COVID-19 Literature Digest – 14/10/2020

Dear all,

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a report three times per week (Mon, Wed, Fri), which includes both preliminary reports of work (preprints) that have NOT been peer-reviewed and research that has been subject to peer review and wider scrutiny.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Report for 14.10.2020 (please note that papers that have NOT been peer-reviewed are highlighted in red).

Sections:
Serology and immunology
Diagnostics
Genomics
Epidemiology and clinical – children / pregnancy
Epidemiology and clinical – risk factors
Epidemiology and clinical – long term complications / sequelae
Epidemiology and clinical – other
Infection control / non-pharmaceutical interventions
# Serology and immunology

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<td>13.10.2020</td>
<td><strong>SARS-CoV-2 immunity: review and applications to phase 3 vaccine candidates</strong></td>
<td>Lancet / Review</td>
<td>• In this Review, the authors discuss what is currently known about human humoral and cellular immune responses to SARS-CoV-2 and relate this knowledge to the COVID-19 vaccines currently in phase 3 clinical trials.</td>
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| 12.10.2020       | **SARS-CoV-2 neutralizing antibody structures inform therapeutic strategies** | Nature / Article       | • To determine structural correlates of SARS-CoV-2 neutralization, the authors solved 8 new structures of distinct COVID-19 human neutralizing antibodies (hNAbs) in complex with SARS-CoV-2 spike trimer or host ACE2 receptor-binding domain (RBD).  
• Structural comparisons allowed classification into 4 categories.  
• These classifications and the structural analyses described provide rules for assigning current and future human RBD-targeting antibodies into classes, evaluating avidity effects, suggesting combinations for clinical use, and providing insight into immune responses. |
| 08.10.2020       | **Absence of SARS-CoV-2 neutralizing activity in pre-pandemic sera from individuals with recent seasonal coronavirus infection** | medRxiv (non-peer reviewed) / Article | • Measured neutralizing activity against SARS-CoV-2 in pre-pandemic sera from patients with prior PCR-confirmed seasonal coronavirus infection.  
• While neutralizing activity against seasonal coronaviruses was detected in nearly all sera, cross-reactive neutralizing activity against SARS-CoV-2 was undetectable. |

# Diagnostics

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| 12.10.2020       | **Pooling for SARS-CoV-2 control in care institutions**                      | BMC Infect Dis / Research article | • A study to describe SARS-CoV-2 prevalence in care homes in Galicia, Spain, during the Coronavirus pandemic, and to evaluate the expected performance of a pooling strategy using RT-PCR for the next rounds of screening of care home residents and workers.  
• Distribution of SARS-CoV-2 infection at Care Homes was uneven (0-60%).  
• The authors demonstrate that pooling of different groups of samples at low prevalence clusters, can be done with a small average delay on Cq values (5 and 2.85 cycles for pools of 20 and 5 samples, respectively). |
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| 09.10.2020      | A CRISPR-Cas12a-based specific enhancer for more sensitive detection of SARS-CoV-2 infection                        | EBioMedicine / Research paper | • A Specific Enhancer for PCR-amplified Nucleic Acid (SENA) was developed based on the Cas12a trans-cleavage activity, which is specifically triggered by the rRT-PCR amplicons of the SARS-CoV-2 Orf1ab (O) and N fragments.  
  • 295 clinical specimens analysed - including 21 uncertain rRT-PCR cases, 4 false negative and 2 false positive samples - characterized by SENA and further verified by next-generation sequencing (NGS). The cut-off values for mix-FCratio were determined as 1.145 for positive and 1.068 for negative.  
  • SENA increases both sensitivity and the specificity of rRT-PCR, providing a simple and low-cost companion diagnosis. |

### Genomics

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  • Were able to detect co-circulating virus variants, some specifically prevalent in England, and to identify changes in viral RNA sequences with time consistent with the recently reported increasing global dominance of Spike protein G614 pandemic variant.  
  • Low levels of viral RNA were detected in a sample from 11th Feb, 3 days before the first case was reported in the sewage plant catchment area.  
  • SARS-CoV-2 RNA concentration increased in March and April, and a sharp reduction was observed in May, showing the effects of lockdown measures.  
  • Conclude that viral RNA sequences found in sewage closely resemble those from clinical samples and that environmental surveillance can be used to monitor SARS-CoV-2 transmission, tracing virus variants and detecting virus importations. |
| 12.10.2020      | Sequences in the cytoplasmic tail of SARS-CoV-2 spike facilitate syncytia formation                                  | bioRxiv (non-peer reviewed) / Article | • The authors applied proteomics to identify cellular factors that interact with the cytoplasmic tail of SARS-CoV-2 spike (S) to elucidate the intracellular trafficking of S protein in host cells.  
  • The study confirmed interactions with components of the COPI, COPII and SNX27/retromer vesicle coats, and with FERM domain actin regulators and the WIPI3 autophagy component.  
  • The interaction with COPII promotes efficient exit from the endoplasmic reticulum (ER), although S leaks to the surface where it accumulates as it lacks an endocytosis motif of the type found in many other coronaviruses.  
  • Suggests the trafficking signals in the cytoplasmic tail of S protein indicate... |
that syncytia formation is not a by-product of infection but a key aspect of the replicative cycle of SARS-CoV-2, and potential cause of pathological symptoms.

### Epidemiology and clinical – children / pregnancy

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| 12.10.2020       | Analysis of SARS-CoV-2 vertical transmission during pregnancy              | Nat Commun / Article         | • Analysed the viral genome on maternal and new-borns nasopharyngeal swabs, vaginal swabs, maternal and umbilical cord plasma, placenta and umbilical cord biopsies, amniotic fluids and milk from 31 mothers with SARS-CoV-2 infection.  
• Detected SARS-CoV-2 genome in one umbilical cord blood and in two at-term placentas, in one vaginal mucosa and in one milk specimen.  
• Report the presence of specific anti-SARS-CoV-2 IgM and IgG antibodies in one umbilical cord blood and in one milk specimen. Finally, in the three documented cases of vertical transmission, SARS-CoV-2 infection was accompanied by a strong inflammatory response.  
• Together, these data support the hypothesis that in utero SARS-CoV-2 vertical transmission, while low, is possible. These results might help defining proper obstetric management of COVID-19 pregnant women, or putative indications for mode and timing of delivery. |
| 12.10.2020       | Outcomes of Neonates Born to Mothers With Severe Acute Respiratory Syndrome Coronavirus 2 Infection at a Large Medical Center in New York City | JAMA Pediatr / Original investigation | • Analysis of a cohort of 101 neonates (54 female [53.5%]) born to 100 mothers positive for or with suspected SARS-CoV-2 infection from 13 March to 24 April 2020 in a New York City hospital.  
• Data suggests no vertical transmission in this cohort, despite most new-borns rooming-in and direct breastfeeding practices. |
• In this national quasi-experimental study, initial implementation of COVID-19 mitigation measures was associated with a substantial reduction in the incidence of preterm births in the following months, in agreement with preliminary observations elsewhere.  
• Integration of comparable data from across the globe is needed to further substantiate these findings and start exploring underlying mechanisms. |
### Epidemiology and clinical – risk factors

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| 08.10.2020       | Elevated antiviral, myeloid and endothelial inflammatory markers in severe COVID-19 | medRxiv (non-peer reviewed) / Article | - Analysed serial plasma samples from 619 patients hospitalised with COVID-19 recruited through the ISARIC clinical characterisation protocol U.K. study and 39 milder community cases not requiring hospitalisation.  
- Elevated levels of mediators including angiopoietin-2, CXCL10, and GM-CSF were seen at recruitment in patients who later died.  
- Markers of endothelial injury (angiopoietin-2 and von-Willebrand factor A2) were detected early in some patients, while inflammatory cytokines and markers of lung injury persisted for several weeks in fatal COVID-19 despite decreasing antiviral cytokine levels.  
- Overall, markers of myeloid or endothelial cell activation were associated with severe, progressive, and fatal disease indicating a central role for innate immune activation and vascular inflammation in COVID-19. |
| 10.10.2020       | Severity of respiratory failure at admission and in-hospital mortality in patients with COVID-19: a prospective observational multicentre study | BMJ Open / Original research | - Investigated the influence of hypoxic acute respiratory failure (hARF) severity on patients’ outcomes - 412 patients (280 males, 68%). Median (IQR) age was 66 (55–76) years with a PaO2/FiO2 at admission of 262 (140–343) mm Hg.  
- Prevalence of mild, moderate and severe hARF was 24.4%, 21.9% and 15.5%, respectively. In-hospital mortality proportionally increased with increasing impairment of gas exchange (p<0.001).  
- A moderate-to-severe impairment in PaO2/FiO2 was independently associated with a threefold increase in risk of in-hospital mortality |
| 13.10.2020       | Longitudinal Profile of Laboratory Parameters and Their Application in the Prediction for Fatal Outcome Among Patients Infected With SARS-CoV-2: A Retrospective Cohort Study | Clin Infect Dis / Article | - Consecutively collected data on 55 laboratory parameters and cytokines from 642 patients with COVID-19 (Wuhan, China) were profiled along the entire disease course, based on which 3 clinical stages (acute stage, days 1–9; critical stage, days 10–15; and convalescence stage, day 15 to observation end) were determined.  
- Laboratory findings based on 75 deceased and 357 discharged patients revealed that, at the acute stage, fatality could be predicted by older age and abnormal lactate dehydrogenase (LDH), urea, lymphocyte count, and procalcitonin (PCT) level.  
- At the critical stage, the fatal outcome could be predicted by age and abnormal PCT, LDH, cholinesterase, lymphocyte count, and monocyte percentage.  
- Interleukin 6 (IL-6) was remarkably elevated, with fatal cases having a more robust production than discharged cases across the whole observation |
13.10.2020  **Sequential infection with influenza A virus followed by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) leads to more severe disease and encephalitis in a mouse model of COVID-19**  
**bioRxiv (non-peer reviewed) / Article**  
- Transgenic mice expressing the human ACE2 receptor driven by the epithelial cell cytokeratin-18 gene promoter (K18-hACE2) were first infected with influenza A virus (IAV) followed by SARS-CoV-2.
- Host response and effect on virus biology was compared to K18-hACE2 mice infected with IAV or SARS-CoV-2 only.
- Infection of mice with each individual virus resulted in a disease phenotype compared to control mice.
- SARS-CoV-2 RNA synthesis appeared significantly reduced in the sequentially infected mice, however these mice had a more rapid weight loss, more severe lung damage and a prolongation of the innate response compared to singly infected or control mice.
- Sequential infection exacerbated the extrapulmonary manifestations associated with SARS-CoV-2, including a more severe encephalitis.

### Epidemiology and clinical – long term complications / sequelae

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| 13.10.2020       | **Sudden irreversible hearing loss post COVID-19** | BMJ Case Rep / Case report | • This paper presents the first UK case of sudden onset sensorineural hearing loss (SSNHL) following COVID-19.  
• Physical examination and imaging excluded any other cause of hearing loss.  
• A literature review showed that four other cases have been previously described.  
• Hearing loss can be a significant cause of morbidity and can easily be missed in the intensive care setting. Being aware and screening for SSNHL following COVID-19 enables an early course of steroids, which offers the best chance of recovering hearing. |
| 12.10.2020       | **Factors associated with re-attendance to emergency services following COVID-19 hospitalisation** | J Med Virol / Letter | • Follow up (median 112 days post-discharge) original cohort, 423/614 (69%) patients discharged alive from index COVID-19 hospitalisation, 3 large London hospitals.  
• 97 (23%) re-attended emergency services; median time from index hospitalisation discharge to first re-attendance was 27 days.  
• Most frequent primary diagnosis at first re-attendance: persisting COVID-19 pneumonia (25, 26%), other infectious diseases (15, 16%; including healthcare-associated infections), cardiovascular disorders (9, 9%) and trauma (7,7%). |
For subsequent re-attendances, most frequent primary diagnosis: other infectious diseases (20, 30%), renal disorders (12, 18%), cardiovascular disorders (6, 9%), with persisting COVID-19 symptoms in only one case.

### Epidemiology and clinical – other

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| 12.10.2020       | Genomic evidence for reinfection with SARS-CoV-2: a case study              | Lancet Infectious Diseases / Article   | • *This paper was previously included in the Digest as a preprint.*  
• Describes an investigation of two instances of SARS-CoV-2 infection in the same individual (25-year-old man who was a resident of Nevada, US).  
• The patient had two positive tests for SARS-CoV-2, the first on April 18, 2020, and the second on June 5, 2020, separated by two negative tests done during follow-up in May, 2020.  
• Findings suggest that the patient was infected by SARS-CoV-2 on two separate occasions by a genetically distinct virus.  
• Thus, previous exposure to SARS-CoV-2 might not guarantee total immunity in all cases. All individuals, whether previously diagnosed with COVID-19 or not, should take identical precautions to avoid infection with SARS-CoV-2. The implications of reinfections could be relevant for vaccine development and application. |
| 09.10.2020       | Reinfection of SARS-CoV-2 in an immunocompromised patient: a case report     | Clin Infect Dis / Accepted manuscript  | • Case report of COVID-19 reinfection in an 89-year-old Dutch woman, suffering from Waldenström’s macroglobulinemia, treated with B-cell-depleting therapy.  
• In the first episode she was discharged after 5 days and besides some persisting fatigue her symptoms subsided completely.  
• Two days after a new chemotherapy treatment, fifty-nine days after the start of the first COVID-19 episode, she developed fever, cough, and dyspnea.  
• She tested positive for COVID-19 on admission, negative for SARS-CoV-2 antibodies on days 4 and 6, and deteriorated on day 8. She died two weeks later.                                                                                                                                                                                                             |
| 09.10.2020       | Development and validation of the 4C Deterioration model for adults hospitalised with COVID-19 | medRxiv (non-peer reviewed) / Article | • The authors developed a multivariable logistic regression model for in-hospital clinical deterioration (defined as any requirement of ventilatory support or critical care, or death) using 11 routinely measured variables, among 75,016 consecutive adults prospectively recruited to the ISARIC Coronavirus Clinical Characterisation Consortium study.  
• Internal-external cross-validation showed consistent measures of... |
discrimination, calibration and clinical utility across eight geographical regions.
• The final model was further validated in held-out data from 8,252 individuals in London, with similarly consistent performance (C-statistic 0.77 (95% CI 0.75 to 0.78); calibration-in-the-large 0.01 (-0.04 to 0.06); calibration slope 0.96 (0.90 to 1.02)).
• The model demonstrated higher net benefit than using other candidate scores to inform decision-making.

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| 08.10.2020 | A linear prognostic score based on the ratio of interleukin-6 to interleukin-10 predicts outcomes in COVID-19 | EBioMedicine / Article | • Studied the relationship between the ratio of interleukin (IL)-6 to IL-10 and clinical outcome in 80 patients hospitalized for COVID-19, and created a simple 5-point linear score predictor of clinical outcome, the Dublin-Boston score.
• The Dublin-Boston score is easily calculated and can be applied to a spectrum of hospitalized COVID-19 patients. More informed prognosis could help determine when to escalate care, institute or remove mechanical ventilation, or drive considerations for therapies. |
| 12.10.2020 | The household secondary attack rate of SARS-CoV-2: A rapid review     | Clin Infect Dis / Article | • Authors analysed data from 22 published / pre-published studies (20,291 household contacts) to combine estimates of household secondary attack rate (SAR).
• Overall pooled random-effects estimate of the household SAR was 17.1% (95% CI: 13.7-21.2%).
• Stratified by testing frequency, SAR estimates 1 test: 9.2% (95% CI: 6.7-12.3%), 2 test: 17.5% (95% CI: 13.9-21.8%), >2 tests: 21.3% (95% CI: 13.8-31.3%).
• SAR reported using single follow-up test may underestimate; multiple testing of COVID-19 household contacts may identify more secondary cases. |
| 12.10.2020 | Sewage as a Possible Transmission Vehicle During a Coronavirus Disease 2019 Outbreak in a Densely populated Community: Guangzhou, China, April 2020 | Clin Infect Dis / Article | • COVID-19 outbreak in a densely populated community in Guangzhou, China: eight cases (four couples) in this community of 2888 residents (attack rate=2.8/1000).
• Cases 1-2 frequented market T; Cases 3-8 never visited market T during incubation period, lived in separate buildings from, and never interacted with, Cases 1-2.
• Of 63 samples collected from street-sewage puddles and sewage-pipe surfaces, 19% tested positive for SARS-CoV-2.
• Viruses identified from squat toilet and shoe-bottom dirt inside apartment of Cases 1-2 homologous with those from Cases 3-8 / identified from sewage samples. |
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<td>10.10.2020</td>
<td>SARS-CoV-2 infects carotid arteries: implications for vascular disease and organ injury in COVID-19</td>
<td>bioRxiv (non-peer reviewed) / Article</td>
<td>• Finding highlighted importance of sewage management, especially in densely-populated places with poor hygiene and sanitation measures.</td>
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| 09.10.2020      | SARS-CoV-2 infects brain astrocytes of COVID-19 patients and impairs neuronal viability | medRxiv (non-peer reviewed) / Article | • An autopsy series of 32 COVID-19 patients investigated whether carotid arteries were infected with SARS-CoV-2 by employing genomic, virologic, histochemical and transcriptomic analyses.  
• Results suggest that SARS-CoV-2 productively infects and modulates vascular responses in carotid arteries. |

**Infection control / non-pharmaceutical interventions**

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<td>12.10.2020</td>
<td>Summary of the effectiveness and harms of different non-pharmaceutical interventions, 21 September 2020</td>
<td>Gov.uk / Research and analysis</td>
<td>• A paper summarising the effectiveness and harms of non-pharmaceutical interventions (NPIs).</td>
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• Concluded that New Zealand’s response resulted in low relative burden of disease, low levels of population disease disparities, and the initial achievement of COVID-19 elimination. |
| 12.10.2020      | Classification of aerosol-generating procedures: a rapid systematic review | BMJ Open Respir Res / Article | • Investigates how official guidance documents and academic publications have classified procedures in terms of whether or not they are aerosol-generating using.  
• 128 documents met the inclusion criteria, containing 1248 mentions of procedures which the authors categorise into 39 procedure groups.  
• Procedures classified as aerosol-generating or possibly aerosol-generating |
• Disagreements existed between sources on some procedure groups, including oral and dental procedures, upper gastrointestinal endoscopy, thoracic surgery and procedures, and nasopharyngeal and oropharyngeal swabbing.
• Some clinically relevant procedures received surprisingly little mention in source documents.

12.10.2020 Concerns and misconceptions about the Australian Government’s COVIDSafe App: A cross-sectional online survey
JMI Public Health Surveill / Article
• Aimed to identify the proportion of people who had downloaded the Australian Government COVIDSafe app and examine the reasons why some did not.
• 1500 participated in the survey. Of survey participants, 37% had downloaded the COVIDSafe app, 19% intended to, 28% refused, and 16% were undecided.
• Equally proportioned reasons for not downloading the app included privacy (25%) and technical concerns (24%). Other reasons included a belief that social distancing was sufficient and the app is unnecessary (16%), distrust in the Government (11%), and apathy (11%). In addition, COVIDSafe knowledge varied with confusion about its purpose and capabilities.
• For the COVIDSafe app to be accepted by the public and used correctly, public health messages need to address the concerns of its citizens, specifically in regards to privacy, data storage, and technical capabilities.

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| 05.10.2020       | Thromboprophylaxis with enoxaparin is associated with a lower death rate in patients hospitalized with SARS-CoV-2 infection. A cohort study | EClinicalMedicine / Article | • Assessed the impact of thromboprophylaxis with enoxaparin on hospital mortality in patients admitted for COVID-19. The effects of enoxaparin on intensive care admission and hospital length-of-stay were evaluated as secondary outcomes.
• This study shows that treatment with enoxaparin during hospital stay is associated with a lower death rate and, while results from randomized clinical trials are still pending, this study supports the use of thromboprophylaxis with enoxaparin in all patients admitted for COVID-19. |
### Modelling

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| 09.10.2020       | A single holiday was the turning point of the COVID-19 policy of Israel | Int J Infect Dis / Article | • An epidemiological investigation of the exponential rise in the accumulation of confirmed cases in Israel, and implementation of a mathematical model to describe the efficiency of the quarantine-isolation policy and the inflow of imported cases.  
• The abrupt change followed the Jewish holiday of Purim in which many public gatherings were held.  
• According to the first model scenario, the accumulation of confirmed cases before Purim was driven by imported cases resulting in controlled regime, with an effective reproduction number, R(e), of 0.69.  
• In the second model scenario which followed Purim, a continuous rise of the local to imported cases ratio began, which led to an exponential growth regime characterized by R(e) of 4.34.  
• It was found that the change of regime cannot be attributed to super-spreader events, as these consisted of approximately 5% of the primary cases which resulted in 17% of the secondary cases. |

### Overviews, comments and editorials

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<td>12.10.2020</td>
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<td>Taking pandemic sequelae seriously: from the Russian influenza to COVID-19 long-haulers</td>
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<td>Combining Rapid PCR and Antibody Tests Improved COVID-19 Diagnosis</td>
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<td>02.10.2020</td>
<td>Global contributions of pharmacists during the COVID-19 pandemic</td>
<td>J Am Coll Clin Pharm / Article</td>
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### Produced by the PHE COVID-19 Literature Digest Team

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