

Randomised controlled trials in child and adolescent health in 2023

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ABSTRACT

In the year July 2022 to June 2023 there were 501 publications from randomised controlled trials (RCTs) in child and adolescent health in developing countries identified through a standardised search strategy that has been going for 20 years. This year, trials addressed the widest range of diseases and conditions that affect the health, development and well-being of children, newborns, adolescents and mothers. RCTs reflected old, neglected and new problems, the changing epidemiology of child health, social and economic circumstances in many countries, local and global priorities of low-income and middle-income countries, environmental causes of poor child health, and inequities. The RCTs tested new and refined treatments, diagnostics, vaccines, holistic management, and prevention approaches, and explored many outcomes, including mortality, nutrition, psychosocial measures, and neurodevelopment. The studies were conducted in numerous hospitals and healthcare clinics, schools, and communities, including among some of the world's most disadvantaged populations in humanitarian and refugee emergencies. Some studies are of the highest quality, and others fall short. Many RCTs will influence guidelines, practice and policies for years to come.

For 20 years I have tried to summarise the evidence on child and adolescent health derived from randomised controlled trials (RCTs) in developing countries and publish it each year. The aim I started with was to make this information accessible to doctors, nurses and other care health workers in resource-poor settings where up-to-date information is hard to find. Working as a paediatrician in a hospital in a rural province, I had known the lack of information in a remote setting, the slowness of the internet when we only had dial-up connections, the high cost of medical journals, and lack of time to search and interpret evidence.

I hoped that this information on RCTs would be helpful in reviewing treatment policies, clinical guidelines, and teaching paediatrics and evidence-based medicine, that if it taught others half as much as what it taught me it would help many people working in similar settings. The world has changed in the last 20 years, and there are now many more sources of information, including the development of open access journals, and social media. Twenty years ago, very few RCTs were published as open access, now a very high proportion are. But still a healthcare worker might not have the time to search and find many publications, and with the vast expansion of information in the social media

age comes added complexity, so I hope such an annual summary remains useful.

The method of searching for studies uses PubMed, a search engine that is freely available and widely used throughout the world (<http://www.ncbi.nlm.nih.gov/sites/entrez>). The search strategy was chosen to capture as many relevant studies as possible and is reproducible by anyone with access to the internet. In 2021–2022 I used a simpler search to save time during the COVID-19 pandemic, but many trials were missed. This year I returned to the more complex search strategy that I had used for over 10 years (box 1). I revised the search weekly and added a system of checking, so I am more confident that virtually all studies are captured.

The search yielded 4216 articles, of which 501 publications reporting results from RCTs were identified. These studies were conducted in countries from all regions of the world.

Most of the papers are accessible free online, which can be found via the hyperlink in the title. Through HINARI (Health Network Access to Research Initiative) (<http://www.partnership.who.int/hinari>) a programme set up by WHO in collaboration with publishers, the full-text versions of over 14 000 journal titles and 30 000 e-books are available to health institutions in over 100 countries. Eligible health institutions (medical school, teaching hospital, nursing school, government office) can check their eligibility and register online with HINARI.

The full list of the 501 trials, are available as an online supplemental appendix to this article, and previous editions (2002–2022) are at <https://pngpaediatricsociety.org/research-2/>

Several trials from this year will lead to significant changes in child health recommendations. A summary of some of the important results from July 2022 to June 2023:

- Multiple studies of the typhoid Vi-polysaccharide conjugate vaccine were published this year, from Malawi,^{1,2} India,^{3,4} Nepal,^{5,6} and Bangladesh⁷ and China,⁸ showing a single dose of the vaccine results in very high levels of seroconversion among children aged 9 months to 12 years and sustained for up to 3 years, and no interference with measles or measles-mumps-rubella vaccines.
- A number of trials this year, including the ODYSSEY trial (in South Africa, Uganda and Zimbabwe showed the greater efficacy of dolutegravir (DTG)-based anti-retroviral therapy (ART) over previous standard of care (mainly protease inhibitor-based) and a lower



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Box 1 Search strategy

Pubmed Advanced strategy, search: ("Developing Countries"(Mesh) OR (austere OR limited resource* OR "resource limited" OR low resource* OR transitioning econom* OR lami countr* OR transitional countri* OR "low gdp" OR "low gnp" OR "low gross domestic" OR "low gross national" OR ((emerging OR developing OR "low income" OR "middle income" OR (low AND middle) OR underdeveloped OR "under developed" OR under-developed OR underserved OR "under served" OR under-served OR (less-developed) OR deprived OR poor) AND (countr* OR nation* OR econom* OR population OR world)) OR "third world" OR LMIC OR LMICs) OR "Africa"(Mesh) OR "caribbean region"(Mesh) OR "central america"(Mesh) OR "latin america"(Mesh) OR "mexico"(Mesh) OR "south america"(Mesh) OR "europe, eastern"(Mesh) OR "indian ocean islands"(Mesh) OR "pacific islands"(Mesh) OR "New Guinea"(Mesh) OR India OR Africa OR Asia OR South-America OR Papua-New-Guinea OR Pacific) AND (newborn* OR new-born* OR baby OR babies OR neonat* OR neo-nat* OR infan* OR boy OR boys OR girl OR girls OR child OR children OR childhood OR pediatric* OR paediatric* OR adolescen* OR youth OR youths OR teen OR teens OR teenage*) AND (randomized controlled trial(pt) OR controlled clinical trial(pt) OR randomized-controlled-trial*(tiab) OR randomised-controlled-trial*(tiab) OR randomized-trial*(tiab) OR randomised-trial*(tiab) NOT (animals(mh) NOT humans(mh))): Publication date between 1 July 2022 and 30 June 2023.

risk of treatment failure in infants and young children living with HIV.⁹ In children with HIV-TB coinfection, twice-daily DTG is safe and itovercomes the rifampicin enzyme-inducing effect in children that reduces DTG blood levels with once daily dosing.¹⁰

- ▶ In a systematic review of studies of children with uncomplicated pneumonia, 5 days of amoxicillin as recommended by WHO was as effective as longer courses.¹¹ In Pakistan, 3 days of amoxicillin for clinical 'fast-breathing' acute respiratory infection, was as effective as longer courses of cotrimoxazole. These studies need to be understood in the context of the high proportion of cases of acute lower respiratory infection (ALRI) being viral, and the power of a study to detect a difference in outcomes for bacterial pneumonia is lower than the sample size suggests.¹²
- ▶ Assessment of risk is increasingly a focus to guide decisions about hospital admission, location and nature of care, and safety of discharge. In a systematic review of 27 RCTs and other trials, postdischarge mortality in children was significantly increased by anaemia (OR 1.72, 95% CI 1.22 to 2.44), severe malnutrition (RR=3.12, 95% CI 2.02 to 4.68; $p < 0.0001$), HIV, bacteraemia and hypoxia.¹³
- ▶ In the Congo, probiotics added to ready-to-use therapeutic feeds for children with severe malnutrition had moderate effects on reduction in the number of days of diarrhoea, the risk of diarrhoea and the proportion of children who had nutritional recovery at 6 weeks.¹⁴ In a small RCT in Indian children, 3 months of a daily probiotic (*Bacillus clausii* UBBC-07) reduced upper respiratory infections; the mechanism seemed to be improving mucosal immunity with decreased IgE and increased salivary IgA.¹⁵
- ▶ Systematic reviews showed that continuous positive airway pressure (CPAP) can be effective in severe ALRI, with the strongest evidence in infants with bronchiolitis, and in a

safe content (adequate staffing, including doctor oversight, intensive monitoring and supportive care, and technician and infrastructure capacity). At the other end of the ALRI spectrum, home management of what WHO calls 'chest indrawing' ALRI can be effective, but again is only safe in certain contexts. To be safe there needs to be a system of risk assessment including clinical danger signs, oxygen saturation, and the presence of comorbidities such as undernutrition, anaemia or HIV, and parental understanding of when to return and ability to do so.^{16 17}

- ▶ Among Malaysian school children with asthma, interactive messages using a mobile phone App, increased asthma knowledge compared with face-to-face education.¹⁸
- ▶ Trials of adolescent leadership and community youth teams in rural India increased school participation; other positive impacts may have been undermined by household poverty.¹⁹
- ▶ Several studies in India aimed to evaluate interventions to improve adolescent mental health in India. Remote online interventions had limited acceptability, a school-based mixed-gender body image intervention with a trained psychologist resulted in sustained improvements in many areas,²⁰ and teaching of problem solving skills by a lay counsellor resulted in such skills being sustained and generalised beyond the original presenting problems.²¹
- ▶ In a trial involving 157 schools in Zambia over 2 years, economic support in combination with comprehensive sexuality education and community dialogue can improve the sexual and reproductive health of adolescent girls. An essential factor was economic support.²² In a trial in Uganda, family based economic strengthening for 613 adolescents living with HIV improved school enrolment, reduced school dropouts, and improved antiretroviral therapy adherence and savings.^{23 24}
- ▶ In Zambia, among adolescent girls in a large cluster RCT of schools over 3 years, addressing the knowledge gaps in sexual and reproductive health through comprehensive sexuality education and improving access to sexual and reproductive health services significantly reduced inschool pregnancies.²⁵
- ▶ In Tanzania, girl-friendly medicine shops increased access to sexual and reproductive health products and services, including HIV self-testing kits and contraception among adolescent girls.²⁶
- ▶ Among Tibetan children aged 9–12 years from single-parent families, 6 weeks of mindfulness training effectively improved self-compassion and resilience when added to the normal school education curriculum, compared with similar children who were randomised to normal education alone, although there was no difference in overall mental health scores.²⁷
- ▶ In Cambodia, daily Spirulina, a nutritional supplement to enhance child nutrition, improved weight gain and reduced anaemia in a small RCT involving 173 preschool children.²⁸
- ▶ In a large trial of over 21 000 births in Burkina Faso, a single dose of azithromycin in the neonatal period did not influence all-cause mortality at 12 months. However the infant mortality rate overall was low at 5.3 per 1000 neonates enrolled.²⁹ Several studies further analysed the earlier trial from Niger which had shown a mortality benefit of biannual azithromycin in very high mortality settings.
- ▶ Among 29 278 women intending to have a vaginal birth, azithromycin resulted in a lower risk of sepsis or death compared with the placebo group (1.6% vs 2.4%), with a

relative risk of 0.67 (95% CI, 0.56 to 0.79); there was no effect on neonatal sepsis, stillbirth or neonatal death.³⁰

- ▶ In a large RCT involving 34 villages in a poor rural area in Maharashtra state, India, village health volunteers that engaged in newborn care, disease management and behaviour change communications resulted in large and sustained reductions in infant and child mortality.³¹
- ▶ The benefits of delayed cord clamping or umbilical cord milking in late-preterm and term infants who are active at birth was again shown in trials and systematic reviews, with improvements in haemoglobin at 48 hours and 6 weeks.^{32–34} However, how best to manage non-vigorous infants where delayed cord clamping is made difficult by the need for some resuscitation was also studied this year. Two RCTs showing blood pressure in the first 6 hours, haemoglobin at 48 hours and 6 weeks, and ferritin levels at 6 weeks were higher in babies who had umbilical cord milking after cutting, compared with those who had early cord cutting alone.³⁵ These results guide what to do for the baby who is not vigorous and needs some resuscitation.³⁶
- ▶ In Kenya, within an RCT of diarrhoea prevention, hand-washing after handling animals (adjusted OR=0.20; 95% CI 0.06 to 0.50) and before eating (adjusted OR=0.44; 95% CI 0.26 to 0.73) were strongly associated with lower risk of diarrhoea. Living in a household with vinyl-covered dirt floors was associated with an increased risk of diarrhoeal pathogen isolation. Reducing animal cohabitation, improving flooring and handwashing are important in diarrhoea prevention.³⁷ In other studies in Kenya, water, hygiene and sanitation, maternal, newborn and child health, nutrition and early childhood development programmes reduced all-cause diarrhoea and led to improvements in water quality.³⁸
- ▶ Several other studies and a large meta-analysis proved that WASH (water, sanitation and hygiene) interventions: sewer connections to houses, water purification at the point of use, and promotion of handwashing with soap consistently and substantially reduced diarrhoea risk.³⁹
- ▶ In a meta-analysis of studies of benzodiazepine-resistant status epilepticus, phenobarbital was the most effective agent for seizure cessation within 60 min of administration, more effective than phenytoin, but phenobarbitone was associated with increased need for intubation. High-dose levetiracetam, high-dose valproate and fosphenytoin were also effective.⁴⁰
- ▶ In poor communities in India, for people living with epilepsy, home care with antiseizure medication provision, adherence reinforcement and epilepsy self-management, and stigma management by a trained primary healthcare worker was associated with improved medication adherence and reduced seizures compared with routine clinic care.⁴¹
- ▶ In neonates with seizures in India, in a small RCT of the acute management with levetiracetam and phenobarbitone were equally efficacious for clinical neonatal seizure control, but need for increased respiratory support was found with phenobarbitone use.⁴²
- ▶ In a meta-analysis of studies of children undergoing surgery, intraoperative intravenous crystalloids substantially reduced postoperative vomiting, nausea, thirst and the need for antiemetics.⁴³
- ▶ In India, another trial of intravenous fluids comparing 0.45% sodium chloride (NaCl) and 0.9% NaCl resulted in significant falls in sodium levels in children in an emergency department treated with the hypotonic fluid at 12 hours and 24 hours, but no difference at 48 hours.⁴⁴ However in neonates >34 weeks gestation in intensive care, 0.9% NaCl was associated with hypernatraemia (serum sodium >145 mmol/L).⁴⁵ So isotonic fluid is the standard of care for children, but not for neonates in intensive care.
- ▶ In children undergoing abdominal surgery in India, intraoperative fluid therapy based on the Plethysmographic Variability Index (PVI) derived from pulse oximetry significantly reduced the volume of intravenous crystalloids administered to children undergoing open bowel surgery. PVI is the percentage difference between the maximum and minimum plethysmographic wave on a pulse oximeter throughout the respiratory cycle.⁴⁶
- ▶ In children in India with ventilator-associated Gram-negative pneumonia, nebulised Colistin and systemic antibiotics compared with systemic antibiotics alone reduced the duration of mechanical ventilation, postoperative ICU and hospital stay.⁴⁷
- ▶ In South African children with sickle-cell disease during a vaso-occlusive pain crisis and acute chest syndrome, oral arginine improves cardiopulmonary haemodynamics, including a significant reduction in tricuspid regurgitant jet velocity, compared with placebo. Arginine administration may improve nitric oxide bioavailability and lead to pulmonary vasodilatation.⁴⁸
- ▶ In Egypt, children with sickle-cell disease or thalassaemia requiring regular blood transfusions in an RCT of oral deferiprone or subcutaneous infusions of deferoxamine as chelating therapy showed that long-term oral chelation with deferiprone led to continued and progressive reduction in iron load, and no safety concerns.⁴⁹
- ▶ In India, in the treatment of acute lymphoblastic leukaemia with high-dose methotrexate, the reduction of prehyperhydration duration (from 12 hours to 6 hours) did not affect the risk of nephrotoxicity and methotrexate levels over 136 cycles in 34 patients. Nephrotoxicity occurred in 1 and 2 per 68 cycles of methotrexate respectively given 12 hours or 6 hours of prehyperhydration.⁵⁰
- ▶ Several studies evaluated point-of-care viral load testing for HIV,⁵¹ and rapid early infant diagnosis of HIV with GeneXpert or other PCR testing.^{52 53}
- ▶ In Papua New Guinea, to eliminate lymphatic filariasis, widespread community administration of the addition of ivermectin to the standard two-drug regimen (diethylcarbamazine, and albendazole) was more effective in reducing microfilariae prevalence to below the target level of <1% at 12 months and 24 months.⁵⁴
- ▶ There has been a rise in pyrethroid-resistant mosquitoes, making many existing insecticide-treated bed nets less effective. Studies this year from Uganda and Benin have shown that chlorfenapyr-pyrethroid⁵⁵ or piperonyl butoxide⁵⁶ insecticide treated bed nets provided greater protection from malaria than standard pyrethroid bed nets.
- ▶ In an RCT in India involving 128 asphyxiated newborns who needed positive pressure respiratory support in the delivery room, using room air resulted in higher treatment failures (27 (46%) vs 16 (25%); relative risk (RR) 1.9 (1.1–3.1)) and took longer time to establish regular respiration (230±231 vs 182±261, mean difference=48 (40–136) seconds), than initiating resuscitation with 100% oxygen.⁵⁷
- ▶ A systematic review of RCTs of neonates with perinatal asphyxia being managed with therapeutic hypothermia showed that enteral feeding is safe and does not increase the risk of necrotising enterocolitis, hypoglycaemia or feed intolerance. Enteral feeding during therapeutic hypothermia

may reduce the incidence of sepsis and all-cause mortality until discharge.⁵⁸

- ▶ In an RCT of a school feeding programme among underprivileged children in northern Pakistan, there was an improvement in cognitive performance in children who received a school meal with and without micronutrient supplementation over a 12-month period, compared with those who did not receive a school meal.⁵⁹
- ▶ In Myanmar, regular, targeted text messages to pregnant women and mothers via mobile phones significantly improved breastfeeding practices (exclusive breastfeeding at 6 months 43% compared with controls 15%; bottle feeding much reduced, and significantly reduced infant diarrhoea during the first 6 months of life).⁶⁰
- ▶ In Uganda, a household solar lighting intervention had far-reaching social implications with improved social integration and social health. Participants felt that lighting mitigated the stigma of poverty, increased the duration and frequency of social interactions, and improved household relationships because of reduced conflicts over light (previously kerosene) rationing. Participants also described a communal benefit of lighting due to improved feelings of safety, improved self-esteem, sense of well-being and reduced stress.⁶¹
- ▶ An RCT of improved oral health and dental hygiene in children living with HIV showed improvements in overall dental health in those with focused teeth brushing, including reduced dental caries, reduced HIV viral load, and improved salivary flow and quality of life scores.⁶²
- ▶ In Brazil, reading aloud to children beginning in pregnancy and early childhood was associated with increased vocabulary and reduced screen time, for families with low parent literacy.⁶³
- ▶ In rural Vietnam, community-based, multicomponent group programmes for mothers and their infants 'Learning Clubs' improved early childhood development compared with the standardised mean.⁶⁴
- ▶ A systematic review of physiotherapy in children with cerebral palsy showed that trunk-targeted exercises improve gross motor function, trunk control and balance, and help in greater functional recovery.⁶⁵
- ▶ In India, children aged 5–18 years with unilateral cerebral palsy given 6 Hz primed, low-frequency, repetitive transcranial magnetic stimulation improved upper limb function, dexterity and strength.⁶⁶

I have been liberal in what is included as an RCT. Some papers are the reports of substudies or subanalyses within an RCT, rather than the efficacy results of the completed RCT. I have not included papers that only report the protocol for an RCT. It is also a grey area as to what is a developing country now, a term that has been superseded by low-income and middle-income country. I have chosen not to include studies from high resource areas in middle-income and high-income countries that formerly were 'developing', such as studies of organ transplantation in China, but I have included studies on basic public child health interventions in Brazil or other Asian countries that have graduated to middle-high income. One factor considered in decision to include is if the trial in some way addresses inequity. Of course, even this can be subjective and arguable.

RCTs are far from the only valuable scientific evidence, and some RCTs, because of problems with design or implementation have limited value. However, the method of the RCT is the gold standard for determining attributable benefit or harm from clinical and public health interventions. When done properly they eliminate bias and confounding. The results should not

be accepted uncritically but they should be evaluated for quality and validity. Before the results of an RCT can be generalised to another setting there must be consideration of wider applicability or reproducibility, feasibility and potential for sustainability.

RCTs often report the 'average effect', that is, the effect on the overall population. However, depending on how specifically that population is defined, within that population may be children who will benefit from the therapy or intervention, children for whom the therapy will have no effect, and some children for whom it may be harmful. The 'average' of these effects may be 'no overall effect', but it is increasingly important that researchers try to understand the effects for individuals or subgroups within trials, and the context in which benefit or not occurs. Prospective subgroup analyses enable this and an understanding of context.

Some of the context differences that may influence the results of a trial include individual or population characteristics, comorbidities, the healthcare environment and healthcare providers, geographical factors, the delivery mechanism for the drug, vaccine or other interventions, the disease stage and specific aetiology, economic, social, and cultural characteristics of the population and individuals within it. Understanding contextual differences even more complex in interpreting systematic reviews of RCTs, where heterogeneity within and between studies is often incompletely reported.

Incorporating an understanding of the observed effect in context requires a nuanced approach, and the RCT design is not always the best method to trial all interventions. This can be the case for complex interventions (ie, a complex clinical therapy or a health system improvement programme) where other methods of evaluation may be more useful.

Since 2002 there have been 3712 trial publications summarised in the 20 editions of this systematic search. It is encouraging to see the evolution in RCT research which aligns with the changing epidemiology of child health in the twenty-first century, and the broader context of the Sustainable Development Goals. There is now more focus on the developmental, psychological and mental health effects of many interventions, including parenting interventions to improve development and nutrition, measures to reduce violence against children, to address maternal depression, and to improve parent-child interactions. And there is more focus on environmental health. Also encouraging is the increased number of trials that address problems relevant to adolescents. This year there were trials of interventions to reduce violence against and by adolescents, to increase adherence in chronic disease management (such as for HIV), improve school retention, improve mental health, self-esteem, and resilience, and to improve sexual health, prevent unwanted pregnancies, and reduce child marriage.

RCTs are being conducted not just in hospitals and health-care settings, but in schools and communities, and some of the world's most disadvantaged settings, including among refugees and in humanitarian emergencies.

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