29th ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Amsterdam, Netherlands
13 – 16 April 2019

The year in Infectious Diseases Part 1

Prof. Pierre TATTEVIN
Infectious Diseases & ICU, Pontchaillou Univ. Hosp., Rennes, France

SOCIETE DE PATHOLOGIE INFECTIEUSE DE LANGUE FRANCAISE
Spilf

CHU Rennes

UNIVERSITÉ DE RENNES 1

Disclosures (2014-2019)

- **Scientific boards, travel expenses, research**
  - Gilead
  - MSD
  - Pfizer
  - Astellas
  - Correvio
  - Mylan

Year in ID – Part 1

1. What was hot for viral diseases ?

2. New strategies to treat ID

3. Antibiotics flowing from the pipeline

Year in ID – Part 1

1. **What was hot for viral diseases ?**
2. **New strategies to treat ID**
3. **Antibiotics flowing from the pipeline**

EBOLA VIRUS DISEASE

Democratic Republic of the Congo

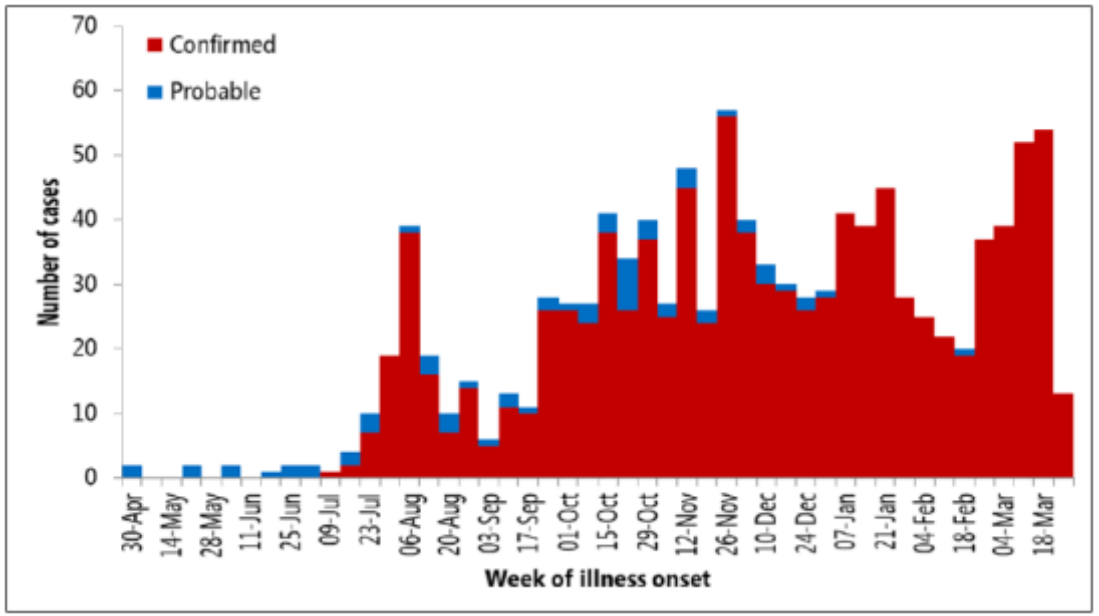
World Health Organization
REGIONAL OFFICE FOR Africa

1. Situation update

Date of issue: 2 April 2019
Data as reported by: 31 March 2019

Cases 1089

Deaths 679



Uncontrolled outbreak, despite:

- ☐ 8 labs with **operational PCR**
- ☐ Contact surveillance
- ☐ **Reinforcement of IPC**
- ☐ Points of entry screening (**42 M**)
- ☐ **Safe** Dignified **Burials**
- ☐ **Ring vaccination** (95,000 to date)
- ☐ *Community engagement ?*

https://www.who.int/ebola/en/

An Epidemic of Suspicion — Ebola and Violence in the DRC

Vinh-Kim Nguyen, M.D.

The epidemic of suspicion that fuels Ebola outbreaks

- 'Perception that *other continents care about Africans only when they get diseases that can harm them*, not when they are dying of diseases that can be treated easily and cheaply'
- Mistrust of public health authorities & international 'Ebola profiteers'

=> Attacks of Ebola treatment units

Most important part of the job is

- Community engagement
- Building trust

Nguyen VK. New Engl J Med 2019

ORIGINAL ARTICLE

A Longitudinal Study of Ebola Sequelae in Liberia

Methods:

- Cohort of **EVD survivors, n=966**
- Enrolled **one year after EVD**
- Controls = close contacts, **Ab neg, n=2350**

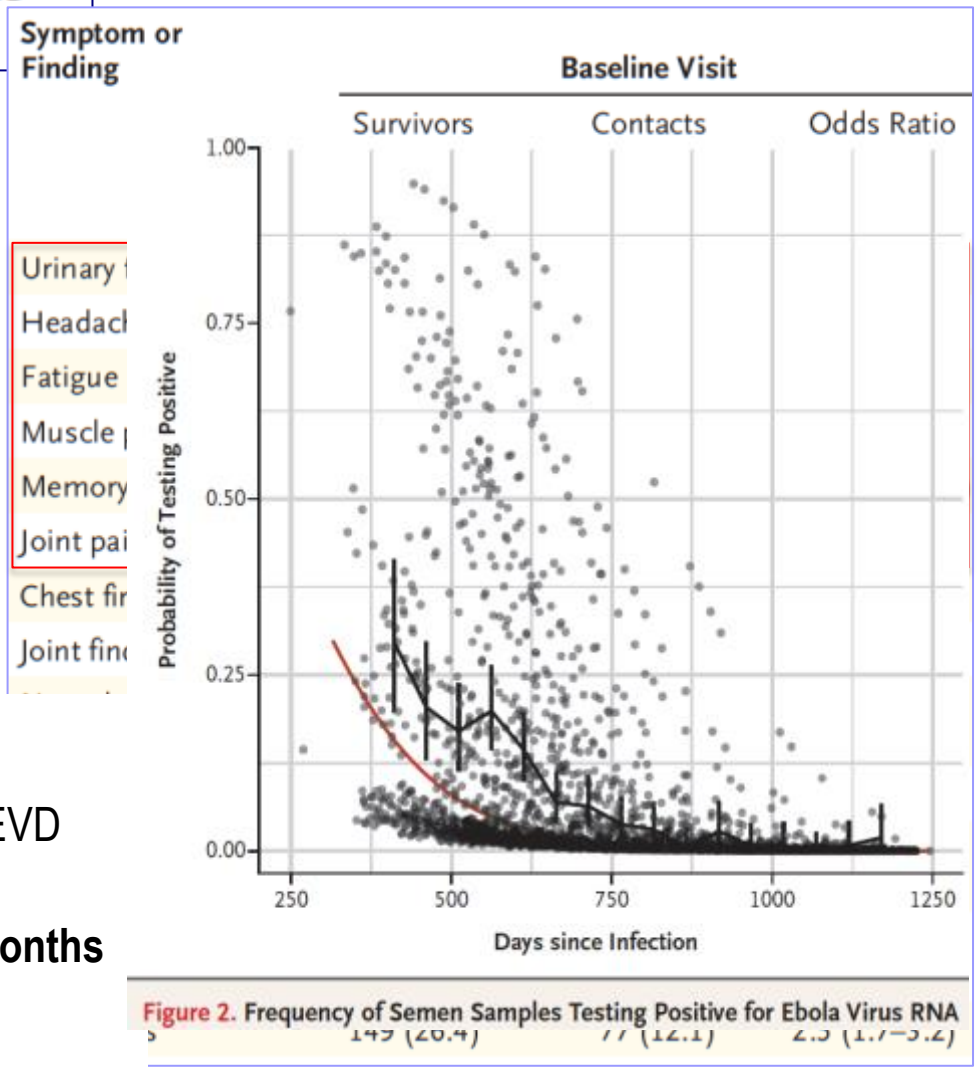


Figure 2. Frequency of Semen Samples Testing Positive for Ebola Virus RNA

Messages:

- **High burden of symptoms one year** post EVD
  - Prevalence decline between year 1 & 2
- Ebola virus **RNA in semen as long as 40 Months**

The Prevail III Study Group, New Engl J Med 2019

ORIGINAL ARTICLE

Persistence of Zika Virus in Body Fluids — Final Report

Zika virus persistence (ZiPer) cohort study, Puerto Rico (2016-2017):

- at enrolment (acute infection, < 7 days)

Detection of ZIKV RNA in Body Fluids and Anti–ZIKV IgM Antibody in Serum

ZIKV RNA					Anti–ZIKV IgM Antibody
Serum	Urine	Saliva	Vaginal Secretions	Semen	Serum
number/total number (percent)					
251/284 (88.4)	136/231 (58.9)	14/291 (4.8)	3/119 (2.5)	48/94 (51.1)	284/294 (96.6)

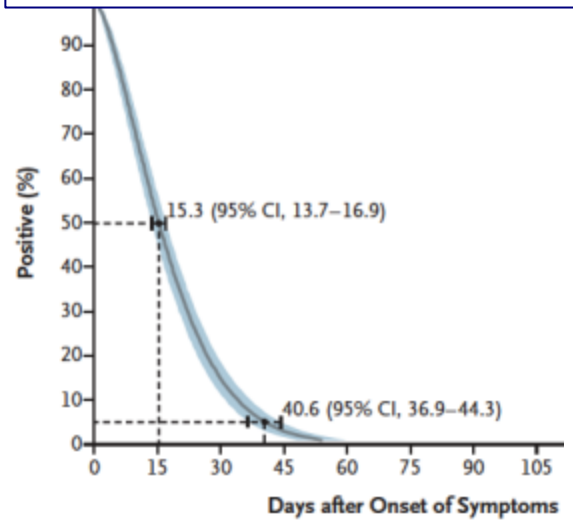
Paz-Bailey G et al. New Engl J Med 2018

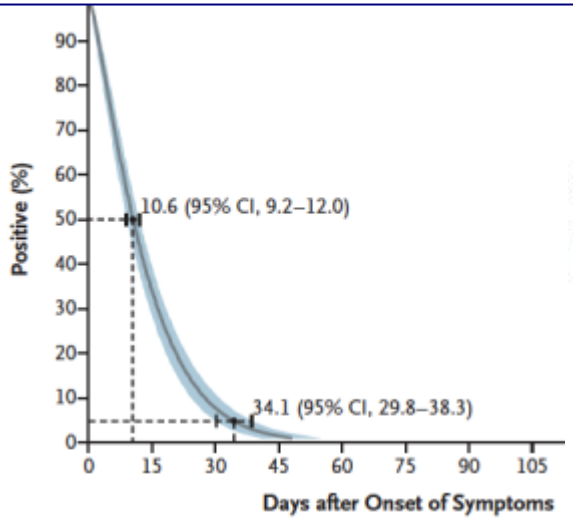
ORIGINAL ARTICLE

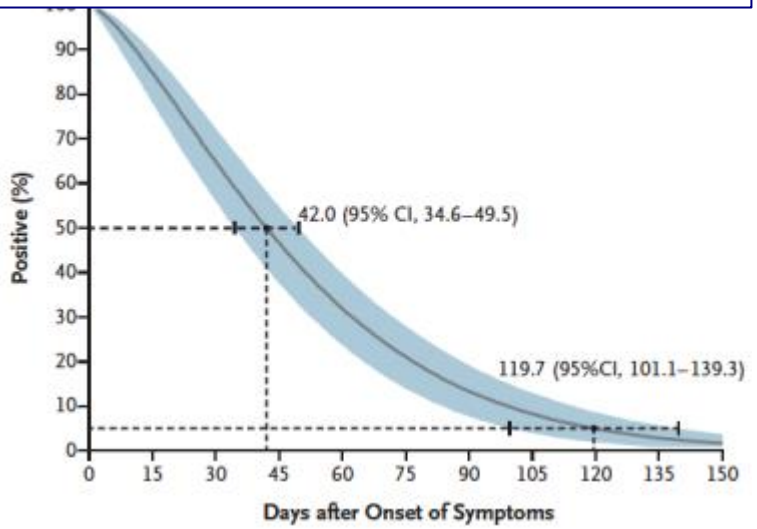
Persistence of Zika Virus in Body Fluids — Final Report

Messages:

- **Men** with ZIKV exposure: **use condom or abstain from sex during 3 months**
- **Women** with ZIKV exposure: wait at least **8 weeks before attempting conception**







Paz-Bailey G et al. New Engl J Med 2018

Immunogenicity, safety, and tolerability of the measles-vectored chikungunya virus vaccine MV-CHIK: a double-blind, randomised, placebo-controlled and active-controlled phase 2 trial

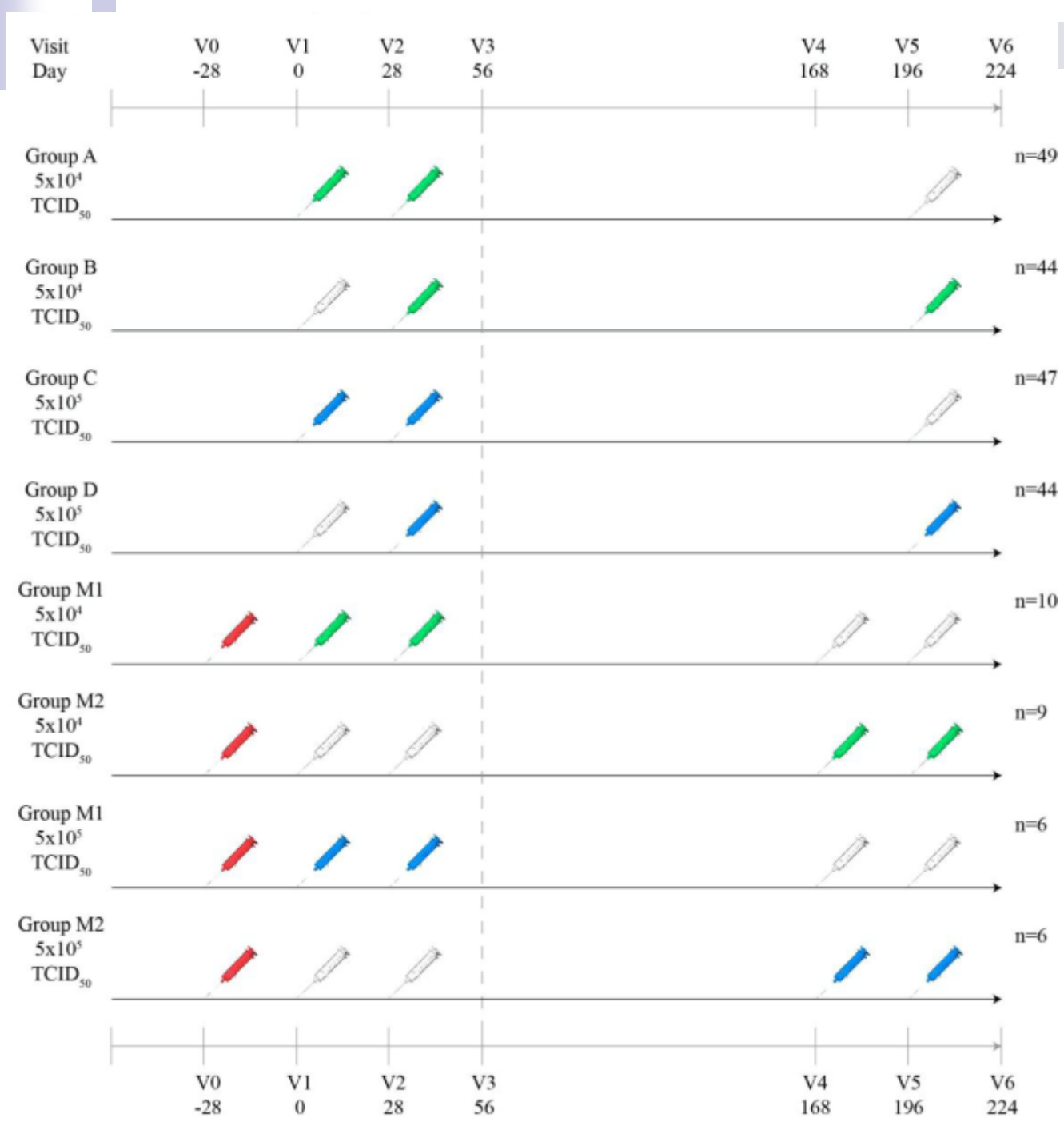
Chikungunya

- ✓ Reported in **106 countries**
- ✓ **1.3 billion** people living in at-risk areas
- ✓ Muskuloskeletal symptoms during months (50% ?)

Live-attenuated, measles-vectored vaccine (MV-CHIK)

Phase 2 trial, healthy volunteers, Austria & Germany

Reisinger EC et al. Lancet 2018



Reisinger EC et al. Lancet 2018

Immunogenicity, safety, and tolerability of the measles-vectored chikungunya virus vaccine MV-CHIK: a double-blind, randomised, placebo-controlled and active-controlled phase 2 trial

Messages:

- **A live-attenuated** measles-vectored **chikungunya virus**
- Good safety & tolerability profiles (n=229)
- **Highly immunogenic in healthy volunteers (>95%)**

(i.e. high dose, **prime-boost vaccination schedule**)

- **Phase 3 study to be started**

Reisinger EC et al. Lancet 2018

ORIGINAL ARTICLE

Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy

Dengue vaccine controversy

- **400 M dengue cases/year** => 3.2 M severe cases => 9000 deaths
- **Tetravalent dengue vaccine => 80% efficacy to prevent hospitalisation for dengue in children 9-16 years**
- Vaccination campaign in schoolchildren in Philippines (n=800,000), 2016
- Halted in 2017 because of **excess severe cases in children seronegative before vaccination**
- Partly responsible for Philippines 2019 measles outbreak ?

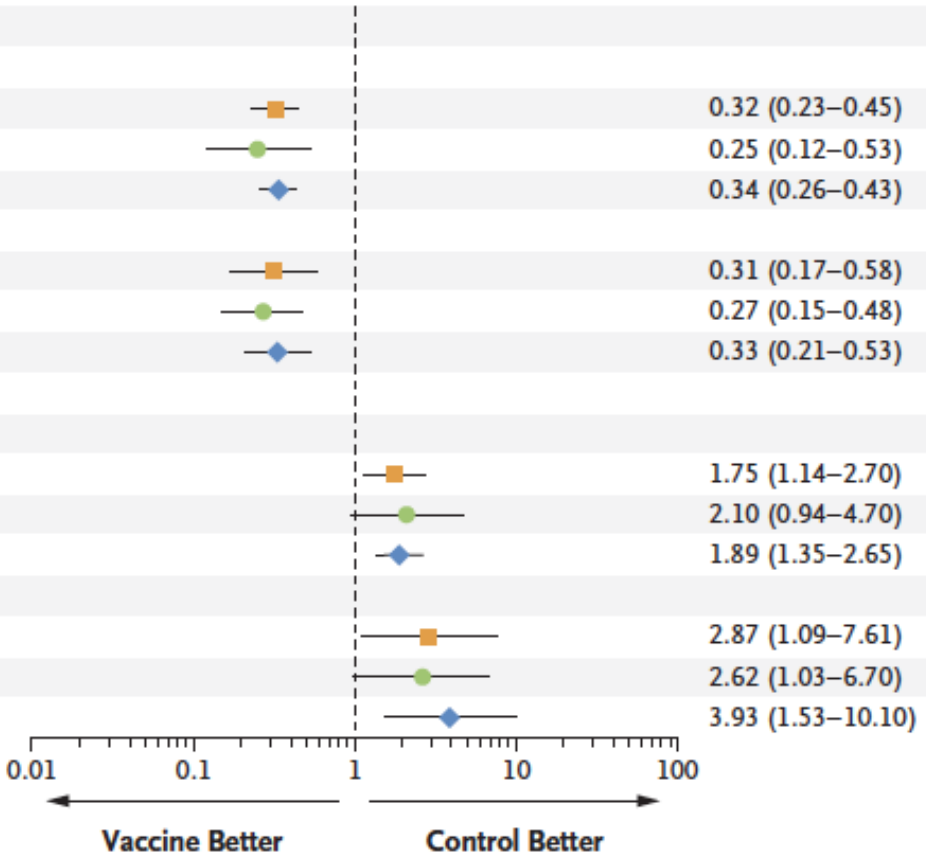
Sridhar S et al. N Engl J Med 2018

ORIGINAL ARTICLE

Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy

2–16 Yr of Age

Serostatus, End Point, and Method	Vaccine Group	Control Group	Relative Risk or Hazard Ratio (95% CI)
	no./total no.		
Seropositive			
Hospitalization for VCD			
MI, month 0 onward	152.4/1816.1	227.5/886.2	0.32 (0.23–0.45)
TMLE, month 0 onward	99.2/1742.3	199.5/846.7	0.25 (0.12–0.53)
NS1, T9, month 13 onward	124/1750	175/822	0.34 (0.26–0.43)
Severe VCD			
MI, month 0 onward	35.1/1816.1	53.4/886.2	0.31 (0.17–0.58)
TMLE, month 0 onward	28.2/1742.3	49.9/846.7	0.27 (0.15–0.48)
NS1, T9, month 13 onward	31/1750	44/822	0.33 (0.21–0.53)
Seronegative			
Hospitalization for VCD			
MI, month 0 onward	201.6/567.9	62.5/307.8	1.75 (1.14–2.70)
TMLE, month 0 onward	244.0/547.2	65.5/296.8	2.10 (0.94–4.70)
NS1, T9, month 13 onward	187/512	53/272	1.89 (1.35–2.65)
Severe VCD			
MI, month 0 onward	44.9/567.9	8.6/307.8	2.87 (1.09–7.61)
TMLE, month 0 onward	44.6/547.2	9.3/296.8	2.62 (1.03–6.70)
NS1, T9, month 13 onward	37/512	5/272	3.93 (1.53–10.10)



Trolleyology and the Dengue Vaccine Dilemma

Lisa Rosenbaum, M.D.

"Trolleyology" refers to a series of moral dilemmas that reveal the tensions between utilitarianism — the idea that a behavior is moral if its consequences maximize public good

Rosenbaum L et al. N Engl J Med 2018

2018, 93, 457–476 No 36

World Health Organization

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

Dengue vaccine: WHO position paper – September 2018

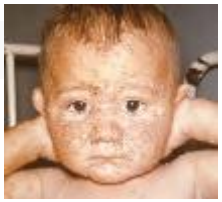
WHO position

Messages

- **Prevaccination screening** is the recomended strategy
- Alternative (if not available) = **vaccination without individual screening only in countries where dengue seroprevalence is >80% by the age of 9 years**

ORIGINAL ARTICLE

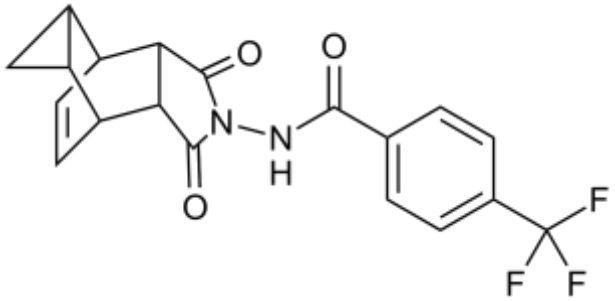
Oral Tecovirimat for the Treatment of Smallpox



Tecovirimat

- Inhibits protein p37 => active on orthopoxviruses
- **Smallpox eradicated**, but potential **bioterrorism** agent

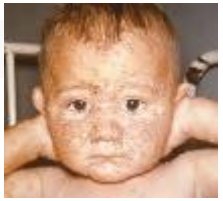
=> FDA animal efficacy rule

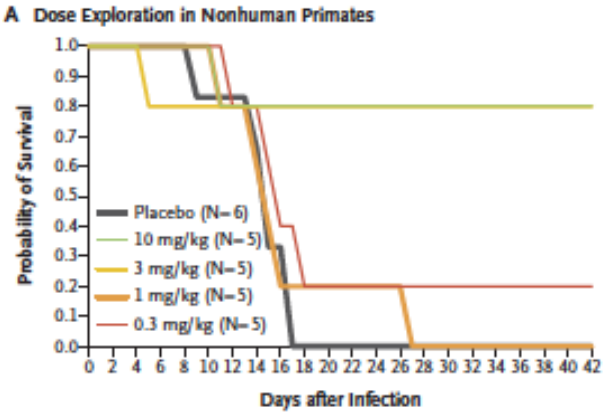


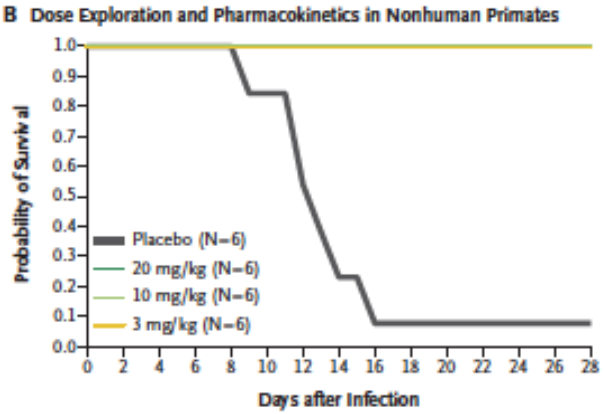
Grosenbach DW et al. N Engl J Med 2018

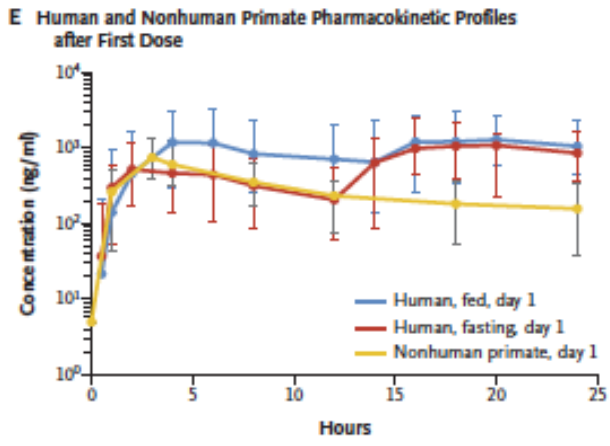
ORIGINAL ARTICLE

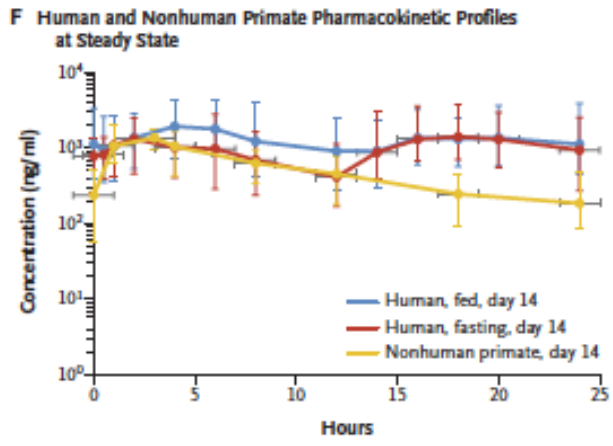
Oral Tecovirimat for the Treatment of Smallpox











Grosenbach DW et al. N Engl J Med 2018

ORIGINAL ARTICLE

Oral Tecovirimat for the Treatment of Smallpox

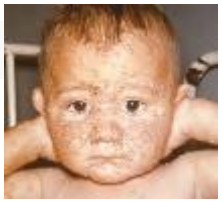


Table 3. Adverse Events That Occurred or Worsened during Receipt of Tecovirimat or Placebo in the Overall Summary Safety Population.

Type of Event*	Placebo (N=90)		Tecovirimat (N=359)		Total (N=449)	
	No. of Participants (%)	No. of Events	No. of Participants (%)	No. of Events	No. of Participants (%)	No. of Events
Any event	30 (33.3)	68	134 (37.3)	318	164 (36.5)	386
Event related to the trial agent	15 (16.7)	32	71 (19.8)	176	86 (19.2)	208
Event leading to discontinuation of trial agent	2 (2.2)	3	6 (1.7)	16	8 (1.8)	19
Serious events and events leading to death	0	0	1 (0.3)†	1	1 (0.2)	1

Messages

- **oral tecovirimat, 600 mg b.i.d. in Humans**
- **PK:** drug exposure > PK targets for treatment of smallpox, based on animal experiments
- **Tolerability** OK (n=359)

Year in ID – Part 1

1. What was hot for viral diseases ?

2. **New strategies to treat ID**

3. Antibiotics flowing from the pipeline

ORIGINAL ARTICLE

Oral versus Intravenous Antibiotics for Bone and Joint Infection

Treatment of complex bone & joint infections

- ✓ Guidelines: surgery + **'at least 2 to 6 weeks of parenteral ATB'**
- ✓ **Hypothesis: highly bioavailable oral antimicrobials may be as good as i.v.**

Pragmatic noninferiority randomized trial (5% noninferiority margin)

- ✓ 26 UK sites, 2010-2015
- ✓ **Prosthetic joint or orthopedic fixation-device infections, osteomyelitis**
- ✓ **Randomization before D7** (post-surgery, or antimicrobials start)
- ✓ **Strategy trial** (i.e. antimicrobials selected by physicians in charge)
- ✓ **Open-label,** but primary outcome (**failure within one year**) categorized by an **end-point committee unaware of trial-group assignment**

Li HK et al. N Engl J Med 2019

ORIGINAL ARTICLE

Oral versus Intravenous Antibiotics for Bone and Joint Infection

Table 1. Baseline Characteristics of the Trial Participants.*

Characteristic	Intravenous Group (N=527)	Oral Group (N=527)	Total (N=1054)
Age — yr			
Median (interquartile range)	61 (49–70)	60 (49–70)	60 (49–70)
Range	18–92	18–91	18–92
Male sex — no. (%)	320 (60.7)	358 (67.9)	678 (64.3)
Baseline surgical procedure — no. (%)			
No implant or device present; débridement of chronic osteomyelitis performed	153 (29.0)	169 (32.1)	322 (30.6)
No implant or device present; débridement of chronic osteomyelitis not performed	25 (4.7)	29 (5.5)	54 (5.1)
Débridement and implant retention	124 (23.5)	123 (23.3)	247 (23.4)
Removal of orthopedic device for infection	89 (16.9)	78 (14.8)	167 (15.8)
Prosthetic joint implant removed	68 (12.9)	67 (12.7)	135 (12.8)
Prosthetic joint implant, one-stage revision	47 (8.9)	43 (8.2)	90 (8.5)

Li HK et al. N Engl J Med 2019

ORIGINAL ARTICLE

Oral versus Intravenous Antibiotics for Bone and Joint Infection

	Intravenous Group (N=527)	Oral Group (N=527)
Organisms identified — no./total no. (%)§		
Staphylococcus aureus	196/500 (39.2)	182/503 (36.2)
Coagulase-negative staphylococcus	137/500 (27.4)	135/503 (26.8)
Streptococcus species	72/500 (14.4)	73/503 (14.5)

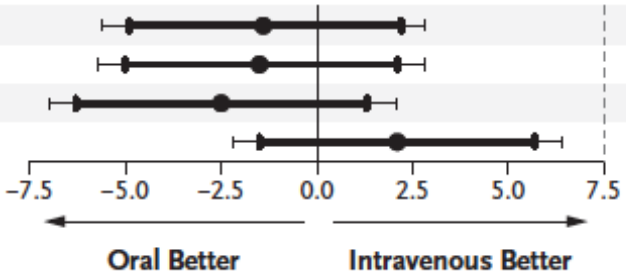
	Participants randomized to IV Antibiotic* (N = 521)	Participants randomized to PO Antibiotic* (N = 523)
Glycopeptides[a] (IV)	214 (41.1%)	22 (4.2%)
Penicillins (IV)	38 (7.3%)	11 (2.1%)
Cephalosporins (IV)	173 (33.2%)	8 (1.5%)
Carbapenems (IV)	41 (7.9%)	5 (1.0%)
Other single IV antibiotic	35 (6.7%)	2 (0.4%)
Combination IV antibiotics	35 (6.7%)	6 (1.1%)
Penicillins (PO)	8 (1.5%)	83 (15.9%)
Quinolones[b] (PO)	33 (6.3%)	191 (36.5%)
Tetracyclines[c] (PO)	4 (0.8%)	57 (10.9%)
Macrolides / Lincosamide [d] (PO)	10 (1.9%)	68 (13.0%)
Other single PO antibiotic (PO)	10 (1.9%)	54 (10.3%)
Combination PO antibiotics (PO)	13 (2.5%)	87 (16.6%)

Li HK et al. N Engl J Med 2019

ORIGINAL ARTICLE

Oral versus Intravenous Antibiotics for Bone and Joint Infection

Subgroup	Oral Group	Intravenous Group	Risk Difference (90% CI; 95% CI)
	patients with treatment failure/ total no. of participants		
Intention-to-treat population	70.0/527	77.3/527	−1.4 (−4.9 to 2.2; −5.6 to 2.9)
Modified intention-to-treat population	67/509	74/506	−1.5 (−5.0 to 2.1; −5.7 to 2.8)
Per-protocol population	61/466	69/443	−2.5 (−6.3 to 1.3; −7.0 to 2.1)
Worst-case sensitivity analysis	85/527	74/527	2.1 (−1.5 to 5.7; −2.2 to 6.4)



Message

- It is safe to switch to oral treatment at D7 for complex bone and joint infections, when susceptible to bioavailable antimicrobial agents

ORIGINAL ARTICLE

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

Left-sided infective endocarditis (IE)

- ✓ European & US Guidelines: **4 to 6 weeks of parenteral ATB**
- ✓ Hypothesis: In **stable patients, shift from i.v. to oral treatment** is safe & effective

Randomized noninferiority trial (10% noninferiority margin)

- ✓ Nationwide study (**Danemark**, 2011-2017)
- ✓ **Prosthetic or native valve, left-sided IE**
- ✓ **Staphylococci, streptococci, or *E. faecalis*** definite IE (Duke)
- ✓ **Randomization if 'stable' after at least 10 days of appropriate i.v. treatment…**
  … and still at least 10 days of IE treatment remaining
- ✓ **Open-label,** but primary outcome (**failure within 6 months**) categorized by an **end-point committee unaware of trial-group assignment**

Iversen K et al. N Engl J Med 2019

ORIGINAL ARTICLE

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

Oral regimens recommended

- ✓ Pre-specified combinations

Methicillin sensitive *Staphylococcus aureus* and coagulase-negative staphylococci

1) Dicloxacillin 1 g x 4 and fusidic acid 0.75 g x 2
2) Dicloxacillin 1 g x 4 and rifampicin 0.6 g x 2
3) Linezolid 0.6 g x 2 and fucidic acid 0.75g x 2
4) Linezolid 0.6 g x 2 and rifampicin 0.6 g x 2

Enterococcus faecalis:

1) Amoxicillin 1 g x 4 and rifampicin 0.6 g x 2
2) Amoxicillin 1 g x 4 and moxifloxacin 0.4 g x 1
3) Linezolid 0.6 g x 2 and rifampicin 0.6 g x 2
4) Linezolid 0.6 g x 2 and moxifloxacin 0.4 g x 1

- ➢ **1954 patients with left-sided IE screened, 400 patients enrolled**

Iversen K et al. N Engl J Med 2019

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

Table 2. Distribution of the Four Components of the Primary Composite Outcome.*

Component	Intravenous Treatment (N=199)	Oral Treatment (N=201)	Difference	Hazard Ratio (95% CI)
	number (percent)		*percentage points (95% CI)*	
All-cause mortality	13 (6.5)	7 (3.5)	3.0 (–1.4 to 7.7)	0.53 (0.21 to 1.32)
Unplanned cardiac surgery	6 (3.0)	6 (3.0)	0 (–3.3 to 3.4)	0.99 (0.32 to 3.07)
Embolic event	3 (1.5)	3 (1.5)	0 (–2.4 to 2.4)	0.97 (0.20 to 4.82)
Relapse of the positive blood culture†	5 (2.5)	5 (2.5)	0 (–3.1 to 3.1)	0.97 (0.28 to 3.33)

Iversen K et al. N Engl J Med 2019

ORIGINAL ARTICLE

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

Message

- It is safe to switch to oral treatment (combination) after D10 for left-sided IE, in stable patients

Iversen K et al. N Engl J Med 2019

ORIGINAL ARTICLE

Procalcitonin-Guided Use of Antibiotics for Lower Respiratory Tract Infection

- ✓ 14 US Hosp.
  - ✓ **high adherence to quality measures** for pneumonia
  - ✓ **Not** PCT users
- ✓ **Step 1: Clinicians trained about**
  - ✓ recommendations for treatment of lower RTI
  - ✓ interpretation of PCT assays
- ✓ **Inclusion (Emergency dept, 2014-2017)**
  - ✓ patients with **suspected lower RTI & physician uncertain whether ATB indicated**
- ✓ **Two arms**
  - ✓ **Treatment guided by PCT results**
  - ✓ **Usual care**

PCT (µg/L)

- If <0.1 => ATB strongly discouraged
- If 0.1-0.25 => ATB discouraged
- If 0.25-0.5 => ATB recommended
- If > 0.5 => ATB strongly recommended

Huang DT et al. N Engl J Med 2018

ORIGINAL ARTICLE

Procalcitonin-Guided Use of Antibiotics for Lower Respiratory Tract Infection

Primary outcome = Antibiotic days by day 30

Table 2. Antibiotic Exposure.*

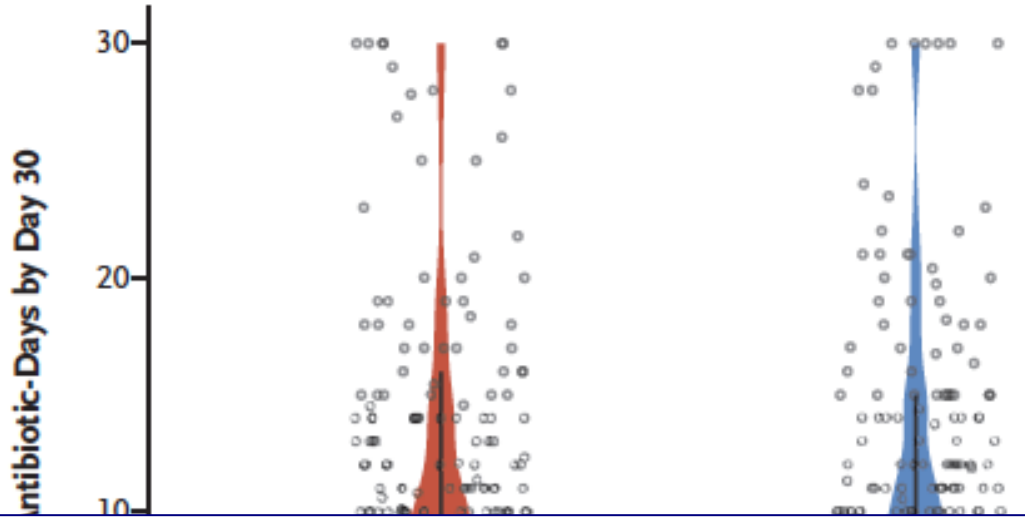
Outcome	Procalcitonin (N=826)	Usual Care (N=830)	Difference (95% or 99.86% CI)†
Intention-to-treat population‡			
Antibiotic-days by day 30§	4.2±5.8	4.3±5.6	−0.05 (−0.6 to 0.5)
Received any antibiotics by day 30 — estimated no. (%)¶	471 (57.0)	513 (61.8)	−4.8 (−12.7 to 3.0)
Antibiotic prescription in ED — estimated no. (%)¶‖	282 (34.1)	321 (38.7)	−4.6 (−12.2 to 3.0)
Antibiotic-days during hospital stay	2.6±3.3	2.7±3.0	−0.1 (−0.8 to 0.6)
Hospital length of stay — days	5.0±4.4	4.7±3.5	0.3 (−0.2 to 0.9)
Per-protocol population**			
No. of patients	696	830	
Antibiotic-days by day 30	4.2±5.7	4.3±5.7	−0.1 (−0.7 to 0.6)

NB. Adverse outcomes similar in both arms (P <0.0001 for noninferiority)

Huang DT et al. N Engl J Med 2018

ORIGINAL ARTICLE

Procalcitonin-Guided Use of Antibiotics for Lower Respiratory Tract Infection

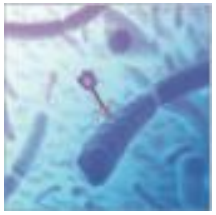


Message

- For well-trained physicians, rapid access to PCT assays does not reduce the use of antibiotics for suspected lower RTI in the emergency department

Huang DT et al. N Engl J Med 2018

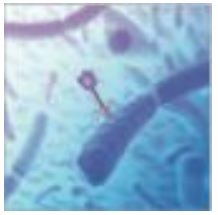
Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by *Pseudomonas aeruginosa* (PhagoBurn): a randomised, controlled, double-blind phase 1/2 trial

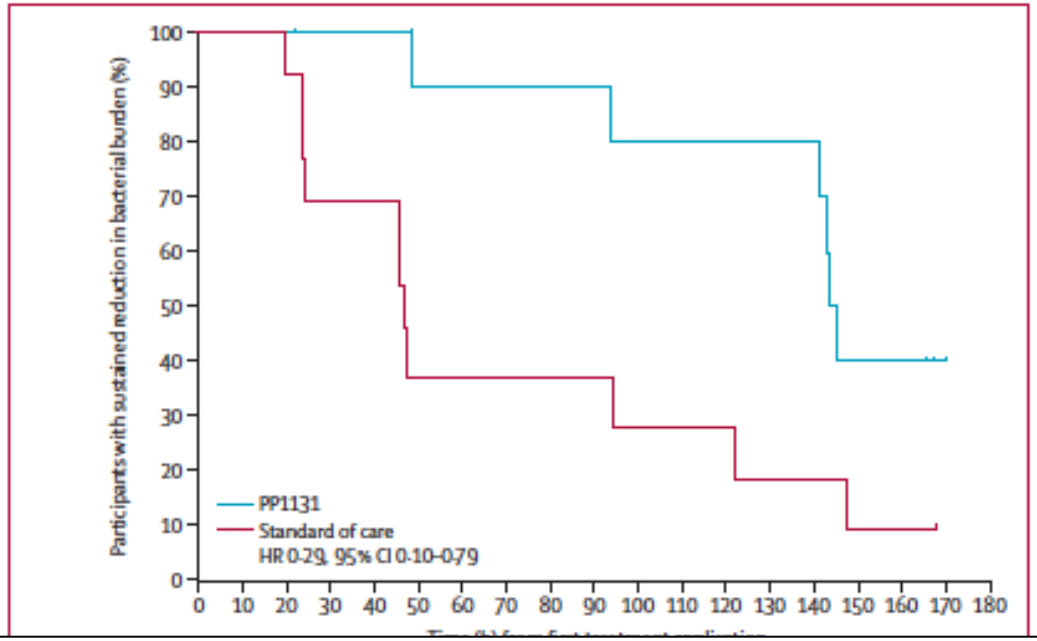


- ✓ **First multicentric, international, RCT on phages**
- ✓ **Nine burn centers (France, Belgium), 2015-2017**
- ✓ Inclusion: patients with **burn wounds clinically infected, *P. aeruginosa***
- ✓ ***Randomization (double-blind)=> 1/d, x 7 days***
  - ✓ ***cocktail of 12 natural lytic anti-P. aeruginosa phages (***10^6 PFU/mL, PP1131)
  - ✓ standard of care = 1% sulfadiazine silver emulsion cream
- ✓ **Primary criteria = microbiologic** (sustained reduction in bacterial burden)
- ✓ **Planned enrolment = 125 patients**

Jault P et al. Lancet Infect Dis 2018

Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by *Pseudomonas aeruginosa* (PhagoBurn): a randomised, controlled, double-blind phase 1/2 trial





Messages

- **Phages efficacy will be complicated to assess**
- RCT on phages are feasible **(& required !)**

Jault P et al. Lancet Infect Dis 2018

ORIGINAL ARTICLE

Azithromycin to Reduce Childhood Mortality in Sub-Saharan Africa



- ✓ **Background**
  - ✓ **Trachoma-control** programs include **mass distribution of azithromycin**
  - ✓ Azithromycin may also **reduce incidence** of **malaria, infectious diarrhea & CAP**
- ✓ **Cluster-randomized trial in Malawi, Niger, and Tanzania** (2014-2017)
  - ✓ Unit of randomization = communities
  - ✓ **Twice yearly mass distributions of azithro (20 mg/kg),** or placebo
- ✓ **Target = children, 1-59 months (n = 190,000)**
- ✓ **Primary criteria = all-cause mortality**

Keenan JD et al. N Engl J Med 2018

ORIGINAL ARTICLE

Azithromycin to Reduce Childhood Mortality in Sub-Saharan Africa



Messages

- **Mass distribution of azithromycin** in children 1-59 months **reduced mortality by 15%** in 3 Sub-Saharan Africa countries
- **Especially**
  - **In young infants (<6 months)**
  - **In countries with highest child mortality (Niger)**
- **Comments**
  - **Causes of death (verbal autopsy): malaria (41%),** diarrhea (18%), and pneumonia (12%)
  - **The effect gradually increased, from 7% (Months 0-6) to 22% (Month 18-24)**
  - **Emergence of macrolide resistance (*S. pneumoniae, E. coli*)**

  => Sustainability ??

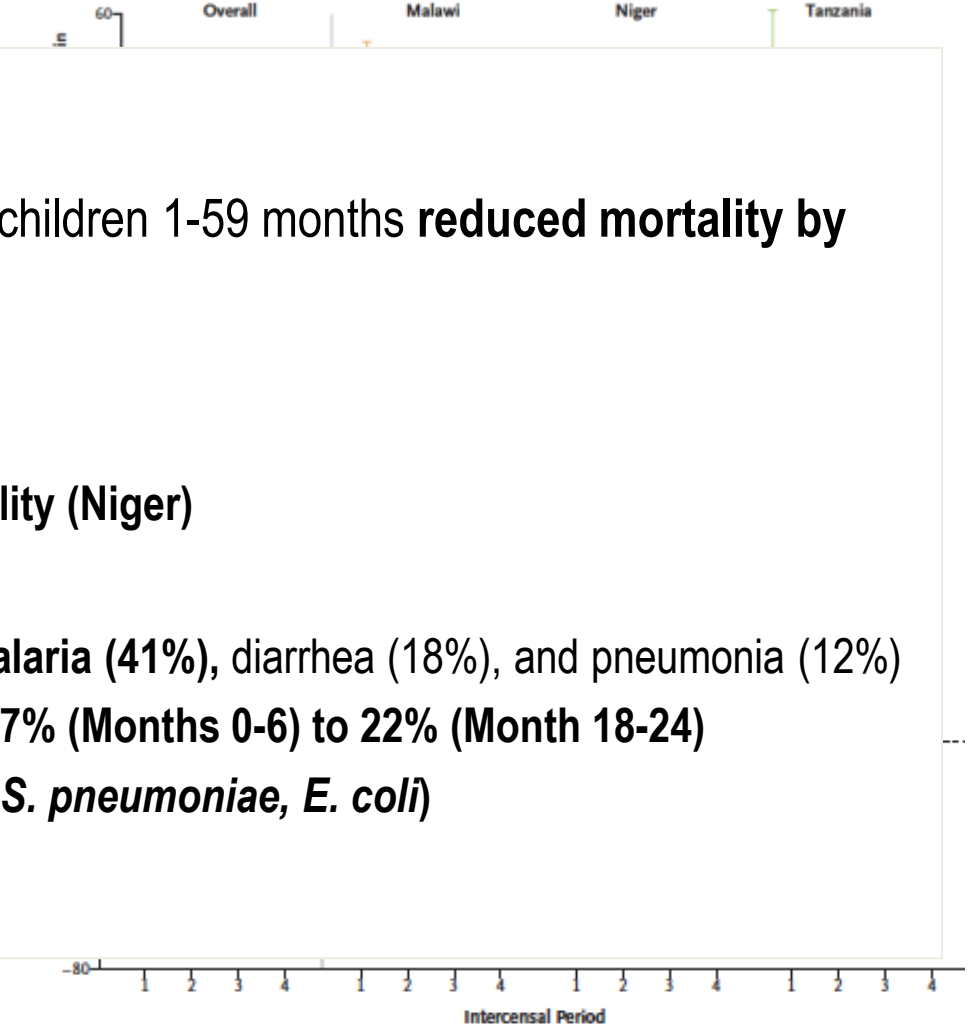


Figure 4. Efficacy of Azithromycin over Time.

Antibiotic prescription for febrile children in European emergency departments: a cross-sectional, observational study

To quantify & explain variability in ATB prescription in European paediatric emergency departments

- Observational study of febrile children attending ED depts (n=28, 11 countries)
- One random sampling day/month, 2014-2016 => 5177 children

	Proportion of children prescribed antibiotics	Proportion of prescriptions for second-line antibiotics
Total population	1454/4560 (32%)	893/1454 (61%)
Per country		
Turkey	450/708 (64%)	363/450 (81%)
UK	57/145 (39%)	45/57 (79%)
Hungary	41/111 (37%)	29/41 (71%)
Italy	149/446 (33%)	120/149 (81%)
Romania	87/282 (31%)	81/87 (93%)
Spain	161/631 (26%)	68/161 (42%)
Portugal	177/698 (25%)	56/177 (32%)
Denmark	6/24 (25%)	2/6 (33%)
France	208/926 (22%)	70/208 (34%)
Netherlands	37/161 (23%)	18/37 (49%)
Switzerland	81/428 (19%)	41/81 (51%)

van de Maat J et al. Lancet Infect Dis 2019

Antibiotic prescription for febrile children in European emergency departments: a cross-sectional, observational study

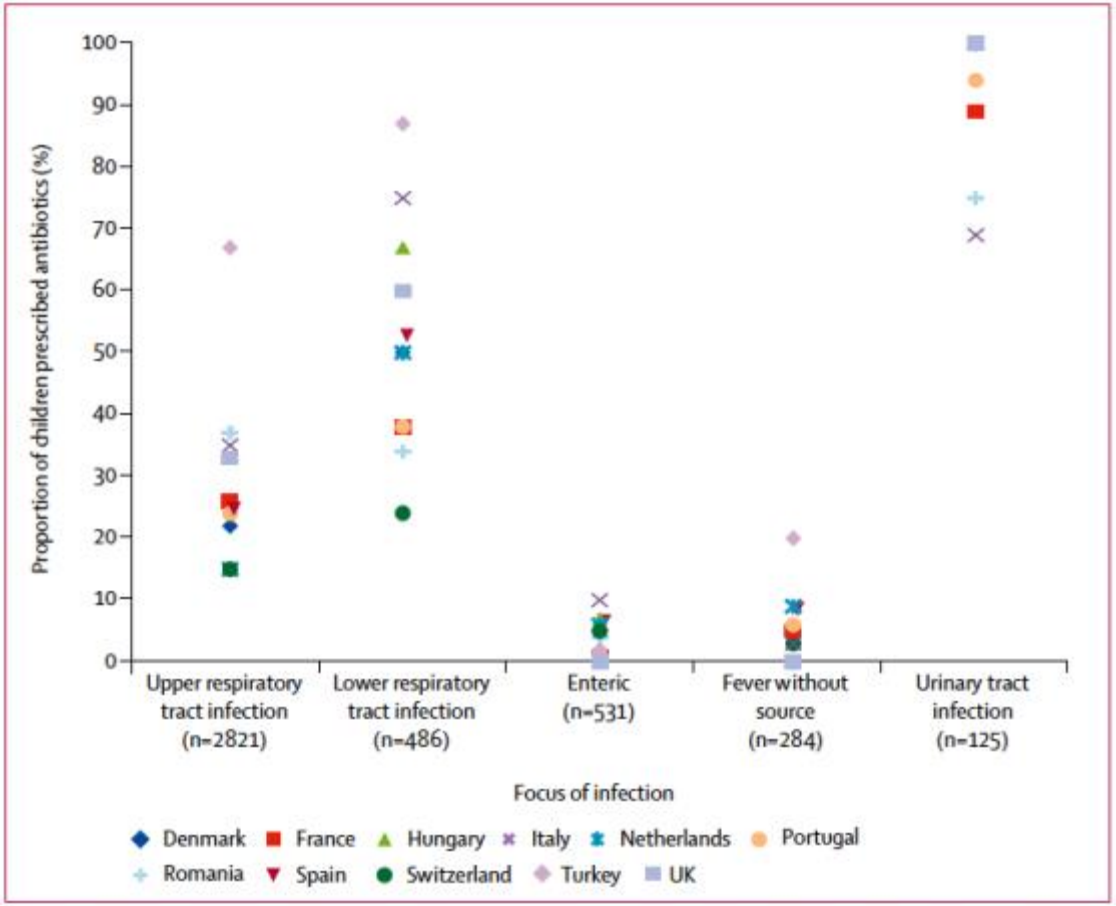


Figure 3: Variability in antibiotic prescription across countries for the most frequent foci of infection in 4560 children without comorbidities

Message. The high variability of ATB use in European ED

van de Maat J et al. Lancet Infect Dis 2019

Year in ID – Part 1

1. What was hot for viral diseases ?

2. New strategies to treat ID

3. **Antibiotics flowing from the pipeline (n=3)**

Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial

- **Cefiderocol**
  - **Siderophore cephalosporin**
  - Broad activity against **Enterobacteriaceae**, and **non-fermenting bacteria, including carbapenem-resistant strains**

- **Inclusion: Complicated UTI** or **non-complicated pyelonephritis** (>18 y)
  - *Arm 1*: Cefiderocol, 2 g (1 h i.v.), x 3/d x 7-14 days
  - *Arm 2*: Imipenem-cilastatin, 1 g x 3/d x 7-14 days

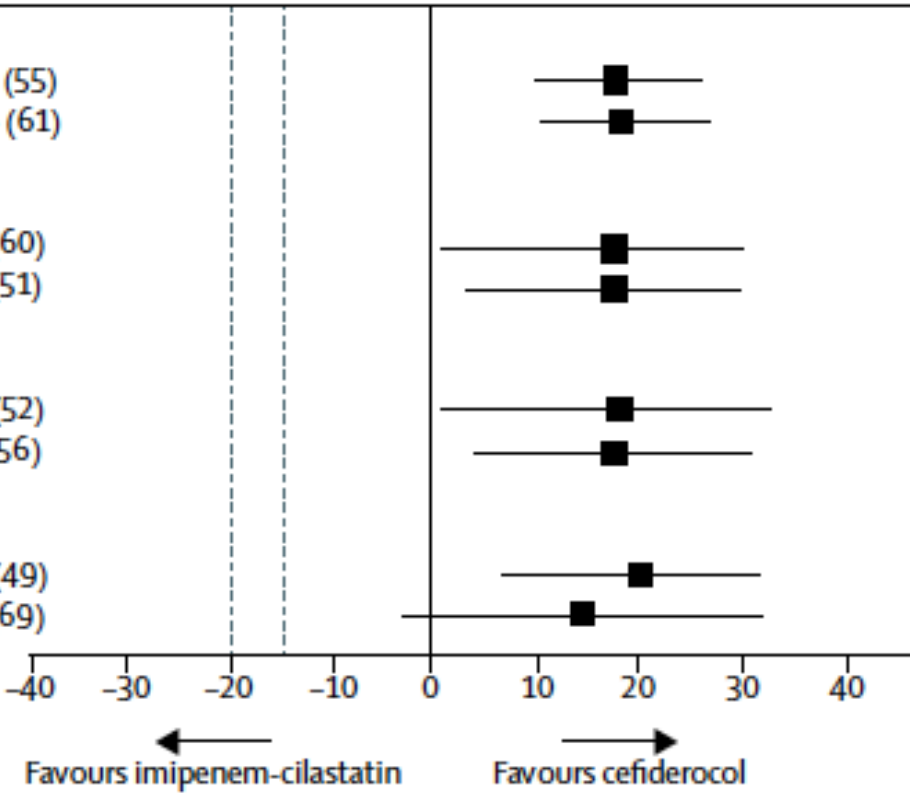
- **2015-2016, 67 sites (15 countries)**

- **Primary criteria,** test of cure (D7 post-treatment) clinical + microbiological

Portsmouth S et al. Lancet Infect Dis 2018

Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial

	n/N (%)	
	Cefiderocol	Imipenem-cilastatin
Analysis population		
mITT population	183/252 (73)	65/119 (55)
Microbiologically evaluable population	182/228 (80)	65/106 (61)
Age, years		
<65	87/113 (77)	32/54 (60)
≥65	96/139 (69)	33/65 (51)
Sex		
Men	84/119 (71)	25/48 (52)
Women	99/133 (74)	40/71 (56)
Clinical diagnosis		
cUTI with or without pyelonephritis	129/187 (69)	41/84 (49)
Acute uncomplicated pyelonephritis	54/65 (83)	24/35 (69)



Portsmouth S et al. Lancet Infect Dis 2018

Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial

Messages

- **Cefiderocol efficacy & tolerability OK (n=303)**
- **50% males, 50% pyelonephritis, mortality < 1%**

NB. For *P. aeruginosa,* success rates 47% (7/15) for cefiderocol, vs. 50% (2/4) for imipenem

Portsmouth S et al. Lancet Infect Dis 2018

Single-Dose Zoliflodacin (ETX0914) for Treatment of Urogenital Gonorrhea

- **Gonorrhea, emerging**
  - **Incidence & resistance**

- **Zoliflodacin**
  - **A new class** (spiropyrimidine-trione **inhibits DNA synthesis)**
  - Active against **ciprofloxacin-resistant & ceftriaxone-resistant** *N. gonorrhae*

- **Uncomplicated** urogenital gonorrhea, 2014-15, sexual health clinics (US)
  - *Arm 1:* **Zoliflodacin, single oral dose, 2 or 3 g**
  - *Arm 2:* **Ceftriaxone, single i.m. dose, 500 mg**

- **Open-label, primary criteria,** TOC (D6±2), microbiological

Taylor N et al. New Engl J Med 2018

Single-Dose Zoliflodacin (ETX0914) for Treatment of Urogenital Gonorrhea

Messages

- **A promising new drug for urogenital gonorrhea**
  (new class, single oral dose…)

- Concerns about **lower efficacy on pharyngeal carriage** (public health issue)

Taylor N et al. New Engl J Med 2018

ORIGINAL ARTICLE

Once-Daily Plazomicin for Complicated Urinary Tract Infections

- **Plazomicin**
  - Aminoglycoside with **bactericidal** activity against **MDR (including carbapenem-resistant) Enterobacteriaceae**
- **Inclusion:** Complicated UTI, including pyelonephritis (adults)
  - *Arm 1:* Plazomicin, 15 mg/kg o.d. x 7-10 days
  - *Arm 2*: Meropenem, 1 g x 3/d x 7-10 days

  Optional oral step-down after D4
- **2016, 68 sites (North America & Europe)**
- **Primary criteria,** D5 & D15-19 post-treatment, clinical + microbiological

Wagenlehner FME et al. New Engl J Med 2019

Once-Daily Plazomicin for Complicated Urinary Tract Infections

Subgroup	Meropenem	Plazomicin	Percentage-Point Difference (95% CI)
	no. of patients with composite cure/no. of patients (%)		
Overall	138/197 (70.1)	156/191 (81.7)	11.6 (2.7 to 20.3)
Diagnosis at baseline			
Complicated UTI	82/119 (68.9)	84/107 (78.5)	9.6 (–2.6 to 21.3)
Acute pyelonephritis	56/78 (71.8)	72/84 (85.7)	13.9 (0.4 to 27.1)
Presence of bacteremia	13/23 (56.5)	18/25 (72.0)	15.5 (–13.7 to 41.9)
Treatment received			
Intravenous only	28/46 (60.9)	29/37 (78.4)	17.5 (–4.3 to 36.6)
Intravenous plus oral	110/151 (72.8)	127/154 (82.5)	9.6 (–0.2 to 19.3)
Catheter			
Present	15/29 (51.7)	18/29 (62.1)	10.3 (–16.6 to 35.5)
Absent	123/168 (73.2)	138/162 (85.2)	12.0 (2.8 to 20.9)
Age			
<65 yr	68/95 (71.6)	90/101 (89.1)	17.5 (5.7 to 29.0)
≥65 yr	70/102 (68.6)	66/90 (73.3)	4.7 (–8.9 to 17.9)
Sex			
Male	68/99 (68.7)	65/84 (77.4)	8.7 (–5.1 to 21.7)
Female	70/98 (71.4)	91/107 (85.0)	13.6 (1.6 to 25.4)
Creatinine clearance			
≤60 ml/min	49/74 (66.2)	43/61 (70.5)	4.3 (–12.5 to 20.3)
>60 ml/min	87/120 (72.5)	112/127 (88.2)	15.7 (5.2 to 25.9)

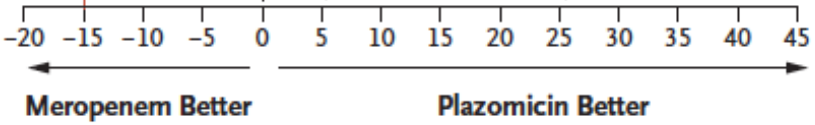


Figure 1. Composite Cure at the Test-of-Cure Visit, According to Patient Subgroups in the Microbiologic Modified Intention-to-Treat Population.

CORRESPONDENCE

Plazomicin for Infections Caused by Carbapenem-Resistant Enterobacteriaceae

Messages

Promising drug for treatment of **Carbapenemase-producing Enterobacteriae (CPE)**

Pending post-marketting data on clinical/microbiological efficacy…

	Days						
No. at Risk							
Plazomicin	17	16	16	15	12	11	9
Colistin	20	18	16	11	9	8	7

No. of Patients with Increase/ Total No. of Patients	2/12	8/16

McKinnell JA et al. New Engl J Med 2019

See you next year !

ECCMID

ESCMID

30th ECCMID, Paris

18-21, April, 2020