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1 Bates M, Mudenda V, Shibemba A, et al. Burden of tuberculosis at post mortem in inpatients at a tertiary referral centre in sub-Saharan Africa: a prospective descriptive autopsy study. *Lancet Infect Dis* 2015; **15:** 544–51 .
2 Rampatige R, Gilks CF. Autopsies and better data on causes of death in Africa. *Lancet Infect Dis* 2015; **15:** 492–94.
3 Punia RS, Mundi I, Mohan H, Chavli KH, Harish D. Tuberculosis prevalence at autopsy: a study from North India. *Trop Doct* 2012; **42:** 46–47.
4 Ozsoy S, Demirel B, Albay A, et al. Tuberculosis prevalence in forensic autopsies. *Am J Forensic Med Pathol* 2010; **31:** 55–57.
5 Lum D, Koelmeyer T. Tuberculosis in Auckland autopsies, revisited. *N Z Med J* 2005; **118:** U1356.
6 Rastogi P, Kanchan T, Menezes RG. Sudden unexpected deaths due to tuberculosis: an autopsy based study. *J Forensic Med Toxicol* 2011; **28:** 81–85.

Evaluating Ebola vaccine trials: insights from simulation

Jolanta Piszczek and Eric Parlow[1] outlined expected benefits of a stepped-wedge cluster trial (SWCT) design, with specific reference to the Sierra Leone Trial to Introduce a Vaccine against Ebola (STRIVE). STRIVE, however, is not an SWCT, but a phased-rollout trial in which randomisation to immediate or delayed vaccination groups occurs at the individual level (a randomised clinical trial [RCT]) within trial clusters.[2] Whereas the SWCT design is advantageous in certain circumstances, many of the benefits described by Piszczek and Parlow[1] would not apply to assessment of Ebola vaccine candidates in Sierra Leone.

In a recently published study, we used simulations to compare statistical validity and power for an SWCT and a STRIVE-like RCT in the same trial population.[3] Piszczek and Parlow[1] contend that an SWCT can achieve greater statistical power than an RCT by many before-and-after and between-group comparisons; however, we found that the declining and heterogeneous epidemic incidence across Sierra Leone undermines such cluster-level comparisons and, consequently, the power of an SWCT. Specifically, we estimated that the SWCT design would be three to ten times less likely than an individually randomised, phased roll-out RCT to definitively identify an efficacious vaccine. For example, an SWCT starting in April 2015 was expected to have a less than 10% chance of detecting the effect of a 90% efficacious vaccine.

As emphasised by Piszczek and Parlow[1] (and the article to which they respond[4]), the primary advantage of an SWCT is that it avoids the ethical problem of withholding a potentially life-saving intervention from trial participants. Phased roll-out RCTs can address this shortcoming, in part, by vaccinating all control participants at the end of the trial, as in STRIVE, although this introduces a delay in vaccination of some participants in the interest of experimental design. When risk is highly variable in space and time, as with Ebola in Sierra Leone, however, a phased roll-out RCT has an additional ethical advantage the SWCT lacks: it allows prioritised vaccination of clusters experiencing high infection risk. Such prioritisation would confer the highest likelihood of benefit to those at highest risk, thereby reducing the total risk to trial participants relative to a non-risk-prioritised design. By contrast, an SWCT needs random-ordered roll-out by definition[5] and therefore cannot allow such prioritisation. An observational impact assessment of risk-prioritised vaccine roll-out without a control group would produce biased efficacy estimates, since vaccination order would be confounded with other factors associated with infection risk.

The relative merits of trial designs are context-specific, and the benefits conventionally associated with certain designs might be achieved by alternative designs, when carefully tailored to local situations. We believe that proposed designs should be rigorously analysed and compared (eg, via simulation) as a matter of course in trial planning, to ensure that trials are valid, efficiently powered, and ethically justified within the setting in which the trial will be done.

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1 Piszczek J, Parlow E. Stepped-wedge trial design to evaluate Ebola treatments. *Lancet Infect Dis* 2015; **15:** 762–63.
2 Centers for Disease Control and Prevention. Sierra Leone to introduce a vaccine against Ebola (STRIVE). April 14, 2015. www.cdc.gov/vhf/ebola/strive/qa.html (accessed July 2, 2015).
3 Bellan SE, Pulliam JRC, Pearson CAB, et al. Statistical power and validity of Ebola vaccine trials in Sierra Leone: a simulation study of trial design and analysis. *Lancet Infect Dis* 2015; **15:** 703–10.
4 Tully C, Lambe T, Gilbert S, et al. Emergency Ebola response: a new approach to the rapid design and development of vaccines against emerging diseases. *Lancet Infect Dis* 2015; **15:** 356–59.
5 Hussey M, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. *Contemp Clin Trials* 2007; **28:** 182–91.