

Prophylactic use of Vaccines (Passive/Active Immunity) to Prevent AMR Infections

Panel 2: Infection Control and Prevention

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Disclosure Statement

Timothy Cooke has the following affiliations:

Consultant, Board Director and shareholder in NovaDigm Therapeutics, a biotechnology company developing vaccines against *Candida* and *Staphylococcus aureus*.

Employee and shareholder in Ology Bioservices, a contract development and manufacturing organization providing R&D services to companies developing vaccines, mAbs and other biologics.

Prophylactic vaccines and mAbs in combating AMR

- Prevention of infections
 - Reduce downstream antibiotic use and further resistance
 - Includes viral targets that could prevent antibiotic use (flu, RSV, rotavirus)
- Lower risk of resistance to vaccines and mAbs vs. antibiotics
 - Prophylaxis can be widely used without generating resistance
- High specificity (“narrow spectrum” prophylaxis)
 - Maintain beneficial elements of microbiome
- Effective against susceptible & AMR strains
 - Proven success with Hib and pneumococcal vaccines
- Complementary to antibiotics

The prevention of bacterial infections is far superior to treatment. Individuals maintain their health and productivity and antibiotics are not utilized, thus reducing the potential for resistance. Viral vaccines play a key role in reducing clinical syndromes that are often treated inappropriately with antibiotics. These currently include influenza vaccines (preventing respiratory infections) and rotavirus (preventing diarrhea in young infants).

The prophylactic use of vaccines and monoclonal antibodies (mAbs) has a very low risk of generating resistance, so they can be employed widely without paying a “penalty” of generating resistance observed with small molecule antibiotics. Vaccines and mAbs are highly specific and do not disrupt the microbiome as much as broad-spectrum antibiotics. Vaccines have been proven to be effective against susceptible and non-susceptible bacterial strains, demonstrated dramatically for Hib and pneumococcal vaccines.

For the some indications, vaccine and mAbs could be complementary with or synergistically with antibiotics.

Prophylactic vaccines and mAbs in combating AMR

Differences in current product profiles

	Vaccines (active immunization)	mAbs* (passive immunization)
Doses	10-100 micrograms	1-5 gms/adult
Administration	Intramuscular/SQ/oral	IV infusion
Time to protection	1 week-months	immediate
Duration of protection	months-years	days-months
Host status of patient	immunocompetent	independent (e.g., toxin neutralization)
Mechanism of protection	Broader (potential B-cell & T-cell stimulation)	Toxin neutralization Blocking adhesion to host cells Opsonophagocytosis

Rapid innovation in mAb design could dramatically improve future product profiles – higher potency, longer half-life, mAb-conjugates and in-vivo generation via nucleic acid approaches.

*Doses/administration based on FDA-approved mAbs against anthrax, RSV, *C. difficile*.

This table shows some of the differences in the product profiles of vaccines and mAbs. The cells tinted green are the more favorable attributes.

To summarize, vaccines are preferred when there is 1) not an immediate need for protection, 2) a long duration of protection is desirable, 3) a host with a competent enough immune system to develop protective responses and 4) a need for T-cell responses for protection. Monoclonal Abs are preferred when there is 1) an immediate need for protection, 2) a short duration of protection is acceptable, 3) an immunocompromised host and 4) protection driven by antibodies alone.

The properties of the mAbs in the table are based on the currently approved mAbs against infectious disease targets. There is tremendous innovation in mAb technology that will lead to improved product profiles in the future.

Vaccine Pipeline 2015 (active immunization) against 2013 CDC AMR Threat List Pathogens

Target	Clinical-Stage Pipeline				FDA Licensed
	Ph 1	Ph 2	Ph 3	Total	
<i>Candida</i>		1		1	
<i>Clostridium difficile</i>		2	1	3	
<i>Escherichia coli</i>	1	1		2	
Group B <i>Streptococcus</i>		1		1	
<i>Pseudomonas aeruginosa</i>		1		1	
<i>Salmonella typhi</i>					2
<i>Shigella</i>		1			
<i>Staphylococcus aureus</i>	3	1		4	
<i>Streptococcus pneumoniae</i>	1	3		4	3
<i>Mycobacterium tuberculosis</i>	1	4		5	1
Totals	6	14	1	21	6

This chart looks at the clinical-stage vaccine pipeline and approved vaccines against the pathogens identified by the CDC as AMR threats in their 2013 report. There are several pathogen targets that have no clinical-stage candidates and these are not shown here.

This is a snapshot from October of 2015, which were included in a presentation made at IDWeek. There were 21 clinical-stage candidates from developed country vaccine developers.

Looking across Phase 1 to 3 candidates, there was an unusual “bell-shaped” distribution, with a higher number of Phase 2 than Phase 1 candidates. One would normally expect a “funnel shape” with the most candidates in Phase 1 and then decreasing by attrition to Phase 2 and 3. The bell shape is indicative of a weak pipeline in which the early candidates are not likely to be able to replace later-stage candidates lost to attrition. Attrition can be caused by clinical attrition (i.e., clinical study failures) or by financial attrition (based on lack of funding rather than clinical failure). For vaccines, the transition from Phase 2 to 3 costs over \$100M, so there is a high rate of financial attrition for candidates, particularly from biotech companies.

Vaccine Pipeline 2015 (active immunization) against 2013 CDC AMR Threat List Pathogens

Target	Clinical-Stage Pipeline				FDA Licensed	Updates
	Ph 1	Ph 2	Ph 3	Total		
<i>Candida</i>		1		1		Positive Ph2 results (NovaDigm) ¹
<i>Clostridium difficile</i>		2	1	3		Ph3- (Sanofi), Ph3+ (Pfizer)
<i>Escherichia coli</i>	1	1		2		
Group B <i>Streptococcus</i>		1		1		Ph2- (GSK), Ph1+ (Pfizer)
<i>Pseudomonas aeruginosa</i>		1		1		Ph2- (Valneva/GSK)
<i>Salmonella typhi</i>					2	
<i>Shigella</i>		1				
<i>Staphylococcus aureus</i>	3	1		4		Ph2/3- (Pfizer), Ph2+ (NovaDigm), Ph1-
<i>Streptococcus pneumoniae</i>	1	3		4	3	Ph3+ (Merck), Ph2+
<i>Mycobacterium tuberculosis</i>	1	4		5	1	Positive Ph2 results (GSK/Aeras) ² , Ph2-
Totals	6	14	1	21	6	21 candidates to 16

Positive results in retrospective case-control study of outer membrane vesicle meningococcal B vaccine against *N. gonorrhoeae*³

An additional column was added to the previous slide showing updates in the pipeline since Oct 2015.

There were some big disappointments in vaccine development. The most impactful ones are the clinical failures of late-stage (Phase 3 or “Ph3”) candidates. These candidates have had a tremendous amount of sustained investment over a long period of time (\$100Ms to billions). Failures in this category included Sanofi Pasteur’s *C. diff* vaccine candidate (Ph3- designates the loss of a Phase 3 candidate). The Sanofi Pasteur study enrolled patients at risk for primary or recurrent *C. diff* infections. Pfizer’s *C. diff* vaccine candidate advanced into Phase 3 (“Ph3+”). Another late-stage failed study was Pfizer’s Phase 2/3 study for their *Staph aureus* vaccine candidate (in pre-surgery patients). Phase 2 candidate failures included Valneva’s *Pseudomonas aeruginosa* vaccine in a study conducted in ICU patients on mechanical ventilators. GSK also removed their GBS vaccine candidate from their publicly disclosed pipeline.

There were several candidates that had advanced since 2015, as seen by the + signs on the chart.

There were positive efficacy results published by NovaDigm on their *Candida* vaccine candidate, the first positive efficacy results for an antifungal vaccine. A team from Aeras and GSK published results on their TB vaccine with 54% efficacy, a landmark result for TB vaccines. The cross-protection of the Novartis OMV meningitis B vaccine against *N. gonorrhoeae* showed 30% efficacy in a large retrospective study in New Zealand, which was also welcome news.

Overall, the number of clinical-stage candidates dropped from 21 to 16 without any new approvals.

Vaccine Pipeline 2018 (active immunization)

against 2013 CDC AMR Threat List Pathogens

Target	Clinical-Stage Pipeline				FDA Licensed
	Ph 1	Ph 2	Ph 3	Total	
<i>Candida</i>		1		1	
<i>Clostridium difficile</i>		1	1	2	
<i>Escherichia coli</i>	1	1		2	
Group B <i>Streptococcus</i>	1			1	
<i>Pseudomonas aeruginosa</i>		0		0	
<i>Salmonella typhi</i>					2
<i>Shigella</i>		1		1	
<i>Staphylococcus aureus</i>	1	1		2	
<i>Streptococcus pneumoniae</i>		3	1	4	3
<i>Mycobacterium tuberculosis</i>	1	2		3	1
Totals	4	10	2	16	6

This is the current pipeline, still showing a bell-shaped curve but fewer candidates.

mAb Pipeline 2015 versus 2018 (passive immunization) against 2013 CDC AMR Threat List Pathogens

2015

Target	Clinical-Stage Pipeline				FDA Licensed
	Ph 1	Ph 2	Ph 3	Total	
<i>Clostridium difficile</i>			1	1	
<i>Escherichia coli</i>		1		1	
<i>Pseudomonas aeruginosa</i>	1	1		2	
<i>Staphylococcus aureus</i>		2		2	
Totals	1	4	1	6	0

2018

Target	Clinical-Stage Pipeline				FDA Licensed	Updates
	Ph 1	Ph 2	Ph 3	Total		
<i>Clostridium difficile</i>					1	Licensed+ (Merck)
<i>Escherichia coli</i>		1		1		Unconfirmed (Taro Pharma)
<i>Pseudomonas aeruginosa</i>		3		3		Ph2+ (Aridis)
<i>Staphylococcus aureus</i>	1	2		3		Ph2- (Arsanis), Ph1+ (Genentech)
Totals	1	6	0	7	1	6 candidates to 8

This is the pipeline for mAbs against the CDC Threat List pathogens. There are far fewer mAb candidates versus vaccines but still a pronounced bell-shaped curve. The 2015 baseline pipeline was derived from a publication by researchers from MedImmune.

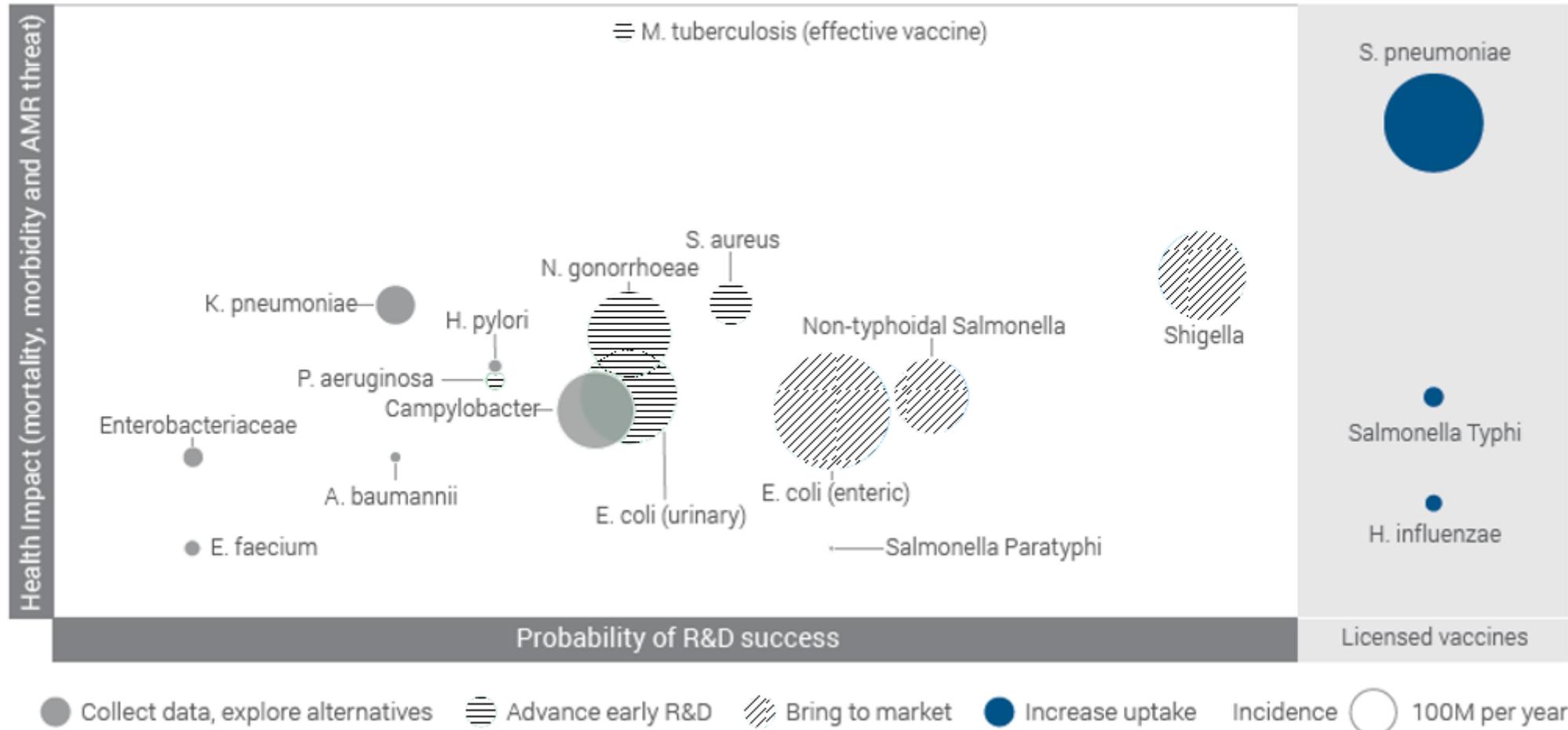
The good news was that the Merck mAb candidate against *C. diff* infections, bezlotoxumab, was approved the FDA. A mAb against *Pseudomonas aeruginosa* was advanced to Phase 2 by Aridis and Genentech moved a mAb against *Staph aureus* into Phase 1.

The Arsanis Phase 2 mAb against *Staph aureus* failed in an efficacy study in ICU patients on mechanical ventilation that were positive for colonization by *Staph aureus*. Aridis and MedImmune are pursuing the same indication in Phase 2 efficacy studies for their mAbs against *Staph aureus*.

Prophylactic vaccines and mAbs in combating AMR

Wellcome/Boston Consulting Group Report Oct 2018

PATHOGEN SEGMENTATION BASED ON ASSESSMENT CREATES CLUSTERS THAT CAN HELP PRIORITISE INTERVENTIONS



There was a recent study funded by the Wellcome Trust and conducted by BCG. The study was the first to segment AMR threat pathogens by their ability to be controlled by vaccines or by other modalities including mAbs, or whether prevention or treatment should be prioritized.

The chart above shows the segmentation criteria, with the probability of successful development on the x-axis and medical need on the y-axis. The size of the bubbles indicate the incidence of infections.

The message here is that prophylactic vaccines are not the solution for all pathogens, mAbs may be preferred for some indications and some targets are best addressed by treatment (i.e., those with low and sporadic incidence).

Prophylactic vaccines and mAbs in combating AMR

Summary

- Healthcare-associated/nosocomial indications remain challenging
 - Low placebo event rates
 - Heterogeneous patient population with significant co-morbidities
- Innovation in vaccines and mAbs remains strong
 - Leverage advances in non-bacterial targets (e.g., HIV, flu, immuno-oncology)
- Need to feed the early- and late-stage pipelines
 - NIH, CARB-X, DoD, Gates funding early stage pipeline for vaccines & mAbs
 - BARDA should receive funding for vaccines & mAbs to combat AMR
- Limited investor funding for infectious disease vaccine/mAb companies*

Indications that are focused on the prevention of healthcare-associated infections remain challenging due to low infection rates in the placebo group, leading to large and expensive clinical studies, often in patients with multiple co-morbidities.

Innovation in vaccines and mAbs is very strong and mostly coming from oncology and viral targets rather than bacteria.

The shape of the clinical stage pipeline across Phase 1-3 studies is indicative of a weak pipeline with very few Phase 1 candidates. There are several efforts to increase the early phase clinical pipeline from the NIH, DoD, Gates and CARB-X. These efforts have not shown up yet in the number of Phase 1 candidates. The other weak aspect of the pipeline is the large number of Phase 2 candidates that may indicate an inability to advance to Phase 3 for financial reasons, and not due to clinical failures. To resolve this issue, funding on the scale of BARDA (>\$100M) would be required. BARDA has not yet funded vaccines and mAbs against pathogens on the CDC threat list, but should be given funds and mandate to do so.

The overall environment for funding ID vaccines and mAbs is very challenging, since investor money has shifted to immuno-oncology and orphan diseases.

This analysis shows the weaknesses in the pipelines for vaccines and mAbs against AMR threat list pathogens. While efforts have been initiated to strengthen the early stage pipeline, there remains a lot of additional funding for late-stage development that is not currently coming from investors. The US government and other funding agencies will have to continue to support the development of vaccine and mAbs against AMR threat list pathogens to make these products available for public health purposes, including the reduction of AMR.