Required Postmarketing Studies

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Application of Pharmacovigilance to
U.S. FDA Regulatory Decisions for Vaccines

June 2, 2012

Vaccine Safety Throughout the Life Cycle

- Ensuring that biologics are as safe as possible is a priority of the FDA

- Vaccine safety occurs throughout the life cycle
  - Preclinical (non-human) testing of candidate vaccines
  - Early phase human studies through large phase III clinical trials
  - Inspection of manufacturing facilities
  - Monitoring of lot release
  - Postlicensure adverse event surveillance

- **Monitoring vaccine safety during development is as important as the postmarketing period**

Marshall V, Baylor NW. Food and Drug Administration regulation and evaluation of vaccines. Pediatrics. 2011 May;127 Suppl 1:S23-30..

Plan for Talk

- Why require postmarketing studies?
- When to require postmarketing studies?
- What are the study options and considerations for a required postmarketing study?
- Examples of FDA required studies

Limits of Clinical Trial Safety Data

- Smaller sample sizes and observation periods limit reliable detection to the most common events
  - Detecting a 2-fold increase of an event normally occurring 1/1000 requires a sample size of 50,000 (two-arm, 80% power, 5% alpha)
- Rare adverse events may not be detected in pre-licensure studies
- Patient enrollment exclusions limit generalizability
- Multiple comparisons and post hoc analyses often limit inferences about safety

Risk Detection Limits in Prelicensure Trials

Power to Detect a 2-Fold Increase

	Clinical Trial Size	
Background rate	**N = 3,000 vaccinees**	**N = 10,000 vaccinees**
1 in 10	**100%**	**100%**
1 in 100	**87%**	**100%**
1 in 1,000	**10%**	**38%**
1 in 10,000	**0.4%**	**2.6%**
1 in 100,000	**0%**	**0%**

Power > 80% Power < 80%

Fisher's exact test. Assuming alpha 0.05, 1:1 ratio of vaccinees to placebo/controls

Interpreting 0 Events in Clinical Trials

Summary of Boys and Men 9 Through 26 Years of Age Who Reported an Incident Condition Potentially Indicative of a Systemic Autoimmune Disorder After Enrollment in Clinical Trials of GARDASIL, Regardless of Causality

Conditions	GARDASIL (N = 3093)	AAHS Control* or Saline Placebo (N = 2303)
	n (%)	n (%)
Alopecia Areata	2 (0.1)	0 (0.0)
Ankylosing Spondylitis	1 (0.0)	2 (0.1)
Arthralgia/Arthritis/Reactive Arthritis	30 (1.0)	17 (0.7)
Autoimmune Thrombocytopenia	1 (0.0)	0 (0.0)
Diabetes Mellitus Type 1	[illegible]	2 (0.1)
Hyperthyroidism	0 (0.0)	1 (0.0)
Hypothyroidism**	[illegible]	0 (0.0)
Inflammatory Bowel Disease***	1 (0.0)	2 (0.1)
Myocarditis	1 (0.0)	1 (0.0)
Proteinuria	1 (0.0)	0 (0.0)
Psoriasis	0 (0.0)	4 (0.2)
Skin Depigmentation	1 (0.0)	0 (0.0)
Vitiligo	2 (0.1)	5 (0.2)

If 0 events are observed, will it never happen in the general population?

***Inflammatory bowel disease includes the following terms: Colitis ulcerative and Crohn's disease
N = Number of individuals who received at least one dose of either vaccine or placebo
n = Number of individuals with specific new Medical Conditions
NOTE: Although an individual may have had two or more new Medical Conditions, the individual is counted only once within a category. The same individual may appear in different categories.

Maximum Risk for Rare Events in Clinical Trials

- Rule of 3* for maximum risk estimate
  - 95% confidence interval = [0, (3/N)]
  - Where N = number of vaccinees

- If N = 3,093 Gardasil vaccinated males aged 9 – 26 years
  - 95% confident that the risk for hyperthyroidism is at most 1 in 1,000 after Gardasil

- Cannot rule out substantial increases in rarer events
  - Example: 5 fold increase in an event normally occurring 1 per 10,000

- Therefore, even if “nothing goes wrong” in clinical trials, we still need postmarketing surveillance to detect meaningful increases in risk for more rare events

*Hanley and Lippman-Hand. JAMA 1983 249(13): 1743-45

Immune Mediated Conditions are Challenging to Assess in Clinical Trials

Table 2. Estimated new cases in 2009 of autoimmune disease in the United States based on mean weighted incidence rates reported in a systematic meta-analysis (*71*). Expected new diagnoses were extrapolated using the 2009 U.S. Census data for population >18 years of age (*73*).

Autoimmune disease	Incidence (per 100,000 persons per year)	Expected new diagnoses (persons >18 years of age)
Adult rheumatoid arthritis	23.7	55,092
Thyroiditis (hypothyroidism)	21.8	50,675
Graves disease (hyperthyroidism)	13.9	32,311
Type 1 diabetes (age >20 years)*	8.1	18,829
Systemic lupus erythematosus	7.3	16,969
Sjogren disease*	3.9	9,065
Multiple sclerosis	3.2	7,438
Primary systemic vasculitis*	2.0	4,649
Polymyositis/dermatomyositis	1.8	4,184
Systemic sclerosis*	1.4	3,254
Addison disease*	0.6	1,394
Myasthenia gravis	0.4	929
Total		204,789

*Additional categories of autoimmune diseases with an age distribution older than 18 years for which missing or updated incidence data were available in a subsequent publication (*72*).

S. Sohail Ahmed et al. *Sci Transl Med* **3**, 93rv2 (2011);

Plan for Talk

- Why require postmarketing studies?
- **When to require postmarketing studies?**
- What are the study options and considerations for a required postmarketing study?
- Examples of FDA required studies

The 3 Criteria for FDA Required Studies

New safety information + **Not evaluable in FDA's Active Surveillance System (Sentinel)** + **Study Purpose**

Study purpose is one of the following:

1. To assess a known serious risk related to the use of the drug
2. To assess signals of serious risk related to the use of the drug
3. To identify an unexpected serious risk when available data indicate the potential for a serious risk

Guidance for Industry: Postmarketing studies and clinical trials — Implementation of Section 505(o)(3)of the Federal Food, Drug and Cosmetic Act (April 2011).

Defining Key Terms in the Criteria

- **New safety information**
  - Information from clinical trial, adverse event report, postapproval study, FDA's Sentinel system, scientific literature
- **Signal of a serious risk**
  - Any information from the above sources about a serious adverse event
- **Unexpected serious risk**
  - Serious event not listed in the labeling, or
  - Listed in label, but differs because of greater severity, specificity, or prevalence

Plan for Talk

- Why require postmarketing studies?
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Match the Safety Issue to the Study Design

Index of Concern → **Study Design**

Strength of association
- Demonstrated vs. theoretical risk

Public health impact
- Population attributable risk
- Seriousness of outcome

Medical complexity
- Strength of confounding
- Availability of comparator

Feasibility
- Availability of data sources
- Confirmation of exposure and outcome

Selected Options for Required Studies

	Patient Outcome Registry	Electronic Database	VAMPSS*
Temporality	Prospective		
Patient recruitment	Voluntary		
Testable hypothesis	No		
Comparator group	No		
Exposure / outcome confirmation	Chart confirmed		
Confounding control	N/A		

* Vaccines and Medications in Pregnancy Surveillance System.
http://www.aaaai.org/about-the-aaaai/strategic-relationships/vampss/vampss-consumer.aspx

Selected Options for Required Studies

	Patient Outcome Registry	Electronic Database	VAMPSS*
Temporality	Prospective	Prospective or retrospective	
Patient recruitment	Voluntary	Identified through billing claims	
Testable hypothesis	No	Yes	
Comparator group	No	Yes	
Exposure / outcome confirmation	Chart confirmed	Chart confirmed	
Confounding control	N/A	Variable	

* Vaccines and Medications in Pregnancy Surveillance System.
http://www.aaaai.org/about-the-aaaai/strategic-relationships/vampss/vampss-consumer.aspx

Selected Options for Required Studies

	Patient Outcome Registry	Electronic Database	VAMPSS*
Temporality	Prospective	Prospective or retrospective	Prospective
Patient recruitment	Voluntary	Identified through billing claims	Voluntary, self-referral
Testable hypothesis	No	Yes	Yes
Comparator group	No	Yes	Yes
Exposure / outcome confirmation	Chart confirmed	Chart confirmed	Chart confirmed
Confounding control	N/A	Variable	Improved with patient interviews

* Vaccines and Medications in Pregnancy Surveillance System.
http://www.aaaai.org/about-the-aaaai/strategic-relationships/vampss/vampss-consumer.aspx

Selected Options for Required Studies

	Patient Outcome Registry	Electronic Database	VAMPSS*
Temporality	Prospective	Prospective or retrospective	Prospective
Patient recruitment	Voluntary	Identified through	Voluntary, self-
Testa			
Comparator group	No	Yes	Yes
Exposure / outcome confirmation	Chart confirmed	Chart confirmed	Chart confirmed
Confounding control	N/A	Variable	Improved with patient interviews

Even more options exist and are dependent on the available resources in each country

* Vaccines and Medications in Pregnancy Surveillance System.
http://www.aaaai.org/about-the-aaaai/strategic-relationships/vampss/vampss-consumer.aspx

Plan for Talk

- Why require postmarketing studies?
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- **Examples of FDA required studies**

3 Examples of FDA Required Studies

	Cervarix	Octagam	Provenge
Safety issue	Spontaneous abortion	Thromboembolic events	Cerebrovascular events

Cervarix PMR

	Cervarix	Octagam	Provenge
Safety issue	**Spontaneous abortion**	Thromboembolic events	Cerebrovascular events

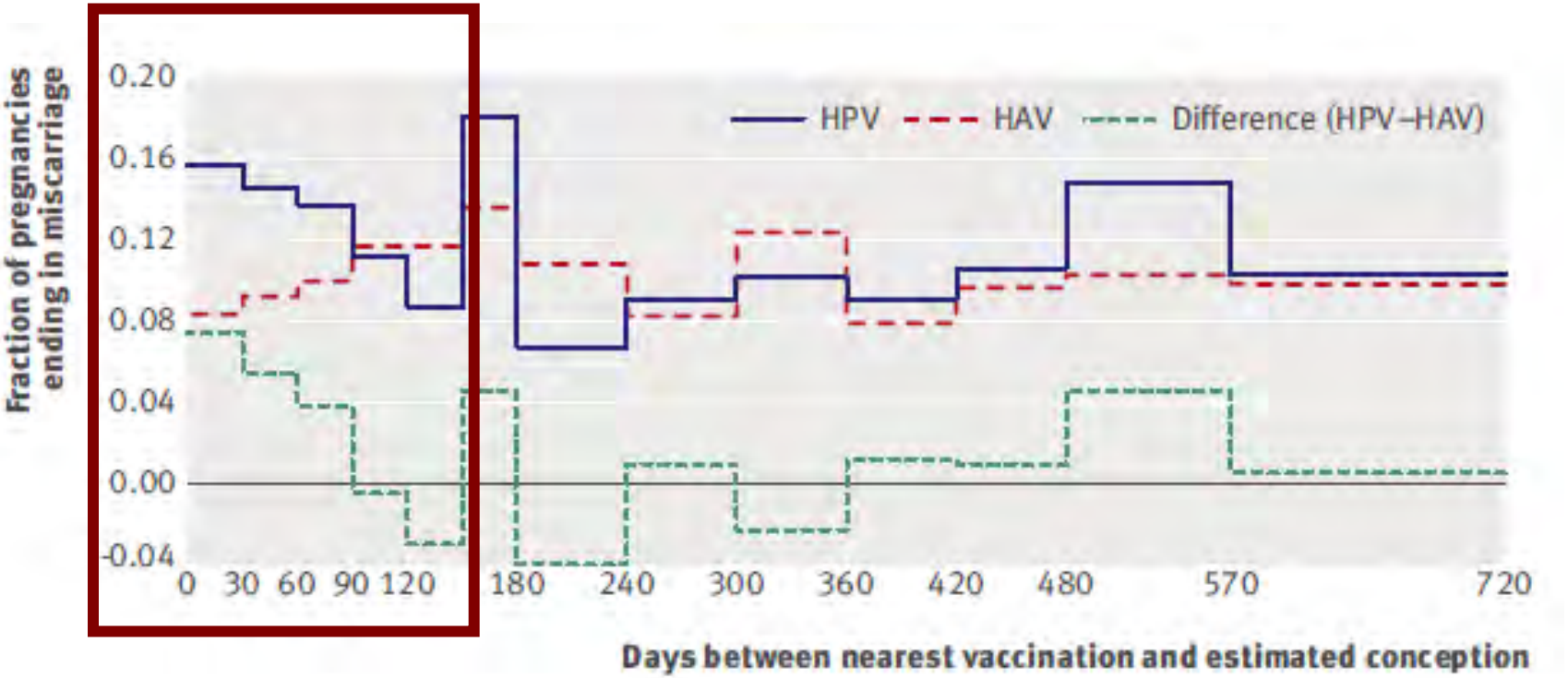
Cervarix and Spontaneous Abortion

- Cervarix is a vaccine that prevents infection by HPV types 16 and 18 that cause cervical cancer

- Not indicated in pregnant women
  - Target population includes women of child-bearing age
  - Risk of inadvertent vaccination during pregnancy

- Safety concern noted in Cervarix clinical trials
  - Imbalance in miscarriage among pregnancies with onset around the time of vaccination (13.8% vs. 9.8%)
  - Overall proportions of pregnancy outcomes were similar between treatment groups

Risk Among Pregnancies Conceived Within 3 Months of Vaccination



- Time frame with the highest prior probability of an effect
- The observed difference (14.7% vs. 9.1%) consistent with a small effect of vaccination or statistical noise

BMJ 2010;340:c712

From Safety Signal to Study

Index of Concern → **Study Design**

Strength of association

– Post-hoc analysis of clinical trials

Public health impact

– Target population at risk
– Potential reproductive adverse events mitigates benefits of cancer prevention

Medical complexity

– Difficult to study pregnant women

Feasibility

– Data sources limited
– Confirmation of exposure, outcome, confounders needed

Summary of Cervarix Required Study

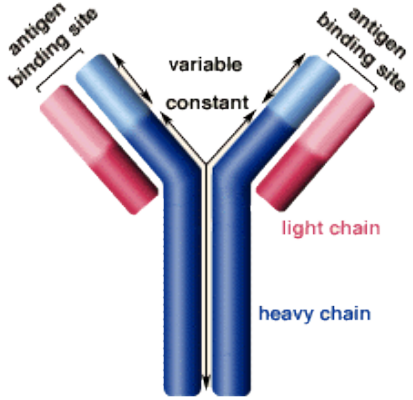
Safety issue	Spontaneous abortion
Study Purpose	To identify an unexpected serious risk when available data indicate the potential for a serious risk
Considerations	▪ Pregnancy difficult to study ▪ Known prenatal confounders, outcome difficult to detect, comparison group difficult to find
Study design	Prospective observational cohort study of Cervarix recipients during pregnancy compared to non-exposed pregnant women (VAMPSS)

Octagam PMR

	Cervarix	Octagam	Provenge
Safety issue	Spontaneous abortion	**Thromboembolic events**	Cerebrovascular events

Octagam and Thrombotic Events

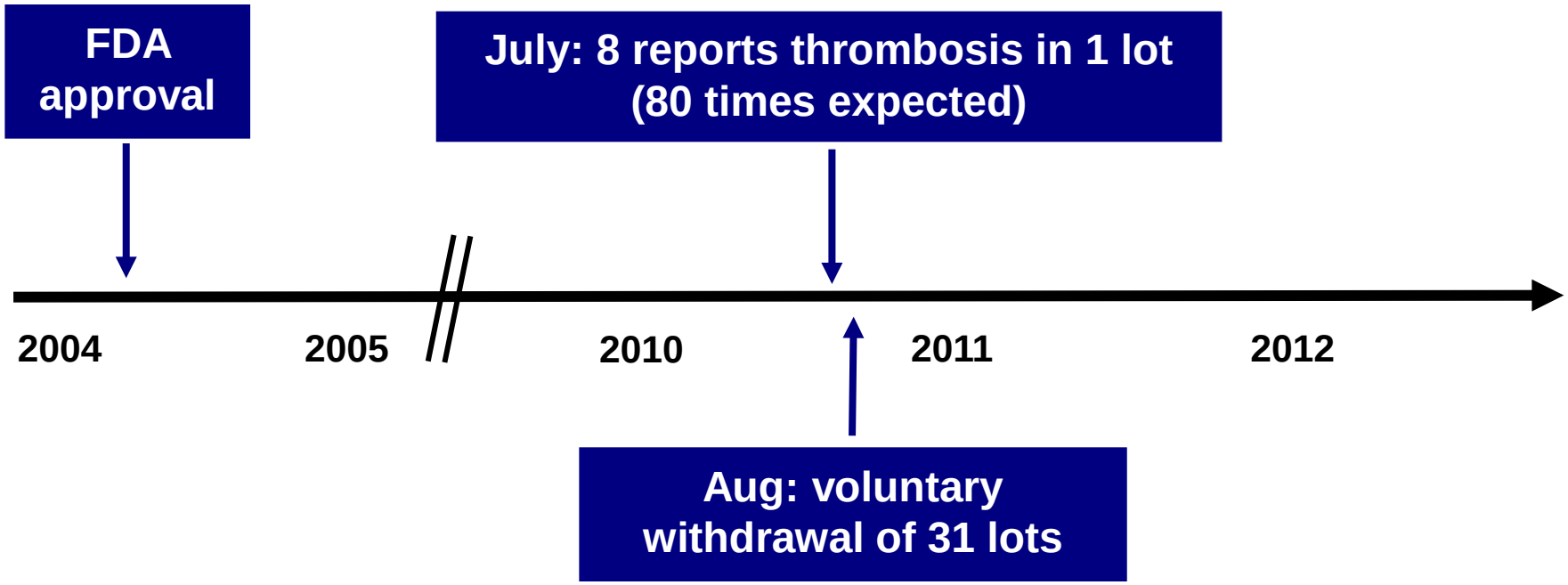
- Purified pooled human-derived antibodies
  - Indicated for treatment of primary immune deficient diseases
  - Administered intravenously



- Thrombotic events (stroke, pulmonary embolism) are known adverse events after all intravenous immunoglobulins
  - Dose-dependent increase in serum viscosity
  - Increased platelet aggregation
  - Preexisting recipient dehydration
  - Residual procoagulant activity after purification

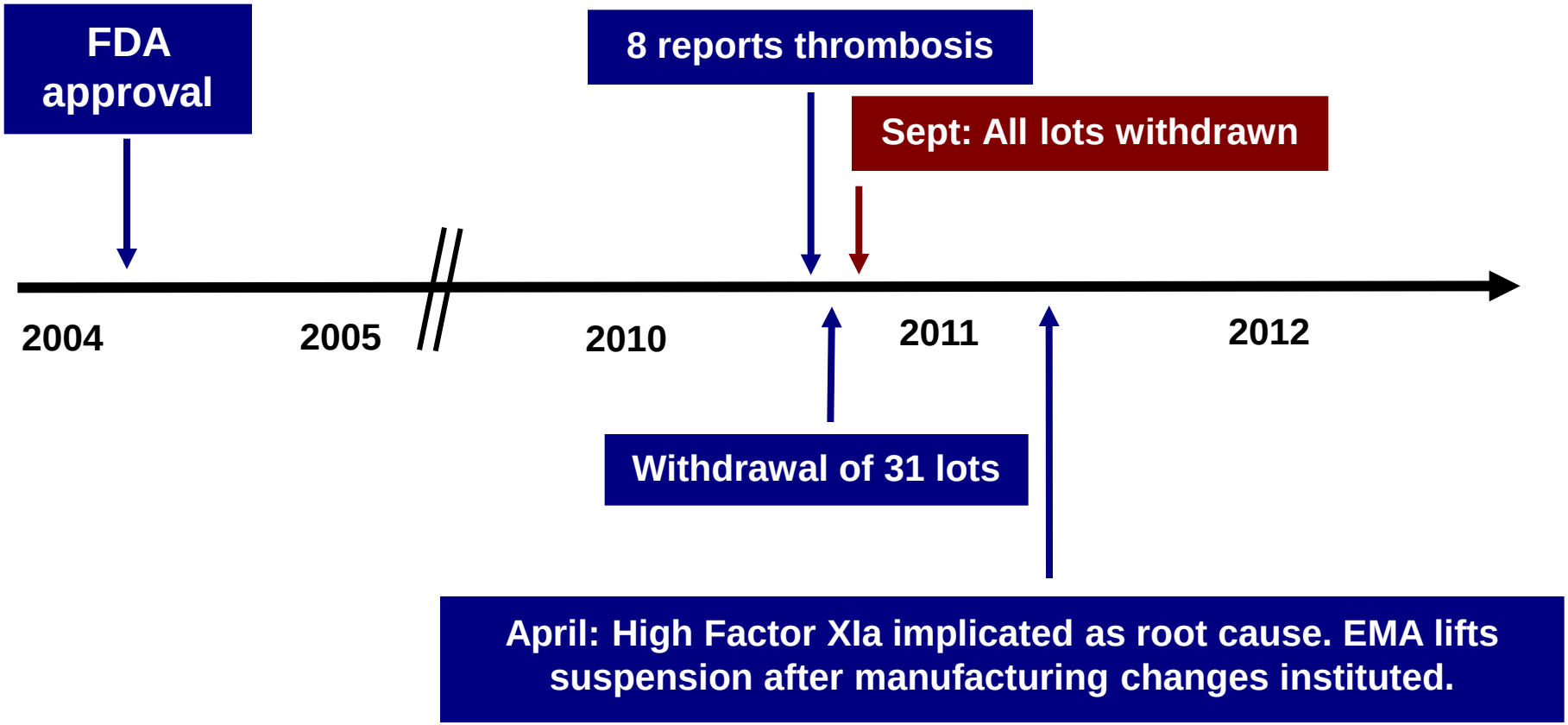
Arch Dermatol. 2003;139:991-993.

Timeline to Octagam Market Withdrawal



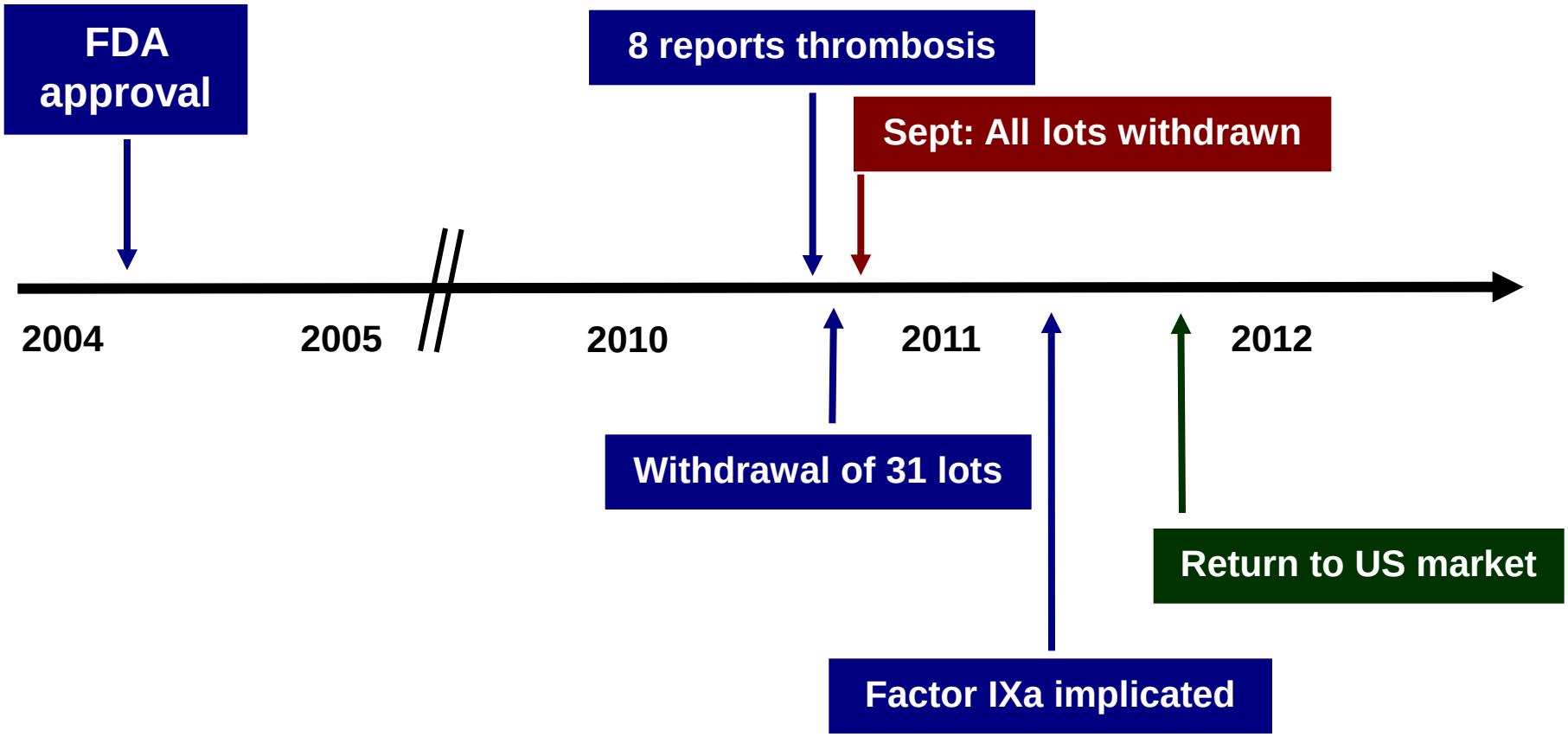
http://www.fda.gov/downloads/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/UCM260769.pdf

Timeline to Octagam Market Withdrawal



http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/Recalls/ucm227133.htm
http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/Recalls/ucm223897.htm
http://www.fda.gov/downloads/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/UCM260769.pdf

Timeline to Octagam Market Withdrawal



http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/Recalls/ucm227133.htm
http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/Recalls/ucm223897.htm
http://www.fda.gov/downloads/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/UCM260769.pdf

From Postlicensure Signal to Postlicensure Study

Index of Concern → **Study Design**

Strength of association

– Passive and active surveillance
– Temporal association, unique presentation (multiple infarcts)

Public health impact

– Death and disability

Medical complexity

– Multiple indications, host factors
– Dosage and dosing regimens

Feasibility

– Confounding adjustment is critical

Summary of Octagam Required Study

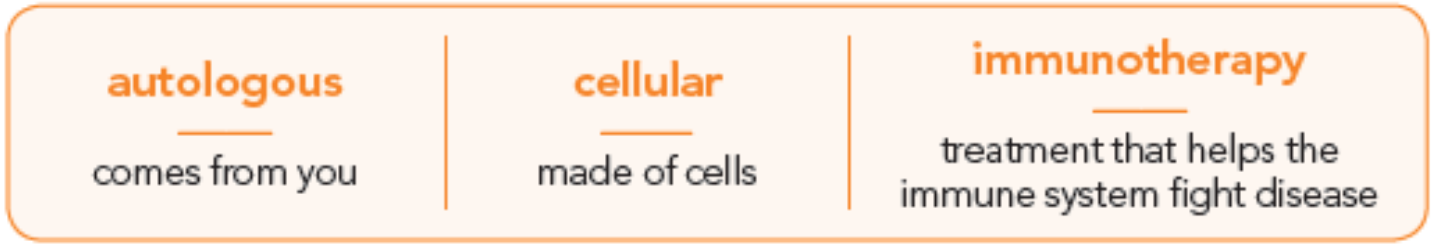
Safety issue	Thrombotic events
Study Purpose	Assess a known serious risk
Considerations	▪ Post-interventional study (started after root cause identified and manufacturing changes instituted) ▪ Goal is to confirm that Octagam is no more thrombogenic compared to other IVIG ▪ Must address between-person confounding
Study design	Observational 2-arm comparator study

Provenge PMR

	Cervarix	Octagam	Provenge
Safety issue	Spontaneous abortion	Thromboembolic events	**Cerebrovascular events**

What is Provenge?

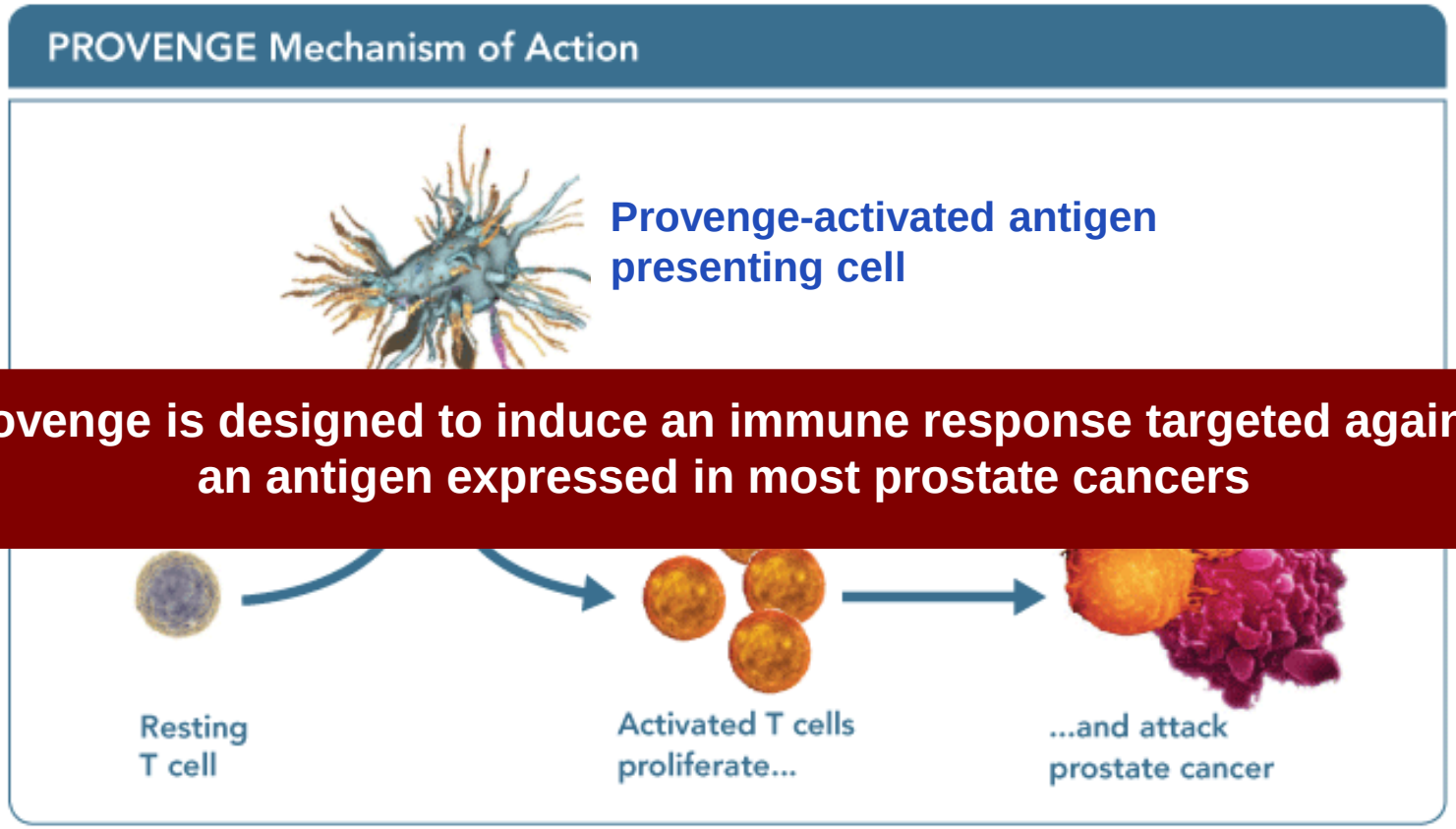
- 1st FDA approved autologous cell based immunotherapy
  - Indicated for late stage metastatic prostate cancer



- White blood cells are obtained by apheresis
  - Grown in culture
  - Activated by a recombinant prostatic protein
  - Reinfused into same patient

http://www.provenge.com/hcp/

Hypothesized Mechanism of Action

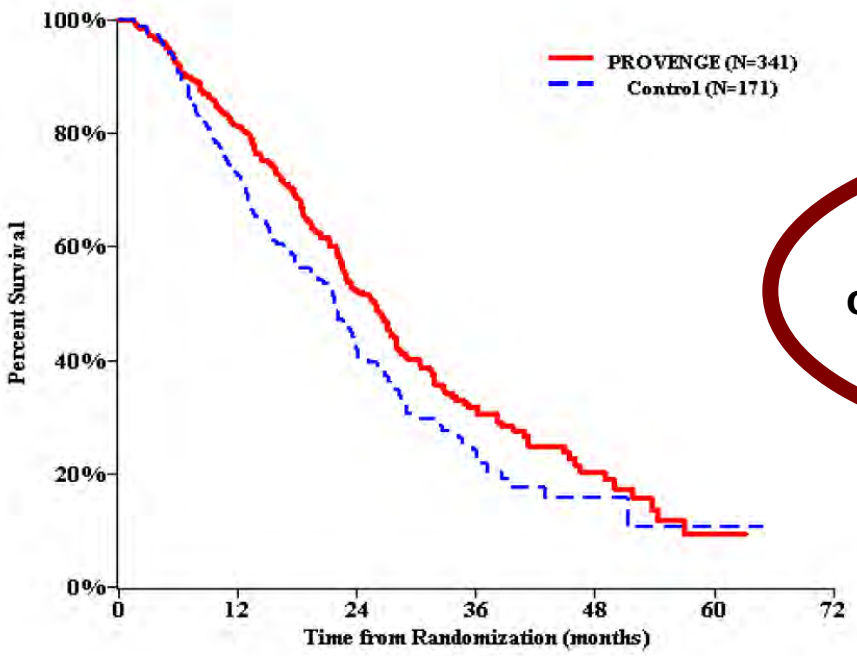


http://www.provenge.com/hcp/

http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/ucm210012.htm

Provenge Clinical Trials

- 600 Provenge recipients compared to 300 patients with prostate cancer receiving non-activated autologous white blood cells
- Course of therapy is 3 doses, given at 0, 2, and 4 weeks

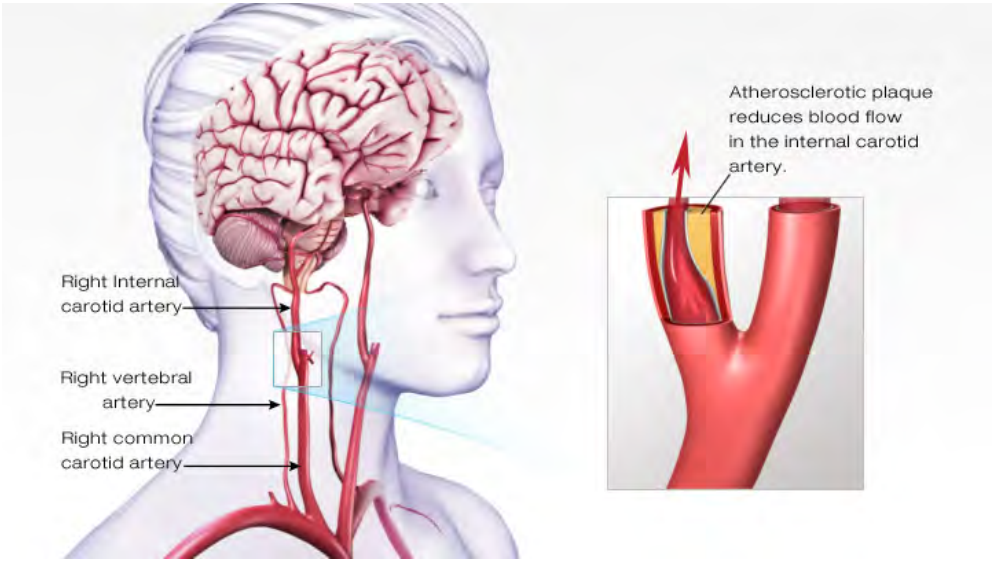


Median increased survival of ~4 months for end-stage prostate cancer patients

Provenge and Cerebrovascular Events

- Statistically significant difference in cerebrovascular events (hemorrhagic and ischemic strokes) observed
  - 3.5% Provenge goup vs. 2.6% control group in crude analyses

- No clear biologic mechanism linking Provenge to stroke



From Prelicensure Signal to Required Study

Index of Concern → **Study Design**

Strength of association

– Statistically significant imbalance in crude rates during clinical trials

Public health impact

– Risk estimates during routine use would improve patient's decision to use product for end stage disease

Medical complexity

– Used in very ill patients

– Cancer is known risk factor for thrombosis

Feasibility

– Exposure easily detected because autologous

– Uptake limited late-stage cancer indication

Summary of Provenge Required Study

Safety issue	Cerebrovascular Events
Study Purpose	Assess signals of serious risk
Considerations	▪ Balance need for better safety data for patients decision making against clear clinical benefit ▪ Confounding must be addressed due to elevated baseline increased risk for thrombosis
Study design	Patient outcomes registry for cerebrovascular events

Summary

- Despite rigorous study prelicensure, postlicensure safety monitoring is necessary due to the known limitations of clinical trials
- FDA may require postmarketing studies when 3 criteria are fulfilled
  - New safety information
  - Safety issue cannot be evaluated in FDA's Sentinel system
  - Meets one of 3 study purposes
- Postmarketing study design should be tailored to answer the surveillance question and the needed degree of certainty

Thank You

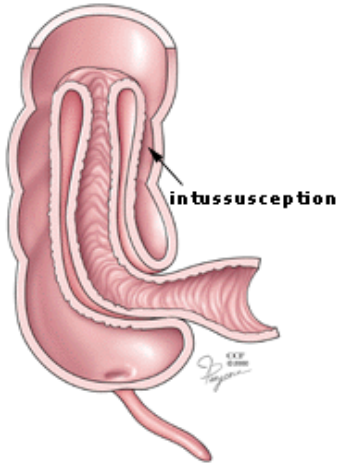
Resources

- FDA's acronym finder:
  - http://www.accessdata.fda.gov/scripts/cder/acronyms/index.cfm
- Complete list of U.S. licensed vaccines (labels, approval letters, reviews, telecons, etc):
  - http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM093833
- CBER's FDAAA Implementation page :
  - http://inside.fda.gov:9003/ProgramsInitiatives/Biologics/Review/UCM019696
- Postmarketing commitments and requirements (PMC versus PMR)
  - Draft Guidance for Industry
    - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf
  - Information on FDA website:
    - http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm
  - CBER's PMR/PMC Administrative Handling SOPP:
    - http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073513.htm
- REMS Draft Guidance Sept 2009:
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf

EXTRA SLIDES

Rotarix and Intussusception

- Rotarix is a live vaccine for preventing serious gastrointestinal infection with rotavirus



- Intussusception (bowel obstruction) has been an outcome of interest since the withdrawal of Rotashield 1999
  - Greatest risk 7 days after first dose Rotashield
  - ~1 excess case in 10,000 Rotashield recipients

- Rotarix licensed 2008 after >60,000 patients in clinical trials demonstrated no increased risk of intussusception
  - RR = 1.23 (95% CI: 0.41–3.90)

http://my.clevelandclinic.org/disorders/intussusception/hic_intussusception.aspx

Evaluating Intussusception After Rotarix

Index of Concern → **Study Design**

Strength of association

– Demonstrated risk in a prior vaccine

– No risk detected in clinical trials

Public health impact

– Universal routine vaccination

– Outcome is serious

Medical complexity

– Confounded by age

– Comparator group available

Feasibility

– Data are available

– Confirmation of exposure and outcome possible

From Safety Concern to Required Study

	Rotarix
Safety issue	Intussusception
Study Purpose	Assess a known serious risk
Considerations	▪ Low tolerance for serious outcome for an otherwise healthy infant population ▪ Rare outcome requires large sample size ▪ Substantial confounding by age
Study design	Observational cohort study in a large electronic database

Background Rates of Select Adverse Events

Predicted numbers of coincident, temporally associated events after a single dose of a hypothetical vaccine, based upon background incidence 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	1440	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)	014	0·98	575	Based upon UK background rate of 0·5 per 100 000 person-years (table 2)[28]

Lancet. 2009 December 19; 374(9707): 2115–2122. doi:10.1016/S0140-6736(09)61877-8.