Wellington-Dufferin-Guelph Public Health
COVID-19 Situational Update
Monday March 23, 2020, 8.30 a.m.

Note: A large and constantly changing volume of information on COVID-19 is available from official sources as well as via the media. The highlights below attempt to summarize the most current information relevant to risk assessment and communication at WDGPH. **New information in the body of this report is typed in *red italicized font.***

Highlights

- ❑ 75% of infected individuals identified from testing of the entire population in Vo, Lombardy Italy were asymptomatic, underscoring the need for widespread testing to successfully identify and isolate infected cases. (Section 3)
- ❑ IgM/IgG antibody test becoming available; UK government has announced intentions to procure and use the test to determine the burden of infection in the population and to screen individuals for return to work. (Section 2)
- ❑ USA case count as of Monday, Mar 23 is 35,070, now third highest worldwide (behind mainland China and Italy), and second highest worldwide among countries with active epidemics.
- ❑ Canadian government working on helping to repatriate Canadians stranded overseas.

Research Findings:

- ❑ Study by Columbia University researchers indicates that COVID-19 has been difficult to contain because of 'silent spreaders'; that transmission by undetected asymptomatic or mildly ill cases has remained "substantially undetected, "and it's flying below the radar." And another study found that "The proportion of pre-symptomatic transmission was 48% (95%CI 32-67%) for Singapore and 62% (95%CI 50-76%) for Tianjin, China." These studies underscore the need for widespread testing and isolation early in an epidemic of COVID-19, in addition to other measures such as social distancing (Section 3).

SECTION 1: Case counts and Outbreak Progression

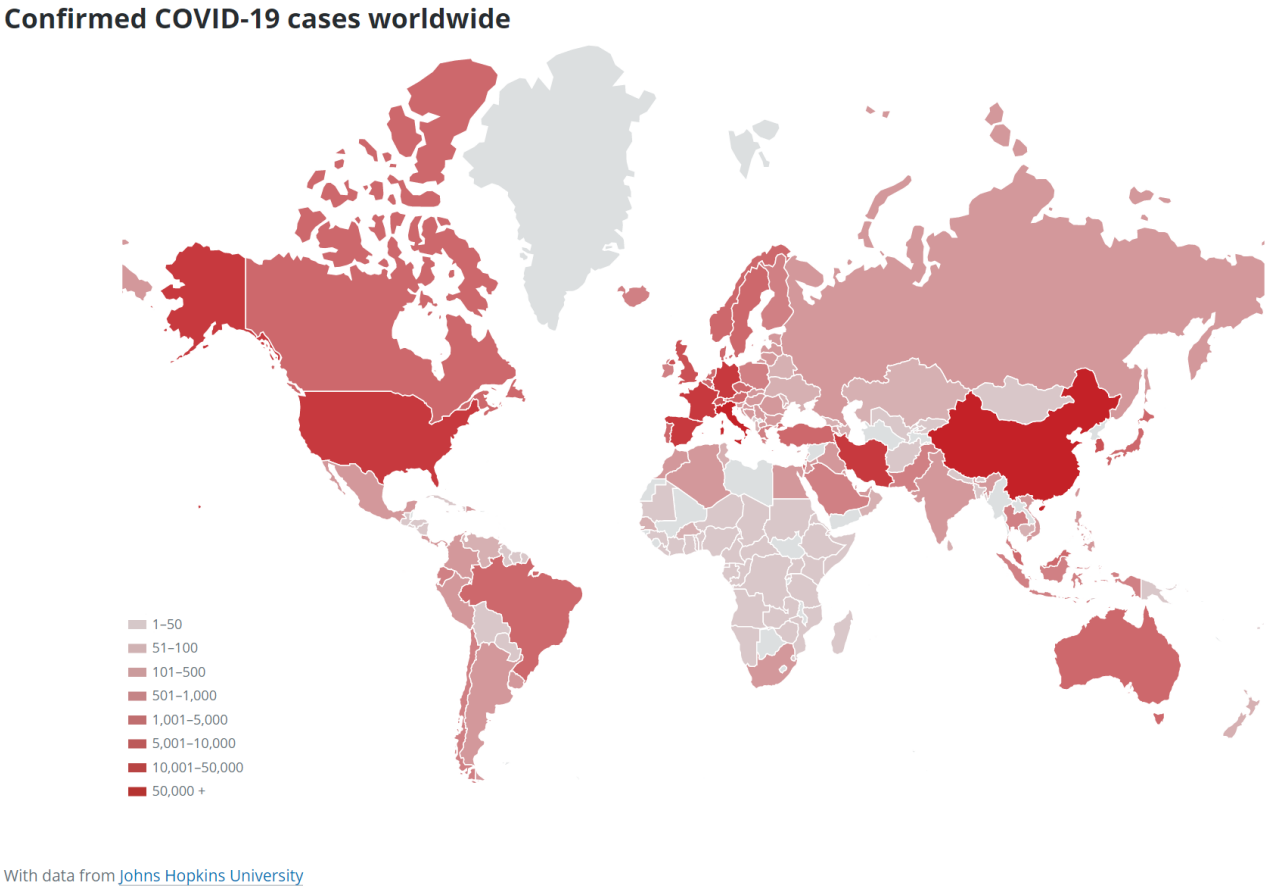
Worldwide spread:

As of Saturday March 21 (counts released by Ontario MOHLTC):

Region	Number of Reported Cases	Percentage of All Cases Worldwide	Number of Reported Deaths	Case Fatality (%)
China: Mainland	81,054	25.88	3,261	4.0
Asia and Oceana	16,971	5.42	239	1.4
Europe	156,595	49.99	7,881	5.0
Midd East	24,963	7.97	1,604	6.4
Africa	1,149	0.37	31	2.7
Latin America/Caribbean	4,151	1.33	51	1.2
USA*	27,021	8.63	344	1.3
Canada	1,318	0.42	19	1.4
TOTAL	**313,222**	**100.0**	**13,430**	**4.3**

**USA case count as of Mon Mar 23 is 35,070, now third highest worldwide (behind mainland China and Italy), and second highest worldwide among countries with active epidemics.*

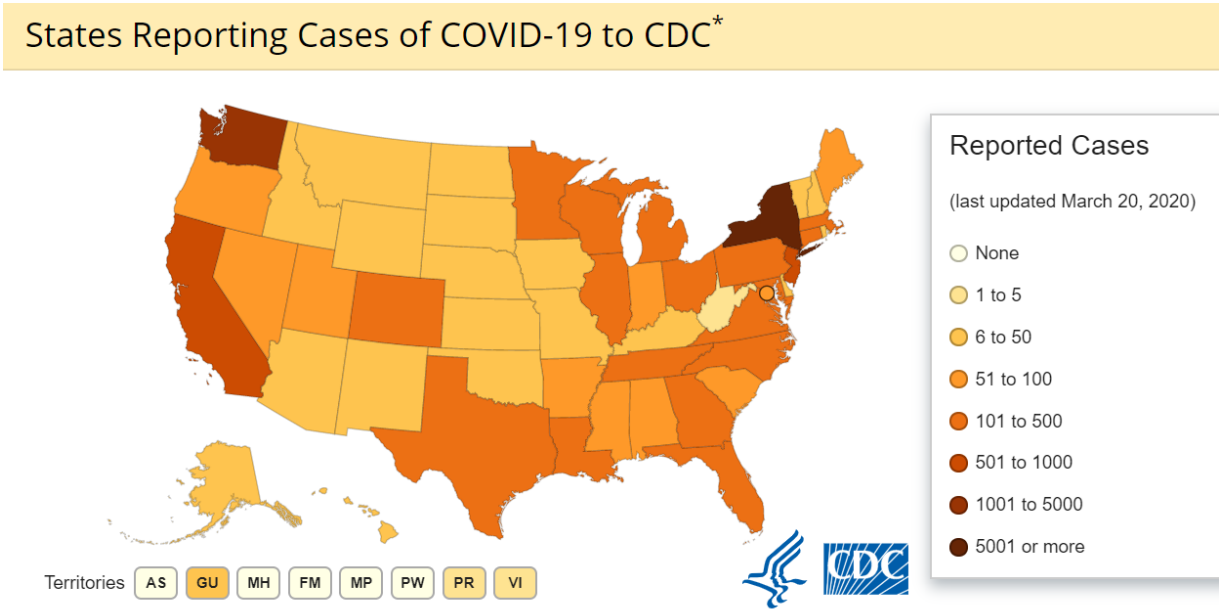
The map below shows the countries reporting confirmed cases of COVID-19 as of Sunday March 22 (source CBC).



For other maps of number of cases by country, see the WHO daily situation reports and the Johns Hopkin dashboard.

US Outbreak [Total US cases as of Mon Mar 23: 35,070]:

The map below shows states in the USA reporting cases of COVID-19 (Source US CDC):



- Marked day-to-day increases in numbers of cases and deaths have begun to be seen in Canada, with several deaths reported to date. The latter, according to previously mentioned research (e.g. Jombart T al. (MedRXiv preprint March 13), may indicate that 'hundreds to thousands' of undetected cases of COVID-19 may have already occurred to date in areas of Canada.
- All US States, including Hawaii, now reporting cases, with extensive community spready widely acknowledged; the source of infection is unknown for 90% of detected cases.
- More cruise ships, some with Canadians on board, have been found to have COVID-19 positive or symptomatic passengers /or crew. Braemar has docked in Cuba.
- *Fenga L (MedRXiv preprint March 18) estimates that instead of the 12,839 cases reported from Italy as of March 12, the true case count could be as high as 105,789.*
- At least four of the Canadian passengers repatriated from the Grand Princess cruise ship in California have tested positive to date, since arrival at Trenton ON for quarantine.
- UK reportedly expects the epidemic to last until spring 2021, with 80% attack rate.
- Number of cases in Italy now over a quarter of those reported from mainland China. Italy has second highest number of detected cases outside mainland China, surpassing South Korea, with a 7.3% confirmed case fatality rate, higher than that of Iran (5.2%) and the US (1.8%). Reasons for relatively high case fatality rate in Italy may include testing being restricted to only those at highest risk, and the fact that 23% of Italy's population is over 65 years old. See this article for more information on this.
- Most experts now believe that containment stage has passed and spread of COVID-19 is inevitable. WHO director-general Tedros Adhanom Ghebreyesus told a news conference that the Geneva-based health agency has "increased our assessment of the risk of spread and the risk of impact of COVID-19 to very high at a global level."
- Pinotti et al. systematically collected and analyzed data on 288 COVID-19 confirmed cases outside China. They analyzed importations that were successfully isolated and those leading to onward transmission and characterized the case timelines, using the information to develop a statistical model to nowcast trends in importations and quantify the proportion of undetected imported cases. The study found that although the time from travel to detection has considerably decreased since the first importation, an estimated 6 out of 10 cases are undetected. The authors conclude that countries outside China should be prepared for the possible emergence of several undetected clusters of chains of local transmissions. This study appears to reflect recent events in several countries, including Italy, the UK and the US.
- In a viewpoint article in JAMA, Swerdlow and Finelli discuss the necessity of being prepared for sustained transmission of SARS-CoV-2. The CDC has also mentioned the need to be prepared for community transmission of the virus in the US (Section 3). Boldog et al. have attempted assess the risk of the SARS-CoV-2 outbreak spreading to countries outside of China. They state that "This risk depends on three key parameters: the cumulative number of cases in areas of China which are not closed, the connectivity between China and the destination country, and the local transmission potential of the virus." As China is not likely to remain isolated indefinitely from other regions of the world, the main determining factor may be the number of cases on the mainland over the long term.

China:

- A study by Li et al. concludes that: "A majority of COVID-19 infections were undocumented prior to implementation of control measures on January 23, and these undocumented infections substantially contributed to virus transmission. These findings explain the rapid geographic spread of COVID-19 and indicate containment of this virus will be particularly challenging. Our findings also indicate that heightened awareness of the outbreak, increased use of personal protective measures, and travel restriction[s] have been associated with reductions of the overall force of infection; however, it is unclear whether this reduction will be sufficient to stem the virus spread." To date, no second wave of new infections has been seen in China, as life gradually returns to normal there.

SECTION 2: Containment efforts and pandemic preparedness:

- *IgM/IgG antibody test becoming available; UK government has announced intentions to procure and use the test to determine the burden of infection in the population and to screen individuals for return to work. (Section 2)*
- The US and Canada working to increase testing. Canada also buying medical supplies in preparation for the surge.
- Quebec has started drive-through testing with the aim of doing 100 tests per day.
- U.K. authorities have abandoned efforts to contain the spread of coronavirus and will focus on delaying the worst of the outbreak, as officials said as many as 10,000 Britons may be infected. Manufacturers there being urged to consider switching some of their production lines to making more ventilators to meet expected demand.
- Many European and North American countries now advising against travel abroad and instituting social distancing measures, including France, Canada.
- In a Lancet editorial (March 16), countries are urged to 'delay, mitigate and communicate' in the face of the growing COVID-19 pandemic. "Robust plans and policies to avoid the disease trajectories seen in the worst-hit countries are urgently needed. These responses must be proportionate to each country's situation and communicated in a clear and balanced way to avoid spreading fear and panic." The editorial also states: The example of Singapore could be informative for many countries: having learned lessons from the severe acute respiratory syndrome epidemic of 2002–03, Singapore has so far managed the outbreak well, with rapid testing of suspected cases, clear public health messages from the outset, and by individuals taking action to protect themselves and others."
- National emergencies declared by several areas of North America including Ontario.

For a summary of other published studies and reports on containment efforts and prevention of SARS-CoV-2 transmission, please see Appendix 6.

SECTION 3: Transmissibility of virus

- *Testing of the entire population of the small town of Vo, in Lombardy, Italy, illustrates the importance of widespread testing to identify and isolate as many cases of COVID-19 as possible: 75% of cases identified were asymptomatic.*
- *Study by Columbia University researchers indicates that COVID-19 has been difficult to contain because of 'silent spreaders', and that transmission by undetected asymptomatic or mildly ill cases has remained "substantially undetected, "and it's flying below the radar." Li R et al. (Science March 16) state: "We estimate 86% of all infections were undocumented (95% CI: [82%–90%]) prior to 23 January 2020 travel restrictions. Per person, the transmission rate of undocumented infections was 55% of documented infections ([46%–62%]), yet, due to their greater numbers, undocumented infections were the infection source for 79% of documented cases. These findings explain the rapid geographic spread of SARS-CoV2 and indicate containment of this virus will be particularly challenging."*
- *Ganyani et al. (MedRXiv preprint March 8) used outbreak data from clusters in Singapore and Tianjin, China to obtain the proportions pre-symptomatic transmission and reproduction numbers of the outbreak. "The proportion of pre-symptomatic transmission was 48% (95%CI 32-67%) for Singapore and 62% (95%CI 50-76%) for Tianjin, China."*
- *Lu S et al. (JMV Mar 19) describe a case series of a familial cluster of COVID-19 cases that included two asymptomatic cases, contacts of another family member who reported only a slight dry cough and no fever. No fever, cough or expectoration occurred in either of the asymptomatic cases; however, both tested positive for SARS-CoV-2 and one had CT findings typical of COVID-19. The first case, with no fever and a slight dry cough the week before diagnosis, was negative for viral detection and was diagnosed on CT findings and history of contact with patients from Hubei.*
- *Adding to the growing body of evidence for asymptomatic and pre-symptomatic transmission, He X et al. (MedRXiv preprint March 18) report temporal patterns of viral shedding in 94 laboratory-confirmed COVID-19*

patients and modelled COVID-19 infectiousness from a separate sample of 77 infector-infectee transmission pairs. The authors observed the highest viral load in throat swabs at the time of symptom onset, and inferred that infectiousness peaked on or before symptom onset. They estimated that 44% of transmission could occur before first symptoms, and suggest that disease control measures should be adjusted to account for probable substantial pre-symptomatic transmission.

For a summary of other published articles and commentaries relevant to transmissibility of SARS-CoV-2 included in previous situation updates, please see Appendix 6.

SECTION 4: Testing and Screening Efficacy

- From a March 17 report: "Biomerica Inc. (NASDAQ: BMRA) today announced it has commenced shipping initial samples of its COVID-19 IgG/IgM Rapid Test (a finger prick blood test with results in 10 minutes, that can be performed by trained professionals anywhere, e.g. airports, schools, work, pharmacies and doctors' offices) to countries outside the US. Evaluation test kits have been requested by Ministries of Health in multiple countries through the Company's distribution partners who are working with their government agencies to assess the tests and forecast demand. This disposable point-of-care serology test is different than the current polymerase chain reaction (PCR) tests in that initial studies indicate that serology tests can identify if someone has been exposed to the COVID-19 virus and can further detect if a person was recently infected with the disease even if they have never shown or are no longer showing symptoms. This can help health agencies focus on prior contacts of persons previously infected."
- *Zhou et al (NEJM) analyzed the viral load in nasal and throat swabs obtained from the 17 symptomatic patients in relation to day of onset of symptoms. "Higher viral loads (inversely related to Ct value) were detected soon after symptom onset, with higher viral loads detected in the nose than in the throat. Our analysis suggests that the viral nucleic acid shedding pattern of patients infected with SARS-CoV-2 resembles that of patients with influenza and appears different from that seen in patients infected with SARS-CoV. The viral load that was detected in the asymptomatic patient was similar to that in the symptomatic patients, which suggests the transmission potential of asymptomatic or minimally symptomatic patients. These findings are in concordance with reports that transmission may occur early in the course of infection and suggest that case detection and isolation may require strategies different from those required for the control of SARS-CoV. How SARS-CoV-2 viral load correlates with culturable virus needs to be determined. Identification of patients with few or no symptoms and with modest levels of detectable viral RNA in the oropharynx for at least 5 days suggests that we need better data to determine transmission dynamics and inform our screening practices."*
- *In the case series described by Lu S et al. (JMV Mar 19; see Section 3), the authors discuss the importance of using several diagnostic approaches to help to overcome the limitations of viral detection methods: "In this case, the results of multiple viral nucleic acid tests of patient A were all negative, suggesting that we should be alert to the negative effects of false negative rate of nucleic acid detection on the prevention and control of COVID-19. It was reported that the sensitivity of RT-PCR method on throat swab samples ranged from 30% to 60% due to the limitations of sample collection and detection method2. Chest CT scan could provide important diagnostic information…. Ground glass shadow was the most common CT manifestation (56.4%) in 1099 COVID-19 patients. The sensitivity of Chest CT scan was 97.0% (580/601) in a diagnostic accuracy study based on 1014 COVID-19 patients. A Rapid IgM-IgG Combined Antibody Test for COVID-19 has been developed for COVID-19 patients. In 397 patients with COVID -19 confirmed by RT-PCR and 128 healthy controls, the sensitivity and specificity of this detection method were 88.7% and 90.6% respectively (Li Z et al. JMV Mar 2020). These previous studies demonstrated that chest CT and serum antibody detection method were helpful to screen asymptomatic COVID-19 patients.*
  In general, the current case suggests that comprehensive rigorous epidemic investigation and the combination of multiple detection methods could help to identify asymptomatic COVID-19 patients."
- Some researchers have suggested serological testing in conjunction with virus detection methods.
- Wang Y and Teunis FM (MedRXiv preprint March 16: see Section 3) state that "Silent transmission has been seen in other infectious diseases where, notably, symptomatically infected subjects appeared to cause fewer

transmissions [than SARS-CoV-2]. As asymptomatic infections would lead to an antibody response, serology could be a valuable tool to assess the importance of asymptomatic transmission."

For a summary of published articles and commentaries relevant to testing and screening for SARS-CoV-2 included in previous situation updates, please see Appendix 7.

SECTION 5: Symptoms, Severity and Clinical Management

- To describe the spectrum of illness in young adults and adolescents, Liao J et al., in MedRxiv preprint (Mar 12) collected data on 46 confirmed COVID-19 patients aged 10 to 35 years. They found that three asymptomatic cases transmitted infections to their family members. Only 1 patient was identified as severe at admission. The common symptoms at admission were dry cough (34, 91.0%), and fever (29, 69.0%). Nearly 60% of the patients had showed ground-glass opacity by chest CT findings. Three patients developed acute kidney injury during treatment. The majority of patients (78.3%) were discharged by the end of the follow-up.
- Tang A et al. (MedRXiv preprint March 10) analyzed the clinical symptoms, laboratory results, chest CT, and treatment of 26 children with laboratory-confirmed COVID-19 admitted to Shenzhen Center of National Infectious Disease Clinical Medical Research from January 16 to February 8, 2020. They found that 9 patients had no obvious clinical symptoms, while 11 developed fever. Other symptoms, including cough (n=11), rhinorrhea (n=2), diarrhea(n=2), vomiting (n=2), were also observed. A small minority of patients had lymphocytopenia. On chest CT scan, 11 patients showed unilateral pneumonia, and 8 had no pulmonary infiltration. No serious complications such as acute respiratory syndrome or acute lung injury occurred in any of the patients. With the cases be generally mild and with a good prognosis.
- For a summary of other studies and reports on this, please see Appendix 4.

Epidemiological Notes

- ❑ *It is becoming increasingly recognized that without testing of, at least, a representative sample of the population, the extent of spread of infection and of community spread will remain unknown. The results of testing in Vo, Italy provide valuable information on the proportion of cases in a population that can represent 'silent spreaders' of the virus, and may explain why so many countries and regions have been taken by surprise by sudden, rapid and seemingly uncontrollable spread of the disease.*
- ❑ Rates of testing and testing criteria vary widely from country to country and often within countries; therefore, the relative numbers of confirmed cases reported by countries or regions do not necessarily reflect differences between the prevalence of infection in those areas.
- ❑ Pinotti et al. have found that although the time from travel to detection has considerably decreased since the first importation, an estimated 6 out of 10 cases are undetected. With evidence indicating that SARS-CoV-2 infections have gone undetected in the US for weeks, and with numbers of detected infections now rising daily in Canada, it cannot be ruled out that a number of infections in Ontario have gone undetected and that community transmission is already taking place in more areas than officially recognized. Countries currently trying to manage epidemics of COVID-19 have tended to realize that community transmission has been taking place only some time after that transmission has begun (e.g. the US). The study by Jombart et al. underscores this: "Our results suggest that by the time a single death occurs, hundreds to thousands of cases are likely to be present in that population…"

List of Scientific References and Additional Reading

Note: Because of the emerging and currently evolving nature of scientific information on 2019nCoV, many/most of the scientific reports listed here have not been peer-reviewed, or have been subjected only to an expedited peer-review process. Conclusions may change as further information becomes available, and should therefore not necessarily be accepted as established.

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Appendices

Appendix 1: Estimates of R_0

Study	Inclusive of data through	Basic Reproductive Number Estimate
Cao, Z. et al. (2020). Estimating the effective reproduction number of the 2019-nCoV in China.	Jan 25	R = 4.08
Cao, Z. et al. (2020). Incorporating human movement data to improve epidemiological estimates for COVID-19. doi: https://doi.org/10.1101/2020.02.07.20021071		R_0 prior to Wuhan quarantine on Jan 23 was 3.24
Imai, N. et al. (2020). Transmissibility of 2019n-CoV	Jan 23	R_e = 2.6
Jung et al. (2020). Real time estimation of the risk of death from novel coronavirus (2019-nCoV) infection: Inference using exported cases.	Jan 24	Two scenarios: 1) R_0 = 2.2 2) R_0 = 3.7
Hermanowicz S.W. (2020). Forecasting the Wuhan coronavirus (2019-nCoV) using a simple (simplistic) model	Jan 28	R_0 ~ 2.4 and decreasing. Don't take this paper seriously though…it was badly off in other estimates the day it was published.
Kucharski, A. et al. (2020). Analysis of early transmission dynamics of nCoV in Wuhan.		Initial R_0 of 1.5 to 4 Declining R_e after mid-January and travel restrictions
Kucharski, A et al. (2020). Early dynamics of transmission and control of 2019-nCoV: A mathematical modelling study.	Mid Dec through Mid Jan	R fluctuated between 1.6 and 2.9
Kucharski, A. et al. (2020). Analysis and projections of transmission dynamics of nCoV in Wuhan.		R_0 of 1.5 to 4.5 prior to Jan 23; Rt decreasing with time
Leung, G. & Wu, J. (2020). Real-time nowcast and forecast on the extent of the Wuhan CoV outbreak, domestic and international spread. Republished in updated form in the Lancet: Wu, J. et al. (2020). Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: A modeling study. *The Lancet*. https://doi.org/10.1016/S0140-6736(20)30260-9	Jan 25	R_0 = 2.13 initially; updated R_0 = 2.68
Li et al. (2020). Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *New England Journal of Medicine*. DOI: 10.1056/NEJMoa2001316	Jan 22	R_0 = 2.2
Liu, T. et al. (2020). Transmission dynamics of 2019 novel coronavirus (2019-nCoV).	Jan 22	R_0 = 2.9
Liu, T. et al. (2020-12 Feb). Transmission dynamics of Novel Coronavirus Pneumonia in China. BioRxiv preprint. https://doi.org/10.1101/2020.01.25.919787	Feb 7	R_0 in Wuhan = 4.4; R_0 elsewhere in China = 4.5; R_t is steadily decreasing
Majumder, M. & Mandl, K.D. (2020). Early transmissibility assessment of a novel coronavirus in Wuhan, China	Jan 24	R_0 = 2.2 to 3.1

Park, Sang Woo et al. (2020). Reconciling early-outbreak preliminary estimates of the basic reproductive number and its uncertainty: a new framework and applications to the novel coronavirus (2019-nCoV) outbreak		Pooled estimate of prior studies: Median R_0 = 3.1 (95% CI: 2.1-5.7) More recent paper says 2.9 (CI: 2.1 – 4.5)
Read, J. et al. (2020). Novel coronavirus 2019-nCoV: Early estimation of epidemiological parameters and epidemic predictions.	Jan 21	R_0 = 3.8 (Twitter update: revised to 2.5 with data through Jan 22) (Further update as of Jan 28 to 3.11)
Riou, J. & Althaus, C. L. (2020). Pattern of early human-to-human transmission of Wuhan 2019-nCoV Updated version published in Eurosurveillance: Riou, J. & Althaus, C.L. (2020). Pattern of rearly human-to-human transmission of Wuhan novel coronavirus (2019-nCoV), December 2019 to Jan 2020. *Eurosurveillance, 25*(4).	Jan 18	R_0 = median 2.2 (high density interval 1.4 – 3.8). Authors suggest high similarlity to SARS-CoV
Sanche, S et al. (2020). The novel coronavirus, 2019-nCoV, is highly contagious and more infectious than initially estimated. Medrxiv preprint.	End of January	Before control measures R_0 = 4.7 to 6.6 depending on the method and data used to calculate Post control measures R_e = 2.3 to 3.0
Shen, M. et al. (2020). Modeling the epidemic trend of the 2019 novel coronavirus outbreak in China.		Initial R_0 = 4.71 (Dec 12) Current R_e = 2.08 (Jan 22) R_e < 1 predicted within 2.5 months
Tuite, A.R. & Fisman, D. N. (2020). Reporting, epidemic growth, and reproduction numbers for the 2019 novel coronavirus (2019-nCoV) epidemic. *Annals of Internal Medicine*. DOI: 10.7326/M20-0358		Initial R_0 = 2.3; R_e ~ 1.5 around 3 Feb
Yang et al. (2020). Epidemiological and clinical features of the 2019 novel coronavirus outbreak in China.		Initial R_0 = 2.2 to 5.2 depending on modeling assumptions. Paper also examines Rt, suggests substantial decrease from peak
You, C et al. (2020—Feb 11). Estimation of the time-varying reproduction number of 2019-nCoV outbreak in China. Medrxiv preprint. https://doi.org/10.1101/2020.02.08.20021253		Initial R_0 = 2.3 to 3.7 for all of China, depending on method ~2 to ~6 for various specific cities Controlled R as of Feb 5: 1.7 to 2.3 for all of China
Zhang, C & Wang, M. (2020). Origin time and epidemic dynamics of the 2019 novel coronavirus.		R_e = 0.2 to 2.2 (varying by time)
Zhao S. et al. (2020). Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: A data-driven analysis in the early phase of the outbreak. Accepted for publication in International Journal of Infectious Diseases: Zhao et al. (2020). Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to	Jan 24	R_0 = 2.24 to 3.58

2020: A data-driven analysis in the early phase of the outbreak. *International Journal of Infectious Diseases*. https://doi.org/10.1016/j.ijid.2020.01.050		
Zhao, Q. et al. (2020). Analysis of the epidemic growth of the early 2019-nCoV outbreak using internationally confirmed cases. doi: https://doi.org/10.1101/2020.02.06.20020941		R_0 = 5.7, based on analysis of international spread
Zhou T et al. (2020-12 Feb). Preliminary prediction of the basic reproduction number of the Wuhan coronavirus 2019-nCoV. *Joural of Evidence-Based Medicine.* https://doi.org/10.1111/jebm.12376		R_0 = 2.8 to 3.9, depending on source of data and parameters
Mizumoto et al Feb 13, 2020. Early epidemiological assessment of the transmission potential and virulence of 2019 Novel Coronavirus in Wuhan City: China, 2019-2020	Feb 13	R_0 = 7.05 (95%CrI: 6.11–8.18) In Wuhan City, China early in epidemic, and 3.24 (95%CrI: 3.16–3.32) after Jan 23 (following enhanced control measures).

Appendix 2: Timelines for Incubation and Disease Progression

New Additions	Study	Sample	Incubation Period Estimate
	Chan et al. (2020). A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *The Lancet*. https://doi.org/10.1016/S0140-6736(20)30154-9	Case study of 7 member extended family, 6 of whom tested positive	First symptoms developed within 4 to 6 days of earliest possible exposure One child case was asymptomatic but was shedding virus.
	Huang et al. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*. https://doi.org/10.1016/S0140-6736(20)30183-5	41 very early patients	While no info is provided on incubation per se (exposure is unclear, as half were on-going exposure to the wet market), on average 7 days passed before the start of symptoms and admission to hospital, 8 days to dyspnoae, 9 days to ARDS, 11 days to ICU admit
	Phan et al. (2020). Importation and Human-to-Human Transmission of a Novel Coronavirus in Vietnam. New England Journal of Medicine. DOI: 10.1056/NEJMc2001272	Case study: Family of three, two of whom tested positive	Son became symptomatic within 3 days of sharing room with father
	Liu et al. (2020). Transmission dynamics of 2019 novel coronavirus (2019-nCoV).	830 cases prior to Jan 23	Average incubation = 4.8 days
	Linton et al. (2020). Epidemiological characteristics of novel coronavirus infection: A statistical analysis of publicly available case data.		Median incubation: 4 to 5 days; 95% CI 2-9 days Median symptom onset to hospitalization: 3 days Median: symptom onset to death: 13.8 days
	Backer et al. (2020). The incubation period of 2019-nCoV infections among travellers from Wuhan, China Accepted in Eurosurvillance: Backer, J.A. et al. Incubation period of 2019 novel coronavirus (2019-nCoV) infections among travellers from Wuhan, China, 20–28 January 2020. *Eurosurveillance*, 25(5).	34 confirmed cases outside of Wuhan	Mean incubation: 5.8 days, ranging from 1.3 to 11.3 days
	Wang et al. (2020). Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. *Journal of Medical Virology*. DOI: 10.1002/jmv.25689	Summary of CNHC report on 17 deaths	Median days from first symptom until death: 14.0 (range 6-41)
	Li et al. (2020). Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *New England Journal of Medicine*. DOI: 10.1056/NEJMoa2001316	First 425 confirmed cases in Wuhan	Mean incubation period 5.2 days, ranging up to 12.5 days (95% of distribution)
	Rothe et al. (2020). Transmission of 2019-nCoV Infection from an Asymptomatic Contact in	5 cases in Germany	Of the four Germany patients with a known exposure history, all developed symptoms with 2-6 days of exposure

	Germany. New England Journal of Medicine. DOI: 10.1056/NEJMc2001468		BUT At least one case was able to infect others within 1-2 days of being exposed himself and several days before he developed symptoms
	Lauer et al. (2020). The incubation period of 2019-nCoV from publicly reported confirmed cases: estimation and application. doi: https://doi.org/10.1101/2020.02.02.20020016	101 confirmed cases in China	Median incubation period is estimated at 5.2 days; 97.5% of those who develop symptoms will do so within 10.5 days of infection. Conservatively estimated, 64 out of 10,000 cases will develop symptoms after 14 days of quarantine.
	Guan et al. (2020). Clinical characteristics of 2019 novel coronavirus infection in China. doi: https://doi.org/10.1101/2020.02.06.20020974	1099 confirmed cases from 31 Chinese provinces	Mean incubation period was 3.0 days (range 0 to 24)
	Sanche, S et al. (2020). The novel coronavirus, 2019-nCoV, is highly contagious and more infectious than initially estimated. Medrxiv preprint.	140 individual case reports	4.2 days from exposure to symptom onset (95% CI 3.5 to 5.1)
	Yang et al. (2020). Epidemiological and clinical features of the 2019 novel coronavirus outbreak in China.	125 patients with clearly defined exposure periods	4.8 days (IQR 3.0, 7.2)

Appendix 3: Comparative Case Definitions for Suspect Cases

Authority	Date Updated	Clinical Presentation		Travel/Exposure History
WHO	31 Jan	Severe acute respiratory infection (SARI), fever and cough, requiring admission to hospital, with no other etiological explanation for infection	AND	Travel to or live in China in the 14 days prior to symptom onset
		Person with any degree of acute respiratory tract illness (ARTI)	AND	Contact with a confirmed or probable nCoV case OR healthcare facility treating nCoV OR visit to live animal market in Wuhan
CDC	4 Mar	Case definition removed from CDC's website. Instead, note indicates that testing will be expanded to "a wider group of symptomatic patients. Clinicians should use their judgment to determine if a patient has signs and symptoms compatible with COVID-19 and whether the patient should be tested. Decisions on which patients receive testing should be based on the local epidemiology of COVID-19, as well as the clinical course of illness. Most patients with confirmed COVID-19 have developed fever1 and/or symptoms of acute respiratory illness (e.g., cough, difficulty breathing). Clinicians are strongly encouraged to test for other causes of respiratory illness, including infections such as influenza. Epidemiologic factors that may help guide decisions on whether to test include: any persons, including healthcare workers, who have had close contact3 with a laboratory-confirmed COVID-19 patient within 14 days of symptom onset, or a history of travel from affected geographic areas… within 14 days of symptom onset."		
European CDPC	2 Mar	**Suspect Case**: Laboratory testing for COVID-19 should be performed for suspected cases according to the following criteria, based on the updated WHO case definition: 1) a patient with acute respiratory tract infection (sudden onset of at least one of the following: cough, fever, shortness of breath) AND with no other aetiology that fully explains the clinical presentation OR 2) a patient with any acute respiratory illness AND having been in close contact with a confirmed or probable COVID-19 case in the last 14 days prior to onset of symptoms; OR 3) A patient with severe acute respiratory infection (fever and at least one sign/symptom of respiratory disease (e.g., cough, fever, shortness breath)) AND requiring hospitalisation (SARI) AND with no other aetiology that fully explains the clinical presentation. **Probable Case:** A suspected case for whom testing for virus causing COVID-19 is inconclusive (according to the test results reported by the laboratory) or for whom testing was positive on a pan-coronavirus assay. **Confirmed case:** A person with laboratory confirmation of virus causing COVID-19 infection, irrespective of clinical signs and symptoms.	AND	with a history of travel or residence in a country/area reporting local or community transmission* during the 14 days prior to symptom onset;

Ireland	26 Feb	**Possible case:** Patients with severe acute respiratory infection requiring admission to hospital with clinical or radiological evidence of pneumonia or acute respiratory distress syndrome. OR Patients with acute respiratory infection of any degree of severity including at least one of the following: fever, cough, shortness of breath OR Fever1 of unknown cause with no other symptoms	AND	In the 14 days prior to onset of symptoms, met at least one of the following epidemiological criteria: • Were in close contact with a case of COVID-19infection; OR • Have visited or lived in areas with presumed ongoing community transmission of COVID-19; OR • Worked in or attended a health care facility where patients with COVID-19infections were being treated. ***Note:*** This interim case definition for COVID-19 was adapted from the European Centre for Disease Prevention and Control's (ECDC) guidanceon European surveillance of human infection with novel coronavirus (COVID-19) andPublic Health England Investigation and initial clinical management of possible cases of novel coronavirus (COVID-19) infection. The case definition for possible cases is based on the current information available on the outbreak and may be subject to revision as new data become available. Changes from Version4.0: 1. List of affected countries has changed-see link below 2. Air flight contacts added to the list of close contacts Interim case definition.
Australia	3 Mar	***Suspect case:*** Suspect case A. If the patient satisfies epidemiological and clinical criteria, they are classified as a suspect case: Clinical criteria • Fever. OR • Acute respiratory infection (e.g. shortness of breath or cough) with or without fever. B. If the patient has severe community-acquired pneumonia (critically ill) and no other cause is identified, with or without recent international travel, they are classified as a suspect case. C. If the patient has moderate or severe community-acquired pneumonia (hospitalised) and is a healthcare worker, with or without international travel, they are classified as a suspect case. ***Confirmed case:*** A person who tests positive to a specific SARS-CoV-2 PCR test or has the virus identified by electron	AND	Epidemiological criteria: • Travel to (including transit through) a country considered to pose a risk of transmission* in the 14 days before the onset of illness. OR • Close or casual contact (see Contact definition below) in 14 days before illness onset with a confirmed case of COVID-19.

		microscopy or viral culture, at a reference laboratory.		
United Kingdom	25 Feb	SARI requiring hospitalization (with evidence of pneumonia or ARDS) OR ARTI or any severity with one of SOB or cough OR fever	AND	In the 14 days before the onset of illness: • travel to specified countries and areas. This includes transit, for any length of time, in these countries OR • contact (see definition below) with confirmed cases of COVID-19 ***Note***: Epidemiological criteria changed on 25 February 2020.
		United Kingdom – Updated Feb 25 Epidemiological criteria Please note these criteria changed on 25 February 2020. In the 14 days before the onset of illness: • travel to specified countries and areas. This includes transit, for any length of time, in these countries OR • contact (see definition below) with confirmed cases of COVID-19		
France	3 Mar	Possible case a) Anyone with clinical signs of acute respiratory infection with fever or feeling of fever	AND	Having traveled or stayed in a risky exposure zone within 14 days before the start date of clinical signs : - The list of risk exposure zones, defined as the countries for which a transmission community-based SARS-CoV-2 is described, is available on the Public Health website France ; - On a case-by-case basis and after consultation with Santé publique France, a proven or potential exposure to a cluster type event (large transmission chain), documented outside these areas risk exposure may also be considered.
		b) Anyone with clinical signs of acute respiratory infection within 14 days	AND	any of the following: - Close contact1 of a confirmed case of COVID-19; - Co-exposed person, defined as having been subject to the same risks of exposure (i.e. a travel or stay in a hazardous area) than a confirmed case.
		c) Anyone, even without the notion of travel / stay in a risky exposure zone or contact close with a confirmed case of COVID-19, presenting: - Pneumonia for which another etiology was previously excluded on the basis of clinical criteria, radiological and / or virological and whose clinical condition requires hospitalization, OR - Signs of acute respiratory distress up to ARDS (Respiratory Distress Syndrome		

		acute) in a possibly viral context with no other etiology obvious from the start.		
Hong Kong	28 Feb	An individual fulfilling the following should be reported to the Centre for Health Protection (CHP) for further investigation: • Fever* OR acute respiratory illness OR pneumonia;	AND	Either one of the following conditions within 14 days BEFORE ONSET OF SYMPTOM: 1. With travel history to a place with active community transmission of COVID-19#; OR 2. Had close contact with a confirmed case of COVID-19.
Germany	14 Feb	Respiratory symptoms of any severity	AND	Within 14 days: Stay in a "Risk area" (Hubei province plus Wenzhou, Hangzhou, Ningbo, Taizhou in Zhejiang province) or contact with a confirmed case ***Contact with a confirmed case*** *is defined as the presence of at least one of the following two criteria within the last 14 days before the onset of illness:* *- Care or care of a person, in particular by medical staff or family members* *- Staying in the same place (e.g. classroom, workplace, apartment / household, extended family, Hospital, other residential facility, barracks or summer camp) like a person while this was symptomatic.* ***Staying in a risk area*** *is defined as traveling or living in an affected area (Risk area) within the last 14 days before the onset of illness. Areas with persistent human-to-human transmission ("community transmission") classified. The risk areas are regularly re-evaluated based on epidemiological criteria and on the RKI website updated: www.rki.de/ncov-risikogebiete*
		Germany updated on Feb 14 (******This is translated from Google as it was only available in German)		
South Korea				Reportedly has done away with travel history requirement for testing; only based on clinical presentation

Appendix 4a: Symptoms and Clinical Management

Study	Population	Symptoms											Notes
		Fever	*Cough*	*Fatigue / Myalgia*	*Rhinor-rhea or Sputum*	*Head-ache*	*Diarrhea*	*SOB*	*Haemo-ptysis*	*Chest Pain*	*Sore Throat*	*Nausea*	
Huang et al.	First 41 patients in Wuhan	98%	76%	44%	28%	8%	3%		5%				Is likely biased towards more severe cases
Chen et al.	99 cases in Wuhan admitted to ID hospital	83%	82%	11%	4%	8%	2%	31%		2%	5%		Is likely biased towards more severe cases
Chan et al.	6 cases in multigenerational family cluster in Shenzhen	5 / 6 (not in child; highest in oldest adults)	3 / 6 dry, 1 /6 product ive	3 / 6 (older adults only)	2 / 6 (middle aged adults only)		2 / 6 (middle aged adults only)			1 / 6	1 / 6		One confirmed pediatric case was asymptomatic
Chang et al.	13 young Chinese cases	12 /13 (1.5 days duratio n, low max)	46% (8 days duratio n)	23%	8%	23%	8%						Median age: 34; includes some pediatric patients. All recovered.
Wang et al.	138 consecutive patients in a single hospital in Wuhan	99%	60%	70%	27%	7%	10%	31%			18%	10%	34.1% of patients discharged, 4.3% died, 61.6% still in hospital
Guan et al.	1099 Chinese cases	44% at present ation	68%	38.1% / 14.8%	4.8% / 33.4%	13.6%	3.7%	18.6%	0.9%		13.9%	5.0%	Unclear how the sample was assembled (represents ~14% of existing Chinese cases at that time); 94% of cases still in hospital, 5% discharged, 1.4% dead
Li et al.	17 patients in Dazhou	67%	83%	42% / 17%			17%						Follow-up is ongoing
WHO report	Chinese data on 18,000 cases												Approximately 82% of cases shed the virus, with 15% of cases being severe and 3% critical. No information has

													been released on the testing criteria for these cases or whether any were asymptomatic.
Dorigatti et al.													Neil Ferguson's group has estimated (Dorigatti et al.) that the confirmed case fatality rate based on early data (26 deaths) from Hubei is 18% (95% CI 11%-81%) and based on data on the spread from outside of China will be between 1.2% and 5.6% depending on the estimation method. They recognize that the Hubei data is likely biased towards more severe cases and that international surveillance is catching more mildly or asymptomatic cases than is surveillance in China. Taking into account the data on the number of positive tests from evacuation flights, the estimated all case fatality rate is about 1%

Appendix 4b: Other studies on symptoms and clinical management of COVID-19

Study	Sample
Hu Z et al.	Hu Z et al., in February 25 MedRXiv preprint, describe their findings in the investigation of 24 asymptomatic contacts of COVID-19 patients who tested positive for SARS-CoV-2: "None of the 24 asymptomatic cases presented any obvious symptoms before nucleic acid screening. Five cases (20.8%) developed symptoms (fever, cough, fatigue and etc.) during hospitalization. Twelve (50.0%) cases showed typical CT images of ground-glass chest and five (20.8%) presented stripe shadowing in the lungs. The remaining seven (29.2%) cases showed normal CT image and had no symptoms during hospitalization. These seven cases were younger (median age: 14.0 years; P = 0.012) than the rest. None of the 24 cases developed severe COVID-19 pneumonia or died."
Yang X et al.	From a study of 52 patients published Feb 24 in The Lancet, Yang X et al. concluded the mortality of critically ill patients with SARS-CoV-2 pneumonia is considerable, with the survival time of non-survivors after ICU admission being approximately 1–2 weeks. The authors state that SARS-CoV-2 pneumonia poses great strain on critical care resources in hospitals, especially if those not adequately staffed or resourced.
Mao et al.	Mao et al report in a MedRXiv preprint posted February 25 that, of 218 COVID-19 patients studied, severe patients tended to show less typical symptoms such as fever and cough, and were also more likely to have neurologic conditions such as acute cerebrovascular diseases and impaired consciousness. Seventy-eight (36.4%) of the patients had neurologic manifestations.
Gao et al.	In a Journal of Digestive Diseases editorial published Feb 25, Gao et al. speculate that, based on recent studies that have found SARS-CoV-2 in oral and anal swabs m infected patients, the disease may have some relationship with the gut microbiota through the angiotensin-converting enzyme 2 (ACE2) receptor. They thus suggest that targeting gut microbiota might be a new therapeutic option for the treatment of virus-related pneumonia.
China CDC Weekly Report	In a study of over 70,000 cases published in the China CDC Weekly Report, case fatality ratios are reported by comorbidities: "While patients who reported no comorbid conditions had a case fatality rate of 0.9%, patients with comorbid conditions had much higher rates—10.5% for those with cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, and 5.6% for cancer." CFRs were also found to be much higher in patients over 70 (8.0% in those 70-79 years of age, and 14.8% for those over 80 and, as in previous studies, higher in males than females. Also, 14.6% of healthcare workers were classified as critical, vs. only 4.7% of the overall study population. The authors do not present any explanation for this; possibly the high viral load present in hospitals and clinics can help to explain to this result.
Xu et al.	In a study published on February 19, Xu et al describe the clinical findings in 62 patients diagnosed in Zhejiang province. Only 2 of the patients developed shortness of breath; the clinical profiles of cases were generally much milder than those of patients diagnosed in Wuhan. The authors apparently attribute this difference to the cases in Zhejiang province being from a later point in the chain of transmission than those at the epicenter: "We found that the clinical features of patients with symptoms for longer than 10 days in Zhejiang province were less severe than those of the primary infected patients from Wuhan. This phenomenon was also apparent during the transmission of MERS-CoV. The global case mortality of MERS-CoV was about 40%, whereas the mortality from second generation MERS-CoV was about 20%."
Wang M et al.	Wang M et al., in a study posted February 18, report that "Clinical testing methods for 2019-nCoV require improvement. Importantly, 5.8% of 2019-nCoV infected and 18.4% of non-2019-nCoV-infected patients had [infections with other pathogens]. It is important to treat combined infections and perform rapid screening to avoid cross-contamination of patients. A test that quickly and simultaneously screens as many pathogens as possible is needed."

Feng et al.	Feng et al, in a study of 15 children diagnosed with SARS-CoV-2 infection, found that early chest CT images of children with 2019-nCoV infection are mostly small nodular ground glass opacities, and that the clinical symptoms are nonspecific. The authors conclude that dynamic reexamination of chest CT and nucleic acid are important.
Wang et al	Wang et al, in a study of 34 children with the virus, concluded that the clinical manifestations of COVID-19 in children are non-specific and are milder than that in adults; 22 (65%) were classified as 'common' cases, 9 (26%) as mild cases and 3 (8.8%) were asymptomatic. No severe or critical cases were identified.
Guan et al.	In a large cohort study of 1099 confirmed cases from across China fever existed on admission to the hospital only among 43% of cases but developed in 88% of cases (Guan et al.). This large study adds significantly to our knowledge on symptoms and disease progression, but the authors are not clear how the cases were selected (the sample represents 14% of known Chinese cases on the date data were extracted), and care is ongoing for more than 90% of the cohort. The proportion of health care workers affected in this outbreak appears to be lower than those infected in the SARS and MERS outbreaks, based on analysis in that study.
Holshue et al.	There is some evidence that antiviral drugs are effective in treating the illness. Holshue et al. describes that the patient improved rapidly when put on remdesivir, a drug in development. A Phase III clinical trial for remdesivir is underway in China. In earlier studies, the drug made by Gilead showed in vitro and in vivo activity against other coronaviruses such as SARS (severe acute respiratory syndrome) and MERS-CoV. The drug isn't licensed or approved, but Gilead has provided it for emergency use in a small number of COVID-19 patients, including at least one in the United States.
Richardson et al; Beck et al; Stockman et al., 2006	Genetic analysis and molecular modeling (Richardson et al) identifies several compounds that may be effective, as does AI-based modeling (Beck et al). There are numerous articles claiming that a variety of antivirals are effective against SARS-CoV as well (e.g., Stockman et al., 2006). However, none of these reports rise to the evidence standard of well designed randomized clinical trials.
Han H	In a MedRXiv preprint February 29, Han H report the results of a study that used chain-of-infection data from outside the Wuhan regions to estimate the incubation period for COVID-19. The study found that the incubation periods of the patients aged >=40 years and age<40 years showed a statistically significant difference, with the former (older) group having a longer incubation period and a larger variance than the latter. It is suggested that different quarantine times should be applied to the groups to reflect this difference. No significant difference was found between the incubation periods of males and females.
Lan et al.	Lan et al. report that four patients treated for COVID-19 and subsequently testing negative twice 24 hours apart became positive again by PCR several days later. "These findings suggest that at least a proportion of recovered patients still may be virus carriers. Although no family members were infected, all reported patients were medical professionals and took special care during home quarantine. Current criteria for hospital discharge or discontinuation of quarantine and continued patient management may need to be reevaluated. Although false-negative RT-PCR test results could have occurred as suggested by a previous study,6 2 consecutively negative RT-PCR test results plus evidence from clinical characteristics and chest CT findings suggested that the 4 patients qualified for hospital discharge or discontinuation of quarantine. The study was limited to a small number of patients with mild or moderate infection. Further studies should follow up patients who are not health care professionals and who have more severe infection after hospital discharge or discontinuation of quarantine. Longitudinal studies on a larger cohort would help to understand the prognosis of the disease."
Cai G.	Cai G. reports that a gene-smoking interaction may explain the findings of a study that revealed a higher level of the ACE2 receptor in Asian smokers than Asian non-smokers, but no difference between Caucasian smokers and non-smokers. The author interprets the results as indicating that smokers, especially former smokers, may be more susceptible to 2019-nCov and have infection paths

	different from those of non-smokers, and that smoking history may provide valuable information in identifying susceptible population and standardizing treatment regimen.
Ji Y et al.	In the Lancet, Ji Y et al. reported on February 26 the results of a study investigating the relationship between health care resources and COVID-19 case fatality rates seen in various affected regions. They found that plotting mortality against the incidence of COVID-19 (cumulative number of confirmed cases since the start of the outbreak, per 10 000 population) showed a significant positive correlation, suggesting that mortality is correlated with health-care burden. The authors state that there are substantial regional disparities in health-care resource availability and accessibility in China and suggest that these might partly explain the low mortality rates—despite high numbers of cases—in the most developed southeastern coastal provinces, such as Zhejiang (0 deaths among 1171 confirmed cases) and Guangdong (four deaths among 1322 cases [0·3%]). This seems to be supported by stories in the media describe an overburdened health care system in Wuhan, with late diagnosis and late or no treatment of cases in the earlier stages of the outbreak, which could possibly have contributed to the much higher fatality ratios seen in Hubei.
Xu et al. **Battegay et al.** **Wilson et al.**	A study published by Xu et al. (see Section 6) showed that cases seen in Zhejiang province were generally milder than those in Wuhan, and attributed this finding to the cases in Zhejiang being further down the chain of transmission of the virus than those in Wuhan. The number of fatalities and cCFR outside of Hubei may continue to increase due to the lag in outbreak start dates in the rest of the mainland compared to Hubei; however, so far, the cCFR outside Hubei, although tripled from 0.2% to 0.6% in the last 2 weeks, remains far lower than that in Hubei. It is possible that there is a true difference between the cCFRs of Hubei and other regions within and outside mainland China because of a difference in the level of preparedness, case management and treatment in Hubei vs. elsewhere, delays in reporting mortalities and/or differences in the criteria for testing for the virus. Of their findings from data from 1,099 patients with COVID-19 from 31 mainland China provinces, Guan et al note that: "The fatality rate was lower (0.88%) when incorporating additional pilot data from Guangdong province (N=603) where effective prevention has been undertaken (unpublished data)… Early isolation, early diagnosis and early management might have collectively contributed to the marked reduction in mortality in Guangdong." However, over 1000 of the 1099 cases followed in the study were still in hospital at the time the manuscript was written, meaning that estimates of mortality in this cohort may have been premature at the time. For a good discussion on the challenges of calculating a true case fatality rate, see Battegay et al. In a study adjusting for the lag in deaths associated with COVID-19, Wilson et al. have estimated a CFR of 1.37% (95%CI: 0.57% to 3.22%) for COVID-19 cases in countries outside China where the healthcare systems are working relatively normally.
Chinese Centres for Disease Control (CCDC)	A large study by the Chinese Centres for Disease Control (CCDC) of 44,672 confirmed cases in China as of Feb 11 reported that, as seen by the numbers of cases and mortalities reported so far, the cCFR is higher in Hubei than the rest of the country (2.9% vs 0.4%). The work points toward the virus being highly transmissible, with 1716 confirmed infections and 5 deaths among health care workers as of Feb 11. The study also identifies which existing illnesses put patients at risk, with cardiovascular disease leading, followed by diabetes, chronic respiratory disease and hypertension (see Section6). The epidemic curve of cases by onset date is reported to have shown a decline from the 23-26 of January up until Feb 11. The peak number of cases diagnosed per day peaked approximately a week and a half later on February 4th (see chart directly above), reflecting the trends seen recently in reported case numbers from other sources. A much higher percentage of health workers were classified as critical compared to the study population in general (14.6% vs. 4.7%). The study reported that 80.9% of infections were classified as mild, 13.8% as severe and 4.7% as critical. Fatality rate increased with age, highest in those over 80 years old, and higher in males.
Jin et al.	Jin et al. propose that the difference in severity and mortality between the sexes may be due to the fact that the ACE2 gene is located on the X-chromosome; it has been shown that circulating levels of the ACE2 receptor, the receptor by which both SARS-CoV-2 and SARS-CoV attack cells, are higher in

	men than in women. The levels of the receptor have also been shown to be higher in patients with diabetes or cardiovascular diseases. In reporting the results of their study on heart injury and COVID-19, Wu C et al. (MedRXiv February 29) conclude that: "Heart injury signs arise in COVID-19, especially in older patients, patients with hypertension and male patients with current smoking. COVID-19 virus might attack heart via inducing inflammatory storm. High levels of heart injury indicators on admission are associated with higher mortality and shorter survival days. COVID-19 patients with signs of heart injury on admission must be early identified and carefully managed by cardiologists, because COVID-19 is never just confined to respiratory injury."
Caramelo et al.	Caramelo et al. have explored the differential case fatality rates observed by determining the risk of categories of patient, given the patients' characteristics. They found age to be the variable most associated with the risk of COVID-19 mortality, with 60y or older patients having an OR of mortality of 18.8 (CI95%[7.2; 41.5]). Regarding comorbidities, cardiovascular disease appeared to be the riskiest (OR=12.8 CI95%[10.3; 15.9], along with chronic respiratory disease (OR=7.8 CI95%[5.5; 10.4]). Findings corroborated those of other studies: males are more likely to die from COVID-19 (OR=1.8 (CI95%[1. 6; 2.1]). Results of a study by Li J et al. (MedRXiv Feb 29) also found this difference between the sexes; men were found to be more likely to have more complicated clinical disease and worse in-hospital outcomes than women.
Guan W et al.	In a study on1,590 laboratory-confirmed hospitalized COVID-19 patients in China, Guan W et al.found that: "Patients with two or more comorbidities had significantly escalated risks of reaching to the composite endpoint compared with those who had a single comorbidity, and even more so as compared with those without (all P<0.05). After adjusting for age and smoking status, patients with COPD (HR 2.681, 95%CI 1.424-5.048), diabetes (HR 1.59, 95%CI 1.03-2.45), hypertension (HR 1.58, 95%CI 1.07-2.32) and malignancy (HR 3.50, 95%CI 1.60-7.64) were more likely to reach to the composite endpoints than those without. As compared with patients without comorbidity, the HR (95%CI) was 1.79 (95%CI 1.16-2.77) among patients with at least one comorbidity and 2.59 (95%CI 1.61-4.17) among patients with two or more comorbidities. Conclusion: Comorbidities are present in around one fourth of patients with COVID-19 in China, and predispose to poorer clinical outcomes."
Chen et al.	Reports indicate that plasma from recovered patients may help in the treatment of critically ill cases. More than 10 have been cases treated to date and results seem promising. Calls for blood donations from recovered patients. China's National Health Commission has listed plasma among treatment measures for critically ill patients in its latest treatment guideline. Chen et al. discuss this in a letter the Lancet published February 27: "Evidence shows that convalescent plasma from patients who have recovered from viral infections can be used as a treatment without the occurrence of severe adverse events. Therefore, it might be worthwhile to test the safety and efficacy of convalescent plasma transfusion in SARS-CoV-2-infected patients."
Stockman et al., 2006 **Beck et al** **Richardson et al**	Reports from Thailand suggest that large doses of lopinavir and ritonavir (both commonly used to treat HIV infection) in combination with oseltamivir (influenza) are also effective. Genetic analysis and molecular modeling (Richardson et al) identifies several compounds that may be effective, as does AI-based modeling (Beck et al). There are numerous articles claiming that a variety of antivirals are effective against SARS-CoV as well (e.g., Stockman et al., 2006). However, none of these reports rise to the evidence standard of well designed randomized clinical trials.

Appendix 5: Estimates of COVID-19 Case Fatality

New Addition or Revision	Citation	Based on Data	Estimate
	Althaus, C.L. (2020, 4 Feb). Estimating case fatality ratio of 2019-nCoV from observed cases outside China. Unpublished Manuscript (University of Bern).	Cases outside of China through ~1 Feb, including a single death	CFR: 3.9% (95%CI: 0.2%-17.9%); while the single death makes this a very preliminary estimate, we include it so that readers can easily find updates to the authors' work
	Jung, Sung-mok et al. Real time estimation of the risk of death from novel coronavirus (2019-nCoV) infection: Inference using exported cases. Medrxiv preprint archive. https://doi.org/10.1101/2020.01.29.20019547		Scenario 1 (based on a growth rate starting Dec 8): 4.6% (95% CI: 3.1, 6.6) Scenario 2 (based on growth of exported cases): 7.7% (CI 4.9-11.3)
	Ferguson, N et al. Report 4: Severity of 2019-novel coronavirus (nCoV)		In Hubei: CFR = 18% (95% CI: 11%-81%) Outside of China: CFR = 1.2% to 5.6% depending on method ~1% (95%CI 0.5% to 4.0%) all case fatality rate
*	Yang et al. (2020). Epidemiological and clinical features of the 2019 novel coronavirus outbreak in China.		CFR estimates are adjusted for based on onset of disease and known outcomes (at the time, 58 confirmed cases were fatal): Based CFR for known outcomes: 1.44% CFR with patients with severe pneumonia: 5.88% Adjusted CFR for all confirmed cases 3.06% CFR for males: 4.45% CFR for females: 1.25% CFR for age >= 60: 5.30% CFR for age <= 60: 1.43% CFR for severe pneumonia: 6.23% CFR for long time until diagnosis: 3.07% CFR for <5 days to diag: 1.34%

Appendix 6a: Studies on transmissibility of COVID-19

Study	Summary
Kang et al	Kang et al have published a study that included analysis of exposures of 100 cases confirmed in Guangdong province during the month of January. They found that 84% of cases had traveled to Hubei. Average duration from onset of symptoms to diagnosis was 5.4 days. Of all of the cases, 84 (44.6%) were identified in 31 cluster infections, including family clusters. Genetic analysis of isolated virus from cases in the study indicated stability in the virus, with no mutations identified, in contrast to SARS early in that epidemic. The authors conclude that the strain is already established in humans, and was already well established in humans when it was first identified and human infections were considered to be spill-over infections from animals.
Lu et al.	in a letter to the Lancet published Feb 6, Lu et al. suggest that, as in the case of SARS, ocular transmission of SARS-CoV-2 may be a possibility. Quote: "On Jan 22, Guangfa Wang, a member of the national expert panel on pneumonia, reported that he was infected by [SARS-CoV-2] during the inspection in Wuhan. He wore an N95 mask but did not wear anything to protect his eyes. Several days before the onset of pneumonia, Wang complained of redness of the eyes. Unprotected exposure of the eyes to [SARS-CoV-2] in the Wuhan Fever Clinic might have allowed the virus to infect the body." Further, the authors state: "The fact that exposed mucous membranes and unprotected eyes increased the risk of SARS-CoV transmission suggests that exposure of unprotected eyes to SARS-CoV-2 could cause acute respiratory infection."
Favre et al.	In a letter to the Lancet published Feb 6, Favre et al express concern that SARS-CoV-2 infection may increase the risk of complications in pregnant women: "Members of the coronavirus family responsible for severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV) are known to be responsible for severe complications during pregnancy." The authors recommend systematic screening of any suspected SARS-CoV-2 infection during pregnancy and follow-up for cases found to be positive during pregnancy.
Wang and Zhang	Comment in the Lancet: The basic and essential strategies that we should stick to remain the early detection, early diagnosis, early isolation, and early treatment of the disease. With the huge efforts from medical professionals to treat patients, substantial public health prevention measures, and accelerated research, we hope the downward turning points for both new cases of COVID-19 and the resulting fatal events might come soon.
Drosten et al.	Additional research on the German cases, confirmed by two laboratories, shows that the virus is reproducing in the nasopharynx and GI tract and is likely communicable even while cases have very mild symptoms resembling the common cold
Holshue et al.	Analysis of information collected on exposure of the first 425 cases in Wuhan for which medical intervention was needed indicated that, like the first case of COVID-19 confirmed in the USA and discussed by Holshue et al., over 70% of cases confirmed after January 1st reported no known contact with a symptomatic case. This may imply that the infection can be easily transmitted by casual or indirect contact with symptomatic cases and/or by close contact with asymptomatic cases. The apparent failure of cases imported by other countries from China to generate large numbers of secondary cases may imply the latter rather than the former.
	The Robert Koch Institute in Germany alleges that NEJM case study on the first German cases, which indicated that the Chinese national who brought the disease to Germany was asymptomatic, is incorrect. The authors did not contact the index case but relied on observations from her colleagues; when contacted by RKI, she indicated that she had experienced very mild symptoms while in Germany. That said, the article still claimed that the first German patient infected two of his contacts within a short period of time of becoming infected himself and several days before he reported symptoms. They also reported a continued high viral load after symptoms ceased. However, the overall credibility of this case study is undermined by the authors' failure to do necessary due diligence.

	Anecdotal evidence and case reports (such as those on the Vietnam case) published to date indicate that transmission occurs primarily by close contact, though no details are available on the exact duration and nature of contact necessary for effective transmission. On the other hand, reports emerging from Singapore indicate that at least two local people were infected by a Chinese tour group that visited their store, indicating that casual contact may be sufficient to transmit the virus, but these reports do not detail the duration of contact.
Holshue et al.	Reports suggest that the gastrointestinal tract may be a potential route of infection for SARS-CoV-2, which is not unexpected in view of the fact that gastrointestinal symptoms of infection can occur, and Holshue et al. isolated the virus from stool of a patient with GI symptoms.
Wang et al.	Wang M et al, in a study posted as a MedRXiv preprint February 25, investigated the effect of ambient temperature on the transmission of SARS-CoV-2, found that an ideal temperature range seems to exist that favours transmission of the virus, and that lower temperatures may increase transmission. They postulate that the lower temperatures in Wuhan may have partly explained the higher levels of transmission seen there, and suggest that countries and regions with lower temperatures should adopt the strictest control measures to prevent or minimize transmission.
Cheung et al.	Cheung et al. published a letter in The Lancet February 24 a letter describing the approach to managing the risks to health-care staff involved in managing the treatment of COVID-19 patients at the ICU at a hospital in Sheung Shui, Hong Kong, while maintaining optimal and high-quality care. The authors make several recommendatios, including that endotracheal intubation be done by an expert specialised in the procedure, and that early intubation should be considered in a patient with deteriorating respiratory condition. The authors also suggest that for all cases, backup airway plans should be ready. For other recommendations, see the article.
Hu Z et al.	Hu Z et al., in February 25 MedRXiv preprint, describe their findings in the investigation of 24 asymptomatic contacts of COVID-19 patients who tested positive for SARS-CoV-2: "The median communicable period, defined as the interval from the first day of positive nucleic acid tests to the first day of continuous negative tests, was 9.5 days (up to 21 days among the 24 asymptomatic cases). Through epidemiological investigation, we observed a typical asymptomatic transmission to the cohabiting family members, which even caused severe COVID-19 pneumonia. Interpretation: The asymptomatic carriers identified from close contacts were prone to be mildly ill during hospitalization. However, the communicable period could be up to three weeks and the communicated patients [secondary cases from asymptomatic transmission] could develop severe illness. These results highlighted the importance of close contact tracing and longitudinal surveillance via virus nucleic acid tests. Further isolation recommendation and continuous nucleic acid tests may also be recommended to the patients discharged."
Zhang W et al.	In an article published in Emerging Microbes and Infections, Zhang W et al. detected SARS-CoV-2 in anal swabs and blood as well as in oral swabs, with more anal than oral swab positive in later stages of infection. Of 15 patients who were found to be still carrying the virus after several days of medical treatment, 2 were positive by both oral swab and anal swab, but none of the blood positive cases were also swab-positive. The conclusion was that viral nucleotide may be found in anal swabs or blood even if not detectable in oral swabs, and although swabs may be negative, the patient might still be viremic. Because of its presence in anal swabs, the authors suggest that the virus can therefore be transmitted via the oral–fecal route as well as the more widely recognized routes of infection. The study also used a serology test and report that it improved the detection rate of cases and therefore should be considered for the diagnosis of cases.
Zhou et al.	Zhou et al. studied viral loads present in nasal and throat swabs from 17 patients with COVID-19. The authors found that, unlike what was observed for SARS-CoV, where transmission occurred mainly after days of illness with viral loads peaking approximately 10 days after symptom onset, "Higher viral loads [of SARS-CoV-2] … were detected soon after symptom onset, with higher viral loads detected in the nose than in the throat." The authors state: "Our analysis suggests that the viral nucleic acid shedding

	pattern of patients infected with SARS-CoV-2 resembles that of patients with influenza and appears different from that seen in patients infected with SARS-CoV. The viral load that was detected in the asymptomatic patient was similar to that in the symptomatic patients, which suggests the transmission potential of asymptomatic or minimally symptomatic patients. These findings are in concordance with reports that transmission may occur early in the course of infection and suggest that case detection and isolation may require strategies different from those required for the control of SARS-CoV."
Hoehl et al	Hoehl et al. describe the repatriation of 126 mostly German nationals from Hubei to Frankfurt, Germany, with and symptom-screening at the airport on arrival. Diagnostic throat-swab testing was also offered, and 114 of the 115 passengers who had passed triage accepted. Of those 114, two passengers were found to be positive for the virus, including by culture which indicated an increased likelihood of infectivity. The authors point out that symptom screening had been ineffective in detecting those asymptomatic infections and shedding. In a letter to The Lancet, Pan et al. also describe asymptomatic infection in two members of a family of three with SARS-CoV-2; the third family member was symptomatic.
Wang X et al.	In a study posted February 19, Wang X et al. retrospectively collected infection data from a hospital of Wuhan University. They found that N95 respirators, disinfection and hand washing helped to reduce the risk of 2019-nCoV infection in medical staff: the medical staff in some departments of the hospital wore N95 respirator and disinfected and cleaned hands frequently, whereas those in other departments wore no medical masks and disinfected and cleaned hands only occasionally. In spite of higher exposure to COVID-19 cases, zero of 278 from the N95 group were infected by 2019-nCoV, while 10 out of 213 (77+136) from the no-mask group were confirmed infected. Similar results were observed at other hospitals. Chang et al. in a letter the Lancet, emphasize the importance of personal protective equipment for healthcare workers in this outbreak: "aggressive measures (such as N95 masks, goggles, and protective gowns) [are warranted] to ensure the safety of health-care workers during this COVID-19 outbreak."
Linton et al.	Linton et al., in a study posted February 18, found that the incubation period for COVID-19 falls within the range of 2-14 days with 95% confidence and has a mean of around 5 days. The mean time from illness onset to hospital admission (for treatment and/or isolation) was estimated at 3-4 days or 5-9 days, depending on the meth of estimation used. Based on the 95th percentile estimate of the incubation period, the authors recommend that the length of quarantine should be at least 14 days. However, Leung C estimated the distribution of incubation periods of patients infected in and outside Hubei province of China using clinical data collected from the individual cases reported by the media as they were not fully available on the official pages of the Chinese health authorities. That study found that the incubation period of patients with no travel history to Hubei was longer and more volatile than that of patients associated with Hubei. Leung recommends that the duration of quarantine should be extended to at least 3 weeks.
Keeling et al.	Using recent estimated for COVID-19 transmission, Keeling et al. have investigated the likely efficacy of the current UK definition of a close contact (within 2 meters for 15 minutes or more) for contact tracing, and the distribution of secondary cases that may go untraced using that definition. They found that that fewer than 1 in 5 cases will generate any subsequent untraced cases, although the use of this definition for a contact results in a high logistical burden, with an average of 36.1 individuals (95th percentiles 0-182) traced per case. The authors state that "Changes to the definition of a close contact can reduce this burden, but with[an] increased risk of untraced cases; we estimate that any definition where close contact requires more than 4 hours of contact is likely to lead to uncontrolled spread."
Nishiura et al.	In a study using dates of illness onset for primary cases (infectors) and secondary cases (infectees) from published research articles and case investigation reports , Nishiura et al estimated a median serial interval (the duration of time between the onset of symptoms in a primary case and the onset of symptoms in a secondary case infected by the primary case) for SARS-CoV-2 of 4.6 days and concluded that a substantial proportion of secondary transmission may occur prior to illness onset,

	providing further evidence of the asymptomatic and pre-symptomatic transmission suggested by several anecdotal accounts to date.
Zhao et al.	In a study posted February 25, Zhao S et al. suggest that the serial interval of the virus may be shorter than the preliminary estimates in previous works. The authors conclude that, as SI could likely be shorter than the incubation period, pre-symptomatic transmission may occur, and that extra efforts on timely contact tracing and quarantine are recommended in combating the COVID-19 outbreak.
Shen et al.	Shen et al. evaluated the impact of lockdown on the 2019-nCov epidemic in Hubei province, China and concluded that it appears to have been effective in reducing about 60% of new infections and deaths, and that its effect also appears to be sustainable even after its removal. However, they acknowledge that the economic impact of the lockdown remains to be seen.
Mizumoto et al	Using an ecological modelling approach, Mizumoto et al have estimated an R_0 of 7.05 in Wuhan City early in the outbreak, with enhanced public health measures apparently decreasing that to about 3.24 since January 23rd.They estimate the total number of infections in Wuhan at nearly 1,000,000 (9.8% of the population), with a crude infection fatality ratio (IFR) and time–delay adjusted IFR is estimated to be 0.07% (95% CrI: 0.05%–0.09%) and 0.23% (95%CrI: 0.17–0.30% respectively - several orders of magnitude smaller than the crude cCFR at 4.06%
Pongpirul et al.;	An account in the New England Journal of Medicine of the infection of a Thai taxi driver who, like a taxi driver in Japan who recently tested positive used his vehicle to transport tourists from China, mentions that all household contacts as well as 10 other close contacts tested negative for the virus, although this Thai case was diagnosed relatively late in the course of his illness. Contrasting with reports of infections apparently having been contracted even by indirect contact or no known contact with a case, this report suggests that the capability of a case to transmit the infection can vary, for reasons that are currently unclear.
Zhou et al.; **Xia et al.**	Zhou et al located SARS-CoV-2 in the ocular fluid of 3 of 67 confirmed and suspected cases; the authors argue that ocular transmission is not supported by this data. Xia et al. reported February 26 that the virus had been found in tear and conjunctival secretions from one of 30 COVID-19 patients, with samples from the other patients being negative.
Yaqian et al.	Yaqian et al. conducted a systematic review of the published literature to compare SARS and COVID-19. They report that fever, cough and malaise/fatigue were the most common symptoms in both SARS and COVID-19, but in general, the clinical symptoms and signs of COVID-19 were not obvious. Compared with SARS, COVID-19 was transmitted in a more diverse way from person to person, with asymptomatic cases and possible fecal-oral transmission, creating the conditions for a large-scale spread. The overall infection rate of healthcare workers of was lower for COVID-19 (3.9%) than for SARS (40.0%). In general, the authors found that the epidemiological and clinical characteristics of SARS and COVID-19 in China are very similar, but in general, COVID-19 is transmitted in more diverse ways and is more infectious, so the early recognition of disease in healthcare workers and patients is very important.
Zhang KK et al.	Through epidemiological analysis, Zhang KK et al. characterized the fast transmission of COVID-19 with a basic reproductive number of 5.6 and have reported that the study proved a sole zoonotic source originating in Wuhan. No changes in transmission was noted across generations of the virus. By evaluating different control strategies through predictive modeling and simulations, a comprehensive quarantine in hospitals and quarantine stations was found to be the most effective approach to control of spread of the outbreak.
Du et al.	Du et al. analyzed the serial intervals of 468 infector-infectee pairs with confirmed COVID-19. The serial intervals ranged from -11 days to 20 days, with a mean of 3.96 days (95% confidence interval: 3.53-4.39) and a standard deviation of 4.75 days (95% confidence interval: 4.46-5.07). The authors found that 12.1% of reports indicating pre-symptomatic transmission. This study adds to the evidence of asymptomatic transmission previously reported by Nishiura et al and Zhao et al..

Mizumoto et al.	Employing a statistical modeling analysis, Mizumoto et al. derived a delay-adjusted asymptomatic ratio of the positive 2019-nCoV infections onboard the Princess Cruises ship along with the timeline of infections. They estimated the percentage of cases that are asymptomatic to be 34.6% (95% CrI: 29.4%-39.8%), with most of the infections occurring before the start of the 2-week quarantine.
Liu Y et al.	Drawing on data from 9 reports of secondary transmission at events, Liu Y et al. estimated 48 secondary infections occurred among 137 attendees. Assuming that all the secondary infections were generated by a single primary case, which was probable given the short-term nature of the exposure events, the authors estimated a secondary attack rate among close contacts of 35% (95% CI 27–44).
Sun X et al.	Sun X et al. did a cross-sectional study of 102 patients with a COVID-19 diagnosis in China from December 30, 2019 to February 7, 2020 to examine whether they could find evidence of ocular transmission of the virus. They found SARS-COV-2 RNA fragments in the ocular discharges of only one of the two patients with conjunctivitis. Authors' conclusions: "Although we suspect the incidence of SARS-COV-2 infection through the ocular surface is extremely low, the nosocomial infection of SARS-CoV-2 through the eyes after occupational exposure is a potential route. The inefficient diagnostic method and the sampling time lag may contribute to the lower positive rate of conjunctival swab samples of SARS-COV-2. Therefore, to lower the SARS-COV-2 nosocomial infection, protective goggles should be worn [by] all health care workers."
Anzhai et al.	Anzhai et al. analyzed data on confirmed cases diagnosed outside China to estimate the impact of travel reduction the number of exported cases, the probability of a major epidemic, and the time delay to a major epidemic. They estimated that 226 exported cases (95% confidence interval: 86, 449) were prevented from 28 January to 7 February 2020 - a 70.4% reduction in incidence compared to the counterfactual scenario. With a median time delay to a major epidemic of only two days or less, the authors conclude that the decision to control travel volume through restrictions on freedom of movement should be balanced between the resulting estimated epidemiological impact and predicted economic fallout.
Jackson ML et al.	Jackson ML et al. estimated the impact of a weather-related social distancing event (closures of schools and workplaces in February 2020 due to weather) on transmission of respiratory viruses in the greater Seattle metropolitan area. They found that reductions in the incidence of viruses were greatest for those viruses that were peaking when the disruption occurred and least for viruses in early epidemic phase. The authors conclude that high-intensity, short-duration social distancing measures may substantially reduce total incidence in a respiratory virus epidemic if implemented near the epidemic peak. This study may be of relevance when appropriate public health measures are being considered for mitigation of COVID-19 epidemics within countries and regions.
Nishiura H et al.	In a March 3 MedRXiv preprint, Nishiura H et al. report the results of a study on secondary transmission data to identify high risk transmission settings. Their findings add to those of the Seattle study (Jackson et al.) with respect to COVID-19: "We show that closed environments contribute to secondary transmission of COVID-19 and promote superspreading events. Closed environments are consistent with large-scale COVID-19 transmission events such as that of the ski chalet-associated cluster in France and the church- and hospital-associated clusters in South Korea. Our findings are also consistent with the declining incidence of COVID-19 cases in China, as gathering in closed environments was prohibited in the wake of the rapid spread of the disease. Reduction of unnecessary close contact in closed environments may help prevent large case clusters and superspreading events."
Kissler et al.	Using data from the United States, Kissler et al. (MedRXiv preprint March 6) measured how seasonality, the duration of immunity, and the strength of cross-immunity to/from the other human coronaviruses affect transmission of human betacoronaviruses HCoV-OC43 and HCoV-HKU1. They then built a mathematical model to simulate transmission of SARS-CoV-2 through the year 2025. The results indicated that recurrent wintertime outbreaks of SARS-CoV-2 will probably occur after an initial pandemic wave. The authors identify key data still needed to distinguish plausible transmission

	scenarios, most importantly longitudinal serological studies to determine the duration of immunity to SARS-CoV-2.
Xia W et al.	Xia W et al. (MedRXiv preprint Mar 8) evaluated transmission of SARS-CoV2 by asymptomatic cases during the incubation period using data from 124 cases. The estimated mean incubation period for COVID-19 was 4.9 days (95% confidence interval [CI], 4.4 to 5.4) days, ranging from 0.8 to 11.1 days (2.5th to 97.5th percentile). The infectious curve showed that in 73.0% of the secondary cases, their date of getting infected was before symptom onset of the first-generation cases, particularly in the last three days of the incubation period. The authors conclude that the transmission of COVID-19 occurs among close contacts during the incubation period, which may lead to a quarantine loophole. They suggest that strong and effective countermeasures should be implemented to prevent or mitigate asymptomatic transmission during the incubation period in populations at high risk.
Tindale L et al. **Qui C et al.**	Tindale L et al., also in a MedRXiv preprint (March 6) describing a similar study, add to the body of evidence supporting pre-symptomatic transmission: "Estimated serial intervals are shorter than incubation periods in both Singapore and Tianjin, suggesting that pre-symptomatic transmission is occurring. Shorter serial intervals lead to lower estimates of R_0, which suggest that half of all secondary infections should be prevented to control spread." Qui C et al. (MedRXiv preprint Mar 6), in their analysis of cases of COVID-19 outside Wuhan, report that "5 asymptomatic infections were found and 2 of them infected their relatives".
Oliveiros et al.	Oliveiros et al., in a Mar 8 MedRXiv preprint, reported the results of a study on cases in China investigating the predicted effect of temperature and humidity on the transmission of SARS-CoV2. Results suggested a decrease in the rate of progression of COVID-19 in the northern hemisphere with the arrival of spring and summer, with a 20^{o}C increase expected to delay the doubling time in 1.8 days.
Zhao Z et al.	Using mathematical modeling, Zhao Z et al. (MedRXiv preprint March 8) investigated age-specific transmissibility of SARS-CoV2 in age groups <= 14 years, 15-44 years, 45-64 years and >= 65 years) in groups <= 5 years, 6-14 years, 15-24 years, 25-59 years and >= 60 years. Results showed that SARS-CoV-2 has high transmissibility among adults and elder people but relatively low transmissibility among children and young people.
Zhuang Z et al.	Zhuang Z et al., in a March 10 MedRXiv preprint, report estimates of R_0 for the outbreaks in South Korea (2.6 [95% CI: 2.3-2.9]) or 3.2 [95% CI: 2.9-3.5]) and Italy (2.6 [95% CI: 2.3-2.9] or 3.3 [95% CI: 3.0-3.6]). The authors report that estimates of dispersion term (k) implied few super-spreading events in both countries.
Zhang L et al. **Tang X et al.**	Two studies indicate that there appear to be two strains of SARS-CoV-2 with different levels of transmissibility: Zhang L et al., in a March 5 MedRXiv preprint, report that their genomic analysis of 169 genomes of the virus suggested two major genotypes, which they denoted Type I (A and B) and Type II, with Type IA most closely resembling the ancestral SARS-CoV-2. The authors propose that Type II likely evolved from Type I and was more prevalent than Type I. as well as more contagious (transmissible) than Type I. And Tang X et al. report similar findings in the National Science Review: population genetic analyses of 103 SARS-CoV-2 genomes indicated that the viruses had evolved into two major types (designated L and S, with the L type (~70%) being more prevalent and more transmissible than the S type (~30%). The S type was found to be the ancestral version. They found that whereas the L type was more prevalent in the early stages of the outbreak in Wuhan, the frequency of the L type decreased after early January 2020. The authors state that it is unclear whether the virulence of the two types differs.
Bi Q et al.	Using case details of 391 SARS-CoV-2 cases in Shenzen, China from January 14 to February 12, 2020 and 1,286 close contacts, Bi Q et al. estimate metrics of disease transmission and analyze factors influencing transmission risk (MedRXiv preprint March 4). They found that household contacts and those travelling with a case where at higher risk of infection (ORs 6 and 7) than other close contacts. The household secondary attack rate was 15%, and children were as likely to be infected as adults, although less likely to have severe symptoms.

Hellewell et al.	Hellewell et al. modeled several scenarios to examine the efficacy of contact tracing and isolation, finding that to achieve control of 90% of outbreaks, 80% of contacts needed to be traced and isolated for scenarios with a reproduction number of 2·5. The proportion of contacts that must be isolated increased as R_0 and the delay between symptom onset and isolation increased. The authors concluded that: "In most scenarios, highly effective contact tracing and case isolation is enough to control a new outbreak of COVID-19 within 3 months. The probability of control decreases with long delays from symptom onset to isolation, fewer cases ascertained by contact tracing, and increasing transmission before symptoms." And in The Lancet (March 5), Wilder-Smith et al. express the view that the COVID-19 epidemic appears to be different from that of SARS in 2003, and that "Clear differences are emerging, such as in transmissibility and severity pyramids; COVID-19 has a higher transmissibility than SARS, and many more patients with COVID-19 rather than SARS have mild symptoms that contribute to spread because these patients are often missed and not isolated. Because of the extent of community spread, traditional public health measures might not be able to halt all human-to-human transmission, and we need to consider moving from containment to mitigation."
Jiang Y et al,	Jiang Y et al, in a Feb 2 MedRXiv preprint, report that: "Viruses [SARS-CoV-2] could be detected on the surfaces of the nurse station in the isolation area with suspected patients and in the air of the isolation ward with an intensive care patient. Conclusion: Comprehensive monitoring of hospital environmental hygiene during pandemic outbreaks is conducive to the refinement of hospital infection control. It is of great significance to ensure the safety of medical treatment and the quality of hospital infection control through the monitoring of environmental hygiene." In the Discussion, the authors report that: " …samples from the same collection points were tested after a series of infection prevention and control measures were taken, such as continuous use of an air disinfection machine for the disinfection of ward air; extending the frequency of disinfection for ground and object surfaces; changing gloves and cleaning hands after operations and leaving the ward; and covering computer keyboards and changing the cover each day. Following the implementation of these measures, the results were negative, showing effectiveness of disinfection." And Ong et al. report in JAMA that in their Singapore study, significant environmental contamination through respiratory droplets and fecal shedding was found in airborne in infection isolation rooms containing symptomatic patients with SARS-CoV-2, suggesting the environment as a potential medium of transmission and supporting the need for strict adherence to environmental and hand hygiene.
Wang Y and Teunis FM	Wang Y and Teunis FM (MedRXiv preprint March 16) investigated the differences in infection rates and transmission patterns across mainland China (Hubei province vs. elsewhere). They found that for early transmission in Wuhan, any infectious case produced as many as four new cases, while transmission outside Wuhan was less intense, with $R_0<2$. "During the rapid growth phase of the outbreak the region of Wuhan city acted as a hot spot, generating new cases upon contact, while locally, in other provinces, transmission was low. Interpretation COVID-19 is capable of spreading very rapidly…" Like other studies, this work found that small children and elderly people were equally likely to transmit infection as any other age group. The authors also state: "The rapid spread of COVID-19 in South Korea (from 31 cases on 18 February to 2,022 cases on 28 February) and Italy (from 20 cases on 21 February to 650 cases on 28 February), shows how missed infectious subjects may cause rapid transmission within a very short period, due to the combination of a short serial interval and an occasionally high reproduction number."
Tan LV et al.	Tan LV et al. (MedRXiv preprint March 16) describe the length of time after infection and treatment for which an COVID-19 patient in Vietnam shed SARS-CoV-2. ‘‘Despite clinical recovery, SARS-CoV-2 RNA remained detectable by real time RT-PCR in throat and rectal swabs until day 11 and 18 of hospitalization, respectively [i.e., 2 and 9 days respectively after patient had improved and no longer required supplemental oxygen]. Because live SARS-CoV-2 has been successfully isolated from a stool sample from a COVID-19 patient in China, the results demonstrate that COVID-19 patients may remain infectious for long periods, and fecal-oral transmission may be possible. Therefore, our finding has important implications for infection control."

Xing Y et al.	Xing Y et al. (MedRXiv preprint March 13) also investigated the length of shedding in cases of COVID-19; three mild to moderate pediatric cases in China were followed and throat and fecal shedding of virus assessed by RT-PCR. The authors report that clearance of SARS-CoV-2 in the respiratory tract occurred within two weeks after abatement of fever, whereas persistent presence of viral RNA was found in stools of all children. In one of the three cases, fecal samples turned negative 8 days after throat swabs cleared of the virus, while in another child fecal samples continued to test positive for an additional 20 days. "At the time of writing, one child still had positive results for RT-PCR analysis in stools after negative conversion of viral RNA in respiratory samples (over 19 days behind)…. Prolonged shedding of SARS-CoV-2 in stools of infected children indicates the potential for the virus to be transmitted through fecal excretion. Massive efforts should be made at all levels to prevent spreading of the infection among children after reopening of kindergartens and schools." However, the authors report that there was no evidence to show that any of these three cases transmitted the infection to others.
Van Doremalen et al.	A US group (Van Doremalen et al., MedRXiv preprint March 10; Lancet correspondence March 17) has investigated the stability of viable HCoV-19 [SARS-CoV-2] on surfaces and in aerosols in comparison with SARS-CoV-1. "Overall, stability is very similar between HCoV-19 and SARS-CoV-1. We found that viable virus could be detected in aerosols up to 3 hours post aerosolization, up to 4 hours on copper, up to 24 hours on cardboard and up to 2-3 days on plastic and stainless steel. HCoV-19 and SARS-CoV-1 exhibited similar half-lives in aerosols, with median estimates around 2.7 hours. Both viruses show relatively long viability on stainless steel and polypropylene compared to copper or cardboard: the median half-life estimate for HCoV-19 is around 13 hours on steel and around 16 hours on polypropylene. Our results indicate that aerosol and fomite transmission of HCoV-19 is plausible, as the virus can remain viable in aerosols for multiple hours and on surfaces up to days."

Other information on transmissibility of SARS-CoV-2:

- **Reproductive number:** Many of the new estimates for the basic reproductive number—the transmissibility of the virus in an immunologically naïve population with no attempts at infection control—of SARS-CoV-2 suggest it exceeds 4 (See Appendix 1). However, measurements of R over time suggest it is decreasing in Hubei and China, at least based on numbers of cases released by the Chinese government. For a reader-friendly discussion on the interpretation of R_0, see this article. For a discussion of the importance of propagating uncertainty estimates through R_0 calculations, see Sang Woo Park.
- With the emergence of COVID-19 on cruise ships, a reminder that the reproductive number of a virus is dependent on context and is generally higher in confined settings. A previous paper (Vynnycky et al.) reviewing the 1918 influenza pandemic estimates R of 1.2 to 3.0 in community settings (with substantial variation between cities) and 2.1 to 7.5 in confined settings such as ships and prisons (with substantial variation between contexts). The apparent high percentage of individuals positive for COVID-19 on the Diamond Princess cruise ship serves to illustrate this concept.
- **Asymptomatic transmission:** Of the 565 Japanese citizens evacuated from Wuhan screened for symptoms and tested using RT-PCR, 4 were positive symptomatic and 4 were positive asymptomatic. Hiroshi Nishiura and colleagues suggests that the asymptomatic ratio is therefore 50%. While Dr Nishiura is a respected modeler of infectious disease, the confidence interval on this estimate (95%CI 12.5%, 87.5%) is too wide to provide much insight, and the data was collected only 7 days after evacuees had left Wuhan, still well within the bounds of the incubation period. The paper does cite a study that influenza shows 56% to 80% asymptomatic infection.
- **Potential fecal transmission:** Hong Kong authorities partially evacuated a block of apartments as a precaution and placed residents in quarantine after a the country's 42nd case, a resident living 10 stories above the 10th

case, was diagnosed with COVID-19 approximately 12 days after the region's 10th case, and 2 of her household contacts became symptomatic. Possibility of airborne transmission via faeces was considered, but initial investigations into the building's drainage system has reduced those concerns, and five symptomatic individuals have all tested negative. Authorities have described the evacuation as a precautionary measure. In the 2003 SARS epidemic, numerous cases resulted from a superspreading event via airborne faecal transmission in Amoy Gardens, a block of apartments in Hong Kong. In the study by Guan et al., 4 (6.5%) of 62 stool specimens from confirmed cases tested positive for the virus. Multiple studies (Appendix 4) suggest that 10% or fewer of patients experience diarrhea, but it is unclear if loose stool and the presence of SARS-CoV-2 in stool usually co-occur. An et al. say that confirmed COVID-19 cases may present only with digestive symptoms. Liang et al suggest that prevalence of diarrhea during COVID-19 is underestimated.

- **Viral persistence:** A review of multiple studies suggests that coronavirus (as a family of viruses, not necessarily SARS-CoV-2) persists on surfaces for up to 9 days but can be efficiently inactivated with ethanol, hydrogen peroxide, or bleach (Kampf et al). The WHO has reported that according to information they have received, the virus can stay on surfaces for 'short periods'.
- **Nosocomial infection**: A review of 138 consecutive cases in a single Wuhan hospital suggests that 41% of cases were hospital acquired, including 40 healthcare workers (Wang et al.); a review of 1099 cases across China say that only 2% were in healthcare workers (Guan et al.). According to a WHO epidemiologist, to the knowledge of the Organization, there has only been one reported incident of an outbreak in a hospital in China. The outbreak involved 15 health workers. The WHO has recently released a clinical case report form to help in the standardized data collection for hospitalized patients. Data collected using this form should provide better quality data for surveillance and assessment of the modes and risk of transmission of the virus.
- **Incubation period:** believed to be between 1 and 10 days; mean seems to be about 5 days with a long tail (Appendix 3). However, a review of 1,099 cases in China estimates a median incubation period of 3.0 days, with a range from 0 to 24 days and with no statistically significant difference for severe vs. non-severe cases (Guan et al.) - ten days longer than previously recognized. However, a maximum observation/isolation period of 14 days seems justified by the data, with the caveat (modeled by Lauer et al.) that a small number of cases will exceed 14 days.
- **Other:** Promising findings from an investigation into the potential for intra-uterine transmission of SARS-CoV-2: 9 pregnant women infested with the virus were followed by Chen et al. through to the births of their babies; no virus was found in amniotic fluid, cord blood, and neonatal throat swab samples at birth, suggesting that no intrauterine fetal infections occurred as a result of COVID-19 infection during a late stage of pregnancy. Breastmilk samples were also negative. The authors state: "Our findings are in accordance with what was observed in SARS, which has a similar sequence to SARS-CoV-2.14 Previous studies have already shown no evidence of perinatal SARS infection among infants born to mothers who developed SARS infection during pregnancy." They acknowledge the limitation of a very small sample size. A comment has been published by Qiao in the Lancet on these findings.

Appendix 6b: Containment Efforts and Prevention of Transmission of SARS-CoV-2

Study	Summary
Teslya A et al.	Teslya A et al. (MedRXiv preprint March 16) developed a transmission model to evaluate the impact of self-imposed prevention measures (handwashing, mask-wearing, and social distancing) due to COVID-19 awareness, and of short-term government-imposed social distancing, on the peak number of diagnoses, attack rate and time until the peak number of diagnoses. The authors found that for fast awareness spread in the population, self-imposed measures can significantly reduce the attack rate and diminish and postpone the peak number of diagnoses. The findings indicated that a large epidemic can be prevented if the efficacy of these measures exceeds 50%. ‘‘Early implementation of short-term government interventions can only delay the peak….We stress the importance of a rapid spread of awareness on the use of self-imposed prevention measures in the population.”
Araujo MB et al.	Using existing data, Araujo MB et al. (MedRXiv preprint March 16) developed models that project monthly variation in climate suitability of SARS-CoV-2 Coronavirus throughout a typical climatological year. Results suggested a preference of SARS-CoV-2 for cool and dry conditions, like SARS-CoV. “Should the spread of SARS CoV-2 continue to follow current trends, a worst-case scenario of synchronous global pandemic is improbable. More probable is the emergence of asynchronous seasonal global outbreaks much like other respiratory diseases. People in temperate warm and cold climates are more vulnerable. Those in arid climates follow next in vulnerability, while the disease will likely marginally affect the tropics. Our projections minimize uncertainties related with spread of SARS CoV-2, providing critical information for anticipating the adequate social, economic and political responses.”
Sugishita Y et al.	Sugishita Y et al. (MedRXiv preprint March 16) evaluated the effect of the voluntary cancellation of sports and entertainment events for 2 weeks in late February and early March on the spread of COVID-19. Results suggested that the basic reproduction number, R_0, before the introduction of voluntary event cancellation (VEC), was 2.50 (95% confidence interval (CI) 2.43, 2.55) and the effective reproduction number, R_v, after VEC introduced was 1. 88 (95% CI 1.68,2.02). “Results demonstrated that VEC can reduce COVID−19 infectiousness by 35%, but R_0 remains higher than one.”
Lai S et al.	Using modeling, Lai S et al. (MedRXiv preprint March 13) assessed the effect of interventions in China on the COVID-19 outbreak in China. The authors found that without the interventions, “the number of COVID-19 cases would likely have shown a 67-fold increase (IQR: 44 - 94), with the effectiveness of different interventions varying. The early detection and isolation of cases was estimated to prevent more infections than travel restrictions and contact reductions, but integrated [interventions] would achieve the strongest and most rapid effect. If [interventions] could have been conducted one week, two weeks, or three weeks earlier in China, cases could have been reduced by 66%, 86%, and 95%, respectively, together with significantly reducing the number of affected areas. However, if [they] were conducted one week, two weeks, or three weeks later, the number of cases could have shown a 3-fold, 7-fold, and 18-fold increase across China, respectively.” Results of the study also suggested that the social distancing intervention should be continued for the next few months in China to prevent case numbers increasing following lifting of travel restrictions on February 17. “Conclusion: The NPIs deployed in China appear to be effectively containing the COVID-19 outbreak, but the efficacy of the different interventions varied, with the early case detection and contact reduction being the most effective. Moreover, deploying the NPIs early is also important to prevent further spread. Early and integrated NPI strategies should be prepared, adopted and adjusted to minimize health, social and economic impacts in affected regions around the World.”
Ferguson NM et al.	Ferguson NM et al. (Imperial College, London) also evaluated the effect of interventions, but specifically their effect on COVID-19 mortality and demands on the health-care system in the UK and US. Like Lai et al., the authors conclude that the effectiveness of any one intervention in isolation is likely to be limited, requiring multiple interventions to be combined to have a substantial impact on transmission. ‘‘We find that that optimal mitigation policies (combining home isolation of suspect

	cases, home quarantine of those living in the same household as suspect cases, and social distancing of the elderly and others at most risk of severe disease) might reduce peak healthcare demand by 2/3 and deaths by half. However, the resulting mitigated epidemic would still likely result in hundreds of thousands of deaths and health systems (most notably intensive care units) being overwhelmed many times over. For countries able to achieve it, this leaves suppression as the preferred policy option. We show that in the UK and US context, suppression will minimally require a combination of social distancing of the entire population, home isolation of cases and household quarantine of their family members. This may need to be supplemented by school and university closures, though it should be recognised that such closures may have negative impacts on health systems due to increased absenteeism. The major challenge of suppression is that this type of intensive intervention package – or something equivalently effective at reducing transmission – will need to be maintained until a vaccine becomes available (potentially 18 months or more) – given that we predict that transmission will quickly rebound if interventions are relaxed. We show that intermittent social distancing – triggered by trends in disease surveillance – may allow interventions to be relaxed temporarily in relative short time windows, but measures will need to be reintroduced if or when case numbers rebound. Last, while experience in China and now South Korea show that suppression is possible in the short term, it remains to be seen whether it is possible long-term, and whether the social and economic costs of the interventions adopted thus far can be reduced."
Bayham J et al.	In a March 13 MedRXiv preprint, Bayham J et al. analyzed data from the US Current Population Survey to measure the potential child care obligations for US healthcare workers that will need to be addressed if school closures are employed as a social distancing measure. Because the US healthcare sector has some of the highest child care obligations in the United States, results suggested that it was unclear whether the potential interruption of transmission resulting from school closures justifies the potential loss of healthcare workers from the standpoint of reducing cumulative mortality.
Kretschmar et al.	Kretschmar et al. (March 13, MedRXiv preprint) evaluated whether and under which conditions it is possible to control and slow down a COVID-19 epidemic in the early stages by isolation and contact tracing. Their analyses showed that transmissibility and the duration of the latent period relative to the duration of incubation period have strong impact on the controllability of the disease. Delays in diagnosis of cases and proportion of asymptomatic cases are key factors for containment and slowing down the epidemic. The authors conclude that Isolation and contact tracing can be an effective means to control early epidemics, but only if transmissibility as measured by R_0 is in the lower ranges of reported values. "Timeliness as well as completeness of tracing and diagnosis of cases are paramount to achieve containment and effective slowing down of the epidemic growth rate"… In conclusion, our results show that isolation and contact tracing are not expected to be able to fully control outbreaks of COVID-19, but are still important ingredients of effective containment strategies, as they are expected to reduce growth rates and increase epidemic doubling times. This is especially true when combined with transmission-reducing behavioral changes and interventions such as school closures and reducing community events."
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	combined with transmission-reducing behavioral changes and interventions such as school closures and reducing community events."
Jombart T et al.	Using a method applicable to the early stages of the COVID-19 epidemic, Jombart T et al. (MedRXiv preprint March 13) estimated, from newly reported deaths in a population without previous reports, the number of COVID-19 cases. "Our results suggest that by the time a single death occurs, hundreds to thousands of cases are likely to be present in that population. This suggests containment via contact tracing will be challenging at this point, and other response strategies should be considered." And Omori R et al. (MedRXiv preprint March 10) analyzed the epidemiological dataset of confirmed cases with COVID-19 in Japan as of 28 February 2020 and estimated the number of severe and non-severe cases, accounting for under-ascertainment. They found an estimated ascertainment rate of non-severe cases of 0.44 (95% confidence interval: 0.37, 0.50), indicating that [the true number of non-severe] cases would be more than twice the reported count, severe cases being twice more likely diagnosed and reported than other cases.
Tuite et al.	Tuite et al. (MedRXiv preprint Mar 6) identified 46 cases of COVID-19 reported in 21 countries between February 25-29, 2020, that were either in individuals with recent travel from Italy, or who had presumed infection by a traveler from Italy. They estimated the size of the underlying epidemic in Italy necessary in order for these cases to be observed with a reasonable probability, finding an estimated true outbreak size of 3971 cases (95% CI 2907-5297), as compared to a reported case count of 1128 on February 29, 2020, suggesting non-identification of 72% (61-79%) of cases. The authors used similar methods to estimate a much larger epidemic size in Iran, with a far greater degree of under-reporting, based on many fewer exported cases due to the relatively low volume of travel from Iran, relative to Italy. The authors suggest that "the numerous COVID-19 case exportations from Italy in recent days suggest an epidemic that is larger than official case counts suggest, and which is approximately on a par with that currently occurring in South Korea, which reports 3526 cases (and fewer deaths) as of February 29, 2020."
Lin et al.	Lin et al. looked at data collected prospectively from Jan. 20 to Feb. 19, 2020, at 8 hospitals from 135 patients tested for COVID-19; which represented 28% of the patients tested within Ontario in that period. The authors concluded that most patients currently being tested in emergency departments have mild illness and that these hospital visits are avoidable. They state that barriers to community-based assessment and testing for COVID-19 need to be urgently addressed in order to minimize emergency department overcrowding, infection of health care workers and risks to other acutely ill patients.
Neher L et al.	Neher L et al. (Feb 5 MedRXiv preprint) have explored how seasonal variation in transmissibility could modulate a SARS-CoV-2 pandemic. "Data from routine diagnostics show a strong and consistent seasonal variation of the four endemic coronaviruses (229E, HKU1, NL63, OC43) and we parameterize our model for SARS-CoV-2 using these data. The model allows for many subpopulations of different size with variable parameters. Simulations of different scenarios show that plausible parameters result in a small peak in early 2020 in temperate regions of the Northern Hemisphere and a larger peak in winter 2020/2021. Variation in transmission and migration rates can result in substantial variation in prevalence between regions. While the uncertainty in parameters is large, the scenarios we explore show that transient reductions in the incidence rate might be due to a combination of seasonal variation and infection control efforts but do not necessarily mean the epidemic is contained… The likely aggregated effect of seasonal variation, infection control measures and transmission rate variation is a prolonged pandemic wave with lower prevalence at any given time, thereby providing a window of opportunity for better preparation of health care systems."
Adalja et al.	Adalja et al. note, in a JAMA Viewpoint article: "As more and more countries report cases, including those with no link to the disease epicenter, it is clear that there are many more unrecognized cases in the world and that community transmission is happening in many countries." The authors also state that: "At this early stage of the epidemic, when numbers of cases are low, public health workers should track contacts of cases to the extent resources allow and have them stay home for the virus'

	incubation period of 2 weeks. However, beyond a certain threshold, it will no longer be feasible to track all contacts."
Anzhai et al.	Anzhai et al. analyzed data on confirmed cases diagnosed outside China to estimate the impact of travel reduction the number of exported cases, the probability of a major epidemic, and the time delay to a major epidemic. They estimated that 226 exported cases (95% confidence interval: 86, 449) were prevented from 28 January to 7 February 2020 - a 70.4% reduction in incidence compared to the counterfactual scenario. With a median time delay to a major epidemic of only two days or less, the authors conclude that the decision to control travel volume through restrictions on freedom of movement should be balanced between the resulting estimated epidemiological impact and predicted economic fallout.

Appendix 7: Testing and Screening Efficacy

<table>
<tr><td><u>Xing Q et al.</u></td><td>In a March 3, 2020 MedRXiv preprint, <u>Xing Q et al</u>. report that 88.5% of COVID-19 patients outside Wuhan in China tested positive for at least one other common respiratory pathogen. The authors recommend that SARS-CoV-2 be added to routine testing assays for respiratory viruses where possible, to prevent misdetection of the virus (i.e., missing COVID-19 co-infections in patients that test positive for common respiratory pathogens).</td></tr>
<tr><td><u>Ge Y et al</u>.</td><td><u>Ge Y et al</u>. state that mass screening and testing intervention (MSTI) might lead to increased transmission if not properly implemented. In a study published February 23, the authors investigate under which conditions MSTI is beneficial. Based on the results, they suggest that the effectiveness of this approach to control could be improved by the use of dedicated testing sites separate from the usual healthcare facilities. “Staff at those sites can be trained to follow protocols that reduce transmission risk. One could also ask symptomatic individuals to call a phone number and schedule a test, instead of allowing individuals to self-report at any time. With a scheduling system, crowding can be reduced, and when individuals show up at the scheduled time, they can be processed rapidly, thus reducing transmission risk.” The authors also suggest having a more specific case definition, ideally without losing sensitivity.” More refined case definitions, screening by experts using telemedicine approaches, or rapid home tests could all be options which reduce the pool of those considered at risk of being infected with the novel pathogen, thus increasing [the effectiveness of MSTI and reducing the total number of individuals going to testing sites].</td></tr>
<tr><td>Yang et al</td><td>Yang et al examined testing accuracy for different respiratory specimens for patients with mild and severe symptoms. Among 213 COVID-19 confirmed patients at varying days after symptom onset in Shenzhen, confirmation of infection via PCR on samples collected from the multiple sites revealed the following rates of samples testing positive:
<table>
<tr><td></td><td colspan="2">Throat</td><td colspan="2">Nasal</td><td colspan="2">Sputum</td><td colspan="2">BALF</td></tr>
<tr><td></td><td>Severe</td><td>Mild</td><td>Severe</td><td>Mild</td><td>Severe</td><td>Mild</td><td>Severe</td><td>Mild</td></tr>
<tr><td>0-7 days</td><td>60%</td><td>61%</td><td>73%</td><td>72%</td><td>89%</td><td>82%</td><td>NA</td><td>NA</td></tr>
<tr><td>8-14 days</td><td>50%</td><td>30%</td><td>72%</td><td>54%</td><td>83%</td><td>74%</td><td>100%</td><td>0%</td></tr>
<tr><td>15+ days</td><td>37%</td><td>11%</td><td>50%</td><td>55%</td><td>61%</td><td>43%</td><td>78%</td><td>NA</td></tr>
</table>
Sputum and bronchoalveolar lavage samples seem to give the highest positive rates. Mild cases tended to test positive less frequently. Viral loads were highest among sputum and BALF samples. Overall, the authors suggest that negative PCR tests should not be enough to exclude patients as potential cases if they have relevant symptoms and exposure history.</td></tr>
<tr><td><u>Chan et al</u></td><td>Repeat testing of initially negative cases appears to be the most reliable way of confirming or excluding SARS-CoV-2 infection. Study by <u>Chan et al</u> concludes that “repeat testing of upper respiratory tract samples or testing of lower respiratory tract samples [is] warranted in clinically suspected cases with an initially negative result in nasopharyngeal or throat swab.”</td></tr>
<tr><td>Gostic et al.

<u>Quilty et al.</u></td><td><u>Gostic et al.</u> estimate that under even optimal circumstances, traveler screening will miss at least half of cases because they are fundamentally undetectable due to lack of symptoms and lack of knowledge of exposure, and <u>Quilty et al.</u> predict that traveler screening will detect less than 40% of cases.</td></tr>
<tr><td><u>Suo T et al</u>.</td><td><u>Suo T et al</u>. (Mar 6 MedRXiv preprint) suggest droplet digital PCR (ddPCR) as an alternative method to real-time PCR (RT-PCR) for testing for SARS-CoV2 infection. The authors describe the disadvantages of RT-PCR for testing: “… the disadvantages of insufficient detection of RT-PCR are more and more prominent, especially the problem of detection dynamic range in the clinical application. At present, it has been found in clinical practice that some patients had fever, and chest CT showed symptoms of suspected viral pneumonia such as lower lobe lesions of the lungs, but the nucleic acid test of pharyngeal swab did not show positive results until 5-6 days after the onset of viral pneumonia. It was estimated that only 30 %-60 % positive results can be obtained among COVID-19 patients that further</td></tr>
</table>

	confirmed by chest CT. This might be explained by the relatively low viral load in the throat of patients and the sensitivity limitation of RT-PCR technology, which inevitably produced the false negatives during the clinical diagnosis, leading to a potential risk of viral transmission. Besides, supposed convalescent, who is about to discharge, also need multiple tests with negative results for confirmation. Therefore, it is a pressing need for a more sensitive and accurate detection method for the pathogenic detection." The authors report increased sensitivity when using ddPCR.
Liu L et al.	Liu L et al., in a March 8 MedRXiv preprint, describe a study of a serological assay for SARS-CoV-2 in 238 admitted hospital patients. Rresults showed that the antibody positive rates were very low in the first five days after initial onset of symptoms, and then rapidly increased as the disease progressed. After 10 days, the antibody positive rates were above 80%, up from less than 50%. On the other hand, while the positive rates of viral RNA stayed above 60% in the first 11 days after initial onset of symptoms, they then rapidly decreased. Half of the suspected patients with symptoms for 6-10 days were detected to be antibody positive. The authors conclude that before the 11th day after initial onset of symptoms, the nucleic acid test is useful for confirmation of viral infection, but the combination of nucleic acid testing and a serological assay can greatly improve the diagnostic efficacy. After the 11th day, the diagnosis for viral infection should be majorly dependent on serological assay.

Summary of studies on serological testing:
In the article by Zhang W et al. described in Section 4, the authors report that none of the patients with viremia had positive swabs. Quote: "These patients would likely be considered as 2019-nCoV negative through routine surveillance, and thus pose a threat to other people. In contrast, we found viral antibodies in near all patients, indicating serology should be considered for 2019-nCoV epidemiology. A possible shift from oral positive during early infection to anal swab positive during late infection can be observed. This observation implied that we cannot discharge a patient purely based on oral swabs negative, who may still shed the virus by oral–fecal route. Above all, we strongly suggest using viral IgM and IgG serological test to confirm an infection, considering the unreliable results from oral swabs detection. Quote from a news article in the British Medical Journal February 26 seems to support this approach: 'Richard Tedder, professor of medical virology at Imperial College London, said the phenomenon of "invisible spreaders" meant definitive testing resources would have to be stepped up. "The fact that so many potential infections are not being recognised is one of the reasons that a number of organisations feel that antibody testing should be developed and should be developed soon," he said.' In a March 3 MedRXiv preprint, Jia X et al. report that in a study on serological testing for SARS-CoV-2, the positive detection rate of combination of IgM and IgG for patients with COVID-19 negative and positive nucleic acid test was 72.73% and 87.50%, respectively. "The results were significantly higher than the nucleic acid or IgM, IgG single detection." The authors suggest this approach as a "quick, simple, accurate aided detection method" for diagnosis of suspected patients and on-site screening of patients in close contact with the population. And Zhao J et al (MedRXiv March 3) report, from a similar study, that: "The presence of antibodies was < 40% among patients in the first 7 days of illness, and then rapidly increased to 100.0%, 94.3% and 79.8% for Ab, IgM and IgG respectively since day 15 after onset. In contrast, the positive rate of RNA decreased from 66.7% (58/87) in samples collected before day 7 to 45.5% (25/55) during days 15 to 39. Combining RNA and antibody detections significantly improved the sensitivity of pathogenic diagnosis for COVID-19 patients ($p < 0.001$), even in early phase of 1-week since onset ($p = 0.007$). Moreover, a higher titer of Ab was independently associated with a worse clinical classification ($p = 0.006$). Interpretation: The antibody detection offers vital clinical information during the course of SARS-CoV-2 infection. The findings provide strong empirical support for the routine application of serological testing in the diagnosis and management of COVID-19 patients." Results and conclusions of a study by Jiang J et al (MedRXiv preprint March 1) seem to also support the use of serological testing for antibodies for the diagnosis of SARS-CoV-2 infection. And Zhang J et al. (MedRXiv preprint March 6) used automated chemiluminescent immunoassay to detect serum IgM and IgG antibodies to 2019-nCoV in736 subjects including patients with and without COVID-19. They found that COVID-19 patients became reactive (positive) for specific anti-2019-nCoV IgM antibodies from 7-12 days after the onset of morbidity, followed closely by the IgG, with the levels of specific IgM and IgG increasing with the progression of the disease. Specific IgM or IgG antibody detection had good sensitivity and specificity for the diagnosis of febrile cases, and was proposed as a good method of differentiating between COVID-19 and other diseases in febrile patients in low epidemic areas.