

International EPI Cell Daily Evidence Digest – 03/06/2020

This Daily Evidence Digest is produced by the PHE COVID-19 Literature Digest Team as a resource for professionals working in public health. We do not accept responsibility for the availability, reliability or content of the items included in this resource and do not necessarily endorse the views expressed within them. The papers are organised under the following themes:

- Serology and immunology
- Diagnostics
- Genomics
- Epidemiology and clinical - children and pregnancy
- Epidemiology and clinical - risk factors
- Epidemiology and clinical - other
- Infection control
- Treatment
- Social sciences
- Modelling
- Overviews, comments and editorials (no digest)

Please note that we are including preprints (**highlighted in red**), which are preliminary reports of work that have NOT been peer-reviewed.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

Serology and immunology

Publication Date	Title/URL	Journal/ Article type	Digest
01.06.2020	Delayed specific IgM antibody responses observed among COVID-19 patients with severe progression	Emerg Microbes Infect / Article	<ul style="list-style-type: none"> • SARS-CoV-2 specific IgM antibodies from patients or healthy people were detected using a SARS-CoV-2 IgM colloidal gold immunochromatographic assay (GICA). • The GICA was found to be positive with the detected 82.2% (37/45) of RT-qPCR confirmed COVID-19 cases, as well as 32.0% (8/25) of clinically confirmed, RT-qPCR negative patients (4-14 days after symptom onset).

			<ul style="list-style-type: none"> Investigation of IgM-negative, RT-qPCR-positive COVID-19 patients showed that half of them developed severe disease. The GICA was found to be a useful test to complement existing PCR-based assays for confirmation of COVID-19, and a delayed specific IgM antibody response was observed among COVID-19 patients with severe progression.
31.05.2020	Population-wide evolution of SARS-CoV-2 immunity tracked by a ternary immunoassay	medRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> Ternary Automated Blood Immunoassay (TRABI) used to assess IgG response against SARS2 in 3,815 pre-pandemic plasma samples and 126 virologically and/or clinically confirmed COVID-19 samples. 429,624 assays on 17,901 blood samples from patients and healthy blood donors: seropositivity in 44 of 8,591 patients /in 26 of 5,388 blood donors, Dec 2019 - May 2020. TRABI identifies seropositive individuals in large unselected cohorts, discriminates between SARS2 immunity and low-affinity cross reactivity; suitable for large-scale nationwide screening campaigns.

Diagnostics

Publication Date	Title/URL	Journal/ Article type	Digest
31.05.2020	Rapid point of care nucleic acid testing for SARS-CoV-2 in hospitalised patients: a clinical trial and implementation study	medRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> Compared a point of care (POC) nucleic acid amplification based platform for rapid diagnosis of COVID-19 against the standard laboratory RT-PCR test and performed an implementation study. SAMBA II SARS-CoV-2 rapid POC test performed as well as standard lab RT-PCR; shorter time to result both in trial and real-world settings.
22.04.2020	Resilient SARS-CoV-2 diagnostics workflows including viral heat inactivation	medRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> Authors compared several commercially available RNA extraction methods plus different 1-step RT-qPCR Master Mix brands. RNA extraction methods provide similar results. For qPCR reagents tested, TaqMan™ Fast Virus 1-Step Master Mix and Luna® Universal Probe One-Step RT-qPCR Kit proved most sensitive. N1 and N2 primer-probes provide more reliable detection than the RdRP-SARSr primer-probe set, particularly in samples with low viral titres. Implemented a protocol using heat inactivation; demonstrated minimal impact on sensitivity of qPCR in clinical samples - potentially making testing portable to settings without CL-3 facilities.

Genomics

Publication Date	Title/URL	Journal/ Article type	Digest
02.06.2020	Host-Viral Infection Maps Reveal Signatures of Severe COVID-19 Patients	Cell / Article	<ul style="list-style-type: none"> • Article introducing Viral-Track, a computational method that globally scans unmapped single-cell RNA sequencing (scRNA-seq) data for the presence of viral RNA, enabling transcriptional cell sorting of infected versus bystander cells. • Applying Viral-Track to bronchoalveolar-lavage samples from severe and mild COVID-19 patients reveals a dramatic impact of the virus on the immune system of severe patients compared to mild cases. • Viral-Track detects an unexpected co-infection of the human metapneumovirus, present mainly in monocytes perturbed in type-I interferon (IFN)-signalling.
03.04.2020	ACE2 gene variants may underlie interindividual variability and susceptibility to COVID-19 in the Italian population	medRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> • This study supports proposal that a predisposing genetic background may explain inter-individual disease susceptibility and/or severity, allowing an evidence-based risk assessment leading to personalized preventive measures and therapeutic options. • Authors mined whole-exome-sequencing data of 6930 Italian control individuals for ACE2 variants. Three more common missense changes, p.(Asn720Asp), p.(Lys26Arg), p.(Gly211Arg) were predicted to interfere with protein structure and stabilization. Rare variants likely interfering with the internalization process, namely p.(Leu351Val) and p.(Pro389His), predicted to interfere with SARS-CoV-2 spike protein binding, were also observed. • Comparison of ACE2 WES data between cohort of 131 patients and 258 controls allowed identifying a statistically significant (P value <0,029) higher allelic variability in controls compared to patients.
31.05.2020	The ABO blood group locus and a chromosome 3 gene cluster associate with SARS-CoV-2 respiratory failure in an Italian-Spanish genome-wide association analysis	medRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> • Genome-wide association analysis of patients with Covid-19 respiratory failure in Italy and Spain, with a total of 8,582,968 single-nucleotide polymorphisms (SNPs) and a meta-analysis of both case-control panels. • They detected cross-replicating associations with rs11385942 at chromosome 3p21.31 and rs657152 at 9q34, which were genome-wide significant (P<5x10-8) in the meta-analysis of both study panels. • Among six genes at 3p21.31, SLC6A20 encodes a known interaction partner with angiotensin converting enzyme 2 (ACE2). The association signal at 9q34 was located at the ABO blood group locus and a blood-

			group-specific analysis showed higher risk for A-positive individuals and a protective effect for blood group O.
31.05.2020	coronapp: a Web Application to Annotate and Monitor SARS-CoV-2 Mutations	bioRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> • The authors present a webtool, coronapp, dedicated to easily processing user-provided SARS-CoV-2 genomic sequences, in order to detect and annotate protein-changing mutations. This results in an up-to-date status of SARS-CoV-2 mutations, both worldwide and in user-selected countries. • The tool allows users to highlight and prioritize the most frequent mutations in specific protein regions, and to monitor their frequency in the population over time. • The tool is available at http://giorgilab.dyndns.org/coronapp/ and the full code is freely shared at https://github.com/federicogiorgi/giorgilab/tree/master/coronapp

Epidemiology and clinical – children and pregnancy

Publication Date	Title/URL	Journal/ Article type	Digest
01.06.2020	Preeclampsia-like syndrome induced by severe COVID-19: a prospective observational study	Bjog / Research article	<ul style="list-style-type: none"> • Prospective, observational study of 42 consecutive pregnancies to investigate the incidence of clinical, ultrasonographic and biochemical findings related to preeclampsia (PE) in pregnancies with COVID-19, and to assess their accuracy to differentiate between PE and the PE-like features associated with COVID-19. • 34 cases were classified as non-severe and 8 as severe COVID-19. Six (14.3%) women presented signs and symptoms of PE, all six being among the severe COVID-19 cases (75.0%). However, abnormal sFlt-1/PIGF and UtAPI could only be demonstrated in one case. Two cases remained pregnant after recovery from severe pneumonia and had a spontaneous resolution of the PE-like syndrome. • Pregnant women with severe COVID-19 can develop a PE-like syndrome that might be distinguished from actual PE by sFlt-1/PIGF, LDH and UtAPI assessment. Health care providers should be aware of its existence.
31.05.2020	A clinical, histopathological and laboratory study of 19 consecutive Italian paediatric patients with chilblain-like lesions: lights and shadows on the relationship with COVID-19 infection	J Eur Acad Dermatol Venereol / Research article	<ul style="list-style-type: none"> • Prospective study of 19 patients, all adolescents (mean age: 14 years). 11/19 (58%) of them and/or their cohabitants reported flu-like symptoms one to two months prior to skin manifestation onset. Lesions were localized to toes and also heels and soles. • Videocapillaroscopy showed pericapillary oedema, dilated and abnormal capillaries, and microhemorrhages both in finger and toe in the majority

		<p>of patients.</p> <ul style="list-style-type: none"> • Major pathological findings included: epidermal basal layer vacuolation, papillary dermis oedema and erythrocyte extravasation, perivascular and perieccrine dermal lymphocytic infiltrate, and mucin deposition in the dermis and hypodermis; dermal vessel thrombi were observed in 2 cases. Blood exams were normal. • Nasopharyngeal swab for SARS-CoV-2 and IgG serology for SARS-CoV-2 nucleocapsid protein were negative. Importantly, IgA serology for S1 domain of SARS-CoV-2 spike protein was positive in 6 patients and borderline in 3.
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Epidemiology and clinical - risk factors

Publication Date	Title/URL	Journal/ Article type	Digest
02.06.2020	Disparities in the risk and outcomes of COVID-19	Public Health England / Review	<ul style="list-style-type: none"> • This is a descriptive review of data on disparities in the risk and outcomes from COVID-19. • The largest disparity found was by age. • Risk of dying among those diagnosed with COVID-19 was also higher in males than females; higher in those living in the more deprived areas than those living in the least deprived; and higher in those in BAME groups than in White ethnic groups. • When compared to previous years, they also found a particularly high increase in all cause deaths among those born outside the UK and Ireland; those in a range of caring occupations including social care and nursing auxiliaries and assistants; those who drive passengers in road vehicles for a living including taxi and minicab drivers and chauffeurs; those working as security guards and related occupations; and those in care homes.
01.06.2020	Greater risk of severe COVID-19 in non-White ethnicities is not explained by cardiometabolic, socioeconomic, or behavioural factors, or by 25(OH)-vitamin D status: study of 1,326 cases from the UK Biobank	medRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> • Study of 4,510 UK Biobank participants tested for COVID-19 (positive, n=1,326). • Multivariate logistic regression models including age, sex, and ethnicity were used to test whether addition of: 1)cardiometabolic factors (diabetes, hypertension, high cholesterol, prior myocardial infarction, smoking, BMI); 2)25(OH)-vitamin D; 3)poor diet; 4)Townsend deprivation score; 5)housing (home type, overcrowding); or 6)behavioural factors (sociability, risk taking) attenuated sex/ethnicity associations with COVID-19 status.

			<ul style="list-style-type: none"> • Male sex, non-White ethnicity, higher BMI, Townsend deprivation score, and household overcrowding were independently associated with significantly greater odds of COVID-19. The pattern of association was consistent for men and women; cardiometabolic, socio-demographic and behavioural factors did not attenuate sex/ethnicity associations.
29.05.2020	Selective CD8 cell reduction by SARS-CoV-2 is associated with a worse prognosis and systemic inflammation in COVID-19 patients	Clin Immunol / research article	<ul style="list-style-type: none"> • The authors analysed comorbidities, indicators of inflammation such as CRP and the ratio of neutrophils/lymphocytes, as well as the count of blood cells with T-lymphocyte subtypes in 172 hospitalized patients with COVID-19, grouped according to their needs for mechanical ventilation (ICU care) or not. • Within the comorbidities studied, obesity was the only associated with greater severity and ICU admission. Both the percentage and the absolute number of neutrophils were higher in patients needing ICU care than non-ICU patients, whereas absolute lymphocyte count, and especially the percentage of lymphocytes, presented a deep decline in critical patients. • There was no difference between the two groups of patients for CD4 T-lymphocytes, however for CD8 T-cells the differences were significant for both parameters which were in decline in ICU patients. There was a firm correlation between the highest values of inflammation indicators with the decrease in percentage of CD8 T-lymphocytes. This effect was not seen with CD4 cells.
24.05.2020	Intellectual and developmental disability and COVID-19 case-fatality trends: TriNetX analysis	Disabil Health J / Research article	<ul style="list-style-type: none"> • Study to compare COVID-19 trends among people with (n=474) and without (n=29,808) intellectual and developmental disability (IDD), overall and stratified by age. • People with IDD had higher prevalence of specific comorbidities associated with poorer COVID-19 outcomes. • Distinct age-related differences in COVID-19 trends were present among those with IDD, with a higher concentration of COVID-19 cases at younger ages. • In addition, while the overall case-fatality rate was similar for those with IDD (5.1%) and without IDD (5.4%), these rates differed by age: ages ≤17 - IDD 1.6%, without IDD <0.01%; ages 18-74 - IDD 4.5%, without IDD 2.7%; ages ≥75- IDD 21.1%, without IDD, 20.7%.
01.06.2020	The impact of COVID-19 on heart failure hospitalization and management: report from a Heart Failure Unit in London during the peak of the pandemic	Eur J Heart Fail / Report	<ul style="list-style-type: none"> • Data from King's College Hospital, London, reported to the National Heart Failure Audit for England and Wales, were used to examine the impact of COVID-19 on acute heart failure (AHF) hospitalization rates, clinical characteristics and management of patients admitted to a tertiary Heart Failure Unit in London during the peak of the pandemic.

			<ul style="list-style-type: none"> • Incident AHF hospitalization significantly declined in the unit during the COVID-19 pandemic, but hospitalized patients had more severe symptoms at admission. • Further studies are needed to investigate whether the incidence of AHF declined or patients did not present to hospital while the national lockdown and social distancing restrictions were in place.
28.05.2020	Rapid Epidemiological Analysis of Comorbidities and Treatments as risk factors for COVID-19 in Scotland (REACT-SCOT): a population-based case-control study	medRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> • Scottish matched case-control study to identify risk factors for severe COVID-19 and to lay the basis for risk stratification based on demographic data and health records. • Severe COVID-19 strongly associated with past medical history across all age groups, as well as older age and male sex. Many comorbidities beyond risk conditions designated by public health agencies contribute to this. • A risk classifier using all information available in health records, rather than limited set of conditions, will more accurately discriminate between low-risk and high-risk individuals who may require shielding until epidemic over.
01.06.2020	Pulmonary Thromboembolic Disease in Patients with COVID-19 Undergoing Computed Tomography Pulmonary Angiography (CTPA): Incidence and Relationship with Pulmonary Parenchymal Abnormalities	medRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> • Retrospective analysis of all patients with confirmed COVID-19 undergoing CT pulmonary angiography (CTPA) in a tertiary centre, reporting the incidence, severity and extent of pulmonary thromboembolic disease (PTD). • Overall incidence of PTD was 41/93 (44%) with a third of patients showing segmental and subsegmental PTD (n=28/93, 30%). D-dimer was elevated in 90/93 (96.8%) of cases. High Wells score did not differentiate between PE and non-PE groups (p=0.801). The inter-observer agreement was fair (Kappa=0.659) for parenchymal pattern and excellent (Kappa = 0.816) for severity. • Lymph node enlargement was found in 34/93 of cases (36.6%) with 29/34 (85.3%) showing no additional source of infection. • Fibrosis was seen in 16/93 (17.2%) of cases, mainly demonstrating fibrotic organising pneumonia.

Epidemiology and clinical – other

Publication Date	Title/URL	Journal/ Article type	Digest
28.05.2020	Echocardiographic Findings in Covid-19 Pneumonia	Can J Cardiol / Research article	<ul style="list-style-type: none"> • Study of 74 Covid-19 patients to characterize the echocardiographic phenotype of patients with Covid-19 pneumonia and its relation to

			<p>biomarkers. A level 1 British Society of Echocardiography TTE assessed chamber size and function, valvular disease and likelihood of pulmonary hypertension.</p> <ul style="list-style-type: none"> • The chief abnormalities were right ventricular (RV) dilatation (41%) and RV dysfunction (27%). • RV impairment was associated with increased D-dimer and CRP levels. In contrast, left ventricular (LV) function was hyper-dynamic or normal in most (89%) patients.
01.06.2020	Clinical Outcomes and Serologic Response in Solid Organ Transplant Recipients with COVID-19: A Case Series from the United States	Am J Transplant / Case series	<ul style="list-style-type: none"> • The authors describe their institutional experience with COVID-19 among ten solid organ transplant patients, including the clinical presentation, treatment modalities, and outcomes of seven renal transplant recipients, one liver transplant recipient, one heart transplant recipient, and one lung transplant recipient. • They also report the serologic response in SOT recipients, documenting a positive IgG response in all seven hospitalized patients.

Infection control

Publication Date	Title/URL	Journal/ Article type	Digest
02.06.2020	Notice of Retraction: Effectiveness of Surgical and Cotton Masks in Blocking SARS-CoV-2	Ann Intern Med / Retraction	<ul style="list-style-type: none"> • Retraction of an article previously featured in this Digest.
02.06.2020	Predictors to use mobile apps for monitoring COVID-19 symptoms and contact tracing: A survey among Dutch citizens	medRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> • Online survey of Dutch citizens acceptance of COVID-19 mobile symptom recognition and monitoring app and contact tracing app: 238 responses, almost 60% female, average age 45.6 years (SD=17.4). • Main reason to use both mobile applications was to control spread of COVID-19 virus. Main reason not to was concerns about privacy. • Age, attitude towards technology, fear of COVID-19 important predictors of acceptance of mobile apps. Consider in development to secure acceptance.
31.05.2020	Exhaled breath is a significant source of SARS-CoV-2 emission	medRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> • 35 COVID-19 subjects were recruited and exhaled breath condensate (EBC), air samples and surface swabs were collected and analysed for SARS-CoV-2 using RT-PCR. • EBC samples had the highest positive rate (16.7%, n=30), followed by surface swabs (5.4%, n=242), and air samples (3.8%, n=26).] • COVID-19 patients were shown to exhale SARS-CoV-2 into the air at an

			<p>estimated rate of 103-105 RNA copies/min; while toilet and floor surfaces represented two important SARS-CoV-2 reservoirs.</p> <ul style="list-style-type: none"> • These results imply that airborne transmission of SARS-CoV-2 plays a major role in COVID-19 spread, especially during the early stages of the disease.
31.05.2020	Detection of SARS-CoV-2 in Exhaled Breath from COVID-19 Patients Ready for Hospital Discharge	medRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> • Study showing that 20% of COVID-19 patients, who were ready for hospital discharge based on current guidelines, had SARS-CoV-2 in their exhaled breath (~105 RNA copies/m³). They were estimated to emit about 1400 RNA copies into the air per minute. • Although fewer surface swabs (1.3%, N=318) tested positive, medical equipment frequently contacted by healthcare workers and the work shift floor were contaminated by SARS-CoV-2 in four hospitals in Wuhan. • All air samples (N=44) appeared negative likely due to the dilution or inactivation through natural ventilation (1.6-3.3 m/s) and applied disinfection.

Treatment

Publication Date	Title/URL	Journal/ Article type	Digest
03.06.2020	HyPE study: hydroxychloroquine prophylaxis-related adverse events' analysis among healthcare workers during COVID-19 pandemic: a rising public health concern	Journal of Public Health / Article	<ul style="list-style-type: none"> • The rising burden of COVID-19 has led to the mass use of hydroxychloroquine by healthcare workers (HCWs). • A retrospective, cross-sectional study was conducted across the country using semi-structured web-based questionnaire among COVID-19 negative and asymptomatic healthcare workers, taking hydroxychloroquine prophylaxis. • A higher incidence of adverse events was observed when results were compared with studies involving patients on long-term hydroxychloroquine therapy. • Younger age and first dose were associated with greater incidence of adverse events though all were self-limiting.
17.05.2020	First case of drug-induced liver injury associated with the use of tocilizumab in a patient with COVID-19	Liver Int / Case report	<ul style="list-style-type: none"> • Case report describing a patient with COVID-19-induced cytokine storm who developed drug-induced liver injury associated with the use of Tocilizumab (TCZ). • One day after TCZ administration, serum transaminase levels increased 40-fold. Nevertheless, TCZ had a positive effect on clinical and laboratory parameters in cytokine storm, with transaminases values normalizing in

10 days.

- This is the first reported case of DILI caused by TCZ in a COVID-19 patient. Intensive liver function monitoring is imperative in COVID-19 patients, because of frequent polypharmacy with potentially hepatotoxic drugs.

Social sciences

Publication Date	Title/URL	Journal/ Article type	Digest
01.06.2020	Factors associated with adherence to self-isolation and lockdown measures in the UK; a cross-sectional survey	medRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> • Online cross-sectional survey of 2240 adult participants living in the UK, to investigate factors associated with adherence to self-isolation and lockdown measures due to COVID-19 in the UK. • Of 217 people reporting symptoms in the household in the last seven days, 75.1% had left the home in the last 24 hours (defined as non-adherent). Factors associated with non-adherence were being male, less worried about COVID-19, and perceiving a smaller risk of catching COVID-19. Adherence was associated with having received help from someone outside your household. Results should be taken with caution as there was no evidence for associations when controlling for multiple analyses. • Of people reporting no symptoms in the household, 24.5% had gone out shopping for non-essentials in the last week (defined as non-adherent). Factors associated with non-adherence and with a higher total number of outings in the last week included decreased perceived effectiveness of Government "lockdown" measures, decreased perceived severity of COVID-19, and decreased estimates of how many other people were following lockdown rules. Having received help was associated with better adherence.

Modelling

Publication Date	Title/URL	Journal/ Article type	Digest
02.06.2020	Effects of non-pharmaceutical interventions on COVID-19 cases, deaths,	The Lancet Public Health / Article	<ul style="list-style-type: none"> • This study assesses the potential impact of different control measures for mitigating the burden of COVID-19 in the UK. • Intensive interventions with lockdown periods would need to be in place

[and demand for hospital services in the UK: a modelling study](#)

for a large proportion of the coming year to prevent health-care demand exceeding availability.

- The characteristics of SARS-CoV-2 mean that extreme measures are probably required to bring the epidemic under control and to prevent very large numbers of deaths and an excess of demand on hospital beds, especially those in ICUs.

Overviews, comments and editorials

Publication Date	Title/URL	Journal/ Article type
29.05.2020	Covid-19: ensuring equality of access to testing for ethnic minorities	British Medical Journal / Editorial
02.06.2020	Potential pitfalls of routine SARS-CoV-2 serology for mass screening	Journal of Medical Virology / Letter
02.06.2020	Expression of concern: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis	The Lancet / Comment
02.06.2020	The need for privacy with public digital contact tracing during the COVID-19 pandemic	The Lancet Digital Health / Comment
02.06.2020	An integrated national scale SARS-CoV-2 genomic surveillance network	The Lancet Microbe / Comment
02.06.2020	Unlocking UK COVID-19 policy	The Lancet Public Health / Comment
03.06.2020	Governments and WHO changed Covid-19 policy based on suspect data from tiny US company	The Guardian / Media

Produced by the PHE COVID-19 Literature Digest Team

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