

Statistical Challenges in the Evaluation of Vaccine Safety

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*The views expressed in this presentation are not
necessarily those of CDE



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Outline

- Reasons for special consideration
- Pre-licensure evaluation
 - Trial testing a specific hypothesis (REST study)
- Post-licensure evaluation
 - Several vaccine safety controversies
- Concluding remarks



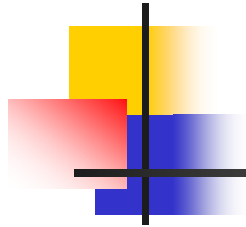
Reasons for special consideration

- Vaccines are given to **healthy individuals**, mostly children and infants
- Vaccines are given to **prevent disease**; this limits tolerability of adverse events
- Vaccines are biological products which are highly complex substances derived from **living materials**, and sometimes comprising living organisms
- Many vaccines are given to children at the ages when developmental and other problems are being recognized for the first time (**cause or coincidence**)



Evaluations of vaccine safety

- More challenging than efficacy
- Assess local (injection-site) and systemic adverse experiences (AE)
- Need large database to detect infrequent AE



Pre-licensure Evaluation



Phase I Studies

- Often uncontrolled, open-label
- Usually enroll small numbers (20-30) of adults
- Careful screening and monitoring
- Conservative stopping criteria based on safety outcomes



Phase II Studies

- Often randomized, may enroll hundreds of individuals
- More rigorous assessment of safety prior to administering vaccine in large phase III efficacy trial



Phase III Studies

- Usually includes subjects who are representative of target population
- Safety is evaluated in a large number of individuals
- Usually not necessary to collect data on common adverse events for all study subjects
 - A subset actively monitored for **common AEs**
 - All subjects actively followed for **serious AEs**

Statistical evaluation in Phase III Studies



- Usually exploratory in nature
- Typical statistical assessment: 95% CI on relative risk of AE in vaccine group relative to control group
- May also look at p-values on rate differences. but **no statistically adjustment for multiple testing** (each test at $\alpha = 0.05$)
- **Minimization of type 2 error** (failure to identify true safety signal) more critical than type I error (detecting false signal)



Sample size considerations

- For evaluation of **common local reactogenicity**, approximately 300 subjects for each comparison group are needed
- More than 5000 subjects may be appropriate to provide reasonable assurance of safety in randomized, controlled trial settings
- “Rule of 3” principle
For a rare event with incidence rate of $1/n$ (e.g. $1/10000$), then the probability to see **at least one event** will be approximately **0.95** when the sample size is **$3n$**



Trial testing a specific hypothesis

- In October 1999, 1st vaccine for infant rotaviral diarrhea (Rhotashield, Wyeth Laboratories licensed in 1998) voluntarily withdrawn after post-marketing surveillance data suggesting strong likelihood of association with intussusception
- Trials of new rotaviral diarrhea vaccines should be designed specifically to detect vaccine-related intussusception



Rotavirus Efficacy and Safety (REST) Study

Study Design

- Double-blinded, placebo-controlled study in 11 countries at over 500 study sites recruiting approximately 70,000 subjects
- The primary event of interest was the incidence of intussusception following receipt of RotaTeq[®] or placebo
- The study employed a group sequential design, which called for a minimum of **60,000** infants with complete safety follow-up, and subsequent groups of 10,000 infants if the end of study criterion was not met, up to a maximum sample size of **100,000**



Rotavirus Efficacy and Safety (REST) Study (cont.)

Lower and Upper Boundaries

- For interim safety monitoring, if at any time during the study, the lower bound of the 95% CI for RR of intussusception in vaccine group as compared with placebo group being >1.0 for the 7-day or 42-day periods after any of three doses, the DSMB could recommend stopping the study due to safety concern
- **10** was chosen as the upper bound criterion at the end of the study. Vaccine/placebo risk ratio were considered clinically acceptable if an upper bound of 95% CI ≤ 10

Rotavirus Efficacy and Safety (REST) Study (cont.)

Statistical Model (Heyse, et al, 2008)

- There are V events in treatment group and C events in control group, with V and C distributed as $Poisson(\lambda_v)$ and $Poisson(\lambda_c)$
- Condition on the total number of events $t=V + C$, V is distributed as a binomial $B(\pi, T)$ where $\pi = \frac{\lambda_v}{\lambda_v + \lambda_c}$
- The relationship between the relative risk $R = \lambda_v / \lambda_c$ and π are given by $R = \frac{\pi}{(1-\pi)}$ and $\pi = \frac{R}{(1+R)}$
- Given t total intussusception events, the upper boundary for V is the **smallest** number of v such that $\sum_{x=v}^t B(x; \pi, T) \leq 0.025$, and the lower boundary is the **maximum** number of v such that $\sum_{x=0}^v B(x; \pi, T) \leq 0.025$

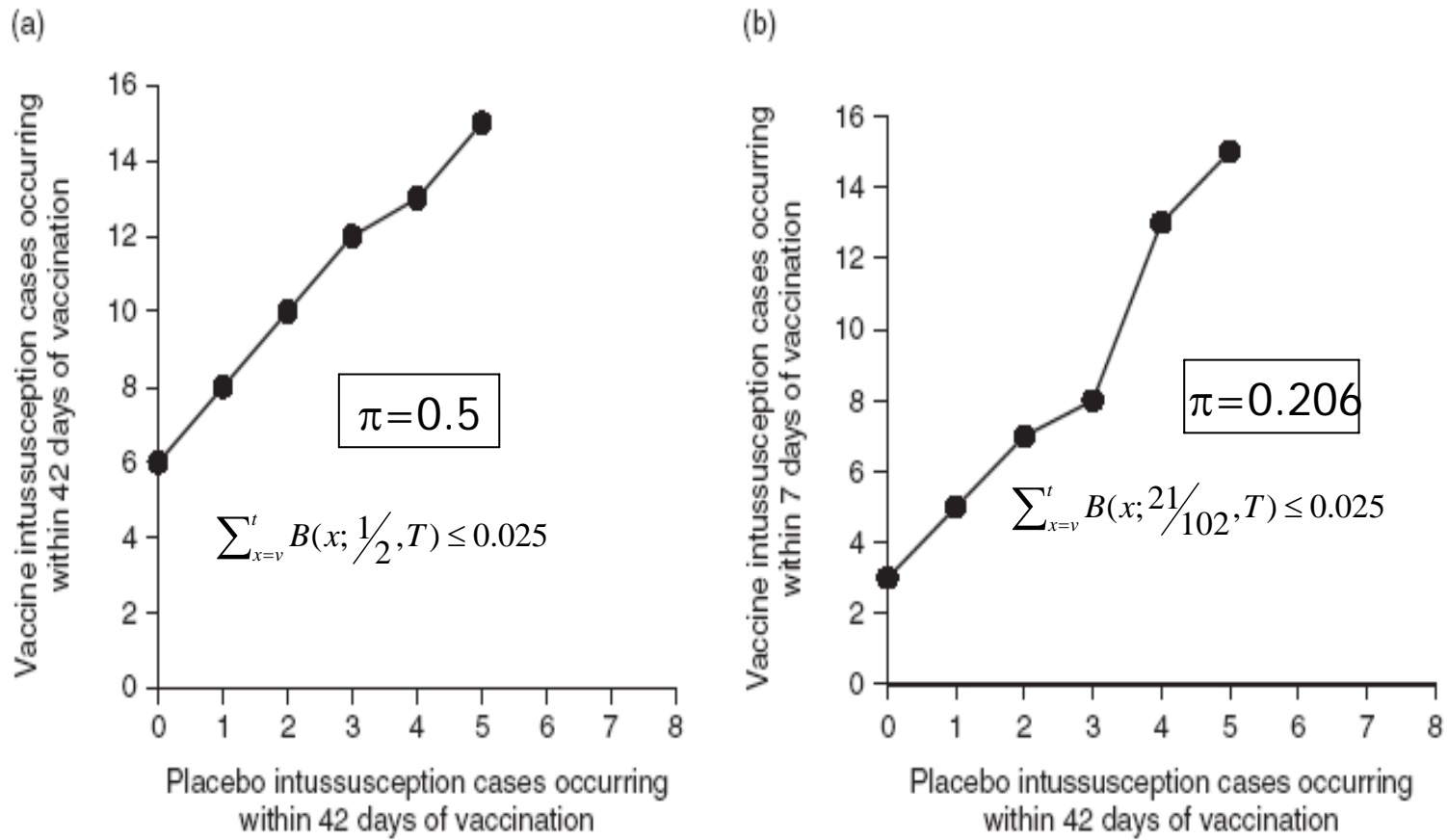


Figure 1 Predefined safety boundaries for the 42 and 7 day ranges after any dose: (a) 42-day period after any dose, (b) 7-day period after any dose

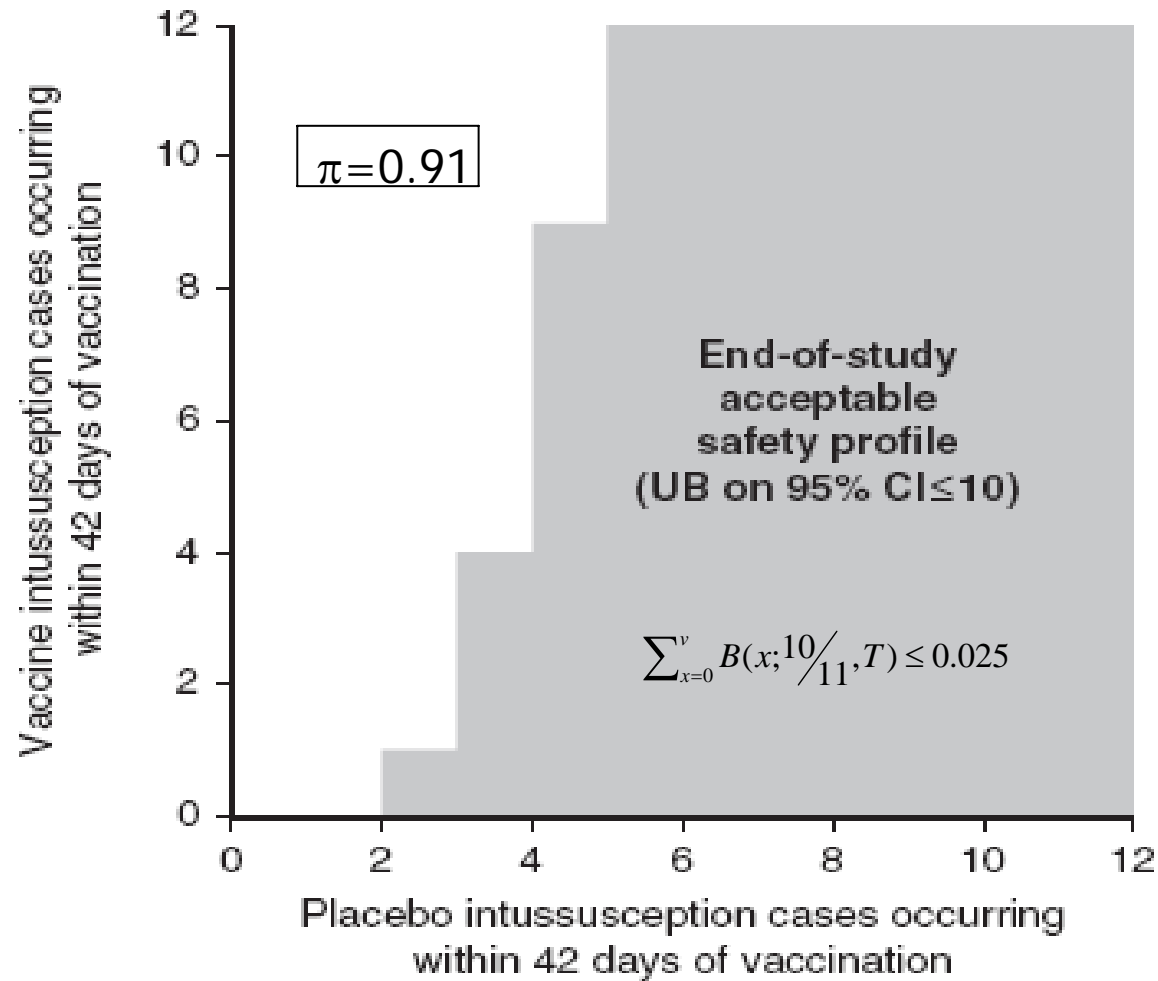
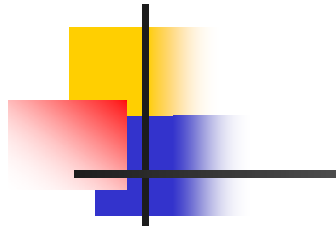


Figure 2 Criteria for stopping enrollment (based on primary hypothesis)

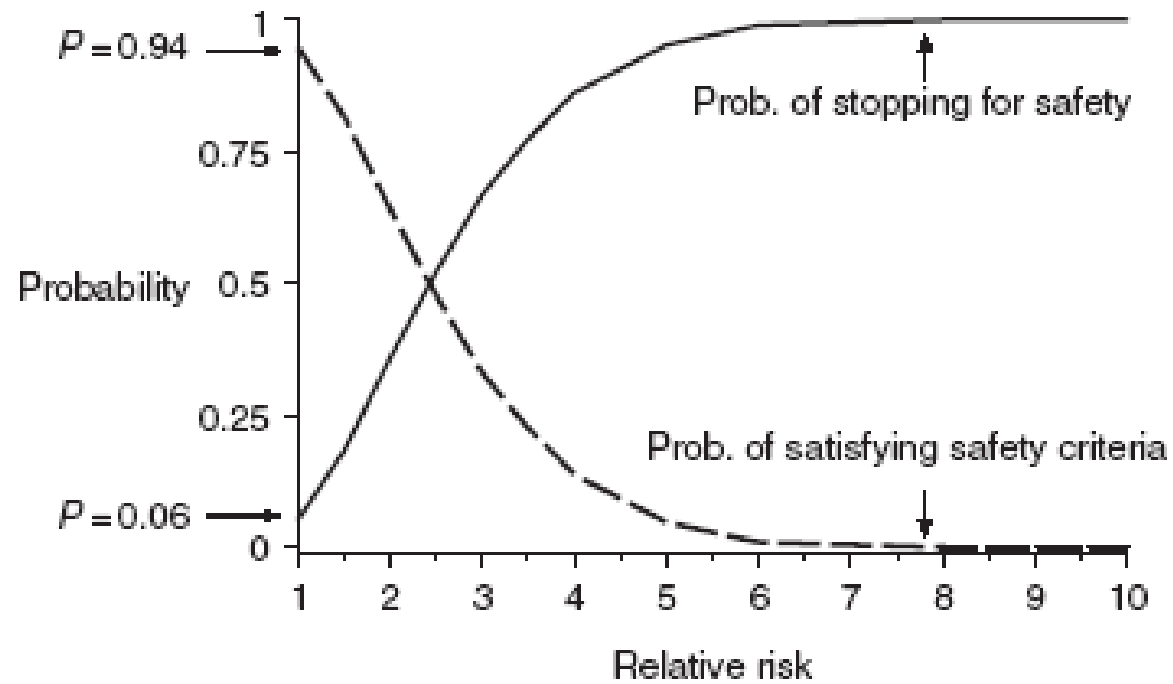
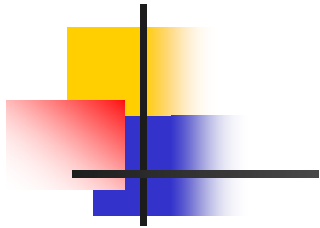
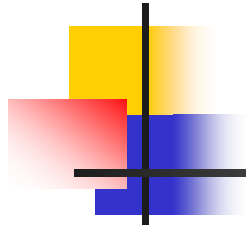


Figure 3 Statistical operating characteristics for REST study design



Post-licensure Evaluation



Data Bases

- Vaccine Adverse Event Reporting System (VAER)
 - jointly managed by US FDA and CDC
 - passive surveillance of vaccine safety
 - Over **11,000** reports received per year
- Vaccine Safety DataLink (VSD)
 - managed by CDC
 - medical record linkage system of patients enrolled in **eight geographically diverse HMO**
 - Covering approximately **3%** of U.S. population
- WHO's VigiBase
 - Managed by the Uppsala Monitoring Centre in Sweden



Key statistical methods

- **Data structure**

- **Denominator-based method**

- longitudinal and cross-sectional data

- **Numerator-based method**

- spontaneous reporting data

- **Frequentist or Bayesian**

- **Frequentist**

- generalized linear model (logistic, Poisson, etc.), sequential probability ratio test (SPRT), proportional reporting ratio (PRR), reporting odds ratio (ROR)


- **Bayesian**

- Bayesian confidence propagation neural network (BCPNN), Gamma-Poisson Shrinker (GPS), multi-item GPS (MGPS)



Key factors in establishing causality

- **Time of onset**
 - Onset of the disease must follow vaccination
- **Virus isolation**
 - In case of a live virus vaccine, causal relationship may often be inferred if the virus is recovered from a normally sterile body site
- **Uniqueness of the clinical syndrome**
 - Causation may be inferred if the adverse event or disease only occur following vaccination and does not occur in persons who did not receive the vaccine
 - Causation may also be inferred if the adverse event occurs a second time after repeat exposure to the same vaccine



Key factors in establishing causality (cont.)

- **Biological mechanism**

- Could potentially explain how the vaccine might cause the adverse event, but not sufficient to prove that vaccine caused the problem

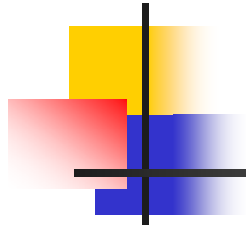
- **Epidemiological studies**

- Often provide **the most important evidence** whether a vaccine caused the problem
- Determine whether the risk of the illness of concern is higher in vaccinated persons compared to unvaccinated persons
- Using the following criteria
 - Strength of association
 - Consistency of association
 - Dose response
- **Cannot prove** that a vaccine dose not cause a disease



Several vaccine safety controversies

- MMR vaccination and autism
- Hepatitis B vaccination and multiple sclerosis
- Influenza vaccination and Guillain Barré Syndrome



MMR vaccination and autism



Autism

Autism is a **complex developmental disability** that typically appears during the first two years of life and is the result of a **neurological disorder** that affects the functioning of the brain, impacting development in the areas of social interaction and communication skills. Both children and adults on the autism spectrum typically show **difficulties in verbal and non-verbal communication, social interactions, and leisure or play activities.**

(Autism Society)



MMR vaccination and autism

(Lancet 1998; 351:637-41)

- **Wakefield and colleagues** postulated causal link between MMR vaccination and autism
- It was based on a reported close **temporal association** between these two events
 - MMR vaccine is given around **12-15 months** of age
 - The mean age at which parents of children with autism first report concern about their child's development is **18-19 months**



MMR vaccination and autism

(Lancet 1999; 353:2026-29)

- Population-based study using **case-series** analysis methods
- 498 cases of autism born since 1979 were identified in eight North Thames health districts, UK
- **Findings:**
 - There was a steady increase in cases by year of birth with **no sudden "step up" or change** in the trend line after the introduction of MMR vaccination (1988) **#**
 - There was **no difference in age at diagnosis** between the cases vaccinated before or after 18 months of age and those never vaccinated
 - There was **no temporal association** between onset of autism within 1 or 2 year after vaccination with MMR (relative incidence compared with control period 0.94 [95% CI: 0.6-1.47] and 1.09 [95% CI: 0.79-1.52] **#**

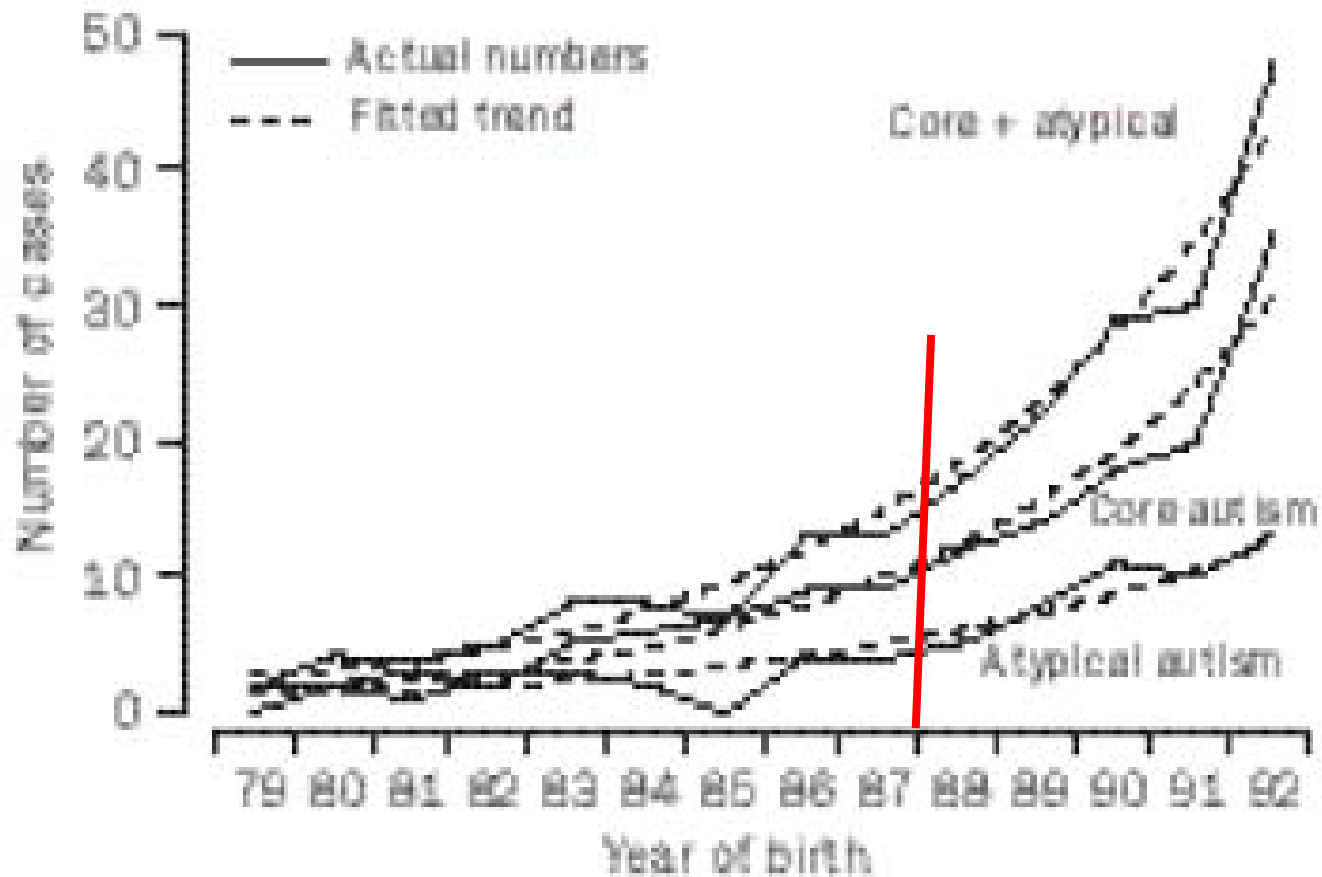
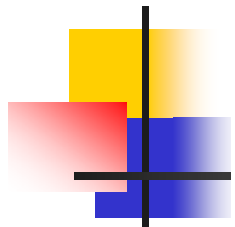


Figure 1: Core and atypical autism cases under 60 months of age and fitted trends by year of birth 1979–92

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MMR vaccination and autism

(Lancet 1999; 353:2026-29)

Event and risk period (months)	MMR vaccine(s)		MMR, measles, mumps and rubella vaccine(s)	
	Relative incidence (95% CI)	Number of events	Relative incidence (95% CI)	Number of events
Autism diagnosis (n=357)				
<12	0.94 (0.60-1.47)	31	0.80 (0.53-1.22)	36
<24	1.09 (0.79-1.52)	138	1.05 (0.76-1.44)	162
Parental concern (n=326)				
<6	1.48 (1.04-2.12)	75	1.19 (0.84-1.69)	82
<12	0.90 (0.63-1.29)	120	0.86 (0.60-1.23)	142
Regression (n=105)				
<2	0.92 (0.38-2.21)	7	1.24 (0.61-2.56)	11
<4	1.00 (0.52-1.95)	17	1.31 (0.73-2.33)	24
<6	0.85 (0.45-1.60)	28	0.99 (0.56-1.75)	35

Table 2: Relative incidence and numbers of events in risk periods after vaccination with one or more MMR vaccine or one or more MMR, single-antigen measles and mumps plus rubella vaccines, by event type in children with core or atypical autism



MMR vaccination and autism

(N Engl J Med 2002; 347 (19):1477-82)

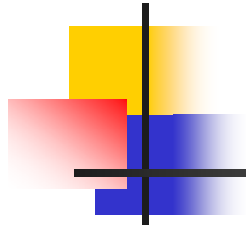
- **Retrospective cohort study** of all children born in Denmark from Jan. 1991 to Dec. 1998
- **MMR-vaccination status** obtained from the Danish National Board of Health. **Children's autism status** obtained from the Danish Psychiatric Central Register
- **Findings:**
 - Of the 537,303 children, 440,655 (82%) had received MMR vaccine, 316 with a diagnosis of autistic disorder, 422 with a diagnosis of other autistic-spectrum disorders
 - After adjusting potential confounders, the relative risk of autistic disorder for vaccination was **0.92 (95% CI: 0.68-1.24)**; the relative risk of another autistic-spectrum disorder was **0.83 (95%CI: 0.65-1.07)#**

TABLE 2. ADJUSTED RELATIVE RISK OF AUTISTIC DISORDER AND OF OTHER AUTISTIC-SPECTRUM DISORDERS IN VACCINATED AND UNVACCINATED CHILDREN.*

VACCINATION	PERSON-YEAR [†]	AUTISTIC DISORDER		OTHER AUTISTIC-SPECTRUM DISORDERS	
		NO. OF CASES	ADJUSTED RELATIVE RISK (95% CI)	NO. OF CASES	ADJUSTED RELATIVE RISK (95% CI)
Total	2,129,864	316		422	
Vaccination					
No	482,360	53	1.00	77	1.00
Yes	1,647,504	263	0.92 (0.68–1.24)	345	0.83 (0.65–1.07)
Age at vaccination					
Not vaccinated	482,360	53	1.00	77	1.00
≤14 mo	200,003	38	1.18 (0.78–1.80)	43	0.88 (0.60–1.28)
15–19 mo	1,320,753	195	0.86 (0.63–1.17)	270	0.83 (0.64–1.08)
20–24 mo	69,242	17	1.19 (0.69–2.07)	12	0.62 (0.33–1.13)
25–35 mo	40,935	11	1.20 (0.63–2.31)	15	1.09 (0.63–1.91)
≥36 mo	16,572	2	0.56 (0.14–2.30)	5	0.64 (0.26–1.59)
Interval since vaccination					
Not vaccinated	482,360	53	1.00	77	1.00
<6 mo	212,805	3	0.39 (0.11–1.32)	8	1.18 (0.51–2.75)
6–11 mo	197,931	21	1.38 (0.76–2.51)	4	0.31 (0.10–0.91)
12–17 mo	183,460	22	1.07 (0.59–1.95)	16	0.92 (0.47–1.80)
18–23 mo	168,045	31	0.86 (0.52–1.41)	16	0.47 (0.26–0.86)
24–29 mo	154,290	42	0.99 (0.61–1.58)	32	0.77 (0.46–1.27)
30–35 mo	139,258	33	0.86 (0.54–1.38)	27	0.69 (0.43–1.11)
36–59 mo	406,320	90	0.99 (0.66–1.50)	158	1.05 (0.77–1.45)
≥60 mo	185,396	21	0.67 (0.34–1.33)	84	0.75 (0.51–1.09)
Date of vaccination					
Not vaccinated	482,360	53	1.00	77	1.00
1991–1992	248,646	31	1.00 (0.59–1.70)	61	0.75 (0.51–1.09)
1993–1994	659,152	81	0.73 (0.50–1.06)	146	0.74 (0.56–0.99)
1995–1996	475,990	96	0.91 (0.63–1.30)	116	1.13 (0.81–1.56)
1997–1999	263,716	55	1.35 (0.84–2.17)	22	0.71 (0.40–1.24)

*The relative risk was adjusted for age, calendar period, sex, birth weight, gestational age, mother's education, and socioeconomic status of the family. The reference group was the group of children who were not vaccinated. The distribution of cases of autistic disorder or other autistic-spectrum disorders according to vaccination status differs from that in Table 1 because, in this analysis, children who were vaccinated after the disorder had been diagnosed were classified according to their vaccination status at the time of the diagnosis (i.e., as unvaccinated). CI denotes confidence interval.

†Because of rounding, the numbers of person-years do not necessarily sum to the total shown.



Hepatitis B vaccination and multiple sclerosis



Multiple sclerosis

Multiple sclerosis (or MS) is a chronic, often disabling disease that attacks the central nervous system (CNS), which is made up of the brain, spinal cord, and optic nerves. Symptoms may be mild, such as numbness in the limbs, or severe, such as paralysis or loss of vision. The progress, severity, and specific symptoms of MS are unpredictable and vary from one person to another.

(National Multiple Sclerosis Society)

Hepatitis B vaccination and multiple sclerosis (MS)

(Neurology 2004;63:838-842)

- A matched case-control study **nested** within the GPRD (General Practice Research Database) cohort
- **Cases** were patients in the GPRD with a confirmed diagnosis of MS between Jan. 1, 1993, and Dec. 31, 2000, with at least 3 years of continuous recording in database before first MS symptoms
- Up to **10 controls** per case were randomly selected, matched on age (± 1 year), sex, practice, and date of joining the practice (± 1 year)
- **Conclusions:**
Immunization with the recombinant hepatitis B vaccine is associated with an increased risk of MS #

Hepatitis B vaccination and multiple sclerosis (MS)

(Neurology 2004;63:838-842)#

Table 2 Association between vaccinations and risk of MS

Immunizations within 3 y before index date	MS cases (%)	Controls (%)	OR (95% CI)
Hepatitis B (recombinant)			
No	152 (93.3)	1565 (97.6)	1.0 (ref.)
Yes	11 (6.7)	39 (2.4)	3.1 (1.5, 6.3)
Influenza			
No	153 (93.9)	1508 (94.0)	1.0 (ref.)
Yes	10 (6.1)	153 (6.0)	1.0 (0.5, 2.0)
Tetanus			
No	144 (88.3)	1325 (82.6)	1.0 (ref.)
Yes	19 (11.7)	279 (17.4)	0.6 (0.4, 1.0)

MS = multiple sclerosis.

Hepatitis B vaccination and multiple sclerosis (MS)

(Neurology 2004;63:838-842)

Table 3 Timing and number of hepatitis B vaccinations in relation to the risk of MS

Hepatitis B vaccination within 3 y before index date	MS cases (%)	Controls (%)	OR (95% CI)
Unvaccinated	152 (93.3)	1,565 (97.6)	1.0 (ref.)
Years since last vaccination before index date			
>0-1	3 (1.8)	17 (1.0)	1.8 (0.5, 6.3)
>1-2	4 (2.5)	11 (0.7)	<u>4.1 (1.3, 13.6)</u>
>2-3	4 (2.5)	11 (0.7)	<u>4.4 (1.3, 14.5)</u>
No. of immunizations before index date			
1-2	5 (3.1)	19 (1.2)	2.8 (1.0, 7.8)
≥3	6 (3.7)	20 (1.2)	<u>3.3 (1.3, 8.5)</u>

MS = multiple sclerosis.

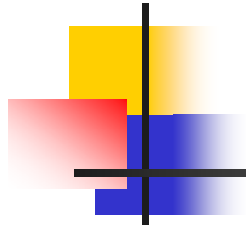
Hepatitis B vaccination and multiple sclerosis (MS)

(WHO Global Advisory Committee on Vaccine Safety)

WHO GAVS response

- Conclusions depend on 11 cases of MS adult patient vaccinated against hepatitis B, the **sample size too small** for a definite interpretation to be made **#**
- The practice of vaccination against hepatitis B in the UK at the time of study was targeted towards **high-risk individuals**, cannot be regarded as a representative sample of general population
- Of the **original 713 cases** of MS 163 were selected, the selection process might have been fraught with methodological problems and with risk of inadvertent bias **#**

The GAVS concluded that the details provided of the methods used and patient data submitted were insufficient to address concerns regarding the likelihood of selection bias that might have distorted conclusions



Influenza Vaccination and Guillain-Barré syndrome



Guillain-Barré syndrome

Guillain-Barré syndrome is a disorder in which **the body's immune system attacks part of the peripheral nervous system**. The first symptoms of this disorder include varying degrees of weakness or tingling sensations in the legs. In many instances, the weakness and abnormal sensations spread to the arms and upper body. These symptoms can increase in intensity until the muscles cannot be used at all and the patient is almost totally paralyzed. In these cases, the disorder is life-threatening and is considered a medical emergency. The patient is often put on a respirator to assist with breathing. Most patients, however, recover from even the most severe cases of Guillain-Barré syndrome, although some continue to have some degree of weakness.

(National Institutes of Health)

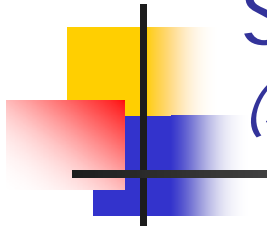
Influenza vaccination and Guillain Barré Syndrome (GBS)

(JAMA 1982; 248:698-700)

- Following the documentation of an epidemiologic association between A/New Jersey (swine) influenza vaccination and the subsequent development of GBS in 1976 (*Am J Epidemiolo* 1979; 110:105-123), a national GBS surveillance system was established by the American Academy of Neurology (AAN)
- This article summarizes the results of surveillance during two seasons (1979-1980 and 1980-1981)
- Findings:
 - 528 cases of GBS (419 adults with vaccination information) with onset between Sept. 1 and March 31, including 7 following recent vaccination (within 8 weeks) were reported by participating neurologist in 1979-1980; 459 cases (359 adults with vaccination information), including 12 following recent vaccination, were reported in 1980-1981
 - The relative risk of acquiring GBS following influenza vaccination is 0.6 (95% CI: 0.45, 1.32) in 1979-1980 and 1.4 (95% CI: 0.8, 1.76) in 1980-1981, was not significantly different from 1.0 in either season#

Influenza vaccination and Guillain Barré Syndrome (GBS)

(JAMA 1982; 248:698-700)



Calculation of Relative Risk of Acquiring Guillain-Barré Syndrome Among Vaccinated* and Unvaccinated Adults, United States, 1979-1980 and 1980-1981				
	Vac- cinated	Unvac- cinated	Relative Risk	95% Confidence Interval
September 1979-March 1980				
Cases	7	412	$\frac{(7) / (123 \times 10^6)}{(412) / (4,486 \times 10^6)} = 0.6$	<u>0.45-1.32†</u>
Susceptible-person-weeks ($\times 10^6$)	123	4,486		
September 1980-March 1981				
Cases	12	347	$\frac{(12) / (114 \times 10^6)}{(347) / (4,641 \times 10^6)} = 1.4$	<u>0.80-1.76†</u>
Susceptible-person-weeks ($\times 10^6$)	114	4,641		

*Designates those persons who received influenza vaccine within eight weeks before onset of illness.

†Test-based confidence limits.

Influenza vaccination and Guillain Barré Syndrome (GBS)

(Clinical Immunology 2003;107: 116-121)

- Acute and severe GBS cases reported following influenza vaccine to the Vaccine Adverse Events Reporting System (VAERS) database from 1991 through 1999 were examined
- The Biological Surveillance Summary Reports of the CDC were used to determine the **incidence** of adverse reactions following vaccination
- Endotoxin concentrations were measured using the **Limulus amebocyte lysate assay** in influenza vaccine
- Findings:
 - A total of **382** cases of GBS following influenza vaccination (male/female ratio of 1.2)
 - The median onset time was **12** days (IQR, 7 to 21 days)
 - An increased risk of acute GBS (**RR, 4.3; 95%CI: 3.0, 6.4**) and severe GBS (**RR, 8.5; 95% CI: 3.7, 18.9**) in comparison to an adult tetanus-diphtheria (Td) vaccine control group#
 - There were significant variation in the incidence of GBS among different influenza manufacturers#
 - Influenza vaccines contained from a 125 to a 1250 fold increase in endotoxin concentrations in comparison to an adult Td vaccine control #

Influenza vaccination and Guillain Barré Syndrome (GBS)

(Clinical Immunology 2003;107: 116-121) #

Table 1

A yearly comparison between Td and influenza vaccination for associated Guillain Barre Syndrome (GBS) adverse reactions reported to VAERS among those residing in the United States from 1991 through 1999

Year	Incidence of GBS per 10 million Td vaccinations	Incidence of GBS per 10 million influenza vaccinations	Relative risk	Attributable risk	Percentage of association	Statistical significance	95% Relative risk confidence interval
1991	0.0	6.7	—	—	100	$P < 0.0001$	—
1992	1.5	7.4	4.9	3.9	83	$P < 0.05$	1.2 to 20.2
1993	1.3	<u>16.3</u>	12.5	11.5	93	$P < 0.0001$	3.0 to 50.4
1994	1.2	7.7	6.4	5.4	86	$P < 0.005$	1.6 to 27.0
1995	2.8	13.4	4.8	3.8	83	$P < 0.002$	1.7 to 12.9
1996	5.5	<u>18.2</u>	3.3	2.3	77	$P = 0.0020$	1.5 to 7.2
1997	2.0	6.8	3.4	2.4	77	$P < 0.05$	1.1 to 11.4
1998	3.8	7.5	2.0	1.0	67	Not significant	0.84 to 4.7
1999	1.2	5.0	4.2	3.2	81	Not significant	0.81 to 14.3

Influenza vaccination and Guillain Barré Syndrome (GBS)

(Clinical Immunology 2003;107: 116-121)#

Table 2

A statistical comparison between manufacturers for the incidence of GBS following influenza vaccination

Manufacturer type (incidence of GBS per million vaccines)	Statistical significance vs A (relative risk)	Statistical significance vs B (relative risk)	Statistical significance vs C (relative risk)	Statistical significance vs D (relative risk)	Statistical significance vs E (relative risk)
A (0.58)	—	Not significant (0.63)	Not significant (1.2)	Not significant (0.67)	$P < 0.0001$ (0.45)
B (0.92)	Not significant (1.6)	—	$P < 0.05$ (2.0)	Not significant (1.1)	Not significant (0.71)
C (0.47)	Not significant (0.81)	$P < 0.05$ (0.51)	—	$P < 0.05$ (0.55)	$P < 0.0001$ (0.36)
D (0.86)	Not significant (1.5)	Not significant (0.93)	$P < 0.05$ (1.8)	—	$P < 0.05$ (0.66)
E (1.3)	$P < 0.0001$ (2.2)	Not significant (1.4)	$P < 0.0001$ (2.8)	$P < 0.05$ (1.5)	—

Influenza vaccination and Guillain Barré Syndrome (GBS)

(Clinical Immunology 2003;107: 116-121)

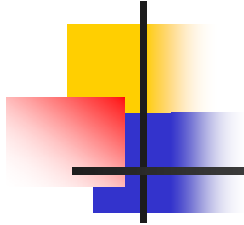
Table 3
Measured concentration of endotoxin present in each lot of vaccine analyzed

Manufacturer	Lot	Type of vaccine	Concentration of endotoxin (EU/ML)
Connaught	1494FK	Influenza	380
Connaught	1505FK	Influenza	380
Connaught	1527FK	Influenza	304
Connaught	1489FK	Influenza	38
Merck Sharp & Dohme	4840G	Influenza	304
Merck Sharp & Dohme	4871G	Influenza	38
Parke-Davis & Co.	913362A	Influenza	38
Parke-Davis & Co.	909515A	Influenza	304
Eli Lilly & Co.	9PB83A	Influenza	38
Lederle	466-340	Td	<u>0.304</u>



Concluding remarks

- As with any drug, there are risks and side effects with vaccines, although serious side effects are mostly rare
- When an adverse event occurs after vaccination, it needs to be determined whether the AE was caused by vaccine or it was just a coincidence
- Although difficult, time consuming and expensive, it is critical that the studies be done to establish causality because vaccines are usually given to healthy individuals, mostly children and infants
- While epidemiologic studies **can** help establish a **causal association** between a vaccine and an adverse event, they **cannot** absolutely **prove coincidence** (reject causation), **they can only infer that coincidence is the most likely explanation**



***Thanks for
your attention!***