EVD Case Management: Updates in Care Package

Therapeutics for EVD: update from DRC

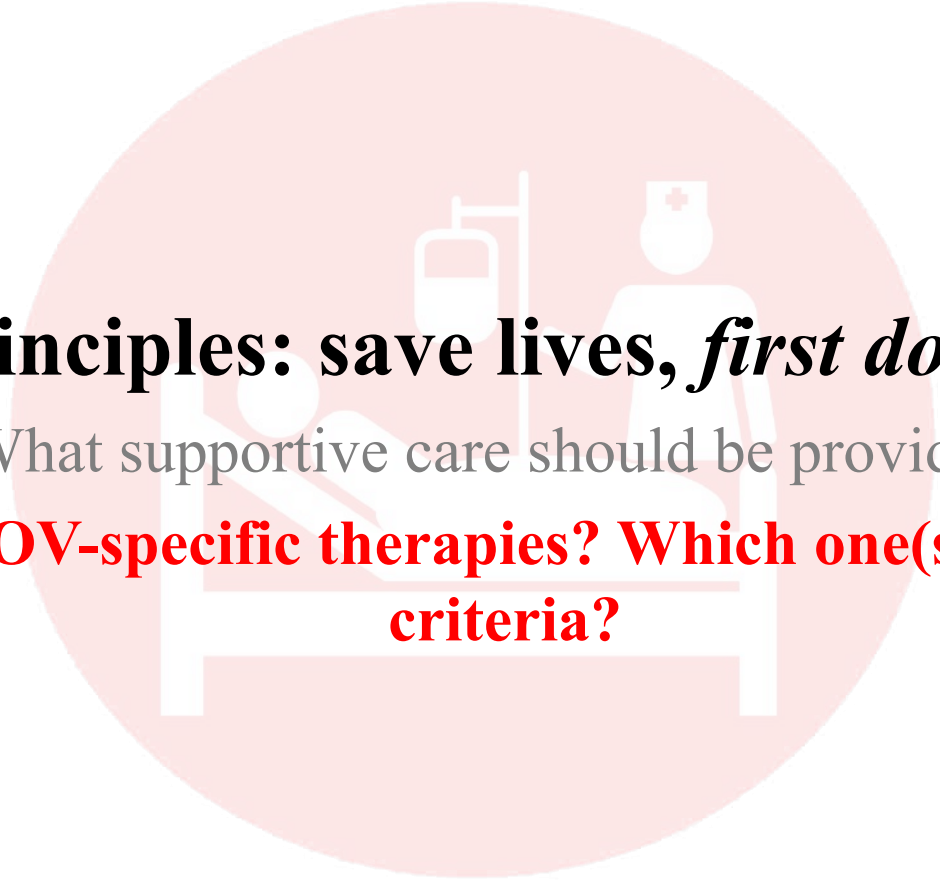
Webinar | February 26, 2020

Ian Crozier, MD
Frederick National Lab, support to NIAID Integrated Research Facility at Fort Detrick

North Kivu EVD bedside (Sep 2018): What best care should be provided to the patient?

A doctor cares for a patient inside an isolate cube at The Alliance for International Medical Action (ALIMA) treatment center in Beni, North Kivu province of the Democratic Republic of Congo September 6, 2018. REUTERS/Fiston Mahamba/File Photo

Good clinical decision-making at the EVD bedside

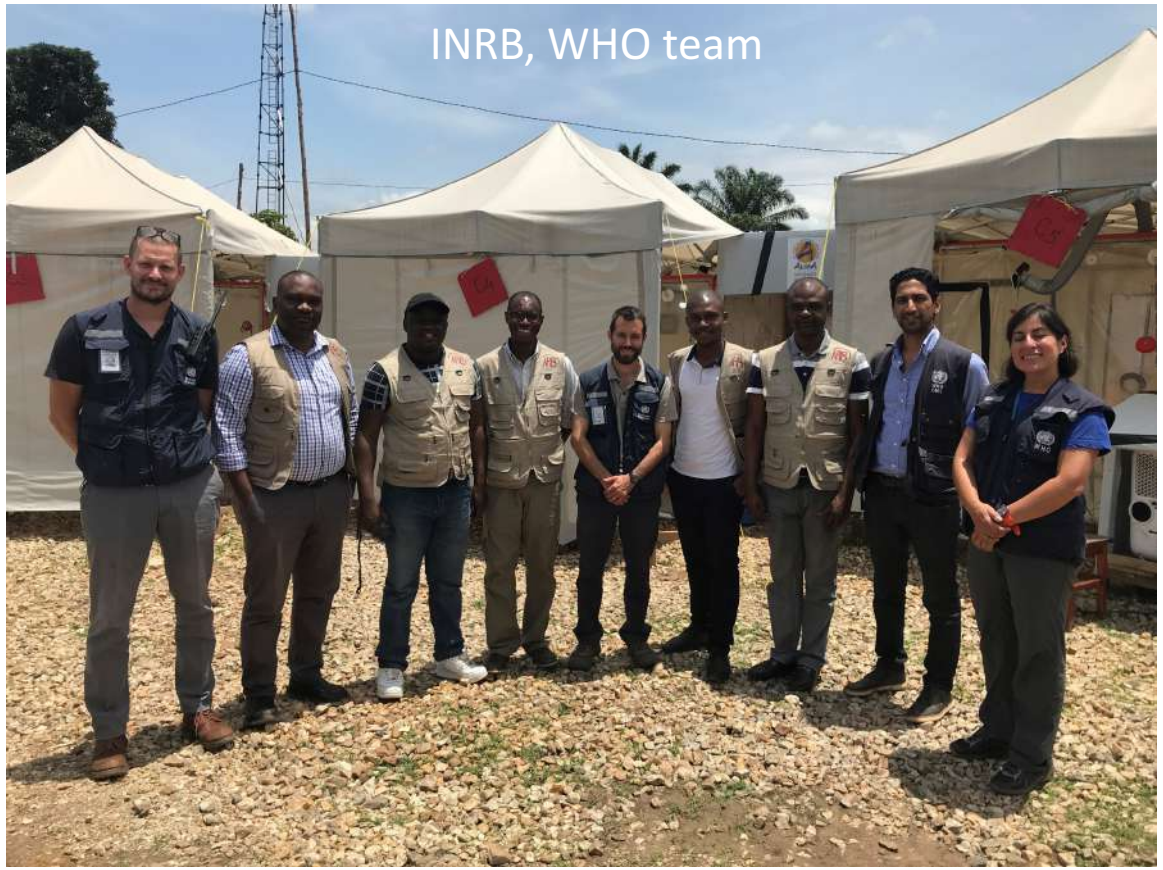


Key principles: save lives, *first do no harm*

What supportive care should be provided?

Would you use EBOV-specific therapies? Which one(s)? According to what criteria?

ALIMA ETU (Beni): ALIMA/INRB/WHO team



Key questions: EVD therapeutics

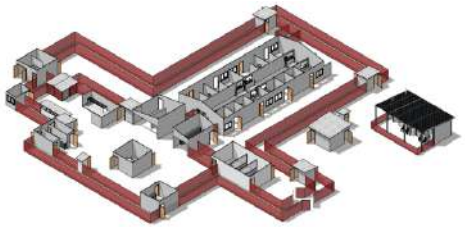
- **WHY** should we use safe and effective therapeutics for EVD? How are they accessed?
- **WHAT** therapeutics that have been shown to be safe and most effective in EVD patients?
- **WHO** should receive therapeutics for EVD?
- **HOW** should these therapeutics be prepared, administered, and monitored?
- **HOW** should that care be documented?

A new strategy that saves lives

Design et Biosecurite

Not a simple isolation unit, but rather a centre centered around patients, staff, families and communities.

A place where patients can receive, quality care with all biosecurity and IPC standards in place.



Optimized supportive care

Oxygen and point of care testing (electrolytes, hemoglobin)

Systematic evaluation et re-evaluation

Resuscitation with fluids

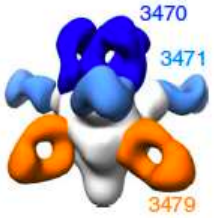
Prevention and care of complications

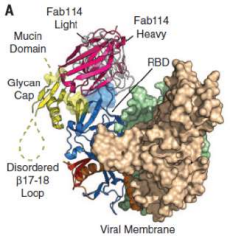
Therapeutics

Proven in hallmark randomized clinical trial (PALM), there are two new molecules available to care for patients with EVD

Inmazeb (REGN-EB3)

Ansuvimab (mAB114, **Ebanga**)





World Health Organization

Source: WHO Case Management

HEALTH EMERGENCIES programme

Access in DRC: the MEURI protocol

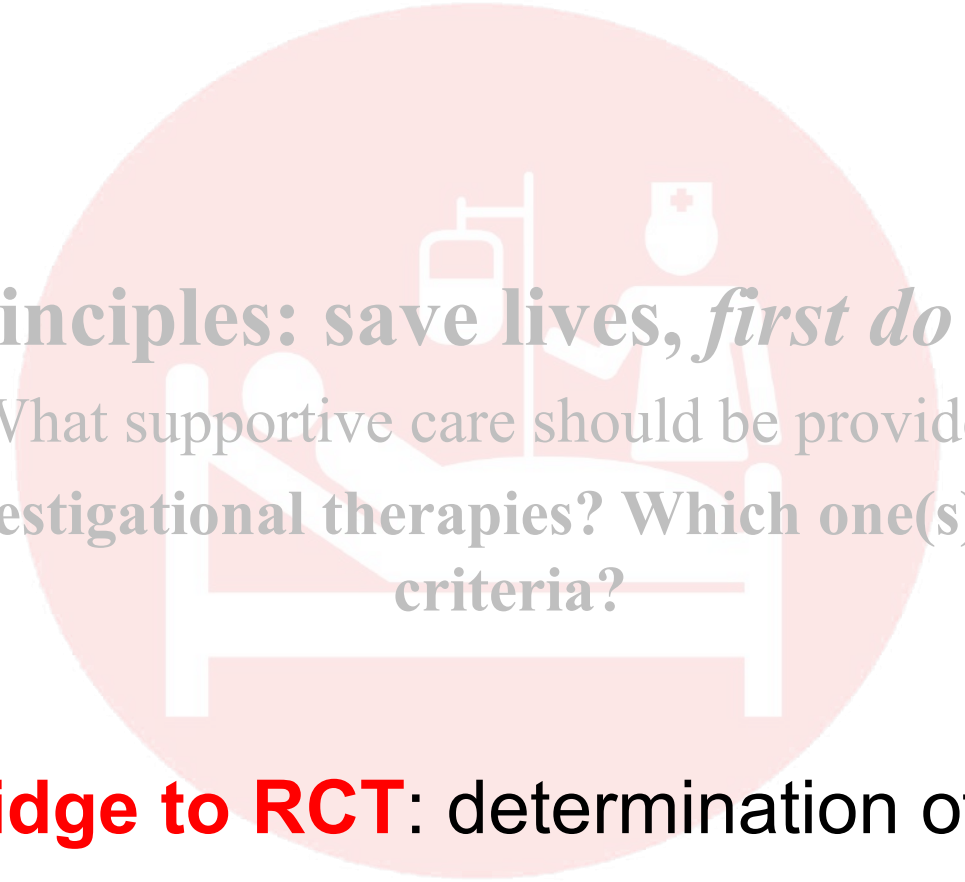
- Early in the 2018-20 DRC outbreak, WHO convened an expert panel to review available evidence and discuss various investigational therapies to use in DRC
- With DRC and Principal Investigators (PI) in country, developed prioritization scheme for use under the **MEURI expanded access protocol (EAP)**, then worked closely with drug developers to facilitate importation under a closely monitored process that required **specific criteria to access**, namely…

Notes for the Record: MEURI (May 17, 2018)

Consultation on **M**onitored **E**mergency **U**se of **Unr**egistered and **I**nvestigational **I**nterventions for EVD → criteria for access:

- **No proven** treatment exists
- It is **not possible** to initiate clinical studies immediately
- Data providing **preliminary support** of the intervention's efficacy and safety are available, at least from laboratory or animal studies, and use of the intervention outside clinical trials has been suggested by an appropriately qualified scientific advisory committee on the basis of a favorable risk–benefit analysis
- **Country authorities**, as well as an appropriately **qualified ethics committee**, have approved such use
- **Adequate resources** are available to ensure that risks can be minimized
- Patient **informed consent** is obtained
- Emergency use of the intervention is **monitored** and the results are **documented** and **shared** in a timely manner with the wider medical and scientific community.

Good clinical decision-making at the EVD bedside



Key principles: save lives, *first do no harm*

What supportive care should be provided?

Would you use investigational therapies? Which one(s)? According to what criteria?

MEURI as a **bridge to RCT**: determination of **safety and efficacy**


PAMOJA TULINDE MAISHA • TOGETHER SAVE LIVES • ENSEMBLE SAUVONS LES VIES

PALM

PALM Randomized Clinical Trial of EVD therapeutics

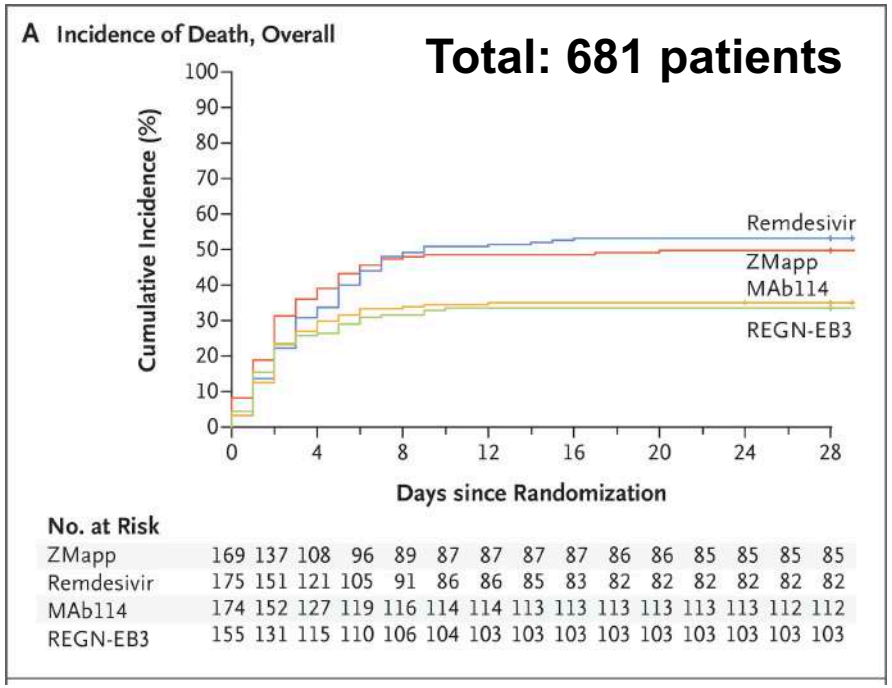
- The PALM study was a **randomized clinical trial** that investigated the safety and efficacy of Ebola virus-specific therapeutics in patients with EVD in the Democratic Republic of Congo.
- It compared each of two monoclonal antibody-based (**mab114**, **REGN-EB3**) and one small molecule antiviral (**remdesivir**) treatment with a control arm that included the **Zmapp** cocktail of monoclonal antibodies.
- Importantly, patients receiving these investigational therapeutics as part of the RCT also received **optimized supportive care** that included clinical and laboratory monitoring
- After starting in November (2018), the trial was conducted at four different sites, then was stopped in August (2019) when the data safety and monitoring board determined that two of the therapeutics (**mab114**, **REG-EB3**) were safe and **more effective**.
- In an follow-on extension study, patients were then only randomized to one of these two therapeutics; additionally, in non-RCT sites, patients could receive only these therapeutics under the MEURI access protocol

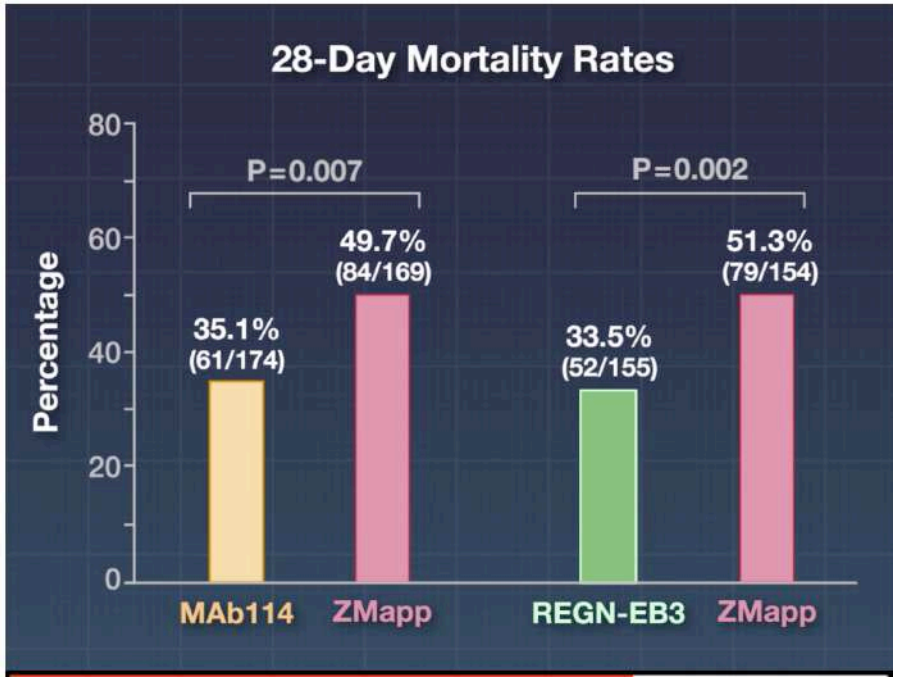
PALM RCT study objectives

- **Primary objective: 28 day mortality** of investigational treatment arms compared to ZMapp control arm
- **Secondary objectives:**
  - Relative changes in viral load over time
  - Comparison of treatment efficacy at low or high risk categories at baseline
  - Evaluation of the comparative safety and efficacy of investigational therapeutics

PALM RCT: overall efficacy of MAb114 and REGN-EB3 in EVD

Take-home: Mab114 and REGN-EB3 improved 28 day mortality rates (versus the Zmapp control arm) and were well-tolerated



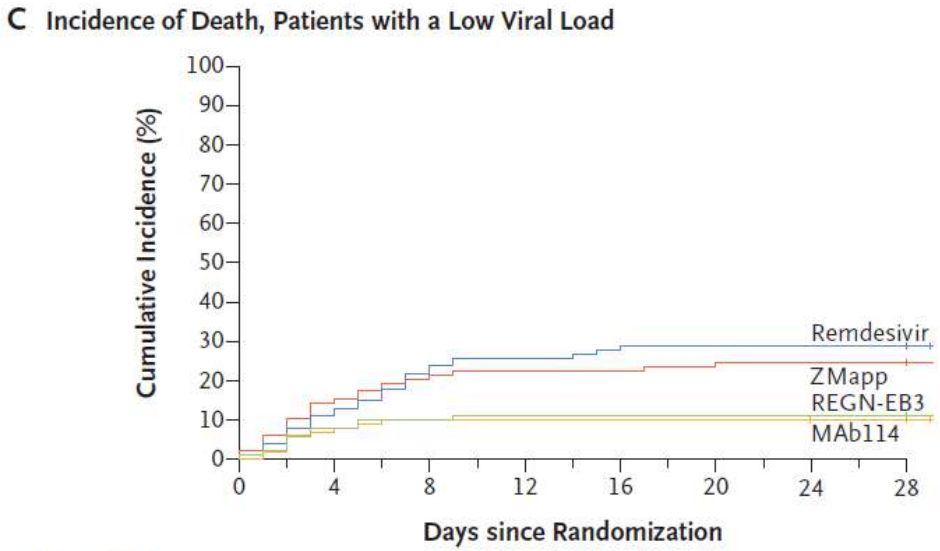


Mulangu et al, NEJM (2019)

PALM RCT: patients with low viral loads

CFR was improved to approximately 10% in patients with CT-NP>22

We need to diagnose EVD EARLY!



No. at Risk

ZMapp	98	92	84	81	78	76	76	76	76	75	75	74	74	74	74
Remdesivir	100	96	89	85	78	74	74	74	72	71	71	71	71	71	71
MAb114	101	99	94	92	91	91	91	91	91	91	91	91	91	90	90
REGN-EB3	89	87	82	80	80	79	79	79	79	79	79	79	79	79	79

24/98 (24.5%)

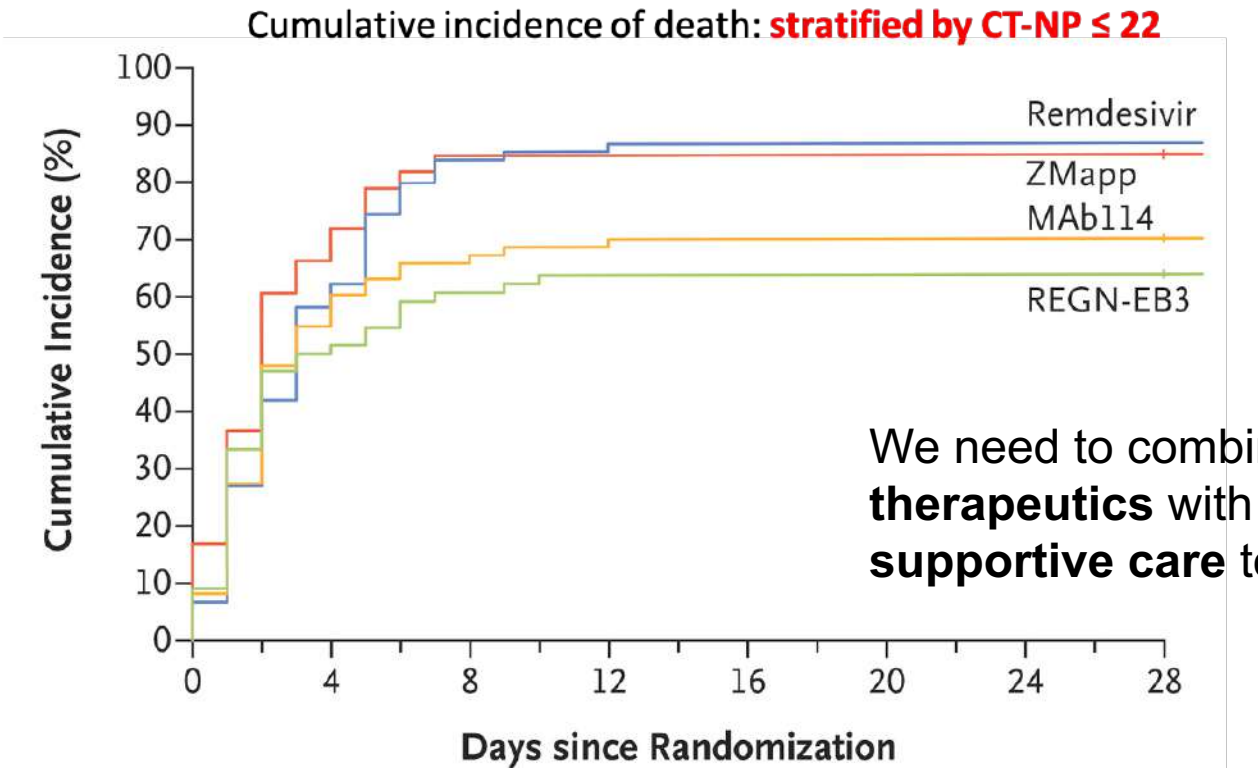
29/100 (29%)

10/101 (9.9)

10/89 (11.2%)

PALM RCT: patients with high viral loads

CFR 64-85% despite EBOV-specific therapeutic, even the most effective ones!

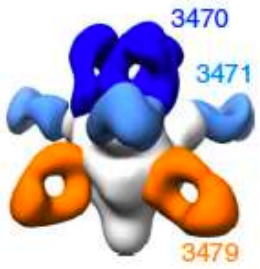


64/75 (85.3%)
60/71 (84.5%)
51/73 (69.9%)
42/66 (63.6%)

We need to combine **early effective therapeutics** with **early and effective supportive care** to improve patient outcomes!

REGN3470-3471-3479 (REGN-EB3, Inmazeb®)

- A cocktail of **3 fully human IgG1** monoclonal antibodies in a 1:1:1 ratio
  - REGN3470
  - REGN3471
  - REGN3479



Supplied in 20 mL glass vials
- Sterile aqueous solution
- 750 mg protein
- **50mg/mL**
- **14.5 mL** withdrawable volume
- 10% (w/v) sucrose

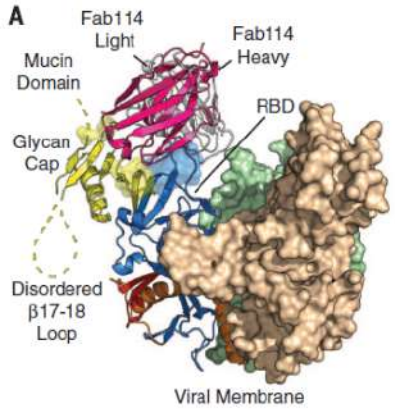
- Advantages:
  - Single 150mg/kg IV dose over 2-4 hours (50mg/kg for each mAb)
  - Each mAb targets a *different epitope* on the Ebola virus glycoprotein AND all 3 mAbs can bind *simultaneously*
- Two distinct MOA: EBOV neutralization *and* immune effector function

mAb114 (ansuvimab, EBANGA)

A single human IgG1 monoclonal antibody, isolated from a Zaire ebolavirus (EBOV) survivor (Kikwit strain) 10 years after infection

Dose: Single 50mg/kg IV dose over 60 min

Mechanism of Action: Targeted to the EBOV glycoprotein (GP) glycan cap and GP1 domains



Supplied as a **lyophilized product** in a glass vial (400 mg/vial, 2-8 degrees C) → reconstitution and further dilution (also as **frozen liquid,** stored at -35 to 15 C)

Since the PALM RCT results:

- These results served as the basis for U.S. FDA approval of REGN-EB3 (**Inmazeb**) and ansuvimab (**EBANGA**) on the basis of the results reported from the PALM RCT
- Both products are being provided and accessed in this outbreak under an expanded access protocol soon to be approved for use in Guinea (and if needed in other countries)
- General principles of establishment of the EAP, inclusion/exclusion criteria, informed consent, monitoring, and documentation will be followed, with some variation depending on specific therapeutic

Steps to take for therapeutics in 2021

- **Global level: IND label thus need protocol**
  - WHO to support coordination function with drug developers.
  - Protocols for expanded use (EAP-MEURI) are available.
  - Informed consent available with protocol and Investigator Brochure

- **National level:**
  - Designate a national PI (responsible), submit protocol to Ethical Review committee
  - Obtain import permits (regulatory bodies)
  - Implementation teams within CM comprehensive strategy (MoH, Partners, WHO etc)
  - Standardized data collection (WHO CRFs available, REDCAP tablet based data entry)

Key questions: EVD therapeutics

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Key principles for safe administration

- Inclusion and exclusion criteria (WHO)
- Patient **informed consent**
- **Shipping and storage** (before and after preparation)
- Correct **dosing and preparation** (step by step instructions)
- Correct **administration and infusion** (specific examples)
- Correct **monitoring** during and after the infusion
- Appropriate **documentation** of all!

Training material contains specific details and case examples useful for the **entire team!**

REG-EB3 (INMAZEB): dosing table

Table 1: INMAZEB Infusion Volumes and Times by Body Weight

Body Weight (kg)	Volume of INMAZEB per kg of Body Weight[a]	Total Infusion Volume After Dilution (mL)[b]	Infusion Time
0.5 to less than 1	3 mL per kg of body weight	7	4 hours
1 to 1.9		15	
2 to 3.9		25	3 hours
4 to 7		50	
8 to 15		100	
16 to 38		250	2 hours
39 to 79		500	
80 to 149		1,000	
150 and above		2,000	4 hours

[a] The dose is 50 mg of atolivimab, 50 mg of maftivimab, and 50 mg of odesivimab per kg of body weight (a volume of 3 mL/kg).

[b] The recommended infusion volume ensures the final concentration of the diluted solution is 9.5 mg/mL to 23.7 mg/mL. 5% Dextrose Injection, USP is recommended for neonates.

mAb114 (ansuvimab, EBANGA): dosing table

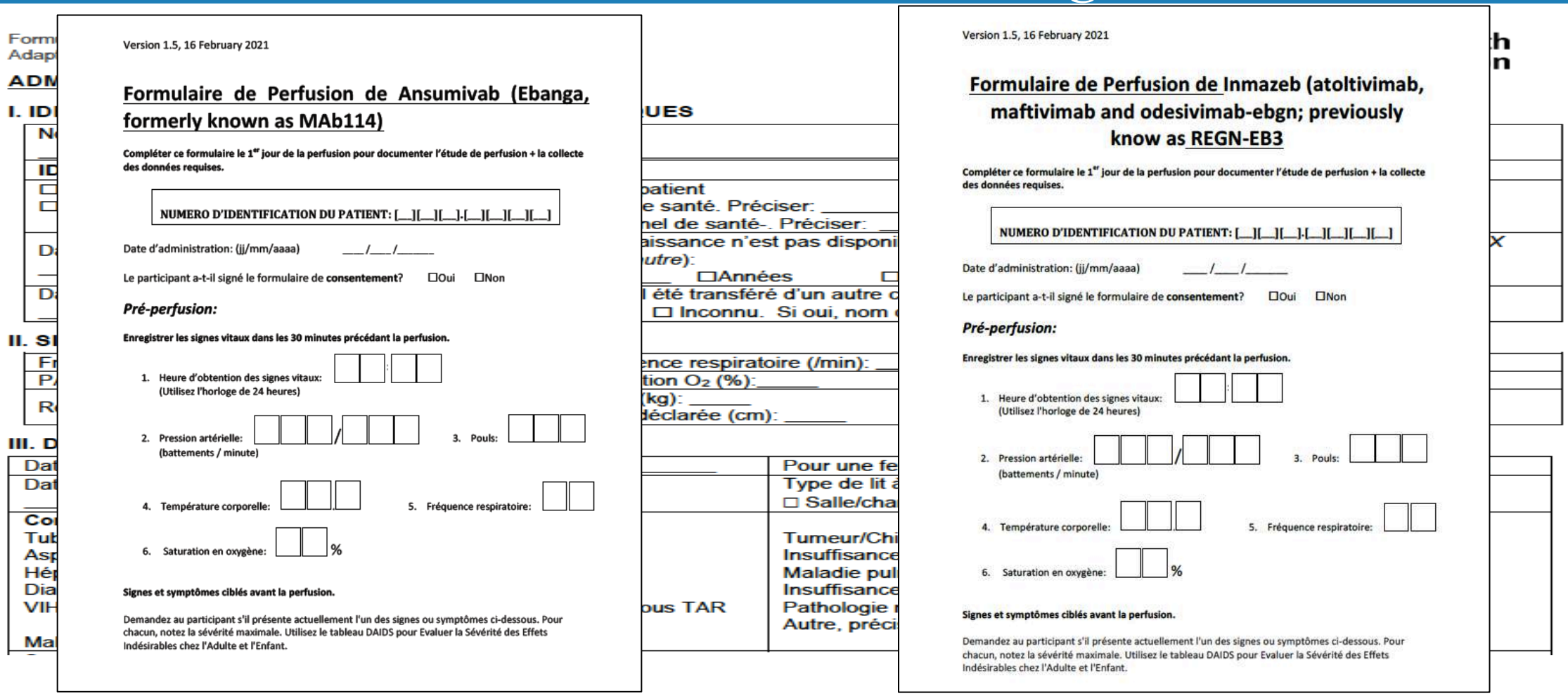
Table 1: EBANGA Volume, Diluent Volume and Total Infusion Volume by Body Weight

Weight in kg	Volume of EBANGA	Diluent Volume (mL)[a,b]	Final Infusion Volume (mL)	Syringe or Infusion Bag Volume for IV Administration
0.5 kg	1 mL/kg	2.5 mL	3 mL	10 mL syringe compatible with IV infusion pump
1 kg		5 mL	6 mL	
2 to 10 kg		10 mL	12 to 20 mL	25 mL IV bag
11 to 25 kg		25 mL	36 to 50 mL	50 mL IV bag
26 to 50 kg		50 mL	76 to 100 mL	100 mL IV bag
51 to 100 kg		100 mL	151 to 200 mL	250 mL IV bag
101 kg and above		150 mL	251 mL and above	500 mL IV bag

[a] The recommended diluent volume ensures the final concentration of the diluted solution is approximately 8-30 mg/mL.

[b] For IV bag administration, the diluent volume column includes the volume of diluent needed to remain in the infusion bag.

Clinical follow-up and monitoring: From admission to discharge!



Version 1.5, 16 February 2021

Formulaire de Perfusion de Ansumivab (Ebanga, formerly known as MAb114)

Compléter ce formulaire le 1er jour de la perfusion pour documenter l'étude de perfusion + la collecte des données requises.

NUMERO D'IDENTIFICATION DU PATIENT: [__][__][__]-[__][__][__][__]

Date d'administration: (jj/mm/aaaa) ___/___/_____

Le participant a-t-il signé le formulaire de **consentement?** ☐Oui ☐Non

Pré-perfusion:

Enregistrer les signes vitaux dans les 30 minutes précédant la perfusion.

1. Heure d'obtention des signes vitaux: (Utilisez l'horloge de 24 heures) ☐☐:☐☐
2. Pression artérielle: ☐☐☐/☐☐☐ (battements / minute) 3. Pouls: ☐☐☐
4. Température corporelle: ☐☐.☐ 5. Fréquence respiratoire: ☐☐
6. Saturation en oxygène: ☐☐ %

Signes et symptômes ciblés avant la perfusion.

Demandez au participant s'il présente actuellement l'un des signes ou symptômes ci-dessous. Pour chacun, notez la sévérité maximale. Utilisez le tableau DAIDS pour Evaluer la Sévérité des Effets Indésirables chez l'Adulte et l'Enfant.

Version 1.5, 16 February 2021

Formulaire de Perfusion de Inmazeb (atoltivimab, maftivimab and odesivimab-ebgn; previously know as REGN-EB3

Compléter ce formulaire le 1er jour de la perfusion pour documenter l'étude de perfusion + la collecte des données requises.

NUMERO D'IDENTIFICATION DU PATIENT: [__][__][__]-[__][__][__][__]

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World Health Organization

HEALTH EMERGENCIES programme

Patient monitoring and data collection

Day	1	2	3	4	5	6	7	10	14	21	29[1] Or at discharge from ETU
ELIGIBILITY											
Informed consent	X										
Eligibility criteria: Positive Ebola Virus Diagnostic Test	X										
Demographics and Medical history	X										
Physical Examination	X										X
INITIATE REGN3470-3471-3479 AND MONITOR PATIENT											
Vital Signs	X[2]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
Weight (kg)	X										X
Signs and Symptoms	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications & Blood Products	X[4]	X	X	X	X	X	X	X	X	X	X
Complete standardized CRF[5]	X[6]	X[7]	X	X	X	X	X	X	X	X	X
REGN-EB3 150 mg/kg IV	X										
Hematology[8]	X[9]		X		X		X		X		X
Blood Chemistry and Liver Function Tests[8]	X[9]		X		X		X		X		X
Pregnancy test[8]	X[9]										
Monitor for and report IRR(s)	X	X	X	X							
Record/Report SAEs	X	X	X	X	X	X	X	X	X	X	X
Exploratory Assessments											
EBOV serum/plasma viral load[8]	X[9]		X		X		X		X		X

1. End of follow up will be at time of discharge from the Ebola Treatment Unit.
2. If feasible, vital signs should be taken pre-infusion, during infusion (at least once), and post-infusion.
3. Vital signs should be taken daily, if feasible.
4. On day 1, collect medications received before dosing with REGN-EB3 and any new medications administered after or during infusion of REGN-EB3.
5. Standardized CRFs will be adapted based on local resources.
6. Complete 'Admission' CRF.
7. Complete 'Daily' and 'Outcome' CRF.
8. Collect if and when it is feasible, based on local personnel expertise on Select Agent regulations and infrastructure availability for laboratory testing and infectious blood sample storage and shipping.
9. Collect pre-treatment on day of dosing.

Patient monitoring and data collection

	Schedule of Evaluations						
Visit Number	01	02	03	04	05	06	**07**
Time After Day 0 Infusion, days		1–2	2–3	7–10	14–21	21	**21+N**
Day on protocol	D0	D1	D2	D7	D14	D21	S
Informed Consent	X						
Study Product Administration	X						
Plasma Sample Collection for Viral Load	X[1]	X		O	O	O	**O**
Serum Sample collection for Ansuvimab PK and sGP quantification	Y[1]		Y[2]	Y[3]	Y[4]		**Y[5]**
Limited Medical Exam, safety evaluation	X[6]	X		X	X	X	**X**
Administration Site Evaluation	**X**	**X**		**X**			

(see slide notes for explanation of symbols)

World Health Organization

(Source: MEURI Expanded Access Protocol)

HEALTH EMERGENCIES programme

Infusion Reaction Guide

Symptoms/Reactions

Suggestions only; Not meant to replace existing clinical guidelines or alter clinical judgment.

Fever

38° - 39° C
1. Continue infusion, monitor VS
2. Administer Paracetamol

39° - 40° C
1. Reduce infusion rate by 50%.
2. Monitor until temp is <39.0, then resume regular rate increase
3. Administer Paracetamol per schedule

>40° C
1. STOP infusion
2. Continue to administer regular IV fluid, Paracetamol
3. External cooling measures (if available)
4. When temp is <39.0º, resume infusion rate at 50%
5. Monitor at 50% rate for 15-30 min with VS q 15 min
6. If reaction does not re-occur, resume regular infusion schedule

Peripheral Neuropathy / Edema / Shivering/ Tremors / Hypotension / Other

Mild
1. Continue infusion, Monitor VS

Moderate
1. Reduce infusion rate by 50%.
2. Monitor until symptoms are reduced to mild
3. Resume regular infusion schedule

Severe
1. STOP infusion
2. When symptoms are reduced to mild, resume infusion rate at 50%
3. Monitor at 50% rate for 15-30 min
4. If reaction does not re-occur, resume regular infusion schedule

Infiltration (Watch for pain, swelling, tightness around injection site; skin cooling/blanching; leakage at insertion site)

1. STOP infusion
2. Discontinue IV site, bandage, apply heat OR cold if available
3. Insert new peripheral IV.

Hypertension

Mild
1. Continue infusion, Monitor VS

BP > 140/90
(OR increase of diastolic pressure >20 mmHg)
1. Reduce infusion rate by 50%.
2. Monitor BP q. 15 minutes until BP is <140/90, then resume regular infusion schedule

BP > 160/100
1. STOP infusion
2. Administer BP medications if available
3. When BP is reduced <140/90, resume infusion rate at 50%
4. Monitor at 50% rate for 15-30 min with VS q 15 min
5. If reaction does not re-occur, resume regular infusion schedule

Seizure

Brief, no loss of consciousness
1. Continue infusion, Monitor patient

Brief generalized (full body) seizure
1. Reduce infusion rate by 50%.
2. Monitor VS q 15 min for 15-30 minutes.
3. If VS are stable and seizure does not recur, resume regular infusion schedule

Extended or multiple full body seizure(s)
1. STOP infusion
2. Continue to administer regular IV fluid, diazepam
3. Monitor VS q 15 min until seizures subside and patient stabilizes
4. When stable, resume infusion at 50% previous rate
5. Monitor for 15-30 min with VS q 15 min
6. If seizures do not re-occur, resume regular infusion schedule

Allergic Reaction (may include rash, flushing, itching)

Mild
1. Continue infusion, Monitor patient

Moderate
1. Reduce infusion rate by 50%.
2. Administer Benadryl
3. Administer IV fluids
4. Monitor patient q 15 minutes until symptoms are reduced to Grade 1 or below, then resume regular infusion schedule

Anaphylaxis

(may include difficulty breathing, chest pain, tachycardia, confusion, dizziness, hypotension, loss of consciousness)

Moderate
1. STOP infusion
2. Administer Benadryl
3. Notify site physician, study team as soon as possible
4. Continue to administer regular IV fluid
5. Monitor VS q 15 min until reaction subsides and patient stabilizes

Severe
1. STOP infusion
2. Administer Epinepherine
3. Notify site physician, study team as soon as possible
4. Continue to administer regular IV fluid
5. Monitor VS q 15 min until reaction subsides and patient stabilizes

World Health Organization

A team approach: the Katwa ETU

Structure | Supplies | Staff | Systems |Security

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- **HOW** should that care be documented?

Learning objectives (from the training session)

At the end of this session, you will be able to:

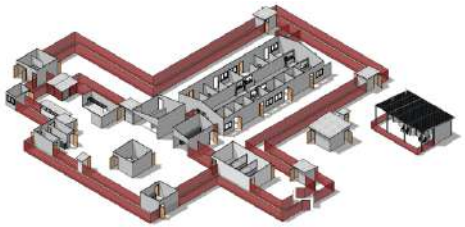
- Review prior experience with the MEURI protocol and evidence from the PALM RCT
- Identify REG-EB3 (Inmazeb) and mab114 (ansuvimab, Ebanga) and describe how they work
- Describe the indications and contraindications for each in patients with EVD
- Outline the preparation and safe administration for each in patients with EVD
- Effectively monitor and respond to adverse effects in EVD patients receiving these therapeutics
- Emphasize the importance of appropriate informed consent and documentation under an approved access protocol for the use of therapeutics in EVD patients
- Emphasize that the use of therapeutics must be combined with optimized supportive care to improve outcomes

A new strategy that saves lives

Design et Biosecurite

Not a simple isolation unit, but rather a centre centered around patients, staff, families and communities.

A place where patients can receive, quality care with all biosecurity and IPC standards in place.



Optimized supportive care

Oxygen and point of care testing (electrolytes, hemoglobin)

Systematic evaluation et re-evaluation

Resuscitation with fluids

Prevention and care of complications

Therapeutics

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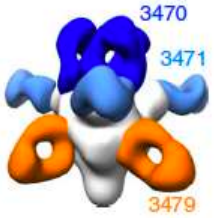
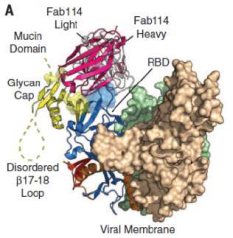
Inmazeb (REGN-EB3)

Ansuvimab (mAB114, **Ebanga**)





World Health Organization

Source: WHO Case Management

HEALTH EMERGENCIES programme