

Randomised trials in child and adolescent health in developing countries

19th Edition 2021-22

RANDOMISED TRIALS IN CHILD AND ADOLESCENT HEALTH IN DEVELOPING COUNTRIES

19th Edition
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Please send suggestions about this booklet to:

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Why RCTs?

- Gold Standard for estimation of attributable benefit or harm
- Eliminates bias and confounding
- However...
 - Need to be evaluated for
 - Quality
 - Relevance
 - Validity
 - Applicability
 - Sustainability

Pubmed search strategy

<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>

- **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 countr* 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 July 1 2018 and June 30 2019.

Pubmed search strategy

<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>

- **Pubmed Advanced strategy, search:** ((child* or neonate or adolescent) and (World Health Organization)) AND ("2021/06/01"[Date - Publication] : "2022/07/01"[Date - Publication])) AND (Randomised trial)

Reading RCTs: PICOT

Population

- In children with disease *X* (*or at risk of disease X*)...

Intervention

- Does treatment with *Y*...

Comparator

- Compared with (Gold Standard)...

Outcome

- Improve predefined outcomes...

Time

- Over a predefined time period...

RCTs in child and adolescent health in developing countries

- 126 trial publications
- Most with free on-line access to full-text

Fluids and feeding in bronchiolitis

Cochrane Database Syst Rev. 2021 12:CD013552.

doi: 10.1002/14651858.CD013552.pub2.

- 3 trials
- >800 infants with moderate-severe bronchiolitis
- Nasogastric fluids / feeding, compared with intravenous fluids
- Marginally better outcomes with NG fluids:
 - 17% relative reduction in the number of ICU admissions
 - 19% relative reduction in re-admissions to hospital
 - Much fewer attempts at insertion (NG vs IV)
 - Care required with either method: IV: extravasation, fluid overload; NG: coughing on insertion; no evidence of aspiration

Malaria vaccine in Africa

N Engl J Med. 2021 Sep 9;385(11):1005-1017

- 6861 children 5-17 months of age randomised to receive
 - (i) intermittent preventative therapy (sulfadoxine-pyrimethamine + amodiaquine)
 - (ii) the malaria vaccine: RTS,S/AS01E
 - (iii) IPT *plus* RTS,S/AS01E
- Primary outcome: uncomplicated and severe malaria
 - IPT: 305 events of uncomplicated clinical malaria
 - Vaccine: 278 events
 - Combination: 113 events
- Protective efficacy of *the combination* was 63% against clinical malaria, 71% against hospital admission with severe malaria, and 73% against death from malaria.

Pulse oximetry in primary care in Bangladesh, Ethiopia, India and Malawi, and Nigeria

BMJ Glob Health. 2021 Aug;6(8):e006578

PLoS One. 2021 Jul 8;16(7):e0254229.

- 2312 children in rural areas of Bangladesh, Ethiopia, India and Malawi with acute lower respiratory infection and chest indrawing
- Children with hypoxaemia ($SpO_2 > 90\%$) excluded:
 - 7 days of amoxicillin with follow up by community health care workers as effective giving the first dose of antibiotics and referral.
 - Clinical failure rates were 5% and 6% respectively
 - 2 deaths in each group.
- Pulse oximetry was key to safe management of pneumonia in primary health facilities, and community health workers could use oximetry effectively.
- Pulse oximetry was also key to improving quality of care for children with pneumonia in a large-scale study involving over 7000 children in Nigeria.

Larvivorous Fish and Dengue vectors in Cambodia

Am J Trop Med Hyg. 2021 Sep 7;105(5):1265-1276.

- Ways to control Dengue vectors: bed-nets, insecticide / larvicide, personal protection. ? Guppy fish that eat mosquitos?
- In Cambodia, in a cluster randomized, controlled trial: 30 clusters of one or more villages allocated either:
 1. all three interventions (guppies, PPF, and COMBI)
 2. two interventions (guppies and COMBI)
 3. control (standard vector control)
- COMBI = community education for changing behavior
- *Aedes* mosquitos reduced by half compared with the control in both guppy arms (RR = 0.49; 95% CI, 0.31-0.77; P = 0.0021).
- *"Where we put little fish in the water there are no mosquitos"*

HIV: studies of dolutegravir

1. Bioavailability of dolutegravir dispersible tablets (both single and FDC) was 1.6-fold higher when compared with conventional tablets
2. DTG + 2 NRTIs highly effective in treating HIV, even in cases of high NRTI resistance: viral load <400 copies / ml in $>90\%$ of the patients
3. Point of care CD-4 testing reduced the time required for patients with advanced HIV to be on effective ART

Timing of initiation of ART in TB-HIV co-infection

J Int AIDS Soc. 2021 24:e25772. doi: 10.1002/jia2.25772

- Meta-analysis of 9 trials
- Among people with all CD4 counts, there was no difference in mortality by earlier ART (≤ 4 week) versus later ART (> 4 week)
- Among people with CD4 count ≤ 50 cells/mm³, earlier ART (≤ 4 weeks) reduced risk of death (RD -6%, -10% to -1%).
- Earlier ART (≤ 4 weeks) increased the risk of IRIS (RD +6%, 95% CI +2% to +10%)

High-dose rifampicin for paediatric tuberculous meningitis

Clin Infect Dis. 2022 Mar 15;ciac208

- **Phase II** open-label randomized trial among children with TBM in India and Malawi. 37 children.
- Participants received isoniazid and pyrazinamide *plus*:
 - (1) high-dose rifampicin (**30 mg/kg**) and ethambutol;
 - (2) high-dose rifampicin and levofloxacin;
 - (3) standard-dose rifampicin and ethambutol:
- for 8 weeks, followed by 10 months of standard treatment
- All arms had good outcomes
- Fine motor, receptive language, and expressive language domains better in Arm 1 than Arm 3, but higher adverse effects.

Trachoma: permethrin-treated scarves in reducing fly-face contact in Ethiopia

EClinicalMedicine. 2022 Jun 8;49:101487

- The eye-seeking fly *Musca sorbens* is a vector for ocular *Chlamydia trachomatis*
- 58 children randomised to wearing a permethrin-treated light cotton scarf for 28 days or control arm.
- Assessments on days 1, 7 and 28 (54 followed for the full 28 days)
- 35% decrease in fly-eye / nose contacts in the treatment arm compared to the control (rate ratio 0.65, 95% CI 0.52-0.83).
- Phase II trial – proof of mechanism

Clinical trial phases

- **Phase I trial** – initial safety data, low dose
- **Phase II trial** – mechanism, biological effect, safety, preliminary efficacy
- **Phase III** – large sample size, strong evidence of efficacy, safety, typically several 100s to 1000s of subjects
- **Phase IV trial** – large scale implementation effectiveness, test in a real-world rare situation, monitoring for rare adverse-effects

Exchange transfusion in neonatal sepsis

Eur J Pediatr. 2022 Jan;181(1):369-381.

- An old therapy
- Many new adjuvant therapies for sepsis, but most expensive and of marginal benefit.
- Meta-analysis of 14 studies of ET: 3 RCTs, and 11 controlled observation studies)
- Mortality benefit in septic neonates who underwent ET - RR 0.72 (CI 0.61-0.86, $p = 0.01$)
- Increase in immunological parameters (immunoglobulin, complement levels), $p = 0.02$) and neutrophil count, $p = 0.03$) and reduction in pro-inflammatory cytokines compared to controls.
- Not convincing trials – small, observational, risk of bias

Exchange transfusion in neonatal sepsis

- Requires fresh whole blood
- 2 x blood volume (170ml/kg) over 60-90 minutes
- Umbilical vein single “push-pull technique” with 3-way tap, or arterial – vein peripheral
- Thrombocytopenia
- Hypocalcaemia (citrate)
- May be repeated

Other trends

- Adolescents, interventions to:
 - reduce violence against adolescents
 - increase retention in chronic disease programs (such as for HIV)
 - improve school retention and self-esteem
- Different outcomes:
 - developmental, psychological and mental health effects
- In praise of cohort studies