IMI Stakeholder Forum, Consultation Workshop: Preparation for Emerging Diseases. Brussels, 29th September 2016

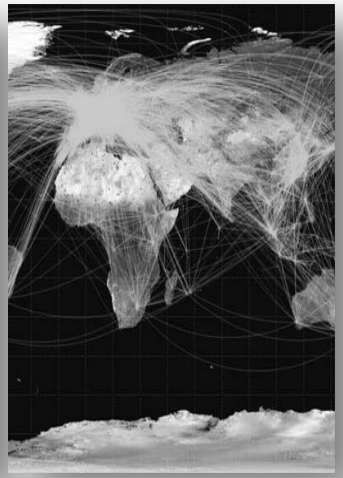
Kenny Simmen, Ph.D.
Vice President, Innovation

Infectious Diseases and Vaccines

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Infectious Diseases are still on the rise…

Population Growth



Travel

Megacities

Climate change

Impact of social media / channels on disease awareness..

Trends/Aspirations:

- Improved prevention & treatment of respiratory infections (influenza /RSV)
- Curing versus chronic management (today – HCV, future – HBV & HIV)
- Disease interception for public health benefit (dengue, ebola, zika)
- Enhanced “bio-preparedness” to tackle novel emerging infections

Which pathogens to prepare for?

The Known:

"Naturally occurring outbreaks"

- Respiratory Infections (influenza/SARs/MERS, coronaviruses)
- Filoviruses (Ebola, Marburg)
- Flaviviruses (dengue, Zika, West Nile)
- Alphaviruses (chikungunya)
- Food and water borne bacterial infections
  - E.coli, Shigella, Salmonella

"Unnaturally occurring epidemics = deliberate disease outbreaks"

- Anthrax / Y. pestis / Burkholderia
- Smallpox
- Synthetic viruses/engineered pathogens

The Unknown:

- ~130 viruses currently known to infect humans
- New pathogenic forms may arise & spread naturally due to intrinsic variation & selection
- Changes in zoonotic vectors
- Malicious synthetic viruses/engineered pathogens derived from "dual use" research of concern (DURC)

Toolbox of current antivirals: saving patients lives

- **Polymerase inhibitors -** nucleoside/tide (HSV, CMV, HIV, HBV, HCV)
- **Polymerase inhibitors -** Non nuc (HIV NNRTIs, HCV NNI)
- **Protease Inhibitors** – HIV, HCV
- **Fusion / Entry Inhibitors** – HIV (gp41, CCR5), RSV
- **Integrase Inhibitors** – HIV
- **Replication Inhibitors** – HCV NS5A
- **Release/Egress Inhibitors –** Influenza (neuraminidase)
- **Antisense** - CMV
- **Ion Channel Blockers** - Influenza
- **Interferons** – HCV, HBV

Examples of therapeutic drug discovery approaches to the "known" viral pathogens:

Targeting conserved features of viral life-cycle:

- **POLYMERASE INHIBITION (with nucleoside analogs).**
- Advantages:
  - Target multiple related viruses with same /similar molecule, due to conservation of enzymatic site.
  - Considerable pharma/academic knowledge base on chemical manufacturing / clinical development pathway.

Targeting pathogen-specific features of viral life-cycle:

- **VIRAL ENTRY / FUSION (with biologics/mAbs)**
- **POLYMERASE INHIBITION (with non-nucleosides)**
- **PROTEASE INHIBITION (small molecules)**
- ***GENOME TARGETING (gene silencing/editing)***
- Advantages:
  - Pathogen-specific molecules. Less chance of generating drug-resistance in co-infecting viruses. *Challenging discovery path…especially gene editing.*

R&D Process - & IMI Antibiotic precedents

- Target identification
- Target validation
- Screening / design
- Lead identification
- Lead optimization
- NME (new molecular entity) declaration

- Scale up & formulation
- IND-enabling TOX/PK
- Phase I
  - PK/PD
  - Safety
  - Dose Definition
- Phase IIa - proof of concept (POC)

- Phase IIb - Phase III
- Manufacturing for commercial product
- NDA (new drug application) filing & approval
- (Line extensions)
- Post-approval studies

IMI ND4BB – ENABLE

IMI ND4BB – COMBACTE

IMI ND4BB – TRANSLOCATION

Proposed "ECRAID" H. Goossens et al

What are the barriers to rapid discovery, development & approval of novel agents today?

- Lack of clarity on when a threat is imminent – need for a clear signal from public health bodies in EU to initiate special programs.
  - Does this require better epidemiology integration across EU states?
- Lack of certainty on sustained state / EU funding for either academic research or biotech/pharma funding for programs on pathogens that may resolve naturally before the next budget cycle…
- Lack of certainty on regulatory approval pathways (how to prove efficacy?), and reimbursement approach.
  - "no profit / no loss", or a "shared risk / shared benefit" approach?
- Industry can work most effectively when an existing basic research knowledge-base has established "R&D toolbox" of reagents and models (preclinical and translational) that can enable drug development.
  - Is there a role for PPPs in enhancing the R&D knowledge in EU on these emerging pathogens, or on the novel technologies themselves (eg biologics/gene editing)? Access to BSL4 facilities.
  - Is there still sufficient pharma / biotech expertise in ID in Europe?
  - Should real drug discovery be initiated, or just the"capability"?

How to overcome the lack of "market pull" to support R&D in these pathogens?

Examples of R&D stimulus: from anthrax to ebola

PROJECT BIOSHIELD (US Dept of Health & Human Services) 2004

- $3.4B in Special Reserve Fund (2004-08), federal acquisition program
- Enhanced NIH ability to expedite R&D of "medical countermeasures against biological, chemical, or radiological agents and to speed their delivery and use in time of an attack"
- Gave FDA authority to grant Emergency Use Authorization before licensure
- Initial focus on four threats: anthrax, smallpox, botulinum toxin & radiological / nuclear agents
- Countermeasures acquired: anthrax vaccines and treatments for anthrax and botulism

How to overcome the lack of "market pull" to support R&D in these pathogens?

Examples of R&D stimulus: from anthrax to ebola

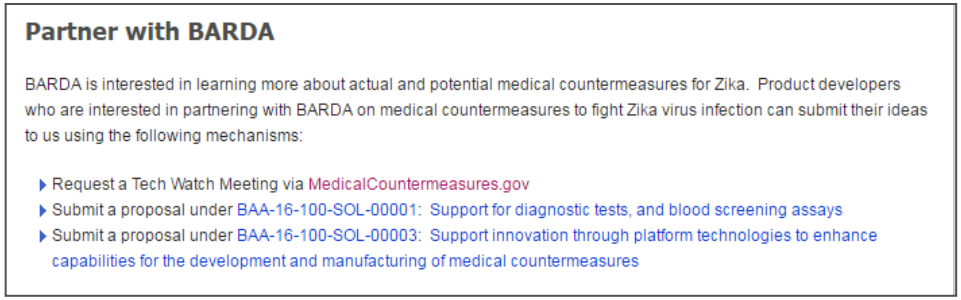
>2009: US Dept of HHS / NIH / BARDA* and the move to broader funding for biosecurity (including natural threats)

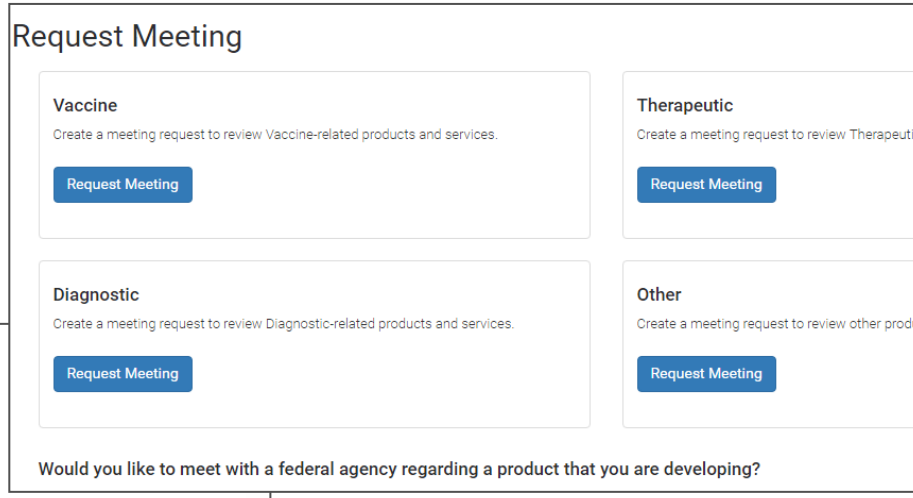
- The National Medical Countermeasures Response Infrastructure
- 2009 Pandemic Influenza Stockpiling Programs (vaccine/antiviral)
- Integrated Portfolio Approach; influenza (Janssen; Visterra), antibiotics (GSK, AZ)
- 2012 HHS awards $400M to establish three Centers for Innovation in Advanced Development and Manufacturing (CI ADMs) – covering 35% of costs over 5 years to increase capacity in response to a need (Novartis, Emergent, Texas A&M)
- 2016 - CARB-X Early stage accelerator for antibiotics (with The Wellcome Trust, UK AMR Centre, California Life Sciences Institute, Mass Biotech Council)
- Zika – coordinated response – funding diagnostics, vaccines & therapeutics

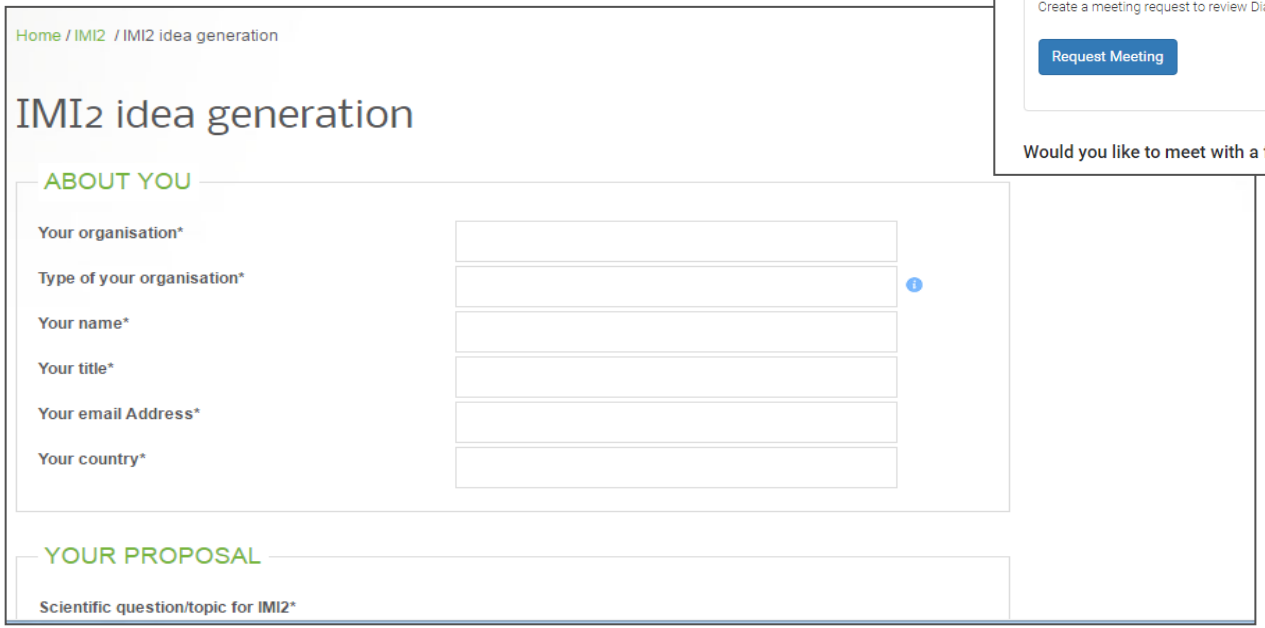
>2014: EU IMI DRIVE-AB, Driving re-investment in R&D and responsible antibiotic use.
>2014: EU IMI / US - EBOLA – diagnostics, therapeutics, vaccines.

On-line interfaces with BARDA and IMI

- Relatively low barrier to contact either







The potential role of European PPPs

ADVANTAGES

- Potential role to link the EU/WW epidemiology trigger to the initiation of rapid action on vaccines or therapeutic programs (if new threat)
- Ability to integrate existing pharma activities with academia/EMA/citizen groups. Helpful for prioritization.
- Enhance EU funding to leading EU researchers in the ID field, and potentially to fund the late-stage clinical development.
- Focus on gaps not yet addressed:
  - disease and pathogen research on neglected threats, including diagnostics
  - Tools / technology platforms – biologics / gene editing / advanced therapies

DISADVANTAGES (real / perceived)

- Lag time to initiate work via IMI is a potential issue, especially given the urgency needed (needs to be months, like Ebola+).
- Clarity needed on true value of incoming platform technology from EfPIA companies, and alignment on responsibilities
- Risk of committing to the "wrong" threat / contract flexibility needed.

Lessons Learned / Janssen

US NIH - collaboration/contract on Influenza biologics (2009-2013)

US BARDA - collaboration/contract on Influenza antiviral (2015-2019)

US NIH/VRC - CRADA on adeno-based Filovirus vaccines (2002-2008)

US NIAID/DMID - contract on multivalent Filovirus vaccines (2008-)

US BARDA – heterologous prime-boost Ebola vaccine regimen (Ad26.ZEBOV and MVA-BN-Filo) – CMC/validation (2015-2020)

EU IMI2 EBOLA+ – heterologous prime-boost Ebola vaccine regimen (Ad26.ZEBOV and MVA-BN-Filo) – clinical development

- EBOMAN (2014-2016) - EBODAC (2014-2017)
- EBOVAC1 (2014-2017) - EBOVAC2 (2014-2017)

- ✓ Long term engagement needed with US & EU.
- ✓ Rapid progress can be made (ebola example).
- ✓ Partners & funders need to be aligned/committed.
- ✓ Best to have smaller, more focussed consortia.
- ✓ Flexibility needed to adapt the workplans.
- ✓ IP is simpler in “bilateral” arrangements (NIH/BARDA)

Multivalent Filovirus Vaccine

NIH-DMID contract HHSN272200800056C

- *IMI-2 EBOLA+*
- *BARDA*

Monovalent Ebola program

Ebola Zaire + MVA-BN®-Filo

MVA-BN®-Filo

Multivalent program

- *NIH-DMID*

Multivalent program
NIH contract 2008

Today

2014

Ebola Zaire, Sudan, Marburg — Ad26.Filo Vaccine

+

Ebola Zaire, Sudan, Marburg — Ad35.Filo Vaccine

Ebola Zaire, Sudan, Marburg — Ad26.Filo Vaccine

+

BAVARIAN NORDIC — MVA-BN®-Filo

Ebola Acknowledgements

Bavarian Nordic

EBOVAC1 IMI2 Consortium

Janssen, London School of Hygiene & Tropical Medicine, Institut National de la Santé et de la Recherche Medicale (Inserm), University of Oxford

EBOVAC2 IMI2 Consortium

Janssen, London School of Hygiene & Tropical Medicine, Institut National de la Santé et de la Recherche Medicale (Inserm), University of Oxford, Inserm Transfert, Le Centre Muraz

EBOMAN Innovative Medicines Initiative (IMI2) Consortium

Janssen, Bavarian Nordic, Vibalogics

EBODAC IMI2 Consortium

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