Public Health England

International EPI Cell Daily Evidence Briefing – 19/03/2020

These papers are organised under the following themes:

- Diagnostics and genomics
- Epidemiology and clinical
- Infection control
- Treatment
- Social sciences
- Miscellaneous
- Modelling

Please note that we are including preprints, which are preliminary reports of work that have <u>NOT</u> been peer-reviewed. They should not be relied on to guide clinical practice or health-related behaviour and should <u>NOT</u> be reported in news media as established information.

Diagnostics and genomics

Publication date	Title/URL	Journal/Type	Digest
17.03.2020	An emergent clade of SARS-CoV-2 linked to returned travellers from Iran	bioRxiv (not peer-reviewed) / Article	•Phylogenetic analyses of whole genome sequencing data identified a distinct SARS-CoV-2 clade linked to travellers returning from Iran to Australia and New Zealand. This study highlights potential viral diversity driving the epidemic in Iran, and underscores the power of rapid genome sequencing and public data sharing to improve the detection and management of emerging infectious diseases.

17.03.2020	[Evidence of the Recombinant Origin and Ongoing Mutations in Severe Acute Respiratory Syndrome 2 (SARS-COV-2)](#)	bioRxiv (not peer-reviewed) / Article	•Whole genome analysis of SARS-CoV-2 revealed ~96% genomic similarity with bat CoV (RaTG13) and clustered together in phylogenetic tree. Furthermore, RaTG13 also showed 97.43% spike protein similarity with SARS-CoV-2 suggesting that RaTG13 is the closest strain. These findings propose that homologous recombination has been occurred between bat and pangolin CoVs that triggered cross-species transmission and emergence of SARS-CoV-2, and, during the ongoing outbreak, SARS-CoV-2 is still evolving for its adaptability.
17.03.2020	[A Cryptic Site of Vulnerability on the Receptor Binding Domain of the SARS-CoV-2 Spike Glycoprotein](#)	bioRxiv (not peer-reviewed) / Article	• The authors report the crystal structure of the SARS-CoV-2 S receptor-binding-domain (RBD) at the highest resolution to date, of 1.95 Å. They identified a set of SARS-reactive monoclonal antibodies with cross-reactivity to SARS-CoV-2 RBD and other betacoronavirus S glycoproteins. This first-ever resolution of a human antibody in complex with SARS-CoV-2 and the broad reactivity of this set of antibodies to a conserved betacoronavirus epitope will allow antigenic assessment of vaccine candidates, and provide a framework for accelerated vaccine, immunotherapeutic and diagnostic strategies against SARS-CoV-2 and related betacoronaviruses.
17.03.2020	[Cross-reactive antibody response between SARS-CoV-2 and SARS-CoV infections](#)	bioRxiv (not peer-reviewed) / Article	• There is currently a lack of knowledge in the antibody response elicited from SARS-CoV-2 infection. One major immunological question is concerning the antigenic differences between SARS-CoV-2 and SARS-CoV. The authors address this question by using plasma from patients infected by SARS-CoV-2 or SARS-CoV, and plasma obtained from infected or immunized mice. The results show that while cross-reactivity in antibody binding to the spike protein is common, cross-neutralization of the live viruses is rare, indicating the presence of non-neutralizing antibody response to conserved epitopes in the spike. Overall, this study not only addresses a fundamental question regarding the antigenicity differences between SARS-CoV-2 and SARS-CoV, but also has important implications in vaccine development.

17.03.2020	International expansion of a novel SARS-CoV-2 mutant	medRxiv (not peer-reviewed) / Letter	•The authors report that a novel SARS-CoV-2 mutation (ORF3a) appears to be spreading worldwide, which deserves close attention.
17.03.2020	Multiple approaches for massively parallel sequencing of HCoV-19 genomes directly from clinical samples	bioRxiv (not peer-reviewed) / Article	•illustrate the application of amplicon and hybrid capture (capture)-based sequencing, as well as ultra-high-throughput metatranscriptomic (meta) sequencing in retrieving complete genomes, inter-individual and intra-individual variations of HCoV-19 from clinical samples covering a range of sample types and viral load. They also examine and compare the bias, sensitivity, accuracy, and other characteristics of these approaches in a comprehensive manner.
17.03.2020	A machine learning-based model for survival prediction in patients with severe COVID-19 infection	MedRxiv (not peer-reviewed) / Article	•This study used a database of blood samples from 404 infected patients in the region of Wuhan, China to identify crucial predictive biomarkers of disease severity. For this purpose, machine learning tools selected three biomarkers that predict the survival of individual patients with more than 90% accuracy: lactic dehydrogenase (LDH), lymphocyte and high-sensitivity C-reactive protein (hs-CRP). In particular, relatively high levels of LDH alone seem to play a crucial role in distinguishing the vast majority of cases that require immediate medical attention. This finding is consistent with current medical knowledge that high LDH levels are associated with tissue breakdown occurring in various diseases, including pulmonary disorders such as pneumonia. Overall, this paper suggests a simple and operable formula to quickly predict patients at the highest risk, allowing them to be prioritised and potentially reducing the mortality rate.

Publication date	Title/URL	Journal/Type	Digest
17.03.2020	Recapitulation of SARS-CoV-2 Infection and Cholangiocyte Damage with Human Liver Organoids	bioRxiv (not peer-reviewed) / Article	•By single-cell RNA sequencing, the authors found that long-term liver ductal organoid culture preserved the human specific ACE2+ population of cholangiocytes. Moreover, human liver ductal organoids were permissive to SARS-CoV-2 infection and support robust replication. These results indicate that control of liver damage caused directly by viral infection should be valued in treating COVID-19 patients. The findings also provide an application of human organoids in investigating the tropism and pathogenesis of SARS-CoV-2, which would facilitate novel drug discovery.
17.03.2020	Deep Learning-based Detection for COVID-19 from Chest CT using Weak Label	MedRxiv (not peer-reviewed) / Article	•A weakly-supervised deep learning-based software system was developed using 3D CT volumes to detect COVID-19.
18.03.2020	Potential T-cell and B-cell Epitopes of 2019-nCoV	bioRxiv (not peer-reviewed) / Article	• There is an immediate need for effective vaccines that contain antigens which trigger responses from human T-cells and B-cells (known as epitopes). Here the authors identify potential T-cell epitopes through an analysis of human antigen presentation, as well as B-cell epitopes through an analysis of protein structure. They identified a list of top candidates, including an epitope located on 2019-nCoV spike protein that potentially triggers both T-cell and B-cell responses. Analyzing 68 samples, they observed that viral mutations are more likely to happen in regions with strong antigen presentation, a potential form of immune evasion.

Epidemiology and clinical

Publication date	Title/URL	Journal/Type	Digest

17.03.2020	COVID-19 in pregnant women-Authors' reply	The Lancet Infectious Diseases / Correspondence	•The authors reply to comments by Schmidt et al about their previous guidelines for pregnant women with suspected severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. They have since updated the guidelines according to the data available at the beginning of March, 2020
18.03.2020	Temporal dynamics in viral shedding and transmissibility of COVID-19	bioRxiv (not peer-reviewed) / Article	Report temporal patterns of viral shedding in 94 laboratory-confirmed COVID-19 patients and modelled COVID-19 infectiousness profile from a separate sample of 77 infector-infectee transmission pairs. They authors observed the highest viral load in throat swabs at the time of symptom onset, and inferred that infectiousness peaked on or before symptom onset. They estimated that 44% of transmission could occur before first symptoms of the index. Disease control measures should be adjusted to account for probable substantial pre-symptomatic transmission.
17.03.2020	Blood single cell immune profiling reveals the interferon-MAPK pathway mediated adaptive immune response for COVID-19	MedRxiv (not peer-reviewed) / Article	•The authors found that the interferon-MAPK pathway and TCR- and BCR-produced antibodies play important roles in the COVID-19 immune response. Immune deficiency or immune overresponse may result in the condition of patients with COVID-19 becoming critical or severe.
17.03.2020	The spread of the COVID-19 coronavirus: Health agencies worldwide prepare for the seemingly inevitability of the COVID-19 coronavirus becoming endemic	EMBO Reports / Article	• As the outbreak continues to develop and new data come out of China, there are at least good prospects of treating patients with anti-viral and antibody treatments until an efficient vaccine becomes available.

Date	Title	Source / Type	Summary
19.03.2020	Rapidly increasing cumulative incidence of coronavirus disease (COVID-19) in the European Union/European Economic Area and the United Kingdom, 1 January to 15 March 2020	Eurosurveillance / Rapid communication	• The authors assess the trends in the cumulative incidence of COVID-19 in each European Union/European Economic Area (EU/EEA) country and the United Kingdom (UK) and compare them to that of Hubei Province, China. :• They also compare the current number of COVID-19 cases in EU/EEA countries and the UK with that in Italy during 31 January–15 March 2020.
18.03.2020	SARS-CoV-2 Infection in Children	NEJM / Correspondence	In order to determine the spectrum of disease in children, the authors evaluated children infected with SARS-CoV-2 and treated at the Wuhan Children's Hospital. Of the 1391 children assessed and tested from January 28 through February 26, 2020, a total of 171 (12.3%) were confirmed to have SARS-CoV-2 infection. The median age of the infected children was 6.7 years. Fever was present in 41.5% of the children at any time during the illness. Other common signs and symptoms included cough and pharyngeal erythema. A total of 27 patients (15.8%) did not have any symptoms of infection or radiologic features of pneumonia. As of March 8, 2020, there was one death. A 10-month-old child with intussusception had multiorgan failure and died 4 weeks after admission. This report describes a spectrum of illness from SARS-CoV-2 infection in children. In contrast with infected adults, most infected children appear to have a milder clinical course. Asymptomatic infections were not uncommon. Determination of the transmission potential of these asymptomatic patients is important for guiding the development of measures to control the ongoing pandemic.
18.03.2020	Am I Part of the Cure or Am I Part of the Disease? Keeping Coronavirus Out When a Doctor Comes Home	NEJM / Prespective	•Perspective from a relative of a person with bronchiolitis obliterans, a chronic, progressive lung condition, on the risk of transmission of COVID-19 in the community.
17.03.2020	Coronavirus Disease 2019 (COVID-19) in Italy	JAMA / Infographic	•This Infographic shows the most recent statistics on COVID-19 emerging from Italy

Infection control

Publication date	Title/URL	Journal/Type	Digest
17.03.2020	Covid-19 and community mitigation strategies in a pandemic	BMJ / Editorial	• No specific drugs or vaccines are available, and health systems are overburdened everywhere.:• We have to rely on targeted, non-coercive, community interventions with sufficient transparency and public engagement and trust, and implement them urgently.
01.06.2020	Identifying and interrupting superspreading events: Implications for control of Severe Acute Respiratory Syndrome Coronavirus 2	Emerging Infectious Diseases / Perspective	• To prevent and control of SSEs, speed is essential. :• Prevention and mitigation of SSEs depends, first and foremost, on quickly recognizing and understanding these events, particularly within healthcare settings.
17.03.2020	If containment is not possible, how do we minimize mortality for COVID-19 and other emerging infectious disease outbreaks?	MedRxiv (not peer-reviewed) / Article	•If COVID-19 containment policies fail and social distancing measures cannot be sustained until vaccines becomes available, the next best approach is to use interventions that reduce mortality and prevent excess infections while allowing low-risk individuals to acquire immunity through natural infection until population level immunity is achieved. In such a situation, allowing some infections to occur in lower-risk groups might lead to an overall greater reduction in mortality than trying to protect everyone equally.
17.03.2020	A high efficient hospital emergency responsive mode is the key of successful treatment of 100 COVID-19 patients in Zhuhai	MedRxiv (not peer-reviewed) / Article	• Outlines a hospital emergency responsive mode for COVID-19 used by a hospital in Zhuhai, which could provide reference for other hospitals and cities in epidemic situations.

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17.03.2020	Efficient inactivation of SARS-CoV-2 by WHO-recommended hand rub formulations and alcohols	bioRxiv (not peer-reviewed) / Article	•The authors determined the virucidal activity of two alcohol-based hand rub solutions for hand disinfection recommended by the World Health Organization (WHO), as well as commercially available alcohols. Efficient SARS-CoV-2 inactivation was demonstrated for all tested alcohol-based disinfectants. These findings show the successful inactivation of SARS-CoV-2 for the first time and provide confidence in its use for the control of COVID-19.
18.03.2020	Covid-19 — The Law and Limits of Quarantine	NEJM / Perspective	•Quarantines and travel bans are often the first response against new infectious diseases. However, these old tools are usually of limited utility for highly transmissible diseases, and if imposed with too heavy a hand, or in too haphazard a manner, they can be counterproductive. This paper discusses this.

Treatment

Publication date	Title/URL	Journal/Type	Digest
18.03.2020	Covid-19: The search for effective therapy	New England Journal of Medicine / Editorial	• Despite the fact that lopinavir–ritonavir does not seem to be highly effective in patients with Covid-19, there are many important takeaways from this study. :• It is clear that rapidly initiated, high-quality randomized clinical trials are possible in epidemic conditions, even in the trying circumstances that prevailed in Wuhan.
18.03.2020	A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19	NEJM / Correspondence	A total of 199 patients with laboratory-confirmed SARS-CoV-2 infection underwent randomization; 99 were assigned to the lopinavir–ritonavir group, and 100 to the standard-care group. Concluded that in hospitalized adult patients with severe Covid-19, no benefit was observed with lopinavir–ritonavir treatment beyond standard care. Future trials in patients with severe illness may help to confirm or exclude the possibility of a treatment benefit.

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01.03.2020	COVID-19, an emerging coronavirus infection: advances and prospects in designing and developing vaccines, immunotherapeutics, and therapeutics	Human Vaccines and Immunotherapeutics / Mini-review	• This article highlights ongoing advances in designing vaccines and therapeutics to counter COVID-19 while also focusing on such experiences and advances as made with earlier SARS- and MERS-CoVs, which together could enable efforts to halt this emerging virus infection.
19.03.2020	Hypothesis: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19	Journal of Travel Medicine / Article	• Patients who take angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) may be at increased risk of severe disease outcomes due to SARS-CoV-2 infections.
19.03.2020	Audio Interview: New Research on Possible Treatments for Covid-19	NEJM / Editorial	•In this audio interview conducted on March 18, 2020, the editors look beyond supportive care to evaluate possible treatments for the disease.

Social Sciences

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17.03.2020	Mental health status among family members of health care workers in Ningbo, China during the Coronavirus Disease 2019 (COVID-19) outbreak: a Cross-sectional Study	MedRxiv (not peer-reviewed) / Article	•A cross-sectional study aimed to investigate the mental health status and related factors of families of HCWs in Designated Hospitals in Ningbo, China (n=822). Psychological responses to COVID-19 have been dramatic among family members of HCWs during the rising phase of the outbreak. The findings provide strong evidence to pay more attention on the mental health status of this vulnerable but often unseen populations during COVID-19 epidemic. :

Miscellaneous

Publication date	Title/URL	Journal/Type	Digest
18.03.2020	SARS-CoV-2, the virus that causes COVID-19: Cytometry and the new challenge for global health	Cytometry Part A / Early view perspective	• This describes the questions about COVID-19 that need to be answered, including why do some patients get infected but do not develop any disease, while others die from the infection? Which are the protective factors, and which are the biomarkers that clinicians could use to predict, and eventually modify, the course of the disease? Why do children seem to develop a milder form of Covid-19, similar to what was described in the case of SARS? Can the immaturity of the immune system protect against immune-mediated damages that could occur during Covid-19? Which assays are useful to monitor the efficacy of an antiviral therapy? How can we help in developing a vaccine?
18.03.2020	The global community needs to swiftly ramp up the response to contain COVID-19	The Lancet / Correspondence	This paper discusses the statement made in the report by the WHO-China Joint Mission on COVID-2019, released publicly on Feb 28, 2020 that "much of the global community is not yet ready for COVID-19 [coronavirus disease 2019]".
18.03.2020	COVID-19 cacophony: is there any orchestra conductor?	The Lancet / Correspondence	•Discusses the COVID-19 pandemic.
18.03.2020	Presidential Powers and Response to COVID-19	JAMA / Viewpoint	How should individual rights be balanced with public health at a critical point in safeguarding the nation's health? Discusses federal emergency powers, travel restrictions, sheltering in place, social distancing and balancing rights and public health in a national emergency (in the US).
18.03.2020	Will COVID-19 generate global preparedness?	The Lancet / Comment	•The authors discuss global preparedness for COVID-19. This includes findings from a paper by Kandel et al which reports their analysis using an operational readiness index to summarise countries national performance across 18 indicators of preparedness to prevent, detect, and respond to an outbreak of a novel infectious disease, the Global Health Security Index and previous assessments from WHO.

18.03.2020	Health security capacities in the context of COVID-19 outbreak: an analysis of International Health Regulations annual report data from 182 countries	The Lancet / Article	•Public health measures to prevent, detect, and respond to events are essential to control public health risks, including infectious disease outbreaks, as highlighted in the International Health Regulations (IHR). In light of the outbreak of 2019 novel coronavirus disease (COVID-19). The authors reviewed existing health security capacities against public health risks and events.
18.03.2020	COVID-19 in Italy: momentous decisions and many uncertainties	The Lancet Global Health / Correspondence	•Discusses the measures taken by the Italian government in responce to the COVID-19 pandemic.
18.03.2020	The resilience of the Spanish health system against the COVID-19 pandemic	The Lancet Public Health / Comment	•Although the Spanish health system has coped well during the 6 weeks since its first case of COVID-19 was diagnosed, it will be tested severely in the coming weeks as there is already widespread community transmission in the most affected regions, Madrid, the Basque Country, and Catalonia. The number of new cases in the country is increasing by more than 1000 each day. A crisis such as this places pressure on all building blocks of a health system, each of which the authors discuss.
18.03.2020	Effects of temperature variation and humidity on the mortality of COVID-19 in Wuhan	MedRxiv (not peer-reviewed) / Article	•Explored the association between coronavirus disease (COVID-19) death and weather parameters. Study findings suggests that temperature variation and humidity may be important factors affecting COVID-19 mortality.

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17.03.2020	Comparative Pathogenesis Of COVID-19, MERS And SARS In A Non-Human Primate Model	bioRxiv (not peer-reviewed) / Article	•To compare the pathogenesis of COVID-19 with that of previously emerging coronaviruses, the authors inoculated cynomolgus macaques with SARS-CoV-2 or MERS-CoV and compared with historical SARS-CoV infections. In SARS-CoV-2-infected macaques, virus was excreted from nose and throat in absence of clinical signs, and detected in type I and II pneumocytes in foci of diffuse alveolar damage and mucous glands of the nasal cavity. In SARS-CoV-infection, lung lesions were typically more severe, while they were milder in MERS-CoV infection, where virus was detected mainly in type II pneumocytes. These data show that SARS-CoV-2 can cause a COVID-19-like disease, and suggest that the severity of SARS-CoV-2 infection is intermediate between that of SARS-CoV and MERS-CoV.
18.03.2020	Facing Covid-19 in Italy — Ethics, Logistics, and Therapeutics on the Epidemic's Front Line	NEJM / Perspective	Provides insites from healthcare workers working on the fronline in Italy during the COVID-19 pandemic.
18.03.2020	COVID-19 battle during the toughest sanctions against Iran	The Lancet / Correspondence	•The economic loss caused by the spread of COVID-19 in Iran coincides with the highest-ever politically induced sanctions against the country. This is discussed in this paper.
13.03.2020	What Does the Coronavirus Disease 2019 (COVID-19) Mean for Families?	JAMA Pediatrics	Lessons learned from China and similar viral diseases can help families prepare for spread. How children will be affected is still mostly unknown. So far, proportionately fewer children have gotten sick in China, and the effects on them have mostly been mild. It is important for families to prepare for spread of COVID-19.

Modelling

Publication date	Title/URL	Journal/Type	Digest

17.03.2020	Excess cases of Influenza like illnesses in France synchronous with COVID19 invasion	medRxiv (not peer-reviewed) / Article	•Several French regions where COVID-19 has been reported currently show a renewed increase in Influenza like illnesses cases in the general practice based Sentinelles network. Here the authors computed the number of excess cases by region and found correlation with the number of reported COVID-19 cases so far. These data suggest larger circulation of SARS-CoV-2 in the French population than apparent from confirmed cases.
18.03.2020	Transmissibility of coronavirus disease 2019 (COVID-19) in Chinese cities with different transmission dynamics of imported cases	bioRxiv (not peer-reviewed) / Article	Examined the time-varying reproduction number (Rt) of COVID-19 and compared its transmissibility between different intervention periods in Hangzhou and Shenzhen. Concluded that the lockdown measures and local outbreak responses helped reduce the potential of local transmission in Hangzhou and Shenzhen. Meanwhile, cities with similar epidemic trend could have different transmission dynamics given the variation in imported cases.
18.03.2020	Demographic science aids in understanding the spread and fatality rates of COVID-19	MedRxiv (not peer-reviewed) / Article	•The authors examine the role of age structure in deaths thus far in Italy and South Korea and illustrate how the pandemic could unfold in populations with similar population sizes but different age structures, showing a dramatically higher burden of mortality in countries with older versus younger populations.
17.03.2020	Temporal relationship between outbound traffic from Wuhan and the 2019 coronavirus disease (COVID-19) incidence in China	MedRxiv (not peer-reviewed) / Article	• This paper investigated the temporal relationship between daily outbound traffic from Wuhan and the incidence of COVID-19 in 31 Chinese provinces during January-February 2020. Concluded that outflowing migration from Wuhan facilitated the COVID-19 transmission to other parts of China with varying time-lagged effects dependent on provincial characteristics. The travel ban led to a significant reduction in COVID-19 outside of Wuhan.
17.03.2020	Modelling the epidemic 2019-nCoV event in Italy: a preliminary note	MedRxiv (not peer-reviewed) / Article	•An analysis of the time evolution of the 2019-nCoV outbreak event in Italy is proposed and is based on the preliminary data at disposal (till March 11th, 2020) on one side, and on an epidemiological model recently used to describe the same epidemic event in the Wuhan region (February 2020) on the other side.

| 17.03.2020 | Indications for healthcare surge capacity in European countries facing an exponential increase in COVID19 cases | MedRxiv (not peer-reviewed) / Article | • The authors calculated pressures on EU healthcare systems by relating both country-specific accumulated COVID-19 deaths (intensity-approach) and active COVID-19 cases (magnitude-approach) to various estimates of hospital beds. On March 14 2020 - relative to Italy on March 11- they found Spain, Luxembourg, Switzerland and France to experience the highest pressure using the intensity-approach, versus Iceland, Denmark, Norway, Sweden, Spain, Switzerland and Slovenia using the magnitude approach. |