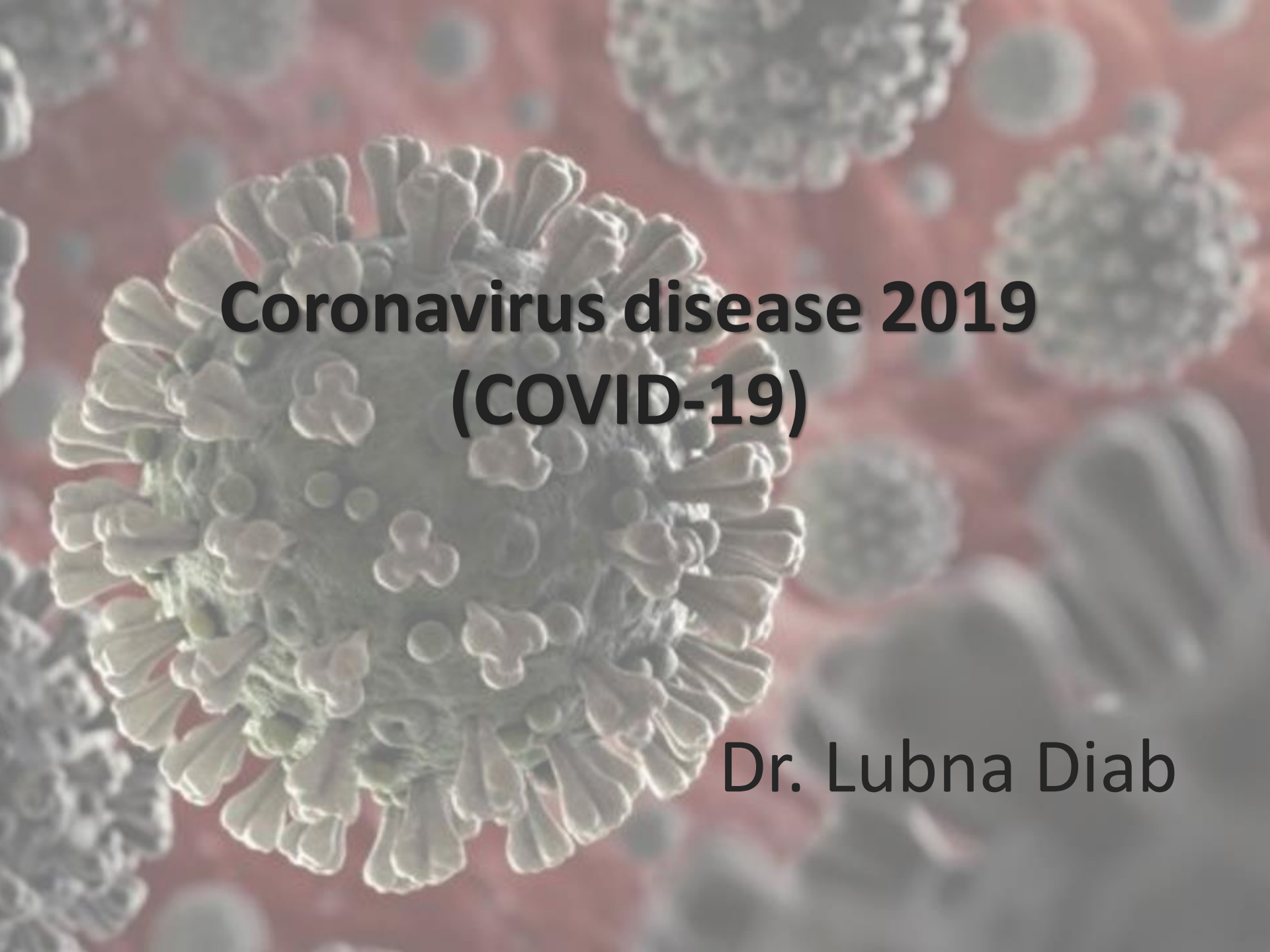

Coronavirus disease 2019 (COVID-19)

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INTRODUCTION

- Coronaviruses (CoVs) are a group of viruses that co-infect humans and vertebrate animals.
- affect the respiratory, gastrointestinal, liver, and CNS, of humans, livestock, birds, bats, mice, & other wild animals.
- **(SARS) in 2002** and **(MERS) in 2012** were both coronaviruses that transmitted from animals to humans.
- On Feb. 11th, 2020, the new coronavirus was renamed **"SARS-CoV-2"** from "2019-nCoV".
- The disease caused by SARS-CoV-2 was called "coronavirus disease 2019" **(COVID-19)**

China *Wuhan*

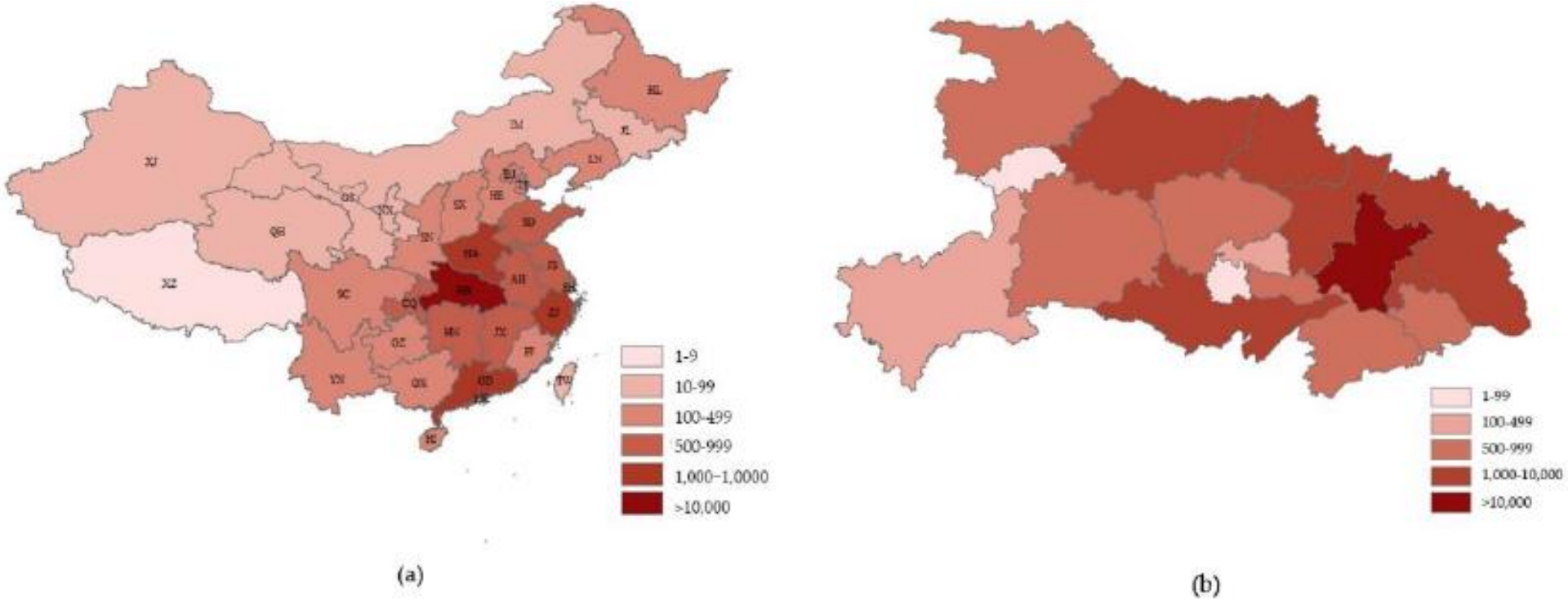

Figure 3. The distribution of COVID-2019 patients in China (a) and Hubei Province (b). XJ, Xinjiang;

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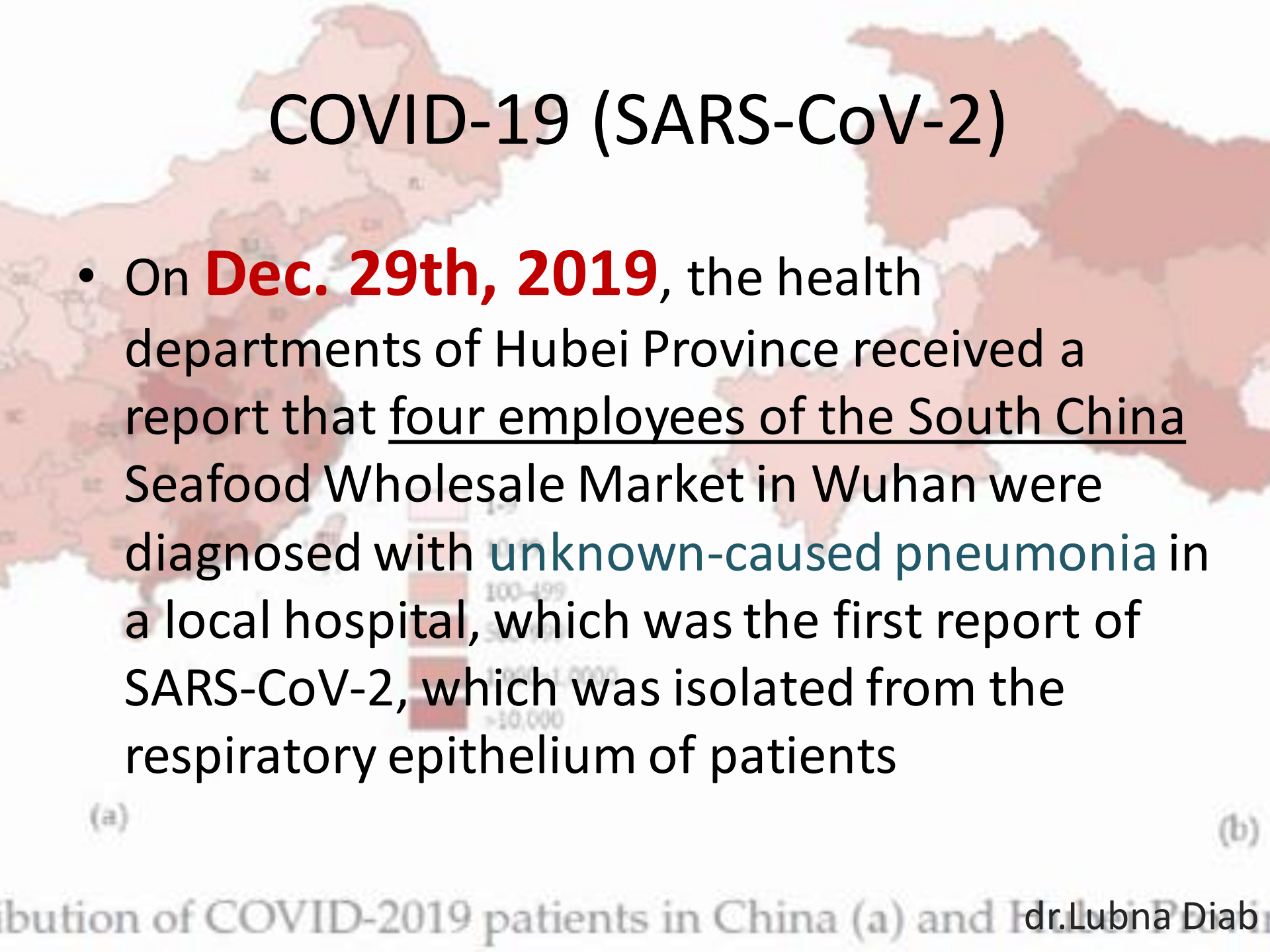
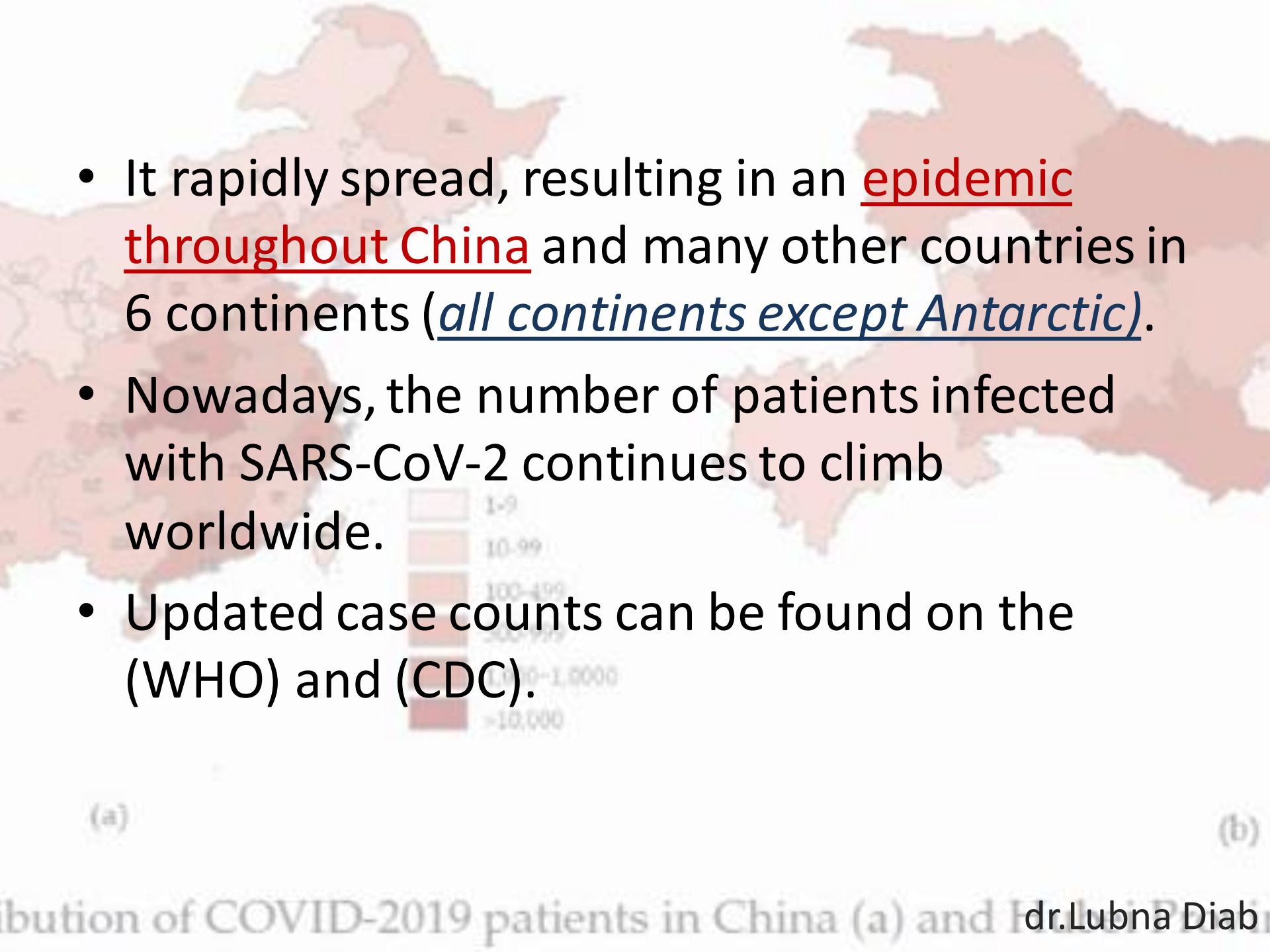
COVID-19 (SARS-CoV-2)

- On **Dec. 29th, 2019**, the health departments of Hubei Province received a report that four employees of the South China Seafood Wholesale Market in Wuhan were diagnosed with unknown-caused pneumonia in a local hospital, which was the first report of SARS-CoV-2, which was isolated from the respiratory epithelium of patients

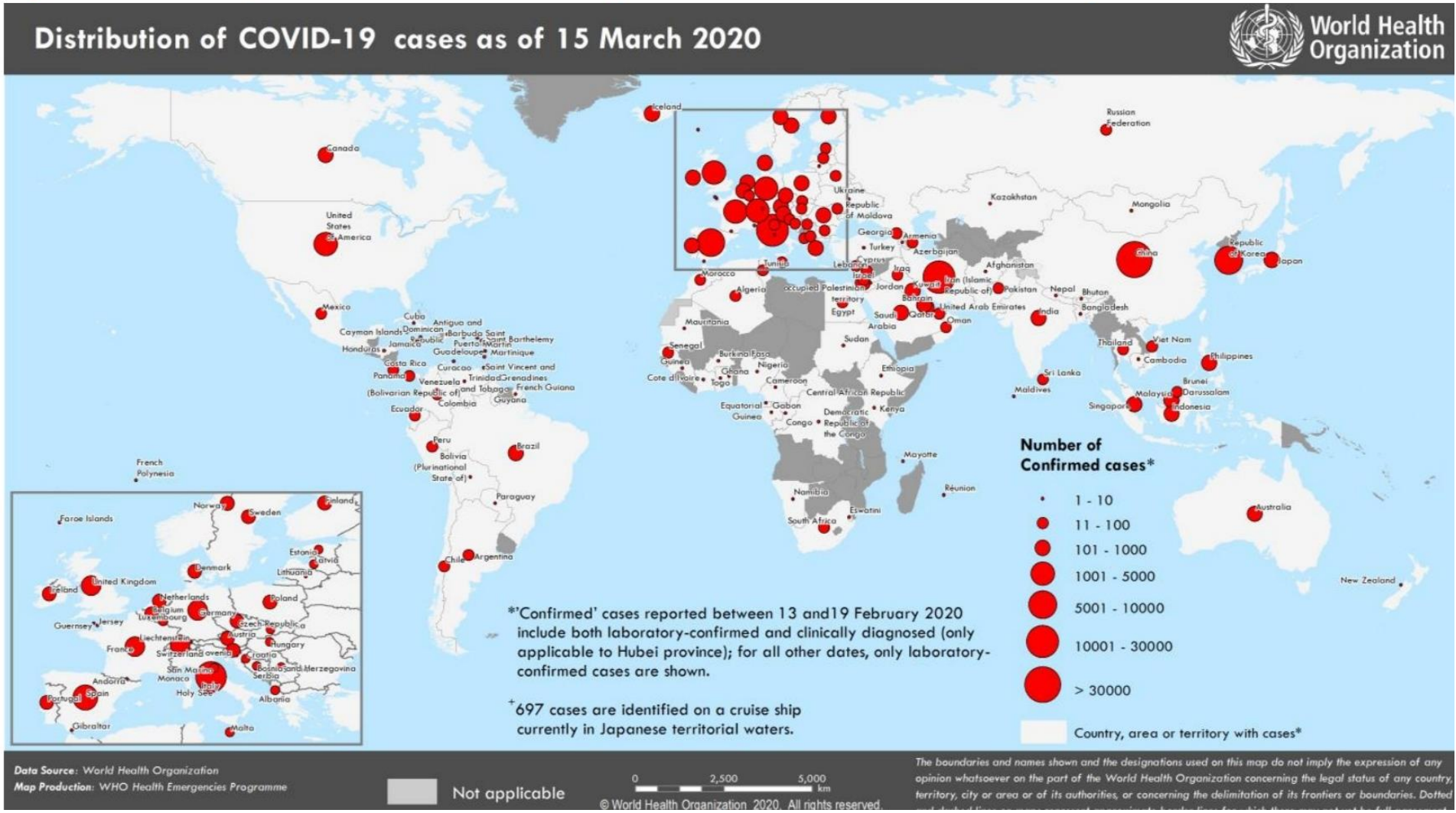


- It rapidly spread, resulting in an epidemic throughout China and many other countries in 6 continents (*all continents except Antarctic)*.
- Nowadays, the number of patients infected with SARS-CoV-2 continues to climb worldwide.
- Updated case counts can be found on the (WHO) and (CDC).



bution of COVID-2019 patients in China (a) and

Figure 1. Countries, territories or areas with reported confirmed cases of COVID-19, 15 March 2020



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SITUATION IN NUMBERS
total and new cases in last 24 hours

Globally
153 517 confirmed
(10 982 new)
5735 deaths (343 new)

China
81 048 confirmed (27 new)
3204 deaths (10 new)

Outside of China
72 469 confirmed (10 955)
2531 deaths (333 new)
143 countries/territories/
areas (09 new)

WHO RISK ASSESSMENT

China	Very High
Regional Level	Very High
Global Level	Very High

COVID-19 ,SARS and MERS— the Initial Events

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SARS-CoV

- On **Nov. 27th, 2002,** a respiratory illness erupted in **Guangdong Province, China**.
- In Feb, 2003, this acute respiratory syndrome resulted in 305 cases and 5 deaths.
- The following month, there were clusters of atypical pneumonia reported in other parts of China, Hong Kong , Canada, and Singapore.
- In Jul, 2003, SARS-CoV spread across 26 countries in six continents, and caused 8,096 cases and 774 deaths (9.6%).

MERS-CoV

- In **September 2012**,
- a case of novel coronavirus infection was reported involving a man in Saudi Arabia admitted to a hospital with pneumonia & acute kidney injury(AKI) in June 2012.
- a few days later, a separate report of a virus detected in a second patient with acute respiratory syndrome & (AKI). Many cases and clusters of infections have been reported.
- This novel coronavirus, has been named Middle East respiratory syndrome coronavirus (MERS-CoV).

MERS-CoV

- MERS-CoV can infect both humans and animals, and transmitted through ***camels***.
- It mainly occurs in Saudi Arabia and has a high mortality rate.
- the clinical course and pathogenesis of SARS and MERS was highly similar.
- The genome of SARS-CoV-2 also shows some similarities to that of MERS-CoV.

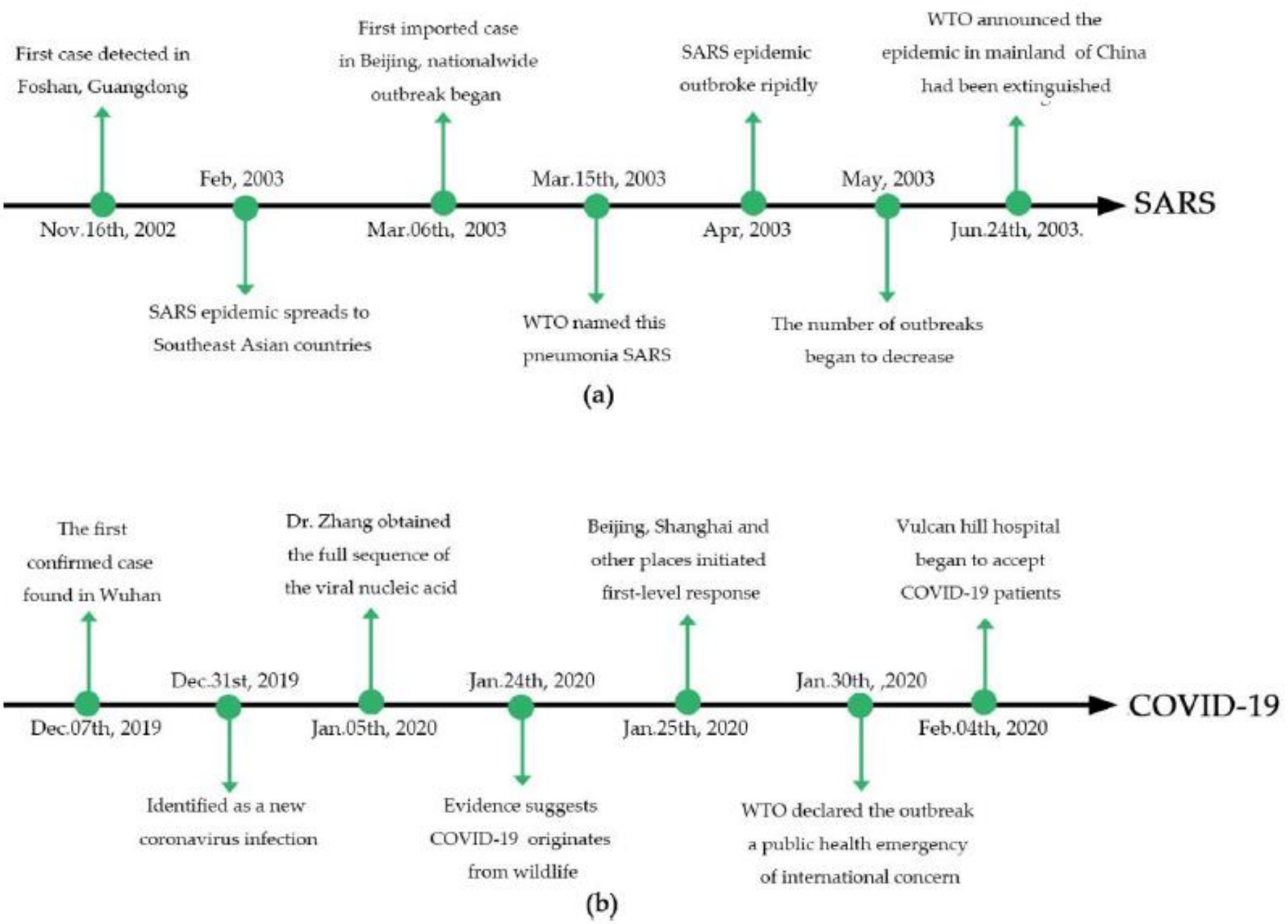

Figure 1. Timeline of SARS (a) and COVID-19 (b) epidemic development.

Table 1. Comparison of SARS and COVID-19.

Items	SARS	COVID-19
First occurrence	Nov. 16th, 2002 in Foshan, Guangdong	Dec. 07th, 2019 in Wuhan, Hubei
Pathogen	SARS-CoV	SARS-CoV-2
Intermediate host	*Paguma larvata*	Pangolin, Mink (Possible)
Definitive host	*Rhinolophus sinicus*	*Rhinolophus affinis* (Possible)
Virus type	RNA virus	RNA virus
Species pathogen	β-coronavirus	β-coronavirus
Total DNA sequence length of pathogen	29,751	29,903
Latency	1–4 days on average	3–7 days on average
Susceptible people	Young adults	People who have not been exposed to SARS-CoV-2
Male–female patient ratio	1:1.25	2.70:1
Mortality	9.60%	2.10%
Clinical symptoms	Fever, cough, myalgia, dyspnea, and diarrhea	Fever, fatigue, and dry cough
Propagation mode	Droplets or close contacts	Droplets or close contacts
Major regional distribution	Beijing, Guangdong, Shanxi in China	Hubei, especially Wuhan in China
Diagnostic methods	RT-PCR, rRT-PCR, RT-LAMP, rRT-LAMP, Coronavirus detection kit	RT-PCR, rRT-PCR, RT-LAMP, rRT-LAMP, Coronavirus detection kit
Treatment	Glucocorticoid and interferon	Lopinavir/ritonavir (in testing)

EPIDEMIOLOGY,
Geographic distribution

- more than 80,000 COVID-19 cases have been reported in China;

  (include laboratory-confirmed & clinically diagnosed cases).
- the epidemic in China **peaked** between late January and early February 2020.
- Case count has been rising daily.
- Increasing numbers of cases also reported in other countries across *all continents except Antarctica*,

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- the rate of *new cases outside of China* has *outpaced* the rate in China *(more than 17000).*

  (mainly among travelers from China and who had contact with those travelers)

- ongoing local transmission outside China, including South Korea, Italy, Iran, Germany, France, Japan, and *travelers from those countries.*

Transmission

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OUTBREAK IN *Wuhan* ,CHINA

- an initial **association with a seafood market** where most patients had worked or visited (which was subsequently closed for disinfection)

- The seafood market also **sold live rabbits, snakes, and other animals**.

However later, most laboratory-confirmed cases had no contact with this market,

Transmission

- Understanding transmission risk is incomplete.
- Mainly Via:
  - respiratory droplets (resembling influenza).
  - airborne precautions.
- as the outbreak progressed, human-to-human spread became the main mode of transmission.
- COVID-19 virus RNA has been detected in blood and stool specimens, (although not known whether they contain infectious virus).

Asymptomatic??

- Detection of viral RNA -from respiratory specimens- of patients with exposure but no symptoms has been reported,

- and transmission from asymptomatic individuals (or within incubation period) has been described.
- Several serologic screening tests are under development *(to detect asymptomatic infections).*

Virology

- 2019-nCoV is a **betacoronavirus**,
- in the same subgenus as the (SARS) virus, but in a different clade.
- has close similarity to ***bat coronaviruses***,
- **SARS-CoV-2 shared almost 80% of the genome with SARS-CoV.**
- it is likely that **bats** are the primary source,

but (*transmitted directly from bats* or *through an intermediate host* is unknown).

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- HCoV-19, SARS-CoV and MERS-CoV, belong to *Beta-coronovirus* genus,
- enveloped,
- positive-stranded RNA viruses with approximately 30,000 nucleotides.
- Angiotensin I converting enzyme 2 (ACE2) is the receptor that engages the Spike surface glycoprotein of SARS-CoV and HCoV-19.
- ACE2 is expressed in many organs, including the lung, heart, kidney, and intestine.

VIROLOGY

- Coronaviruses are from **Nidovirales** family, *viruses that replicate using a nested set of mRNAs ("nido-" for "nest").*

- subfamily is further classified into four genera:

human coronaviruses

avian coronaviruses

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- **The human coronaviruses** (HCoVs) are in two of these genera:
  - alpha coronaviruses :
    - (HCoV-229E and HCoV-NL63)
  - beta coronaviruses :
    1. HCoV-HKU1,
    2. HCoV-OC43,
    3. Middle East respiratory syndrome coronavirus [MERS-CoV],
    4. severe acute respiratory syndrome coronavirus [SARS-CoV]

- The gamma & delta *coronavirus* are **avian coronaviruses**, (gamma cause respiratory &reproductive tract disease in chickens, and delta found in songbirds).

So..

- Seven type of CoVs identified to cause human disease .
- The two highly pathogenic viruses, SARS-CoV and MERS-CoV, cause severe respiratory syndrome in humans.
- The other four human CoVs (HCoV-NL63, HCoV-229E, HCoV-OC43 and HKU1) induce only mild upper respiratory diseases.
- The latest one is SARS-CoV-2.

- clinical drugs and therapies for treating SARS may be used as a reference for COVID-19 treatment.

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CLINICAL FEATURES

Incubation period:

- **5-14** days following exposure.

Clinical presentation:

- very similar to winter influenza
- **Pneumonia** is the most frequent serious manifestation of infection,
- Fever(99%), dry cough(59%), dyspnea(31%), myalgias(35%)
- bilateral infiltrates on chest imaging (**bilateral patchy shadows** or **ground-glass opacities** on CT).
- Most infections are not severe, although many patients have had critical illness.
- Some patient developed ARDS(20%), and mechanical ventilation was implemented(12%)
- gastrointestinal symptoms (nausea & diarrhea)_uncommon.

disease severity

- a report from China (44,500 confirmed infections):
- 81% were mild (no or mild pneumonia),
- 14% were severe (eg, with dyspnea, hypoxia, or >50% lung involvement on imaging within 24 to 48 hours),
- 5% were critical (eg, with respiratory failure, shock, or multiorgan dysfunction).
- The overall case-fatality rate was 2.3 percent; no deaths were reported among noncritical cases

COVID-19 can be classified into light, normal, severe, and critical types based on the severity of the disease :

- (1) Mild cases—clinical symptoms were mild, and no pneumonia was found on the chest-CT.
- (2) normal cases—fever, respiratory symptoms, and patients found to have imaging manifestations of pneumonia;
- (3) severe cases—one of the following three conditions: Respiratory distress, respiratory rate ≥ 30 times / min (in resting state, refers to oxygen saturation ≤ 93 (PaO2)/(FiO2) ≤300 mmHg.
- (4) critical cases—one of the following three conditions: Respiratory failure and need for mechanical ventilation, shock, or associated failure of other organs requiring the (ICU).

Fatality??

- According to (WHO), the case-fatality rate ranged from 2 to 4 % in Wuhan and 0.7% in the rest of China.
- Most of the fatal cases occurred in patients with advanced age or underlying medical comorbidities.

recovery time

- around two weeks for mild infections
- 3-6 weeks for severe disease

Laboratories

- WBC count can vary. Leukopenia, leukocytosis, and lymphopenia (most common).
- Elevated aminotransferase levels.
- normal serum procalcitonin (viral pneumonia); but may elevate in (ICU) patient.
- High d-dimer level & severe lymphopenia, **associated with mortality.**

Radiologic findings

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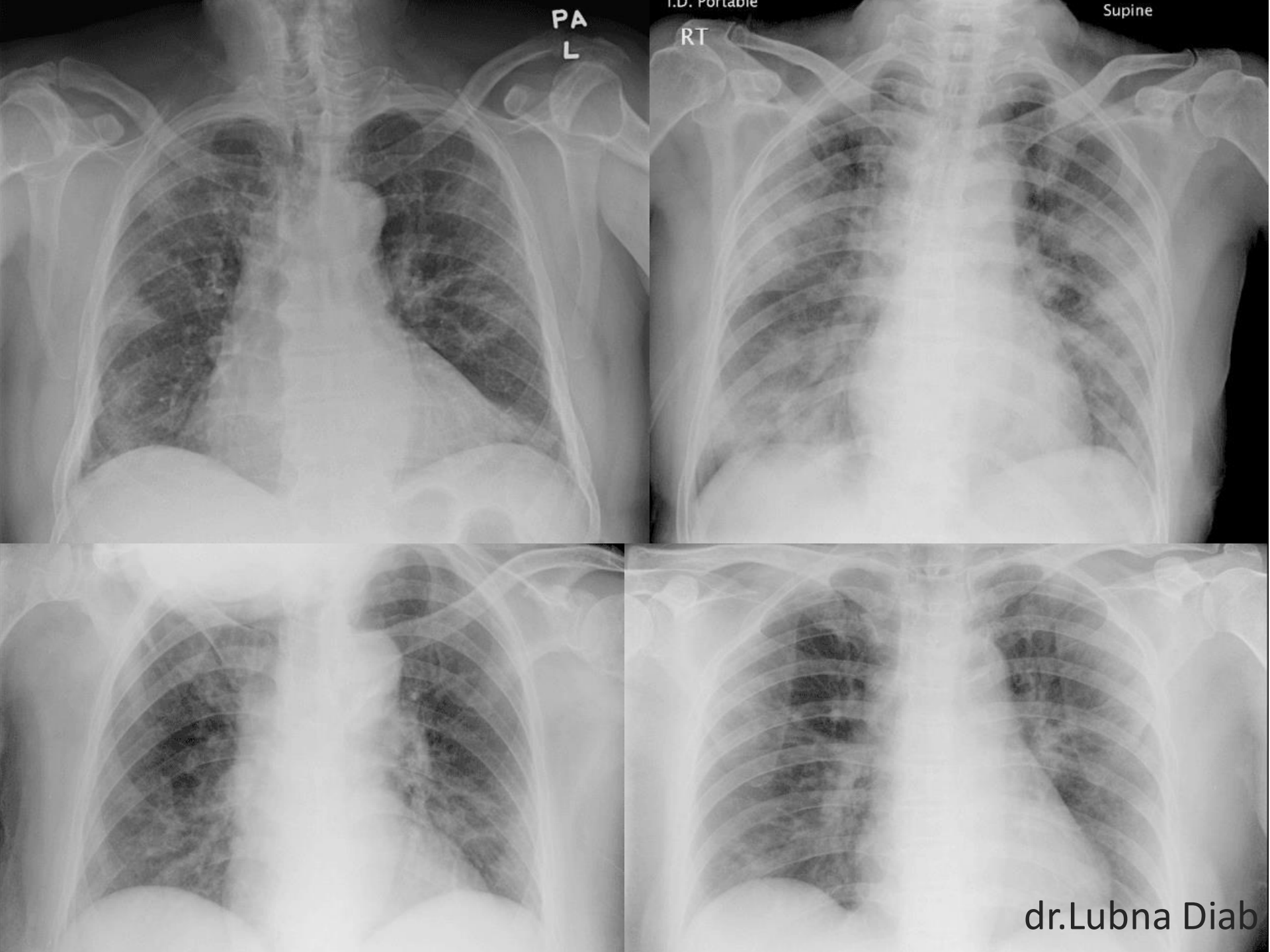
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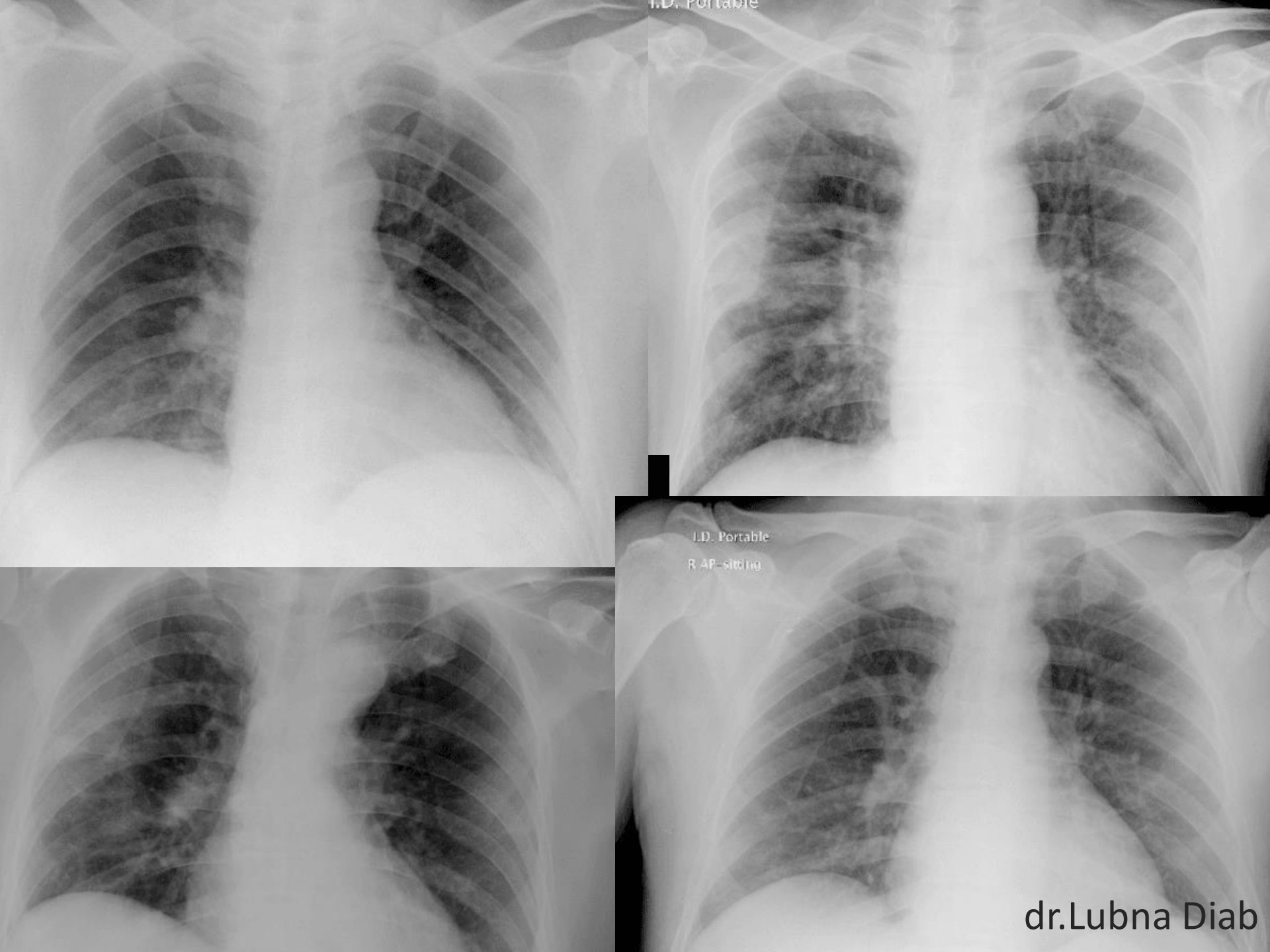

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Radiologic findings:

CXR

- CXR findings are non-specific
- Findings in common:
  - Bilateral air-space opacities/ infiltrates
  - No pleural effusion

- Chest-CT: bilateral, peripheral, lower lobes.
- Ground glass opacification with or without consolidative abnormalities (viral pneumonia).

Chest-CT

The Key +ve CT Findings :

1. Ground-glass opacities (100%)
2. Involvement of **multiple lobes** (100%)
3. Subpleural or **peripheral** distribution (often central-sparing) (100%)
4. Consolidations (77.8%)
5. Septal thickening (55.6%)
6. Bronchial dilation and wall thickening (55.6%)

The Important –ve CT Findings :

1. Pleural effusion (0%)
2. Lymphadenopathy (0%)
3. Lung nodule (0%)
4. Specific zonal predominance (variable, upper/basal/diffuse distribution each 33.3%)

Why imaging is important

- There have been reports of cases with serial –ve PCR test results ending up +ve later
- Typical CT findings in combination of suspicious clinical findings probably warrant management as potential carriers even if PCR tests show –ve results
- Community outbreak is inevitable
- Some outpatient/ routine scans may be performed for other indications
- If typical nCoV CT findings are seen, these reports require early attention and possible further investigations ASAP

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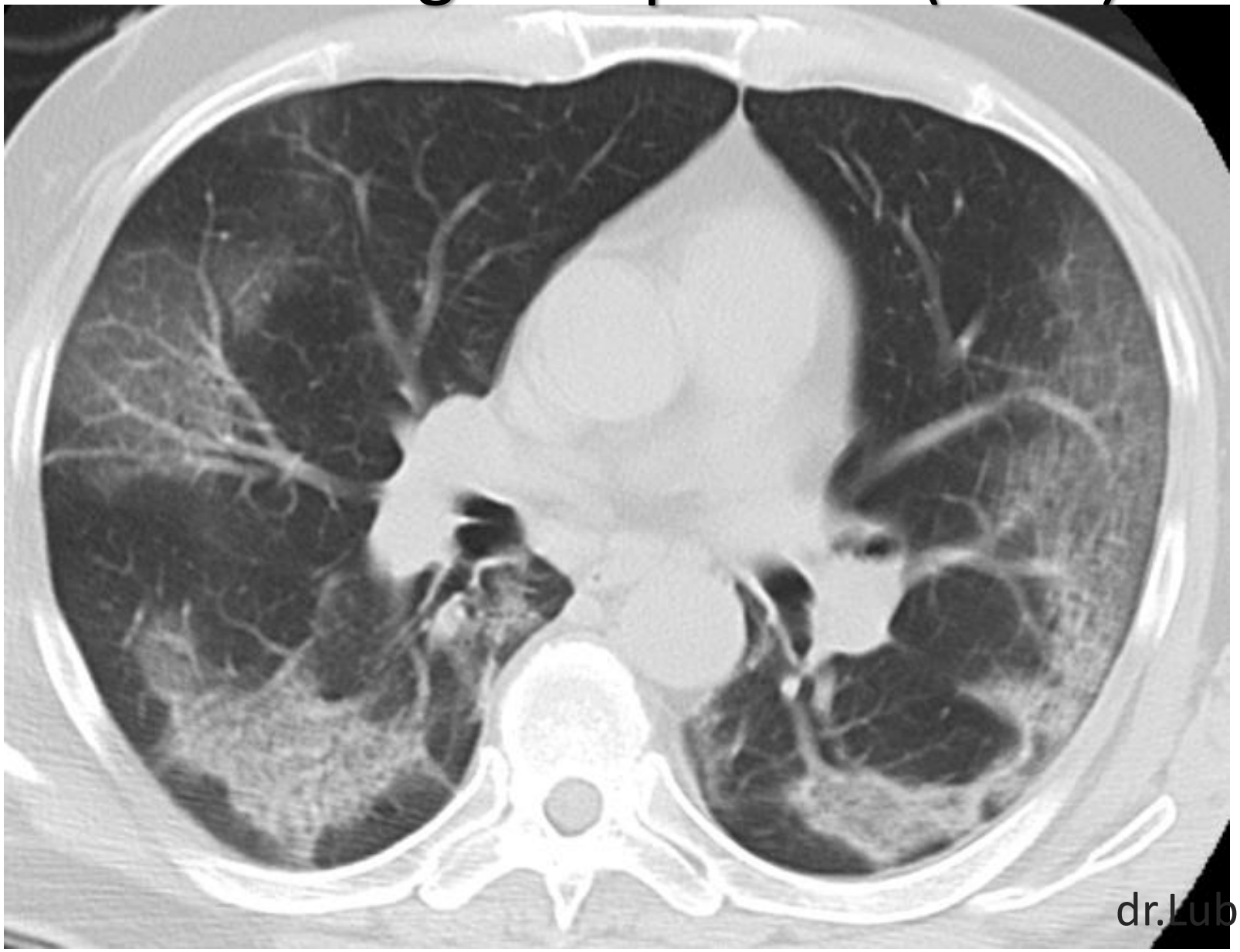
Patient demographics and imaging features	
Total scans included	9
Age	63.7 (39-75)
Sex	
Male	6
Female	3
Days from diagnosis to CT	2.8 (39-75)
CT technique	
HRCT	7
Conventional CT	2
CT findings	
GGO	9 (100%)
All lobes involvement	8 (88.9%)
Upper lobes sparing	1
Peripheral subpleural distribution	9 (100%)
Zonal predominance	
Upper	3 (33.3%)
Basal	3 (33.3%)
Diffuse	3 (33.3%)
Interlobular/ intralobular septal thickening	5 (55.6%)
Consolidation	7 (77.8%)
Bronchial wall thickening or dilatation	5 (55.6%)
Centrilobular nodule	0 (0%)
Pleural effusion	0 (0%)
Lymph node enlargement	0 (0%)

Age and days expressed in means with range in brackets
CT findings expressed in case number with proportions in brackets

Ground-glass opacities (GGO)



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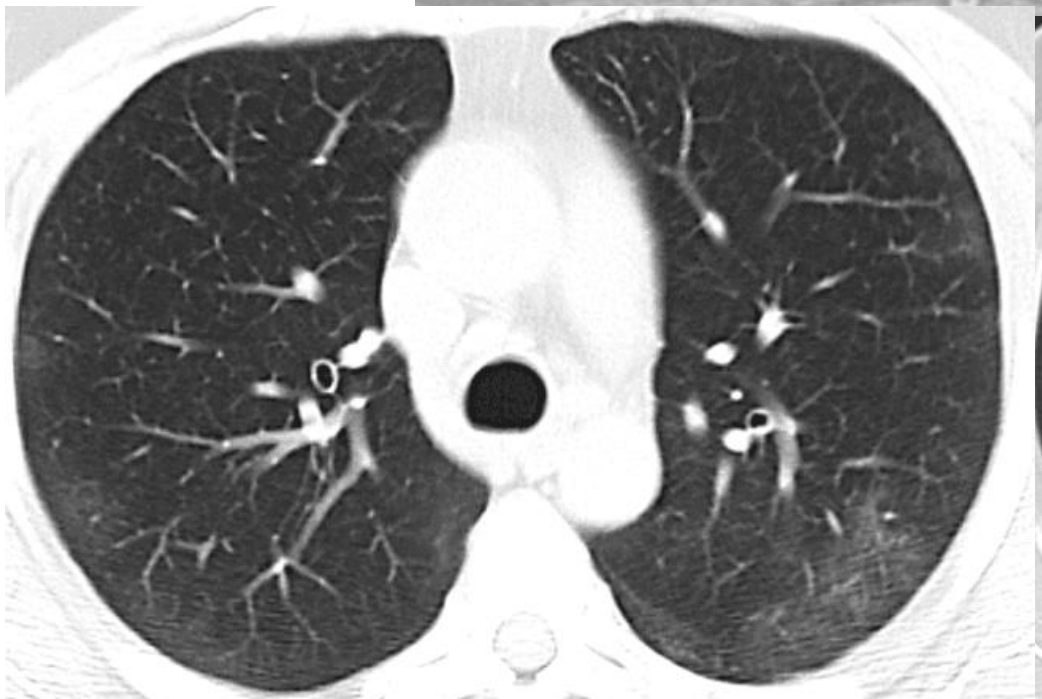

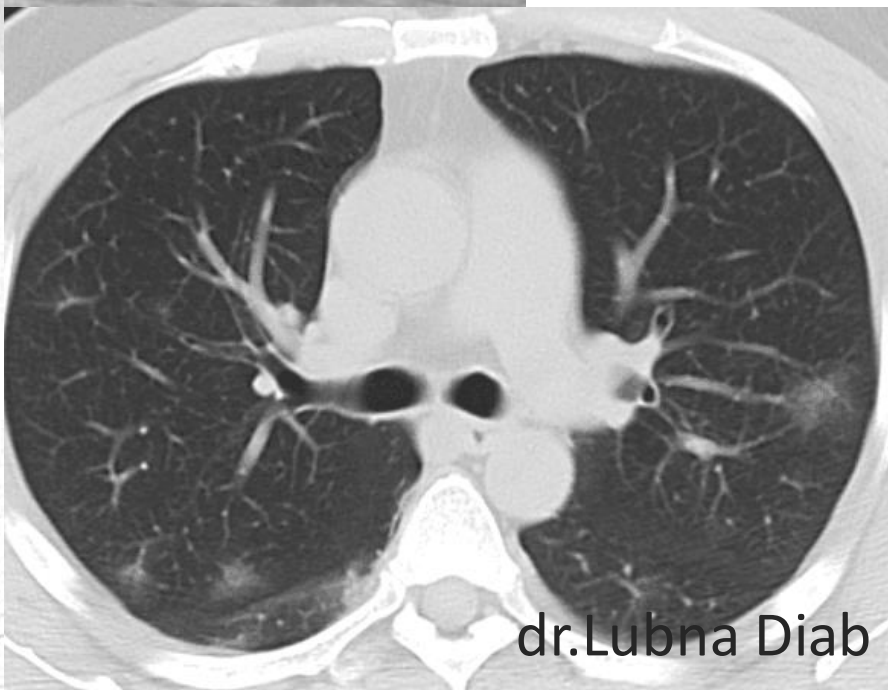

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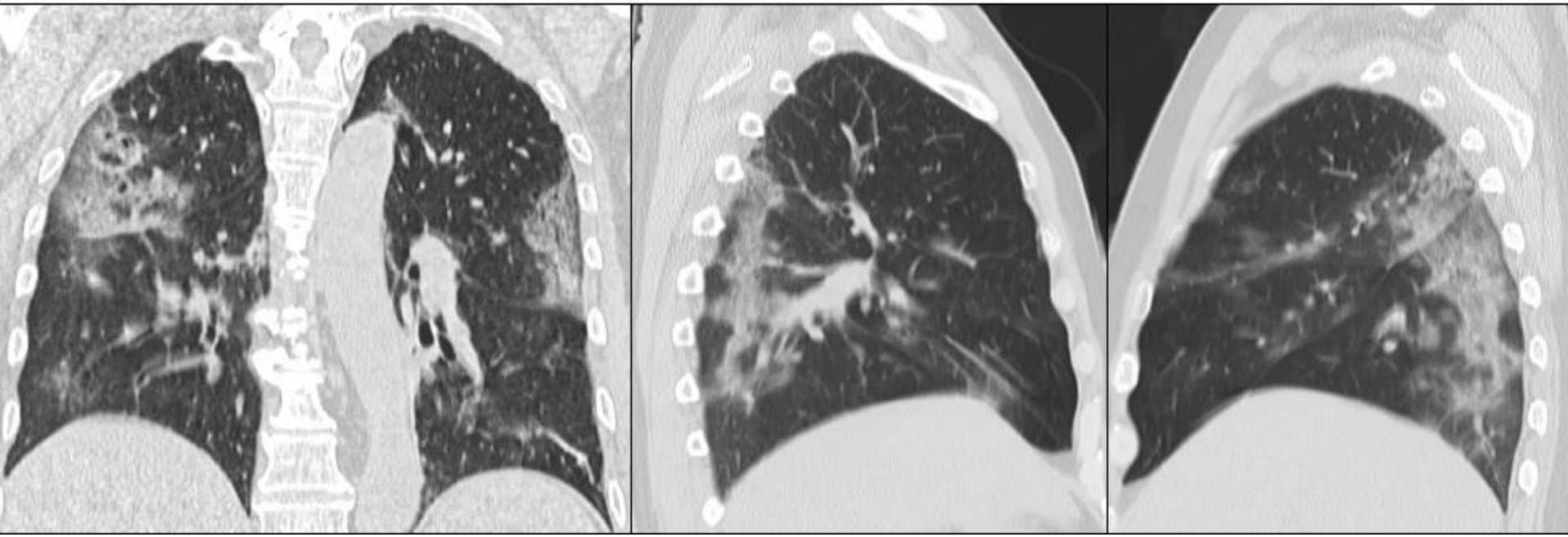
Involvement of multiple lobes

- Often more than one lobes (if not all) show GGO +/- consolidations



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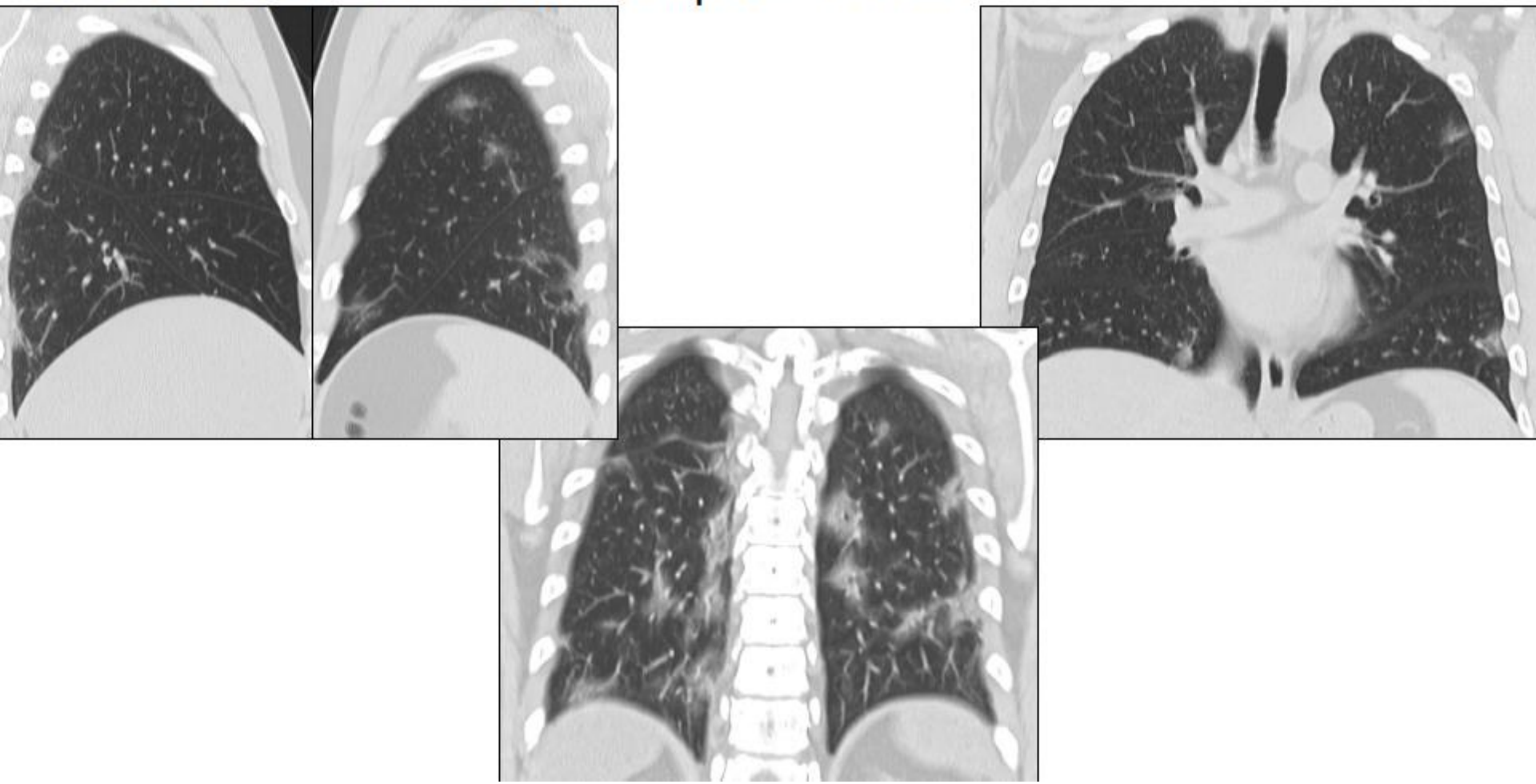
Involvement of multiple lobes



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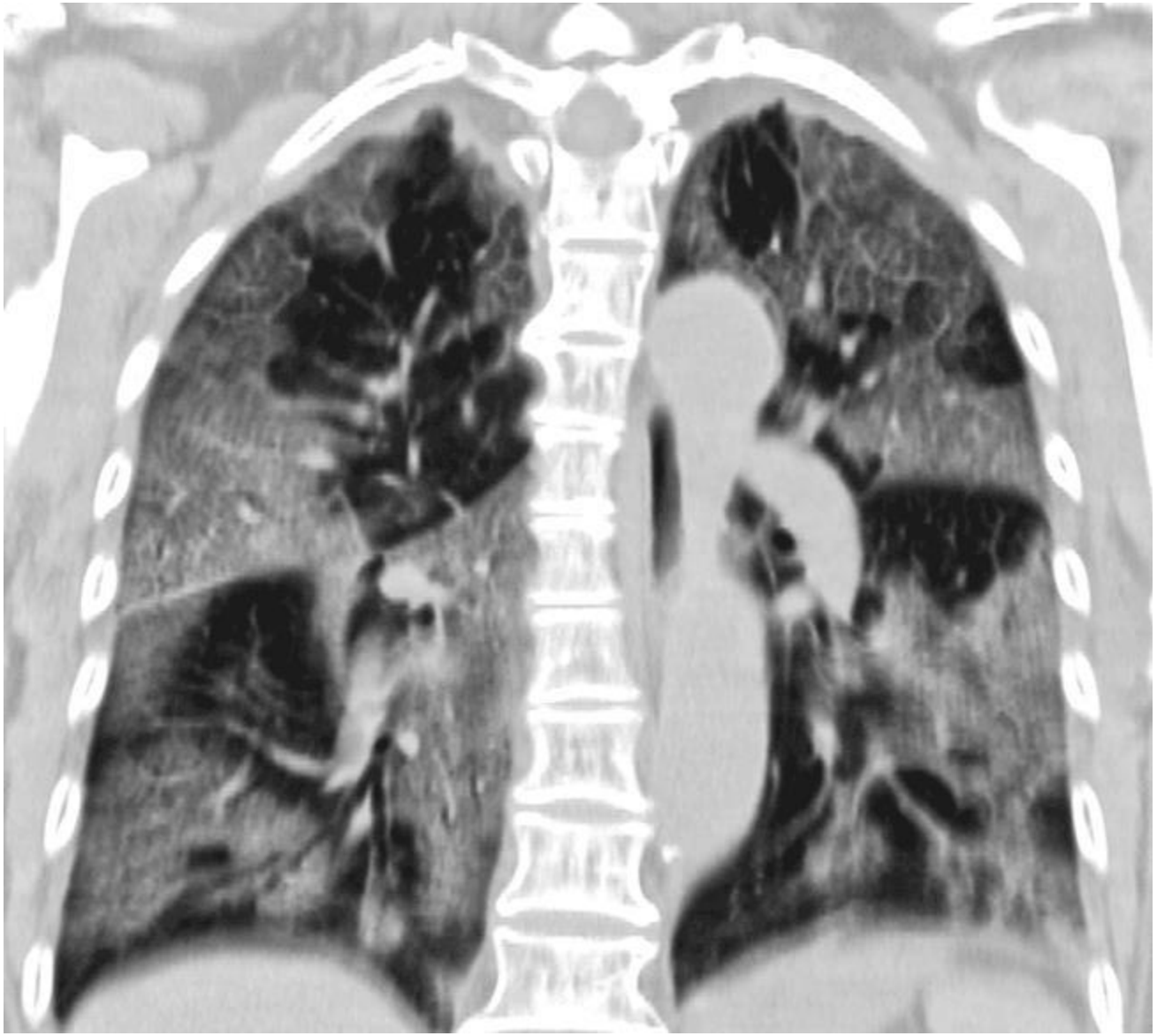

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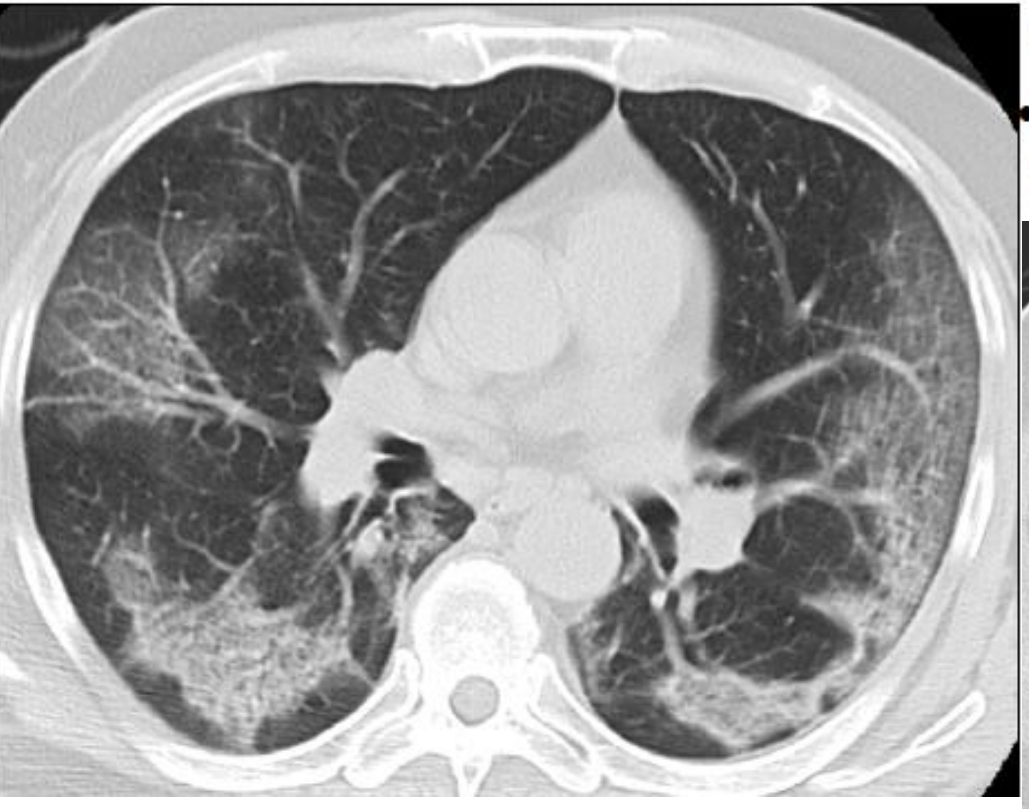
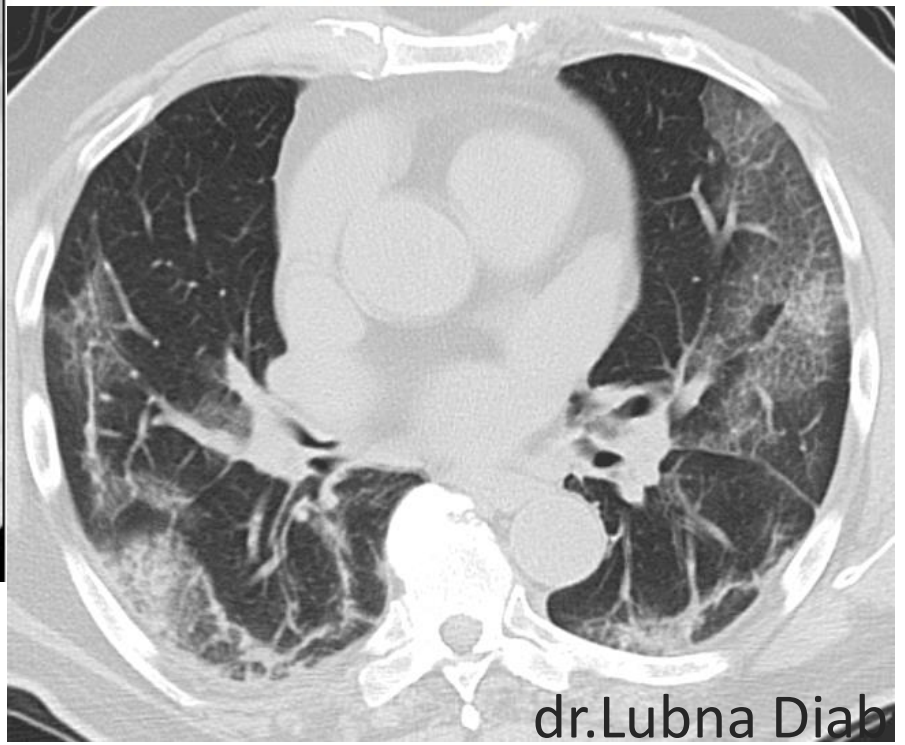
Peripheral/ subpleural distribution



- Peripheral/ subpleural regions are almost invariably involved
- Central regions are often spared/ or involved in a later stage



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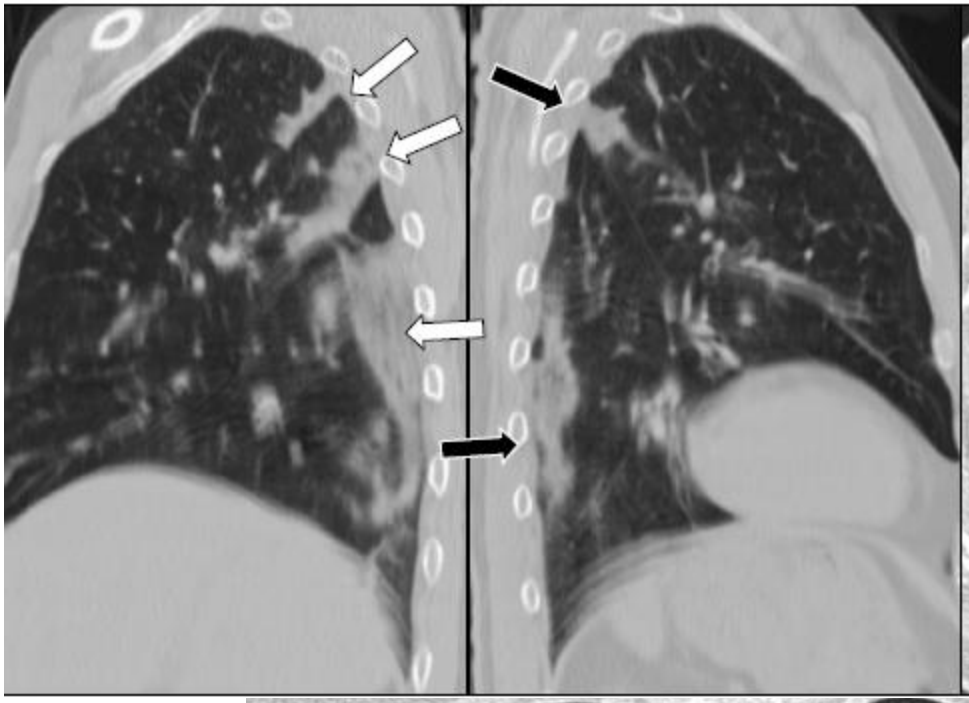
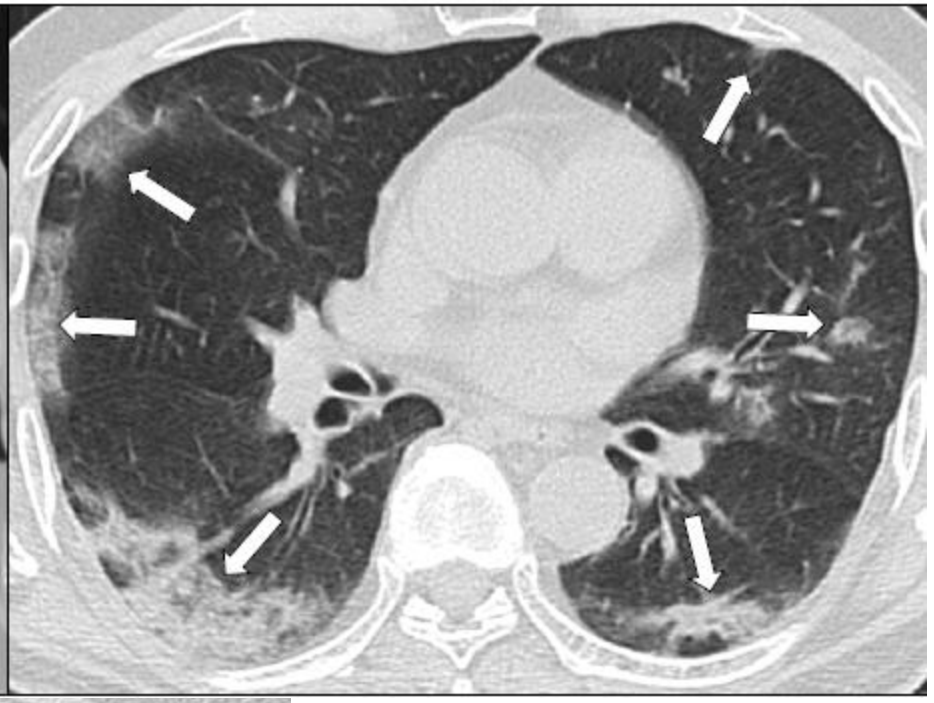
Peripheral/ subpleural distribution





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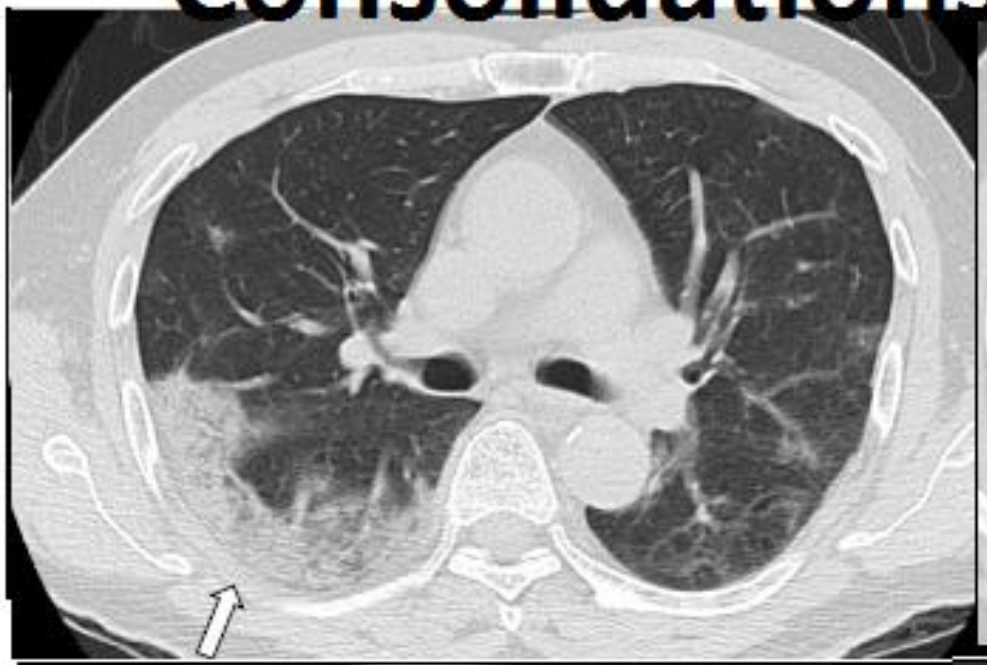
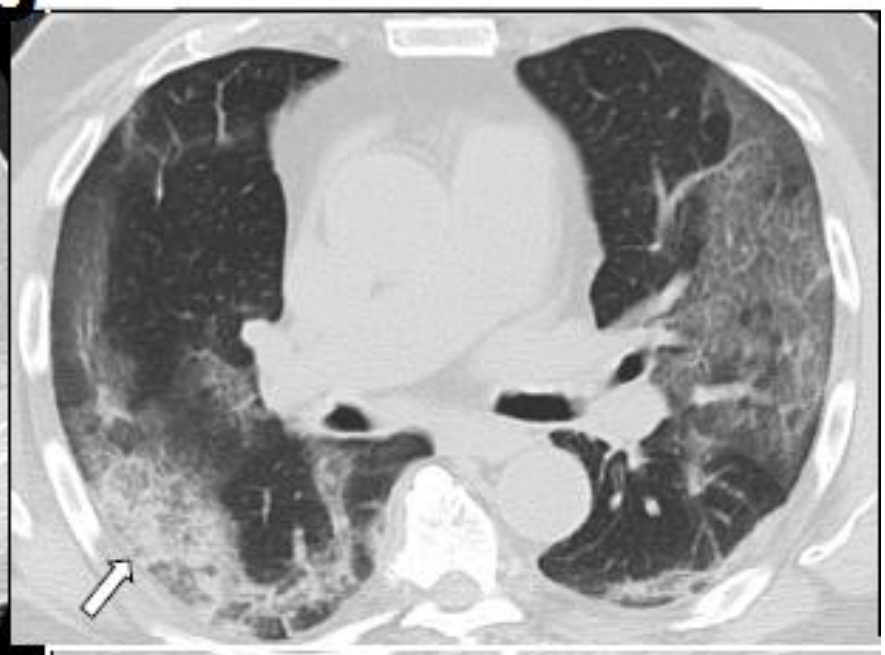
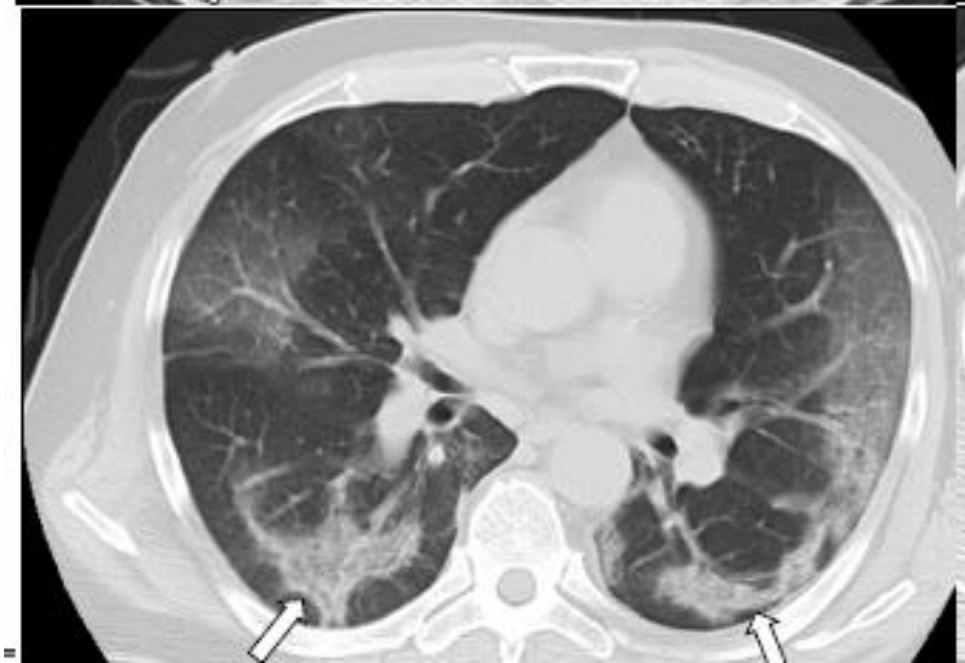
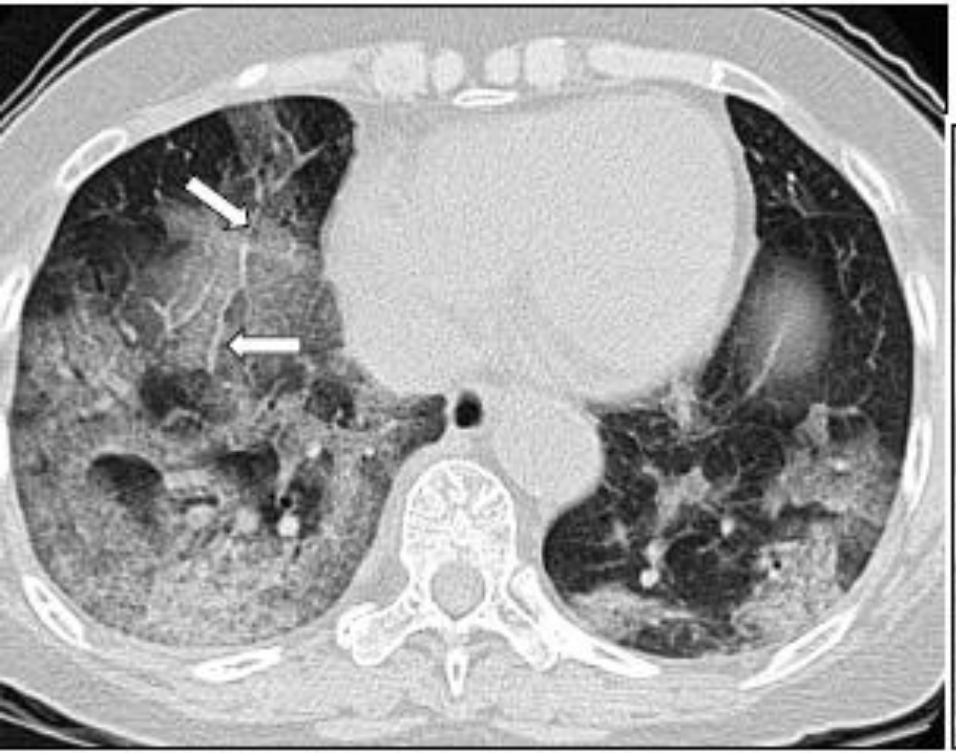
Consolidations

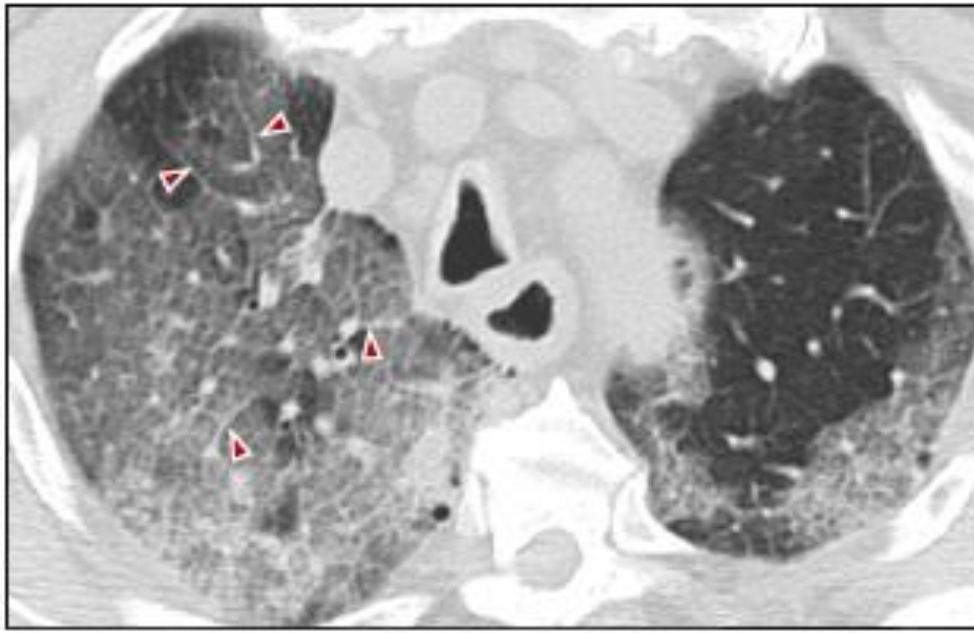








Septal thickening



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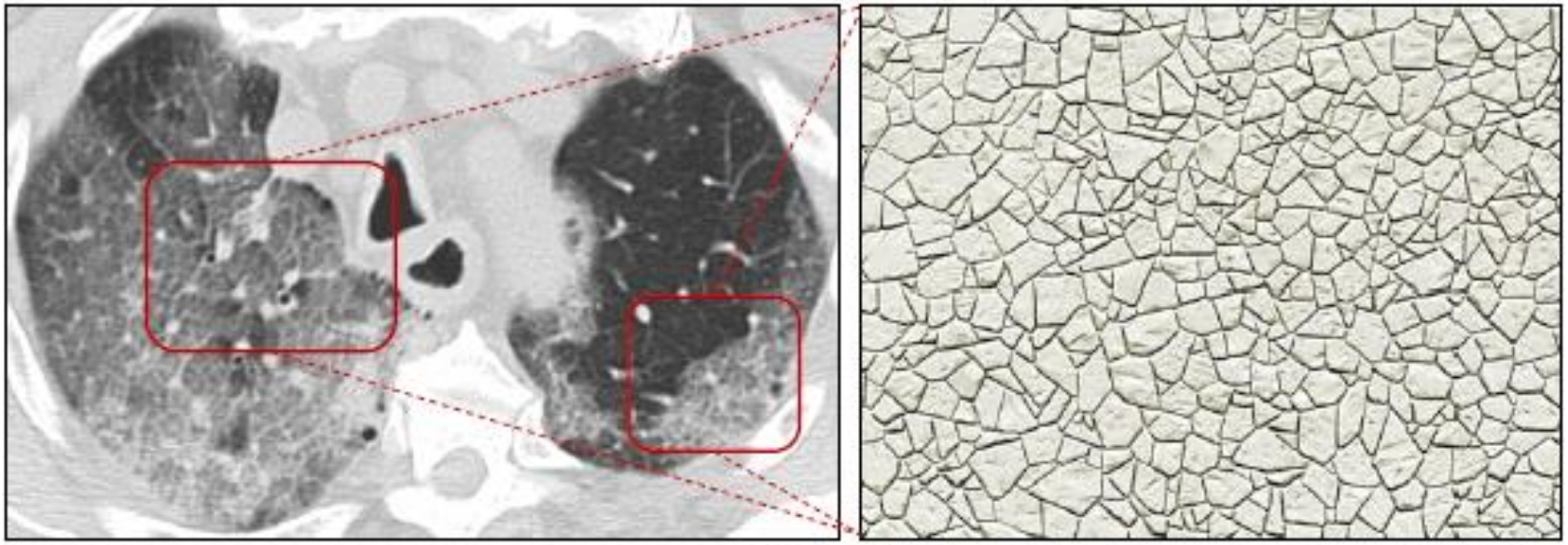
Septal thickening + GGO → crazy-paving pattern



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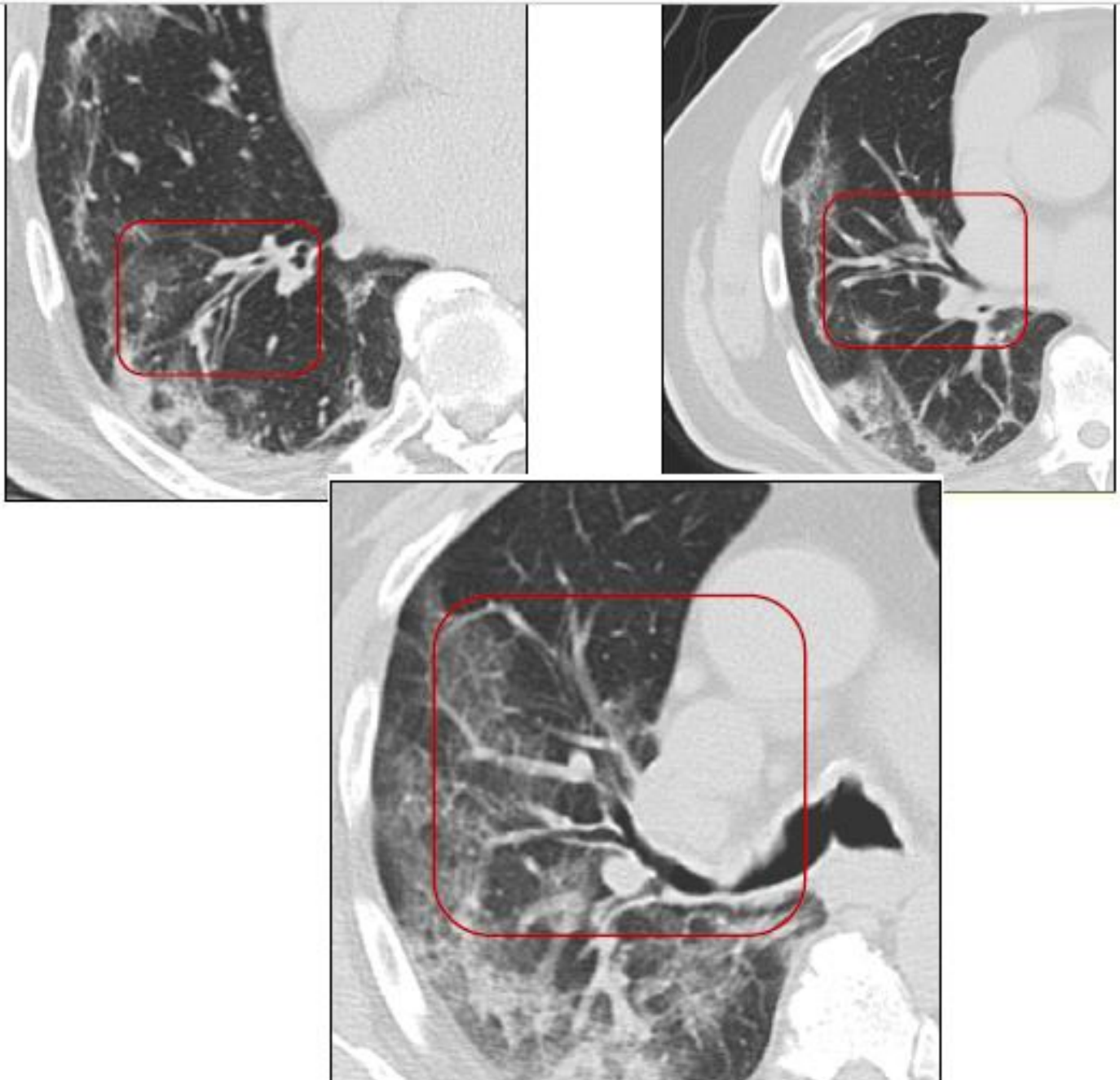
Bronchial dilatation + wall thickening



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EVALUATION AND DIAGNOSIS

1. early recognition of suspect cases,
2. immediate isolation,
3. institution of infection control measures.
4. testing for SARS-CoV-2 (the virus that causes COVID-19), in addition to testing for other respiratory pathogens.

Clinical suspicion

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CDC clinical criteria for patients under investigation for COVID-19

Clinical features		Epidemiologic risk
Fever* **or** signs/symptoms of lower respiratory illness (eg, cough or shortness of breath)	**PLUS**	Any person, including health care workers, who has had close contact[¶] with a laboratory-confirmed[Δ◊] COVID-19 patient within 14 days of symptom onset
Fever* **and** signs/symptoms of lower respiratory illness (eg, cough or shortness of breath)	**PLUS**	A history of travel from Hubei Province, China[§] within 14 days of symptom onset
Fever* **and** signs/symptoms of lower respiratory illness (eg, cough or shortness of breath) **requiring hospitalization**[◊]	**PLUS**	A history of travel from mainland China[§] within 14 days of symptom onset

CASE DEFINITIONS

- **Suspect case**

A. A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease (e.g., cough, shortness of breath), AND with no other etiology that fully explains the clinical presentation AND a history of travel to or residence in a country/area or territory reporting local transmission of COVID-19 disease during the 14 days prior to symptom onset.

- OR

B. A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case in the last 14 days prior to onset of symptoms;

- OR

C. A patient with severe acute respiratory infection (fever and at least one sign/symptom of respiratory disease (e.g., cough, shortness breath) AND requiring hospitalization AND with no other etiology that fully explains the clinical presentation.

- **Probable case**
- A suspect case for whom testing for COVID-19 is inconclusive)result of the test reported by the laboratory)
- **Confirmed case**
- A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

CDC definition of close contact (any of the following):

- Being within 6 feet (2 meters) of a patient with COVID-19 *for a prolonged period of time while not wearing recommended personal protective equipment* **(eg, gowns, gloves, NIOSH-certified disposable N95 respirator, eye protection);**

  *(**close contact** : caring for, living with, visiting, or sharing a health care waiting area or room with a patient with COVID-19.)*

- direct contact with **infectious secretions** of a patient with COVID-19 **(eg, being coughed on) while not wearing recommended personal protective equipment.**

- For severely ill patients (severe lower respiratory tract illness), *and another etiology* cannot be identified *:*

Test for COVID-19 , even if no clear exposure.
(uncertain or no known travel or exposure)

Confirm diagnosis

- collection of specimens (*under airborne precautions)* from:
  - the upper respiratory tract (nasopharyngeal and oropharyngeal swab)
  - lower respiratory tract (sputum, tracheal aspirate, or bronchoalveolar lavage).
  - Serum, urine, stool can also be collected.

PCR

reverse-transcription polymerase chain reaction (RT-PCR)

For safety reasons, **specimens should not go viral culture.**

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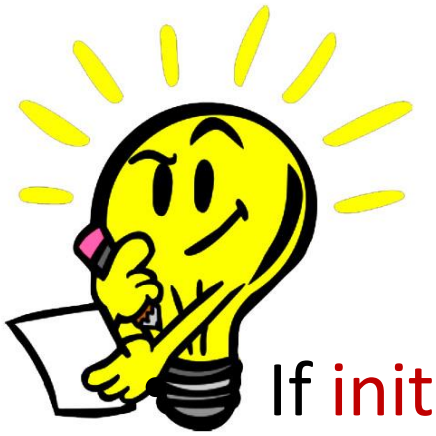

If initial PCR test is negative but the suspicion for COVID-19 remains,

resampling and testing from multiple respiratory tract sites (WHO).

testing for other pathogens (respiratory viral pathogen) is important at the same time.

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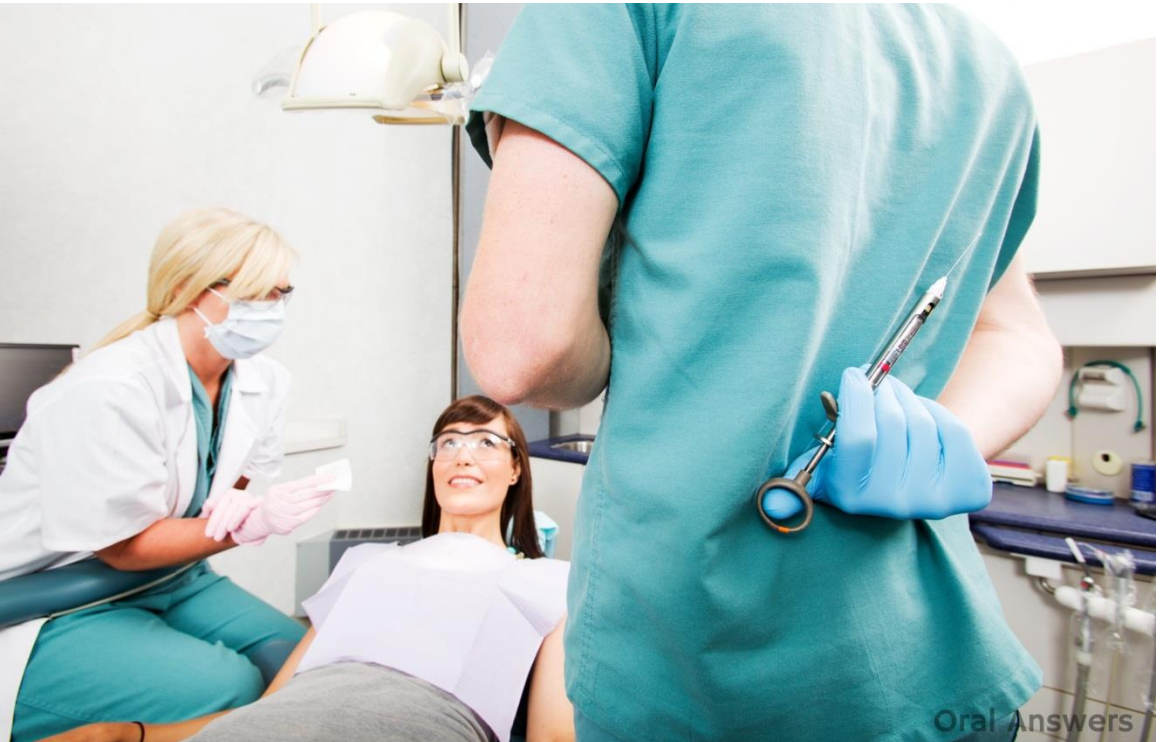
MANAGEMENT



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Hospital care

- Patient with suspected infection in the community or hospital should :
  - wear a mask (to contain their respiratory secretions).
  - Immediatilly isolate in a negative pressure room if available or a private room with the door closed,
  - any personnel entering the room should wear the appropriate personal protection equipment.
  - supportive care for sepsis and ARDS if evolved.

glucocorticoids

- WHO and CDC **recommended not be used in COVID-19 pneumonia, unless there are other indications** (eg, exacerbation of COPD).
  1. increased risk for mortality in patients with influenza
  2. delayed viral clearance in patients with (MERS-CoV).

- *widely used in management of (SARS),*

(no benefit, adverse short- and long-term harm)

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antiviral treatment

Remdesivir (for moderate or severe COVID-19)

- a novel nucleotide analogue that has activity against SARSCoV-2 *in vitro*, and related coronaviruses (SARS and MERS-CoV) both *in vitro* and *in animal studies*.

- *Any clinical impact of remdesivir on COVID-19 remains unknown*

lopinavir-ritonavir: (combined protease inhibitor)

- Used for the treatment of HIV infection,
- Has anti coronavirus activity in vitro (for SARS-CoV, MERS-CoV), in animal studies (MERS-CoV)
- its efficacy in COVID-19 is unclear (effective in some case reports),
- being evaluated in larger randomized trials.

Home management

- for patients with **mild infection**
- Management should focus on:
  - prevention of transmission to others (isolation).
  - monitoring for clinical deterioration, which should prompt hospitalization

PREVENTION

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Types of precautions for infection control

Type of precaution	Selected patients	Major specifications
Standard	All patients	Perform hand hygiene before and after every patient contact.* Gloves, gowns, eye protection as required. Safe disposal or cleaning of instruments and linen. Cough etiquette: Patients and visitors should cover their nose or mouth when coughing, promptly dispose used tissues, and practice hand hygiene after contact with respiratory secretions.
Contact[¶]	Colonization of any bodily site with multidrug-resistant bacteria (MRSA, VRE, drug-resistant gram-negative organisms) Enteric infections (Norovirus, *Clostridioides* [formerly *Clostridium*] *difficile**, *Escherichia coli* O157:H7) Viral infections (HSV, VZV, RSV[Δ], parainfluenza, enterovirus, rhinovirus[◊], certain coronaviruses [eg, 2019 nCoV, MERS-CoV]) Scabies Impetigo Noncontained abcesses or decubitus ulcers (especially for *Staphylococcus aureus* and group A *Streptococcus*)[§]	**In addition to standard precautions:** Private room preferred; cohorting allowed if necessary. Gloves required upon entering room. Change gloves after contact with contaminated secretions. Gown required if clothing may come into contact with the patient or environmental surfaces or if the patient has diarrhea. Minimize risk of environmental contamination during patient transport (eg, patient can be placed in a gown). Noncritical items should be dedicated to use for a single patient if possible.

Droplet[¶]	**Known or suspected:** *Neisseria meningitidis* *Haemophilus influenzae* type B *Mycoplasma pneumoniae* *Bordetella pertussis* Group A *Streptococcus*[§] Diphtheria Pneumonic plague Influenza Rubella Mumps Adenovirus Parvovirus B19 Rhinovirus[◊]	**In addition to standard precautions:** Private room preferred; cohorting allowed if necessary. Wear a mask when within three feet of the patient. Mask the patient during transport. Cough etiquette: Patients and visitors should cover their nose or mouth when coughing, promptly dispose used tissues, and practice hand hygiene after contact with respiratory secretions.
Airborne	**Known or suspected:** Tuberculosis Varicella Measles Smallpox Certain coronaviruses[¥] Ebola[‡]	**In addition to standard precautions:** Place the patient in an AIIR (a monitored negative pressure room with at least 6 to 12 air exchanges per hour). Room exhaust must be appropriately discharged outdoors or passed through a HEPA filter before recirculation within the hospital. A certified respirator must be worn when entering the room of a patient with diagnosed or suspected tuberculosis. Susceptible individuals should not enter the room of patients with confirmed or suspected measles or chickenpox. Transport of the patient should be minimized; the patient should be masked if transport within the hospital is unavoidable. Cough etiquette: Patients and visitors should cover their nose or mouth when coughing, promptly dispose used tissues, and practice hand hygiene after contact with respiratory secretions.

Wearing level-D protective clothing can protect medical staff from infection of respiratory viruses.

Pregnant women

- no laboratory evidence of transmission of the virus to the neonate or through breast milk.
- **two neonatal cases of infection have been documented .**
  - The first diagnosed at day 17 of life after close contact with the infant's mother & a maternity matron who were both.
  - The other case diagnosed 36 hours after birth; source and time of transmission were unclear.
- The approach is similar to that in nonpregnant, but more vulnerable to developing severe illness.

Pregnant women

- infants born to mothers with confirmed COVID-19 should be considered a patient under investigation, isolated and evaluated.

- droplet transmission could occur through close contact during breastfeeding.
- So mothers should (hand hygiene and use a facemask) or consider another individual to feed the infant.

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Pregnant women with SARS-CoV-2 exposure

- Travelled to an affected country within the previous 14 days
- Close contact with a confirmed case of COVID-19 (ie, <1 metre for >15 minutes, living together, direct contact with body fluids)

CLINICAL EXAMINATION + RT-PCR (SARS-CoV-2) on deep nasopharyngeal and pharyngeal samples

ASYMPTOMATIC

No isolation room

MONITORING at home

(T° + Respiratory symptoms)

SARS-CoV-2 NEGATIVE

Stop monitoring

SARS-CoV-2 POSITIVE*

Isolation at home for 14 days

If delivery:
- No breastfeeding
- Mother isolated from newborn until viral shedding clears

US Fetal surveillance : Growth + Doppler / 2 weeks

SYMPTOMATIC

Fever >38°C **AND** respiratory symptoms

MONITORING AT HOSPITAL
- Isolated room with negative pressure (IRNP)
- Protective gear* for visitors / health personnel
- Delivery and neonatal procedure equipment on site

SARS-CoV-2 NEGATIVE

Isolation at home 14 days
+ Clinical self-monitoring

If symptoms persist:
RETEST (possible false negative)

SARS-CoV-2 POSITIVE*

HOSPITALISATION IN A TERTIARY CARE CENTER

Maternal surveillance:
+ T°, HR, BP, RR (3-4x/day)
+ Chest imaging (high resolution CT-scan or X-ray)

Fetal:
+ FHR (1x/day)
+ Fetal maturation by Betamethasone injection depending on maternal status (until 34 to 37 WG)
+ IV Antibiotics treatment (depending local protocol)

RECOVERY

INTENSIVE CARE UNIT ADMISSION (Quick SOFA Score)
More than 1 following criteria:
- Systolic blood pressure <100mmHg
- Respiratory rate >22
- Glasgow conscious score <15

SEVERE FAILURE CRITERIA (consider cesarean delivery)
- SEPTIC SHOCK
- ACUTE ORGAN FAILURE
- FETAL DISTRESS

DELIVERY

Before 24 WG (fetal viability)
- in case of severe maternal illness, consider TOP (if legal)

After 24 WG
- On site / IRNP
- Vaginal delivery (induction of labor ± instrumental delivery when possible unless severe failure criteria)
- Early clamping of the umbilical cord
- Early cleaning of the newborn
- Newborn monitoring in IRNP
- SARS-CoV-2 RT-PCR of the newborn
- No breastfeeding
- Mother isolated from newborn until viral shedding resolves

vaccine

- **on Jan. 26th, 2020**, **China CDC** started to develop the vaccine.

- **Afew days ago**, claims the first coronavirus vaccine could be in clinical use **in April** (not sure ??)

Thank you,

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