Município da Estância Balneária de Praia Grande
Estado de São Paulo

Gabinete do Prefeito

Em 15 de maio de 2020.

OFÍCIO GP Nº 285/2020

A Sua Excelência o Senhor
EDNALDO DOS SANTOS PASSOS
Presidente da Câmara Municipal de Praia Grande
PRAIA GRANDE – SP

Senhor Presidente,

Em atenção aos questionamentos feitos por meio do **REQUERIMENTO Nº 93/2020**, de autoria do nobre vereador **EDUARDO PÁDUA SOARES JARDIM**, referentes às políticas públicas de prevenção e proteção da população que a Administração Municipal vem adotando para combater a incidência da COVID-19 no Município, encaminho, anexa, cópia da manifestação da Subsecretaria de Planejamento em Saúde da Secretaria de Saúde Pública (Sesap), recebida pelo Departamento de Processo Legislativo deste Gabinete, bem como do MEMORANDO Nº 009/2020/SESAP 10.3 (Plano de Contingência), com os respectivos esclarecimentos.

Sem mais para o momento, aproveito o ensejo para externar os meus protestos de elevada estima e apreço.

Atenciosamente,

ALBERTO PEREIRA MOURÃO
Prefeito

APM/ed

Papel para informação, rubricado como folha nº. ####

do PA nº ***** de 2020 , 30/04/2020 (a) _____

À SESAP 10
Ilmo. Sr. Secretário,

Assunto: Requerimento n°. 093/2020.

Mediante respeitosas saudações, em atenção ao requerimento do nobre Edil, Sr. Eduardo Pádua Soares Jardim, submeto a vossa ilustre apreciação a sugestão de esclarecimento aos quesitos formulados pelo nobre vereador, conforme abaixo:

Quesito 1: A municipalidade adotou ampla estratégia de divulgação de ações de promoção e prevenção em enfrentamento à Pandemia por COVID-19. Entre estas, destacam-se as ações de esclarecimento disponíveis publicamente no endereço eletrônico da Prefeitura com endereços específicos para tal finalidade.

Quesito 2: Sim, ações de orientação para o uso de máscara e estratégia de distanciamento dos idosos em fila foram adotadas.

Quesito 3: Não foi necessária a adoção de medidas excepcionais posta a grande capilaridade da Atenção Primária à Saúde do município (100% de Cobertura) e o sucesso dos resultados da campanha.

Quesito 4: Sim, ação em andamento, conforme ampla divulgação em mídias digitais.

Quesito 5: Adotado medidas gerais, conforme recomendações do Decreto Municipal n°. 6.943, de 08 de abril de 2020.

Quesito 6: Sim. Segue anexo Memorando n°. 009/2020/SESAP 10.3, de 13 de março de 2020, que dimensiona os quesitos formulados, sem prejuízo dos demais estudos de dimensionamento da rede municipal para o enfrentamento da Pandemia por COVID-19.

Reiterando saudações, coloco-me à disposição para informações complementares.

Atenciosamente,

Praia Grande, 30 de abril de 2020.

Rodrigo França Gomes
Resp. Subsecretaria de Planejamento em Saúde

MUNICÍPIO DA ESTÂNCIA BALNEÁRIA DE PRAIA GRANDE
Estado de São Paulo

MEMORANDO Nº 009/2020/ SESAP 10.3

Praia Grande, 13 de março de 2020.

À SESAP 10
Ilmo. Sr. Secretário,

Assunto: Plano de Contingência COVID 19: dimensionamento de leitos hospitalares.

Mediante respeitosas saudações, em atenção ao tema em epígrafe e objetivando a operacionalização das discussões abordadas na sala de situações sobre Doenças Virais Epidêmicas da Vigilância Epidemiológica da Secretaria de Saúde Pública de Praia Grande, no que tange ao planejamento de riscos para o componente hospitalar, segue reflexão – à luz das escassas evidências ainda disponíveis na literatura médica mundial sobre a modelagem epidemiológica da taxa de crescimento da pandemia por COVID 19 – de sorte a dimensionar o número de leitos hospitalares, a partir de futuro caso índice municipal.

Adota-se como modelagem, a prévia do estudo publicado no *Emerging Infectious Diseases*® pelo *Centers for Disease Control e Prevention* dos autores DU et al.(2020), que, em 13 de fevereiro de 2020, apresentou a taxa de crescimento epidêmica para outras cidades, previamente à quarentena, da síndrome respiratória aguda severa de coronavírus 2 em Wuhan, China (grifos nosso em amarelo), conforme modelo probabilístico a partir do índice abaixo (anexo I):

$$1 - \exp\left[-\int_{u=t_0}^{t} (\gamma_{j,u} + \Psi'_{j,u})du\right]$$

De acordo com o estudo, o tempo de duplicação apresentado pelo modelo foi de 7,31 dias (I.C. 95% [6,26-9,66]). Esta taxa foi corroborada pelo *StatPearls Publishing LLC*® da *National Center for Biotechnology Information, U.S. National Library of Medicine*, em sua atualização de 08 de março de 2020 (Cascella M, Rajnik M, Cuomo A, et al, 2020).

Segundo os autores (anexo II), revisando a literatura mundial, a experiência vivenciada pela China (Li et al., 2020) revelou não existir diferença significante entre gêneros (56% dos casos no sexo masculino), atingindo predominantemente uma faixa etária de 15 a 89 anos (média de 59

anos), tendo a infecção por COVID-19, em seu espectro clínico, variações de assintomáticos ou com doença leve (86%), até a evolução com casos severos (14%) e críticos (5%), com intervalo até aparecimento de dispneia de 8 dias [5;13] (Li et al., 2020), anexo III, e taxa de letalidade geral de 2,3% (Wu e McGoogan, 2020), conforme tabela abaixo:

Características e lições importantes do surto de doença de coronavírus 2019 (COVID-19) na China.

Doença leve: não-pneumonia e pneumonia leve (86% dos casos).
Doença grave: dispnéia, frequência respiratória ≥ 30 / min, saturação de oxigênio no sangue (SpO2) ≤ 93%, razão PaO2 / FiO2 <300 e / ou infiltração pulmonar> 50% em 24 a 48 horas (14% dos casos).
Doença crítica: insuficiência respiratória, choque séptico e / ou disfunção de múltiplos órgãos (5% dos casos).

Fonte: Wu e McGoogan, 2020 apud Cascella M, Rajnik M, Cuomo A, et al, 2020.

Em observância aos apontamentos da nobre Vigilância Epidemiológica Municipal e perante a manifestação do Ministério de Saúde, junto à imprensa de grande circulação na data de ontem (anexo IV), 12 de março de 2020, apontando a rápida evolução da doença na Europa e anunciando a previsão de abertura de 2 mil leitos de UTI no Brasil, **o presente memorando busca dimensionar,** conforme tabela abaixo, **a potencial necessidade de leitos hospitalares, nos próximos 60 dias, a partir da deflagração do caso índice à luz do modelo probabilístico supracitado, até que o Ente Federal esclareça – por meio de portarias oficiais – como ocorrerá a expansão e financiamento da oferta dos novos leitos anunciados,**

Plano de Contingência de leitos hospitalares para pandemia COVID – 2019 Complexo Hospitalar Irmã Dulce			
Parâmetro (modelo probabilístico de Du et al., 2020)	$\lambda - Z_{\alpha/2}\sqrt{\frac{\lambda}{n}}$	λ	$\lambda + Z_{\alpha/2}\sqrt{\frac{\lambda}{n}}$
Tempo de Duplicação (dias)	6,26	7,31	9,66
Estimativa de casos, próximos 60 dias, a partir do índice	768	295	74
Estimativa de casos graves (14%)	107,5	41,4	10,4
Estimativa de casos críticos (5%)	38,4	14,8	3,7

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Assim, atendo-se ao modelo de regressão adotado, para uma Taxa de duplicação estimada em 7,31 dias, o município de Praia Grande, a partir do caso índice, assistiria ao crescimento estimado no período de 295 casos, com 41 pacientes com manifestação clínicas graves e 14 pacientes críticos no período. Frente a esta taxa de crescimento, segue abaixo a estimativa de leitos de enfermaria e leitos de UTI para utilização em 60 dias de expansão exponencial da doença.

Plano de Contingência de leitos hospitalares para pandemia COVID – 2019
Análise de eficiência Alocativa – Taxa de Ocupação Hospitalar em 100%
Complexo Hospitalar Irmã Dulce

Leitos de Enfermaria - Atenção ao paciente com espectro grave

Parâmetro	N° estimado de internações	Média de Permanência (dias)	Pacientes/dia (60 dias a partir do índice)	Leitos estimados
Limite superior (p=0,975)	10,4	7	72,8	2
Taxa média	41,4	7	289,8	10
Limite inferior (p=0,025)	107,5	7	752,5	25

Leitos de UTI - Atenção ao paciente com espectro crítico

Parâmetro	N° estimado de internações	Média de Permanência (dias)	Pacientes/dia (60 dias a partir do índice)	Leitos estimados
Limite superior (p=0,975)	3,7	21	77,7	3
Taxa média	14,78	21	310,38	10
Limite inferior (p=0,025)	38,39	21	806,19	27

Posto que o Complexo Hospitalar Irmã Dulce seja a principal Porta de Entrada da RUE/RRAS 07, com grande volume diário de cirurgias de urgência e eletivas, com previsão de descontos por não cumprimento de metas cirúrgicas eletivas em seu Plano Operativo Anual vigente e, considerando que o enfrentamento da pandemia implique na necessidade de realocação do capital humano, submeto a Vossa ilustre apreciação, a juízo de oportunidade e conveniência, a reflexão – junto a equipe técnica da Sala de Situação de Doenças Virais Epidêmicas – quanto a necessidade

de suspensão de componentes eletivos e reserva de leitos hospitalares, sem prejuízo das demais ações previstas no cronograma do Plano de Contingência.

Reitero saudações e me prontifico a prestar informações complementares.

Atenciosamente,

Rodrigo França Gomes
Resp. Subsecretaria de Planejamento em Saúde

(RFG)

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Du Z, Wang L, Chauchemez S, Xu X, Wang X, Cowling BJ, et al. Risk for transportation of 2019 novel coronavirus disease from Wuhan to other cities in China. ***Emerg Infect Dis***. 2020 May [date cited]. https://doi.org/10.3201/eid2605.200146

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ANEXO I

(MEMO n°. 009/2020/SESAP 10.3)

PubMed Risk for Transportation of 2019 Novel Coronavirus Disease from Wuh

Full text links

Format: Abstract

See 1 citation found by title matching your search:

Emerg Infect Dis. 2020 May 17;26(5). doi: 10.3201/eid2605.200146. [Epub ahead of print]

Risk for Transportation of 2019 Novel Coronavirus Disease from Wuhan to Other Cities in China.

Du Z, Wang L, Cauchemez S, Xu X, Wang X, Cowling BJ, Meyers LA.

Abstract

On January 23, 2020, **China** quarantined **Wuhan** to contain **2019 novel coronavirus disease** (COVID-19). We estimated the probability of **transportation** of COVID-19 from **Wuhan** to 369 **other cities** in **China** before the quarantine. Expected COVID-19 **risk** is >50% in 130 (95% CI 89-190) **cities** and >99% in the 4 largest metropolitan areas.

KEYWORDS: 2019 novel coronavirus disease; COVID-19; **China**; SARS-CoV-2; **Wuhan**; **coronavirus**; epidemiology; importation; outbreak; severe acute respiratory syndrome **coronavirus** 2; viruses

PMID: 32053479 DOI: 10.3201/eid2605.200146

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Article DOI: https://doi.org/10.3201/eid2605.200146

Risk for Transportation of 2019 Novel Coronavirus Disease from Wuhan to Other Cities in China

Appendix

Data

We analyzed the daily number of passengers traveling between Wuhan and 369 other cities in mainland China. We obtained mobility data from the location-based services of Tencent (https://heat.qq.com). Users permit Tencent to collect their realtime location information when they install applications, such as WeChat (≈1.13 billion active users in 2019) and QQ (≈808 million active users in 2019), and Tencent Map. By using the geolocation of users over time, Tencent reconstructed anonymized origin–destination mobility matrices by mode of transportation (air, road, and train) between 370 cities in China, including 368 cities in mainland China and the Special Administrative Regions of Hong Kong and Macau. The data are anonymized and include 28 million trips to and 32 million trips from Wuhan, during December 3, 2016–January 24, 2017. We estimated daily travel volume during the 7 weeks preceding the Wuhan quarantine, December 1, 2019–January 22, 2020, by aligning the dates of the Lunar New Year, resulting in a 3-day shift. To infer the number of new infections in Wuhan per day during December 1, 2019–January 22, 2020, we used the mean daily number of passengers traveling to the top 27 foreign destinations from Wuhan during 2018–2019, which were provided in other recent studies (*1*–*3*).

Model

We considered a simple hierarchical model to describe the dynamics of 2019 novel coronavirus disease (COVID-19) infections, detections, and spread.

Epidemiologic Model

By using epidemiologic evidence from the first 425 cases of COVID-19 confirmed in Wuhan by January 22, 2020 (*4*), we made the following assumptions regarding the number of new cases, $dI_\omega(t)$, infected in Wuhan per day, t.

- The COVID-19 epidemic was growing exponentially during December 1, 2019–January 22, 2020, as determined by the following:

  $$dI_\omega(t) = i_0 \times \exp(\lambda \times t)$$

  in which i_0 denotes the number of initial cases on December 1, 2019 (*5*), and λ denotes the epidemic growth rate during December 1, 2019–January 22, 2020.

- After infection, new cases were detected with a delay of $D = 10$ days (*6*), which comprises an incubation period of 5–6 days (*4,7–11*) and a delay from symptom onset to detection of 4–5 days (*12,13*). During this 10-day interval, we labeled cases as infected. Given the uncertainty in these estimates, we also performed the estimates by assuming a shorter delay ($D = 6$ days) and a longer delay ($D = 14$ days) between infection and case detection (Appendix Table 2).

Our model can be improved by incorporating the probability distribution for the delay between infection and detection, as reconstructed linelists (*14–17*) and more granular epidemiologic data are becoming available.

Under these assumptions, we calculated the number of infectious cases at time, t, by the following:

$$I_\omega(t) = \int_{u=t-D}^{t} dI_\omega(u)du$$

The prevalence of infectious cases is given by the following:

$$\xi(t) = \frac{I_\omega(t)}{N_\omega}$$

in which $N_\omega = 11.08$ million, the population of Wuhan.

Mobility Model

We assumed that visitors to Wuhan have the same daily risk for infection as residents of Wuhan and constructed a nonhomogenous Poisson process model (*18–20*) to estimate the risk for exportation of COVID-19 by residents of and travelers to Wuhan. In this model, $W_{j,t}$ denotes the number of residents of Wuhan that travel to city j on day t and $M_{j,t}$ denotes the number of from city j traveling to Wuhan on day t. Then, the rate at which infected residents of Wuhan travel to city j at time t is given as $\gamma_{j,t} = \xi(t) \times W_{j,t}$ and the rate at which travelers from city j get infected in Wuhan and return to their home city while still infected is $\Psi_{j,t} = \xi(t) \times M_{j,t}$. This model assumes that newly infected visitors to Wuhan will return to their home city while still infectious. By using this model, the probability of introducing ≥1 case of COVID-19 from Wuhan to city j by time t is given by

$$1 - \exp\left[-\int_{u=t_0}^{t} (\gamma_{j,u} + \Psi_{j,u})du\right]$$

in which t_0 denotes the beginning of the study period, December 1, 2019.

Inference of Epidemic Parameters

We applied a likelihood-based method to estimate our model parameters, including the number of initial cases i_0 and the epidemic growth rate λ, from the arrival times of the 19 reported cases transported from Wuhan to 11 cities outside of China, as of January 22, 2020 (Appendix Table 1). All 19 cases were Wuhan residents. We aggregated all other cities without cases reported by January 22, 2020 into a single location ($j = 0$).

In this model, N_j denotes the number of infected residents of Wuhan who were detected in location j outside of China, and $\chi_{j,i}$ denotes the time at which the i-th COVID-19 case was detected in a Wuhan resident in location j; $\chi_{j,0}$ denotes the time at which international surveillance for infected travelers from Wuhan began, January 1, 2020 (*21*); and E denotes the end of the study period on January 22, 2020. As indicated above, the rate at which infected residents of Wuhan arrive at location j at time t is $\gamma_{j,t}$. Then the log-likelihood for all 19 cases reported outside of China by January 22, 2020 is given by:

$$\prod_{j=0}^{11} \exp\left(-\int_{\chi_j, N_j}^{E} \gamma_{t,j} dt\right) \prod_{l=0}^{N_j} \gamma_{\chi_{j,l},j} \exp\left(-\int_{\chi_{j,l-1}}^{\chi_{j,l}} \gamma_{t,j} dt\right)$$

which yields the following log-likelihood function:

$$\sum_{j=1}^{11} \sum_{l=1}^{N_j} \log\left(\gamma_{j,\chi_{j,l}}\right) - \frac{\sum_{j=0}^{11} W_{j,t}}{N_\omega} \times \frac{i_0}{\lambda^2} \times \left[\exp(\lambda \times E) - \exp\left(\lambda \times \chi_{j,0}\right) + \exp\left(\lambda \times \left(\chi_{j,0} - D\right)\right) - \exp(\lambda \times (E - D))\right]$$

Parameter Estimation

We directly estimated the number of initial cases, i_0, on December 1, 2019, and the epidemic growth rate, λ, during December 1, 2019–January 22, 2020. We infer the epidemic parameters in a Bayesian framework by using the Markov Chain Monte Carlo (MCMC) method with Hamiltonian Monte Carlo sampling and noninformative flat prior. From these, we derive the doubling time of incident cases as $d_T = \log(2)/\lambda$ and the cumulative number of cases and of reported cases by January 22, 2020. We also derived the basic reproduction number, by assuming a susceptible-exposed-infectious-recovery (SEIR) model for COVID-19 in which the incubation period is exponentially distributed with mean L in the range of 3–6 days and the infectious period is also exponentially distributed with mean Z in the range of 2–7 days. The reproduction number is then given by $R_0 = (1 + \lambda \times L) \times (1 + \lambda \times Z)$.

We estimated the case detection rate in Wuhan by taking the ratio between the number of reported cases in Wuhan by January 22, 2020 and our estimates for the number of infections occurring ≥10 days prior (i.e., by January 12, 2020). We truncated our estimate 10 days before the quarantine to account for the estimated time between infection and case detection, assuming a 5–6 day incubation period (*4,7–11*) followed by 4–5 days between symptom onset and case detection (*12,13*). Given the uncertainty in these estimates, we also provide estimates assuming shorter and longer delays in the lag between infection and case reporting (Appendix Table 3).

We ran 10 chains in parallel. Trace plot and diagnosis confirmed the convergence of MCMC chains with posterior median and 95% CrI estimates as follows:

- Epidemic growth rate, λ: 0.095 (95% CrI 0.072–0.111), corresponding to an epidemic doubling time of incident cases of 7.31 (95% CrI 6.26–9.66) days;
- Number of initial cases in Wuhan on December 1, 2019: 7.78 (95% CrI 5.09–18.27);
- Basic reproductive number, R_0: 1.90 (95% CrI 1.47–2.59);
- Cumulative number of infections in Wuhan by January 22, 2020: 12,400 (95% CrI 3,112–58,465);
- Case detection rate by January 22, 2020: 8.95% (95% CrI 2.22%–28.72%). This represents the ratio between the 425 confirmed cases in Wuhan during this period (22) and our estimate that 4,747 (95% CrI 1,480–19,151) cumulative infections occurred by January 12, 2020 (i.e., ≥10 days before the quarantine to account for the typical lag between infection and case detection).

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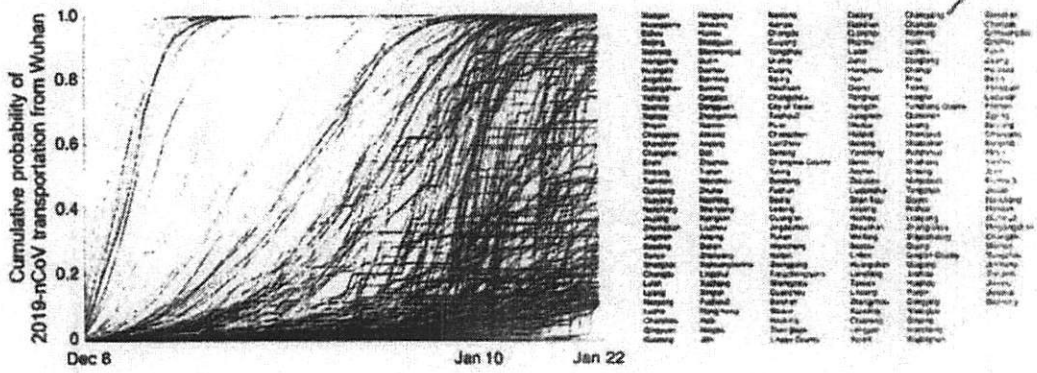
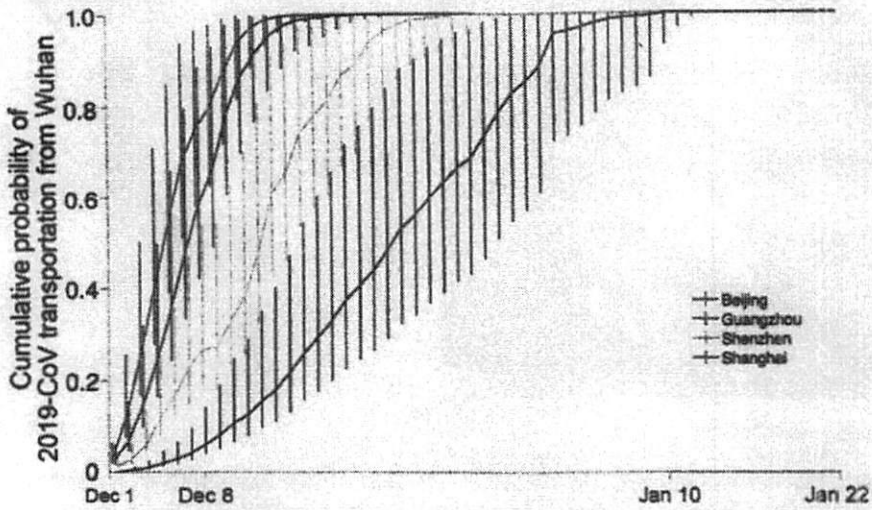
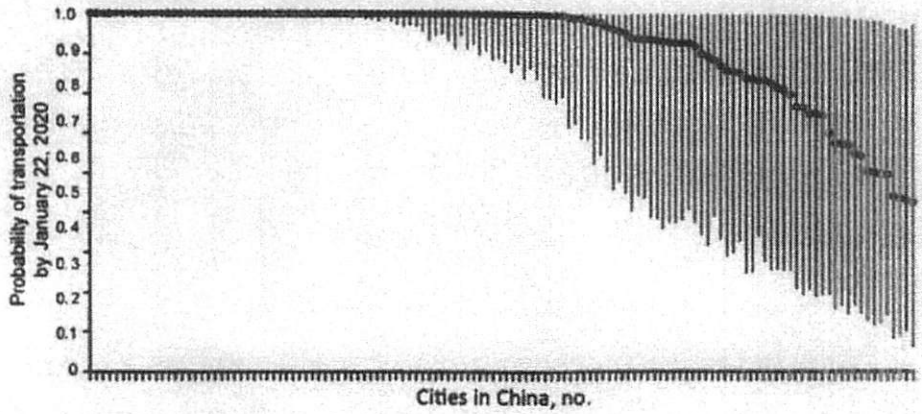


Appendix Figure 1. The risk for introduction of 2019 novel coronavirus disease (COVID-19) from Wuhan to other cities in China before the January 23, 2020 quarantine of Wuhan. Lines indicate probabilities that at ≥1 person infected with COVID-19in Wuhan arrived in a listed city by the date indicated on the x-axis. The estimates were calculated by using mobility data collected from the location-based services of Tencent (https://heat.qq.com) during December 10, 2017–January 24, 2018, the timeframe that corresponds to the Spring Festival travel period of December 8, 2019–January 22, 2020. All cities with an expected importation probability >10% by January 22, 2020 (n = 212) are shown.



Appendix Figure 2. Uncertainty analysis representing the number of 2019 novel coronavirus disease (COVID-19) exposures in Wuhan per day. Lines show the probability that ≥1 transportation of COVID-19 infection occurred from Wuhan to Beijing, Guangzhou, Shenzhen, and Shanghai during December 8, 2020–January 22, 2020. Error bars indicate 95% credible intervals.



Appendix Figure 3. Risk for transportation of 2019 novel coronavirus disease (COVID-19) from Wuhan to 130 cities in China by January 23, 2020. All cities represented have mean importation probability >50%. As of January 26, 2020, 82.3% (107/130) of these cities had reported cases. Grey circles indicate cities that were included in the quarantine as of January 24, 2020. Red circles indicate cities outside the quarantine area with confirmed cases; blue circles indicate cities outside the quarantine area without confirmed cases as of January 26th, 2020.

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Research Letter

Risk for Transportation of 2019 Novel Coronavirus Disease from Wuhan to Other Cities in China

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Suggested citation for this article

Abstract

On January 23, 2020, China quarantined Wuhan to contain 2019 novel coronavirus disease (COVID-19). We estimated the probability of transportation of COVID-19 from Wuhan to 369 other cities in China before the quarantine. Expected COVID-19 risk is >50% in 130 (95% CI 89–150) cities and >99% in the 4 largest metropolitan areas.

In December 2019, a novel coronavirus, since named severe acute respiratory syndrome coronavirus 2, emerged in Wuhan, China (*1*), causing a respiratory illness that the World Health Organization has named 2019 novel coronavirus disease (COVID-19). On January 30, 2020, the World Health Organization declared the outbreak a public health emergency of international concern (*2*). By January 31, 2020, a total of 192 fatalities and 3,215 laboratory-confirmed cases had been reported in Wuhan; 8,576 additional cases were spread across >300 cities in mainland China, and 127 exported cases were reported in 23 countries spanning Asia, Europe, Oceania, and North America. The rapid global expansion, rising fatalities, unknown animal reservoir, and evidence of person-to-person transmission potential (*3*,*4*) initially resembled the 2003 SARS epidemic and raised concerns about global spread.

On January 22, 2020, China announced a travel quarantine of Wuhan and by January 30 expanded the radius to include 16 cities, encompassing a population of 45 million. At the time of the quarantine, China was already 2 weeks into the 40-day Spring Festival, during which residents and visitors make several billion trips throughout China to celebrate the Lunar New Year (*5*). Considering the timing of exported COVID-2019 cases reported outside of China, we estimate that only 8.95% (95% credibility interval [CrI] 2.22%–28.72%) of persons infected in Wuhan by January 12 might have had COVID-19 confirmed by January 22. By limiting our estimate to infections occurring ≥10 days before the quarantine, we account for an ≈5–6-day incubation period and 4–5 days between symptom onset and case detection (Appendix) (*2*–*4*,*6*). The low detection rate coupled with an average lag of 10 days between infection and detection (*7*) suggest that newly infected persons who traveled out of Wuhan just before the quarantine might have remained infectious and undetected in dozens of cities in China for days to weeks. Moreover, these silent importations already might have seeded sustained outbreaks that were not immediately apparent.

We estimated the probability of transportation of infectious COVID-2019 cases from Wuhan to cities throughout China before January 23 by using a simple model of exponential growth coupled with a stochastic model of human mobility among 369 cities in China (Appendix). Given that ≈98% of all trips taken during this period were made by train or car, our analysis of air, rail, and road travel data yields more granular risk estimates than possible with air passenger data alone (*6*).

Figure. Risks for transportation of 2019 novel coronavirus disease (COVID-19) from Wuhan, China, before a quarantine was imposed on January 23, 2020. A) Daily travel volume to and from Wuhan, given as...

By fitting our epidemiologic model to data on the first 19 cases reported outside of China, we estimate an epidemic doubling time of 7.31 days (95% CrI 6.26–9.66 days) and a cumulative total of 12,400 (95% CrI 3,112–58,465) infections in Wuhan by January 22 (Appendix). Both estimates are consistent with a similar epidemiologic analysis of the first 425 cases confirmed in Wuhan (*4*). Assuming these rates of early epidemic growth, we estimate that 130 cities in China have a ≥50% chance of having a COVID-2019 case imported from Wuhan in the 3 weeks preceding the quarantine (Figure). By January 26, a total of 107 of these 130 high-risk cities had reported cases. However, 23 had not, including 5 cities with importation probabilities >99% and populations >2 million: Bazhong, Fushun, Leibin, Ziyang, and Chuxiong.

Under our lower bound estimate of 6.26 days for the doubling time, 190/369 cities lie above the 50% threshold for importation. Our risk assessment identified several cities throughout China likely to be harboring yet undetected cases of COVID-19 a week after the quarantine, suggesting that early 2020 ground and rail travel seeded cases far beyond the

Wuhan region under quarantine.

Our conclusions are based on several key assumptions. To design our mobility model, we used data from Tencent (https://heat.qq.com), a major social media company that hosts applications including WeChat (≈1.13 billion active users in 2019) and QQ (≈808 million active users in 2019) (Statista, https://www.statista.com); consequently, our model might be demographically biased by the Tencent user base. Further, considerable uncertainty regarding the lag between infection and case detection remains. Our assumption of a 10-day lag is based on early estimates for the incubation period of COVID-19 (*4*) and prior estimates of the lag between symptom onset and detection for SARS (*9*). We expect that estimates for the doubling time and incidence of COVID-19 will improve as reconstructed linelists and more granular epidemiologic data become available (Appendix). However, our key qualitative insights likely are robust to these uncertainties, including extensive prequarantine exportations throughout China and far greater case counts in Wuhan than those reported before the quarantine.

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Code for estimating epidemiological parameters and probabilities of case introductions, as well as aggregate mobility data, are available from GitHub (https://github.com/linwangidd/2019nCoV_EID). Aggregate data also are available (Appendix Table 3). Additional code and data requests should be addressed to L.A.M. (laurenmeyers@austin.utexas.edu).

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Figure

Figure. Risks for transportation of 2019 novel coronavirus disease (COVID-19) from Wuhan, China, before a quarantine was imposed on January 23, 2020. A) Daily travel volume to and from Wuhan, given...

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ANEXO II

(MEMO n°. 009/2020/SESAP 10.3)

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Features, Evaluation and Treatment Coronavirus (COVID-19)

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Introduction

According to the World Health Organization (WHO), viral diseases continue to emerge and represent a serious issue to public health. In the last twenty years, several viral epidemics such as the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 to 2003, and H1N1 influenza in 2009, have been recorded. Most recently, the Middle East respiratory syndrome coronavirus (MERS-CoV) was first identified in Saudi Arabia in 2012.

In a timeline that reaches the present day, an epidemic of cases with unexplained low respiratory infections detected in Wuhan, the largest metropolitan area in China's Hubei province, was first reported to the WHO Country Office in China, on December 31, 2019. Published literature can trace the beginning of symptomatic individuals back to the beginning of December 2019. As they were unable to identify the causative agent, these first cases were classified as "pneumonia of unknown etiology." The Chinese Center for Disease Control and Prevention (CDC) and local CDCs organized an intensive outbreak investigation program. The etiology of this illness is now attributed to a novel virus belonging to the coronavirus (CoV) family, COVID-19.

On February 11, 2020, the WHO Director-General, Dr. Tedros Adhanom Ghebreyesus, announced that the disease caused by this new CoV was a "COVID-19," which is the acronym of "coronavirus disease 2019". In the past twenty years, two additional coronavirus epidemics have occurred. SARS-CoV provoked a large-scale epidemic beginning in China and involving two dozen countries with approximately 8000 cases and 800 deaths, and the MERS-CoV that began in Saudi Arabia and has approximately 2,500 cases and 800 deaths and still causes as sporadic cases.

This new virus seems to be very contagious and has quickly spread globally. In a meeting on January 30, 2020, per the International Health Regulations (IHR, 2005), the outbreak was declared by the WHO a Public Health Emergency of International Concern (PHEIC) as it had spread to 18 countries with four countries reporting human-to-human transmission. An additional landmark occurred on February 26, 2020, as the first case of the disease, not imported from China, was recorded in the United States.

Initially, the new virus was called 2019-nCoV. Subsequently, the task of experts of the International Committee on Taxonomy of Viruses (ICTV) termed it the SARS-CoV-2 virus as it is very similar to the one that caused the SARS outbreak (SARS-CoVs).

The CoVs have become the major pathogens of emerging respiratory disease outbreaks. They are a large family of single-stranded RNA viruses (+ssRNA) that can be isolated in different animal species.[1] For reasons yet to be explained, these viruses can cross species barriers and can cause, in humans, illness ranging from the common cold to more severe diseases such as MERS and SARS. Interestingly, these latter viruses have probably originated from bats and then moving into other mammalian hosts — the Himalayan palm civet for SARS-CoV, and the dromedary camel for MERS-CoV — before jumping to humans. The dynamics of SARS-Cov-2 are currently unknown, but there is speculation that it also has an animal origin.

The potential for these viruses to grow to become a pandemic worldwide seems to be a serious public health risk. Concerning COVID-19, the WHO raised the threat to the CoV epidemic to the "very high" level, on February 28, 2020. Probably, the effects of the epidemic caused by the new CoV has yet to emerge as the situation is quickly evolving. World governments are at work to establish countermeasures to stem possible devastating effects. Health organizations coordinate information flows and issues directives and guidelines to best mitigate the impact of the threat. At the same time, scientists around the world work tirelessly, and information about the transmission mechanisms, the clinical spectrum of disease, new diagnostics, and prevention and therapeutic strategies are rapidly developing. Many uncertainties remain with regard to both the virus-host interaction and the evolution of the epidemic, with specific reference to the times when the epidemic will reach its peak.

At the moment, the therapeutic strategies to deal with the infection are only supportive, and prevention aimed at reducing transmission in the community is our best weapon. Aggressive isolation measures in China have led to a progressive reduction of cases in the last few days. In Italy, in geographic regions of the north of the peninsula, political and health authorities are making incredible efforts to contain a shock wave that is severely testing the health system.

In the midst of the crisis, the authors have chosen to use the "Statpearls" platform because, within the PubMed scenario, it represents a unique tool that may allow them to make updates in real-time. The aim, therefore, is to collect information and scientific evidence and to provide an overview of the topic that will be continuously updated.

Etiology

CoVs are positive-stranded RNA viruses with a crown-like appearance under an electron microscope (*coronam* is the Latin term for crown) due to the presence of spike glycoproteins on the envelope. The subfamily *Orthocoronavirinae* of the *Coronaviridae* family (order *Nidovirales*) classifies into four genera of CoVs: Alphacoronavirus (alphaCoV), Betacoronavirus (betaCoV), Deltacoronavirus (deltaCoV), and Gammacoronavirus (gammaCoV). Furthermore, the betaCoV genus divides into five sub-genera or lineages.[2] Genomic characterization has shown that probably bats and rodents are the gene sources of alphaCoVs and betaCoVs. On the contrary, avian species seem to represent the gene sources of deltaCoVs and gammaCoVs.

Members of this large family of viruses can cause respiratory, enteric, hepatic, and neurological diseases in different animal species, including camels, cattle, cats, and bats. To date, seven human CoVs (HCoVs) — capable of infecting humans — have been identified. Some of HCoVs were identified in the mid-1960s, while others were only detected in the new millennium.

In general, estimates suggest that 2% of the population are healthy carriers of a CoV and that these viruses are responsible for about 5% to 10% of acute respiratory infections.[3]

- Common human CoVs: HCoV-OC43, and HCoV-HKU1 (betaCoVs of the A lineage); HCoV-229E, and HCoV-NL63 (alphaCoVs). They can cause common colds and self-limiting upper respiratory infections in immunocompetent individuals. In immunocompromised subjects and the elderly, lower respiratory tract infections can occur.
- Other human CoVs: SARS-CoV, SARS-CoV-2, and MERS-CoV (betaCoVs of the B and C lineage, respectively). These cause epidemics with variable clinical severity featuring respiratory and extra-respiratory manifestations. Concerning SARS-CoV, MERS-CoV, the mortality rates are up to 10% and 35%, respectively.

Thus, SARS-CoV-2 belongs to the betaCoVs category. It has round or elliptic and often pleomorphic form, and a diameter of approximately 60–140 nm. Like other CoVs, it is sensitive to ultraviolet rays and heat. Furthermore, these viruses can be effectively inactivated by lipid solvents including ether (75%), ethanol, chlorine-containing disinfectant, peroxyacetic acid and chloroform except for chlorhexidine.

In genetic terms, Chan et al. have proven that the genome of the new HCoV, isolated from a cluster-patient with atypical pneumonia after visiting Wuhan, had 89% nucleotide identity with bat SARS-like-CoVZXC21 and 82% with that of human SARS-CoV[4]. For this reason, the new virus was called SARS-CoV-2. Its single-stranded RNA genome contains 29891 nucleotides, encoding for 9860 amino acids. Although its origins are not entirely understood, these genomic analyses suggest that SARS-CoV-2 probably evolved from a strain found in bats. The potential amplifying mammalian host, intermediate between bats and humans, is, however, not known. Since the mutation in the original strain could have directly triggered virulence towards humans, it is not certain that this intermediary exists.

Transmission

Because the first cases of the CoVID-19 disease were linked to direct exposure to the Huanan Seafood Wholesale Market of Wuhan, the animal-to-human transmission was presumed as the main mechanism. Nevertheless, subsequent cases were not associated with this exposure mechanism. Therefore, it was concluded that the virus could also be transmitted from human-to-human, and symptomatic people are the most frequent source of COVID-19 spread. The possibility of transmission before symptoms develop seems to be infrequent, although it cannot be excluded. Moreover, there are suggestions that individuals who

remain asymptomatic could transmit the virus. This data suggests that the use of isolation is the best way to contain this epidemic.

As with other respiratory pathogens, including flu and rhinovirus, the transmission is believed to occur through respiratory droplets from coughing and sneezing. Aerosol transmission is also possible in case of protracted exposure to elevated aerosol concentrations in closed spaces. Analysis of data related to the spread of SARS-CoV-2 in China seems to indicate that close contact between individuals is necessary. The spread, in fact, is primarily limited to family members, healthcare professionals, and other close contacts.

Based on data from the first cases in Wuhan and investigations conducted by the China CDC and local CDCs, the incubation time could be generally within 3 to 7 days and up to 2 weeks as the longest time from infection to symptoms was 12.5 days (95% CI, 9.2 to 18).[5] This data also showed that this novel epidemic doubled about every seven days, whereas the basic reproduction number (R0 - R naught) is 2.2. In other words, on average, each patient transmits the infection to an additional 2.2 individuals. Of note, estimations of the R0 of the SARS-CoV epidemic in 2002-2003 were approximately 3.[6]

It must be emphasized that this information is the result of the first reports. Thus, further studies are needed to understand the mechanisms of transmission, the incubation times and the clinical course, and the duration of infectivity.

Epidemiology

Data provided by the WHO Health Emergency Dashboard (March 03, 10.00 am CET) report 87,137 confirmed cases worldwide since the beginning of the epidemic. Of these, 2977 (3.42%) have been fatal. About 92% (79,968) of the confirmed cases were recorded in China, where almost all the deaths were also recorded (2,873, 96.5%). Of note, the "confirmed" cases reported between February 13, 2020, and February 19, 2020, include both laboratory-confirmed and clinically diagnosed patients from the Hubei province.

Outside China, there are 7169 confirmed cases in 59 countries including the Republic of Korea (3736 cases), Italy (1128), international conveyance (Diamond Princess, 705 cases), the Islamic Republic of Iran (593), Japan (239), Singapore (102), France (100), United States of America (62), Germany (57), Kuwait (45), Spain (45), Thailand (42), Bahrain (40), Australia (25), Malaysia (24), United Kingdom (23), Canada (19), United Arab Emirates (19), Switzerland (18), Viet Nam (16), Norway (15), Iraq (13), Sweden (13), Austria (10), Croatia (7), Israel (7), Netherlands (7), Oman (6), Pakistan (4), Azerbaijan (3), Denmark (3), Georgia (3), Greece (3), India (3), Philippines (3), Romania (3). Moreover, two cases were recorded respectively in Brazil, Finland, Lebanon, Mexico, the Russian Federation, and a single case each in Afghanistan, Algeria, Belarus, Belgium, Cambodia, Ecuador, Egypt, Estonia, Ireland, Lithuania, Monaco, Nepal, New Zealand, Nigeria, North Macedonia, Qatar, San Marino, and Sri Lanka.

The most up-to-date source for the epidemiology of t[illegible]emerging pandemic can be found at the foll[illegible]ing sources:

- The WHO Novel Coronavirus (COVID-19) Situation Board
- The Johns Hopkins Center for Systems Science and Engineering site for Coronavirus Global Cases COVID-19, which uses openly public sources to track the spread of the epidemic.

Pathophysiology

CoVs are enveloped, positive-stranded RNA viruses with nucleocapsid. For addressing pathogenetic mechanisms of SARS-CoV-2, its viral structure, and genome must be considerations. In CoVs, the genomic structure is organized in a +ssRNA of approximately 30 kb in length — the largest known RNA viruses — and with a 5′-cap structure and 3′-poly-A tail. Starting from the viral RNA, the synthesis of polyprotein 1a/1ab (pp1a/pp1ab) in the host is realized. The transcription works through the replication-transcription complex (RCT) organized in double-membrane vesicles and via the synthesis of subgenomic RNAs (sgRNAs) sequences. Of note, transcription termination occurs at transcription regulatory sequences, located between the so-called open reading frames (ORFs) that work as templates for the production of subgenomic mRNAs. In the atypical CoV genome, at least six ORFs can be present. Among these, a frameshift between ORF1a and ORF1b guides the production of both pp1a and pp1ab polypeptides that are processed by virally encoded chymotrypsin-like protease (3CLpro) or main protease (Mpro), as well as one or two papain-like proteases for producing 16 non-structural proteins (nsps). Apart from ORF1a and ORF1b, other ORFs encode for structural proteins, including spike, membrane, envelope, and nucleocapsid proteins.[1] and accessory proteic chains. Different CoVs present special structural and accessory proteins translated by dedicated sgRNAs.

Pathophysiology and virulence mechanisms of CoVs, and therefore also of SARS-CoV-2 have links to the function of the nsps and structural proteins. For instance, research underlined that nsp is able to block the host innate immune response.[7] Among functions of structural proteins, the envelope has a crucial role in virus pathogenicity as it promotes viral assembly and release. However, many of these features (e.g., those of nsp 2, and 11) have not yet been described.

Among the structural elements of CoVs, there are the spike glycoproteins composed of two subunits (S1 and S2). Homotrimers of S proteins compose the spikes on the viral surface, guiding the link to host receptors.[8] Of note, in SARS-CoV-2, the S2 subunit — containing a fusion peptide, a transmembrane domain, and cytoplasmic domain — is highly conserved. Thus, it could be a target for antiviral (anti-S2) compounds. On the contrary, the spike receptor-binding domain presents only a 40% amino acid identity with other SARS-CoVs. Other structural elements on which research must necessarily focus are the ORF3b that has no homology with that of SARS-CoVs and a secreted protein (encoded by ORF8), which is structurally different from those of SARS-CoV.

In international gene banks such as GenBank, researchers have published several Sars-CoV-2 gene sequences. This gene mapping is of fundamental importance allowing researchers to trace the phylogenetic tree of the virus and, above all, the recognition of strains that differ according to the mutations. According to recent research, a spike mutation, which probably

occurred in late November 2019, triggered jumping to humans. In particular, Angeletti et al. compared the Sars-Cov-2 gene sequence with that of Sars-CoV. They analyzed the transmembrane helical segments in the ORF1ab encoded 2 (nsp2) and nsp3 and found that position 723 presents a serine instead of a glycine residue, while the position 1010 is occupied by proline instead of isoleucine.[9] The matter of viral mutations is key for explaining potential disease relapses.

Research will be needed to determine the structural characteristics of SARS-COV-2 that underlie the pathogenetic mechanisms. Compared to SARS, for example, initial clinical data show less extra respiratory involvement, although due to the lack of extensive data, it is not possible to draw definitive clinical information.

Histopathology

Tian et al.[10] and others reported histopathological data obtained on the lungs of two patients who underwent lung lobectomies for adenocarcinoma and retrospectively found to have had the infection at the time of surgery. Apart from the tumors, the lungs of both 'accidental' cases showed edema and important proteinaceous exudates as large protein globules. The authors also reported vascular congestion combined with inflammatory clusters of fibrinoid material and multinucleated giant cells and hyperplasia of pneumocytes.

History and Physical

The clinical spectrum of COVID-19 varies from asymptomatic or paucisymptomatic forms to clinical conditions characterized by respiratory failure that necessitates mechanical ventilation and support in an intensive care unit (ICU), to multiorgan and systemic manifestations in terms of sepsis, septic shock, and multiple organ dysfunction syndromes (MODS). In one of the first reports on the disease, Huang et al. illustrated that patients (n. 41) suffered from fever, malaise, dry cough, and dyspnea. Chest computerized tomography (CT) scans showed pneumonia with abnormal findings in all cases. About a third of those (13, 32%) required ICU care, and there were 6 (15%) fatal cases.[11]

The case studies of Li et al. published in the New England Journal of Medicine (NEJM) on January 29, 2020, encapsulates the first 425 cases recorded in Wuhan.[5] Data indicate that the patients' median age was 59 years, with a range of 15 to 89 years. Thus, they reported no clinical cases in children below 15 years of age. There were no significant gender differences (56% male). Clinical and epidemiological data from the Chinese CDC and regarding 72,314 case records (confirmed, suspected, diagnosed, and asymptomatic cases) were shared in the Journal of the American Medical Association (JAMA) (February 24, 2020), providing an important illustration of the epidemiologic curve of the Chinese outbreak.[12] There were 62% confirmed cases, including 1% of cases that were asymptomatic, but were laboratory-positive (viral nucleic acid test). Furthermore, the overall case-fatality rate (on confirmed cases) was 2.3%. Of note, the fatal cases were primarily elderly patients, in particular those aged ≥ 80 years (about 15%), and 70 to 79 years (8.0%). Approximately half (49.0%) of the critical

patients and affected by preexisting comorbidities such as cardiovascular disease, diabetes, chronic respiratory disease, and oncological diseases, died. While 1% of patients were aged 9 years or younger, no fatal cases occurred in this group.

The authors of the Chinese CDC report divided the clinical manifestations of the disease by there severity:

- Mild disease: non-pneumonia and mild pneumonia; this occurred in 81% of cases.
- Severe disease: dyspnea, respiratory frequency ≥ 30/min, blood oxygen saturation (SpO2) ≤ 93%, PaO2/FiO2 ratio [the ratio between the blood pressure of the oxygen (partial pressure of oxygen, PaO2) and the percentage of oxygen supplied (fraction of inspired oxygen, FiO2)] < 300, and/or lung infiltrates > 50% within 24 to 48 hours; this occurred in 14% of cases.
- Critical disease: respiratory failure, septic shock, and/or multiple organ dysfunction (MOD) or failure (MOF); this occurred in 5% of cases.[12]

Data obtainable from reports and directives provided by health policy agencies, allow dividing the clinical manifestations of the disease according to the severity of the clinical pictures. The COVID-19 may present with mild, moderate, or severe illness. Among the severe clinical manifestations, there are severe pneumonia, ARDS, sepsis, and septic shock. The clinical course of the disease seems to predict a favorable trend in the majority of patients. In a percentage still to be defined of cases, after about a week there is a sudden worsening of clinical conditions with rapidly worsening respiratory failure and MOD/MOF. As a reference, the criteria of the severity of respiratory insufficiency and the diagnostic criteria of sepsis and septic shock can be used.[13]

Uncomplicated (mild) Illness

These patients usually present with symptoms of an upper respiratory tract viral infection, including mild fever, cough (dry), sore throat, nasal congestion, malaise, headache, muscle pain, or malaise. Signs and symptoms of a more serious disease, such as dyspnea, are not present. Compared to previous HCoV infections, non-respiratory symptoms such as diarrhea are challenging to find.

Moderate Pneumonia

Respiratory symptoms such as cough and shortness of breath (or tachypnea in children) are present without signs of severe pneumonia.

Severe Pneumonia

Fever is associated with severe dyspnea, respiratory distress, tachypnea (> 30 breaths/min), and hypoxia (SpO2 < 90% on room air). However, the fever symptom must be interpreted carefully as even in severe forms of the disease, it can be moderate or even absent. Cyanosis can occur in children. In this definition, the diagnosis is clinical, and radiologic imaging is used for excluding complications.

Acute Respiratory Distress Syndrome (ARDS)

The diagnosis requires clinical and ventilatory criteria. This syndrome is suggestive of a serious new-onset respiratory failure or for worsening of an already identified respiratory picture. Different forms of ARDS are distinguished based on the degree of hypoxia. The reference parameter is the PaO2/FiO2:

- Mild ARDS: 200 mmHg < PaO2/FiO2 ≤ 300 mmHg. In not-ventilated patients or in those managed through non-invasive ventilation (NIV) by using positive end-expiratorypressure (PEEP) or a continuous positive airway pressure (CPAP) ≥ 5 cmH2O.
- Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤ 200 mmHg.
- Severe ARDS: PaO2/FiO2 ≤ 100 mmHg.

When PaO2 is not available, a ratio SpO2/FiO2 ≤ 315 is suggestive of ARDS.

Chest imaging utilized includes chest radiograph, CT scan, or lung ultrasound demonstrating bilateral opacities (lung infiltrates > 50%), not fully explained by effusions, lobar, or lung collapse. Although in some cases, the clinical scenario and ventilator data could be suggestive for pulmonary edema, the primary respiratory origin of the edema is proven after the exclusion of cardiac failure or other causes such as fluid overload. Echocardiography can be helpful for this purpose.

Sepsis

According to the International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), sepsis represents a life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection, with organ dysfunction.[14] The clinical pictures of patients with COVID-19 and with sepsis are particularly serious, characterized by a wide range of signs and symptoms of multiorgan involvement. These signs and symptoms include respiratory manifestations such as severe dyspnea and hypoxemia, renal impairment with reduced urine output, tachycardia, altered mental status, and functional alterations of organs expressed as laboratory data of hyperbilirubinemia, acidosis, high lactate, coagulopathy, and thrombocytopenia. The reference for the evaluation of multiorgan damage and the related prognostic significance is the Sequential Organ Failure Assessment (SOFA) score, which predicts ICU mortality based on lab results and clinical data.[15] A pediatric version of the score has also received validation.[16]**Septic Shock**

In this scenario, which is associated with increased mortality, circulatory, and cellular/metabolic abnormalities such as serum lactate level greater than 2 mmol/L (18 mg/dL) are present. Because patients usually suffer from persisting hypotension despite volume resuscitation, the administration of vasopressors is required to maintain a mean arterial pressure (MAP) ≥ 65 mmHg.

Evaluation

Most countries are utilizing some type of clinical and epidemiologic information to determine who should have testing performed. In the United States, criteria have been developed for persons under investigation (PUI) for COVID-19. According to the U.S. CDC, most patients with confirmed COVID-19 have developed fever and/or symptoms of acute respiratory illness (e.g., cough, difficulty breathing). If a person is a PUI, it is recommended that practitioners immediately put in place infection control and prevention measures. Initially, they recommend testing for all other sources of respiratory infection. Additionally, they recommend using epidemiologic factors to assist in decision making. There are epidemiologic factors that assist in the decision on who test. This includes anyone who has had close contact with a patient with laboratory-confirmed COVID-19 within 14 days of symptom onset or a history of travel from affected geographic areas (presently China, Italy, Iran, Japan, and South Korea) within 14 days of symptom onset.

The WHO recommends collecting specimens from both the upper respiratory tract (naso- and oropharyngeal samples) and lower respiratory tract such as expectorated sputum, endotracheal aspirate, or bronchoalveolar lavage. The collection of BAL samples should only be performed in mechanically ventilated patients as lower respiratory tract samples seem to remain positive for a more extended period. The samples require storage at four degrees celsius. In the laboratory, amplification of the genetic material extracted from the saliva or mucus sample is through a reverse polymerase chain reaction (RT-PCR), which involves the synthesis of a double-stranded DNA molecule from an RNA mold. Once the genetic material is sufficient, the search is for those portions of the genetic code of the CoV that are conserved. The probes used are based on the initial gene sequence released by the Shanghai Public Health Clinical Center & School of Public Health, Fudan University, Shanghai, China on Virological.org, and subsequent confirmatory evaluation by additional labs. If the test result is positive, it is recommended that the test is repeated for verification. In patients with confirmed COVID-19 diagnosis, the laboratory evaluation should be repeated to evaluate for viral clearance prior to being released from observation.

The availability of testing will vary based on which country a person lives in with increasing availability occurring nearly daily.

Concerning laboratory examinations, in the early stage of the disease, a normal or decreased total white blood cell count and a decreased lymphocyte count can be demonstrated. Lymphopenia appears to be a negative prognostic factor. Increased values of liver enzymes, LDH, muscle enzymes, and C-reactive protein can be found. There is a normal procalcitonin value. In critical patients, D-dimer value is increased, blood lymphocytes decreased persistently, and laboratory alterations of multiorgan imbalance (high amylase, coagulation disorders, etc.) are found.

Treatment / Management

There is no specific antiviral treatment recommended for COVID-19, and no vaccine is currently available. The treatment is symptomatic, and oxygen therapy represents the major treatment intervention for patients with severe infection. Mechanical ventilation may be necessary in cases of respiratory failure refractory to oxygen therapy, whereas hemodynamic support is essential for managing septic shock.

On January 28, 2020, the WHO released a document summarizing WHO guidelines and scientific evidence derived from the treatment of previous epidemics from HCoVs. This document addresses measures for recognizing and sorting patients with severe acute respiratory disease; strategies for infection prevention and control; early supportive therapy and monitoring; a guideline for laboratory diagnosis; management of respiratory failure and ARDS; management of septic shock; prevention of complications; treatments; and considerations for pregnant patients.

Among these recommendations, we report the strategies for addressing respiratory failure, including protective mechanical ventilation and high-flow nasal oxygen (HFNO) or non-invasive ventilation (NIV).

Intubation and protective mechanical ventilation

Special precautions are necessary during intubation. The procedure should be executed by an expert operator who uses personal protective equipment (PPE) such as FFP3 or N95 mask, protective goggles, disposable gown long sleeve raincoat, disposable double socks, and gloves. If possible, rapid sequence intubation (RSI) should be performed. Preoxygenation (100% O2 for 5 minutes) should be performed via the continuous positive airway pressure (CPAP) method. Heat and moisture exchanger (HME) must be positioned between the mask and the circuit of the fan or between the mask and the ventilation balloon.

Mechanical ventilation should be with lower tidal volumes (4 to 6 ml/kg predicted body weight, PBW) and lower inspiratory pressures, reaching a plateau pressure (Pplat) < 28 to 30 cm H2O. PEEP must be as high as possible to maintain the driving pressure (Pplat-PEEP) as low as possible (< 14 cmH2O). Moreover, disconnections from the ventilator must be avoided for preventing loss of PEEP and atelectasis. Finally, the use of paralytics is not recommended unless PaO2/FiO2 < 150 mmHg. The prone ventilation for > 12 hours per day, and the use of a conservative fluid management strategy for ARDS patients without tissue hypoperfusion (strong recommendation) are emphasized.

Non-invasive ventilation

Concerning HFNO or non-invasive ventilation (NIV), the experts' panel, points out that these approaches performed by systems with good interface fitting do not create widespread dispersion of exhaled air, and their use can be considered at low risk of airborne transmission.[17] Practically, non-invasive techniques can be used in non-severe forms of respiratory failure. However,

if the scenario does not improve or even worsen with a short period of time (1–2 hours) the mechanical ventilation must be preferred.

Other therapies

Among other therapeutic strategies, systemic corticosteroids for the treatment of viral pneumonia or acute respiratory distress syndrome (ARDS) are not recommended. Moreover, unselective or inappropriate administration of antibiotics should be avoided. Although no antiviral treatments have been approved, alpha-interferon (e.g., 5 million units by aerosol inhalation twice per day), and lopinavir/ritonavir have been suggested. Preclinical studies suggested that remdesivir (GS5734) — an inhibitor of RNA polymerase with in vitro activity against multiple RNA viruses, including Ebola — could be effective for both prophylaxis and therapy of HCoVs infections.[18] This drug was positively tested in a rhesus macaque model of MERS-CoV infection.[19]

When the disease results in complex clinical pictures of MOD, organ function support in addition to respiratory support, is mandatory. Extracorporeal membrane oxygenation (ECMO) for patients with refractory hypoxemia despite lung-protective ventilation should merit consideration after a case-by-case analysis. It can be suggested for those with poor results to prone position ventilation.

Prevention

Preventive measures are the current strategy to limit the spread of cases. Because an epidemic will increase as long as R0 is greater than 1 (COVID-19 is 2.2), control measures must focus on reducing the value to less than 1.

Preventive strategies are focused on the isolation of patients and careful infection control, including appropriate measures to be adopted during the diagnosis and the provision of clinical care to an infected patient. For instance, droplet, contact, and airborne precautions should be adopted during specimen collection, and sputum induction should be avoided.

The WHO and other organizations have issued the following general recommendations:

- Avoid close contact with subjects suffering from acute respiratory infections.
- Wash your hands frequently, especially after contact with infected people or their environment.
- Avoid unprotected contact with farm or wild animals.
- People with symptoms of acute airway infection should keep their distance, cover coughs or sneezes with disposable tissues or clothes and wash their hands.
- Strengthen, in particular, in emergency medicine departments, the application of strict hygiene measures for the prevention and control of infections.

- Individuals that are immunocompromised should avoid public gatherings.

The most important strategy for the populous to undertake is to frequently wash their hands and use portable hand sanitizer and avoid contact with their face and mouth after interacting with a possibly contaminated environment.

Healthcare workers caring for infected individuals should utilize contact and airborne precautions to include PPE such as N95 or FFP3 masks, eye protection, gowns, and gloves to prevent transmission of the pathogen.

Meanwhile, scientific research is growing to develop a coronavirus vaccine. In recent days, China has announced the first animal tests, and researchers from the University of Queensland in Australia have also announced that, after completing the three-week in vitro study, they are moving on to animal testing. Furthermore, in the U.S., the National Institute for Allergy and Infectious Diseases (NIAID) has announced that a phase 1 trial has begun for a novel coronavirus immunization in Washington state.

Differential Diagnosis

The symptoms of the early stages of the disease are nonspecific. Differential diagnosis should include the possibility of a wide range of infectious and non-infectious (e.g., vasculitis, dermatomyositis) common respiratory disorders.

- Adenovirus
- Influenza
- Human metapneumovirus (HmPV)
- Parainfluenza
- Respiratory syncytial virus (RSV)
- Rhinovirus (common cold)

For suspected cases, rapid antigen detection, and other investigations should be adopted for evaluating common respiratory pathogens and non-infectious conditions.

Pertinent Studies and Ongoing Trials

Multiple studies globally are investigating the use of remdesivir, a broad-spectrum antiviral.

Prognosis

Preliminary data suggests the reported death rate ranges from 1% to 2% depending on the study and country. The majority of the fatalities have occurred in patients over 50 years of age. Young children appear to be mildly infected but may serve as a vector for additional transmission.

Complications

Long term complications among survivors of infection with SARS-CoV-2 having clinically significant COVID-19 disease are not yet available. The mortality rates for cases globally remain between 1% to 2%.

Deterrence and Patient Education

Patients and families should receive instruction to:

- Avoid close contact with subjects suffering from acute respiratory infections.
- Wash their hands frequently, especially after contact with sick people or their environment.
- Avoid unprotected contact with farm or wild animals.
- People with symptoms of acute airway infection should keep their distance, cover coughs or sneezes with disposable tissues or clothes and wash their hands.
- Immunocompromised patients should avoid public exposure and public gatherings. If an immunocompromised individual must be in a closed space with multiple individuals present, such as a meeting in a small room; masks, gloves, and personal hygiene with antiseptic soap should be undertaken by those in close contact with the individual. In addition, prior room cleaning with antiseptic agents should be undertaken and performed before exposure. However, considering the danger involved to these individuals, exposure should be avoided unless a meeting, group event, etc. is a true emergency.
- Strict personal hygiene measures are necessary for the prevention and control of this infection.

Enhancing Healthcare Team Outcomes

Since the first outbreak of coronavirus (COVID-19) in Wuhan, China, the disease is spreading worldwide. Individuals at the extreme of ages and those that are immunocompromised are at the most significant risk. All health care workers should understand the presentation of the disease, workup, and supportive care. Further, health professionals should be aware of the precautions necessary to avoid the contraction and spread of the disease. [Level 5]

Questions

To access free multiple choice questions on this topic, click here.

Figure

Transmission electron microscopic image of an isolate from the first U.S. case of COVID-19, formerly known as 2019-nCoV. The spherical viral particles, colorized blue, contain cross-sections through the viral genome, seen as black dots. Coronavirus, COVID-19. (more...)

Figure

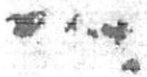
This illustration, created at the Centers for Disease Control and Prevention (CDC), reveals ultrastructural morphology exhibited by coronaviruses. Note the spikes that adorn the outer surface of the virus, which impart the look of a corona surrounding (more...)

Figure

This illustration, created at the Centers for Disease Control and Prevention (CDC), reveals ultrastructural morphology exhibited by coronaviruses. Note the spikes that adorn the outer surface of the virus, which impart the look of a corona surrounding (more...)

Figure

Centers for Disease Control and Prevention (CDC) activated its Emergency Operations Center (EOC) to coordinate with the World Health Organization (WHO), federal, state and local public health partners, and clinicians in response to the coronavirus disease (more...)



Figure

Map of the COVID-19 outbreak as of 2 March 2020. Be aware that since this is a rapidly evolving situation, new cases may not be immediately represented visually. Refer to the primary article 2019–20 coronavirus outbreak or the World Health Organization's (more...)

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ANEXO III

(MEMO n°. 009/2020/SESAP 10.3)

Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China

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Summary

Background A recent cluster of pneumonia cases in Wuhan, China, was caused by a novel betacoronavirus, the 2019 novel coronavirus (2019-nCoV). We report the epidemiological, clinical, laboratory, and radiological characteristics and treatment and clinical outcomes of these patients.

Methods All patients with suspected 2019-nCoV were admitted to a designated hospital in Wuhan. We prospectively collected and analysed data on patients with laboratory-confirmed 2019-nCoV infection by real-time RT-PCR and next-generation sequencing. Data were obtained with standardised data collection forms shared by WHO and the International Severe Acute Respiratory and Emerging Infection Consortium from electronic medical records. Researchers also directly communicated with patients or their families to ascertain epidemiological and symptom data. Outcomes were also compared between patients who had been admitted to the intensive care unit (ICU) and those who had not.

Findings By Jan 2, 2020, 41 admitted hospital patients had been identified as having laboratory-confirmed 2019-nCoV infection. Most of the infected patients were men (30 [73%] of 41); less than half had underlying diseases (13 [32%]), including diabetes (eight [20%]), hypertension (six [15%]), and cardiovascular disease (six [15%]). Median age was 49·0 years (IQR 41·0–58·0). 27 (66%) of 41 patients had been exposed to Huanan seafood market. One family cluster was found. Common symptoms at onset of illness were fever (40 [98%] of 41 patients), cough (31 [76%]), and myalgia or fatigue (18 [44%]); less common symptoms were sputum production (11 [28%] of 39), headache (three [8%] of 38), haemoptysis (two [5%] of 39), and diarrhoea (one [3%] of 38). Dyspnoea developed in 22 (55%) of 40 patients (median time from illness onset to dyspnoea 8·0 days [IQR 5·0–13·0]). 26 (63%) of 41 patients had lymphopenia. All 41 patients had pneumonia with abnormal findings on chest CT. Complications included acute respiratory distress syndrome (12 [29%]), RNAaemia (six [15%]), acute cardiac injury (five [12%]) and secondary infection (four [10%]). 13 (32%) patients were admitted to an ICU and six (15%) died. Compared with non-ICU patients, ICU patients had higher plasma levels of IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNFα.

Interpretation The 2019-nCoV infection caused clusters of severe respiratory illness similar to severe acute respiratory syndrome coronavirus and was associated with ICU admission and high mortality. Major gaps in our knowledge of the origin, epidemiology, duration of human transmission, and clinical spectrum of disease need fulfilment by future studies.

Funding Ministry of Science and Technology, Chinese Academy of Medical Sciences, National Natural Science Foundation of China, and Beijing Municipal Science and Technology Commission.

Introduction

Coronaviruses are enveloped non-segmented positive-sense RNA viruses belonging to the family Coronaviridae and the order Nidovirales and broadly distributed in humans and other mammals.[1] Although most human coronavirus infections are mild, the epidemics of the two betacoronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV)[2–4] and Middle East respiratory syndrome coronavirus (MERS-CoV),[5,6] have caused more than 10 000 cumulative cases in the past two decades, with mortality rates of 10% for SARS-CoV and 37% for MERS-CoV.[7,8] The coronaviruses already identified might only be the tip of the iceberg, with potentially more novel and severe zoonotic events to be revealed.

In December, 2019, a series of pneumonia cases of unknown cause emerged in Wuhan, Hubei, China, with clinical presentations greatly resembling viral pneumonia.[9] Deep sequencing analysis from lower respiratory tract samples indicated a novel coronavirus, which was named 2019 novel coronavirus (2019-nCoV). Thus far, more than 800 confirmed cases, including in health-care workers, have been identified in Wuhan, and several exported cases have been confirmed in other provinces in China, and in Thailand, Japan, South Korea, and the USA.[10–12]

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See Comment pages 469 and 470

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(methylprednisolone 40–120 mg per day) was given as a combined regimen if severe community-acquired pneumonia was diagnosed by physicians at the designated hospital. Oxygen support (eg, nasal cannula and invasive mechanical ventilation) was administered to patients according to the severity of hypoxaemia. Repeated tests for 2019-nCoV were done in patients confirmed to have 2019-nCoV infection to show viral clearance before hospital discharge or discontinuation of isolation.

Data collection

We reviewed clinical charts, nursing records, laboratory findings, and chest x-rays for all patients with laboratory-confirmed 2019-nCoV infection who were reported by the local health authority. The admission data of these patients was from Dec 16, 2019, to Jan 2, 2020. Epidemiological, clinical, laboratory, and radiological characteristics and treatment and outcomes data were obtained with standardised data collection forms (modified case record form for severe acute respiratory infection clinical characterisation shared by WHO and the International Severe Acute Respiratory and Emerging Infection Consortium) from electronic medical records. Two researchers also independently reviewed the data collection forms to double check the data collected. To ascertain the epidemiological and symptom data, which were not available from electronic medical records, the researchers also directly communicated with patients or their families to ascertain epidemiological and symptom data.

Cytokine and chemokine measurement

To characterise the effect of coronavirus on the production of cytokines or chemokines in the acute phase of the illness, plasma cytokines and chemokines (IL1B, IL1RA, IL2, IL4, IL5, IL6, IL7, IL8 (also known as CXCL8), IL9, IL10, IL12p70, IL13, IL15, IL17A, Eotaxin (also known as CCL11), basic FGF2, GCSF (CSF3), GMCSF (CSF2), IFNγ, IP10 (CXCL10), MCP1 (CCL2), MIP1A (CCL3), MIP1B (CCL4), PDGFB, RANTES (CCL5), TNFα, and VEGFA were measured using Human Cytokine Standard 27-Plex Assays panel and the Bio-Plex 200 system (Bio-Rad, Hercules, CA, USA) for all patients according to the manufacturer's instructions. The plasma samples from four healthy adults were used as controls for cross-comparison. The median time from being transferred to a designated hospital to the blood sample collection was 4 days (IQR 2–5).

Detection of coronavirus in plasma

Each 80 µL plasma sample from the patients and contacts was added into 240 µL of Trizol LS (10296028; Thermo Fisher Scientific, Carlsbad, CA, USA) in the Biosafety Level 3 laboratory. Total RNA was extracted by Direct-zol RNA Miniprep kit (R2050; Zymo research, Irvine, CA, USA) according to the manufacturer's instructions and 50 µL elution was obtained for each sample. 5 µL RNA was used for real-time RT-PCR, which targeted the *NP* gene using AgPath-ID One-Step RT-PCR Reagent (AM1005; Thermo Fisher Scientific). The final reaction mix concentration of the primers was 500 nM and probe was 200 nM. Real-time RT-PCR was performed using the following conditions: 50°C for 15 min and 95°C for 3 min, 50 cycles of amplification at 95°C for 10 s and 60°C for 45 s. Since we did not perform tests for detecting infectious virus in blood, we avoided the term viraemia and used RNAaemia instead. RNAaemia was defined as a positive result for real-time RT-PCR in the plasma sample.

Definitions

Acute respiratory distress syndrome (ARDS) and shock were defined according to the interim guidance of WHO

For the International Severe Acute Respiratory and Emerging Infection Consortium-WHO case record form for severe acute respiratory infections see https://isaric.tghn.org/protocols/severe-acute-respiratory-infection-data-tools/

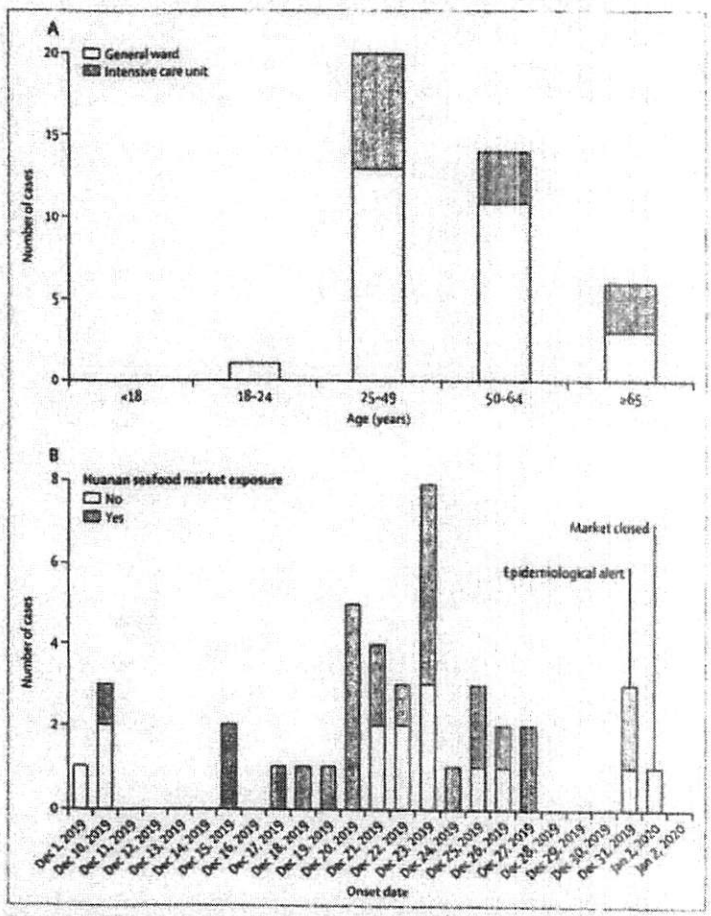

Figure 1: Date of illness onset and age distribution of patients with laboratory-confirmed 2019-nCoV infection

(A) Number of hospital admissions by age group. (B) Distribution of symptom onset date for laboratory-confirmed cases. The Wuhan local health authority issued an epidemiological alert on Dec 30, 2019, and closed the Huanan seafood market 2 days later.

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Research in context

Evidence before this study

Human coronaviruses, including hCoV-229E, OC43, NL63, and HKU1, cause mild respiratory diseases. Fatal coronavirus infections that have emerged in the past two decades are severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus. We searched PubMed and the China National Knowledge Infrastructure database for articles published up to Jan 15, 2020, using the keywords "novel coronavirus", "2019 novel coronavirus", or "2019-nCoV". No published work about the human infection caused by the 2019 novel coronavirus (2019-nCoV) could be identified.

Added value of this study

We report the epidemiological, clinical, laboratory, and radiological characteristics, treatment, and clinical outcomes of 41 laboratory-confirmed cases infected with 2019-nCoV. 27 (66%) of 41 patients had a history of direct exposure to the Huanan seafood market. The median age of patients was 49·0 years (IQR 41·0–58·0), and 13 (32%) patients had underlying disease. All patients had pneumonia. A third of patients were admitted to intensive care units, and six died. High concentrations of cytokines were recorded in plasma of critically ill patients infected with 2019-nCoV.

Implications of all the available evidence

2019-nCoV caused clusters of fatal pneumonia with clinical presentation greatly resembling SARS-CoV. Patients infected with 2019-nCoV might develop acute respiratory distress syndrome, have a high likelihood of admission to intensive care, and might die. The cytokine storm could be associated with disease severity. More efforts should be made to know the whole spectrum and pathophysiology of the new disease.

We aim to describe epidemiological, clinical, laboratory, and radiological characteristics, treatment, and outcomes of patients confirmed to have 2019-nCoV infection, and to compare the clinical features between intensive care unit (ICU) and non-ICU patients. We hope our study findings will inform the global community of the emergence of this novel coronavirus and its clinical features.

Methods

Patients

Following the pneumonia cases of unknown cause reported in Wuhan and considering the shared history of exposure to Huanan seafood market across the patients, an epidemiological alert was released by the local health authority on Dec 31, 2019, and the market was shut down on Jan 1, 2020. Meanwhile, 59 suspected cases with fever and dry cough were transferred to a designated hospital starting from Dec 31, 2019. An expert team of physicians, epidemiologists, virologists, and government officials was soon formed after the alert.

Since the cause was unknown at the onset of these emerging infections, the diagnosis of pneumonia of unknown cause in Wuhan was based on clinical characteristics, chest imaging, and the ruling out of common bacterial and viral pathogens that cause pneumonia. Suspected patients were isolated using airborne precautions in the designated hospital, Jin Yin-tan Hospital (Wuhan, China), and fit-tested N95 masks and airborne precautions for aerosol-generating procedures were taken. This study was approved by the National Health Commission of China and Ethics Commission of Jin Yin-tan Hospital (KY-2020-01.01). Written informed consent was waived by the Ethics Commission of the designated hospital for emerging infectious diseases.

Procedures

Local centres for disease control and prevention collected respiratory, blood, and faeces specimens, then shipped them to designated authoritative laboratories to detect the pathogen (WHO Key Laboratory of Systems Biology of Pathogens and Christophe Mérieux Laboratory, Beijing, China). A novel coronavirus, which was named 2019-nCoV, was isolated then from lower respiratory tract specimen and a diagnostic test for this virus was developed soon after that.[1] Of 59 suspected cases, 41 patients were confirmed to be infected with 2019-nCoV. The presence of 2019-nCoV in respiratory specimens was detected by next-generation sequencing or real-time RT-PCR methods. The primers and probe target an envelope gene of CoV were used and the sequences were as follows: forward primer 5′-ACITCITTTTCTTGGTTGGTGGT-3′; reverse primer 5′-GCAGCAGTAGGCACACAATC-3′; and the probe 5′CY5-CTAGTTAGACTAGGGATCCTACTGC-3′BHQ1. Conditions for the amplifications were 50°C for 15 min, 95°C for 3 min, followed by 45 cycles of 95°C for 15 s and 60°C for 30 s.

Initial investigations included a complete blood count, coagulation profile, and serum biochemical test (including renal and liver function, creatine kinase, lactate dehydrogenase, and electrolytes). Respiratory specimens, including nasal and pharyngeal swabs, bronchoalveolar lavage fluid, sputum, or bronchial aspirates were tested for common viruses, including influenza, avian influenza, respiratory syncytial virus, adenovirus, parainfluenza virus, SARS-CoV and MERS-CoV using real-time RT-PCR assays approved by the China Food and Drug Administration. Routine bacterial and fungal examinations were also performed.

Given the emergence of the 2019-nCoV pneumonia cases during the influenza season, antibiotics (orally and intravenously) and oseltamivir (orally 75 mg twice daily) were empirically administered. Corticosteroid therapy

were sputum production (11 [28%] of 39), headache (three [8%] of 38), haemoptysis (two [5%] of 39), and diarrhoea (one [3%] of 38; table 1). More than half of patients (22 [55%] of 40) developed dyspnoea. The median duration from illness onset to dyspnoea was 8·0 days (IQR 5·0–13·0). The median time from onset of symptoms to first hospital admission was 7·0 days (4·0–8·0), to shortness of breath was 8·0 days (5·0–13·0), to ARDS was 9·0 days (8·0–14·0), to mechanical ventilation was 10·5 days (7·0–14·0), and to ICU admission was 10·5 days (8·0–17·0; figure 2).

The blood counts of patients on admission showed leucopenia (white blood cell count less than 4×10^9/L; ten [25%] of 40 patients) and lymphopenia (lymphocyte count $<1·0\times10^9$/L; 26 [63%] patients; table 2). Prothrombin time and D-dimer level on admission were higher in ICU patients (median prothrombin time 12·2 s [IQR 11·2–13·4]; median D-dimer level 2·4 mg/L [0·6–14·4]) than non-ICU patients (median prothrombin time 10·7 s [9·8–12·1], p=0·012; median D-dimer level 0·5 mg/L [0·3–0·8], p=0·0042). Levels of aspartate aminotransferase were increased in 15 (37%) of 41 patients, including eight (62%) of 13 ICU patients and seven (25%) of 28 non-ICU patients. Hypersensitive troponin I (hs-cTnI) was increased substantially in five patients, in whom the diagnosis of virus-related cardiac injury was made.

Most patients had normal serum levels of procalcitonin on admission (procalcitonin <0·1 ng/mL; 27 [69%] patients; table 2). Four ICU patients developed secondary infections. Three of the four patients with secondary infection had procalcitonin greater than 0·5 ng/mL (0·69 ng/mL, 1·46 ng/mL, and 6·48 ng/mL).

On admission, abnormalities in chest CT images were detected among all patients. Of the 41 patients, 40 (98%) had bilateral involvement (table 2). The typical findings of chest CT images of ICU patients on admission were bilateral multiple lobular and subsegmental areas of consolidation (figure 3A). The representative chest CT findings of non-ICU patients showed bilateral ground-glass opacity and subsegmental areas of consolidation (figure 3B). Later chest CT images showed bilateral ground-glass opacity, whereas the consolidation had been resolved (figure 3C).

Initial plasma IL1B, IL1RA, IL7, IL8, IL9, IL10, basic FGF, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1A, MIP1B, PDGF, TNFα, and VEGF concentrations were higher in both ICU patients and non-ICU patients than in healthy adults (appendix pp 6–7). Plasma levels of IL5, IL12p70, IL15, Eotaxin, and RANTES were similar between healthy adults and patients infected with 2019-nCoV. Further comparison between ICU and non-ICU patients showed that plasma concentrations of IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα were higher in ICU patients than non-ICU patients.

All patients had pneumonia. Common complications included ARDS (12 [29%] of 41 patients), followed by RNAaemia (six [15%] patients), acute cardiac injury (five [12%] patients), and secondary infection (four [10%] patients; table 3). Invasive mechanical ventilation was required in four (10%) patients, with two of them (5%) had refractory hypoxaemia and received extracorporeal membrane oxygenation as salvage therapy. All patients were administered with empirical antibiotic treatment, and 38 (93%) patients received antiviral therapy (oseltamivir). Additionally, nine (22%) patients were given systematic corticosteroids. A comparison of clinical features between patients who received and did not receive systematic corticosteroids is in the appendix (pp 1–5).

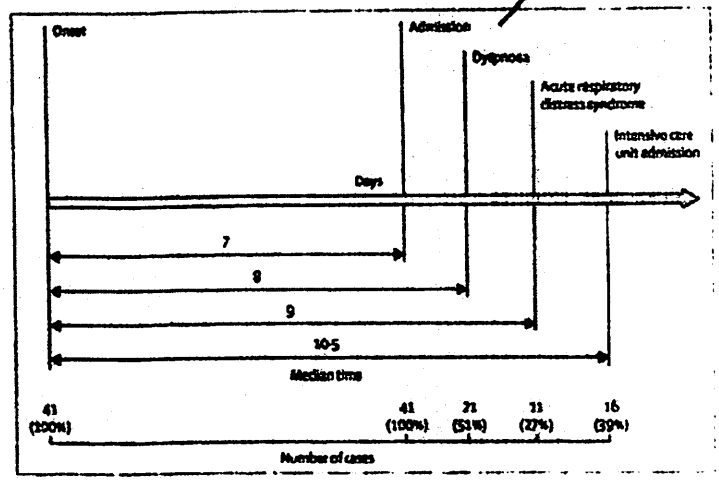

Figure 2: Timeline of 2019-nCoV cases after onset of illness

As of Jan 22, 2020, 28 (68%) of 41 patients have been discharged and six (15%) patients have died. Fitness for discharge was based on abatement of fever for at least 10 days, with improvement of chest radiographic evidence and viral clearance in respiratory samples from upper respiratory tract.

Discussion

We report here a cohort of 41 patients with laboratory-confirmed 2019-nCoV infection. Patients had serious, sometimes fatal, pneumonia and were admitted to the designated hospital in Wuhan, China, by Jan 2, 2020. Clinical presentations greatly resemble SARS-CoV. Patients with severe illness developed ARDS and required ICU admission and oxygen therapy. The time between hospital admission and ARDS was as short as 2 days. At this stage, the mortality rate is high for 2019-nCoV, because six (15%) of 41 patients in this cohort died.

The number of deaths is rising quickly. As of Jan 24, 2020, 835 laboratory-confirmed 2019-nCoV infections were reported in China, with 25 fatal cases. Reports have been released of exported cases in many provinces in China, and in other countries;

See Online for appendix

	All patients (n=41)	ICU care (n=13)	No ICU care (n=28)	p value
Characteristics				
Age, years	49·0 (41·0-58·0)	49·0 (41·0-61·0)	49·0 (41·0-57·5)	0·66
Sex	–	–	–	0·24
Men	30 (73%)	11 (85%)	19 (68%)	–
Women	11 (27%)	2 (15%)	9 (32%)	–
Huanan seafood market exposure	27 (66%)	9 (69%)	18 (64%)	0·75
Current smoking	3 (7%)	0	3 (11%)	0·31
Any comorbidity	13 (32%)	5 (38%)	8 (29%)	0·53
Diabetes	8 (20%)	1 (8%)	7 (25%)	0·16
Hypertension	6 (15%)	2 (15%)	4 (14%)	0·93
Cardiovascular disease	6 (15%)	3 (23%)	3 (11%)	0·32
Chronic obstructive pulmonary disease	1 (2%)	1 (8%)	0	0·14
Malignancy	1 (2%)	0	1 (4%)	0·49
Chronic liver disease	1 (2%)	0	1 (4%)	0·68
Signs and symptoms				
Fever	40 (98%)	13 (100%)	27 (96%)	0·68
Highest temperature, °C	–	–	–	0·037
<37·3	1 (2%)	0	1 (4%)	–
37·3–38·0	8 (20%)	3 (23%)	5 (18%)	–
38·1–39·0	18 (44%)	7 (54%)	11 (39%)	–
>39·0	14 (34%)	3 (23%)	11 (39%)	–
Cough	31 (76%)	11 (85%)	20 (71%)	0·35
Myalgia or fatigue	18 (44%)	7 (54%)	11 (39%)	0·38
Sputum production	11/39 (28%)	5 (38%)	6/26 (23%)	0·32
Headache	3/38 (8%)	0	3/25 (12%)	0·10
Haemoptysis	2/39 (5%)	1 (8%)	1/26 (4%)	0·48
Diarrhoea	1/38 (3%)	0	1/25 (4%)	0·66
Dyspnoea	22/40 (55%)	12 (92%)	10/27 (37%)	0·0010
Days from illness onset to dyspnoea	8·0 (5·0-13·0)	8·0 (5·0-17·0)	6·5 (3·0-10·0)	0·22
Days from first admission to transfer	5·0 (1·0-8·0)	8·0 (5·0-14·0)	1·0 (1·0-6·5)	0·0033
Systolic pressure, mm Hg	125·0 (119·0-135·0)	145·0 (123·0-157·0)	122·0 (118·5-129·5)	0·018
Respiratory rate >24 breaths per min	12 (29%)	8 (62%)	4 (14%)	0·0023

Data are median (IQR), n (%), or n/N (%), where N is the total number of patients with available data. p values comparing ICU care and no ICU care are from χ^2 test, Fisher's exact test, or Mann-Whitney U test. 2019-nCoV=2019 novel coronavirus. ICU=intensive care unit.

Table 1: Demographics and baseline characteristics of patients infected with 2019-nCoV

for novel coronavirus.[7] Hypoxaemia was defined as arterial oxygen tension (PaO_2) over inspiratory oxygen fraction (FIO_2) of less than 300 mm Hg.[8] Acute kidney injury was identified and classified on the basis of the highest serum creatinine level or urine output criteria according to the kidney disease: improving global outcomes classification.[9] Secondary infection was diagnosed if the patients had clinical symptoms or signs of nosocomial pneumonia or bacteraemia, and was combined with a positive culture of a new pathogen from a lower respiratory tract specimen (including the sputum, transtracheal aspirates, or bronchoalveolar lavage fluid, or from blood samples taken >48 h after admission).[9] Cardiac injury followed the definition used in our previous study in H7N9 patients.[8] In brief, cardiac injury was diagnosed if serum levels of cardiac biomarkers (eg, troponin I) were above the 99th percentile upper reference limit, or new abnormalities were shown in electrocardiography and echocardiography.

Statistical analysis

Continuous variables were expressed as median (IQR) and compared with the Mann-Whitney U test; categorical variables were expressed as number (%) and compared by χ^2 test or Fisher's exact test between ICU care and no ICU care groups. Boxplots were drawn to describe plasma cytokine and chemokine concentrations.

A two-sided α of less than 0·05 was considered statistically significant. Statistical analyses were done using the SAS software, version 9.4, unless otherwise indicated.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

By Jan 2, 2020, 41 admitted hospital patients were identified as laboratory-confirmed 2019-nCoV infection in Wuhan. 20 (49%) of the 2019-nCoV-infected patients were aged 25–49 years, and 14 (34%) were aged 50–64 years (figure 1A). The median age of the patients was 49·0 years (IQR 41·0-58·0; table 1). In our cohort of the first 41 patients as of Jan 2, no children or adolescents were infected. Of the 41 patients, 13 (32%) were admitted to the ICU because they required high-flow nasal cannula or higher-level oxygen support measures to correct hypoxaemia. Most of the infected patients were men (30 [73%]); less than half had underlying diseases (13 [32%]), including diabetes (eight [20%]), hypertension (six [15%]), and cardiovascular disease (six [15%]).

27 (66%) patients had direct exposure to Huanan seafood market (figure 1B). Market exposure was similar between the patients with ICU care (nine [69%]) and those with non-ICU care (18 [64%]). The symptom onset date of the first patient identified was Dec 1, 2019. None of his family members developed fever or any respiratory symptoms. No epidemiological link was found between the first patient and later cases. The first fatal case, who had continuous exposure to the market, was admitted to hospital because of a 7-day history of fever, cough, and dyspnoea. 5 days after illness onset, his wife, a 53-year-old woman who had no known history of exposure to the market, also presented with pneumonia and was hospitalised in the isolation ward.

The most common symptoms at onset of illness were fever (40 [98%] of 41 patients), cough (31 [76%]), and myalgia or fatigue (18 [44%]); less common symptoms

before and after their exposure to 2019-nCoV for identification of asymptomatic infections.

Similarities of clinical features between 2019-nCoV and previous betacoronavirus infections have been noted. In this cohort, most patients presented with fever, dry cough, dyspnoea, and bilateral ground-glass opacities on chest CT scans. These features of 2019-nCoV infection bear some resemblance to SARS-CoV and MERS-CoV infections.[20,21] However, few patients with 2019-nCoV infection had prominent upper respiratory tract signs and symptoms (eg, rhinorrhoea, sneezing, or sore throat), indicating that the target cells might be located in the lower airway. Furthermore, 2019-nCoV patients rarely developed intestinal signs and symptoms (eg, diarrhoea), whereas about 20–25% of patients with MERS-CoV or SARS-CoV infection had diarrhoea.[21] Faecal and urine samples should be tested to exclude a potential alternative route of transmission that is unknown at this stage.

The pathophysiology of unusually high pathogenicity for SARS-CoV or MERS-CoV has not been completely understood. Early studies have shown that increased amounts of proinflammatory cytokines in serum (eg, IL1B, IL6, IL12, IFNγ, IP10, and MCP1) were associated with pulmonary inflammation and extensive lung damage in SARS patients.[22] MERS-CoV infection was also reported to induce increased concentrations of proinflammatory cytokines (IFNγ, TNFα, IL15, and IL17).[23] We noted that patients infected with 2019-nCoV also had high amounts of IL1B, IFNγ, IP10, and MCP1, probably leading to activated T-helper-1 (Th1) cell responses. Moreover, patients requiring ICU admission had higher concentrations of GCSF, IP10, MCP1, MIP1A, and TNFα than did those not requiring ICU admission, suggesting that the cytokine storm was associated with disease severity. However, 2019-nCoV infection also initiated increased secretion of T-helper-2 (Th2) cytokines (eg, IL4 and IL10) that suppress inflammation, which differs from SARS-CoV infection.[22] Further studies are necessary to characterise the Th1 and Th2 responses in 2019-nCoV infection and to elucidate the pathogenesis. Autopsy or biopsy studies would be the key to understand the disease.

In view of the high amount of cytokines induced by SARS-CoV,[22,24] MERS-CoV,[23,25] and 2019-nCoV infections, corticosteroids were used frequently for treatment of patients with severe illness, for possible benefit by reducing inflammatory-induced lung injury. However, current evidence in patients with SARS and MERS

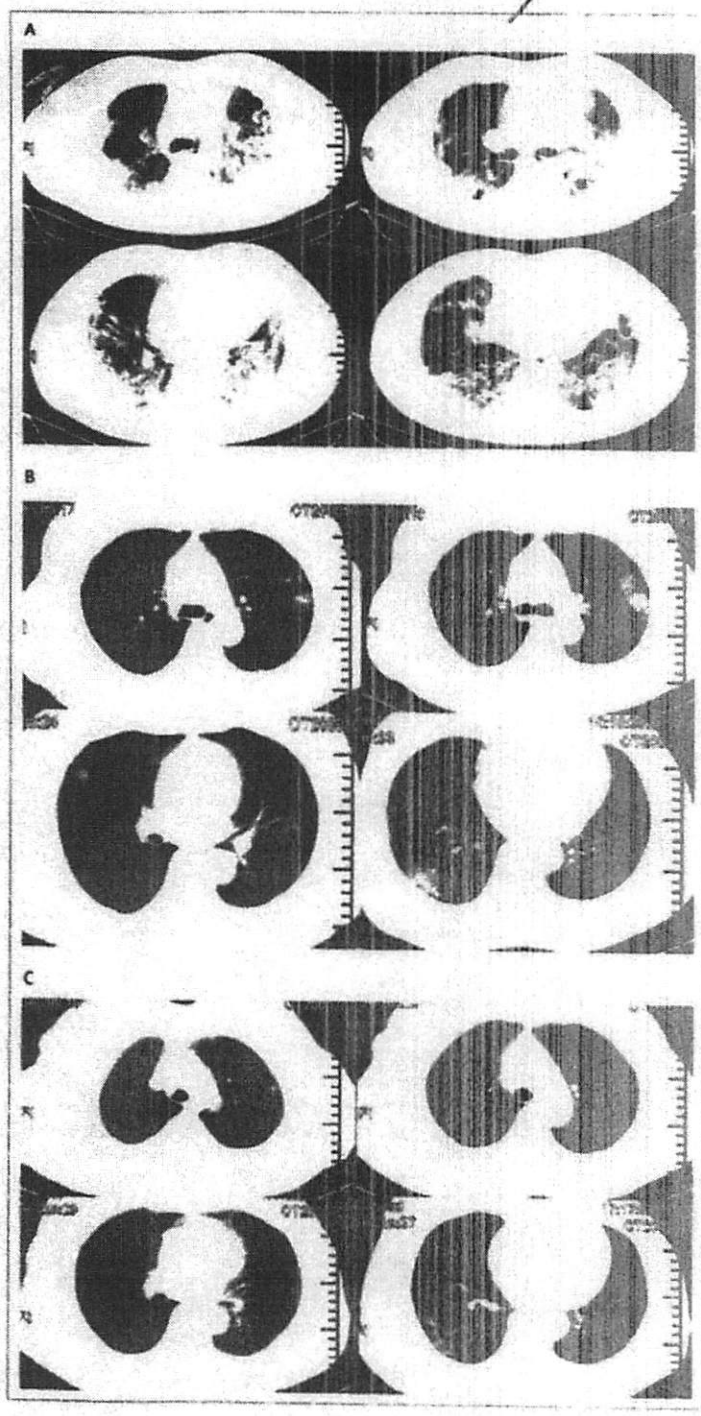

Figure 3: Chest CT images
(A) Transverse chest CT images from a 40-year-old man showing bilateral multiple lobular and subsegmental areas of consolidation on day 15 after symptom onset. Transverse chest CT images from a 53-year-old woman showing bilateral ground-glass opacity and subsegmental areas of consolidation on day 8 after symptom onset (B), and bilateral ground-glass opacity on day 12 after symptom onset (C)

	All patients (n=41)	ICU care (n=13)	No ICU care (n=28)	p value
White blood cell count, × 10⁹ per L	6·2 (4·1–10·5)	11·3 (5·8–12·1)	5·7 (3·1–7·6)	0·011
<4	10/40 (25%)	1/13 (8%)	9/27 (33%)	0·041
4–10	18/40 (45%)	5/13 (38%)	13/27 (48%)	..
>10	12/40 (30%)	7/13 (54%)	5/27 (19%)	..
Neutrophil count, × 10⁹ per L	5·0 (3·3–8·9)	10·6 (5·0–11·8)	4·4 (2·0–6·1)	0·00069
Lymphocyte count, × 10⁹ per L	0·8 (0·6–1·1)	0·4 (0·2–0·8)	1·0 (0·7–1·1)	0·0041
<1·0	26/41 (63%)	11/13 (85%)	15/28 (54%)	0·045
≥1·0	15/41 (37%)	2/13 (15%)	13/28 (46%)	..
Haemoglobin, g/L	126·0 (118·0–140·0)	122·0 (111·0–128·0)	130·5 (120·0–140·0)	0·20
Platelet count, × 10⁹ per L	164·5 (131·5–263·0)	196·0 (165·0–263·0)	149·0 (131·0–263·0)	0·45
<100	2/40 (5%)	1/13 (8%)	1/27 (4%)	0·45
≥100	38/40 (95%)	12/13 (92%)	26/27 (96%)	..
Prothrombin time, s	11·1 (10·1–12·4)	12·2 (11·2–13·4)	10·7 (9·8–12·1)	0·012
Activated partial thromboplastin time, s	27·0 (24·2–34·1)	26·2 (22·5–33·9)	27·7 (24·8–34·1)	0·57
D-dimer, mg/L	0·5 (0·3–1·3)	2·4 (0·6–14·4)	0·5 (0·3–0·8)	0·0042
Albumin, g/L	31·4 (28·9–36·0)	27·9 (26·3–30·9)	34·7 (30·2–36·5)	0·00066
Alanine aminotransferase, U/L	32·0 (21·0–50·0)	49·0 (29·0–115·0)	27·0 (19·5–40·0)	0·038
Aspartate aminotransferase, U/L	34·0 (26·0–48·0)	44·0 (30·0–70·0)	34·0 (24·0–40·5)	0·10
≤40	26/41 (63%)	5/13 (38%)	21/28 (75%)	0·025
>40	15/41 (37%)	8/13 (62%)	7/28 (25%)	..
Total bilirubin, mmol/L	11·7 (9·5–13·9)	14·0 (11·9–32·9)	10·8 (9·4–12·3)	0·011
Potassium, mmol/L	4·2 (3·8–4·8)	4·6 (4·0–5·0)	4·1 (3·8–4·6)	0·27
Sodium, mmol/L	139·0 (137·0–140·0)	138·0 (137·0–139·0)	139·0 (137·5–140·5)	0·26
Creatinine, μmol/L	74·2 (57·5–85·7)	79·0 (53·1–92·7)	73·3 (57·5–84·7)	0·84
≤133	37/41 (90%)	11/13 (85%)	26/28 (93%)	0·42
>133	4/41 (10%)	2/13 (15%)	2/28 (7%)	..
Creatine kinase, U/L	132·5 (62·0–219·0)	132·0 (82·0–493·0)	133·0 (61·0–189·0)	0·31
≤185	27/40 (68%)	7/13 (54%)	20/27 (74%)	0·21
>185	13/40 (33%)	6/13 (46%)	7/27 (26%)	..
Lactate dehydrogenase, U/L	286·0 (242·0–408·0)	400·0 (323·0–578·0)	281·0 (233·0–357·0)	0·0044
≤245	11/40 (28%)	1/13 (8%)	10/27 (37%)	0·036
>245	29/40 (73%)	12/13 (92%)	17/27 (63%)	..
Hypersensitive troponin I, pg/mL	3·4 (1·1–9·1)	3·3 (3·0–163·0)	3·5 (0·7–5·4)	0·075
>28 (99th percentile)	5/41 (12%)	4/13 (31%)	1/28 (4%)	0·017
Procalcitonin, ng/mL	0·1 (0·1–0·1)	0·1 (0·1–0·4)	0·1 (0·1–0·1)	0·031
<0·1	27/39 (69%)	6/12 (50%)	21/27 (78%)	0·029
≥0·1 to <0·25	7/39 (18%)	3/12 (25%)	4/27 (15%)	..
≥0·25 to <0·5	2/39 (5%)	0/12	2/27 (7%)	..
≥0·5	3/39 (8%)	3/12 (25%)*	0/27	..
Bilateral involvement of chest radiographs	40/41 (98%)	13/13 (100%)	27/28 (96%)	0·68
Cycle threshold of respiratory tract	32·2 (31·0–34·5)	31·1 (30·0–33·5)	32·2 (31·1–34·7)	0·39

Data are median (IQR) or n/N (%), where N is the total number of patients with available data. p values comparing ICU care and no ICU care are from χ², Fisher's exact test, or Mann-Whitney U test. 2019-nCoV=2019 novel coronavirus. ICU=intensive care unit. *Complicated typical secondary infection during the first hospitalisation.

Table 2: Laboratory findings of patients infected with 2019-nCoV on admission to hospital

some health-care workers have also been infected in Wuhan. Taken together, evidence so far indicates human transmission for 2019-nCoV. We are concerned that 2019-nCoV could have acquired the ability for efficient human transmission.[19] Airborne precautions, such as a fit-tested N95 respirator, and other personal protective equipment are strongly recommended. To prevent further spread of the disease in health-care settings that are caring for patients infected with 2019-nCoV, onset of fever and respiratory symptoms should be closely monitored among health-care workers. Testing of respiratory specimens should be done immediately once a diagnosis is suspected. Serum antibodies should be tested among health-care workers

data and the accuracy of the data analysis. YWa, GF, XG, JiXu, HL, and BC contributed to writing of the report. BC contributed to critical revision of the report. YWa, GF, XG, JiXu, and HL contributed to the statistical analysis. All authors contributed to data acquisition, data analysis, or data interpretation, and reviewed and approved the final version.

Declaration of interests
All authors declare no competing interests.

Data sharing
The data that support the findings of this study are available from the corresponding author on reasonable request. Participant data without names and identifiers will be made available after approval from the corresponding author and National Health Commission. After publication of study findings, the data will be available for others to request. The research team will provide an email address for communication once the data are approved to be shared with others. The proposal with detailed description of study objectives and statistical analysis plan will be needed for evaluation of the reasonability to request for our data. The corresponding author and National Health Commission will make a decision based on these materials. Additional materials may also be required during the process.

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	All patients (n=41)	ICU care (n=13)	No ICU care (n=28)	p value
Duration from illness onset to first admission	7·0 (4·0–8·0)	7·0 (4·0–8·0)	7·0 (4·0–8·5)	0·87
Complications				
Acute respiratory distress syndrome	12 (29%)	11 (85%)	1 (4%)	<0·0001
RNAaemia	6 (15%)	2 (15%)	4 (14%)	0·93
Cycle threshold of RNAaemia	35·1 (34·7–35·1)	35·1 (35·1–35·1)	34·8 (34·1–35·4)	0·35
Acute cardiac injury*	5 (12%)	4 (31%)	1 (4%)	0·037
Acute kidney injury	3 (7%)	3 (23%)	0	0·027
Secondary infection	4 (10%)	4 (31%)	0	0·0014
Shock	3 (7%)	3 (23%)	0	0·027
Treatment				
Antiviral therapy	38 (93%)	13 (92%)	25 (93%)	0·45
Antibiotic therapy	41 (100%)	13 (100%)	28 (100%)	NA
Use of corticosteroid	9 (22%)	6 (46%)	3 (11%)	0·013
Continuous renal replacement therapy	3 (7%)	3 (23%)	0	0·027
Oxygen support	–	–	–	<0·0001
Nasal cannula	27 (66%)	1 (8%)	26 (93%)	–
Non-invasive ventilation or high-flow nasal cannula	10 (24%)	8 (62%)	2 (7%)	–
Invasive mechanical ventilation	2 (5%)	2 (15%)	0	–
Invasive mechanical ventilation and ECMO	2 (5%)	2 (15%)	0	–
Prognosis	–	–	–	0·014
Hospitalisation	7 (17%)	1 (8%)	6 (21%)	–
Discharge	28 (68%)	7 (54%)	21 (75%)	–
Death	6 (15%)	5 (38%)	1 (4%)	–

Data are median (IQR) or n (%). p values are comparing ICU care and no ICU care. 2019-nCoV=2019 novel coronavirus. ICU=intensive care unit. NA=not applicable. ECMO=extracorporeal membrane oxygenation. *Defined as blood levels of hypersensitive troponin I above the 99th percentile upper reference limit (>28 pg/mL) or new abnormalities shown on electrocardiography and echocardiography.

Table 3: Treatments and outcomes of patients infected with 2019-nCoV

suggests that receiving corticosteroids did not have an effect on mortality, but rather delayed viral clearance.[17,18] Therefore, corticosteroids should not be routinely given systemically, according to WHO interim guidance.[19] Among our cohort of 41 laboratory-confirmed patients with 2019-nCoV infection, corticosteroids were given to very few non-ICU cases, and low-to-moderate dose of corticosteroids were given to less than half of severely ill patients with ARDS. Further evidence is urgently needed to assess whether systematic corticosteroid treatment is beneficial or harmful for patients infected with 2019-nCoV.

No antiviral treatment for coronavirus infection has been proven to be effective. In a historical control study,[20] the combination of lopinavir and ritonavir among SARS-CoV patients was associated with substantial clinical benefit (fewer adverse clinical outcomes). Arabi and colleagues initiated a placebo-controlled trial of interferon beta-1b, lopinavir, and ritonavir among patients with MERS infection in Saudi Arabia.[21] Preclinical evidence showed the potent efficacy of remdesivir (a broad-spectrum antiviral nucleotide prodrug) to treat MERS-CoV and SARS-CoV infections.[22,23] As 2019-nCoV is an emerging virus, an effective treatment has not been developed for disease resulting from this virus. Since the combination of lopinavir and ritonavir was already available in the designated hospital, a randomised controlled trial has been initiated quickly to assess the efficacy and safety of combined use of lopinavir and ritonavir in patients hospitalised with 2019-nCoV infection.

Our study has some limitations. First, for most of the 41 patients, the diagnosis was confirmed with lower respiratory tract specimens and no paired nasopharyngeal swabs were obtained to investigate the difference in the viral RNA detection rate between upper and lower respiratory tract specimens. Serological detection was not done to look for 2019-nCoV antibody rises in 18 patients with undetectable viral RNA. Second, with the limited number of cases, it is difficult to assess host risk factors for disease severity and mortality with multivariable-adjusted methods. This is a modest-sized case series of patients admitted to hospital; collection of standardised data for a larger cohort would help to further define the clinical presentation, natural history, and risk factors. Further studies in outpatient, primary care, or community settings are needed to get a full picture of the spectrum of clinical severity. At the same time, finding of statistical tests and p values should be interpreted with caution, and non-significant p values do not necessarily rule out difference between ICU and non-ICU patients. Third, since the causative pathogen has just been identified, kinetics of viral load and antibody titres were not available. Finally, the potential exposure bias in our study might account for why no paediatric or adolescent patients were reported in this cohort. More effort should be made to answer these questions in future studies.

Both SARS-CoV and MERS-CoV were believed to originate in bats, and these infections were transmitted directly to humans from market civets and dromedary camels, respectively.[24] Extensive research on SARS-CoV and MERS-CoV has driven the discovery of many SARS-like and MERS-like coronaviruses in bats. In 2013, Ge and colleagues[25] reported the whole genome sequence of a SARS-like coronavirus in bats with that ability to use human ACE2 as a receptor, thus having replication potentials in human cells.[26] 2019-nCoV still needs to be studied deeply in case it becomes a global health threat. Reliable quick pathogen tests and feasible differential diagnosis based on clinical description are crucial for clinicians in their first contact with suspected patients. Because of the pandemic potential of 2019-nCoV, careful surveillance is essential to monitor its future host adaption, viral evolution, infectivity, transmissibility, and pathogenicity.

Contributors

BC and JW had the idea for and designed the study and had full access to all data in the study and take responsibility for the integrity of the

ANEXO IV

(MEMO n°. 009/2020/SESAP 10.3)

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BEM ESTAR

CORONAVÍRUS

SUS prevê 2 mil leitos de UTI para tratar pacientes com Covid-19

Nível de preocupação aumentou após piora da situação na Itália.

Por Brenda Ortiz, Fabio Manzano e Lara Pinheiro, G1 e G1 DF
12/03/2020 12h44 · Atualizado há 15 horas

Secretário-executivo do Ministério da Saúde, João Gabbardo — Foto: TV Globo/Reprodução

O Brasil vai direcionar 2 mil leitos de UTI para o tratamento de pacientes com Covid-19 pelo Sistema Único de Saúde (SUS). Na quinta-feira (12), o **Ministério da Saúde** explicou que a previsão de aumento nos atendimentos do SUS foi motivada pela rápida evolução da doença na Europa.

O secretário-executivo do Ministério da Saúde, João Gabbardo, disse em entrevista coletiva que o nível de preocupação com leitos aumentou após registros dos casos na Itália.

- **Saúde convoca 5 mil profissionais pelo programa Mais Médicos para combate ao coronavírus**
- **Pessoas que tiverem contato com infectados por coronavírus também podem ser colocadas em isolamento, define governo**

"Quando pensamos em mil leitos, foi uma estimativa, sem nenhum dado concreto", disse o secretário-executivo. "Hoje, depois da Itália, nosso nível de preocupação aumentou. Por isso estamos colocando dois mil leitos."

Gabbardo disse também que o SUS deve mudar os critérios para o uso de leitos nas Unidades de Tratamentos Intensivos (UTI) e explicou que pacientes terminais, por exemplo, não serão levados a este setor.

"Estamos pensando em sugestões e alterações do uso dos leitos", disse. "Não vamos colocar pacientes de forma desnecessária em um hospital. Tem critérios na utilização para situação de emergência."

A pasta também anunciou, nesta quinta (12), a **convocação de 5 mil profissionais** pelo programa **Mais Médicos** para contribuir no combate ao surto de novo coronavírus.

Covid-19: Ministério da Saúde faz chamamento público de leitos hospitalares

Isolamento e quarentena

O Ministério da Saúde também definiu as regras para isolamento e quarentena de pacientes com Covid-19. O texto prevê que agentes de vigilância epidemiológica podem recomendar o isolamento para pessoas que tiveram contato próximo com alguém infectado enquanto o caso delas estiver sendo investigado.

A decisão sobre manter em isolamento ou não uma pessoa que teve contato com alguém infectado ficará a cargo do profissional, segundo afirmou o Ministério da Saúde ao G1.

A portaria diz que quem descumprir as medidas de isolamento ou quarentena recomendadas será responsabilizado nos termos previstos na lei, mas não detalha a quais tipos de sanções essas pessoas podem ser submetidas.

Ministério da Saúde anuncia medidas para combater o coronavírus

Casos no Brasil

O número de casos confirmados de coronavírus no Brasil passou de 70. O Ministério da Saúde contabiliza 60 casos pelo país, segundo balanço divulgado na manhã desta quinta. Esse número, porém, não leva em conta outros 19 casos já informados por outros órgãos. São eles:

- Os 2 primeiros casos confirmados pela Secretaria Estadual de Saúde de Pernambuco nesta quinta
- 16 casos confirmados na quarta (11) pelo Hospital Albert Einstein em São Paulo
- O 3º caso confirmado pela Secretaria de Estado da Saúde na Bahia, na quarta

O balanço aponta que São Paulo é o estado com mais casos e soma ao todo 30 pacientes com a Covid-19. Na sequência aparecem Rio de Janeiro (13), Bahia (2), Rio Grande do Sul (4), Distrito Federal (2), Alagoas (1), Pernambuco (2), Minas Gerais (1), Espírito Santo (1) e Paraná (5).