Statistical Methods for Infectious Disease Using Validation Sets for Outcomes in Vaccine Studies

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Vaccine efficacy for susceptibility

$$\begin{aligned} \mathrm{VE}_S &= 1 - \mathrm{RR} \\ \mathrm{RR} &= \text{relative risk in vaccinated} \\ &\quad \text{compared to unvaccinated} \end{aligned}$$

- incidence rates, hazard rates, incidence proportion, transmission probability
- if all ascertained cases actually disease of interest

The problem

- In many diseases, influenza, rotavirus, pertussis, and cholera,
  $\longrightarrow$ confirmatory diagnosis of suspected case by culture or quick test of specimen
- Often difficult or expensive
  $\longrightarrow$ use nonspecific case definition
  $\longrightarrow$ lower estimates than with specific case definition.

Example: Influenza vaccine studies

- Live attenuated influenza vaccine in children (RCT): with culture confirmed influenza:
  $\longrightarrow$ $VE_S = 0.89$ (Belshe, et al,1998)

- Similar vaccine in adults (RCT): case definition: "upper respiratory tract illness with either fever or cough":
  $\longrightarrow$ $VE_S = 0.25$ (Nichol, et al 1999).

Studies with validation sets for outcomes

- In small validation sample, measure both
  $\longrightarrow$ good outcome of interest
  $\longrightarrow$ correlated auxiliary outcome that is easier or cheaper.
- In the large main study, measure
  $\longrightarrow$ just easy, cheap correlated auxiliary outcome
- Validation sample $\longrightarrow$ corrects bias
- Main study $\longrightarrow$ improves efficiency

Final value data

- Estimating Efficacy of Trivalent, Cold-Adapted, Influenza Virus Vaccine (CAIV-T) Using Surveillance Cultures
- Halloran, Longini, Gaglani, Piedra, Chu, Herschler, Glezen
- American Journal of Epidemiology, 2003, 158:305–311.

Field Investigators

- W. Paul Glezen, Pedro A. Piedra, Department of Molecular Virology and Microbiology and Pediatrics, Baylor College of Medicine, Houston, Texas
- Manjusha J. Gaglani, Gayla B. Herschler, Charles Fewlass, Section of Pediatric Infectious Diseases, Department of Pediatrics, Scott & White Memorial Hospital & Clinic, Scott, Sherwood and Brindley Foundation, Texas A & M College of Medicine, Temple, Texas

Field Study of Flumist (Medimmune)

- Originally for estimating indirect effects in adults of vaccinating children 1.5-18 years old.
- Study in three communities, one with vaccination, two without
- Here we use only community with vaccination to estimate direct protective effects, VE_S

Field Study of Flumist

- Community-based non-randomized, open-label study of experimental vaccine.
- Temple-Belton, Texas, August 1998 - June 2001.
- All children 1.5–18 years old offered Flumist through Scott & White Clinics.
- Beginning in Fall 2003, vaccinated 5 –18 years old after licensure

This analysis

- Concerned with epidemic year 2000-01
- Children vaccinated either
  $\longrightarrow$ 1999 (and possibly 1998, not 2000)
  $\longrightarrow$ 2000 (and possibly 1999, 1998)
- Members of Scott & White Health Plan

Non-specific case definition

- Medically-attended acute respiratory illness (MAARI)
- ICD-9 codes 381-383, 460-487
- upper and lower respiratory track infections, otitis media, sinusitis, and asthma (with other diagnosis)
- influenza season defined by surveillance cultures

Influenza surveillance cultures

- Any individual presenting with history of fever and any respiratory illness was eligible.
- Throat swab or nasal wash at discretion of health care provider with informed verbal consent
- Influenza A and B viruses characterized by CDC

Viral Strain Information

Vaccine virus	Circulating wild type
1999-2000	
A/Sydney (H3N2)	
A/Beijing (H1N1)	not
B/Beijing	relevant
2000-01	
A/Sydney (H3N2)	—
A/New Caledonia (H1N1)	A/New Caledonia (H1N1)
B/Beijing	B/Sichuan

Efficacy using actual influenza cases:

- N_1, N_0 = number of children in vaccinated and unvaccinated groups, respectively.
- y_1, y_0 = number of true influenza cases in vaccinated and unvaccinated groups, respectively.
- IP_1 and IP_0 = incidence (binomial) proportion in vaccinated and unvaccinated groups, respectively.

$$\widehat{VE}_S = 1 - \frac{IP_1}{IP_0} = 1 - \frac{y_1/N_1}{y_0/N_0},$$

Using nonspecific case definition:

- z_1, z_0 = number of flu-like cases that are not true flu in vaccinated and unvaccinated groups, respectively.
- $w_\nu = z_\nu + y_\nu$ = number of total MAARI cases in group ν, $\nu = 0, 1$.
- Based on total number of influenza-like illnesses,

$$\widehat{VE}_{S,a} = 1 - \frac{IP_{1,a}}{IP_{0,a}} = 1 - \frac{w_1/N_1}{w_0/N_0},$$

- a = all influenza-like illness, auxiliary outcome.

Confidence intervals for $VE_{S,a}$ and VE_S

- normal approximation of the log of the ratio of two independent binomial random variables

Estimates using the surveillance samples, $VE_{S,v}$

- Auxiliary outcome and the mean score method by Pepe, Reilly and Fleming (1994)
- Estimate score contribution for main study member with only auxiliary outcome data from
  $\longrightarrow$ average score contributions of validation sample with same observed covariate and auxiliary outcome values.

Semiparametric method

- Parametric model for good data
- Nonparametric estimation or no estimation of relation between good data and surrogate measure
- Avoids misspecification of relation and resulting bias

Auxiliary outcome and mean score method

- Pepe, Reilly and Fleming (1994)
- Y = outcome of interest (influenza status)
- A = auxiliary outcome (MAARI, yes, no)
- X = set of covariates (vaccination, age group)
- $P_\beta(Y|X)$ = probability model
- β = parameters to estimate in probability model
- S_β = score function
- $V, \overline{V}$ = in validation set or not

Estimation

- Estimating equation:

$$\sum_{i \in V} S_\beta(Y_i|X_i) + \sum_{j \in \overline{V}} \hat{E}\{S_\beta(Y|X_j)|A_j, X_j\} = 0$$

- Unbiased estimator for nonvalidation set person:

$$\hat{E}\{S_\beta(Y|X_j)|A_j, X_j\} = \sum_{i \in V(A_j, X_j)} S_\beta(Y_i|X_i)/n^V(A_j, X_j)$$

- Inference makes allowance for not having all data.

Inverse proportional weighting

- Basically equivalent to analytic methods that weight observed or sampled case inversely to the probability of being observed.
- Horwitz-Thompson (1952) type estimators

Advantages of this method

- Proven consistent
- Easy computation of variance estimator
- Simple expression for optimal sampling fractions
- Simple to explain to epidemiologists

Potential drawbacks

- Restricted to categorical data
- Need validation members in every cell
- Assumes missing at random (MAR)

Conditional independence assumption (MAR)

- $Y =$ disease (influenza)
- $A =$ non-specific disease (MAARI)
- $X =$ observed covariates (vaccine, age)
- $\Delta = 0, 1$ whether sampled in to validation set
- negative MAARI assumed negative influenza !
  $\longrightarrow (Y \perp \Delta \mid A, X)$
  $\longrightarrow [Y \mid X, A, \Delta = 1] = [Y \mid X, A]$

Likely MAR does not hold

- Ad hoc sampling due to physician's choice likely not random
- Likely physicians may choose to culture cases that they believe are influenza, say more severe.
- Unvaccinated cases may be more severe than vaccinated cases

Oversampling of severe cases

- If unvaccinated influenza cases are oversampled because they look more like influenza,
- $\longrightarrow$ then the data are missing for reasons that depend on the outcome that is missing in some.
- Therefore, Y and Δ likely not independent conditional on X and A.

Sensitivity Analysis

More details later.

Table: Epidemic year 2000-2001. N is the number of children in each group by vaccine status.

Age (years)	Vaccine	N	MAARI cases	MAARI attack rate	MAARI cases cultured	Number positive cultures	Fraction cultures positive	Fraction cultured
Vaccinated in 2000.								
1.5-4	CAIV-T	537	389	0.72	16	0	0	0.041
	None	1844	1665	0.90	86	24	0.28	0.052
5-9	CAIV-T	807	316	0.39	17	2	0.12	0.054
	None	2232	1156	0.52	118	53	0.45	0.102
10-18	CAIV-T	937	219	0.23	19	3	0.16	0.087
	None	5249	1421	0.27	123	56	0.46	0.087
Total	CAIV-T	2281†	924	0.41	52	5	0.10	0.056
	None	9325	4242	0.45	327	133	0.41	0.077

† 848 children received CAIV-T in 2000 only

Table: Epidemic year 2000-2001: Vaccine effectiveness ($VE_{S,a}$) against MAARI and efficacy ($VE_{S,v}$) against combined influenza A (H1N1) and B taking missing influenza status into account.

Age (years)	$VE_{S,a}$ MAARI	(95% CI)	$VE_{S,v}$ influenza	(95% CI)
Vaccinated in 2000.				
1.5-4	0.20	(0.14,0.25)	0.91	$(-0.34, 0.99)$
5-9	0.25	(0.15,0.34)	0.80	(0.26,0.95)
10-18	0.14	(0.01,0.26)	0.70	(0.13,0.90)
Total	0.18	(0.11,0.24)	0.79	(0.51,0.91)

Esimates for influenza A (H1N1) and B

	Positive	A (H1N1)	B
Vaccinated 2000	5	1	4
Vaccinated 1999	4	1	3
Never Vaccinated	133	68	65

Estimates for influenza A (H1N1) and B

- $\longrightarrow$ Vaccinated in 2000
- A (H1N1): 0.92 [95% CI 0.42,0.99]
- B: 0.66 [95% CI 0.09,0.87],

- $\longrightarrow$ Vaccinated in 1999
- A (H1N1): 0.84 [95% CI -0.11,0.98]
- B: 0.50 [95% CI -0.49,0.83]

Summary of results

- demonstrate substantial efficacy of CAIV-T against influenza during an epidemic of influenza A (H1N1) and B
- protection more than a year after vaccination
- evidence for cross-protection
- estimates accounting for missing influenza status compare favorably to those from randomized, double-blinded studies with culture-confirmed outcomes.
- first analysis to use validation set approach in vaccine studies.

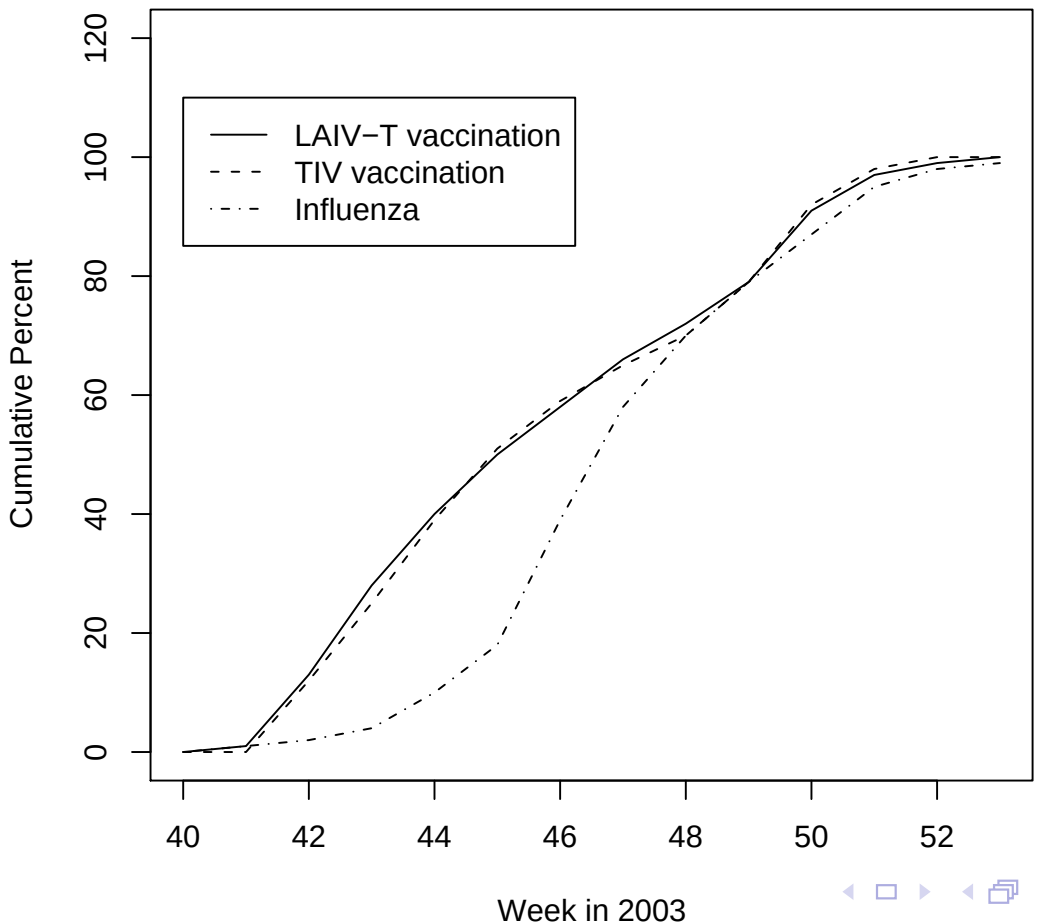
Time-to-event data

- Efficacy of Trivalent, Cold-Adapted, Influenza Virus Vaccine Against Influenza A (Fujian), a Drift Variant, during 2003-2004
- M. Elizabeth Halloran, Pedro A. Piedra, Ira M. Longini, Jr, Manjusha J. Gaglani, Brian Schmotzer, Charles Fewlass, Gayla B. Herschler, W. Paul Glezen
- 2007, *Vaccine*

The 2003-2004 Influenza Season

- In the 2003-2004 influenza season, the predominant circulating influenza A (H3N2) virus in the United States was similar antigenically to A/Fujian/411/2002 (H3N2), a drift variant of A/Panama/2007/99 (H3N2), the vaccine strain.
- The influenza season started early in Texas, so vaccination occurred during the influenza season.
- The analysis allows a child's vaccination status to change during the influenza season.
- Healthy children aged 5 – 18 years were offered LAIV-T vaccination, TIV offered if LAIV-T contraindicated

Figure: Cumulative distribution of vaccine uptake and positive influenza cultures



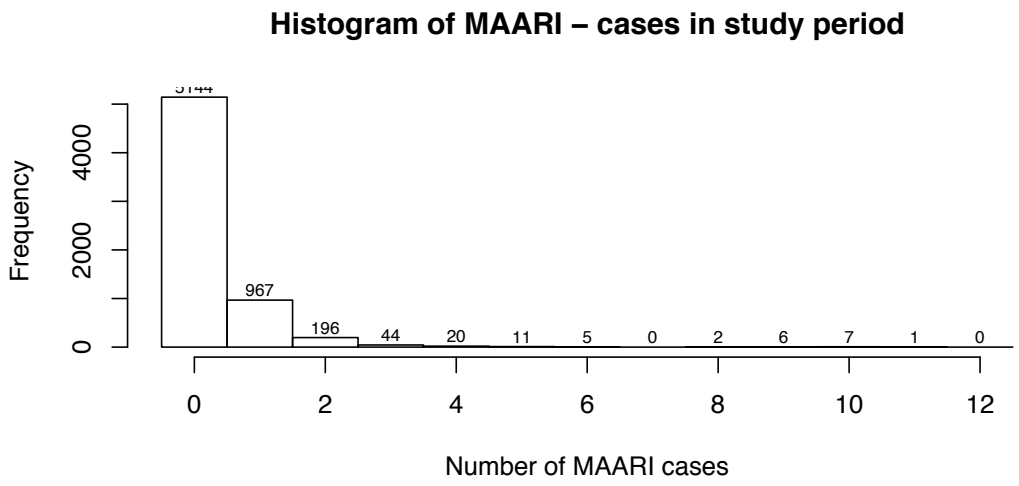
Analysis

- We estimate the incidence rate of true influenza in each vaccine group, and from that, the group specific vaccine efficacy, $\mathrm{VE}_{k,v}$, based on the validation set as

$$\widehat{\mathrm{VE}}_{k,v} = 1 - \frac{[\sum_{\tau=1}^{T} \hat{\rho}_{k1\tau} w_{k1\tau}]/[\sum_{\tau=1}^{T} d_{k1\tau}]}{[\sum_{\tau=1}^{T} \hat{\rho}_{k0\tau} w_{k0\tau}]/[\sum_{\tau=1}^{T} d_{k0\tau}]} \ .$$

- Overall VE_v is computed by weighting the contributions of the age groups by the combined number of child-days at risk in the vaccinated and unvaccinated groups in each age group.
- Confidence intervals were based on the bootstrap (Efron and Tibshirani 1993).

Figure: Distribution of MAARI cases



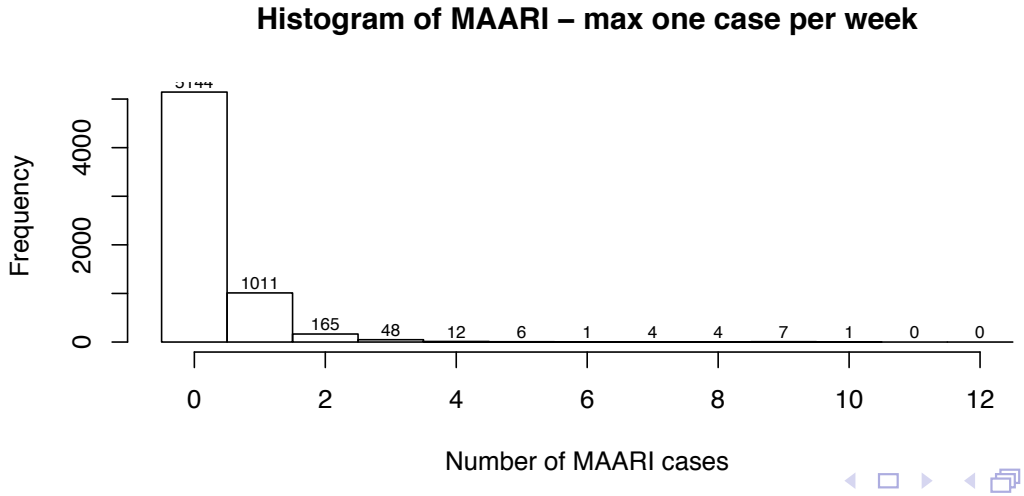


Table: LAIV-T Vaccine Strains in the 1998-2002 and 2003-2004 Seasons in this Study

	A(H3N2)	A(H1N1)	B
Current			
2003-2004	A/Panama/2007/99	A/New Caledonia/20/99	B/Hong Kong/330/2001
Previous			
2001-2002	A/Panama/2007/99	A/New Caledonia/20/99	B/Sichuan/379/99-like
2000-2001	A/Sydney/5/97	A/New Caledonia/20/99	B/Beijing/184/93-like (B/Ann Arbor/1/94)
1998-2000	A/Sydney/5/97	A/Beijing/262/95	B/Beijing/184/93-like (B/Ann Arbor/1/94)

Table: Covariates by Vaccine Group

	Vaccine status at end of period				Total
	LAIV-T no. (%)	TIV no. (%)	PREV no. (%)	UNVAC no. (%)	
Total	1706	548	983	3166	6403
5–9 years	757(44)	225(41)	224(23)	739(23)	1945(30)
10-18 years	949(56)	323(59)	759(77)	2427 (77)	4458(70)
Male	820(48)	296(54)	516(52)	1637(52)	3269 (51)
Female	886(52)	252(46)	467 (48)	1529 (48)	3134(49)
Group 1*	82(5)	190(35)	60(6)	227(7)	618(10)
Group 2 †	73(4)	37(7)	52(5)	158 (5)	379(6)
Both‡	10(0.3)	13(2)	8(0.8)	28(0.9)	59(1)
Either§	165(10)	240(44)	120(12)	413(13)	938(15)

* Chronic obstructive pulmonary disease (COPD), including asthma (ICD-9-CM codes 490-496)

† Numerous other chronic underlying conditions, including HIV

‡ Having conditions from both categories

§ Total number with COPD or other chronic condition

Table: MAARI events, child-days at risk and rate per 1,000 child-days at risk by age group and vaccine status.

Age (years)	Vaccination status	MAARI Events	Child-days at Risk	Rate/1,000 Child-days at risk
5-9				
	LAIV-T	105	35,886	2.93
	TIV	80	10,598	7.55
	PREV	143	26,902	5.32
	UNVAC	261	61,522	4.24
10-18				
	LAIV-T	117	42,991	2.72
	TIV	82	13,741	5.97
	PREV	273	71,424	3.82
	UNVAC	641	179,828	3.56
Combined				
	LAIV-T	222	78,883	2.81
	TIV	162	24,383	6.64
	PREV	416	98,297	4.23
	UNVAC	902	241,331	3.74
Totals				
5-9		589	134,908	4.37
10-18		1113	307,984	3.61
Combined		1702	442,896	3.84

Table: Influenza Surveillance Data (Number positive/Number cultured (proportion)), Temple-Belton, Texas, 2003-2004.

Age Group (years)	SWHP		non-SWHP		Combined	
	Unvaccinated	LAIV-T	Unvaccinated	LAIV-T	Unvaccinated	LAIV-T
5-9	8/20 (0.40)	3/15 (0.20)	19/34 (0.56)	4/9 (0.44)	27/54 (0.50)	7/24 (0.29)
10-18	35/56 (0.63)	5/13 (0.38)	30/49 (0.61)	4/11 (0.36)	65/105 (0.62)	9/24 (0.38)
Total	43/76 (0.57)	8/28 (0.29)	49/83 (0.59)	8/20 (0.40)	92/159 (0.58)	16/48 (0.33)
	TIV	PREV	TIV	PREV	TIV	PREV
5-9	2/5 (0.40)	3/9 (0.33)	0/3 (0.33)	7/21 (0.33)	2/8 (0.25)	10/30 (0.33)
10-18	3/3 (1.0)	15/29 (0.52)	5/6 (0.83)	8/15 (0.53)	8/9 (0.89)	23/44 (0.52)
Total	5/8 (0.63)	18/38 (0.47)	5/9 (0.56)	15/36 (0.42)	10/17 (0.59)	33/74 (0.44)

Table: Vaccine effectiveness of LAIV-T: VE^{a} against MAARI (95% CI), against culture-confirmed influenza using just SWHP surveillance cultures VE^{in} (95% CI), and against culture-confirmed influenza using surveillance cultures from the children in the SWHP database and children not in the SWHP database, VE^{ex} (95% CI).

Vaccine status	Age group (years)	VE^{a} (95% CI)‡ MAARI	VE^{in} (95% CI) influenza	VE^{ex} (95% CI) influenza
LAIV-T*				
	5-9	0.31 (0.11,0.47)	0.66 (−0.03,1.0)	0.60 (0.25,0.84)
	10-18	0.24 (0.03,0.40)	0.53 (0.12,0.86)	0.54 (0.23,0.78)
	All	0.26 (0.11,0.39)	0.56 (0.24,0.84)	0.56 (0.32,0.75)
PREV†				
	5-9	−0.25 (−0.61,0.05)	−0.04 (−1.9,1.0)	0.17 (−0.50,0.61)
	10-18	−0.07 (−0.28,0.10)	0.11 (−0.37,0.46)	0.09 (−0.28, 0.39)
	All	−0.13 (−0.30,0.03)	0.08 (−0.38,0.44)	0.11 (−0.19,0.37)

∗ vaccinated with LAIV-T in 2003, regardless previously vaccinated or not

† previously vaccinated in 1998-2001, but not in the 2002-2003 season or in 2003

‡ Percentile bootstrap confidence intervals based on 2000 bootstrap samples.

Validation Samples with Selection Bias

- Scharfstein, Halloran, Chu, Daniels. On estimation of vaccine efficacy using validation samples with selection bias.
- *Biostatistics*, 2006, 7:615-629.

Methods

- Frequentist varied over range of possibilities
- Bayesian with elicitation of priors: full posterior distributions.

Figure: Frequentist sensitivity analysis of $P_{z,x}[Y = 1]$.

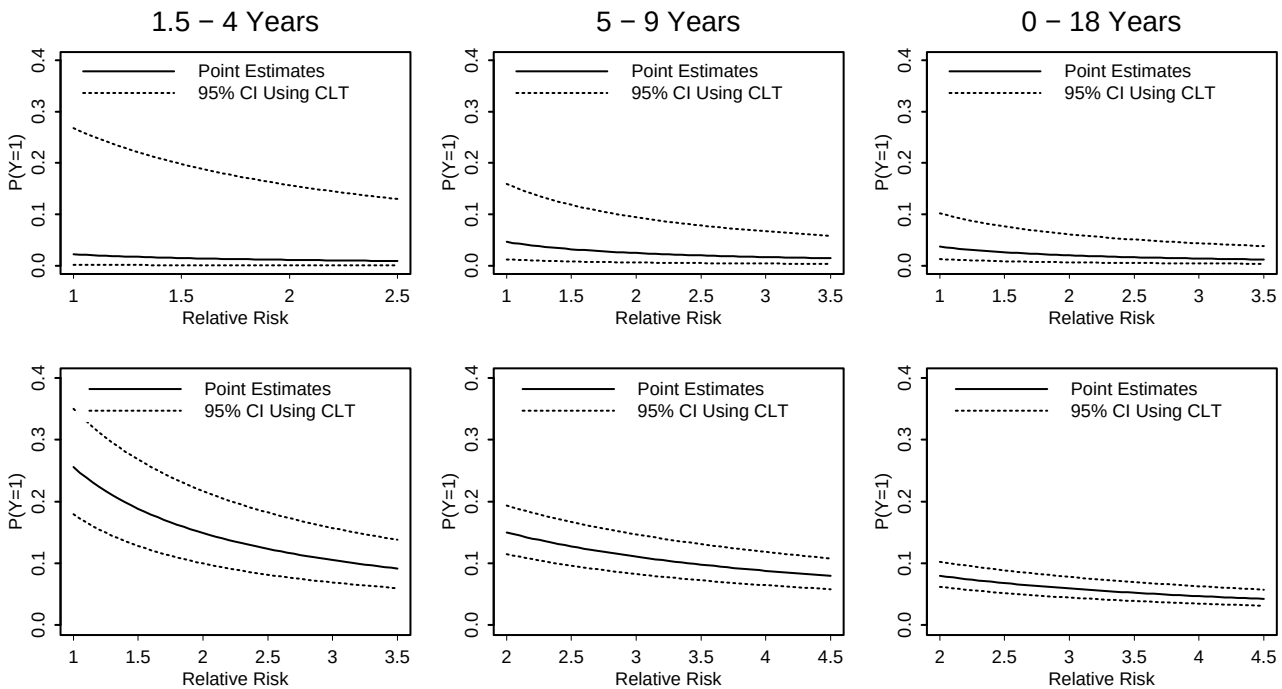


Figure: Frequentist sensitivity analysis of point estimates and lower 95% confidence bounds of age-group specific VE as function of relative risk selection bias parameter varied over 90% of range elicited from the expert.

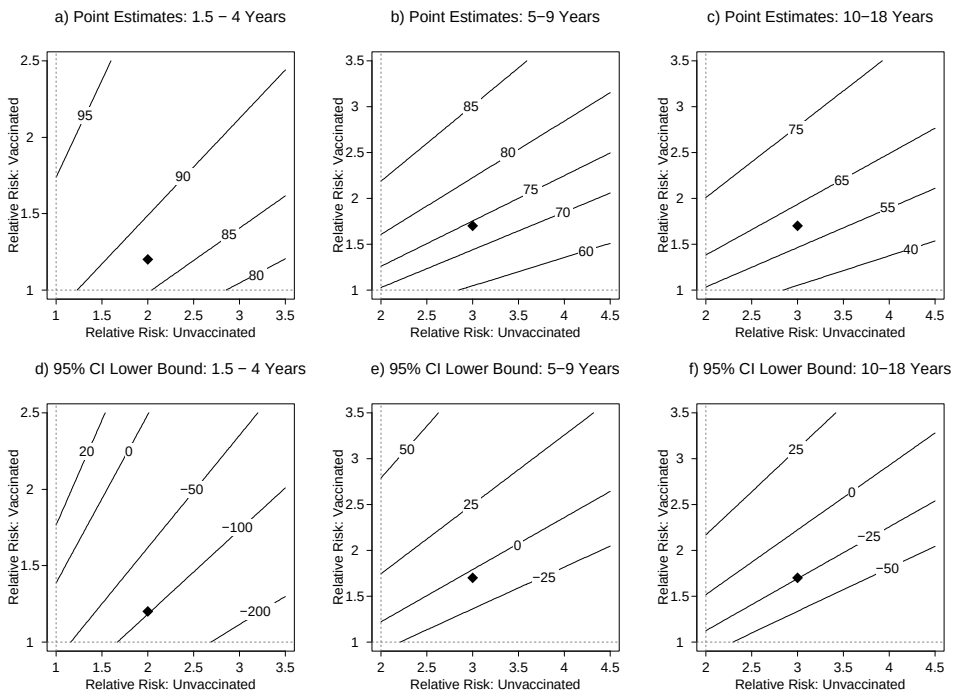
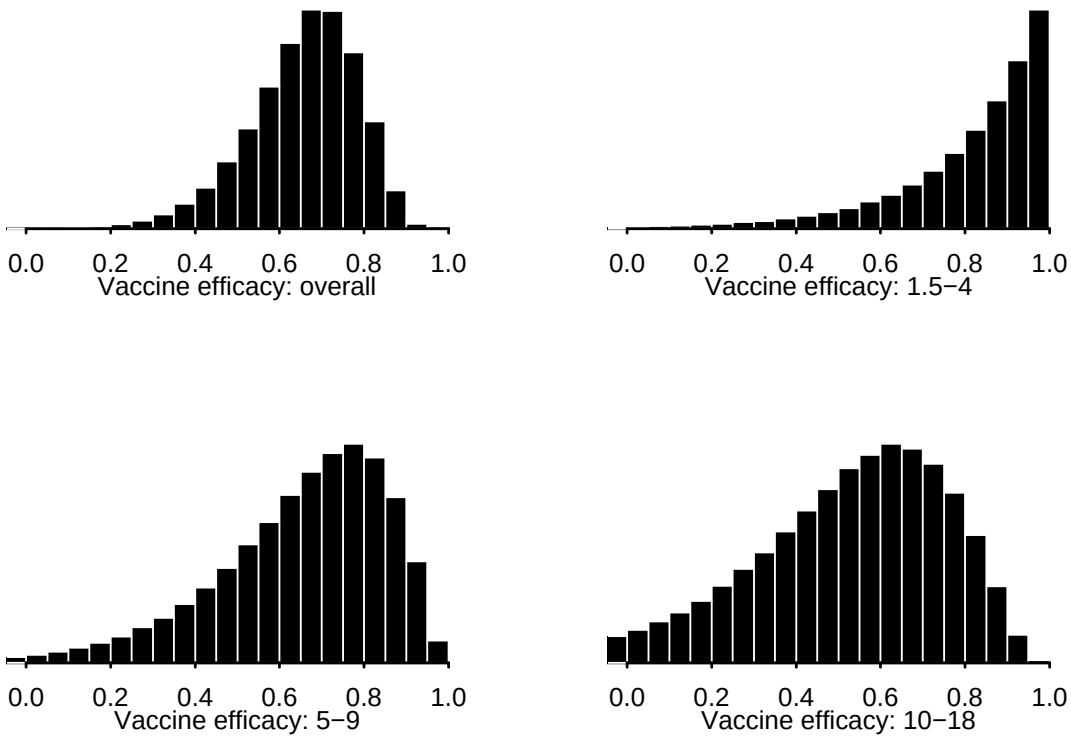


Figure: Posterior distributions of the overall VE and by age group using the informative prior distributions.



Other

- Commentary in Am J Epidemiol, Halloran and Longini (2001):
  $\longrightarrow$ suggested using validation sets for outcomes and exposure to infection in vaccine studies
- Greg Golm, Halloran, Longini: Validation sets for exposure to infection in HIV Vaccine Studies
  $\longrightarrow$ (*Biometrics* 1999; *Statist in Med*, 1999)

Challenges of flu

- Fast temporal changes of influenza (true flu)
- Fast temporal changes of background flu-like illness
- Time-dependence of ratio of true flu to fake flu
- Age- and vaccine-status dependence
- Repeated outcomes of flu-like illness
- Influence of vaccine status on culture outcome
- No gold standard for outcome

Sampling considerations

- Sample every 10th nonspecific case
- Determine before the study which 10% people are in the validation sample, then culture them with at every illness

Example: Community trials

- increased interest in indirect effects of vaccination
- trials in Texas(flu), southwest US (pneumococcal), cholera (Vietnam)
- unit of analysis: population, not individual
- large size of community trials makes use of validation sets even more compelling

Thank You!