Public Health England

COVID-19 Literature Digest – 21/10/2020

Dear all,

This week's guest editor is Professor Cliodna McNulty – Consultant Medical Microbiologist and Joint Clinical Lead and Head of PHE's Primary Care and Interventions Unit. Cliodna continues to support the COVID-19 response via her role within the Clinical Guidance Cell.

If you only read three papers this week…

This week I would like to draw your attention to a Lancet infectious disease review detailing recent cases of reinfection which has significant public health implications. Additionally, Tillett et al describe a previously fit 25 year old who recovered well from a minor COVID-19 illness, to be reinfected 6 weeks later with a second genetically different SARS-CoV-2 variant, which resulted in a more severe illness requiring oxygen support and hospitalisation. The researchers cleverly ruled out the possibility of specimen mishandling or mislabelling errors during RNA extractions through forensic identity testing using short tandem repeat (STR) analysis, to confirm the specimens were from the same individual. The report has considerable implications for public health. What are the possible reasons for albeit rare reinfections with more severe illness? Firstly, a very high dose of virus might lead to reinfection, inducing more severe disease; in this case a parent in the same household was symptomatic before the reinfection. According to a paper also included in last week's Digest by Fung et al, secondary attack rates in household contacts can reach 21% if over two repeat specimens are taken from household contacts. Secondly, it is possible that reinfection is caused by a more virulent COVID-19 strain for a particular individual. Thirdly, a mechanism of antibody-dependent enhancement might be the cause, a means by which specific Fc-bearing immune cells become infected with virus by binding to specific antibodies. Fourthly, protective antibody may not be generated.

Another paper from China published this week gives us more insight into the immunity of COVID-19 patients post-hospitalisation. Hu et al found that 90% of patients who had persistent COVID-19 tests post discharge produced low titres of RBD-specific antibodies, whereas 97% of those with negative retests had high titres of viral RBD-specific IgG and/or IgA. The persistent COVID-19 spreaders were more likely to have positive anal tests pre and post admission, which is consistent with the high number of ACE2 binding receptors in the gastrointestinal tract which facilitate SARS-COC-2 viral infection.

The lancet review concludes that we cannot rely on immunity acquired by natural infection to prevent reinfection or confer herd immunity, and that herd immunity requires safe and effective vaccines and robust vaccination implementation will be required.

With my behavioural background I also include a behavioural publication. Although young people are at very low risk of severe COVID-19 illness, 19-23 years accounted for 32% of cases in this USA study by Wilson et al. A mixed method design allowed the generation of both generalisable quantitative data, and the more detailed qualitative data which helped explain drivers of the numerical data. 58% of 19-23 years with positive COVID-19 tests reported working outside the home during the incubation period (IP). Qualitative data revealed young people voiced concerns about being infected while at work due to conflicting messaging, misinformation and opposing views around

the effectiveness of masks at work. Some business owners reported discontinuing staff mask wearing to avoid offending clients. 38% of young people reported attending a social gathering during the incubation period. Interviews indicated although young people wore masks while shopping, they reported feeling social or peer pressure to not wear a mask when with peers. Furthermore, although they "limited" their social activities during the IP, they visited bars and took part in other social activities. Lack of concern for their own risk of severe disease decreased motivation to comply with COVID-19 infection prevention, although some were concerned about infecting older relatives. We need to motivate the young to protect themselves as well as others, focusing on social norms and perceived pressure to not wear face coverings. Maybe we need face coverings to become more of a fashion item!

Please find today's report below.

PHE's COVID-19 Literature Digest has been produced since February 2020. A selection of our previous Digests can be found here. This resource aims to highlight a small selection of recent COVID-19 papers that are relevant to UK settings, contains new data / insights or emerging trends. The Digest team generate a report three times per week (Mon, Wed, Fri), which includes both preliminary reports of work (preprints) that have NOT been peer-reviewed and research that has been subject to peer review and wider scrutiny. The Digest is very rapidly produced and does not claim to be a perfect product; the inclusion or omission of a publication should not be viewed as an endorsement or rejection by PHE. We do not accept responsibility for the availability, reliability or content of the items included in this resource.

To join our email distribution list please send a request to COVID.LitDigest@phe.gov.uk. If you are interested in papers relating to behaviour and social science please contact COVID19.behaviouralscience@phe.gov.uk to sign up to receive the PHE Behavioural Sciences Weekly Report.

Best wishes,

Bláthnaid Mahon, Emma Farrow, James Robinson
On behalf of the PHE COVID-19 Literature Digest Team

Report for 21.10.2020 (please note that papers that have **NOT been peer-reviewed** are highlighted in red).

Sections:

Overviews, comments and editorials (no digest)

Diagnostics

Publication Date	Title / URL	Journal / Article type	Digest
14.10.2020	Specificity and positive predictive value of SARS-CoV-2 nucleic acid amplification testing in a low prevalence setting	Clin Microbiol Infect / Article	• When prevalence is low a significant proportion of initially positive results fail to confirm and confirmatory testing substantially reduces false positive detections. • Of 19,597 samples, SARS-CoV-2 RNA was detected in 107. 52 corresponded to first-time detection (0.27% of tests on samples without previous detection); further testing detected SARS-CoV-2 RNA ≥1 time ("confirmed") in 29 (56%), and failed to detect SARS-CoV-2 RNA ("not confirmed") in 23 (44%).
15.10.2020	FebriDx point-of-care test in patients with suspected COVID-19: a pooled diagnostic accuracy study	medRxiv (non-peer reviewed) / Article	• Systematic review and pooled diagnostic test accuracy study of available individual patient data to evaluate the diagnostic accuracy of a commercial POC test (FebriDx) in patients with suspected COVID-19. • Included two published studies with 527 hospitalised patients. • A total of 523 patients had valid FebriDx results for Myxovirus resistance protein A (MxA), an antiviral host response protein. • FebriDx produced a pooled sensitivity of 0.920 (95% CI: 0.875-0.950) and specificity of 0.862 (0.819-0.896) compared with RT-PCR, where there was an estimated true COVID-19 prevalence of 0.405 (0.364-0.448) and overall FebriDx test yield was 99.2%. • No differences were found in a sub-group analysis of time tested since the onset of symptoms (median 4 days after symptom onset).

Genomics

Publication Date	Title / URL	Journal / Article type	Digest
12.10.2020	SARS-CoV-2 sequencing reveals rapid transmission from college student clusters resulting in morbidity and deaths in vulnerable populations	medRxiv (non-peer reviewed) / Article	• Substantial SARS-CoV-2 outbreak (2,002 cases in Sept) in La Crosse County, Wisconsin coincided with return to in-person instruction at three local academic institutions. • Genomic sequencing found rapid expansion of two viral substrains. Majority of cases among college-age individuals; rapid transmission into more vulnerable populations identified. • Eight sampled genomes represented two independent transmission events

			into two skilled nursing facilities, resulting in two fatalities. • Study highlights significant risks imposed by college reopening decisions, on college-associated populations and vulnerable individuals in surrounding communities.

Epidemiology and clinical – children / pregnancy

Publication Date	Title / URL	Journal / Article type	Digest
01.11.2020	Sociodemographic Predictors of SARS-CoV-2 Infection in Obstetric Patients, Georgia, USA	Emerg Infect Dis / Research	• A cohort study (1,882 women) examined sociodemographic risk factors for COVID-19 infection among obstetric patients in 2 urban hospitals in Atlanta, Georgia, USA. • Prevalence of infection was highest among women who were Hispanic (15.8%, 95% CI 9.8–21.9; p<0.001), were uninsured (10.1%, 95% CI 5.5–14.6; p<0.001), lived in areas with smaller average household size (5.2%, 95% CI 3.8–6.6. vs. 3.0%, 95% CI 1.9–4.1; p = 0.02), or lived in high-density neighbourhoods (5.1%, 95% CI 3.7–6.5, vs. 3.1%, 95% CI 2.0–4.2; p = 0.03).

Epidemiology and clinical – risk factors

Publication Date	Title / URL	Journal / Article type	Digest
01.01.2021	Coronavirus Disease among Workers in Food Processing, Food Manufacturing, and Agriculture Workplaces	Emerg Infect Dis / Dispatch (early release)	• Describes COVID-19 among US food manufacturing and agriculture workers and provide updated information on meat and poultry processing workers. • Among 742 food and agriculture workplaces in 30 states, 8,978 workers had confirmed COVID-19; 55 workers died.
19.10.2020	Excess mortality in the first COVID pandemic peak: cross-sectional analyses of the impact of age, sex, ethnicity, household size, and long-term conditions in people of known SARS-Cov-2 status in England	Br J Gen Pract / Research	• Authors describe the mortality in England and its association with SARS-CoV-2 status and other demographic and risk factors. • People living in households of ≥9 had a fivefold increase in relative mortality (RHR = 5.1, 95% CI = 4.87 to 5.31, P<0.0001). • Male sex, population density, black ethnicity (compared to white), and people with long-term conditions, including learning disability (OR = 1.96, 95% CI = 1.22 to 3.18, P = 0.0056) had higher odds of mortality.
16.10.2020	Deaths in people from Black, Asian and minority ethnic communities from both COVID-19 and non-COVID causes in the first weeks of the pandemic in London: a hospital case note review	BMJ Open / Original research	• Case review of deaths in London teaching hospital during a 6-week period during pandemic, from first death on 12 Mar, and contrast same period in 2019. • No evidence of COVID-19 deaths occurring disproportionately in elderly compared with non-COVID deaths in this period in 2020 and 2019.

			• Deaths in BAME communities over-represented in both COVID-19 (OR=2.43, 95% CI=1.60–3.68, p<0.001) and non-COVID groups (OR=1.76, 95% CI=1.09–2.83, p=0.02) during pandemic. • Detailed research needed to fully understand influence of ethnicity on susceptibility to illness, mortality and health-seeking behaviour during the pandemic.
20.10.2020	Rapid Epidemiological Analysis of Comorbidities and Treatments as risk factors for COVID-19 in Scotland (REACT-SCOT): A population-based case-control study	PLoS Med / Research article	• *This paper was previously included in the Digest as a preprint.* • First systematic study of relationship of severe/fatal COVID-19 to pre-existing health conditions and other risk factors in Scotland, based on electronic health records. • Residents in care homes 21 times more likely to develop severe disease than people of same age and sex not living in care homes. • Conditions associated with increased risk include diagnoses that are associated with frailty and poor health such as strokes and a history of falls. When no listed conditions, use of prescribed drugs acting on digestive system or nervous system associated with increased risk of severe COVID-19.
20.10.2020	Excess Deaths Associated with COVID-19, by Age and Race and Ethnicity — United States, January 26–October 3, 2020	MMWR Morb Mortal Wkly Rep / Early release	• As of Oct 15, 216,025 deaths from COVID-19 have been reported in the US; however, this might underestimate the total impact of the pandemic on mortality. • Overall, an estimated 299,028 excess deaths occurred from late Jan through October 3, 2020, with 198,081 (66%) excess deaths attributed to COVID-19. • The largest percentage increases were seen among adults aged 25–44 years and among Hispanic or Latino persons.
19.10.2020	Estimating the infection-fatality risk of SARS-CoV-2 in New York City during the spring 2020 pandemic wave: a model-based analysis	Lancet Infectious Diseases / Article	• Estimated the infection-fatality risk of SARS-CoV-2 in New York City, USA. • From Mar 1 to June 6, 2020, 205 639 people had a laboratory-confirmed infection with SARS-CoV-2 and 21 447 confirmed and probable COVID-19-related deaths occurred among residents of NY City. Estimated an overall infection-fatality risk of 1·39% (95% credible interval 1·04–1·77). • Estimated IFR for the two oldest age groups (65–74 and ≥75 years) was much higher than the younger age groups. • Weekly IFR was estimated to be as high as 6·72% (5·52–8·01) for those aged 65–74 years and 19·1% (14·7–21·9) for those aged 75 years and older.
20.10.2020	Risk for In-Hospital Complications Associated with COVID-19 and Influenza — Veterans Health Administration, United States, October 1, 2018–May 31, 2020	MMWR Morb Mortal Wkly Rep / Early release	• Hospitalized patients with COVID-19 in the Veterans Health Administration had a more than five times higher risk for in-hospital death and increased risk for 17 respiratory and non-respiratory complications than did hospitalized patients with influenza. • The risks for sepsis and respiratory, neurologic, and renal complications of

			COVID-19 were higher among non-Hispanic Black or African American and Hispanic patients than among non-Hispanic White patients.
20.10.2020	Variation in racial/ethnic disparities in COVID-19 mortality by age in the United States: A cross-sectional study	PLoS Med / Article	• Authors used national data on COVID-19 deaths by racial/ethnic group and age, along with US Census population data, to explore variation in mortality risk. • More years of life were lost before 65 years among non-Hispanic Black and Hispanic populations, despite smaller size of these groups, than among non-Hispanic White population.
26.08.2020	Individuals with obesity and COVID-19: A global perspective on the epidemiology and biological relationships	Obes Rev / Article	• Systematic review of COVID-19 risk, mortality, and mechanistic pathways in individuals with obesity (75 studies selected from Chinese and English language literature). • Discussed in recent JAMA article https://dx.doi.org/10.1001/jama.2020.18637

Epidemiology and clinical – other

Publication Date	Title / URL	Journal / Article type	Digest
15.10.2020	Excess mortality in England and Wales during the first wave of the COVID-19 pandemic	J Epidemiol Community Health / Original research	• *This paper was previously included in the Digest as a preprint.* • Authors quantified excess mortality in regions of England and Wales during the pandemic, for all causes and for non-COVID-19-associated deaths. • Mar 7 - May 8: 47 243 (95% CI: 46 671 to 47 815) excess deaths in England and Wales, of which 9948 (95% CI: 9376 to 10 520) not associated with COVID-19. • Excess mortality varied, from 49 per 100 000 (95% CI: 49 to 50) in South West to 102 per 100 000 (95% CI: 102 to 103) in London. • Non-COVID-19 associated excess mortality rates ranged from −1 per 100 000 (95% CI: −1 to 0) in Wales (ie, mortality rates not higher than expected) to 26 per 100 000 (95% CI: 25 to 26) in West Midlands.
08.10.2020	Updated hospital associated venous thromboembolism outcomes with 90-days follow-up after hospitalisation for severe COVID-19 in two UK critical care units	Thromb Res / Letter	• Prolonged follow-up of cohorts in 2 UK critical care centres (Cambridge, n=63; London, n=66) found that although some patients remained hospitalised after 90 days, there were minimal rates of further venous thromboembolism (VTE) in hospital and following discharge. • Data does not support the use of extended thromboprophylaxis post-hospitalisation for patients with COVID-19 following critical care admission.

Infection control / non-pharmaceutical interventions

Publication Date	Title / URL	Journal / Article type	Digest
19.10.2020	The Safety of Contemporary Planned Cancer Surgery During the COVID-19 Pandemic	medRxiv (non-peer reviewed) / Article	• An audit of all patients undergoing elective cancer surgery in Greater Manchester between 1 May and 31 June 2020, following the introduction of specific peri operative COVID-19 safety measures. • Of 1501 patients undergoing surgery, one (<0.1%) was diagnosed with COVID-19 in hospital within 14 days of surgery. • Suggests peri operative COVID-19 infection prevention strategies allow for the safe continuation of elective cancer surgery during this pandemic in all surgical units.
01.01.2021	Impact of a Nationwide Lockdown on SARS-CoV-2 Transmissibility, Italy	Emerg Infect Dis / Dispatch (early release)	• On Mar 11, 2020, Italy imposed a national lockdown to curtail the spread of SARS-CoV-2. Authors estimate that, 14 days after lockdown, the net reproduction number had dropped below 1 and remained stable at »0.76 (95% CI 0.67–0.85) in all regions for >3 of the following weeks.
13.10.2020	Community engagement for COVID-19 prevention and control: a rapid evidence synthesis	BMJ Glob Health / Original research	• Rapid evidence review of community engagement approaches in past epidemics may support more robust implementation within COVID-19 response. • Six main community engagement factors: local leaders, community / faith-based organisations, community groups, health facility committees, individuals and key stakeholders. • COVID-19's global presence and social transmission pathways require social and community responses, especially to reach marginalised populations and support equity-informed responses.

Treatment

Publication Date	Title / URL	Journal / Article type	Digest
20.10.2020	Association Between Early Treatment With Tocilizumab and Mortality Among Critically Ill Patients With COVID-19	JAMA Intern Med / Original investigation	• In this multicentre cohort study that included 3924 critically ill COVID-19 patients, risk of in-hospital death estimated to be lower with tocilizumab treatment in first 2 days of ICU admission compared with no early use of tocilizumab. • Estimated 30-day mortality 27.5% (95% CI, 21.2%-33.8%) in tocilizumab-treated patients; 37.1% (95% CI, 35.5%-38.7%) in non-tocilizumab–treated patients (risk difference, 9.6%; 95% CI, 3.1%-16.0%). • Findings may be susceptible to unmeasured confounding, and further research from randomized clinical trials is needed.

20.10.2020	Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial	JAMA Intern Med / Original investigation	• In a randomised clinical trial of patients with COVID-19 and pneumonia requiring oxygen support but not admitted to the intensive care unit, 63 were randomised to tocilizumab (TCZ) and 67 to usual care. • TCZ did not reduce World Health Organization 10-point Clinical Progression Scale (WHO-CPS) scores lower than 5 at day 4 but might have reduced the risk of non-invasive ventilation, mechanical ventilation, or death by day 14. • No significant difference on day 28 mortality was found.
20.10.2020	Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial	JAMA Intern Med / Original investigation	• Hospitalised adult patients with COVID-19 pneumonia (n=126; median age 60; male 61.1%) were randomised to tocilizumab (n=60) or standard care (n= 66). • Seventeen patients of 60 (28.3%) in the tocilizumab arm and 17 of 63 (27.0%) in the standard care group showed clinical worsening within 14 days since randomization (rate ratio, 1.05; 95% CI, 0.59-1.86). • Two patients in the experimental group and 1 in the control group died before 30 days from randomisation, and 6 and 5 patients were intubated in the 2 groups, respectively. • The trial was prematurely interrupted after an interim analysis for futility. • Authors suggest further trials are needed to evaluate application of tocilizumab in different stages of the disease.
15.10.2020	Clinical characteristics and outcomes among hospitalized adults with severe COVID-19 admitted to a tertiary medical center and receiving antiviral, antimalarials, glucocorticoids, or immunomodulation with tocilizumab or cyclosporine: A retrospective observational study (COQUIMA cohort)	EClinicalMedicine / Article	• Describes the characteristics and impact of different therapies on clinical outcomes in a cohort of severe COVID-19 patients. • 607 patients were included. Median age was 69 years, 65% male. • Risk of death increased with older age, tocilizumab therapy (2·4, [1·13 - 5·11]), C-reactive protein at admission (1·07, per 10 mg/L, [1·04 - 1·10]), d-dimer > 2·5 µg/mL (1·99, [1·03 - 3·86]), diabetes mellitus (2·61, [1·19 - 5·73]), and the PaO2/FiO2 at admission (0·99, per every 1 mmHg, [0·98 - 0·99]). • Among the prescribed therapies (tocilizumab, glucocorticoids, lopinavir/ritonavir, hydroxychloroquine, cyclosporine), only cyclosporine was associated with a significant decrease in mortality (0·24, [0·12 - 0·46]; p<0·001).

Vaccine development

Publication Date	Title / URL	Journal / Article type	Digest
20.10.2020	A global survey of potential acceptance of a COVID-19 vaccine	Nature Medicine / Brief communication	• Surveyed 13,426 people in 19 countries to determine potential acceptance rates and factors influencing acceptance of a COVID-19 vaccine. • Of these, 71.5% of participants reported that they would be very or

			somewhat likely to take a COVID-19 vaccine, and 61.4% reported that they would accept their employer's recommendation to do so. • Differences in acceptance rates ranged from almost 90% (in China) to less than 55% (in Russia). Respondents reporting higher levels of trust in information from government sources were more likely to accept a vaccine and take their employer's advice to do so.
10.10.2020	Caregiver willingness to vaccinate their children against COVID-19: Cross sectional survey	Vaccine / Article	• International cross sectional survey of 1541 caregivers visiting 16 paediatric Emergency Departments (ED) across six countries from Mar 26 to May 31, 2020. • 65% (n = 1005) of caregivers reported that they intend to vaccinate their child against COVID-19, once a vaccine is available. • Most common reason for acceptance was to protect the child / for refusal was the vaccine's novelty. • Child age, chronic illness, vaccination history affects willingness / Caregiver gender, vaccination history, concern about infection affect willingness. • Public health strategies: evidence about an upcoming vaccine's safety and efficacy, highlight risks and consequences of infection in children, educate caregivers on the role of vaccination.

Modelling

Publication Date	Title / URL	Journal / Article type	Digest
18.10.2020	Evaluating the use of the reproduction number as an epidemiological tool, using spatio-temporal trends of the Covid-19 outbreak in England	medRxiv (non-peer reviewed) / Article	• Estimated time-varying reproduction number (Rt) using a model that mapped unobserved infections to observed test-positive cases, hospital admissions, and deaths with confirmed Covid-19, in seven regions of England, Mar-Aug 2020. • Divergence between estimates from each source was not consistent within or across regions over time, although estimates based on hospital admissions and deaths were more spatio-temporally synchronous than compared to estimates from all test-positives. • Differences between Rt may be linked to biased representations of sub-populations in each data source: from uneven testing rates, or increasing severity of disease with age. • Suggests policy makers should consider the source populations of Rt estimates.

Overviews, comments and editorials

Publication Date	Title / URL	Journal / Article type
20.10.2020	Time to Reassess Tocilizumab's Role in COVID-19 Pneumonia	JAMA Intern Med / Editorial
19.10.2020	Herd Immunity and Implications for SARS-CoV-2 Control	JAMA / Insights
19.10.2020	Use of adenovirus type-5 vectored vaccines: a cautionary tale	Lancet / Correspondence
20.10.2020	COVID-19 Vaccine: What Physicians Need to Know	Ann Intern Med / Article
15.10.2020	Fixing England's COVID-19 response: learning from international experience	J R Soc Med / Article Commentary

Produced by the PHE COVID-19 Literature Digest Team

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