Stepped Wedge Test-Negative Trials

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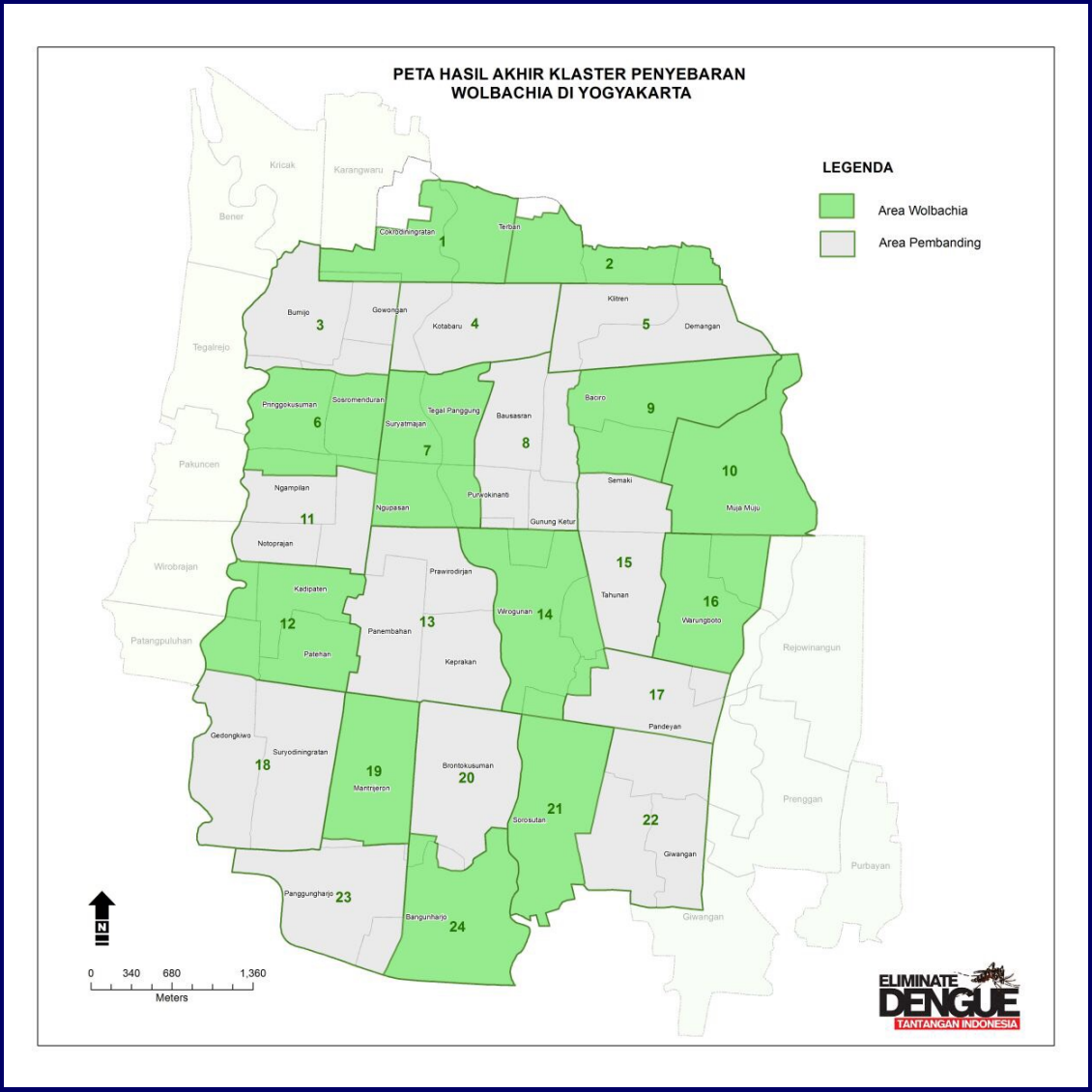
Current developments in cluster randomized trials and stepped wedge designs

Prototypical Example

- Outcome = # of dengue cases ascertained in a ‘cluster”
- Intervention: Measure to suppress dengue infection
  - Vaccine
  - Mosquito suppression
  - Modified mosquitoes (CRISPR, *Wolbachia*, etc)
- Clusters randomly assigned to intervention
  - Parallel arm design
  - Stepped wedge design
- Statistical methods used to compare cluster-level counts by cluster intervention status (denominators unknown)
  - For stepped wedge, cluster counts are further broken down by time period which raises the challenge of assessing time effects on counts

Randomization: January 2017

Currently ~ 275 dengue cases, but now some contamination



CRT Design – Outcome Ascertainment

- Most CRT trials use cohort assessment of “outcomes”
- Often small numbers of clusters
  - Use permutation tests/randomization inference
- Why no case-control efforts when outcomes are rare
  - By case-control, I mean hear case-control surveillance superimposed on top of randomized intervention assignment to clusters
  - How are controls sampled?
- Most CRT trials don’t employ “negative controls”
  - Negative controls are outcomes for whom no intervention response is expected (allows for control of ascertainment bias due to unblinding)
  - Negative controls need to be ascertained at the same relative frequency as cases for the outcome of interest ; i.e. non-differential ascertainment across intervention ‘arms’ is ok but not if the ascertainment also differs between cases and negative controls
    - Tall order?

Example—Test-Negative Designs (TND)

- TNDs used in at least 358 studies to date
  - Often used to assess vaccine effectiveness
- TND studies enroll subjects who seek care for a non-specific clinical syndrome
- Enrolled participants are definitively tested for outcome (e.g. pathogen of interest)
  - Test-positives (e.g. dengue infections)
  - Test-negatives (e.g. other febrile illness that is not dengue)
    - blinded interventions often not possible
- Can compare test-positive counts across arms (arm-periods for stepped wedge)
  - But subject to bias despite randomization if health-care seeking behaviour differs across arms (cluster intervention is often not blinded)
- Test-negatives play role of negative controls

Observational TND: Efficacy Measure

	Test-Positives	Test-Negatives	Not Infected	Total
Intervention (Exposed)	*A*	*B*	*C*	N_I
Control (Unexposed)	*G*	*H*	*I*	N_C

Stratification of *Care-Seeking* Population based on Intervention Status, Infection Testing

$$RR = \frac{A/N_I}{G/N_C} \quad B/N_I \approx H/N_C \quad \Rightarrow \quad OR \equiv \frac{AH}{GB} \approx RR \equiv \lambda$$

- **Intervention does not affect test-negative conditions**
- **Efficacy is the same in the non-care seeking population**
- **No (unmeasured) confounding**

CR-TND: Parallel Arm-–Test Positives Only

Cluster *j*	Test-Positives	Test-Negatives	Not Infected	Total
Intervention (Exposed)	A_j	B_j	C_j	N_{Ij}
Control (Unexposed)	G_j	H_j	I_j	N_{Cj}

Stratification of *Care-Seeking* Population based on Intervention Status, Infection Testing

- **Only A_j and G_j are observed**
- **Test statistic:** $T = \frac{\sum A_j - \sum G_j}{\sqrt{2m\hat{V}_{\mathcal{P}}}}$ $V_{\mathcal{P}}$ **is variance of A_js and G_js**
- ***t*-test:** **Approximation to permutation test at the null**

$$\hat{RR} = \frac{\sum A_j}{\sum G_j}$$

$$Var(\log(\hat{RR})) \approx \frac{16}{n_D^2}\frac{m}{2}V_{\mathcal{P}}$$

CR-TND: Parallel Arm--Test Positives and Negatives

Cluster *j*	Test-Positives	Test-Negatives	Not Infected	Total
Intervention (Exposed)	A_j	B_j	C_j	N_{Ij}
Control (Unexposed)	G_j	H_j	I_j	N_{Cj}

- **Compute cumulative Odds Ratio**

$$OR = \frac{(\sum_j A_j)(\sum_j H_j)}{(\sum_j G_j)(\sum_j B_j)}$$

Approximation to permutation test at the null

- **Straightforward to estimate variance term**

$$\text{var}\left(\log(\text{OR})\right) \approx \frac{16}{n_D^2}(m/2)V_D + \frac{16}{n_{\bar{D}}^2}(m/2)V_{\bar{D}} - 2 \times \frac{n_D n_{\bar{D}}}{A_+(n_D - A_+)B_+(n_{\bar{D}} - B_+)}\text{cov}(A_+, B_+)$$

CR-TND: Stepped Wedge–-Test Positives Only

		Time Period				
		0	1	2	3	4
Cluster	1	0	1	1	1	1
	2	0	0	1	1	1
	3	0	0	0	1	1
	4	0	0	0	0	1

Hughes *et al* (2019)
Schematic representation of stepped wedge design with 4 intervention sequences (1 cluster each) and 5 time periods

$$A_T = \sum_{i=1}^{m} \sum_{j=0}^{k} x_{ij} Y_{ij} \qquad G_T = \sum_{i=1}^{m} \sum_{j=0}^{k} (1 - x_{ij}) Y_{ij}$$

$$\begin{aligned} E_{\mathcal{P}}(x_{ij}) &= \overline{x}_j = j/M \\ V_{\mathcal{P}}(x_{ij}) &= \overline{x}_j (1 - \overline{x}_j) \\ \mathrm{Cov}_{\mathcal{P}}(x_{ij}, x_{i'j'}) &= \overline{x}_j (1 - \overline{x}_{j'}) \qquad i = i', j \le j' \\ &= -\frac{1}{M-1} \overline{x}_j (1 - \overline{x}_{j'}) \quad i \ne i', j \le j'. \end{aligned}$$

$$T = A_T - G_T$$

has non-zero mean under the permutation distribution

CR-TND: Stepped Wedge–-Test Positives Only

		Time Period				
		0	1	2	3	4
Cluster	1	0	1	1	1	1
	2	0	0	1	1	1
	3	0	0	0	1	1
	4	0	0	0	0	1

Normalize the comparison

$$T = (A_T - G_T) - E_{\mathcal{P}}(A_T - G_T) = \sum_{j=0}^{k} \frac{2j}{M}(M - j)\bar{T}_j$$

where T_j is just the treatment comparison across clusters at time period j (ignores first and last time period).

- **this suggests using a weighted average of treatment effects, A_j/G_j, for an estimate of the Relative Risk**
- **weights?**
- **permutation variance more of a challenge due to covariance across time periods in same cluster**

CR-TND: Stepped Wedge–-Test Positives and Negatives

		Time Period				
		0	1	2	3	4
Cluster	1	0	1	1	1	1
	2	0	0	1	1	1
	3	0	0	0	1	1
	4	0	0	0	0	1

$$A_T = \sum_{i=1}^{m} \sum_{j=0}^{k} x_{ij} Y_{ij}$$

$$G_T = \sum_{i=1}^{m} \sum_{j=0}^{k} (1 - x_{ij}) Y_{ij}$$

$$B_T = \sum_{i=1}^{m} \sum_{j=0}^{k} x_{ij} Z_{ij}$$

$$H_T = \sum_{i=1}^{m} \sum_{j=0}^{k} (1 - x_{ij}) Z_{ij}$$

where Z_{ij} counts test-negatives in cluster/time period

test-positive only analysis suggests using weighted combination of parallel arm comparisons in each time period

- **weights?**
- **permutation variance more of a challenge due to covariance across time periods in same cluster and correlations between test-positive and test-negative counts in both the same and different time periods**

References

- Anders KL, Cutcher Z, Kleinschmidt I, Donnelly CA, Ferguson N, Indriani C, Ryan PA, O'Neill S, Jewell N, & Simmons C, "Cluster-randomized test-negative design trials: A novel and efficient method to assess the efficacy of community-level dengue interventions" *Amer. J. Epidemiol.* 2018. 187(9): 2021-2028
- Jewell NP, Dufault S, Cutcher Z, Simmons CP & Anders KL, "Analysis of cluster-randomized test-negative designs: cluster-level methods" *Annals of Statistics*, 1992, 10(2): 479-494.
- Dufault S & Jewell NP, "Analysis of counts for cluster randomized trials: An application to test-negative designs" *Statistics in Medicine,* under revision.
- Hughes JP, Heagerty PJ, Xia F & Ren Y, "Robust inference for the stepped wedge design" *Biometrics,* 2019, in press.
- Jewell NP & Dufault S, "Inference for stepped wedge randomized test-negative designs," 2019, in preparation.