Universitätsklinikum Hamburg-Eppendorf

Ebola

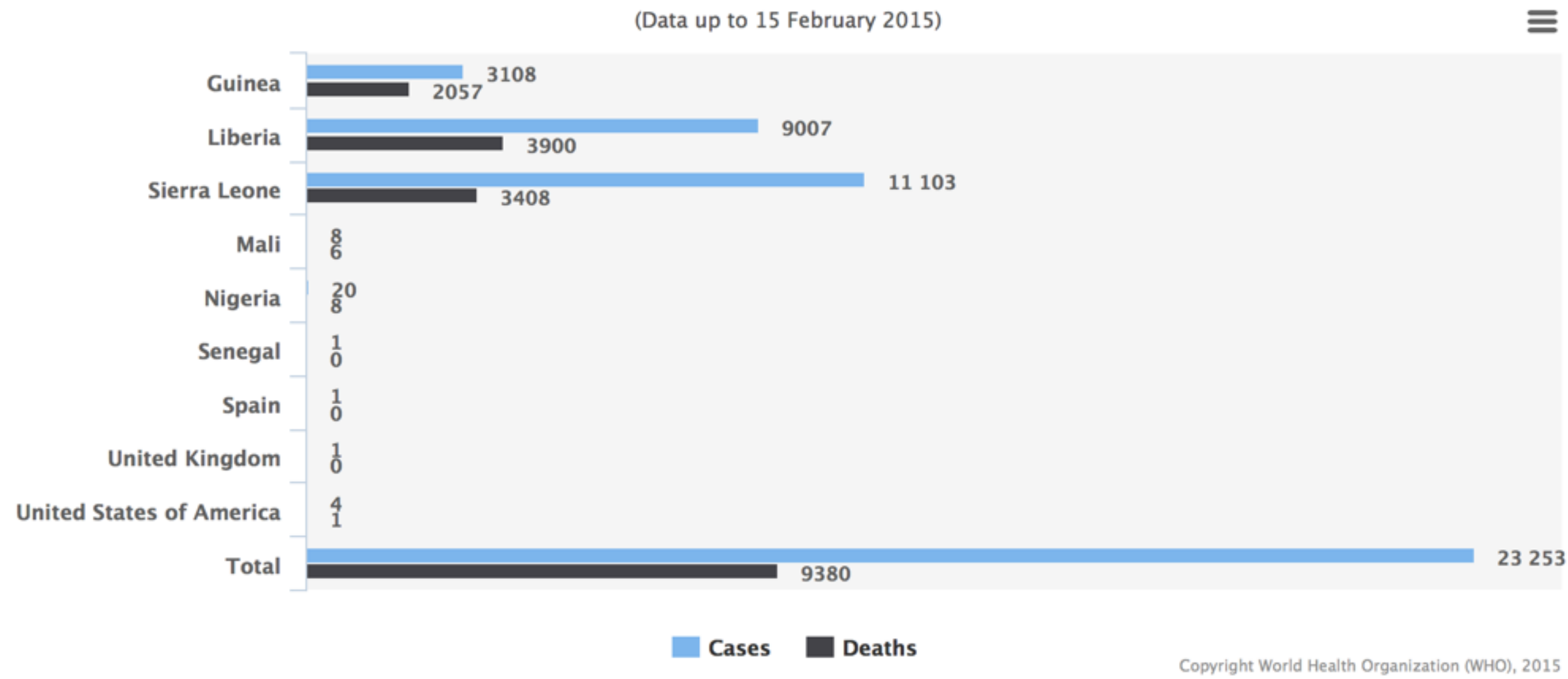
klinische Erfahrungen aus Hamburg

PD Dr. D. Wichmann
UKE - Hamburg

Universitätsklinikum Hamburg-Eppendorf

Die aktuelle Situation in Westafrika

Ebola Situation Report - 18 February 2015



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Health Care Worker

Wesentliche Risikofaktoren:

- Schlechtes / fehlendes *Personal Protection Equipment* (PPE)
- Probleme beim Dekontaminationsprozess

Intensive Care Med
DOI 10.1007/s00134-014-3582-3

Dominic Wichmann
Stefan Schmiedel
Stefan Kluge

Isolation in patients with Ebola virus disease

Wichmann *Int Care Med* 2014

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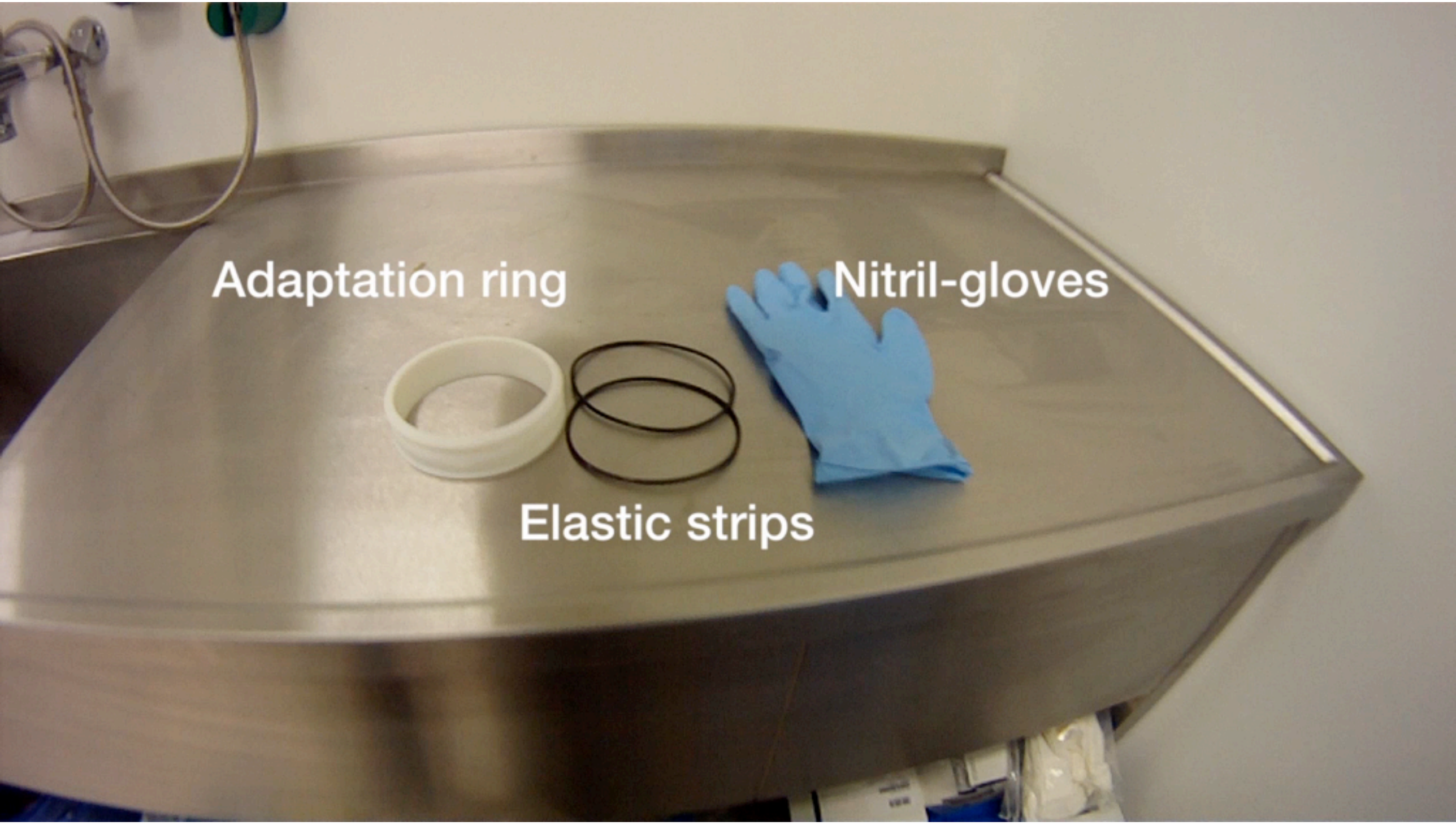

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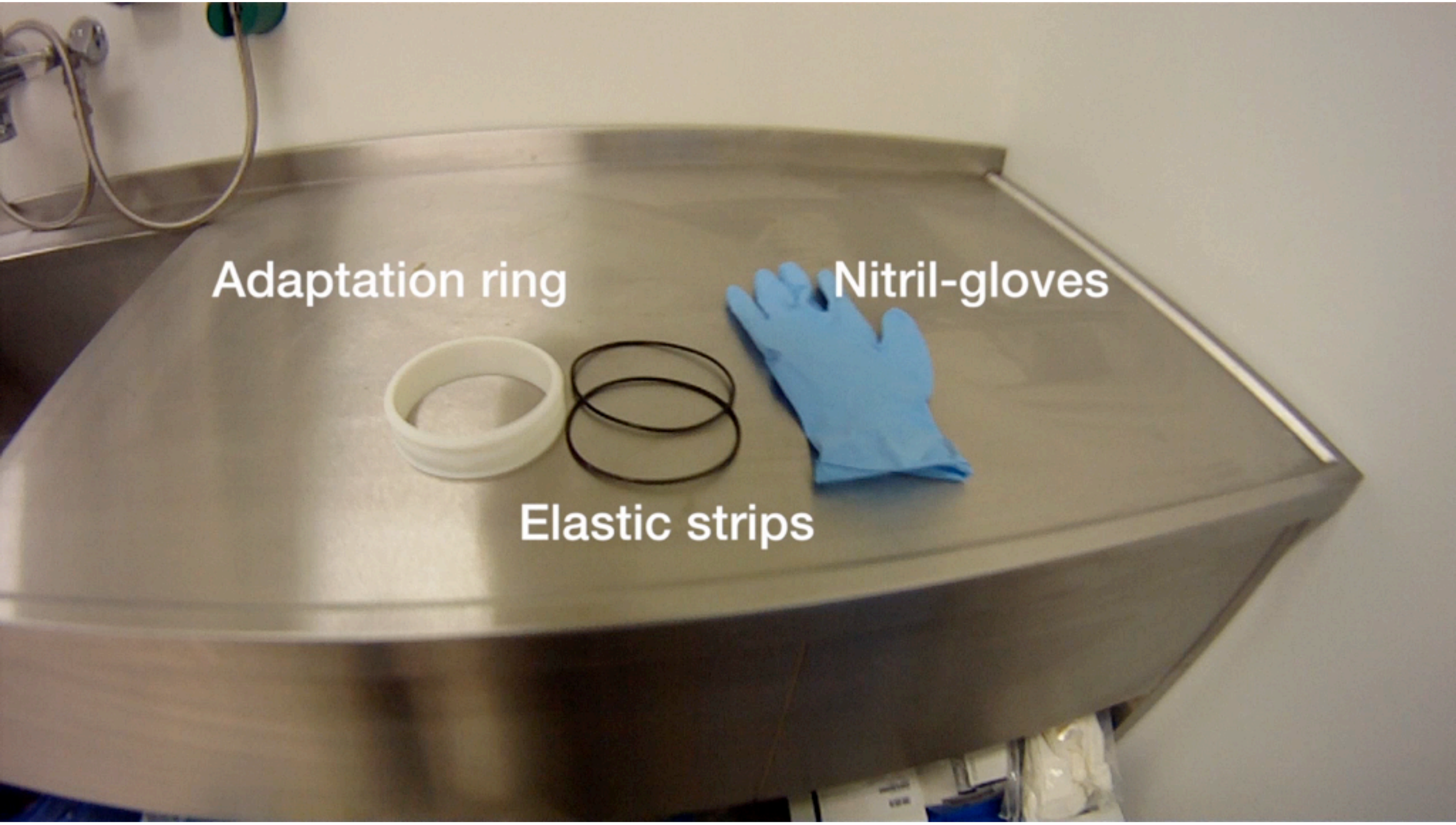

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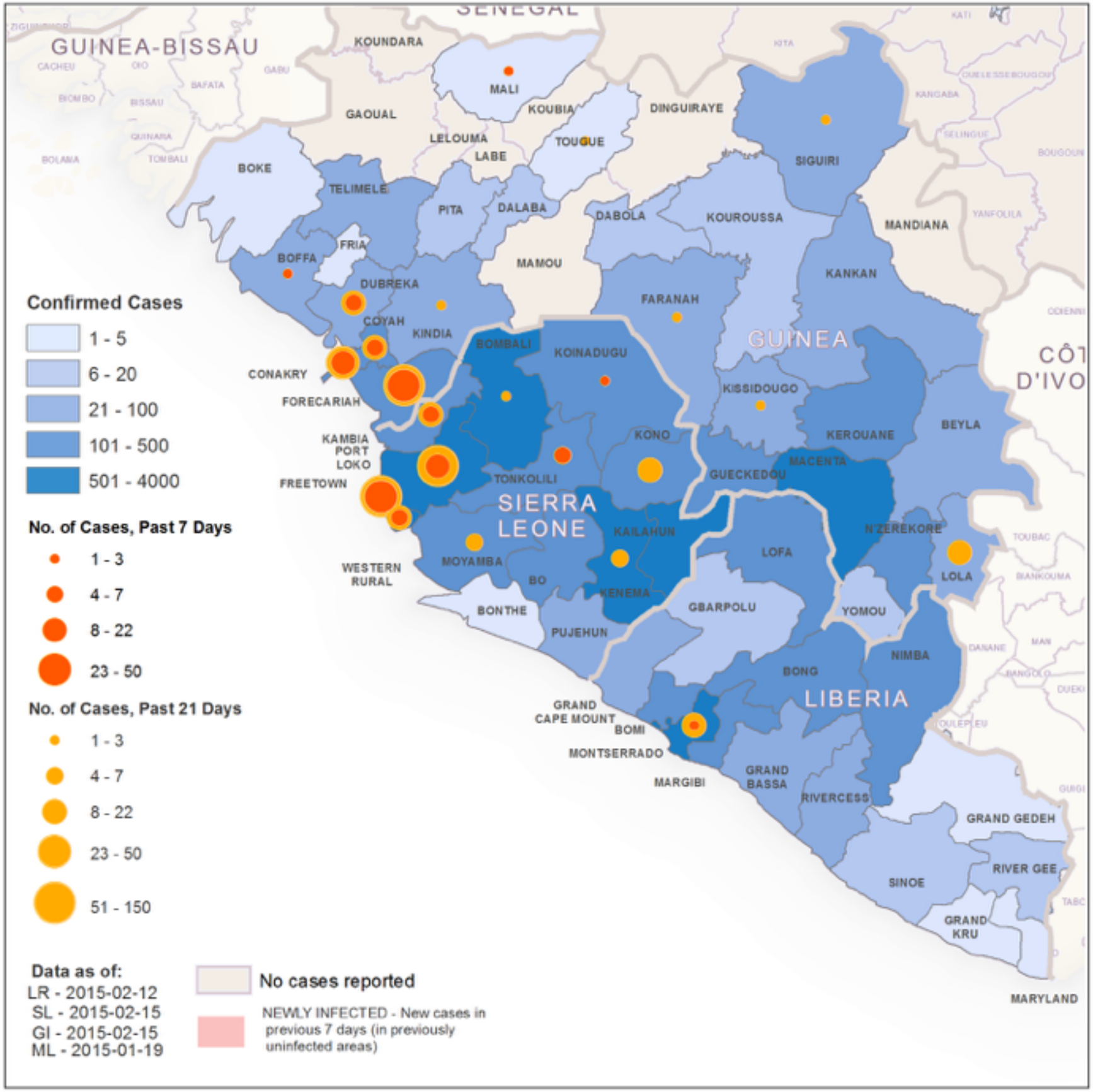
Lokale Entwicklungen



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Ebola Virus Disease

Inkubationszeit: **2-21 Tage**

Symptome: **Fieber**

Diarrhö / Erbrechen

Arthralgien / Myalgien

Schleimhautblutungen

Komplikationen: **DIC**

GI-Blutungen

Epistaxis

Multiorganversagen

- (Leber/Niere)

Table 1. Characteristics, Symptoms, Vital Signs, and Time Course of Clinical Progression of 37 Patients with Confirmed Ebola Virus Disease (EVD).*

Variable	Value
Median age (IQR) — yr	38 (28–46)
Male sex — no. (%)	24 (65)
Health care worker — no. (%)	
Yes	14 (38)
No	23 (62)
Known mechanism of contact — no./total no. (%)†	
Health care	12/34 (35)
Household	23/37 (62)
Funeral	6/37 (16)
Known coexisting medical condition — no. (%)	
Hypertension	2 (5)
Human immunodeficiency virus	2 (5)
Diabetes	1 (3)
Renal insufficiency	1 (3)
Tuberculosis	1 (3)
Malaria at presentation — no. (%)	4 (11)
Symptoms — no./total no. (%)	
Fever	31/37 (84)
Fatigue	24/37 (65)
Diarrhea	23/37 (62)
Headache	12/21 (57)
Vomiting	21/37 (57)
Anorexia	16/37 (43)
Vital signs at admission	
Temperature — °C	38.6±1
Heart rate — beats/min	93±14
Systolic blood pressure — mm Hg	125±25
Median interval from onset of symptoms (IQR) — days	
To hospital admission	5 (3–7)
To death	8 (7–11)

* Plus–minus values are means ±SD. IQR denotes interquartile range.
† Some patients had more than one exposure.

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Virus Charakteristika

Primärwirt: Fledermäuse

Infektionquellen: Primaten / bush meat

Übertragung: Scheimhautkontakt mit infektiösem Material

Schmierinfektion

Hygienemängel

Nadelstichverletzungen

Geschlechtsverkehr

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Virus Charakteristika

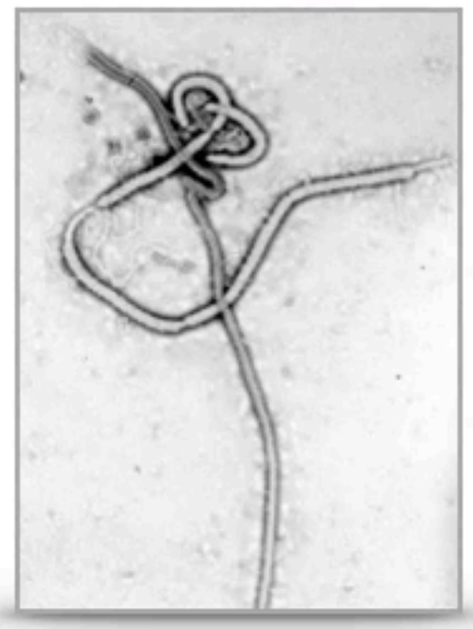
Gruppe: **Mononegavirales**

Familie: ***Filoviridae***

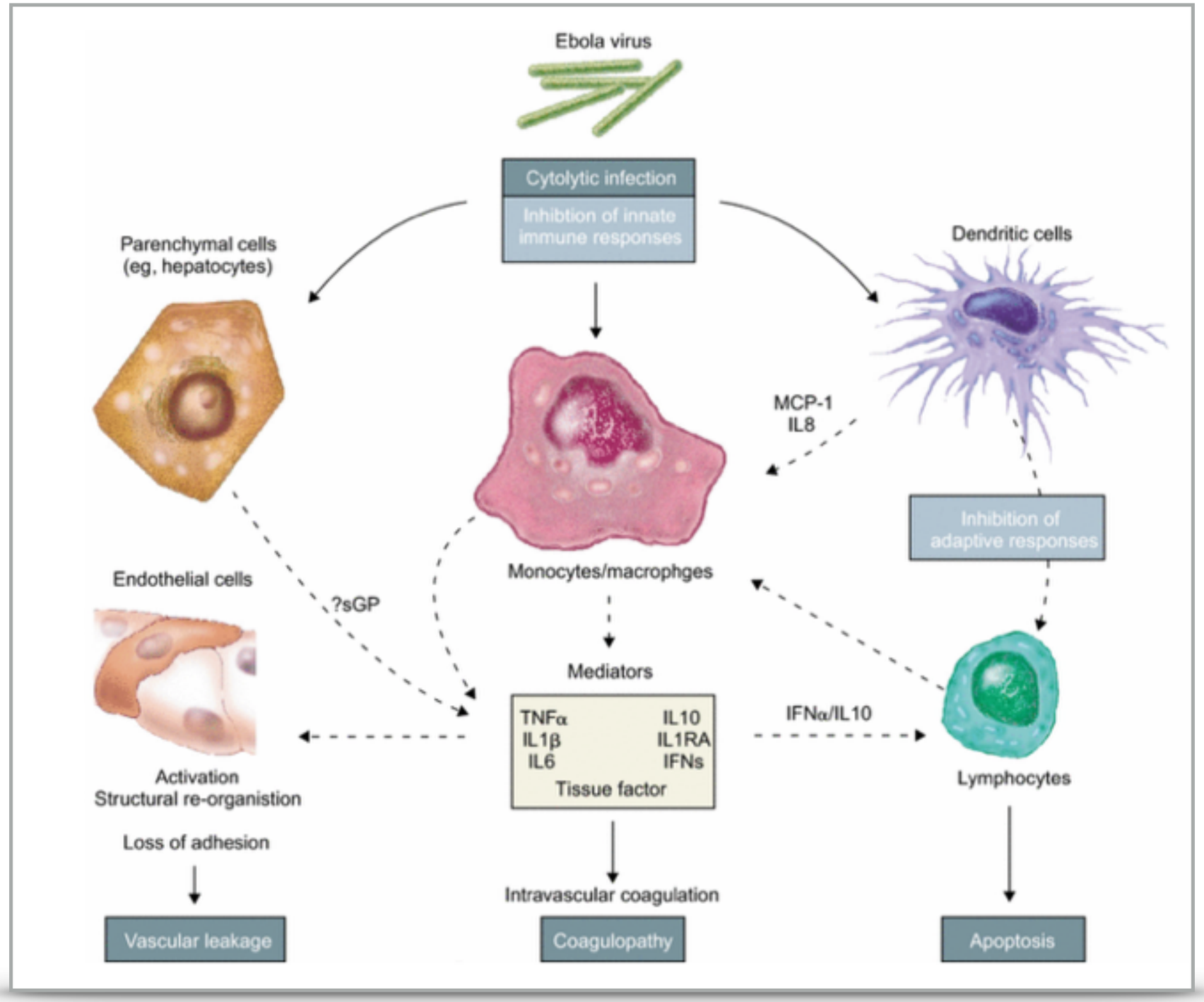
5 Serotypen: **Zaire; Sudan, Bundibugyo, Taï Forest und Reston**

Genomstruktur: **⊖ssRNA**

Struktur: **fadenfömig, 14 x 0,8µm**



Pathogenese



Fletcher *Int Care Med* 2014

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

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Antikörper-Antwort

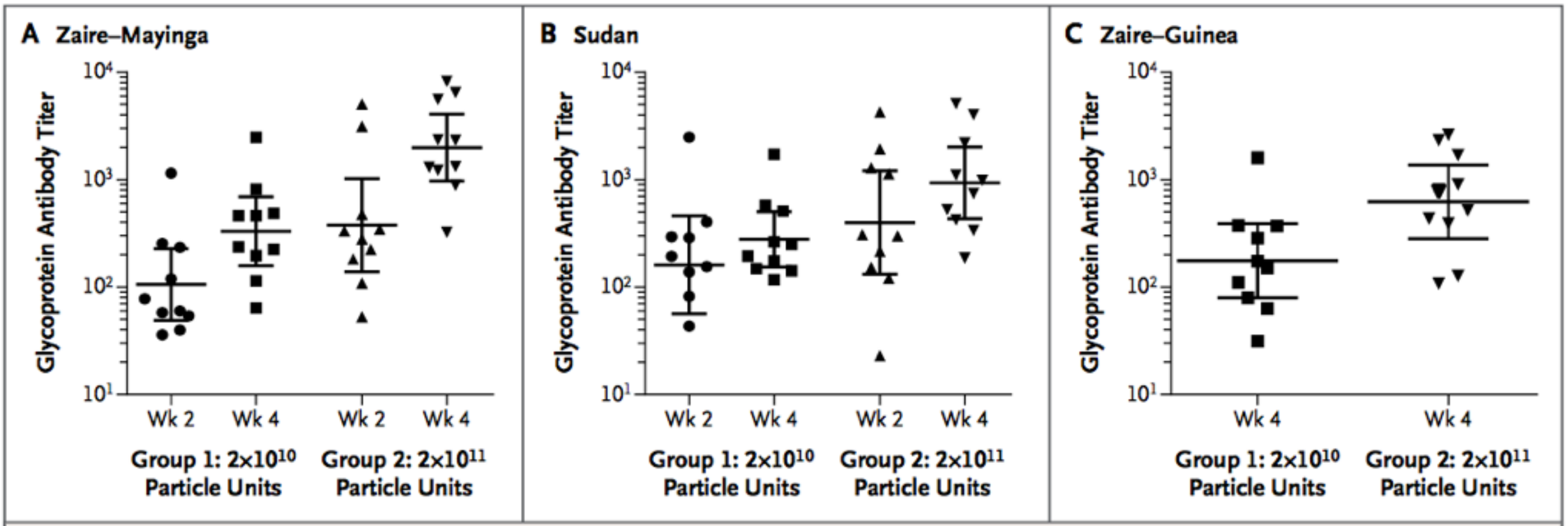

Figure 2. Glycoprotein Antibody Titers in Groups 1 and 2 as Assessed by an Enzyme-Linked Immunosorbent Assay (ELISA), According to Antigen.

Individual antibody titers as assessed by glycoprotein ELISA at 2 and 4 weeks after vaccination are shown according to antigen and vaccine-dose group. Geometric mean titers (horizontal lines) are shown for each group and time point; I bars indicate 95% confidence intervals. Vaccine-induced antibodies against Zaire–Mayinga glycoprotein (Panel A) were higher at week 4 than at week 2 in both group 1 and group 2 ($P=0.001$ and $P<0.001$, respectively), and the difference between the groups reached significance at both week 2 and week 4 ($P=0.03$ and $P=0.001$, respectively). Vaccine-induced antibodies against Sudan glycoprotein (Panel B) were higher at week 4 than at week 2 in group 2 ($P=0.004$), and the difference between group 1 and group 2 reached significance at week 4 ($P=0.01$). Vaccine-induced antibodies against Zaire–Guinea glycoprotein (Panel C) were higher in group 2 than in group 1 at week 4 ($P=0.02$).

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T-Zell-Antwort

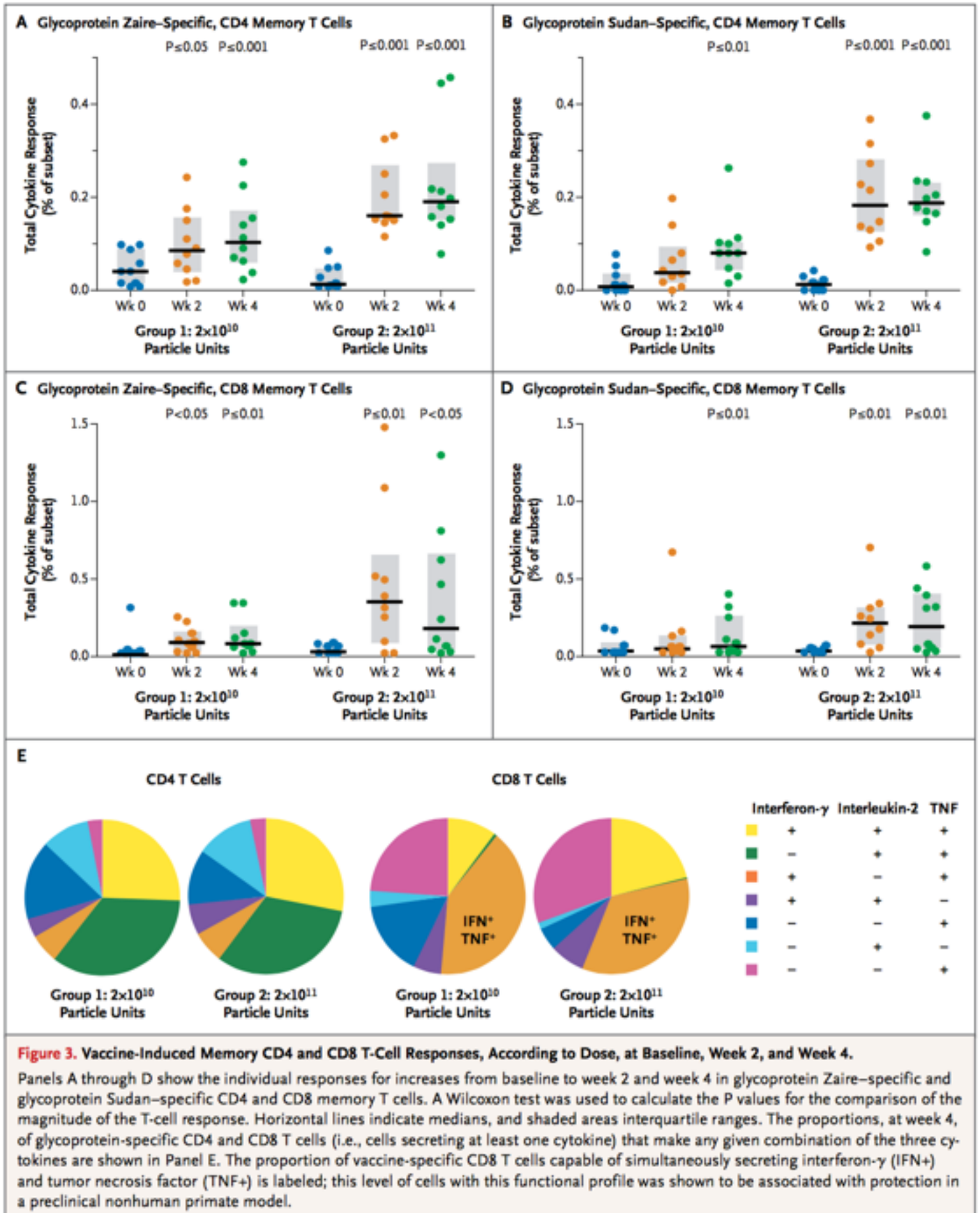

Figure 3. Vaccine-Induced Memory CD4 and CD8 T-Cell Responses, According to Dose, at Baseline, Week 2, and Week 4.

Panels A through D show the individual responses for increases from baseline to week 2 and week 4 in glycoprotein Zaire–specific and glycoprotein Sudan–specific CD4 and CD8 memory T cells. A Wilcoxon test was used to calculate the P values for the comparison of the magnitude of the T-cell response. Horizontal lines indicate medians, and shaded areas interquartile ranges. The proportions, at week 4, of glycoprotein-specific CD4 and CD8 T cells (i.e., cells secreting at least one cytokine) that make any given combination of the three cytokines are shown in Panel E. The proportion of vaccine-specific CD8 T cells capable of simultaneously secreting interferon-γ (IFN+) and tumor necrosis factor (TNF+) is labeled; this level of cells with this functional profile was shown to be associated with protection in a preclinical nonhuman primate model.

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(Experimentelle) Therapieoptionen

Präparat	Wirkmechanismus	Stand der Entwicklung
Brincidofovir	orales Nukleosidanalogon	Phase-3 für CMV und Adenoviren FDA-Zulassung für „emergency-use“
ZMapp	MaB-Cocktail	Tierexperimente z.Z. nicht lieferbar
TKM-Ebola	small interfering RNA	FDA-Zulassung für „emergency-use“
Rekonvaleszenz-Serum/Blut	passiver Immuntransfer Ig (?)	sehr limitiert

Der Hamburger Patient

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

A Case of Severe Ebola Virus Infection Complicated by Gram-Negative Septicemia

Benno Kreuels, M.D., Dominic Wichmann, M.D., Petra Emmerich, Ph.D., Jonas Schmidt-Chanasit, M.D., Geraldine de Heer, M.D., Stefan Kluge, M.D., Abdourahmane Sow, M.D., Thomas Renné, M.D., Ph.D., Stephan Günther, M.D., Ansgar W. Lohse, M.D., Marylyn M. Addo, M.D., Ph.D., and Stefan Schmiedel, M.D.

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36jähriger senegalesischer WHO-Mitarbeiter aus Sierra Leone

Tag 1-5: Fieber, Cephalgien, Arthalgien, Myalgien

Therapie: orale Antimalariamedikation, Ceftazidim

Tag 6: PCR-Nachweis von EBOV

Tag 6-7: unblutige Diarrhö, Übelkeit, abdominelle Beschwerden

Therapie: i.v. Volumen, Ciprofloxacin + Metronidazol

Tag 10: Evakuierung ins Behandlungszentrum für Hochkontagiöse Infektionen

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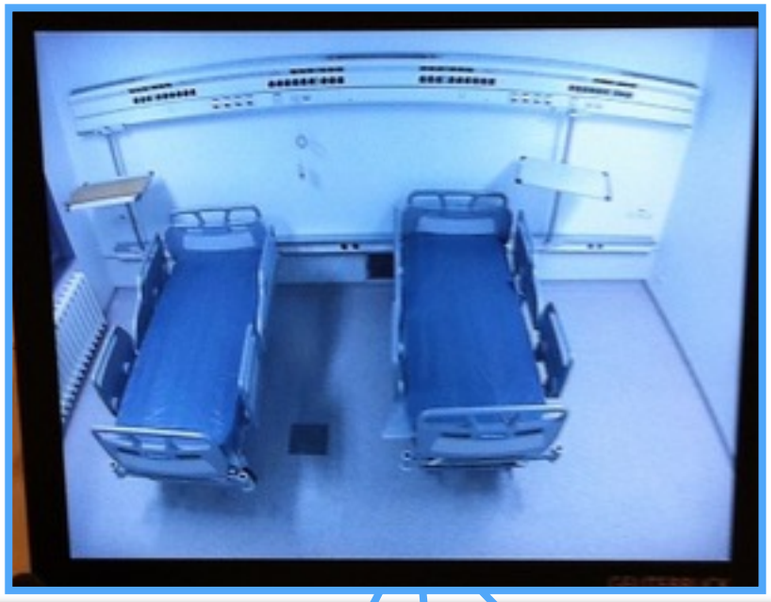
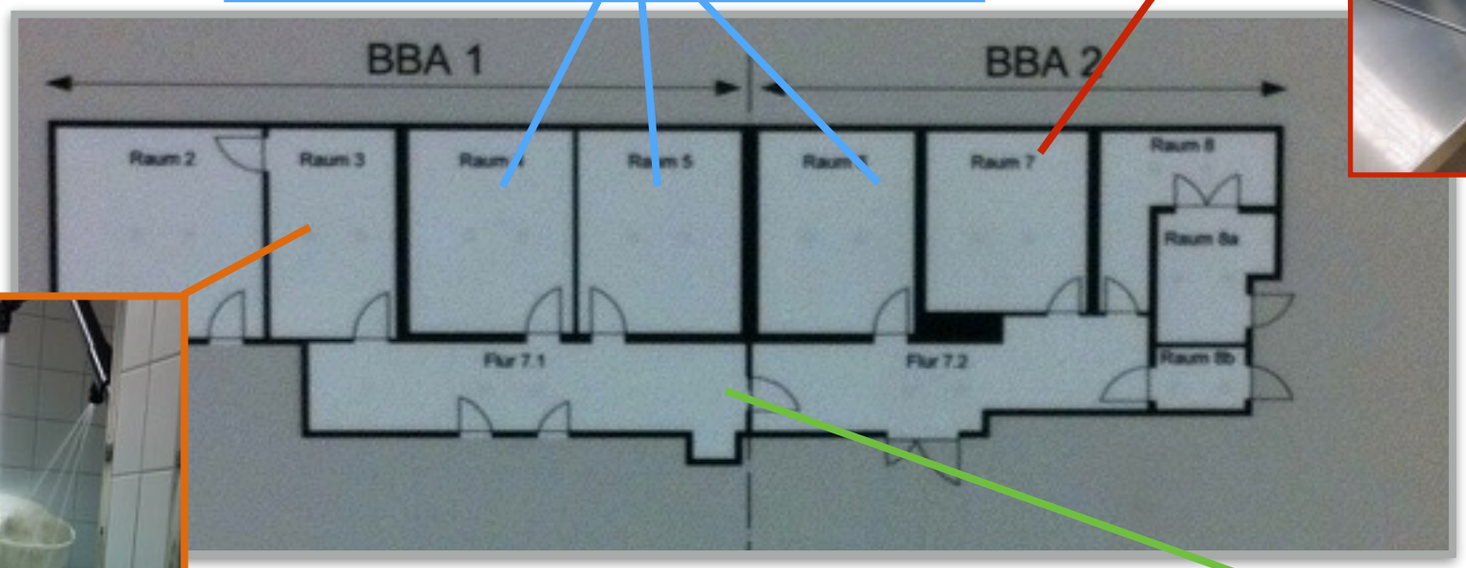
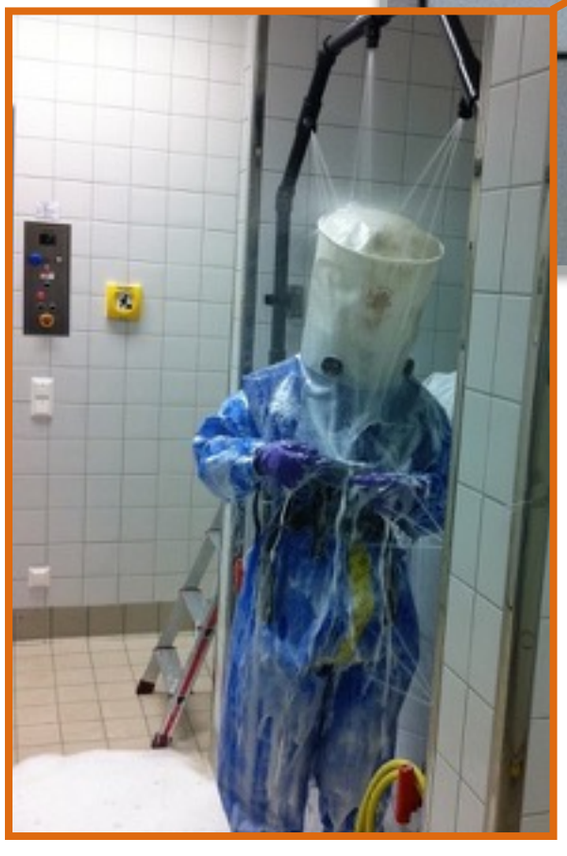
Das BZHI Hamburg







Das primäre Problem

Beginnendes Multiorganversagen (unklarer Genese)

- metabolische Azidose
- Oligurie
- Transaminasenerhöhung und verminderte Lebersyntheseleistung

Direkter Viruseffekt **versus** **Hypovolämer Schock**

- Endothelschädigung
- Hepatitis
- cytokine-storm

- Diarrhö
- Erbrechen
- Unfähigkeit zur ausreichenden oralen Kompensation

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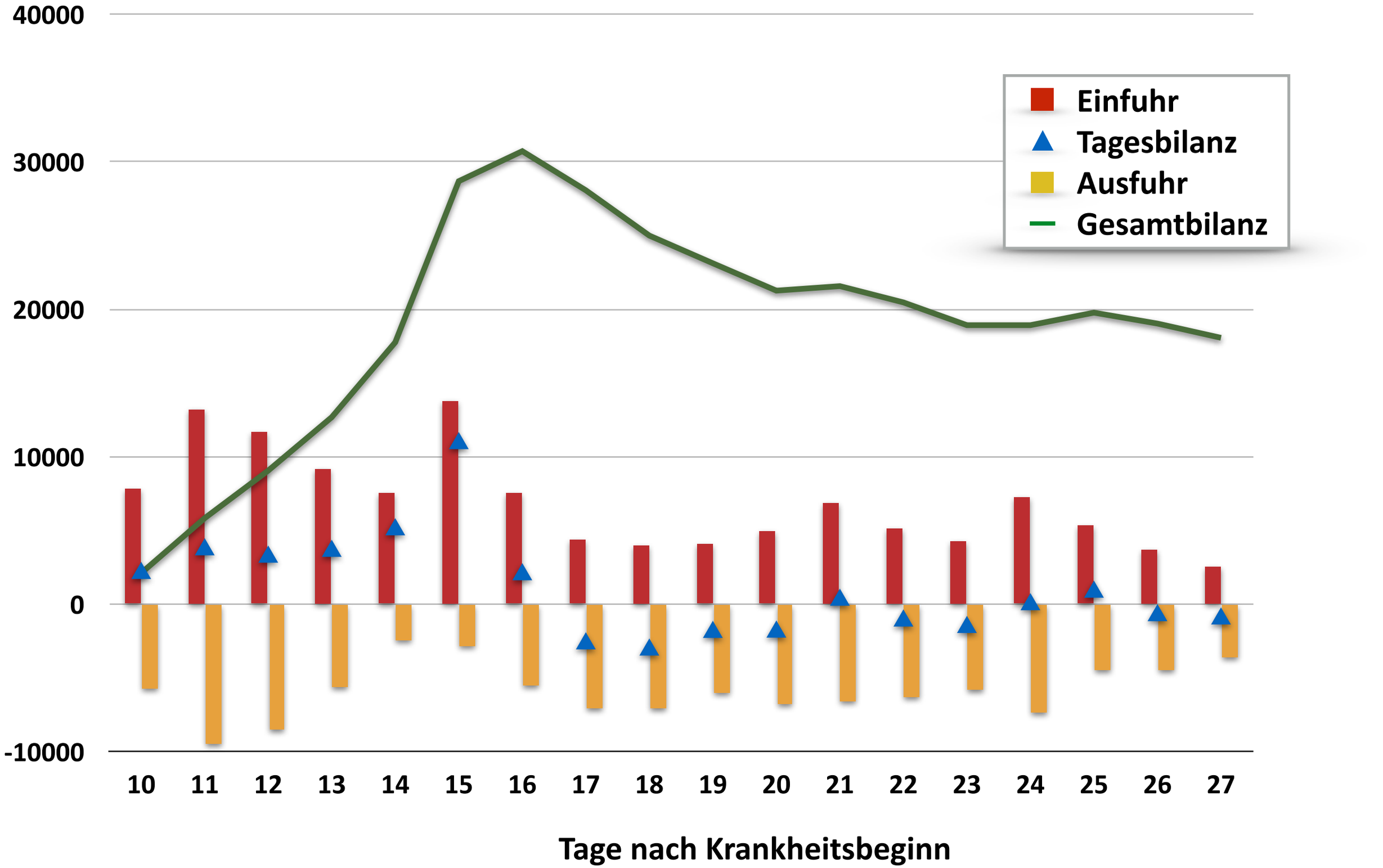
Volumenstatus



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Intensivmedizin im Bio-Safety-Level-4 Umfeld

Herausforderungen:

Große Volumenverschiebungen

- Einfuhr / Ausfuhr
- ausgeprägte Bildung peripherer Ödeme

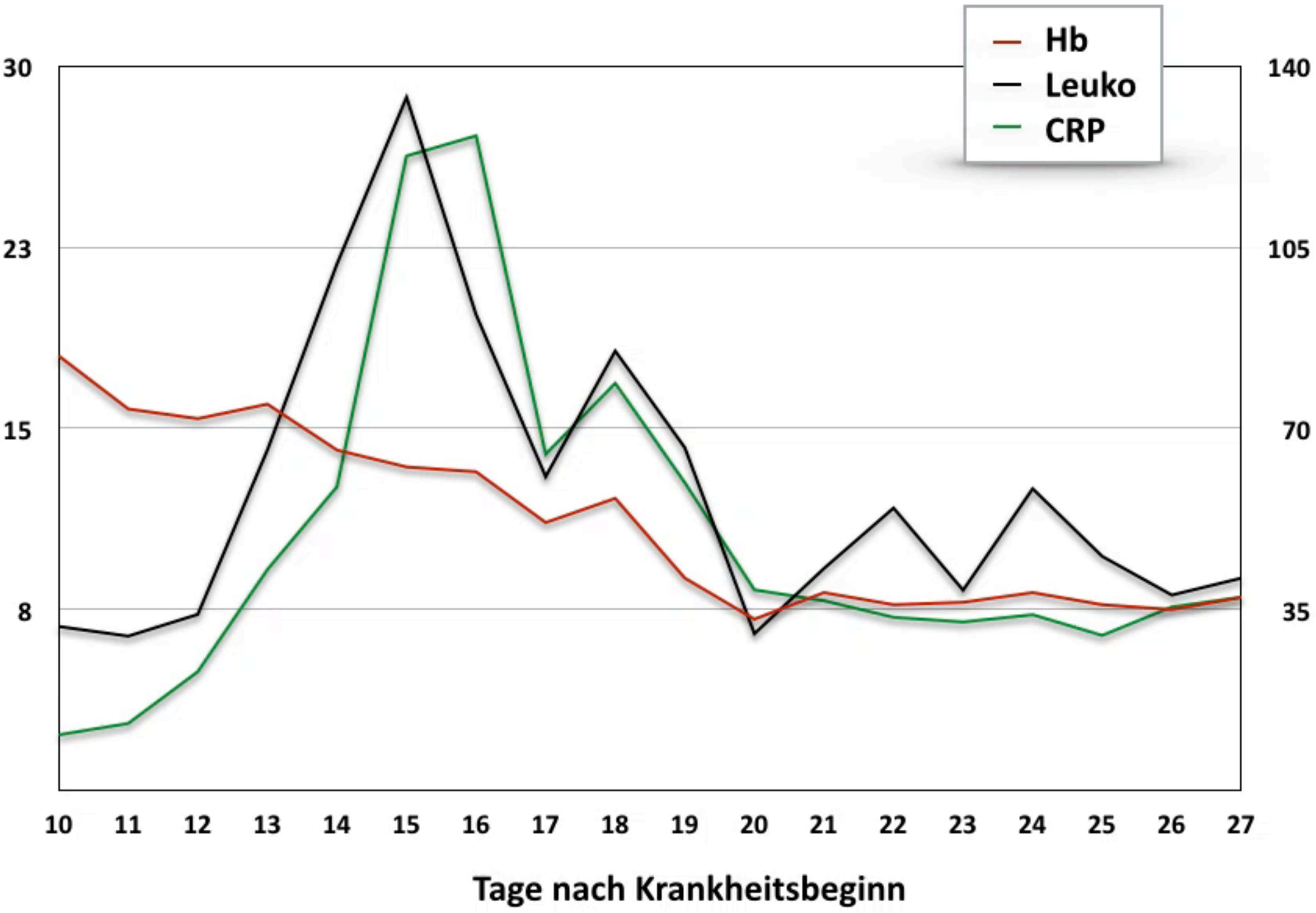
Ausgeprägte Elektrolytveränderungen

- Notwendigkeit engmaschiger Kontrollen
- Möglichkeit zur schnellen Korrektur

Lösungsansatz:

Zentralvenöser Zugang

Hämatologie + Infektparameter



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Sekundärkomplikation Sepsis

Klinik:

paralytischer Ileus

- massiv distendierte flüssigkeitsgefüllte Darmschlingen
- ausgeprägte Schwellung der Darmwand (bis zu 10mm)

Vigilanzminderung

respiratorische Insuffizienz

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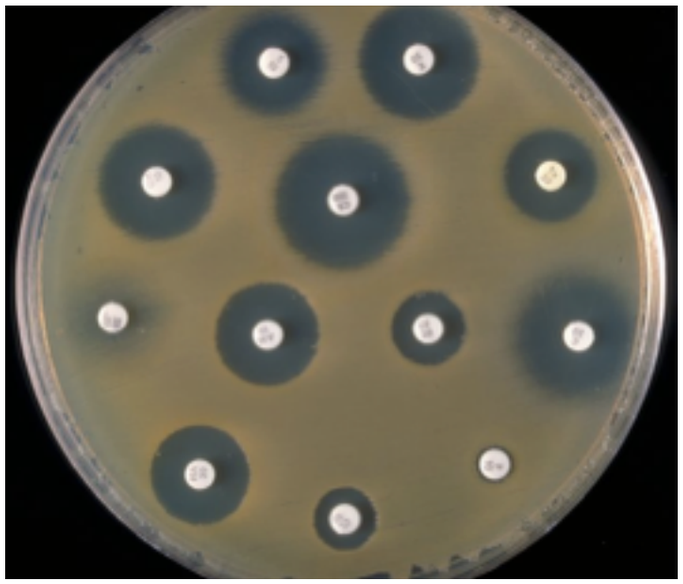
Sepsisdiagnostik unter BSL-4 Bedingungen

Herausforderung:

- Anlage von Blutkulturen
- Transport/Verarbeitung in der Mikrobiologie ist nicht möglich

Lösungsansatz:

- Kultivieren im Brutschrank
- Trübung 3x täglich visuell kontrollieren
- Ausplattieren auf Standardagarplatte
- Resistenztestung durch Agardiffusionstest



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Nachweis eines 3-MRGN der mit Ceftriaxon nicht abgedeckt war.

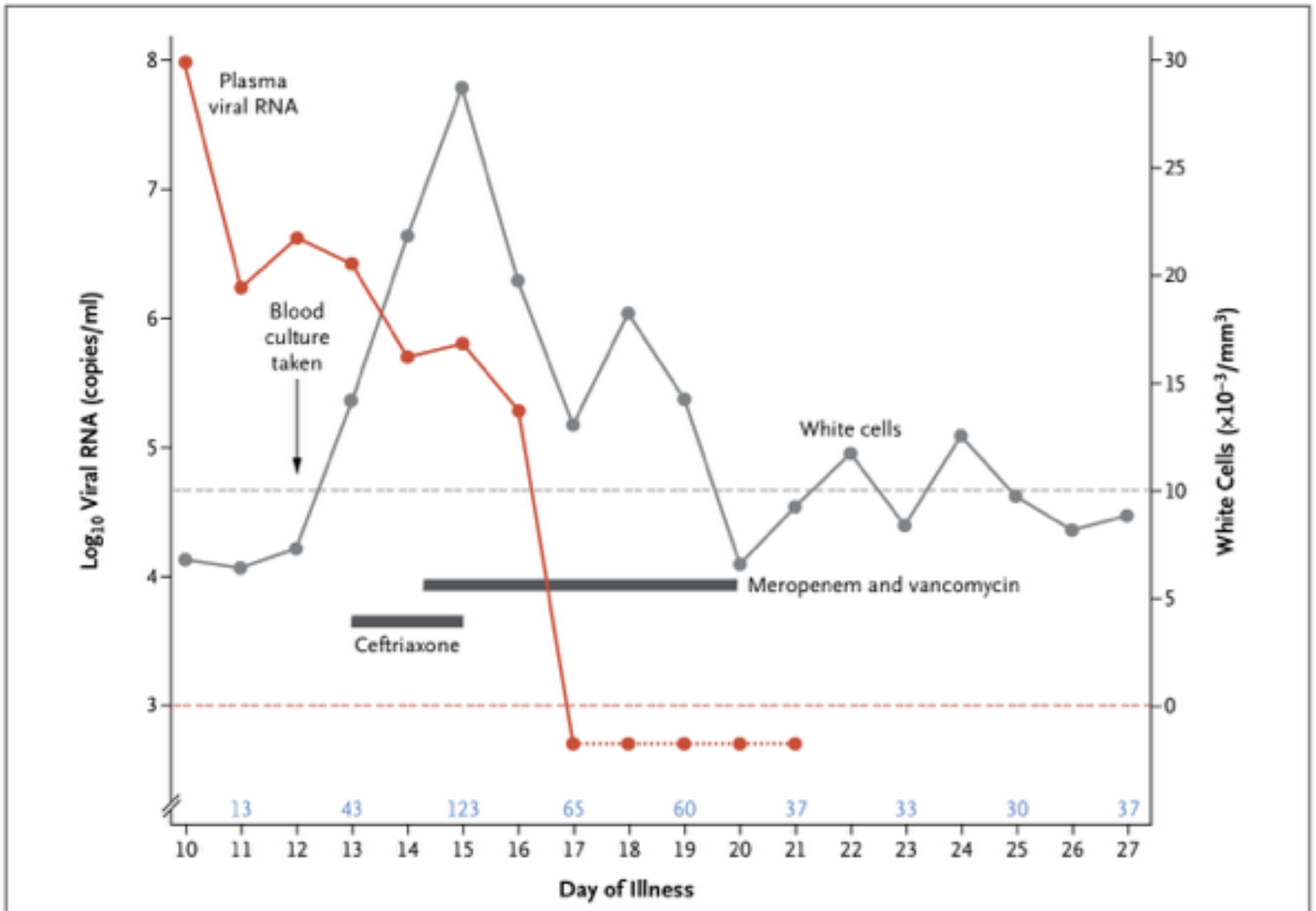

Figure 1. Timeline of Plasma Viral RNA Load, Septicemia, and Antimicrobial Therapy in a Patient with Severe Ebola Virus Disease.

The decline in viral copies in plasma (red line) and the development and course of leukocytosis (gray line) are shown. The maximum C-reactive protein levels (in milligrams per liter) are shown in blue above the respective day numbers. The time when the blood culture was performed is marked by an arrow at day 12. The duration of antimicrobial therapy is shown by the gray bars. The dashed gray line represents the upper limit of the normal range for white cells. The dashed red line represents the lower limit of detection of viral RNA in plasma on reverse-transcriptase–polymerase-chain-reaction assay.

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Therapie der Sekundärkomplikation Sepsis

paralytischer Ileus

- parenterale Ernährung
- Glutamin-Substitution (Zottentrophismus)

Sepsis

- Meropenem bei klinischem Versagen nach Tag 2
- Im Verlauf Nachweis eines **3-MRGN** in der Blutkultur

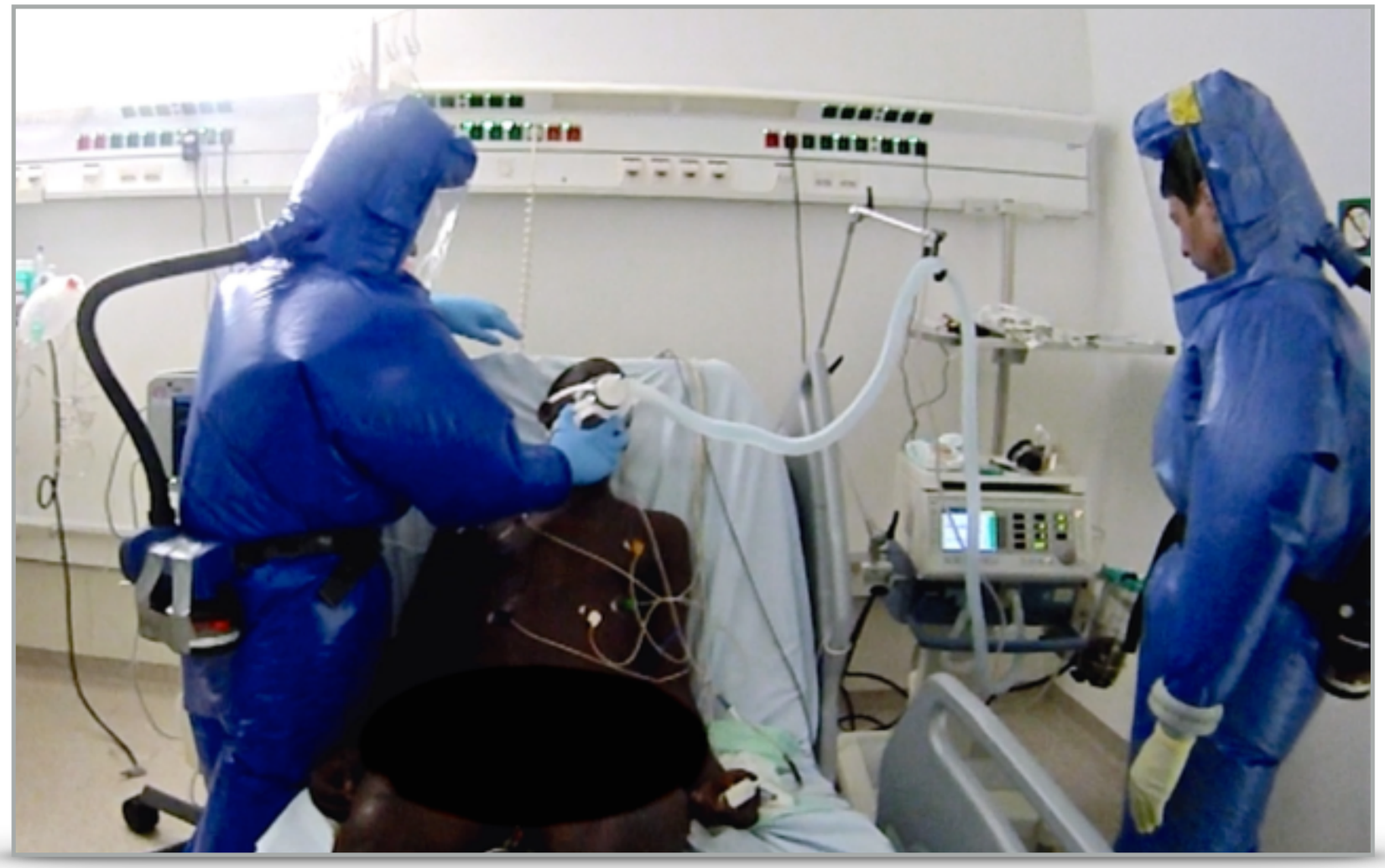
Sekundärkomplikation respiratorische Insuffizienz

Hypoventilation und Lungenödem

- Nicht-Invasive Beatmung unter Magensondenschutz

- Risk-/Benefit-Abwägung

  (Ileus und eingeschränktem Monitoring für invasive Beatmung)



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Erfahrungen aus den USA

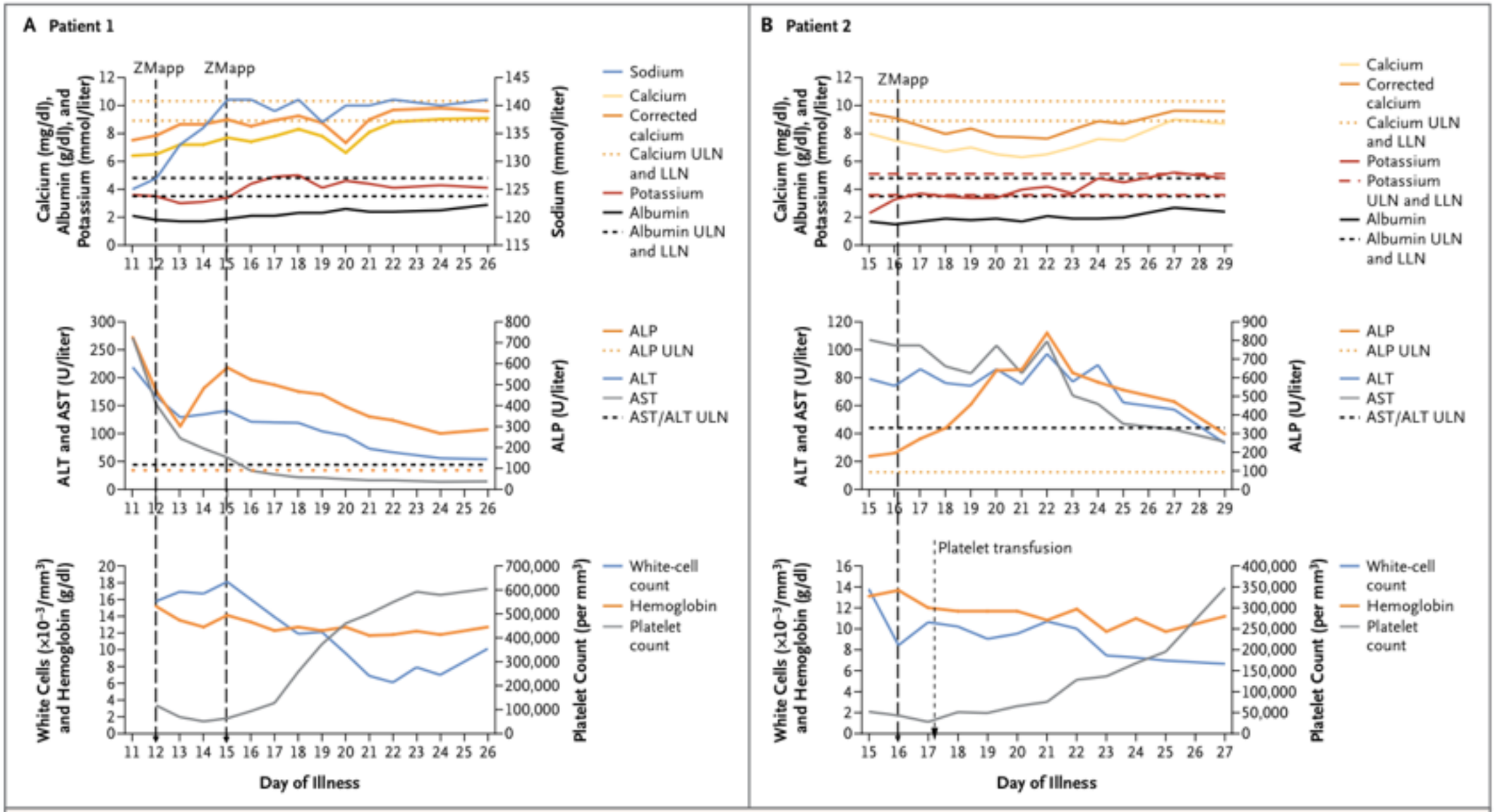

Figure 1. Laboratory Values over the Course of Ebola Virus Disease (EVD) in Patients 1 and 2.

Shown are the changes in laboratory values during hospitalization in Patient 1 (Panel A) and Patient 2 (Panel B) after transfer to Emory University Hospital from Liberia. In both panels, the vertical dashed lines point to the days on which the patients received an experimental antibody cocktail called ZMapp. For the two patients, values are provided for pertinent electrolytes (top graphs), liver enzymes (middle graphs), and blood counts, including white-cell counts, hemoglobin levels, and platelet counts (bottom graphs). The administration of a platelet transfusion in Patient 2 is indicated by the dashed line in the bottom graph of Panel B. To convert the values for calcium to millimoles per liter, multiply by 0.250. ALP denotes alkaline phosphatase, ALT alanine aminotransferase, AST aspartate aminotransferase, LLN lower limit of the normal range, and ULN upper limit of the normal range.

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Prädiktoren für das Outcome im Endemiegebiet

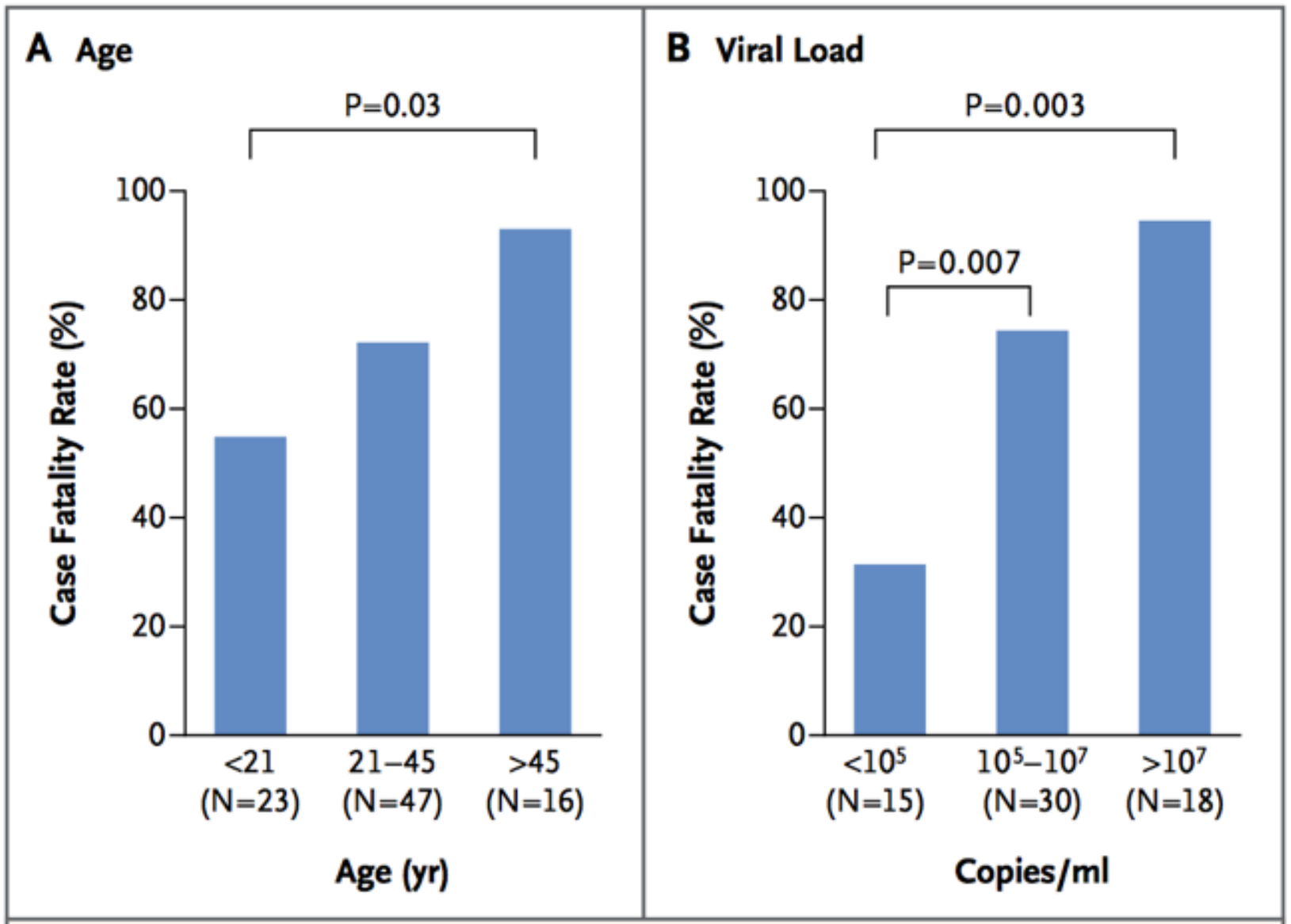

Figure 1. Case Fatality Rates among Patients with Ebola Virus Disease (EVD) in Sierra Leone.

Shown are case fatality rates among patients with confirmed EVD, a known outcome, and available data, according to age and viral load.

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Zusammenfassung

Herausforderungen:

- Große Volumenschwankungen
- Ausgeprägte Elektrolytimbalancen
- Herzrhythmusstörungen
- Sekundärkomplikationen (Sepsis/Peritonitis/Hyperkapnie)

Lösungsansätze:

- eingespieltes interdisziplinäres/interprofesionelles Team
  - ICU-Team, Infektiologen, MTAs, Blutbank, Versorgungstechnik
- Frühzeitige Anlage eines Zentralvenösen Zugangs
- Engmaschige Kontrolle intensivmedizinischer Basisparameter
- Balanciertes Ernährungskonzept