The costs and effectiveness of large pre-licensure phase III clinical trials:

time for a new paradigm?"

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Disclosures

- I am a consultant for GSK Vaccines, Protein Sciences, Takeda and WHO.
- As a clinical trialist, I performed or participated in many of the trials I am going to discuss.

Overview

- The goal of phase three studies
- An historical perspective on the size of phase three clinical trials for vaccine licensure
- Large phase III safety trials – How well have we done?
- Large phase III efficacy trials - How well have we done?
- What are the financial and opportunity costs of mandating large phase III trials before licensure
- The alternatives:
  - The evolution of post-licensure safety surveillance
  - Epidemiologic disease surveillance infrastructure
  - The potential for further mutual regulatory reciprocity
  - What might a new paradigm look like?

Goals of Large Phase III trials
for vaccines

- Efficacy: Obtain a precise estimate of vaccine efficacy in a target population
  - To allow licensure
  - To inform public health decisions
  - To evaluate cost effectiveness
  - To prioritize introductions
- To assure the safety of the vaccine in the target population

Historical Trends in Phase III Trial Size

Year	Vaccine	Clinical Trial Size Phase III
1980	Hepatitis B inactivated	1,083[1]
1985	Hepatitis B recombinant	2,200[2]
1990	Hib (HbOC)	61,080
1993	DTaP	17,995[3]
2000	PCV7	37,868
2006	Rotarix	63,225
2006	Rotateq	34,035
2007	HPV (Gardasil)	17,662
2008	HPV (Cervarix)	16,162

1. Szmuness, Wolf, et al. "Hepatitis B vaccine: demonstration of efficacy in a controlled clinical trial in a high-risk population in the United States." *New England Journal of Medicine* 303.15 (1980): 833-841.
2. Zajac, B. A., et al. "Overview of clinical studies with hepatitis B vaccine made by recombinant DNA." *Journal of Infection* 13 (1986): 39-45.
3. Greco, Donato, et al. "A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis." *New England journal of medicine* 334.6 (1996): 341-349.

How is trial size determined?

- Initially sample sizes for large trials were based upon efficacy considerations and safety evaluation was a secondary concern
  - Hib efficacy trials – > 60,000 vaccinated children
  - Pneumococcal conjugate efficacy trials- PCV 7: > 37,000 children
- This changed following identification of the risk of intussusception for Rotashield rotavirus vaccine post licensure
  - Safety trials for GSK and Merck rotavirus vaccines were sized based upon the outcome of intussusception. > 35,000 vaccinees

Considerations of Statistical Power

Total Study Population Size Required to Detect a Selected Increased Levels of Risk

Control Incidence (person-yrs)	Study Population to Detect 2 Fold Increased Relative Risk	Study Population to Detect 3 Fold Increased Relative Risk	Study Population to Detect 5 Fold Increased Relative Risk
1/100	4,638	1,538	570
1/1000	47,036	15,670	5,870
1/10,000	471,000	156,992	58,866
1/100,000	4,710,650	1,570,208	588,822

Assuming the test and control group have a 1:1 ratio , that the background incidence in treated = incidence in controls, two tailed alpha=0.05, 80% power.

Strom, B.L., Pharmacoepidemiology, 2nd Ed., John Wiley and Sons, 1994

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Phase Three Safety and Efficacy Trials

SO HOW HAVE WE DONE?

Phase III **Safety** Trials
How well have we done?
Rotateq and Rotarix as examples

Vaccine	Clinical Trial Result for Intussusception Risk
Rotateq	Clinical Trial 34,035 infants **RR= 1.6** (95% CI= 0.4-6.4) "Met trial safety criteria" "No evidence of increased risk"[1]
Rotarix	Clinical Trial in 63,225 infants 6 cases in vaccinees, 7 in placebo **RR= 0.86** (P= ns) "No evidence of an increased risk" [2]

1. Vesikari, Timo, et al. "Safety and efficacy of a pentavalent human–bovine (WC3) reassortant rotavirus vaccine." *New England Journal of Medicine* 354.1 (2006): 23-33.
2. Ward, Richard L., David I. Bernstein, and Stanley Plotkin. "Rotarix: a rotavirus vaccine for the world." *Clinical Infectious Diseases* 48.2 (2009): 222-228.
3. Carlin, John B., et al. "Intussusception risk and disease prevention associated with rotavirus vaccines in Australia's national immunization program." *Clinical infectious diseases* 57.10 (2013): 1427-1434.

Phase III Safety Trials
How well have we done?
Rotateq and Rotarix as examples

Vaccine	Clinical Trial Result for Intussusception Risk	Intussusception Risk Post Licensure ≤ 7 days of Dose One Total Birth Cohort ~ 1 million
Rotateq	Clinical Trial 34,035 infants **RR= 1.6** (95% CI= 0.4-6.4) "Met trial safety criteria" "No evidence of increased risk"[1]	**RR= 9.9** 95% CI= 3.7–26.4[3]
Rotarix	Clinical Trial in 63,225 infants 6 cases in vaccinees, 7 in placebo **RR= 0.86** (P= ns) "No evidence of an increased risk" [2]	**RR= 6.8** 95% CI = 2.4–19.0;[3]

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Phase III **Efficacy** Trials
How well have we done?
PCV7 as an example

Outcome	Clinical Trial Result
Invasive Disease	93.9 %[1] (95% CI=79.6-98.5)
Otitis Media	7.0 %[1] (95% CI =4.1-9.7)
All Cause Pneumonia < 5 yo	6 %[2] (95% CI= -1.5 to 11%)
Cost Effectiveness Of Childhood Vaccination	US$ 80,000/ QALY[3]

1. Black, Steven, et al. "Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children." *PIDJ* 19.3 (2000): 187-195.
2. Black, Steven B., et al. "Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than five years of age for prevention of pneumonia." *PIDJ* 21.9 (2002): 810-815.
3. Ray T, Lieu T, Black S, et al. "Projected Cost Effectiveness of Pneumococcal Conjugate Vaccine in Infants and Young Children" JAMA 2000;283(11):1460-1468.
4. http://www.cdc.gov/pneumococcal/surveillance.html
5. Grijalva, Carlos G., et al. "National impact of universal childhood immunization with pneumococcal conjugate vaccine on outpatient medical care visits in the United States." *Pediatrics* 118.3 (2006): 865-873.
6. Grijalva, Carlos G., et al. "Decline in pneumonia admissions after routine childhood immunization with PCVin the USA: a time-series analysis." *Lancet* 369.9568 (2007): 1179-1186.
7. Ray, G. Thomas, et al. "Cost-effectiveness of pneumococcal conjugate vaccine: evidence from the first 5 years of use in the United States incorporating herd effects." *PIDJI* 25.6 (2006): 494-501.

Phase III Efficacy Trials
How well have we done?
PCV7 as an example

Outcome	Clinical Trial Result	Post Introduction Result
Invasive Disease	93.9 %[1] (95% CI=79.6-98.5)	**> 99 %[4]**
Otitis Media	7.0 %[1] (95% CI =4.1-9.7)	20%[5] (95% CI= 4-34%)
All Cause Pneumonia < 5 yo	6 %[2] (95% CI= -1.5 to 11%)	39%[6] (95% CI 22–52)
Cost Effectiveness Of Childhood Vaccination	US$ 80,000/ QALY[3]	US$7500/ QALY[7]

1. Black, Steven, et al. "Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children." *PIDJ* 19.3 (2000): 187-195.
2. Black, Steven B., et al. "Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than five years of age for prevention of pneumonia." *PIDJ* 21.9 (2002): 810-815.
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Other Examples

- Rotavirus effectiveness
- Acellular Pertussis Effectiveness

Rotavirus Vaccine Effectiveness

Vaccine	Primary Efficacy Trial Severe Disease	Other Sites
Pentavalent Rotavirus (Merck)	98% (88.3-100%)[1]	Asia: 48.3% (22.3-66.1%)[2]

1. Vesikari et al NEJM 2006; 354:23-33. 2. Zaman et al *Lancet* 2010; 376: 615–23

Pertussis Vaccine Effectiveness

- Acellular pertussis vaccines were evaluated in numerous large phase three trials in Europe leading to licensure of several vaccines based upon short term efficacy

- Post licensure follow up has revealed
  - A lack of duration of protection
  - Lack of ability to prevent transmission

What are the financial and opportunity costs of the current system?

Time and financial cost

- Current cost for large phase III trials is estimated to be up to 150 million Euros.
- Time from inception to completion is 4-5 years .

Impact

- **Opportunity Cost:** Manufacturers will only consider bringing a very few potential candidates into clinical development
  - This increases risk of vaccine development for each manufacturer and likely increases cost for successful vaccines
  - Risk limits manufacturer interest and investment
  - Limiting development decreases the number of vaccines available to prevent disease
- Time lost: There is a delay in the time until a beneficial vaccine becomes available.
- Risk of a false assessment – rejecting a useful vaccine

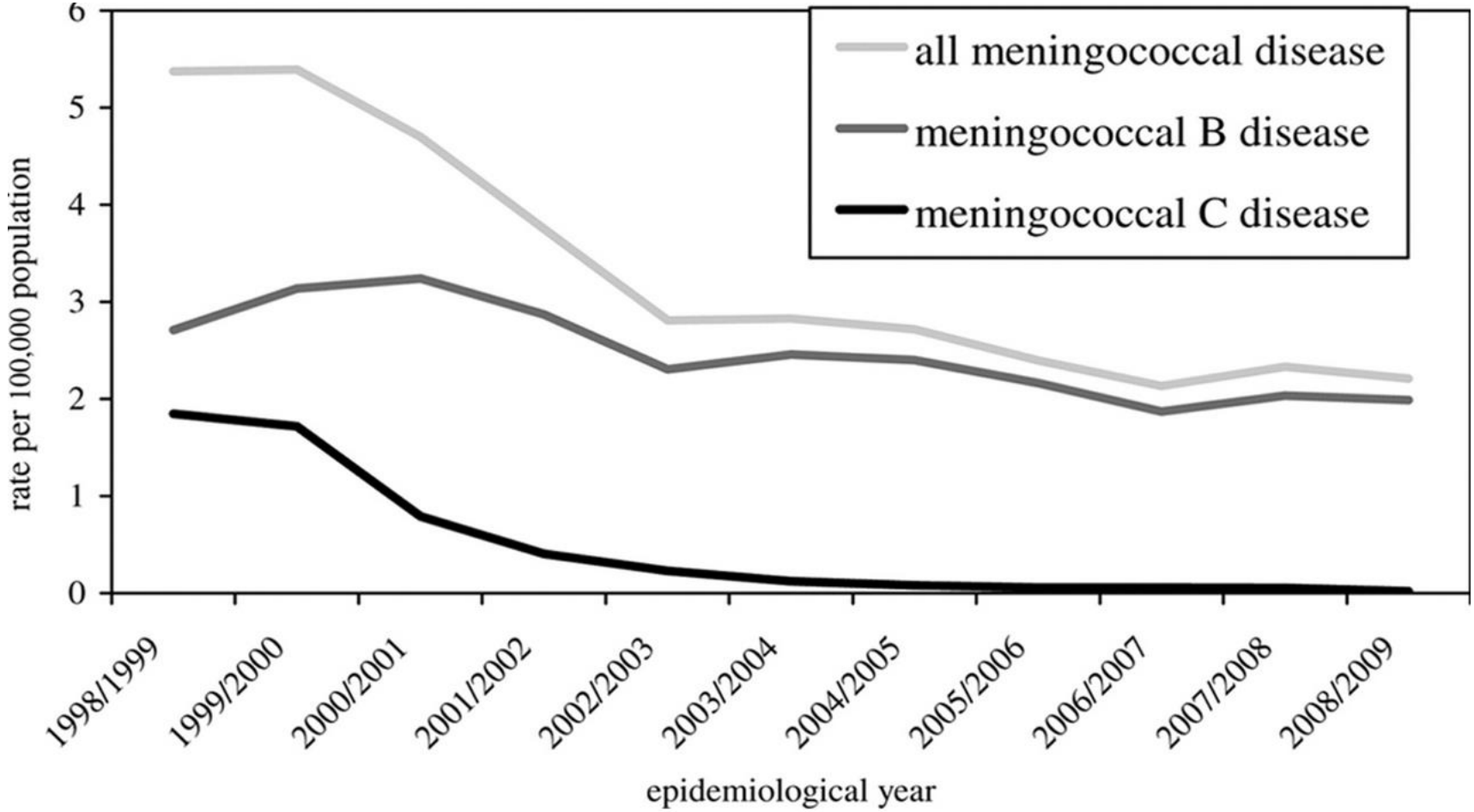
Summary so far

- In the last three decades, the size of phase III trials has increased dramatically
  - This has caused
    - An increase in the time to market and the cost of pre-licensure evaluation
    - A reduction and slowing in the vaccine development pipeline
  - This has not resulted in a concomitant
    - Increase in the predictive value of pre-licensure evaluations of efficacy or cost-effectiveness
    - A dramatic increase in our ability to assess safety

What resources might an alternative approach employ?

- Efficacy: Extensive disease surveillance networks exist in the US, UK, several countries in Europe, Asia, and Latin America.
  - **Example**: the approach used by the UK for Men C
- Safety
  - More rapid and comprehensive techniques
    - VSD routine, rapid cycle, outcome scanning
    - ADVANCE in Europe
    - Beginning network within PAHO

Skipping Phase III: Men C Epidemiology in the UK post introduction Men C conjugate

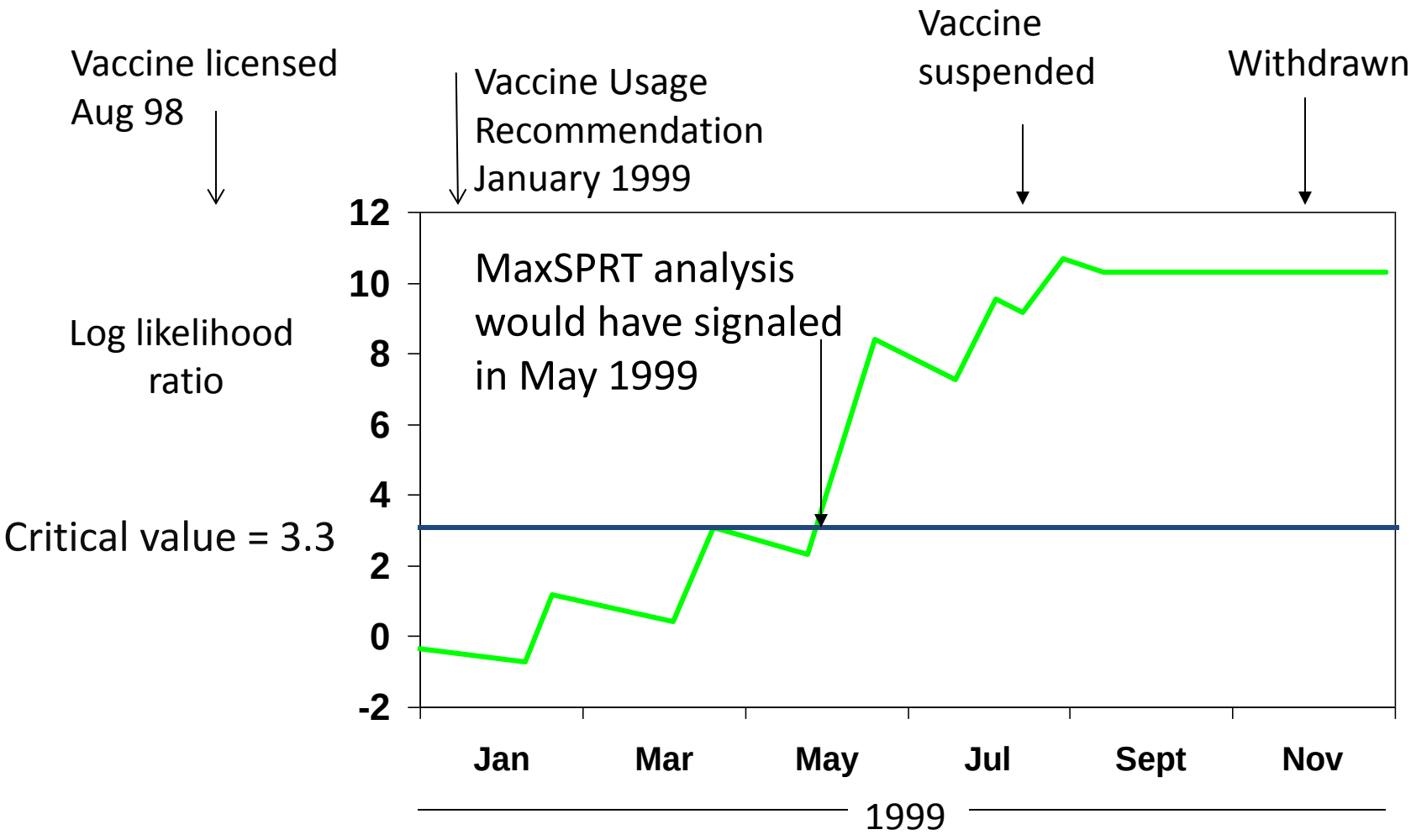


http://cvi.asm.org/content/17/5/840/F1.large.jpg

VSD Rapid Cycle Analysis (RCA)

- Sequential monitoring of adverse events following immunization
  - Automated weekly updates of files
- Basic technique
  - For each vaccine, choose specific outcomes to monitor
  - Each week, evaluate the number of events in vaccinated persons
  - Compare it to the expected number of events based on a comparison group
  - Adjust for multiple comparisons

Rapid Cycle Analysis Example:
Rotavirus vaccine and intussusception (historical analysis)



Thanks to Roger Baxter & Tracy Lieu for slide

Outcome Based Surveillance (OBS)

A Technique for Surveillance on a Large Number of Outcomes

- RCA requires that you pre-specify outcomes of interest
- OBS makes it possible to do surveillance on large numbers of outcomes
- Can use all ICD9/ICD10 codes alone or in groupings

Thanks to Roger Baxter for slide

Hepatitis A vaccine: ED Visits

Elevated Odds Ratios, p< 0.01

Risk Interval	Diagnosis	Risk Interval Cases	Rest of 9 months Cases	Odds Ratio	95% CI	P-Value
3 Days	Syncope	37	1417	2.29	(1.63,3.15)	<.001
	Skin infections	48	1825	2.15	(1.59,2.84)	<.001
2 Weeks	Other skin disorders	111	1347	1.34	(1.10,1.62)	0.004
	Allergic reactions	249	3093	1.32	(1.16,1.50)	<.001
	Fever	739	9592	1.22	(1.13,1.31)	<.001
6 Weeks	Other skin disorders	299	1160	1.24	(1.09,1.41)	0.001
	Fever	1963	8370	1.10	(1.04,1.15)	<.001
	Respiratory infections	3303	15555	1.05	(1.02,1.10)	0.006

Thanks to Roger Baxter for slide

Another issue

- Currently there is lack of mutual recognition by US regulatory authorities and the EMA.
- This can lead to duplication of large studies for US submission and delays in vaccine availability.
  - The is very inefficient especially for well characterized vaccine (increase in valency, known platform, etc.)

And yet Another issue

- Phase III trials have tended to be performed in developed country settings in Europe or the US.
- The morbidity and mortality associated with diseases such as rotavirus is in poor LMICs
- The results of RCTs are difficult to generalize
  - Difference in impact on mortality following PCV in Gambia versus US
- Vaccine introduction “vaccine probe” demonstration studies (much as was done for Men C in the UK) might be better suited to define impact in LMIC

Putting this all together: possible approaches

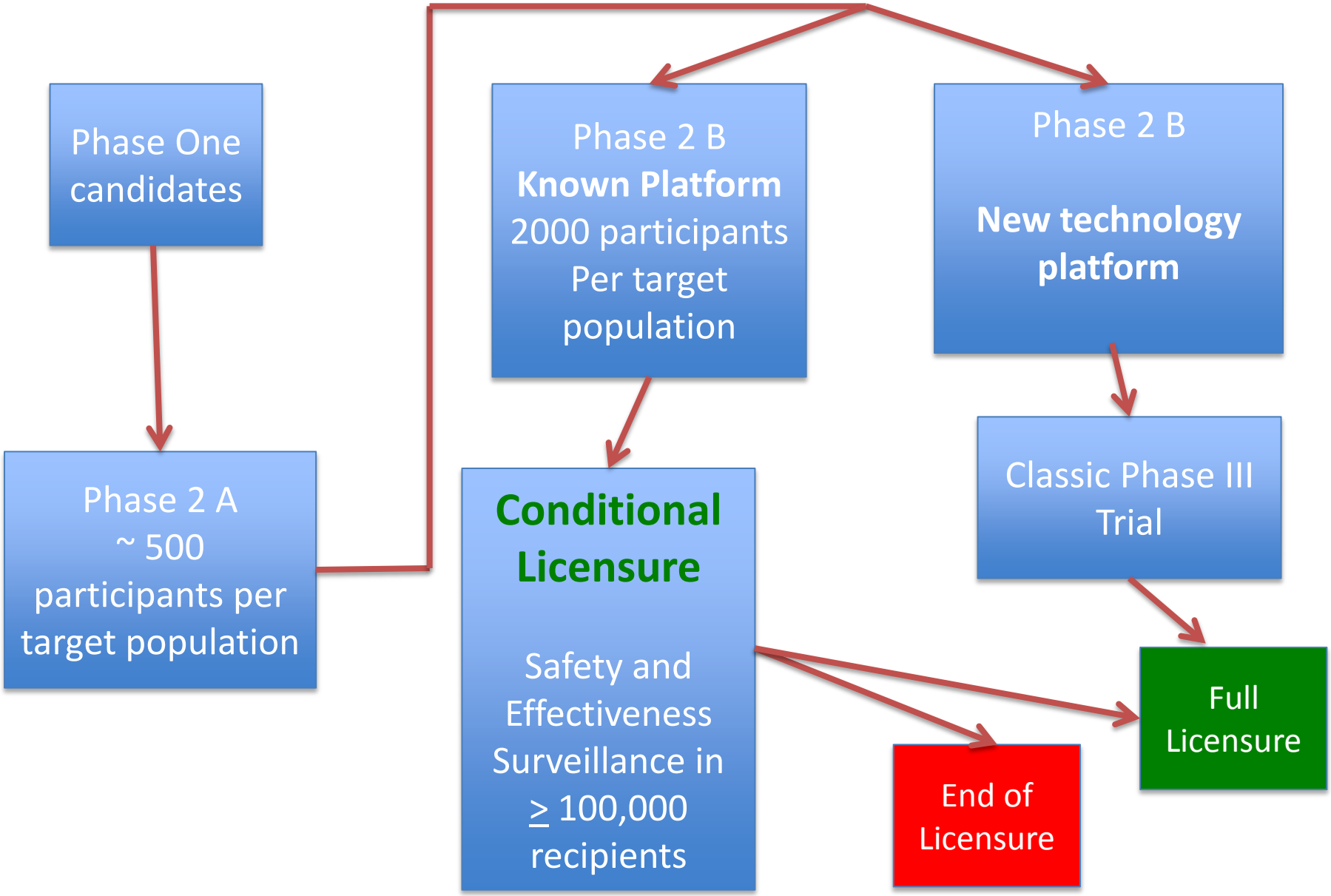
- “Conditional” licensure of vaccines

- Regulatory harmonization and increased mutual recognition by the EU and FDA.

One possible approach: Conditional Licensure

- “Conditional” licensure of vaccines could be considered following phase 2b studies with permanent licensure linked to results of mandated safety evaluations within a two year period.
- Manufacturers could charge for vaccine and the vaccine would be approved for use during this period
- A conditional licensure fee could be assessed to fund the post-conditional licensure evaluations.
- The relevant regulatory agency would review data at the end of the conditional period to consider routine licensure and recommending bodies could adjust vaccine use recommendations if warranted.

Conditional Licensure Schematic



A different path for “known” entities

- For vaccines where there is only a change in valency (PCV7 to PCV13 for example)
- For vaccines where the platform is well known
  - CRM or tetanus conjugates

- One could envision a much reduced pre-licensure requirement augmented by post licensure surveillance for safety and effectiveness.

Another option
Increased Reciprocity and Harmonization

- Currently, the FDA, EMA and others set trial requirements and path to licensure separately
- This can lead to different population and study requirements which can dictate that two studies be performed.
- This introduces resource and time constraints and time delays to vaccine availability.

What are the barriers?

- Inertia
- False assurance that “large” RCTs provide a “better” assessment of safety and efficacy.
  - RCTs do indeed avoid some potential biases
  - However, they are limited in scope, have limited power, are time consuming and have difficulty assessing
    - Indirect effects
    - Effects in special populations which may be excluded from phase three studies.

What is the risk of the status quo?

- Opportunity cost for vaccine development
  - Limitation of pipeline
  - Focus on “high ROI” targets by manufacturers
- False conclusions regarding potential impact from RCT
  - Inappropriate CE analysis
  - Over or underestimation of impact in target population

The challenge

I would propose that stakeholders review the track record of the past three decades, the new post licensure technologies available and the negative impact of the requirement for large phase three studies on vaccine development pipelines and timelines and consider how our current approach might be improved.

Thank you.