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COVID19 KIDS EVIDENCE UPDATE

WHAT THE MELBOURNE
CHILDREN'S CLINICIANS,
SCIENTISTS, EPIDEMIOLOGISTS,
AND MEDICAL STUDENTS HAVE
BEEN READING THIS WEEK

Weekly Update No. 1

15 April 2020

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ADULT MEDICINE

Jun Hua Bowen Lim - 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

Meta-analysis of 4,243 COVID-19 patients from six countries and data collected from a COVID-19 cohort in Hong Kong

<https://doi.org/10.1053/j.gastro.2020.03.065>

- > Meta-analysis of >60 studies revealed the pooled prevalence of gastrointestinal symptoms to be 17.6%
- > Anorexia is the most common (26.8%) followed by diarrhoea (12.5%), nausea/vomiting (10.2%) then abdominal pain/discomfort (9.2%)
- > Severe disease is more common in patients with gastrointestinal symptoms than those without (17.1% vs 11.8%)
- > Pooled prevalence of stool samples positive for virus RNA was 48.1%; 70.3% of stool samples collected after loss of virus from the respiratory specimens tested positive (one patient had viral RNA in stool >33 days from illness onset)
- > Limitations: gastrointestinal symptoms may be underreported, large sample size studies of non-Chinese ethnic groups are lacking
- > In this cohort study (n=59), stool viral RNA was detected in 38.5% with diarrhoea and 8.7% without diarrhoea with higher fecal viral load in those with diarrhoea

Reviewed by: Professor Julie Bines

CLINICAL MEDICINE

Evelyn Andrews - 4th Year Medical Student,
Department of Paediatrics, The University of Melbourne.

Clinical Examination versus Lung Ultrasound in the setting of COVID-19 (Correspondence)

<https://www.sciencedirect.com/science/article/pii/S221326002030120X>

- > Standard evaluation of respiratory conditions involves examination with a stethoscope and investigation by imaging. Stethoscopes are difficult to cover and may accidentally become contaminated during use. Imaging (e.g. with CT or x-ray) usually requires movement between units and contact with several hospital personnel.
- > By contrast, lung ultrasound allows concomitant clinical examination and lung imaging at the bedside by a single doctor. It can accurately detect various lung pathologies, including pneumonia and ARDS. Previous studies have proved its non-inferiority to chest x-ray and clinical examination for detection of such pathologies.
- > Use of lung ultrasound alone, instead of stethoscopes + x-ray/CT, is strongly recommended in order to reduce nosocomial spread of COVID-19.
- > How to undertake the procedure is described

Reviewed by: Dr Shidan Tosif

CRITICAL CARE

Rachel Leong - 4th Year Medical Student,
Department of Paediatrics, The University of Melbourne

What are the baseline characteristics and outcomes of patients with confirmed COVID-19 admitted to ICU in Lombardy, Italy?

https://jamanetwork.com/journals/jama/articlepdf/2764365/jama_grasselli_2020_oi_200037.pdf

Retrospective analysis of 1591 ICU patients admitted between 20th February - 18th March 2020 with follow-up on 25th March 2020 in Lombardy, Italy.

- > Of the 1591 patients admitted to ICU during this time period, only 4 under 20 years of age (less than 1% of the sample), this is consistent with data from China and the US, which indicates COVID-19 is a much milder disease in children (children comprise only 1.7% of total cases in US, and 0.59-2% of paediatric cases need PICU, for example: CDC data MMW 6th April 2020; and in China only 5% of 2143 infected children needed hospitalisation for oxygen and only 0.6% required ICU: Dong Y, CDC data Pediatrics 2020).
- > 3 of the 4 paediatric / adolescent patients in this Italian series had comorbidities, again consistent with larger paediatric data-sets which indicate an over-representation of children with chronic health problems in PICUs around the world (cerebral palsy, diabetes, obesity, cardiac and metabolic conditions).
- > Hypertension and diabetes (49% and 17% of adults in this sample) are major risk factors for ICU admission and death from COVID-19 in adults. Both conditions are associated with high IL-6 levels (J Clin Endo and Metabol 2001; 86: 1154-59). Very high IL-6 is part of the inflammatory cytokine release seen in many adults with COVID-19 who develop hyperinflammatory deterioration with shock: elevated D-dimers, ferritin, hypercoagulable state, pulmonary microemboli, renal failure and hypotension.
- > The pathophysiology of severe COVID-19 in adults is yet to be worked out, but it is clear it is a multi-phasic illness, and has some atypical features to ARDS, including severe hypoxaemia despite good lung compliance, and the inflammatory escalation which looks like a cytokine storm / HLH, but is different in some ways. Fortunately, very few children have developed such severe disease.

Reviewed by: Trevor Duke

DIAGNOSTICS AND SAMPLING

Dr Danielle Wurzel - Respiratory Physician, RCH; Honorary post-doctoral Research Fellow in the Respiratory Diseases Group, MCRI: and honorary Senior Fellow, Department of Paediatrics, The University of Melbourne.

Virological assessment of hospitalized patients with COVID-2019

<https://www.nature.com/articles/s41586-020-2196-x>

Virological assessment of 9 (middle-age, otherwise healthy professionals) with mild COVID:

- > 100% diagnostic yield on nasal and throat swabs day 1-5 of symptoms, detection rate dropped to average of 40% later in illness
- > Evidence for active pharyngeal shedding from upper respiratory tract early in illness
- > Also, independent viral replication found to be occurring in different sites.
- > Sequence-distinct virus populations found in throat and lung.
- > Live virus detectable in throat and lung, but not stool (despite high viral RNA in stool) – implications for transmission.
- > No virus yield in blood or urine

Kieren Fahey – 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

Which is the best swab for SAR-CoV-2 detection?

<https://jamanetwork.com/journals/jama/fullarticle/2762997>

Comparison of different sampling sites with respect to SARS-CoV-2 detection (1070 samples from 205 adults and children, median age 44 years):

- > Virus was detected using RT-PCR, with the cycle threshold (CT) used as a proxy for viral load. CT value of <40 on RT-PCR considered positive.
- > Lower airway samples (BAL/sputum) showed highest positivity followed by nasal swab (BAL n= 14/15; 93%; sputum n=72/104; 72%; nasal swabs n=5/ 8; 63%). Nasal swabs had the highest

- > Lower positivity seen in faeces (44 of 153; 29%), and blood (3 of 307; 1%). None of the 72 urine specimens tested positive.
- > Limitations
 - Many results were in the 35-40 range which may indicate low viral numbers or non-specific amplification
 - Samples were collected at different points in the admission, and so may not be directly comparable
 - Nasopharyngeal swabs are currently recommended for testing by many agencies, but were not included in this study
- > Transmission of the virus by extra-pulmonary routes may be possible

Can SARS-CoV-2 antibodies be used to reflect the progress of viral infection?

<https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25820>

Analysis of 60 convalescent patients (onset of illness 6-7 weeks previously) in Wuhan, China that were tested for SARS-CoV-2 antibodies

- > All 60 patients tested positive for IgG, while 13 patients tested negative for IgM
- > A significant drop in titer for both IgM and IgG was found when 10 patient samples were tested one week apart. In these patients, two consecutive negative SARS-CoV-2 RNA tests correlated with improved CT findings
- > Antibody detection therefore may be used as an indicator for stage of COVID-19 disease – with previous studies indicating that SARS-CoV-2 RNA can be positive in the acute phase, whilst antibodies may be negative
- > Detection of IgM and IgG against SARS-CoV-2 may be useful in identifying past infection (especially if mild or asymptomatic) and may assist in determining prognosis in more severe disease - future research is needed
- > Limitations
 - Small sample size, particularly in the sub-analysis of serology one week post initial test
 - PCR and Serology were not performed in the same study, therefore giving us limited clinical information on the relationship between a positive PCR and positive Serology
- > Summary: Declining IgM & IgG titres, combined with a negative pharyngeal swab result, may indicate resolving infection

Is SARS-CoV-2 RNA detectable in stool samples?

<https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25825>

Retrospective analysis of stool samples from 42 COVID-19 patients that had a previous positive pharyngeal swab in Wuhan, China

- > 28 out of 42 patients tested positive for SARS-CoV-2 RNA in faeces.

- > Positive tests were not associated with the presence of gastrointestinal symptoms or severity of illness
- > 18/28 (64%) of patients stool samples tested positive for an average of 7 days after a negative pharyngeal swab result, suggestive of prolonged faecal shedding
- > This study raises the possibility of faecal-oral transmission of SARS-CoV-2 however further research is needed
- > Limitations
 - As detectable CoV2 RNA in faecal samples does not confirm presence of live virus, we are unable to determine from this study if these patients remained infectious after they returned a negative pharyngeal swab result
- > Summary: Prolonged faecal shedding of SARS-CoV-2 RNA occurs in a proportion of patients, but currently the clinical significance of this is unknown

Reviewed by: Dr Danielle Wurzel and Associate Professor Catherine Satzke

EMERGENCY MEDICINE

Natalie Commins - 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

What changes to basic and advanced life support procedures should be made when patients have suspected or confirmed COVID-19?

<https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.120.047463>

New adult and paediatric guidelines and algorithms for basic and advanced life support in patients with suspected or confirmed COVID-19, developed from existing AHA CPR guidelines with the aim of preventing disease transmission to healthcare workers.

- > Manual chest compressions should be replaced by mechanical CPR devices if available
- > Strategies to reduce the risk of aerosolisation of the virus
 - HEPA filters should be attached to any manual or mechanical ventilation devices
 - Use cuffed endotracheal tubes if possible
 - Use a bag-mask device with a HEPA filter during CPR
- > Out of hospital cardiac arrest (Lay rescuers)
 - Compressions only for adults, a cloth/face mask over mouth and nose of rescuer and/or victim may decrease risk of COVID-19 transmission to non-household bystanders
 - For children, Perform chest compressions and if responder is willing also give mouth-to-mouth ventilation given the higher incidence of respiratory arrest

Reviewed by: Dr Wonie Uahwatanasakul

EPIDEMIOLOGY AND PUBLIC HEALTH

Samar Hikmat - 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

Epidemiological characteristics of COVID-19 among Children in China

<https://pediatrics.aappublications.org/content/pediatrics/early/2020/03/16/peds.2020-0702.1.full.pdf>

Retrospective study based on 2135 paediatric patients with COVID-19 reported to the Chinese Center for Disease Control and Prevention from 16th January – 8th February 2020. Children were defined as being <18 years old.

- > Out of the total 2135 patients, 34.1% were laboratory confirmed cases and 65.9% were suspected cases. Suspected cases were defined based on clinical symptoms, results of blood tests/imaging, and risks of getting the disease from being exposed to a known case of COVID-19. Confirmed cases were defined as those with nasal and pharyngeal swabs or blood specimens being positive or having a highly homologous genetic sequence with COVID-19.
- > Children of all ages were susceptible to COVID-19 and there was no significant sex difference.
- > Compared with the adult population, most cases of COVID-19 in children were mild. About 5.8% were severe and critical; with the largest proportion of those being in infants (< 1 year). Only 1 child died.
- > The reasons why children appear less vulnerable than adults to COVID-19 still needs to be determined. Suggested theories include:
 - Angiotensin-converting enzyme II (ACE2) is likely the receptor of COVID-19. The maturity and binding ability of this receptor in children may be lower than in adults.
 - Children often experience respiratory infections in winter and may have higher levels of antibody against the virus than adults.
 - Childrens' immune systems are still developing and may respond differently to pathogens compared with adults.
- > There is a strong evidence for human-to-human transmission because children were unlikely to visit the Huanan Seafood Wholesale Market, where the early adult patients were reported to have obtained COVID-19.

Reviewed by: Professor Fiona Russell

Associate Professor Margie Danchin - General and Immunisation paediatrician, Department of General Medicine, Royal Children's Hospital Melbourne, Group Leader, Vaccine Uptake, MCRI, Clinician Scientist Fellow, Department of Paediatrics and School of Population and Global Health, The University of Melbourne

Understanding and Addressing Sources of Anxiety Among Health Care Professionals During the COVID-19 Pandemic

<https://jamanetwork.com/journals/jama/fullarticle/2764380>

Summarises specific sources of anxiety and fear and key considerations for supporting the health care workforce

- > Critical that leaders understand the sources of concern, assure health care professionals that their concerns are recognised, and work to develop approaches that mitigate concerns to the extent that they are able
- > 8 main sources of anxiety, including (1) access to appropriate PPE, (2) being exposed to COVID-19 at work and taking the infection home to their family, (3) not having rapid access to testing if they develop COVID-19 symptoms and concomitant fear of propagating infection at work, (4) uncertainty that their organization will support/take care of their personal and family needs if they develop infection, (5) access to childcare during increased work hours and school closures, (6) support for other personal and family needs as work hours and demands increase (food, hydration, lodging, transportation), (7) being able to provide competent medical care if deployed to a new area (eg, non-ICU nurses having to function as ICU nurses), and (8) lack of access to up-to-date information and communication
- > Specific responses include
 - HCWs need to be part of the decision-making process
 - Adequate PPE and testing, information to avoid taking the infection home and accommodation if needed
 - Adequate PPE training
 - Physical and psychological first aid ie meals, webinars on how to deal with anxiety and distress

Jim Owens - 4th Year Medical Student,
Department of Paediatrics, The University of Melbourne

Are school closures effective and cost-effective in coronavirus outbreaks, including COVID-19, SARS and MERS?

<https://www.ncbi.nlm.nih.gov/pubmed/32272089>

Systematic review on the effectiveness of school closures and school-based social distancing practices during coronavirus outbreaks

- > Data on school distancing measures was found to be of relatively low quality due to school closure implementation coinciding within broader infection-control “suites”, and a lack of dedicated studies
- > Modelling and statistical studies support the effectiveness of school closures during influenza outbreaks. However, modelling which incorporates critical differences in the transmission dynamics between influenza and coronaviruses, including higher reproductive numbers and lower rates of symptomatic cases in children, predicts that the independent effect of school closures in reducing outbreak size will be marginal
- > Modelling studies of SARS produced conflicting results
- > Recent modelling studies of COVID-19 predict that school closures alone would prevent only 2-4% of deaths, much less than other social distancing interventions. However, data quality is poor.
- > Policy-makers must balance the economic and social impacts of school closures with their public health benefits and the strain placed on schools due to staff absenteeism due to illness
- > Suggestions of alternative measures to be explored, including the restricted opening of schools to children of healthcare and other essential workers

Reviewed by: Professor Fiona Russell

Professor Sharon Goldfeld – Paediatrician, public health physician, Co-Group Leader of Policy and Equity at the MCRI and Director of the Centre for Community Child Health at The Royal Children's Hospital Melbourne

What are the adverse consequences of school closures on children?

<https://www.ncbi.nlm.nih.gov/pubmed/18552649>

- > Schools closures during a pandemic may be problematic: evidence for their efficacy has not been established; and they have the potential to create adverse consequences that disproportionately affect vulnerable populations
- > Adverse effects include: school meal programs may be compromised; working parents may rely on self-care (leaving a child in their own care or with a sibling under 13 years); and disrupted education

- > More evidence on the efficacy of school closures during a pandemic is needed; intermediate options such as partially closing schools should be considered; and school closures must be implemented in a way that does not unduly burden vulnerable populations.

What are the needs of children during pandemic planning, including their mental health needs?

<https://www.ncbi.nlm.nih.gov/pubmed/19797738>

- > During a severe pandemic, school closures and social distancing strategies are likely to cause stress and confusion, as well as disrupting children's routines
- > Family stress levels are likely to be higher, and hospitalisations lead to parent and child separations
- > Children may experience the loss of loved ones, and there is likely to be a high demand for mental health services
- > Need for national, state and local plans to include an organised mental health response to children's needs.

IMMUNOLOGY

Associate Professor Paul Licciardi, Team Leader, New Vaccines Group, MCRI, Professor Philip Sutton – Group Leader, Mucosal Immunology Group, MCRI, Dr Dan Pellicci- Group Leader, Cellular Immunology Group, MCRI

Breadth of concomitant immune responses prior to patient recovery: case report of non-severe COVID-19

<https://www.nature.com/articles/s41591-020-0819-2>

Measurement of host immune response in a non-severe adult patient with COVID-19

- > A 47-year old patient requiring hospitalisation with mild-moderate COVID-19
- > The main findings included the appearance of both an increased cellular immune response (antibody-secreting cells, follicular helper T cells, activated CD4+ and CD8+ T cells) and humoral responses (IgG and IgM) by day 7-9 following symptom onset
- > Importantly, the appearance of these immunological responses preceded recovery, suggesting they might be associated with protection against SARS-CoV-2 infection.
- > Responses persisted for at least 7 days following symptom resolution
- > Results need to be confirmed in larger cohorts and across the age and clinical spectrum
- > This paper provides the first published analysis of the immunological response factors that occur concomitant with recovery from COVID-19, albeit only in a single patient

Dahlia Hawari - 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

Does convalescent plasma therapy have a role in the treatment of severe COVID 19 patients?

<https://doi.org/10.1073/pnas.2004168117>

Clinical review of 10 patients with severe COVID 19 treated with convalescent plasma therapy

- > Prior to treatment, 3 patients received mechanical ventilation, 3 received high flow nasal prongs and another 3 received oxygenation through low-flow nasal prongs.

- > Primary endpoint = safety of transfusion; secondary endpoints = clinical and laboratory endpoints
- > All 10 patients (6 males and 4 females) demonstrated improvement of clinical symptoms within 1-3 days of treatment
- > Treatment outcome was then matched with a historic control group matched by age, gender and severity of disease which showed a significant difference in treatment outcomes, with the CP group having no deaths and 3 discharges from hospital, compared with three deaths in the control group
- > No significant adverse effects of treatment reported.
- > Study limited by a small sample size; need a larger RCT

Reviewed by: Associate Professor Paul Licciardi

INFECTION CONTROL

Dr Vanessa Clifford - Infectious Diseases physician and Microbiologist, RCH/RWH; Honorary Research Fellow in the Infection and Immunity Group, MCRI; and honorary Senior Fellow, Department of Paediatrics, The University of Melbourne.

Respiratory virus shedding in exhaled breath and efficacy of face masks

<https://www.nature.com/articles/s41591-020-0843-2.pdf>

- > Hong Kong study- measurement of respiratory viruses detectable in exhaled breath collection of droplet and aerosol particles from 123 adult patients with respiratory tract infection (primarily influenza, seasonal coronaviruses (n=17), rhinoviruses) attending a hospital outpatient clinic randomised to wear (or not wear) a surgical mask during breath collection.
- > Viral RNA in droplets and aerosols could be detected in expired air samples from approximately one third of patients with respiratory infection
- > Wearing a surgical mask reduced detection of influenza in droplets and detection of coronaviruses in aerosols.
- > This study does not provide direct evidence around transmission risk for these viruses detected in aerosols and droplets
- > The study supports existing recommendations that patients attending hospital with respiratory tract infection should wear a surgical mask when moving outside their room in order to protect other patients and health care workers.

MENTAL HEALTH

Dr Sharon Goldfeld - Paediatrician, public health physician, Co-Group Leader of Policy and Equity at the MCRI and Director of the Centre for Community Child Health at The Royal Children's Hospital Melbourne.

What are the potential negative effects of prolonged school closure and home confinement on children's physical and mental health in China during COVID-19?

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)30547-X/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30547-X/fulltext)

- > In China, nationwide school closures were implemented during the COVID-19 outbreak, with rigorous implementation of an emergency home schooling plan
- > Schools and teachers created online courses and delivered them through TV broadcasts and the internet
- > Possible physical health effects include: being physically less active, having longer screen time, and eating less healthy diets
- > Potential mental health effects include: fears of infection, frustration, boredom, lack of in-person contact with peers and teachers, lack of personal space in the home, and family financial hardship
- > Call for the government, community, schools, and families to recognise these issues, and to develop strategies for addressing the needs of children during this time.

What are the psychosocial responses of children and their parents to pandemic disasters?

<https://www.ncbi.nlm.nih.gov/pubmed/24618142>

- > Important to consider needs of children and their families during pandemic planning, to avoid long-term trauma
- > Pandemics share factors in common with other disasters (impact on community and unpredictability), but are unique in requiring separation, quarantine, and isolation of victims
- > Almost a third of isolated / quarantined children and 86% of their parents met the threshold for PTSD
- > Collaboration during pandemic responses is necessary to minimise negative psychosocial consequences for children and families

- > Post-pandemic mental health surveillance in parents and children should be integrated into public health responses.

What is the psychological impact of quarantine? A review

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)30460-8/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30460-8/fulltext)

- > Stressors following quarantine include finances and stigma
- > Quarantine is associated with a substantial psychological effect that can persist for months or years
- > Effective mitigation measures are an essential part of quarantine planning
- > Officials should provide clear communication around what is happening, why it is happening, and how long it will continue
- > Meaningful activities to do during quarantine, and basic supplies, should be made available
- > Highlighting that quarantine helps keep vulnerable populations safe, and that health authorities are grateful, should be communicated

Thomas Hill - 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

Detecting early behavioral and emotional responses to COVID-19 in children

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7127630/>

Early behavioral and emotional responses were screened in 320 Chinese children using an online survey.

- > Children aged 3-6 years were more likely to exhibit clinginess and fear that a family member would contract the disease.
- > Children and adolescents aged 6-18 years were more likely to exhibit inattention and persistent questioning about the virus.
- > Clinginess, inattention and irritability were the most common behaviors expressed across all ages.
- > Families reported that digital media devices were more effective in relieving their children's distress than books and exercise.
- > This study stresses the importance of screening methods for early recognition of negative emotions in children to address the need for further assessment and to provide timely intervention.

How does COVID-19 implicate addiction?

<https://onlinelibrary.wiley.com/doi/10.1111/add.15080>

- > Self-isolation and social distancing lead to more anxiety and less positive reinforcement in everyday life increasing risk of substance misuse or relapse.
- > People living with addiction are at greater risk of poverty, financial hardship and mental illness, for which they are unable to receive adequate support due to the attenuation of face to face community services.
- > Individuals with addictive disorders have higher rates of homelessness and residence in under-resourced public housing with higher population densities and are therefore particularly vulnerable to disease outbreak.
- > Supply of narcotics may be limited leading to increased use of alcohol, benzodiazepines and other easier to source substances. Alternatively, supply may be intermittent possibly increasing the risk of overdose.
- > There is an urgent need for local and international collaboration to address the public health needs of people living with addictive disorders.

Reviewed by: Professor David Coghill

PERINATAL HEALTH

Jenny Pham - 4th Year Medical Student, Department of Paediatrics, The University of Melbourne

Global interim guidance on coronavirus disease 2019 (COVID-19) during pregnancy and puerperium: Information for healthcare professionals.

<https://obgyn.onlinelibrary.wiley.com/doi/abs/10.1002/ijgo.13156?af=R>

- > Currently no evidence of:
 - Pregnant women having Increased susceptibility to COVID-19 infection but also a lack of data
 - COVID-19 infection being associated with fetal or placental complications
 - Vertical transmission of COVID-19 but lack of data
- > Triage
 - Most common presentations of COVID infection include fever and cough. Two thirds had lymphopaenia and increased CRP
 - Chest CT scan should be included in workup. May show ground glass opacity in lungs.
- > Intrapartum management of women infected with COVID-19
 - Occur in negative pressure isolation rooms with minimal foot traffic
 - COVID-19 infection is not an indication for delivery, unless maternal oxygenation needs to be improved
 - COVID-19 infection is not a contraindication for vaginal delivery
 - Low threshold to expedite delivery
 - For protection of the medical team, water births should be avoided (evidence of virus in faeces)
- > Postpartum management and neonatal care
 - Currently insufficient evidence regarding breastfeeding and mother/baby separation
 - For women with mild disease: consider breastfeeding and colocation. Mothers should wash their hands carefully and wear a mask before touching the baby.
 - For women with severe disease: separation seems to be the best option, continue to express breast milk

- > Psychological impact:
 - Increased anxiety and depression if suspected/confirmed COVID
 - Mother/baby separation hinders bonding, further increasing stress

Reviewed by: Professor Fiona Russell

Chuyi Katherine Liao - 3rd Year Medical Student, Department of Paediatrics, The University of Melbourne

Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: case series

[https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(20\)30176-6/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30176-6/fulltext)

- > 7 women aged 29-34 diagnosed with COVID19 admitted at 37-41 weeks gestation to Tongji Hospital (Wuhan, China)
- > clinical features include: fever (6/7) +/- cough (1/7), less commonly diarrhoea and dyspnea. This manifestation is similar to that of non-pregnant women.
- > Laboratory tests showed that absolute lymphocyte counts were reduced; neutrophil count, C-reactive protein, erythrocyte sedimentation rate, and D-dimer were increased
- > 2 women also had influenza H1N1 diagnosed by RT-PCR, 1 was diagnosed with legionella (method unknown)
- > Women received a wide range of antiviral medications including oseltamivir, ganciclovir, interferon and chinese herbal medicines. Corticosteroid was used as part of the treatment regimen post delivery in most.
- > No maternal complications. Neonatal Apgars and follow-up to day 28 were normal
- > All newborns were tested for SARS-CoV-2 shortly after birth- 1 tested positive at 36 hours of age
- > Compared with SARS, COVID-19
 - Pneumonia demonstrated better maternal, fetal and neonatal outcomes compared with SARS.
 - Demonstrated possible vertical transmission

Reviewed by: Professor Jim Buttery

Benjamin Watson - 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

Novel Coronavirus Infection in Newborn Babies Under 28 Days in China

<https://erj.ersjournals.com/content/erj/early/2020/04/01/13993003.00697-2020.full.pdf>

- > Systematic review identified 4 possible SARS-CoV-2 infections in newborn babies in China as of 13th March 2020 (age range 30hrs to 17 days) out of the 81 026 confirmed cases
- > Symptomatology profiles included: fever, shortness of breath, cough and asymptomatic
- > All mothers were infected by SARS-CoV-2, with 3 showing symptoms before, and 1 after delivery.
- > All newborns received supportive treatment, none required NICU or mechanical ventilation
- > Symptoms in newborns were milder and outcomes less severe compared with adults
- > Intrauterine vertical transmission is possible but direct evidence is still lacking

Reviewed by: Professor Fiona Russell

Professor Fiona Russell - Director Child and Adolescent PhD Program; Department of Paediatrics, The University of Melbourne, Asia-Pacific Health Research, Group Leader, MCRI

Universal screening for SARS-CoV-2 at delivery?

<https://www.nejm.org/doi/full/10.1056/NEJMc2009316>

- > Universal of SARS-CoV-2 instigated in a New York hospital for women admitted for delivery (n=215)
- > Most women who were positive for SARS-CoV-2 at delivery were asymptomatic
- > More than one of eight asymptomatic patients who were admitted to the labor and delivery unit were positive for SARS-CoV-2
- > Universal testing includes the ability to use COVID-19 status to determine hospital isolation practices and bed assignments, inform neonatal care, and guide the use of personal protective equipment

THERAPEUTICS

Dr Amanda Gwee - Infectious Diseases Physician, RCH; Team leader & Clinician-Scientist Fellow in the Infectious Diseases Group, MCRI; and Senior Lecturer, Department of Paediatrics, The University of Melbourne

Which is the evidence for hydroxychloroquine for COVID-19?

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102549/>

- > Open-label non-randomized clinical trial of hospitalised patients age >12 years with confirmed COVID-19. The study included 26 patients treated with hydroxychloroquine 600 mg daily (6 also received azithromycin) and 16 controls.
- > Main results on day 6 post-inclusion:
 - 70% of hydroxychloroquine-treated patients had negative nasopharyngeal PCR compared to 12.5% in the control group.
 - All 6 patients treated with hydroxychloroquine + azithromycin had negative PCRs on day 6.
- > Significant bias – 6 patients in the hydroxychloroquine group were excluded from the final results (3 transferred to ICU, 1 died, 1 discharged from hospital, 1 ceased treatment due to nausea).

Nicholas Baxter - 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

COVID-19: combining antiviral and anti-inflammatory treatments

<https://www.sciencedirect.com/science/article/pii/S1473309920301328>

- > Severe cases of COVID-19 are characterised by the host inflammatory response causing major long damage and subsequent mortality
- > There is a need to repurpose existing drugs to tackle the pandemic
 - Computational modelling was used to assess the pharmacokinetic properties of Baricitinib suggested as a JAK/NAK inhibitor known for its anti-inflammatory properties and ameliorate chronic inflammation in interferonopathies

- Fedratinib and ruxolitinib additionally potent JAK inhibitors that are approved for indications such as rheumatoid arthritis and myelofibrosis, and likely to be effective against the consequences of the elevated levels of cytokines (including interferon-gamma) observed in people with COVID-19
- > The author has hypothesised that these compounds are unlikely to reduce viral infectivity at tolerated doses, but they may reduce the host inflammatory response through JAK inhibition. To date there is no clinical data to support their use as treatment for COVID-19

Reviewed by: Professor Julie Bines

TRANSMISSION

Professor Fiona Russell - Director Child and Adolescent PhD Program; Department of Paediatrics, The University of Melbourne, Asia-Pacific Health Research, Group Leader, MCRI

A case of mother-child transmission of SARS-CoV-2?

https://protect-au.mimecast.com/s/Dw_vCmOxr6sj5VZpphGlyr5?domain=jamanetwork.com

- > Case report of a newborn with elevated IgM antibodies to SARS-CoV-2 born to a mother with COVID-19 in China
- > Elevated IgM antibody level suggests that the neonate was infected in utero. IgM antibodies are not transferred to the fetus via the placenta
- > No PCR testing of amniotic fluid or placenta was performed. Additional examination of maternal and newborn samples needs to be done

Professor Andrew Steer - Infectious Diseases paediatrician, RCH; Director of Infection and Immunity Theme, MCRI; Tropical Diseases, Group Leader, MCRI

COVID-19 in children: the link in the transmission chain

[https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(20\)30236-X/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30236-X/fulltext)

- > Children are susceptible to SARS-CoV-2 infection, but frequently do not have notable disease, raising the possibility that children could be facilitators of viral transmission
- > If children are important in viral transmission and amplification, social and public health policies (eg, avoiding interaction with elderly people) could be established to slow transmission and protect vulnerable populations
- > Urgent need to for further investigation of the role children have in the chain of transmission

Age dependent effects in the transmission and control of COVID-19 epidemics

<https://www.medrxiv.org/content/10.1101/2020.03.24.20043018v1.full.pdf>

- > This study showed a strong age dependence in the probability of displaying clinical symptoms for COVID-19, from around 20% in under 10s, to over 70% in older adults
- > The authors suggest that the age-specific severity and age-specific clinical fraction is more likely than age-specific susceptibility to infection
- > The authors highlight the need for serological surveys to provide critical information on the true distribution of subclinical infections

Chuyi Katherine Liao - 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

What role do children play in terms of COVID-19 transmission?

[https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(20\)30236-X/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30236-X/fulltext)

This commentary on first report of 36 paediatric cases from China

([https://doi.org/10.1016/S1473-3099\(20\)30198-5](https://doi.org/10.1016/S1473-3099(20)30198-5))

- > Overall, a milder clinical picture compared with other demographics was demonstrated: high proportion of children (10%) were asymptomatic, and none of children had severe illness or died
- > The milder disease could be attributed to different immune regulators in children
- > Most importantly, the similar susceptibility but milder presentation of clinical disease raises the possibility that children are facilitators of COVID-19
- > This possibility has important implications in terms of social and public health policy guidance in relation to slowing viral transmission and protecting vulnerable populations.
- > More research and review is urgently needed in the role of children in transmission

Reviewed by: Professor Fiona Russell

Jim Owens - 4th Year Medical Student,
Department of Paediatrics, The University of Melbourne

What is the rate of asymptomatic infection and how does this impact on transmission and efforts to control COVID-19 in the community?

<https://www.bmj.com/content/369/bmj.m1375>

- > Review of current epidemiological studies indicating asymptomatic infection rates may be higher than previously identified
- > Chinese authorities began publishing daily figures on 1st April 2020 on the number of new coronavirus cases that are asymptomatic, so far indicating four out of five infections were asymptomatic and could pose as a source of transmission
- > A completely isolated village of ~3000 people in northern Italy showed symptomatic COVID-19 decreased by 90% when symptomatic and asymptomatic infected people were isolated for 10 days.
- > As more data becomes available, it may help to identify the potential impact of asymptomatic infection rates on the transmission of COVID-19 in the community and whether lockdown measures are effective.

Reviewed by: Professor Fiona Russell

VACCINES

A/Prof Nigel Crawford, General Paediatrician, The Royal Children's Hospital; Medical Head, Immunisation Services, Department of General Medicine, The Royal Children's Hospital; Director of SAEFVIC (Surveillance of Adverse Events Following Vaccination in the Community); Senior Fellow, Department of Paediatrics, University of Melbourne.

Developing Covid-19 Vaccines at Pandemic Speed

<https://www.nejm.org/doi/full/10.1056/NEJMp2005630>

- > Describe the activities of CEPI (Coalition for Epidemic Preparedness Innovation) an international nongovernmental organisation, that includes academia, biotech, industry and governments- with established vaccine platforms waiting to be activated in the setting of a pandemic
- > Outlines CEPI's role and tabulates current vaccine platforms - including a subunit vaccine from the University of Queensland
- > In exciting developments - the Moderna mRNA SARS-CoV-2 vaccine candidate [supported by the NIH] entered a phase 1 Human clinical trial on March 16, only 63 days after activating the platform
- > Ongoing international efforts to understand the virus and how vaccines may induce a correlate of protection are essential - including against clinical outcomes like severe pneumonia.

Daniel Lindholm - 4th Year Medical Student,
Department of Paediatrics, The University of Melbourne

What is the current status of COVID-19 Vaccine Development?

<https://link.springer.com/content/pdf/10.1007/s40475-020-00201-6.pdf>

- > Summary of the immunology surrounding COVID-19
- > Provides an overview of the advantages and disadvantages of varied production platforms and technologies for COVID-19 vaccines.
- > The S protein which interacts with ACE2 receptors in human lungs has been the major antigen targeted for vaccine development

Where is the mRNA vaccine candidate (Moderna) up to?

<https://science.sciencemag.org/content/sci/368/6486/14.full.pdf>

- > Moderna's mRNA vaccine candidate is discussed in this Science Magazine article, alongside commentary on the overall vaccine landscape for COVID-19
- > Phase I human trials began on the 16th March 2020

Could the microneedle array vaccine design be a viable candidate in COVID-19?

<https://www.sciencedirect.com/science/article/pii/S2352396420301183>

- > Development of a microneedle array (MNA) for the delivery of a MERS-CoV vaccine is discussed, and how they leveraged this experience to rapidly develop a similar COVID-19 subunit vaccine
- > Pre-clinical immunogenicity studies of MERS-CoV vaccines in mice were undertaken by delivering subcutaneously, or intracutaneously by dissolving microneedle arrays (MNAs), and evaluating virus specific IgG antibodies in the serum of vaccinated mice by ELISA and using virus neutralization assays
- > MNA delivered MERS-S1 subunit vaccines elicited strong and long-lasting antigen-specific antibody responses
- > Robust antigen-specific responses were found two weeks following immunisation, comparable in gamma irradiated and non-irradiated vaccines
- > Plan to evaluate these SARS-CoV-2 vaccines for other important predictors of vaccine efficacy in humans, including the induction of neutralizing antibodies and for their ability to prevent infection in animal challenge models, when these assays and preclinical models become available

Reviewed by: Professor Fiona Russell

VIROLOGY

Dr Lien Anh Ha Do - Virologist, New Vaccines, Infection & Immunity Theme, MCRI and Honorary Fellow, Department of Paediatrics, The University of Melbourne.

Evidences of prolonged viral shedding and the correlation between viral load and antibody responses in COVID-19

<https://www.nature.com/articles/s41586-020-2196-x>

This study reported the correlations of the viral kinetics of SARS-CoV-2, the causative virus of the COVID-19, the antibody responses and clinical presentations over the course of disease among nine non-severe COVID-19 cases. The sampling was collected at early phase of disease when these individuals had very mild symptoms or even prodromal.

- > SARS-CoV-2 was effectively replicated in both upper (throat) and lower respiratory tracts (sputum) with a very high viral load and a long viral shedding (virus was still detected on day 28 post-onset on sputum).
- > Viral RNA was detected in the stools but not in urine and in blood. The in vitro infectivity of the virus was demonstrated for throat/sputum, not for stools.
- > Seroconversion by detecting IgM and IgG (immunofluorescence platform and S protein of SARS-CoV-2) occurred by day 7. Neutralising antibody seems not correlated to the clinical presentations and not abrupt viral replications
- > Evidence to explain why SARS-CoV-2 is easily transmitted (high viral load and asymptomatic and prolong viral shedding in sputum)
- > Warning about the possible lack of efficacy of neutralising antibody against the viral replication
- > No comparisons groups e.g no severe cases
- > No cellular immunity profiles

Professor Julie Bines, Paediatric Gastroenterologist, RCH; Lead Enteric Disease Group MCRI; Victor and Loti Smorgon Professor of Paediatrics, The University of Melbourne and Dr Celeste Donato- Virologist, Enteric Diseases Group, MCRI; Lecturer, Department of Paediatrics, The University of Melbourne

How sewerage could reveal the true scale of coronavirus outbreak

<https://www.nature.com/articles/d41586-020-00973-x>

- > SARS-CoV-2 is shed in the faeces of a significant proportion of SARS-CoV-2 patients
- > Sewerage sampling of 7 cities and the airport in the Netherlands were tested using RT-PCR against 3 fragments of the nucleocapsid gene (n1-3) and 1 fragment of the envelope protein (E)
- > On 6th February 2020, 3 weeks before the first case was reported in the Netherlands no SARS-CoV-2 was detected in the sewerage samples, 5th March 2020 N1 fragment was detected at 5 sites and 15th / 16th March 2020 the N1 And N3 fragments were detected at 4-5 sites.
- > This is the first report of detection of SARS-CoV-2 in sewerage
- > SARS-CoV-2 is detected in sewerage even when the COVID-19 prevalence is low, sewerage surveillance could be a sensitive tool to monitor the circulation of the virus in the population

OTHER RESOURCES

<https://dontforgetthebubbles.com/evidence-summary-paediatric-covid-19-literature/>

Focuses on clinical, epidemiological, transmission and neonatal aspects

<https://www.ncbi.nlm.nih.gov/research/coronavirus/> All

COVID-19 literature

<https://www.cebm.net/oxford-covid-19/> Oxford

COVID-19 Evidence Service

https://docs.google.com/forms/u/0/d/e/1FAIpQLSfOxCoAuLV0aJdf_z2uWV7r3FaPzAOr86q9ZXBcTZ1QcCE_Nw/formResponse

Subscription link to daily updates on new literature compiled by Canadian medical students

<https://www.dhhs.vic.gov.au/coronavirus-covid-19-daily-update>

Victorian Department of Health and Human Services

<https://www.health.gov.au/news/health-alerts/novel-coronavirus-2019-ncov-health-alert/coronavirus-covid-19-current-situation-and-case-numbers>

Australian Government

<http://www.nephjc.com/covid19>

COVID-19 and the kidney, which is currently the recommended US resource

<https://www.birmingham.ac.uk/university/colleges/mds/Coronavirus/COVID-19-research-briefing.aspx>

University of Birmingham COVID-19 Research Briefing

<https://www.health.gov.au/news/health-alerts/novel-coronavirus-2019-ncov-health-alert/coronavirus-covid-19-advice-for-the-health-and-aged-care-sector/webinars-on-the-coronavirus-covid-19-response-for-primary-care-practitioners>

Australian Government Department of Health Webinars on the COVID-19 response for primary care practitioners

<https://epiforecasts.io/covid/posts/global/>

Global summary, identifying changes in the reproduction number, rate of spread, and doubling time during the course of the COVID-19 outbreak whilst accounting for potential biases due to delays in case reporting both nationally and sub-nationally

<https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen>

WHO Rolling updates on COVID-19

<https://www.scimex.org/newsfeed/bubs-born-to-mums-with-covid-19-in-china>

Scimex.org – breaking science news portal: COVID-19 stories (research and expert commentary)

<https://www.covid19-hpc-consortium.org/>

Active projects incl: COVID-19, scientific literature, summarization, Text mining
PI: Karan Uppal, Emory University

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