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Putting Vaccine Safety in Perspective

Detecting and Evaluating Post Licensure Vaccine Safety Concerns

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Vaccine Safety in Perspective
What Have We Accomplished?

Disease	Baseline 20th Century Cases	1998 Cases	Decrease (%)
Smallpox	48,164	0	100
Diphtheria	175,885	1	100
Pertussis	147,271	6279	95.7
Tetanus	1314	34	97.4
Poliomyelitis (paralytic)	16,136	0	100
Measles	503,282	89	100
Mumps	152,209	606	99.6
Rubella	47,745	345	99.3
Congenital rubella syndrome	823	5	99.4
Hib	20,000	54	99.7

MMWR. April 2, 1999;48(12):243-248. . http://www.cdc.gov/mmwr/preview/mmwrhtml/00056803.htm#00003752.htm. Accessed July 15, 2011.

Impact on Latin America

http://www.paho.org/vwa/?p=1898&l
=es.

A View in an Age Without Disease Awareness – Vaccine Safety in Perspective

	Pre-Vaccine Era	2003	%Change
Total Vaccine AEFIs*	0	8616*	++
Total Disease	1,064,854	8957	-99%

* Reports to VAERS for common vaccines

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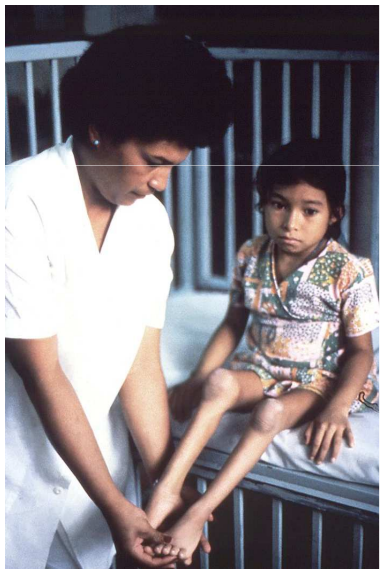
Courtesy of Robert Chen from Chen RT, et al. *Vaccine.* 1994;12:542-550.

Vaccine Safety in the Age of Widespread Disease

- Prior to the introduction of vaccinia vaccine in 1796, smallpox
  - Killed an estimated 400,000 Europeans per year during the closing years of the 18th century
  - Was responsible for one-third of all blindness
  - Killed 20%–60% of infected adults and >80% of infected children.
  - Was responsible for an estimated 300 million–500 million deaths during the 20th century
- Poliomyelitis was first recognized as a distinct condition by Heine in 1840
  - Its causative agent, polio virus, was identified in 1908 by Karl Landsteiner
  - Although major polio epidemics were unknown before the late 19th century, polio was one of the most dreaded diseases of the 20th century
  - Acceptance of vaccine was very high when it was introduced



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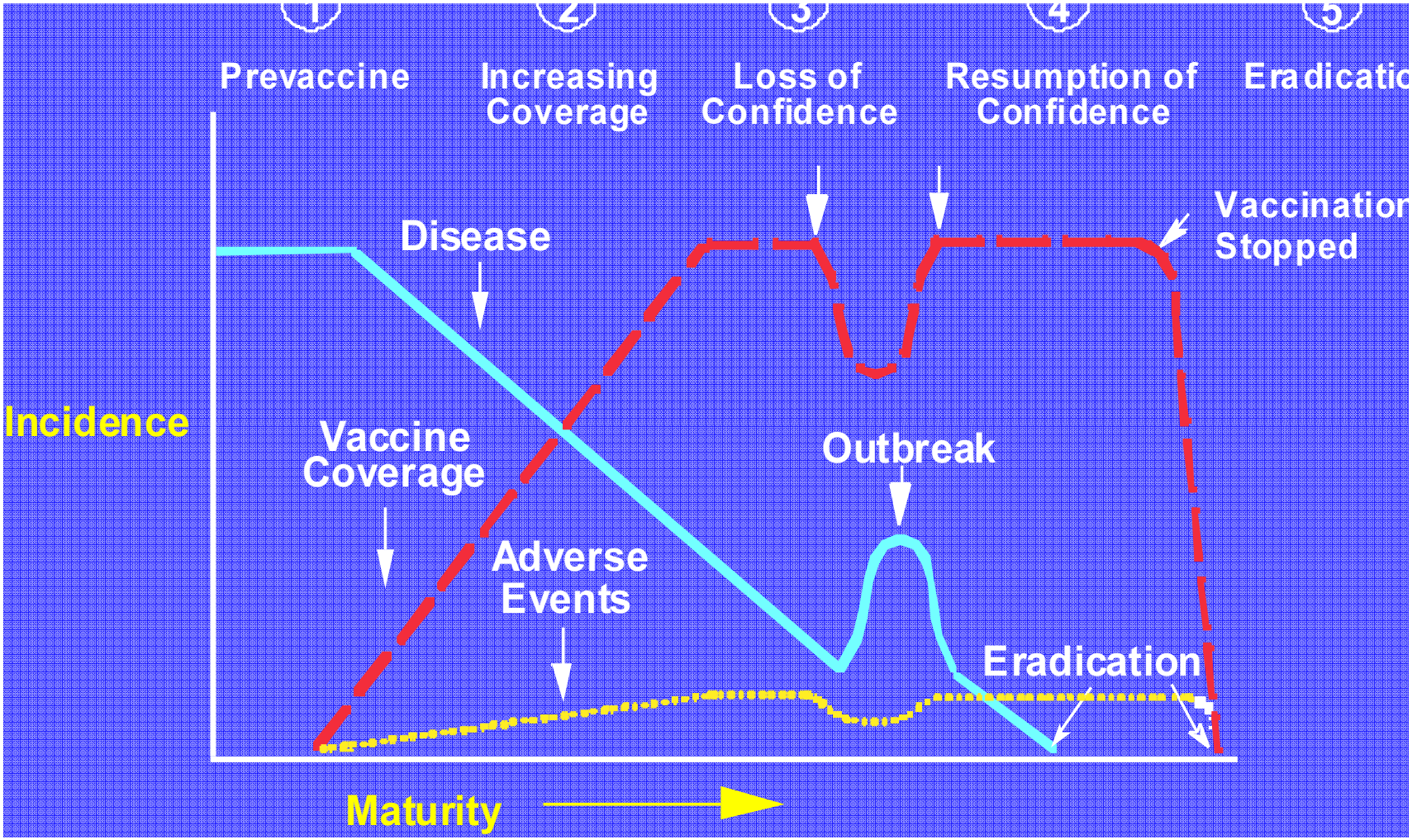
Images courtesy of CDC image library.

Vaccine Safety Concerns Began with the First Vaccination

1802 Cartoon Showing Recipients of Vaccinia Turning into Cows

Vaccine Safety in Perspective

Evolution of Vaccine Use and Safety Concerns



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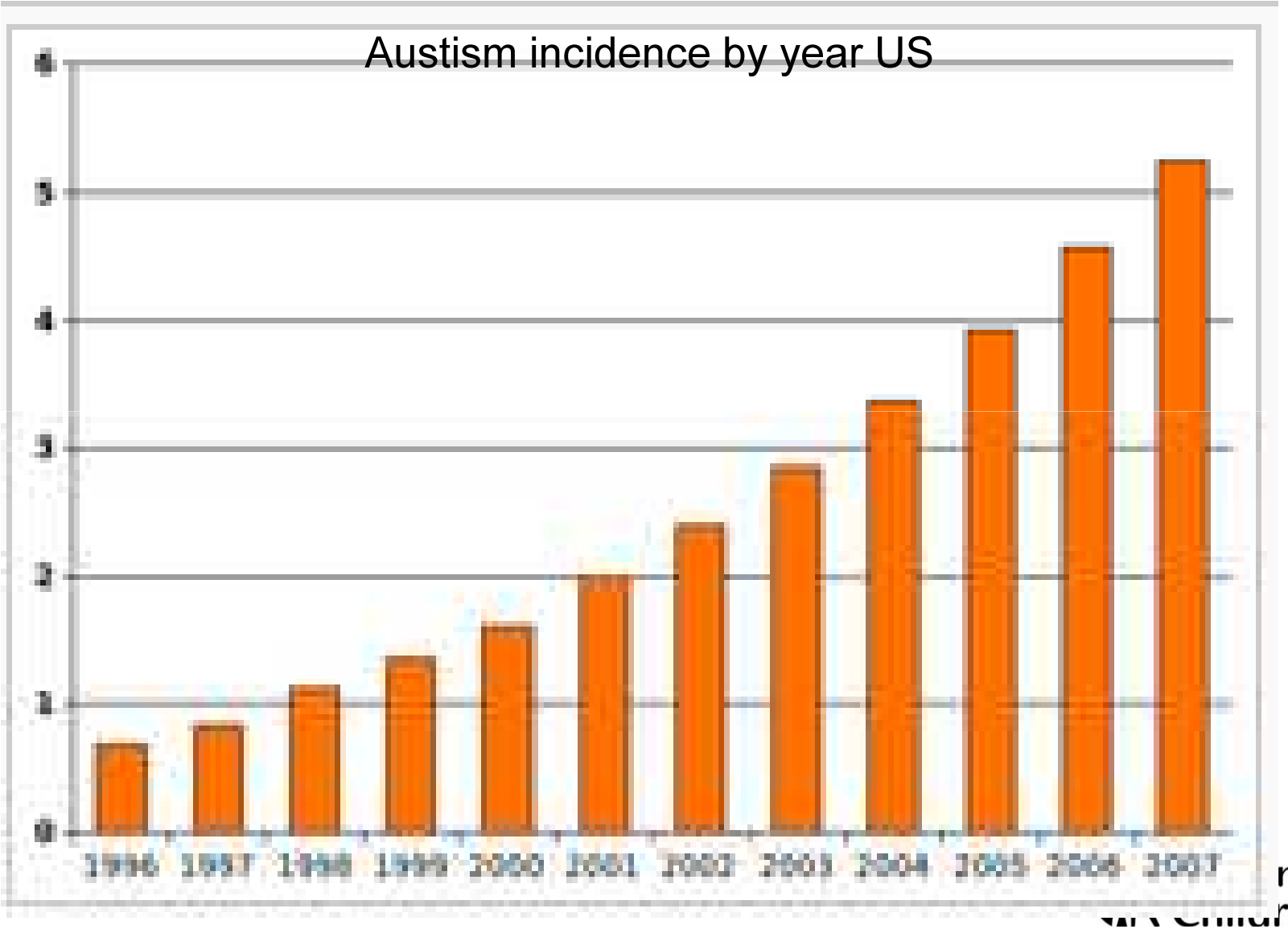
Courtesy of Robert Chen from Chen RT et al. Vaccine 1994;12:542-550.

Pseudo Science and Vaccine Safety
The Perils of Observational Epidemiology



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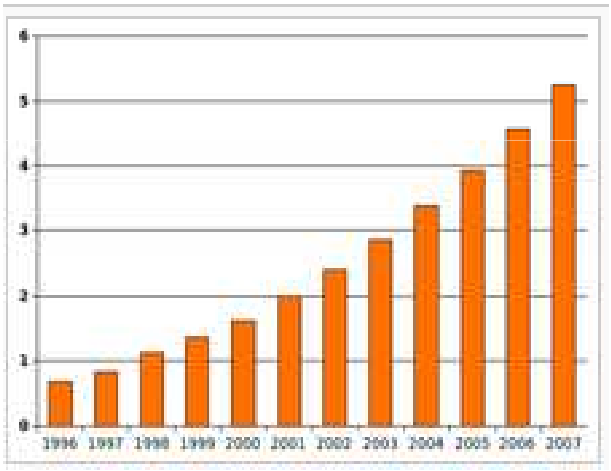
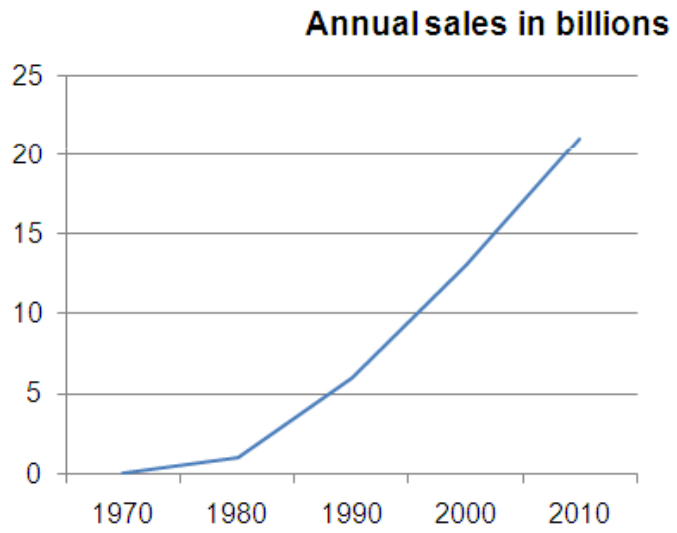
Pseudo Science and Vaccine Safety: Coincidence versus Causality

Austism incidence by year US



McDonald's annual sales



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How Are Public Concerns Regarding Vaccine Safety Being Addressed?

The Advent of New Vaccine Safety Assessment Technology

- Understanding coincidence through generation of background rates of events
- Larger clinical trials pre- and post-licensure
- Passive reporting systems
  - e.g., data mining in VAERS
- Database studies
  - Rapid cycle techniques
- Use of new technology
  - Genomics studies
  - Biomarkers and system's biology

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Black S, et al. *Lancet*. 2009;374:2115-2122.

What is an adverse event following immunization (AEFI)?

A medical incident that takes place after an immunization, causes concern, and is believed to be caused by immunization (but not necessarily caused by vaccination)

- Vaccine reaction - caused by vaccine's inherent properties
- Program error - caused by error in vaccine preparation, handling, or administration
- Coincidental - happens after immunization but not caused by it
- Injection reaction - anxiety or pain of injection not vaccine

Without causality assessment

Evidence supporting a causal relationship

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Slide adapted from Philippe Duclos

Passive Reporting

- **May allow reporting only by health personnel or alternatively also vaccinees and parents for any adverse events following immunization (AEFI) .**
- **Enhanced reporting may be facilitated for prespecified adverse events of special interest (AESI).**
- **To be useful, requires collation and monitoring of data.**
- **Utility limited by reporting bias**
  - **Known associations are reported much more frequently**
    - **This may generate a lot of data that is not useful**
    - **Unanticipated events not thought to be associated with vaccination may not be reported or part of an AESI list.**
- **No denominator data**

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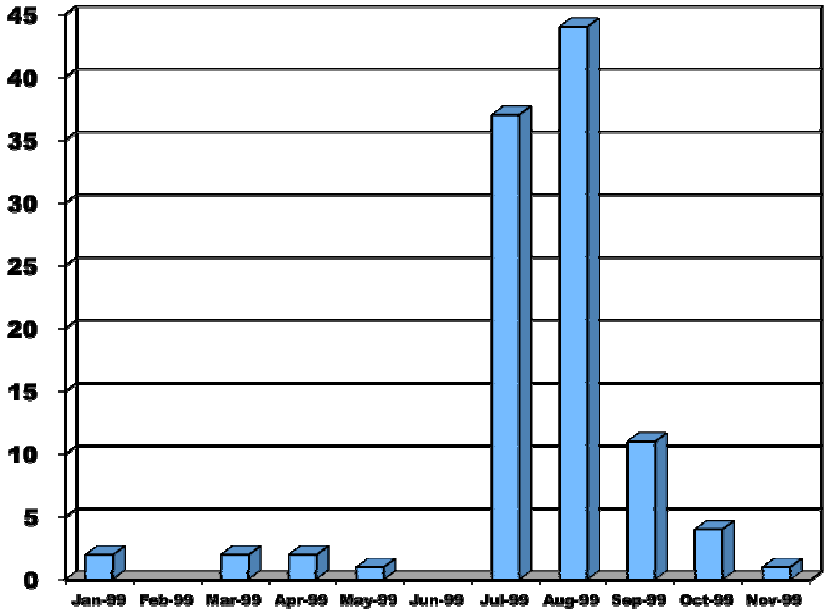
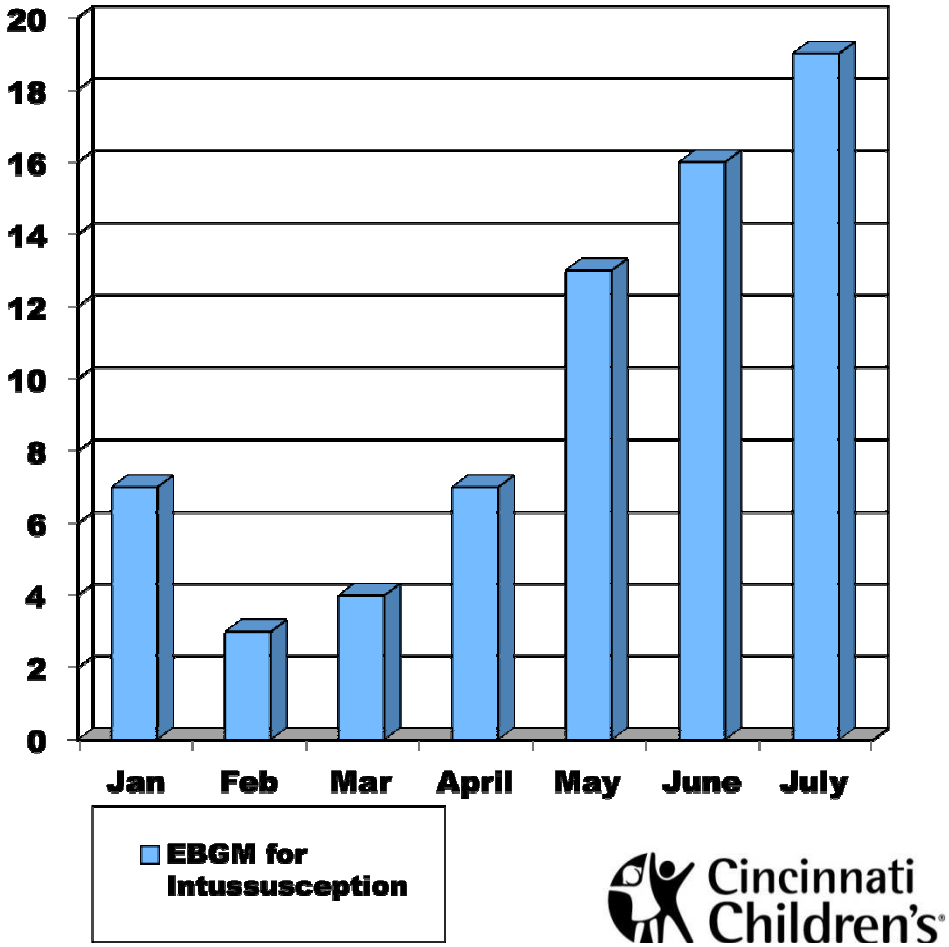
Passive Reporting Systems
VAERS

Intussusception cases reported to VAERS after introduction of RRV-TV vaccine:





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Passive Reporting Summary

- **Statistical techniques can be used for earlier detection of vaccine safety signals.**
- **Major Limitations of passive reporting systems:**
  - **Are prone to bias in that events closest to vaccine are reported preferentially**
  - **Underreporting can occur.**
  - **Misclassification of events can occur.**
  - **Information on cases may be limited.**
  - **Unrecognized events may not be reported.**
  - **Do not allow assessment of relative or attributable risk.**
  - **Enhanced reporting systems are limited to anticipated outcomes.**
  - **In a safety scare, large numbers of events may be reported without there being a true association with vaccination.**

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Active Surveillance studies vs Passive Reporting Systems.

Unlike passive reporting systems, active surveillance data based studies have the potential to

- **Identify cases of events in an unbiased way.**
- **Allow access to medical records to better characterize and understand cases.**
- **Calculate rates of events, relative risk and attributable risk.**
- **Evaluate vaccine impact and changes in disease epidemiology**

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What Data Do You Need?

Computerized Hospital And/or Clinic Diagnoses

Identify the Outcome or Possible "Adverse Event" in an unbiased manner

vaccine Data

Exposure information at a minimum for cases from database or chart

Demographic Data on A Population

- Can do case series with Outcome alone or case control with Outcome and Demographics.
- With all three, can calculate rates and attributable risk

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Summary: advantages of Active Surveillance and Population Based Studies

- Identifies cases in an unbiased manner
- Can identify unanticipated associations.
- Allow calculation of incidence on AEFI and background rates of disease without vaccination
- Allow calculation of relative risk
- Allow calculation of attributable risk.
- Allow adjustment for confounders
- Allow assessment of trends including vaccine impact on disease

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What do active surveillance analyses look like?

A Case Study: MMR-V

- **Pre-licensure studies of safety are usually small**
  - **Focus on common local and systemic events**
  - **Analyses done within predefined windows**
- **Post licensure studies are usually much larger and have ability to look at events more flexibly**

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MMR-V Pre-licensure Safety

Black et al. PIDJ 24:8-12, 2005

	MMRV N=323	MMR & V N=157	P-value
Fever 0-42 days s/p vax	39.6%	34.8%	ns
Fever 5-12 days s/p vax	27.7%	18.7%	0.034
Seizures	1 on day 9	1 on day 1	ns

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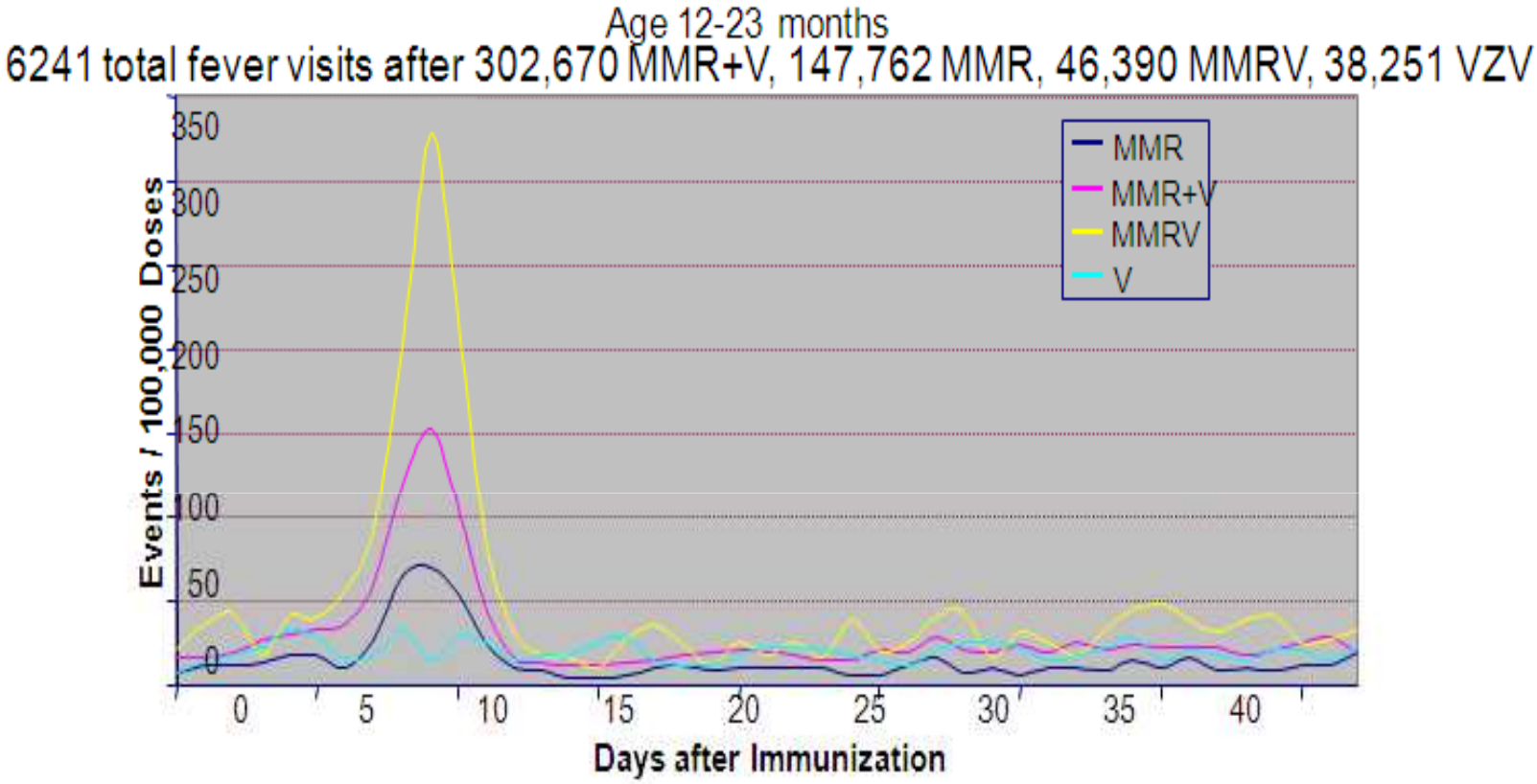
Rapid Cycle Studies
Approximating Real Time Surveillance



Risk of Seizure

	Odds ratio	95% Confidence Interval	P-value
MMRV versus MMR + Varicella*	2.3	1.6, 3.2	<0.0001
	Attributable Risk	95% Confidence Interval	
MMRV versus MMR + Varicella*	5.2 / 10,000	2.2, 8.1	

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Courtesy of Nicola Klein, Northern California Kaiser Permanente at PAS/SPR in Honolulu May 2008

Background Rates

What happens without vaccines?

The importance of knowing background epidemiology

What happens without vaccines?

"AEFI" without Vaccines: Outpatient visits in 30 days

Outpatient care		# events Adolescents	Rate/100,000 py Teens	Rate Adults
(…)	Thyroid disorders	859	396	1412.05
556.x	Ulcerative colitis	76	35.4	117.52
555.x	Regional enteritis	68	31.6	97.18
7100	Systemic lupus erythematosus	63	52.9	120.23
7140	Rheumatoid arthritis	29	13.5	119.33
37730	Optic neuritis	10	4.7	13.56
340	Multiple sclerosis	9	4.2	64.18
71659	Polyarthritis	7	3.3	30.74

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Understanding Coincidence and Background Rates

	Number of coincident events since a vaccine dose			Baseline rate used for estimate
	Within 1 day	Within 7 days	Within 6 weeks	
Guillain-Barré syndrome (per 10 million vaccinated people)	0·51	3·58	21·50	1·87 per 100 000 person-years (all ages; UK Health Protection Agency data)
Optic neuritis (per 10 million female vaccinees)	2·05	14·40	86·30	7·5 per 100 000 person-years in US females (table 2)[16]
Spontaneous abortions (per 1 million vaccinated pregnant women)	397	2780	16 684	Based on data from the UK (12% of pregnancies)[34]
Sudden death within 1 h of onset of any symptoms (per 10 million vaccinated people)	0·14	0·98	5·75	Based upon UK background rate of 0·5 per 100 000 person-years (table 2)[28]

Table 6: Predicted numbers of coincident, temporally associated events after a single dose of a hypothetical vaccine, based upon background incidence rates

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Reprinted from Black S, et al. *Lancet*. 2009;374:2115-2122.

What to do if you observe a safety signal?

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What to do if you observe a possible signal?

- **Evaluation of a possible consistent time association of the event with vaccination**
  - **As we saw with MMRV and seizure**
- **Comparison with background rates - are there more events than you would expect?**
- **Possible associations can serve as a source of hypothesis generation for further studies**
  - **case-control study conducted for intussusception following Rotashield vaccine.**

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Population Based Post-licensure Surveillance

Overall Summary

- There are multiple modalities to evaluate safety in the post-licensure setting
  - Passive reporting signal detection systems such as VAERS
  - Enhanced reporting systems such as CRIE in Brazil
  - Population based systems such as VSD, HPA.
  - International collaborations such as VAESCO in Europe
  - The global vaccine safety data network.
- The globalization of manufacturing and the development of vaccines targeting developing countries dictates that vaccine safety assessment and communication is now the responsibility of all countries.
  - At a minimum, passive reporting, analysis of data and communication needs to exist at the country level
  - Enchanced active surveillance is necessary in all manufacturing countries
    - Active surveillance offers advantages that should encourage all countries with appropriate capacity to perform this function.
- Global collaborations can increase efficiency and capacity

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The Future

New Vaccine safety methods

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New Approaches to Vaccine Safety

- Identifying safety concerns preclinically
  - Biomarkers
  - Immune signatures predicting higher risk of AEFI
- Identifying patients at risk
  - Genomics and vaccine safety

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Biomarkers and Systems Biology

- Systems biology studies biological systems
  - Classically we study vaccines by looking at one characteristic at a time
    - IgG immune response
    - T cell response
    - Induction of IL-2
    - Febrile response
  - Systems biology looks at multiple systems simultaneously and attempts to develop a model to integrate these measurements to better understand and predict response
- An analogy is meteorology:
  - One could measure temperature, atmospheric pressure, prior trends in isolation and attempt to predict the weather
  - Or analogous to systems biology, one could integrate many factors into a predictive model to improve accuracy of prediction
- So far this has been done for yellow fever immunogenicity but not for safety

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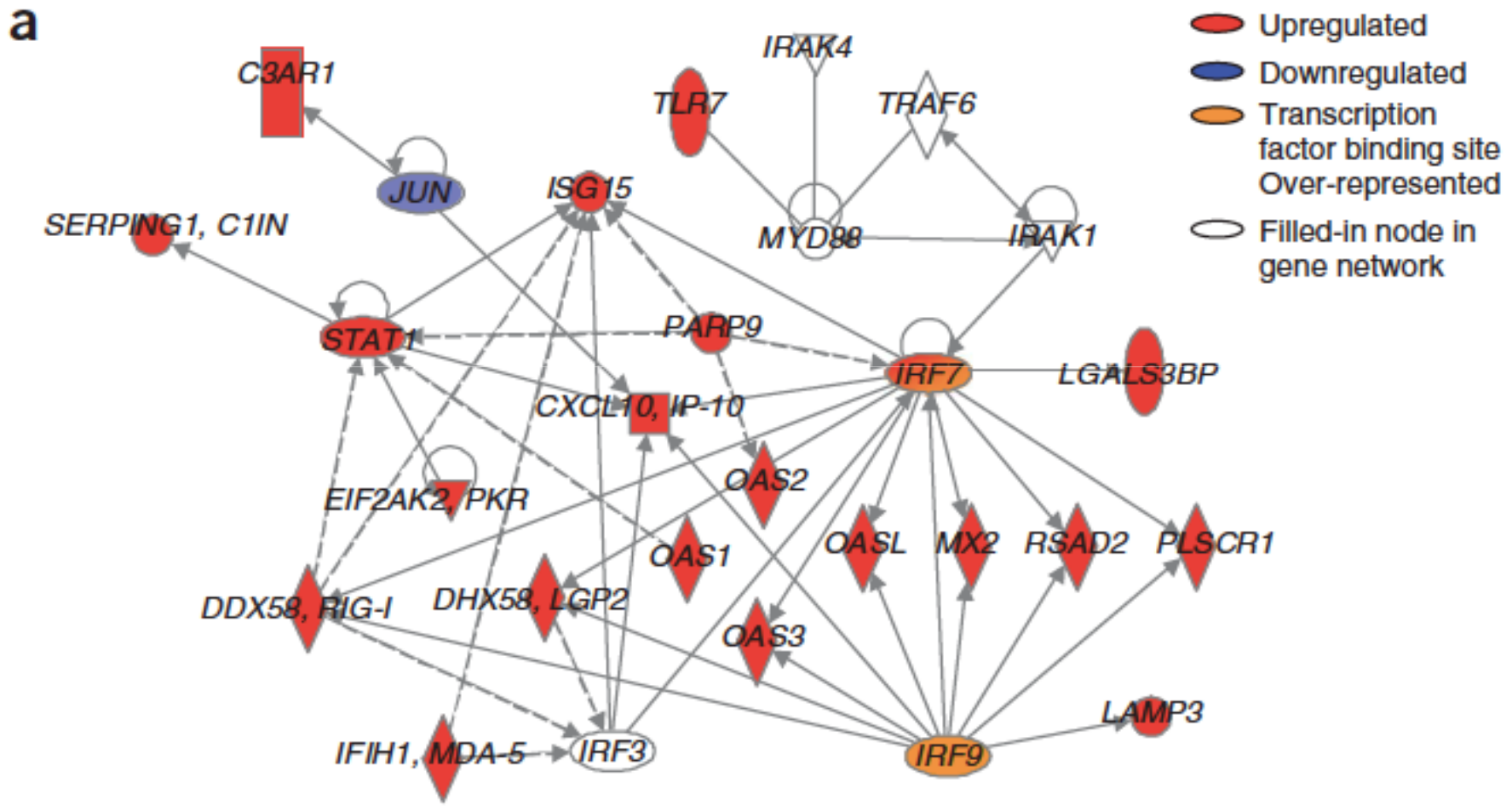
(Ideker et al, 2001)

Pulendran et al: Systems Biology of Yellow Fever Vaccination



In Nature Immunology 10: in 2009

Genomics: The Potential to Identify Individuals at Risk

- In the next 10-40 years, screening at birth for predisposition to disease, drug response, drug adverse events will be technically feasible and cheap and likely part of newborn screening.
  - Already drug adverse event (e.g., carbamazepine; abacavir)
  - Costs for sequencing falling rapidly – large-scale whole genome sequencing of large population segments on horizon

- This information will (eventually) be detailed enough to enable personalized vaccine and drug delivery based on the underlying genetics of the recipient

- Major challenge will not be technology, but rather will be in
  - collecting and interpreting the data to identify who is at risk (doing the studies)
  - collecting the data on what should be done with this information (alternate treatments, modified prevention strategies, etc.)

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So How is this Applicable to Clinical Practice?

- Before discussing safety, parents need to understand
  - The risks of vaccine-preventable diseases
  - That all vaccine-preventable diseases except smallpox are still out there ready to cause disease
  - That there is extensive infrastructure to assure the vaccines we use are safe
  - That “bad things” happen all the time and sometimes they will happen coincidentally after vaccination
- While genomic testing and systems biology offer potential, this is still not a reality for vaccine safety.

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