

RESEARCH SUMMARY

Intravenous Doxycycline, Azithromycin, or Both for Severe Scrub Typhus

Varghese GM et al. DOI: 10.1056/NEJMoa2208449

CLINICAL PROBLEM

Scrub typhus, a life-threatening infection caused by *Orientia tsutsugamushi* and transmitted by trombiculid mite larvae, accounts for an estimated 150,000 deaths each year. The best treatment option for severe scrub typhus is unclear.

CLINICAL TRIAL

Design: A multicenter, double-blind, randomized, three-group trial in India compared the efficacy and safety of intravenous doxycycline, intravenous azithromycin, or both in patients with severe scrub typhus.

Intervention: 809 patients ≥ 15 years of age with severe disease involving at least one organ were assigned to receive an in-hospital, 7-day, intravenous course of doxycycline (200 mg twice daily on day 1, then 100 mg twice daily thereafter), azithromycin (500 mg twice daily on day 1, then 500 mg once daily), or a combination of the two. The primary efficacy outcome was a composite of death from any cause at day 28, persistent complications at day 7, and persistent fever at day 5.

RESULTS

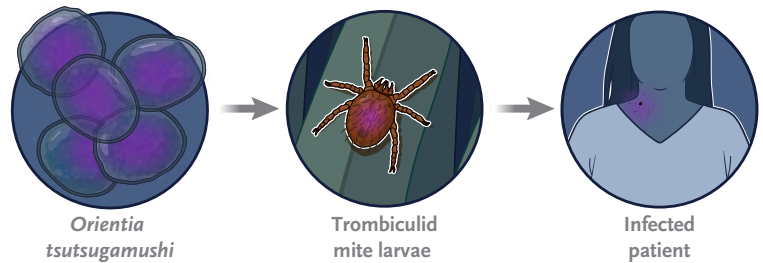
Efficacy: Among evaluable patients, primary-outcome events occurred significantly less often with combination therapy than with either treatment alone.

Safety: The incidence of grade ≥ 3 adverse events or serious adverse events was similar across the groups.

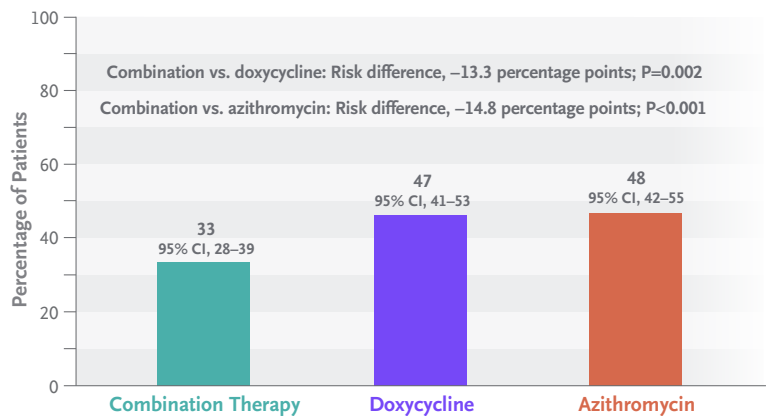
LIMITATIONS AND REMAINING QUESTIONS

- Children and pregnant women were excluded from the trial, so the safety findings cannot be generalized to these populations (although extrapolation of the efficacy findings may be reasonable).
- Some critically ill patients discontinued their randomized treatment assignments to receive open-label treatment.
- The reason for the greater clinical effectiveness of combination therapy is uncertain.

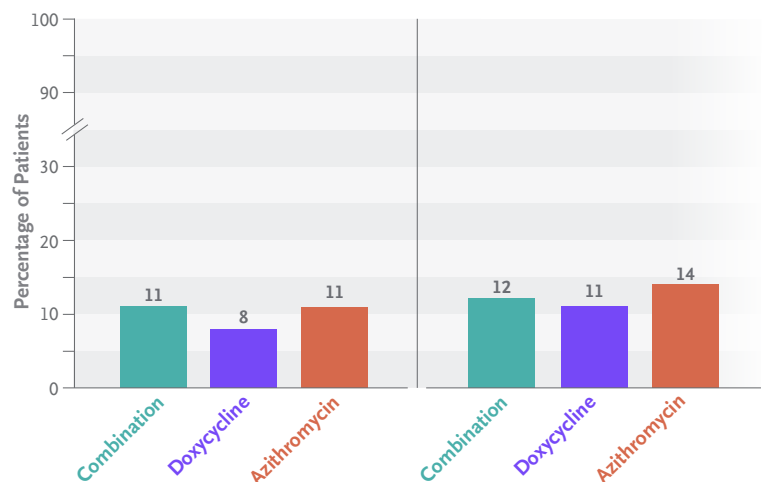
Transmission of Scrub Typhus



Death from Any Cause at Day 28, Persistent Complications at Day 7, or Persistent Fever at Day 5

Grade ≥ 3 Adverse Events

Serious Adverse Events



CONCLUSIONS

In patients with severe scrub typhus, a 7-day intravenous course of doxycycline plus azithromycin was superior to either treatment alone with regard to a composite outcome of death, persistent complications, and persistent fever.

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