ADDRESSING EBOLA: VACCINE & THERAPEUTIC DEVELOPMENT AND THE ANIMAL RULE

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ALLIANCE FOR BIOSECURITY

Mission

The Alliance for Biosecurity promotes a stronger, more effective partnership between government, the biopharmaceutical industry, and other stakeholders in order to advance their shared goal of developing critically needed medical countermeasures. The Alliance also seeks to develop sound public policy proposals that could bolster national efforts to rapidly develop, produce, stockpile, and distribute medical countermeasures.

Alliance for Biosecurity Regulatory Science Subteam:

- Convened to address regulatory science issues relevant to Alliance members and serve as a resource to coordinate comments to FDA and respond to Hill requests for technical, scientific feedback.
- Focus on FDA Animal Model Rule issues.
- Proactively consider opportunities for engaging FDA on regulatory science issues unique to medical countermeasures.

Alliance for Biosecurity

www.allianceforbiosecurity.org

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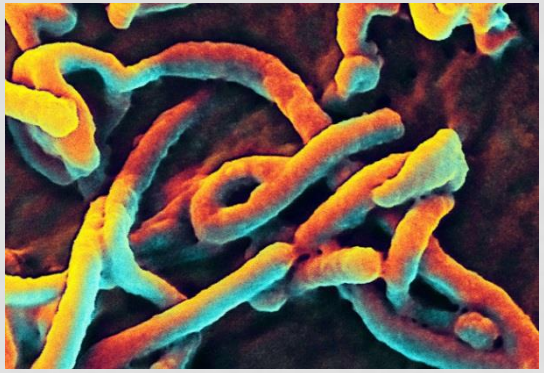
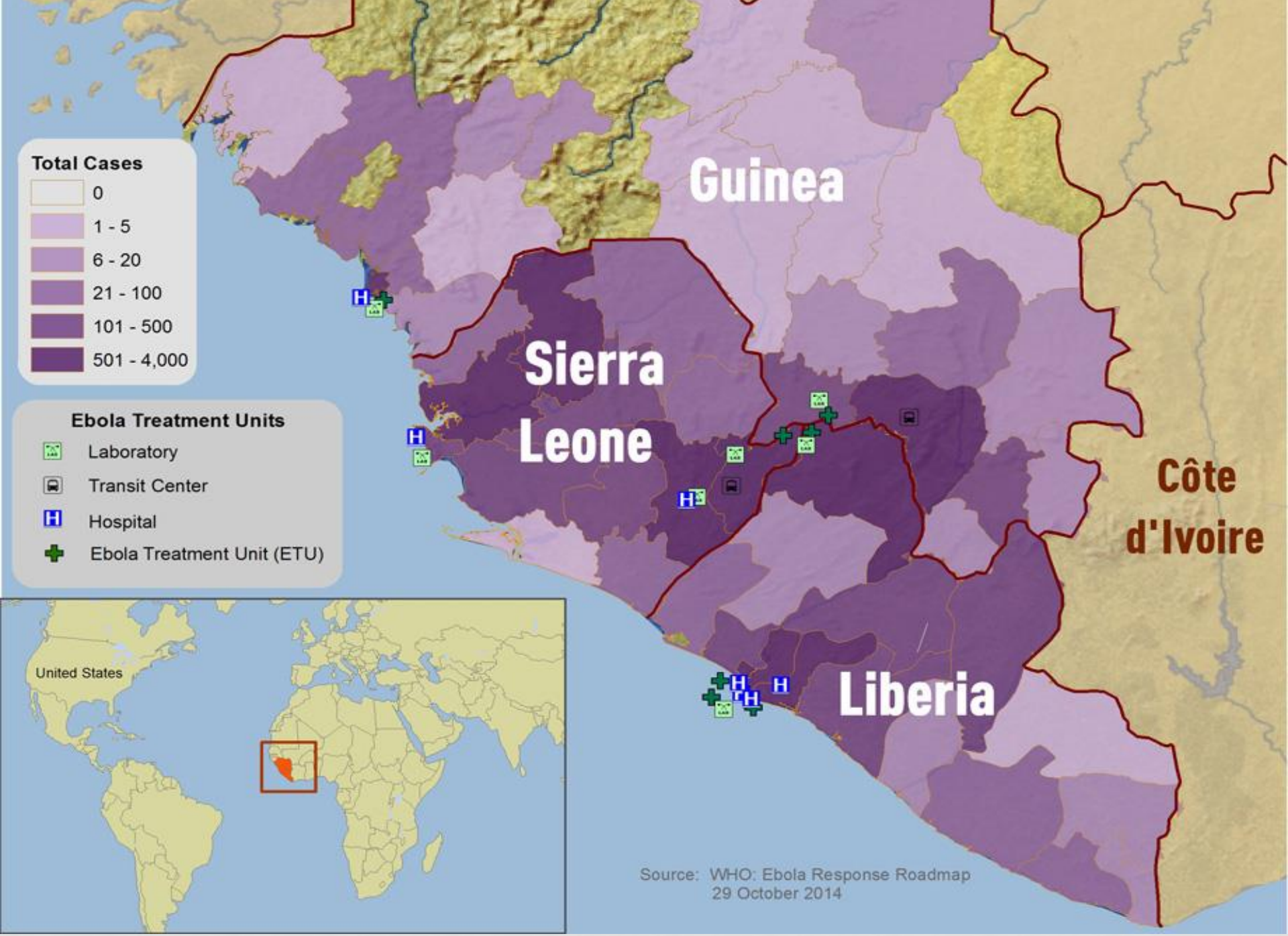
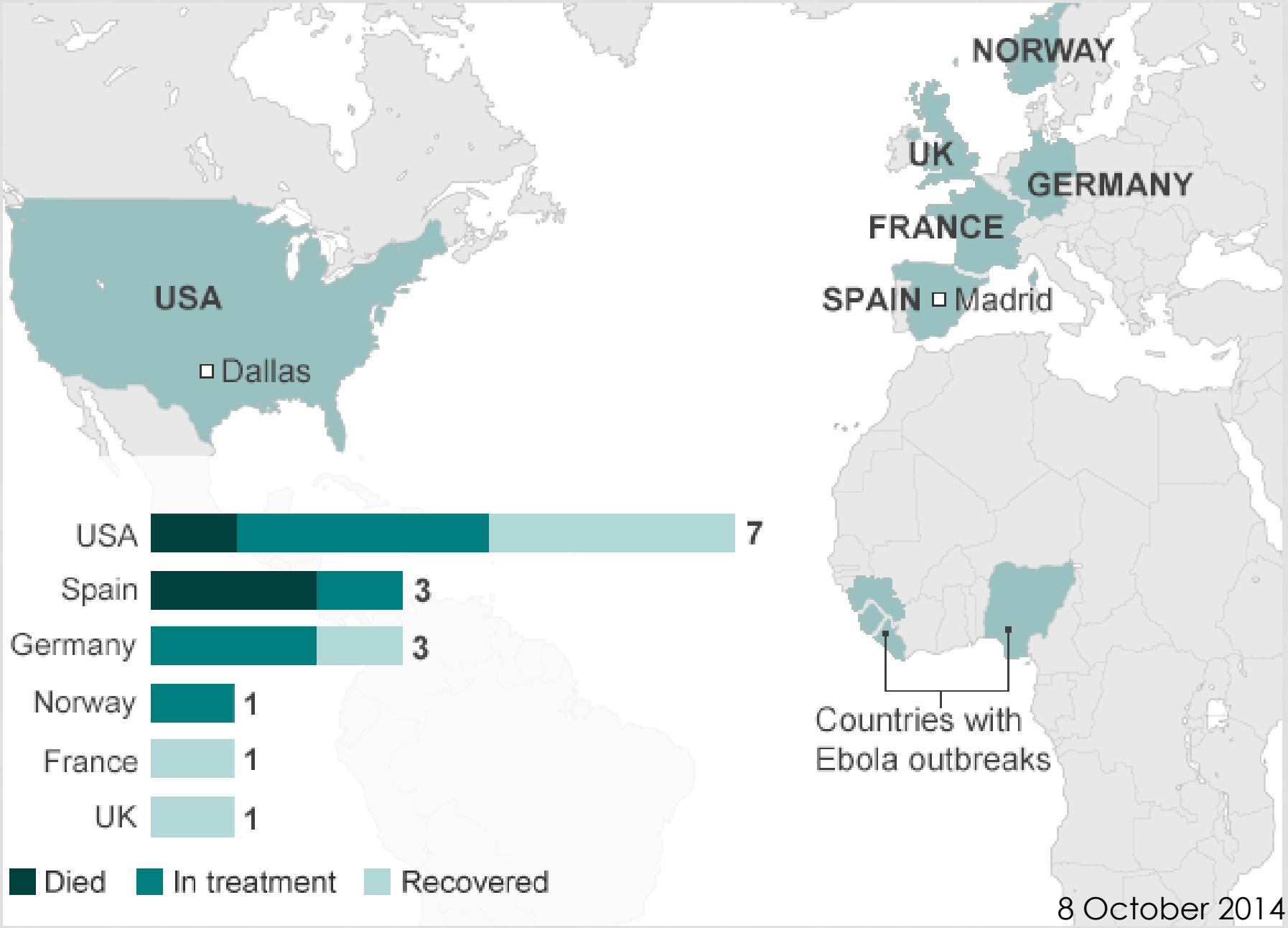
OUTLINE



- Update: Incidence
- FDA Animal Rule: What's the deal?
- The virus, the animal model
- Update: Vaccine Development
- Update: Therapeutic Development
- Discussion


Total Cases
0
1 - 5
6 - 20
21 - 100
101 - 500
501 - 4,000
Ebola Treatment Units
Laboratory
Transit Center
Hospital
Ebola Treatment Unit (ETU)
Guinea
Sierra Leone
Liberia
Côte d'Ivoire
United States
Source: WHO: Ebola Response Roadmap
29 October 2014



8 October 2014

http://www.bbc.com/news/world-africa-26835233

World Health Organization

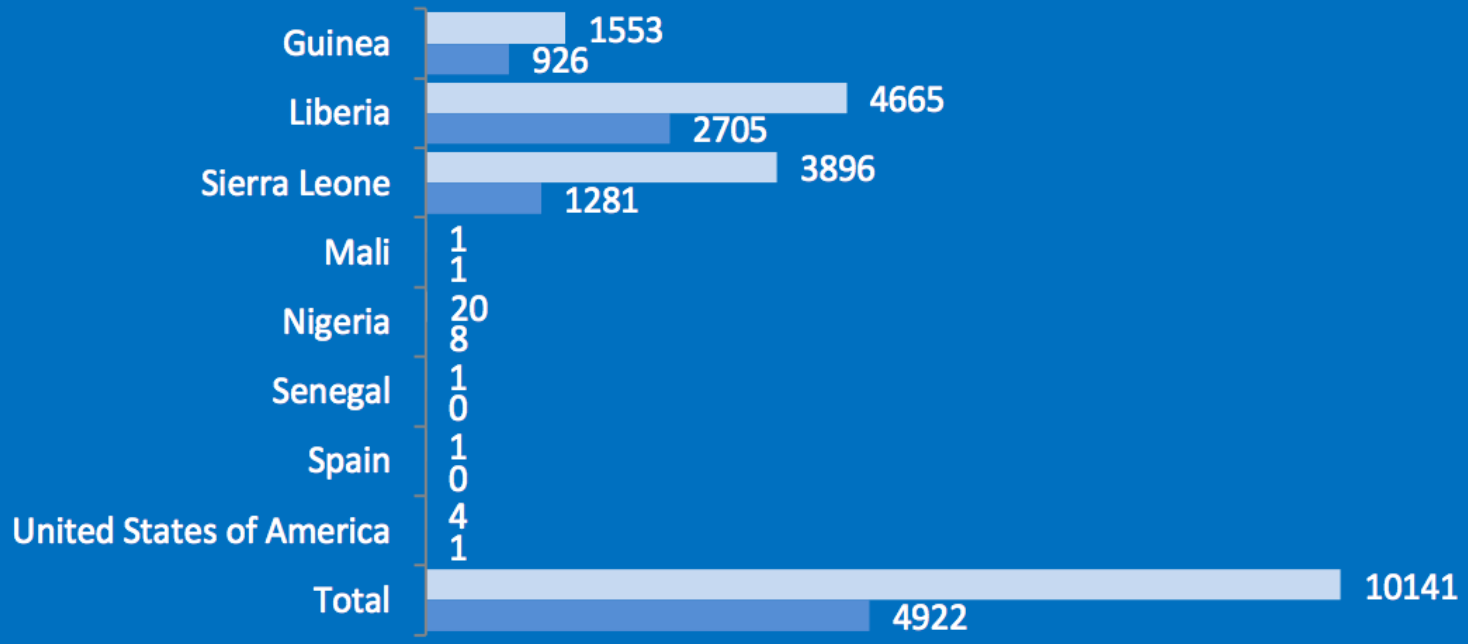
EBOLA RESPONSE ROADMAP SITUATION REPORT UPDATE

25 OCTOBER 2014

HIGHLIGHTS

- There have been 10 141 EVD cases in eight affected countries since the outbreak began, with 4922 deaths
- Mali has reported its first confirmed case of EVD
- A confirmed case has been reported in New York City, in the United States of America

CASES / DEATHS



FDA ANIMAL RULE

- The rule, located at 21 CFR 314.600-650 (drugs) and 601.90 (biologics), is meant to allow FDA to approve products for "serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances."
- Approval based on animal efficacy data when "human efficacy studies are not ethical or feasible."
- Does **NOT** apply to products that can be approved based on efficacy standards described elsewhere in FDA regulations.

FDA ANIMAL RULE – NEW GUIDANCE DOCUMENT (1)

- Approval based on well-controlled animal studies that establish that the product is reasonably likely to produce clinical benefit in humans.

  1) There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product;

  2) The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans;

FDA ANIMAL RULE – NEW GUIDANCE DOCUMENT (2)

3) The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity; and

4) The data or information on the pharmacokinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans.

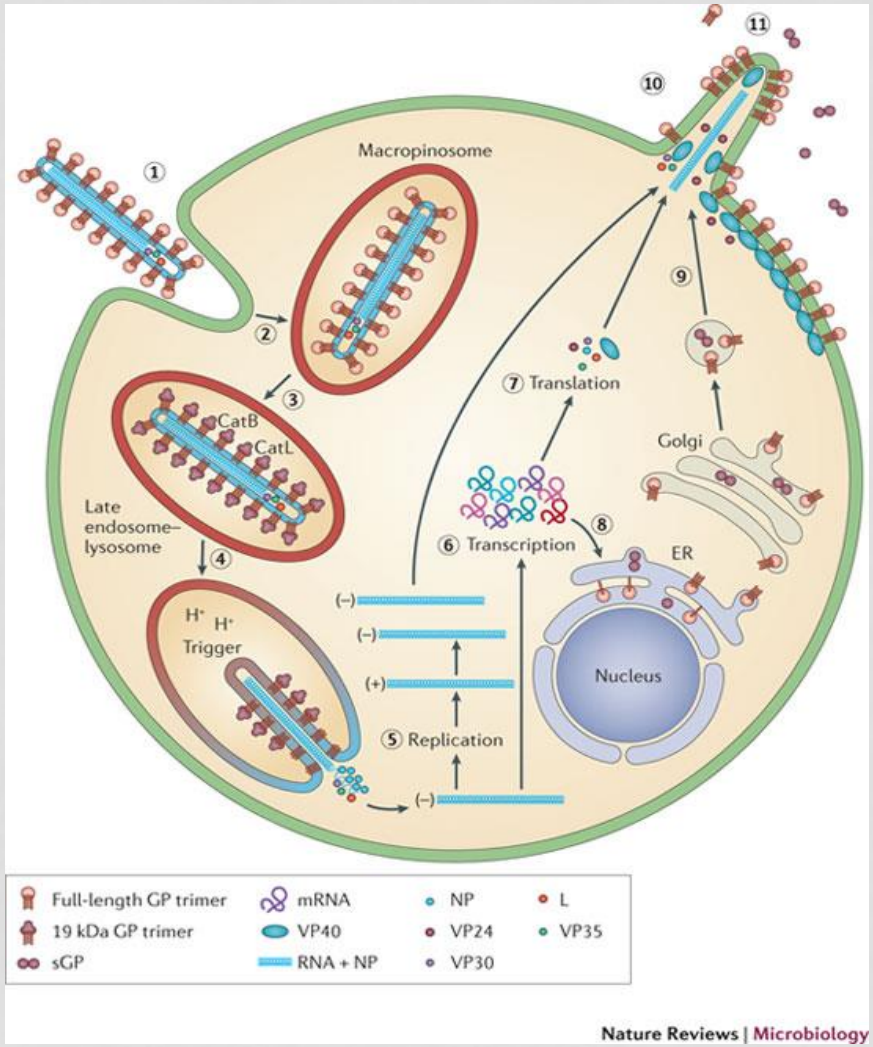
FDA ANIMAL RULE

- What it is not……
  - Faster than "traditional" drug development.
  - Cheaper than "traditional" drug development.
  - Easier than "traditional" drug development.
- Nonclinical pharmacology and toxicology study requirements aren't different.
- Safety must still be demonstrated in healthy human volunteers.

FDA ANIMAL RULE

- FDA approval based on the Rule
  - J&J: Levaquin (levofloxacin, plague), in April 2012
  - GSK: Raxibacumab (inhalation anthrax), December 2012
  - Cangene: botulism antitoxin, March 2013
  - EMD Pharmaceuticals: Cyanokit, December 2006
  - Pyridostigmine bromide (soman pre-exposure), 2003

EBOLA VIRUS LIFE CYCLE



1) Glycoprotein (GP)-dependent viral attachment to host cell
2) Endocytosis/Internalization
3) Fusion of viral & endosomal membranes after cathepsin digestion of GP
4) Nucleocapsid release into cytoplasm
5) Genome replication
6) Transcription
7) Translation
8) Heterotrimers of modified GPs formed
9) GP delivered to plasma membrane
10) Assembly of viral RNA & protein, packaging into viral particles, fusion with host membrane and release by budding
11) Secretion of GP

White & Schonberg,
Nat Rev Micro (2012) 10:317

'GOLD STANDARD' FOR TESTING

- 2000 – sequential sampling study in cynomolgus macaque to characterize disease in the nonhuman primate (NHP)

  - 21 NHPs challenged IM with 1,000pfu Ebola virus (EBOV)-Zaire
  - Uniformly lethal in 6-9 days; mean time to death = 6.7 days

- 2000 – smaller study completed in Rhesus macaques
  - 16 NHPs challenged IM with 1,000pfu Ebola virus (EBOV)-Zaire
  - Uniformly lethal in 7-10 days; mean time to death = 8.4days

VACCINE UPDATE

- Two lead candidates – recombinant vaccines
  - ChAd3
  - rVSV-EVD
- Efficacy data available for nonhuman primates (NHPs)
- Clinical trials in some stage of progression

WHO Background Document – Potential Therapies and Vaccines; Sept 2014; DRAFT

VACCINE UPDATE:
ChAd3 MONOVALENT/BIVALENT

- Developed by GlaxoSmithKline (GSK) in collaboration with the National Institute of Infectious Diseases (NIAID)
- Vector is a chimp-derived adenovirus 3 inserted with glycoproteins (GP) from Ebola & Sudan along with monovalent GP Ebola
- Phase I safety (healthy volunteers) in US, UK, Mali, and Switzerland
- Phase II anticipated to begin in early 2015 in 1,000+ healthcare workers in Sierra Leone, Guinea and Liberia

VACCINE UPDATE:
ChAd3 MONOVALENT/BIVALENT

- Nonhuman primates (NHP) – 100% protection
  - 16 out of 16 survived lethal challenge
  - Single vaccine dose
- Human safety/efficacy – no data yet
  - 1,300+ people have received similar vaccines for other diseases, seemingly safe vector
- 10,000-15,000 doses available by end of 2014

VACCINE UPDATE:
VESICULAR STOMATITIS VIRUS (VSV)
rVSV-EVD

- Developed by Public Health Agency of Canada (PHAC) and licensed by NewLink Genetics / BioProtection Systems
- Attenuated VSV with Ebola Zaire glycoprotein (GP) exchanged for native glycoprotein (GP)
- Has been in clinical trials in the US
- ~800 doses available

VACCINE UPDATE:
VESICULAR STOMATITIS VIRUS (VSV)
rVSV-EVD

- Nonhuman primates (NHP) – 100% protection
  - 20 out of 20 survived lethal challenge
  - Single vaccine dose
- Human safety/efficacy – no data yet
  - One lab worker received rVSV after needle-stick injury and remained well
  - Tested in Phase I (healthy volunteers) in US; "soon" in Geneva, Germany, Gabon, Kenya

OTHER VACCINE CANDIDATES

- Profectus Biosciences: rVSV platform
- Bavarian Nordic: Modified Vaccinia (MVA)
- Crucell: Adenovirus platform
- Crucell: Combination Modified Vaccinia (MVA)/adenovirus
- Thomas Jefferson University: based on the established rabies virus vaccine
- Vaxart: oral tablet based on Ad5

THERAPEUTIC UPDATE

- Eight lead candidates
  - Convalescent plasma
  - Zmapp cocktail
  - Hyperimmune globulin
  - TKM-100802
  - AVI 7537
  - Favipivavir/T-705
  - BCX4430
  - Interferons
- Varied information in both nonclinical models and stages of clinical trials in some stage of progression

WHO Background Document – Potential Therapies and Vaccines; Sept 2014; DRAFT

HUMAN CONVALESCENT PLASMA

- NHP efficacy studies suggest passive transfers can provide partial protection
- First used unsuccessfully on 1 patient in 1976. However in 1995, successful in 7/8 patients.
- In recent epidemic, used in patients with seemingly positive results. Difficult interpretation due to multiple therapies
- In Sept. 2014, WHO released a guidance: "Use of convalescent whole blood or plasma collected from patients recovered from Ebola virus disease: Empirical treatment during outbreaks"

INTERFERONS

- Multiple interferon products and manufacturers
- Approved for multiple indications, but not EVD
- NHP efficacy, delayed time to death, but no overall effect on survival:
  - IFN-β
  - IFN-a2b
  - HuIFN-alpha-Le
  - DEF201 (Ad-IFNa)

THERAPEUTIC UPDATE

Company	Candidate	NHP Efficacy	Phase 1	Notes
MappBio	Zmapp (monoclonal antibody)	Yes (EBOV)	No	Used to treat multiple healthcare workers
Tekmira	TKM-100802 (siRNA)	Yes (EBOV)	In progress (partial clinical hold)	
Sarepta/AVI	AVI 7537 (antisense)	Yes (EBOV)	Completed	
Toyoma Chemical / Fuji Film	Favipivavir/T-705 (nucleoside analog)	No	Yes	Phase 3 - influenza
Biocryst	BCX4430 (nucleoside analog)	No (EBOV) Yes (MARV)	No	

ZMAPP™

- Mapp Biopharmaceutical, Inc.
- Cocktail of 3 chimeric mouse-human mAbs, produced in tobacco plants
- MOA is unknown (www.mappbio.com) and current supplies have been exhausted
- "Strong survival" in NHPs up to 5 days after infection; data submitted for publication
- No controlled human safety data
  - In a few cases (n=7) of compassionate use, no safety issues reported
  - Benefit is inconclusive
- Production scale-up may yield few 100 doses by end of 2014

TKM-100802 (TKM-EBOLA)

- Tekmira Pharmaceuticals
- Cocktail of two small interfering RNAs (siRNAs) in lipid nanoparticles
- NHP efficacy: 100% protection from a lethal dose of Zaire Ebola virus (Geisbert et al., The Lancet, Vol 375, May 29, 2010)
- TKM-EBOLA is being developed via the FDA Animal Rule
- Phase I initiated; headaches, dizziness, chest tightness and increased heart rate at high doses. Single dose phase complete
- Partial clinical hold prior to initiating multi-doses, to evaluate cytokine release
- FDA has authorized Emergency Use in infected patients
- Production of 900 doses by early 2015

AVI-7537

- Sarepta
- Phosphoro-diamidate oligonucleotide which blocks viral protein production
- NHP efficacy: 60–80%, depending on dose, when administered at time of infection
- Phase I completed; well tolerated
- Up to 25 treatment courses by mid-October; 100 treatment courses by early 2015

WHO Background Document – Potential Therapies and Vaccines; Sept 2014; DRAFT. Table 1

FAVIPIRAVIR (T-705)

- Toyoma Chemical / Fuji Film
- Small molecule, viral polymerase inhibitor
- Approved under special circumstances in Japan for Influenza
- Effective in mouse model studies but no promising NHP data to date
- Approx. 1,000 people have received it for influenza, without adverse effects
- Up to 10,000 treatment courses may be available, depending on dose regimen for EVD

BCX4430

- BioCryst
- Small molecule, viral polymerase inhibitor
- Developed by FDA Animal Rule
- Efficacy in mouse models (83-100%)
- NHP efficacy for Marburg virus: 100% when administered 48 hours after challenge
- No human data

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