

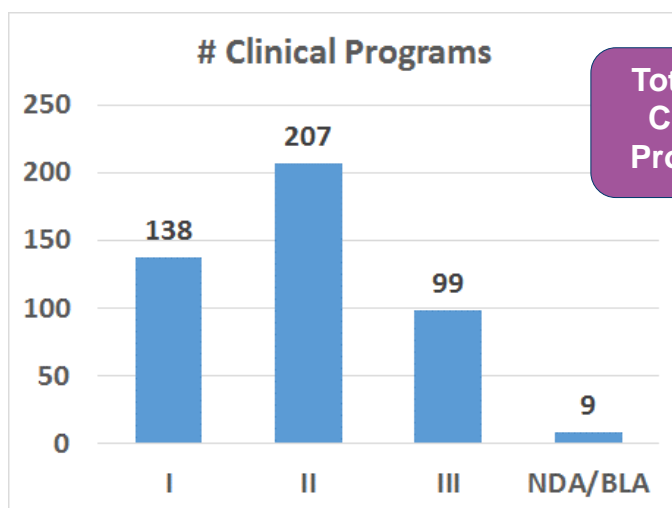
New Vaccines on the Horizon: The Clinical-Stage Pipeline

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Kelly Cappio
Director
Vaccines & Biodefense Policy
kcappio@bio.org



Infectious Disease Pipeline



Source: BIO Industry Analysis, BioMedTracker, April 2016

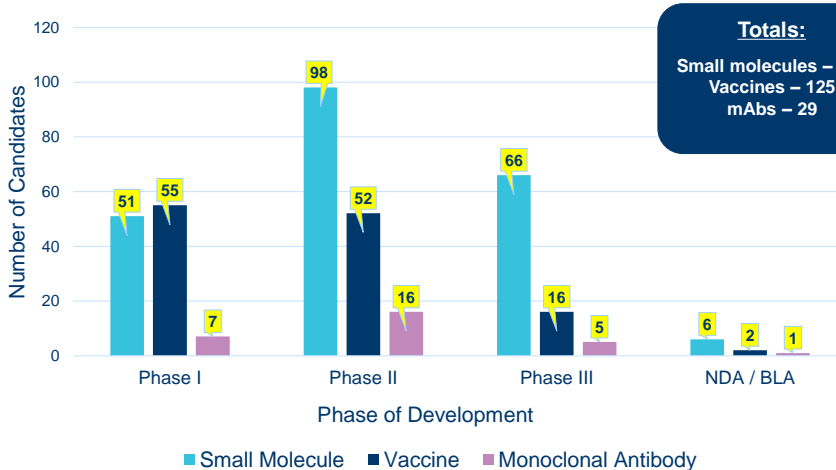
Infectious Disease Pipeline By Target

Indication_Name	I	II	III	NDA/BLA	Total
Hepatitis C (HCV) (Antiviral)	16	30	8	1	55
HIV / AIDS	13	19	13	0	45
Skin and Skin-Structure Infections (Antibacterial)	2	11	9	0	22
Urinary Tract and Reproductive Tract Infections (A	5	7	8	0	20
Hepatitis B (HBV) Treatment (Antiviral)	6	12	1	1	20
Pandemic Influenza Vaccines	14	5	0	0	19
Influenza therapeutics (excluding vaccines)	5	10	3	0	18
Clostridium difficile-Associated Diarrhea/Infection	2	9	4	1	16
Staphylococcal Vaccines and Other Staphylococ	7	8	0	0	15
Respiratory Syncytial Virus (RSV)	4	8	2	0	14
Seasonal Influenza Vaccines	3	9	2	0	14
Malaria	4	6	2	1	13
Tuberculosis	4	6	2	0	12
Hospital Acquired (Nosocomial) Pneumonia (HAP	0	3	9	0	12
Fungal Infections - Non-Systemic	2	7	1	0	10
Ebola	4	3	3	0	10



Source: BIO Industry Analysis, BioMedTracker, April 2016

Infectious Disease Pipeline by Modality (type of product)



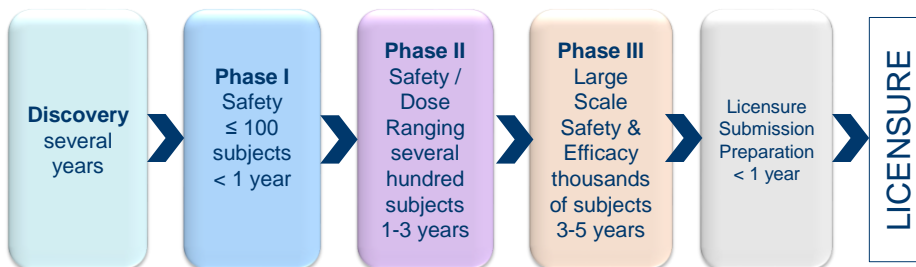
Source: BIO Industry Analysis, BioMedTracker, April 2016

Decision to Pursue New Vaccines Has Numerous Criteria

- Vaccine companies assess new vaccine targets based on general criteria used for all biopharmaceutical investments:
 - Unmet medical and public health need
 - Scientific feasibility
 - Ability to scale up production to meet demand
 - Cost and time to develop
 - Global burden of disease
 - Treatment availability
 - Market size
 - Potential revenue
 - Fit with the company's existing portfolio or platform
 - Status of intellectual property
- Development process for vaccines is unique. It is also long, highly capital intensive, and risky.
- The science is complex. The "low-hanging fruit" has been picked.



Vaccine Development Process



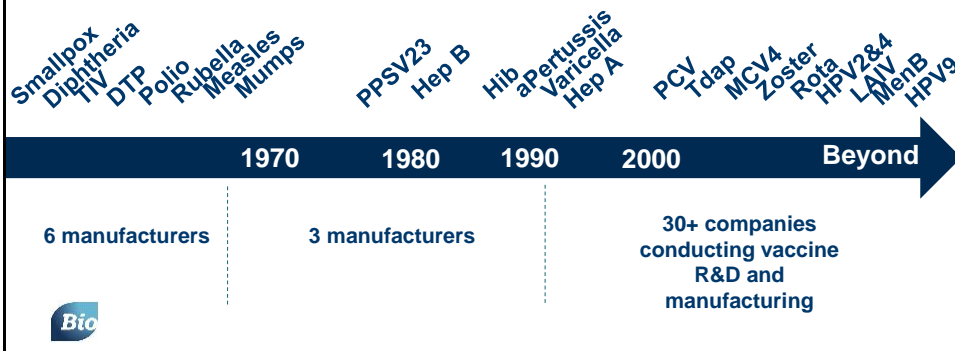
On average, vaccine development requires **10-15 years** and total development costs can reach **\$1 billion**.



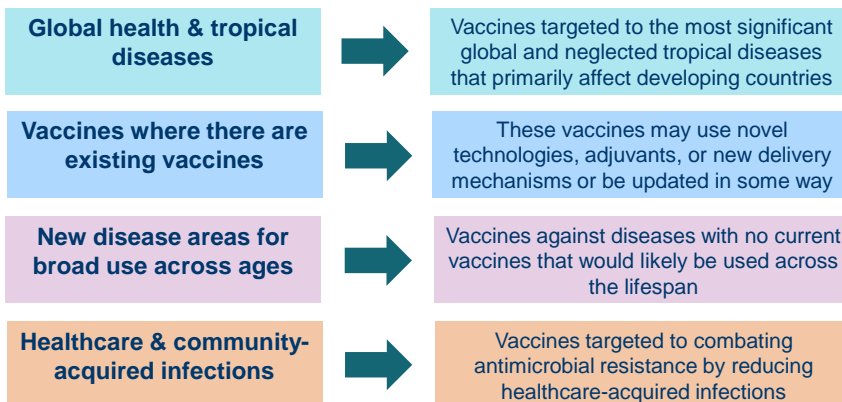
Source: PhRMA Vaccine Fact Book 2013

Changes to Landscape Have Helped Stimulate New Company Entrants into Vaccine Development

- Over the last 2 decades, more than a dozen new vaccines have been introduced and the number of companies developing products has increased.
- Companies can increase investment in vaccines because new vaccines can often demonstrate comparable returns on investment (ROI) relative to new biologicals and pharmaceuticals.
- Large and small companies, as well as investors, are continually assessing ROI and opportunity costs, and making decisions on resource allocation priorities.



4 Areas of Vaccine Development with Implications for Adult IZ Programs



Global Health & Tropical Diseases

- Vaccines targeted to global diseases affecting many countries, primarily developing ones; many of these vaccines may be used as travel vaccines in developed countries.
- R&D for these vaccines is generally funded through global public-private partnerships, or Product Development Partnerships (PDPs) with the Bill & Melinda Gates Foundation, PATH, Wellcome Trust, the Global Fund and other global funding partners.
- In addition to long-standing Neglected Tropical Diseases (NTDs), emerging infectious diseases, such as Ebola and Zika, also fall into this category.
- These vaccines are considered high volume and are typically made available through programs like UNICEF, PAHO and Gavi or US government programs.
- Investment is required in large-scale manufacturing facilities in preparation for global demand.



Global Health & Tropical Diseases – Vaccines in Development

Target	Clinical-Stage Pipeline				
	Ph 1	Ph 2	Ph 3	BLA	Total
<i>Malaria</i>	3				3
<i>Tuberculosis</i>	3	4			7
<i>HIV</i>	3	1			4
<i>Dengue</i>	5	2	1		8
<i>Ebola</i>	2		3		5
<i>Pandemic Influenza</i>	14	4			18
<i>MERS</i>	1				1
<i>Leishmaniasis</i>	1				1
			4		47



Sources: BIO Industry Analysis, BioMedTracker, April 2016;
Dengue Vaccine Initiative

New Vaccines in Development Where There Are Existing Vaccines

- Many vaccines in this category use novel technologies, such as novel adjuvants, in their development, production, or delivery.
- Some of the vaccines will be targeted to specific populations or sub-sets of existing recommended populations, cover additional strains, or help with an emergency response in the event of a pandemic / outbreak.
- This category could include clinical activities undertaken by vaccine companies in support of maternal immunization recommendations.
- In addition, this category could include improvements to vaccine storage or delivery, for example, improved heat stability, patches, use in multiple injection technologies, nasal spray delivery, etc.



New Vaccines in Development Where There Are Existing Vaccines

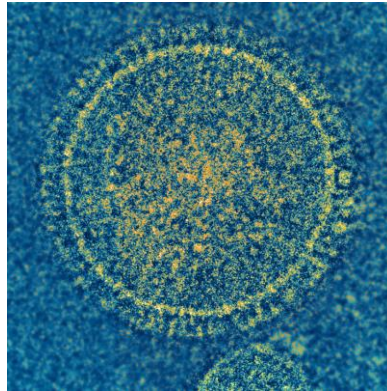
Target	Clinical-Stage Pipeline				TOTAL
	Ph 1	Ph 2	Ph 3	BLA	
<i>Seasonal influenza</i>	3	8	2		13
<i>Herpes zoster (shingles)</i>			1		1
<i>Hepatitis B</i>	2		1	1	4
<i>Pertussis (generally included w DT)</i>	1				1
<i>Human Papilloma virus (HPV)</i>		1			1
<i>Pneumococcal</i>		3			3
<i>Hib (Haemophilus influenzae b)</i>	1	1			2
			4	1	25



Source: BIO Industry Analysis, BioMedTracker, April 2016

New Disease Areas for Adult Vaccines

- Many vaccines in this category could potentially be indicated in multiple age categories based on the epidemiology of the disease and unmet medical or public health need.
- Some of these vaccines also may be indicated as part of a maternal immunization platform.



Respiratory syncytial virus (RSV). Credit: NIAID



New Disease Areas with Vaccines in Development

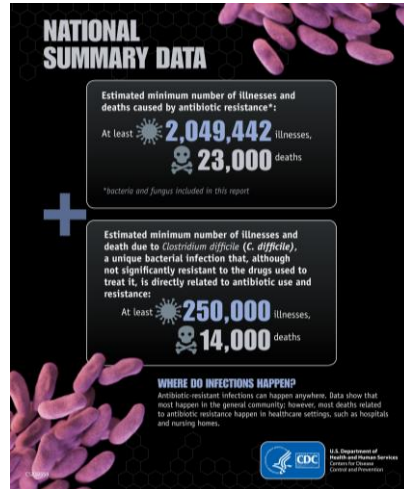
Target	Clinical-Stage Pipeline				TOTAL
	Ph 1	Ph 2	Ph 3	BLA	
Norovirus		2			2
Respiratory Syncytial Virus (RSV)	3	2	1		6
Hepatitis C		2			2
Herpes Simplex Virus (HSV)	1	3			4
Cytomegalovirus (CMV)	2	1			3
Group B Streptococcus		1			1
			1		18



Source: BIO Industry Analysis, BioMedTracker, April 2016

Healthcare & Community-Acquired Infections / AMR - Vaccines

- AMR = antimicrobial resistance
- In 2013, CDC identified & prioritized 18 threats.
- Companies are actively pursuing vaccines as part of solution to combat drug-resistant bacteria, fungi, and viruses.
- AMR vaccines are often designed to protect limited populations (e.g., hospitalized patients at risk of healthcare-associated infections).



Vaccines against Healthcare-Acquired Infections Face Unique Development Issues

- 79% of deaths reported in 2013 CDC AMR Report are due to HAIs.

Challenges	Opportunities
Limited populations vs. routine vaccines	Prevention of infections can:
Defining at-risk patients to vaccinate	<ul style="list-style-type: none"> reduce morbidity & mortality reduce hospitalizations reduce antibiotic use increase the effectiveness of hospital infection control programs increase quality of life and productivity
Target populations with high co-morbidities	
Level of immunocompetence may affect vaccine response	Durable protection
Rapid protection may be required	<ul style="list-style-type: none"> reduce recurrent infections/readmission



AMR Vaccines in Development

Target	Clinical-Stage Pipeline				FDA Licensed	Expected New*
	Ph 1	Ph 2	Ph 3	Total		
2013 CDC AMR Threat List - includes pathogens with clinical-stage or FDA-approved vaccines						
<i>Candida</i>		1		1		0.3
<i>Clostridium difficile</i>		2	1	3		1.2
<i>Escherichia coli</i>	2			2		0.4
<i>Group B Streptococcus</i>		1		1		0.3
<i>Pseudomonas aeruginosa</i>		1		1		0.3
<i>Salmonella typhi</i>					2	
<i>Staphylococcus aureus</i>	3	1		4		0.9
<i>Streptococcus pneumoniae</i>	1	3		4	3	1.1
<i>Mycobacterium tuberculosis</i>	1	4		5	1	1.4
Totals	7	13	1	21	6	5.9

Credit: Tim Cooke, PhD, "Role of Vaccines in Combating Antimicrobial Resistance: Big Opportunities & Big Challenges," IDWeek 2015.

Data Sources: BioMedTracker, FDA website, clinicaltrials.gov, company websites

* Number of new vaccines from current pipeline expected post-attrition (20% probability of licensure Ph1, 30% Ph2, 60% Ph3, from Hay et al, Nature Biotech, 2014, 40)

Summary

- Development process for vaccines is unique. It is also long, highly capital intensive, and risky.
- There are **125 vaccine candidates in the pipeline** that could help:
 - Improve global health & reduce NTD burden;
 - Add new technologies in categories with existing vaccines;
 - Prevent diseases that were previously not "vaccine-preventable"; and
 - Reduce drug-resistant infections and slow the growth of resistance.
- Less than 1 in 10 vaccines achieve licensure; however there are a number of promising products in mid/late stage development.
 - > **11 vaccines in Phase III or BLA**
 - > **48 vaccines in Phase II**
- The scientific, regulatory, and commercial issues affecting vaccine development can differ depending on disease targets, populations, epidemiology, medical need, and plans for global access.



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