Fever diagnostics in low-income settings

Iruka N Okeke

Haverford College
Biology Department

The Clinical Importance of Microbiological Findings in the Diagnosis and Management of Bloodstream Infections

Harald Seifert

Institute for Medical Microbiology, Immunology and Hygiene, University of Cologne, Cologne, Germany

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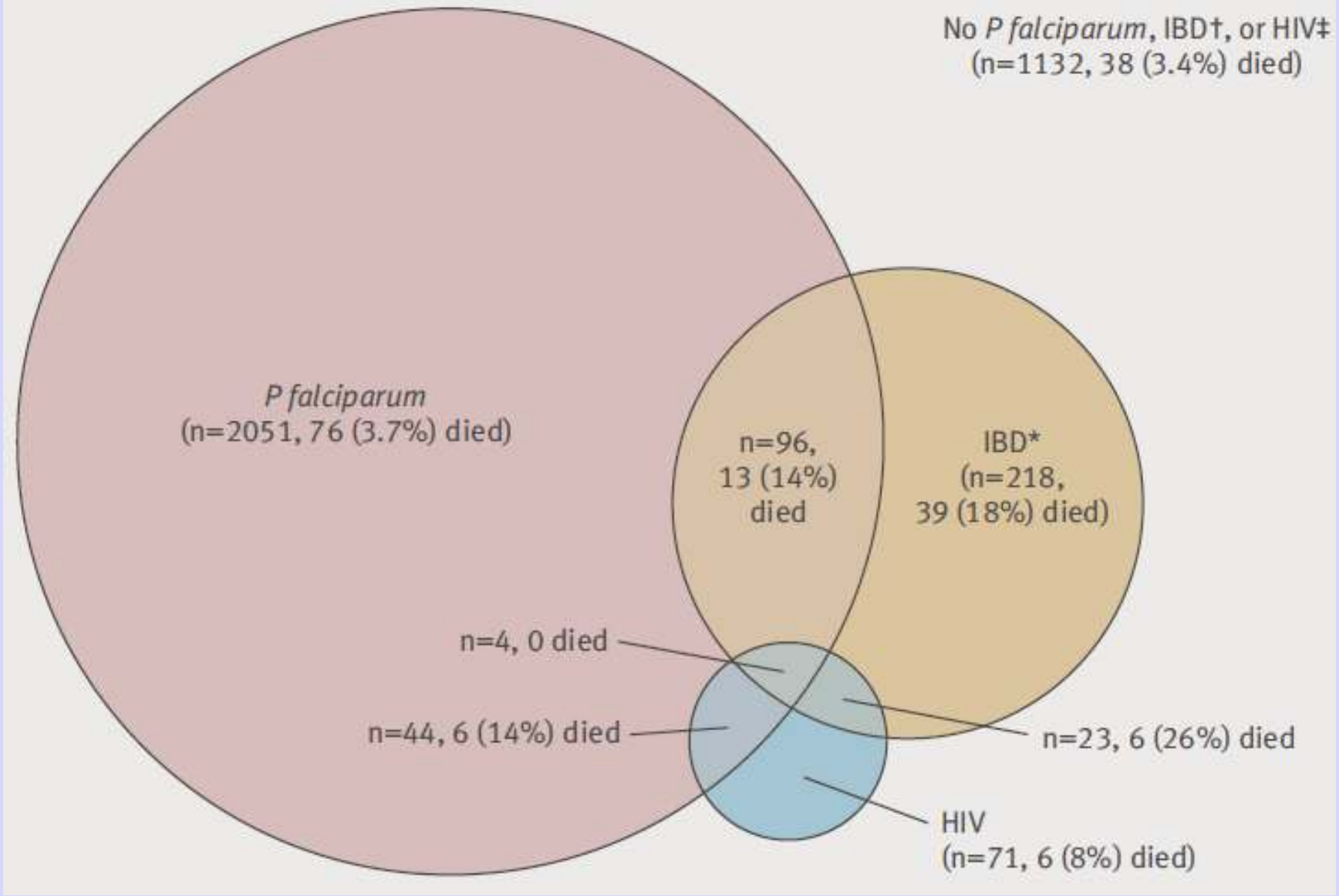
Bloodstream infections are associated with high morbidity and mortality. Accurate identification of blood isolates to the species level and identification of the source of infection and/or the portal of entry are crucial for optimal management of these infections. These investigations—in addition to clinical findings and laboratory and imaging studies—are central to informing and directing efficient and effective diagnostic examinations and to choosing the optimal antimicrobial regimen. Four case studies that demonstrate the importance of identifying the causative agents and the source of infection are discussed to illustrate the central importance of microbiological findings in the diagnosis of bacteremia and bloodstream infections associated with infections at other sites.

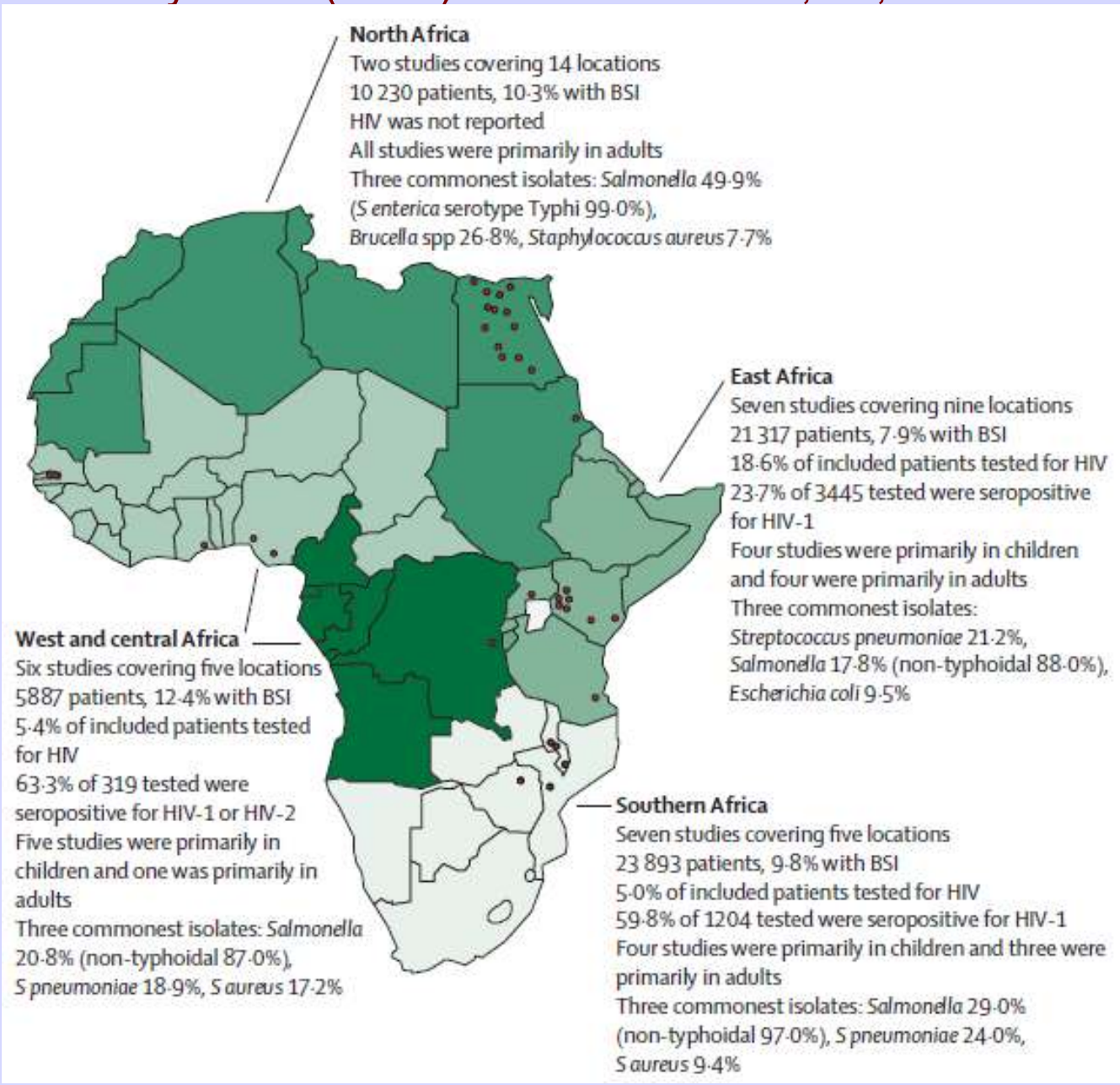
Seifert H (2009) The clinical importance of microbiological findings in the diagnosis and management of bloodstream infections. *Clin Infect Dis* 48 Suppl 4:S238-245

Pediatric patients in Muheza district hospital, Tanzania, infected with *Plasmodium falciparum*, invasive bacterial disease or HIV

Nadjm et al. (2010) BMJ, 340, c1340



Community-acquired bloodstream infections accross Africa
Reddy et al. (2010) Lancet Infect Dis, 10, 417-432



Approaches to dealing with the febrile diagnostic dilemma

- Sequential chemotherapy
  - The patient as the diagnostic test tube
- Extended-spectrum chemotherapy
  - Cover all bases
- Evidence based, rational medicine
  - Treat based on diagnosis

“Without diagnosis, there is no rational treatment”

Rene Laënnec (1781-1826)

Laënnec Exhibit at the Semmelweiss Museum, Budapest

Parasitology Laboratory, UTH, Lusaka. October 2005.

“ This [quick identification of the pathogen] is spectacularly demonstrated by the rapid response to the highly publicised outbreak of Ebola virus in Kitwit, Zaire in 1995: glycoprotein sequences from the Kitwit strains were obtained within 48 hours of the virus arriving at the CDC in Atlanta”

Holmes, EC. Molecular epidemiology and evolution of emerging infectious diseases. British Medical Bulletin 54 (3) 533-543, 1998.

Date (1995)	Event
Jan 13th	Death of index case
April 10-14th	Identification of first cases among health personnel
April 27th-29th	"Emergency" message sent to health authorities; Lab technician dispatched
May 1st-3rd	Evaluation of preliminary lab findings and clinical signs establishes a diagnosis of viral hemorrhagic fever
May 4th-5th	First blood specimens sent to CDC. First anti-epidemic measures taken
May 9th	Specimens arrive at CDC
May 10th	Results of serological and RT-PCR test confirming Ebola Hemorrhagic Fever conveyed to Kikwit.

There were 317 documented cases of Ebola virus infection in Kikwit in 1995. 245 of these died

Muyembe-Tamfum, JJ, Kipasa, M, Kiyungu, C and Colebunders, R. J. Infect Dis 179 (Suppl 1):S259-262

ELSEVIER

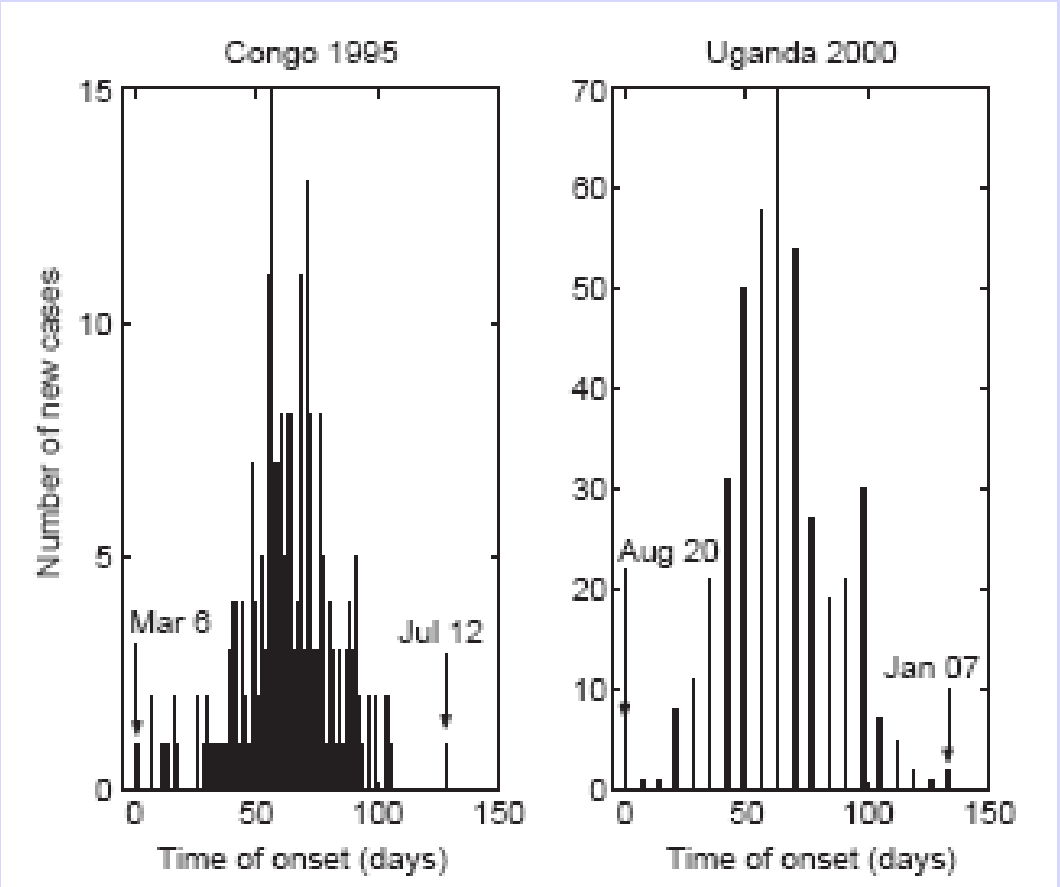
Journal of Theoretical Biology 229 (2004) 119–126

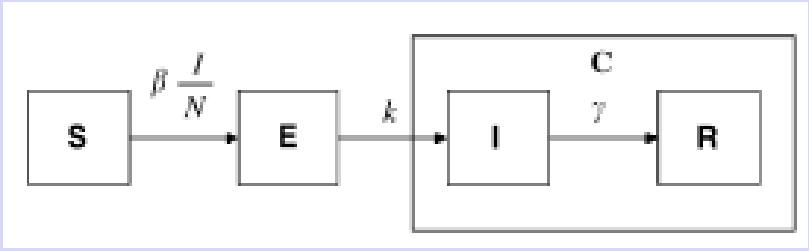
Biology

www.elsevier.com/locate/jtbi

The basic reproductive number of Ebola and the effects of public health measures: the cases of Congo and Uganda

G. Chowell[a,d,*], N.W. Hengartner[b], C. Castillo-Chavez[a,d], P.W. Fenimore[a], J.M. Hyman[c]





Computer simulated Ebola epidemics

Pfeiffer, T, Zhang P, Okeke I and Manning R. Unpublished data

Susceptible, Exposed, Infected, Recover (SEIR)

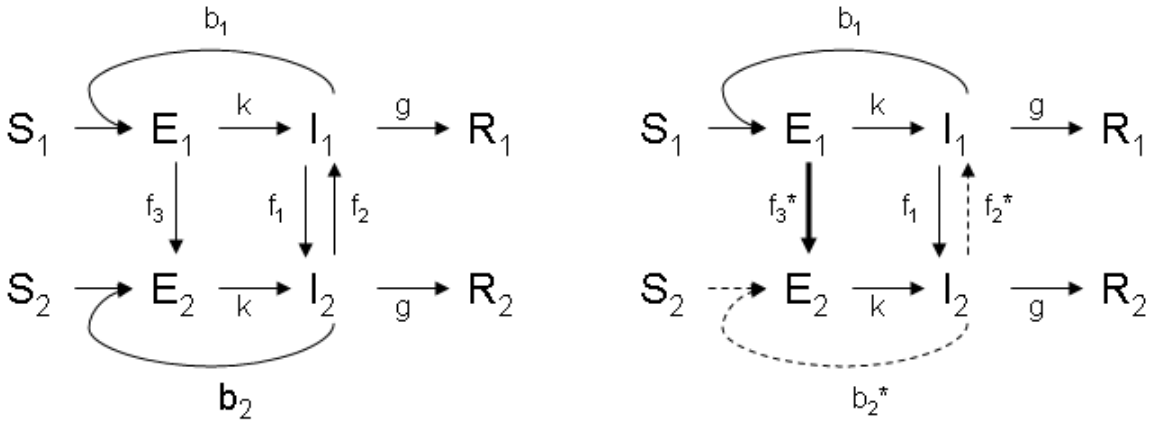
Ebola/Lassa model

A two compartment model to accommodate a health workers subpopulation was used.

pre-intervention *post-intervention*

Population
Size: $p_1=10^6$

Hospital population
Size: $p_2=10^3$



Parameters

p_1 – population size
p_2 – size of health workers pool
b_1 – within population transmission
b_2 – within hospital transmission*
k – disease progression
g – recovery/mortality
f_1 – hospitalization
f_2 – release from hospital*
f_3 – hospitalization of exposed*
* – affected by interventions

Interventions

Quarantine decreases release from hospital f_2 and within hospital transmission b_2, increases hospitalization of exposed individuals f_3

Equations

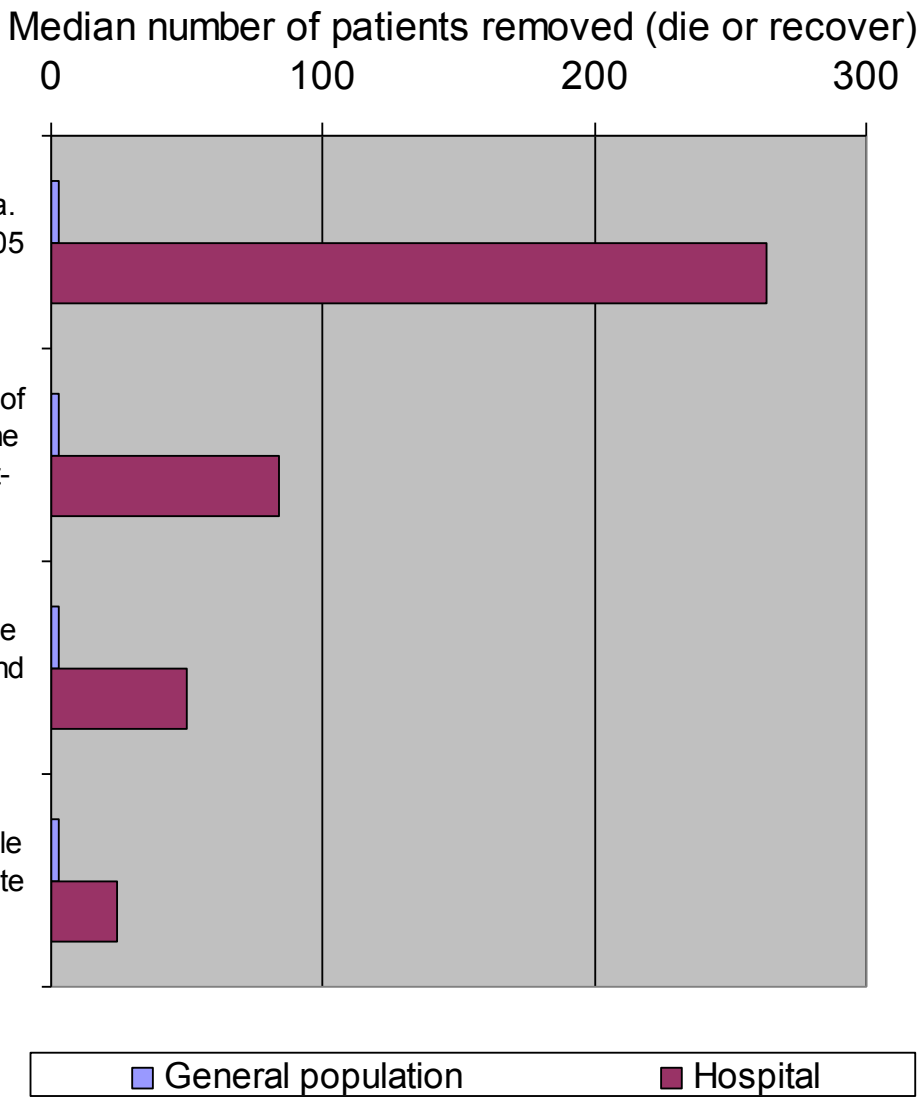
$dS_1/dt = - b_1 S_1 I_1/p_1$
$dE_1/dt = b_1 S_1 I_1/p_1 - kE_1 - f_3 E_1$
$dI_1/dt = kE_1 - gI_1 - f_1 I_1 + f_2 I_2$
$dR_1/dt = gI_1$
$dS_2/dt = - b_2 S_2 I_2/p_2$
$dE_2/dt = b_2 S_2 I_2/p_2 - kE_2 + f_3 E_1$
$dI_2/dt = kE_2 - gI_2 + f_1 I_1 - f_2 I_2$
$dR_2/dt = gI_2$

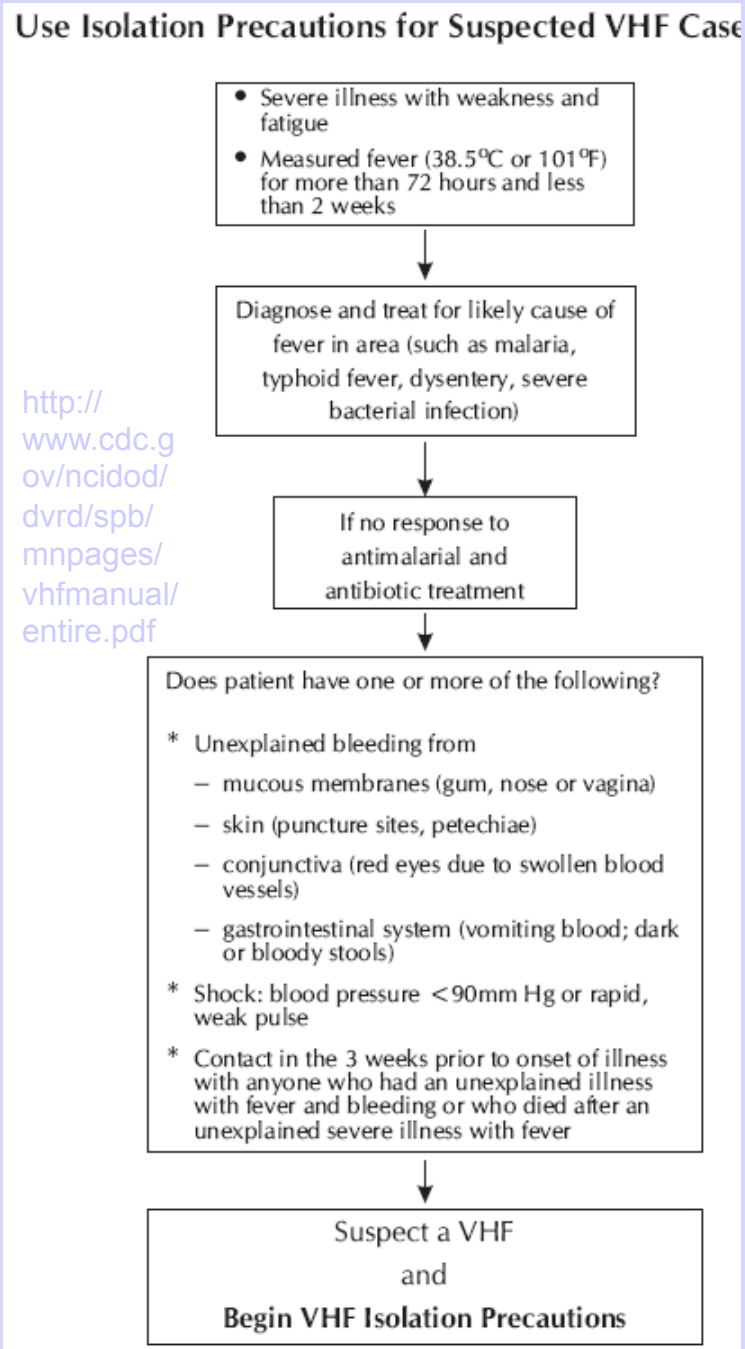
1: No active diagnosis of individual with a fever for Ebola. Everyone (inside or outside of the hospital) is given a .0005 chance of being detected with Ebola per day.

2: In addition to 1, post-mortem diagnosis with the probability of 1- .9*exp(-# of R in hospital)/50)); i.e. the higher the # of R in the hospital, the stronger and more accurate the diagnosis in post-mortem. Diagnositc turnaround = 3 days.

3: In addition to 1 and 2, Ebola is actively diagnosed in febrile health workers. The probability of successful diagnosis is .9 and diagnostic turnaround = 2 days. # of health workers = 100.

4: In addition to 1 to 3, all in hospital population who are febrile are actively diagnosed for Ebola. The test has a .9 success rate and diagnostic turnaround = 2 days.





http://www.cdc.gov/ncidod/dvrd/spb/mnpages/vhfmanual/entire.pdf

No diagnostic lab support	Diagnostic support for Endemic fevers only
Day 0	Day 0
Day 1	Day 1
Day 14	Not needed
Day 15	Day 3-4

The Feasibility of Laboratory Diagnosis in African Settings: unpacking the myths

- *Too many patients, too little time.*
- *Laboratory facilities are too expensive.*
- *Local technical expertise is insufficient to support diagnostic testing.*
- *Diagnostic tests are superfluous.*

Diagnostic testing is not cheap but it is cost effective:

	Clinical diagnosis	Microscopy	New rapid diagnostic tests
n	6520	10,460	6685
Total cost of diagnosis and treatment/ patient	4.2	8.8	5.2
# (%) of cases correctly diagnosed	1,598 (25)	8,303 (79)	6,082 (91)
Average cost effectiveness ratio (ACER)	17.1	11.0	5.7

Chanda, Pascalina ASTMH abstract #87, December 2007

Shifting the health delivery emphasis is from prescription to diagnosis in Africa and other limited resource areas could:

- Improve therapeutic success overall
- Reduce disability and mortality from as well as duration of illnesses
- Prevent spread of pathogens
- Inspire confidence in the ‘orthodox’ medical system
- **Address the drug resistance problem by conserving antimicrobial effectiveness**

The Feasibility of Laboratory Diagnosis in African Settings: unpacking the myths

- *Too many patients, too little time.*
- *Laboratory facilities are too expensive.*
- *Local technical expertise is insufficient to support diagnostic testing.*
- *Diagnostic tests are superfluous.*
- *Laboratory diagnostics make no contribution to disease prevention.*
- ***The ideal tests for resource-limited health systems have not been invented yet.***

Community case management of fever due to malaria and pneumonia in children under five in Zambia: a cluster randomized controlled trial.

Yeboah-Antwi K, et al. PLoS Med. 2010 Sep 21;7(9):e1000340.

	Intervention arm (Malaria RDTs and antibiotics)	Control arm (Syndromic diagnosis and referral)	Risk ratio (95% CI)
Treatment failure day 5–7	11.3% (41/362)	20.2% (41/203)	0.44 (0.21–0.93)
Children with fever that received ACT	27.5% (265/963)	99.1% (2066/2084)	0.23 (0.14–0.38)
Early and appropriate antibiotics for pneumonia	68.2% (247/362)	13.3% (22/203)	5.32 (2.19–8.94)

Proportion seeking care during all illnesses or fast breathing during baseline and post-study surveys

Source of care	Intervention Baseline	Intervention Poststudy	Control Baseline	Control Poststudy
All illnesses	**(*n* = 174)**	**(*n* = 190)**	**(*n* = 163)**	**(*n* = 203)**
Home	12.7%	2.6%	7.4%	4.9%
CHW	47.1%	78.9%	50.9%	77.3%
RHC/CMH	40.2%	18.5%	41.7%	17.8%
Fast breathing	**(*n* = 61)**	**(*n* = 66)**	**(*n* = 59)**	**(*n* = 34)**
Home	6.6%	3.0%	6.8%	8.8%
CHW	50.8%	77.3%	54.2%	55.9%
RHC/CMH	42.6%	19.7%	39.0%	35.3%

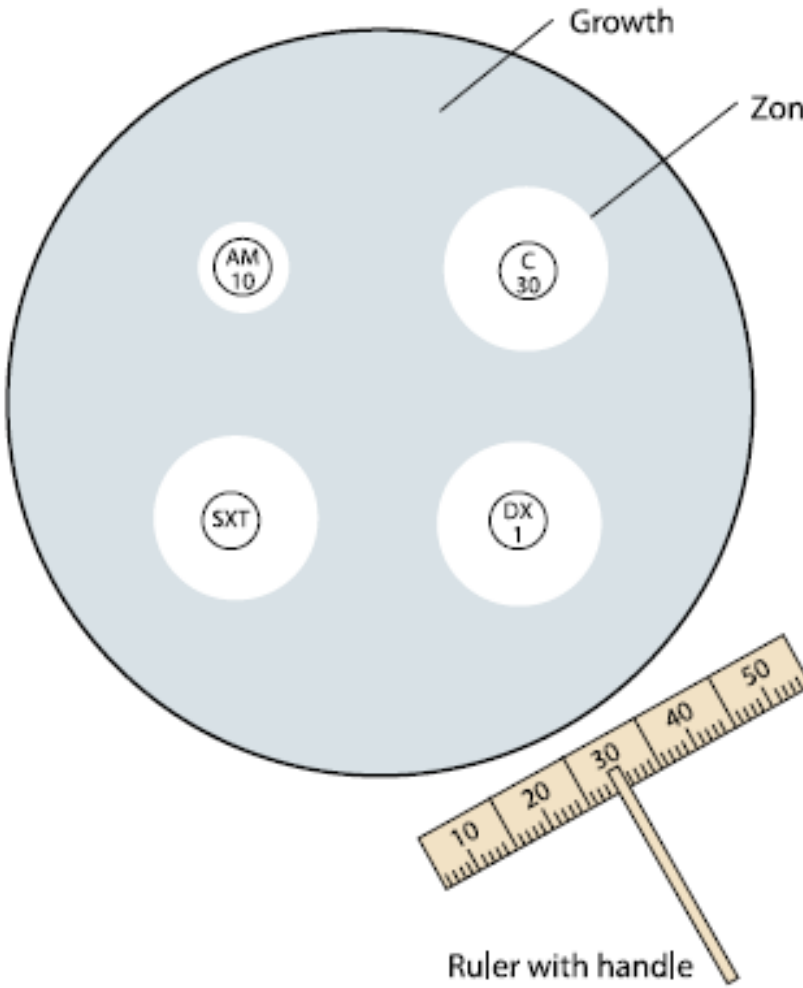
CMH, Chikankata Mission Hospital; RHC, rural heath center.

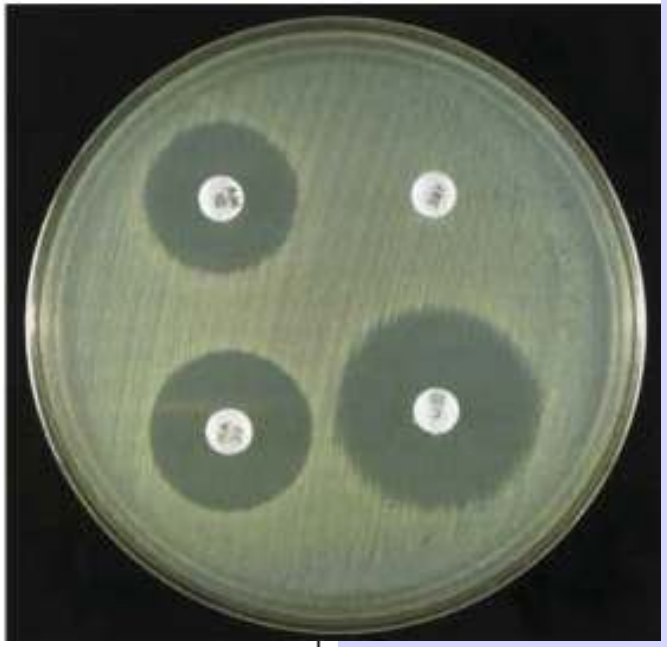
Community case management of fever due to malaria and pneumonia in children under five in Zambia: a cluster randomized controlled trial. Yeboah-Antwi K, et al. PLoS Med. 2010 Sep 21;7(9):e1000340.

The parable of the blind leading the blind

Bruegel, Pieter the Elder, 1568

FIGURE 6: The antimicrobial susceptibility disk diffusion test: disk placement and measurement of inhibition zone diameters





A ruler on a stick can be used to measure zone inibition diameters if calipers are not available.

http://www.who.int/csr/resources/publications/drugresist/en/IAMRmanual.pdf

Candidate diagnostic targets

	Ease of access and detection*	Ease of interpretation*	Likely predictive value
Host marker	high	low	Medium to low
Host antibody	Medium	Low	Medium
Whole pathogen	Dependable	High	High
Pathogen antigen	Low	High	High

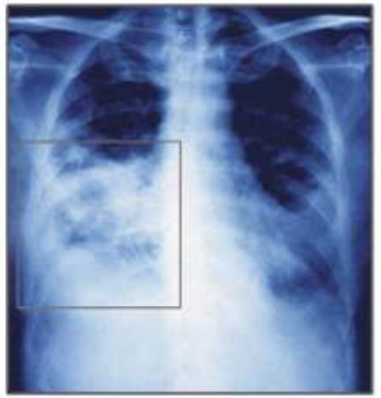
*(in most cases: varies for different pathogens)

Diagnostic needs

Mabey, D., Peeling, R.W., Ustianowski, A., Perkins, M.D., 2004. Diagnostics for the developing world. Nat. Rev. Microbiol. 2, 231–240.

- **A**ffordable,
- **S**ensitive,
- **S**pecific,
- **U**ser friendly (requiring minimal training)
- **R**apid and **R**obust, (possible to transport, store and use in hot and humid climates),
- **E**quipment-free
- **D**eliverable to areas of need

PCT algorithm for patients with respiratory tract infection



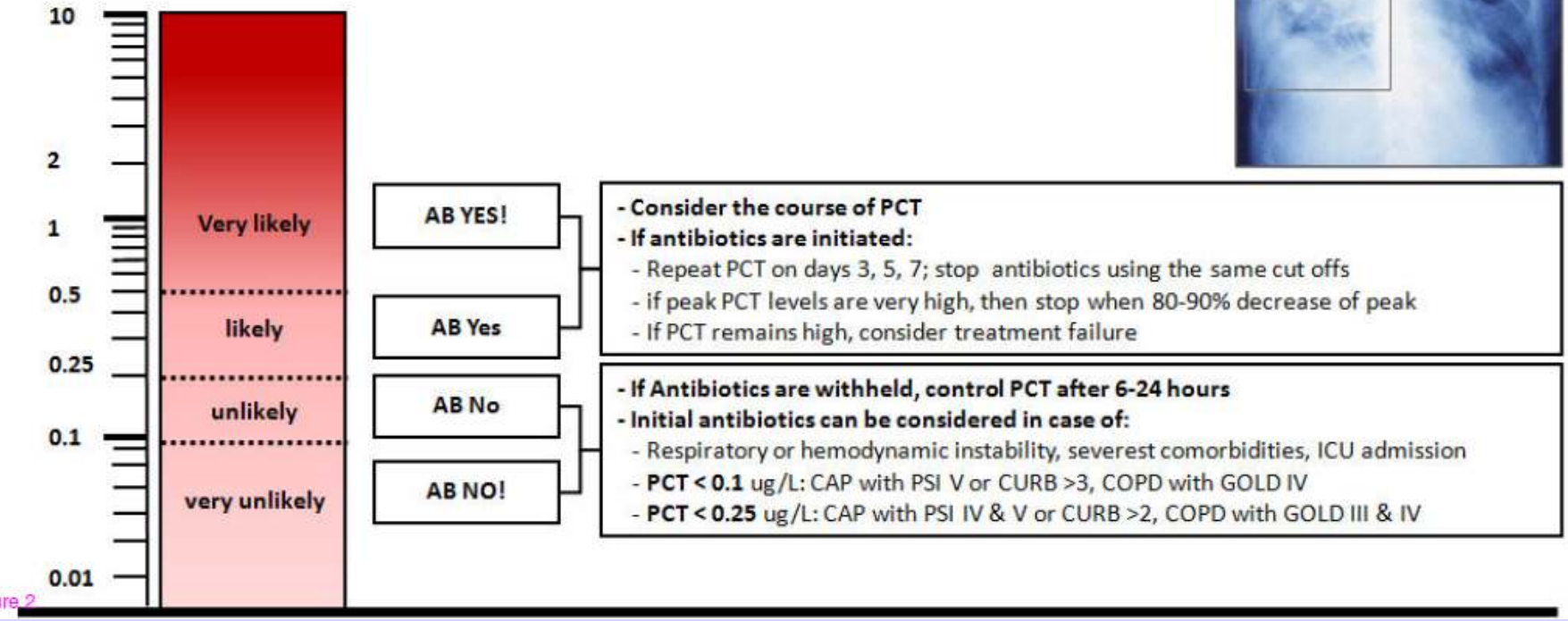
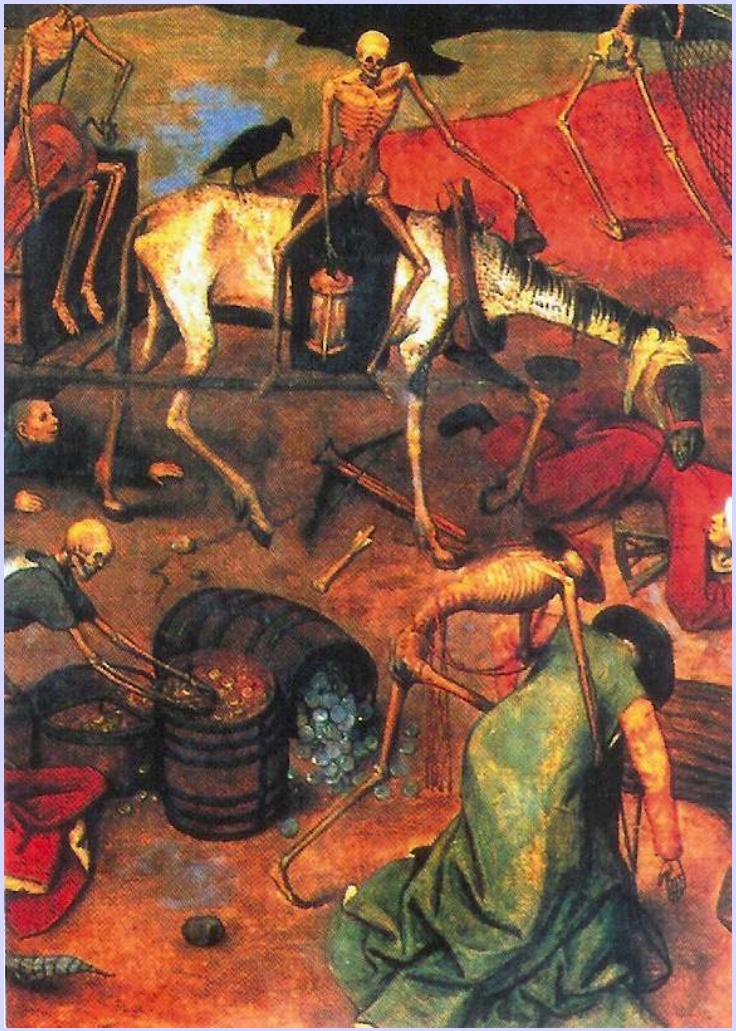


Figure 2

Schuetz et al **Procalcitonin can guide antibiotic treatment**
BMC Medicine 2011, **9**:107



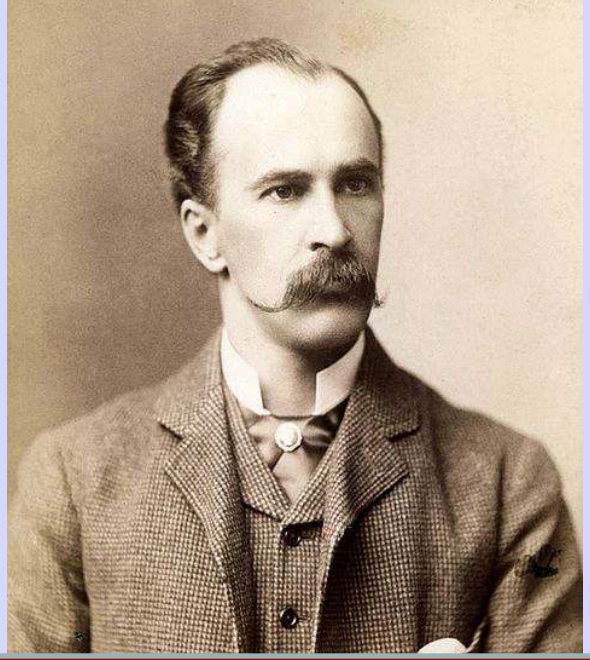
Detail from
Triumph over death
Pieter Breugel 1562
The British museum

"Advances in biomedicine in the last 50 or 100 years have been great, but for the average rural health worker, operating often in a situation of economic crisis and chronic underfudning of medical services, these advances may seem more theoretical than real".

Megan Vaughan
Curing their Ills. pg 155.

I confess myself unable to differentiate certain cases of malarial remittent from typhoid fever, without the blood examination

Sir William Osler, 1892



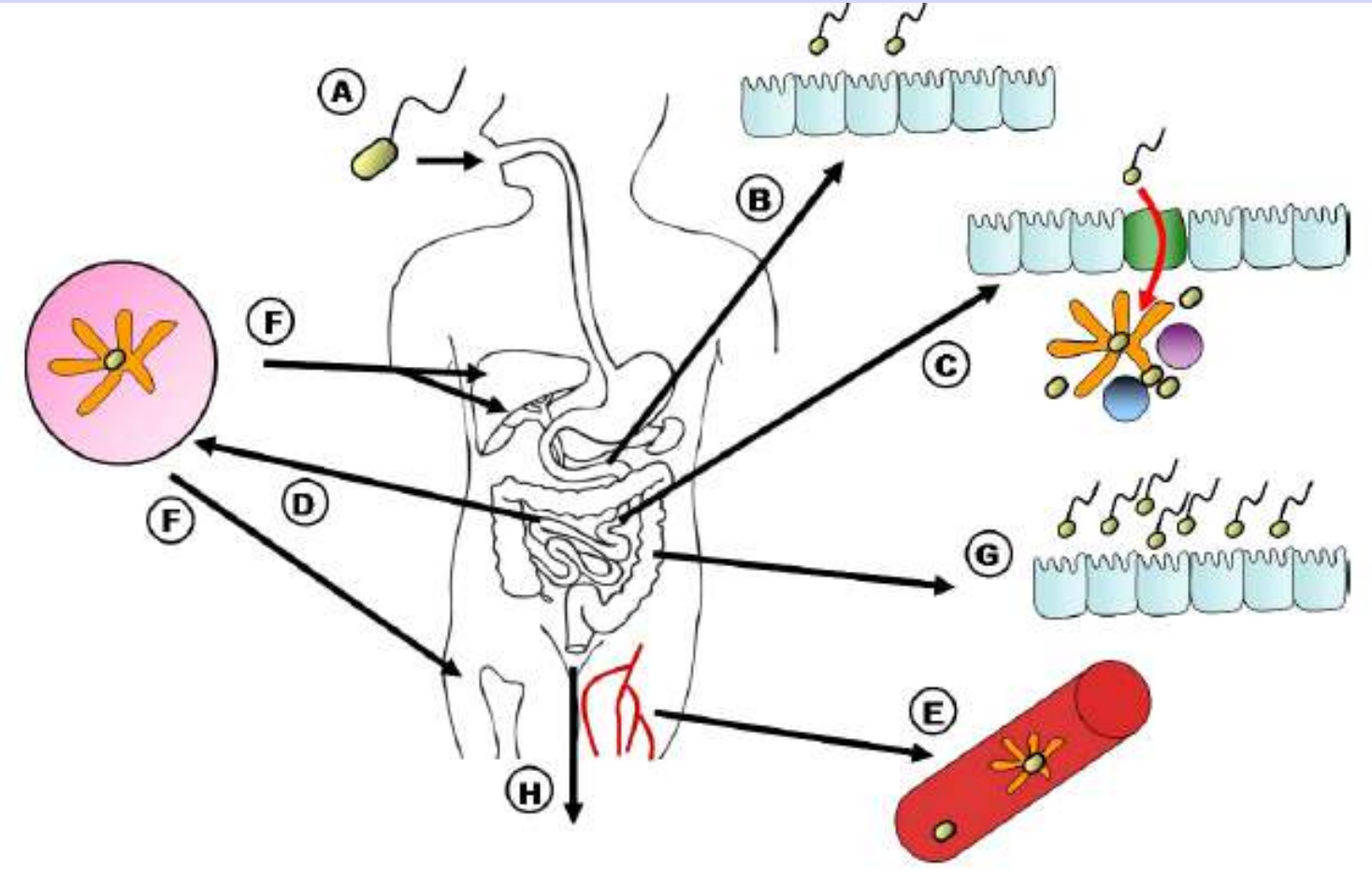
On typhoid diagnostics:

"Its in the dark ages"

Gordon 'Doog' Dougan, 2005

Searching for the elusive typhoid diagnostic

Baker et al. BMC Infectious Diseases 2010, 10:45



Searching for the elusive typhoid diagnostic

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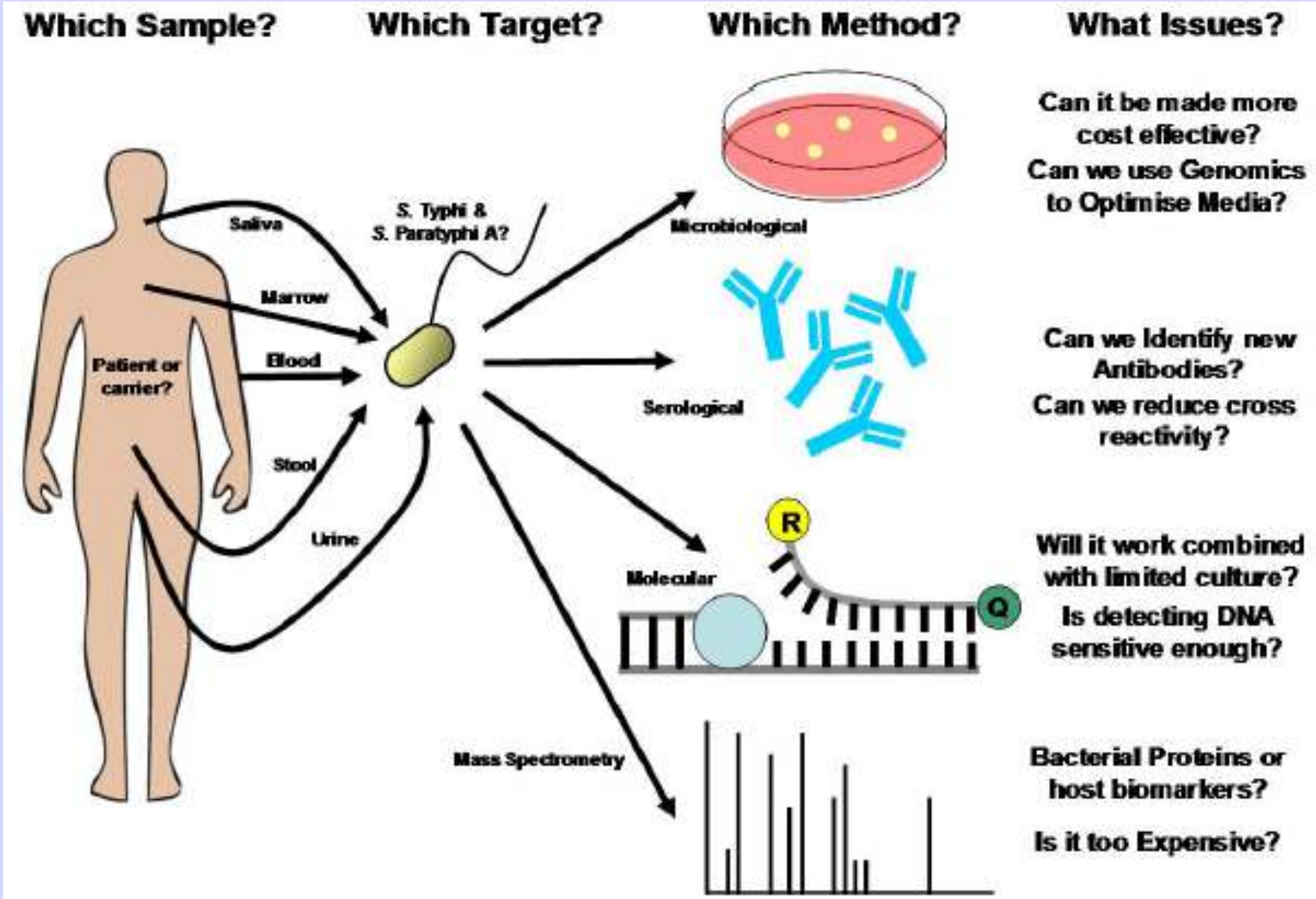

Translation Research Pathway for Appropriate Diagnostics

Okeke, IN, Peeling RW, Goosens, H, Aukenthaler, R, Olmsted, SS, de Lavison, J-F, Zimmer, B, Nordqvist, K (2011) *Drug Res Updat,* 14:95.

"We are begging for a Lab, so we can go there for a proper check up…so we can be serious and fast to know which is the sickness, instead of giving blind treatment to people. …As far as Lassa is concerned, you have to be very much more serious, you don't have to be hypothetical, you have to be correct in your diagnosis when you are treating Lassa Fever… we need a lab."

Patient advocates from Kenema, Sierra Leone, where Lassa fever is hyper-endemic.

Moving forward

- Prioritize multiplex tests for common syndromes
- Guidelines for use of diagnostics in complex emergencies
- Test development must be accompanied by interventions to assure appropriate use. We need to learn what these are now.
  - "perhaps the most significant barrier to laboratory use was physicians' reliance on clinical judgment" Polage et al 2006

Acknowledgements: Diagnostic insufficiency

- Society-in-Science
- Colleagues and Students at Haverford College
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  - Obafemi Awolowo Univ and Teaching Hospitals Complex, Nigeria
  - Wellcome Trust Sanger Institute, Cambridge
  - University Teaching Hospital, Lusaka, Zambia
  - MRC labs, Fagara, The Gambia
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- Fran Benson and Suzanne Gordon, Cornell Univ Press; Grey Osterud and Cris Fuller

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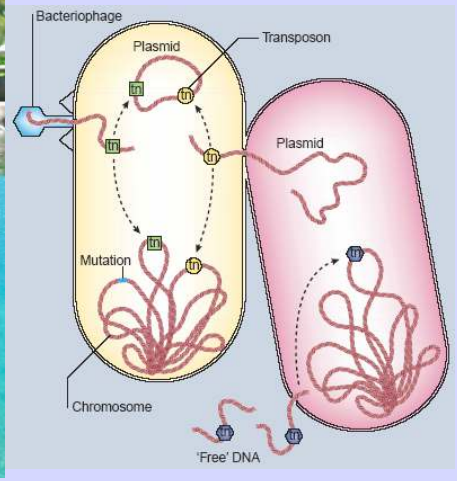
Biology Department

society in science
The Branco Weiss Fellowship



[Without diagnosis, there is no rational treatment. Examination comes first, then judgment, and then one can give help]

- Carl Gerhadt, Würsburg, 1873