

Maintaining the Future of Immunizations

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Disclosures

- I have received honoraria from Pfizer Vaccines and Sanofi Pasteur for service as a scientific consultant.
 - My honoraria is donated to the IAC
- I do NOT intend to discuss an unapproved or investigative use of a commercial product/device in my presentation.

Disclaimer

The opinions expressed in this presentation are solely those of the presenter and do not necessarily represent the official positions of the Immunization Action Coalition, or the National Adult and Influenza Immunization Summit

Outline

- Review the historical environment of vaccine research and development
- Review the process of getting a new vaccine to market
- Discuss the changing environment for vaccine research and development

A perspective on the evolution of the vaccine environment

- Pre-1980s, the “public health” years...
- 1980s to 2010, the “ROI” years...
- 2010 to the near future
 - A rocky path ahead?
 - How does the immunization community continue to evolve and recognize that we are all in this together...

Evolution of vaccine R & D environment over the years – pre-1980, the “public health” years

- No strong leadership to recommend use of vaccines
- Vaccines seen as a public health good
 - Vaccine prices were low
 - No significant return on investment to vaccine manufacturers
 - No commitment to invest in vaccines and vaccination programs to improve prevention
 - Liability to manufacturers real and costly, leading to crisis in the early 1980s
- Manufacturers beginning to leave vaccine R & D

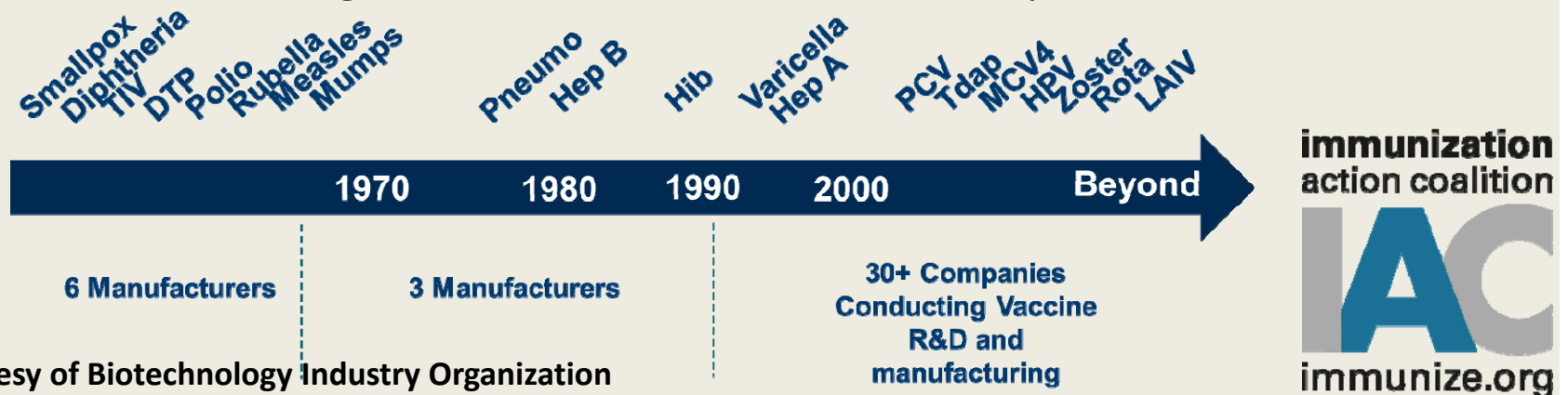
Evolution of vaccine R & D environment over the years – 1980s to 2010, the “ROI” years

- Vaccines seen as good public health value AND good commercial investments
 - Vaccination programs developed to support use of vaccines
 - Leadership commitment to address unmet medical need by preventing disease via immunization
 - Liability to manufacturers and providers ameliorated with the Vaccine Injury Compensation Program
 - New vaccines introduced into programs were paid at prices that were comparable to therapeutic interventions
 - That allowed Returns on Investment (ROI)

Evolution of vaccine R & D environment over the years – 1980s to 2010, the “ROI” years

These Changes Helped Stimulate New Manufacturers to enter a Growing Market

- Over the last 2 decades, more than a dozen new vaccines have been introduced and the number of companies developing products has increased.
- There was re-investment of profits from new vaccines into improving current vaccines and developing new ones as there was now comparable ROI relative to new biologicals and pharmaceuticals.
- Large and small companies, as well as investors, are continually assessing these ROI's and making decisions on resource allocation priorities.



Graphic courtesy of Biotechnology Industry Organization

Evolution of vaccine R & D environment over the years – 1980s to 2010, the “ROI” years

- A positive ROI assessment leads to a win-win situation
 - We have seen drops in infectious diseases as a result of new vaccines, such as pneumococcal conjugate vaccine, rotavirus vaccine, varicella vaccine, and HPV vaccine, when we can get high coverage
- And we see new vaccines in the pipeline, and new delivery technologies, when the ROI assessment shows promise

Evolution of vaccine R & D environment over the years – 1980s to 2010, the “ROI” years

Targets for vaccine development include traditional viruses and bacteria, and also non-communicable diseases. Vaccines may become a key part of anti-microbial stewardship programs.

Over the next decade, we may see:

New Vaccines for Global Health	New Adult or Pediatric Vaccines	New Healthcare-acquired Infection Vaccines
Malaria	Universal influenza	Clostridium difficile
Dengue	Meningococcal A,C, Y, W-135	Staphylococcus aureus
Ebola	Meningococcal B	Tuberculosis
Tuberculosis	CMV	Pseudomonas aeruginosa
Chikungunya	RSV	Candida
Zika	Streptococcus vaccines	
	Norovirus	
	New combinations of existing pediatric vaccines	

BUT...



Evolution of vaccination paradigms over the years – Now and Beyond...

- Challenges are showing up
 - To vaccine development for prevalent diseases (eg, CMV, RSV, Group A Strep, etc)
 - To vaccine development for emerging diseases (eg, Ebola, MERS, Zika, etc)
 - To developing improved versions of available vaccines (eg, pertussis, influenza, etc)
 - To applying scientific advances to develop new vaccines and improve existing vaccines (eg, novel adjuvants, combination vaccines, novel delivery routes, greater thermostability, etc)

We are all in this together? Right?

- We must now think about how we can align both private and public sector stakeholders to address vaccinology/vaccine gaps and share risks
- If we fail, promising scientific progress will not be effectively translated into public health progress
- Our ability to prepare for, and respond to, emerging public health threats, will be greatly diminished

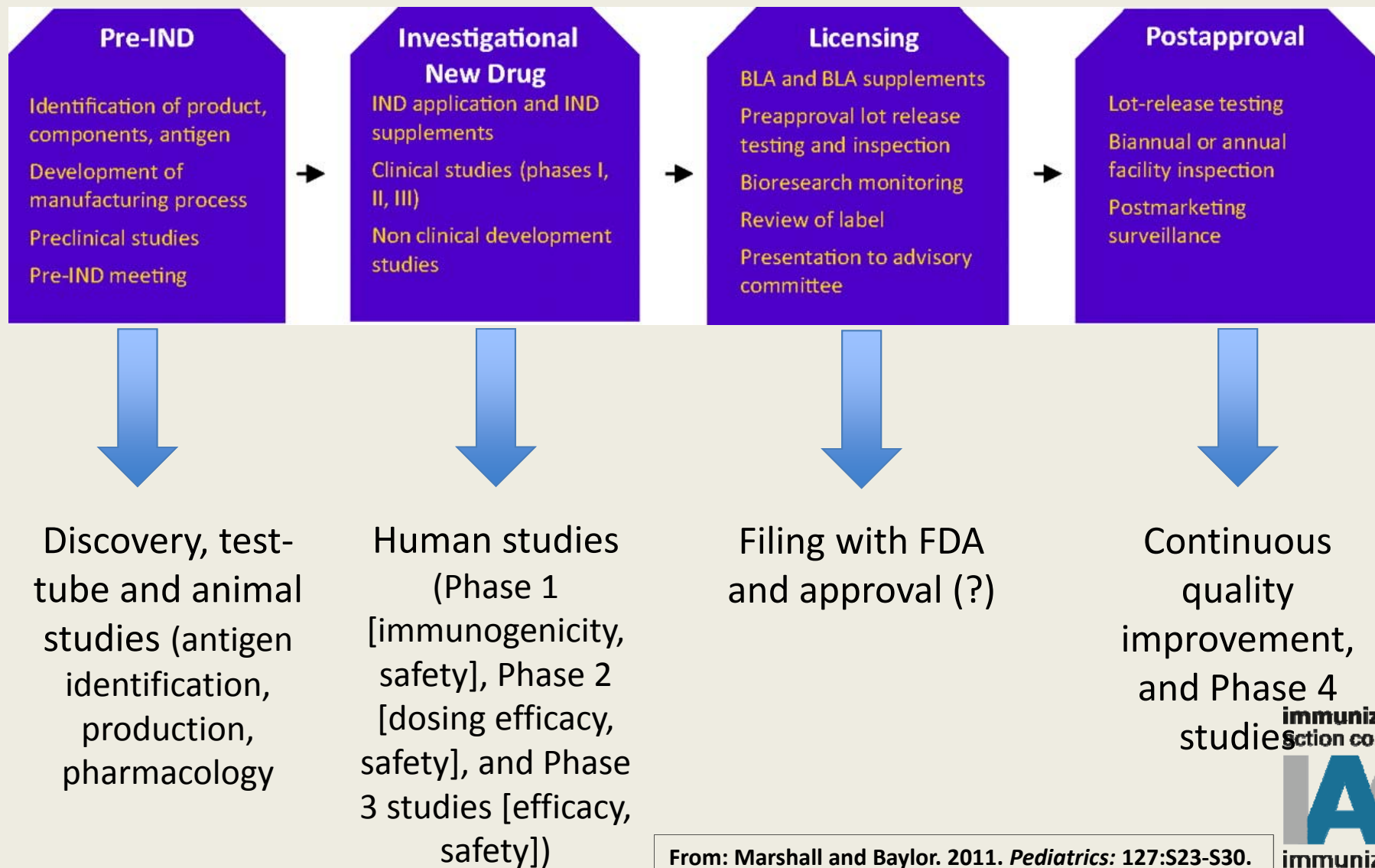
Vaccine development is not simple

- Vaccine development can take from 15 to 20 years and cost as much as US\$800 million or more.¹
 - Including costs to build a vaccine manufacturing facility and maintain equipment, that figure can rise to well over USD 1 billion.²
- Clinical development involves a large number of subjects.
 - Vaccines must meet a high threshold of efficacy and safety.
- Manufacturing processes must meet stringent quality control criteria.
- Final filing initiates an in-depth evaluation by governmental regulatory authorities.

1. Plotkin SA. Health Aff. 2005;24(3):631–634.

2. Center for Global Development. Making Markets for Vaccines: Ideas to Action. Center for Global Development; 2005.

Vaccine development is not simple



From: Marshall and Baylor. 2011. *Pediatrics*: 127:S23-S30.

The Challenge of Evolving Vaccination Paradigms – Now and Beyond...

- New vaccine targets are more difficult – “the easy ones are all done”
 - Biological risks/uncertainties are now greater - complex natural histories, incompletely understood pathogenesis, lack of natural immunity to natural infection, lack of available immune correlate of protection, safety concerns
 - Clinical trials are consequently more complicated and efficacy trials are not always possible (eg. Zika)
 - Very difficult to detect rare events
- Development risks/uncertainties are more complex - populations, pathways, endpoints, duration and scope of clinical trials needed to support licensure

From: Feinberg, M. Presentation to NVAC, February 2016

The Challenge of Evolving Vaccination Paradigms – Now and Beyond...(cont.)

- Programmatic risks/uncertainties have increased - lack of “line of sight” from discovery to development to licensure to recommendation to reimbursement to implementation to in-use monitoring/follow-up [safety and duration of efficacy] to population impact demonstration
- Significant upfront investment at risk needed - efficacy trials need to be enrolled before all supporting data is in, manufacturing facilities before efficacy is demonstrated and probability of licensure
- Long timelines for development exacerbate impact of uncertainties (eg, changing epidemiology or priority placed on prevention by policy makers and the public)

From: Feinberg, M. Presentation to NVAC, February 2016

The Challenge of Evolving Vaccination Paradigms – Now and Beyond...(cont.)

- If policy makers and payers are not willing to pay higher prices for improved vaccines (eg, enhanced efficacy, combination, improved presentation, delivery), there is no possibility of realizing a return on investment in any traditional commercial model
- Renewed focus on the price of vaccines, as opposed to the value...

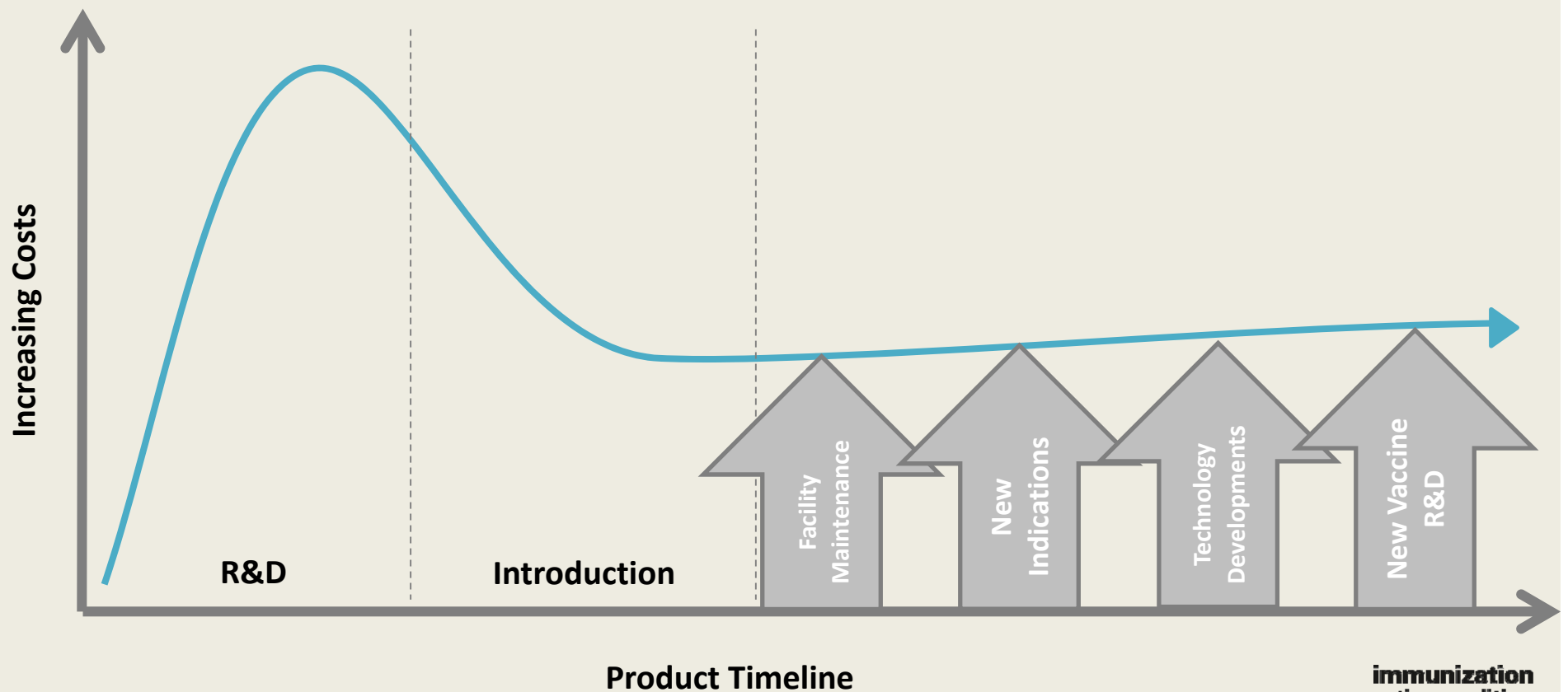
Tom Frieden, CDC Director, to ACIP...

- The development and availability of newer vaccines since VFC began 17 years ago has expanded the prevention impact of our programs, but most newer products and new formulations of old products have come at substantially higher prices. We have also seen prices rising after initial federal contracts were set, and prices failing to fall when vaccine schedules are compressed or a second vaccine manufacturer enters the market. These are not things that we would expect under normal economic conditions.
- At a time when budgets are under intense review, ACIP considerations and the public value and risk-benefit ratios of various vaccine recommendations are made even more difficult with the rising prices of vaccines. While the budget pressures I mentioned are not unique to CDC or to immunization, I know that ACIP members have been wrestling with complex policy decisions. Certainly, if vaccine prices were coming down instead of going up or were responding as we would expect them to under market conditions, there would be an easier set of decisions

The Challenge of Evolving Vaccination Paradigms – Now and Beyond...(cont.)

- Renewed focus on the price of vaccines, as opposed to the value – but costs HAVE to go up, and hence prices
 - Constant quality control and FDA-required upgrades of facilities
 - Constant requirement to assess and improve current vaccines
 - New clinical development programs
 - Large clinical trial sizes
 - Post-marketing requirements for safety

Vaccines Present a Unique Need for Continuous Investment



Graphic courtesy of Biotechnology Industry Organization

Expectations for Vaccine Pricing

- **The U.S healthcare system and workforce are more expensive and better paid.**
 - Thus existing vaccines come out as cost effective and usually cost saving over time.
- **The US healthcare market drives the innovation engine of the world.**
 - The US sits at the top of the tiered pricing hierarchy
 - Pricing pressure in the US to drop prices would compress the value of the global market for vaccines that likely will not be picked up by other countries
 - Note that new vaccines do not generally come from Europe unless they have a viable market in the US
- **Recall that conversely, many other consumables (eg. gas, produce) are much cheaper in the US as compared to other countries. Should global pricing not be based on ability to pay?**

The Challenge of Evolving Vaccination Paradigms – Now and Beyond...(cont.)

- Challenges to the ROI years are showing up
 - Under-developed vaccination programs, eg adults!
 - Remember that ROI is dependent on market size
 - Example: relative success of influenza and Tdap vaccination during pregnancy has stimulated development of new vaccines targeted at maternal immunization, such as GBS and RSV
- Increased concerns over safety
 - Increased risk management/risk communications issue for providers and patients
 - What's the impact on vaccine acceptance? And hence ROI?
 - Spillover into regulatory? How will new vaccine technology be approved? Detection of rare event difficult...

The Challenge of Evolving Vaccination Paradigms – Now and Beyond...(cont.)

- And will a vaccine get a recommendation?!
 - It is now difficult to predict whether a new vaccine will achieve a “use” recommendation
 - Focus on medical necessity in past years is now replaced with a focus on cost effectiveness (ACIP has much power in the US due to ACA)
 - Vaccines that clearly qualify for a “routine” recommendation are mostly done; new vaccines now prevent diseases with low incidence, eg meningococcal disease
 - Cost of R & D is now very high
 - Phase III trials are large and complicated
 - Manufacturing facility needs to be built prior to the recommendation

Why are clinical trials getting more expensive?

- **The demands of the regulatory agencies are increasing in terms of data requested, populations covered.**
 - For example, the need (quite justified) to be powered for race differences or underlying conditions
- **Trials are more likely to be global from the beginning so the upfront early R&D costs are higher before you launch and start to garner revenue.**
 - more clinical trials monitors, more complex protocols as the concomitant use is more complex.
- **Regulatory filing both in the US and internationally is more expensive.**
- **Disease epidemiology of newer targets is more sporadic and of lower incidence forcing clinical trial size to be bigger.**
- **The rare adverse event...**

Number of subjects enrolled in pivotal vaccine efficacy clinical trials

Trial	Number subjects enrolled	Year trial completed
PCV7	~38,000	1998
HPV4	~18,000	2004
HPV4	~19,000	2005
Rotavirus (pentavalent)	~70,000	2006
Influenza high dose	~32,000	2013
PCV13 (CAPiTA)	~85,000	2014
Dengue	~40,000	2014

Evolution of vaccination paradigms over the years – Now and Beyond...

Uncertainty over a vaccine use recommendation combined with increasing resource intensity (fiscal and otherwise) of development, has increased the risk associated with vaccine R & D

So where does that leave us? Aren't we in this together?

- Academic institutions may start basic research into new vaccines but partnership with a large manufacturer is needed to scale up production
- There is a high barrier to entry for new manufacturers
 - They will need partners with competency
 - Joint ventures/partnerships are increasingly important in investment decisions
 - Or their project may be sold to a large multinational, who has to satisfy its investors
 - And there is internal competition for dollars

So where does that leave us? Aren't we in this together?

- Most vaccine companies are publicly traded and ROI is a major driver for strategic investment
 - A medical need is no longer enough to drive investment, there has to be an expected ROI
 - The availability and size of the market for the vaccine, if it is licensed, will determine ROI
- Decisions to develop a new vaccine are no longer based on “just” medical and public health need
 - Will national governments recommend the vaccine?
 - Will there be public funding for the vaccine?
 - Is the price controlled?
 - What else is already in the market?
 - Relying on the private market for revenue is insufficient for investment purposes

So where does that leave us?

- And the investment decision WILL compete for resources with other potentially more profitable products, which may have bigger revenues
 - Significant pressures exist for maximizing pipeline productivity and value, with other projects with higher and faster potential return on investment (eg, novel biologics)
 - In this environment, the impact of opportunity costs is often greater than those of direct costs
- Ultimately, investment in development in new vaccines and technology will occur where there is a commercial reason to do so.

How can we all get together to keep preventing diseases through vaccination?

- Strengthen/advance regulatory science and regulatory policy
 - To allow for innovative clinical trial designs that shorten development timelines and reduce costs without impacting safety and efficacy
 - To identify the potential basis for licensure and clinical endpoints that will be used by regulators to assess vaccine efficacy, and the regulatory considerations for novel vaccine innovations
 - Proactively engage all stakeholders on new vaccine technology
 - Need balance on safety and efficacy end points

How can we all get together to keep preventing diseases through vaccination?

- Establish clear transparent recommendation processes and regular dialogue between stakeholders and manufacturers during all phases of development
 - Need dialogue on which vaccines are considered to address unmet medical/public health need – prioritization of the key pathogens?
 - How will cost effectiveness come into play?

How can we all get together to keep preventing diseases through vaccination?

- Improve vaccine science
 - To advance understanding of epidemiology and biology of prioritized diseases to fill in knowledge gaps, develop essential enabling tools (eg, case definitions and validated assays) and contribute to robust vaccine design and clinical trial design
- ACIP Policy Recommendation
 - Provide a reasonable expectation for a favorable recommendation and public sector funding if the target vaccine is developed
- Explore new development partnerships between private and public sector entities to advance vaccine innovation

So, how can we all get together to keep preventing diseases through vaccination?

- Return on investment needs to be comparable to other therapeutic areas to encourage continued participation in vaccine science, and R & D
- Improve coverage rates in the adult and pregnancy platforms to drive a market
 - Communicate on the known benefits of vaccination for adults and pregnant women
 - Improve access to vaccines for all
 - All providers must give strong recommendations to all patients

We ARE all in this together....

- For the future to remain positive, there must be increased cooperation and communication between the public and private sector
- Working together, all stakeholders can succeed
- In order to work together, the value, and the needs, of all partners have to be understood, recognized, and integrated.

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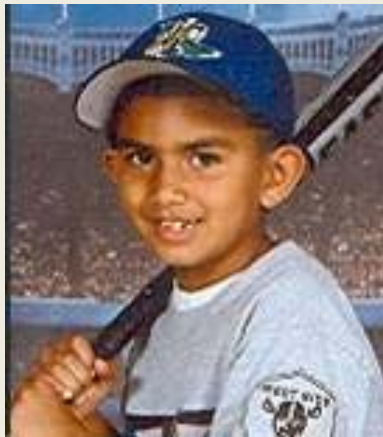


Amanda, died at age 4½ yrs from influenza

Why do we immunize against influenza?



Breanne, died at age 15 mos from influenza complications



Lucio, died at age 8 yrs from influenza complications



Alana, died at age 5½ yrs from influenza



Barry, a veteran fire-fighter, died at age 44 yrs from influenza

Slide Courtesy of Families Fighting Flu

Thank You!