

Recent Advances

Pediatric Infectious Disease (2019): 10.5005/jp-journals-10081-1208

Source: Biswal S, Reynales H, Saez-Llorens X, et al. Efficacy of a tetravalent dengue vaccine in healthy children and adolescents. *N Engl J Med* 2019;381(21):2009–2019. DOI: 10.1056/NEJMoa1903869

The researchers have reported the primary efficacy data from part 1 of an ongoing phase three randomized trial of TAK-003, a tetravalent dengue vaccine candidate, in regions of Asia and Latin America in which the disease is endemic. Two doses of vaccine or placebo were administered 3 months apart to healthy children and adolescents aged 4–16 years. At least one dose of vaccine or placebo (safety population) was received by 20,071 participants; of these, 19,021 (94.8%) received both injections and were included in the per-protocol analysis. In the safety population, the researchers noted an overall vaccine efficacy of 80.9% (95% CI 75.2–85.3; 78 cases per 13,380 [0.5 per 100 person-years] in the vaccine group vs 199 cases per 6,687 [2.5 per 100 person-years] in the placebo group). In per-protocol analyses, they identified a vaccine efficacy of 80.2% (95% CI 73.3–85.3; 61 cases of virologically confirmed dengue in the vaccine group vs 149 cases in the placebo group); the vaccine also showed 95.4% efficacy against dengue leading to hospitalization (95% CI 88.4–98.2; 5 hospitalizations in the vaccine group vs 53 hospitalizations in the placebo group).

Overall, the researchers' findings support that, in countries in which the disease is endemic, TAK-003 may be efficacious against symptomatic dengue. This trial is ongoing, and longer-term data will be important in better defining the efficacy and safety profile of this vaccine candidate.

Source: Ståhlgren GS, Tyrstrup M, Edlund C, et al. Penicillin V four times daily for 5 days vs three times daily for 10 days in patients with pharyngotonsillitis caused by group A streptococci: randomised controlled, open label, non-inferiority study. *BMJ* 2019;367:l5337. DOI: 10.1136/bmj.l5337

A 10-day course of penicillin is a standard therapy for streptococcal pharyngitis. To evaluate whether a shorter course using higher doses could be equally effective while reducing total antibiotic exposure, a randomized trial compared 5 days of penicillin V dosed at 800 mg four times daily with 10 days of penicillin V dosed at 1,000 mg three times daily in 433 children and adults with microbiologically confirmed streptococcal pharyngitis.

Primary outcome was clinical cure 5–7 days after the end of antibiotic treatment. Secondary outcomes were bacteriologic eradication, time to the relief of symptoms, the frequency of relapses, complications and new tonsillitis, and patterns of adverse events.

The authors conclude that penicillin V four times daily for 5 days was non-inferior in clinical outcome to penicillin V three times daily for 10 days in patients with pharyngotonsillitis caused by group I streptococci. The number of relapses and complications did not differ between the two intervention groups. 5-day treatment with penicillin V four times daily might be an alternative to the currently recommended 10-day regimen.

A closer look at the study shows that while clinical cure rates were similar (90 vs 93%), bacterial eradication rates were lower in the 5-day treatment group (80 vs 91%). Because complications of streptococcal pharyngitis, particularly immune sequelae, can be severe and are likely related to the presence of group I *Streptococcus* in the oropharynx, should we continue to a 10-day course of therapy?

Source: Karabay M, Kaya G, Hafizoglu T, et al. Effect of camera monitoring and feedback along with training on hospital infection rate in a neonatal intensive care unit. *Ann Clin Microbiol Antimicrob* 2019;18(1):35. DOI: 10.1186/s12941-019-0332-y

Given that neonatal intensive care units (NICU) constitute the greatest risk in terms of pediatric healthcare-associated infections (HAI), researchers retrospectively investigated the impact of the training along with camera monitoring and feedback (CMAF) to control infection following a small outbreak.

At the isolation room of Sakarya University Hospital NICU, ESBL producing *Klebsiella pneumoniae* was detected on three infants in May 2014. To prevent further spread of the infection, isolation of infected infants, and initiation of their decolonization were performed. For this aspect, training was provided to healthcare workers (HCWs) in NICU for infection control measures. The HCWs were monitored by an infection control committee by installing cameras in the NICU. The CMAF period exhibited a significant decrease in the infection rate in this study. Moreover, a crucial increase in handwashing compliance was noted following the implementation of camera monitoring. Before the onset of the CMAF, HAI density of 9.59% was reported; it reduced to 2.24% during the CMAF period.

The researchers conclude that HCWs should be monitored in order to increase their compliance for infection control measures and emphasized that CMAF of health workers may contribute significantly in reducing the HAI rate in the NICU.

Source: <https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treatment-resistant-forms-tuberculosis-affects-lungs>

First new tuberculosis drug approved in 50 years.

A treatment regimen for extensively drug-resistant (XDR) tuberculosis could help stem the growing problem of hard-to-treat TB infections in developing countries. Approved by the US Food and Drug Administration on August 14, the therapy includes two existing drugs, bedaquiline and linezolid, and a new antibiotic called pretomanid—only the third new TB drug in nearly half a century to reach the market.

In clinical trials for XDR TB, nearly 90% of patients receiving the medication recovered after 6 months of treatment—almost three times the success rate of current treatment options, which involves taking antibiotic cocktails for up to 2 years.

Pretomanid was developed by the nonprofit TB Alliance. “One definite advantage of a not-for-profit is you don’t have to look at things like returning your profits to shareholders,”—says Mel Spigelman, president and chief executive of TB Alliance. Helen Boucher, a professor and director of the Tufts Center for Integrated Management of Antimicrobial Resistance says that “There isn’t a market to sell [a TB drug] to make money, so it was imperative that a nonprofit take that on.”

The TB Alliance has also filed for approval of pretomanid as part of a combo regimen for TB with European regulatory authorities.

Source: Roy P, Vekemans J, Clark A, et al. Potential effect of age of BCG vaccination on global paediatric tuberculosis mortality: a modelling study. *Lancet Glob Health* 2019;7(12):e1655–e1663. DOI: 10.1016/S2214-109X(19)30444-9

Age-specific bacillus Calmette Guerin (BCG) coverage in 152 high-burden countries using data from large, nationally representative household surveys were predicted, to parameterize a static mathematical model, calibrated to global childhood tuberculosis deaths in 2016 in order to evaluate the potential global tuberculosis mortality advantage of administering BCG on time and consequences of later administration. It was discovered that decreasing delays and raising coverage at birth would considerably decrease global pediatric tuberculosis mortality. Modeled scenarios whereby BCG was added later in the infant schedule were all supposed to boost tuberculosis deaths, even with progressed coverage. Moreover, the WHO recommendation for BCG at birth should be sustained and affirmed.

Source: Mina MJ, Kula T, Leng Y, et al. Measles virus infection diminishes preexisting antibodies that offer protection from other pathogens. *Science* 2019;366(6465):599–606. DOI: 10.1126/science.aay6485

Many of the deaths attributable to measles virus are caused by secondary infections because the virus infects and functionally impairs immune cells. Whether measles infection causes long-term damage to immune memory has been unclear. This question has become increasingly important given the resurgence in measles epidemics worldwide. Using a blood test called VirScan, Mina et al. comprehensively analyzed the antibody repertoire in children before and after natural infection with measles virus and in children before and after measles vaccination. They found that measles infection can greatly diminish previously acquired immune memory, potentially leaving individuals at risk of infection by other pathogens. These adverse effects on the immune system were not seen in vaccinated children.

One of the authors says, people use seatbelts to prevent serious injuries in car accidents, and the study shows that “measles is like an accident to your immune system.” The vaccine is “like a seatbelt,” and people should “buckle up.”

Source: Salvatore P, Johnson K, Vojnov L, et al. Clinical consequences of using an indeterminate range for early infant diagnosis of HIV: a decision model. *J Acquir Immune Defic Syndr* 2019;82(3):287–296. DOI: 10.1097/QAI.0000000000002155

Given the World Health Organization recommendation for confirmatory testing for all infants initiating antiretroviral therapy (ART) in order to minimize false-positive diagnoses of HIV in exposed infants, researchers examined if semi-quantitative cycle thresholds (Cts) that identify positive results most likely to be false-positive may aid in clinical decisions in settings where confirmatory testing is not feasible or intermittently performed.

For infants with weakly positive (“indeterminate”) results, a decision analysis model of HIV-exposed infants in sub-Saharan Africa was generated to determine the clinical consequences of deferring ART. The degree to which “indeterminate” results may decrease the number of infants commencing ART unnecessarily was determined while missing a small number of HIV-infected infants.

The analysis revealed that the benefits of classifying weakly positive results as “indeterminate” may outweigh the risks when it is implemented in settings where confirmatory testing is not universal. Accordingly, a recommendation by the World Health Organization has been made to consider Ct values ≥ 33 indeterminate for infant HIV diagnosis.

Source: Yoon SH, Kim EH, Kim HY, et al. Presepsin as a diagnostic marker of sepsis in children and adolescents: a systemic review and meta-analysis. *BMC Infect Dis* 2019;19(1):760. DOI: 10.1186/s12879-019-4397-1

The researchers while performing this meta-analysis, investigated the overall diagnostic accuracy of presepsin in pediatric sepsis. In addition, they compared its diagnostic accuracy with those for C-reactive protein (CRP) and procalcitonin (PCT). Four studies comprising 308 patients (aged between 1 month and 18 years) were included in the final analysis. Findings suggest that relative to PCT or CRP, presepsin has higher sensitivity and diagnostic accuracy, but lower specificity, in detecting sepsis in children. However, they recommend careful interpretation of these results as the number of studies included was small and the studies were statistically heterogeneous.

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