Accelerating R&D for public health emergencies – a Blueprint

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Year(s)	Country	Virus subtype	N=Human cases	Mortality
Aug-Nov 2014	DRC	Zaire	66	49 (74%)
Mar 2014-Present	Multiple countries	Zaire	21121	8304
Nov 2012-Jan 2013	Uganda	Sudan	6*	3* (50%)
Jun-Nov 2012	DRC	Bundibugyo	36*	13* (36.1%)
Jun-Oct 2012	Uganda	Sudan	11*	4* (36.4%)
May 2011	Uganda	Sudan	1	1 (100%)
Dec 2008-Feb 2009	DRC	Ebola	32	15 (47%)
Nov 2008	Philippines	Reston	6 (asymptomatic)	0
Dec 2007-Jan 2008	Uganda	Bundibugyo	149	37 (25%)
2007	DRC	Ebola	264	187 (71%)
2004	Russia	Ebola	1	1 (100%)
2004	South Sudan	Sudan	17	7 (41%)
Nov-Dec 2003	Rep of the Congo	Ebola	35	29 (83%)
Dec 2002-Apr 2003	Rep of the Congo	Ebola	143	128 (89%)
Oct 2001-Mar 2002	Rep of the Congo	Ebola	57	43 (75%)
Oct 2001-Mar 2002	Gabon	Ebola	65	53 (82%)
2000-2001	Uganda	Sudan	425	224 (53%)
1996	Russia	Ebola	1	1 (100%)
1996	South Africa	Ebola	2	1 (50%)
1996-1997 (Jul-Jan)	Gabon	Ebola	60	45 (74%)
1996 (Jan-Apr)	Gabon	Ebola	37	21 (57%)
1995	DRC	Ebola	315	250 (81%)
1994	Côte d'Ivoire	Taï Forest	1	0
1994	Gabon	Ebola	52	31 (60%)
1989-1990	Philippines	Reston	3 (asymptomatic)	0
1990	USA	Reston	4 (asymptomatic)	0
1979	South Sudan	Sudan	34	22 (65%)
1977	Zaire	Ebola	1	1 (100%)
1976	South Sudan	Sudan	284	151 (53%)
1976	DRC	Ebola	318	280 (88%)

Knowledge gaps at the beginning of the epidemic

- Natural history of the illness in humans
- Immunopathology in humans, including aspects of the immune response
- Routes of transmission/acquisition
- Transmission dynamics
- Environmental survival of the pathogen
- Essential interventions for disease control

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Current Situation for EIDs

- Lack essential countermeasures for most severe emerging diseases
- Control measures simplistic and sometimes brutal
- Control measures usually too late
- Lack essential scientific knowledge
- Diseases are sporadic and to a large extent unpredictable
- Often occur in countries with poor health and biomedical infrastructure
- Countries feel threatened because they cannot control the consequences
- ***We do not know what the next new one will be***

Challenges during the EVD epidemic in evaluating vaccines, therapeutics and diagnostics

- The need for a more rapid research response
- Overall coordination of the R&D response
- To focus R&D on scientifically credible interventions
- Community engagement for clinical research in emergencies
- Moving to scale with interventions
- Money!

Therapeutics proposed at the start of the outbreak

Interferons

Vulture Gastric Fluid

Monoclonal antibodies

Brincidofovir

Chamomile Tea

Micronutrients

Ayurvedic Oils

HIV therapy: Lamivudine

Crystals

Vitamins

Anti-influenza: favipiravir

Anti-malarials

Magnets

Bath salts

Si-RNA

Electromagnetic Waves

Root Extracts

Those for which there was evidence to support conducting clinical trials

Interferons

Monoclonal antibodies

Brincidofovir

Anti-influenza: favipiravir

Si-RNA

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Those for which there is now evidence of efficacy in humans

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Therapeutics : issues faced

- No best practices for preclinical screening (vitro, vivo)

  → conflicting data on utility: difficult to select products to use.

  - NHP data did not always predict human efficacy: NHP method ??

- Results (+ve and –ve) not shared

  → repetition of studies wasting rare BSL4 resources

  - Critical studies delayed

  - Promising candidate drug use delayed by safety studies

  ➢ → safety + PKPD studies need to be done before outbreaks

Issues faced with clinical trials

- Prioritization: hundreds of candidates, only space for a few trials
  - available drug with poor data vs not available with strong data
- Design of protocol: RCT vs single arm vs …
  - statistically perfect vs population wishes etc
- Overlapping/competing trials:
  - few trial sites with capacity, multiple trials, dwindling patients
- Lack of communication…
  - A) journals don't publish studies that don't meet 'perfection'
  - B) investigators don't publish until data meets 'perfection'

The challenge

To compress the usual timeline for unproven interventions from years to months, by working in parallel on:

Development

Testing

Licensure

Use

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Lessons learned (1)

WHO Ebola R&D Summit (11-12 May)

- Need for new R&D funding models to support the development of products where the market is non-existent, unknown, or unreliable
- Future R&D must encompass far more than vaccines, diagnostics and drugs
- Need to establish target product profiles (TPPs), and global R&D roadmaps, for priority novel interventions
- Arrangements for carrying out clinical trials should be agreed in advance e.g protocols, review mechanisms, reference preparations for assays, approved standards of care

Policy context of the Blueprint

- WHO Executive Board (January 2015)[1]
- WHO Summit on Ebola R&D (May 2015)
- World Health Assembly (May 2015)

*"welcomed the development of a **Blueprint**—in consultation with Member States and relevant stakeholders— for **accelerating research and development in epidemics** or other health emergency situations where there are no, or insufficient, preventive, and curative solutions…"*

Declaration of G7 Health Ministers

- "In the R&D response ….we stress that progress should be made …**on lead candidate products… pre-established protocols, and capacity** ….
- We highlight the need for a more **comprehensive applied and translational research in partnership with at-risk countries**.
- We underline the importance of direct collaboration **between countries and health research funders**
- We call for **continued financing, collaboration and coordination** ….through initiatives such as the proposed **WHO blueprint for R&D preparedness and rapid research response** during future public health emergencies**…"** ***(8-9 October, 2015)***

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Five work-streams

designed to identify key actions required to achieve the objectives

1	2	3	4	5
Prioritisation of pathogens & operational plan	Identification of research priorities	Coordination of stakeholders & expansion of capacity	Assessment of preparedness and impact of intervention	Development of innovative funding options

Workstream 1

Key questions

- For which severe emerging pathogens do we urgently need knowledge and tools, as they are most likely to generate a public health emergency?
- What are the key gaps which must be addressed to prepare for the emergence of a new severe infectious disease?
- How can we streamline and coordinate the operational aspects of moving from research preparedness to actions

Workstream 2

Key questions

- What is the current status of basic and applied research for the 5-10 priority epidemic-prone diseases identified through workstream 1?
- Which health technology platforms are the most efficacious and versatile?
- How can R&D for appropriate diagnostics, vaccines, therapeutics, and other biomedical and behavioural sciences, and information technology, be accelerated for priority epidemic-prone diseases?

Workstream 3

Key questions

- What governance structure would allow national and international actors to work in concert in support of global R&D efforts before and during an outbreak?
- What existing capacities, platforms, tools and templates are available or should be developed to conduct an efficient R&D response during a public health emergency?
- How best to encourage collaborative research inclusive of scientists of countries at risk?

Workstream 4

Key questions

- How can WHO ensure regular implementation of actions and reporting of progress to stakeholders?
- What would be the attributes of an “enabling environment” in support of efficient and timely R&D actions?
- What would be the elements of an evaluation plan to determine the effects of the R&D emergency actions?

Workstream 5

Key questions

- How to ensure adequate and sustainable funding for the research identified as priority?
- How to align and make more efficient use of existing funding?
- How to make use of existing mechanisms and avoid overlap and duplication?
- How to ensure appropriate governance mechanisms for any selected funding model?

Outcome

- The implementation of the Blueprint will guide future planning and execution of R&D activities before and during emergencies, including effective mechanisms for e.g. efficient collaboration, funding, sharing of knowledge and benefits
- Covers research preparedness and research response

Development of the Blueprint

- Data sharing: September, Geneva
- Biobanking: 3d meeting - December; Geneva
- ECBS: October – 2 standards now approved; will be made available
- Pre-clinical models: October, Washington DC
- Clinical trial design: October, London
- Funding - innovative models & governance: October; Oslo
- Clinical trials: November, Bethesda
- Collaboration and Partnerships: November, London
- MERS-CoV Roadmap: December; Geneva….

Anticipated Challenges

- ***The next one will not be like the last one***
- Must be prepared for strain variation – challenge to diagnostics, drugs and vaccines
- Impossible to predict if a known pathogen may display new characteristics- altered transmission dynamics; different population susceptibilities; behavioural/economic practices which lead to public health events
- Must have a portfolio of countermeasures and interventions
- Must be prepared with platforms which can be rapidly adapted to something novel – call for ideas

Anticipated Challenges (2)

- Different groups will have differing perspectives on the most relevant diseases, risks, and solutions
- WHO must take a global perspective,
  - serve the needs of developing countries and all MSs
- Keeping up and adapting to new developments
  - Assessments must be regularly refreshed
- Must be able to move smoothly from preparedness to action when an event begins
  - Risk assessment, involving partners and initiating actions, how we step up and scale up

Science will only fulfill its promises when the benefits are equally shared

—César Milstein, *Un Fueguito*

Not The END

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