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Layered, Integrated Medical Intervention Technologies (LIMIT) Concept



DTRA FUNDED RESEARCH

Kimberly A Hofmeyer, PhD
2019 CBD S&T Conference
20 November 2019

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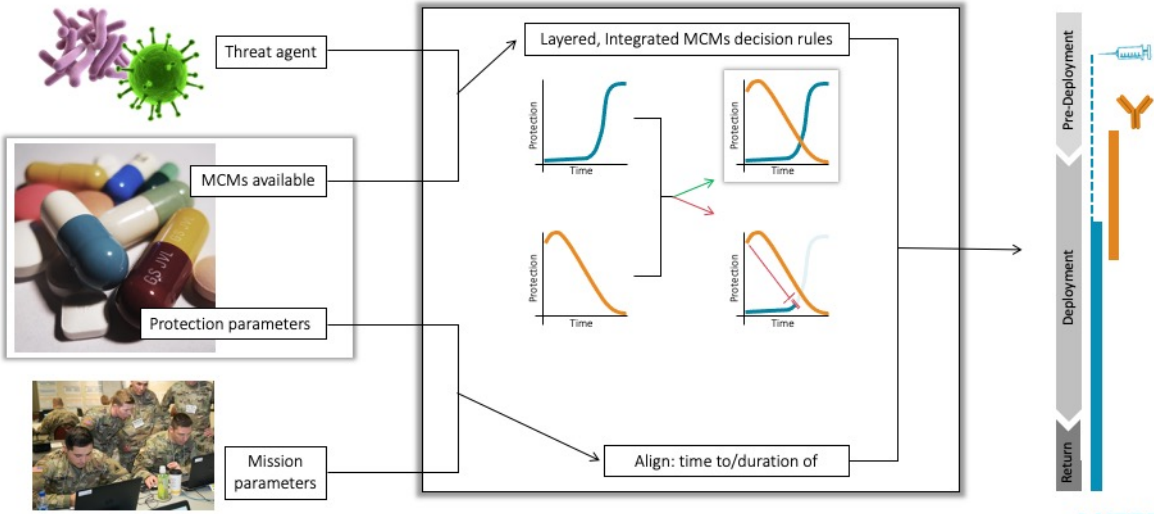
Layered and Integrated Medical Intervention Technologies (LIMIT) Concept



- **Medical countermeasures (MCM) – biologics and drugs – are a defensive solution against biological threat agents;**
 - This may be limited if a single medical intervention does not meet all efficacy requirements in a biological threat environment
- **Solution:** develop a concept for layered, integrated MCM defense that is science-based and can be tailored to mission needs
 - Expand protective barrier
 - Avoid single point of failure
 - Strengthen Joint Force resiliency and operational readiness
- **Concept scope:**
 - *Bacillus anthracis (Ba)* and *Zaire ebolavirus (EBOV)* MCM
 - Phase 1 through FDA approved MCM (active use/development)
 - MCM administration pre-deployment (i.e. prophylactic)

LIMIT - A layered, integrated MCM defense that can be tailored to mission needs

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MCM Layering Rules – mAb and vaccine layering

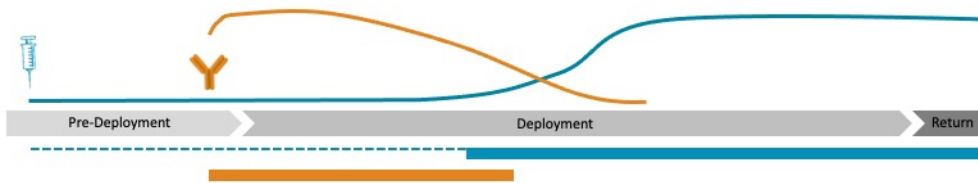
■ **Scoping:**

- MCM that could be administered during pre-deployment (vaccines; mAb)
- Anthrax and Ebola MCMs

MCM	Time to protection	Duration of Protection
mAb	Immediate	Short
Vaccine	Delayed	Long

■ **Goals:**

- **Interoperable MCM layers to expand the protective barrier**
- Avoid MCM interference
- Tailor to mission timelines



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MCM Layering Rules – mAb and vaccine layering

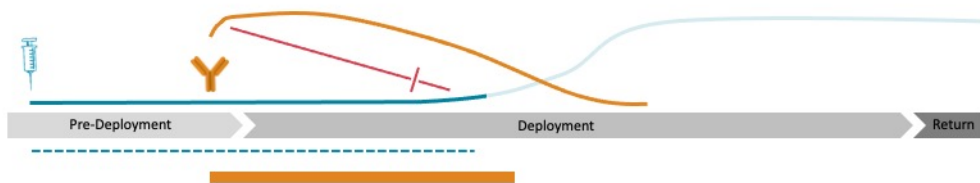
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MCM Layering Rules – mAb and vaccine layering

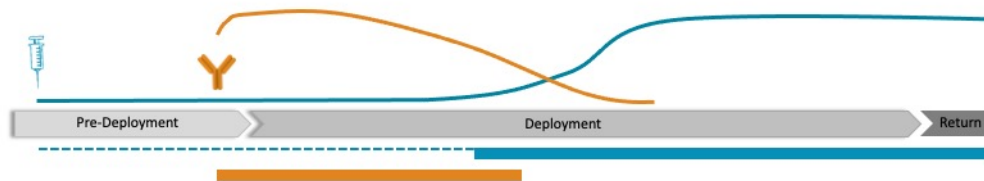
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Anthrax MCM – Empirically tested layering

- MCM layering empirically tested for some agents/MCM

	Biothrax	Nuthrax	NasoShield	Anthrasil	Raxibacumab	Anthim	Cipro	Doxy
Biothrax								
Nuthrax	NA							
NasoShield	NA	NA						
Anthrasil	NO	ND	ND					
Raxibacumab	OK	ND	ND	NA				
Anthim	ND	ND	ND	NA	NA			
Cipro	OK	ND*	ND	OK	OK	OK		
Doxy	OK	ND*	ND	ND	ND	OK	NA	
	Biothrax	Nuthrax	NasoShield	Anthrasil	Raxibacumab	Anthim	Cipro	Doxy

OK OK to combine
NO Not OK to combine
ND Not directly determined
NA Not applicable
 *Testing in progress

- ... where not empirically determined, develop agent-agnostic layering rules

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- Ad4-PA (PaxVax) – Trial in 2013; PaxVax acquired by Emergent BioSolutions and not currently listed as a vaccine in their pipeline
- Velocity 2 Trial – Phase 2 trial to test AV7909 with Cipro and Doxy
- Anthim = ETI-204; obiltoxaimab
- NasoShield = 2017/2018 Phase 1
- Fraunhofer Center for Molecular Biotechnology completed phase I clinical trials for PA83-FhCMB for anthrax vaccine in healthy adults in year 2015
- Px563L (Pfenex) – Phase 1 results reported in 2016 - After Pfenex disclosed that it received notice that BARDA has decided not to exercise its options to fund further development of anthrax vaccine candidates, Px563L and RPA563

MCM Layering Rules – Agent Agnostic

- **Priority is to avoid negative interactions**
 - Vaccine impact on mAb – competitive inhibition
 - However, not observed in anthrax testing of Ab + vaccine
 - mAb impact on vaccine – inhibit processes critical to vaccine immunogenicity
- **Key considerations for impact of mAb on vaccine**
 - Shared antigen target
 - Is the vaccine antigen accessible to mAb (i.e. how is the antigen expressed)
 - mAb mechanism of action
 - Does vaccine antigen mediate cellular uptake necessary for immunogenicity (i.e. infection)
- **Goal:** define high-level, agent agnostic characteristics of MCM that address key considerations for avoiding mAb interference with vaccine immunogenicity

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Define high-level, agent agnostic MCM characteristics for avoiding mAb interference with vaccine immunogenicity

- **Process:** Intuitive immunology-based rules followed by supporting literature review

Agent	Vaccines				
	Name	Vaccine antigen			
		Target	Expression	Accessible	Mediates cell uptake
Ba	Biothrax	PA	Purified protein	Yes	No
	NasoShield	PA	Viral vector DNA	No	No
EBOV	INO-4212	GP	Plasmid DNA	No	No
	cAd3-EBO Z	GP	Viral vector DNA	No	No
	Ad26.ZEBOV	GP	Viral vector DNA	No	No
	MVA-BN Filo	GP	Viral vector surface	Yes	Yes
	rVSV-ZEBOV	GP	Viral vector surface	Yes	Yes
	HPIV3-EboZ GP	GP	Viral vector surface	Yes	Yes
EBOV GP	GP	Recombinant protein	Yes	?	

(Select vaccine examples)

Agent	Monoclonal Antibodies (mAb)		
	Name	Ag Target	MoA includes neutralization
Ba	Raxibacumab	PA	Yes
EBOV	Zmapp	GP	Yes
	REGN-EB3	GP	Yes
	mAb114	GP	Yes

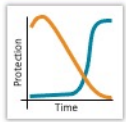
(Select mAb examples)

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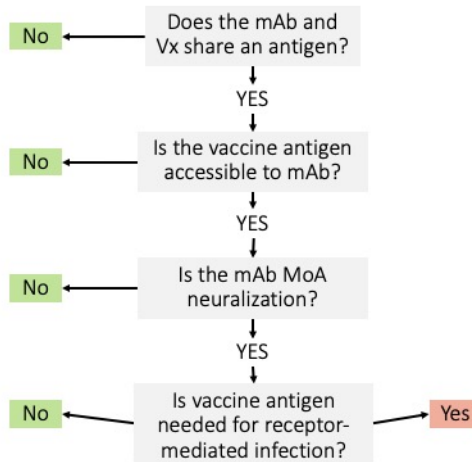
MCM Layering Rules – Avoid mAb interference with vaccine

- **Process:** Intuitive immunology-based rules followed by supporting literature review

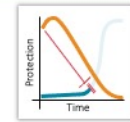
Layering OK



mAb interference with vaccine immunogenicity **unlikely**



Layering NOT OK



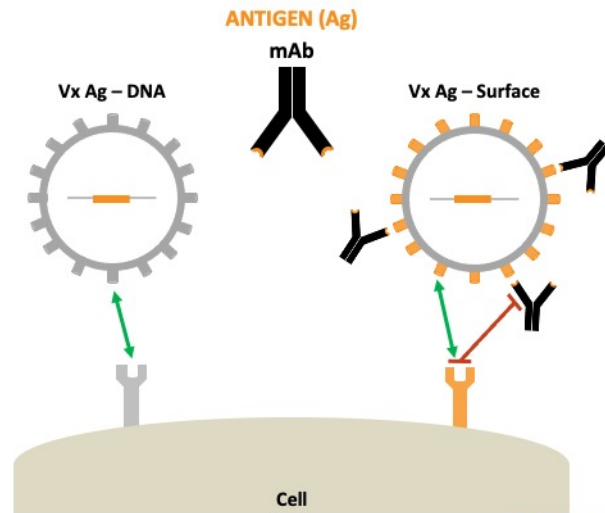
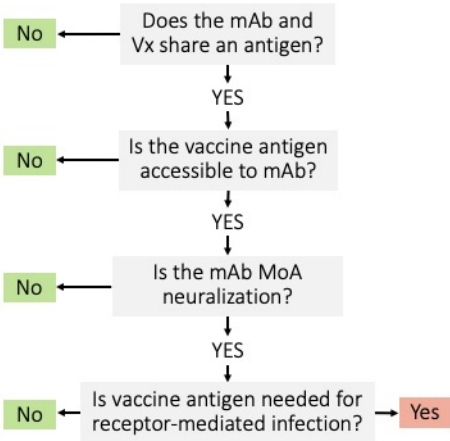
mAb interference with vaccine immunogenicity **likely**

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MCM Layering Rules – Avoid mAb interference with vaccine (Vx)

Layering OK

Layering NOT OK

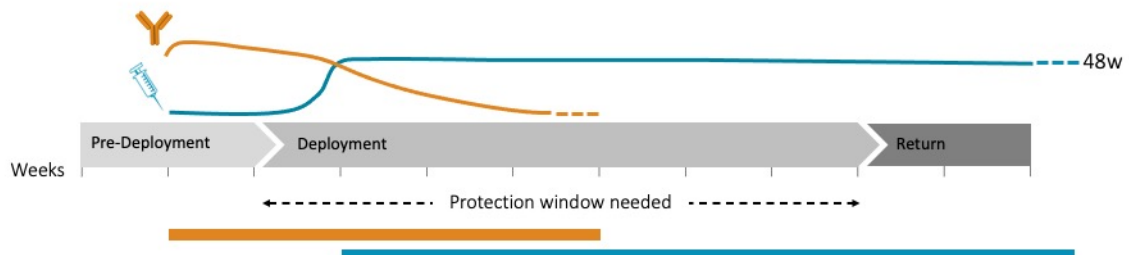


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Alignment of MCM protection parameters with mission planning

	MCM Type	Name	Antigen	Protection Parameters*	
				Time to	Duration
EBOV	mAb	mAb114	GP	0d	~24-30d (Est)
	Vaccine	cAd3-EBO Z	GP	14d	336d (48w)

*Estimated based on available data



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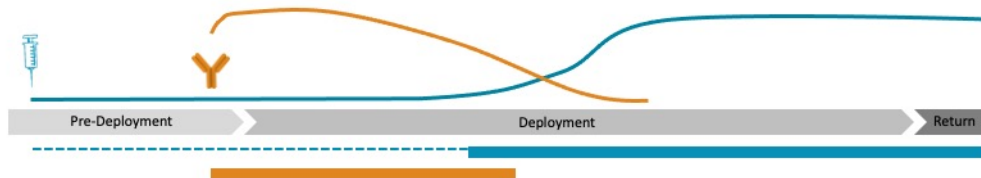
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- **mAb114:** In NHP: C_{max} of 50mg/kg dose 1349.73 μ g/mL protective, given up to 5d after lethal EBOV exposure; in unpublished data, 30mg/kg dose protective 5d after lethal EBOV infection. In human Ph1 PK study, C_{max} of 25mg/kg dose 829.38 μ g/mL. (Guadinski, Lancet, 2019)
- **cAd3-EBO Z:** In human Ph1 study, Vx Abs in the range associated with Vx-induced protective immunity in NHP and responses were sustained to week 48 (48w study duration). (Ledgerwood, NEJM, 2017)

Layered and Integrated Medical Intervention Technologies (LIMIT) Concept

- **Operational readiness in a biological threat environment depends on prioritizing preparedness to ensure a more lethal and resilient Joint Force**
 - Single defensive solutions = single points of failure
 - Layering MCMs has the potential to overcome singular limitations

To avoid single points of failure in MCM protection against biological threat agents and expand the protective barrier, developing a concept to layer MCMs while avoiding interference



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LIMIT Concept – Future Considerations and Next Steps

- **Expand LIMIT concept**
 - Additional MCM types (small molecule drugs; immunomodulators; etc.)
 - Expanded timeframe (pre- and post-deployment MCM use)
 - Layering for incident response (post-exposure prophylaxis (PEP) or treatment)
 - Layering impact on MCM efficacy requirements across pre-deployment (i.e. pre-exposure MCM) and during deployment (PEP or treatment)
 - Additional threat agents
- **Rational MCM development & program design**
 - Develop MCMs with layering principles in mind
 - MCM layering impact on efficacy requirements for individual MCMs

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