Statistical efficiencies in 'the' etiologic study of near-immediate sequelae of infant vaccination

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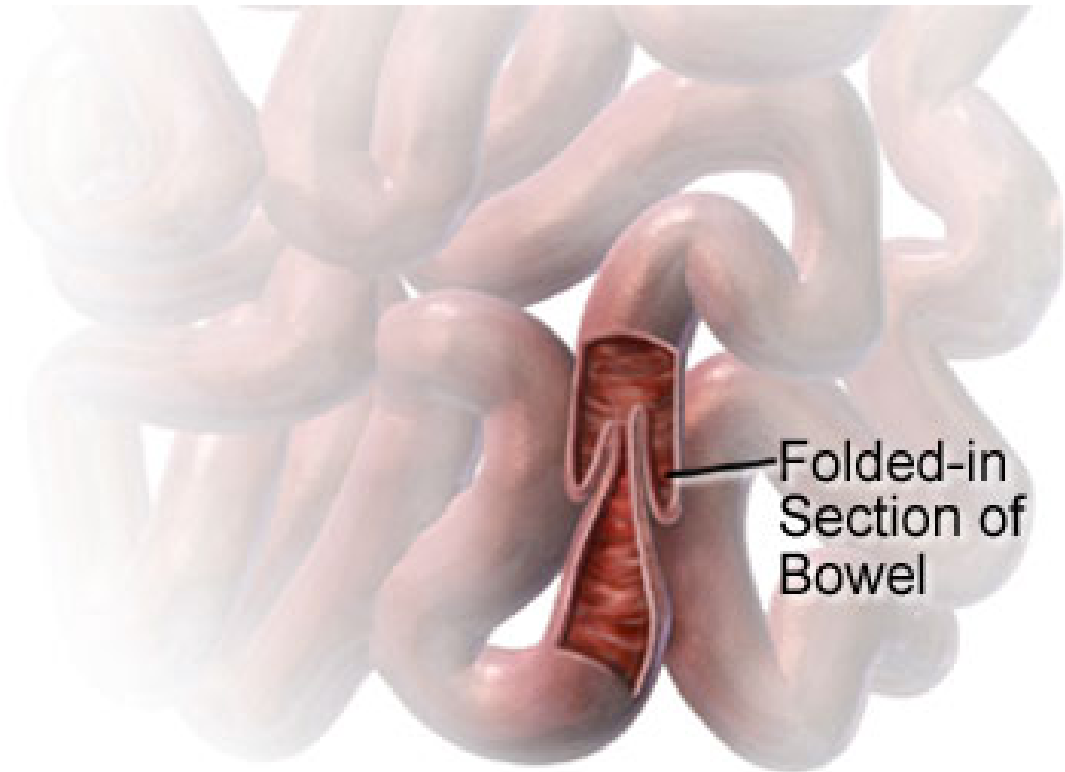
3 take-home messages

- Infants are special
- 'Case-control' studies of possible adverse effects of vaccinations in infancy/early childhood permit
  - data-displays
  - data-analysis approaches
  - statistical efficiencies

  that are not usually possible in other 'case-control' studies.
- and provide insights into the form of 'the' etiologic study.

Intussusception* Risk and Health Benefits of Rotavirus Vaccination in Mexico and Brazil NEJM, June 16, 2011

*Intussusception: Inversion of one portion of the intestine within another



Intussusception of the Bowel

http://www.drugs.com/cg/intussusception-in-children.html

Intussusception* Risk and Health Benefits of Rotavirus Vaccination in Mexico and Brazil NEJM, June 16, 2011

Background Because post-licensure surveillance determined that a previous rotavirus vaccine, RotaShield, caused intussusception in 1 of every 10,000 recipients, we assessed the association of the new monovalent rotavirus vaccine (RV1) with intussusception after routine immunization of infants.

Methods We used case-series and case-control methods to assess the association between RV1 and intussusception.

Infants with intussusception were identified through active surveillance at 69 hospitals (16 in Mexico and 53 in Brazil), and age-matched infants from the same neighborhood were enrolled as controls. Vaccination dates were verified by a review of vaccination cards or clinic records.

Results

We enrolled 615 case patients (285 in Mexico and 330 in Brazil) and 2050 controls. An increased risk of intussusception **1 to 7 days after** the first dose of RV1 was identified among infants in Mexico with the use of both the case-series method (incidence ratio, 5.3; 95% confidence interval [CI], 3.0 to 9.3) and the case-control method (odds ratio, 5.8; 95% CI, 2.6 to 13.0). No significant risk was found after the first dose among infants in Brazil, but an increased risk, albeit smaller than that seen after the first dose in Mexico – an increase by a factor of 1.9 to 2.6 – was seen 1 to 7 days after the second dose.

A combined annual excess of 96 cases of intussusception in Mexico (approximately 1 per 51,000 infants) and in Brazil (approximately 1 per 68,000 infants) and of 5 deaths due to intussusception was attributable to RV1.

However, RV1 prevented approximately 80,000 hospitalizations and 1300 deaths from diarrhea each year in these two countries.

Methods: **case-series analysis**.. "dose-specific incidence ratios

using a conditional Poisson regression model by comparing for each infant the incidence of intussusception within each risk period with the incidence within all other observation periods.

We adjusted for age in 14-day intervals to account for the varying background incidence of intussusception during the observation period and included an interaction term for country.

The occurrence of intussusception before RV1 vaccination could decrease the probability that the infant would receive subsequent doses in the short term or could perhaps contraindicate subsequent vaccination. To account for this effect, only the time after exposure to the vaccine was included in the observation period."

Methods: **case-control analysis**, “conditional logistic-regression model

used to assess the ratio of the odds that case patients were vaccinated within the risk windows to the odds that age-matched controls were vaccinated within those windows, including an interaction term for country.

The season of birth and regional variations in the incidence of intussusception and vaccination were implicitly adjusted for by matching case patients with controls according to neighborhood and date of birth.

In addition, the infants in each matched set of case patient and controls in the final model were the same age in days. This was accomplished by creating a “reference date” for controls, which was the date on which the matched control was the same age as the case patient was at the time of hospitalization.

Exposure to vaccination was determined within risk windows before this reference date. Therefore, exposure status was age-matched between case patients and controls. Strata of cases with the same reference date were collapsed.

Table 1. Characteristics of the Infants with Intussusception, According to Country.

Characteristic	Mexico (N = 285)	Brazil (N = 330)
Age — mo		
Median	5.2	5.5
Range	1.5–8.0	1.5–8.0
Duration of symptoms before hospitalization — days		
Median	1	1
Range	0–7	0–7
Duration of hospitalization — days		
Median	4	15
Range	0–37	0–24
Male sex — no. (%)	174 (61)	189 (57)

Male sex — no. (%)	174 (61)	189 (57)
Death — no. (%)	3 (1)	16 (5)
Surgical treatment — no./total no. (%)	242/278 (87)	314/330 (95)
Surgery with resection — no./total no. (%)	63/265 (24)	153/330 (46)
Rotavirus vaccination*		
Dose 1	272 (95)	314 (95)
Dose 2	200 (70)	243 (74)
Age at dose 1 — days		
Median	68	64
Range	25–238	5–136
Age >105 days or >14 wk at dose 1 — no. (%)	37 (13)	10 (3)
Breast-fed — no. (%)†	—	314 (95)

* Included are all vaccinations that were administered during the observation period, before or after the onset of intussusception.
† Data on breast-feeding were not available for the Mexican cohort.

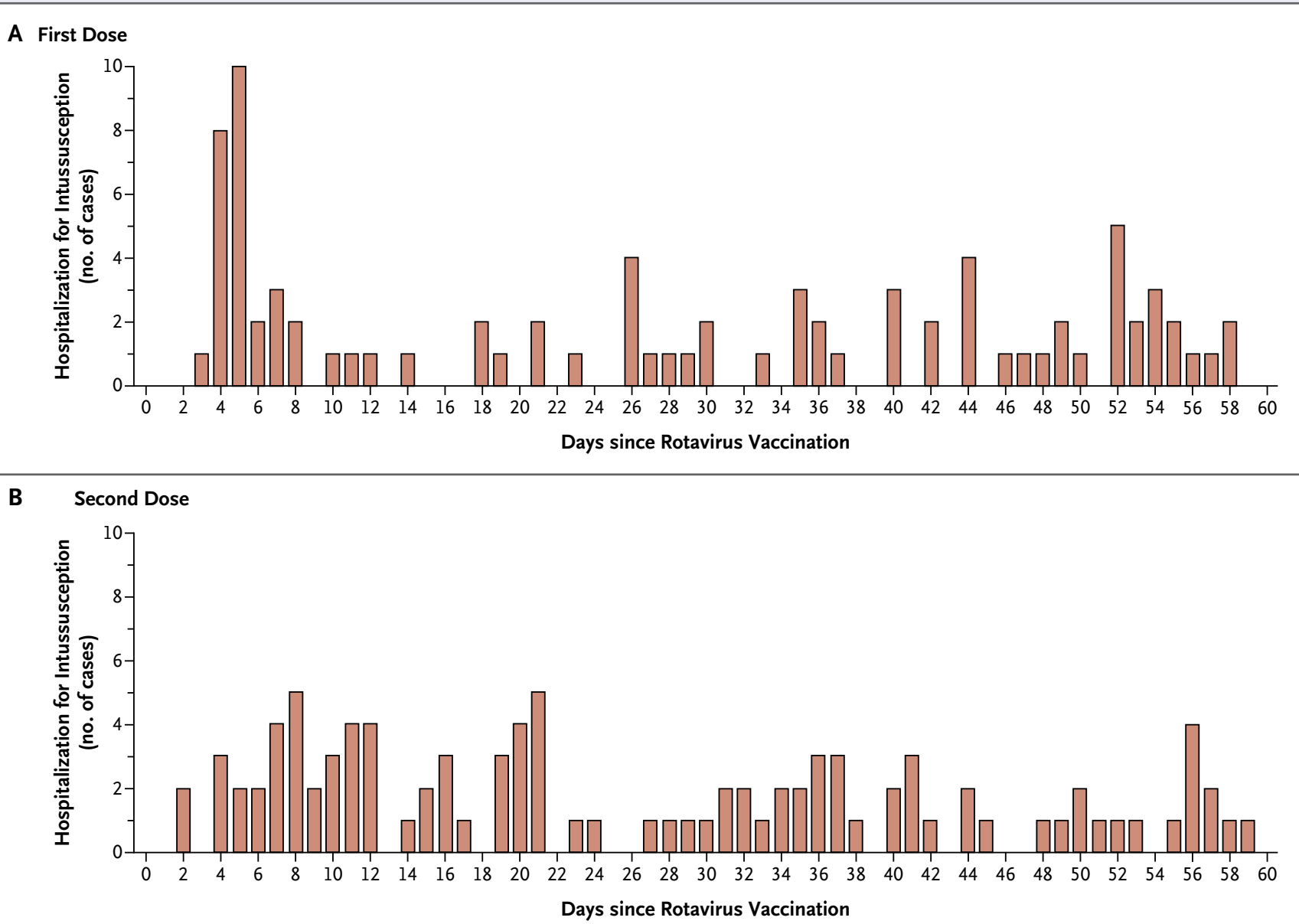


Figure 1. Interval between Rotavirus Vaccination and Hospitalization for Intussusception in Mexico.

Not shown are 12 cases of intussusception that occurred before the first dose, 31 that occurred more than 60 days after the first dose, and 49 that occurred more than 60 days after the second dose.

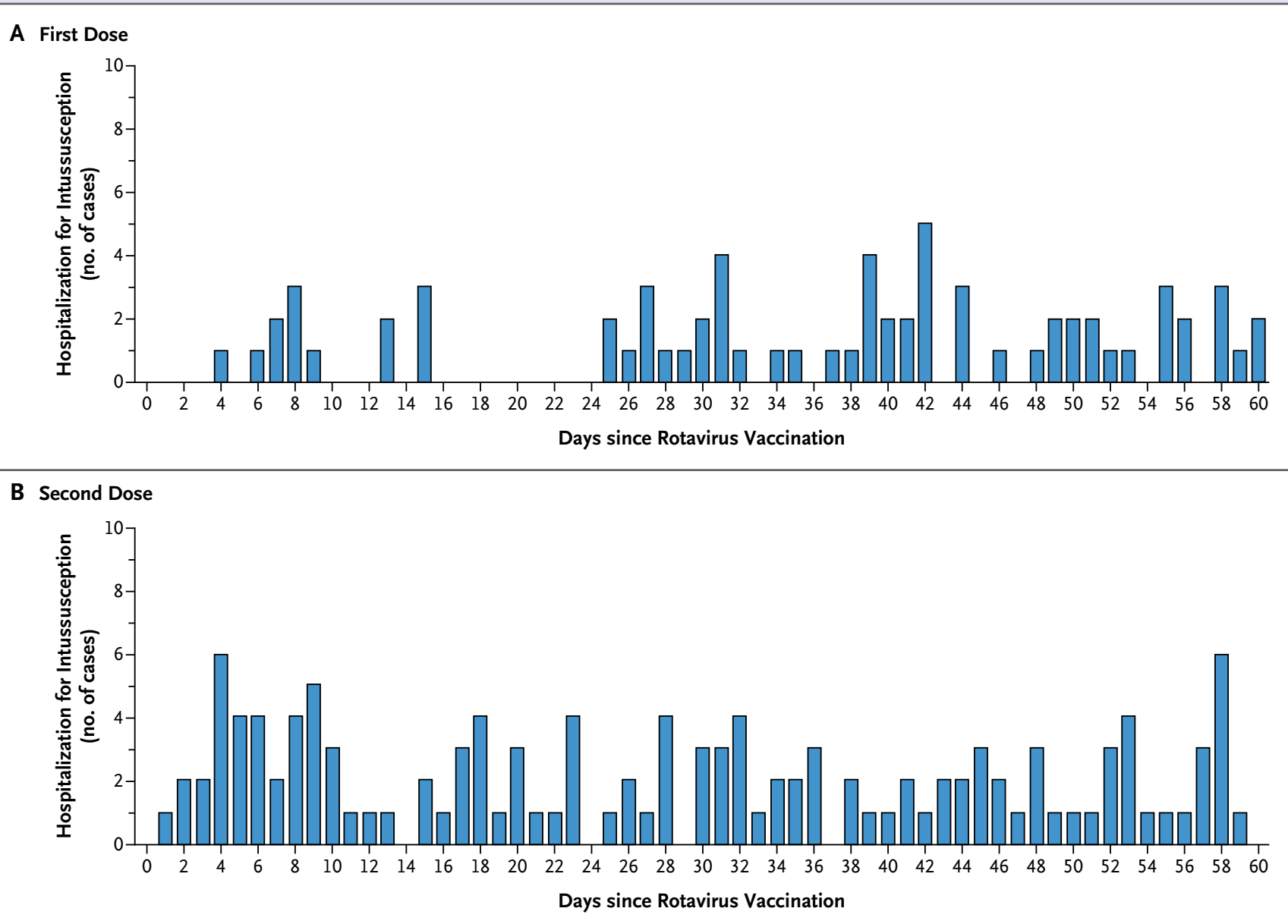


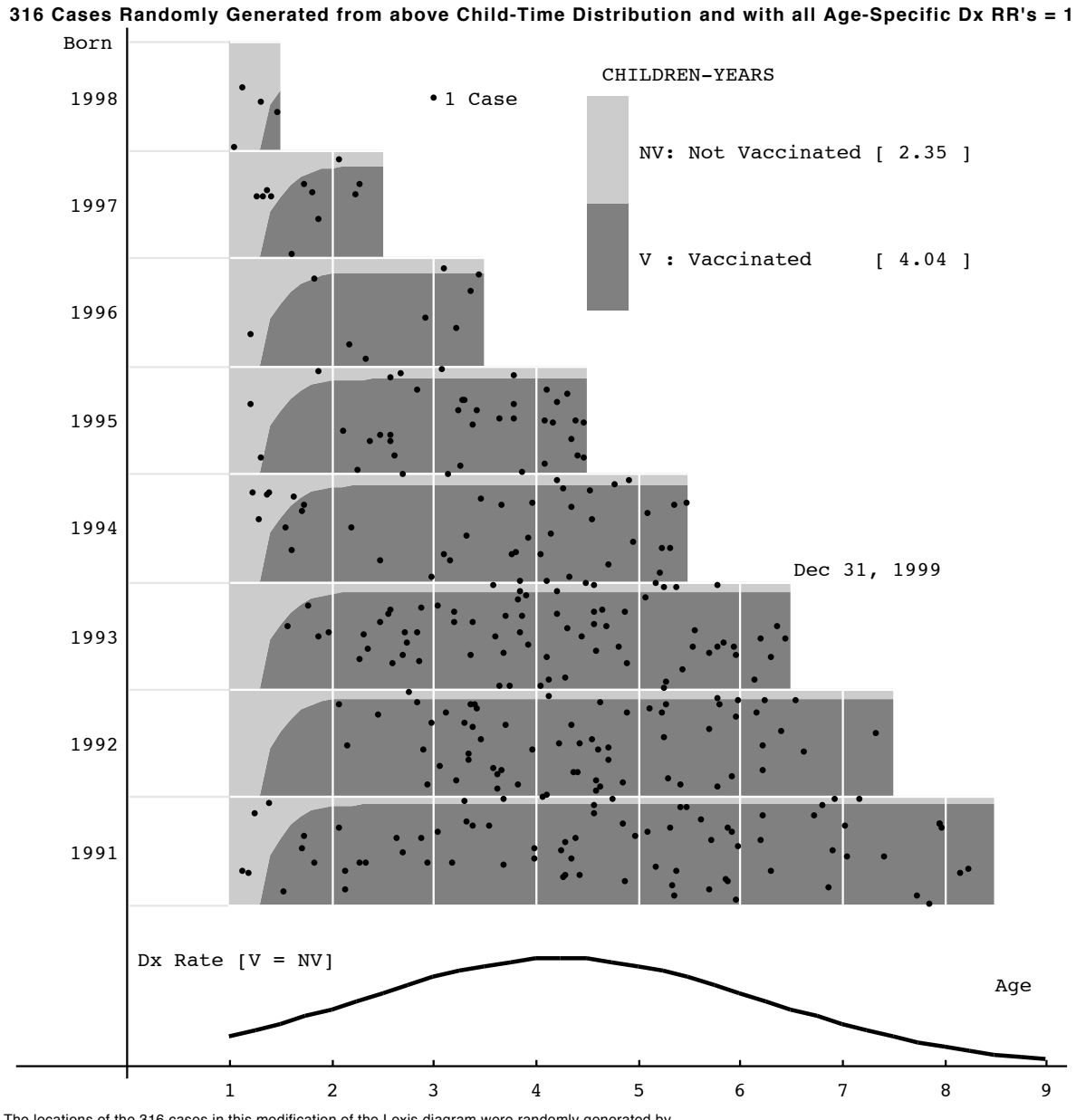
Figure 2. Interval between Rotavirus Vaccination and Hospitalization for Intussusception in Brazil.

Not shown are 2 cases of intussusception that occurred before the first dose, 28 that occurred more than 60 days after the first dose, and 90 that occurred more than 60 days after the second dose.

Using Danish electronic vaccination registry

investigators (NEJM 2002) had data on ...

MMR vaccination / Autism cases : 9 birth-cohorts



The locations of the 316 cases in this modification of the Lexis diagram were randomly generated by

They didn't compare rates in (older) V^{ed} vs. (younger) $\overline{V}^{ed}$ child-years (CY)

$$\textit{Crude } RR = \frac{\sum_{ages} n.cases.V / \sum_{ages} CY_V}{\sum_{ages} n.cases.\overline{V} / \sum_{ages} CY_{\overline{V}}} = \frac{263/1,647,504}{53/482,360} = 1.45$$

They compared rates in same-age V and $\overline{V}$ child-years:

$$\text{M-H}^* \; RR = \frac{\sum_{ages} \; n.cases.V \; \times \; CY_{\overline{V}} \; / CY}{\sum_{ages} \; n.cases.\overline{V} \; \times \; CY_V \; / CY} = 0.92$$

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* Full disclose: They used Poisson regression.

ASIDE: a tribute to Mantel's statistical intuition

$$\text{M-H}^{*}\ RR = \frac{\sum_{ages}\ n.cases.V\ \times\ CY_{\overline{V}}\ /CY}{\sum_{ages}\ n.cases.\overline{V}\ \times\ CY_{V}\ /CY}.$$

$$RR_{MLE} = \frac{\sum_{ages}\ n.cases.V\ \times\ CY_{\overline{V}}\ /(CY_{\overline{V}} + RR_{MLE} \times CY_{V})}{\sum_{ages}\ n.cases.\overline{V}\ \times\ CY_{V}\ /(CY_{\overline{V}} + RR_{MLE} \times CY_{V})}.$$

M-H* *RR* is 1st iteration, from $RR_0 = 1$, towards RR_{MLE} !

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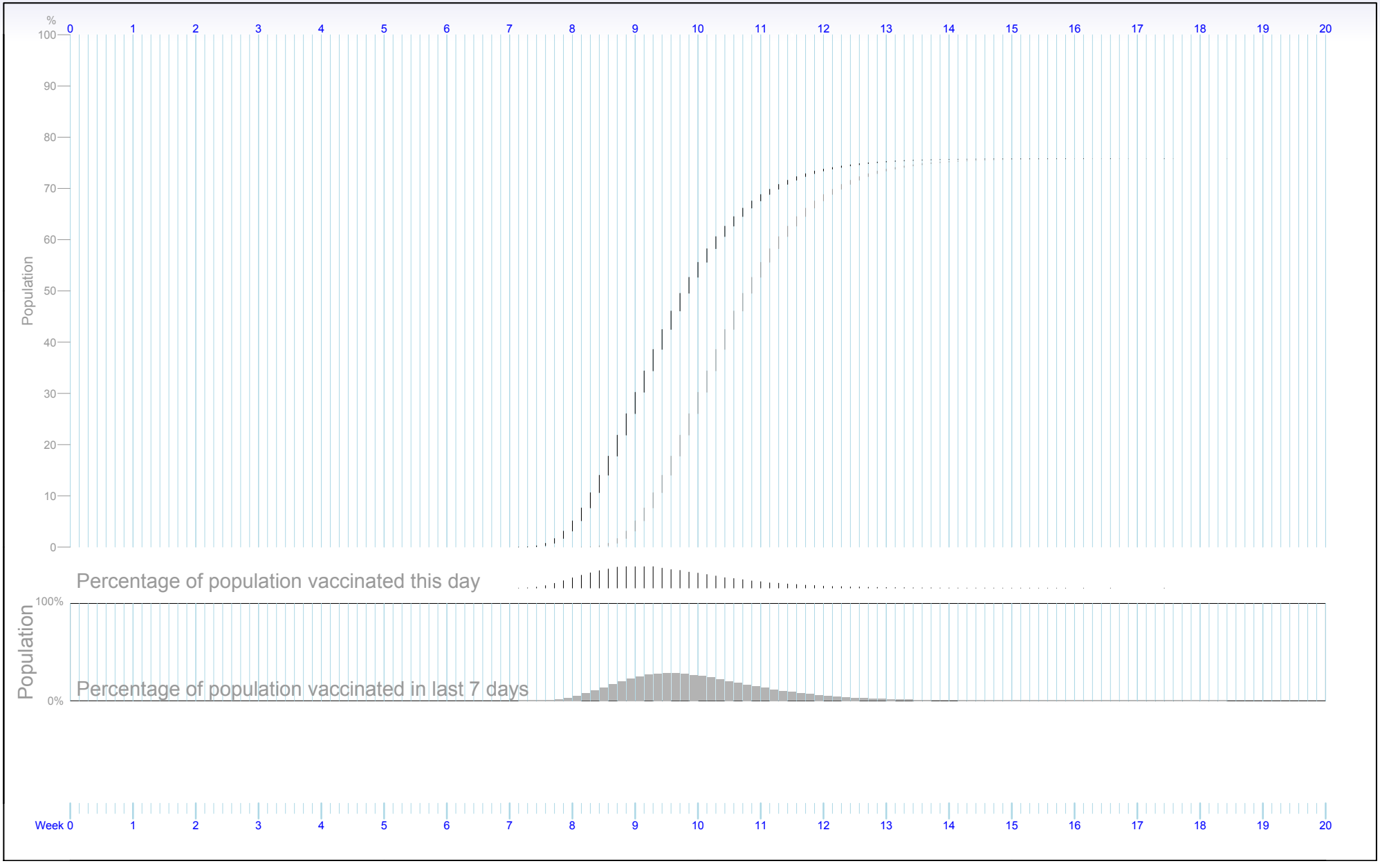
* Clayton & Hills, Ch 15, page 144. Applies only to 'known CY denominators' case.

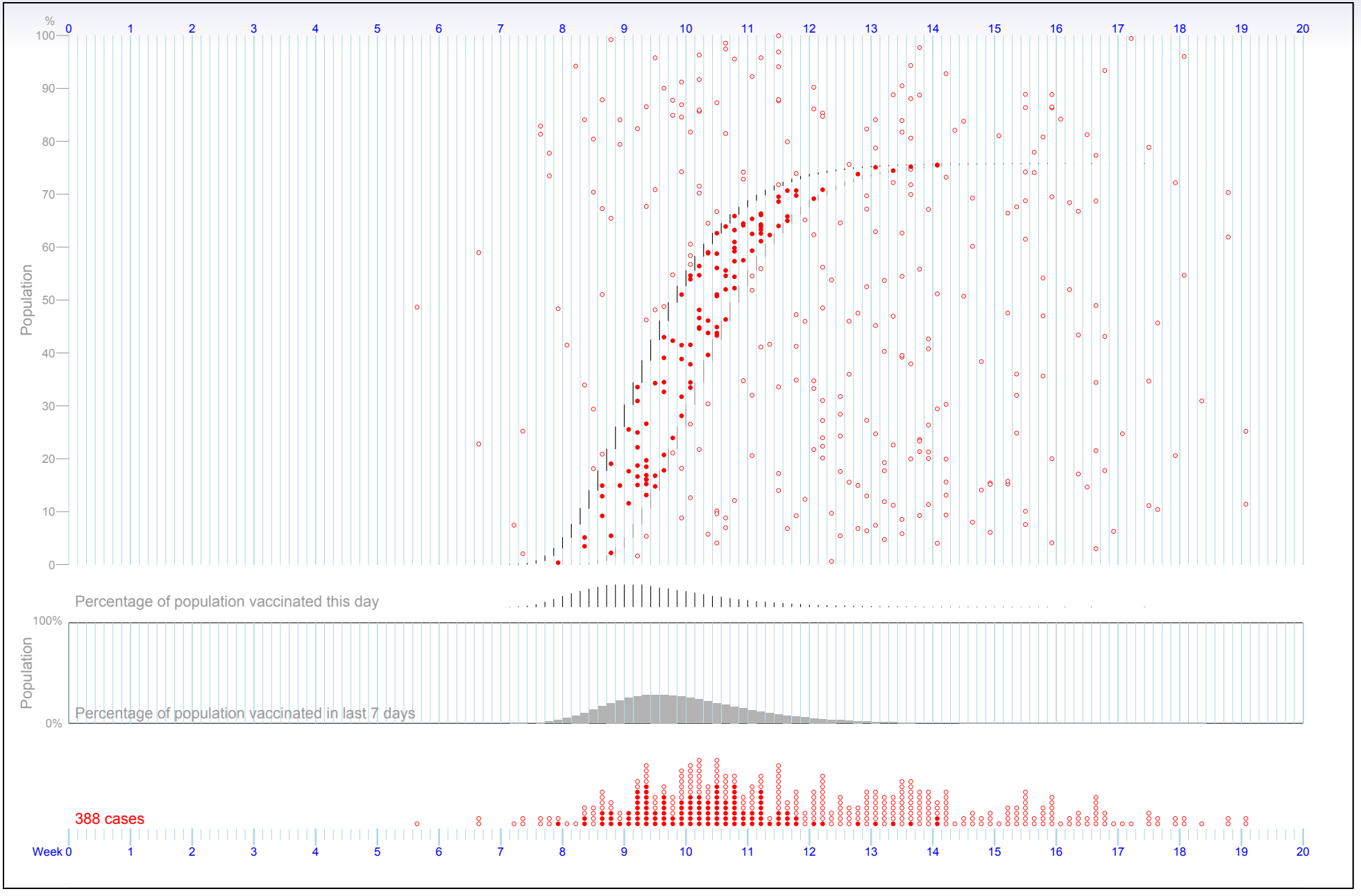
If there were such a registry for RV1, it *would* provide

% of children who received RV1 vaccine each day

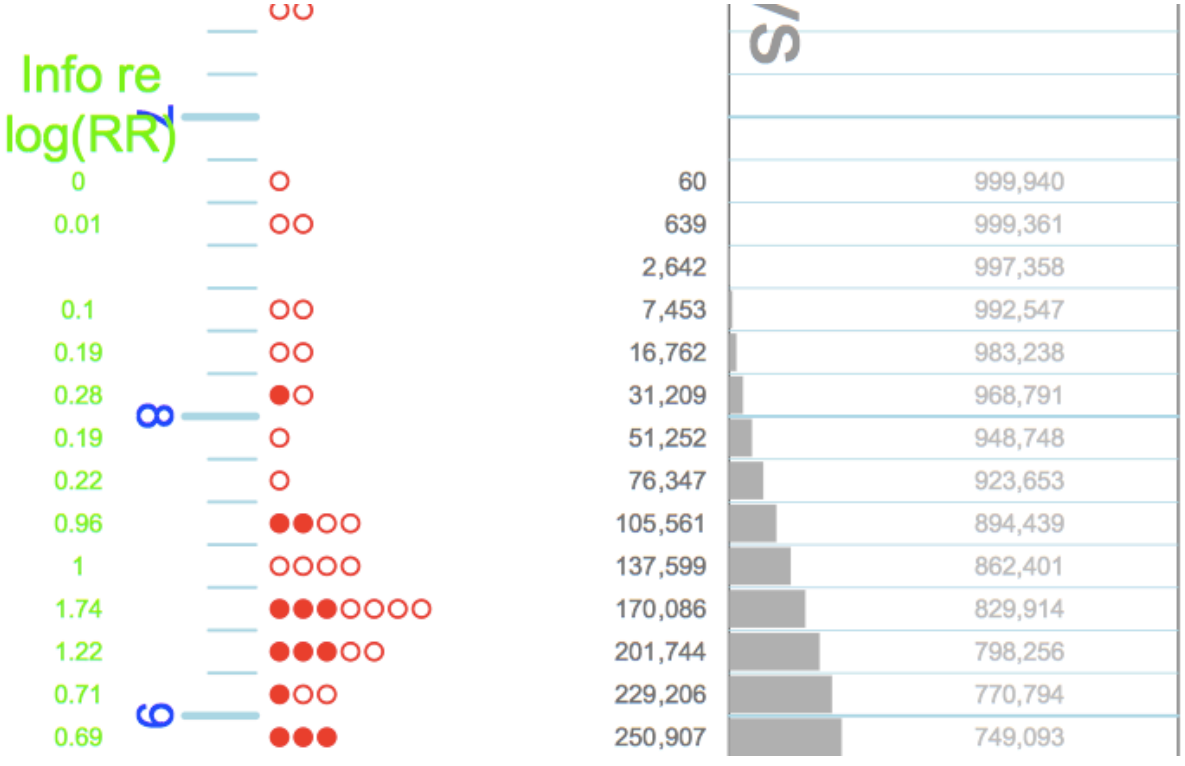

%
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
100
90
80
70
60
50
40
30
20
10
0
Population
Percentage of population vaccinated this day
100%
Population
Percentage of population vaccinated in last 7 days
0%
Week 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

and one could superimpose on it ..

the distribution of the cases


%
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
100
90
80
70
60
50
40
30
20
10
0
Population
Percentage of population vaccinated this day
100%
Population
Percentage of population vaccinated in last 7 days
0%
388 cases
Week 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

and estimate (Inc.) Rate Ratio ['V': 1-7 days post vacc'n. ; CD='Child-Days']



Information = Variance^{-1}

Information re log(RR) :

$$\sum n.cases \; \frac{RR \times P_V \times P_{\overline{V}}}{(1+(RR-1)P_V)^2}$$

(P_V : prop'n of CDs 1-7 days post vacc'n)

RR=1: $\left\{\frac{1}{n.cases}\right\}^{-1} \times \left\{\frac{1}{P_V} + \frac{1}{P_{\overline{V}}}\right\}^{-1}$

- M-H: $\frac{\sum_{days} n.cases.V \times CD_{\overline{V}} \; / \; CD}{\sum_{days} n.cases.\overline{V} \times CD_V \; / \; CD}$

Cf. first 1/2 of usual 'Woolf' variance:

$$\frac{1}{n.exposed.cases} + \frac{1}{n.unexposed.cases}$$

- Poisson (unconditional):

```
glm(  n.cases ~ I(V), family = poisson, offset = log[CD] )
```

- Poisson (conditional):

```
glm(n.cases.V ~ 1, family = binomial, offset = log[CD-V / CD-not-V] )
```

Variance = function(no.s of cases)

Risk of Guillain-Barré Syndrome Following H1N1 Influenza Vaccination in Quebec

Context In fall 2009 in Quebec, Canada, an immunization campaign was launched against the 2009 influenza A(H1N1) pandemic strain, mostly using an AS03 adjuvant vaccine. By the end of the year, 57% of the 7.8 million residents had been vaccinated.

Objective To assess the risk of Guillain-Barré syndrome (GBS) following pandemic influenza vaccine administration.

Design Population-based cohort study with follow-up over the 6-month period October 2009 through March 2010. The investigation was ordered by the chief medical officer of health in accordance with the Quebec Public Health Act.

Setting All acute care hospitals and neurology clinics in Quebec.

Population Suspected and confirmed GBS cases reported by physicians, mostly neurologists, during active surveillance or identified in the provincial hospital summary discharge database. Medical records were reviewed and cases classified according to Brighton Collaboration definitions (categorized as level 1, 2, or 3, corresponding to criteria of decreasing certainty in diagnosis). Immunization status was verified and denominators were estimated from the provincial immunization registry (4.4 million vaccinated) and census data (total target population aged ≥6 months, 7.8 million), with a total of 3 623 046 person-years of observation.

Main Outcome Measures Relative and attributable risks were calculated using a Poisson model and the self-controlled case-series method.

The mass immunization campaign started on October 26, 2009. The target population included all residents aged 6 months or older (total=7.8 million). Pandemic vaccines were administered by the public health service only. All immunizations were recorded in a specific registry linked to the universal provincial health insurance database.
DeWals et al. JAMA July 11, 2012

What if no such RV1 vaccination registry available?

For each case patient, we enrolled as controls up to $k = 4$ infants in the same neighborhood whose dates of birth were individually matched (within 30 days before or after) to the date of birth of the case patient.

- M-H:

$$\frac{\sum_{sets} I[case.V] \times \widehat{CD_{\overline{V}}} \;/\; 5}{\sum_{sets} I[case.\overline{V}] \times \widehat{CD_{V}} \;/\; 5}$$

- Conditional logistic regression:

```
clogit(I[case] ~ V +
strata(case.control.set))
```

Information (Variance^{-1}) re log(*RR*) in an informative {1: k} matched set

	V	$\overline{V}$	
case			1
'controls'			k
	≥ 1	$\leq$ k	1 + k

$$\sum_{sets} \frac{k+1}{k} \left\{ \underbrace{\frac{1}{E[case.V]} + \frac{1}{E[case.\overline{V}]}} + \underbrace{\frac{1}{E[n.cntrls.V]} + \frac{1}{E[n.cntrls.\overline{V}]}} \right\}^{-1}$$

↑ variance: price for estimating child-day (CD) denominators

Variance = function(no.s of cases) + function(no.s of 'controls')

How to interpret the data from these matched sets?

matched set	day	no. ctls 'exposed'	% *of CDs 'exposed'*
1	55	0	0%
2	56	0	0%
3	57	0	0%
4	58	0	0%
5	59	0	0%
6	60	1	25%
7	61	0	0%
8	62	1	25%
9	63	2	50%
..	...	.	....%

‘Case-control’ studies in infants are special

For each case, why not view the entire (merged) sample of children in the ‘control’ series as a representative denominator sample of the child-days base in which that case occurred?

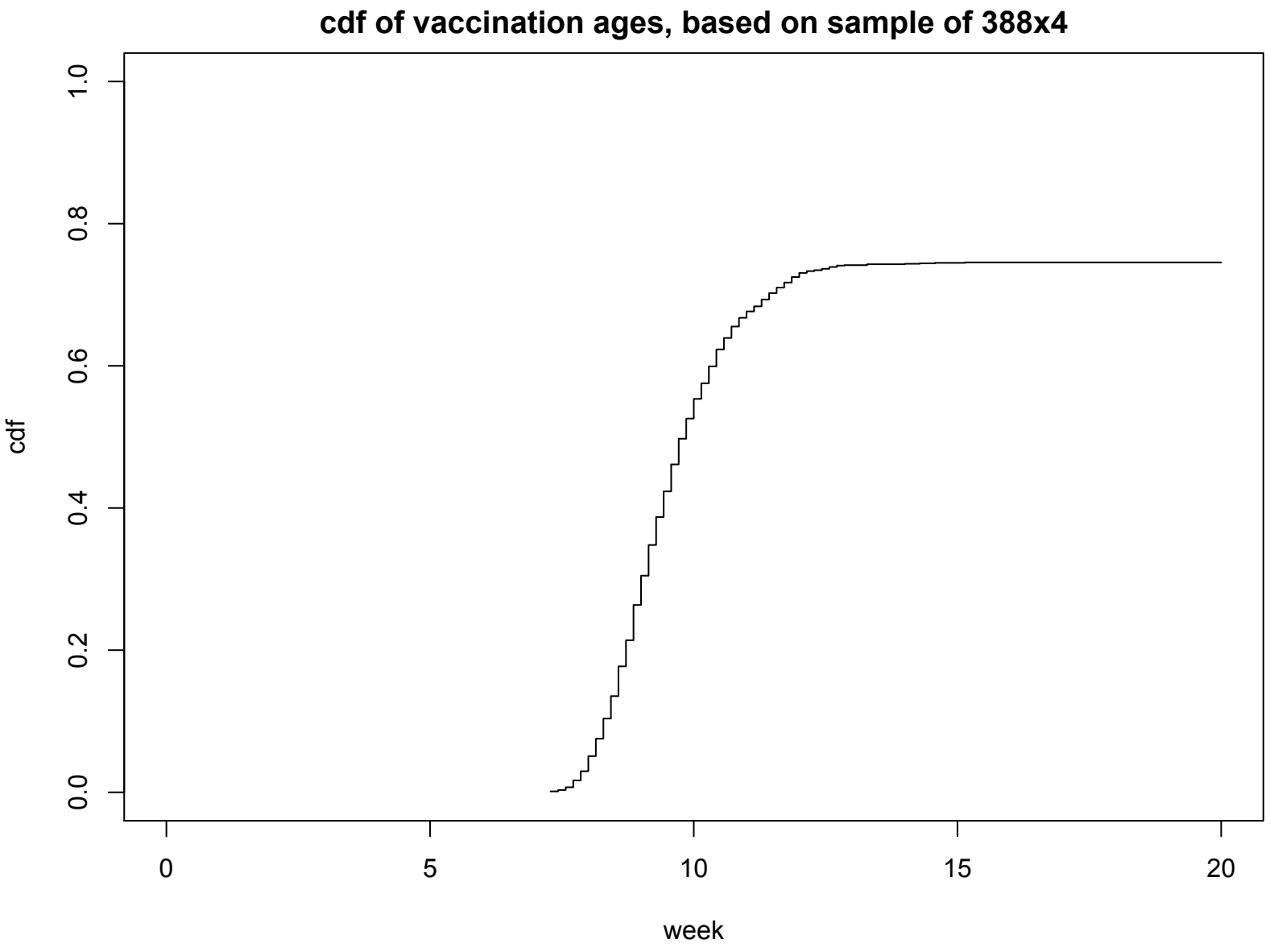
- denominator (‘control’) sample was matched on age (and almost on date of birth) by use of ‘reference date’

- and thus (to within 1 mo.) on season;

- little emigration/attrition;

- effectively a ‘case-cohort’ study.

Estimate each daily denominator from ENTIRE denominator series (i.e., 'control' series) of size 4 x 388



Upsides / Downsides

Complement of K-M curve (or a smoothed version) can be used (i.e., entire denominator sample can be 're-used') to provide [almost-without sampling error] denominator estimates (i.e., $CD_V : CD_{\overline{V}}$ ratios) at the time of each case.

We should not treat the estimated denominators as entirely-without-sampling error (i.e., as 'Danish denominators')

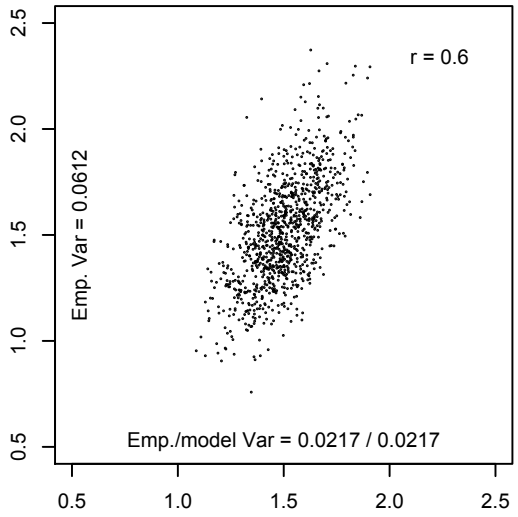
And the extra sampling variance ('price' of estimation) is somewhat complicated by the fact that each estimated percentage 'vaccinated within the last 7 days' is now a sum of 7 slightly-correlated multinomial percentages, and that these 7-day sums are themselves correlated.

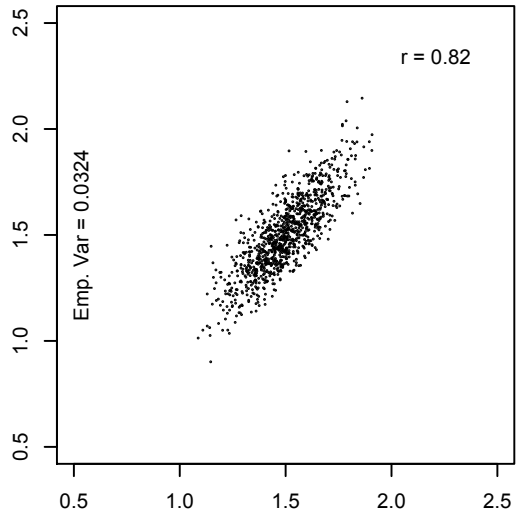
$\widehat{RR}$ if $RR = exp[1.5] = 4.5$: daily denominator ratios known (x) estimated (y)

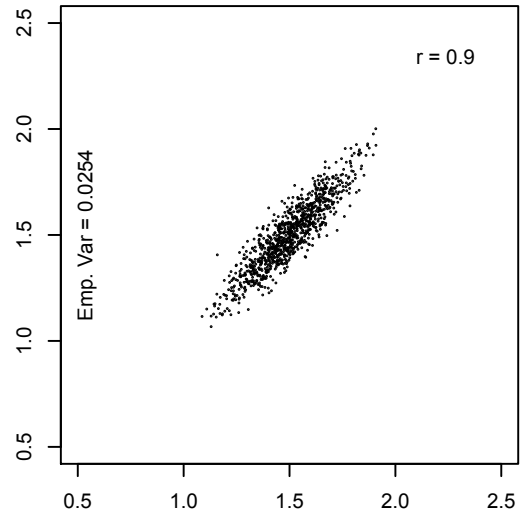
Base-case ratio: $k = 1$ $k = 4$ $k = 10$

Denominator

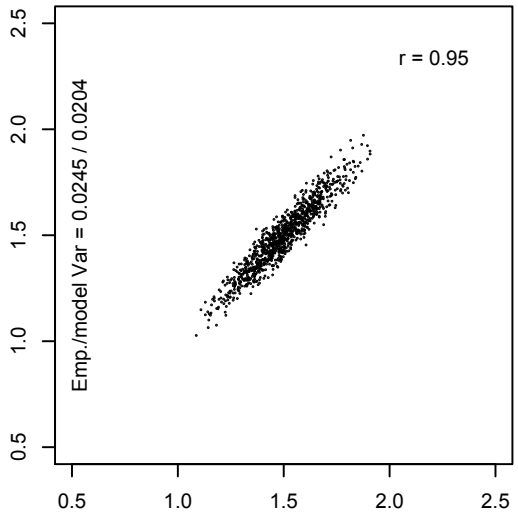
k per case

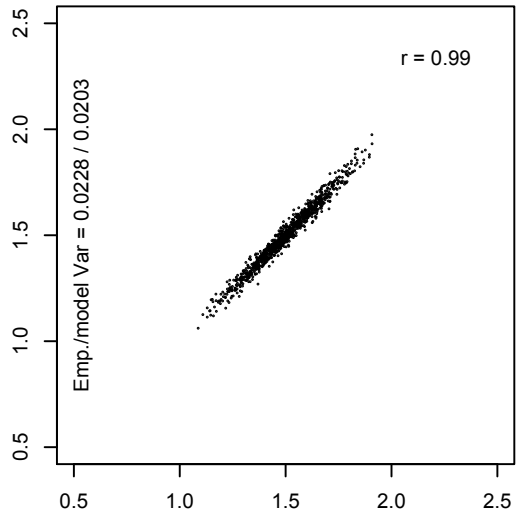


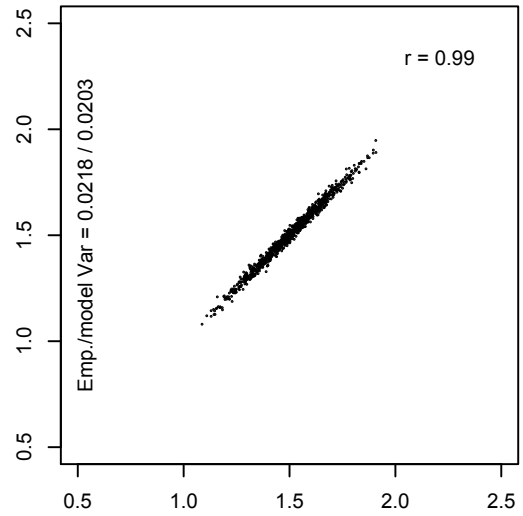




all $n \times k$ for every case







n = 300 cases expected if RR=1.

Concluding remarks

- 'Exposure' (recent vaccination) distribution in the source population at time of each case can be estimated
  - (conventionally) from the k matched to that one case, or
  - (here), more efficiently, from all $n \times k$ in the 'control' series.
- The population uptake of vaccinations follows a relatively smooth time pattern that can be described by a smooth time-function – further reducing the sampling variation.
- The vaccination data can be presented graphically, the rate ratio can be estimated from the $n + n \times k$ observations, and its precision can be measured.
- Infants teach us what 'the' etiologic study should be:

  Are population-time denominators

  - known Danish CY ?
  - estimated Mexican $\widehat{CY}$?

FUNDING, CO-ORDINATES, DOWNLOADS

Natural Sciences and Engineering Research Council of Canada

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