

Intervention Options against Ebola

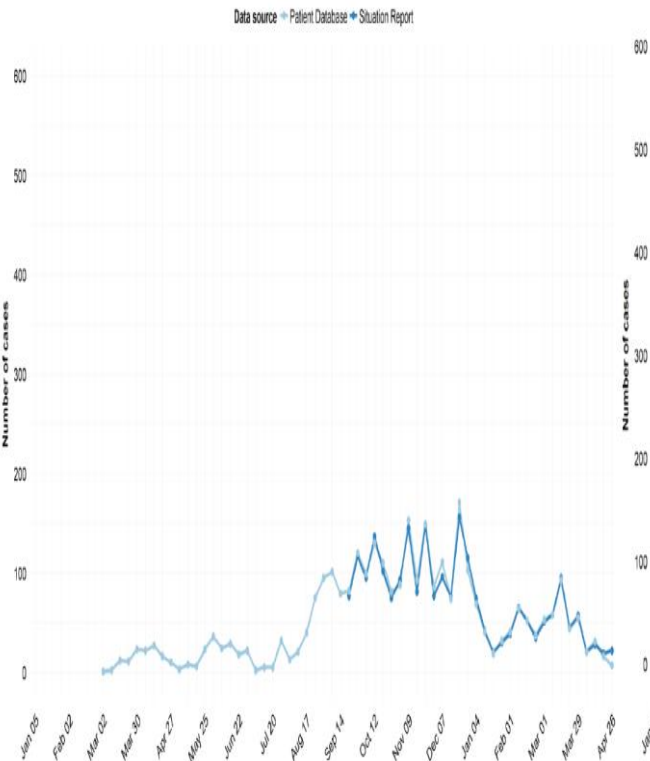
Experience and Outlook



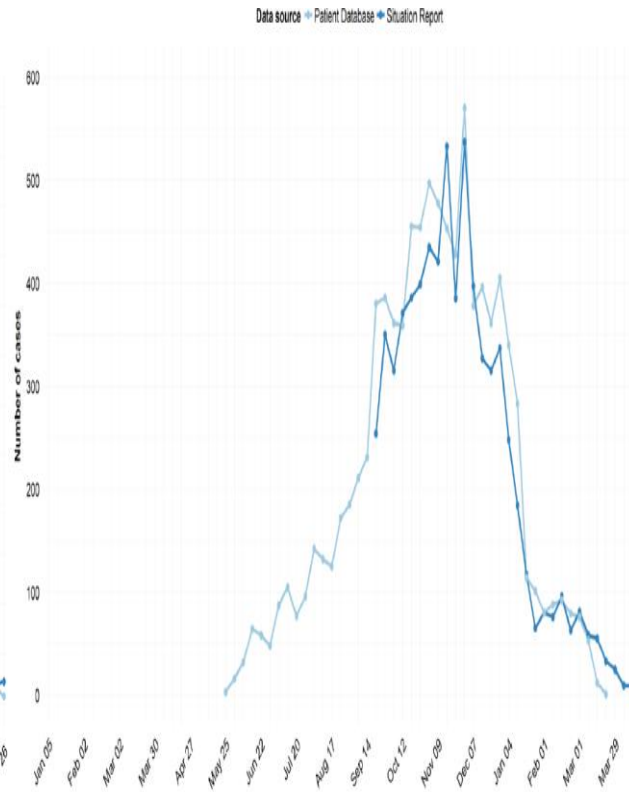
Micha Nübling, 20 May 2015

Ebola epidemiological curve

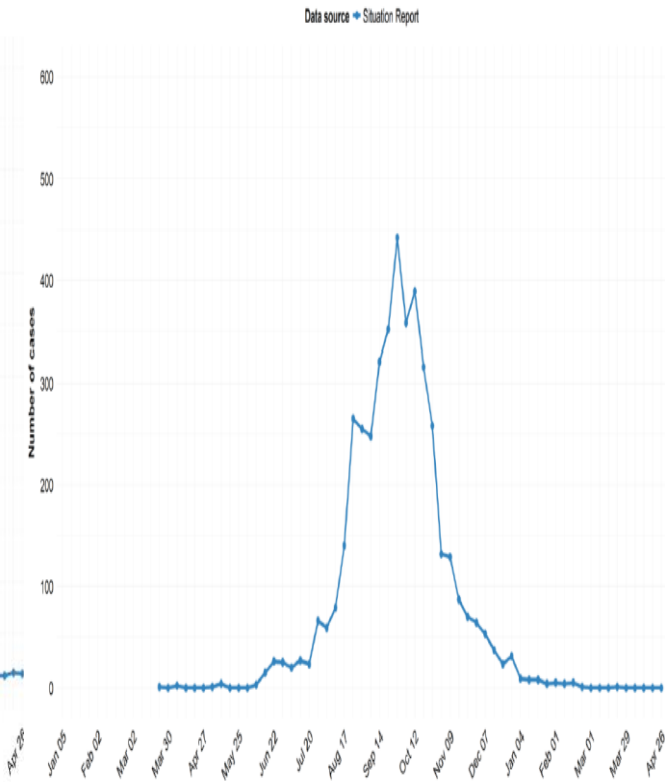
Guinea



Sierra Leone



Liberia



The map displays the following data series:

- Confirmed Cases (by region):**
 - 1 - 5 (Lightest blue)
 - 6 - 20 (Light blue)
 - 21 - 100 (Medium blue)
 - 101 - 500 (Dark blue)
 - 501 - 4000 (Darkest blue)
- No. of Cases, Past 7 Days (by area):**
 - 1 (Small orange dot)
 - 2 - 5 (Small orange circle)
 - 6 - 10 (Medium orange circle)
 - 11 - 20 (Large orange circle)
 - 21 - 50 (Very large orange circle)
- No. of Cases, Past 21 Days (by area):**
 - 1 (Small yellow dot)
 - 2 - 5 (Small yellow circle)
 - 6 - 10 (Medium yellow circle)
 - 11 - 20 (Large yellow circle)
 - 21 - 50 (Very large yellow circle)
 - 51 - 150 (Extremely large yellow circle)
- Legend:**
 - No cases reported (Light grey)
 - NEWLY INFECTED - New cases in previous 7 days (in previously uninfected areas) (Pink)
- Data as of:**
 - LR - 2015-05-05
 - SL - 2015-05-10
 - GI - 2015-05-10

Week
13.05.2015: 9 cases

Context

- The World Health Organization's response to Ebola virus disease (EVD) comprises four elements:
 - Response in affected countries
 - Preparedness in non-affected countries
 - Research and Development for health products
 - Health systems recovery/reconstruction

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 - Response in affected countries
 - Preparedness in non-affected countries
 - **Research and Development for health products**
 - Health systems recovery/reconstruction

Accelerating access to vaccines and therapeutics is a
high priority

In parallel...

Development

Testing

Licensure

Plan for use

Gathering knowledge

- Since August 2014, series of consultations with key international experts and stakeholders to identify potential preventive, diagnostic or therapeutic solutions for Ebola
- Based on concerted expert advice, WHO has prioritized a number of products for further investigation through human testing:
 - two candidate vaccines
 - a shortlist of antiviral drugs
 - Ebola diagnostics
 - convalescent whole blood and plasma



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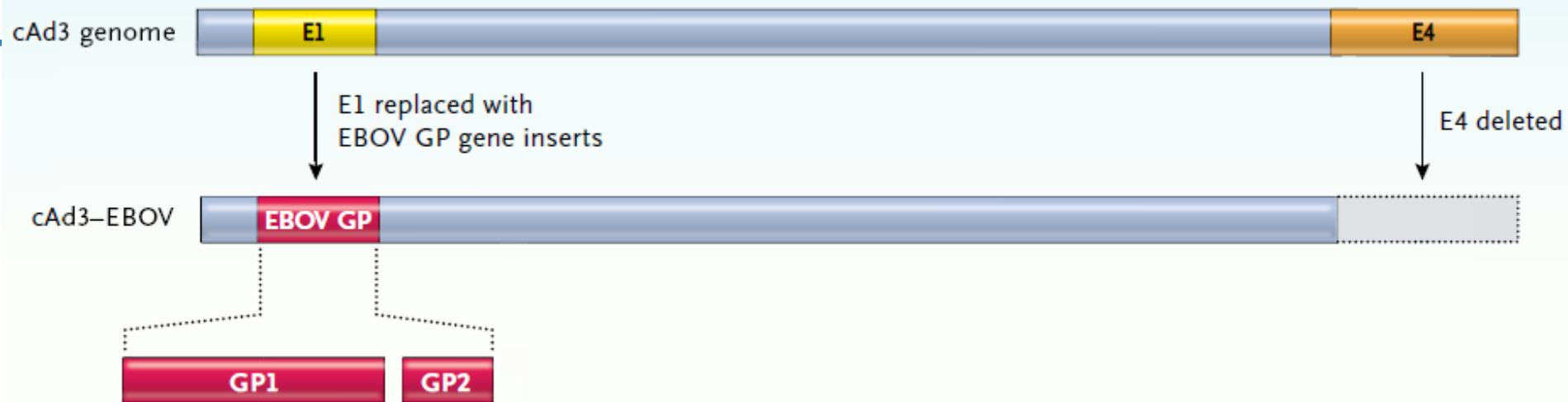
Gathering knowledge

Candidate Vaccines

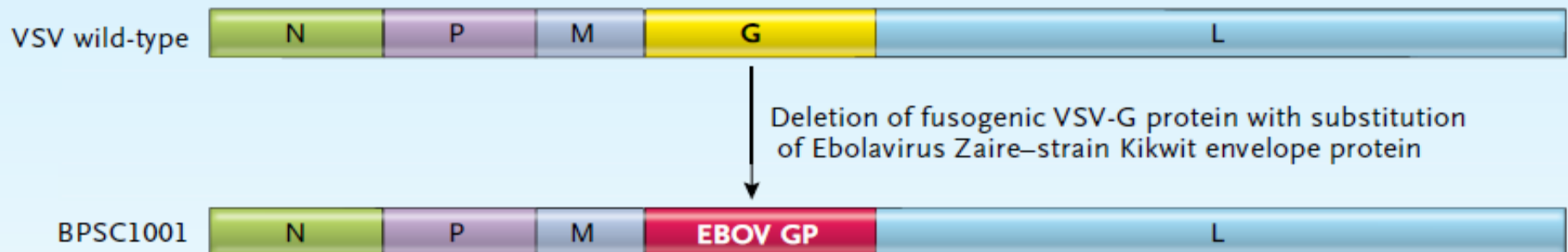
**100% efficacy in non-human primates
but not tested in humans so far**

- **Recombinant vesicular stomatitis virus (rVSV-ZEBOV)**
replicating recombinant virus
- **Chimpanzee adenovirus serotype 3 (ChAD3-ZEBOV)**
non-replicating recombinant virus

ChAD3-ZEBOV



rVSV-ZEBOV

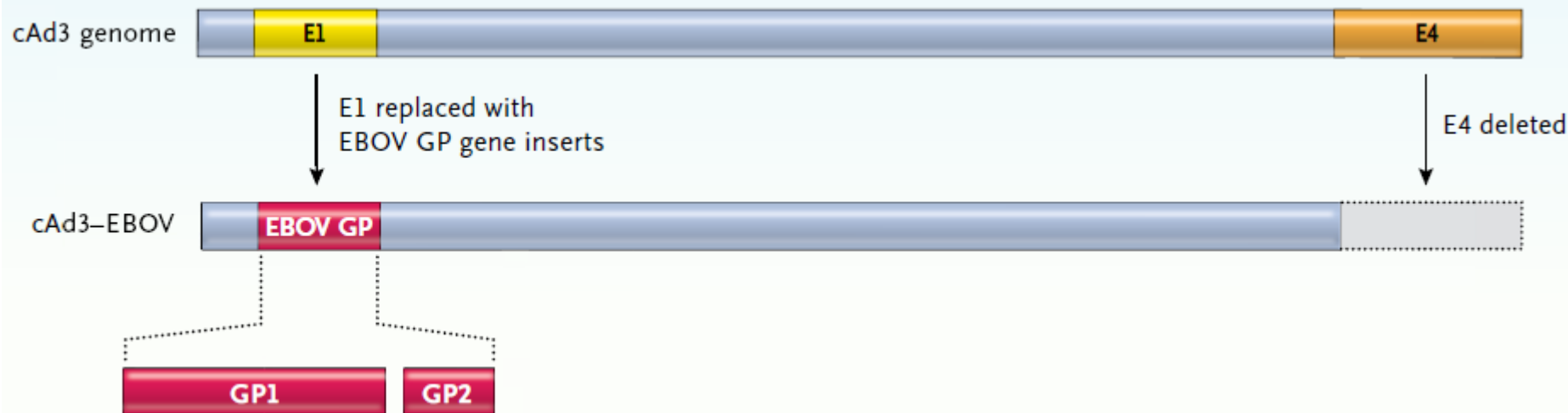


Gathering knowledge

Joint efforts by international consortia to obtain authorisation of clinical trials in short time frame

- joint assessments, work sharing
FDA / EMA / WHO / NRAs from different countries, including African
Ethnic commissions
Study sites in the US, Europe, Africa
Authorisation of Phase 1 – 3 trials

ChAD3-ZEBOV



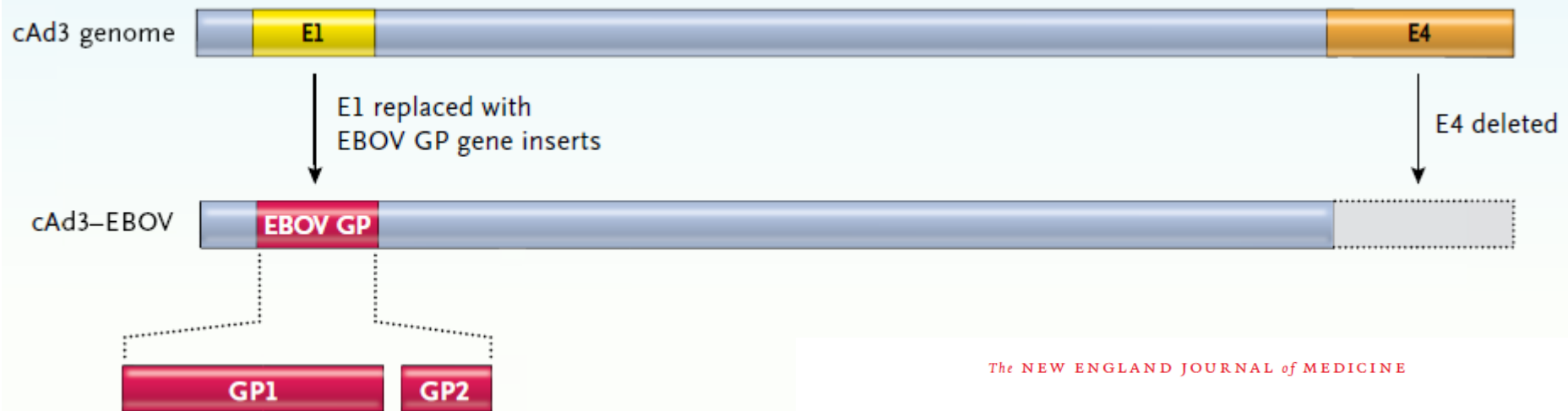
Glaxo Smith Kline, U.S. Nat Inst Allergy Infect Dis

Safety profile in humans of related ChAD experimental vaccines:

no safety concerns

GSK, NIAID (USA)

ChAD3-ZEBOV



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Chimpanzee Adenovirus Vector Ebola Vaccine — Preliminary Report

Julie E. Ledgerwood, D.O., Adam D. DeZure, M.D., Daphne A. Stanley, M.S., Laura Novik, M.A., Mary E. Enama, M.A., Nina M. Berkowitz, M.P.H., Zonghui Hu, Ph.D., Gyan Joshi, M.S., Aurélie Ploquin, Ph.D., Sandra Sitar, M.S., Ingelise J. Gordon, R.N., Sarah A. Plummer, C.R.N.P., LaSonji A. Holman, F.N.P., Cynthia S. Hendel, C.R.N.P., Galina Yamshchikov, M.S., Francois Roman, M.D., Alfredo Nicosia, Ph.D., Stefano Colloca, Ph.D., Riccardo Cortese, M.D., Robert T. Bailer, Ph.D., Richard M. Schwartz, Ph.D., Mario Roederer, Ph.D., John R. Mascola, M.D., Richard A. Koup, M.D., Nancy J. Sullivan, Ph.D., Barney S. Graham, M.D., and the VRC 207 Study Team

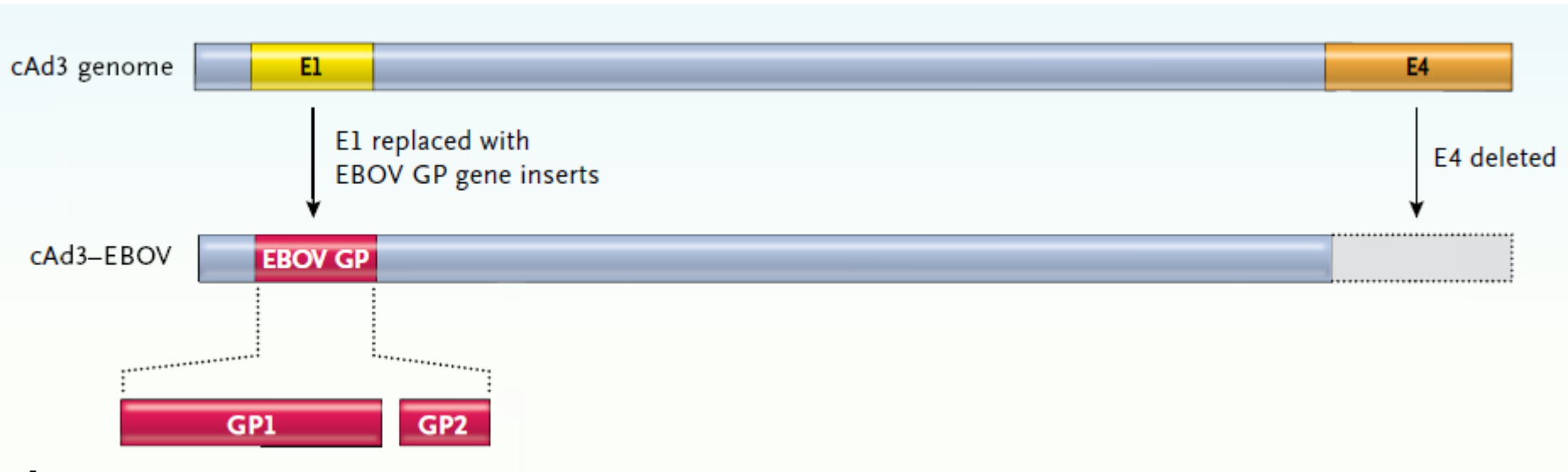
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Monovalent Chimpanzee Adenovirus Ebola Vaccine — Preliminary Report

Tommy Rampling, M.R.C.P., Katie Ewer, Ph.D., Georgina Bowyer, B.A., Danny Wright, M.Sc., Egeruan B. Imoukhuede, M.D., Ruth Payne, M.R.C.P., Felicity Hartnell, M.B., B.S., Malick Gibani, M.R.C.P., Carly Bliss, B.A., Alice Minhinnick, M.B., Ch.B., Morven Wilkie, M.R.C.P., Navin Venkatraman, M.R.C.P., Ian Poulton, Dip.H.E., Natalie Lella, B.A., Rachel Roberts, M.Sc., Kailan Sierra-Davidson, B.A., Verena Krähling, Ph.D., Eleanor Berrie, Ph.D., Francois Roman, M.D., Iris De Ryck, Ph.D., Alfredo Nicosia, Ph.D., Nancy J. Sullivan, Ph.D., Daphne A. Stanley, M.S., Julie E. Ledgerwood, D.O., Richard M. Schwartz, Ph.D., Loredana Siani, Ph.D., Stefano Colloca, Ph.D., Antonella Folgori, Ph.D., Stefania Di Marco, Ph.D., Riccardo Cortese, M.D., Stephan Becker, Ph.D., Barney S. Graham, M.D., Richard A. Koup, M.D., Myron M. Levine, M.D., Vasee Moorthy, D.Phil., Andrew J. Pollard, Ph.D., Simon J. Draper, D.Phil., W. Ripley Ballou, M.D., Alison Lawrie, Ph.D., Sarah C. Gilbert, Ph.D., and Adrian V.S. Hill, D.M.

ChAD3-ZEBOV



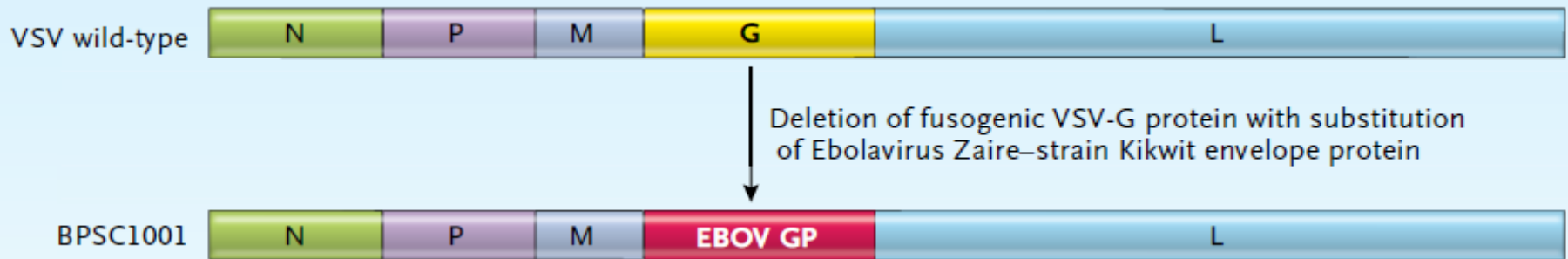
Phase 1

Antibody, cytotoxic T-cells in humans < in macaques efficacy studies

Ab gp binding activity: as rec VSV vaccine

monovalent vaccine sufficient (MVA vector boost)

rVSV-ZEBOV



NewLink Genetics, PHA Canada

postexposure (needle-stick) treatment in a laboratory worker

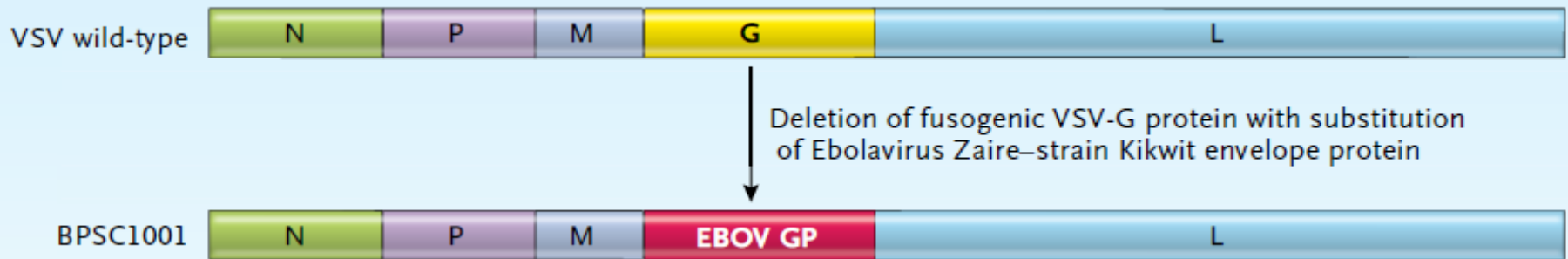
Preliminary Communication

Emergency Postexposure Vaccination With Vesicular Stomatitis Virus-Vectored Ebola Vaccine After Needlestick

Lilin Lai, MD; Richard Davey, MD; Allison Beck, MPAS; Yongxian Xu, MD; Anthony F. Suffredini, MD; Tara Palmore, MD; Sarah Kabbani, MD; Susan Rogers, RPh; Gary Kobinger, PhD; Judie Alimonti, PhD; Charles J. Link Jr, MD; Lewis Robinson, MD; Ute Ströher, PhD; Mark Wolcott, PhD; William Dorman, BS; Timothy M. Uyeki, MD; Heinz Feldmann, MD, PhD; H. Clifford Lane, MD; Mark J. Mulligan, MD

JAMA. 2015;313(12):1249-1255. doi:10.1001/jama.2015.1995
Published online March 5, 2015.

rVSV-ZEBOV



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 1 Trials of rVSV Ebola Vaccine in Africa and Europe — Preliminary Report

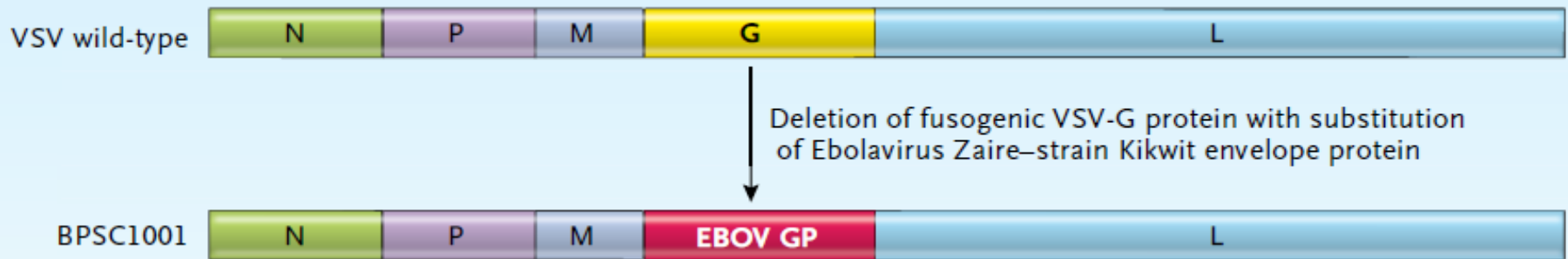
S.T. Agnandji, A. Huttner, M.E. Zinser, P. Njuguna, C. Dahlke, J.F. Fernandes, S. Yerly, J.-A. Dayer, V. Kraehling, R. Kasonta, A.A. Adegnik, M. Altfeld, F. Auderset, E.B. Bache, N. Biedenkopf, S. Borregaard, J.S. Brosnahan, R. Burrow, C. Combescure, J. Desmeules, M. Eickmann, S.K. Fehling, A. Finckh, A.R. Goncalves, M.P. Grobusch, J. Hooper, A. Jambrecina, A.L. Kabwende, G. Kaya, D. Kimani, B. Lell, B. Lemaître, A.W. Lohse, M. Massinga-Loembe, A. Matthey, B. Mordmüller, A. Nolting, C. Ogwang, M. Ramharter, J. Schmidt-Chanasit, S. Schmiedel, P. Silvera, F.R. Stahl, H.M. Staines, T. Strecker, H.C. Stubbe, B. Tsofa, S. Zaki, P. Fast, V. Moorthy, L. Kaiser, S. Krishna, S. Becker, M.-P. Kieny, P. Bejon, P.G. Kremsner, M.M. Addo, and C.-A. Siegrist*

Phase 1/2 trials: Europe / Africa

transient viral replication (3 d)
short viraemia
(peripheral replication)
(“arthritis”)

antibodies: gp binding
neutralizing: dose dep

rVSV-ZEBOV



Phase 3 , April 2015

**frontline workers
ring vaccination in Guinea (23.03.2015)**

Contribution to current decline of numbers?

Proof for efficacy ?

Gathering knowledge

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- Based on concerted expert advice, WHO has prioritized a number of products for further investigation through human testing:
 - two candidate vaccines
 - **a shortlist of antiviral drugs**
 - Ebola diagnostics
 - convalescent whole blood and plasma



Therapeutics

- >100 drugs proposed to WHO: “potential antiEBOV activity”
- Priorization according to data from clinical trials
 - Category A- D according to information on Ebola-related efficacy in humans from clinical trials
- Table on WHO continuously updated
- Depriorization
- Prevention of competition for patients for clinical trials

Therapeutics

- **Favipiravir**: viral RNA polymerase inhibitor, NHP efficacy: 2 log reduction in viremia (Toyama Chemical, Japan)
- **TKM-100802**: NHP efficacy 30 min post challenge (Tekmira pharmaceuticals; BC, Canada),
- **Zmapp**: NHP efficacy 5 days after challenge (MappBio, USA)
- **AVI 7537**: phosphoramidate oligonucleotide, antiVP24 (Sarepta Therapeutics, MA, USA)
- **Brincidofovir** (Chimerix; NC, USA)
- **BCX4430**: adenosine analogue (BioCryst, NC, USA)
- **Interferons**

Therapeutics

Currently ongoing clinical trials

- **TKM-100802:** lipid nanoparticle delivering small interfering RNA (siRNA), NHP efficacy 30 min post challenge (Tekmira pharmaceuticals; BC, Canada)
- **Zmapp:** Cocktail of three monoclonal antibodies produced in tobacco plants, NHP efficacy 5 days after challenge (MappBio, USA)

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 - **Ebola diagnostics**
 - convalescent whole blood and plasma



Ebola diagnostics

- Diagnosis of symptomatic patients; therapy monitoring
 - NAT assays
 - Antigen tests
- Screening of contact persons
 - NAT assays
- Vaccine trials
 - antiEBOV-gp titre
 - EBOV neutralisation
- Characterization of convalescent plasma / blood
 - EBOV antibody patterns
 - EBOV neutralising antibodies



Ebola diagnostics

- WHO emergency use assessment and listing procedure (EUAL)
(IVD prequalification team)
 - Review of assay design; performance data, if available
 - Review of QMS
 - Antigen RDT: independent field study: basic assay features
 - NAT: independent lab evaluation: limit of detection

Ebola diagnostics

Currently listed (WHO EUAL)

- ReEBOV™ Antigen Rapid Test Kit (Corgenix)

=====

- RealStar® Filovirus Screen RT-PCR Kit 1.0 (Altona)
- Liferiver™ - Ebola Virus (EBOV) Real Time RT-PCR Kit (Shanghai ZJ BioTech)
- Xpert® Ebola Assay (Cepheid AB)
-

Ebola diagnostics

WHO guidance on selection and use of Ebola IVDs

- Setting (remote testing, reference lab)
- Confirmation of test results
- PPV, NPV

Ebola diagnostics

Standardization (NIBSC)

- NATs

- Antibody tests

- vaccine trials
- convalescent plasma

- Antigen tests

Materials available

- ❖ recomb constructs

- lentiviral
- flu

- ❖ sera / plasma

- transchromosomal (bovine)
- convalescent
- vaccinees

- ❖

Gathering knowledge

There is consensus that the use of whole blood and convalescent blood serums needs to be considered as a matter of priority.

(WHO meeting 4/5 Sep 2014)

Convalescent Whole Blood (CWB) and Plasma CP)

- Effective in treatment of infections
 - Diphtheria, Tetanus serum therapy (Behring, 1890)
 - Influenza H1N1
 - CMV
 - Hantavirus (Vial, 2014)
 - Junin virus, AHF (Maiztegui, 1979)
 - Ebola (?): CP treatment of 1 patient (Edmond, 1977)
CWB treatment of 8 patients (Mupapa, 1999)
non-human primates (Jahrling, 1996, 1999, 2007)

• b



WHO Blood Regulators Network (BRN)

Position Paper on Collection and Use of Convalescent Plasma or Serum as an Element in Filovirus Outbreak Response*

August 14, 2014

- **Potential suitability of CP/CWB**

- Clinical use of Ebola CP/CWB investigational
 - Characterization of CP/CWB: neutralizing Abs?
 - Virus inactivation of CP

- **Regulatory Agencies**

- screening of donors
 - design of trials
 - evaluation

- **Need for controlled studies**

- pilot studies in humans
 - NHP models
 - negative human plasma / whole blood as comparator



Use of Convalescent Whole Blood or Plasma Collected from Patients Recovered from Ebola Virus Disease for Transfusion, as an Empirical Treatment during Outbreaks

WHO advice on

- CWB/CP donors
- Products
- CWB/CP recipients

Use of Convalescent Whole Blood or Plasma Collected from Patients Recovered from Ebola Virus Disease for Transfusion, as an Empirical Treatment during Outbreaks

CWB/CP donors

28 days after discharge from ETU
2 x Ebola PCR neg, ≥ 2 days apart
TTI screening neg, ABO, RhD

apheresis plasma: 2 weeks interdonation
whole blood: 12 – 16 weeks interdonation

informed consent (Annex)

Use of Convalescent Whole Blood or Plasma Collected from Patients Recovered from Ebola Virus Disease for Transfusion, as an Empirical Treatment during Outbreaks

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Clinical Aspects of Ebola Virus Disease

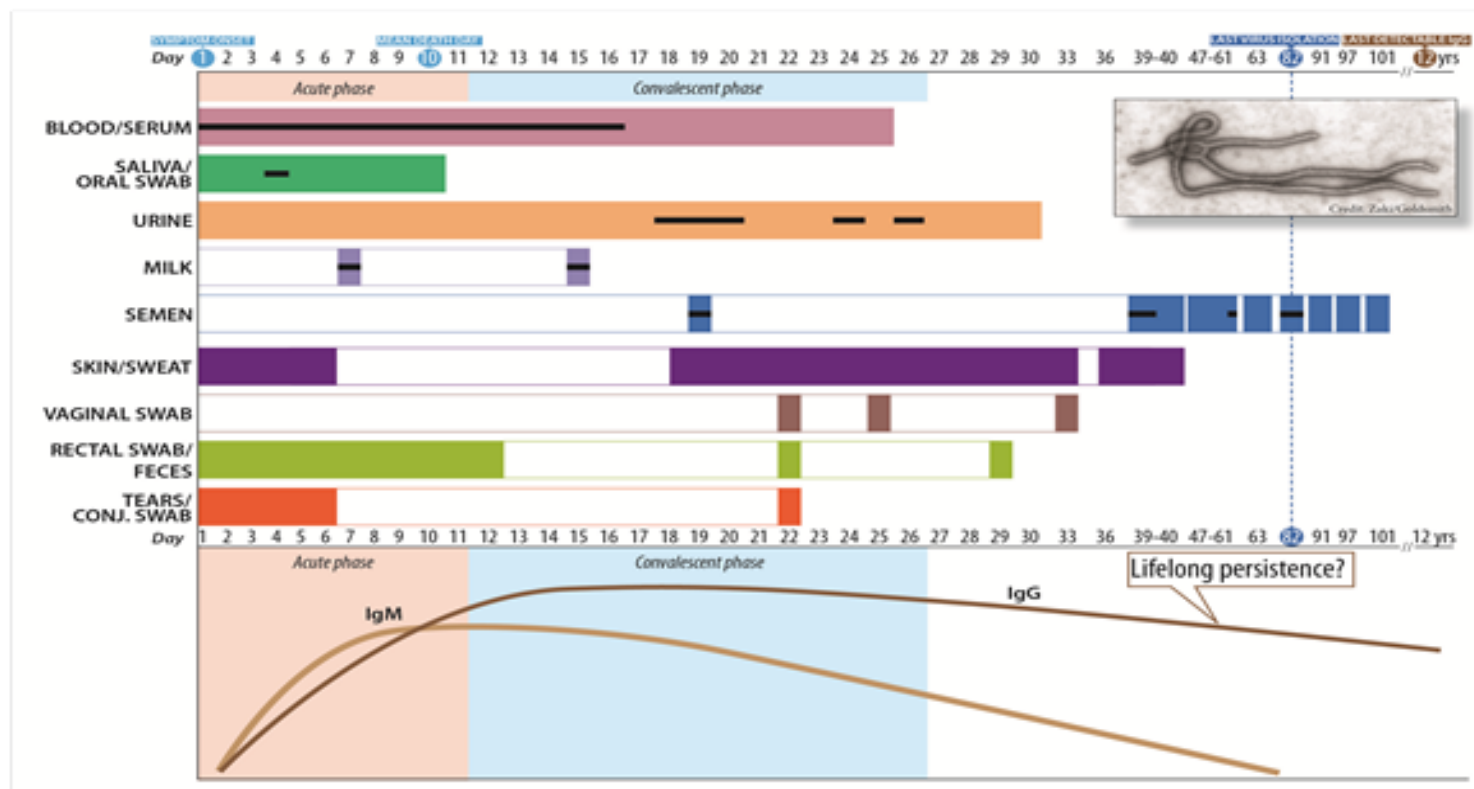


Figure 2. Ebola virus shedding in body fluids. Colors=PCR positive. Bars=culture positive.

Source: Pierre Rollin/CDC

Use of Convalescent Whole Blood or Plasma Collected from Patients Recovered from Ebola Virus Disease for Transfusion, as an Empirical Treatment during Outbreaks

Products (CWB/CP)

- Storage
- Traceability
- Back-up specimens

CWB/CP recipients

- preferably early stage of disease
- administration of CWB/CP
- patient monitoring, including viral load
- informed consent (Annex)

Blood Products Clinical Trials

Liberia		
Government US (Clin RM/BMGF)	few patients use of “excess” plasma?	Whole blood Plasma
Sierra Leone		
Government SL/UK/US	>50 patients, data eval ?	Whole Blood Plasma
Guinea		
Guinea/Belgium/UK/France	Running started 02/15, 86 patients	Plasma

Expatriated patients – receiving convalescent plasma

Blood Products Clinical Trials

Experiences

- Clinical trials
 - Infrastructure
 - Logistical issues
 - Agreement of local authorities
 - no control group
 - improvement of clinical care
 - patients enter ETUs at earlier stage of disease (ct-values)

Blood Products Clinical Trials

Experiences

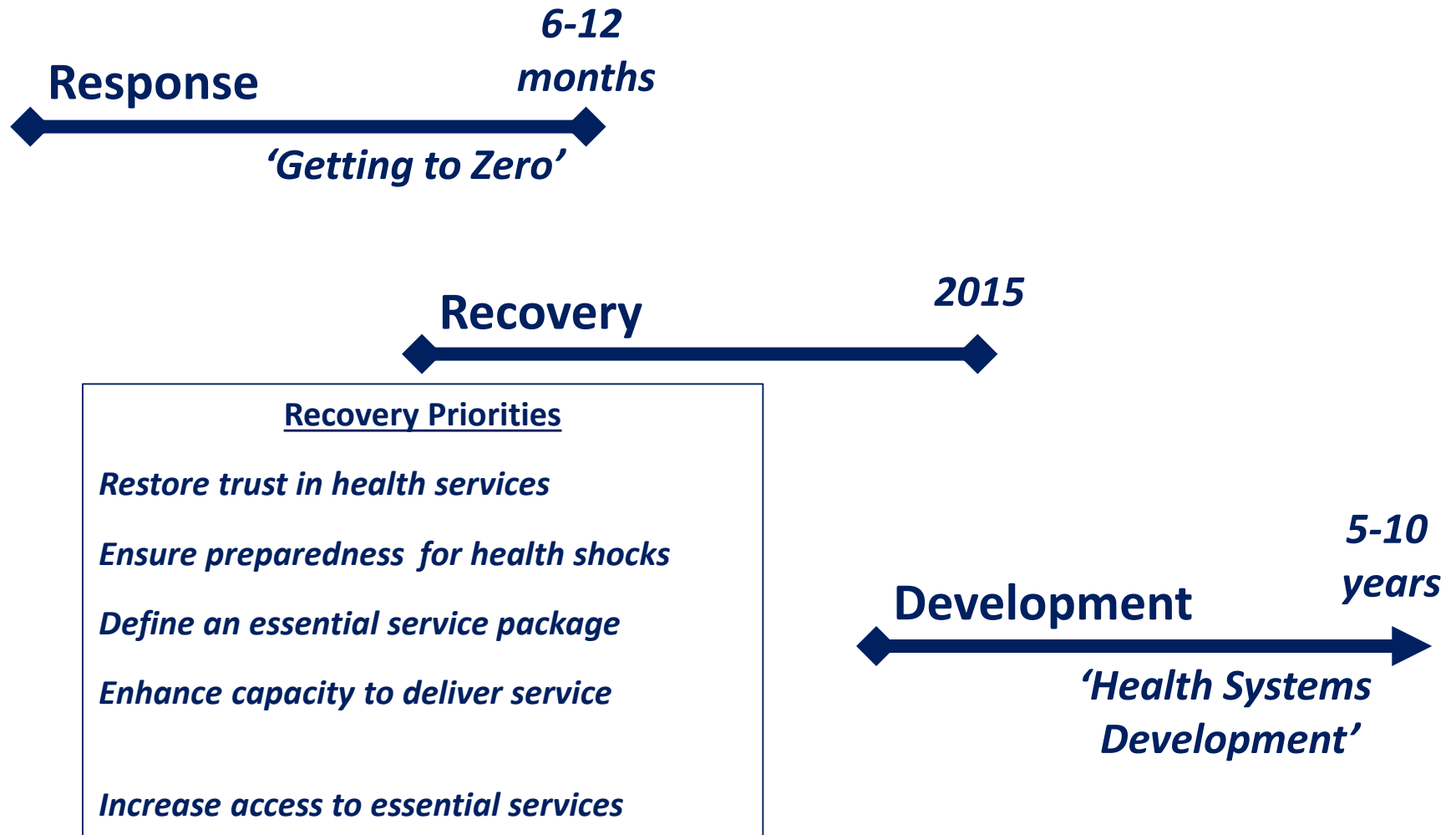
- Clinical trials

- CWB donors (Sierra Leone)
60 / 200 candidates suitable for donation (health conditions)
- Declining Ebola epidemiology

collection and storage of CP

immunoglobulin fractionation?

Conceptual Framework for Health Sector Response, Recovery & Resilience from the Ebola Crisis



Turning crisis into opportunity

Blood collection systems in Ebola-affected countries

Convalescent plasma: spotlight on blood system infrastructures

Ebola affected countries with rudimentary blood system infrastructure before Ebola

No separation of whole blood into components

- 90% replacement / paid donations
- 30% maternal deaths due to blood shortage
- many child deaths due to anemia caused by malaria

Blood collection stopped completely with Ebola crisis

25-27 Feb 2015, 2-4 June 2015

Meetings on developing plan to strengthen the blood systems in Ebola-affected countries

Country-specific proposals for recovery and development of blood collection systems

“The cloud of Ebola may have a silver lining by bringing attention and support to blood services when they have never previously had sufficiently high priority.”

Dr Samuel H. Baker, Programme Manager, National Safe Blood Transfusion Service, Sierra Leone

Thanks to...

Dr David Wood (WHO)

Community Engagement and Education, Recruitment and Retention of People Recovered from Ebola as Potential Donors for Convalescent Whole Blood and Plasma



- WHO document on key considerations for effective community engagement in blood donation for compassionate use and clinical trials
- Prevention of stigmatisation of EVD survivors
- Draft model to enable national health authorities, blood transfusion services and trial investigators to effectively engage with communities to prepare EVD survivors and the communities for blood donation and the clinical trials
- Aims to help to ensure informed participation of survivors and communities and avoid the additional pressure and anxiety inappropriate and/or insufficient community engagement can place on already vulnerable groups.