Raising the Standard for Global Collaboration in Infectious Disease

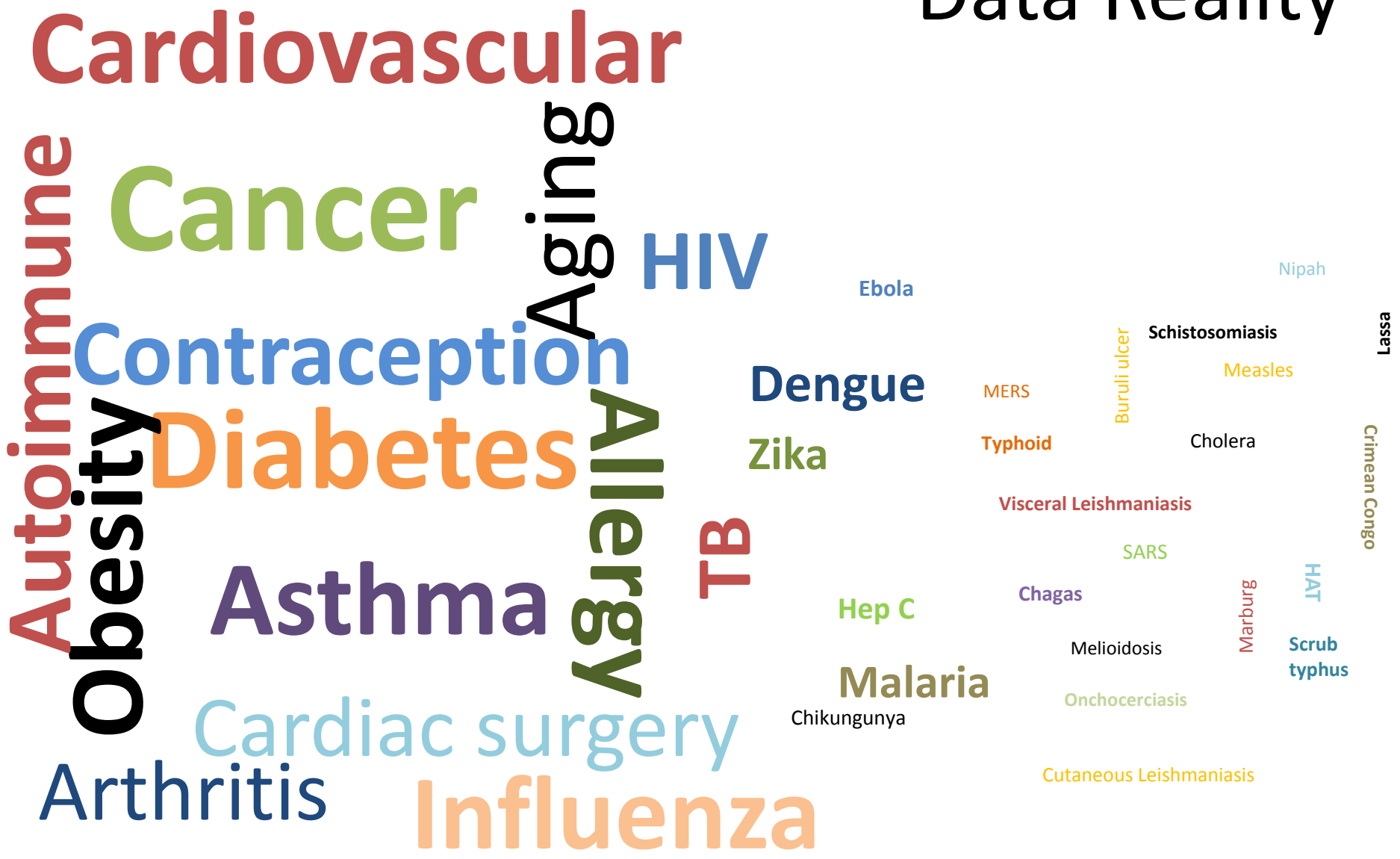
Laura Merson

IDDO

INFECTIOUS DISEASES DATA OBSERVATORY

UNIVERSITY OF OXFORD

Data Reality

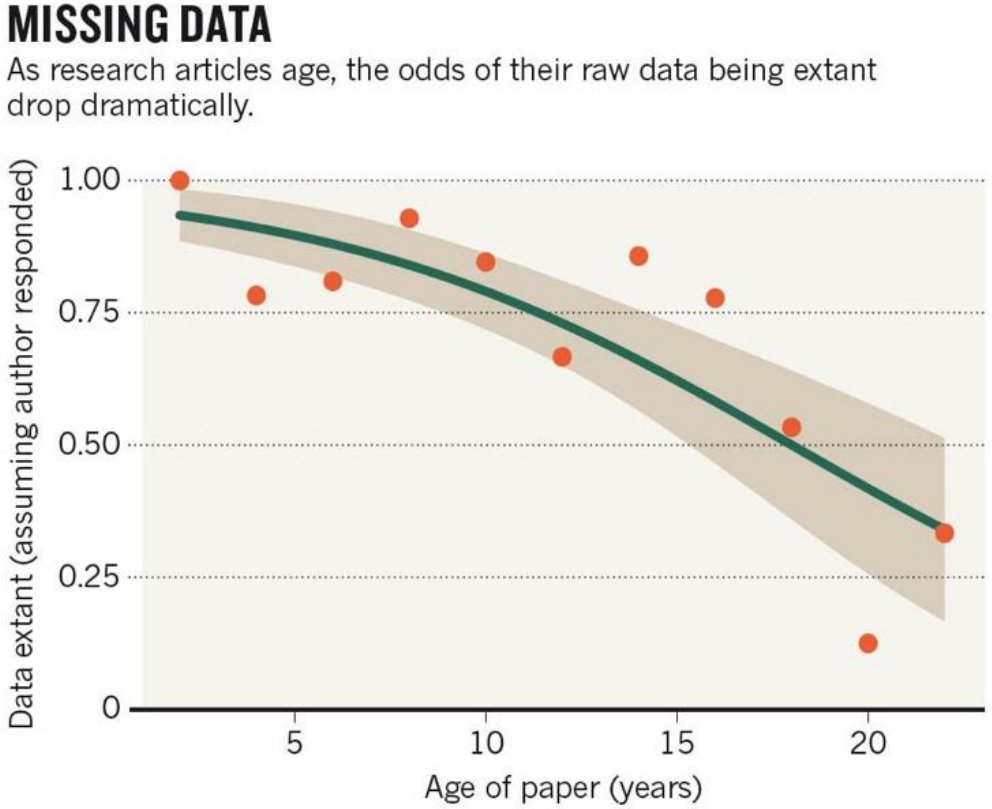



Svalbard
Global Seed Vault


SVALBARD GLOBAL SEED VAULT
Sign in
Svalbard
Greenland Sea
Baffin Bay
Norwegian Sea
Greenland
Iceland
Northwestern Passages
Canada
Hudson Bay
Sweden
Finland
Norway
Russia
United Kingdom
Ireland
Denmark
Belarus
Poland
Germany
Ukraine
France
Austria
Romania
Kazakhstan
Mongolia
Italy
Spain
Portugal
Greece
Turkey
Uzbekistan
Kyrgyzstan
Turkmenistan
China
South Korea
Japan
Sea of Japan
East China Sea
Syria
Iraq
Iran
Afghanistan
Pakistan
Nepal
India
Myanmar (Burma)
Thailand
Vietnam
Philippines
Tunisia
Morocco
Algeria
Libya
Egypt
Western Sahara
Saudi Arabia
Oman
Yemen
Mauritania
Mali
Niger
Chad
Sudan
Burkina Faso
Guinea
Ghana
South Sudan
Ethiopia
Gulf of Aden
Arabian Sea
Bay of Bengal
Gulf of Thailand
Laccadive Sea
United States
North Atlantic Ocean
Gulf of Mexico
Mexico
Cuba
Puerto Rico
Guatemala
Nicaragua
Caribbean Sea
Venezuela
Guyana
Suriname
Colombia
Satellite
Google
Map data ©2017 Google, INEGI
Terms
Send feedback
1000 km

Guarding the Value of Data

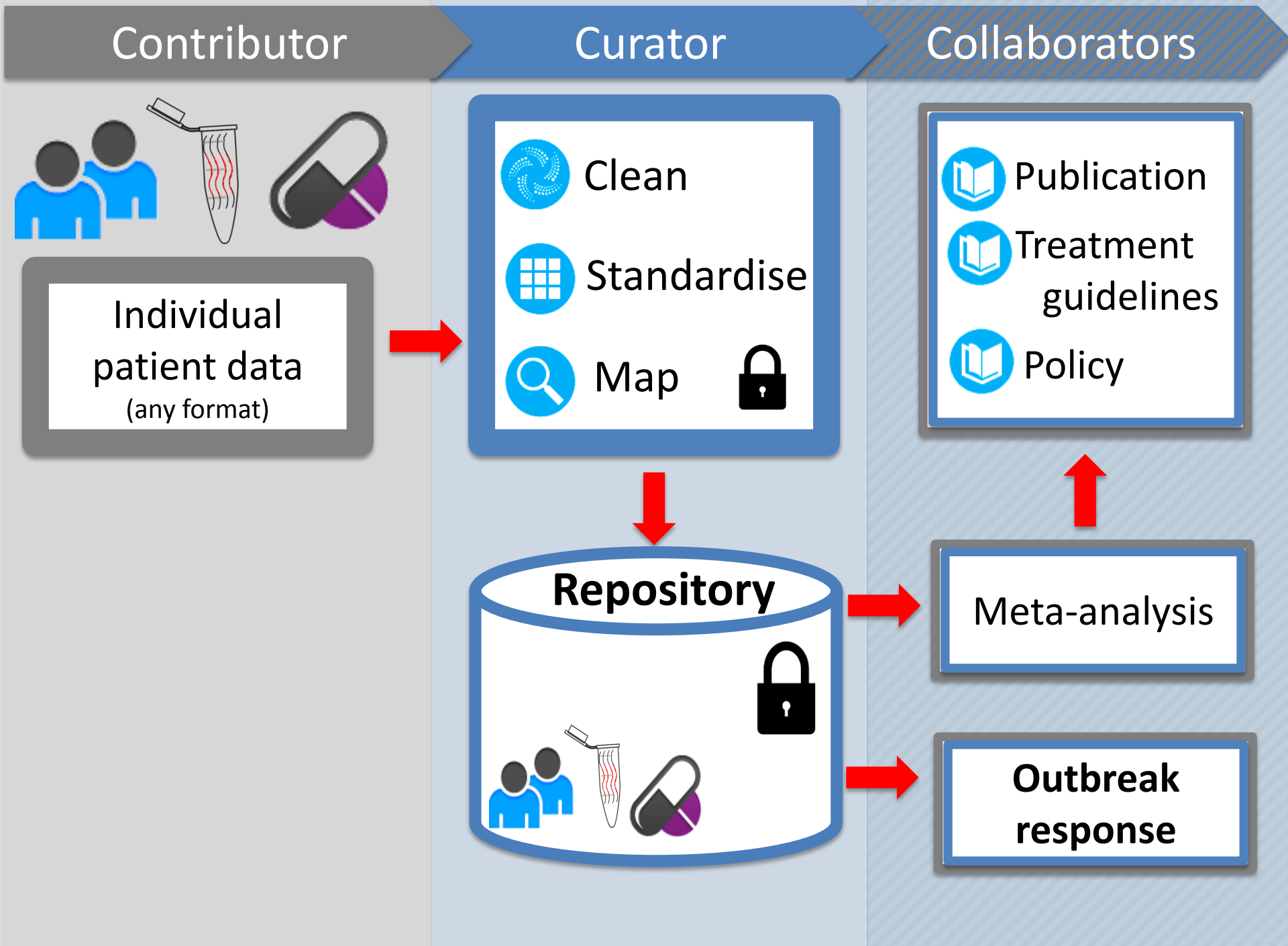
Providing an insurance policy for research investment and outputs



Upholding the **ethical** imperative to **protect against loss** of invaluable human health data held in traditional resources around the world

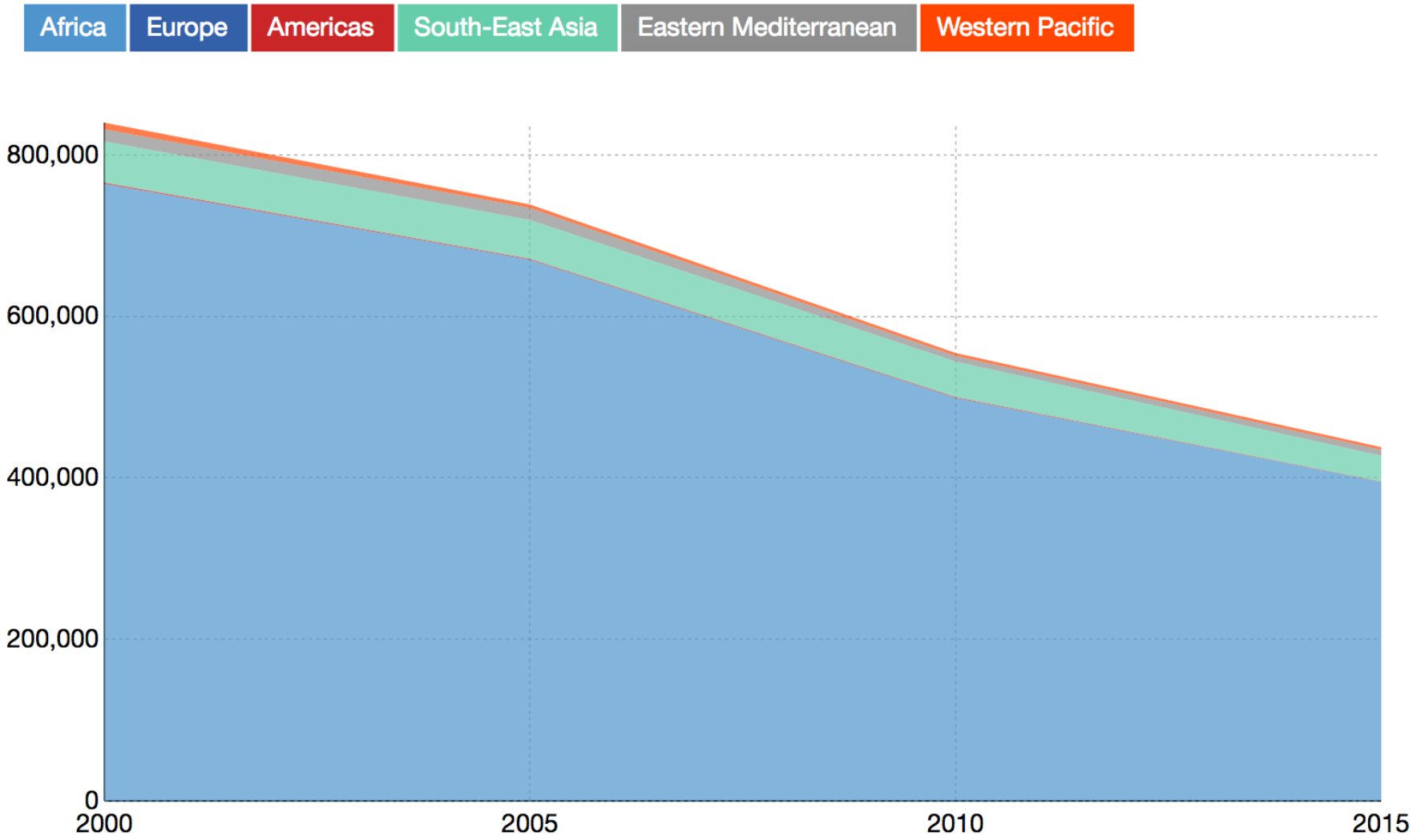
Vines *et al.* Current Biology 2014

IDDO
INFECTIOUS DISEASES DATA OBSERVATORY


Contributor
Curator
Collaborators
Individual patient data (any format)
Clean
Standardise
Map
Repository
Publication
Treatment guidelines
Policy
Meta-analysis
Outbreak response

Global malaria deaths by world region

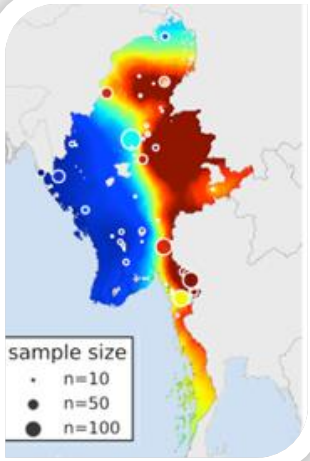
Our World in Data



Source: Deaths by World Region (WHO)

Understanding factors driving resistance

Young children and pregnant women

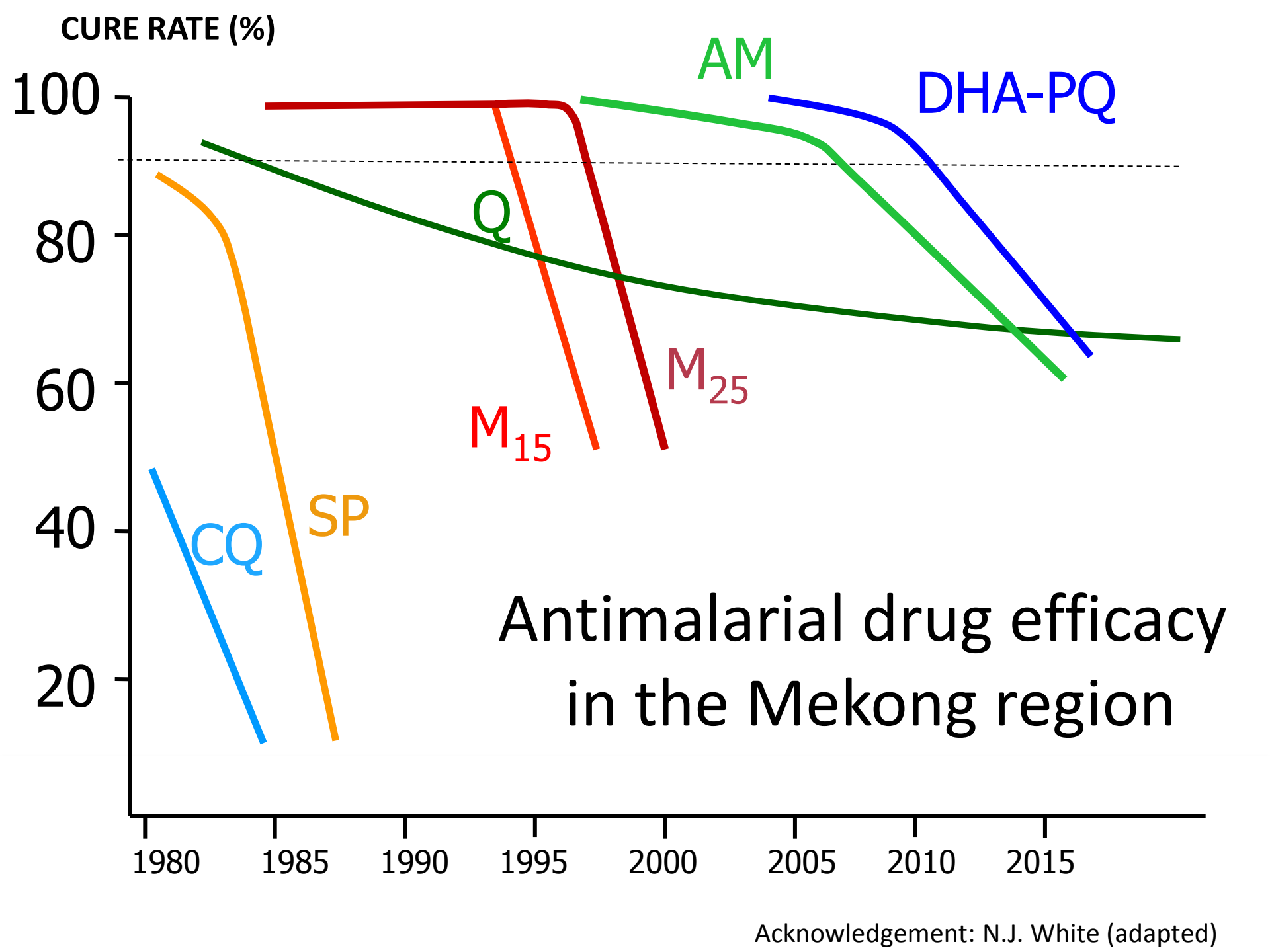


Regional diversity

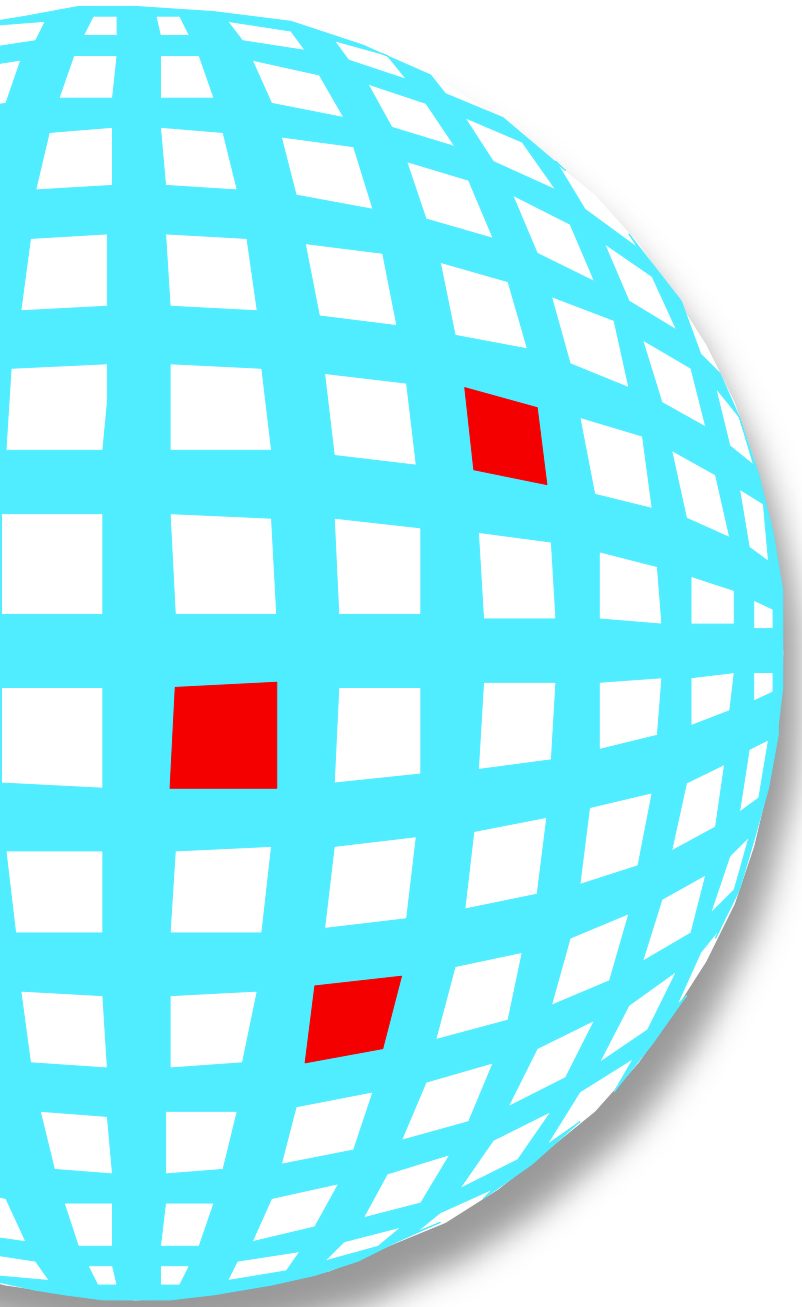
Poor quality medicines

Comorbidities:
e.g. malnutrition, HIV

Drug interactions
e.g. ARV



Acknowledgement: N.J. White (adapted)



WorldWide Antimalarial Resistance Network

WWARN

Responding to key public health needs

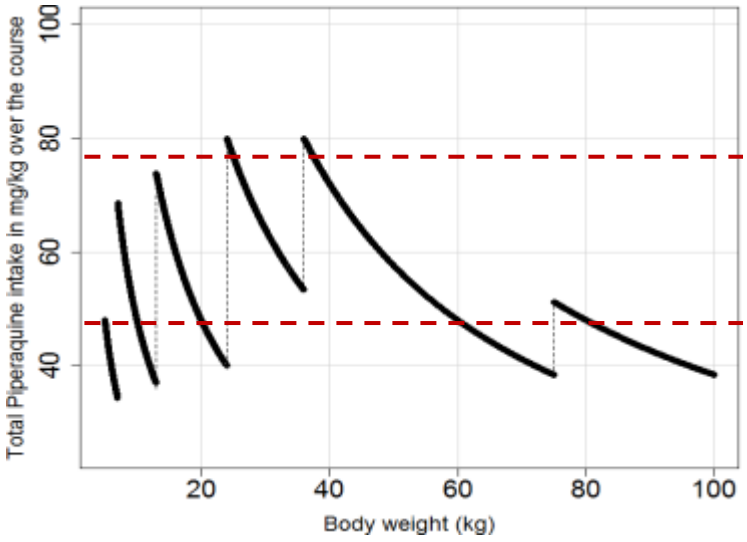
Is dosing of DHA-Piperaquine in young children adequate ?

Power of pooled data

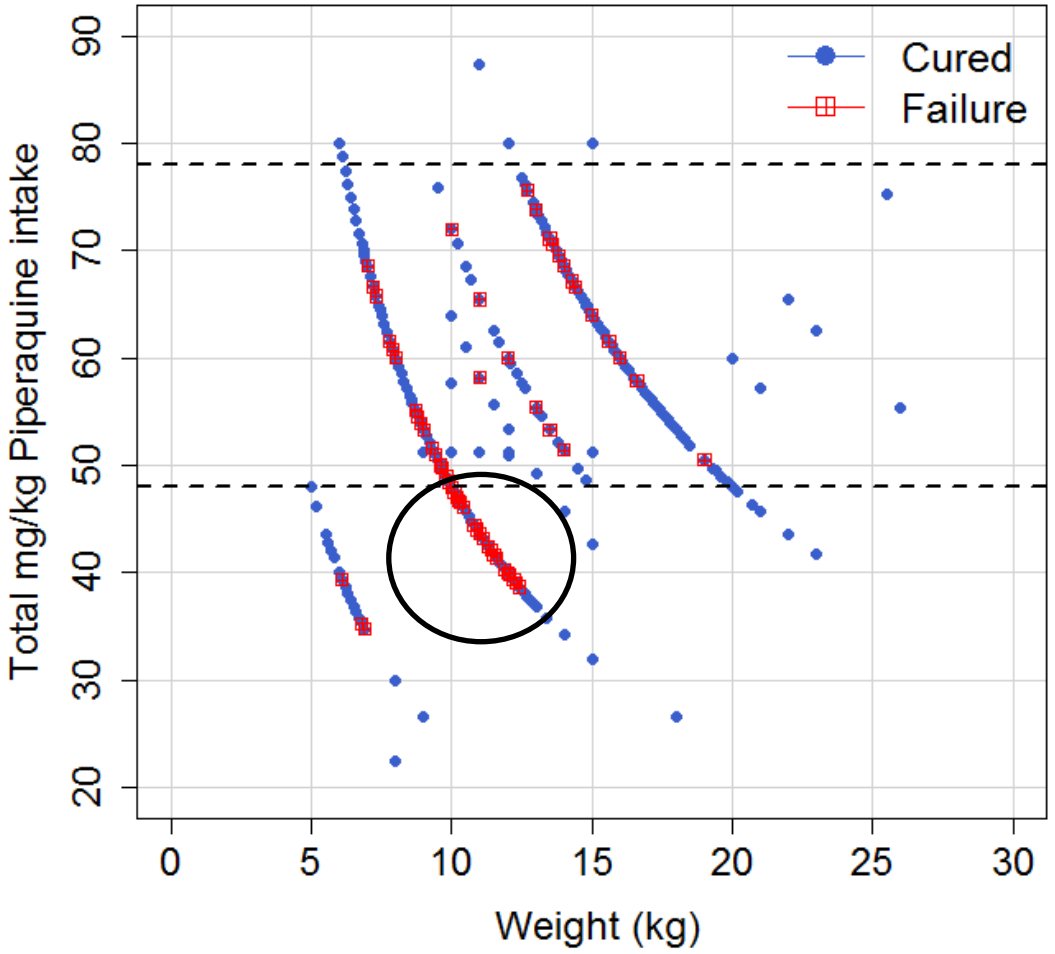
Dihydroartemisinin-Piperaquine study sites

- 26 studies
- 7,072 patients enrolled between 2002–2011

Suboptimal DHA-PQ dosing in young children



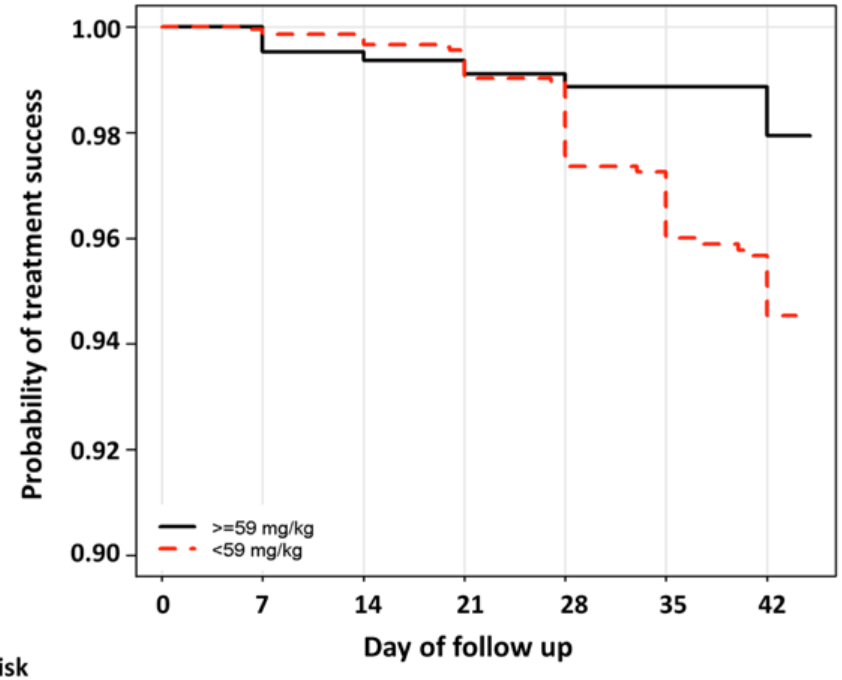
WHO recommended therapeutic range
(48 -78 mg/kg) for piperaquine



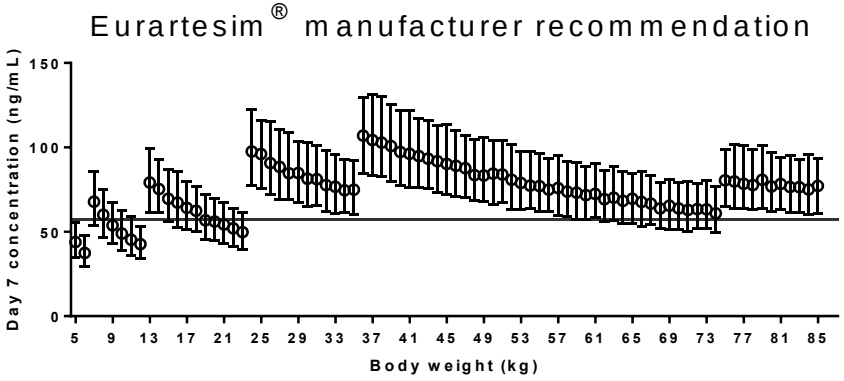
Young children administered suboptimal doses

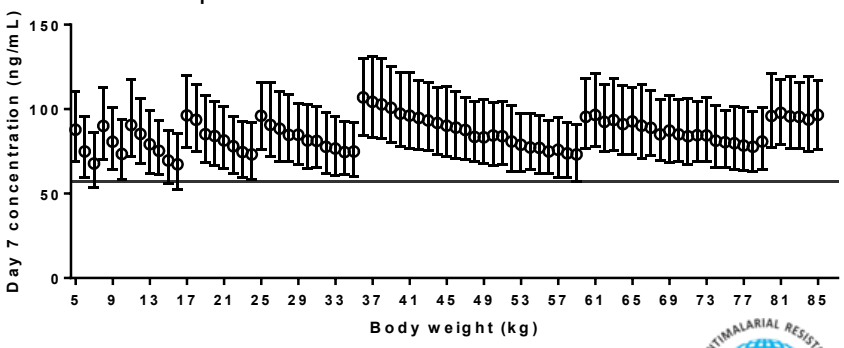
WWARN DP Study Group. *Plos Med*. 2013

Risk of recrudescence in 1-4 year olds, by dose



Double risk of failure for patients receiving piperaquine <59mg/kg



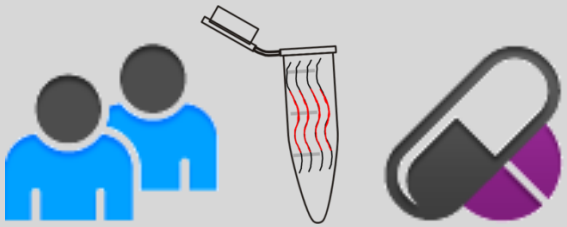


WWARN

Contributor

Curator

Collaborators



Individual patient data
(any format)

Repository

Clean

Standardise

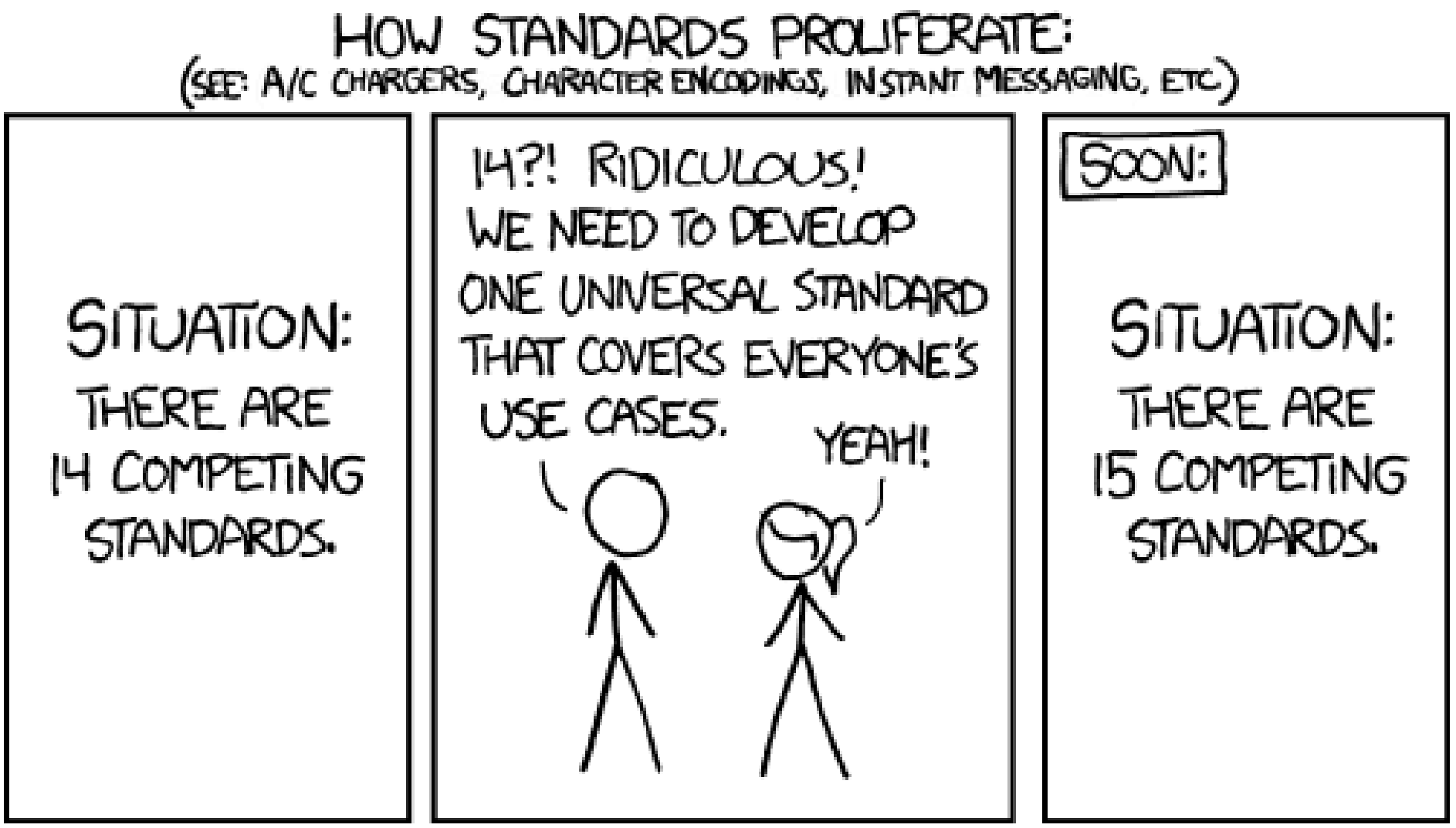
Map

Meta-analysis

Publication

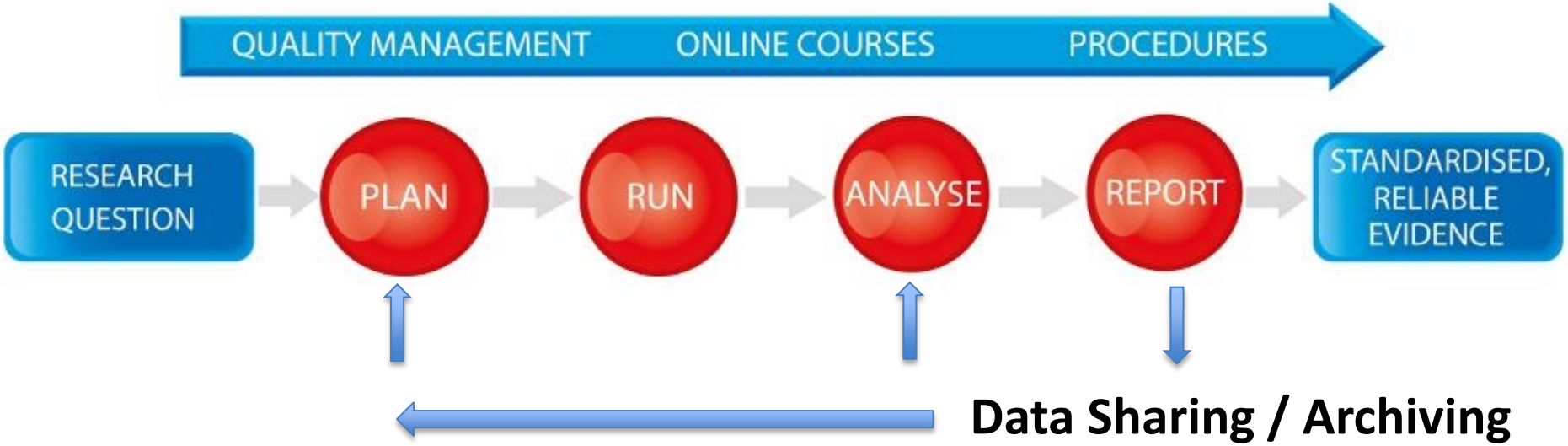
Treatment guidelines

Policy



Source: xkcd.com

Role of WWARN

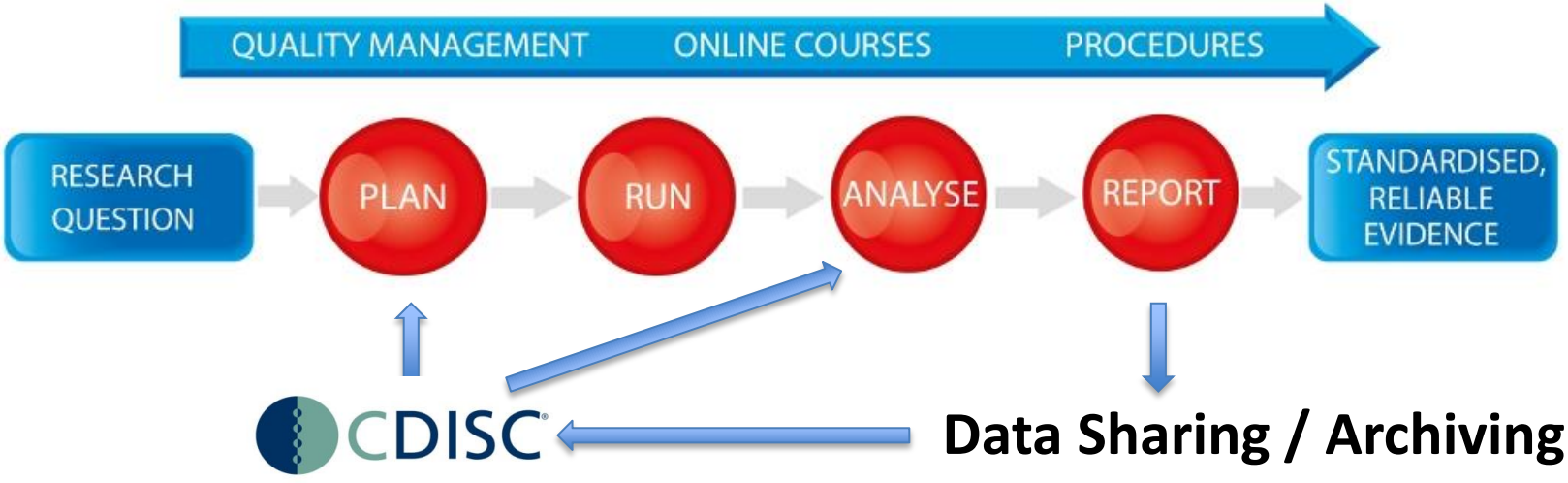


Role of WWARN

To facilitate the development of a CDISC data standard for malaria.

Aligns with WWARN goals to:

- Enable data sharing
- Conduct pooled data analyses to quantify effects of different standards.
- Provide the (long-term) storage infrastructure and maintaining the antimalarial data repository / archive



The role of stakeholders

Stakeholders include:

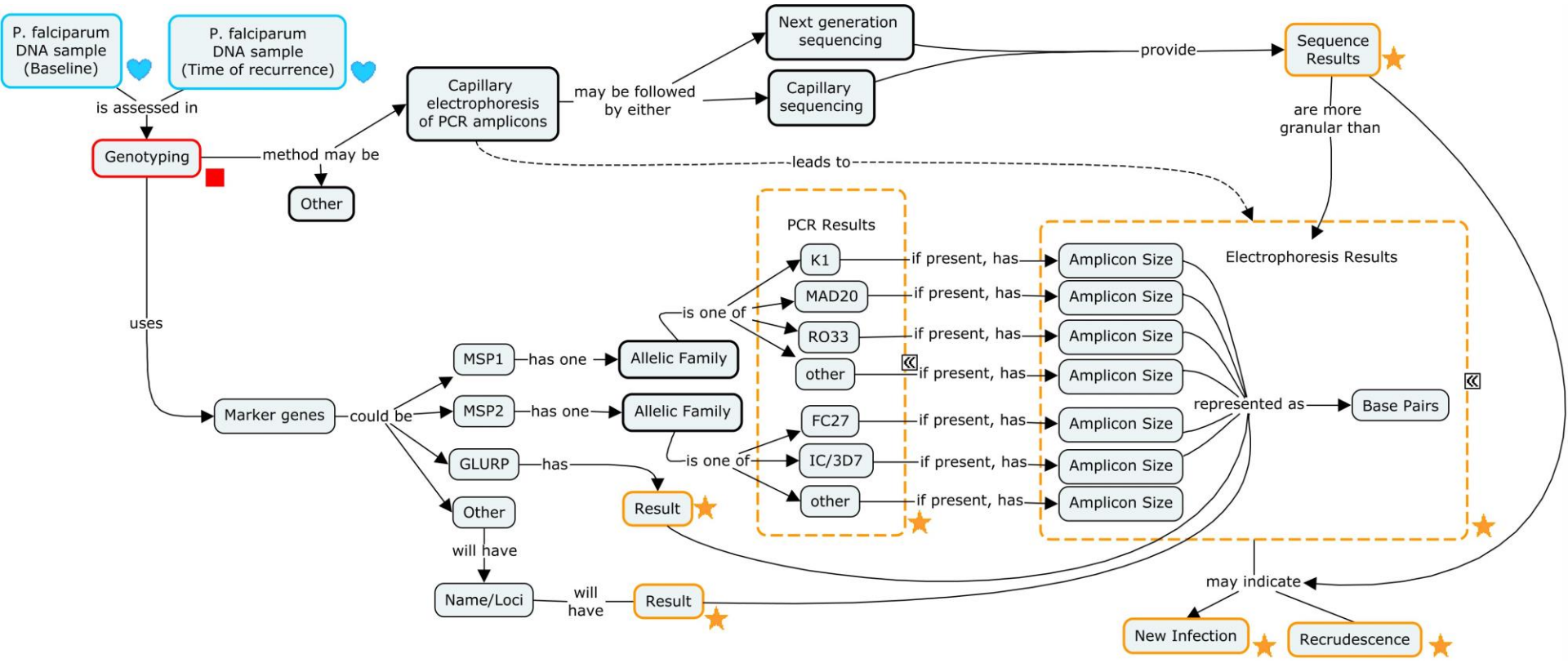
- *CDISC, CPATH*
- *WWARN members*
- *WHO GMP / TDR*
- *BMGF*
- *GHT, LSTM,*
- *Pharma:*
  - *GlaxoSmithKline*
  - *Medicines for Malaria Venture*
  - *Merck*
  - *Novartis*
  - *Sanofi*
  - *Shin Poon*
  - *Sigma Tau*
  - *Takeda*
  - *UCB*

Review draft data standards

Share relevant experience:

- Recent CRF templates / Database Structures / Statistical Analysis Plans
- Identification of critical issues in regulatory submissions.

P. falciparum recrudescence vs. reinfection



Known issues

- Reproducibility, Sensitivity, and Specificity
- In high malaria transmission intensity settings, MoI, a minor population at D0 may be the genotype that recurs.
- In the very low malaria transmission intensity settings, the lack of diversity in the population of parasites means that a reinfecting parasite may have a high probability of sharing the same genotype as the original infection.

WORLDWIDE ANTIMALARIAL RESISTANCE NETWORK
WWARN

Reviewers comments

3.2 Baseline Assessments

Evaluating malaria subjects may include the collection of medical history, as well as recording symptoms of the disease, and characteristics of the subject based on physical examination and special investigations, such as laboratory tests and electrocardiograms (ECGs). Medical history helps to confirm the diagnosis, exclude severe malaria, and identify underlying risk factors that may also be exclusion criteria (e.g., pregnancy, co-morbidities such as HIV, malnutrition MAL-244 RESOLVED MAL-205 RESOLVED). Data regarding recent antimalarial treatment, as well as any concomitant medication use (including traditional, alternative and complementary medicines) MAL-206 RESOLVED and previous medical history may be exclusion criteria and, if not, are necessary for the interpretation of possible adverse events (AEs). Physical characteristics of the subject can include age, body weight, and pregnancy status for women of child-bearing age, as well as whether or not any abnormalities were detected on physical examination and special investigations.

CDISC JIRA tickets

MAL-296	Routinely Collected Data - Adverse Events of Special Interest	Bess LeRoy	Colleen Ratliffe	RESOLVED	Done	22/Nov/16	28/Nov/16
MAL-293	Known Issue 2	Bess LeRoy	Colleen Ratliffe	RESOLVED	Done	22/Nov/16	29/Nov/16
MAL-291	Routinely Collected Data - Dosing with Food	Bess LeRoy	Colleen Ratliffe	RESOLVED	Done	22/Nov/16	29/Nov/16
MAL-288	Routinely Collected Data - Site and Trial Level Data	Bess LeRoy	Colleen Ratliffe	RESOLVED	Done	22/Nov/16	24/Nov/16
MAL-282	Disease Assessment - Parasite Genotyping	Jon Neville	Colleen Ratliffe	RESOLVED	Done	22/Nov/16	24/Nov/16
MAL-284	Disease Assessment - Parasite Genotyping	Jon Neville	Colleen Ratliffe	RESOLVED	Done	22/Nov/16	24/Nov/16
MAL-286	Routinely Collected Data - Site and Trial Level Data	lesley Workman	Colleen Ratliffe	RESOLVED	Fixed	22/Nov/16	26/Nov/16
MAL-290	Known Issue 1	Bess LeRoy	Colleen Ratliffe	RESOLVED	Done	22/Nov/16	26/Nov/16

WWARN

CDISC Strength Through Collaboration

Subscribe Contact Members Only Logout

Enter your keywords SEARCH

About Standards Partnerships Resources News Education Events Membership

HOME / STANDARDS / THERAPEUTIC AREAS / MALARIA

Malaria

Malaria Therapeutic Area User Guide v1.0

1.0 Release Date: 9 Jan 2017

Version 1.0 of the Malaria Therapeutic Area User Guide (TAUG-Malaria) was dev
Program and the CDISC Standards Development Process. TAUG-Malaria describ
biomedical concepts relevant to Malaria, and the necessary metadata to repres
consistently with CDISC standards, such as the SDTM and CDASH.

An example CRF developed by the team can be accessed here: Malaria Case Re

TA Standards extend the Foundational Standards to represent data that pertai
within disease areas. CDISC Standards specify how to structure the data; they c
should be collected or how to conduct clinical trials, assessments or endpoints

CDISC posts Public Review comments and resolutions to ensure transparency a
how comments were addressed in the standard development process.

TA Specifications show how to modify TAUG examples for various versions of th

ALL CURRENT PUBLIC REVIEWS

BRIDG v5.0 Public Review
Comments Due by: 4 May 2017

Define-XML v2.1 Public

ENGLISH FRANÇAIS

WWARN

Share Data CRM Low bandwidth Register Login People Contact

ABOUT US TRACKING RESISTANCE WORKING TOGETHER TOOLS & RESOURCES NEWS & INFORMATION IMPACT

Home > Tools & resources > Procedures > Malaria Case Record Form (CRF)

Malaria Case Record Form (CRF)

Author: WWARN

To help investigators implement the Malaria Therapeutic Area Data Standard (TAUG-malaria) developed in partnership with CDISC we are delighted to share a standardised Case Record Form (CRF) which facilitates the collection of relevant clinical data according to CDASH (Clinical Data Acquisition Standards Harmonization) standards* and will map the data to the SDTM (Study Data Tabulation Model). Our CDASH compliant CRF is intended to be used by persons involved in the planning, collection, management and analysis of antimalarial clinical trials and clinical studies to ensure compliance to regulatory requirements for submission. We also hope it will promote data interchange allowing data to be pooled and shared, and ensure that clinical malaria data is appropriately archived and available for further analysis and reporting. We will develop training materials to accompany this CRF and the malaria standards in the coming months.

Download the malaria case record form (CRF)

Share

Malaria Case Record Form CRF

DOCX 9 January 2017
Malaria Case Record Form CRF
v1.0
DOCX • 202.66 KB

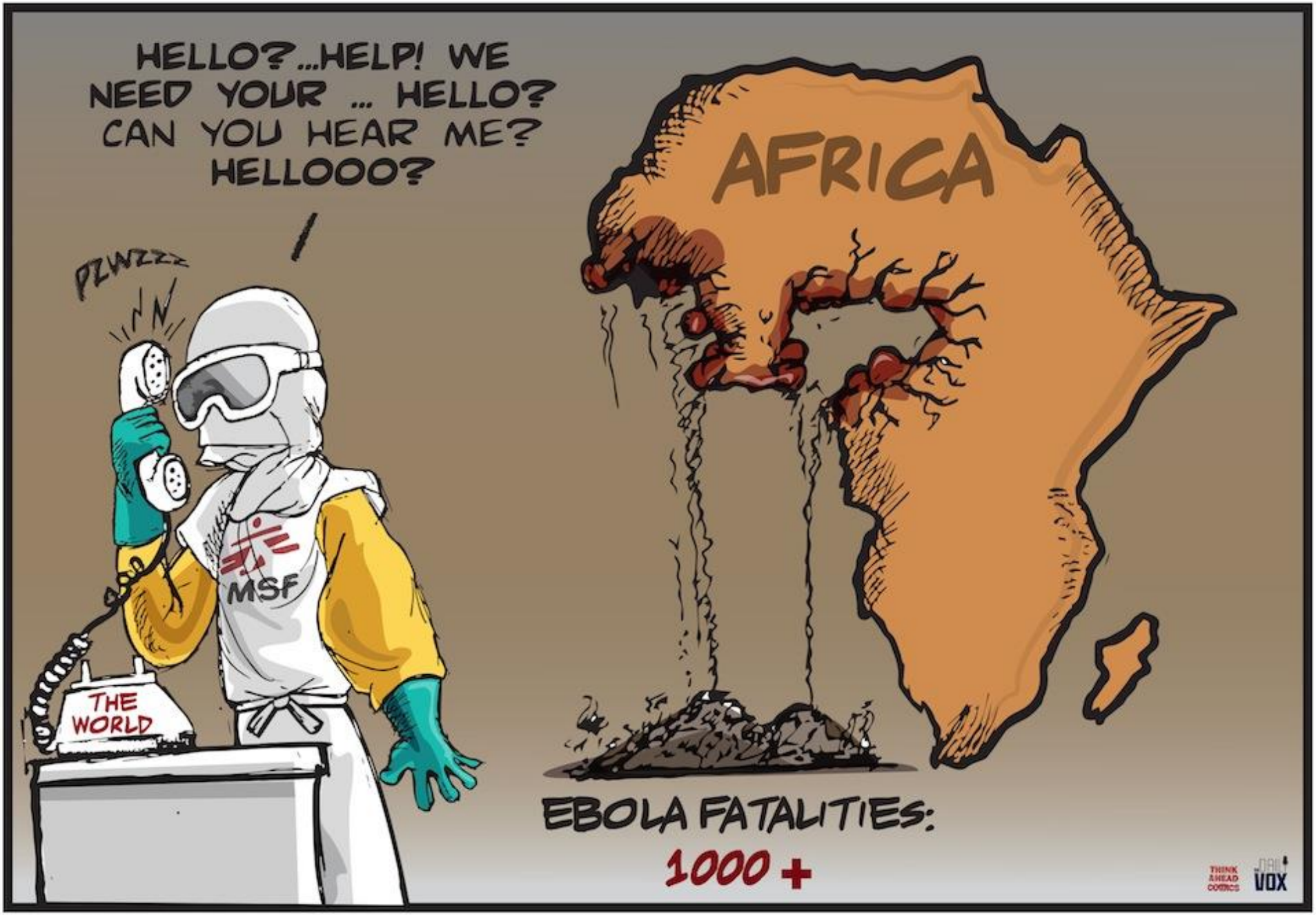
Dominique Faget/AFP/Getty Images


CAPITAL
CAPITAL
CAPITAL


I LOVE U OH LORD
NIGERIA
Innovationiseverywhere.com


Pete Muller, Prime for National Geographic

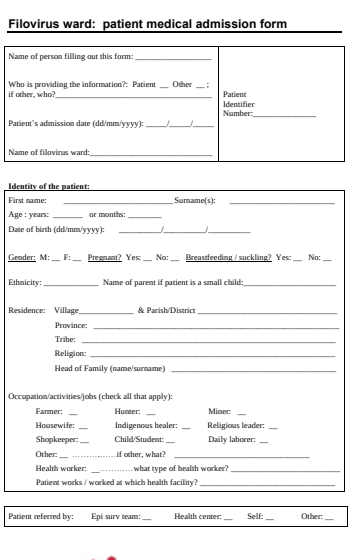
John Moore/Getty Images


HELLO?...HELP! WE NEED YOUR ... HELLO? CAN YOU HEAR ME? HELLOOO?
PZWZZZ
MSF
THE WORLD
AFRICA
EBOLA FATALITIES:
1000 +
THINK AHEAD COMICS
VOX

Core Dataset Development

1: AMALGAMATE AVAILABLE RESOURCES

- Collect existing data forms from a range of organisations



Filovirus ward: patient medical admission form

Name of person filling out this form: _____

Who is providing the information?: Patient __ Other __ ; if other, who?_____

Patient's admission date (dd/mm/yyyy): ____/____/____

Name of filovirus ward:_____

Patient Identifier Number:_____

Identity of the patient:

First name: _____ Surname(s): _____

Age : years: _____ or months: _____

Date of birth (dd/mm/yyyy): _____/_____/_____

Gender: M: __ F: __ Pregnant? Yes: __ No: __ Breastfeeding / suckling? Yes: __ No: __

Ethnicity: _____ Name of parent if patient is a small child:_____

Residence: Village_____ & Parish/District _____

Province: _____

Tribe: _____

Religion: _____

Head of Family (name/surname) _____

Occupation/activities/jobs (check all that apply):

Farmer: __ Hunter: __ Miner: __

Housewife: __ Indigenous healer: __ Religious leader: __

Shopkeeper: __ Child/Student: __ Daily laborer: __

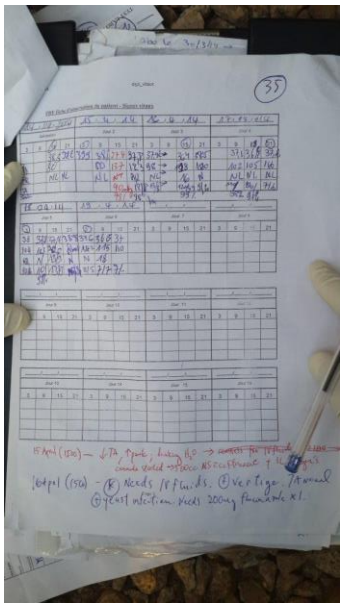
Other: __ ……if other, what? _____

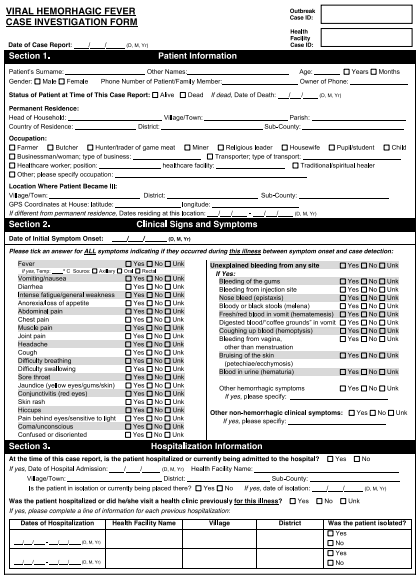
Health worker: __…… what type of health worker? _____

Patient works / worked at which health facility? _____

Patient referred by: Epi surv team: __ Health center: __ Self: __ Other: __

Patient identifier number:_____ 2





VIRAL HEMORRHAGIC FEVER CASE INVESTIGATION FORM

Outbreak Case ID:

Health Facility Case ID:

Date of Case Report: ___/___/___ (D, M, Y)

Section 1. Patient Information

Patient's Surname: _____ Other Names: _____ Age: _____ ☐ Years ☐ Months

Gender: ☐ Male ☐ Female Phone Number of Patient/Family Member: _____ Owner of Phone: _____

Status of Patient at Time of This Case Report: ☐ Alive ☐ Dead *If dead,* Date of Death: ___/___/___ (D, M, Y)

Permanent Residence:

Head of Household: _____ Village/Town: _____ Parish: _____

Country of Residence: _____ District: _____ Sub-County: _____

Occupation:

☐ Farmer ☐ Butcher ☐ Hunter/trader of game meat ☐ Miner ☐ Religious leader ☐ Housewife ☐ Pupil/student ☐ Child

☐ Businessman/woman; type of business: _____ ☐ Transporter; type of transport: _____

☐ Healthcare worker; position: _____ healthcare facility: _____ ☐ Traditional/spiritual healer

☐ Other; please specify occupation: _____

Location Where Patient Became Ill:

Village/Town: _____ District: _____ Sub-County: _____

GPS Coordinates at House: latitude: _____ longitude: _____

If different from permanent residence, Dates residing at this location: ___/___/___ - ___/___/___ (D, M, Y)

Section 2. Clinical Signs and Symptoms

Date of Initial Symptom Onset: ___/___/___ (D, M, Y)

Please tick an answer for ALL symptoms indicating if they occurred during this illness between symptom onset and case detection:

Fever	☐ Yes	☐ No	☐ Unk	
If yes, Temp: ___ °C Source: ☐ Axillary ☐ Oral ☐ Aural				
Vomiting/nausea	☐ Yes	☐ No	☐ Unk	
Diarrhea	☐ Yes	☐ No	☐ Unk	
Intense fatigue/general weakness	☐ Yes	☐ No	☐ Unk	
Anorexia/loss of appetite	☐ Yes	☐ No	☐ Unk	
Abdominal pain	☐ Yes	☐ No	☐ Unk	
Chest pain	☐ Yes	☐ No	☐ Unk	
Muscle pain	☐ Yes	☐ No	☐ Unk	
Joint pain	☐ Yes	☐ No	☐ Unk	
Headache	☐ Yes	☐ No	☐ Unk	
Cough	☐ Yes	☐ No	☐ Unk	
Difficulty breathing	☐ Yes	☐ No	☐ Unk	
Difficulty swallowing	☐ Yes	☐ No	☐ Unk	
Sore throat	☐ Yes	☐ No	☐ Unk	
Jaundice (yellow eyes/gums/skin)	☐ Yes	☐ No	☐ Unk	
Conjunctivitis (red eyes)	☐ Yes	☐ No	☐ Unk	
Skin rash	☐ Yes	☐ No	☐ Unk	
Hiccups	☐ Yes	☐ No	☐ Unk	
Pain behind eyes/sensitive to light	☐ Yes	☐ No	☐ Unk	
Coma/unconscious	☐ Yes	☐ No	☐ Unk	
Confused or disoriented	☐ Yes	☐ No	☐ Unk	

Unexplained bleeding from any site ☐ Yes ☐ No ☐ Unk

If Yes:

Bleeding of the gums	☐ Yes	☐ No	☐ Unk
Bleeding from injection site	☐ Yes	☐ No	☐ Unk
Nose bleed (epistaxis)	☐ Yes	☐ No	☐ Unk
Bloody or black stools (melena)	☐ Yes	☐ No	☐ Unk
Fresh/red blood in vomit (hematemesis)	☐ Yes	☐ No	☐ Unk
Digested blood "coffee grounds" in vomit	☐ Yes	☐ No	☐ Unk
Coughing up blood (hemoptysis)	☐ Yes	☐ No	☐ Unk
Bleeding from vagina, other than menstruation	☐ Yes	☐ No	☐ Unk
Bruising of the skin (petechiae/ecchymosis)	☐ Yes	☐ No	☐ Unk
Blood in urine (hematuria)	☐ Yes	☐ No	☐ Unk
Other hemorrhagic symptoms *If yes,* please specify: _____	☐ Yes	☐ No	☐ Unk

Other non-hemorrhagic clinical symptoms: ☐ Yes ☐ No ☐ Unk

If yes, please specify: _____

Section 3. Hospitalization Information

At the time of this case report, is the patient hospitalized or currently being admitted to the hospital? ☐ Yes ☐ No

If yes, Date of Hospital Admission: ___/___/___ (D, M, Y) Health Facility Name: _____

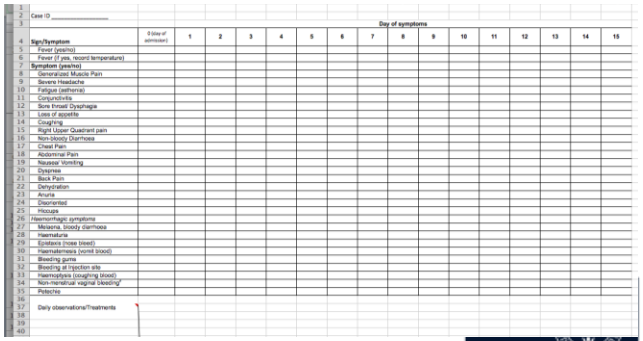
Village/Town: _____ District: _____ Sub-County: _____

Is the patient in isolation or currently being placed there? ☐ Yes ☐ No *If yes,* date of isolation: ___/___/___ (D, M, Y)

Was the patient hospitalized or did he/she visit a health clinic previously for this illness? ☐ Yes ☐ No ☐ Unk

If yes, please complete a line of information for each previous hospitalization:

Dates of Hospitalization	Health Facility Name	Village	District	Was the patient isolated?
___/___/___ - ___/___/___ (D, M, Y)				☐ Yes ☐ No
___/___/___ - ___/___/___ (D, M, Y)				☐ Yes ☐ No



Case ID _____

Day of symptoms

Sign/Symptom	0 (day of admission)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Fever (yes/no)																
Fever (if yes, record temperature)																
Symptom (yes/no)																
Generalized Muscle Pain																
Severe Headache																
Fatigue (asthenia)																
Conjunctivitis																
Sore throat/ Dysphagia																
Loss of appetite																
Coughing																
Right Upper Quadrant pain																
Non-bloody Diarrhoea																
Chest Pain																
Abdominal Pain																
Nausea/ Vomiting																
Dyspnea																
Back Pain																
Dehydration																
Anuria																
Disoriented																
Hiccups																
Haemorrhagic symptoms																
Melaena, bloody diarrhoea																
Haematuria																
Epistaxis (nose bleed)																
Haematemesis (vomit blood)																
Bleeding gums																
Bleeding at injection site																
Haemoptysis (coughing blood)																
Non-menstrual vaginal bleeding																
Petechiae																
Daily observations/Treatments																

ISARIC

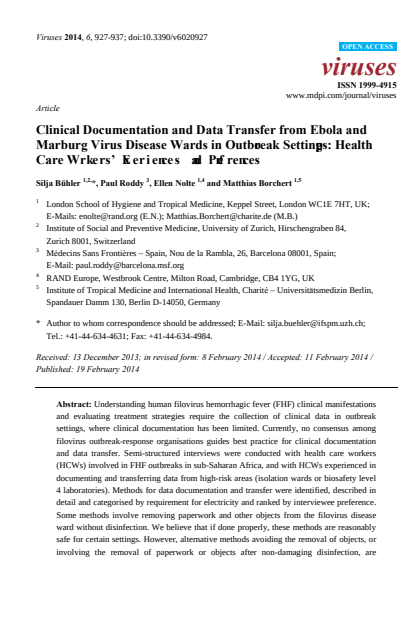
wellcome trust

UNIVERSITY OF OXFORD

Core Dataset Development

1: AMALGAMATE AVAILABLE RESOURCES

- Collect existing data forms from a range of organisations
- Literature search to identify additional variables



Viruses **2014**, *6*, 927-937; doi:10.3390/v6020927

OPEN ACCESS

viruses

ISSN 1999-4915

www.mdpi.com/journal/viruses

Article

Clinical Documentation and Data Transfer from Ebola and Marburg Virus Disease Wards in Outbreak Settings: Health Care Workers' Experiences and Preferences

Silja Bühler [1,2,*], Paul Roddy [3], Ellen Nolte [1,4] and Matthias Borchert [1,5]

1 London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK; E-Mails: enolte@rand.org (E.N.); Matthias.Borchert@charite.de (M.B.)

2 Institute of Social and Preventive Medicine, University of Zurich, Hirschengraben 84, Zurich 8001, Switzerland

3 Médecins Sans Frontières – Spain, Nou de la Rambla, 26, Barcelona 08001, Spain; E-Mail: paul.roddy@barcelona.msf.org

4 RAND Europe, Westbrook Centre, Milton Road, Cambridge, CB4 1YG, UK

5 Institute of Tropical Medicine and International Health, Charité – Universitätsmedizin Berlin, Spandauer Damm 130, Berlin D-14050, Germany

* Author to whom correspondence should be addressed; E-Mail: silja.buehler@ifspm.uzh.ch; Tel.: +41-44-634-4631; Fax: +41-44-634-4984.

Received: 13 December 2013; in revised form: 8 February 2014 / Accepted: 11 February 2014 / Published: 19 February 2014

Abstract: Understanding human filovirus hemorrhagic fever (FHF) clinical manifestations and evaluating treatment strategies require the collection of clinical data in outbreak settings, where clinical documentation has been limited. Currently, no consensus among filovirus outbreak-response organisations guides best practice for clinical documentation and data transfer. Semi-structured interviews were conducted with health care workers (HCWs) involved in FHF outbreaks in sub-Saharan Africa, and with HCWs experienced in documenting and transferring data from high-risk areas (isolation wards or biosafety level 4 laboratories). Methods for data documentation and transfer were identified, described in detail and categorised by requirement for electricity and ranked by interviewee preference. Some methods involve removing paperwork and other objects from the filovirus disease ward without disinfection. We believe that if done properly, these methods are reasonably safe for certain settings. However, alternative methods avoiding the removal of objects, or involving the removal of paperwork or objects after non-damaging disinfection, are

SUPPLEMENT ARTICLE

Filovirus Hemorrhagic Fever Outbreak Case Management: A Review of Current and Future Treatment Options

Paul Roddy,[1] Robert Colebunders,[2,3] Benjamin Jeffs,[1] Pedro Pablo Palma,[1] Michel Van Herp,[1] and Matthias Borchert[3]

[1]Médecins Sans Frontières—Spain, Barcelona, Spain; [2]Institute of Tropical Medicine, and [3]University of Antwerp, Antwerp, Belgium; [4]Médecins Sans Frontières—Belgium, Brussels; and [5]Institute of Tropical Medicine and International Health, Charité Universitätsmedizin Berlin, Berlin, Germany

Testing an innovative therapy for filovirus hemorrhagic fever (FHF) in an outbreak setting may be years away. Moreover, beyond anecdotal evidence, little is known about best practice for outbreak case management. Currently, Médecins Sans Frontières and others provide FHF patients with basic supportive treatment. We describe and discuss treatment possibilities, challenges, and potential next steps for FHF outbreak case management. More comprehensive supportive treatment, including vital sign monitoring, intensive care components, and goal-directed interventions may contribute to improved clinical outcomes; the feasibility and effectiveness of this more comprehensive supportive treatment should be assessed. Our outlined summary may assist future FHF outbreak case management teams to create collaborative platforms and develop relevant treatment protocols aimed at improving clinical outcome.

Filovirus virions are filamentous, enveloped particles with a negative-sense, single-stranded RNA genome [1]. Filoviruses are taxonomically separated into 2 genera, *Ebolavirus* and *Marburgvirus*, and comprise the family Filoviridae. Respectively, they cause Ebola hemorrhagic fever (EHF) and Marburg hemorrhagic fever (MHF) in human and nonhuman primates, and are characterized by person-to-person transmission and high case fatality [2]. To date, 34 filovirus hemorrhagic fever (FHF) outbreaks and laboratory-acquired infections are known to have occurred in humans (23 EHF and 11 MHF), all in or originating from sub-Saharan Africa and yielding approximately 2800 laboratory-confirmed, suspect, or putative cases [3–7].

Herein, we review treatment possibilities, challenges, and potential next steps for improving FHF outbreak case management during outbreaks. Topics include: (1) innovative treatment, (2) standard supportive treatment, (3) past and current challenges for outbreak case management, and (4) recommendations for improved case management. This review may assist future FHF outbreak case management teams to deliver improved treatment for patients.

INNOVATIVE TREATMENT

Efforts by researchers working in high-containment laboratories to address the absence of an effective, approved, and available filovirus treatment in humans are ongoing. Evaluated in nonhuman primates (NHPs) and other animals, some postexposure prophylaxes have achieved promising results [8–10] and have the potential to be innovative components of human treatment [8–12]. Innovative treatment can be divided into 2 categories: (1) disease-modifying agents, and (2) inhibitors of viral replication [8].

Disease-Modifying Agents

The pathophysiology of FHF resembles sepsis and septic shock, with strong inflammatory responses and disseminated intravascular coagulation (DIC) [13]. This similarity served as the impetus for animal-model

Potential conflicts of interest: none reported.

Correspondence: Paul Roddy, MPH, Nou de la Rambla, 26 Barcelona 08001, Spain (paul.roddy@barcelona.msf.org).

The Journal of Infectious Diseases 2011;204:S783–S790

0022-1899 (print)/1537-6613 (online)/2011/204S2-0058$14.00
DOI: 10.1093/infdis/jir297

OPEN ACCESS Freely available online

PLOS ONE

Clinical Manifestations and Case Management of Ebola Haemorrhagic Fever Caused by a Newly Identified Virus Strain, Bundibugyo, Uganda, 2007–2008

Paul Roddy[1]*, Natasha Howard[2], Maria D. Van Kerkhove[3], Julius Lutwama[4], Joseph Wamala[5], Zabulon Yoti[6], Robert Colebunders[7], Pedro Pablo Palma[1], Esther Sterk[1], Benjamin Jeffs[1], Michel Van Herp[1], Matthias Borchert[10,11]

1 Medical Departments of Médecins Sans Frontières, Barcelona, Spain, 2 Medical Departments of Médecins Sans Frontières, Geneva, Switzerland, 3 Medical Departments of Médecins Sans Frontières, Brussels, Belgium, 4 Department of Global Health and Development, London School of Hygiene & Tropical Medicine, London, United Kingdom, 5 Medical Research Council Centre for Outbreak Analysis and Modelling, Department of Infectious Disease Epidemiology, Imperial College London, London, United Kingdom, 6 Department of Arbovirology, Emerging, and Re-Emerging Viral Infections, Uganda Virus Research Institute, Entebbe, Uganda, 7 National Disease Control, Uganda Ministry of Health, Kampala, Uganda, 8 Disease Surveillance and Response Cluster, World Health Organization Regional Office for Africa, Kampala, Uganda, 9 Department of Clinical Sciences, Institute of Tropical Medicine Antwerp and Department of Epidemiology and Social Medicine, University of Antwerp, Antwerp, Belgium, 10 Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, United Kingdom, 11 Institute of Tropical Medicine and International Health, Charité-Universitätsmedizin Berlin, Berlin, Germany

Abstract

A confirmed Ebola haemorrhagic fever (EHF) outbreak in Bundibugyo, Uganda, November 2007–February 2008, was caused by a putative new species (*Bundibugyo ebolavirus*). It included 93 putative cases, 56 laboratory-confirmed cases, and 37 deaths (CFR = 25%). Study objectives are to describe clinical manifestations and case management for 26 hospitalised laboratory-confirmed EHF patients. Clinical findings are congruous with previously reported EHF infections. The most frequently experienced symptoms were non-bloody diarrhoea (81%), severe headache (81%), and asthenia (77%). Seven patients reported or were observed with haemorrhagic symptoms, six of whom died. Ebola care remains difficult due to the resource-poor setting of outbreaks and the infection-control procedures required. However, quality data collection is essential to evaluate case definitions and therapeutic interventions, and needs improvement in future epidemics. Organizations usually involved in EHF case management have a particular responsibility in this respect.

Citation: Roddy P, Howard N, Van Kerkhove MD, Lutwama J, Wamala J, et al. (2012) Clinical Manifestations and Case Management of Ebola Haemorrhagic Fever Caused by a Newly Identified Virus Strain, Bundibugyo, Uganda, 2007–2008. PLoS ONE 7(12): e52986. doi:10.1371/journal.pone.0052986

Editor: Mark N. Wass, Oracle Senguis, University of Liverpool, United Kingdom

Received August 31, 2012; **Accepted** November 23, 2012; **Published** December 28, 2012

Funding: MSW acknowledges funding from the Medical Research Council UK and the Bill and Melinda Gates Foundation. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: roddypd@gmail.com

Introduction

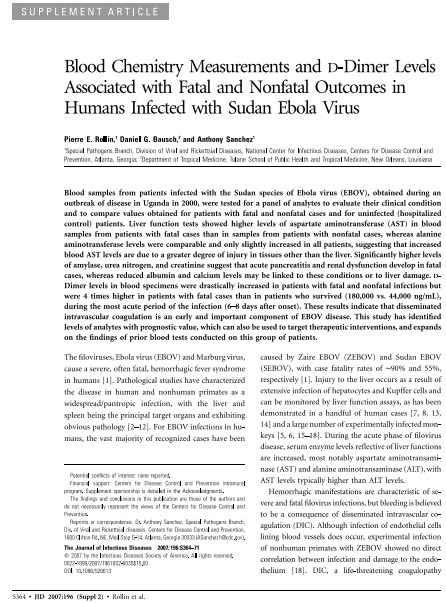
Filoviridae family members are characterized by filamentous enveloped particles with a negative-sense single-stranded RNA genome. They are divided into two genera, *Ebolavirus* and *Marburgvirus*, respectively causing Ebola and Marburg haemorrhagic fever (EHF, MHF) in human and non-human primates [1]. Filovirus haemorrhagic fever (FHF) outbreaks are characterized by secondary transmission and high case fatality [2,3], although species-specific case fatality ratios (CFR) vary considerably: *Zaire ebolavirus* (ZEBOV; 80–90%) [2,4,5], *Sudan ebolavirus* (SEBOV; 40–65%) [2], *Bundibugyo ebolavirus* (BEBOV; 25%) [6–8], *Côte d'Ivoire ebolavirus* (CIEBOV; 0%; based on a single patient) [9–11], *Reston ebolavirus* (REBOV; 0%; possibly non-pathogenic for humans) [12–16], and *Lake Victoria marburgvirus* (MARV; 20–88%) [17–20]. To date, 35 FHF outbreaks are known to have occurred in humans (24 EHF and 11 MHF), all in or originating from sub-Saharan Africa [2,21–27].

Suspect and laboratory-confirmed patient categorisation

In sub-Saharan Africa, when a medical professional suspects a filovirus infection, the patient's blood sample is typically sent abroad to a biosafety level-4 (BSL-4) laboratory for diagnostic confirmation. If positive, an outbreak is declared and an international response initiated, consisting of case identification and contact tracing, with isolation and treatment of suspect and laboratory-confirmed patients in a filovirus ward [28–33].

Due to delays between outbreak onset, recognition, and response, some individuals potentially infected with filovirus convalesce, die and are buried, or are lost to follow-up before having their blood sampled for disease confirmation. Likewise, if clinical disease and outcome occur prior to a filovirus ward's existence or functionality, not all patients are hospitalized and treated on a filovirus ward. Outbreaks therefore habitually conclude with putative, suspected, and laboratory-confirmed patient categorisations, with only some patients receiving supportive treatment on a filovirus ward.

Once case identification and contact tracing activities commence, individuals matching epidemiological and clinical case



SUPPLEMENT ARTICLE

Blood Chemistry Measurements and D-Dimer Levels Associated with Fatal and Nonfatal Outcomes in Humans Infected with Sudan Ebola Virus

Pierre E. Rollin,[1] Daniel G. Bausch,[1] and Anthony Sanchez[1]

[1]Special Pathogens Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; [2]Department of Tropical Medicine, Tulane School of Public Health and Tropical Medicine, New Orleans, Louisiana

Blood samples from patients infected with the Sudan species of Ebola virus (EBOV), obtained during an outbreak of disease in Uganda in 2000, were tested for a panel of analytes to evaluate their clinical condition and to compare values obtained for patients with fatal and nonfatal cases and for uninfected (hospitalized control) patients. Liver function tests showed higher levels of aspartate aminotransferase (AST) in blood samples from patients with fatal cases than in samples from patients with nonfatal cases, whereas alanine aminotransferase levels were comparable and only slightly increased in all patients, suggesting that increased blood AST levels are due to a greater degree of injury in tissues other than the liver. Significantly higher levels of amylase, urea nitrogen, and creatinine suggest that acute pancreatitis and renal dysfunction develop in fatal cases, whereas reduced albumin and calcium levels may be linked to these conditions or to liver damage. D-Dimer levels in blood specimens were drastically increased in patients with fatal and nonfatal infections but were 4 times higher in patients with fatal cases than in patients who survived (180,000 vs. 44,000 ng/mL), during the most acute period of the infection (6–8 days after onset). These results indicate that disseminated intravascular coagulation is an early and important component of EBOV disease. This study has identified levels of analytes with prognostic value, which can also be used to target therapeutic interventions, and expands on the findings of prior blood tests conducted on this group of patients.

The filoviruses, Ebola virus (EBOV) and Marburg virus, cause a severe, often fatal, hemorrhagic fever syndrome in humans [1]. Pathological studies have characterized the disease in human and nonhuman primates as a widespread/pantropic infection, with the liver and spleen being the principal target organs and exhibiting obvious pathology [2–12]. For EBOV infections in humans, the vast majority of recognized cases have been caused by Zaire EBOV (ZEBOV) and Sudan EBOV (SEBOV), with case fatality rates of ~90% and 55%, respectively [1]. Injury to the liver occurs as a result of extensive infection of hepatocytes and Kupffer cells and can be monitored by liver function assays, as has been demonstrated in a handful of human cases [7, 8, 13, 14] and a large number of experimentally infected monkeys [5, 6, 15–18]. During the acute phase of filovirus disease, serum enzyme levels reflective of liver functions are increased, most notably aspartate aminotransaminase (AST) and alanine aminotransaminase (ALT), with AST levels typically higher than ALT levels.

Hemorrhagic manifestations are characteristic of severe and fatal filovirus infections, but bleeding is believed to be a consequence of disseminated intravascular coagulation (DIC). Although infection of endothelial cells lining blood vessels does occur, experimental infection of nonhuman primates with ZEBOV showed no direct correlation between infection and damage to the endothelium [18]. DIC, a life-threatening coagulopathy

Potential conflicts of interest: none reported.

Financial support: Centers for Disease Control and Prevention intramural program, facilities sponsorship is detailed in the Acknowledgments.

The findings and conclusions in this publication are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Reprints or correspondence: Dr. Anthony Sanchez, Special Pathogens Branch, Div. of Viral and Rickettsial diseases, Centers for Disease Control and Prevention, 1600 Clifton Rd, NE, Mail Stop G-14, Atlanta, Georgia 30333 (ASanchez1@cdc.gov).

The Journal of Infectious Diseases 2007;196:S364–71

0022-1899/2007/19601S2-0055$15.00
DOI: 10.1086/520615

Core Dataset Development

#2: DETERMINE WHAT IS NEEDED

- Survey experienced health care workers, public health agencies, clinical researchers to collect recommendations on important data variables.

ISARIC

wellcome trust

UNIVERSITY OF OXFORD

Core Dataset Development

#3: CREATE A MASTER LIST

	A	B	C	D	E	F	G	H	I	J	K	L
		Master Content Table		Green=General Demo	Yellow=Vitals	Orange=Signs/Symptoms	Blue=History	Purple=Diagnostic Tests	Grey=Medications Given	Beige=Treatments Performed	RED=Discharge Information	Black=Operational Research
		CRITICAL: READ ME BEFORE PROCEEDING: To all persons editing/viewing it is important to note that the software will have sufficient intelligence to add variables as needed. This table is in no way meant to serve as the final list of clinical variables collected. This table is meant to serve as 'most robust' starting point for administrators to create/modify clinical line lists.										
	#	VARIABLE LIST (ROBUST)	START POINT: 1. Baseline=first patient contact 2. First Consult=First MD patient interaction 3. Vitals=Nurse or physician basic patient assessment 4. Repeat Consult:	POINT: 1. Baseline=first patient contact 2. First Consult=First MD patient interaction 3. Vitals=Nurse or physician basic patient assessment 4. Repeat Consult: more thorough patient assessment throughout	Data Collection Location	Frequency of Collection: (Total possible collection frequency)	Coding Method	Coding Schema	Mandatory Variable (not able to be manipulated on line list generator software) 1==yes 0==no	FINAL JUSTIFICATION FOR Variable BEING MANDATORY OR OPTIONAL (Write rationale here)		
	108	Specimen Type (LABS)	1 or 2	2,3,4,5	triage, consultation, vitals, discharge	multiple (triage-discharge)	Categorical all levels NOTE: SKIP PATTERN BUILT FOR PATIENTS THAT RECEIVED SPECIMEN DRAW ONLY (user able to select all relevant fields)	1==Filovirus PCR	1			
								2==Filovirus ELISA	1			
								3==Na+, K+, Cl-, HCO3-	0			
								4==Ionized Ca++	0			
								5==Ionized Ca++	0			
								6==Hemoglobin/Hematocrit	0			
								7==WBC	0			
								8==Platelet	0			
								9==Glucose	0			
								10==BUN/Creatinine	0			
								11==Lactate	0			
								12==Malaria RDT	0			
								13==D-dimer	0	Prognostic value important for patient management		
								14==APTT & PT & INR	0			
								15==Amylase	0			
								16==Bilirubin	0			
								17==AST/SGOT and ALT/SGPT	0	Prognostic value important for patient management		
								18==Creatine kinase	0			
								19==Albumin	0			
								20==Urinalysis	0			
								99==other (open for entry)	0			
	109	Lab (specimen) Results (LABS)	2	3,4,5,6	consultation, dishcarge	multiple (triage-discharge)	Categorical all levels NOTE: SKIP PATTERN BUILT FOR PATIENTS THAT RECEIVED SPECIMEN DRAW ONLY (user able	Categorical results populated based on lab tests drawn	0			
	110	Fluid Given	2	2,3,4,5	consultation	multiple (triage-discharge)	Binary all levels	1==yes	0			
								0==no				
	111	Fluid Given (Type)	2	2,3,4,5	consultation	multiple (consultation/vitals)	Binary by type of fluid given with aggregate 'Fluids Y/N at all levels NOTE: SKIP PATTERN ONLY PATIENTS THAT WERE GIVEN FLUIDS	1==ORS	0			
								2==Lactated Ringers	0			
								3==D10	0			
								4=Others (open)	0			

Core Dataset Development

#4: DETERMINE WHAT IS NOT NEEDED TO ACHIEVE THE OBJECTIVES

- Iterative series of reviews and input from a range of experts

SEPERATELY

- Survey of experienced health care workers to select and justify what variables are needed

ISARIC

wellcome trust

UNIVERSITY OF OXFORD

Core Dataset Development

#5: ONGOING REVIEW & UPDATE

- Addition of variables as required by stakeholders to accommodate research, interventions and new findings
- Data dictionary development
- Dictionary standardization – CDISC standards

ISARIC

wellcome trust

UNIVERSITY OF OXFORD

World Health Organization

centre | Publications | Countries | Programmes | Governance | About WHO

Media centre

Ethical considerations for use of unregistered interventions for Ebola virus disease (EVD)

Summary of the panel discussion

WHO statement
12 August 2014

West Africa is experiencing the largest, most severe and most complex outbreak of Ebola virus disease in history. Ebola outbreaks can be contained using available interventions like early detection and isolation, contact tracing and monitoring, and adherence to rigorous procedures of infection control. However, a specific treatment or vaccine would be a potent asset to counter the virus.

Over the past decade, research efforts have been invested into developing drugs and vaccines for Ebola virus disease. Some of these have shown promising results in the laboratory, but they have not yet been evaluated for safety and efficacy in human beings. The large number of people affected by the 2014 west Africa outbreak, and the high case-fatality rate, have prompted calls to use investigational medical interventions to try to save the lives of patients and to curb the epidemic.

Therefore, on 11 August 2014, WHO convened a consultation to consider and assess the ethical implications for clinical decision-making of the potential use of unregistered interventions.

In the particular circumstances of this outbreak, and provided certain conditions are met, the panel reached consensus that it is ethical to offer unproven interventions with as yet unknown efficacy and adverse effects, as potential treatment or prevention.

"investigators have a moral duty to evaluate these interventions in the best possible clinical studies that can be conducted under the circumstances of the epidemic."

World Health Organization

1. EBOLA THERAPIES AND VACCINES: WHAT'S IN THE PIPELINE?

The following table lists potential therapies and vaccines for EVD and provides information about how the interventions might work. It also summarises the research, which has been conducted, what is known about safety and availability, and the feasibility of use under current conditions. The list has been produced after a review of studies exploring the effects of potential therapies and vaccines *in vitro* and in animal models, and following discussions with clinicians and virologists conducted by WHO and partners from the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC)[1].

1.1 Lead experimental therapies

Table1. Overview of scientific information on potential therapies under development (Annex 2)

Therapy	What it does?/ State of research	Safety	Availability/feasibility
Convalescent plasma	Studies suggest blood transfusions from EVD survivors might prevent or treat Ebola virus infection in others, but the results of the studies are still difficult to interpret. It is not known whether antibodies in the plasma of survivors are sufficient to treat or prevent the disease. More research is needed.	Safe if provided by well-managed blood banks. Risks are like those associated with the use of any blood products, such as the transmission of blood-borne pathogens that cause disease. There is a theoretical concern about antibody-dependent enhancement of EVD infection, which can increase infectivity in the cells.	Blood transfusion is culturally acceptable in West Africa. Potential donors are Ebola survivors, but the logistics of blood collection are an issue. Options to conduct studies in patients are being explored. The first batches of convalescent plasma might be available by the end of 2014.
ZMapp Cocktail of three	The three antibodies in this mixture block or neutralize the virus, by	There have been no formal safety studies in humans. Very small	A very limited supply (fewer than 10 treatment courses) has been

Facilities, power, access, internet, security.

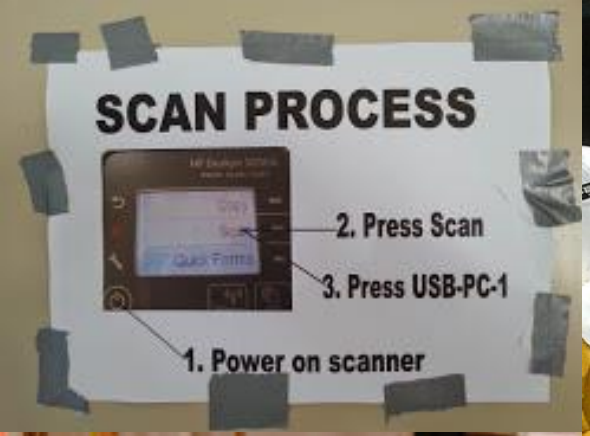
Diagnostic methods, kits & standards.

John Moore/Getty Images

John Moore/Getty Images

Staff, time, priorities.

Many patients, some very sick, some not, coming from many places speaking many languages


SCAN PROCESS
2. Press Scan
3. Press USB-PC-1
1. Power on scanner


ISHLEY

MSF


Standard Abbreviations:
OK - Ok
C - Concern
i.v. - i.v. Line
B - Bleeding
D - Diarrhea
F - Fever
HA - Headache
P - Pain
V - Vomit
W - Weakness (if intense)
DH - Dehydration
A - Anorexia
ST - Sore throat
Abdominal P.
B. Pain

Infection control means nothing comes out:

Everything is burned

First trials for Ebola treatments to start at MSF sites in December

13 November 2014

Geneva – In the absence of specific treatments for Ebola, international medical humanitarian organisation Médecins Sans Frontières (MSF) announced today that it will host clinical trials in three Ebola treatment centres in West Africa. The separate trials, which are aimed at quickly finding an effective therapy that can be used against the disease which has so far taken around 5,000 lives in the current outbreak in the region, will be led by three different research partners.

The French National Institute of Health and Medical Research (INSERM) will lead a trial using antiviral drug favipiravir in Guéckédou, Guinea; the Antwerp Institute of Tropical Medicine (ITM) will lead a trial of convalescent whole blood and plasma therapy at the Donka Ebola centre in Conakry, Guinea; and The University of Oxford will lead, on behalf of the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC), a Wellcome Trust-funded trial of the antiviral drug brincidofovir at a site yet to be determined. The World Health Organization (WHO) and health authorities of the affected countries are also taking part in this collaborative effort.

Helena gets a chance to talk to her son Moses who is an Ebola confirmed patient. A MSF health promoter supports this difficult moment for the young mother as she is too overwhelmed with what to say. The health promoter advises her to say positive things such as „I am waiting here outside for you" or „I am thinking of you non Stop"


OXFORD

Data Standards

CDISC

Therapeutic Area Data Standards User Guide for Ebola Virus Disease

Version 1.0 (Provisional)

Developed by the
Ebola Team

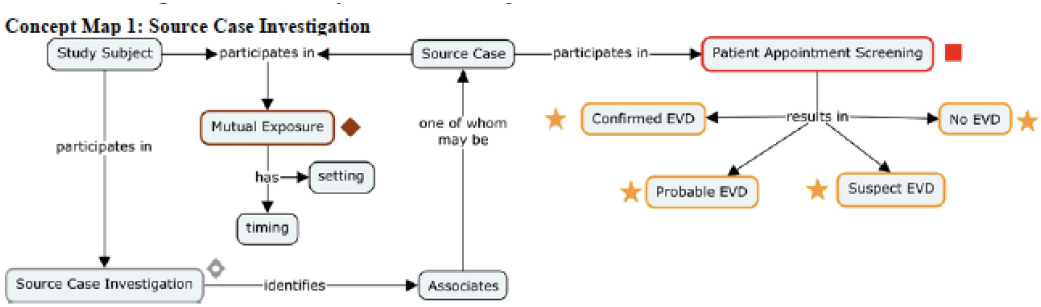
Notes to Readers

- This is version 1.0 of the Therapeutic Area Data Standards User Guide for Ebola Virus Disease.
- This document is based on CDASH v1.1 and CDASHUG v1.0, SDTM v1.4 and SDTMIG v3.2, but incorporates some modeling based on proposed changes to these foundational standards.

Revision History

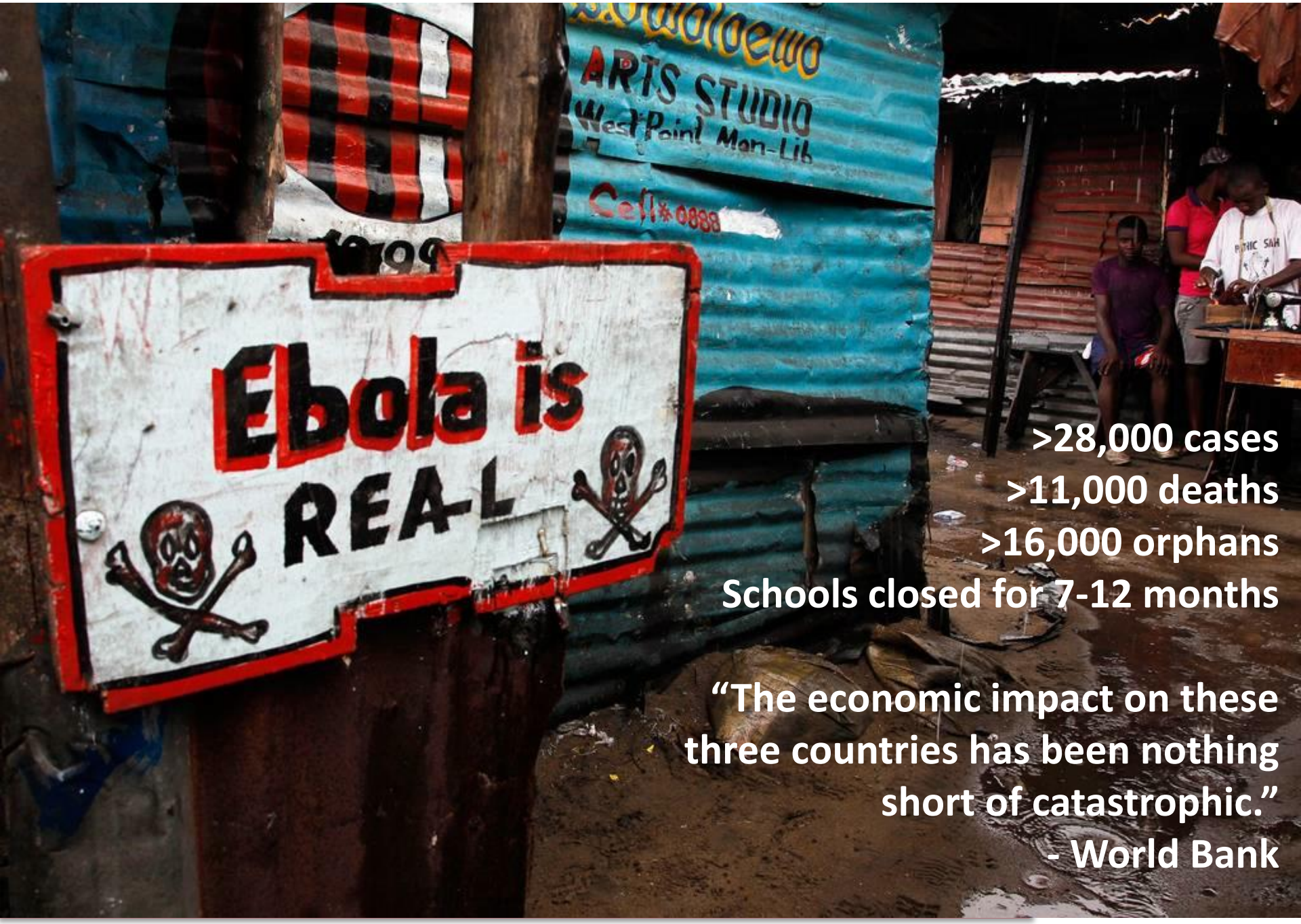
Date	Version
2016-12-19	1.0 Provisional
2016-09-30	1.0 Draft

See Appendix E for Representations and Warranties, Limitations of Liability, and Disclaimers.



EVD Entry Symptom and Diagnosis Type	
Visit VISIT *Pre-specified*	VISIT 1
Domain DOMAIN *Hidden/pre-specified*	MH
Did the subject experience fever? MHOCCUR where MHTERM = "Fever"	☐ Yes ☐ No
Start Date FEVER_MHSTDAT MHSTDTC where MHTERM = "Fever"	__/___/____
Ongoing FEVER_MHONGO MHENRTPT MHENRF	☐ Yes ☐ No
End Date FEVER_MHENDDAT MHENDTC where MHTERM = "Fever"	__/___/____
Did the subject experience vomiting? MHOCCUR where MHTERM = "Vomiting"	☐ Yes ☐ No
Start Date VOMIT_MHSTDAT MHSTDTC where MHTERM = "Vomiting"	__/___/____

IDDO
INFECTIOUS DISEASES DATA OBSERVATORY



>28,000 cases
>11,000 deaths
>16,000 orphans
Schools closed for 7-12 months

"The economic impact on these three countries has been nothing short of catastrophic."
- World Bank

Drivers of infectious disease outbreaks are strengthening and shifting.

Flights over 24 hours: 3JUL17 (Guardian.com)