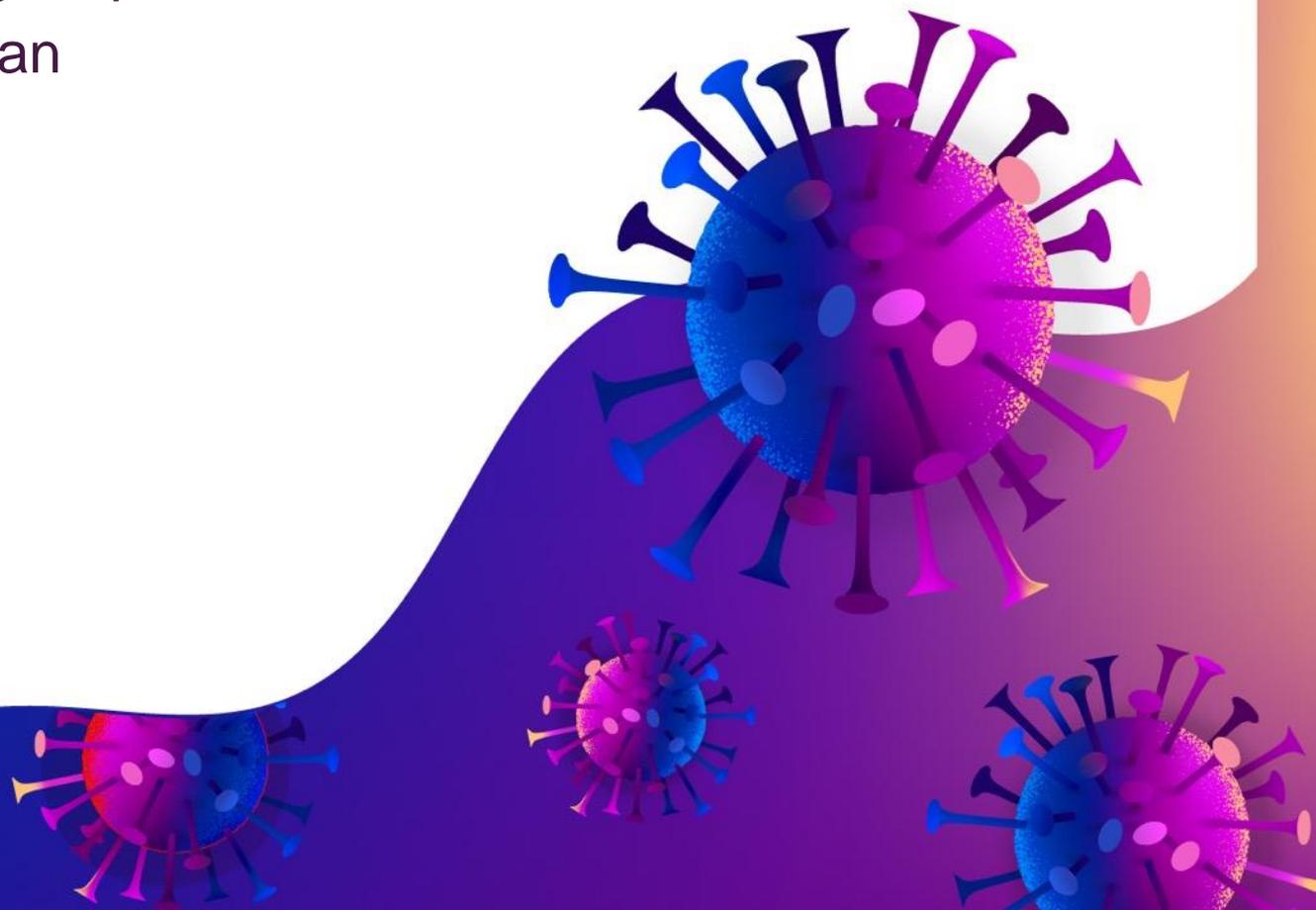




COVID-19 Patient Journey

Progression, Diagnosis, and Treatments in Development

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COVID-19 PATIENT JOURNEY

Together we advance

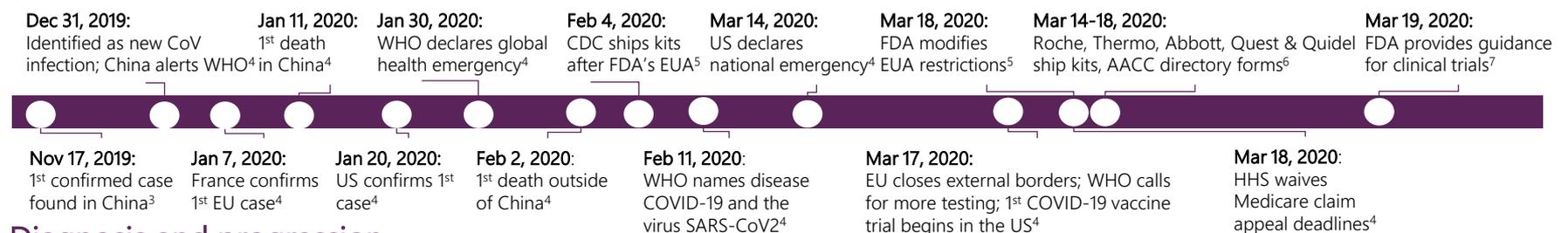
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Background and epidemiology

We developed this patient journey to help us all start to separate the signal from the noise. Coronaviruses (CoVs) are major pathogens that target the human respiratory system.¹ Previous outbreaks of CoVs in the last decade include the severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV, previously characterized as agents that are great public health threats.¹

In late December 2019, a cluster of critically ill patients, epidemiologically linked to a seafood and wet animal wholesale market in Wuhan, Hubei Province, China,^{1,2} were admitted to hospitals with an initial diagnosis of pneumonia of unknown cause. The most common symptoms were fever, cough, and fatigue.

The clinical features, e.g. chest scans indicating pneumonia, were similar to infection from other CoVs. Genomic sequence analysis of COVID-19 showed >88% of the same identity as two bat-derived severe acute respiratory syndrome (SARS)-like CoVs.¹ This evidence of bat-origin CoVs indicates that mammals were the link for transmission into humans.¹



Diagnosis and progression

Symptoms of COVID-19 disease present after an incubation period of approximately 5 days and are generally mild in young adults.⁸ Depending on patients' symptoms and risk factors, they may be triaged to either home monitoring, respiratory screening clinic, or the ER.

Most common symptoms: Fever, cough, and fatigue, which are considered mild.⁹

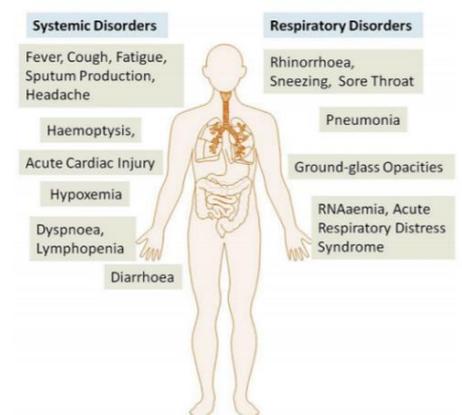
Emergency warning signs to indicate moderate to severe disease: Difficulty breathing, persistent chest pain or pressure, confusion, or bluish lips.¹⁰

Diagnostic testing: Upper respiratory tract specimens (nasopharyngeal swab) and lower respiratory tract specimens (bronchoalveolar lavage).¹¹

Recovery process: More than 80% of the population will experience mild symptoms and can stay home to recover without further testing.¹² People with pre-existing medical conditions (high blood pressure, heart/lung disease, cancer, diabetes) are at risk for developing serious illness. Critically ill patients will develop pneumonia and need to be admitted to the hospital, isolated, and provided antibiotics, antivirals, steroids, and ventilation. Most will recover with proper care.

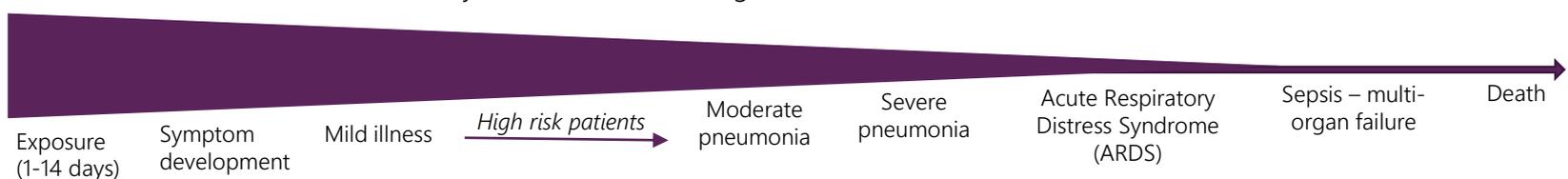
Complications and mortality rate:

- In Northern Italy less than 0.1% deaths were observed for patients under 50.¹³
- A retrospective study of 191 COVID-19 adult critically-ill patients from Wuhan² revealed for high-risk critically ill patients, the period from the onset of COVID-19 symptoms to death had a median of 14 days¹⁴ and was dependent on the age of the patient and status of the patient's immune system. Common complications were respiratory failure/acute respiratory distress syndrome, sepsis/septic shock, and heart failure.^{2,11} Half of the non-survivors experienced a secondary infection, and ventilator-associated pneumonia occurred in 31% of the patients.²
- Another smaller study on 59 COVID-19 adult patients in China found that kidney dysfunction from the viral infection was common and may contribute to multi-organ failure and death.¹⁵



Systemic and respiratory disorders for COVID-19

Cell entry of coronaviruses depends on binding of the viral spike (S) proteins to the host's cellular ACE2 receptors and on S protein priming by the host cell serine proteases (TMPRSS2),¹⁶ both druggable targets. Early Type I Interferon (IFN-1) signaling or reduced inflammatory monocyte-macrophages (IMMs) result in mild disease.⁹



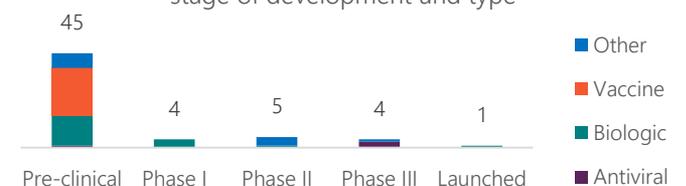
Diagnostics

The FDA recently changed their Emergency Use Authorization (EUA) rules,¹⁷ and currently Roche, Thermo, Abbott, Quest, and Quidel are shipping tests. The American Association of Clinical Chemistry (AACC) also has launched the COVID-19 Testing Directory, a new resource for healthcare professionals seeking access to clinical laboratory testing services for SARS-CoV-2. Molecular diagnostic tests still follow CDC protocols¹⁸ for the real-time RT-polymerase chain reaction (rRT-PCR) detection of the SARS-CoV-2 virus. Rapid diagnostics also are in development for IgM and IgG antibodies, and analysis of secondary predictors are currently underway, e.g. increased C-Reactive Protein (CRP) levels.¹⁸

Treatments in development

Today at least 60 drugs are in development globally,¹⁹ with one launched (Acentra, China). Most are early-stage (discovery and pre-clinical) and vaccines. Some repurposed drugs (camostat mesylate, chloroquine) suggest the rapid mobilization of global R&D. The high number of therapies in development since the first confirmed case points to an unprecedented urgency for intervention.

Pipeline of COVID-19 therapies by stage of development and type



Impact and next steps

There has been a large, global mobilization to solve the coronavirus pandemic and to maintain a functional healthcare system. Pharmaceutical companies and research groups have come together to share data and work together in diagnosing, screening, and treating patients.

DISCLAIMER: Please check with local city and state public health departments to coordinate local response; call your doctor if symptoms appear.

References

1. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun.* 2020 Feb 26:102433. doi: 10.1016/j.jaut.2020.102433. [Epub ahead of print]
2. Zhou F, Yu T, Du R et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020 Mar 11. pii: S0140-6736(20)30566-3. doi: 10.1016/S0140-6736(20)30566-3. [Epub ahead of print]
3. South China Morning Post. Coronavirus: China's first confirmed Covid-19 case traced back to November 17. Accessed March 21, 2020. <https://www.scmp.com/news/china/society/article/3074991/coronavirus-chinas-first-confirmed-covid-19-case-traced-back>.
4. RNZ. COVID-19 pandemic timeline. Accessed March 21, 2020. <https://shorthand.radionz.co.nz/coronavirus-timeline/index.html>.
5. AACC. How labs in the US are responding to COVID-19. Accessed March 19, 2020. <https://www.aacc.org/publications/cln/articles/2020/march/how-laboratories-in-the-us-are-responding-to-covid19>
6. Modern Healthcare. Commercial COVID-19 test developers race to get products out. Accessed March 21, 2020. <https://www.modernhealthcare.com/operations/commercial-covid-19-test-developers-race-get-products-out>.
7. FDA. FDA Guidance on conduct of clinical trials of medical products during COVID-19 pandemic. Accessed March 21, 2020. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-pandemic>.
8. Lauer SA, Grantz KH, Bi Q et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. *Ann Intern Med.* 2020 Mar 10. doi: 10.7326/M20-0504. [Epub ahead of print]
9. CDC. Symptoms of coronavirus disease 2019. Accessed March 21, 2020. <https://www.cdc.gov/coronavirus/2019-ncov/downloads/COVID19-symptoms.pdf>.
10. CDC. Coronavirus disease 2019 (COVID-19). Symptoms. Accessed March 21, 2020. <https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html>.
11. CDC. Coronavirus disease 2019 (COVID-19). Interim guidelines for collecting, handling, and testing clinical specimens from persons for coronavirus disease 2019 (COVID-19). Accessed March 21, 2020. <https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html>.
12. The New York Times. Most coronavirus cases are mild. That's good and bad news. Accessed March 21, 2020. <https://www.nytimes.com/2020/02/27/world/asia/coronavirus-treatment-recovery.html>.
13. AMA Ed Hub. Coronavirus in Italy—report from the front lines. Accessed March 21, 2020. <https://edhub.ama-assn.org/jn-learning/video-player/18315311>.
14. Wang W, Tang J, Wei F. Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. *J Med Virol.* 2020 Apr;92(4):441-447. doi: 10.1002/jmv.25689. Epub 2020 Feb 12.
15. Anti-2019-nCoV Volunteers, Zhen L, Ming W et al. Caution on kidney dysfunctions of 2019-nCoV Patients. *MedRxiv.* Accessed March 17, 2020. <https://www.medrxiv.org/content/10.1101/2020.02.08.20021212v1>.
16. Hoffmann M, Kleine-Weber H, Schroeder S et al. (2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically-proven protease inhibitor. *Cell*, DOI: 10.1016/j.cell.2020.02.052
17. FDA. Coronavirus Disease 2019 (COVID-19). Accessed March 21, 2020. <https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/coronavirus-disease-2019-covid-19>.
18. CDC. Coronavirus disease 2019 (COVID-19). Frequently asked questions on COVID-19 testing at laboratories. Accessed March 21, 2020. <https://www.cdc.gov/coronavirus/2019-ncov/lab/testing-laboratories.html>.
19. Clarivate Analytics. Cortellis. Accessed March 17, 2020. <https://www.cortellis.com/>.