COVID-19 Literature Digest – 08/01/2021

Dear all,

Firstly, we would like to say a huge thank you to our 24 amazing guest editors of 2020, both for their time and useful insights. This week’s guest editorial was prepared by five of our earliest guest editors, who have each selected one paper to highlight from the immense collection of COVID-19 literature produced in 2020.

Some highlights of 2020...

Dr. Jake Dunning

Just as I was honoured to be the first guest editor to share some ‘top picks’ earlier this year, I am equally honoured to have been asked to share what I think is one of the most important COVID-19 papers of 2020. That is not an easy task, as there have been so many papers across many different disciplines. Sometimes it can feel like there is little to celebrate from 2020; for most of us, the coronavirus outbreak will have been the worst pandemic we’ve experienced to date, and it’s not over yet. I have learned, however, that even during major outbreaks it is okay - and indeed healthy - to celebrate excellent science, particularly research that improves our understanding of a disease and helps bring a crisis to an end. The reporting of important discoveries now extends beyond papers published in scientific journals. We have seen pre-print publishing really take off in the last twelve months and, while non-peer reviewed papers need to be treated with caution, the benefits of rapid information-sharing are undeniable. We’ve also seen great science from PHE, other government departments and expert groups appear as papers for SAGE and NERVTAG, many of which have since been made available on gov.uk.

Given the wealth of papers, which one have I chosen then? I think many may expect me to pick the obvious, headline-grabbing papers, such as those about vaccine efficacy, which experimental treatments work and which don’t work, how the virus spreads, or the types of illness that are caused by the virus. PHE departments, and also researchers based at or linked to PHE, have contributed to many of these important papers, which is fantastic; however, I have chosen a less well known clinical virology paper, and one that I am proud to say has come from the National Infection Service.

In August 2020, Eurosurveillance published a paper from Anika Singanayam and colleagues working in PHE Reference Virology, Data and Analytical Sciences, and Immunisations and Countermeasures. They set out to provide answers to quite obvious but important questions: how long can you detect SARS-CoV-2 RNA by RT-PCR following onset of infection, and for how long do people typically remain infectious? RT-PCR is the highly sensitive method used for detecting SARS-COV-2 virus and is now the standard diagnostic test for COVID-19 used across the world. The team found that SARS-CoV-2 PCR cycle threshold (Ct) values correlate strongly with cultivable...
(infectious) virus and likelihood of infectiousness. The level of SARS-CoV-2 RNA in nose and throat swabs was greatest around symptom onset, steadily decreased during the first 10 days after illness onset, and then plateaued. After 10 days, the probability of culturing virus declines to a very low level, just 6%.

Others have done work addressing these questions, but this study included samples from many people, including a large number of samples collected 7 days after symptom onset. Such data are really important in ensuring that our initial, reasonable assumptions and recommendations are correct. Indeed, the PHE study and others informed and helped justify revisions of public health policies, such as increasing the isolation period for infected people from 7 days to 10 days. They also help inform appropriate use of PCR and point of care tests in the new “test to release” initiatives. But I like this paper most because it demonstrates the unique position of PHE departments: delivering essential laboratory services as part of the public health response, right from the start of the pandemic, but also making use of the valuable data we generate in the process, some of which relies on highly specialised skills like virus isolation. Such information is important to the UK, but also to the pandemic response efforts around the world. It’s just one of many examples of PHE delivering essential public health services while producing meaningful and important research outputs at the same time. Long may that continue, whether we are PHE or The National Institute for Health Protection.

Cat O Connor

My selection for the 2020 highlights reel takes us back to 24 January 2020 and the first peer reviewed case series of COVID-19 cases, although at that stage it was still referred to as 2019-nCOV. Huang and colleagues describe clinical features of the first 41 hospitalised cases of COVID-19 in Wuhan, revealing the potential severity of infection. On the same day another publication from China (Chan et al) described the first familial cluster with clear evidence of human-to-human transmission and asymptomatic infection. Together these papers demonstrated the complexity of this emerging virus. For reference, by 24 January a total of 849 cases and 25 fatalities had been reported from 10 countries or territories globally.

Our understanding of SARS-CoV-2 infection and transmission dynamics has come a long way since then, but these papers were pivotal in shaping our initial response to the pandemic in terms of clinical and public health guidance.

Professor Bernie Hannigan

The paper I have chosen is a review, by Gracia-Hernandez et al., titled ‘Targeting Macrophages as a Therapeutic Option in Coronavirus Disease 2019’. I love macrophages and for quite a chunk of my career I observed how they are affected by biological or chemical agents. Macrophages are tissue cells, many arising from white blood cells – monocytes. Macrophages orchestrate immune responses to reduce the burden of pathogens both directly, e.g. phagocytosis, and indirectly by releasing molecules called cytokines that initiate beneficial immune / inflammatory responses and then repair tissues to restore normal function. Over-production of cytokines (cytokine storm) damages cells and tissues. Coronaviruses infect and dysregulate macrophages. Non-survivors of COVID-19 show increased migration of monocytes into lungs to become macrophages and cytokine storm effects are evident, e.g. excessive inflammation, intravascular coagulation (that leads to organ failure when small blood vessels are blocked), and pulmonary fibrosis. The many functions of macrophages provide targets for pharmacological intervention and laboratory and clinical studies include attempts to block pro-inflammatory cytokine production, inhibit responses to cytokines or prevent intravascular coagulation using anticoagulant combinations.

Iona Smith
The COVID-19 pandemic has been an unforeseen global challenge for governments, healthcare systems and individuals. It has, however, also provided an opportunity to evaluate different countries’ approaches to public health and how their health systems have impacted their response. The paper I have selected for my 2020 highlight by Lal et al., investigates different health systems and their response to COVID-19. What I found fascinating about this paper, was its analysis of countries COVID-19 response while keeping two global health policy approaches in mind – global health security and universal health coverage. As a staunch supporter of both universal health coverage and global health security the paper raises important criticisms, comments and suggestions about how to reimagine global healthcare infrastructure to build a more sustainable future. Whilst no-one would have chosen for this to be how 2020 went, I think it is imperative to ensure that the scientific and global community takes stock of the many lessons learnt and looks at how we can improve for the future.

Dr. Ebere Okereke

There have been so many interesting publications about the epidemiology, virology, clinical manifestations, treatment options, control measures and vaccines for COVID-19 throughout 2020. I have decided to go slightly off message and have selected the new chapter of The Green Book on COVID-19 SARS-CoV-2 vaccination. I have selected this for two reasons: it is a practical summary of the current knowledge of the disease, the available vaccines and the UK vaccination strategy, and because it demonstrates the phenomenal work of developing complex vaccination policy and health professional guidance while evidence is still being generated, and regulatory approvals obtained. It is a classic example of what a colleague Dr Chikwe Ihekweazu of Nigeria Centre for Disease Control, describes as ‘building the ship while sailing it’.

Although this specialist guidance is aimed at health professionals, it is written in clear accessible language and could be easily understood by an informed lay person seeking understanding of the UK vaccination plans. The authors are to be commended for this phenomenal work.

1 Head of Emerging Infections and Zoonoses at PHE, infectious diseases consultant at the Royal Free Hospital and one of the PHE national Incident Directors for the COVID-19 response.
2 Principal Scientist for Emerging Infections in the National Infection Service, PHE. Cat led the COVID-19 International Epidemiology team since day 1 of PHE’s COVID-19 response but has since returned to business as usual to monitor for emerging threats.
3 Leads PHE’s Research, Translation & Innovation division and has been supporting the COVID-19 response via the Public Health Advice, Guidance and Expertise (PHAGE) function.
4 Epidemiologist within the Emerging Infections and Zoonoses team at PHE. Iona has been extensively involved in the work of the International Epidemiology Cell in the COVID-19 response.
5 Consultant in Global Public Health and Communicable Disease Control. Ebere leads PHE’s UK-Aid funded IHR Strengthening Project, building capacity for global health security in six countries in Africa and Asia.

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, contain new data, insights or emerging trends. The Digest Team generate a report three times per week (Mon, Wed, Fri). The reports include both preprints, which should be treated with caution as they are NOT peer-reviewed and may be subject to change, and also 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

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Report for 08.01.2021 (please note that papers that have NOT been peer-reviewed are highlighted in red).

Sections:
Serology and immunology
Vaccines
Diagnostics and 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
Transmission
Treatment
Overviews, comments and editorials (no digest)

Serology and immunology

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<th>Publication Date</th>
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<th>Journal / Article type</th>
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| 06.01.2021      | Fever, Diarrhea, and Severe Disease Correlate with High Persistent Antibody Levels against SARS-CoV-2 | medRxiv (non-peer reviewed) / Article | • Evaluated anti-SARS-CoV-2 antibodies in a clinically diverse COVID-19 convalescent cohort (n=120) at defined time points to determine persistence of antibodies, and to identify clinical and demographic factors that correlate with high titres.  
• Demonstrates for the first time that COVID-19 symptoms, namely fever, abdominal pain, diarrhoea and low appetite, correlated consistently with higher anti-SARS-CoV-2 antibody levels. |
### Vaccines

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<tr>
<td>06.01.2021</td>
<td>Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine — United States, December 14–23, 2020</td>
<td>MMWR / Report</td>
<td>During Dec 14–23, 2020, monitoring by the Vaccine Adverse Event Reporting System in the US detected 21 cases of anaphylaxis after administration of a reported 1,893,360 first doses of the Pfizer-BioNTech COVID-19 vaccine (11.1 cases per million doses); 71% of these occurred within 15 minutes of vaccination.</td>
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### Diagnostics and genomics

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| 07.01.2021       | Impact of mass testing during an epidemic rebound of SARS-CoV-2: a modelling study using the example of France | Eurosurveillance / Rapid communication | Authors used a mathematical model to evaluate the impact of mass testing in the control of SARS-CoV-2.  
• Under optimistic assumptions, one round of mass testing may reduce daily infections by up to 20–30%. Consequently, very frequent testing would be required to control a quickly growing epidemic if other control measures were to be relaxed.  
• Mass testing is most relevant when epidemic growth remains limited through a combination of interventions. |
| 06.01.2021       | Saliva viral load is a dynamic unifying correlate of COVID-19 severity and mortality | medRxiv (non-peer reviewed) / Article | In a study of saliva and nasopharyngeal (NP) viral load, saliva viral load was significantly higher in those with COVID-19 risk factors, correlated with increasing levels of disease severity, and showed a superior ability over NP viral load as a predictor of mortality over time (AUC=0.90).  
• Patients with fatal COVID-19 exhibited higher viral loads, which correlated with depletion of cTfh cells, and lower production of anti-RBD and anti-S IgG levels. |
| 06.01.2021       | Impaired performance of SARS-CoV-2 antigen-detecting rapid tests at elevated temperatures | medRxiv (non-peer reviewed) / Article | Assesses analytical sensitivity and specificity of 11 commercially available SARS-CoV-2 rapid antigen-detecting tests (Ag-RDTs) using different storage and operational temperatures.  
• In summary, short- and long-term exposure to elevated temperatures likely impairs sensitivity of several SARS-CoV-2 Ag-RDTs that may translate to false-negative test results at clinically relevant virus concentrations compatible with inter-individual transmission. |
| 06.01.2021       | SARS-CoV-2 spike downregulates tetherin to enhance viral spread | bioRxiv (non-peer reviewed) / Article | Study demonstrates that SARS-CoV-2 downregulates an interferon-induced protein, tetherin, to aid its release from cells, and investigates potential proteins involved in this process. |
• Loss of tetherin from cells caused an increase in SARS-CoV-2 viral titre.
• Findings suggest SARS-CoV-2 spike protein is responsible for tetherin downregulation, rather than ORF7a as previously described for the 2002-2003 SARS-CoV.
• Found that ORF7a is responsible for Golgi fragmentation, and expression of ORF7a in cells recapitulates Golgi fragmentation observed in SARS-CoV-2 infected cells.

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<tr>
<th>Epidemiology and clinical – children / pregnancy</th>
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| **06.01.2021** | [Open Schools, Covid-19, and Child and Teacher Morbidity in Sweden](#) | N Engl J Med / Correspondence | • Swedish preschools and schools kept open; authors present data on Covid-19 among children 1 to 16 years of age and their teachers.  
• March through June 2020, 15 children with Covid-19 (including those with MIS-C) were admitted to an ICU (0.77 per 100,000 children in this age group).  
• Fewer than 10 preschool teachers and 20 schoolteachers received intensive care for Covid-19 up until June 30, 2020 (20 per 103,596 schoolteachers, which is equal to 19 per 100,000).  
• Among 1.95 million children 1 to 16 years of age, 15 children had Covid-19, MIS-C, or both conditions and were admitted to an ICU, which is equal to 1 child in 130,000. |
| **03.01.2021** | [Longitudinal testing for respiratory and gastrointestinal shedding of SARS-CoV-2 in day care centres in Hesse, Germany](#) | Clin Infect Dis / Accepted manuscript | • Longitudinal study (18 June 2020 to 10 Sep 2020) screened 859 children (age range 3 months to 8 years) and 376 staff members from 50 day care centres in the state of Hesse, Germany, for both respiratory and gastrointestinal shedding of SARS-CoV-2.  
• 7,366 buccal mucosa swabs and 5,907 anal swabs were analysed.  
• No respiratory or gastrointestinal shedding of SARS-CoV-2 was detected in any of the children.  
• Shedding of SARS-CoV-2 could be detected in two staff members from distinct day care centres.  
• One was asymptomatic at the time of testing, and one was symptomatic and did not attend the facility on that day. |
### Epidemiology and clinical – risk factors

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| 02.01.2021       | Re-emergence of coronavirus disease in Chinese cities associated with chilled and frozen food products | J Infect / Letter to the editor     | • Authors concluded that recent localized epidemics in China demonstrate that chilled and frozen food products can cause SARS-CoV-2 infections.  
• On November 8, 2020, the Chinese government introduced a comprehensive preventive disinfection work plan for imported chilled and frozen food to help prevent further COVID-19 outbreaks caused by imported chilled and frozen products.  
• State that to prevent similar epidemics during the winter ahead, other countries should strengthen the monitoring and management of the processing and sale of chilled food products.                                                                                                                                 |
• 62% of cohort of non-white ethnic background; prevalence of diabetes 38%.  
323 (36%) patients met primary outcome of death/admission to the ICU within 30 days of COVID-19 diagnosis.  
• Male gender, lower platelet count, advancing age and higher Clinical Frailty Scale (CFS) score (but not diabetes) independently predicted poor outcomes. Antiplatelet medication associated with lower risk of death/ICU admission.  
• Comorbidity (i.e., diabetes with ischemic heart disease; increasing CFS score in older patients) was a major determinant of poor outcomes with COVID-19. Antiplatelet medication should be evaluated in randomized clinical trials among high-risk patient groups.                                                                                                                                 |

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

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| 05.01.2021       | Prevalence and 6-month recovery of olfactory dysfunction: a multicentre study of 1363 COVID-19 patients | J Intern Med / Brief report         | • Study of prevalence and recovery of olfactory dysfunction (OD) in COVID-19 patients (n=2581) from 18 European hospitals.  
• Concluded that OD is more prevalent in mild COVID-19 forms than in moderate-to-critical forms. OD disappeared in 95% of patients regarding objective olfactory evaluations at 6 months.                                                                                                                                                                                |
### Epidemiology and clinical - other

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| 07.01.2021       | Control of a COVID-19 outbreak in a nursing home by general screening and cohort isolation in Germany, March to May 2020 | Eurosurveillance / Outbreaks | • Describe an outbreak of COVID-19 in a nursing home in Germany from 8 Mar to 4 May 2020 (58 days), and the effect of an intervention of general screening and cohort isolation.  
  - Eighty of 160 residents (50%) and 37 of 135 staff members (27%) tested positive for SARS-CoV-2. Twenty-seven of the 80 residents were asymptomatic but tested positive during the first general screening.  
  - Cohort isolation of SARS-CoV-2 positive residents by reorganising the facility proved to be a major effort. After the intervention, four further asymptomatic residents tested positive in follow-up screenings within a period of 6 days, and were possibly infected prior to the intervention. Thereafter, no further infections were recorded among residents.  
  - The described outbreak was controlled by implementing general screening and rigorous cohort isolation, providing a blueprint for similar facilities. |

| 05.01.2021       | Estimation of US SARS-CoV-2 Infections, Symptomatic Infections, Hospitalizations, and Deaths Using Seroprevalence Surveys | JAMA Netw Open / Original investigation | • Cross-sectional study of U.S respondents of all ages, data from 4 regional and 1 nationwide CDC seroprevalence surveys (April [n = 16 596], May, June, and July [n = 40 817], and August [n = 38 355]) were used to estimate infection underreporting multipliers and symptomatic underreporting multipliers.  
  - An estimated 14.3% (IQR, 11.6%-18.5%) of the US population were infected by SARS-CoV-2 as of mid-November 2020.  
  - The SARS-CoV-2 disease burden may be much larger than reported COVID-19 cases owing to underreporting. Even after adjusting for underreporting, a substantial gap remains between the estimated proportion of the population infected and the proportion infected required to reach herd immunity. |

### Infection control / non-pharmaceutical interventions

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| 17.12.2020       | Measures implemented in the school setting to contain the COVID-19 pandemic: a rapid scoping review | Cochrane Database of Systematic Reviews / Rapid review | • Rapid review of evidence on the impacts of measures implemented in the school setting to reopen schools, or keep schools open, or both, during the COVID-19 pandemic (42 studies).  
  - The majority of studies used mathematical modelling designs (n = 31).  
  - Three broad intervention categories emerged from the included studies: organisational measures to reduce transmission (n = 36), |
structural/environmental measures to reduce transmission (n = 11), and surveillance and response measures to detect infections (n = 19).

- Most studies assessed transmission-related outcomes (n = 29), while others assessed healthcare utilization (n = 8), other health outcomes (n = 3), and societal, economic, and ecological outcomes (n = 5).
- Studies assessed both harmful and beneficial outcomes across all outcome categories.

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<td>07.01.2021</td>
<td>Early transmissibility assessment of the N501Y mutant strains of SARS-CoV-2 in the United Kingdom, October to November 2020</td>
<td>Eurosurveillance / Rapid communication</td>
<td>• Two new SARS-CoV-2 lineages with the N501Y mutation in the receptor-binding domain of the spike protein spread rapidly in the United Kingdom. • Authors estimated that the earlier 501Y lineage without amino acid deletion Δ69/Δ70, circulating mainly between early Sept and mid-Nov, was 10% (6–13%) more transmissible than the 501N lineage, and the 501Y lineage with amino acid deletion Δ69/Δ70, circulating since late Sept, was 75% (70–80%) more transmissible than the 501N lineage.</td>
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<td>08.01.2021</td>
<td>Opening of Large Institutions of Higher Education and County-Level COVID-19 Incidence - United States, July 6-September 17, 2020</td>
<td>MMWR Morb Mortal Wkly Rep / Article</td>
<td>• U.S. counties with large colleges or universities with remote instruction (n = 22) experienced a 17.9% decrease in incidence. University counties with in-person instruction (n = 79) experienced a 56% increase in incidence, comparing the 21-day periods before and after classes started. • Counties without large colleges or universities (n = 3,009) experienced a 6% decrease in incidence during similar time frames. • In-person instruction at colleges and universities was associated with increased county-level COVID-19 incidence and percentage test positivity. Implementation of increased mitigation efforts at colleges and universities could minimize on-campus COVID-19 transmission.</td>
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| 07.01.2021 | Minimal transmission of SARS-CoV-2 from paediatric COVID-19 cases in primary schools, Norway, August to November 2020 | Eurosurveillance / Rapid communication | • An intense debate on school closures to control the COVID-19 pandemic is ongoing in Europe. • Authors prospectively examined transmission of SARS-CoV-2 from confirmed paediatric cases in Norwegian primary schools between Aug and Nov 2020. • All in-school contacts were systematically tested twice during their quarantine period. With preventive measures implemented in schools, they found minimal child-to-child (0.9%, 2/234) and child-to-adult (1.7%, 1/58)
transmission, supporting that under 14 year olds are not the drivers of SARS-CoV-2 transmission.

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| 07.01.2021       | SARS-CoV-2 Transmission From People Without COVID-19 Symptoms | JAMA Netw Open / Original investigation | - In this decision analytical model assessing multiple scenarios for the infectious period and the proportion of transmission from individuals who never have COVID-19 symptoms, transmission from asymptomatic individuals was estimated to account for more than half of all transmission.  
- The findings of this study suggest that the identification and isolation of persons with symptomatic COVID-19 alone will not control the ongoing spread of SARS-CoV-2.  
- Additional measures to reduce risk of transmission from people with infection who do not have symptoms - such as wearing masks, hand hygiene, social distancing, and strategic testing of people who are not ill - will be foundational to slowing the spread of COVID-19 until safe and effective vaccines are available and widely used. |

**Treatment**

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| 07.01.2021       | Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 - Preliminary report | medRxiv (non-peer reviewed) / Article | - Tocilizumab and sarilumab both met the pre-defined triggers for efficacy in this preliminary report of an ongoing international trial.  
- At the time of full analysis 353 critically ill patients had been assigned to tocilizumab (8mg/kg), 48 to sarilumab (400mg) and 402 to control (standard care).  
- Median organ support-free days were 10, 11 and 0 for tocilizumab, sarilumab and control, respectively.  
- Hospital mortality was 28.0% (98/350) for tocilizumab, 22.2% (10/45) for sarilumab and 35.8% (142/397) for control.  
- In critically ill patients with Covid-19 receiving organ support in intensive care, treatment with the IL-6 receptor antagonists, tocilizumab and sarilumab, improved outcome, including survival. |
| 06.01.2021       | Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults | N Engl J Med / Article | - Authors conducted a randomized, double-blind, placebo-controlled trial of convalescent plasma with high IgG titres against SARS-CoV-2 in 160 older adult patients within 72 hours after onset of mild Covid-19 symptoms.  
- Severe respiratory disease developed in 13 of 80 patients (16%) who received convalescent plasma and 25 of 80 patients (31%) who received placebo (relative risk, 0.52; 95% confidence interval [CI], 0.29 to 0.94; P=0.03), with a relative risk reduction of 48%. |
• Exclusion of 6 patients who had a primary end-point event before infusion of convalescent plasma or placebo showed a larger effect size (relative risk, 0.40; 95% CI, 0.20 to 0.81).
• Early administration of high-titre convalescent plasma against SARS-CoV-2 to mildly ill infected older adults reduced the progression of Covid-19.

Overviews, comments and editorials

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<th>Publication Date</th>
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<tbody>
<tr>
<td>05.01.2021</td>
<td>Should children be vaccinated against COVID-19 now?</td>
<td>Arch Dis Child / Viewpoint</td>
</tr>
<tr>
<td>06.01.2021</td>
<td>Covid-19 vaccination: What’s the evidence for extending the dosing interval?</td>
<td>Bmj / News analysis</td>
</tr>
<tr>
<td>06.01.2021</td>
<td>Genetic Variants of SARS-CoV-2-What Do They Mean?</td>
<td>JAMA / Viewpoint</td>
</tr>
<tr>
<td>23.12.2020</td>
<td>The Importance and Challenges of Identifying SARS-CoV-2 Reinfections</td>
<td>J Clin Microbiol / Minireview</td>
</tr>
</tbody>
</table>

Produced by the PHE COVID-19 Literature Digest Team

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