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Lessons learnt from the Ebola outbreak
A regulatory position

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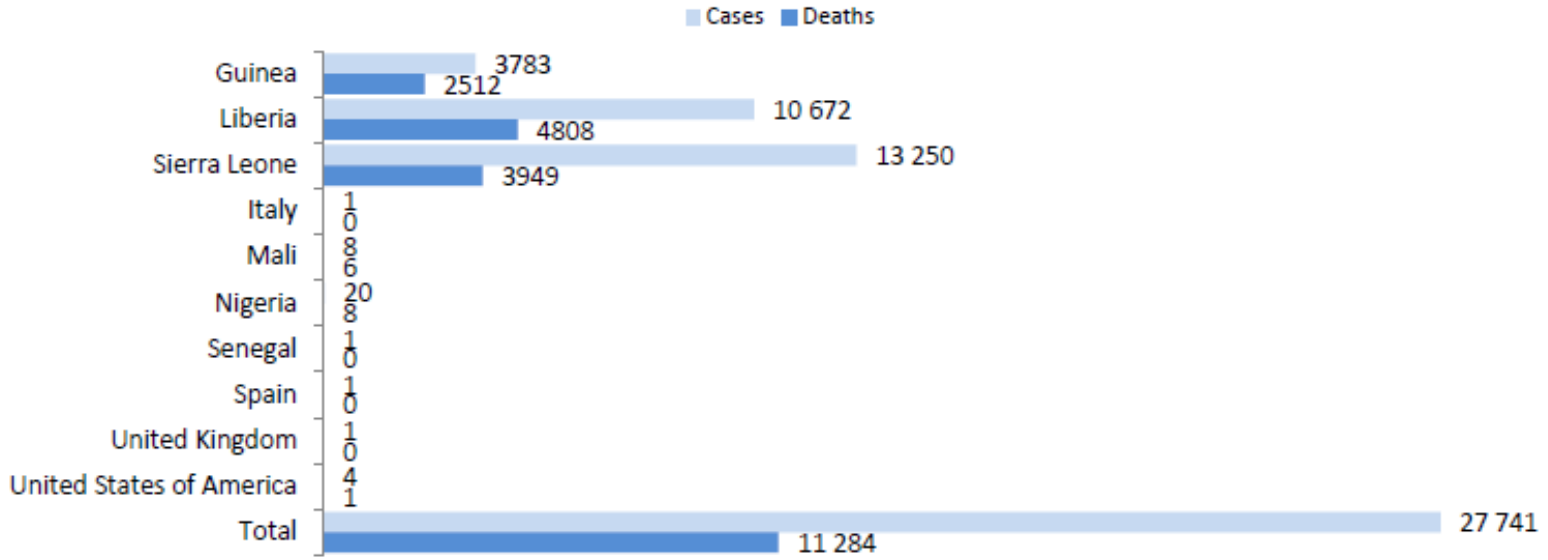
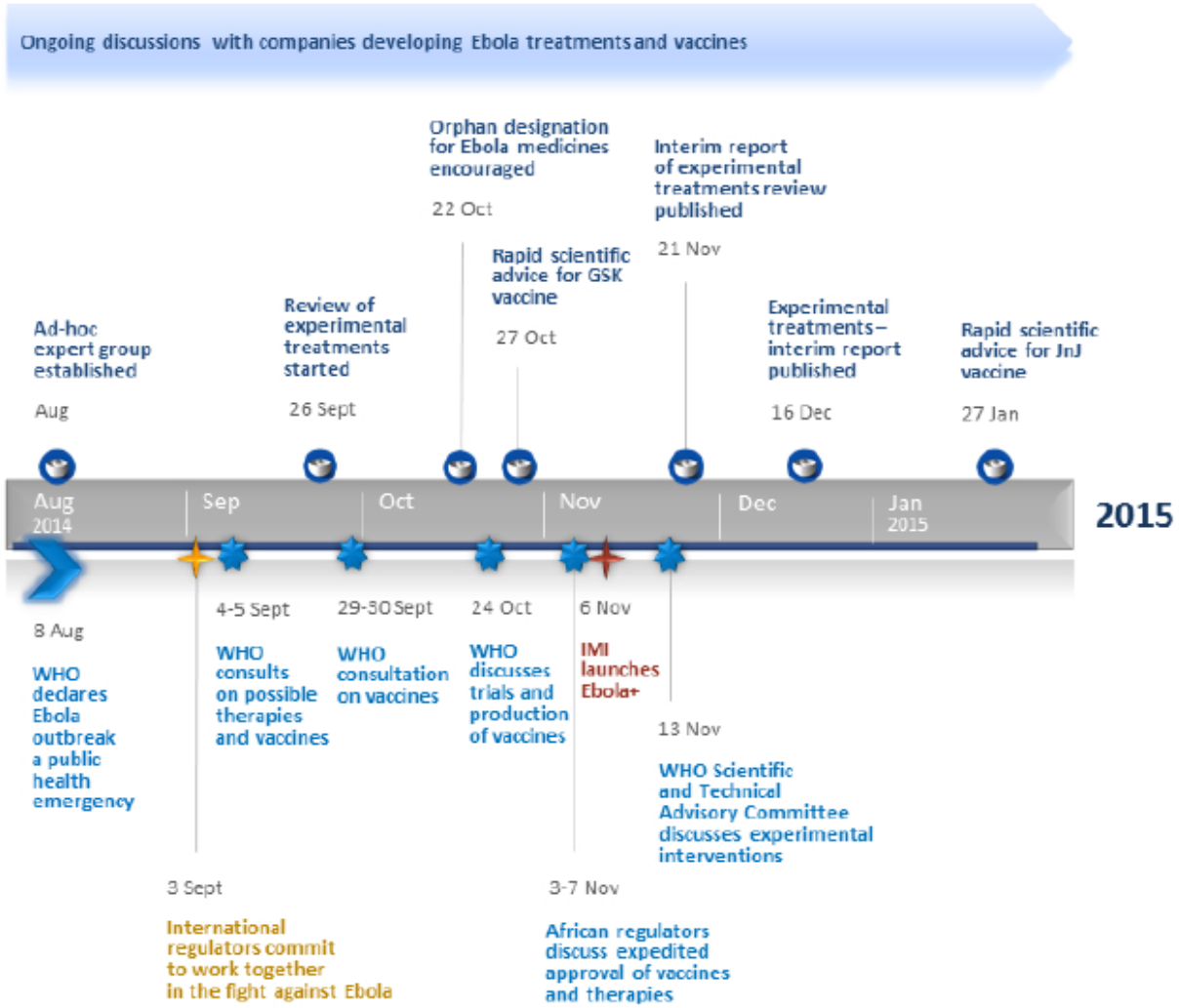
Figure 1: Confirmed, probable, and suspected EVD cases worldwide (data up to 19 July 2015)




Ongoing discussions with companies developing Ebola treatments and vaccines
Ad-hoc expert group established
Aug
Review of experimental treatments started
26 Sept
Orphan designation for Ebola medicines encouraged
22 Oct
Rapid scientific advice for GSK vaccine
27 Oct
Interim report of experimental treatments review published
21 Nov
Experimental treatments – interim report published
16 Dec
Rapid scientific advice for JnJ vaccine
27 Jan
Aug 2014
Sep
Oct
Nov
Dec
Jan 2015
2015
8 Aug
WHO declares Ebola outbreak a public health emergency
4-5 Sept
WHO consults on possible therapies and vaccines
29-30 Sept
WHO consultation on vaccines
24 Oct
WHO discusses trials and production of vaccines
6 Nov
IMI launches Ebola+
13 Nov
WHO Scientific and Technical Advisory Committee discusses experimental interventions
3 Sept
International regulators commit to work together in the fight against Ebola
3-7 Nov
African regulators discuss expedited approval of vaccines and therapies

Composition of Ad hoc expert group

- EMA scientific committee and working party members
- Relevant experience in
  - Vaccines
  - Infectious diseases
  - Quality of biological medicinal products
  - Preclinical
  - Clinical trial design

  - Paediatric aspects

Ad hoc expert group tasks

- Exploratory **review** of current investigational products for treatment or prevention of EVD including TCs with developers.
- To identify the **most appropriate regulatory pathway** to ensure that potential treatments and/or vaccines are approved/made available as swiftly as possible.
- **Rapid scientific advice** on questions from manufacturers on their development plans, endorsed by CHMP (response in 3-4 weeks maximum)

- Discussion with FDA, Health Canada, WHO on available treatments/vaccines and clinical trial design
- Discussions with European Commission (EC), Health Security Committee (HSC), European CDC

Interim assessment report

Review under Article 5(3) of Regulation (EC) No 726/2004

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Ebola vaccines

- ChAd3-EBO-Z , GSK
- rVSV ΔG-ZEBOV, Merck
- Ad26-EBOV und MVA-EBOV, Crucell/J&J

- Additional vaccine candidates
  - Ad5 Ebola, Tianjin CanSino Biotech (China)
  - Rekombinant, adjuvanted, Novavax (USA)
  - Etc…..

Regulatory standards for new vaccines

- Proof of efficacy requires studies that demonstrate protection against clinical disease
- Sufficient number of vaccinees (at least 3,000)
- Demonstration of consistent manufacturing, acceptable quality, potency
- Paediatric investigation plan (mandatory)

Ebola vaccines –considerations for clinical development

- Randomized controlled clinical trials including a placebo arm are the most efficient way of collecting information on vaccine efficacy and safety
- Definition of the target population for these efficacy trials: HCWs? Contacts of cases? Adults only?
- Primary outcome in efficacy studies should be definite EVD

Ebola vaccines –considerations for clinical development

- Pre-existing neutralising antibodies to the vector should be measured at least in a subset
- Adult populations including elderly should be the primary target
- Adolescents could be included in adult trials
- Dedicated paediatric studies expected to be conducted in parallel or shortly after start of adult PhII trials
- Phase II studies are an opportunity to collect extensive data on safety and reactogenicity of the vaccines

Ebola vaccines –considerations for clinical development

- However, in the current context the following needs to be considered:
  - Public health authorities and WHO views on best way to use vaccines supply
  - Ethical aspects and approval of the clinical trials are entirely in the remit of the local authorities of affected countries
  - Challenging field conditions may hamper the feasibility

Regulatory approach to Ebola vaccines

- Open for interaction,
- Open to multiple interactions over time
- Facilitate interaction (e.g. no fees, speed)

- Multi-tiered, pragmatic approach, i.e. explore and investigate all possible regulatory
  - Ethical aspects
  - Uncertainty how outbreak develops
  - Feasibility of different study designs
  - Availability of manufacturing capacity
  - Funding

- „Our heads are round so our thoughts can change directions.“ (Francis Picabia)

Regulatory precedence (if clinical efficacy study not feasible)

- Smallpox vaccine (modified vaccinia Ankara, MVA)
  - Need of alternatives for people contraindicated conventional vaccinia
  - Bridging from animal models
  - Approval under exceptional circumstances

- Meningococci B vaccine
  - Low incidence
  - Immunological correlate for protection (hSBA)

Immunobridging

- Investigate immunogenicity in animal challenge model, e.g. functional antibodes
- Correlate immune parameter to protection in animal model

- Investigate immunogenicity in humans using the same immune parameters

- Build the bridge

- Confirm after marketing authorisation in effectiveness studies

Conditional Marketing Authorisation

- *Justification that medicinal product in scope for CMA:*
  - Seriously debilitating or life-threatening diseases
  - Medicinal products to be used in emergency situations
  - Orphan medicinal products

- *Fulfilment of the requirements for CMA:*
  - The risk-benefit balance of the product is positive and it is likely that the applicant will be able to provide comprehensive data
  - Fulfilment of unmet medical need
  - The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required

Marketing authorisation under exceptional circumstances

- Products for which the applicant can demonstrate that **comprehensive data** (in line with the requirements laid down in Annex I of Directive 2001/83/EC, as amended) **cannot be provided** (due to specific reasons foreseen in the legislation) might be eligible for marketing authorisation under exceptional circumstances.

Article 58 of Regulation (EC) No. 726/2004

The Agency may give a scientific opinion, in the context of cooperation with the World Health Organization, for the evaluation of certain medicinal products for human use intended **exclusively for markets outside the Community**. For this purpose, an application shall be submitted to the Agency in accordance with the provisions of Article 6. The Committee for Medicinal Products for Human Use may, after consulting the World Health Organisation, draw up a scientific opinion in accordance with the provisions of Articles 6 to 9. The provisions of Article 10 shall not apply.

Why Art. 58?

- Responds to the unavailability of medicinal products whose Marketing Authorizations are no longer in place in EU for commercial reasons but are still of use for countries outside the EU

- Access to essential medicines for countries lacking the regulatory capacity for assessing new medicinal products for their markets

- Responds to the need to protect public health and to give scientific assistance to non-member countries in the context of cooperation with WHO while at the same time allowing rapid access to those countries for important new medicinal products

Regulatory learnings and tasks for the future

- Engage stakeholders early and facilitate interaction
- Maintain flexible approach
- Improve network of stakeholders
- Increase awareness for financing institutions (philantropy, governments) of need for long-term committment
- Encourage investigation of vaccine platform technologies and proactively develop regulatory approach

Acknowledgments

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