The Urgent Countermeasures in Infection Control for Diagnosis of Severe Acute Respiratory Syndrome Coronavirus 2 Infection in Taiwan

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Abstract

The emergence of the coronavirus disease 2019 (COVID-19) caused a large-scale outbreak and has rapidly spread across China and multiple countries. We reported countermeasures in infection control for diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the experiences of point of care diagnostics and medical quarantine for presumed SARS-CoV-2-infected subjects. We conducted a retrospective cohort study on subjects came to Chung Shan Medical University Hospital with suspicion of SARS-CoV-2 infection during January to March, 2020. We performed the real-time reverse-transcription polymerase chain reaction testing (rRT-PCR) for SARS-CoV-2-infection and reported the results of testing and treatment. A total of 212 participants were enrolled due to suspicion of SARS-CoV-2 infection. Five of those were confirmed COVID-19 cases after monitoring for a period of 14 days and were cured. The time to rRT-PCR test conversion after treatment is variate. The infection control measures of home quarantine and mandatory medical quarantine combined with rapid diagnosis seem to postpone the speed of transmission of SARS-CoV-2 infection at once in Taiwan. Due to lack of vaccination and confirmed antiviral therapy, it is important to strictly abide by the infection control measures.

Introduction

In December 2019, an outbreak of severe pneumonia caused by an unknown pathogen emerged in Wuhan, Hubei Province and the first report stated that 66% coronavirus disease 2019 (COVID-19) cases had a history of exposure to the Huanan Seafood Wholesale Market.\(^1\) Soon after the COVID-19 disseminated widely to multiple countries, included Taiwan.\(^2\) The World Health Organization (WHO) declared the coronavirus outbreak a public health emergency of international concern on 30 January, 2020 and announced global pandemic of COVID-19 on 11 March, 2020. Previous studies identified the clinical features of the case series, incubation period, attack rate, case fatality rate and basic reproduction number.\(^3,4\) Currently, antiviral treatment and vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are under investigation.\(^5\) There is available information about the natural course of transmission in the community and the measures of infection control for SARS-CoV-2 infection. The epidemic of COVID-19 has raised global health concerns on the emergence of a large-scale outbreak, pandemic or endemic in human community.\(^6,7\)

Around 0.4 million Taiwanese work in China, of which more than 2,000 are Taiwanese businessmen and women. They maintain very close links between Taiwan and China.\(^2,8\) The total number of suspected SARS-CoV-2 cases in Taiwan increased to more than 432 confirmed COVID-19 cases, most of them imported to Taiwan by the time we initiated writing this paper. We highlighted some key issues in infection control measures for SARS-CoV-2 infection, compared with Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) according to published studies.\(^7,9\) The case-fatality rate of COVID-19 appears to be relatively milder as compared with SARS and MERS, estimated to be more than 5.7%.\(^7,9,10\) The clinical features and the mode of transmission were comparatively different
than them. The majority of SARS and MERS were spread through hospitals and resulted in health care-associated infections (HCAIs).\textsuperscript{1,7,9} Therefore, stringent infection control measures need be applied to prevent outbreaks in family clusters and healthcare settings. As Taiwan experienced a large-scale outbreak of SARS in 2003, the government has ever since been alert and prepared for the management of epidemic emergencies due to infectious diseases.\textsuperscript{11,12} In this study, we have reported the practices of performing point of care diagnostics following the guidance of Taiwan Centres for Disease Control (CDC) and we have particularly reported the infection control measures under the COVID-19 challenges in Taiwan.

**Results**

During the 2-month study period, we enrolled a total of 212 subjects with acute respiratory infection (ARI) suspected to have SARS-CoV-2 related COVID-19, who sought medical attention at the Out-patient or Emergency Department of Chung Shan Medical University Hospital (CSMUH). The demographic, clinical characteristics, laboratory, and microbiology tests of the enrolled participants shown in Table 1. All of the presumed COVID-19 subjects had pneumonia on chest radiography (CXR) examination who would be compulsively admitted to negative pressure wards to receive medical treatment at once. In case of negative real-time reverse-transcription polymerase chain reaction (rRT-PCR) test for SARS-CoV-2, the presumed COVID-19 subjects should receive sequential 24 hours second testing. And, the presumed COVID-19 subjects were discharged home after resolution of illness and sequential negative SARS-CoV-2 rRT-PCR. After discharge from hospital, they would stay home for self-health care management for 14 days (Fig. 1, 2 and 3). For confirmed COVID-19 subjects (positive SARS-CoV-2 rRT-PCR; first time positive test or sequential 24 hours second testing positive), they would continuously stay at negative pressure ward to receive medical treatment until resolution of illness and negative results of rRT-PCR testing for SARS-CoV-2 on three consecutive oropharyngeal or sputum specimens, with each specimen collected over 24 hours apart (Fig. 3). Of the 212 subjects, 120 (56.6%) were women and 41 subjects (19.3%) were diagnosed as pneumonia initially. The risk factors of 41 presumed COVID-19 pneumonia included travel history 35 (85.4%), contact history 3 (7.3%), healthcare workers 1 (2.4%) (Table 1). The most common signs and symptoms were cough (75.6%), fever (34.1 %), rhinorrhoea (31.7%), sore throat (31.7%), myalgia or fatigue (24.4%), dyspnoea (24.4%), loss of smell and taste (4.9%), and 31.7 % subjects had more than three signs and symptoms. The table 1 shows the results of laboratory and microbiology tests of enrolled participants. A total of 43.9% (18/41) subjects were empirically treated with oseltamivir 75 mg orally every 12 hours. The other organisms isolated in order of frequency were 7.3% *Mycoplasma pneumoniae (M. pneumoniae)* in 3 subjects, *Streptococcus pneumoniae* (4, 9.8%), *Legionella pneumophila* (3, 7.3%), and influenza virus (2, 4.9%).

For the presumed COVID-19 subjects with normal CXR examination, they would receive SARS-CoV-2 rRT-PCR test. In case of negative rRT-PCR test for SARS-CoV-2, they would be discharged from hospital and would stay home for a self-health care management for 14 days (Fig. 3 and Table 1). For the presumed
COVID-19 subjects with mild illness (normal chest x-ray), they would come to hospital and receive the rRT-PCR testing in case of their illness deterioration. When the result of SARS-CoV-2 rRT-PCR testing was negative, the subjects should stay home for self-health care management for 14 days, but those subjects with positive test results would be admitted to negative pressure ward for treatment (Fig. 1 and 3). The results of 171 presumed subject with SARS-CoV-2 infection showed in the table 1. The risk factors of presumed SARS-CoV-2 infection included travel history 132 (77.2%), healthcare workers 10 (5.8%), transportation services 5 (2.9%), contact history 25 (14.6%).

The most common signs and symptoms were cough (59.6%), fever (45.0 %), rhinorrhoea (32.2%), sore throat (33.9%), myalgia or fatigue (19.9%), diarrhoea or vomiting (12.3%), dyspnoea (12.3%), and 40.9 % subjects had more than three signs and symptoms. A total of 17.0% (29/171) subjects were empirically treated with oseltamivir. The average time lapse from specimen collection to the results was 14.1 hours. The isolated organisms were \textit{M. pneumoniae} (2, 1.2%) and influenza virus (1, 0.6%). According to the definition of confirmed COVID-19 case, those of 171 presumed subjects would not be excluded after monitoring for a period of 14 days. (Fig.1 and 3)

The demographic, clinical characteristics, laboratory data, and treatment of the COVID-19 patients showed in Table 2. In our cohort, we had five confirmed COVID-19 patients after monitoring for a period of 14 days. All patients were treated with hydroxychloroquine (HCQ) 200mg daily every 12 hours for 10 to 14 days. Four of them were treated with HCQ and oseltamivir. Three patients were treated with two drugs in combination HC and azithromycin (AZ). Serial rRT-PCRs for SARS-CoV-2 were performed in the oropharyngeal swab of two COVID-19 patients who survived until discharge. Duration of rRT-PCR positivity in our study, the time to rRT-PCR test conversion after treatment is variate range from 10 to 38 days in our cohort. One patient developed respiratory failure with mechanic ventilation and had positive rRT-PCR test in sputum specimens at the 7-day HCQ treatment (Table 2). The patient was treated with one dose of tocilizumab 400mg infusion, an Interleukin 6 (IL-6) targeting drug, for critical COVID-19. The criteria to be considered to discontinue medical quarantine or hospitalization included resolution of clinical signs and symptoms and negative results of RT-PCR testing for SARS-CoV-2 on three sequential oropharyngeal or sputum specimens, with each specimen collected over 24 hours apart.\textsuperscript{13} Finally, all of the patients were fully recovery.

**Discussion**

We reported 212 subjects with presumed COVID-19 presenting with pneumonia or mild symptoms of ARIs with travel history or the possibility of person-to-person transmission from close contact between family and healthcare facilities. Our findings are consistent with the previous studies, the risk factors were travel history, contact history, and occupation exposure history of COVID-19.\textsuperscript{1,3,14,15} As the manifestation of COVID-19 is nonspecific, it is similar with viral respiratory symptoms or asymptomatic.\textsuperscript{1,16} The physicians would take medical history for risk assessment when new recruits sought medical attention (Supplementary Table 2).\textsuperscript{17} As a result, we strongly emphasized the key point of travel history, occupational exposure, contact history, cluster history (T.O.C.C.) medical history at clinic for initial
surveillance subjects. COVID-19 could transmit to person in one two days before symptoms appear. As a result, the high-risk subjects could receive rRT-PCR testing and isolation quickly and prevent the spread of coronavirus. Furthermore, as the outbreak of coronaviruses (such as SARS, MERS, and COVID-19) have widely occurred in healthcare settings, it would emphasise HCWs to wear personal protective equipment (PPE) when managing high-risk subjects in healthcare settings.\textsuperscript{1,7,9}

Our study showed that most subjects presented mild illness similar to ARI. Some subjects were confirmed for influenza and treated with oseltamivir 75 mg orally every 12 hours. However, COVID-19 produce many common features similar to viral ARIs, especially influenza commonly occurring during winter season.\textsuperscript{18} Recent studies reported that oseltamivir has been used for confirmed COVID-19 cases.\textsuperscript{19} Hence, we provided oseltamivir for the 47 patients despite being negative for influenza PCR testing. But we cannot evaluate the efficacy of oseltamivir in our cohort. The HCQ has also been reported for COVID-19 and potentially could be an alternative agent for the treatment of COVID-19.\textsuperscript{13,20} Our small case report showed HCQ with or without AZ tested negative for the virus on an oropharyngeal swab on day 7. We found the tested negative is variate. Notably, one of our patients treated with HCQ progressed to severe illness with respiratory failure during the hospitalization and was eventual cured for one dose of tocilizumab 400mg infusion. The recent study showed that the use of HCQ shall be limited to the acute emergency situation of fighting the COVID-19 patients and chemoprophylaxis for post-exposure HCWs.\textsuperscript{21}

Our Critical COVID-19 Patient was successfully treated with tocilizumab. Cytokine storm syndrome was proposed as the main cause of ARDS; IL-6 is suggested as acting as a critical mediator in the development of shock, ARDS, and multiorgan failure in severe COVID-19 patients.\textsuperscript{20} Furthermore, recent study reported that severe COVID-19 patients received tocilizumab infusion had clinical improvement: respiratory function, rapid afebrile, and a successful discharge.\textsuperscript{22} However, therapeutic options for the COVID-19 are urgently needed, it was recommended that larger studies are required to measure the efficacy of the use of tocilizumab.\textsuperscript{22}

Our study had five confirmed COVID-19 cases. We suggest that there may be a relatively low prevalence of SARS-CoV-2 infection in Taiwan. This could be a result of implementation of personnel infection control measures (wear surgical mask and hand hygiene) in healthcare settings, quarantine measures, and the point of care (POC) diagnostics in Taiwan.\textsuperscript{12} The average time lapse from specimen collection to the results of rRT-PCR test was 14.3 hours in our study. Consequently, we could quickly diagnose COVID-19 cases. The POC diagnostics (rapid diagnosis) for infectious diseases is a well-known method for preventing and controlling an outbreak.\textsuperscript{23,24} At present, the rRT-PCR test is performed widely in many countries according to WHO’s recommended protocol and primers.\textsuperscript{25} Our study performed POC diagnostics by using risk assessment and rRT-PCR test for COVID-19. Taiwan CDC rapidly established more than one hundred Designated Laboratories and freely provided rRT-PCR test by using Taiwan Health Insurance.\textsuperscript{12} By the time we initiated writing this paper, more than 63,713 subjects, accounting for around 2.8% Taiwan population, underwent the rRT-PCR test. Total of 432 cases of SARS-CoV-2 infection
included 55 indigenous cases and obliviously decreased from 138 on 2020 12th week to 3 on 18th week and the number of fatality cases were sex (Figure 4). 

The agency claims to have the capacity to test about 1200 specimens a day and the results would be available around 4 hours. But, rRT-PCR test is expensive and laborious. As such, development of an easy diagnostic testing technique is urgently required to screen for coronavirus. These reports substantiate the need for a rapid detection method and portable detection devices to confirm suspected cases, screen patients, and outbreak surveillance.

Taiwan government has rapidly responded to the crisis of deadly coronavirus outbreak by implementation of policies through board control and quarantine measures in January 27, 2020 for the containment of the epidemic. Following the 2003 epidemic of SARS, Taiwan CDC was aware of the importance of infection control measures for HCAs health care-associated infections (HCAIs) and implemented the pandemic or a large-outbreak of Communicable Disease Preparedness and Response, and Infection Control Program. According to the program, Taiwan government established the National Health Command Centre for the operational command point, which acts as directorate for communications among central, regional, and local authorities. This program also involved the establishment of The Communicable Disease Control Medical Network and implemented regular inspections and audits of isolation beds at hospitals responsible for pandemic responses. There are 134 isolation hospitals and 1100 negative pressure wards. Importantly, in 2015, Taiwan government implemented all necessary quarantine measures with regard to ships, aircraft, and people; port and airport authorities as required to establish health and safety; team work to prevent the importation and exportation of communicable diseases. In accordance with the guidelines of Taiwan CDC, our study carried out the quarantine measures implementation including mandatory medical quarantine at hospital for severe COVID-19 as well as home quarantine or self-health care management for 14 days for mild illness or asymptotic subjects. Similarly, recent published study detailed the contents of infection control measures implemented big data analytics, new technology, and proactive testing to manage this crisis of COVID-19 in Taiwan. 

Due to lack of vaccination and antiviral therapy, the quarantine measures are mandatory to avoid rapid transmission in the community. Taiwan CDC implemented the Nosocomial Infection Control and Quality Improvement Project, which commissioned the Taiwan Joint Commission on Hospital Accreditation (TJCHA) for hospital accreditation systems annually since 2007. Taiwan CDC performed standardized operations to audit hospital infection control measures, communicable disease monitoring, reporting, and preventive measures in line with policies of competent authorities. Importantly, Taiwan government launched the special law to require hospitals to have a stockpile for preparing a large-scale outbreak, all hospital need to have medical supplies including PPE for 30 days. The CSMUH was audited for compliance with the infection control measures from 2007– 2019 by the Taiwan CDC and TJCHA. The hospital secured accreditation at the level of medical centre. Hence, for the prevention of large-scale outbreaks in our hospital, we strictly distributed and implemented an infection control manual with
specific protocols for prevention of infection by various routes (e.g. airborne, droplets, and contact),
execution of communicable disease monitoring and reporting, maintained clean hospital environment,
and followed strict hand hygiene program.

This study had several limitations. First, we did not perform all the microbiologic tests in the study. As the
manifestations of COVID-19 are indistinguishable from viral ARIs and epidemic of influenza or many
other viral ARIs developed at the same time, we decided to perform the microbiologic tests for precise
diagnosis and empirically used oseltamivir for possible influenza co-infection. Second, pneumonia was
diagnosed by CXR and clinical signs and symptoms in our study. We did not perform chest computed
tomography (CT) scan for diagnosis due to the risk for contamination of all CT scan equipment. The
chest CT scan is recommended as the precise method for confirming COVID-19 cases. Third, sensitivity of rRT-PCR test was not available in oropharyngeal swabs in our study. This may be due to
inadequate specimen in swab procedures. In a case where our study could have undetected the COVID-19
cases with mild illness, these subjects who abided to stay at home quarantine, performed hand hygiene,
and wore face mask when they went outside might have helped to decrease the spread of coronavirus
transmission in the community.

In conclusions, under the crisis of pandemic, the measures of home quarantine and mandatory medical
quarantine combined with rapid diagnosis seem to postpone the speed of transmission of SARS-CoV-2 at
once in Taiwan. For slowing spread transmission, we recommend that it is important to adhere to
infection control measures and prepare pandemic emergency strategies to combat the coronavirus.

Methods

We performed a retrospective study at the CSMUH, which is a 1100-bed Medical Centre in Central Taiwan.

We recruited consecutive patients admitted from the emergency department with suspected pneumonia
after an evaluation based on standard practice including clinical evaluation, routine blood tests, and CXR.
We included all participants with fever $\geq 38^\circ$C with or without ARIs initially presented at our out-patient or
emergency department during the period of January 21 to March 27, 2020 and who underwent the rRT-
PCR test of SARS-CoV-2 and had sufficient follow-up data. We excluded the patients did not have the rRT-
PCR test of SARS-CoV-2 and they did not have any follow-up visit (Fig.1). Presence of an acute infiltrate
was interpreted by the physician in charge of the patient. The diagnosis of pneumonia on the CXR
examination would be presented by the expert radiologist on duty at the same time. We noted the clinical
characteristics, fever, respiratory symptoms, CXR, and laboratory and microbiological findings of patients
suspected with SARS-CoV-2-infection. In present study, the data was collected from electronic medical
records by retrospective review.

Framework followed by the government to identify SARS-
CoV-2 (COVID-19) Cases
Individuals with respiratory syndrome who sought medical attention at clinics were given the notice of mandatory home quarantine, or self-home quarantine, or self-health management and were informed to report to the physician of their medical history (T.O.C.C.), residence history, and whether anyone else has similar symptoms. Fig. 2 and Supplementary Table 1 and 2. The other scenario was when the patients had ARI and sought medical attention, physician took medical history of T.O.C.C. and used risk assessment for patients having the possibility of COVID-19 (Fig. 2 and Supplementary Table 2). Those who met the criteria of definition of confirmed COVID-19 case were reported to the Communicable Diseases Network Taiwan CDC to be presumed a COVID-19 case. Subsequently, we used rRT-PCR assay to survey coronavirus in the nasopharynx, oropharynx, or sputum specimens (Fig. 2 and 3).

Definition of Confirmed Coronavirus Disease 2019 (COVID-19) Case

We obtained the clinical information based on the guidelines of WHO and Taiwan CDC. Then, we established the urgent countermeasures of SARS-CoV-2 related COVID-19 at the Centre of Infection control of CSMUH in February 2020. (Fig. 2 and 3) For confirmation of SARS-CoV-2 infections, Taiwan CDC recommends fitting in the case definition and diagnostic testing of patients who meet the clinical, or laboratory, or epidemiologic criteria for a SARS-CoV-2 person under investigation.

Case definition for reporting SARS-CoV-2 infection:

A. Clinical criteria is a patient with at least one of the following symptoms:

1. Fever \(\geq 38^\circ\text{C}\) or patients with acute respiratory infection (sudden onset of cough, sore throat, shortness of breath)

2. Patients with pneumonia diagnosed by clinical signs and symptoms, or by radiological or histopathologic means

3. Patients with community-acquired-pneumonia with unknown pathogens

B. Laboratory Criteria at least one of the following:

Collected specimens from lower or upper respiratory tracts, including expectorated sputum, bronchoalveolar lavage, endotracheal aspirate, nasopharyngeal swab or oropharyngeal swab.

1. Isolation and confirmed SARS-CoV-2

2. Positive testing by SARS-CoV-2 rRT-PCR assay

C. Epidemiologic criteria
In the 14 days prior to the onset of symptoms, met at least one of the following:

1. Had a history of live in or travel to warning level 3 destinations or were in close contact with a symptomatic person with presumed ongoing community transmission of SARS-CoV-2.

2. Had a history of close contact with a symptomatic probable case or confirmed case having had face-to-face contact or without airway protection

3. Health-care-workers

4. A familial cluster or a hospital cluster

D. Reported illnesses, meets at least one of the following:

1. Meets at least one of the clinical criteria plus epidemiologic criteria (1) or (3)

2. Clinical criteria (2) plus epidemiologic criteria (2)

3. Meets the clinical criteria (3)

4. Meets at least one of the laboratory Criteria

E. Classification of the disease

1. Presumed case

A presumed case meets clinical criteria, but SARS-CoV-2 for testing is inconclusive (the result of the test reported by the laboratory) or a suspected case had close contact with a symptomatic confirmed case of SARS-CoV-2 infection in the 14 days prior to onset of symptoms.

2. Confirmed case:

Patients with laboratory confirmation of SARS-CoV-2 infection, irrespective of clinical signs and symptom

Real-Time Reverse-transcription Polymerase Chain Reaction

We obtained the respiratory samples including nasopharyngeal or oropharyngeal swabs, or sputum specimens in the negative pressure room from hospitalized patients or patients who sought medical attention at the emergency department and it was stored in viral-transport medium. The physicians wore PPE, including gloves, face shield or goggles, water resistant gown, and N95 mask or respirator, when they collected the specimens (Fig. 2). All samples were processed at the central laboratory of the CSMUH for diagnostic detection of SARS-CoV-2 and influenza by rRT-PCR. The protocol was performed according to the guidelines of WHO and Taiwan CDC as described in detail in other researches.\textsuperscript{25,31} We detected of
respiratory pathogens using FilmArray™ Respiratory Panel (BioFire Diagnostics, bioMérieux, Utah, USA) from the nasopharyngeal specimens collected from the presumed COVID-19 patients.33

Statistical analysis

We used SPSS for Windows Version 22.0 (SPSS Inc., Chicago, IL, USA) to analyse the data. Continuous variables were expressed as mean and standard deviation; categorical variables were expressed as number (%) and Chi-square test was used to compare between pneumonia and presumed infection groups. Statistical significance was defined as a $p$-value less than 0.05 and all tests were two-tailed.

Abbreviations

ARI: Acute respiratory infection

AZ: azithromycin

CDC: Centres for Disease Control

CSMUH: Chung Shan Medical University Hospital

COVID-19: Coronavirus disease 2019

CT: Computed tomography

CXR: Chest radiography

HCAIs: Health care-associated infections

HCQ: Hydroxychloroquine

MERS: Middle East Respiratory Syndrome

POC: point of care

PPE: Personal protective equipment

rRT-PCR: Real-time reverse-transcription polymerase chain reaction

SARS: Severe Acute Respiratory Syndrome

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

TJCHA: Taiwan Joint Commission on Hospital Accreditation

T.O.C.C.: Travel history, occupational exposure, contact history, cluster history
Declarations

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Author information

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Contributions

Y.T.L conceived and designed the study and drafted the manuscript. C.F.L, H.H.P, Y.H.C, H.J.H, and S.F.Y participated in research design. M.C.H performed the experiments, S.Y.L analyzed the data. C.S.P, S.W.H, M.C.T, C.H.Y, K.C.C, and Y.T.W collectively contributed to the data collection. C.N.H, C.Y.C, Y.S.T, G.P.J, W.J.L, T.C.C, C.H.L and Y.F.H interpreted data and provided critical comments. L.H.H, T.J.W, L.M.C, C.Y.T, Y.H.W., M.H.T, C.H.Y, S.J.H, Y.H.H, P.C.C, S.Y.L, and W.C.L helped to interpret the results from the analysis. All authors reviewed and approved the final manuscript.

Ethics declarations

Ethics approval and consent to participate

The Institutional Review Board of The CSMUH approved the research study (Number: CS2-20032). A written informed consent was waived from the subjects due to the retrospective nature of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing financial interests.

References

1. Huang, C. et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* **395**, 497-505 (2020).
2. Liu, Y. C., Liao, C. H., Chang, C. F., Chou, C. C. & Lin, Y. R. A Locally Transmitted Case of SARS-CoV-2 Infection in Taiwan. *Engl. J. Med.* **382**, 1070-1072 (2020).

3. Guan, W. J. *et al.* Clinical Characteristics of Coronavirus Disease 2019 in China. *Engl. Med.* 10.1056/NEJMo2002032 (2020). [Epub ahead of print]

4. Riou, J. & Althaus, C. L. Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV), December 2019 to January 2020. *Surveill.* 2020;25(4):pii=2000058. https://doi.org/10.2807/1560-7917.ES.2020.25.4.2000058 (2020).

5. Holshue, M. L. *et al.* First case of 2019 novel coronavirus in the United States. *Engl. J. Med.* **382**, 929-936 (2020).

6. Li, Q. *et al.* Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. *Engl. J. Med.* **82**:1199-1207 (2020).

7. Munster, V. J., Koopmans, M., van Doremalen, N., van Riel, D. & de Wit, E. A novel coronavirus emerging in China—key questions for impact assessment. *Engl. J. Med.* **382**:692-694 (2020).

8. Wang, C. J., Ng, C. Y. & Brook, R. H. Response to COVID-19 in Taiwan: Big Data Analytics, New Technology, and Proactive Testing. 10.1001/jama.2020.3151 (2020). [Epub ahead of print]

9. Wang, C., Horby, P. W., Hayden, F. G. & Gao, G. F. A novel coronavirus outbreak of global health concern. **395**, 470-473 (2020).

10. Baud, D. *et al.* Real estimates of mortality following COVID-19 infection. *Infect. Dis.* 10.1016/S1473-3099(20)30234-6 (2020). [Epub ahead of print]

11. Centers for Disease Control, Taiwan. Coronavirus Disease 2019 Preparedness and Response, and Infection Control Program. https://cdc.gov.tw/File/Get/v-d6pbsormuOP2EvVM-e6Q (2020).

12. Lin, C. *et al.* Policy Decisions and Use of Information Technology to Fight 2019 Novel Coronavirus Disease, Taiwan. *Infect. Dis.* **26**, 10.3201/eid2607.200574 (2020). [Epub ahead of print]

13. Centers for Disease Control, Taiwan. Interim Guidance for Clinical management of Patients with COVID-19. https://cdc.gov.tw/File/Get/S-10ceXtvVG8D33DgODUkA (2020).

14. Chan, J. F. W. *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.* **395**, 514-523 (2020).

15. Chen, N. *et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. **395**, 507–13 (2020).

16. Bai, Y. *et al.* Presumed Asymptomatic Carrier Transmission of COVID-19. *JAMA.* 10.1001/jama.2020.2565 (2020). [Epub ahead of print]

17. Centers for Disease Control, Taiwan. COVID 2019 Patient Risk Assessment Form. https://cdc.gov.tw/File/Get/tqZ0SYvAQAm_D050wqMKGA (2020).

18. Ding, Q., Lu, P., Fan, Y., Xia, Y. & Liu, M. The clinical characteristics of pneumonia patients coinfected with 2019 novel coronavirus and influenza virus in Wuhan, China. *Med. Virol.* 10.1002/jmv.25781 (2020). [Epub ahead of print]
19. Wu, Y., Xie, Y.-l. & Wang, X. Longitudinal CT Findings in COVID-19 Pneumonia: Case Presenting Organizing Pneumonia Pattern. *Cardiothorac. Imaging*. 2, e200031, 10.1148/ryct.2020200031 (2020).

20. Zhao, M. Cytokine storm and immunomodulatory therapy in COVID-19: Role of chloroquine and anti-IL-6 monoclonal antibodies. I *J. Antimicrob. Agents*. 10.1016/j.ijantimicag.2020.105982 (2020). [Epub ahead of print]

21. Lee, S. H., Son, H. & Peck, K. R. Can post-exposure prophylaxis for COVID-19 be considered as an outbreak response strategy in long-term care hospitals? *J. Antimicrob. Agents*. 10.1016/j.ijantimicag.2020.105988 (2020). [Epub ahead of print]

22. Xu, X. et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc. Natl. Acad. Sci. U.S.A*. 10.1073/pnas.2005615117 (2020).

23. Lan, L. *et al.* Positive RT-PCR Test Results in Patients Recovered From COVID-19. *JAMA*. 10.1001/jama.2020.2783 (2020). [Epub ahead of print]

24. Gubala, V., Harris, L. F., Ricco, A. J., Tan, M. X. & Williams, D. E. Point of Care Diagnostics: Status and Future. *Chem*. 84, 487-515 (2012).

25. Nguyen, T., Duong Bang, D. & Wolff, A. 2019 Novel Coronavirus Disease (COVID-19): Paving the Road for Rapid Detection and Point-of-Care Diagnostics. 11, 2072-2666X (2020).

26. World Health Organization. Diagnostic detection of 2019-nCoV by real-time RT-PCR. https://who.int/docs/default-source/coronaviruse/protocol-v2-1.pdf?sfvrsn=a9ef618c_2 (2020).

27. Centers for Disease Control, Taiwan. Coronavirus Disease (COVID-2019) Situation Reports in Taiwan. https://cdc.gov.tw/En (2020).

28. Centers for Disease Control, Taiwan. The Strategies of Quarantine for People Having Risk for COVID 2019. https://cdc.gov.tw/File/Get/mA-0-AbiABrCA_w0wH1L_g (2020).

29. Centers for Disease Control, Taiwan. Case Definition for Reporting Patients with COVID-19 Pneumonia. https://cdc.gov.tw/File/Get/6jclqnbR6Q8w203x1nXilg (2020).

30. Lee, Y.T. *et al.* Decline in the incidence of healthcare-associated methicillin-resistant Staphylococcus aureus (HA-MRSA) correlates with deceased antimicrobial consumption at a tertiary care hospital in Taiwan, 2001–2009. *J. Antimicrob. Agents*. 36, 523-530 (2010).

31. Shi, H. *et al.* Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Infect. Dis*. 20, 425-434 (2020).

32. Centers for Disease Control, Taiwan. Diagnostic detection of 2019-nCoV by real-time RT-PCR. https://cdc.gov.tw/File/Get/5772dH56Jtb7eJtQK0BNvw (2020).

33. World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected Interim Guidance 13 March 2020. https://who.int/publications-detail клиничное-управление-острого-заболевания-дыхательной-системы-когда-нового-вируса-коронавируса-(ncov)-инфицирование-тестирования (2020).
34. Hsih, W.H. et al. Featuring COVID-19 cases via screening symptomatic patients with epidemiologic link during flu season in a medical center of central Taiwan. J. Microbiol. Immunol. Infect. 10.1016/j.jmii.2020.03.008 (2020). [Epub ahead of print]

Tables

Table 1. The Demographic, Clinical Characteristics, Laboratory, and Microbiology Tests of Enrolled Participants (N= 212)
|                                | All patients (n=212) | Pneumonia case (n=41) | Presumed infection case (n=171) | p value |
|--------------------------------|-----------------------|-----------------------|---------------------------------|---------|
| **Age (± SD)**                 | 34.7±18.4             | 32.2±18.7             | 35.3±18.3                       |         |
| **Age < 18 (n %)**             | 29(13.9%)             | 9(23.7%)              | 20(11.7%)                       | 0.053   |
| **Age ≥18 (n %)**              | 183(86.3%)            | 32(78.0%)             | 151(88.3%)                      |         |
| **Sex**                        |                       |                       |                                 |         |
| Men                            | 92(43.4%)             | 22(53.7%)             | 70(40.9%)                       | 0.188   |
| Women                          | 120(56.6%)            | 19(46.3%)             | 101(59.1%)                      |         |
| **Travel history**             | 169(79.7%)            | 35(85.4%)             | 132(77.2%)                      | >0.99   |
| Asia                           | 142 (67.0%)           | 26(63.4%)             | 116(67.8%)                      | 0.205   |
| China                          | 31(14.6%)             | 20(48.8%)             | 11(6.4%)                        |         |
| Japan                          | 53(25.0%)             | 1(2.4%)               | 52(30.4%)                       |         |
| Korea                          | 16(7.5%)              | 5(12.2%)              | 11(6.4%)                        |         |
| United States                  | 5(2.4%)               | 2(4.9%)               | 3(1.8%)                         |         |
| European                       | 13(6.1%)              | 6(14.6%)              | 7(4.1%)                         |         |
| Other areas                    | 9(4.2%)               | 3(7.3%)               | 6(3.5%)                         |         |
| **Occupation history**         |                       |                       |                                 |         |
| Healthcare workers             | 11(5.2%)              | 1(2.4%)               | 10(5.8%)                        | 0.681   |
| Transportation services        | 5(2.4%)               | 0(0.0%)               | 5(2.9%)                         |         |
| Other                          | 118(55.7%)            | 1741.5%)              | 101(59.1%)                      | >0.99   |
| Contact history                | 28(13.2%)             | 3(7.3%)               | 25(14.6%)                       |         |
| Cluster history                | 0(0.0%)               | 0(0.0%)               | 0(0.0%)                         |         |
| **Signs and symptoms**         |                       |                       |                                 |         |
| Fever≥38℃                      | 91(42.9%)             | 14(34.1%)             | 77(45.0%)                       | <0.001  |
| Cough                          | 133(62.7%)            | 31(75.6%)             | 102(59.6%)                      |         |
| Rhinorrhoea                    | 68(32.1%)             | 13(31.7%)             | 55 (32.2%)                      |         |
| Sore throat                    | 64(30.2%)             | 6(14.6%)              | 58(33.9%)                       |         |
| Myalgia or fatigue             | 44(20.8%)             | 10(24.4%)             | 34(19.9%)                       |         |
| Diarrhoea or vomiting          | 21(9.9%)              | 0(0.0%)               | 21(12.3%)                       |         |
| Dyspnea                        | 27(12.7%)             | 6(14.6%)              | 21(12.3%)                       |         |
| Loss of smell and taste        | 2(0.9%)               | 2(4.9%)               | 0(0.0%)                         |         |
| 3≥ Signs and symptoms          | 83(39.2%)             | 13(31.7%)             | 70(40.9%)                       |         |
| **Laboratory tests**           |                       |                       |                                 |         |
| WBC×10^9 cells per L, ≥1.2    | 16(7.5%)              | 1(2.4%)               | 15(8.8%)                        | >0.99   |
| Hb g/dL, <12                   | 20(9.4%)              | 4(9.8%)               | 16(9.4%)                        |         |
| BUN, mg/dL, ≥20                | 6(2.8%)               | 0(0.0%)               | 6(3.5%)                         |         |
| Cr., μmol/L, ≥1.3              | 10(4.7%)              | 2(4.9%)               | 8(4.7%)                         |         |
|                                | Value 1 (%) | Value 2 (%) | Value 3 (%) | p-value |
|--------------------------------|-------------|-------------|-------------|---------|
| ALT, U/L, ≥40                  | 12(5.7%)    | 7(17.1%)    | 5(2.9%)     |         |
| hs-CRP, mg/L, ≥1               | 31(14.6%)   | 7(17.1%)    | 24(14.0%)   |         |

Results of Microbiology test (Positive findings)

|                                | Value 1 (%) | Value 2 (%) | Value 3 (%) | p-value |
|--------------------------------|-------------|-------------|-------------|---------|
| SARS CoV-2                     | 5(2.4%)     | 5(12.2%)    | 0(0.0%)     | >0.99   |
| Time from collection of specimens to results (hours); mean | 14.3        | 14.8        | 14.1        | >0.99   |
| Case number of Consecutive specimen collection (n) | 36 (17.0%)  | 36(87.8%)   | 0(0.0%)     | >0.99   |
| Influenza virus PCR (n)        | 179 (84.4%) | 2(4.9%)     | 1 (0.6%)    | >0.99   |
| Use of oseltamivir single (n)  | 47(22.2%)   | 18 (43.9%)  | 29(17.0%)   | >0.99   |
| Use of HCQ (n)                 | 5(2.4%)     | 5(12.2%)    | 0(0.0%)     | >0.99   |
| Mycoplasma pneumoniae          | 18(8.5%)    | 3(16.7%)    | 2(11.1%)    | >0.99   |
| Streptococcus pneumoniae (urine) | 13(6.1%)   | 4(30.8%)    | 0(0.0%)     | >0.99   |
| Legionella pneumophila (urine) | 10(4.8%)    | 3(23.1%)    | 0(0.0%)     | >0.99   |

ALT = Alanine aminotransferase, BUN = Blood urea nitrogen; Cr. = Creatinine; HCQ = Hydroxychloroquine; Hb = Hemoglobin; hs-CRP = high-sensitivity C-reactive protein; N = Numbers of the participants; PCR = polymerase chain reaction; (%) represent column percentage; SARS CoV-2= Severe acute respiratory syndrome coronavirus 2; SD = standard deviation; WBC = White blood cell count. p ≤ 0.05 were considered statistically significant

Table 2. COVID-19 patients demographic, clinical characteristics, laboratory data, and treatment.
| Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | % |
|----------|----------|----------|----------|----------|---|
| Age      | 30       | 23       | 66       | 45       | 50 |
| Sex      | Female   | Female   | Male     | Female   | Male |
| Risk Assessment | Turkey  | travel history USA | travel history USA | contact with patient 5 | travel history Spain |
| Comorbidities | Hypertension | No | No | Yes | No | No | 20% |

**Signs and symptoms**

| Days of illness onset (days) | 11 | 6 | 2 | 6 | 5 |
|-----------------------------|----|---|---|---|---|
| Fever≧38℃                   | No | Yes | Yes | Yes | No | 60% |
| Cough                       | Yes | Yes | Yes | Yes | Yes | 100% |
| Rhinorhoea                  | Yes | Yes | Yes | Yes | No | 80% |
| Sore throat                 | Yes | Yes | No | No | No | 40% |
| Myalgia or fatigue          | Yes | Yes | Yes | No | No | 60% |
| Diarrhoea                   | Yes | Yes | No | No | No | 40% |
| Dyspnea                     | No | No | No | Yes | No | 20% |
| Loss of smell and taste     | No | Yes | No | Yes | No | 40% |

**Laboratory tests**

- **WBC × 10^9 cells per L, ≧1.2**: No, No, No, Yes, No | 20%
- **Hb, g/dL, <12**: No, No, No, No, No | 0%
- **BUN, mg/dL ≧20**: No, No, No, No, No | 0%
- **Cr., µmol/L, ≧1.3**: No, No, No, No, No | 0%
- **ALT, U/L, ≧40**: No, Yes, Yes, Yes, No | 60%
- **hs-CRP, mg/L, ≧1**: No, No, Yes, Yes, No | 60%
- **Influenza A/B virus**: No, No, NA, No, No | 0%

**Treatment**

- **HCQ**: Yes, Yes, Yes, Yes, Yes | 100%
- **Oseltamivir**: Yes, Yes, No, Yes, Yes | 80%
- **Azithromycin**: No, No, Yes, Yes, Yes | 60%
- **Tocilizumab**: No, No, No, Yes, No | 20%
- **Test to virus conversion after HCQ (7-day)**: 10, 38, 21, 21, 10 | 20%
- **Respiratory failure**: No, No, No, Yes, No | 20%
- **In hospitalization (days)**: 12, 40, 24, 32, 12

ALT = Alanine aminotransferase, BUN = Blood urea nitrogen; Cr. = Creatinine; HCQ = Hydroxychloroquine; Hb = Hemoglobin; hs-CRP = high-sensitivity C-reactive protein; N = Numbers of the participants; PCR = polymerase chain reaction; (%) represent row percentage; SARS CoV-2= Severe acute respiratory syndrome coronavirus 2; WBC = White blood cell count.

**Figures**
Figure 1

The flow chart of clinical diagnosis to confirm coronavirus disease 2019 (COVID-19) case. COVID-19, Coronavirus Disease 2019; RT-PCR, reverse-transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2
Figure 2

The flow chart of laboratory diagnosis to confirm coronavirus disease 2019 (COVID-19) Case. COVID-19, Coronavirus Disease 2019; rRT-PCR, reverse-transcription polymerase chain reaction; SARS-CoV-2: acute respiratory syndrome coronavirus 2
Figure 3

The countermeasures of COVID-19 in Taiwan. COVID-19, Coronavirus Disease 2019; rRT-PCR, reverse-transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2
Figure 4

Timeline of Events and Trend of Confirmed COVID-19 Cases in Taiwan N=432 (2020 January 01 to 2020 May 11). CDC: Centres for Disease Control; CECC: Central Epidemic Command Center; COVID-19: Coronavirus Disease 2019; rRT-PCR: reverse-transcription polymerase chain reaction; SARS-CoV-2: acute respiratory syndrome coronavirus 2; T.O.C.C.: Travel history, occupational exposure, contact history, cluster history; WHO: World Health Organization

Supplementary Files

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