Public Health England

International EPI Cell Daily Evidence Digest – 05/06/2020

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
- Genomics
- Epidemiology and clinical - children and pregnancy
- Epidemiology and clinical - risk factors
- Epidemiology and clinical - other
- Infection control
- Treatment
- Social sciences
- 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Please note that we are including preprints (highlighted in red), which are preliminary reports of work that have NOT been peer-reviewed.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.

Two retracted papers are included under the 'Overviews, comments and editorials' section. For a list of retracted COVID-19 papers click here.

Serology and immunology

Publication Date	Title/URL	Journal/Article type	Digest
04.06.2020	Serodiagnostics for Severe Acute Respiratory Syndrome-Related Coronavirus-2: A Narrative Review	Ann Intern Med / review	• This article discusses key use cases for SARS-CoV-2 antibody detection tests and their application to serologic studies, reviews currently available assays, highlights key areas of ongoing research, and proposes potential strategies for test implementation.

02.06.2020	Increased serum levels of sCD14 and sCD163 indicate a preponderant role for monocytes in COVID-19 immunopathology	medRxiv (non-peer reviewed) / Article	• Investigation of two soluble markers of monocyte activation, sCD14 and sCD163, in covid19 patients with the aim of characterizing their potential role in monocyte-macrophage disease immunopathology. • Compared to a healthy control group, sCD14 and sCD163 levels were significantly higher among COVID-19 patients, independently of ICU admission requirement. • There was a significant correlation between sCD14 levels and other inflammatory markers, particularly Interleukin-6, in the non-ICU patients group. • sCD163 showed a moderate positive correlation with the time at sampling from admission, increasing its value over time, independently of severity group.
02.06.2020	Comparative assessment of multiple COVID-19 serological technologies supports continued evaluation of point-of-care lateral flow assays in hospital and community healthcare settings	medRxiv (non-peer reviewed) / Article	• Study which evaluated the performance of ten commercial serological assays and their potential as diagnostic tools on an identical panel of 110 SARS−CoV−2−positive samples and 50 pre−pandemic negatives. • The head to head comparison of multiple serodiagnostic assays on identical sample sets revealed that performance is highly dependent on the time of sampling, with sensitivities of over 95% seen in several tests when assessing samples from more than 20 days post onset of symptoms. • Furthermore, these analyses identified clear outlying samples that were negative in all tests, but were later shown to be from individuals with mildest disease presentation.
03.06.2020	Regional Difference in Seroprevalence of SARS-CoV-2 in Tokyo: Results from the community point-of-care antibody testing	medRxiv (non-peer reviewed) / Article	• In two community clinics in Tokyo, the overall positive percentage of SARS-CoV-2 IgG antibody is 3.83% (95% confidence interval: 2.76-5.16) for the entire cohort (n =1,071). • Central Tokyo exhibited a significantly higher prevalence compared to suburban Tokyo (p =0.02, 4.68% [95%CI: 3.08-6.79] versus 1.83 [0.68-3.95] in central and suburban Tokyo, respectively). • The seroprevalence of the cohort surveyed in this study is low for herd immunity, which suggests the need for robust disease control and prevention.
23.05.2020	COVIDep platform for real-time reporting of vaccine target recommendations for SARS-CoV-2: Description and connections with COVID-19 immune responses and preclinical vaccine trials	bioRxiv (non-peer reviewed) / Article	• Description of COVIDep (https://COVIDep.ust.hk), a web-based platform that provides immune target recommendations for guiding SARS-CoV-2 vaccine development. • COVIDep implements a protocol that pools together publicly-available genetic data for SARS-CoV-2 and epitope data for SARS-CoV to identify B cell and T cell epitopes that present potential immune targets for SARS-

			CoV-2. • Correspondences between outputs of COVIDep and immune responses recorded in COVID-19 patients and preclinical vaccine trials are also indicated.

Genomics

Publication Date	Title/URL	Journal/Article type	Digest
04.06.2020	Genetic structure of SARS-CoV-2 reflects clonal superspreading and multiple independent introduction events, North-Rhine Westphalia, Germany, February and March 2020	Eurosurveillance / Rapid communication	• Report of the genetic structure of SARS-CoV-2 in North-Rhine Westphalia, Germany's most populous state (18 million inhabitants). • The analysis includes the 'Heinsberg outbreak', which started in the second half of February 2020 – comprising a superspreading event at a carnival session in Gangelt, a small municipality of ca 12,000 inhabitants on the border between Germany and the Netherlands – and subsequent outbreak dynamics in March, in the state capital Düsseldorf, located 70 km from Gangelt and an international economic and air travel hub of ca 600,000 inhabitants.
26.05.2020	Impact of Comorbidities on SARS-CoV-2 Viral Entry-Related Genes	bioRxiv (non-peer reviewed) / Article	• The authors show that the expression levels of ACE2, TMPRSS2 and other viral entry-related genes are modulated in target organs of select disease states. • In tissues such as heart, which normally express ACE2 but minimal TMPRSS2, they found that TMPRSS2 as well as other TTSPs are elevated in individuals with comorbidities vs healthy individuals. • They also found increased expression of viral entry-related genes in the settings of hypertension, cancer or smoking across target organ systems.
03.06.2020	Early phylodynamics analysis of the COVID-19 epidemics in France	medRxiv (non-peer reviewed) / Article	• Phylodynamics analysis of 196 SARS-Cov-2 genomes collected in France between Jan 24 and Mar 24 2020. • A slowing down of the epidemic spread can be detected in Mar, which is consistent with the implementation of the national lock-down on Mar 17. • The inferred distributions for the infection duration and Rt are in line with those estimated from contact tracing data.

Epidemiology and clinical – children and pregnancy

Publication Date	Title/URL	Journal/Article type	Digest
04.06.2020	SARS-CoV-2-related paediatric inflammatory multisystem syndrome, an epidemiological study, France, 1 March to 17 May 2020	Eurosurveillance / Rapid communication	• On 28 April 2020, French clinicians alerted the French Public Health Agency about an abnormal increase in cases of Kawasaki-like disease (KLD) and myocarditis in children requiring critical care support that occurred during of the ongoing coronavirus disease (COVID-19) epidemic in France. • To investigate this emerging inflammatory disease in children, now named paediatric inflammatory multisystem syndrome (PIMS) or multisystem inflammatory syndrome in children (MIS-C), a nationwide surveillance was launched on 30 April, coordinated by the French Public Health Agency and French paediatric scientific societies
03.06.2020	Characteristic of COVID-19 infection in pediatric patients: early findings from two Italian Pediatric Research Networks	Eur J Pediatr / Research article	• Among a case series of 130 children, mostly diagnosed at hospital level, and with a relatively high rate (26.2%) of comorbidities, about three-quarter had an asymptomatic or mild disease. • 57.7% were hospitalized, 11.5% needed some respiratory support, and 6.9% were treated in an intensive care unit. • More studies are needed to further understand the presentation and outcomes of children with COVID-19 in children with special needs.

Epidemiology and clinical - risk factors

Publication Date	Title/URL	Journal/Article type	Digest
01.06.2020	Ethnic Disparities in Hospitalisation for COVID-19 in England: The Role of Socioeconomic Factors, Mental Health, and Inflammatory and Pro-inflammatory Factors in a Community-based Cohort Study	Brain Behav Immun / Article	• Of 340,966 men and women (mean age 56.2 years) from the UK Biobank study, there were 640 COVID-19 cases (571/324,306 White, 31/4,485 Black, 21/5,732 Asian, 17/5,803 Other). • Compared to the White study members and after adjusting for age and sex, Black individuals had over a 4-fold increased risk of COVID-19 infection, and there was a doubling of risk in the Asian group and the 'other' non-white group. • There were clear ethnic differences in risk of COVID-19 hospitalisation and these do not appear to be fully explained by other explanatory measured factors.

01.06.2020	Neurological complications in patients with SARS-CoV-2 infection: a systematic review	Arq Neuropsiquiatr / Systematic review	• Systematic review of 43 articles, including data ranging from common, non-specific symptoms, such as hyposmia and myalgia, to more complex and life-threatening conditions, such as cerebrovascular diseases, encephalopathies, and Guillain-Barré syndrome. • Recognition of neurological manifestations of SARS-CoV-2 should be emphasized despite the obvious challenges faced by clinicians caring for critical patients who are often sedated and presenting other concurrent systemic complications.
04.06.2020	Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study	Eur Heart J / article	• While hypertension and the discontinuation of antihypertensive treatment are suspected to be related to increased risk of mortality, in this retrospective observational analysis, the authors did not detect any harm of RAAS inhibitors in patients infected with COVID-19.
04.06.2020	Distribution of ACE2, CD147, CD26 and other SARS-CoV-2 associated molecules in tissues and immune cells in health and in asthma, COPD, obesity, hypertension, and COVID-19 risk factors	Allergy / Article	• Study to analyse the expression of known and potential SARS-CoV-2 receptors and related molecules in primary human cells and tissues from healthy subjects and patients with risk factors and known comorbidities of COVID-19. • ACE2 and TMPRSS2 were coexpressed at the epithelial sites of the lung and skin, whereas CD147 (BSG), cyclophilins (PPIA and PPIB), CD26 (DPP4) and related molecules were expressed in both, epithelium and in immune cells, with a distinct age-related expression profile of these genes in healthy children and adults. • Asthma, COPD, hypertension, smoking, obesity, and male gender status generally led to the higher expression of ACE2- and CD147-related genes in the bronchial biopsy, BAL or blood. Additionally, CD147-related genes correlated positively with age and BMI.
03.06.2020	Lactate dehydrogenase and susceptibility to deterioration of mild COVID-19 patients: a multicenter nested case-control study	BMC Med / Case control study	• 85 confirmed COVID-19 patients were enrolled into a multicentre nested case-control study , including 16 in the progression group and 69 in the stable mild group. • Compared to stable mild group (n = 69), patients in the progression group (n = 16) were more likely to be older, male, presented with dyspnoea, with hypertension, and with higher levels of lactase dehydrogenase and c-reactive protein. • In multivariate logistic regression analysis, advanced age and the higher level of lactase dehydrogenase were independently associated with exacerbation in mild COVID-19 patients.
10.05.2020	Estimating the extent of asymptomatic COVID-19 and its potential for community	medRxiv (non-peer reviewed) / Systematic review	• Synthesis of available research on the asymptomatic rates and transmission rates to estimate the prevalence of true asymptomatic COVID-19 cases.

	transmission: systematic review and meta-analysis		• Nine low risk-of-bias studies from six countries were included, that tested 21,035 at-risk people, of which 559 were positive and 83 were asymptomatic. • The proportion of asymptomatic cases ranged from 4% to 41%. Meta-analysis (fixed effect) found that the proportion of asymptomatic cases was 15% (95% CI: 12% - 18%) overall; higher in non-aged care 16% (13% - 19%), and lower in long-term aged care 8% (3% - 18%). • Four studies provided direct evidence of forward transmission of the infection by asymptomatic cases but suggested considerably lower rates than symptomatic cases.
02.06.2020	Decreased plasma levels of the survival factor renalase are associated with worse outcomes in COVID-19	medRxiv (non-peer reviewed) / Article	• Study to test the hypothesis that reduced plasma RNLS levels could be a marker of COVID-19 disease severity, comparing plasma from 51 hospitalized COVID-19 patients and 15 uninfected non-hospitalized controls. • Plasma RNLs levels were negatively correlated with inflammatory markers, including IL-1b, IL-6, and TNFa ($p = 0.04$, $p = 0.03$, $p = 0.01$, respectively). • Patients with COVID-19 disease had lower levels of RNLS than controls, and these were associated with more severe disease and worse survival among COVID-19 patients.

Epidemiology and clinical – other

Publication Date	Title/URL	Journal/Article type	Digest
04.06.2020	Active case finding with case management: the key to tackling the COVID-19 pandemic	The Lancet / Health Policy	• Describes China's strategies for prevention and control of COVID-19 (containment and suppression) and their application, from the perspective of the COVID-19 experience to date in China. • The authors report case finding and management, with identification and quarantine of close contacts, are vitally important containment measures and are essential in China's pathway forward.
04.06.2020	Thrombosis in COVID-19: clinical outcomes, biochemical and pathological changes, and treatments	Oxford COVID-19 Evidence Service / Treatments for COVID	• Reports that COVID-19 is associated with venous and arterial thrombosis and pulmonary embolism and increased rates of thrombosis in cannulae and extracorporeal circuits for renal replacement or membrane oxygenation, have drawn attention to the coagulant effects of the disease. • The best current strategies for confronting large vessel thrombosis in

			COVID-19 are prophylaxis with low-molecular-weight heparin and treatment with full-dose low-molecular-weight heparin with monitoring of anti-Factor Xa. • There are no strong hypotheses regarding the pathogenesis of the coagulant effect of COVID-19 to guide therapy. • Until the results of masked randomized controlled trials are available, treatments directed against components of putative pathogenic pathways, such as interleukin and complement, should be regarded as experimental.
04.06.2020	High impact of COVID-19 in long-term care facilities, suggestion for monitoring in the EU/EEA, May 2020	Eurosurveillance / Rapid communication	• COVID-19 affects elderly residents in LTCF considerably, causing high morbidity and mortality. • In the absence of vaccination or effective pharmaceutical measures, early identification of virus circulation in LTCF through comprehensive surveillance will help protect LTCF residents and staff. • Early testing to identify symptomatic and asymptomatic cases and immediate implementation of additional IPC and occupational safety and health measures as well as cohorting of infected residents will help minimise outbreaks and the overall impact of COVID-19 on the elderly.
04.06.2020	Influenza and COVID-19 Co-infection: Report of 6 cases and review of the Literature	J Med Virol / Case series	• 6 patients (0.54%) out of 1103 patients with COVID-19 were diagnosed co-infected with influenza. • Thorax radiology findings were compatible with COVID-19 in five and with influenza in one patient. Cases were mild-to-moderate in severity. • The reported cases in the literature included patients died (n=2) and those living ventilator dependent or under mechanical ventilation. • Screening studies report more cases, suggesting that unless screening COVID-19 patients, the co-infection remains undiagnosed and underestimated.
04.06.2020	COVID-19 polyradiculitis in 24 patients without SARS-CoV-2 in the cerebro-spinal fluid	J Med Virol / article	• SARS-CoV-2 can cause Guillain-Barre syndrome (GBS) and SARS-CoV-2-associated GBS occurs in the absence of the virus in the cerebrospinal fluid. • Clinical presentation, course, response to treatment, and outcome do not vary between SARS-CoV-2-associated GBS and GBS due to other triggers.
01.06.2020	A Follow-up Study of Recovered Patients with COVID-19 in Wuhan, China	Int J Infect Dis/ article	• Of 1673 cured patients who were followed up in two different fever clinics from March 1 to March 20 2020, 13 (13/1673, 7.7‰) patients with COVID-19 were relapsed, and all of these patients presented with related symptoms of COVID-19.

02.06.2020	Quantifying the prevalence of SARS-CoV-2 long-term shedding among non-hospitalized COVID-19 patients	medRxiv (non-peer reviewed) / Article	• Among a cohort of 379 COVID-19 patients with at least one positive follow-up SARS-CoV-2 PCR test, 53 patients remain SARS-CoV-2-positive after four weeks of initial diagnosis, with a majority not hospitalized and having no enrichments among symptoms, demographics, or medical history. • In a cohort of 370 COVID-19 patients that transition to a confirmed negative status, the upper bound of viral shedding duration has a mean of 21.2 days with standard deviation of 9.3 days. • Of the 81 PCR-confirmed COVID-19 patients who have undergone serologic testing, 68 patients have developed anti-SARS-CoV-2 IgG to date, with a mean upper bound of time to seroconversion of 38.1 days.

Infection control

Publication Date	Title/URL	Journal/Article type	Digest
04.06.2020	Correlation Between N95 Extended Use and Reuse and Fit Failure in an Emergency Department	JAMA / Research letter	• This study found duckbill N95s had a high failure rate. • Failure of dome-shaped masks was associated with increased use. • N95 failure may contribute to SARS-CoV-2 transmission despite PPE use and deserves further study. • Based on these preliminary data, health systems should closely evaluate N95 fit during extended use or reuse and limit duckbill mask use if alternatives are available.
01.06.2020	The Role of Children in the Dynamics of Intra Family Coronavirus 2019 Spread in Densely Populated Area	Pediatr Infect Dis J / Article	• In a study to examine the dynamics of Covid-19 transmission within families, there were significantly lower rates of Covid-19 positivity in children compared with adults residing in the same household. • Children of 5-17 years of age were 61% and children of 0-4 years of age were 47% less likely to have positive polymerase chain reaction results compared with adults residing in the same household.
5.202	No infectious risk of COVID-19 patients with long-term fecal 2019-nCoV nucleic acid positive	Eur Rev Med Pharmacol Sci / Article	• To determine whether COVID-19 patients with positive long-term faecal nucleic acid tests have the risk of self-infection, 5 patients with negative respiratory tract nucleic acid and positive faecal nucleic acid were studied to explore whether these patients can re-infect themselves. • All 5 patients had symptoms of fever and diarrhoea upon admission. The faecal nucleic acid and throat swab were positive, all had positive IgM antibodies on the 7th day of admission and positive IgM and IgG at

			the time of discharge, and there were no abnormalities in the gastrointestinal examination on discharge. • All 5 faecal nucleic acid tests were positive at the time of discharge. After continuous dynamic follow-up for 3-15 days, no clinical symptoms recurred, and the last nucleic acid test was negative.
30.05.2020	Evaluating the Efficacy of Stay-At-Home Orders: Does Timing Matter?	medRxiv (non-peer reviewed) / Article	• Observational analysis of countries and US states with known stay-at-home orders, focussing specifically on the efficacy of stay-at-home orders, both nationally and internationally, in the control of COVID-19. • A larger number of days between the first reported case and stay-at-home mandates was associated with a longer time to reach the peak daily case and death counts. • The largest effect was among regions classified as the latest 10% to implement a mandate, which in the US, predicted an extra 35.3 days to the peak number of cases, and 38.3 days to the peak number of deaths.

Treatment

Publication Date	Title/URL	Journal/Article type	Digest
03.06.2020	Efficacy and safety of antiviral treatment for COVID-19 from evidence in studies of SARSCoV-2 and other acute viral infections: a systematic review and meta-analysis	Cmaj / review	• Systematic review on the benefits and harms of 7 antiviral treatments for COVID-19 (ribavirin, chloroquine, hydroxychloroquine, umifenovir (arbidol), favipravir, interferon and lopinavir/ritonavir). • Persuasive evidence of important benefit in COVID-19 does not exist for any antiviral treatments, although for each treatment evidence has not excluded important benefit. • Additional randomized controlled trials involving patients with COVID-19 will be needed before such treatments can be administered with confidence.
30.05.2020	Missing clinical trial data: the knowledge gap in the safety of potential COVID-19 drugs	medRxiv (non-peer reviewed) / Article	• Analysis of the knowledge gap in safety data by quantifying the number of missing clinical trial results for drugs potentially being repurposed for COVID-19. • Of 3754 completed trials, 1516 (40.4%) did not post results on ClinicalTrials.gov or in the academic literature. 1172 (31.2%) completed trials had tabular results on ClinicalTrials.gov. A further 1066 (28.4%) completed trials had results from the literature search, but did not report results on ClinicalTrials.gov. • Key drugs missing clinical trial results include hydroxychloroquine

			(37.0% completed trials unreported), favipiravir (77.8%) and lopinavir (40.5%). • There is an important evidence gap for the safety of drugs being repurposed for COVID-19. This uncertainty could cause a large burden of additional morbidity and mortality during the pandemic.

Social sciences

Publication Date	Title/URL	Journal/Article type	Digest
02.06.2020	The Relationship Between COVID-19 Infection and Risk Perception, Knowledge, Attitude As Well As Four Non-pharmaceutical Interventions (NPIs) During the Late Period Of The COVID-19 Epidemic In China — An Online Cross-sectional Survey of 8158 Adults	medRxiv (non-peer reviewed) / Article	• Online survey of 8158 Chinese adults to study the relationship between COVID-19 infection and public risk perception, information source, knowledge, attitude and four non-pharmaceutical interventions. • The study found high levels of risk perception, positive attitude, desirable knowledge as well as a high level of adopting four NPIs. • The relevant knowledge, risk perception and attitude were strong predictors of adapting the four NPIs. • Mask wearing, among four personal NPIs, was the most effective protective measure against COVID-19 infection with added preventive effect among those who practised all or part of the other three NPIs.
03.06.2020	Trajectories of depression and anxiety during enforced isolation due to COVID-19: longitudinal analyses of 59,318 adults in the UK with and without diagnosed mental illness	medRxiv (non-peer reviewed) / Article	• This study explored trajectories of anxiety and depression over the first two months of lockdown using data from 53,328 adults in the UCL COVID -19 Social Study, and compared the experiences of individuals with and without diagnosed mental illness. • 24.4% of the sample had scores indicating moderate-severe anxiety, and 31.4% indicating moderate-severe depressive symptoms. • Over the first two months of lockdown, there was only a slight decrease in anxiety levels amongst participants as a whole and a very small decrease in depression levels between weeks 3-6 that then increased again in weeks 7-8. • Adults with pre-existing diagnoses of mental health conditions had higher levels of anxiety and depression but there was no evidence of widening inequalities in mental health experiences compared to people without existing mental illness.
02.06.2020	Are adversities and worries during the COVID-19 pandemic related to sleep quality? Longitudinal analyses of 45,000 UK adults	medRxiv (non-peer reviewed) / Article	• Study using data from 45,109 adults in the UK COVID-19 Social Study, exploring whether either worries about adversities during the pandemic or the experience of adversities were associated with impaired sleep.

			• Six categories of adversity were studied, with both the total number of adversity experiences and total number of adversity worries associated with lower quality sleep. All worries and experiences were significantly related to poorer quality sleep except experiences relating to employment and finances. • Having a larger social network offered some buffering effects on associations but there was limited further evidence of moderation by social or psychiatric factors.

Overviews, comments and editorials

Publication Date	Title/URL	Journal/Article type
04.06.2020	Retraction: "Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis"	The Lancet / **Retraction**
04.06.2020	Retraction: Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2007621	New England Journal of Medicine / **Retraction**
04.06.2020	Covid-19: Validity of key studies in doubt after leading journals issue expressions of concern	British Medical Journal / News
04.06.2020	Quantifying additional COVID-19 symptoms will save lives	The Lancet / Correspondence

Produced by the PHE COVID-19 Literature Digest Team

Bláthnaid Mahon, Caroline De Brún, Nicola Pearce-Smith, Ruth Muscat, Rachel Gledhill, Emma Farrow, Cath Hayes, Paul Rudd