DARPA Biotechnologies: Diagnostics on Demand

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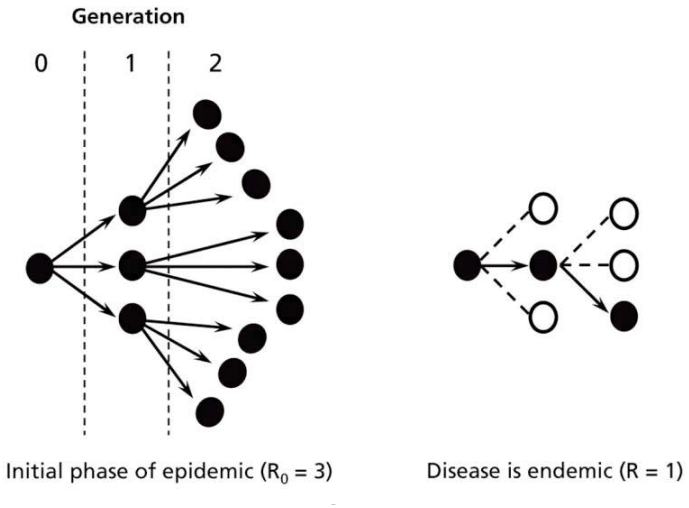
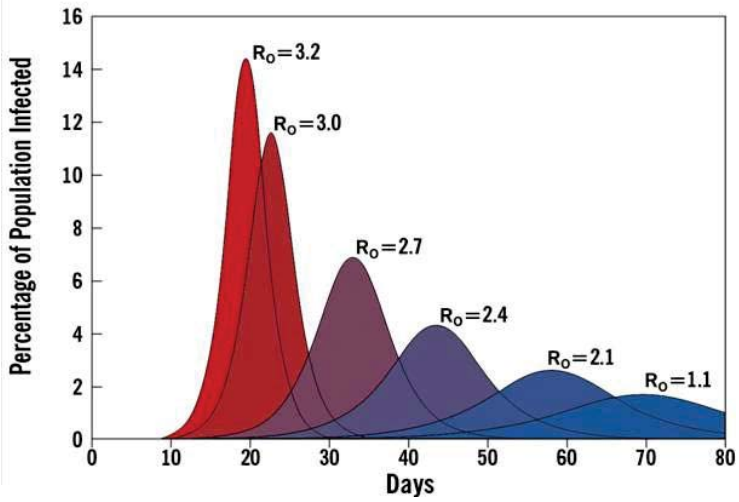
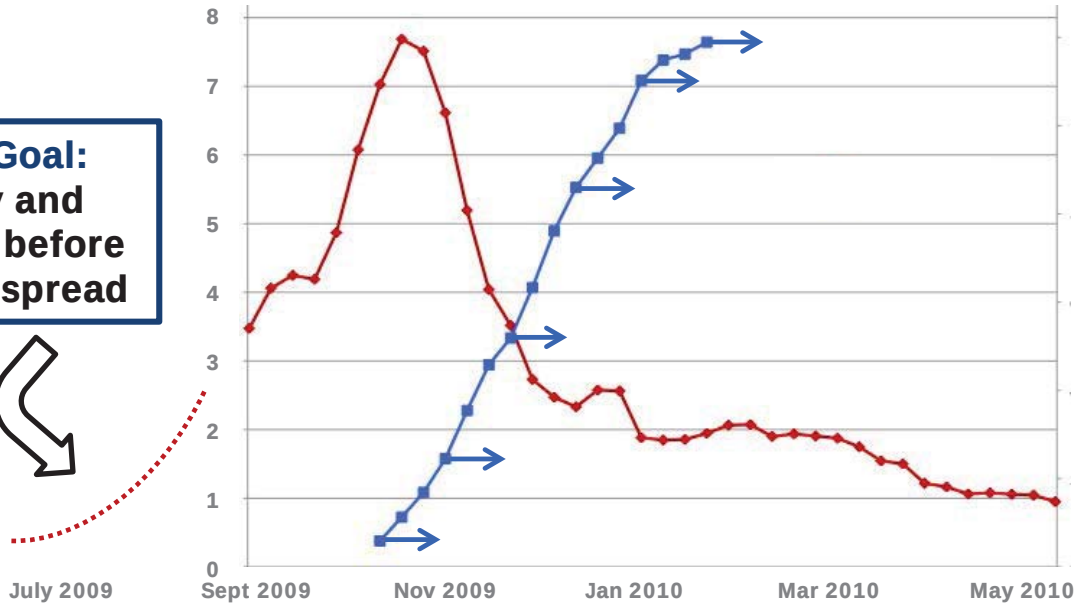
Challenge: Transmissibility of infectious disease





DARPA Goal:
Identify and intervene before extensive spread

Vaccines provided too late: 2009 H1N1

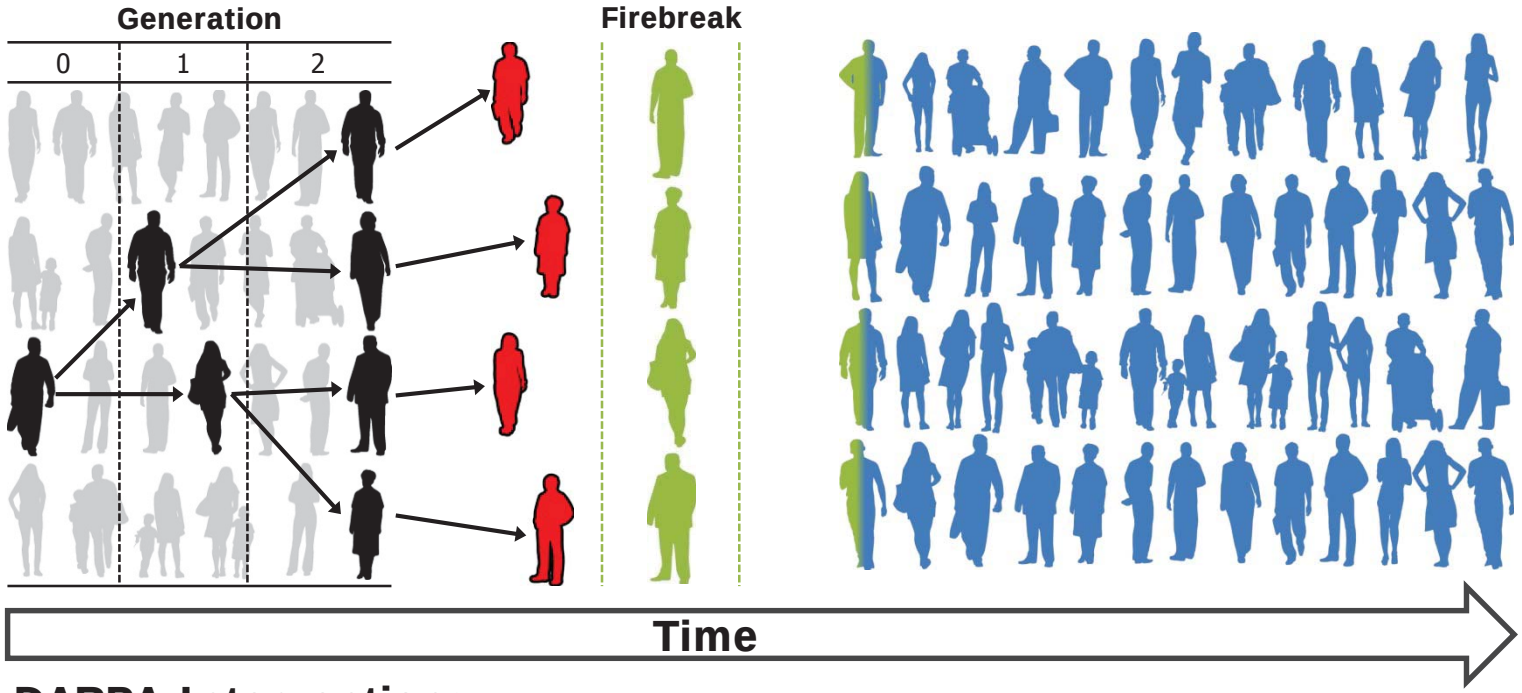


Doses shipped (in millions)

Earliest protection: 2 weeks post-vaccination

% Hospital visits for flu-like illness

Challenge: Outpace the Spread of Infectious Disease



DARPA Interventions

- **Distributed diagnostics:** Molecular and analytical methods suitable for use outside hospital settings
- **Transfer of immune responses:** Nucleic acid constructs and delivery for *in vivo* production of protective antibodies that impart immediate prophylaxis or treatment
- **New vaccine platforms:** RNA-based vaccines with controlled immunogenicity able to be designed and manufactured up rapidly

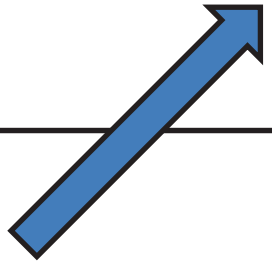
Solution: Biochemical monitoring & testing outside of traditional healthcare settings

Why not now?

- Limited testing in physician offices or homes and no continuous monitoring for key biochemical markers
- Limited information integration
- Minimal participation

Technology capability for distributed testing

Rapid Test / (molecule detected)	LOD (molecules/mL)	
Home pregnancy test / protein	10^8	today
Flu rapid test / protein	10^8	
DARPA platform / protein	**10^5**	
DARPA platform / nucleic acid	**10^{1-2}**	



DARPA technology for increased diagnostic sensitivity

Information integration: Mobile health today

Situational Awareness
> 50,000 mobile health apps

- e.g.: behavior, fitness information
- Efforts underway to link to EMRs

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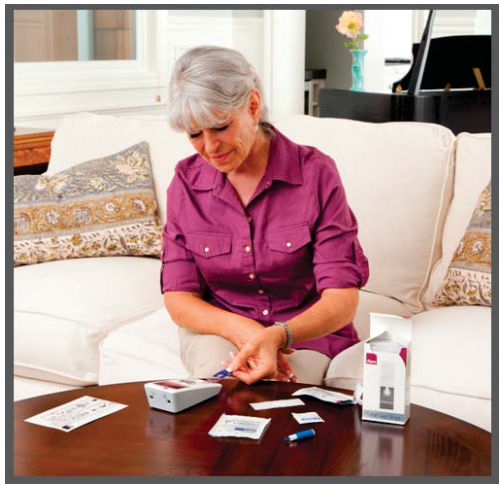
Biochemical Ground Truth
< 10 tests

- e.g.: warfarin INR, glucose
- DARPA diagnostics efforts



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Clinical trial participation

An overwhelming majority of people (77%), say that they would consider getting involved in an appropriate clinical research study if asked.
(www.ciscrp.org)

About 2% of the United States population gets involved with clinical research trials each year. Among people who suffer from severe, chronic illnesses, only 6% participate. As a result, an increasing number of clinical trials are delayed because too few people...even knew they had the opportunity to get involved.
(Getz, The Gift of Participation, 42)

Biochemical Testing Outside of Traditional Settings: DARPA Diagnostics on Demand

New formats for self-collected biospecimens

Eliminate refrigeration & reduce pain

Vision: Painless self-collection and room temperature preservation

Strategy:

- Preserve self-collected biospecimens without refrigeration
- Reduced pain with minimally invasive self-collection
- Biospecimen source: blood, urine, nasal swab, etc.
- Analyte class: DNA, RNA, proteins, whole cells, live viruses
- Stable storage for future functional assays

Courtesy of Spot on Sciences

Courtesy of GenTegra

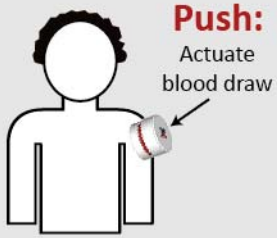
Biospecimen collection for immediate testing and preservation for future additional analysis

HemoLink™

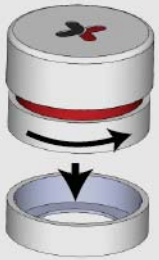
Self-administered, ultra-simple, large-volume blood collection

- ✓ No training required
- ✓ Safe and convenient
- ✓ Large blood volumes
- ✓ Integrated sample stabilization

Step 1
Blood draw



Step 2
Preserve sample



Direct elution for on-site analysis

Stabilized sample for future lab analyses

qiagen.com

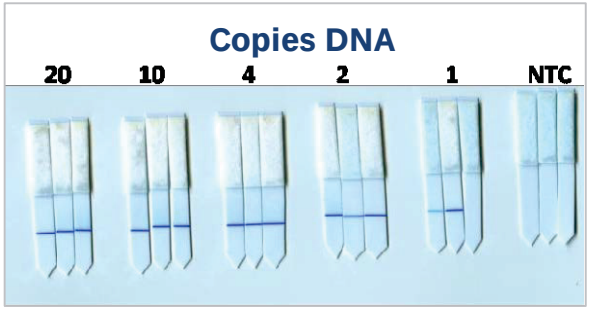
Advanced methods for limited resource settings

Move the diagnostic device

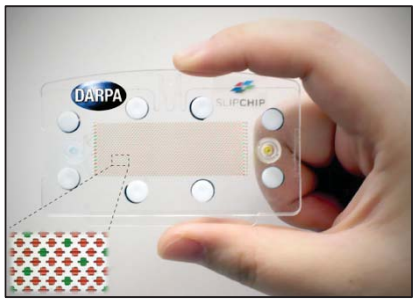
Vision: Clinical diagnostics for home use

Strategy:

- Materials and devices that are disposable with no/low power
- Self-collected sample integration
- New molecular signal amplification methods
- Nucleic acid and protein-based assays
- Simple to use (CLIA-waived), sample to answer diagnostics with positive predictive value



Courtesy of Paul Yager,
University of Washington



Courtesy of Rustem Ismagilov,
Caltech

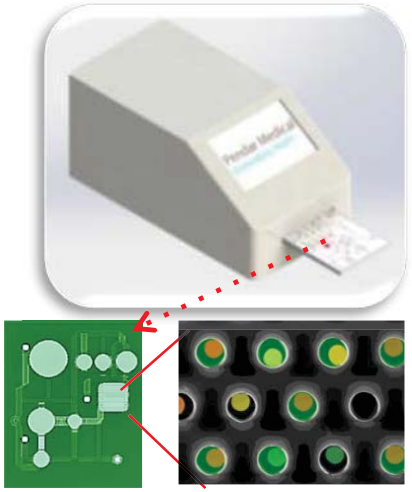
Multiplex analysis for POC settings

Move the lab analysis

Vision: Automated, highly multiplexed diagnostics at point of care

Strategy:

- Automated sample preparation and processing
- Broad dynamic range and high sensitivity, multiplex analysis methods
- Disease specific (nucleic acid) and host response (proteins) detection
- Integrated instruments for simple operation (CLIA-waived for physician office use)
- Advanced data handling and strategies for emerging disease detection



Courtesy of J. Michael Ramsey, UNC-Chapel Hill

Proteomics vision

Current protein blood tests are based on only 250 currently measurable proteins

Total number of currently detectable serum proteins

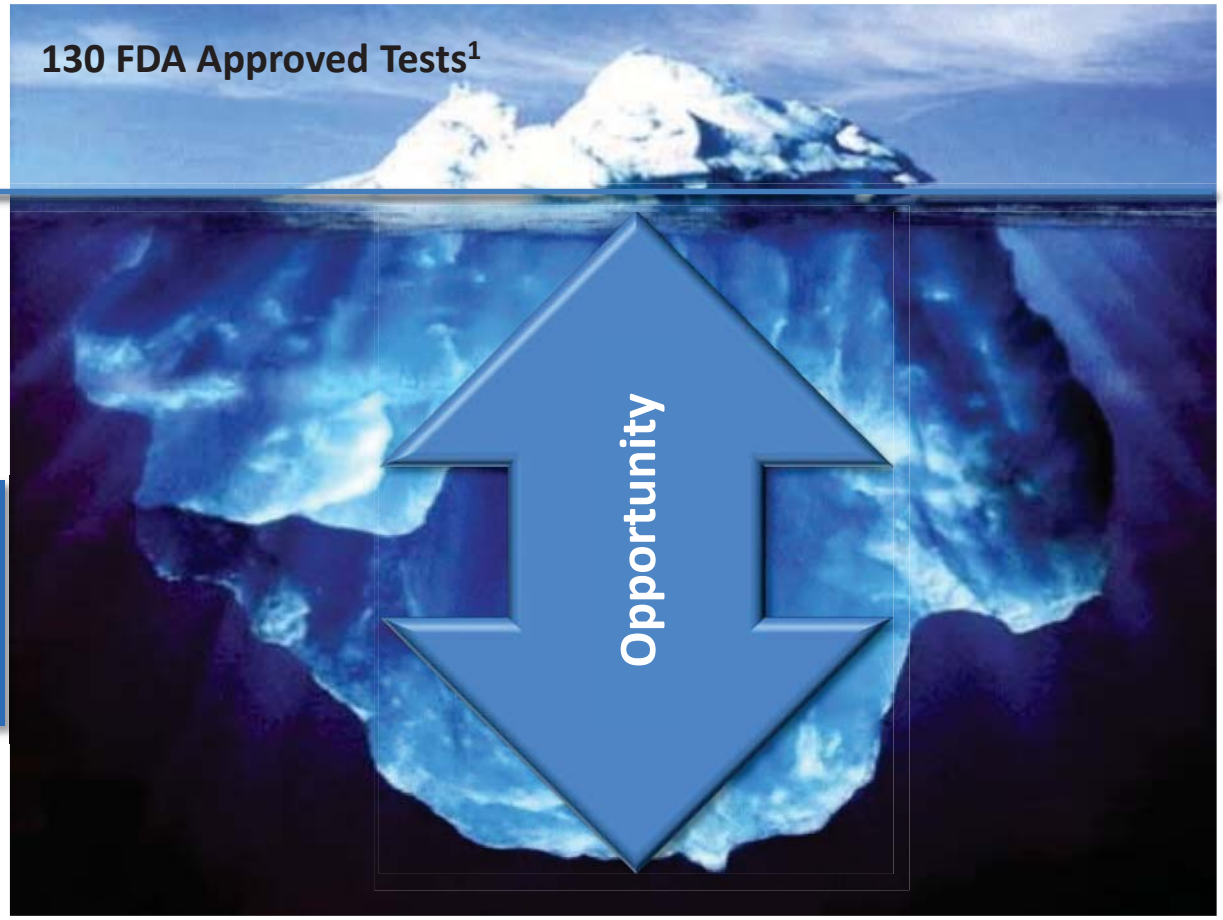
250[1]

How many proteins are below currently detectable levels?

Potential is Large:

Human Proteome = 25,000 genes

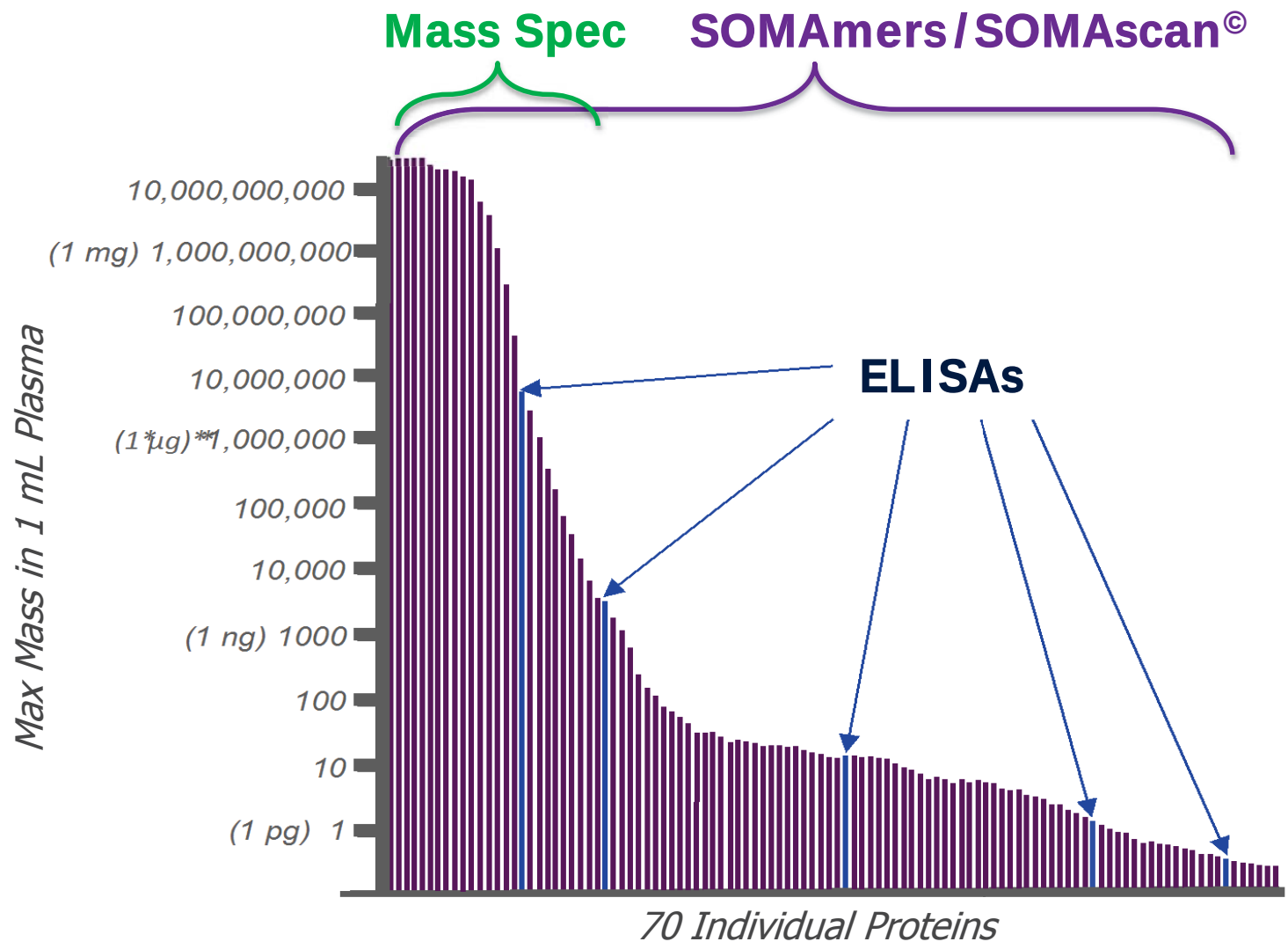
Secreted Proteins >2,500



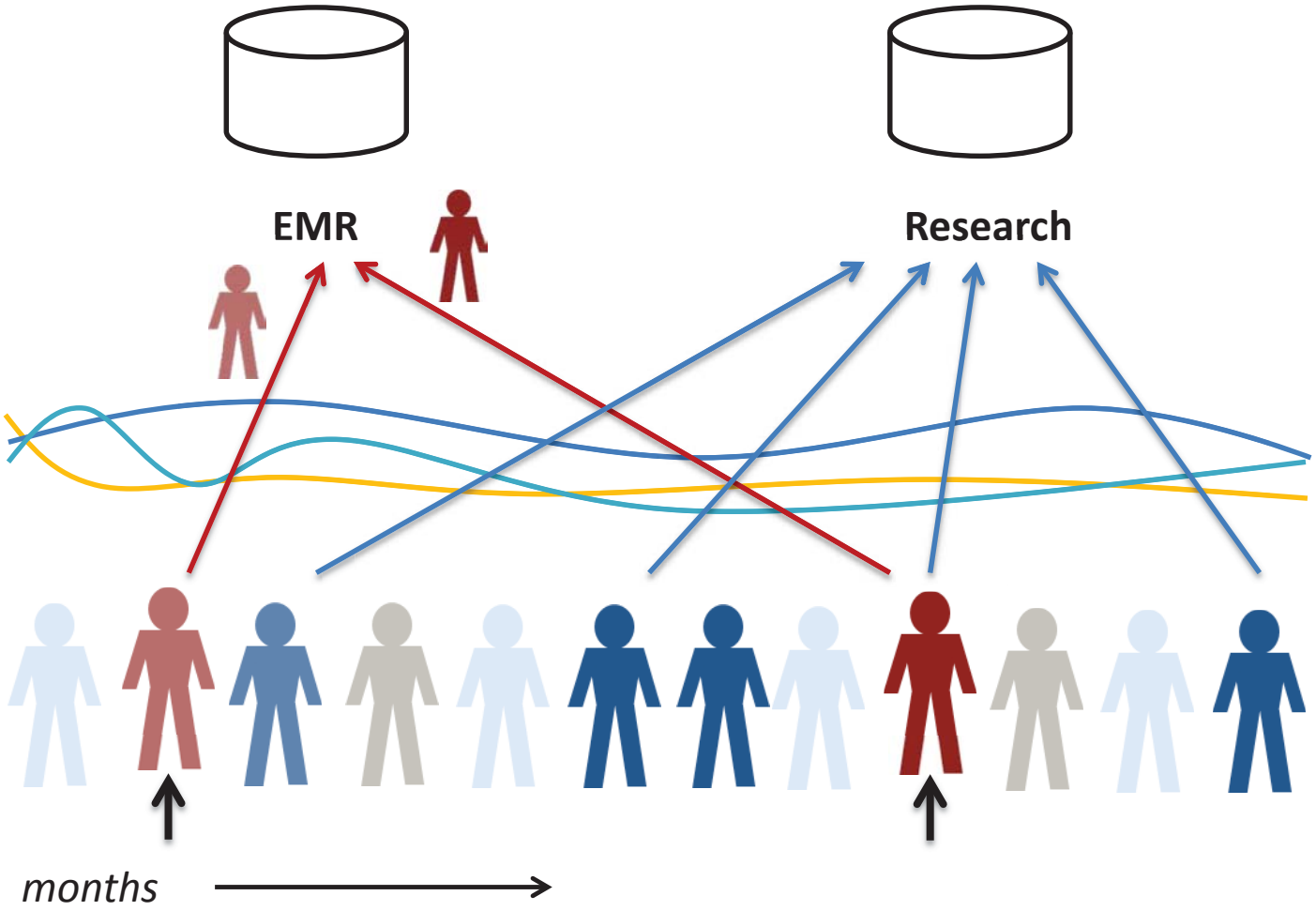
[1]Anderson and Anderson, Molecular & Cellular Proteomics 2002: 1.11 845-867

Courtesy of David Walt, Tufts University

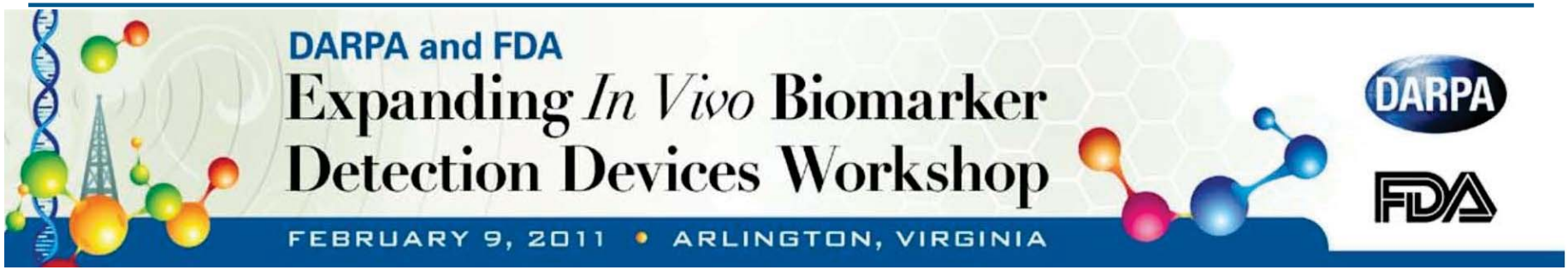
Proteomics: current methods



More biochemical inputs from one person



Continuous Monitoring:
DARPA *In-Vivo* Diagnostics

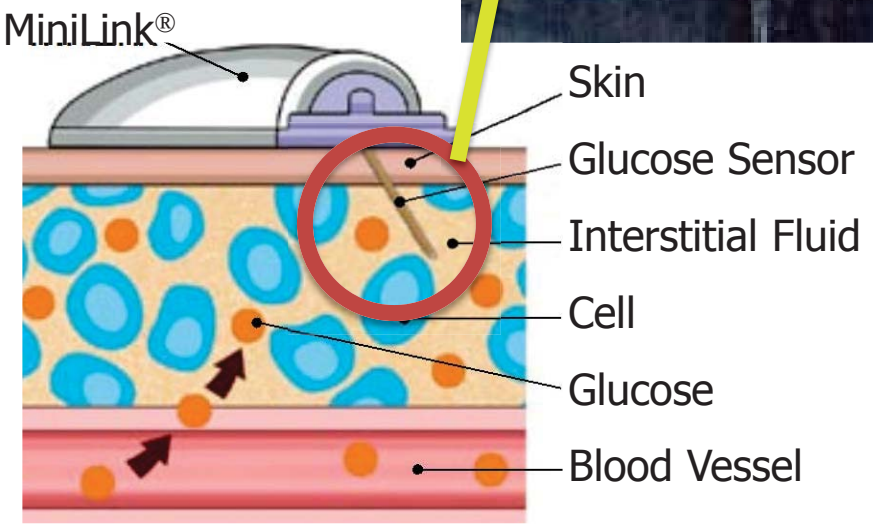


Current *in-vivo* biochemical measurements

Commercial blood oxygen monitor

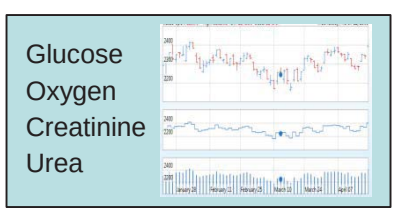
Commercial glucose sensors: last 2-7 days

Commercial tissue oxygen sensor: non-wearable



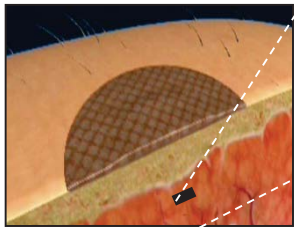
The future of *in-vivo* nanosensors

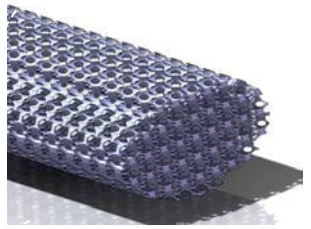
DATA

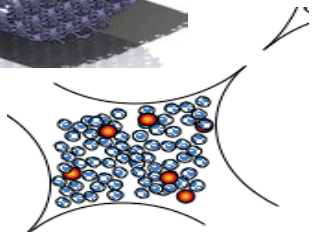


- Real-time streaming
- Controlled data distribution: Patient, Care provider, Physician

SENSOR





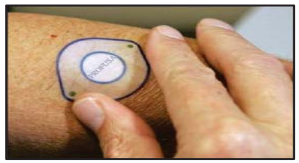


- Ultra small, hydrogel scaffold
- Tissue integration – overcome foreign body response and no embedded electronics
- Fluorescent sensing nanospheres

ELECTRONIC HEALTH RECORDS

- Doctors/caregivers real-time access
- Complete historical perspective

READER

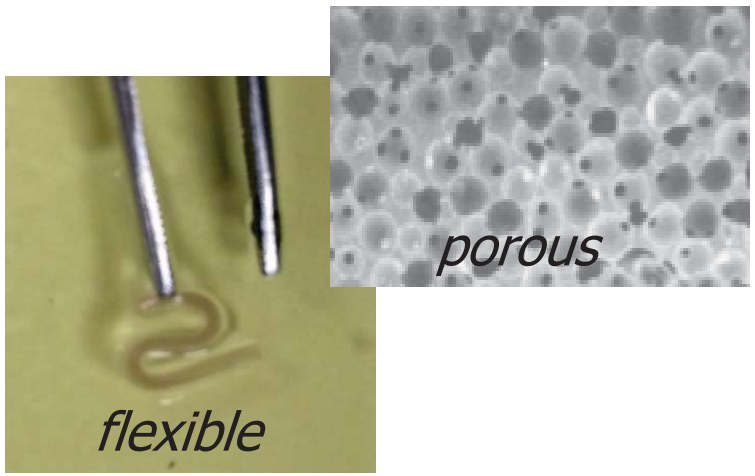


- Thin patch or hand-held wand
- Self-calibrating optics
- Multi-channel/color capable

Sensor synthesis

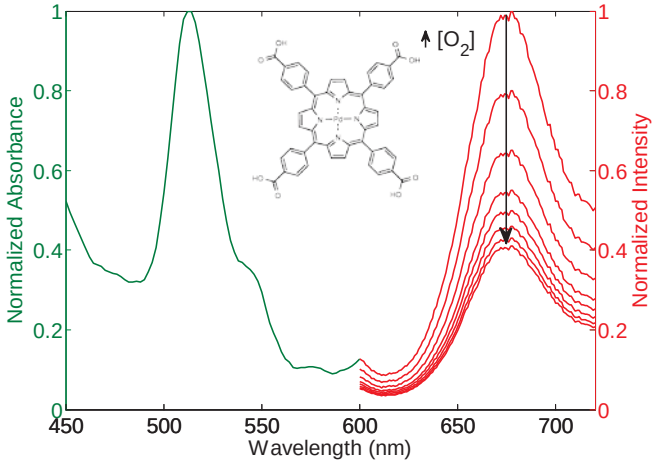
Tissue-integrating Biomaterials

- Flexible yet strong formulation
- pHEMA-based hydrogel
- Sphere-templated to produce interconnected pores



Fluorescent Chemistry

- Oxygen, glucose and lactate sensitive dyes developed



- Other near-term analytes: pH, urea, creatinine, histamine, Na^+, ethanol, and billirubin

Discussion

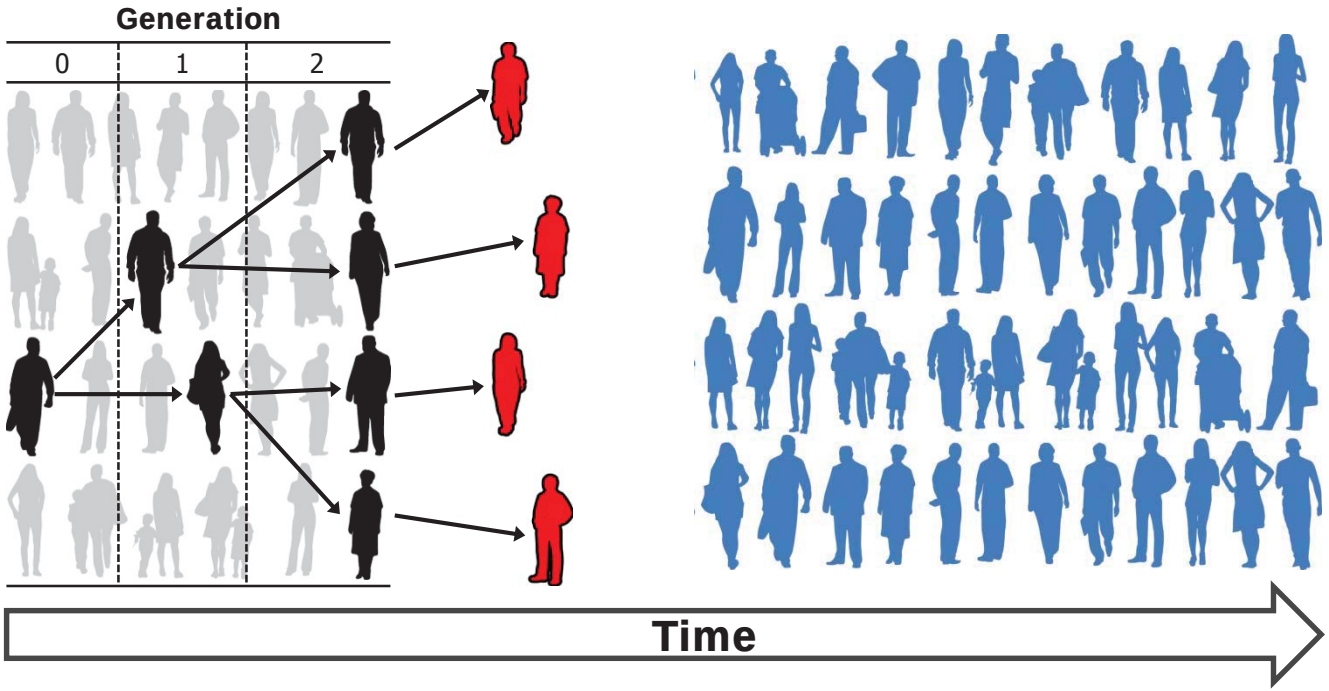
Future health paradigm:

- Individual health monitoring based on rapid, distributed, sensitive biochemical tests
- DARPA technology for new devices with seamless integration of biospecimen collection/continuous monitoring, analysis, and electronic reporting

Opportunity space:

- New business models that leverage information to incentivize the cost of clinical validation
- Health IT tools for increased patient access and autonomy, e.g.:
  - fine control of data privacy/sharing with specific recipients
  - electronic enrollment in clinical trials and remote participation
  - user authentication and data provenance

Outpace the Spread of Infectious Disease

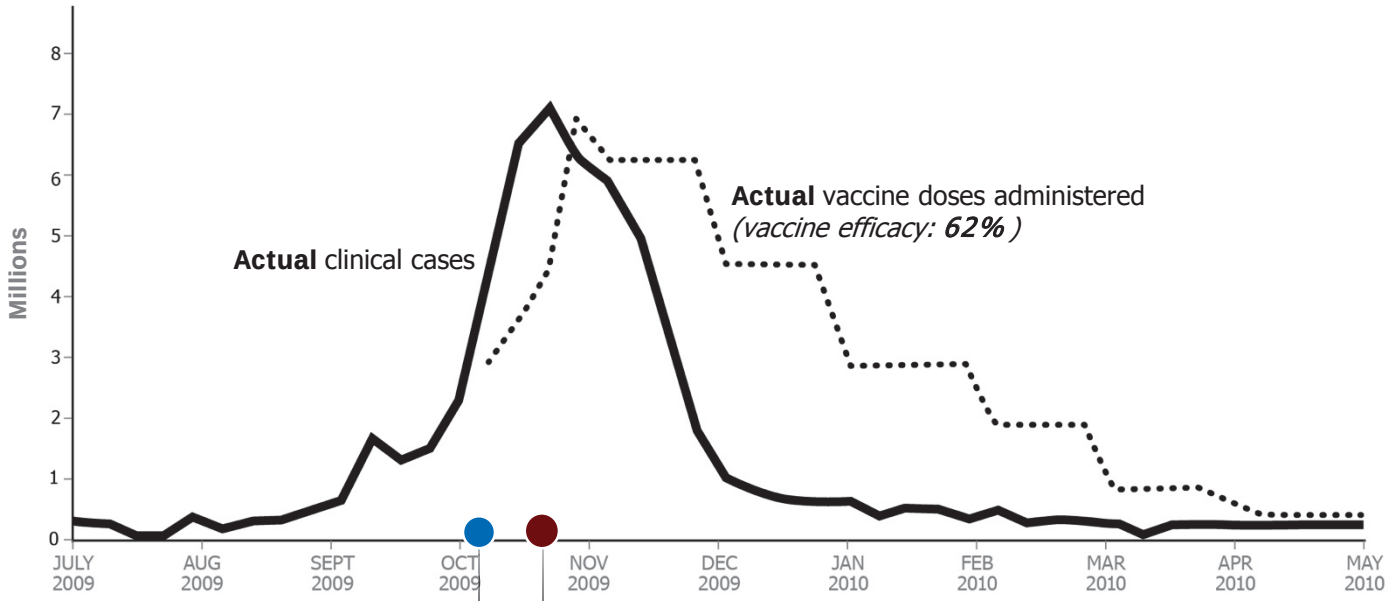


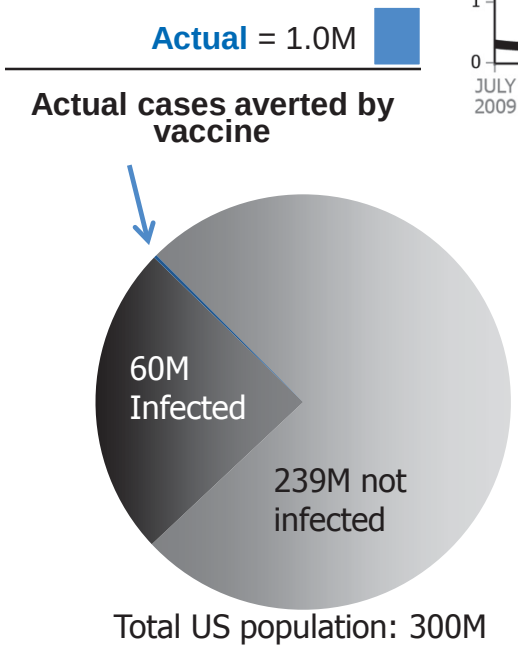
DARPA Interventions

- **Distributed diagnostics:** Molecular and analytical methods suitable for use outside hospital settings
- **New vaccine platforms:** RNA-based vaccines with controlled immunogenicity able to be designed and manufactured up rapidly

Case Study: H1N1 2009-2010 Vaccine Program

1.0M actual clinical cases averted

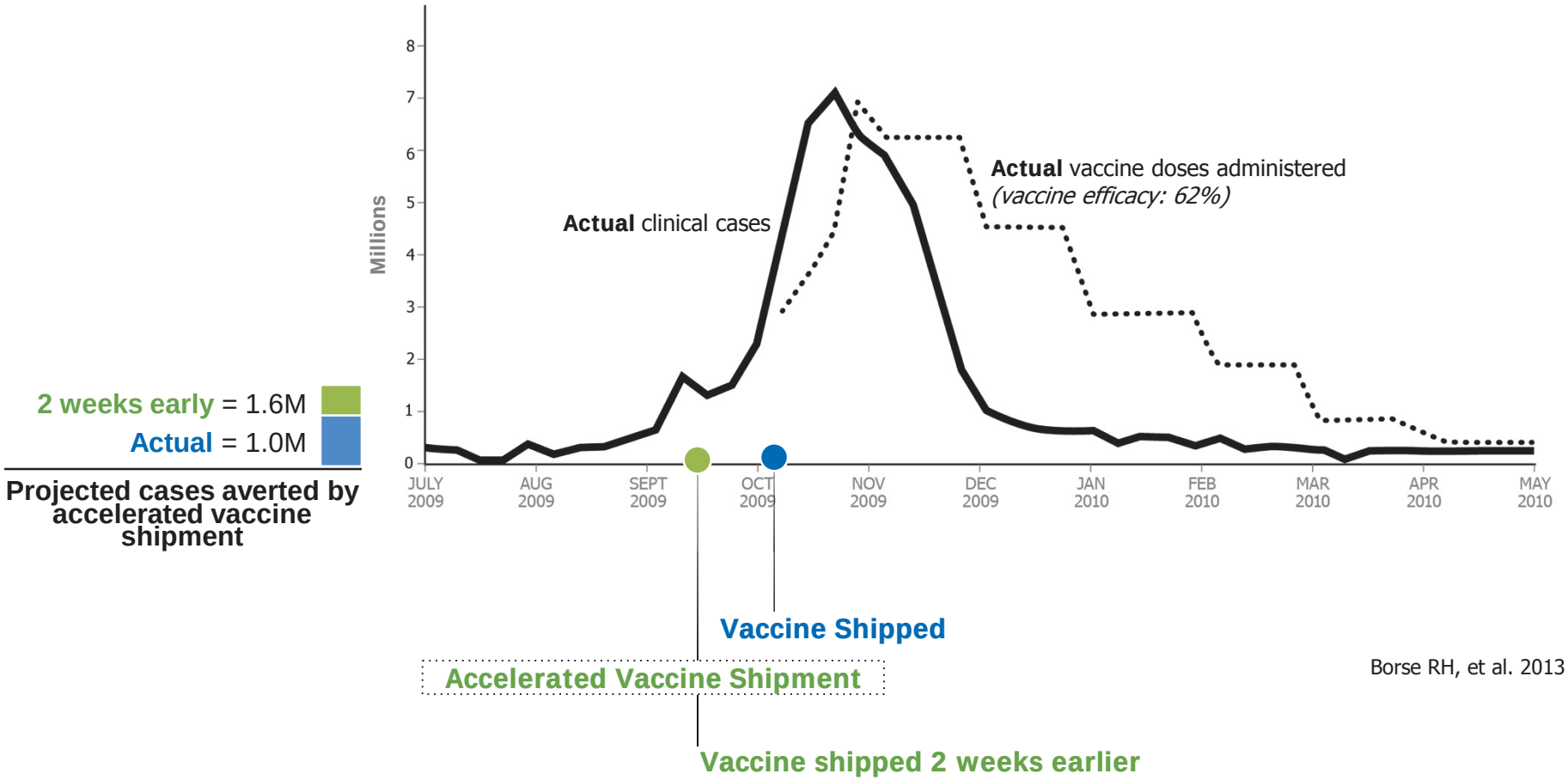




Borse RH, et al. 2013

CDC Projected Improvements from Accelerated Shipping

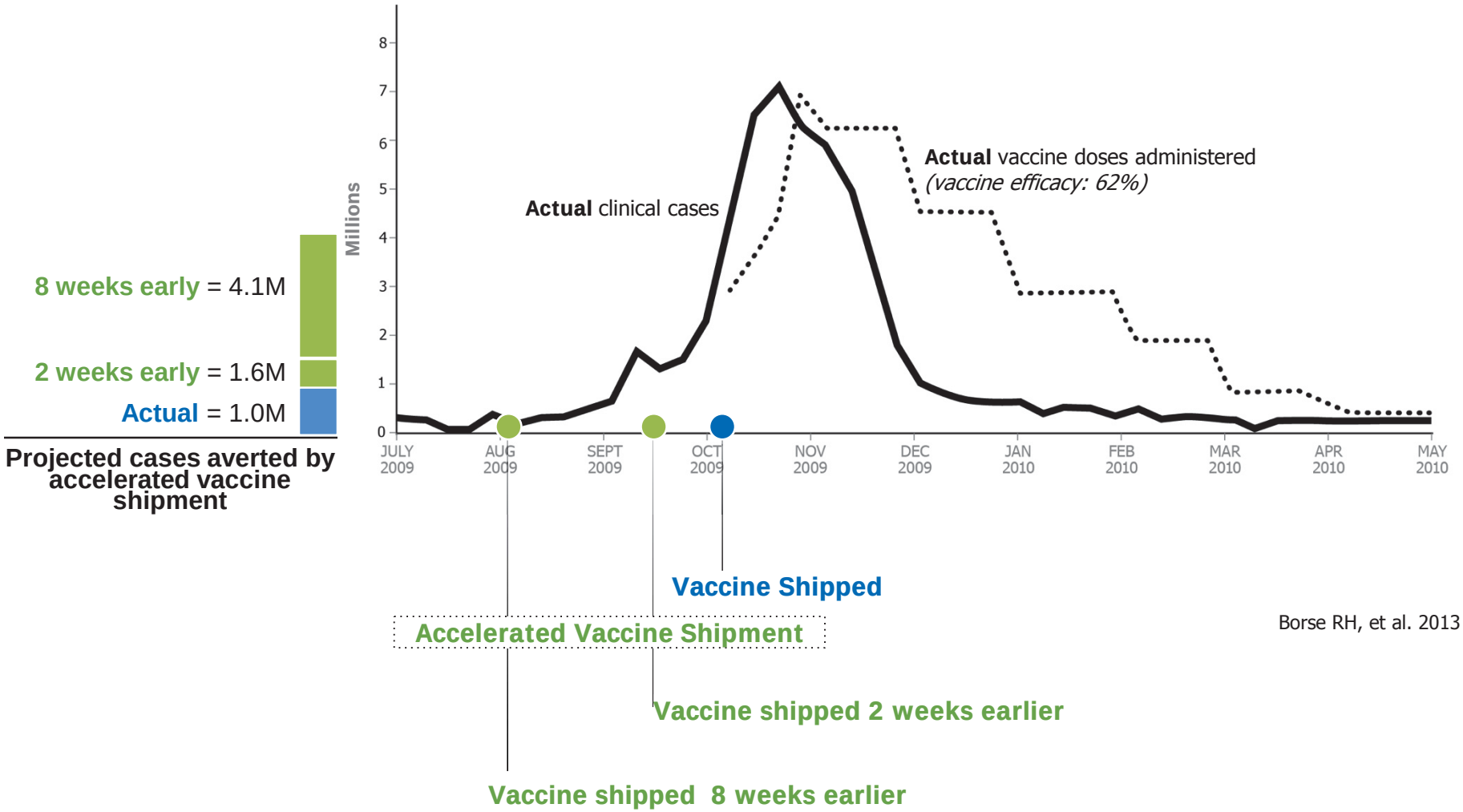
1.6M clinical cases averted from shipping 2 weeks earlier



Borse RH, et al. 2013

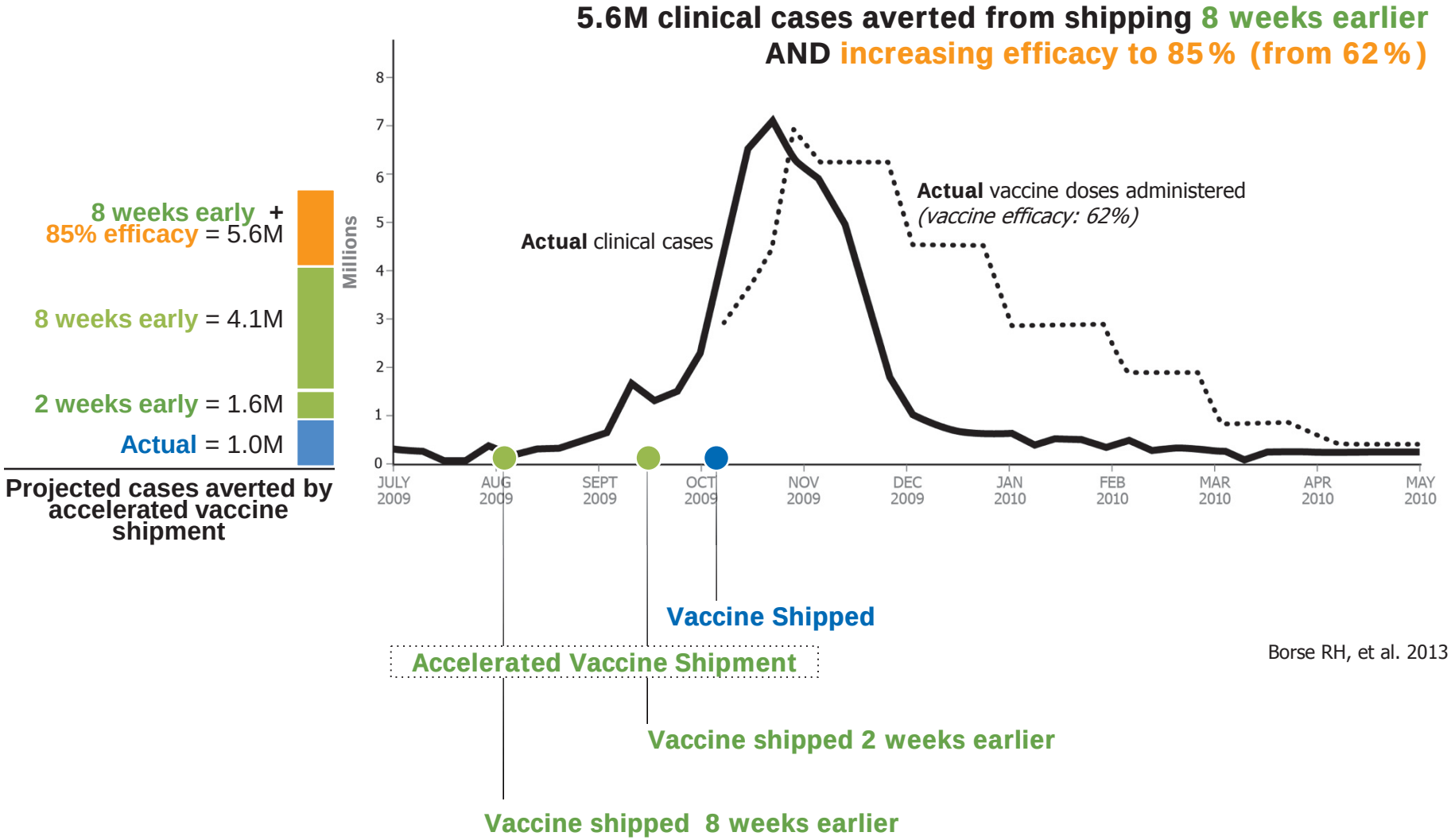
CDC Projected Improvements from Accelerated Shipping

4.1M clinical cases averted from shipping 8 weeks earlier



Borse RH, et al. 2013

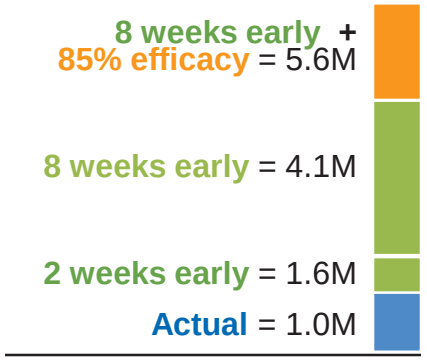
CDC Projected Improvement from Accelerated Shipping and Increased Vaccine Efficacy

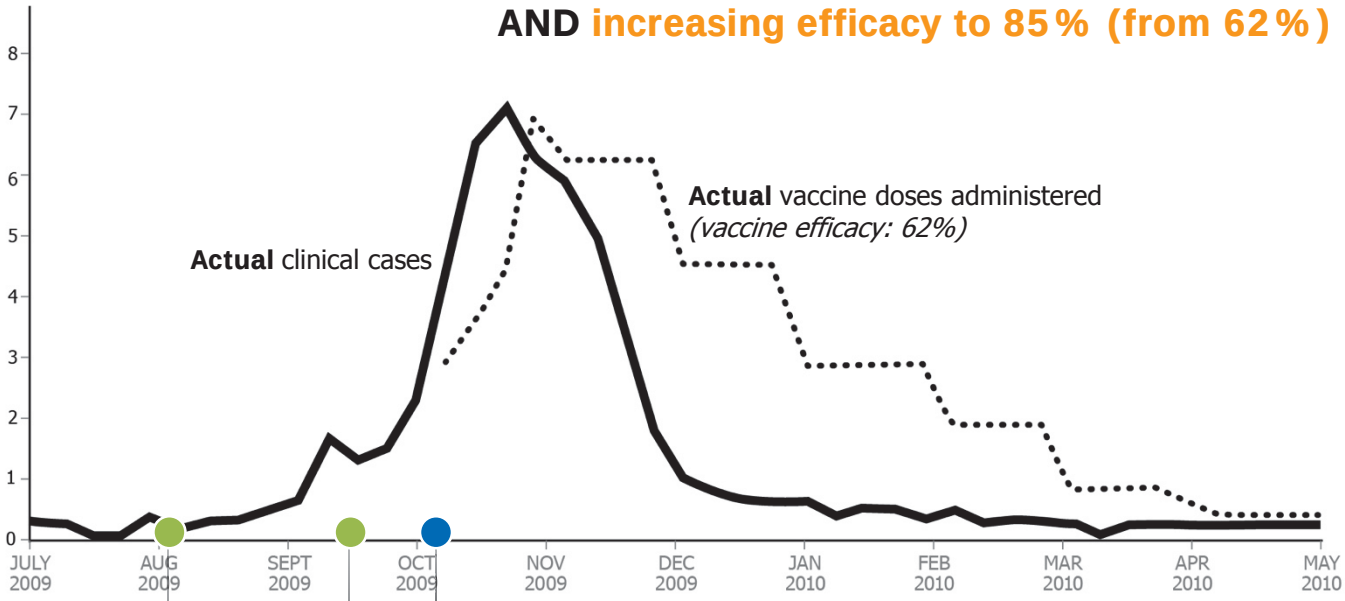


Borse RH, et al. 2013

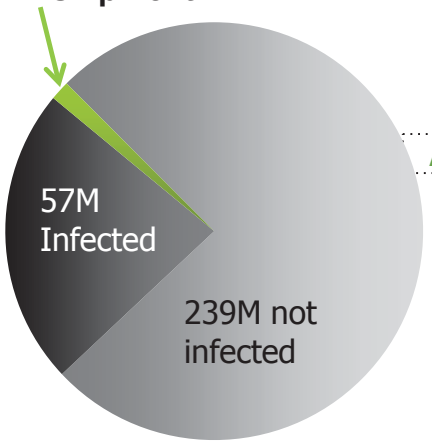
CDC Projected Improvement from Accelerated Shipping and Increased Vaccine Efficacy

5.6M clinical cases averted from shipping 8 weeks earlier AND increasing efficacy to 85% (from 62%)





Projected cases averted by accelerated vaccine shipment



Total US population: 300M

Vaccine Shipped

Accelerated Vaccine Shipment

Vaccine shipped 2 weeks earlier

Vaccine shipped 8 weeks earlier

Borse RH, et al. 2013

Selection: Speed and Effectiveness

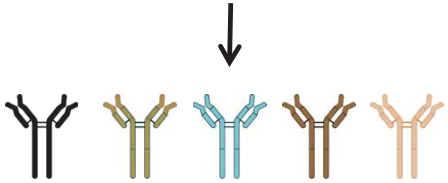
Immunize mice/animals against a known pathogen or protein antigen

Phage Display

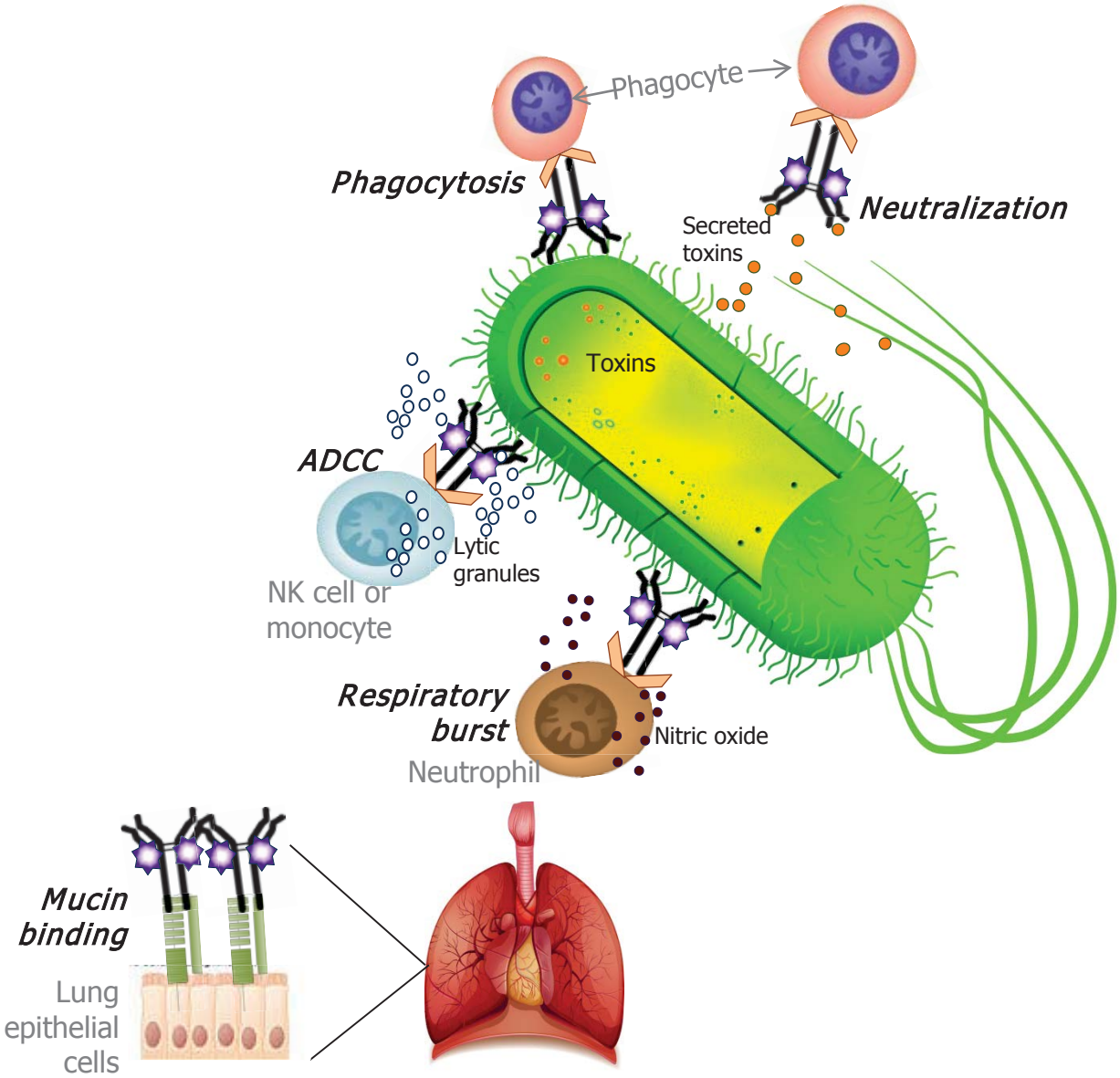
Single B-cell technology (antigen sorting, supernatant screening)

Hybridoma Technologies

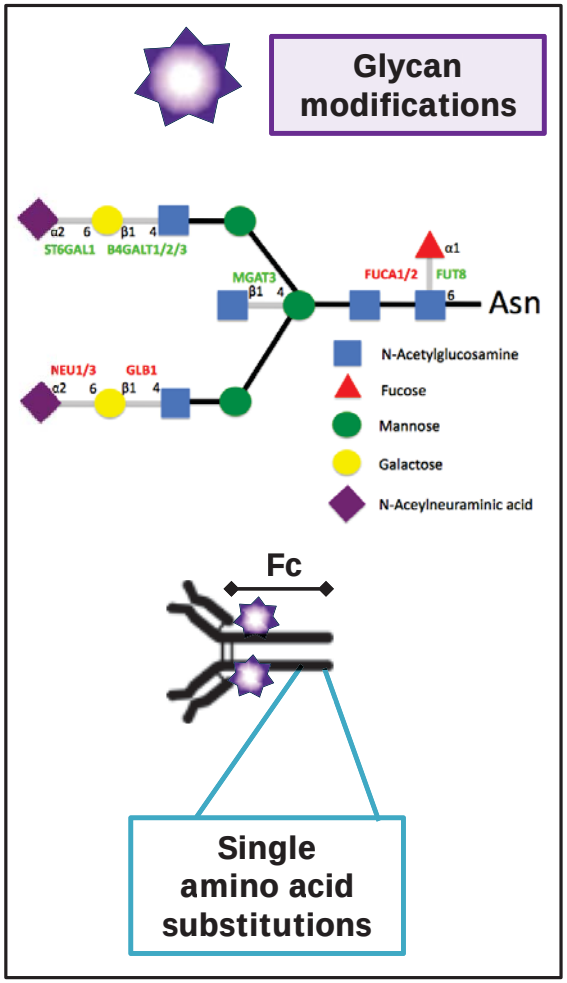
NGS of the Immune Repertoire



Modification to Enhance Effect, Duration, Location



Fc Enhancement



Selection, Modification, and Design

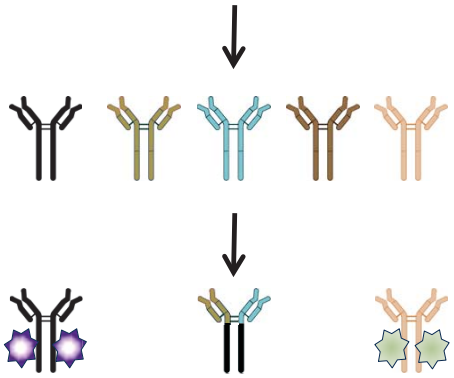
Immunize mice/animals against a known pathogen or protein antigen

Phage Display

Single B-cell technology (antigen sorting, supernatant screening)

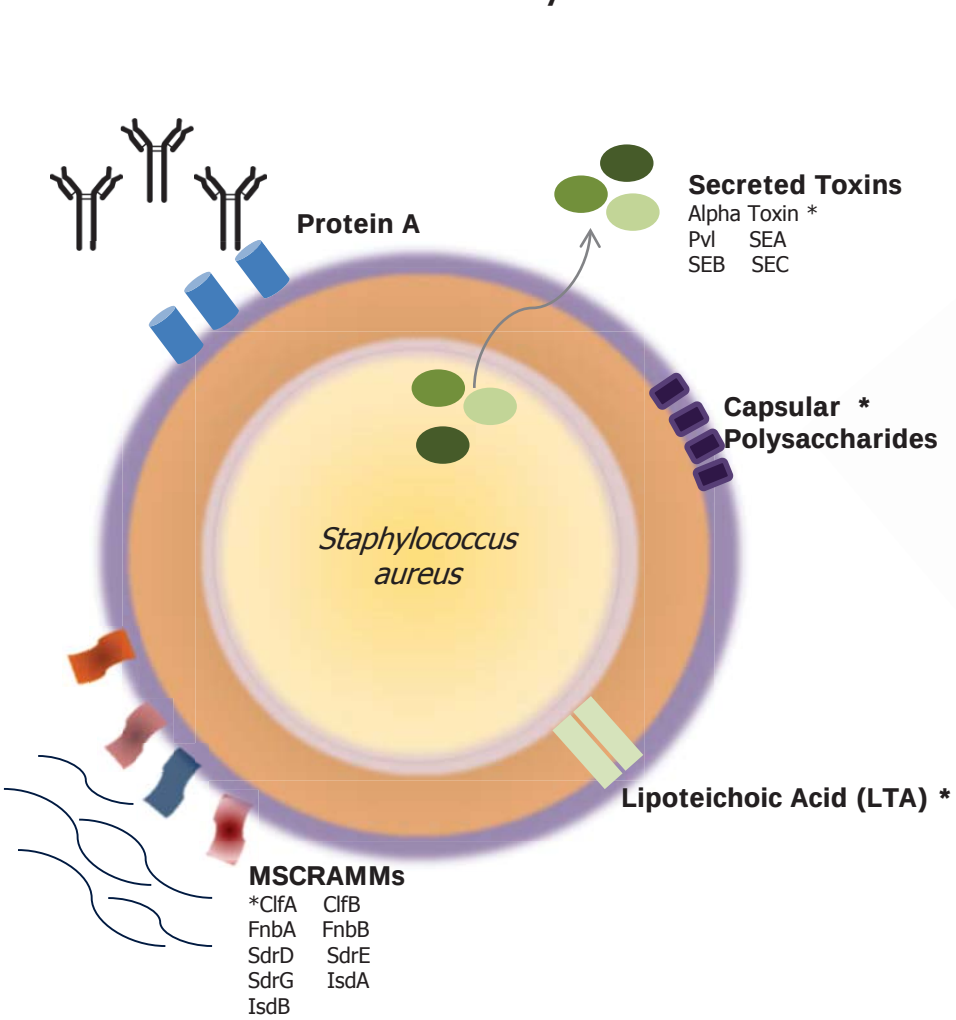
Hybridoma Technologies

NGS of the Immune Repertoire

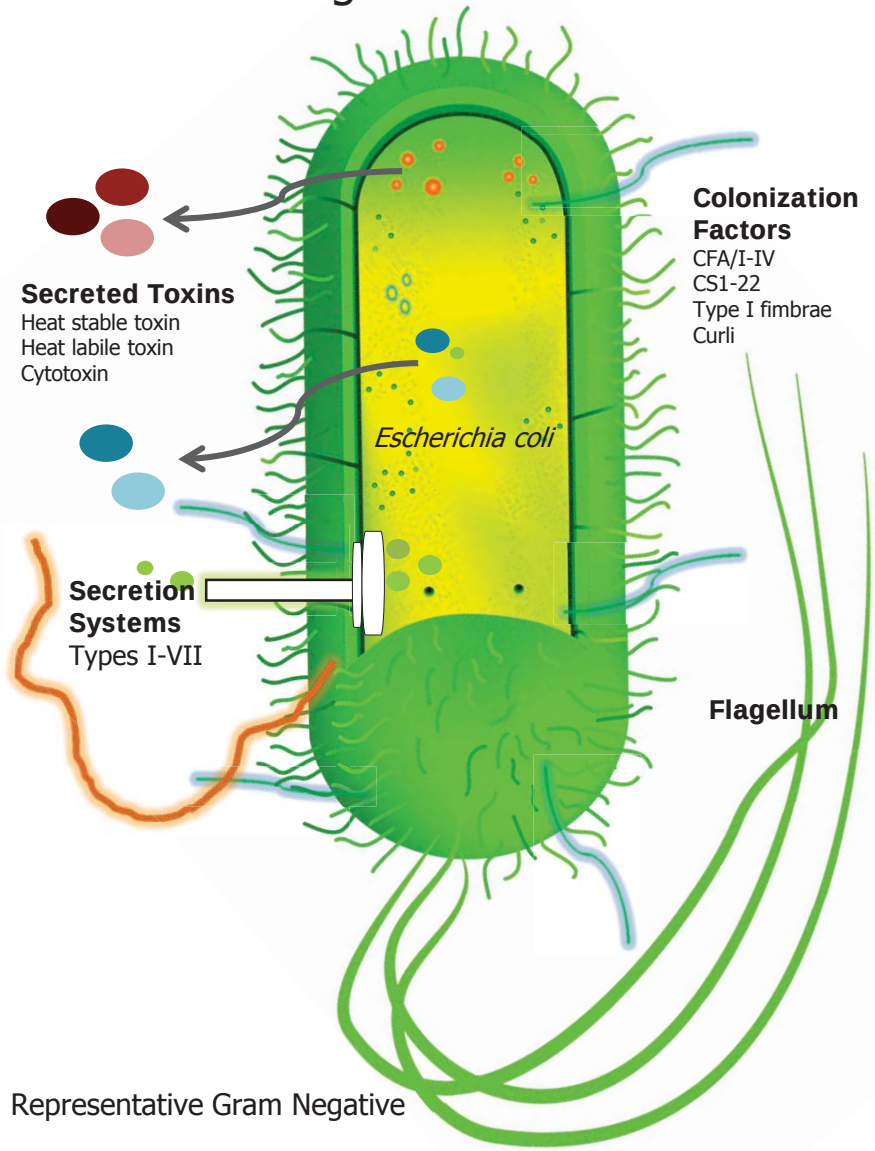


Antibodies and Bacterial Pathogenesis

Many Virulence Factor & Mechanistic Targets



Representative Gram Positive



Representative Gram Negative

Approaches to Combating Antibiotic Resistant Bacteria

Antibody Discovery Platforms

- Rapid, accurate technologies for antibody discovery against bacterial pathogens

Antibodies Effective Against Various ARB

- Effective antibodies targeting various aspects of bacterial virulence (currently available and/or discovered with new platforms
- Antibody cocktails
- Multi-specific Antibodies

Effector Function Modification/ Novel Delivery

- Fc modifications
- Nucleic acid delivery