# Paediatrics Research Review™

Making Education Easy

Issue 46 - 2023


## In this issue:



**Abbreviations used in this issue:**

**COVID-19** = coronavirus disease 2019; **CSF** = cerebrospinal fluid; **EEG** = electroencephalogram; **FDA** = Food and Drug Administration; **HIE** = hypoxic-ischaemic encephalopathy; **ICU** = intensive care unit; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2; **WHO** = World Health Organization.



## Welcome to the latest issue of Paediatrics Research Review.

In this issue, we report a number of studies regarding COVID-19 in children, including the effectiveness of the BNT162b2 vaccine in young children, the effectiveness of maternal COVID-19 vaccination during pregnancy, changes in the severity of COVID-19 symptoms in children over the course of the pandemic, and the manifestation of long COVID symptoms in children. Also in this issue, the Australian MIST trial finds that intranasal saline is useful in children with sleep-disordered breathing, a meta-analysis looks at various dietary therapies in children with drug-resistant epilepsy, and we are reminded of the dangers associated with button battery ingestion.

We hope you find these and the other selected articles interesting and welcome any feedback you may have.

Kind Regards,


**Prof Nicholas Freezer**
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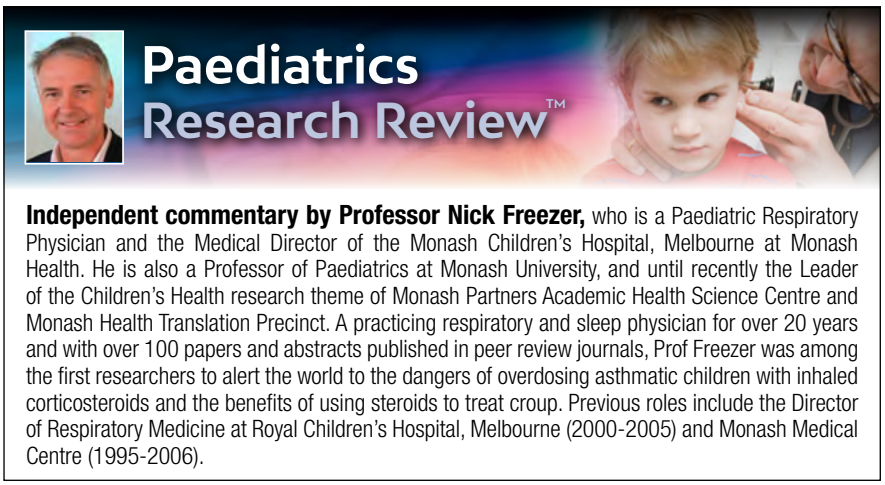
### Evaluation of BNT162b2 COVID-19 vaccine in children younger than 5 years of age

**Authors:** Muñoz FM et al., for the C4591007 Clinical Trial Group


**Summary:** This study investigated the efficacy and safety of the BNT162b2 vaccine in healthy young children. After an initial dose-finding study, 4526 children aged 6 months to 4 years were randomised 2:1 to receive two 3-µg doses of BNT162b2 or placebo. On the basis of preliminary immunogenicity results, a third 3-µg dose (≥8 weeks after the second dose) was administered from Jan 2022 (coinciding with the emergence of the Omicron variant). The overall vaccine efficacy of BNT162b2 against symptomatic COVID-19 was 73.2% from 7 days after dose 3 (on the basis of 34 cases). Reactogenicity events were mostly mild to moderate, and the incidence of fever after receipt of BNT162b2 was similar to that after placebo.


**Comment:** In June 2022 the FDA authorised BNT162b2 (Pfizer COVID-19 vaccine) and mRNA-1273 (Moderna COVID-19 vaccine) for use in children 6 months and older. Trials in children aged 6 months to 11 years have demonstrated that these vaccines, given at lower doses, elicit neutralising immune responses comparable to those in adolescents and adults following standard doses. Vaccination also reduces the risk of symptomatic COVID-19, although the estimates of effect vary, in part because of different variants prevalent during the trials. There were no cases of vaccine-associated myocarditis in the trials. Clinicians should be aware that the dose and formulation used for children are different from those for adolescents and adults.

***Reference: N Engl J Med 2023;388:621-34***
Abstract




**Independent commentary by Professor Nick Freezer,** who is a Paediatric Respiratory Physician and the Medical Director of the Monash Children's Hospital, Melbourne at Monash Health. He is also a Professor of Paediatrics at Monash University, and until recently the Leader of the Children's Health research theme of Monash Partners Academic Health Science Centre and Monash Health Translation Precinct. A practicing respiratory and sleep physician for over 20 years and with over 100 papers and abstracts published in peer review journals, Prof Freezer was among the first researchers to alert the world to the dangers of overdosing asthmatic children with inhaled corticosteroids and the benefits of using steroids to treat croup. Previous roles include the Director of Respiratory Medicine at Royal Children's Hospital, Melbourne (2000-2005) and Monash Medical Centre (1995-2006).

## Effectiveness of BNT162b2 vaccination during pregnancy in preventing hospitalization for severe acute respiratory syndrome coronavirus 2 in infants

**Authors:** Danino D et al.

**Summary:** This retrospective case-control study in Israel evaluated the effectiveness of the BNT162b2 vaccine during pregnancy for preventing hospitalisations for severe SARS-CoV-2 infection in infants. 116 symptomatic hospitalised infants aged <6 months with a positive SARS-CoV-2 test result were matched by age and time to 348 negative controls that were hospitalised with symptoms compatible with SARS-CoV-2 infection. Mothers were considered fully vaccinated if they had received 2 doses of BNT162b2 (with the second given between 2 weeks and 6 months before delivery) or partially vaccinated if they received only 1 or 2 doses and the second was given more than 6 months or less than 2 weeks before delivery. The effectiveness of fully vaccinated mothers in reducing infant hospitalisations was 61.6% but the effectiveness of partially vaccinated mothers was not significant. Effectiveness was higher in infants aged 0–2 months than in those aged 3–6 months.

**Comment:** During periods of Delta and Omicron variant circulation, maternal completion of both doses of a primary mRNA COVID-19 vaccination series during pregnancy was associated with reduced risk for COVID-19 hospitalisation among infants <6 months of age (vaccine efficacy 52%) (N Engl J Med 2022;387(2):109). Vaccine efficacy was lower during circulation of the Omicron variant than during the Delta-predominant period (38% vs 80%) and higher when the second vaccine dose was given after 20 weeks' gestation compared with before 20 weeks (69% vs 38%). Vaccine efficacy against admission to an ICU for COVID-19 was 70%, with 90% of the infants admitted to an ICU for COVID-19 born to mothers who were unvaccinated. The only two infants who died were born to unvaccinated mothers.

***Reference: J Pediatr 2023;254:48-53.e1***
Abstract

## Severe COVID-19 outcomes in pediatrics: An observational cohort analysis comparing Alpha, Delta, and Omicron variants

**Authors:** Bahl A et al.

**Summary:** This multicentre cohort study investigated changes in the severity of COVID-19 symptoms in children over the course of the pandemic. 4517 consecutive children who presented with a primary diagnosis of COVID-19 to Detroit emergency departments in 2021–2022 were included. Data were gathered from three distinct time intervals that coincided with Alpha (T1), Delta (T2), and Omicron (T3) variant predominance. The primary outcome was composite severe disease (ICU admission, mechanical ventilation, multisystem inflammatory syndrome in children, myocarditis, or death). 24.4%, 31.6%, and 44.0% of admissions occurred during T1, T2 and T3, respectively, indicating that Omicron cases had the highest admission frequency. However, composite severe disease decreased throughout the pandemic, occurring in 36.2% of children in T1, 27.4% in T2, and 18.9% in T3. Viral coinfection was more common during T2 than T3 or T1, and was more likely in younger children (median age 1.2 years). Severe outcomes occurred more often in cases with viral coinfection than in cases without coinfection (45.6% vs 22.1%; p<0.001).

**Comment:** Like other viruses, SARS-CoV-2 evolves over time. The Alpha variant was first identified in the UK in 2020 and subsequently became the globally dominant variant until the emergence of the Delta variant. Alpha was approximately 50–75% more transmissible than previously circulating strains and was associated with greater disease severity. The Delta variant was first identified in India in Dec 2020 and was the most prevalent variant worldwide until emergence of the Omicron variant in 2021. Compared with the Alpha variant, the Delta variant was more transmissible and was associated with a higher risk of severe disease and hospitalisation. The Omicron variant was first reported from South Africa in Nov 2021. It was associated with an increase in regional infections, and was promptly identified in many other countries. Multiple studies suggest that the risk of severe disease or death with Omicron infection is lower than with prior variants. An analysis from England estimated that the risk of hospital admission or death with Omicron was approximately one-third of that with Delta, adjusted for age, sex, vaccination status, and prior infection (Lancet 2022;399(10332):1303).

***Reference: Lancet Reg Health Am 2023;18:100405***
Abstract

## Long COVID symptoms in Israeli children with and without a history of SARS-CoV-2 infection

**Authors:** Adler L et al.

**Summary:** This cross-sectional study in Israel evaluated long COVID symptoms in children. 3240 parents of children aged 5–18 years with and without a history of SARS-CoV-2 infection completed an online questionnaire (11.9% response rate). 1148 children had a history of SARS-CoV-2 infection and 2092 did not. Most long COVID symptoms were significantly more prevalent (p<0.001) in children with a history of SARS-CoV-2 infection: headache (18.4% vs 5.4%), weakness (15.1% vs 3.3%), fatigue (12.3% vs 6.4%) and abdominal pain (9.5% vs 3.8%). However, some symptoms were more prevalent in children without a history of SARS-CoV-2 infection, including attention problems in school (10.8% vs 8.5%; p=0.05), stress (9.1% vs 5.7%; p<0.001), social problems (7.8% vs 2.8%) and weight changes (6.8% vs 3.7%; p<0.001). Long COVID symptoms were more prevalent in older children (aged 12–18 years) than in younger children (5–11 years).

**Comment:** The WHO provides a consensus clinical case definition for long COVID that can be applied to children of all ages and includes confirmed or probable SARS-CoV-2 infection and symptoms lasting ≥2 months that initially occurred within 3 months of acute COVID-19. In a systematic review, fatigue, altered smell/anosmia, and anxiety were more frequent among children with post-COVID-19 condition than controls without post-COVID-19 condition. A wide range of other potential symptoms may also occur including cough, cognitive difficulty, and diarrhoea. Symptoms may be persistent and may fluctuate or recur over time and can affect everyday function (e.g., eating habits, physical activity, interaction with friends and family, and school performance).

***Reference: BMJ Open 2023;13(2):e064155***
Abstract

## Association of hospital resource utilization with neurodevelopmental outcomes in neonates with hypoxic-ischemic encephalopathy

**Authors:** Cardona VQ et al.

**Summary:** This retrospective analysis of neonates with HIE who underwent therapeutic hypothermia at various US children's hospitals investigated whether higher hospital resource utilisation during the first 4 days of life is associated with survival without neurodevelopmental impairment (NDI). 381 infants with HIE who underwent therapeutic hypothermia and who had neurodevelopmental outcomes assessed at age >11 months were divided into 2 groups: those who died or survived with NDI (n=144), and those who survived without NDI (n=237). Overall, there was no association between high- or medium-hospitalisation cost centres and death or NDI when compared with low-cost centres. However, high- and medium-EEG cost centres had lower odds of death or NDI compared with low-cost centres; high- and medium-laboratory cost centres had higher odds of death or NDI compared with low-cost centres; and high-antiseizure medication cost centres had higher odds of death or NDI compared with low-cost centres.

**Comment:** Therapeutic hypothermia is the only proven neuroprotection intervention for HIE and perinatal asphyxia in term and late preterm infants (gestational age ≥35 weeks). It is initiated for infants with pH of ≤7 or a base deficit of ≥16 mmol/L, moderate to severe encephalopathy, and the need for ongoing resuscitative efforts. If hypothermia is not available at the birth centre, it is imperative that infants who meet the criteria are transferred immediately to a centre with expertise, as hypothermia needs to be initiated within the first 6h after delivery. Mortality and long-term development outcomes for infants with perinatal asphyxia have improved with the advent of therapeutic hypothermia. It remains uncertain whether therapeutic hypothermia has similar benefits for other organ systems (e.g., heart, kidney, and liver).

***Reference: JAMA Netw Open 2023;6(3):e233770***
Abstract

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**Now PBS listed for PGTCS[1]**

**VIMPAT is now PBS listed as add-on therapy for the treatment of PGTCS in patients with IGE aged ≥4 years who have failed two ASMs and are currently taking one ASM.[1]**

# Take control of PGTCS with add-on VIMPAT[2,3*]

*Significantly more patients were free from PGTCS with add-on VIMPAT vs placebo (K-M estimate of proportion of PGTCS-free patients, 31.3% vs 17.2% respectively [p=0.011]) at 24 weeks[3]

**CLICK HERE to watch Terry O'Brien present the findings from the VALOR study** – a phase 3, double-blind, placebo-controlled study assessing the efficacy and safety of VIMPAT as add-on therapy for patients with IGE experiencing uncontrolled PGTCS.

**PBS INFORMATION: Partial seizures and primary generalised tonic-clonic seizures.**
**Tablets and Oral solution:** Authority Required (STREAMLINED). Refer to the PBS schedule for full authority information. **Injection:** This product is not listed on the PBS.

**Please review the full Product Information before prescribing.**
The Product Information can be accessed at
**www.ucbpharma.com.au/Vimpat-oral | www.ucbpharma.com.au/Vimpat-IV**

**Abbreviations: ASM,** anti-seizure medication; **IGE,** idiopathic generalised epilepsy; **K-M,** Kaplan-Meier; **PGTCS,** primary generalised tonic-clonic seizure.

**References: 1.** PBS indication: https://www.pbs.gov.au/pbs/search?term=lacosamide. **2.** VIMPAT® Australian Approved Product Information. **3.** Vossler *DG et al. J Neurol Neurosurg Psychiatry* 2020; 91(10):1067–1075.

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## Effectiveness of intranasal mometasone furoate vs saline for sleep-disordered breathing in children

**Authors:** Baker A et al.

**Summary:** The Australian MIST study compared the efficacies of intranasal mometasone furoate and intranasal saline in children with sleep-disordered breathing (SDB). 276 children aged 3–12 years who were referred to a specialist for significant SDB symptoms were randomised to receive intranasal mometasone furoate 50µg or saline 0.9% (one spray in each nostril daily) in a double-blind design. 44% of patients in the mometasone group and 41% in the saline group had resolution of significant SDB symptoms at 6 weeks (p=ns). The most commonly reported adverse events were epistaxis (9.7% of mometasone recipients and 15% of saline recipients) and nasal itch/irritation (9.7% and 18% of patients in the respective groups).

**Comment:** Whether the findings of this study are a result of an equivalence in treatment effect between mometasone and saline or if they reflect natural resolution of the condition is uncertain. It appears possible that a large proportion of children with SDB may be able to be treated successfully by their primary care physician, using 6 weeks of intranasal saline as a first-line treatment to increase the quality of life of children with SDB. There is now an opportunity to further assess the effect of intranasal saline on SDB symptoms in children and to examine the effects of a corticosteroid and saline on the sequelae of SDB. Follow-up of the MIST trial patient cohort is ongoing in the MIST+ study to understand the effect of 6 weeks of intranasal sprays on the rates of tonsillectomy and adenoidectomy over the following 2 years.

***Reference: JAMA Pediatr 2023;177(3):240-7***
Abstract

## Efficacy and safety of dietary therapies for childhood drug-resistant epilepsy

**Authors:** Devi N et al.

**Summary:** This systematic review and meta-analysis evaluated the effects of various dietary therapies in children with drug-resistant epilepsy. A search of PubMed, Embase, Cochrane, and Ovid identified 12 randomised controlled trials of dietary interventions (including the ketogenic diet, modified Atkins diet, and low glycaemic index therapy) involving a total of 907 children that were suitable for inclusion. Short-term (≤3 months) primary outcomes were ≥50% or ≥90% reduction in seizure frequency, and treatment withdrawal due to adverse events. Meta-analysis of the data showed that all dietary interventions were more efficacious than usual care for ≥50% seizure reduction (low glycaemic index therapy: OR 24.7, 95% CI 5.3–115.4; modified Atkins diet: OR 11.3, 95% CI 5.1–25.1; ketogenic diet: OR 8.6, 95% CI 3.7–20.0). In addition, ketogenic diet (OR 6.5, 95% CI 2.3–18.0) and modified Atkins diet (OR 5.1, 95% CI 2.2–12.0) were better than usual care for ≥90% seizure reduction. However, treatment withdrawals due to adverse events were more common with ketogenic diet (OR 8.6, 95% CI 1.8–40.6) and modified Atkins diet (OR 6.5, 95% CI 1.4–31.2) compared with usual care.

**Comment:** The ketogenic diet and the modified Atkins diet are effective therapies for intractable epilepsy. A meta-analysis of 19 observational studies (1084 patients) found that after 6 months, approximately 60% of children started on the classic ketogenic diet had a greater than 50% seizure reduction, with 30% having greater than 90% seizure reduction (J Child Neurol 2006;21(3):193). The modified Atkins diet is an alternative designed to mimic some aspects of the classic ketogenic diet but allowing more ad lib protein, fluids, and calories. The efficacy of the diet has been reported in more than 25 studies, including one randomised trial in children. Overall, 45% of patients have had at least a 50% reduction in seizures after 6 months, with 25% having >90% seizure reduction.

***Reference: JAMA Pediatr 2023;177(3):258-66***
Abstract

## Assessment of infant position and timing of stylet removal to improve lumbar puncture success in neonates (NeoCLEAR)

**Authors:** Marshall ASJ et al.

**Summary:** This open-label trial investigated the impact of infant position and timing of stylet removal on lumbar puncture success in neonates. In 21 UK neonatal and maternity units, 1082 infants requiring lumbar puncture at 27–44 weeks' corrected gestational age and weighing ≥1000g were randomised 1:1:1:1 to sitting position and early stylet removal, sitting position and late stylet removal, lying position and early stylet removal, or lying position and late stylet removal. The primary outcome was successful first lumbar puncture, defined as obtaining a CSF sample with a red blood cell count of <10,000 cells/µl. Successful first lumbar puncture was more frequently observed in sitting than in lying position (63.7% vs 57.6%; adjusted risk ratio 1.10, 95% CI 1.01–1.21; p=0.029; number needed to treat, 16). Timing of stylet removal had no effect on the primary outcome.

**Comment:** Careful positioning is required to accurately identify landmarks and successfully perform a lumbar puncture. An experienced assistant must be available to hold the child in an optimal position. Children should be observed for adequate respiratory function throughout the procedure because positioning may compromise respiratory status and apnoea can occur, especially in young infants. Monitoring should be performed throughout the procedure, with continuous cardiorespiratory monitoring and pulse oximetry. The sitting position may be preferred in children who have the potential for developing respiratory compromise because of hyperflexion of the neck in the lateral recumbent position. This position may also improve flow of CSF in very small infants, but it does not permit accurate measurement of opening pressure and should be avoided when manometry is necessary.

***Reference: Lancet Child Adolesc Health 2023;7(2):91-100***
Abstract



## Resuscitation with intact cord versus clamped cord in late preterm and term neonates

**Authors:** Raina JS et al.

**Summary:** This open-label study in India compared the effect of intact cord versus clamped cord resuscitation on physiological transition in neonates receiving positive-pressure ventilation (PPV) at birth. Neonates born at ≥34 weeks' gestation after a complicated pregnancy or labour were randomised just before birth to receive resuscitation with either an intact cord or after early cord clamping. The allocated intervention was administered if the neonate needed PPV at birth. Among neonates who received PPV, the expanded Apgar score at 5 min (primary outcome) was significantly higher in the intact cord resuscitation group than in the early cord clamping resuscitation group (median 15 vs 14; p<0.001).

**Comment:** The American College of Obstetricians and Gynecologists recommends delaying umbilical cord clamping for at least 30–60 sec after birth in both vigorous term and preterm infants (Obstet Gynecol 2020;136(6):e100). The main advantage of delayed cord clamping is higher infant iron stores at 6 months of age, which may be particularly advantageous when the mother has a low ferritin level or plans to breastfeed without supplementing with iron or fortified formula. This may have favourable long-term developmental effects, since iron deficiency has been associated with impaired neurodevelopment. In preterm infants, an advantage of delayed cord clamping is that it provides more time for the physiological transition from foetal to newborn life. Although a benefit has not been demonstrated consistently, delayed cord clamping is unlikely to be harmful in preterm infants, even those who are small for gestational age (Am J Obstet Gynecol 2022;226(2):247).

***Reference: J Pediatr 2023;254:54-60.e4***
Abstract

## Pediatric button battery ingestion: A single center experience and risk score to predict severe outcomes

**Authors:** Scalise PN et al.

**Summary:** The medical records of 143 patients who ingested a button battery in 2008–2021 and were evaluated at a single high-volume centre in the US were analysed. 24 (17%) patients had a severe outcome (at least one of the following: deep/circumferential mucosal erosion, perforation, mediastinitis, vascular or airway injury/fistula, or development of oesophageal stricture). Multivariate analysis determined that independent predictors of a severe outcome included location of the battery in the oesophagus on imaging (96%), battery size ≥2cm (95%), and presence of any symptoms on presentation (96%). The predicted probability of a severe outcome ranged from 88% when all three risk factors were observed to 0.3% when none of them were present.

**Comment:** Most battery ingestions occur in children younger than 6 years of age, with the peak frequency between 1–2 years of age. Most batteries are ingested immediately after removal from a product. For asymptomatic children with acute (within 12h) button battery ingestions who are older than 1 year, one oral dose of pure honey (e.g., 5–10ml) should be given as soon as possible after ingestion. Button batteries that are lodged in the oesophagus are of particular concern and should be removed promptly with direct endoscopic visualisation by an appropriate specialist (paediatric gastroenterologist, otolaryngologist, or surgeon). Complications from button battery ingestion include tracheoesophageal fistula, vocal cord paralysis, subglottic and tracheal stenosis, oesophageal perforation or stenosis, and intestinal perforation. As with other ingestions, primary prevention is preferable to treatment, with close supervision of children and the proper disposal of batteries.

***Reference: J Pediatr Surg 2023;58(4):613-8***
Abstract