or avoiding the aggregation infection through individuals with no clinical symptoms is crucial and possible as its occurrence is mainly attributed to the local environment as opposed to the super spreader with or without clinical symptoms. As infected cases are not necessarily positive with gene test by definition, proper application of gene test is crucial in the identification of asymptomatic cases. In the early stage of an outbreak of infectious disease, gene test can be used to identify asymptomatic cases but it should not be used to exclude cases with typical clinical symptoms and signs. In the middle or late stages of an outbreak gene test should be applied in evaluation of infection rate of the population of a region, in addition to be used in spreader identification and isolation. Although asymptomatic cases are attributed to the overwhelming effect of personalized defense against pathogens, they are still a source of infection. Asymptomatic cases are considered to be Qi deficiency and with lingering toxicity in traditional Chinese medicine (TCM). Treatment in such cases, typically, involves therapy focused on replenishing the Qi, tonifying the lung, clearing the fever, and detoxification in order to return to a normal health condition. The recommended Chinese medicines include Qing Fei Pai Du Decoction, Yi Qi Qu Du Decoction, Xuan

Fei Bai Du Granule, Lian Hua Qing Wen Capsule (Granule), and Jin Hua Qing Gan Granule, etc.

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1 Introduction

In the past several months, millions of coronavirus disease 2019 (COVID-19) cases caused by SARS-CoV-2 have been reported, and tens of thousands of patients have died. This shows that SARS-CoV-2 has a higher reproductive number (R0) and is more contagious than SARS. Although the R0 was initially reported to be between 2.24 - 3.58 [1, 2], the aggregation infections in Diamond Princess Cruise [3] and the South Korea Shincheonji Church [4] suggest that the real R0 is much higher than the initial reports. Several points can be learned from these two infections: (1) the initial virus spreaders, who caused these two aggregation infections, are reported cases but it is theoretically possible they could have been from individuals without clinical symptoms; (2) R0 cannot simply be calculated by the final number of infected cases as some of the infected cases are not directly transmitted from the initial virus spreaders; (3) the higher infection rate in these aggregation infections compared to sporadic infections, are possibly attributed to their local environments in which there was a relatively higher concentration of virus in the air [5]. The third point has been, unfortunately, indirectly supported by the higher rates of infection, the number of serious cases, and the number of deaths in Iran, Italy, Spain and USA compared to China and other countries.

2 The values of SARS-CoV-2 Infected Cases with Untraceable Epidemic Origin

The eventual severity of the COVID-19 outbreak mainly depends on three factors: (1) the virulence; (2) the season; (3) the preventive strategies targeting isolation and identification of infected individuals without clinical symptoms. Notably, the third factor is the only one that can be controlled to some extent. The first wave of SARS-CoV-2 spreading in China is nearly ending; significant differences in the severity have been found between Wuhan and other regions of Hubei Province and among different provinces or major cities in China, as well as in the USA and Europe, depending on the timing and the stringency of isolation strategy. When and how an isolation strategy should be initiated is a highly sensitive and political issue in all nations, which could vary among countries based on the population density, cultural difference, the weather, and the risk of aggregation infection from social factors such as school sizes, transportation systems, sporting events, religious events, etc.

With SARS-CoV-2 spreading worldwide, more identified infected cases with untraceable epidemic origin will be reported in regions involved in the outbreak. To efficiently fight the epidemic outbreak of COVID-19, the recognition of the triple values of newly identified cases with untraceable infection origin could help in guiding current strategies and in preparing for the future. The first one indicates that the region already has community transmission and needs preparation for the coming risk; the number of untraceable epidemic cases can be used as a parameter to assess the severity of community transmission of the virus to match medical facilities and material resources. The second and the third values are relevant and opposite: a certain portion of the population with such cases is getting immunized and more have already been immunized, and an unpredictable future risk exists in regions where there are no infected cases with untraceable epidemic origin. Based on this triple values approach, minimizing sporadic infection and eliminating aggregation infection should be our major aims.

3 Identification of the Epidemically Untraceable Cases

Identification of infected cases can be confirmed by either detecting the antigen of the pathogen itself or the antibodies to the pathogen, depending on the stage (early or late) of an outbreak. Some common diagnostic experences in China in the past several months are helpful for the outbreak of COVID-19. The first experence is, gene testing should not be simply used as the gold standard to confirm or reject the diagnosis of COVID-19. On February 13, we submitted a commentary letter to New England Journal of Medicine (NEJM) with the title, “Genetic testing of SARS-CoV-2: its improper and proper applications” (Manuscript ID: NMED-C102279). In the submitted version, our main comments and suggestions are as follows:

On February 12th, 2020, China reported a total of 13 436 newly confirmed cases including cases identified by clinic diagnosis of individuals infected with SARS-CoV-2 in Wuhan [6]*. Compared to the accumulated total of 32 994 cases in the city, this nearly 41% increase in confirmed cases has very clear and essential values to the world. Firstly, more patients will be hospitalized and fewer individuals will die from the disease. Secondly, positive results from genetic testing of SARS-CoV-2 has been excluded from the confirmation of infection and hospitalization. The adequate method to apply genetic testing in the fight against SARS-CoV-2 outbreak has been debated. At early period, the positive result from genetic test has always been required for the confirmed cases of SARS-CoV-2 infection from the 1st to the 5th Diagnosis and Treatment Criteria. Therefore, the report of a day increase of 13 436 infected cases does not mean worsening of the outbreak in Wuhan, it is rather, the change of diagnostic criteria. When positive results of genetic test are excluded from diagnostic criteria, more patients can be confirmed. It has marvelous benefits to the people and to the war against the outbreak of COVID-19.*

Since January 25th, 2020, we repeatedly suggested how to properly use genetic testing of SARS-CoV-2 in the world. One experience we have learnt from Wuhan fighting against SARS-CoV-2 is, the diagnosis of a patient should be mainly based on clinical manifestations combining with gene testing and etiological identification, particularly when the cause is a type of virus without effective drugs. However, the crucial role of genetic testing for SARS-CoV-2 cannot be overemphasized. One outstanding example is the identification of infected cases in the Diamond Princess Cruise in Japan [3]*. Genetic testing has a crucial role that is not replaceable in the screening and identification of infected individuals who have no clinical manifestation.*

Considering the limited resources globally, genetic testing of SARS-CoV2 should be used in the screening of individuals, particularly of those without clinical manifestation. The sad event of Diamond Princess Cruise should be avoided as much as possible.

Although this submitted letter was not accepted, some opinions and points of the letter from Chinese experts are of importance for the world, particularly the suggestion regarding more efficient use of limited medical resources to minimize asymptomatic cases in order to avoid occurrence of aggregation infection.

Currently, RT-PCR and next generation sequencing (NGS) are the two methods employed in gene testing of SARS-CoV-2. The assay with RT-PCR is faster and less expensive compared to that of NGS and hence, should be used as the first choice in clinical application. For suspected COVID-19 individuals who have no typical clinical symptoms, genetic testing using RT-PCR is urgently required. When the RT-PCR analysis is positive for the SARS-CoV-2 infection, an etiological diagnosis is then confirmed. However, for patients with a negative RT-PCR, the second gene testing should use the NGS because even though it is not as sensitive as RT-PCR, it can identify multiple pathogens including SARS-CoV-2. NGS will provide three possible results: (1) positive for SARS-CoV-2; (2) negative for SARS-CoV-2 and seasonal flu viruses; and (3) negative for SARS-CoV-2 but positive for seasonal flu viruses. The etiological diagnosis for the first and third results is evident in view of the positive results of the gene test. The second possibility is more questionable since it should be considered as a SARS-CoV-2 positive equivalent; in this situation, the patients need to be treated as COVID-19 cases, particularly when supported by typical clinical features including CT scanning [7, 8].

Positive gene testing as the gold standard in diagnosis has no clinical values in patient management. From a therapeutic point of view, no specific drug is available to inhibit SARS-CoV-2 and the clinical management of isolation is the only treatment approach. Practically, throat swabs have very low copies of SARS-CoV-2, which is part of the reason why some patients scored several consecutive negative tests before positive gene testing was reported. Treating these patients as seasonal flu patients will most likely result in an iatrogenic infection. In addition to its proper applications in diagnosis, RT-PCR is the assay of choice for the follow-up of cured cases. Most of the cured cases showed persistent negative results in gene testing. However quite a few returned positive in gene testing, which indicates that SARS-CoV-2 is not eliminated from the body in parallel with the clinical symptoms. In the worst situation, some fatal cases were reported for those whose gene test returned positive after the initial standard COVID-19 treatment.

Gene testing employing RT-PCR assay is routinely applied, to screening individuals with epidemic history of close contact with identified SARS-CoV-2 infected cases, whether they are symptomatic or asymptomatic. Discharged patients whose gene testing returned positive were monitored as virus carrier even without clinical symptoms. As aforementioned, identification of SARS-CoV-2 infection with untraceable contact history indicates that the virus has spread in the community, and the number of these cases can guide the stringency of general strategies including personal isolation, and social gathering bans. In January, China initiated personal isolation in Wuhan as high stringent nationwide strategies have shown their efficiency in decreasing R0 and prolonging the incubation period as well as the reducing the ratio of mild to severe cases. Presently, immunoassay targeting IgM against SARS-CoV-2 are tested in China for diagnostic purposes but gave some false positive and false negative results. Better assay kits for targeting IgM are needed as screening large population with RT-PCR and NGS is not financially possible and is limited to laboratory output. However IgM assay can give information about the infection and immunization rate of the COVID-19 outbreak [9, 10]; this is a very important data for predicting future risk and for preparing future strategies.

4 Characteristics and Individualized Treatment of the Epidemically Untraceable Cases

The origin and the intermediate host of SARS-CoV-2 is not known yet [11, 12]. At the molecular level, its gene sequence showed several crucial mutations that indicate that, its matured virulence may not be formed via repeated cycling of viral mutations, and mild infections of the host. It is highly contagious to almost the whole population as no subpopulation had the chance to be previously immunized against the early less virulent form of the virus. Thus, regions or local communities without identified epidemic untraceable case, as well as children born after this outbreak are at a risk of a local outbreak of COVID-19, either this year or the coming years. Long incubation period and the efficient replication for weeks or months in some patients, together with much higher R0 than SARS, have shown that SARS-CoV-2 has a completely different performance than SARS and will repeatedly infect humans from now on. Recently, the report of a positive gene testing in a Hong Kong dog [13] further warned the world that SARS-CoV-2 may host many species such as dogs and cats and this as a result of a substitution at the 82 amino acid residue (Met to Tyr) which is one of the 6 binding residues at ACE2 [14]. Some species such as macaca and gorilla, which have no substitution at these 6 binding amino acid residues, can be ideal hosts for SARS-CoV-2 as well.

Epidemic outbreak of new airborne infectious diseases always develop from a sporadic infection to an aggregation infection in one region and then spreads by repeating similar cycles. So far, the worst aggregation infection event in the outbreak of COVID-19 was in the “gathering party” of New World Church (Shincheonji Church) Daegu, South Korea, which pushed up the severity of the infected cases in the city [4]. Similarly, the Diamond Princess Cruise [3] event ignited and scaled up the viral spreading internationally. The most important warning from the second and third values of the identified source-untraceable cases is about the regions where no such cases were identified. If no specific vaccine or medicine become available in a short time, the lifestyle of the population may have to be adjusted in the coming months before the summer to avoid the outbreak of the virus similar to what happened in New York, and on the Diamond Princess Cruise. For example, NBA games and many other games with large crowds should either be canceled or delayed. Hopefully, a COVID-19 vaccine [15] and effective drugs (such as remdesivir) [16] are in development and should be available soon.

On the other hand, the concept of super spreader [17], with or without clinical symptoms, linked to aggregation infection is somehow misleading. Most or all aggregation infection events are attributed to the particular local environment instead of the viral spreader. When viral concentrations in the air accumulate to the levels higher than the nonspecific immunity of people exposed, aggregation occurs. The triple values of the identified epidemically untraceable cases strongly recommend a more stringent regulation for social activities with large crowds, including public transportation, sporting events, and a variety of meetings. Only the region with a relatively large number of untraceable cases are considered to have been immunized by community spreading of SARS-CoV-2 and are at a lesser risk of occurrence than other regions. Possibly, we will have to change our life style to a certain extent to minimize aggregation infection and the occurrence of COVID-19 in the coming months before an effective vaccine is available.

Finally, there are some advantages of Chinese traditional medicine in decreasing the ratio of asymptomatic to symptomatic cases. According to Chinese Medicine, the syndromes of asymptomatic patients belong to Qi deficiency and toxicity lingering, and the related therapies should be focused on replenishing the Qi, tonifying the lung, clearing the fever, and detoxification in order to support a normal health condition of the body [18]. The recommended Chinese medicines include Qing Fei Pai Du Decoction, Yi Qi Qu Du Decoction, Xuan Fei Bai Du Granule, Lian Hua Qing Wen Granule, Jin Hua Qing Gai Granule, etc. Those Chinese medicines contain herbs such as: Astragali Radix (Huang Qi, 黄芪), Codonopsis Radix (Dang Shen, 党参), Bupleuri Radix (Chai Hu, 柴胡), Lonicerae Japonicae Flos (Jin Yin Hua, 金银花), Citri Reticulatae Pericarpium (Chen Pi, 陈皮), Forsythiae Fructus (Lian Qiao, 连翘) and Glycyrrhizae Radix Et Rhizoma (Gan Cao, 甘草), etc. The different combinations of these herbs possess functionality of replenishing the Qi, tonifying the lung, clearing the fever, and detoxification, and thus can relax the anxiety caused by inhibition of the immune system. In fact, asymptomatic cases cover two types of individuals: some are, indeed, asymptomatic cases and some are future patients who are temporarily in an incubation period. The reason for the differences between these two types of individuals is dependent on the interactions between body's defense functionality and viral virulence. Both modern medicine such as vitamins and aforementioned Chinese traditional medicines can benefit the asymptomatic cases, increasing their defense functionality and shortening the duration of being viral carriers. Viral carriers are part of the risk factors related to aggregation infection. Recently, the Treatment Protocol (Expert Guide) for Convalescence of COVID-19 with Traditional Chinese Medicine was recommended by China Association of Chinese Medicine [19], which will be an effective measure.

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About the main points of this paper, we submitted a Commentary to ***Nat Med*** with the title, "Identified SARS-CoV-2 infected cases with untraceable epidemic origin: Triple values" on March 6th, 2020 (Manuscript ID: NMED-C102279). Unfortunately, the two papers were not accepted for publication.

Competing Interests

The authors declare no conflict of interest.

References

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[1] ZHAO S, LIN Q, RAN J, et al. Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: a data-driven analysis in the early phase of the outbreak. International Journal of Infectious Diseases, 2020, 92: 214–217.

[2] LI K, DENG J, HUANG R. Suppressing R0 requires the identification of super spreader by genetic screening of individuals without fever. International Journal of Family Medicine and Primary Care, 2020, March 30. doi: 10.25107/IJFMPC-v1-id1006.

[3] VOA Special English. Thousands Trapped on Cruise Ship in Japan Over COVID-19 Virus Fears. Available from: https://www.51voa.com/VOA_Special_English/thousands-trapped-on-cruise-ship-in-japan-over-covid--virus-fears-83897.html.

[4] VOA Special English. South Korea Tries "Social Distancing" to Prevent Coronavirus Spread. Available from: https://www.51voa.com/VOA_Special_English/south-korea-tries-social-distancing-to-prevent-coronavirus-spread-84046.html.

[5] YANG D, CHUAN J, LUO D, et al. Preliminary study of the association between SARS-CoV-2 exposure dose and COVID-19. Medical Science Journal of Central South China, 2020, 48(2): 122–127.

[6] http://news.chinaxiaokang.com/shehuipindao/minsheng/20200213/892424.html.

[7] GUAN W, NI Z, HU Y, et al. Clinical characteristics of coronavirus disease 2019 in China. The New England Journal of Medicine, 2020, 382(18): 1708–1720.

[8] SHI H, HAN X, JIANG N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. The Lancet Infectious Diseases, 2020, 20(4): 425–434.

[9] LIPPI G, SALVAGNO GL, PEGORARO M, et al. Assessment of immune response to SARS-CoV-2 with fully automated MAGLUMI 2019-nCoV IgG and IgM chemiluminescence immunoassays. Clinical Chemistry and Laboratory Medicine. 2020 Apr 16. pii: cclm-2020-0473. doi: 10.1515/cclm-2020-0473. [Epub ahead of print].

[10] PADOAN A, COSMA C, SCIACOVELLI L, et al. Analytical performances of a chemiluminescence immunoassay for SARS-CoV-2 IgM/IgG and antibody kinetics. Clinical Chemistry and Laboratory Medicine. 2020 Apr 16. pii: cclm-2020-0443. doi: 10.1515/cclm-2020-0443. [Epub ahead of print].

[11] BENVENUTO D, GIOVANETTI M, CICCOZZI A, et al. The 2019-new coronavirus epidemic: Evidence for virus evolution. Journal of Medical Virology, 2020, 92(4): 455–459.

[12] LU R, ZHAO X, LI J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet, 2020, 395(10224): 565–574.

[13] https://www.sohu.com/a/377740938_119759.

[14] LIU Z, XIAO X, WEI X, et al. Composition and divergence of coronavirus spike proteins and host ACE2 receptors predict potential intermediate hosts of SARS-CoV-2. Journal of Medical Virology, 2020, 92(6): 595–601.

[15] NELSON R. COVID-19 disrupts vaccine delivery. The Lancet Infectious Diseases, 2020, 20(5): 546.

[16] GORDON CJ, TCHESNOKOV EP, WOOLNER E, et al. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. Journal of Biological Chemistry. 2020 Apr 13. pii: jbc.RA120.013679. doi: 10.1074/jbc.RA120.013679. [Epub ahead of print].

[17] AI-TAWFIQ JA, RODRIGUEZ-MORALES AJ. Super-spreading events and contribution to transmission of MERS, SARS, and COVID-19. Journal of Hospital Infection, 2020, (105): 111–112.

[18] Beijing Association of Chinese Medicine. Treatment Protocol (Expert Guide) for Convalescenc of COVID-19 with Traditional Chinese Medicine (TCM). Journal of Beijing University of Traditional Chinese Medicine. Available from: http://kns.cnki.net/kcms/detail/11.5635.

r.20200221.1334.002.html.

[19] China Association of Chinese Medicine. Diagnosis and Treatment Protocol for COVID-19 (Trial Version 7) -- Traditional Chinese medicine (TCM) treatment. Available from: https://www.thepaper.cn/newsDetail_forward_6631169.

SARS-CoV-2 不可溯源感染者在防止疫情再爆发中的价值、确认与中医药治疗

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【摘要】COVID-19爆发过程中，不可朔源感染病例具有三方面意义：首先，表明该地区存在社区蔓延；其次，显示该社区已有一定数量人群获得了自然免疫和更多个体正在获得自然免疫；再次，提示对于没有出现不可朔源感染病例的地区，未来存在随时爆发局部流行的未知风险。认请局部微环境是导致聚集感染的关键因素，而不是仅仅注重超级传染源，有利于减少和避免聚集感染的发生。因为感染病例不一定由基因检测阳性确定，因此正确应用基因检测对无症状病例的确认至关重要。在疫情暴发的早期阶段，基因检测可用于识别无症状病例，但不应用于排除具有典型临床症状和体征的病例。在疫情暴发的中后期，基因检测除了用于传播者的识别和隔离外，还可应用于评价一个地区的人口感染率。关于无症状感染者，虽然显示其自身对病原体反应具有很强抑制力，但仍是传染源。中医认为，无症状感染者属于气虚毒恋型，临床治疗以益气补肺、清热解毒、扶正固本为主，防治建议采用清肺排毒汤、益气祛毒汤、宣肺败毒颗粒或莲花清温胶囊、金花清感胶囊等。

【关键词】SARS-CoV-2；流行病溯源；中医药治疗；无症状感染者；聚集性感染