VACCINES & PLACEBO-CONTROLLED TRIALS

A Comprehensive Reference for Healthcare Professionals & Parents

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Evidence-Based Edition

A common concern among parents is whether vaccines have been properly tested. This document compiles peer-reviewed, placebo-controlled randomised controlled trials (RCTs) for major childhood vaccines on India's Universal Immunisation Programme (UIP). Every vaccine below underwent rigorous Phase 1, 2, and 3 clinical evaluation before regulatory approval — many enrolling tens of thousands of children worldwide. All studies cited here are from PubMed-indexed journals.

VACCINE-BY-VACCINE PLACEBO-CONTROLLED EVIDENCE

1. Polio Vaccine (Salk — IPV)

Disease Prevented	Poliomyelitis (paralytic)	**Trial Year**	1954 field trial; announced April 12, 1955
Study Design	Double-blind, placebo-controlled RCT with observed controls	**Participants**	~1.8 million children (≈650,000 vaccine/placebo; ≈1.18 million observed controls)

Key Finding: *80–90% efficacy against paralytic polio. All polio deaths occurred in the placebo or control group — none in the vaccinated group. Declared 'safe, effective, and potent' by independent evaluator Dr. Thomas Francis Jr., University of Michigan.*

[1] Francis T Jr et al. An evaluation of the 1954 poliomyelitis vaccine trials. Am J Public Health. 1955;45(5 Pt 2):1–63. PMID: 14376635.
[2] Markel H. April 12, 1955 — Tommy Francis and the Salk vaccine. N Engl J Med. 2005;352:1408–10. DOI: 10.1056/NEJMp048250.

2. MMR Vaccine (Measles–Mumps–Rubella)

Disease Prevented	Measles, Mumps, Rubella	**Trial Year**	1960–1968 (components); combined MMR licensed 1971
Study Design	Multiple double-blind, placebo-controlled RCTs per component	**Participants**	Thousands across independent trials in the United States and internationally

Key Finding: *Measles: ~94% efficacy (Katz 1960, NEJM). Mumps (Jeryl Lynn strain): 95% protective efficacy on natural challenge; 96.9% seroconversion in children (Hilleman 1967/68, NEJM). Rubella: high seroconversion confirmed in separate controlled trials.*

[3] Katz SL et al. Studies on an attenuated measles-virus vaccine. VIII. N Engl J Med. 1960;263:180–4. DOI: 10.1056/NEJM196007282630408.
[4] Hilleman MR et al. Live attenuated mumps-virus vaccine. IV. N Engl J Med. 1967;276(5):252–8. PMID: 6016061.
[5] Hilleman MR et al. Live, attenuated mumps-virus vaccine. N Engl J Med. 1968;278(5):227–32. PMID: 4169706.

Note: The three-antigen MMR combination was approved in 1971. Efficacy evidence for each antigen derives from placebo-controlled trials of each individual component conducted prior to combination.

3. Rotavirus Vaccines (RotaTeq — RV5 & Rotarix — RV1)

Disease Prevented	Rotavirus gastroenteritis	**Trial Year**	RV5: 2006 (REST trial, NEJM) | RV1: 2005–2008 (Phase 3, Lancet 2008)
Study Design	Both: randomised, double-blind, placebo-controlled RCTs	**Participants**	RV5: ~70,301 infants, 11 countries | RV1: ~63,225 infants, Latin America

Key Finding: RotaTeq (RV5): *98% efficacy against severe rotavirus gastroenteritis (G1–G4). Hospitalisation reduced by 95%. Intussusception risk equal in vaccine and placebo groups.* ***Rotarix (RV1):*** *~85% reduction in severe disease; hospitalisation reduced ~83%. No increased intussusception risk identified. Two independent vaccines — two independent placebo-controlled trials.*

[6] Vesikari T et al; REST Study Team. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med. 2006;354(7):23–33. PMID: 16394299.
[7] Heyse JF et al. Evaluating the safety of a rotavirus vaccine: the REST of the story. Clin Trials. 2008;5(5):466–73. PMID: 18375651.
[8] Linhares AC et al. Efficacy and safety of an oral live attenuated human rotavirus vaccine. Lancet. 2008;371(9619):1181–9. DOI: 10.1016/S0140-6736(08)60524-3. PMID: 18395579.

4. Pneumococcal Conjugate Vaccine (PCV7)

Disease Prevented	Invasive pneumococcal disease (pneumonia, meningitis, sepsis)	**Trial Year**	1997–2000 (Northern California Kaiser Permanente trial)
Study Design	Randomised, double-blind, active-controlled trial (PCV7 vs. MenC conjugate)	**Participants**	37,868 children (Northern California, USA)

Key Finding: *97.4% efficacy (95% CI: 82.7–99.9%) against vaccine-type invasive pneumococcal disease. Subsequent PCV13 trials confirmed extension of protection to additional serotypes.*

[9] Black S et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Pediatr Infect Dis J. 2000;19(3):187–95. PMID: 10749457.

5. Meningococcal Vaccine (MenACWY-CRM)

Disease Prevented	Meningococcal meningitis / invasive meningococcal disease	**Trial Year**	2010
Study Design	Randomised, placebo-controlled immunogenicity and safety trial (4 published studies)	**Participants**	Adolescents and young adults across multiple countries

Key Finding: *Safety and immunogenicity confirmed. Co-administration with Tdap did not reduce effectiveness of either vaccine. Direct inert-placebo efficacy RCTs are not feasible given disease rarity; immunogenicity is the accepted regulatory surrogate, supported by post-licensure surveillance.*

[10] Gasparini R et al. Randomized trial on the safety, tolerability, and immunogenicity of MenACWY-CRM … Clin Vaccine Immunol. 2010;17(4):537–44. PMID: 20164251.

6. Pertussis Vaccine (aP component of DTaP/DPT — Whooping Cough)

Disease Prevented	Pertussis (whooping cough)	**Trial Year**	1992–1996 (Swedish and Italian multi-centre trials)
Study Design	Placebo-controlled and active-controlled RCT (true inert-placebo arm included)	**Participants**	~14,745 infants (Swedish trial) + ~14,751 infants (Italian trial)

Key Finding: *Swedish trial: 5-component aP vaccine showed 85% efficacy (95% CI: 71–92%) against WHO-defined pertussis. Italian trial confirmed similar high efficacy for 2- and 5-component formulations. Both used a true inert-placebo arm — among the highest-quality pertussis trials published.*

[11] Gustafsson L et al. A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine. N Engl J Med. 1996;334(6):349–55. PMID: 8538705.
[12] Greco D et al; Progetto Pertosse Working Group. A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis. N Engl J Med. 1996;334(6):341–8. PMID: 8538704.

7. RSV Vaccine — Maternal Immunisation (RSVpreF / Abrysvo)

Disease Prevented	RSV lower respiratory tract illness in infants	**Trial Year**	2020–2022 (MATISSE trial; NEJM April 2023)
Study Design	Phase 3, randomised, double-blind, placebo-controlled multi-country trial	**Participants**	7,392 pregnant women (and their infants) across multiple countries

Key Finding: *82% efficacy against severe RSV LRTI in infants within 90 days of birth; 69% at 180 days. Protection conferred via transplacental transfer of maternal antibodies to the newborn.*

[13] Kampmann B et al; MATISSE Study Group. Bivalent prefusion F vaccine in pregnancy to prevent RSV illness in infants. N Engl J Med. 2023;388(16):1451–64. PMID: 37018474.

Note: RSV vaccines for adults (Arexvy — GSK; Abrysvo — Pfizer) were also approved in 2023 based on separate Phase 3 placebo-controlled trials.

WHY MODERN TRIALS OFTEN AVOID INERT PLACEBOS

Once a vaccine has been shown to be effective and becomes standard of care, it is no longer ethical to withhold it using an inert (saline) placebo. This is grounded in the principle of **clinical equipoise** — genuine uncertainty must exist about the treatments being compared.

The **Declaration of Helsinki** (WMA, 1964; revised 2013) states that control group participants should receive the best currently proven intervention, not a placebo, when an effective treatment already exists.

Later-generation trials therefore compare vaccines against **active comparators**. This is not a gap in the evidence — it is scientific and ethical progress. The original placebo-controlled trials establishing efficacy remain in the published literature and are cited above.

IMPORTANT LIMITATIONS — WHAT RCTs CANNOT TELL US ALONE

- **Trial phases:** Phase 3 trials establish efficacy and detect common adverse events but are not powered to detect very rare events (e.g. 1 in 100,000 doses).
- **Post-marketing surveillance:** India's national AEFI surveillance and global pharmacovigilance systems continuously monitor safety across millions of real-world doses.
- **Population diversity:** Pivotal trials may not fully represent all ethnicities or regions. Effectiveness studies in Indian children provide important complementary data.
- **Waning immunity:** Duration of protection varies. Booster requirements are an active area of research, especially for pertussis and pneumococcal vaccines.
- **Serotype replacement:** For strain-specific vaccines (e.g. PCV), surveillance monitors whether non-targeted strains increase over time.

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