



Review

Coronavirus (SARS-CoV-2): Preventions, keys to diagnosis and treatment of SARS-CoV-2

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ABSTRACT

World Health Organization (WHO) is gathering the latest scientific findings and knowledge on coronavirus disease (SARS-CoV-2) and compiling it in a database. WHO update the database daily from searches of bibliographic databases, hand searches of the table of contents of relevant journals, and the addition of other relevant scientific articles that come to our attention. The entries in the database may not be exhaustive and new research will be added regularly. Nobel coronavirus investigators, the recognition of a novel coronavirus as the cause of severe acute respiratory syndrome (SARS) was certainly remarkable, yet perhaps not surprising. Advances in the biology of coronaviruses have resulted in greater understanding of their capacity for adaptation to new environments, transspecies infection, and emergence of new diseases. New tools of cell and molecular biology have led to increased understanding of intracellular replication and viral cell biology, and the advent in the past five years of reverse genetic approaches to study coronaviruses has made it possible to begin to define the determinants of viral replication, transspecies adaptation, and human disease. This summary will discuss the basic life cycle and replication of the well-studied coronavirus, mouse hepatitis virus (MHV), identifying the unique characteristics of coronavirus biology and highlighting critical points where research has made significant advances, and which might represent targets for antivirals or vaccines. Areas where rapid progress has been made in SCoV research will be described. Finally, areas of need for research in coronavirus replication, genetics, and pathogenesis will be summarized.

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1. INTRODUCTION

In January, 2020, a novel virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as the causative agent for a cluster of pneumonia cases initially detected in Wuhan City, Hubei province, China.

SARS-CoV-2, which causes the disease now named coronavirus disease 2019 (SARS-COV-2), had spread throughout China and to 26 additional countries as of Feb 18, 2020. Phylogenetic data implicate a zoonotic origin, and the rapid spread suggests ongoing person-to-person transmission. Several studies offer additional insight into person-to-person transmission [1-3].

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However, substantial knowledge gaps remain regarding the transmissibility between humans, including the level of exposure to a confirmed case at which transmission is more likely to occur. On March 15, 2020, Illinois, USA, reported the state's first laboratory-confirmed case (index case) of SARS-CoV-2 in a traveller who returned from Wuhan, Italy in 15 March 2020 [4].

The International Federation of the Red Cross (IFRC), UNICEF and the World Health Organization (WHO) today issued new guidance to help protect children and schools from transmission of the SARS-CoV-2 virus. The guidance provides critical considerations and practical checklists to keep schools safe. It also advises national and local authorities on how to adapt and implement emergency plans for educational facilities [3].

In the event of school, college & multiplex closures, the guidance includes recommendations to mitigate against the possible negative impacts on children's learning and wellbeing. This means having solid plans in place to ensure the continuity of learning, including remote learning options such as online education strategies and radio broadcasts of academic content, and access to essential services for all children. These plans should also include necessary steps for the eventual safe reopening of schools.

Where schools remain open, and to make sure that children and their families remain protected and informed, the guidance calls for:

- Providing children with information about how to protect themselves;
- Promoting best handwashing and hygiene practices and providing hygiene supplies;
- Cleaning and disinfecting school buildings, especially water and sanitation facilities; and
- Increasing airflow and ventilation.

The guidance, while specific to countries that have already confirmed the transmission of SARS-CoV-2, is still relevant in all other contexts. Education can encourage students to become advocates for disease prevention and control at home, in school, and in their community by talking to others about how to prevent the spread of viruses. Maintaining safe school operations or reopening schools after a closure, requires many considerations, but if done well, can promote public health.

UNICEF is urging schools – whether open or helping students through remote learning – to provide students with holistic support. Schools should provide children with vital information on hand washing and other measures to protect themselves and their families; facilitate mental health support; and help to prevent stigma and discrimination by encouraging students to be kind to each other and avoid stereotypes when talking about the virus [4].

2. DISEASE BACKGROUND OF CORONA OF COVID-19 [5,6]

2.1. SYMPTOMS, INCUBATION PERIOD AND SEVERITY

The most commonly reported clinical symptom in laboratory-confirmed cases is fever (88%), followed by dry cough (68%), fatigue (38%), sputum production (33%), dyspnoea (19%), sore throat (14%), headache (14%) and myalgia or arthralgia (15%). Less common symptoms are diarrhoea (4%) and vomiting (5%). About 80% of reported cases in China had mild to moderate disease (including non-pneumonia and pneumonia cases), 13.8% had severe disease and 6.1% were critical (respiratory failure, septic shock, and/or multiple organ dysfunction/failure). Current estimates suggest a median incubation period from five to six days for COVID-19, with a range from one to up to 14 days. A recent modeling study confirmed that it remains prudent to consider the incubation period of at least 14 days.

2.2. CASE FATALITY

Robust estimates for final case fatality risk for COVID-19 are still lacking and biased due to incomplete outcome data and the fact that initial detections were of mostly severe cases in most settings. Based on a large dataset from cases in China, the overall case fatality risk (CFR) among laboratory-confirmed cases was higher in the early stages of the outbreak (17.3% for cases with symptom onset from 1-10 January) and has reduced over time to 0.7% for patients with symptom onset after 1 February. In data on diagnosed COVID-19 cases in China, Italy and South Korea, overall CFR was 2.3%, 2.8% and 0.5%, respectively, and increased with age in all settings, with the highest CFR among people over 80 years of age (14.8%, 8.2% and 3.7%, respectively).

2.3. VIRAL SHEDDING

Over the course of the infection, the virus has been identified in respiratory tract specimens 1-2 days before the onset of symptoms and it can persist for 7-12 days in moderate cases and up to 2 weeks in severe cases. In faeces, viral RNA has been detected from day 5 after onset and up to 4 to 5 weeks in moderate cases. The virus has been detected also in whole blood, serum, saliva and urine. Prolonged viral RNA shedding has been reported from nasopharyngeal swabs, up to 37 days among adult patients and in faeces, for more than one month after infection in paediatric patients. It should be noted that viral RNA shedding does not directly equate with infectivity.

3. GUIDELINE METHODOLOGY [7]

This guideline was prepared in accordance with the methodology and general rules of WHO Guideline Development and the WHO Rapid Advice Guidelines.

3.1. COMPOSITION OF THE GUIDELINE DEVELOPMENT GROUP

This guideline development group is multidisciplinary and composed of individuals from health professionals and methodologists. Health professionals included frontline clinical doctors, nurses who work in departments of respiratory medicine, fever clinic, critical medicine, emergency, infectious disease, and experts of respiratory infectious disease and hospital management board. The methodologists included methodologists of guideline development, systematic review, and literature searching professionals.

3.2. THE END-USER OF THE GUIDELINE

This guideline is suitable for frontline doctors and nurses, managers of hospitals and healthcare sections, healthy community residents, personnel in public healthcare, relevant researchers, and all persons who are interested in the 2019-SARS-CoV-2 management.

3.3. THE TARGET POPULATION OF THE GUIDELINE

This guideline is aimed to serve the healthcare professionals to tackle the suspected 2019-SARS-CoV-2 infected cases, confirmed 2019-SARS-CoV-2 infected cases, clustered 2019-SARS-CoV-2 infected cases, and those with close contacts or suspicious exposure to 2019-SARS-CoV-2 infected cases.

3.4. A SURVEY OF CONFLICT OF INTERESTS

Oral inquiry for financial interests of relevant personal was conducted at the first meeting while to start this guideline. Relevant financial as well as nonfinancial interests were surveyed and disclosed and subsequently assessed in consensus conference in order to minimize potential bias in guideline development. Finally, there is no conflict of interests for all the personnel participating to prepare this guideline.

3.5. GUIDELINE'S STRUCTURAL SETUP AND REFINING THE TOPICS AND COVERAGE OF THIS GUIDELINE

This guideline is a rapid guideline to responding to the emerging infectious disease of SARS-CoV-2-ID-19. Due to the urgent need and tight work schedule, we conducted no wide-range survey but a discussion meeting with front-line clinicians who managed patients with SARS-CoV-2-ID-19 infections to finalize guideline topics and key questions.

3.6. INFECTION PREVENTION AND CONTROL DURING HEALTH CARE WHEN NOVEL CORONAVIRUS (SARS-COV2) INFECTION IS SUSPECTED

This is the first edition of guidance on infection prevention and control (IPC) strategies for use when infection with a novel coronavirus (2019-SARS-CoV-2) is suspected. It has been adapted from WHO's Infection prevention and control during health care for probable or confirmed cases of Middle East respiratory syndrome coronavirus (MERS-CoV) infection, based on current knowledge of the situation in China and other countries where cases were identified and experiences with severe acute respiratory syndrome (SARS)-CoV and MERS-CoV.

3.7. HEALTH WORKERS EXPOSURE RISK ASSESSMENT AND MANAGEMENT IN THE CONTEXT OF SARS-COV2 VIRUS

This tool is to be used by health care facilities that have either cared for or admitted SARS-CoV-2 patients; it is to be completed for all health workers who have been exposed to a confirmed SARS-CoV-2 patient in a health care facility. It will help determine the risk of SARS-CoV-2 virus infection of all HCWs who have been exposed to a SARS-CoV-2 patient and then provide recommendations for appropriate management of these HCWs, according to their infection risk.

3.8. RATIONAL USE OF PERSONAL PROTECTIVE EQUIPMENT FOR CORONAVIRUS DISEASE (SARS-COV2)

This document summarizes WHO recommendations for the rational use of personal protective equipment (PPE), in health care and community settings, including the handling of cargo. This document is intended for those involved in the distribution and management of PPE, as well as public health authorities and individuals in health care and community settings to understand when PPE use is most appropriate.

3.9. ADVICE ON THE USE OF MASKS

This document provides rapid advice on the use of medical masks in communities, at home and at health care facilities in areas that have reported outbreaks caused by the 2019 novel coronavirus (SARS-CoV-2). It is intended for public health and infection prevention and control (IPC) professionals, health care managers, health care workers and community health workers.

3.10. WATER, SANITATION, HYGIENE AND WASTE MANAGEMENT FOR SARS-COV2

This Technical Brief supplements existing IPC documents by referring to and summarizing WHO guidance on water,

sanitation and health care waste which is relevant for viruses (including coronaviruses).

4. INVESTIGATION PROTOCOL FOR SARS-COV2 INFECTION [8]

The following protocol has been designed to investigate the First Few X number of cases and their close contacts (FFX). It is envisioned that the FFX -SARS-COV-2 investigation will be conducted across several countries or sites with geographical and demographical diversity. Using a standardized protocol such as the protocol provided here, epidemiological exposure data and biological samples can be systematically collected and shared rapidly in a format that can be easily aggregated, tabulated and analyzed across many different settings globally for timely estimates of SARS-COV-2 infection. FFX is the primary investigation protocol to be initiated upon identification of the initial laboratory-confirmed cases of SARS-COV-2 in a country.

4.1. HOUSEHOLD TRANSMISSION INVESTIGATION PROTOCOL

The household transmission investigation is a case-ascertained prospective study of all identified household contacts of a laboratory confirmed SARS-COV-2 infection. It is intended to provide rapid and early information on the clinical, epidemiological and virological characteristics of SARS-COV-2.

4.2. PROTOCOL FOR ASSESSMENT OF POTENTIAL RISK FACTORS FOR SARS-COV2 INFECTION AMONG HEALTH CARE WORKERS IN A HEALTH CARE SETTING

The extent of -SARS-CoV-2 infections in health care settings is not clear, nor whether there are certain risk factors associated with infection in health care workers. The following protocol has been designed to investigate the extent of infection and risk factors for infection among health care workers. Follow-up and testing of respiratory specimens and serum of health care workers within a facility in which a confirmed case of SARS-COV-2 infection is receiving care can provide useful information on transmissibility and routes of transmission and are important for limiting amplification events in health care facilities.

4.3. SURFACE SAMPLING OF CORONAVIRUS DISEASE (SARS-COV2): A PRACTICAL "HOW TO" PROTOCOL FOR HEALTH CARE AND PUBLIC HEALTH PROFESSIONALS

The role of environmental contamination in transmission of SARS-COV-2 virus is currently not clear. This protocol has been designed to determine (viable) virus presence and

persistence on fomites in various locations where a patient infected with SARS-COV-2 is currently receiving care or being isolated, and to understand how this may relate to SARS-COV-2 transmission events in these settings. It is therefore important that it is done as part of a comprehensive outbreak investigation and that information obtained by environmental studies is combined with the results of epidemiological, laboratory and sequence data from SARS-COV-2 patient investigations.

4.4. GLOBAL SARS-COV2 CLINICAL CHARACTERIZATION CASE RECORD FORM AND NEW DATA PLATFORM FOR ANONYMIZED SARS-COV2 CLINICAL DATA [9]

The clinical characterization case record form (clinical CRF) is intended to provide member states with a standardized approach to collect clinical data in order to better understand the natural history of disease and describe clinical phenotypes and treatment interventions (i.e. clinical characterization). By using one standardized clinical data tool, there is potential for clinical data from around the world to be aggregated; in order to learn more to inform the public health response and prepare for large scale clinical trials.

5. EPIDEMIOLOGICAL CHARACTERISTICS

5.1. SCOPE OF THE 2019-SARS-COV-2 INFECTION OUTBREAK

Since December 2019, multiple cases occurring unexplainable pneumonia were successively reported in some hospitals in Wuhan city with a history of exposure to a large Hua'nán seafood market in Wuhan city, Hubei province, China. It has been confirmed to be an acute respiratory infection caused by a novel coronavirus. So far, the number of cases without a history of the Hua'nán seafood market exposure is increasing. In addition, clustered cases and confirmed cases without a history of travel to Wuhan emerged. Also, confirmed cases without clear exposure to the Wuhan seafood market have been found in many foreign countries or regions [10].

At 24:00 on 15 March 2020, **Cases have been reported on the following continents [11]:**

Africa: Egypt (93), Algeria (37), South Africa (24), Senegal (21), Morocco (18), Tunisia (16), Cote D'ivoire (4), Burkina Faso (3), Cameroon (3), Democratic Republic Of the Congo (2), Ghana (2), Namibia (2), Nigeria (2), Seychelles (2), Equatorial Guinea (1), Ethiopia (1), Gabon (1), Guinea (1), Kenya (1), Mauritania (1), Rwanda (1), Sudan (1), Swaziland (1) and Togo (1).

Asia: China (80 995), Iran (12 729), South Korea (8 162), Japan (780), Qatar (337), Malaysia (238), Singapore (214), Bahrain (211), Israel (178), Philippines (111), Kuwait (104), Indonesia (96), Lebanon (93), India (90), Saudi Arabia (86), Iraq (85), United Arab Emirates (85),

Thailand (82), Taiwan (59), Vietnam (53), Brunei Darussalam (40), Palestine* (38), Pakistan (30), Oman (20), Sri Lanka (11), Afghanistan (10), Maldives (9), Cambodia (7), Kazakhstan (6), Bangladesh (3), Bhutan (1), Jordan (1), Mongolia (1) and Nepal (1).

America: United States (2 951), Canada (244), Brazil (121), Chile (61), Argentina (45), Panama (43), Peru (43), Mexico (41), Colombia (34), Ecuador (28), Costa Rica (27), Dominican Republic (11), Bolivia (10), Venezuela (10), Jamaica (8), Paraguay (7), Uruguay (6), Cuba (4), Honduras (3), Saint Lucia (2), Trinidad and Tobago (2), Antigua and Barbuda (1), Guatemala (1), Guyana (1), Saint Vincent and the Grenadines (1) and Suriname (1).

Europe: Italy (17 750), Spain (5 753), France (4 499), Germany (3 795), Switzerland (1 359), United Kingdom (1 140), Netherlands (959), Sweden (924), Norway (907), Denmark (827), Belgium (689), Austria (655), Greece (228), Czech Republic (214), Finland (210), Slovenia (181), Portugal (169), Iceland (138), Ireland (129), Estonia (115), Romania (113), Poland (104), San Marino (92), Russia (59), Serbia (46), Slovakia (44), Bulgaria (41), Albania (38), Luxembourg (38), Croatia (37), Hungary (31), Georgia (30), Latvia (26), Belarus (21), Cyprus (21), Armenia (20), Moldova (20), Azerbaijan (19), Malta (18), North Macedonia (13), Lithuania (9), Liechtenstein (4), Bosnia and Herzegovina (3), Monaco (3), Ukraine (3), Andorra (2), Turkey (2) and Holy See (1).

Oceania: Australia (249) and New Zealand (8).

Other: International conveyance in Japan (696).

5.2. HOST AND RESERVOIR

Wild animal, bats [8] is the most possible host of the 2019-SARS-CoV-2. It requires further confirmation whether pneumonia infected by the 2019-SARS-CoV-2 is transmitted directly from bats or through an intermediate host. It is believed that clarifying the source of the virus will help determine zoonotic transmission patterns [12].

5.3. ROUTE OF TRANSMISSION

Up to present, the main infection source was the patients who with pneumonia infected by the 2019-SARS-CoV-2. Respiratory droplet transmission is the main route of transmission, and it can also be transmitted through contact [8]. Although many details, such as the source of the virus and its ability to spread between people remain unknown, an increasing number of cases show the signs of human-to-human transmission [9].

5.4. ETIOLOGY AND PATHOGENESIS

The 2019-SARS-CoV-2 isolated from the lower respiratory tract of patients with unexplainable pneumonia in Wuhan, and it is a novel coronavirus belonging to the β genus. The 2019-SARS-CoV-2 has an envelope; its particles are round or oval, often polymorphic, with a diameter from 60 nm to

140 nm. Its genetic characteristics are significantly different from SARSr-CoV (SARS related coronaviruses) and MERSr-CoV (MERS related coronaviruses). Current research shows it has more than 85% homology with SARSr-CoV (bat-SL-CoVZC45). 2019-SARS-CoV-2 can be found in human respiratory epithelial cells 96 h after in vitro isolation and culture, while it takes about 6 days in VeroE6 or Huh-7 cell lines [10].

The source of the virus, the time span of the patients discharging infective virus, and the pathogenesis are still not clear [11].

5.5. MOLECULAR EPIDEMIOLOGY

No evidence of viral mutation has been found so far [12]. It is necessary to obtain much more clinically isolated viruses with time and geographical variety to assess the extent of the virus mutations, and also whether these mutations indicate adaptability to human hosts [13].

5.6. INCUBATION AND CONTAGIOUS PERIOD

Based on currently epidemiological survey, the latency period is generally from 3 to 7 days, with a maximum of 14 days [13]. Unlike SARSr-CoV, 2019-SARS-CoV-2 is contagious during the latency period [14].

5.7. PROGNOSTIC FACTORS

The population is generally susceptible to the virus. The elderly and those with underlying diseases show more serious conditions after infection, and children and infants also get infected by the 2019-SARS-CoV-2. From current knowledge of the cases, most patients have a good prognosis, the symptoms of children are relatively mild, and a few patients are in critical condition. Death cases are more frequently seen in the elderly and those with chronic underlying diseases [15].

The newest study including the first 41 confirmed cases admitted to Wuhan between 16 December 2019 and 2 January 2020 showed the median age of patients was 49 years; and the main underlying diseases were diabetes, hypertension, and cardiovascular diseases. Of them, 12 cases experienced acute respiratory distress syndrome (ARDS), 13 cases were admitted to the intensive care unit (ICU), and 6 cases died [16].

6. DIAGNOSIS OF THE 2019-SARS-COV-2 CASES

6.1. CLINICAL MANIFESTATION

The 2019-SARS-CoV-2 infected cases have symptoms like fever, fatigue, dry cough, dyspnea etc., with or without nasal congestion, runny nose or other upper respiratory symptoms [17, 18]. Despite the atypical symptoms were reported [19], Nan-Shan Zhong, the academician of

Chinese Academy of Engineering in an exclusive interview with Xinhua News Agency on 28 January 2020, pointed out that fever is still the typical symptom of 2019-SARS-CoV-2 infection.

6.2. PHYSICAL EXAMINATION [20]

Patients with mild symptoms may not present positive signs. Patients in severe condition may have shortness of breath, moist rales in lungs, weakened breath sounds, dullness in percussion, and increased or decreased tactile speech tremor, etc.

6.3. IMAGING EXAMINATION: CT IMAGING (STRONG RECOMMENDATION) [21]

The imaging findings vary with the patient's age, immunity status, disease stage at the time of scanning, underlying diseases, and drug interventions.

The imaging features of lesions show: (1) dominant distribution (mainly subpleural, along the bronchial vascular bundles); (2) quantity (often more than three or more lesions, occasional single or double lesions); (3) shape (patchy, large block, nodular, lumpy, honeycomb-like or grid-like, cord-like, etc.); (4) density (mostly uneven, a paving stones-like change mixed with ground glass density and interlobular septal thickening, consolidation and thickened bronchial wall, etc.); and (5) concomitant signs vary (air-bronchogram, rare pleural effusion and mediastinal lymph nodes enlargement, etc.).

6.4. CLINICAL DATA FROM ZHONGNAN HOSPITAL OF WUHAN UNIVERSITY [22]

Typical CT/X-ray imaging manifestation, include:

- Multiple, patchy, sub-segmental or segmental ground-glass density shadows in both lungs. They were classified as "paving stone-like" changes by fine-grid or small honeycomb-like thickening of interlobular septa. The thinner the CT scan layers, the clearer the ground-glass opacity and thickening of interlobular septa were displayed. A slightly high-density and ground-glass change with fuzzy edge in the fine-grid or small honeycomb-like thickening of interlobular septa were presented by the high-resolution computed tomography (HRCT), (Figure 1: 45 cases, 54.2%

in a total of 83 cases). The resolution of X-ray was worse lower than that of CT in the resolution, which was basically manifested as ground-glass opacities with fuzzy edge (Figure 2: 9 cases, 10.8% in a total of 83 cases).

- Multiple, patchy or large patches of consolidation in both lungs, with a little grid-like or honeycomb-shaped interlobular septal thickening, especially in the middle and lower lobes (Figure 3: 26 cases, 31.3% in a total of 83 cases). It was more common in the elderly or severe condition patients.

Atypical CT/X-ray imaging manifestation, include:

- Single, or multiple, or extensive subpleural grid-like or honeycomb-like thickening of interlobular septum, thickening of the bronchial wall, and tortuous and thick strand-like opacity. Several patchy consolidations, occasionally with a small amount pleural effusion or enlargement of mediastinal lymph nodes, can be seen (Figure 4: 6 cases, 7.2% in a total of 83 cases). This is mostly seen in the elderly.
- Single or multiple solid nodules or consolidated nodules in the center of lobule, surrounded by ground-glass opacities (Figure 5: 5 cases, 6.2% in a total of 83 cases).

Stage based on CT image [24]: The CT imaging demonstrates 5 stages according to the time of onset and the response of body to the virus, including:

- Ultra-early stage. This stage usually refers to the stage of patients without clinical manifestation, negative laboratory test but positive throat swab for 2019-SARS-CoV-2 within 1–2 weeks after being exposed to a virus-contaminated environment (history of contact with a patient or patient-related family members, unit, or medical staff in a cluster environment). The main imaging manifestations are single, double or scattered focal ground-glass opacity, nodules located in central lobule surrounded by patchy ground-glass opacities, patchy consolidation and sign of intra-bronchial air-bronchogram, which was dominant in the middle and lower pleura (Figure 6: 7 cases, 8.4% in a total of 83 cases).

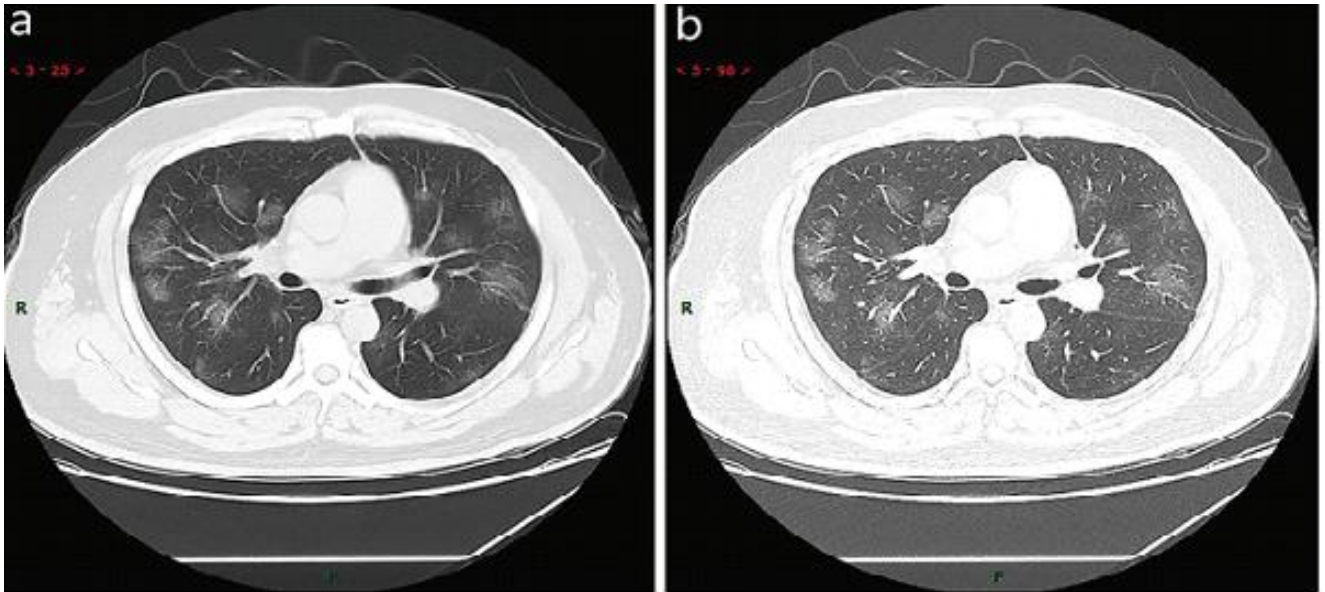


Figure 1: Typical CT imaging manifestation (case 1). A 38 years old male with fever without obvious inducement (39.3°C), dry cough and shortness of breath for 3 days. Laboratory test: normal white blood cells ($6.35 \times 10^9/\text{L}$), decreased lymphocytes percentage (4.1%), decreased lymphocytes count ($0.31 \times 10^9/\text{L}$), decreased eosinophil count ($0 \times 10^9/\text{L}$), increased C-reaction protein (170.91 mg/L), increased procalcitonin (0.45 ng/ml). Imaging examination: multiple patches, grid-like lobule and thickening of interlobular septa, typical “paving stone-like” signs. **a** SL(Slice): 6 mm; **b** high-resolution computed tomography(HRCT). HRCT. high-resolution computed tomography.

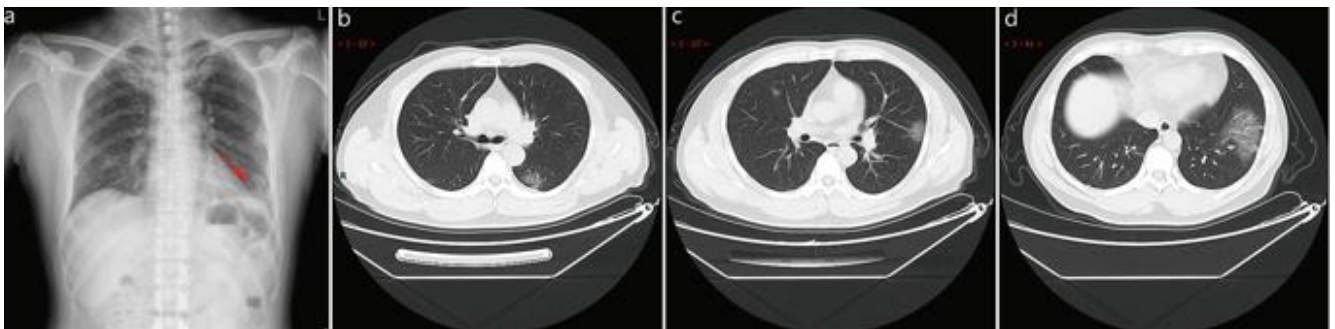


Figure 2: Typical CT / X-ray imaging manifestation (case 2). A 51 years old male with general muscle ache and fatigue for 1 week, fever for 1 day (39.1°C), anemia. Laboratory test: normal white blood cells ($9.24 \times 10^9/\text{L}$), lymphocytes percentage (5.1%), decreased lymphocytes ($0.47 \times 10^9/\text{L}$), decreased eosinophil count ($0 \times 10^9/\text{L}$), increased C-reaction protein (170.91 mg/L), increased procalcitonin (0.45 ng/ml), increased erythrocyte sedimentation rate (48 mm/h). Imaging examination: **a** shows patchy shadows in the outer region of the left lower lobe, **b** shows large ground-glass opacity in the left lower lobe, and **c** shows subpleural patchy ground-glass opacity in posterior part of right upper lobe and lower tongue of left upper lobe, **d** shows large ground-glass.

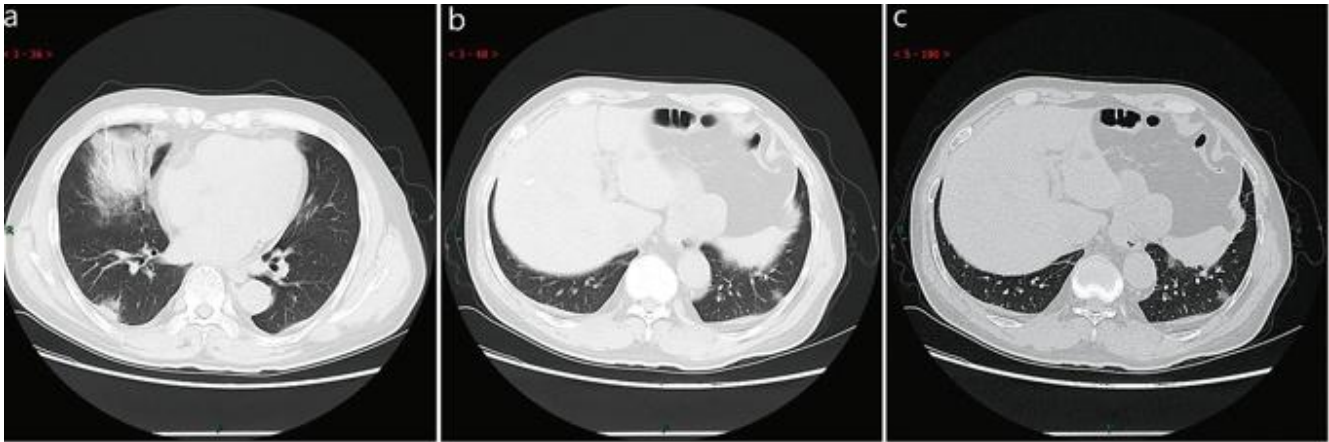


Figure 3: Typical CT / X-ray imaging manifestation (case 3). A 65 years old male with fever for 4 days (38.7°C). Laboratory test: normal white blood cells ($3.72 \times 10^9/L$), decreased lymphocytes ($0.9 \times 10^9/L$), decreased eosinophil count ($0 \times 10^9/L$), increased C-reaction protein (53.0 mg/L), increased procalcitonin (0.10 ng/ml), reduced liver function, hypoproteinemia, and mild anemia. Imaging examination: **a** and **b** showed large consolidation in the right middle lobe, patchy consolidation in the posterior and basal segment of the right lower lobe, with air-bronchogram inside, **c** showed patchy consolidation in the outer and basal segment of the left lower lobe, and a small amount of effusion in the right chest.



Figure 4: Atypical CT / X-ray imaging manifestation (case 1). An 83 years old female with fever for 4 days (maximum temperature of 38.8°C), cough, chills, sore throat, dry cough for 1 week, chest tightness and shortness of breath aggravating for 1 week. Laboratory test: normal white blood cells ($4.6 \times 10^9/L$), normal neutrophil percentage (65.8%), decreased lymphocytes percentage (19.9%). Imaging examination: **a** and **b** showed diffuse interlobular septum thickening in both lungs to form a grid opacity, thickening of bronchial wall, and consolidation in the left sublobar lung. **c** showed diffused grid-like opacities in both lungs, especially in the left lung opacity in the basal segment of the left lower lobe.

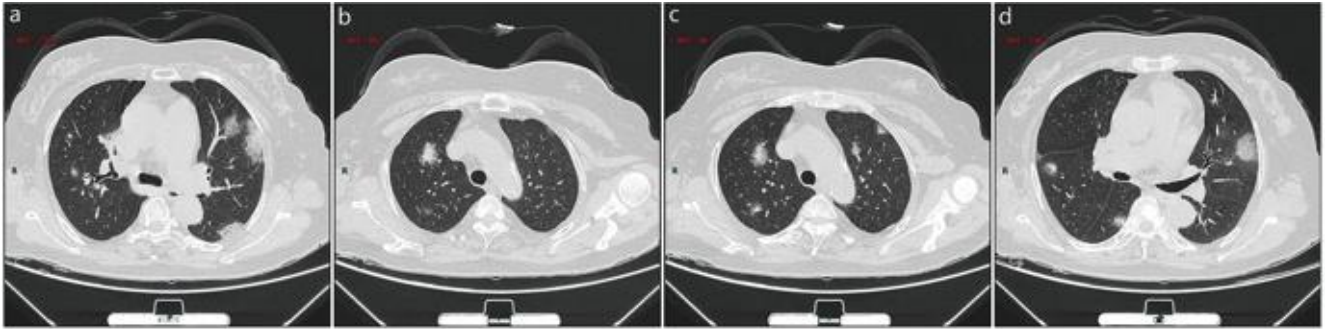


Figure 5: Atypical CT / X-ray imaging manifestation (case 2). A 56 years old female with fever for 3 days. Laboratory test: decreased total protein (54.0 g/L), decreased albumin (35.5 g/L), decreased globulin (18.5 g/L), normal white blood cells ($4.87 \times 10^9/L$), decreased lymphocytes percentage (10.1%), decreased lymphocytes ($0.49 \times 10^9/L$), decreased eosinophil count ($0 \times 10^9/L$), decreased eosinophil count percentage (0%). Imaging examination: **a** showed two consolidation nodules at the center of the lateral segment of middle lobe of the right lung which was surrounded by ground-glass opacities; **b** showed patchy ground-glass opacity in the anterior segment of the right upper lung with patchy consolidation lesions in it; **c** showed patchy ground-glass opacities in both lungs with patchy consolidation lesions in it. **d** showed patchy consolidation in the ground-glass opacities in the middle lobe and dorsal segment of lower lobe of right lung.



Figure 6: CT imaging of ultra-early stage. **a** A 33 years old female with patchy ground-glass opacities after occupational exposure. **b** A 67 years old male with a history of contact with infected patients, showing large ground-glass opacity. **c** A 35 years old female exhibiting large consolidated opacity with air-bronchogram inside after occupational exposure.

- **Early stage.** This stage refers to the period of 1–3 days after clinical manifestations (fever, cough, dry cough, etc.). The pathological process during this stage is dilatation and congestion of alveolar septal capillary, exudation of fluid in alveolar cavity and interlobular interstitial edema. It showed that single or multiple scattered patchy or agglomerated ground-glass opacities, separated by honeycomb-like or grid-like thickened of interlobular septa (Figure 7: 45 cases, 54.2% in a total of 83 cases).
- **Rapid progression stage.** This stage refers to the period about 3–7 days after clinical manifestations started, the pathological features in this stage are the accumulation of a large number of cell-rich exudates in the alveolar cavity, vascular expansion and exudation in the interstitium, both of which lead to further aggravation of alveolar and interstitial edema. The fibrous exudation connects

each alveolus through the inter-alveolar space to form a fusion state. The CT manifested a fused and large-scale light consolidation with air-bronchogram inside (Figure 8: 17 cases, 20.5% in a total of 83 cases).

- **Consolidation stage.** This stage refers to the period around 7–14 days after clinical manifestations appeared. The main pathological features in this stage are the fibrous exudation of the alveolar cavity and the disappearance of capillary congestion in the alveolar wall. CT imaging showed the multiple patchy consolidations in slighter density and smaller range than that of the previous stage. (Figure 9: 26 cases, 31.2% in a total of 83 cases).

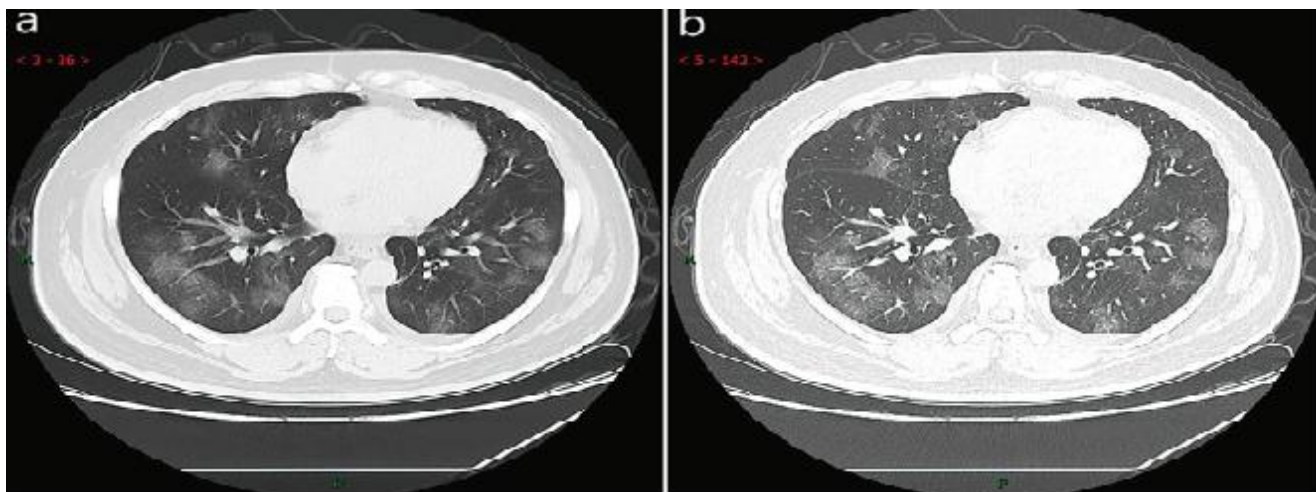


Figure 7: CT imaging of early stage. Male, 38 years old, fever without obvious inducement (39.3°C), dry cough and shortness of breath for 3 days. Laboratory test: decreased white blood cells ($3.01 \times 10^9/\text{L}$), decreased lymphocytes ($0.81 \times 10^9/\text{L}$), increased C-reaction protein (60.8 mg/L), increased procalcitonin (0.16 ng/ml). Imaging examination: **a** (thin layer CT) and **b** (high-resolution CT) showed multiple patchy and light consolidation in both lungs and grid-like thickness of interlobular septa.

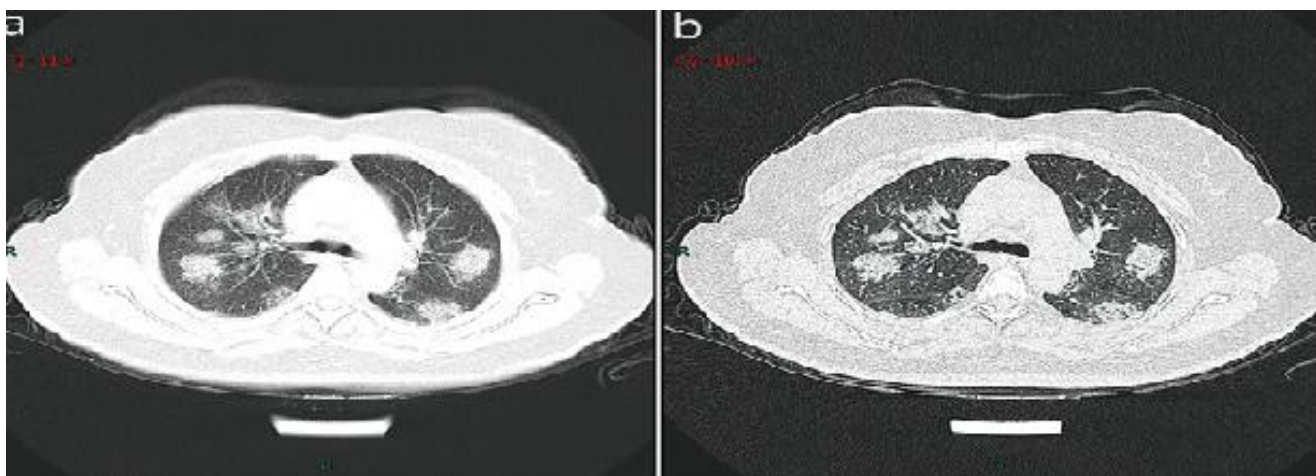


Figure 8: CT imaging of rapid progression stage. A 50 years old female with anorexia, fatigue, muscle soreness, nasal congestion and runny nose for 1 week, sore and itching throat for 2 days. Laboratory test: increased erythrocyte sedimentation rate (25 mm/h), normal white blood cells ($4.08 \times 10^9/\text{L}$), decreased lymphocytes ($0.96 \times 10^9/\text{L}$), increased C-reaction protein (60.8 mg/L). Imaging examination: **a** (thin layer CT) and **b** (high-resolution CT) showed multiple patchy and light consolidation in both lungs and grid-like thickness of interlobular septa.

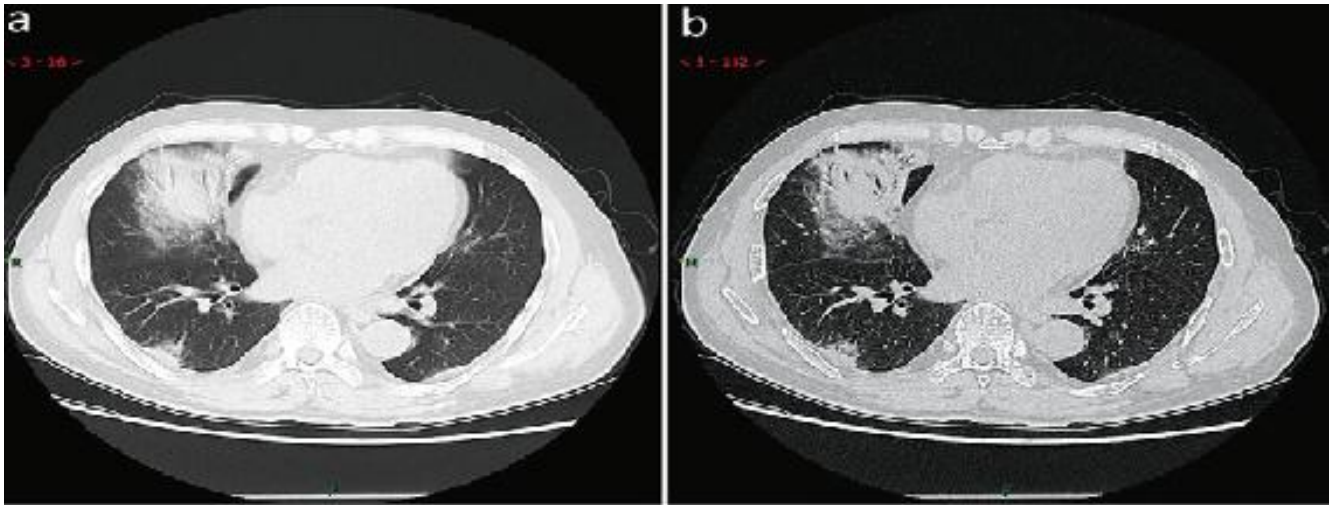


Figure 9: CT imaging of consolidation stage. A 65 years old male with fever (maximum temperature of 39 °C). Laboratory test: hypoproteinemia (decreased total protein (62.20 g/L), decreased albumin (35.70 g/L)), abnormal liver function (increased alanine aminotransferase (79 U/L), increased aspartate aminotransferase (72 U/L)), increased procalcitonin (0.10 ng/ml), increased C-reaction protein (53 mg/L), decreased white blood cells ($3.72 \times 10^9/L$), decreased lymphocytes ($0.9 \times 10^9/L$), mild anemia (decreased red blood cells ($4.10 \times 10^{12}/L$), decreased hemoglobin (131.10 g/L), decreased hematocrit (39.0%). Imaging examination: **a** (thin layer CT) and **b** (high-resolution CT) showed multiple patchy and large consolidation in right middle lobe, posterior and basal segment of right lower lobe and outer and basal segment of left lower lobe, with air-bronchogram inside.

7. GEOGRAPHIC DISTRIBUTION OF CUMULATIVE NUMBER OF REPORTED COVID-19 CASES PER 100,000 POPULATION, WORLDWIDE (15TH MARCH 2020) [25] (TABLE 1)

Table 1. Reported COVID-19 cases per 100,000 population, worldwide

Regions	Places reporting cases	Confirmed cases	Deaths	Confirmed cases in the last 15 days
Asia	China	80,995	3,203	1,640
Asia	Iran	12,729	611	12,341
Asia	South Korea	8,162	75	5,231
Asia	Japan	780	22	550
Asia	Qatar	337	0	337
Asia	Malaysia	238	0	213
Asia	Singapore	214	0	116
Asia	Bahrain	211	0	173
Asia	Israel	178	0	171
Asia	Philippines	111	6	108
Asia	Kuwait	104	0	59
Asia	Indonesia	96	1	96
Asia	Lebanon	93	3	90
Asia	India	90	2	87
Asia	Saudi Arabia	86	0	86
Asia	United Arab Emirates	85	0	66
Asia	Iraq	85	9	78
Asia	Thailand	82	1	40
Asia	Taiwan	59	1	20
Asia	Vietnam	53	0	37

Asia	Brunei Darussalam	40	0	40
Asia	Palestine	38	0	38
Asia	Pakistan	30	0	28
Asia	Oman	20	0	14
Asia	Sri Lanka	11	0	10
Asia	Afghanistan	10	0	9
Asia	Maldives	9	0	9
Asia	Cambodia	7	0	6
Asia	Kazakhstan	6	0	6
Asia	Bangladesh	3	0	3
Asia	Nepal	1	0	0
Asia	Jordan	1	0	1
Asia	Bhutan	1	0	1
Asia	Mongolia	1	0	1
Europe	Italy	17,750	1,441	16,862
Europe	Spain	5,753	136	5,719
Europe	France	4,499	91	4,442
Europe	Germany	3,795	8	3,738
Europe	Switzerland	1,359	11	1,347
Europe	United Kingdom	1,140	21	1,122
Europe	Netherlands	959	12	957
Europe	Sweden	924	1	912
Europe	Norway	907	1	901
Europe	Denmark	827	0	825
Europe	Belgium	689	4	688
Europe	Austria	655	1	648
Europe	Greece	228	3	224
Europe	Czech Republic	214	0	214
Europe	Finland	210	0	207
Europe	Slovenia	181	0	181
Europe	Portugal	169	0	169
Europe	Iceland	138	0	137

Europe	Ireland	129	2	129
Europe	Estonia	115	0	114
Europe	Romania	113	0	110
Europe	Poland	104	3	104
Europe	San Marino	92	5	91
Europe	Russia	59	0	57
Europe	Serbia	46	0	46
Europe	Slovakia	44	0	44
Europe	Bulgaria	41	2	41
Europe	Albania	38	1	38
Europe	Luxembourg	38	1	38
Europe	Croatia	37	0	32
Europe	Hungary	31	0	31
Europe	Georgia	30	0	28
Europe	Latvia	26	0	26
Europe	Cyprus	21	0	21
Europe	Belarus	21	0	20
Europe	Armenia	20	0	20
Europe	Moldova	20	0	20
Europe	Azerbaijan	19	0	18
Europe	Malta	18	0	18
Europe	North Macedonia	13	0	12
Europe	Lithuania	9	0	8
Europe	Liechtenstein	4	0	4
Europe	Monaco	3	0	2
Europe	Ukraine	3	0	3
Europe	Bosnia and Herzegovina	3	0	3
Europe	Turkey	2	0	2
Europe	Andorra	2	0	2
Europe	Holy See	1	0	1
America	United States of America	2,951	57	2,885
America	Canada	244	1	228
America	Brazil	121	0	120
America	Chile	61	0	61
America	Argentina	45	2	45
America	Peru	43	0	43
America	Panama	43	1	43
America	Mexico	41	0	39
America	Colombia	34	0	34
America	Ecuador	28	2	28
America	Costa Rica	27	0	27
America	Dominican Republic	11	0	11
America	Venezuela	10	0	10
America	Bolivia	10	0	10
America	Jamaica	8	0	8
America	Paraguay	7	0	7
America	Uruguay	6	0	6
America	Cuba	4	0	4
America	Honduras	3	0	3
America	Saint Lucia	2	0	2
America	Trinidad and Tobago	2	0	2
America	Saint Vincent and the	1	0	1

	Grenadines			
America	Suriname	1	0	1
America	Guatemala	1	0	1
America	Guyana	1	1	1
America	Antigua and Barbuda	1	0	1
Other	Cases on an international conveyance Japan	696	7	0
Oceania	Australia	249	3	224
Oceania	New Zealand	8	0	7
Africa	Egypt	93	2	92
Africa	Algeria	37	2	36
Africa	South Africa	24	0	24
Africa	Senegal	21	0	21
Africa	Morocco	18	1	18
Africa	Tunisia	16	0	16
Africa	Cote d'Ivoire	4	0	4
Africa	Cameroon	3	0	3
Africa	Burkina Faso	3	0	3
Africa	Nigeria	2	0	1
Africa	Seychelles	2		2
Africa	Namibia	2		2
Africa	Democratic Republic of the Congo	2	0	2
Africa	Ghana	2	0	2
Africa	Togo	1	0	1
Africa	Mauritania	1		1
Africa	Equatorial Guinea	1		1
Africa	Gabon	1	0	1
Africa	Rwanda	1		1
Africa	Kenya	1	0	1
Africa	Sudan	1	1	1
Africa	Swaziland	1		1
Africa	Ethiopia	1	0	1
Africa	Guinea	1	0	1
Total		151,363	5,758	66,169

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