



COVID-19 Literature Digest – 09/09/2020

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

This week’s editorial was prepared by the Literature Digest Team - Dr. Bláthnaid Mahon is a Senior Scientist (a microbiologist by background), and Emma Farrow and James Robinson are both Knowledge and Evidence Specialists within PHE’s National Infection Service. They continue to support the COVID-19 response via their roles on the Literature Digest Team, within the Clinical Guidance Cell.

If you only read three or four papers this week...

It has long been recognised that the health of humans, animals and the environment are inextricably linked. The papers we would like to highlight this week focus on potential transmission routes, and in doing so emphasise the importance of using a ‘One Health’ perspective when gaining an understanding of the current epidemic.

The first paper is [a preprint by Oude Munnink et al](#), which is aptly titled “Jumping back and forth: anthrozoönotic and zoonotic transmission of SARS-CoV-2 on mink farms”. Here the authors outline “an in-depth investigation into the SARS-CoV-2 outbreak in mink farms and mink farm employees in the Netherlands, combining epidemiological information, surveillance data and WGS on the human-animal interface”. They describe the first animal to human transmissions of SARS-CoV-2 in mink farms. Screening of farm workers and/or their contacts found 68% to be infected with SARS-CoV-2, suggesting contact with SARS-CoV-2 infected mink is a risk factor for contracting COVID-19. To the best of the authors knowledge, these are the first animal to human SARS-CoV-2 transmission events documented.

While the first paper focused on the animal aspect of the One Health triad, the remaining papers focus on the environmental aspect – specifically the built environment. [A paper by de Man et al describes an outbreak of COVID-19 in a Dutch nursing home](#), where COVID-19 infections were almost simultaneously detected among residents (17 (81%)) and healthcare workers (17 (50%)) (HCWs) within a particular ward (in which HCWs wore surgical masks). In contrast, all 106 HCWs and 95 residents in the six other wards tested negative for SARS-CoV-2. The outbreak investigation led the team to examine the ventilation systems in the wards. A key difference between the ventilation systems in the outbreak ward (which recirculated unfiltered inside air) vs. the other six wards (which all circulated outside air) was identified. SARS-CoV-2 RNA was subsequently detected on the ventilation system filters in the outbreak ward. The authors state that the possibility of aerosol transmission in healthcare facilities and other buildings where ventilation systems recirculate unfiltered inside air should be considered in the prevention of COVID-19 infection.

Similarly, [a paper by Shen et al](#) highlights suspected transmission of SARS-CoV-2 via poor ventilation, this time in a public transport setting. The study involved 128 individuals who rode one of two buses to attend a worship event in Eastern China, a 100-minute round trip. In both buses, central air conditioners were on indoor recirculation mode. On bus 2, 24 of 68 individuals (35.3% [including the index patient]) were diagnosed with COVID-19 after the event. No-one on bus 1 (60 individuals) was infected. Within bus 2, individuals in high-risk zones (in closer proximity to the index patient) had moderately, but non-significant, higher risk for COVID-19, suggesting airborne spread may partially explain the markedly high attack rate among these bus riders.

In keeping with the built environment theme, [in the final paper](#) we would like to mention, the authors report an outbreak of nine confirmed COVID-19 cases in three vertically aligned flats in Guangzhou, China, during a period of social distancing. The first household had a history of travel to the COVID-19 epicentre, Wuhan, while the remaining two households had no travel history and a later onset of symptoms. The households were connected vertically by drainage pipes in the master bathrooms. Environmental samples were taken, and drainage airflow dispersion was measured using a tracer gas. Observed infections and the locations of positive environmental samples were both consistent with the spread of virus-laden aerosols via vertical drainage stacks and vents, while no evidence was found for transmission via the elevator or elsewhere. The authors outline a number of limitations of the study and state that “on basis of circumstantial evidence, faecal aerosol transmission may have caused the community outbreak of COVID-19 in this high-rise building”.

Collectively, these research findings highlight the importance of using a ‘One Health’ approach in order to gain a more comprehensive understanding of this novel virus and its potential transmission routes.

*The Literature Digest Team,
Bláthnaid, Emma and James.*

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- Serology and immunology
- Genomics
- Epidemiology and clinical - children and pregnancy
- Epidemiology and clinical - risk factors
- Epidemiology and clinical - other
- Treatment
- Guidance, consensus statements and hospital resources (no digest)
- 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
08.09.2020	Ultra-sensitive Serial Profiling of SARS-CoV-2 Antigens and Antibodies in Plasma to Understand Disease Progression in COVID-19 Patients with Severe Disease	Clin Chem / Article	<ul style="list-style-type: none"> • The authors report on SARS-CoV-2 Simoa antigen assay's detection of viral antigens in the plasma of COVID-19 positive patients. • These data show that SARS-CoV-2 viral antigens in the blood are associated with disease progression, such as respiratory failure, in COVID-19 cases with severe disease.
08.09.2020	In vivo antiviral host transcriptional response to SARS-CoV-2 by viral load, sex, and age	PLoS Biol / Article	<ul style="list-style-type: none"> • Examined host response gene expression across infection status, viral load, age, and sex among shotgun RNA sequencing profiles of nasopharyngeal (NP) swabs from 430 individuals with PCR-confirmed SARS-CoV-2 and 54 negative controls. • Concluded that collectively, their data demonstrate that host responses to SARS-CoV-2 are dependent on viral load and infection time course, with observed differences due to age and sex that may contribute to disease severity.
04.09.2020	In severe COVID-19, SARS-CoV-2 induces a chronic, TGF-β-dominated adaptive immune response	medRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> • The authors analysed the dynamics of the adaptive immune response triggered by SARS-CoV-2 in severely affected COVID-19 patients, as reflected by activated B cells egressing into the blood, at the single cell level. • In the sustained immune reaction of the COVID-19 patients, until day 59, activated peripheral B cells shifted to expression of IgA2, reflecting instruction by TGF-β. Despite the continued generation of activated B cells, those cells were not found in the lungs of deceased COVID-19 patients, nor did the IgA2 bind to dominant antigens of SARS-CoV-2.
06.09.2020	Kynurenic acid underlies sex-specific immune responses to COVID-19	medRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> • In males with COVID-19, kynurenic acid (KA) and a high KA to kynurenine (K) ratio was positively correlated with age, inflammatory cytokines, and chemokines and was negatively correlated with T cell responses, revealing that KA production is linked to immune responses in males. • Males that clinically deteriorated had a higher KA:K ratio than those that stabilized. • In females with COVID-19, this ratio positively correlated with T cell responses and did not correlate with age or clinical severity. • This study reveals that KA has a sex-specific link to immune responses and clinical outcomes, in COVID-19 infection.

08.09.2020	A prefusion SARS-CoV-2 spike RNA vaccine is highly immunogenic and prevents lung infection in non-human primates	bioRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> The authors report the design, preclinical development, immunogenicity and anti-viral protective effect in rhesus macaques of the BNT162b2 vaccine candidate. BNT162b2 is currently being evaluated in a global, pivotal Phase 2/3 trial (NCT04368728).
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Genomics

Publication Date	Title / URL	Journal / Article type	Digest
02.09.2020	Genomic characterization of SARS-CoV-2 identified in a reemerging COVID-19 outbreak in Beijing's Xinfadi market in 2020	Biosaf Health / Article	<ul style="list-style-type: none"> After 56 days of no cases, reemergent COVID-19 cases were reported in Beijing on June 11, 2020. According to the full-length genome of SARS-CoV-2, all the six Xinfadi sequences (from the clinical specimens of 4 human cases and 2 environmental samples) belong to the L lineage European branch 1. A unique shared nucleotide substitution, nt6026(C → T), is the characteristic nucleotide substitution of SARS-CoV-2 in Beijing Xinfadi outbreak. An amino acid D614G mutation caused by nt23403 substitution was found in all Xinfadi strains.
08.09.2020	Analysis of SARS-CoV-2 genomes from across Africa reveals potentially clinically relevant mutations	bioRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> In silico analyses and comparisons were conducted to identify if there are distinguishing mutations in the African SARS-CoV-2 genomes compared to genomes from other countries, including disease hotspots. Results showed a similarity between the African SARS-CoV-2 genomes and those in countries including China, Brazil, France, the UK, Italy, France and the USA.

Epidemiology and clinical – children and pregnancy

Publication Date	Title / URL	Journal / Article type	Digest
04.09.2020	Multisystem inflammatory syndrome in children: A systematic review	EclinicalMedicine / Systematic review	<ul style="list-style-type: none"> This systematic review summarizes the clinical presentation of MIS-C from 662 patients (n = 39 studies). They report the most common signs and symptoms, quantify laboratory findings, and describe imaging characteristics of children with MIS-C. They summate outcomes, treatments, and compare MIS-C to COVID-19.

08.09.2020	Comparison of Clinical Features of COVID-19 vs Seasonal Influenza A and B in US Children	JAMA Netw Open / Original investigation	<ul style="list-style-type: none"> • In this cohort study of 315 children with COVID-19 and 1402 children with seasonal influenza, there were no statistically significant differences in the rates of hospitalization, admission to the intensive care unit, and mechanical ventilator use between the 2 groups. • More patients with COVID-19 than with seasonal influenza reported fever, diarrhoea or vomiting, headache, body ache, or chest pain at the time of diagnosis.
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Epidemiology and clinical - risk factors

Publication Date	Title / URL	Journal / Article type	Digest
07.09.2020	Prevalence of suspected COVID-19 infection in patients from ethnic minority populations: a cross-sectional study in primary care	Br J Gen Pract / Article	<ul style="list-style-type: none"> • The authors quantified the prevalence and time course of clinically suspected COVID-19 presenting to general practices, to report the risk of suspected COVID-19 by ethnic group, and to identify whether differences by ethnicity can be explained by clinical data in the GP record. • GPs recorded 8985 suspected COVID-19 cases between 10 Feb and 30 Apr 2020. • Using data from GP records, black and South Asian ethnicity remain as predictors of suspected COVID-19, with levels of risk similar to hospital admission reports. Further understanding of these differences requires social and occupational data.
05.09.2020	Ethnicity and clinical outcomes in COVID-19 A Systematic Review and Meta-analysis	medRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> • A systematic review and meta-analysis (13,535,562 patients from 35 studies) examined whether the risk of SARS-CoV-2 infection, COVID-19 ICU admission and mortality are associated with ethnicity. • Black, Asian and Hispanic individuals had a greater risk of infection compared to White individuals. • Black individuals were significantly more likely to be admitted to ICU than White individuals (pooled adjusted RR: 1.61, 95% CI: 1.02-2.55). • Risk of mortality was similar across ethnicities among hospitalised patients, but increased among Asian and Mixed ethnic groups in the general population.
08.09.2020	Adverse outcomes and mortality in users of non-steroidal anti-inflammatory drugs who tested positive for SARS-CoV-2: A Danish nationwide cohort study	PLoS Med / Article	<ul style="list-style-type: none"> • The authors identified all Danish residents who tested positive for the infectious agent of COVID-19 (n=9,236) and grouped them into users and non-users of NSAIDs. • The risks of being hospitalized, admitted to the ICU, or dying were compared between the 2 groups.

		<ul style="list-style-type: none"> • Overall, risks for all studied outcomes were similar between users and non-users of ibuprofen and other NSAIDs. • NSAIDs do not lead to more severe coronavirus disease according to this study.
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Epidemiology and clinical – other

Publication Date	Title / URL	Journal / Article type	Digest
03.09.2020	COVID-19 Report: 03 September 2020	ISARIC / Report	<ul style="list-style-type: none"> • The results in this report were produced using data from the ISARIC COVID-19 database. • Up to the date of this report, data have been entered for 96074 individuals from 562 sites across 42 countries, of which 81705 met inclusion criteria. • The report outlines demographics and presenting features, outcomes and treatment.
04.09.2020	The timing of COVID-19 transmission	medRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> • The authors examined the distribution of transmission events with respect to exposure and onset of symptoms. • Overall, the fraction of transmission from strictly pre-symptomatic infections was high (41%; 95%CI 31-50%), which limits the efficacy of symptom-based interventions, and the large fraction of transmissions (35%; 95%CI 26-45%) that occur on the same day or the day after onset of symptoms underlines the critical importance of individuals distancing themselves from others as soon as they notice any symptoms, even if they are mild. • Rapid or at-home testing and contextual risk information could greatly facilitate efficient early isolation.

Treatment

Publication Date	Title / URL	Journal / Article type	Digest
29.08.2020	Effect of Calcifediol Treatment and best Available Therapy versus best Available Therapy on Intensive Care Unit Admission and Mortality Among Patients Hospitalized	J Steroid Biochem Mol Biol / Article	<ul style="list-style-type: none"> • Evaluated the effect of calcifediol treatment, on ICU admission and mortality rate among Spanish patients hospitalized for COVID-19 in a parallel pilot randomized open label, double-masked clinical trial. • Of 50 patients treated with calcifediol, one required admission to the ICU

	for COVID-19: A Pilot Randomized Clinical study		(2%), while of 26 untreated patients, 13 required admission (50%) p value X2 Fischer test $p < 0.001$. <ul style="list-style-type: none"> • Administration of calcifediol or 25-hydroxyvitamin D to hospitalized COVID-19 patients significantly reduced their need for ICU admission. • Calcifediol seems to reduce severity of the disease.
04.09.2020	The link between vitamin D deficiency and Covid-19 in a large population	medRxiv (non-peer reviewed) / Article	<ul style="list-style-type: none"> • In a population study, 52,405 infected patients were matched with a cohort of 524,050 control individuals to assess the relationship between baseline vitamin D levels, acquisition of vitamin D supplements in the last 4 months, and positive Covid-19. • A highly significant correlation between prevalence of vitamin D deficiency and Covid-19 incidence, and between female-to-male ratio for severe vitamin D deficiency and female-to-male ratio for Covid-19 incidence in localities ($P < 0.001$) was observed. • In the matched cohort, a significant association between low vitamin D levels and the risk of Covid-19 was found, with the highest risk observed for severe vitamin D deficiency. • A significant protective effect was observed for members who acquired liquid vitamin D formulations (drops) in the last 4 months.

Guidance and consensus statements

Publication Date	Title / URL	Journal / Article type
07.09.2020	SARS-CoV-2 RNA testing: assurance of positive results during periods of low prevalence	Gov.uk / Research and analysis

Overviews, comments and editorials

Publication Date	Title / URL	Journal / Article type
07.09.2020	T cells in COVID-19 - united in diversity	Nat Immunol / News and views
08.09.2020	Detection of SARS-CoV-2 RNA in Blood of Patients with COVID-19: What Does It Mean?	Clin Infect Dis / Article
07.08.2020	We need better evidence on non-drug interventions for covid-19	Bmj / Views and reviews

08.09.2020	“When Will We Have a Vaccine?” — Understanding Questions and Answers about Covid-19 Vaccination	N Engl J Med / Perspective
08.09.2020	Preparing for a pandemic: highlighting themes for research funding and practice-perspectives from the Global Research Collaboration for Infectious Disease Preparedness (GloPID-R)	BMC Med / Commentary

Produced by the PHE COVID-19 Literature Digest Team

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

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