Vaccine Risk Management

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Vaccines vs. Therapeutic Drugs

- **↓ risk of serious and life-threatening infectious diseases**
- **Primary prevention**
- **Generally highly effective**
- **Mechanism of action may be unknown but evolutionary adaptive**
- **Eradication of disease and diminishing returns**
- **Vaccines with treatment and mitigation indications may compete with drugs**
- **Mass vaccination with novel adjuvants, novel technologies**

- Life-style to life-threatening
- Mild to severely affected pts
- Efficacy from 5-30% on avg
- Mechanism of action is unknown
- Chronic diseases, rarely curative
- Reductions in morbidity and mortality for serious diseases leads to non-inferiority trials
- Chronic exposure and long-term adverse events

Vaccines vs. Preventive Drugs

- **Medical practice and immunization practice system highly developed**
- **Development risks**
  - **Crowding of vaccine schedule**
  - **New manufacturing**
  - **Disease on the decline/↓risk tolerance**

- New medical understanding and paradigm except CV

- Development risks
  - Long term effectiveness studies
  - Long term side effects
  - Changing B/R

DEPARTMENT OF HEALTH AND HUMAN SERVICES • CENTERS FOR DISEASE CONTROL AND PREVENTION

Recommended Immunization Schedule for Persons Aged 0–6 Years—UNITED STATES • 2007

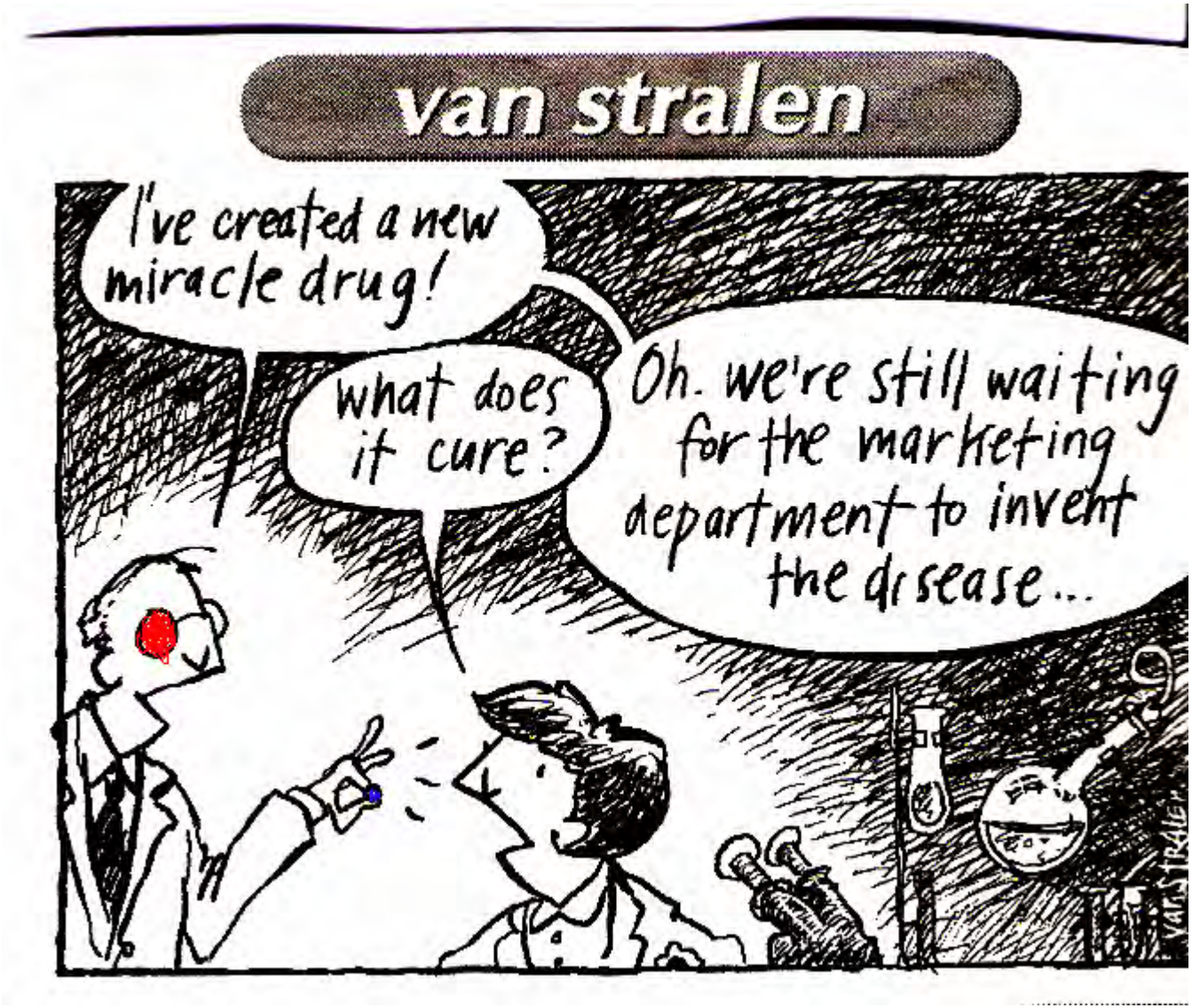
Vaccine ▼ / Age ►	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19–23 months	2–3 years	4–6 years
Hepatitis B[1]	HepB	HepB		see footnote 1	HepB				HepB Series		
Rotavirus[2]			Rota	Rota	Rota						
Diphtheria, Tetanus, Pertussis[3]			DTaP	DTaP	DTaP		DTaP				DTaP
Haemophilus influenzae type b[4]			Hib	Hib	*Hib*[4]	Hib		Hib			
Pneumococcal[5]			PCV	PCV	PCV	PCV				PCV PPV	
Inactivated Poliovirus			IPV	IPV	IPV		IPV				IPV
Influenza[6]					Influenza (Yearly)						
Measles, Mumps, Rubella[7]						MMR					MMR
Varicella[8]						Varicella					Varicella
Hepatitis A[9]						HepA (2 doses)				HepA Series	
Meningococcal[10]										MPSV4	

Range of recommended ages

Catch-up immunization

Certain high-risk groups

This schedule indicates the recommended ages for routine administration of currently licensed childhood vaccines, as of December 1, 2006, for children aged 0–6 years. Additional information is available at http://www.cdc.gov/nip/recs/child-schedule.htm. Any dose not administered at the recommended age should be administered at any subsequent visit, when indicated and feasible. Additional vaccines may be licensed and recommended during the year. Licensed combination vaccines may be used whenever any components of the combination are indicated and other components of the vaccine are not contraindicated and if approved by the Food and Drug Administration for that dose of the series. Providers should consult the respective Advisory Committee on Immunization Practices statement for detailed recommendations. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete a VAERS form is available at http://www.vaers, hhs.gov or by telephone, 800-822-7967.


van stralen
I've created a new miracle drug!
what does it cure?
Oh. we're still waiting for the marketing department to invent the disease...

Cancer Prevention Drug/Vaccine

- Identify an agent that is effective as a cancer prevention intervention
  - Lowers risk of developing the cancer
  - Will lower cancer morbidity and/or mortality
  - Favorable: long and short term safety (risks)
  - Favorable: rare and frequent adverse events
- How to use the product to get desired effect, safely
  - How long to use, ok with other meds

Raloxifene: Risk vs. Benefit

Raloxifene Placebo-controlled Trials

- Reduced risk of invasive breast cancers
  - Mammography (NEJM Oct. 27,2005)
- Variability of raloxifene effect size (44%-71% risk reduction)
  - **Number of women needed to treat (NNT) for one year to prevent one invasive breast cancer:**
  - **RUTH** **862 (Women with ≥4 CV risk score)**
  - **MORE** **323 (Women with osteoporosis)**
  - **CORE** **335 (Women with osteoporosis)**
  - **NSABP P-1** **300 (Women ≥35 y old, at high risk)**
- Increased risk of thromboembolic adverse events
- Comparison of Risk vs. Benefit:
  - **Reduction in invasive breast cancer incidence/osteoporosis Rx vs. increased risk of thromboembolic AEs**
- RUTH: No diff in CV events, but ↑ risk stroke death

Source: P.Cortazar, FDA, ODAC, July 24, 2007

Raloxifene: Risk vs. Benefit
Active Control Trial in Postmenopause

- For prevention, not clear what the minimum percent retention of an active control effect should be for an efficacy claim based on non-inferiority.
  - For adjuvant breast cancer Rx, the FDA requires at least a 75% retention of an active control effect for an efficacy claim based on non-inferiority.
- Benefits:
  - The size of the benefit is uncertain when compared to tamoxifen
  - A non-inferiority analysis shows that raloxifene could lose up to 35% of the Tamoxifen effect in reducing risk of invasive breast cancer
- Risks:
  - Generally less risks compared with Tamoxifen.

Source: B. Mann, FDA, ODAC
July 24, 2007

HPV Vaccine: Risk vs. Benefit

- Prevention of cervical cancer by HPV in girls age 9-16
  - Pap testing
- >10,000 US women develop cervical cancer annually and 3,000 deaths
  - HPV 16 and 18 cause ~25,000 of cases of CIN (25% of CIN 1)
- Per Protocol Efficacy CIN 2/3 or worse due to HPV in vaccine **100%** [93-100%; 0 vax vs.53 cases PL]
- Overall efficacy CIN 2/3 or worse due to any HPV type **12.2%** [-3.2%, 25.3%]
- Adverse events < benefits
- Long term effectiveness unknown for both vaccine and drug

Source: Merck and FDA slides
VRBPAC May 18, 2006

Some Drug Adverse Events of Interest

- Hepatoxicity
  - 3x ↑ AST/ALT with 2x↑ TBili
    - Rate in CT x 10% ≈ rate of acute liver failure in general pop
  - Ximelagantran
- QTc prolongation
  - Active control for assay sensitivity
    - Warnings/Precaution
- Cardiovascular events
  - Unpredictable (opposing actions by drugs)
  - Study population's baseline risk for MI may overwhelm modest increases so signal is lost
- Suicidality
  - Accidents, injuries, drownings

Some Vaccine Adverse Events of Interest

- GBS w/Swine Flu Vaccine
  - 1 per 100,000 (1 per 1,000,000 background)
- Intussusception with Rotashield
  - 5 cases per 10,000 vs 1 case per 4,600 placebo
- Hypotonic Hyporesponsive Episodes w/WC Pertussis
  - 0.5 cases per 1000 doses (Sweden II HCPDT)
  - whole-cell rates reported to vary from 36 to 250 episodes and acellular rates 4 to 140 episodes (per 100,000 doses)
- Myopericarditis with Vaccinia
  - 5-6 cases per 1000 primary vaccinees (ACAM2000: 5 per 873 and Dryvax 3 per 289)
- Wheezing/Hosp with LAIV vs. TIV (6-23 mon)
  - Δ 21/10 cases per 1000 (MICPIII data)

Limitations in Drug/Vaccine Risk Identification and Quantification

- Most pre and post marketed studies are sized between a total of 1,000-20,000 patients;
- Moderate-high frequency events
  - 100/10,000→2,000 patients
  - 10/10,000→20,000 patients
  - 1-5/10,000→40-200,000 patients
    90% power to rule out 3 fold increase; alpha 0.025

Causal inference

Can we detect long term events and rare but life-threatening events?

Class of Agents **and** **Example members**	**Phase 3 & 4 Clinical Trials: Sample Size and Duration of follow-up**	**Bkgd Rate/ 10Kpy**	**RR**	**# cases Target'd /Seen in the Study**
Cox 2 inhibitors Celebrex, Vioxx, Bextra	*20,000 pt PRECISION , 2+y fu*	CV 100	R/O 1.333	500
Long Acting β-Agonists Salmeterol	26,000 pt SMART Trial, 6 m fu	Resp. 5	4 (7 Blks)	(7 vs 1)
Tysabri	Limited controlled trial data (3,000-Crohn's/Rheum/MS) Accelerated Approval	PML <0.01?		> 3 ?
Rotavirus Vaccine RotaTeq Rotashield	70,000 person study (1:1 pl) 14,600 person study (2:1)	Intuss 1	 >10 ?>20	6v5@42d (5:1)
Inact. Influenza Vaccines	Accelerated Approval 3,000	GBS .01		0
HiB vaccine	*Epi study using US CDC data to r/o risk of disease if vaccine is less effective*	HiB cases ≈0.002	5-10	6-9> comparison

What can be detected?

Table 2: Sample Sizes Needed During Clinical Trials to Detect Increases in Rates of Rare Events After Vaccination

Rates (%)	Sample Size*	No. Potentially Affected Annually
0.1 vs. 0.2	50,000	4,000
0.1 vs. 0.3	17,500	8,000
0.05 vs. 0.1	100,000	2,000
0.01 vs. 0.02	500,000	400
0.01 vs. 0.03	175,000	800

* Two-arm, power=80%, alpha (2 sided)=5%

Adapted from Ellenberg SS, Safety considerations for new vaccine development. Pharmacoepidemiol Drug Saf. 2001 Aug-Sep;10(5):411-5.

Concerns w/Prevention Trials

- New adverse events may arise in longer trials
- Long development time for cancer preventive for collection of cases
- Drugs studied in high AE rate populations (elderly) now studied in healthy at risk
- Immediate versus delayed safety events
  - Risk assessed over time interval, even if intervention is stopped earlier in time
  - Risks and duration of exposure: dependent? Independent?
- Risk/Benefit profile changes over time
  - AERS reporting ↓ after 5-10 years

Pharmacovigilance Plan

- ICH E2E
- Reviewed by Division of Epi/OBE/CBER
- Phase 4 studies for further risk assessment
  - Assessment of known or serious risk or signal, post approval studies may be required. CT can be required if pa studies will not be sufficient.
- Phase 4 studies to demonstrate meeting risk management goals

FDAAA 2007

- Sec 905: Active Postmarket Risk Identification and Analysis System (PMRIAS)
  - 25,000,000 patient July 1, 2010
  - 100,000,000 pts July 1, 2012
- Develop validated methods to link and analyze data
- Establish PMRIAS
- Biannual AC on priority safety questions
- Sec 901: If PMRIAS is not sufficient, post approval studies or clinical trials may be required.

FDAAA 2007 (cont)

- Labeling changes and timelines for new safety information
- Risk Evaluation and Mitigation Strategy (REMS)
  - REMS may be required
  - Postmarketing studies (evaluations) are required for assessment of REMS
  - 18 month, 3 yr, 7 yr evaluation

Vaccine RM Tools at FDA

- Labeling
  - Indication, W/P
  - New authority for labeling changes with timelines and an order.
- Medications guide
- RiskMAPs
  - ACAM2000
- Approval w/restrictions for safe use
  - 21 CFR 601.42 Subpart E

Smallpox vaccinia vaccine, Live: RiskMAP

- RiskMAP Goals and Objectives
  - Education for vaccinees and vaccine providers to achieve
    - Vaccine is administered safely and effectively
    - Vaccinees informed of risks and benefits
      - Myo-pericarditis, transmission, autoinoculation
    - Risks of transmission and autoinoc are minimized
- This RiskMAP is broad, not prescriptive
    - Process control is not lynchpin for safety
    - Approaches will differ for specific risks/controls

Smallpox vaccinia vaccine, Live: RiskMAP

- Conditions of use in approval letter for national emergency declared by the Sec. of HHS
  - "In the event of an actual emergency, declared by the Secretary under Section 319 of the PHS Act, the conditions of use for the vaccine would change, altering the vaccine's risk/benefit balance. Consequently, the postmarketing restrictions needed to assure safe use would change accordingly…alternative approaches that meet the RiskMAP Goals and Objectives may be immediately implemented…"
- Vaccine is only distributed by the manufacturer to entities that educate providers on administration, benefits/risk—Subpart E Approval
- Outcomes-based RMP to allow flexibility
- Evaluation is via outcomes of interest
  - Rates of transmission vaccinia, autoinoculation, and eczema vaccinatum

RM and RC Tools in the US

- National Childhood Vaccine Injury Act 1986
  - VIS required for certain childhood vaccines
  - VAERS reporting mandatory
- ACIP
  - Recommendations for inclusion in the immunization schedule affect VFC, NVICP, medical practice standards
- Academic & professional org. recommendations
- State laws
- Reimbursement incentives and liability
- Distribution system direct to providers

Influenza Vaccines

- On the cusp of fundamental change
- New paradigm for population protection
  - Priming the population for a pandemic
    - Yearly rotations of antigens? Separate inoculations? Coordinated?
  - How do you conduct the priming studies?
  - Level of tolerance for adverse events for preventing a pandemic which may not come for that strain?
- Post-marketing collection of effectiveness and safety
  - What systems do we have now? Can they provide timely feedback? Do they cover the right strain? Protocols?

Closing Thoughts

- Drug and vaccine risk management have parallels and divergences.
- Labeling is cornerstone for risk management.
- New paradigms for vaccine development
  - More data for informed decision making re: R/Bs
- Global versus US public health considerations
  - Sec. 1102: Priority review to encourage tropical disease applications…“any other infection for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations, designated by regulations”
    - Priority review vouchers (may be sold or transferred)