



COVID-19 Literature Digest – 16/09/2020

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

This week’s guest editor is Dr Catherine Crawford – Head of the UK Focal Point on Drugs in PHE’s Alcohol, Drugs, Tobacco and Justice Division. Catherine has been working for the past 6 months in the External Guidance Cell, which is part of the COVID-19 response.

If you only read three papers this week...

Having spent the past few weeks being involved with guidance for educational settings, and with a five-year-old now back to school after the summer holidays, I was interested to read the paper by [Ehrhardt et al](#), looking at the transmission of SARS-CoV-2 after the reopening of schools in Baden-Württemberg, Germany. In this region of 10.8 million people, schools were closed to most children on 17 March, and were reopened in a stepwise fashion from 4 May until 29 June. The authors identified 557 cases among those aged 0-19 between 25 May and 5 August; 453 of these also had information on school attendance available. 137 cases had attended school or childcare for at least 1 day during their infectious period. Using the available contact tracing data, the authors found that 6 of the 137 cases had infected a total of 11 additional pupils. Four pupils had also been infected by 2 teachers. All other remaining cases with information on school attendance available (n=437) were believed to be caused by sources outside of school and childcare facilities, most commonly within the household.

As seen recently in the UK, a large proportion of newer COVID-19 infections in the US are among young adults. The recent paper by [Cunningham et al](#) focused on the clinical effects among this group, as the authors state that few such studies have included younger people. Just over three thousand (n=3,222) non-pregnant patients aged 18-34 were identified as having been discharged from hospital between April and June, 5% of all adults in the dataset. One-fifth (n=684) of these patients required intensive care, with 10% requiring mechanical ventilation. 88 of the 3,222 (2.7%) died. More than half of the patients (n=1,669) were black and/or Hispanic. From what we know about the disease already, there were few surprises in the results regarding the patients’ characteristics: those who required ventilation or who died were more likely to be male, obese, or have high blood pressure. Those with multiple risk factors (morbid obesity, hypertension and diabetes) experienced the same risks of those aged 35-64 with COVID-19 infection who didn’t have these risk factors, once again underlining the importance of good general health among the population of all ages when it comes to fighting infections such as COVID-19.

If you go to hospital, what are your chances of catch COVID-19 while there? This is the question [Rhee et al](#) have been trying to answer. Looking at 9,149 patients admitted to one US hospital in Boston, Massachusetts between 7 March and 30 May, they identified 697 COVID-19 cases. Of these, only 12 tested positive in hospital day 3 or later; none had had known exposures to staff members with COVID-19 or shared a room with another case. Only 1 patient definitely acquired COVID-19 while in the hospital: they were most likely to have been infected by their visiting spouse. The other 11 cases were deemed to be either definitely or likely community-acquired. The authors also looked at 8,370 patients who weren’t hospitalised with COVID-19 to see whether they went on to develop the disease following discharge: they found 11 such patients. Only 1 case was deemed to have been definitely hospital-acquired. One significant limitation of the paper was how hospital-acquired cases were determined – this was done using a set

of criteria by infection control physicians, rather than by genome sequencing of the strain of SARS-CoV-2 present in the cases. However, despite the limitations, the paper points to the efficacy of infection control measures in place in hospitals, which should give people confidence in attending hospital should they need to.

Catherine

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
- Epidemiology and clinical - children and pregnancy
- Epidemiology and clinical - risk factors
- Epidemiology and clinical – long term complications / sequelae
- 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
14.09.2020	Change in Donor Characteristics and Antibodies to SARS-CoV-2 in Donated Blood in the US, June-August 2020	JAMA / Research letter	<ul style="list-style-type: none"> • Authors examined whether COVID-19 antibody testing (an incentive to donate) was associated with changes in donor characteristics and reactivity of donated blood. • First-time donors increased. Donations from younger / racial and ethnic minority donors more likely to be reactive. Reactivity rates increased with time. • Of 953 926 donations tested, 17 336 (1.82% [95% CI, 1.79%-1.84%]) were reactive; 4786 (28%) were from first-time donors and 12 550 (72%) from repeat donors for anti-SARS-CoV-2 rates of 2.99% (95% CI, 2.90%-

			3.07%) among first-time donors and 1.58% (95% CI, 1.55%-1.61%) among repeat donors (P < .001).
10.09.2020	Complete mapping of mutations to the SARS-CoV-2 spike receptor-binding domain that escape antibody recognition	bioRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> • The authors describe a deep mutational scanning method to map how all amino-acid mutations in the SARS-CoV-2 spike receptor-binding domain (RBD) affect antibody binding, and apply this method to 10 human monoclonal antibodies. • Escape mutations cluster on several surfaces of the RBD that broadly correspond to structurally defined antibody epitopes. • The complete escape maps predict which mutations are selected during viral growth in the presence of single antibodies, and enable the authors to design escape-resistant antibody cocktails.

Diagnostics

Publication Date	Title / URL	Journal / Article type	Digest
21.08.2020	Evidence summary for accuracy of molecular and antigen detection tests for the diagnosis of COVID-19 using alternative clinical specimens or sites	HIQA / Review	<ul style="list-style-type: none"> • This evidence summary focused on the accuracy of molecular and antigen detection tests using saliva or nasal specimens in SARS-CoV2 detection compared with RT-PCR tested nasopharyngeal specimens. Twenty four studies were identified with 16 including data relevant to saliva specimens and nine to nasal specimens. • Concluded that depending on the test environment and purpose, saliva and nasal specimens may offer a viable alternative to traditional test specimens for RT-PCR testing. • Use should be contingent on validation studies confirming performance in the intended setting. • No study within this review reported on differences in resource use, or assessed provider and patient satisfaction with the different specimen types.
08.09.2020	A role for Biofoundries in rapid development and validation of automated SARS-CoV-2 clinical diagnostics	Nat Commun / Article	<ul style="list-style-type: none"> • The authors present a reagent-agnostic automated SARS-CoV-2 testing platform that can be quickly deployed and scaled. • Using an in-house-generated, MS2-virus-like particle (VLP) SARS-CoV-2 standard, RNA extraction and RT-qPCR workflows are validated, in addition to two detection assays based on CRISPR-Cas13a and RT-loop-mediated isothermal amplification (RT-LAMP). • Overall workflow and detection of SARS-CoV-2 in patient samples using RT-qPCR, CRISPR-Cas13a, and RT-LAMP are reported.

- The validated RNA extraction and RT-qPCR platform has been installed in NHS diagnostic labs, increasing testing capacity by 1000 samples per day.

Epidemiology and clinical – children / pregnancy

Publication Date	Title / URL	Journal / Article type	Digest
21.08.2020	Evidence summary of potential for children to contribute to transmission of SARS-CoV-2	HIQA / Review	<ul style="list-style-type: none"> • In total, 28 studies were identified. 19 investigated household and close contact transmission, six examined transmission of SARS-CoV-2 in schools and three were modelling studies estimating age-specific transmissibility of SARSCoV-2. • From the studies identified, based on low certainty evidence, transmission from child-to-adult or child-to-child does occur in household and educational settings, but reported transmission rates for children remain low. Few definitive cases of virus transmission from children have been published to date with no clear evidence to support a higher rate of transmission for children than adults.
15.09.2020	SARS-CoV-2–Associated Deaths Among Persons Aged <21 Years — United States, February 12–July 31, 2020	MMWR Morb Mortal Wkly Rep / Report	<ul style="list-style-type: none"> • Among 121 SARS-CoV-2–associated deaths in persons aged <21 years reported to CDC by July 31, 2020, 12 (10%) were infants and 85 (70%) were aged 10–20 years. • Hispanic, non-Hispanic Black and non-Hispanic American Indian/Alaskan Native persons accounted for 94 (78%) of these deaths; 33% of deaths occurred outside of a hospital.
14.09.2020	Frequency of Children vs Adults Carrying Severe Acute Respiratory Syndrome Coronavirus 2 Asymptotically	JAMA Pediatr / Research letter	<ul style="list-style-type: none"> • Investigated the frequency of individuals carrying SARS-CoV-2 among children admitted for non-infectious conditions and without any SARS-CoV-2–associated symptoms or signs and compare it with the frequency of individuals carrying SARS-CoV-2 among a similar adult population in Milan. • Children less frequently positive than adults (1 in 83 children [1.2%] vs 12 in 131 adults [9.2%]; P = .02), with an odds ratio of 0.12 (95% CI, 0.02-0.95) compared with adults.

Epidemiology and clinical – risk factors

Publication Date	Title / URL	Journal / Article type	Digest
11.09.2020	Update Alert 4: Epidemiology of and Risk Factors for Coronavirus Infection in Health Care Workers	Ann Intern Med / Letter	<ul style="list-style-type: none"> The fourth monthly update alert for a living rapid review on the epidemiology of and risk factors for coronavirus infection in health care workers (HCWs) - added 17 studies.
15.09.2020	Characteristics of COVID-19 in Homeless Shelters : A Community-Based Surveillance Study	Ann Intern Med / Original research	<ul style="list-style-type: none"> A total of 1434 study encounters were done in shelter residents and staff, regardless of symptoms, across 14 US homeless shelters. 29 (2% [95% CI, 1.4% to 2.9%]) cases of SARS-CoV-2 infection were detected across 5 shelters. Most (n = 21 [72.4%]) were detected during surge testing events rather than routine surveillance. Most (n = 21 [72.4% {CI, 52.8% to 87.3%}]) were asymptomatic at the time of sample collection. Those testing positive: frequently aged 60+ (44.8% vs. 15.9% testing negative); slept in a communal space (86%) rather than in a private or shared room.
15.09.2020	Risk of severe coronavirus disease in imported and secondary cases in Zhejiang province, China	J Public Health (Oxf) / Article	<ul style="list-style-type: none"> Retrospectively explored the differences in the risk of severe or critical COVID-19 among imported, secondary and tertiary cases in Zhejiang, China. Of 1187 COVID-19 cases, 227 (19.1%, 95% CI: 16.9-21.4) manifested severe or critical illness. Adjusted risk difference for severe or critical illness was lower for second- (odds ratio (OR) = 0.84, 95% CI: 0.52-1.36) and third-generation (OR = 0.55, 95% CI: 0.37-0.83) cases than for first-generation cases. Concluded that second- and third-generation cases of COVID-19 have a lower risk of developing severe or critical illness than first-generation cases.

Epidemiology and clinical – long term complications / sequelae

Publication Date	Title / URL	Journal / Article type	Digest
26.09.2020	Medium- and long-term health sequelae of COVID-19	NSW COVID-19 Critical Intelligence Unit / Review	<ul style="list-style-type: none"> Investigated the medium and long-term health sequelae of COVID-19 infection among survivors. Outlines general health, respiratory health, cardiovascular health, neurological, and mental health sequelae.

- The empirical evidence on direct medium- and long-term health sequelae of COVID-19 is limited and still developing. Given the short timeline COVID-19 pandemic, studies included in this evidence check are limited to those that describe symptoms that persist or develop a few weeks or months after recovering from COVID-19 infection.

Epidemiology and clinical – other

Publication Date	Title / URL	Journal / Article type	Digest
09.09.2020	Investigation of SARS-CoV-2 outbreaks in six care homes in London, April 2020	EclinicalMedicine / Article	<ul style="list-style-type: none"> • Conducted detailed investigations in six London care homes reporting suspected COVID-19 outbreaks during April 2020. • Across the six care homes, 105/264 (39.8%) residents were SARS CoV-2 positive, including 28 (26.7%) symptomatic, 10 (9.5%) post-symptomatic, 21 (20.0%) pre-symptomatic and 46 (43.8%) who remained asymptomatic. • Among staff, 53/254 (20.9%) were SARS-CoV-2 positive and 26/53 (49.1%) remained asymptomatic. • A high prevalence of SARS-CoV-2 positivity was found in care homes residents and staff, half of whom were asymptomatic and potential reservoirs for on-going transmission. A third of symptomatic SARS-CoV-2 residents died within 14 days. • Symptom-based screening alone is not sufficient for outbreak control.
12.09.2020	Characterizing COVID-19 Clinical Phenotypes and Associated Comorbidities and Complication Profiles	medRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> • Retrospective analysis of 1,022 COVID-19 patient admissions from 14 Midwest U.S. hospitals (median age 62.1 years; 48.6% male; 46.7% caucasian) identified three clinical phenotypes. • Adjusted odds of respiratory ($p<0.001$), renal ($p<0.001$), and metabolic ($p<0.001$) complications were highest for patients with phenotype I, followed by phenotype II. • Patients with phenotype I had a far greater odds of hepatic ($p<0.001$) and haematological ($p=0.02$) complications. • Phenotypes I and II were associated with significantly increased hazard of death when compared to phenotype III.
14.09.2020	Predicting clinical outcome with phenotypic clusters in COVID-19 pneumonia: an analysis of 12,066 hospitalized patients from the Spanish registry SEMI-3 COVID-19	medRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> • Cluster analysis of a large Spanish cohort (12,066 patients; 58.5% male) identified 4 phenotypic clusters in patients with COVID-19 pneumonia, which predicted the in-hospital prognosis of clinical outcomes.

11.09.2020	Post-Mortem Findings in Italian Patients with COVID-19 - a Descriptive Full Autopsy Study of cases with and without co-morbidities	J Infect Dis / Article	<ul style="list-style-type: none"> • Autopsies on 22 COVID-19 patients. Tissues from lung, heart, liver, kidney, spleen, bone marrow (not the brain) examined. Only lung tissues subject to transmission electron microscopy. • COVID-19 causes multisystem pathology. Pulmonary and cardiovascular involvement are dominant pathological features. Extra-pulmonary manifestations include hepatic, kidney, splenic and bone marrow involvement, and microvascular injury and thrombosis were also detected. • These findings were similar in patients with or without pre-existing medical co-morbidities.
------------	--	------------------------	--

Infection control

Publication Date	Title / URL	Journal / Article type	Digest
15.09.2020	Evidence summary for the duration of infectiousness in those that test positive for SARS-CoV-2 RNA	HIQA / Review	<ul style="list-style-type: none"> • Investigated the duration of isolation for those that test positive for SARS-CoV-2 RNA. • Fifteen studies were included; 13 viral culture studies and two contact tracing studies. • The evidence to date suggests that patients with mild-to-moderate COVID-19 symptoms are unlikely to be infectious beyond 10 days from onset of symptoms. However, evidence from a limited number of studies indicates that patients with severe-to-critical symptoms and or those who are immunocompromised, may be infectious for 20 days or more.
14.09.2020	Quarantine alone or in combination with other public health measures to control COVID-19: a rapid review	Cochrane Database of Systematic Reviews / Review	<ul style="list-style-type: none"> • Updated review. • Assessed the effects of quarantine (alone or in combination with other measures) of individuals who had contact with confirmed or suspected cases of COVID-19, who travelled from countries with a declared outbreak, or who live in regions with high disease transmission. • Included a total of 51 studies. • The current evidence is limited because most studies on COVID-19 are mathematical modelling studies that make different assumptions on important model parameters. • Findings consistently indicate that quarantine is important in reducing incidence and mortality during the COVID-19 pandemic, although there is uncertainty over the magnitude of the effect.

21.08.2020	Evidence summary for airborne transmission of SARS-CoV-2 via aerosols	HIQA / Review	<ul style="list-style-type: none"> • Investigated if airborne transmission via aerosols contribute to the spread of SARS-CoV-2. • This review included 28 studies with various designs; epidemiological case series (n=8), air sampling (n=16), and microbiological (n=4). • Concluded that while there is some limited, low certainty evidence that SARSCoV-2 may transmit via aerosols, it is not known if this is restricted to specific contexts, such as in low temperature, enclosed or poorly ventilated environments. It is also uncertain what contribution aerosol transmission makes to the COVID-19 pandemic relative to other transmission modes (contact and droplet).
21.08.2020	Evidence summary for the relative importance of droplet versus contact transmission to the spread of SARS-CoV-2	HIQA / Review	<ul style="list-style-type: none"> • Investigated the relative importance of droplet versus contact transmission (in other words, direct versus indirect droplet transmission) to the spread of SARS-CoV-2. • This review included six studies with various designs: systematic reviews (n=2), mathematical modelling studies (n=3), and a cross-sectional survey (n=1). • Concluded that there is currently insufficient evidence to determine the relative importance of droplet versus contact transmission to the spread of SARS-CoV-2 and other similar enveloped respiratory viruses. However, it is likely that the relative importance of these modes of transmission is context-specific.
21.08.2020	Evidence summary for face mask use by healthy people in the community	HIQA / Review	<ul style="list-style-type: none"> • 19 studies that provide direct evidence on the effectiveness of face mask use in community settings to reduce transmission of respiratory viruses were identified. • There is limited, low certainty evidence based on four observational studies conducted during the COVID-19 pandemic that face masks may reduce the risk of transmission of SARS-CoV-2. • Studies from previous pandemic settings and for other respiratory viruses also provide low certainty evidence that the wearing of face masks in community settings reduces the risk of transmission of respiratory pathogens. However, their applicability to COVID-19 is uncertain given possible differences between viruses in their pathogenicity and infectivity and the potential differences in the relative contribution of the different modes of transmission (droplet, aerosol, contact).
15.09.2020	COVID-19 infection and transmission in domestic animals	NSW COVID-19 Critical Intelligence Unit / Review	<ul style="list-style-type: none"> • Investigated if domestic animals become infected with COVID-19, and is there evidence of transmission of COVID-19? • There have been isolated incidents of domestic animals testing

		<p>positive for the COVID-19 virus. Generally, in these cases, the pet owners have been COVID-19 positive.</p> <ul style="list-style-type: none"> • The infected domestic animals reported in the literature are mainly dogs and cats, and studies reported either natural or experimental infection with the SARS-CoV-2. • Infected pets may show clinical symptoms, or they may remain asymptomatic. Most of the pets that were infected with COVID-19 had mild symptoms and fully recovered. • There is currently no evidence that pets transmit SARS-CoV-2 via animal-to-human transmission or via animal interspecies infection. The risk of animals spreading the COVID-19 virus to human is considered low.
--	--	---

Treatment

Publication Date	Title / URL	Journal / Article type	Digest
11.09.2020	Update to living systematic review on drug treatments for covid-19	BMJ / Research	<ul style="list-style-type: none"> • A living systematic review of drug treatments for covid-19 by Siemieniuk et al (2020) has been updated.
14.09.2020	Currently prescribed drugs in the UK that could upregulate or downregulate ACE2 in COVID-19 disease: a systematic review	BMJ Open / Original research	<ul style="list-style-type: none"> • Systematic review of evidence on routinely prescribed drugs in the UK that could upregulate or downregulate ACE2 and potentially affect COVID-19 disease. • Authors screened 3360 titles and included 112 studies with 21 different drug classes identified as influencing ACE2 activity. • No convincing evidence to justify starting or stopping currently prescribed drugs to influence outcomes of COVID-19 disease. • Impact of currently prescribed drugs on ACE2 poorly studied in vivo, particularly in human lungs where SARS-CoV-2 virus appears to enact its pathogenic effects.
09.09.2020	Compassionate use of convalescent plasma for treatment of moderate and severe pneumonia in COVID-19 patients and association with IgG antibody levels in donated plasma	EClinicalMedicine / Article	<ul style="list-style-type: none"> • Assessed outcome of patients with moderate and severe COVID-19 following treatment with convalescent plasma (CP) and the association with IgG levels in transfused CP. • Concluded that treatment with CP with higher levels of IgG against S1 may benefit patients with moderate and severe COVID-19. IgG against S1 level in CP predicts neutralization antibodies titres.
14.09.2020	Successful awake proning is associated with improved clinical outcomes in patients with	BMJ Open Respir Res / Article	<ul style="list-style-type: none"> • A single-centre retrospective study (n=565) assessed whether successful awake proning of patients with COVID-19, requiring

	COVID-19: single-centre high-dependency unit experience		<p>respiratory support (continuous positive airways pressure (CPAP) or high-flow nasal oxygen (HFNO)) on a respiratory high-dependency unit (HDU), was associated with improved outcomes.</p> <ul style="list-style-type: none"> • Patients managed with CPAP alone (22/48 (45.8%)) were significantly less likely to die than patients who required transfer onto HFNO (26/48 (54.2%)): CPAP mortality 36.4%; HFNO mortality 69.2%, (p=0.023). • However, increasing age and inability to awake prone were the only independent predictors of COVID-19 mortality.
--	---	--	--

Overviews, comments and editorials

Publication Date	Title / URL	Journal / Article type
15.09.2020	Coronavirus research updates	Nature / Article
14.09.2020	Intention to vaccinate against COVID-19 in Australia	The Lancet Infectious Diseases / Correspondence
15.09.2020	Bridging the Gap at Warp Speed — Delivering Options for Preventing and Treating Covid-19	NEJM / Perspective
09.09.2020	Antibody-dependent enhancement and SARS-CoV-2 vaccines and therapies	Nat Microbiol / Perspective
14.09.2020	Covid-19: An efficient and effective test trace regime is not a numbers game	BMJ / Views and Reviews
14.09.2020	Lancet COVID-19 Commission Statement on the occasion of the 75th session of the UN General Assembly	The Lancet / Commission statement
15.09.2020	Addressing racial inequalities in a pandemic: data limitations and a call for critical analyses	The Lancet Global Health / Correspondence
15.09.2020	The COVID-NMA Project: Building an Evidence Ecosystem for the COVID-19 Pandemic	Ann Intern Med / Ideas and Opinions
16.09.2020	Developing Guidelines Before, During, and After the COVID-19 Pandemic	Ann Intern Med / Ideas and Opinions

Produced by the PHE COVID-19 Literature Digest Team

To sign-up, email COVID.LitDigest@phe.gov.uk

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