The need for quantitative bias analysis in HIV/AIDS research: The case of nevirapine vs. efavirenz on virologic failure in Johannesburg, South Africa

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Introduction

- **Observational studies are prone to bias**
  - Confounding, selection bias and information bias
- **While random error is nearly always quantified, systematic error typically only speculated about**
  - Without quantification of magnitude/direction of bias, difficult to speculate on total error, can lead to erroneous conclusions
- **Quantitative bias analysis (QBA) is an attempt to overcome this problem by using assumptions about sources of bias in a study and simulating the data we expect in the absence of the bias**
  - Use probabilistic Monte Carlo simulations to create uncertainty intervals (UI) accounting for total error (systematic and random)
  - Used Excel™ https://sites.google.com/site/biasanalysis/

Primary Study

- **Studied association between nevirapine (NVP) vs. efavirenz (EFV) in first-line ART and risk of one-year virologic failure at Themba Lethu, Johannesburg, South Africa**
  - Excluded pregnant women, those with TB
  - Virologic failure defined as 2 viral loads >1000 copies/ml
  - 711 initiated NVP and 9355 EFV, 3.5% (N=353) failure
  - Conventional analysis, those given NVP were 1.83-times (95%CI: 1.34-2.49) more likely to fail than those given EFV
- **Results are subject to bias**
  - Unmeasured confounding if sicker patients prescribed NVP
  - Non-differential exposure misclassification in recording regimens
  - Differential outcome misclassification if patients given NVP have better surveillance for failure than those given EFV

Bias Analysis Methods

- **Specify distributions for each bias parameters**
  - Sensitivity, specificity, strength/distribution of the confounder
  - Parameters defined as beta or trapezoidals
- **For each bias, draw randomly from distribution**
  - Use simple formulas* to "correct" the association between NVP vs. EFV on failure as if the source of bias had been absent
- **Monte Carlo simulation - repeat 40,000 times each time saving the corrected estimate of effect**
  - Summarize corrections using median and 2.5^{th}-97.5^{th} percentiles
  - Combine each estimate corrected for systematic error with random error by subtracting a randomly sampled standard normal deviate times the conventional standard error

Bias Parameters

Description	Parameter	Mean	Distribution
Unmeasured Confounder			
Moderate strength with higher prevalence in those given NVP than EFV that would increase the appearance of effect of NVP	Pr(C+|NVP)	65%	beta (66, 36)
	Pr(C+|EFV)	30%	beta (31, 71)
	$RR_{C\text{-}Failure}$	3.0	trap(min=2, mode1=2.5, mode2=3.5, max=4))
Non-differential Exposure Misclassification (NVP)			
Mild misclassification from data entry errors	Se/Sp	98%	beta(100, 2))
Differential Outcome Misclassification (Virologic Failure)			
Perfect specificity but higher sensitivity in those given NVP than EFV if better surveillance for failure in those given NVP	Se|NVP	99%	beta(101,1))
	Se|EFV	82%	beta (84, 18))
	Sp	100%	None

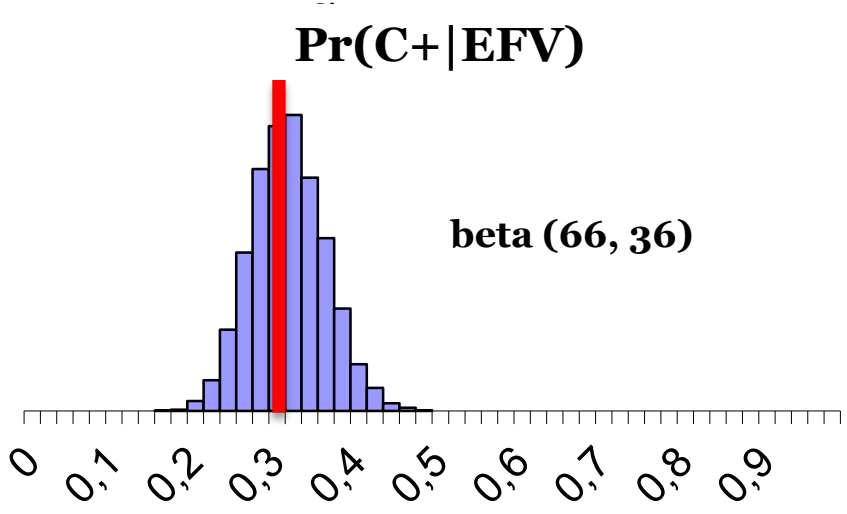
Formulas for corrections

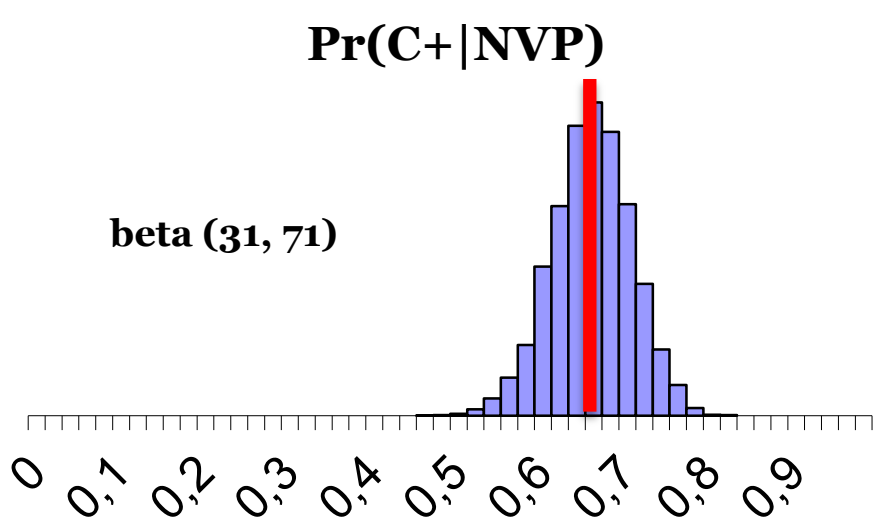
- Misclassification (exposure)
  - $A = [a - D+ * (1 - SP_{D+})] / [SE_{D+} - (1 - SP_{D+})]$
  - $C = [c - D- * (1 - SP_{D-})] / [SE_{D-} - (1 - SP_{D-})]$
  - $B = D+ - A$ and $D = D- - C$
- Confounder
  - $N_1 = n * p_o$ and $M_1 = m * p_1$
  - $N_o = n - N_1$ and $M_o = m - M_1$
  - $A_1 = [RR_{CD} * M_1 * a] / [RR_{CD} * M_1 + m - M_1]$
  - $B_1 = [RR_{CD} * N_1 * b] / [RR_{CD} * N_1 + n - N_1]$
  - $C_1 = M_1 - A_1$, $D_1 = N_1 - B_1$
  - $C_o = c - C_1$ and $D_o = d - D_1$
  - Where p1 and po=prev confounder in C+ and C-

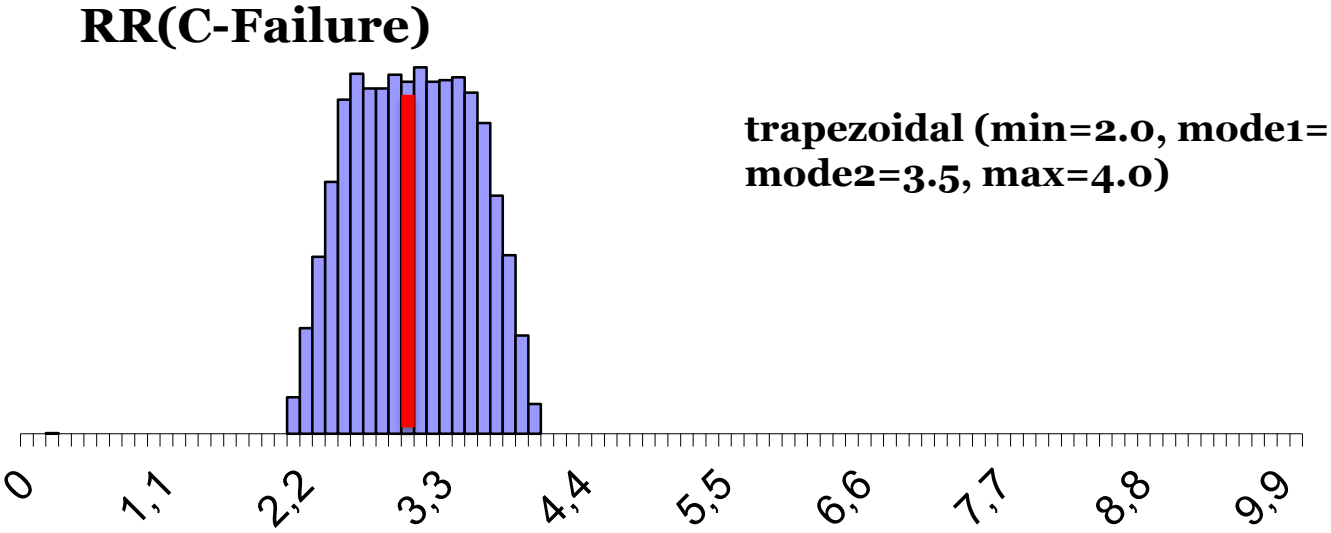
	"Truth"		Observed	
	E_+	**E-**	**E+**	**E-**
D_+	A	B	a	b
D-	C	D	c	d
	M	N	m	n

	Observed		Unmeasured Confounder			
	Total		C_1		C_0	
	E_1	**E_0**	**E_1**	**E_0**	**E_1**	**E_0**
D_1	a	b	A_1	B_1	A_0	B_0
D_0	c	d	C_1	D_1	C_0	D_0
	m	n	M_1	N_1	M_0	N_0

Example: Unmeasured Confounder







https://sites.google.com/site/biasanalysis/

PROBABILISTIC SENSITIVITY ANALYSIS UNMEASURED CONFOUNDING — Chapter 8

This spreadsheet can be used to conduct a probabalistic sensitivity analysis to correct for unknown of unmeasured counfounding and random error simultaneously. The example follows the example in chapter 8.

Input Bias Parameters	alpha	beta	Pos	N	Mean	Error
p_1	66.00	36.00	65	100	0.65	Corr p
p_0	31.00	71.00	30	100	0.30	0.00
RR_{DC}	2.00	2.50	3.50		4.00	
Sims	50000					

Instructions

Enter distributions for the bias parameters in the blue cells to the left and the crude data in the blue cells below. Cells in green give the results after adjusting for the unmeasured confounder. Note that white cells are expected values and therefore do not have to be integers.

Run Simulation

Variable Names		Exposure	NVP
Confounder	Unknown	Outcome	Viral failure

Data (Enter Crude NVP-Viral failure Data in Blue Cells)

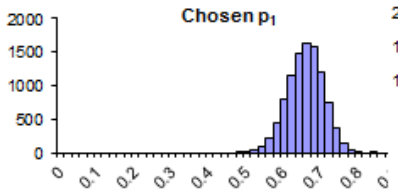
	Total		Unknown +		Unknown -	
	NVP +	NVP -	NVP +	NVP -	NVP +	NVP -
Viral failure +	43 a	310 b	36.9 A_1	168.7 B_1	6.1 A_0	141.3 B_0
Viral failure -	668 c	9045 d	409.2 C_1	2157.6 D_1	258.8 C_0	6887.4 D_0
Total	711 m	9355 n	446.2 M_1	2326.3 N_1	264.8 M_0	7028.7 N_0

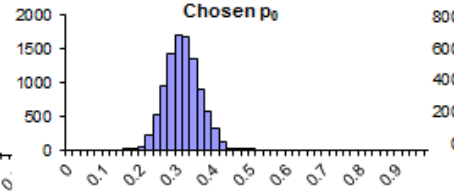
Crude and Adjusted Measures of NVP-Viral failure Relationship

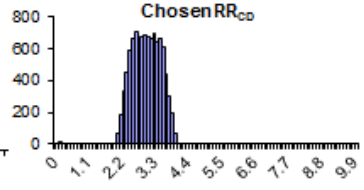
Crude	Measure (95% CI)	Adjusted SMR		Chosen Values	
RR (NVP-Viral	1.83 (1.34 - 2.49)	RR (NVP-Viral failure)	1.14	p_1	62.8%
OR (NVP-Viral	1.88 (1.35 - 2.61)	OR (NVP-Viral failure)	1.15	p_0	24.9%
				RR_{DC}	3.61

NVP-Viral failure Relationship Adjusted for Unknown

RR Simulation Results (N=20001)		OR Simulation Results (N=20001)		Illegal Values
Analysis	Median (2.5th-97.5th percentile)	Analysis	Median (2.5th-97.5th percentile)	
Conventional	1.83 (1.34 - 2.49)	Conventional	1.88 (1.35 - 2.61)	0
Systematic	1.29 (1.09 - 1.49)	Systematic	1.31 (1.09 - 1.53)	
Total Error	1.28 (0.91 - 1.82)	Total Error	1.31 (0.9 - 1.89)	







Calculations

OR	1.15	RR	1.14
SE(LN(OR))	0.1676	SE(LN(RR))	0.158
Negative cell	FALSE		

Correlation

u	0.905
e1	0.334
e0	0.109
t	2.253
f1	-0.691
f0	-2.099
p1	0.334
p0	0.109

Single Iteration

Syst Error		+ Rand Error		Chosen Bias Parameters		
SMR_{RR}	SMR_{OR}	SMR_{RR}	SMR_{OR}	p1	p0	RR_{DC}
1.14	1.15	0.99386	1.161	62.8%	24.9%	3.6
1.3647097	1.39041	1.3531	1.338	0.706	0.314	2.1792
1.2301847	1.24825	1.0472	1.364	0.64	0.289	3.2837
1.1309903	1.14071	1.3583	1.437	0.66	0.173	2.6148
1.2540581	1.27417	1.2653	1.236	0.614	0.28	3.195
1.0152387	1.01636	0.9652	1.038	0.766	0.238	3.3579
1.130837	1.14103	1.2703	1.177	0.688	0.284	3.6656
1.4117767	1.44268	1.3235	1.333	0.599	0.312	2.498
1.2005058	1.21621	1.2822	1.167	0.644	0.273	3.2787
1.2493755	1.26808	1.8166	1.061	0.707	0.337	3.1364
1.1434549	1.15425	0.9173	1.028	0.704	0.267	3.152
1.1528667	1.16441	1.2191	1.195	0.676	0.24	2.9663
1.4874078	1.52613	1.2134	1.393	0.593	0.396	3.1072
1.2752627	1.29647	1.4865	1.21	0.646	0.304	3.0496
1.3769474	1.40452	1.6212	1.278	0.657	0.325	2.4385
1.2515038	1.27136	1.153	1.349	0.628	0.292	3.2638
1.4306732	1.46286	1.5095	1.508	0.581	0.301	2.4005
1.442333	1.47652	1.2678	1.697	0.541	0.295	2.5812
1.1166177	1.1253	1.0382	0.664	0.747	0.299	3.4646
1.2986327	1.32311	1.206	1.479	0.606	0.322	3.6451
1.1907452	1.2056	1.1845	1.288	0.631	0.245	3.0836

Conventional and QBA Results

Analysis	Risk Ratio (95% Uncertainty Interval)	Interval accounts for:
Conventional:		
Crude	1.83 (1.34 – 2.49)	Random Error
Adjusted*	1.70 (1.24 – 2.33)	Random Error

*** Adjusted for baseline CD4 count, age at ART initiation, and sex**

Conclusions

- **Bias is common in observational epidemiology**
  - Quantitative bias analysis can be implemented in freely available software
  - Can reduce overconfidence by appropriately shifting point estimates, widening intervals
  - We used Excel™ with summary data but can be done in SAS, etc. with record level data
- **For analysis of the association between NVP vs. EFV and treatment failure**
  - Our results suggest while we likely overestimated the effect of nevirapine on failure, some effect remains
  - However, we should reduce our confidence in study findings

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