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Comparing Bounds for Vaccine Effects on Infectiousness

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Halloran and Hudgens¹ and VanderWeele and Tchetgen Tchetgen² (henceforth HH and VT) consider inference about causal vaccine effects for infectiousness. The two papers make assumptions that result in different bounds. Assume a random sample of N households with two individuals. Let $Z_{ij} = 1$ if individual j in household i receives vaccine and 0 otherwise, $i = 1, \dots, N, j = 1, 2$. Let $\mathbf{Z}_i = (Z_{i1}, Z_{i2})$ denote the treatment assignment vector for household i , and z_i, z_{ij} denote possible values of $\mathbf{Z}_i, \mathbf{Z}_{ij}$. Let $Y_{ij}(z_{i1}, z_{i2})$ denote the potential infection outcome for individual j in household i if the two individuals in household i have vaccine status (z_{i1}, z_{i2}) . Let Y_{ij}^{obs} be the observed value of Y_{ij} under an actual assignment, i.e., $Y_{ij}^{obs} = Y_{ij}(\mathbf{Z}_i)$. Assume throughout only individual 1 can be assigned to vaccine or control, vaccine assignment is randomized, and there is no interference across transmission units.

Let $p_1 = E[Y_{i2}^{obs} | Z_{i1} = 1, Y_{i1}^{obs} = 1]$ and $p_0 = E[Y_{i2}^{obs} | Z_{i1} = 0, Y_{i1}^{obs} = 1]$. The net vaccine effect on infectiousness based on the observed data when the exposed individual has vaccine status 0 is $RD_i^{net}(0) = p_1 - p_0$. This net vaccine effect is difficult to interpret without additional assumptions because of selection bias, i.e., households that become infected when randomized to vaccine might not be comparable to households that become infected under control. Let $p_v = E[Y_{i2}(1, 0) | Y_{i1}(1, 0) = Y_{i1}(0, 0) = 1]$ and $p_u = E[Y_{i2}(0, 0) | Y_{i1}(1, 0) = Y_{i1}(0, 0) = 1]$. The causal risk difference in the stratum of households where individual 1 becomes infected whether receiving vaccine or control is $CRD_{\lambda}(0) = p_v - p_u$. The $CRD_{\lambda}(0)$ is not subject to selection bias. Even though this causal effect is not identifiable, the observable data provide information such that bounds can be estimated.

Monotonicity assumes the vaccine does not increase the risk that individual 1 becomes infected. HH develop bounds on $CRD_{\lambda}(0)$ assuming monotonicity. Under monotonicity, there are three principal strata based on the joint potential outcomes under vaccine and control of person $j = 1$ (eTable 1), namely the immune stratum (never infected), the protected stratum (not infected if vaccinated, infected if not vaccinated), and the doomed stratum (always infected). Under monotonicity, $p_1 = p_v$. Given the observed data, the proportion ρ of households where individual 1 is randomized to control and becomes

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infected that is in the doomed principal stratum is identifiable, just not which ones. Thus the HH bounds on $CRD_I(0)$ are

$$CRD_I^{H, low}(0) = p_1 - \min\{1, p_0/\rho\}, \quad (1)$$

$$CRD_I^{H, up}(0) = p_1 - \max\{0, (p_0 - (1 - \rho))/\rho\}. \quad (2)$$

In contrast, VT make the additional assumption that in the absence of vaccination, individuals who become infected regardless of whether they are vaccinated are more infectious than individuals who are protected by the vaccine. Under this assumption, VT show the net risk difference is an upper bound for the causal risk difference. The net risk difference is always less than or equal (2). The main difference between the VT and HH bounds is the reliance on this assumption, which is untestable.

Consider the study of 3000 households with two individuals in Table 1. The net vaccine effect on infectiousness is $RD_I^{net}(0) = 0.2 - 0.4 = -0.2$. Because $p_0 = 0.4$ and $\rho = 0.5$, $\min\{1, p_0/\rho\} = 0.8$ and $\max\{0, (p_0 - (1 - \rho))/\rho\} = 0$. Thus $CRD_I^{H, low}(0) = 0.2 - 0.8 = -0.6$ and $CRD_I^{H, up}(0) = 0.2 - 0 = 0.2$. The HH upper bound is positive, allowing that vaccination might actually enhance infectiousness. The VT upper bound is $RD_I^{net}(0) = -0.2$, indicating that, ignoring statistical variability, vaccination decreases infectiousness. Thus, in contrast to the HH bounds, the VT bound leads to the conclusion the vaccine is beneficial in reducing secondary transmissions. The different bounds could lead to different qualitative conclusions about whether the vaccine decreases, or possibly increases, infectiousness. Thus, one needs to examine critically the underlying biological and selection assumptions when determining bounds. Rather than relying on untestable assumptions, the bounds (1) and (2) can be combined with a sensitivity analysis (as in Hudgens and Halloran³) to make clear the degree to which conclusions about the vaccine having an effect on infectiousness depend on merging the data with strong prior beliefs. Further details are in the Online Supporting Material.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Identifiability and bounds on the causal risk difference $CRD_{\mathcal{I}}(0)$. 3000 households of size 2 with individual 1 randomized to vaccine or control 1:1. In the 1500 households with $\mathbf{Z}_j = (0, 0)$, individual 1 became infected in 1000, and individual 2 became infected in 400 of those, so $p_0 = 0.4$. In the 1500 households with $\mathbf{Z}_j = (1, 0)$, individual 1 became infected in 500, and individual 2 became infected in 100 of those, so $p_1 = 0.2$. The 500 transmission units where individual 1 was randomized to vaccine and became infected must be in the doomed stratum. The 500 transmission units where individual 1 was randomized to control and was not infected must be in the immune stratum. Thus, ignoring sampling variability, the proportions in the three principal strata π_i , π_p , and π_d all equal $1/3$, and $\rho = (1/3)/(2/3) = 0.5$. The number of households with $Y_{i1} = 1$, $Z_{i1} = 0$ in which $Y_{i2} = 1$ is 400. It is not known which of these 400 households are in the doomed or protected stratum. The number assumed in the doomed stratum under different selection assumptions is denoted by x (eSection 2.1). If individual 1 does not become infected, then $Y_{i2}(z_{i1}, z_{i2})$ is undefined and denoted by $*$.

Basic Principal Stratum	Prop.	Potential infection outcomes $Y_{i1}(z_i)$			Observed transmission outcomes $Y_{i2}^{obs} = 1$		Selection assumptions $Y_{i2}(z_i)$		
		(0,0)	(1,0)	(1,0)	(0,0)	(1,0)	(0,0)	(0,0)	(0,0)
Immune	π_i	0	0		*	*			
		500	500						
Protected	π_p	1	0			*			
		500	500		$\uparrow ?$		200	0	400
Doomed					400				
	π_d	1	1		$\downarrow ?$				
		500	500			100	$x = 200$	400	0
						CRD $_I(0)$	-0.2	-0.6	0.2