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Journal Review

Journal watch: Neonatology, allergies and more

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Source: Branagan A, Yu I, Gurusamy K, Miletin J. (2023). Thresholds for surfactant use in preterm neonates: A network meta-analysis. *Archives of Disease in Childhood. Foetal and Neonatal Edition*, 108(4), 333–341. https://doi.org/10.1136/archdischild-2022-324184

The researchers conduct a network meta-analysis of various surfactant treatment strategies for respiratory distress syndrome (RDS) with a focus on determining whether a specific fraction of inspired oxygen (FiO_2) is more effective for selective surfactant therapy.

To achieve this, the researchers carried out a systematic review and network meta-analysis using Bayesian analysis of randomised and controlled trials. The trials compared prophylactic versus selective surfactant treatments for RDS. The participants in the studies were infants under 32 weeks of gestational age. All infants received intratracheal surfactant and the type or dosage of surfactant was not a factor in the analysis. The primary outcome measure was neonatal mortality and the researchers compared this outcome among groups receiving selective surfactant therapy at different FiO_2 thresholds. Secondary outcomes included respiratory morbidity and major complications of prematurity. After identifying and including 14 studies involving 5298 participants out of 4643 references, the researchers found no statistically significant differences between the 30%, 40% and 50% FiO_2 thresholds. However, in a sensitivity analysis of infants treated during a period of high antenatal steroid use and nasal continuous positive airway pressure as the initial mode of respiratory support, the results indicated no difference in mortality, RDS or intraventricular haemorrhage alone. Yet, there was a potential increase in combined major morbidities observed at the 60% of FiO_2 threshold.

In conclusion, the study suggests that surfactant treatment does not show a clear advantage at any specific FiO_2 threshold. The 60% of FiO_2 threshold may lead to increased morbidity, but no advantage was observed with prophylactic treatment. The researchers emphasise the urgent need for randomised trials exploring different surfactant delivery thresholds to provide more conclusive evidence and guidance to clinicians.

Source: Bhattacharjee E, Thiruvengadam R, Ayushi Das C, GARBH-Ini Team, Wadhwa N, Natchu UC, *et al.* (2023). Genetic variants associated with spontaneous preterm birth in women from India: A prospective and cohort study. *The Lancet Regional Health. South-east Asia*, 14, 100190. https://doi.org/10.1016/j.lansea.2023.100190

Despite being a region with the highest number of pre-term births worldwide, there is a notable absence of genomic studies on pre-term birth in India and other South-Asian countries. To address this gap, the authors undertook a groundbreaking genome-wide association study of spontaneous pre-term birth (sPTB) in a cohort of 6211 women from India.

In their study, the authors employed a novel resampling technique to identify relevant single nucleotide polymorphisms (SNPs) associated with sPTB, followed by haplotype association analysis and imputation. They discovered that 512 maternal SNPs showed a significant association with sPTB ($P < 2.51e-3$) and after Bonferroni correction, the minor allele of 19 SNPs exhibited an increased genotype relative risk. Notably, six of these 19 SNPs (rs13011430, rs8179838, rs2327290, rs4798499, rs7629800 and rs13180906) were found to be part of haplotypes that were also associated with sPTB ($P < 9.9e-4$; Bonferroni adjusted $P < 0.05$).

Furthermore, through imputation in the vicinity of the 19 SNPs, the researchers identified 15 additional imputed SNPs that were significantly associated with sPTB (Bonferroni adjusted $P < 0.05$). Interestingly, one of these imputed SNPs, rs35760881, along with three other SNPs (rs17307697, rs4308815 and rs10983507), had previously been reported to be linked to sPTB in women of European ancestry.

Moreover, the study revealed that the GG genotype at rs1152954, one of the associated SNPs, not only increased the risk of sPTB but also led to a reduction in telomere length. This study marks the first-ever genomic investigation in South Asia to identify maternal SNPs associated with sPTB. These specific SNPs were found to impact genes associated with critical pathways in sPTB, including inflammation, apoptosis, cervical ripening, telomere maintenance, selenocysteine biosynthesis, myometrial contraction and innate immunity.

From a public health perspective, the discovery of four transethnic associated SNPs identified in this study could aid in stratifying women at risk of sPTB across diverse populations, making a significant contribution to managing and preventing preterm births worldwide.

Source: Mani S, Hazra S, Hagan J, Sisson A, Nair J, Pammi M. (2023). Viral infections and neonatal necrotising enterocolitis: A meta-analysis. *Pediatrics,* 152(1), e2022060876. https://doi.org/10.1542/peds.2022-060876

Necrotising enterocolitis (NEC) is a severe intestinal disease that affects premature infants. Recent research has implicated viral infections in its development. To investigate the connection between viral infections and NEC comprehensively, a systematic review and meta-analysis were conducted. The analysis included 29 observational studies examining the association between viral infections and NEC, with 24 of these studies used for the meta-analysis.

The results of the meta-analysis demonstrated a significant association between viral infections and NEC, with an odds ratio (OR) of 3.81 (95% confidence interval [CI]: 1.99–7.30) based on the 24 studies analysed. Even after removing outliers and studies with poor methodology, the association remained significant, showing an OR of 2.89 (95% CI: 1.56–5.36) from 22 studies and an OR of 3.33 (95% CI: 1.73–6.43) from 22 studies, respectively.

Subgroup analyses based on the birth weight of participants revealed that studies focusing solely on very low birth weight infants showed a significant association with NEC, yielding an OR of 3.62 (95% CI: 1.63–8.03) from eight studies. Similarly, studies involving non-very low birth weight infants also exhibited a significant association, with an OR of 5.28 (95% CI: 1.69–16.54) from six studies.

In addition, subgroup analyses based on specific viruses found that infections with rotavirus (OR: 3.96, 95% CI: 1.12–13.95, 10 studies), cytomegalovirus (OR: 3.50, 95% CI: 1.60–7.65, 5 studies), norovirus (OR: 11.95, 95% CI: 2.05–69.84, 2 studies) and astrovirus (OR: 6.32, 95% CI: 2.49–16.02, 2 studies) were significantly associated with NEC.

It is essential to acknowledge that this study had limitations, particularly the heterogeneity among the included studies. Nevertheless, the findings highlight a clear association between viral infections and an increased risk of NEC in premature infants. To further understand the impact and potential preventive measures against viral infections and NEC incidence, future well-designed and prospective studies are warranted.

Source: Nivins S, Klingberg T. (2023). Effects of prenatal exposure to maternal diabetes mellitus on deep grey matter structures and attention deficit hyperactivity disorder symptoms in children. *Acta Paediatrica* (*Oslo, Norway: 1992*), 112(7), 1511–1523. https://doi.org/10.1111/apa.16756

A study investigated the neurological mechanism that links maternal diabetes mellitus (DM) to the risk of attention deficit hyperactivity disorder (ADHD) symptoms and working memory deficits in children. The research included 6291 children (52% boys) born after 28 weeks of gestation, who underwent brain magnetic resonance imaging scans at 9–10 years of age. The study estimated subcortical brain volumes from the T1-weighted images, assessed ADHD symptoms through parental/caregiver reports using the Child Behaviour Checklist and evaluated working memory performance with the NIH Toolbox.

Comparing children exposed to DM ($n = 422$) to unexposed children, those exposed to DM had smaller pooled deep grey matter (GM) volumes ($\beta = -0.15$, $P = 0.001$). Further analysis revealed smaller volumes in the caudate nucleus, putamen, thalamus and cerebellum, but not in the hippocampus. In addition, altered cortico-striatal white matter projection tracts were observed in children exposed to DM.

Although DM exposure during pregnancy was not associated with working memory deficits or inattention, it was linked to increased hyperactivity/impulsivity and sluggish cognitive tempo symptoms in boys. Notably, the hyperactivity/

impulsivity symptoms in boys were partially mediated by smaller deep GM volume. This suggests that exposure to DM during pregnancy impacts the development of deep GM in offspring during late childhood, contributing to an elevated risk of hyperactivity/impulsivity symptoms in boys.

These findings provide novel insights into the neurobiological underpinning of ADHD in offspring with prenatal exposure to maternal diabetes.

Source: Meyer A, Mazzara C, Lava SA, Treglia G, Bianchetti MG, Goeggel Simonetti B, *et al*. (2023). Neurological complications of rotavirus infection in children: A systematic review and meta-analysis. *Acta Paediatrica* (*Oslo, Norway: 1992*), 112(7), 1565–1573. https://doi.org/10.1111/apa.16775

In a comprehensive investigation, the clinical characteristics and outcomes of paediatric patients experiencing neurological complications related to rotavirus infection were systematically reviewed. The study encompassed a systematic literature review and meta-analysis, analysing articles published between 1984 and 2020.

The identified neurological complications were categorised into four groups: Encephalitis, cerebellitis, encephalo-cerebellitis and benign convulsions with mild gastroenteritis (CwG). A total of 68 reports meeting the research criteria were analysed, resulting in the collection of 99 cases of CwG, 39 cases of encephalitis, 18 cases of encephalo-cerebellitis and five cases of cerebellitis. The majority of patients (95) were from Asia and the median age at diagnosis was 22 months (with an interquartile range of 14–29 months). It was observed that children who developed CwG were significantly younger (median age of 19 months, interquartile range 12–24 months) compared to those with other neurological complications ($P < 0.0001$).

Among the patients, 23% of those with encephalitis and 5% of those with CwG experienced status epilepticus. The most commonly reported neuroimaging finding was lesions of the splenium of the corpus callosum. Fatal events were reported in four cases of encephalitis, whereas no fatalities were documented in the other groups. Among the surviving children, the encephalo-cerebellitis group showed the most severe long-term outcome. Conversely, all cases of CwG achieved full recovery.

The study findings suggest that older age at diagnosis and the development of encephalo-cerebellitis are associated with a higher risk of long-term complications. This comprehensive analysis sheds light on the clinical presentation and outcomes of paediatric patients with neurological complications related to rotavirus infection and highlights potential risk factors for adverse long-term effects.

Source: Lisik D, Ermis SS, Ioannidou A, Milani GP, Nyassi S, Spolidoro GC, *et al*. (2023). Siblings and risk of allergic rhinitis: A systematic review and meta-analysis. *Paediatric Allergy and Immunology: Official Publication of the European Society of Paediatric Allergy and Immunology,* 34(7), e13991. https://doi.org/10.1111/pai.13991

Based on the 'hygiene hypothesis' and the rising prevalence of allergic rhinitis and other atopic diseases, various studies have explored whether sibship composition could act as a protective factor, but the results have been contradictory. This study aimed to comprehensively analyse global literature to investigate the connection between birth order, sibship size (number of siblings) and the risk of allergic rhinitis.

To conduct this analysis, 15 databases were systematically searched without any restrictions on publication date or language. The researchers included observational studies that defined sibship composition (birth order or sibship size) as the exposure and allergic rhinitis or allergic rhinoconjunctivitis (self-reported or clinically diagnosed) as the outcome. The process of study selection, data extraction and quality assessment was carried out independently in pairs and relevant data were summarised.

In total, 76 reports involving over two million subjects were identified and analysed. The results showed that being a second- or later-born child was associated with a protective effect against both current (pooled risk ratio [RR]: 0.79, 95% confidence interval [CI]: 0.73–0.86) and ever (RR: 0.77, 95% CI: 0.68–0.88) allergic rhinitis. Having siblings, regardless of birth order, was also linked to a reduced risk of current allergic rhinitis (RR: 0.89, 95% CI: 0.83–0.95) and allergic rhinoconjunctivitis (RR: 0.92, 95% CI: 0.86–0.98). These effects remained consistent across different age groups, time periods and geographical regions.

In conclusion, the study's findings suggest that primarily, higher birth order and to a lesser extent, the number of siblings is associated with a lower risk of developing allergic rhinitis. This analysis adds valuable insights into the potential protective role of sibship composition in the context of allergic rhinitis and its association with the hygiene hypothesis.

Source: Shaikh N, Hoberman A, Shope TR, Jeong JH, Kurs-Lasky M, Martin JM, *et al*. (2023). Identifying children likely to benefit from antibiotics for acute sinusitis: A randomised and clinical trial. *JAMA,* 330(4), 349–358. https://doi.org/10.1001/jama.2023.10854

A study aimed to investigate the potential benefit of antibiotic therapy in specific subgroups of children diagnosed with acute sinusitis. The symptoms of acute sinusitis often overlap with viral upper respiratory tract infections, which may indicate that some children receiving antibiotics may not experience significant benefits from this treatment. The researchers conducted a randomised and clinical trial involving 515 children aged 2–11 years diagnosed with acute sinusitis based on clinical criteria.

The trial, conducted between February 2016 and April 2022 at primary care offices affiliated with 6 US institutions, assessed symptom burden in subgroups defined by nasopharyngeal bacterial cultures of *Streptococcus pneumoniae*, *Haemophilus influenzae* or *Moraxella catarrhalis* and the presence of coloured nasal discharge. The children were randomly assigned to receive either oral amoxicillin and clavulanate (antibiotic group) or placebo for a duration of 10 days.

The primary outcome measured was symptom burden based on daily symptom scores using a validated scale over the 10-day period after diagnosis. Secondary outcomes included treatment failure, adverse events (including clinically significant diarrhoea) and resource use by families.

Most of the 510 included children aged 2–5 years, male, White and non-Hispanic. The study found that the mean symptom scores were significantly lower in the antibiotic group compared to the placebo group. The time to symptom resolution was also shorter in the antibiotic group than in the placebo group.

Interestingly, children without nasopharyngeal bacterial pathogens detected did not benefit as much from antibiotic treatment as those with detected pathogens. The difference in mean symptom scores between the two groups was smaller in those without pathogens detected compared to those with pathogens detected.

Furthermore, the presence of coloured nasal discharge did not significantly affect the efficacy of antibiotic treatment. The study suggests that testing for specific bacteria on presentation may serve as a strategy to reduce unnecessary antibiotic use in children with acute sinusitis.

Overall, the study highlights the potential limited benefit of antibiotics in certain subgroups of children with acute sinusitis, emphasising the importance of targeted and appropriate use of antibiotics to reduce antibiotic resistance and adverse effects.

Source: Knuf M, Charkaluk ML, The Nguyen PN, Salamanca de la Cueva I, Köbrunner P, Mason L, *et al*. (2023). Penta- and hexavalent vaccination of extremely and very-to-moderate preterm infants born at <34 weeks and/or under 1500 g: A systematic literature review. *Human Vaccines and Immunotherapeutics*, 19(1), 2191575. https://doi.org/10.1080/21645515.2023.2191575

Combined vaccines, such as penta and hexavalent vaccines used to protect against multiple childhood diseases, are commonly administered to healthy full-term babies. However, there is ongoing debate regarding the effectiveness of these vaccines in high-risk infants, including those born prematurely at <34 weeks of pregnancy, those with a birth weight below 1500 g or babies with chronic diseases.

To address this uncertainty, we conducted a systematic literature search to identify studies focusing on high-risk infants vaccinated with penta or hexavalent vaccines. Our investigation centred on examining their antibody levels post-vaccination, potential side effects and the extent of protection conferred against the targeted diseases. In addition, we analysed whether these high-risk infants received vaccinations on schedule, in line with recommendations for healthy full-term babies.

Among the 14 studies identified that included premature infants, the results indicated that the immune systems of premature babies generally respond similarly to penta and hexavalent vaccines as those of full-term infants. Most side effects observed in premature infants were comparable to those experienced by full-term infants, but some adverse effects, such as pauses in breathing, slow heart rate or low blood oxygen levels, appeared to be more frequent in preterm babies. Therefore, close monitoring of these infants after vaccination is recommended for safety purposes.

It was also noted that preterm babies often received vaccinations with a delay compared to the recommended schedule for full-term babies. However, no studies provided data on the level of protection achieved against the diseases covered by penta and hexavalent vaccinations in preterm infants.

While the available evidence sheds light on the response of premature infants to penta and hexavalent vaccines, further research is needed to investigate the vaccination outcomes in other high-risk populations beyond those born prematurely. This would help to better understand the efficacy and safety of these combined vaccines in a wider range of vulnerable infants, including those with other underlying health conditions.

Source: GBD 2019 Meningitis Antimicrobial Resistance Collaborators (2023). Global, regional and national burden of meningitis and its aetiologies, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *The Lancet. Neurology,* 22(8), 685–711. https://doi.org/10.1016/S1474-4422(23)00195-3

Despite efforts to prevent meningitis, it continues to cause a significant number of deaths worldwide each year. The World Health Organization has set ambitious goals to reduce meningitis cases by 2030 and monitoring trends in the global burden of meningitis can help assess progress and identify areas that need improvement. To achieve this, the researchers utilised data from the Global Burden of Diseases, Injuries and Risk Factors Study (GBD) 2019.

Their aim was to assess incident cases and deaths related to acute infectious meningitis, categorised by age and aetiology, from 1990 to 2019 across 204 countries and territories. Meningitis mortality was modelled using data from vital registration, verbal autopsy, sample-based vital registration and mortality surveillance. Meningitis morbidity was

modelled using a Bayesian compartmental model, which combined data from published literature identified through a systematic review, surveillance data, inpatient hospital admissions, health insurance claims and cause-specific meningitis mortality estimates.

For aetiology estimation, a network analysis model was applied to analyse data from various sources, including causes of death, vital registration, hospital discharge, microbial laboratory and literature studies. This allowed them to estimate the proportion of meningitis deaths and cases attributable to specific pathogens.

The results showed that in 2019, there were approximately 236,000 deaths and 2.51 million incident cases of meningitis globally. The burden was highest among children under 5 years old, with 112,000 deaths and 1.28 million incident cases in that year. Age-standardised mortality rates decreased from 1990 to 2019.

The most significant contributors to meningitis deaths in 2019 were *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Klebsiella pneumoniae*. Notably, *Haemophilus influenzae* showed the most substantial reduction in deaths among children under 5 years between 1990 and 2019.

While progress has been made in reducing meningitis mortality, more deaths could be prevented by rapidly scaling up immunisation efforts and improving access to healthcare services. Further reduction in the global meningitis burden can be achieved through the use of low-cost multivalent vaccines, enhanced access to accurate and rapid diagnostic tests, improved surveillance and early treatment. These measures play a crucial role in combating meningitis effectively.

Source: Dahan E, El Ghazal N, Nakanishi H, El Haddad J, Matar RH, Tosovic D, *et al*. (2023). Dexamethasone versus prednisone/prednisolone in the management of paediatric patients with acute asthmatic exacerbations: A systematic review and meta-analysis. *The Journal of Asthma: Official Journal of the Association for the Care of Asthma,* 60(8), 1481–1492. https://doi.org/10.1080/02770903.2022.2155189

The frequent occurrence of acute asthmatic exacerbation in paediatric emergency visits has led to the increasing use of dexamethasone (DEX) as an alternative to prednisone in managing this condition. To assess the safety and efficacy of DEX compared to prednisone/prednisolone (PRED) in paediatric patients with acute asthma exacerbation, a systematic review was conducted.

The review involved searching Cochrane, Embase, PubMed, Scopus and Web of Science for articles from their inception to August 2022. Seventeen studies, involving 5967 paediatric patients with asthma exacerbation treated with either DEX (n = 2865) or PRED (n = 3102), met the eligibility criteria. Baseline patient characteristics, such as age, sex, paediatric respiratory assessment measure, previous corticosteroid and beta-agonist inhaler use, were comparable between the two groups.

After treatment administration, the DEX group exhibited fewer incidents of vomiting (odds ratio [OR] = 0.24, 95% confidence interval [CI]: 0.11, 0.51, I^2 = 58%) and reduced noncompliance events (OR = 0.12, 95% CI: 0.04, 0.34, I^2 = 0%) compared to the PRED group. However, there were no significant differences between the two groups in terms of hospital admission rates (OR = 0.83, 95% CI: 0.58, 1.19, I^2 = 15%), time spent in the emergency department (mean difference = −0.11 h, 95% CI: −0.52; 0.30, I^2 = 82%) or relapse occurrences (OR = 0.67, 95% CI: 0.30, 1.49, I^2 = 52%).

In conclusion, while there were no substantial differences in hospital admission rates, time spent in the emergency department or relapse events between the DEX and PRED groups, paediatric patients receiving DEX experienced lower rates of non-compliance and vomiting incidents. This suggests that DEX may be a favourable option for managing acute asthmatic exacerbation in paediatric patients due to its better tolerability in terms of adverse events. However, further research may be required to fully assess the long-term safety and efficacy of DEX compared to prednisone/prednisolone in this population.

Source: Gould L, Delavale V, Plovnick C, Wisniewski T, Devinsky O. (2023). Are brief febrile seizures benign? A systematic review and narrative synthesis. *Epilepsia, 10.1111/epi.17720. Advance Online Publication*. https://doi.org/10.1111/epi.17720

Febrile seizures are a relatively common occurrence in 2–5% of U.S. children and are generally considered harmless, although they do carry an increased risk of epilepsy and, in rare cases, sudden unexplained death. To understand the impact of simple and complex febrile seizures on young children, the authors compared rates of mortality, neurodevelopmental disorders and neuropathology with healthy controls.

For this analysis, they systematically reviewed studies that included 3–72-month-old children with simple or complex febrile seizures lasting <30 min. The search for outcome measures related to mortality, neurodevelopment or neuropathology was conducted up to 18 July 2022. Bias risk was assessed based on the study design and each outcome measure was analysed separately.

A total of 26 studies met the criteria, comprising 2665 children with febrile seizures and 1206 seizure-free controls. The study designs varied, including cohort studies, cross-sectional studies, case–control studies, series and case reports. Mortality outcomes showed significant variations, with cohort studies reporting no deaths among children after febrile seizures, while child death series and case reports

identified a mortality rate of 24.1% (108/449) associated with simple and brief complex febrile seizures.

Minor hippocampal histopathological anomalies were commonly observed in sudden deaths, regardless of febrile seizure history. Most electroencephalogram studies showed normal results and neuroimaging studies suggested increased right hippocampal volumes. Neurodevelopmental issues were often present before febrile seizure onset. Bias risk was higher in cohort and case–control studies compared to other study designs.

The research on outcomes after simple or brief complex febrile seizures is currently limited, with cohort studies suffering from small sample sizes, bias risk and inadequate follow-up durations. Sudden death registries, although focused on a small percentage of cases, strongly suggest an association between simple febrile seizures and increased mortality. Most children with febrile seizures tend to have positive outcomes, but longer-term prospective studies are required to gain a more comprehensive understanding of the implications of these seizures on children's health and well-being.

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