Incentives for Vaccines that Combat Antimicrobial Resistance: *BIO's Perspective*

PACCARB Meeting

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Timothy Cooke, Ph.D.
CEO, NovaDigm Therapeutics

Member of:
National Vaccine Advisory Committee
BIO Vaccine Policy Advisory Committee
BIO Antimicrobial Resistance Working Group
U.S. Stakeholder Forum on Antimicrobial Resistance

Bio Biotechnology Innovation Organization

Disclosures

Timothy Cooke is an employee, Board director and shareholder in NovaDigm Therapeutics, Inc., a company engaged in the development of vaccines against antimicrobial resistant pathogens including *Candida*, *Staphylococcus aureus* and *Acinetobacter baumannii*.

Vaccine Development Summary

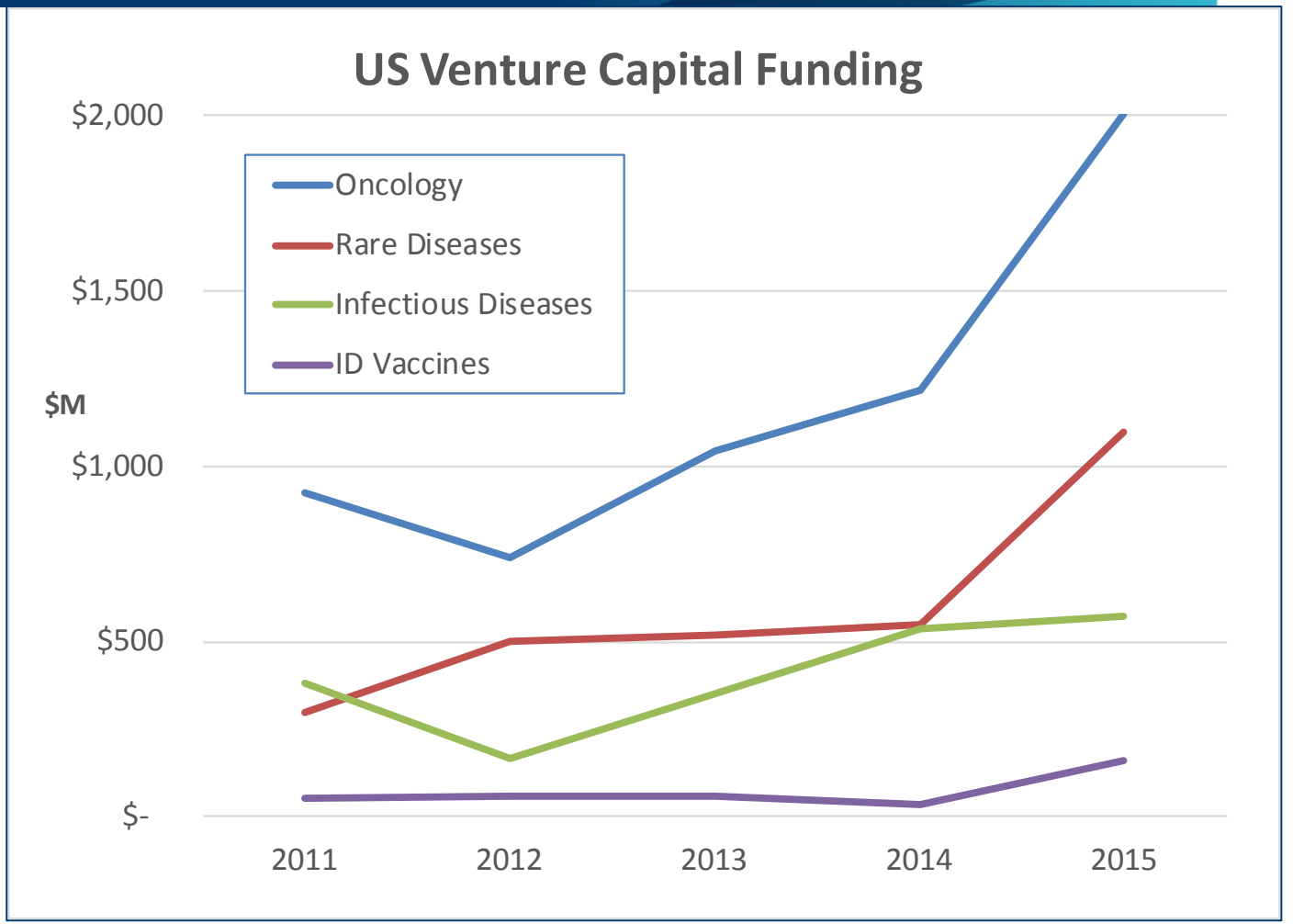
- Long development timelines and costs
  - 10-20 years and up to $1.5B for human vaccines
  - High capital equipment costs for manufacturing pre-licensure
- High product complexity
  - Increased cost of goods versus small molecules
  - High post-approval costs to meet increasing quality standards
- Markets driven by gov't recommendations and purchase
  - Adds additional risk following regulatory approval

Vaccine Investment Landscape

- Companies/investors use similar valuation methods
  - Risk-adjusted net present value (rNPV) models assuming development costs & time, probability of success, market forecasts
  - Applied to vaccines vs. pharmaceuticals vs. high tech investments
  - Drives resource allocations within Big Pharma/biotech portfolios
  - Drives private and public investments
- rNPV assumptions for infectious disease vaccines
  - Longer timelines, higher costs & greater market risk decrease value
  - Lack of generic or “follow-on” vaccines increases value but benefit is discounted since it occurs later

Vaccine Investment Landscape

1.6% of U.S. VC funding for therapeutics went to ID vaccine companies (2006-2015)

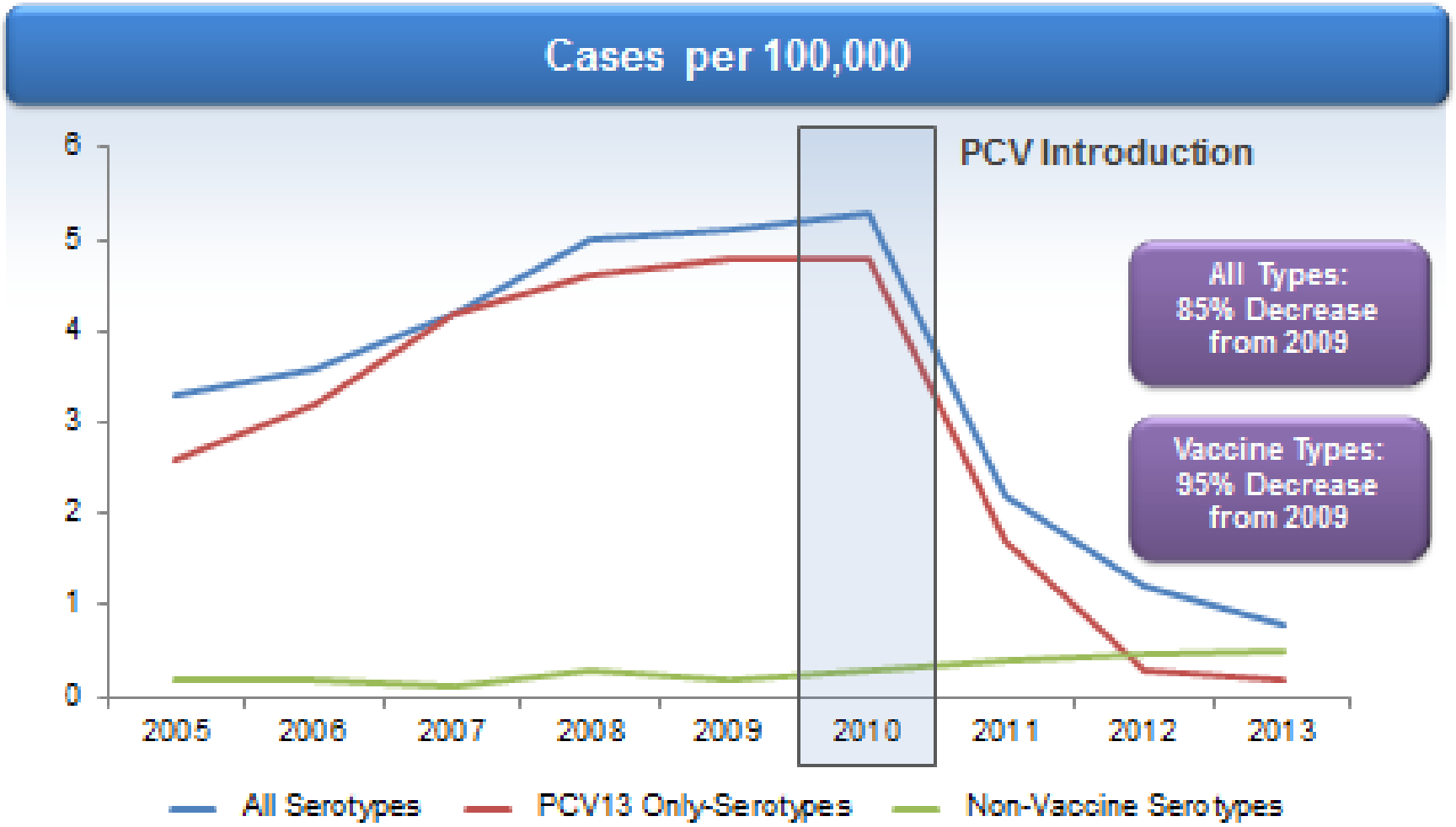


BIO Report on Emerging Therapeutic Company Investment and Deal Trends, Thomas & Wessel, 2016

Opportunities for Vaccines in Combating AMR

- Prevention of infections in humans and animals
  - Reduce downstream antibiotic use and further resistance
  - Includes viral vaccines that could prevent antibiotic use (flu, RSV)
- Low risk of resistance to AMR vaccines
  - Prophylaxis can be widely used without generating resistance
- Longer duration of protection vs. antibiotics
  - Reduce recurrent infections and hospital readmissions
- Vaccines effective against susceptible & AMR strains
  - Demonstrated with Hib and pneumococcal vaccines

Rates of Multidrug-Nonsusceptible IPD Among US Children <5 years, 2005–2013



Adapted from oralsession35; abstract78 by Tomczyk S, et al. Prevention of antimicrobial resistant infection among children aged <5 years with the 13-valent pneumococcal conjugate vaccine – Selected U.S. areas, 2005–2013. ID Week 2014; October 8–12, 2014; Philadelphia PA. USA.

Challenges for New Vaccines in Combating AMR

- Novel pathogen targets
  - Lower probability of success
- Novel indication: prevention of healthcare-associated infections (HAIs)
  - Clinical development, regulatory pathway, ACIP recommendation and market risks
- Target populations limited vs. routine vaccines
  - More difficult to make economic case for development

AMR Vaccines
Clinical stage or FDA-approved

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*						
Candida		1		1		0.3
Clostridium difficile		2	1	3		1.2
Escherichia coli	1	1		2		0.5
Group B Streptococcus		1		1		0.3
Pseudomonas aeruginosa		1		1		0.3
Salmonella typhi					2	
Shigella		1				0.3
Staphylococcus aureus	3	1		4		0.9
Streptococcus pneumoniae	1	3		4	3	1.1
Mycobacterium tuberculosis	1	4		5	1	1.4
Totals	7	14	1	22	6	6.3

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)

AMR Vaccines
No clinical-stage candidates

Target	Clinical-Stage Pipeline			
	Ph 1	Ph 2	Ph 3	Total
2013 CDC AMR Threat List – *pathogens with no clinical-stage or approved candidates*				
Acinetobacter				0
Campylobacter				0
Enterococcus				0
Group A Streptococcus				0
Klebsiella				0
Neisseria gonorrhoeae				0
Non-typhoidal Salmonella				0

Pipeline to Address AMR Pathogens

Target	Clinical-Stage Pipeline			
	Ph 1	Ph 2	Ph 3	Total
Products targeted for 2013 CDC AMR Threat List Pathogens				
Small molecules	10	22	8	40
Vaccines	6	15	1	22
Monoclonal antibodies	3	4	1	8
Novel technologies (e.g., microbiome, phages)	1	4		5
Totals	20	44	10	74

Sources: clinicaltrials.gov & company websites
Antibiotics: PEW Trust Antibiotic Pipeline Mar 2015
Antifungals: Denning & Bromley, Science 2015, 1414
ID mAbs: DiGiandomenico & Sellman, Curr Opin Microlbiol, 2015, 78
Novel technologies: BEAM Alliance Position Paper (EU AMR-focused biotechs, 9/30/15) http://beam-alliance.eu/assets/2015-Position-Paper.pdf

What incentives have been tried & worked?

- **Push R&D funding**
  - NIH, DoD, IMI and BARDA
- **Regulatory incentives**
  - Accelerated review for Orphan Drugs
  - GAIN Act QIDP designation for novel antibiotics – Fast Track & Priority Review at FDA
- **Pull incentives**
  - GAVI Advanced Market Commitments – pneumococcal vaccines
  - BARDA/CDC stockpiling for biodefense/pandemic influenza vaccines

Are there opportunities for early successes (the "low-hanging fruit")?

- **Increase global uptake of existing vaccines!**
  - Pneumococcal, influenza, Hib vaccines
- **Increase/enhance USG push incentives for R&D**
  - Increase funding for Phases 1-3 of AMR vaccine development at NIH & BARDA
  - Use new CARB Biopharmaceutical Accelerator for AMR vaccines
  - Ease access to USG push incentives by:
    - Making product transitions between agencies more seamless
    - Reducing bureaucratic and contracting hurdles generally
    - Considering use of OTA for contracts (not used for vaccines yet)

The “low-hanging fruit” (cont.)

- **Fund supporting research by USG on AMR pathogens**
  - Epidemiology & definition of target populations
  - Potential correlates of protection for vaccines

- **Regulatory incentives**
  - QIDP designation for therapeutic & prophylactic biologics, including vaccines, to ensure Fast Track & Priority Review at FDA and linkage to any future incentives for QIDPs

What additional incentives are needed for AMR Vaccines?

- **Push incentives**
  - Create tax credit for clinical trial expenses for all AMR products
- **Regulatory incentives**
  - Publish FDA guidelines for use of correlates of protection
  - Harmonize regulatory requirements for AMR vaccines between FDA, EMA and others
- **Risk-sharing for vaccines against HAIs**
  - High clinical & market size risk due to targeted patient population
  - Advanced recommendations for use of vaccines assuming target product profile (e.g. advanced ACIP recommendations)

What additional incentives are needed for AMR Vaccines? (cont.)

- **Attractive market is <u>best</u> driver of investment**
  - Recognize full value of AMR vaccines to society, including Abx stewardship, in economic evaluations by gov’ts, payors
  - Eliminate cost-sharing in Medicare Part D for new vaccines & address provider billing issues to help drive uptake in older adults
  - Explore other novel pull mechanisms, such as transferrable market exclusivity; punitive measures such as “pay or play” proposals should be avoided

Potential Roles for PACCARB

- Champion a broad approach to the problem of AMR and emphasize the important role of vaccines, recognizing the full value of vaccines & the savings they bring to society.
- Make vaccines part of the stewardship discussion – if providers are being stewards of antibiotics, they should also be immunizers.
- **Include USG-funded push incentives & market-based pull incentives for vaccines in your recommendations to HHS & the President.**
- **Increase attention on alternative modalities to combat AMR**, e.g. microbiome products, phage therapies, mAbs, anti-biofilms, and examine specific incentives needed.

Thank You