



COVID-19 Literature Digest – 04/09/2020

Over coming weeks, we are trialling a weekly "top picks" section. Guest editors will be invited to review the week's literature digests (Monday, Wednesday and Friday) and choose three papers, explaining why they are of interest. The Digest team aims to have guest editors with different scientific backgrounds, to get different perspectives.

The [Evidence Digest](#) continues after the "Top picks".

This week's guest editor is Cat O'Connor, Principal Scientist for Emerging Infections in the National Infection Service, PHE. Cat led the COVID-19 International Epidemiology team since day 1 of PHE's COVID-19 response, but recently returned to business as usual to monitor for emerging threats.

If you only read three papers this week...

Since joining the Emerging Infections and Zoonoses team in 2012, my primary focus has been enhancing our methods of epidemic intelligence; detecting, assessing and communicating the risks to the UK public from new and emerging infectious disease threats. Working in epidemic intelligence means you are always alert to the unusual or anything that could indicate a variation in epidemiology or pathogenicity. The papers I have selected for highlighting this week act as a reminder that we still do not fully understand the limits of normality for COVID-19.

I cannot do this editorial spot without mentioning the publication that garnered an awful lot of press attention this past week, so let's get it out of the way first. Colleagues in Hong Kong ([To et al., CID](#)) published the (I believe) first genomic evidence of SARS-CoV-2 re-infection, 4.5 months after initial infection. In subsequent days, identical cases were reported from Belgium, the Netherlands, Ecuador and the [USA](#). Despite the alarmist headlines, these reports were not unexpected and as further re-infection cases emerge we will start to gather an understanding of what lies ahead in the coming months.

My second selection is a publication from Boston, USA describing two "superspreading events" in late February ([Lemieux et al., medRxiv](#)). Please note this publication is still awaiting peer review. Of particular interest is the superspreading event associated with an international meeting, widely reported in the media as a Biogen conference. Based on a crude prevalence estimate of the variant hypothesised to have been introduced into Boston from Europe by a single conference participant, the authors believe that the conference could have been responsible for approximately 20,000 cases in the Boston area in the following months. Despite there being previous incursions of COVID-19 into the Boston area, it was this event that was a major contributor to sustained community transmission.

My final selection describes a single case report from colleagues in Austria ([Lang et al., Lancet Resp Med](#)) which reports the first case of a successful lung transplantation for a patient with a persistently positive SARS-CoV-2 PCR test. The 44yo patient, with no serious underlying conditions, required intubation six days after initial diagnosis. From there her condition continued to deteriorate, to the point where on day 52 a consensus was reached that the lungs of the patient had no potential for recovery. On day 58 a sequential bilateral lung transplantation was performed, and on day 144 (postoperative day 86) the patient remains well. Even as a non-medic, I understand this patient is

an exception. Transplantation will only be seen as a [viable consideration for a handful of cases](#), and successes will be limited. This case acts as a stark reminder of our vital role in public health, because preventing infection is our best strategy to save lives from this horrid disease. Thank you all for your incredible work.

Cat

This 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
- 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
04.09.2020	Seroprevalence of SARS-CoV-2 Among Frontline Health Care Personnel in a Multistate Hospital Network - 13 Academic Medical Centers, April-June 2020	MMWR Morb Mortal Wkly Rep / Report	<ul style="list-style-type: none"> • Among 3,248 frontline Health care personnel (HCP) who worked with COVID-19 patients at 13 geographically diverse academic medical centres in the USA, 194 (6.0%) tested positive for COVID-19 antibodies. • Of these 194 testing positive, 56 (29%) reported no symptoms since 1 Feb 2020, 86 (44%) did not believe that they previously had COVID-19, and 133 (69%) did not report a previous COVID-19 diagnosis. Seroprevalence by hospital ranged from 0.8% to 31.2%. • Seroprevalence was lower among personnel who reported

			always wearing a face covering while caring for patients (5.6%), compared with that among those who did not (9.0%) (p = 0.012).
24.08.2020	COVID-19 patients display distinct SARS-CoV-2 specific T-cell responses according to disease severity	J Infect / Letter	<ul style="list-style-type: none"> • Study of adaptive Immune responses for 60 COVID-19 convalescent patients (1-month post infection) in two cohorts: mild illness and severe pneumonia. • T-cell responses in term of frequency and intensity are clearly distinct between mild illness and severe pneumonia patients. • High levels of IFN_γ production observed with all CoV proteins support that SARS-CoV-2 elicit potent memory immune responses.
24.08.2020	SARS-CoV-2 IgG and IgA antibody response is gender dependent; and IgG antibodies rapidly decline early on	J Infect / Letter	<ul style="list-style-type: none"> • In cohort study of patients with a history of positive COVID-19 PCR test (n=159; 52.2% female) antibody tests were performed every week in the first month and then after another four weeks in the second month. • Upon the first sampling (corresponding to the median of 5 weeks after the PCR test), 4.6%, 4.6% and 6.5% of participants had not developed measurable anti-SP IgG, anti-SP IgA or anti-NC IgG. • Antibody response peaked 4-5 weeks after positive PCR, followed by an early decline. The decline is statistically significant for anti-SP and anti-NC IgG at weeks 8-10. • Significantly higher antibody concentrations are seen in men for all antibodies. • A subgroup of individuals with extremely high values had a significantly higher fraction of men than the rest of the cohort (77% of samples with OD > 20, p < 0.01).
02.09.2020	Phase 1-2 Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine	N Engl J Med / Article	<ul style="list-style-type: none"> • Randomized, placebo-controlled, phase 1–2 trial to evaluate safety and immunogenicity of the rSARS-CoV-2 vaccine (in 5-μg and 25-μg doses, with or without Matrix-M1 adjuvant, and with observers unaware of trial-group assignments) in 131 healthy adults. • At 35 days, NVX-CoV2373 appeared to be safe, and it elicited immune responses that exceeded levels in Covid-19 convalescent serum. The Matrix-M1 adjuvant induced CD4+ T-cell responses that were biased toward a Th1 phenotype.
02.09.2020	Evolution of Early SARS-CoV-2 and Cross-Coronavirus Immunity	mSphere / Article	<ul style="list-style-type: none"> • The authors profiled the immune response across multiple coronavirus receptor binding domains (RBDs), respiratory viruses, and COVID-19, to determine whether heterologous

		immunity to other CoV-RBDs or other infections influenced evolution of the COVID-19 humoral immune response. <ul style="list-style-type: none"> • Findings suggest that common viral infections including common CoV immunity, targeting the receptor binding domain involved in viral infection, do not appear to influence the rapid functional evolution of COVID-19 immunity.
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Diagnostics

Publication Date	Title / URL	Journal / Article type	Digest
02.09.2020	Temporal profile and determinants of viral shedding and of viral clearance confirmation on nasopharyngeal swabs from SARS-CoV-2-positive subjects: a population-based prospective cohort study in Reggio Emilia, Italy	BMJ Open / Article	<ul style="list-style-type: none"> • Population-based prospective cohort study (1162 subjects) to determine timings from diagnosis and from symptom onset to viral clearance. • Viral clearance achieved by 60.6% (704/1162) of patients, with a median time of 30 days from diagnosis (IQR 23-40) and 36 days from symptom onset (IQR 28-45). • Of those negative and retested, 78.7% (436/554) had viral clearance confirmation, suggesting one in five false negative tests. • Probability of confirmed viral clearance reached 86.8% after 34 days from symptom onset and increased with time, even when adjusting for age and sex.

Genomics

Publication Date	Title / URL	Journal / Article type	Digest
01.09.2020	Tracking the COVID-19 pandemic in Australia using genomics	Nat Commun / Article	<ul style="list-style-type: none"> • The authors report high-throughput genomics for COVID-19, sequencing 80% of cases in Victoria, Australia (population 6.24 million) between 6 Jan and 14 Apr 2020 (total 1,333 COVID-19 cases). • Seventy-six distinct genomic clusters were identified, including large clusters associated with social venues, healthcare and cruise ships.

			<ul style="list-style-type: none"> Sequencing sequential samples from 98 patients reveals minimal intra-patient COVID-19 genomic diversity.
01.09.2020	Spike mutation D614G alters SARS-CoV-2 fitness and neutralization susceptibility	bioRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> The authors engineered the D614G mutation in the COVID-19 USA-WA1/2020 strain and characterized its effect on viral replication, pathogenesis, and antibody neutralization. The G614 virus produced higher infectious titres in the nasal washes and trachea, but not lungs, than the D614 virus. Results confirm clinical evidence that the D614G mutation enhances viral loads in the upper respiratory tract of COVID-19 patients and may increase transmission. Sera from D614 virus-infected hamsters consistently exhibit higher neutralization titres against G614 than those against D614, indicating that (i) the mutation may not reduce the ability of vaccines in clinical trials to protect against COVID-19, and (ii) therapeutic antibodies should be tested against G614 before clinical development.
31.08.2020	Determinants of SARS-CoV-2 receptor gene expression in upper and lower airways	medRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> An assessment of the expression patterns in genes required for COVID-19 entry into cells and replication, and their regulation, throughout the respiratory tract using upper (nasal) and lower airways (bronchi) samples. Smoking status was found to increase expression of the majority of COVID-19 related genes including ACE2 and TMPRSS2, but only in the lower airways. Acute and second hand smoke were both found to increase ACE2 expression in the bronchus. Inhaled corticosteroids decrease ACE2 expression in the lower airways.

Epidemiology and clinical – children and pregnancy

Publication Date	Title / URL	Journal / Article type	Digest
01.09.2020	Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis	Bmj / Article	<ul style="list-style-type: none"> Living systematic review and meta-analysis to determine clinical manifestations, risk factors, maternal / perinatal outcomes of COVID-19 in pregnancy. 77 studies included. Pregnant and recently pregnant women are less likely to manifest COVID-19 related symptoms of fever and myalgia than

			<p>non-pregnant women of reproductive age and are potentially more likely to need intensive care treatment for COVID-19.</p> <ul style="list-style-type: none"> • Pre-existing comorbidities, high maternal age, and high body mass index seem to be risk factors for severe covid-19. Preterm birth rates are high in pregnant women with covid-19 than in pregnant women without the disease.
31.08.2020	Seroprevalence of SARS-CoV-2 antibodies in children - A prospective multicentre cohort study	medRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> • An observational cohort study at 5 UK sites (992 children; median age 10.1 years) aimed to report the presence of SARS-CoV-2 antibodies, consistent with previous infection, and to report the symptomatology of infection in children. • 68 (6.9%) participants had positive COVID-19 antibody tests indicative of previous COVID-19 infection. Of these, 34/68 (50%) reported no symptoms. • Four independent variables were identified as significantly associated with COVID-19 infection: known infected household contact; fatigue; gastrointestinal symptoms; and changes in sense of smell or taste.
01.09.2020	Serological identification of SARS-CoV-2 infections among children visiting a hospital during the initial Seattle outbreak	Nat Commun / Article	<ul style="list-style-type: none"> • Authors serologically screen 1,775 residual samples from Seattle Children’s Hospital collected from 1,076 children seeking medical care during March - April 2020. • One child seropositive in March; seven in April for a period seroprevalence of ≈1%. Most seropositive children (6/8) were not suspected of having had COVID-19.
01.09.2020	Prognostic accuracy of emergency department triage tools for children with suspected COVID-19: The PRIEST observational cohort study	medRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> • A retrospective observational cohort study in 44 EDs across the UK aimed to estimate the accuracy of triage tools for predicting severe illness in children presenting to the emergency department (ED) with suspected COVID-19 infection. • Data suggests four existing triage tools (WHO algorithm, SFHPC, POPS, and COAST) have good but not excellent prediction for adverse outcome in children with suspected COVID-19. • POPS and COAST could achieve an appropriate balance of sensitivity and specificity for supporting decisions to discharge home by considering any score above zero to be positive.

Epidemiology and clinical - risk factors

Publication Date	Title / URL	Journal / Article type	Digest
01.09.2020	Ethnicity and risk of death in patients hospitalised for COVID-19 infection in the UK: an observational cohort study in an urban catchment area	BMJ Open Respir Res / Article	<ul style="list-style-type: none"> • <i>This paper was previously included in the Digest as a preprint.</i> • All patients admitted to University Hospitals Birmingham NHS Foundation Trust with COVID-19 during study period were included (2217 in total). 58% male, 69.5% white; majority (80.2%) had comorbidities. • 18.5% South Asian ethnicity. These patients more likely to be younger and have no comorbidities, but twice the prevalence of diabetes than white patients. • More admissions and deaths in South Asian patients than would be predicted; more likely to present with severe disease despite no delay in presentation since symptom onset.
02.09.2020	Infection Fatality Ratios for COVID-19 Among Noninstitutionalized Persons 12 and Older: Results of a Random-Sample Prevalence Study	Ann Intern Med / Letter	<ul style="list-style-type: none"> • Authors estimate infection fatality ratio (IFR) among noninstitutionalized (that is, community-dwelling) populations by age, race, ethnicity, and sex by using the first U.S. state-wide random-sample study of SARS-CoV-2 prevalence. • By using SARS-CoV-2 population prevalence data, authors found that the risk for death among infected persons increased with age. • Indiana's IFR for noninstitutionalized persons older than 60 years is just below 2% (1 in 50). In comparison, the ratio is approximately 2.5 times greater than the estimated IFR for seasonal influenza, 0.8% (1 in 125), among those aged 65 years and older. • Of note, the IFR for non-Whites is more than 3 times that for Whites, despite COVID-19 decedents in that group being 5.6 years younger on average.
03.09.2020	Association of Vitamin D Status and Other Clinical Characteristics With COVID-19 Test Results	JAMA Netw Open / Original investigation	<ul style="list-style-type: none"> • In this cohort study of 489 patients who had a vitamin D level measured in the year before COVID-19 testing, the relative risk of testing positive for COVID-19 was 1.77 times greater for patients with likely deficient vitamin D status compared with patients with likely sufficient vitamin D status, a difference that was statistically significant.
02.08.2020	Characteristics and outcomes of 627 044 COVID-19 patients with and without obesity	medRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> • A cohort study of 627,044 COVID-19 patients (US: 502,650; Spain: 122,058; UK, 2336) and 4,549,568 influenza patients (US:

	in the United States, Spain, and the United Kingdom	<p>4,431,801; Spain: 115,224; UK: 2543) aimed to describe and compare the demographics, comorbidities, and outcomes of obese and non-obese patients.</p> <ul style="list-style-type: none"> • Obese hospitalized COVID-19 patients were more often female and younger than non-obese COVID-19 patients or obese influenza patients. • Obese COVID-19 patients were more likely to have prior comorbidities, present with cardiovascular and respiratory events during hospitalization, require intensive services, or die compared to non-obese COVID-19 patients. • Obese COVID-19 patients were more likely to require intensive services or die compared to obese influenza patients, despite presenting with fewer comorbidities.
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Epidemiology and clinical – other

Publication Date	Title / URL	Journal / Article type	Digest
24.08.2020	Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19	J Infect / Letter	<ul style="list-style-type: none"> • Single-centre study assessing post-discharge persistent symptoms and health-related quality of life (HRQoL) after hospitalization for COVID-19. 100+ days after admission. • 120 patients answered phone questionnaire: 96 in ward group, 24 in ICU group for artificial ventilation. • After a mean of 110.9 days, most frequently reported persistent symptoms: fatigue (55%), dyspnoea (42%), loss of memory (34%), concentration and sleep disorders (28% and 30.8%, respectively). Loss of hair reported by 24 (20%) patients - 20 women and 4 men. • Comparisons between ward and ICU patients led to no statistically significant differences regarding those symptoms.
03.09.2020	COVID-19 outbreaks in a transmission control scenario: challenges posed by social and leisure activities, and for workers in vulnerable conditions, Spain, early summer 2020	Eurosurveillance / Rapid communication	<ul style="list-style-type: none"> • SARS-CoV-2 community-wide transmission declined in Spain by early May 2020, being replaced by outbreaks and sporadic cases. • In this study, outbreaks notified to the national level in Spain during early summer of 2020 are reported. Moreover, certain settings where outbreaks were most frequently identified are described, as well as national, regional and local efforts to further investigate and control the outbreaks.

01.09.2020	Jumping back and forth: anthrozoootic and zoonotic transmission of SARS-CoV-2 on mink farms	bioRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> • Describes an in-depth investigation of COVID-19 outbreaks on 16 mink farms and humans living or working on these farms, using whole genome sequencing. • Concludes the virus was introduced from humans and has evolved, most likely reflecting widespread circulation among mink in the beginning of the infection period several weeks prior to detection. • At present, despite enhanced biosecurity, early warning surveillance and immediate culling of infected farms, there is ongoing transmission between mink farms with three big transmission clusters with unknown modes of transmission. • The first animal to human transmissions of COVID-19 in mink farms are described.
02.09.2020	COVID-19 pulmonary pathology: a multi-institutional autopsy cohort from Italy and New York City	Mod Pathol / Article	<ul style="list-style-type: none"> • Systematically evaluated lungs of 68 autopsies from 3 institutions in heavily hit areas (2 USA, 1 Italy). • The cohort consisted of 47 males and 21 females with a median age of 73 years (range 30–96). Co-morbidities were present in most patients with 60% reporting at least three conditions. • Concluded that COVID-19 pneumonia is a heterogeneous disease (tracheobronchitis, DAD, and vascular injury), but with consistent features in three centres. The pulmonary vasculature, with capillary microthrombi and inflammation, as well as macrothrombi, is commonly involved.
02.09.2020	Ocular conjunctival inoculation of SARS-CoV-2 can cause mild COVID-19 in rhesus macaques	Nat Commun / Article	<ul style="list-style-type: none"> • This study shows that infection via the conjunctival route is possible in non-human primates; further studies are necessary to compare the relative risk and pathogenesis of infection through these different routes in more detail.

Infection control

Publication Date	Title / URL	Journal / Article type	Digest
04.09.2020	Preventing and Mitigating SARS-CoV-2 Transmission - Four Overnight Camps, Maine, June-August 2020	MMWR Morb Mortal Wkly Rep / Report	<ul style="list-style-type: none"> • During the 2020 summer camp season, four Maine overnight camps with 1,022 attendees from 41 states and international locations implemented a multi-layered prevention and mitigation strategy that was successful in identifying and

			isolating three asymptomatic COVID-19 cases and preventing secondary transmission.
03.09.2020	Enhanced contact investigations for nine early travel-related cases of SARS-CoV-2 in the United States	PLoS One / Article	<ul style="list-style-type: none"> • 404 close contacts of 9 US early travel-related cases were identified and monitored daily for development of symptoms (active monitoring). • Two additional symptomatic COVID-19 cases (i.e., secondary cases) were identified; both spouses of travel-associated case patients. • When considering only household members (all of whom had ≥ 1 respiratory sample tested for SARS-CoV-2) the secondary attack rate (i.e., the number of secondary cases as a proportion of total close contacts) was 13% (95% CI: 4–38%). • Contact tracing investigation results suggest that household members, especially significant others, of COVID-19 cases are at highest risk of becoming infected.

Treatment

Publication Date	Title / URL	Journal / Article type	Digest
02.09.2020	Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis	JAMA / Original investigation	<ul style="list-style-type: none"> • In this prospective meta-analysis of 7 randomized trials that included 1703 patients of whom 647 died, 28-day all-cause mortality was lower among patients who received corticosteroids compared with those who received usual care or placebo (summary odds ratio, 0.66). • Administration of systemic corticosteroids, compared with usual care or placebo, was associated with lower 28-day all-cause mortality in critically ill patients with COVID-19.
02.09.2020	Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial	JAMA / Original investigation	<ul style="list-style-type: none"> • In this bayesian randomized clinical trial that included 403 patients and was stopped early after results from another trial were released, treatment with a 7-day fixed-dose course of hydrocortisone or shock-dependent dosing of hydrocortisone, compared with no hydrocortisone, resulted in 93% and 80% probabilities of superiority, respectively, with regard to the odds of improvement in organ support-free days within 21 days. • Although suggestive of benefit for hydrocortisone in patients with severe COVID-19, the trial was stopped early and no

			treatment strategy met prespecified criteria for statistical superiority, precluding definitive conclusions.
02.09.2020	Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19: A Randomized Clinical Trial	JAMA / Original investigation	<ul style="list-style-type: none"> • In this randomized clinical trial that included 149 patients and was terminated early following the recommendation of the data and safety monitoring board, there was no significant difference in the rate of treatment failure (defined as death or persistent respiratory support with mechanical ventilation or high-flow oxygen therapy) on day 21 between the hydrocortisone and placebo groups (42.1% vs 50.7%, respectively). • Low-dose hydrocortisone did not significantly reduce treatment failure in patients with COVID-19–related acute respiratory failure; however, the study was stopped early and was therefore likely underpowered.
02.09.2020	Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial	JAMA / Original investigation	<ul style="list-style-type: none"> • In this randomized clinical trial that included 299 patients, the number of days alive and free from mechanical ventilation during the first 28 days was significantly higher among patients treated with dexamethasone plus standard care when compared with standard care alone (6.6 days vs 4.0 days). • Intravenous dexamethasone plus standard care, compared with standard of care alone, resulted in a statistically significant increase in the number of days alive and free of mechanical ventilation over 28 days.

Overviews, comments and editorials

Publication Date	Title / URL	Journal / Article type
02.09.2020	Corticosteroids in COVID-19 ARDS: Evidence and Hope During the Pandemic	Jama / Editorial
04.09.2020	COVID-19 prevention and treatment: A critical analysis of chloroquine and hydroxychloroquine clinical pharmacology	PLoS Med / Policy forum
03.09.2020	COVID-19 and mRNA Vaccines-First Large Test for a New Approach	Jama / Medical news & perspectives
05.09.2020	COVID-19: a new lens for non-communicable diseases	The Lancet / Editorial
02.09.2020	“A Menace to the Public Health” — Contact Tracing and the Limits of Persuasion	N Engl J Med / Perspective
04.09.2020	The COVID-19 dashboard: bringing together data and statistics in one place	Public Health England / Blog
03.09.2020	Italy's first wave of the COVID-19 pandemic has ended: no excess mortality in May, 2020	The Lancet / Correspondence

Produced by the PHE COVID-19 Literature Digest Team

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A selection of previous digests [can be found here](#)