Do This, Don’t Do That

Infectious Diseases Edition

DATE: SEPTEMBER 2022 PRESENTED BY: ERIN BONURA, MD, MCR

Objectives for the next 30 min

- By the end of this session, the audience will be able to state
  - State the key indicators for complicated staphylococcus aureus bacteremia (SAB)
  - Identify the oral treatment options for SAB
  - State the indications for dalbavancin
  - State the epidemiology of hMPXV and identify the errors in messaging.

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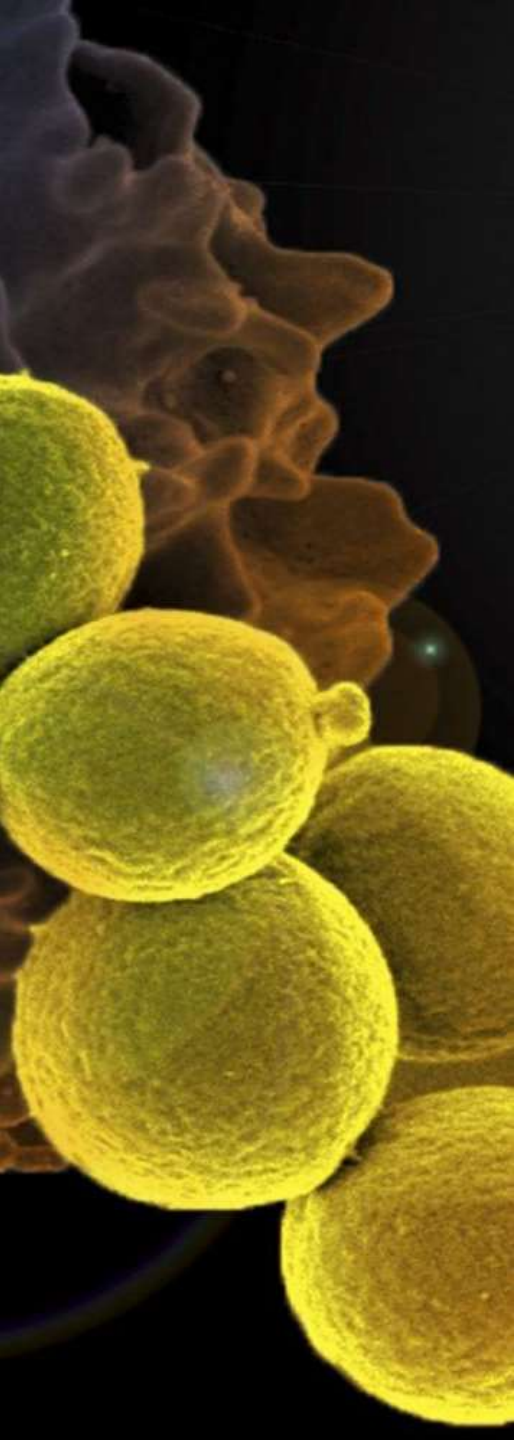

Question 1: Sam Adams

Mr. SA is a 64 year old man with diabetes who presents with fevers, chills, and generally feeling unwell. His exam is remarkable for a temp of 38.4 C, HR 98, BP 160/84, RR 16 PO2 98%RA. He appears unwell but not toxic. Only notable exam finding is a II/VI murmur that he says is old. Blood cultures are obtained and grown MSSA the next day. He is placed on Cefazolin and defervesce on day 2. Cultures at 48 hours are positive but negative at 96.

Which of the following is most correct?

a) The patient should be treated for 2 weeks

b) The patient should have a TEE

c) The most predictive indicator is lack of fever at 72 hours

d) The patient should be treated with Nafcillin instead

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~COMPLICATED~

ORIGINAL INVESTIGATION

Clinical Identifiers of Complicated *Staphylococcus aureus* Bacteremia

Vance G. Fowler, Jr, MD, MHS; Maren K. Olsen, PhD; G. Ralph Corey, MD; Christopher W. Woods, MD, MPH; Christopher H. Cabell, MD; L. Barth Reller, MD; Allen C. Cheng, MB, BS; Tara Dudley, MS; Eugene Z. Oddone, MD, MHS

- Prospective observational cohort 1994-99
- 724 patients with *S.aureus* bacteremia

Arch Intern Med. 2003;163:2066-72

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Predictors of SAB

Table 4. Reduced Prognostic Model of Complicated *Staphylococcus aureus* Bacteremia*

Variable	Odds Ratio (95% Confidence Interval)	*P* Value
Community acquired†	3.10 (1.96-4.87)	<.001
Skin examination findings suggesting the presence of acute systemic infection	2.04 (1.30-3.18)	.002
Positive follow-up blood culture result‡	5.58 (3.93-7.95)	<.001
Persistent fever at 72 h	2.23 (1.55-3.12)	<.001

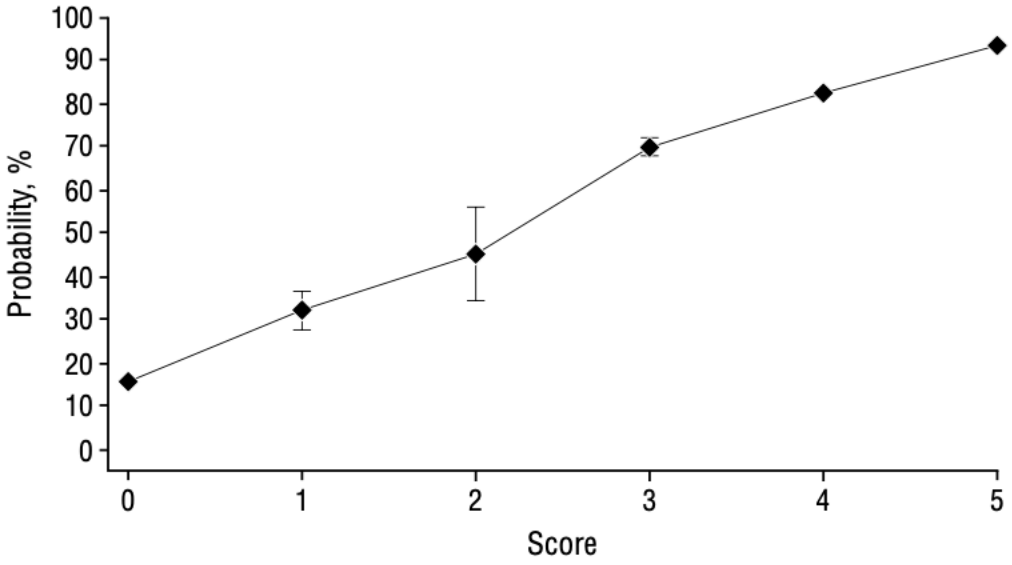

Table 3. Predictors of Complicated *Staphylococcus aureus* Bacteremia*

iable	Odds Ratio (95% CI)	*P* Value
nographic characteristics		
urgical hospital service†	1.83 (1.18-2.82)	.006
ommunity acquired‡	3.08 (1.80-5.28)	<.001
rthopedic or other prosthetic device	1.77 (1.01-3.11)	.05
ardiac device	1.70 (0.82-3.51)	.16
ex	0.84 (0.58-1.22)	.37
IV positive or injection drug use	1.89 (0.92-3.86)	.09
ge	1.01 (1.00-1.02)	.05
iabetes mellitus	1.10 (0.74-1.64)	.62
lace	1.15 (0.76-1.72)	.51
icators of existing complications		
kin examination findings suggesting the presence of acute systemic infection	1.80 (1.10-2.95)	.02
ew or diastolic murmur	2.46 (1.01-6.02)	.05
linical evidence of embolic/autoimmune events	2.05 (0.85-4.95)	.11
linical evidence of central nervous system involvement	1.30 (0.74-2.30)	.36
eported duration of symptoms	1.04 (1.00-1.08)	.06
eptic shock	1.22 (0.77-1.94)	.40
ersistent fever at 72 h	2.00 (1.36-2.92)	<.001
ositive follow-up blood culture result	4.94 (3.37-7.25)	<.001
tment-related variables		
ancomycin therapy	1.16 (0.78-1.74)	.46
minoglycoside use	1.42 (0.78-2.59)	.25
ifampin use	0.87 (0.50-1.50)	.62
ppropriate empiric antibiotic therapy	0.80 (0.44-1.46)	.46
orticosteroid use	1.63 (0.96-2.77)	.07
emovable source of *S aureus* bacteremia not removed	1.23 (0.69-2.20)	.49

SUPPLEMENT ARTICLE

Staphylococcus aureus Bloodstream Infections: Definitions and Treatment

G. Ralph Corey
Duke University Medical Center, Durham, North Carolina

This supplement is based on the proceedings of a Novartis-sponsored session at the 9th International Symposium of Modern Concepts in Endocarditis and Cardiovascular Infections, June 2007; for sponsorship details, see p. S258.

- **Uncomplicated = negative follow up cultures, defervescence in 72 hours, normal TEE, no prosthetic material (joints, IV), no symptoms of metastatic disease**
- **Catheter associated… variable**
- **Clinical Infectious Diseases 2009; 48:S254–9**

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Do This

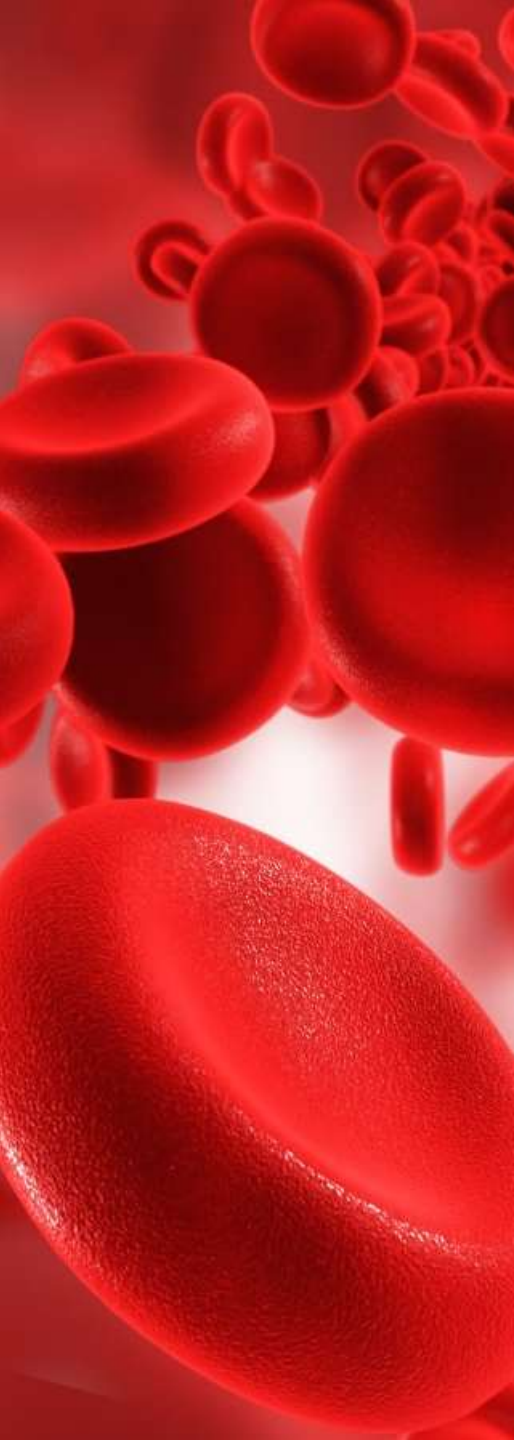
- Check for metastatic sites of infection and prosthetic material
- Note the date of defervescence
- Get daily cultures initially
- Order a TTE
- Treat at least 2 weeks

Don't Do That

- Don't treat SAB <2 weeks
- Don't disregard aches/Pains
- Don't demand TEE

Ok, we are going to treat a LONG time…

But, do we have to use IV?



Question 2: Igor Villanueva

“ Mr. IV is 42 year old man with obesity who presents with pain in his right leg. He states it started 3 days ago and has progressively gotten more warm and red. On exam he has a temperature of 38C, HR 88, BP 142/68, RR 14 and pO2 10% RA. His RLE is erythematous from ankle to tibial tuberosity with pain upon palpation. No bullae noted, no purulence. Cultures are dawn and he is started on vancomycin. The next day cultures return for MRSA. Repeat cultures at 48 hours are negative and the patient slowly improves. ”

What would you suggest?

A. Treat with cefazolin x 2 weeks
B. Treat with vancomycin x 4 weeks.
C. Treat with linezolid x 2 weeks
D. Treat with clindamycin x 4 weeks.

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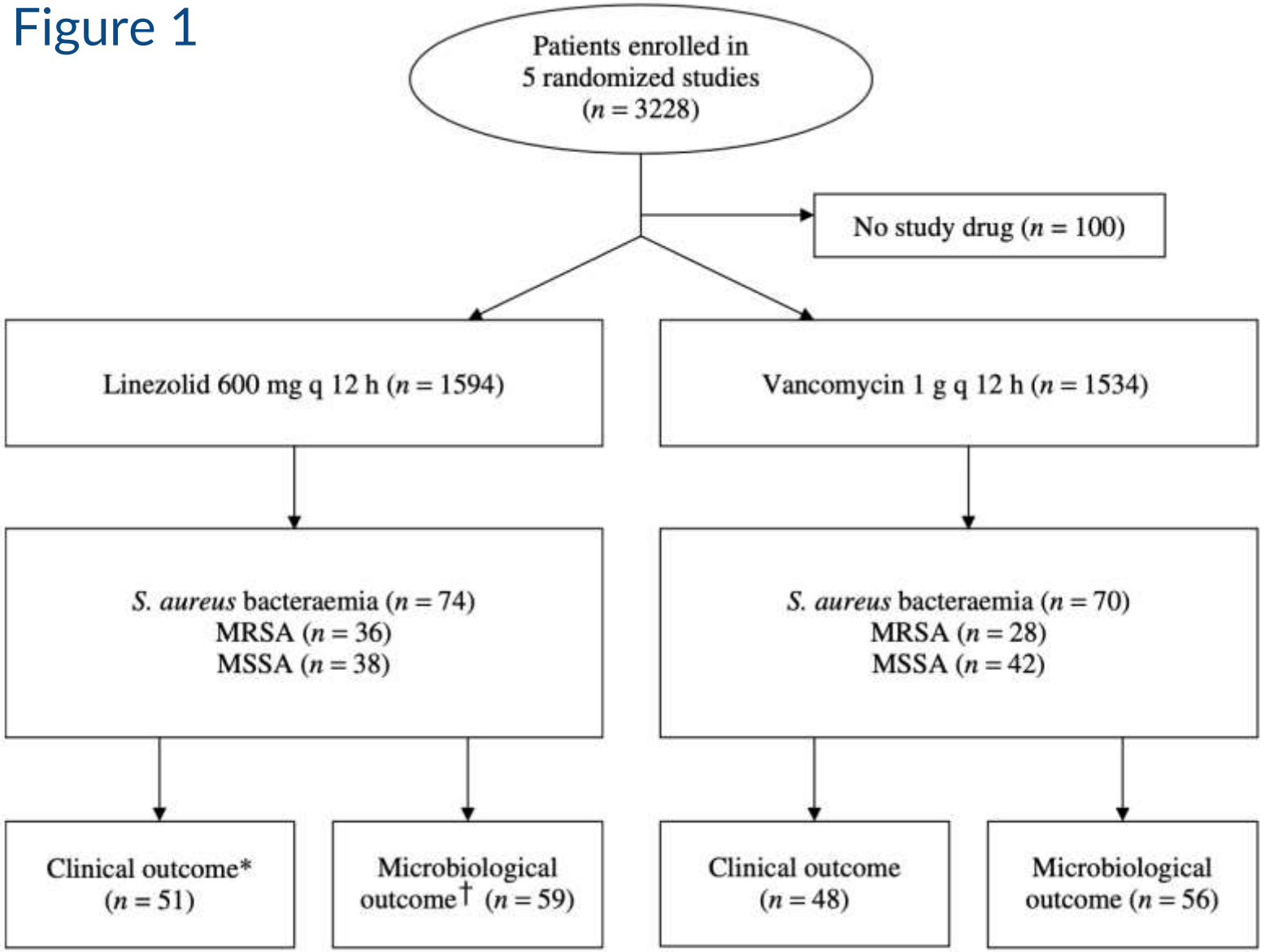
Figure 1



Journal of Antimicrobial Chemotherapy (2005) 56, 923–929

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Table 1

Characteristics	Number of patients (%), unless otherwise stated: linezolid (n = 74)	vancomycin (n = 70)	P value[a]
Age			
mean ± SD, years	63.5 ± 17.1	59.3 ± 18.9	0.163
<65 years	29 (39.2)	39 (55.7)	0.047
Sex, men	51 (68.9)	41 (58.6)	0.196
APACHE II score available	41 (55.4)	41 (58.6)	0.915
APACHE II score (mean ± SD)	13.9 ± 6.8	14.1 ± 7.5	0.915
Mechanical ventilation	25 (33.8)	26 (37.1)	0.660
Comorbidities			
congestive heart failure	12 (16.2)	13 (18.6)	0.709
diabetes	26 (35.1)	19 (27.1)	0.301
malignancy, active	13 (17.6)	7 (10.0)	0.189
renal insufficiency (creatinine > 1.5 mg/dL)	32 (43.2)	22 (31.4)	0.155
Primary infection			0.924
pneumonia	33 (44.6)	27 (38.6)	
skin and soft tissue infection	22 (29.7)	21 (30.0)	
bacteraemia	8 (10.8)	8 (11.4)	
urinary tract infection	1 (1.4)	1 (1.4)	
other, not specified	10 (13.5)	13 (18.6)	
MRSA infection	36 (48.6)	37 (52.9)	0.614
Duration of therapy (days) (mean ± SD)			
intravenous therapy	8.6 ± 5.5	11.7 ± 6.8	0.004
intravenous and oral therapy	12.1 ± 6.5	11.7 ± 6.8	0.666

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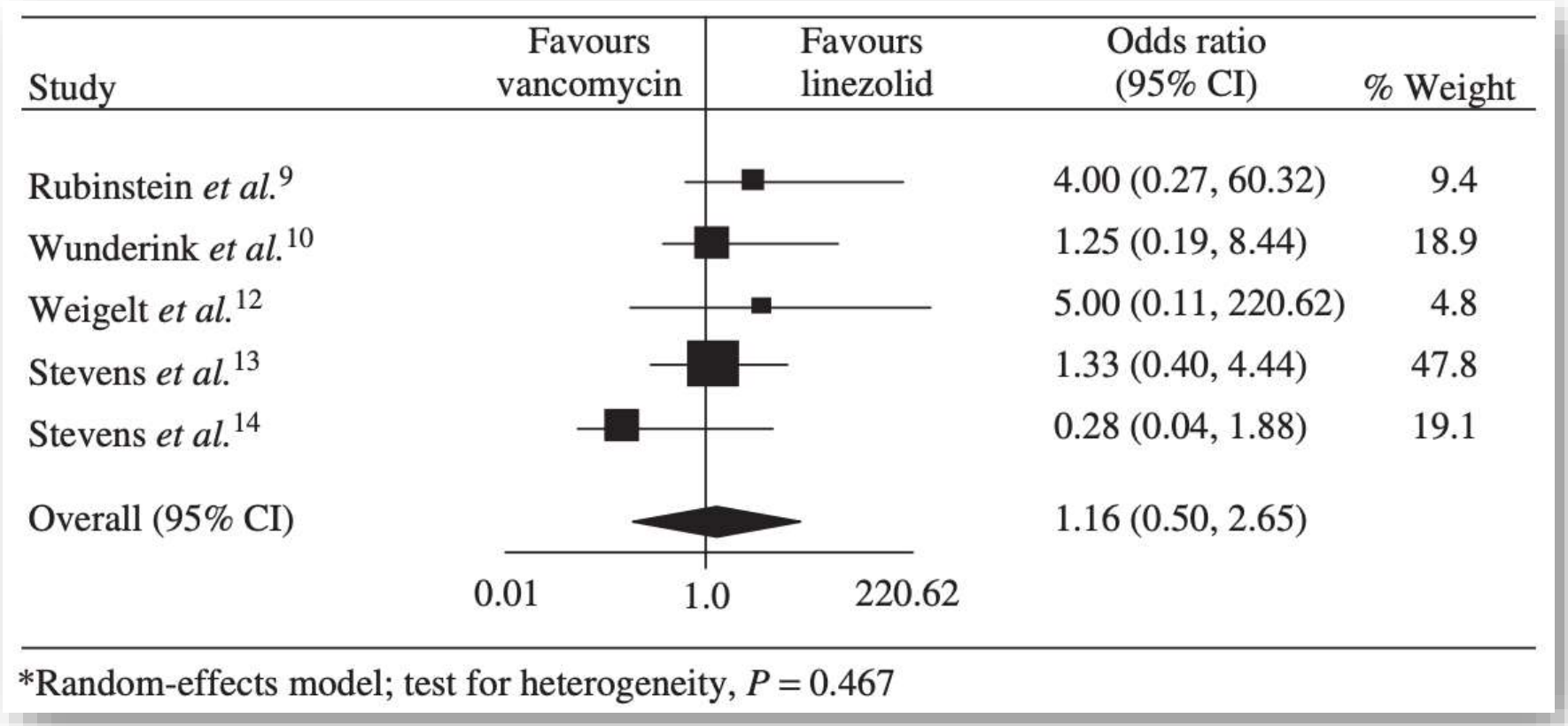
Figure 2


Study
Favours vancomycin
Favours linezolid
Odds ratio (95% CI)
% Weight
Rubinstein et al.[9]
4.00 (0.27, 60.32)
9.4
Wunderink et al.[10]
1.25 (0.19, 8.44)
18.9
Weigelt et al.[12]
5.00 (0.11, 220.62)
4.8
Stevens et al.[13]
1.33 (0.40, 4.44)
47.8
Stevens et al.[14]
0.28 (0.04, 1.88)
19.1
Overall (95% CI)
1.16 (0.50, 2.65)
0.01
1.0
220.62
*Random-effects model; test for heterogeneity, P = 0.467

MAJOR ARTICLE

Linezolid in Methicillin-Resistant *Staphylococcus aureus* Nosocomial Pneumonia: A Randomized, Controlled Study

Richard G. Wunderink,[1] Michael S. Niederman,[2] Marin H. Kollef,[3] Andrew F. Shorr,[4] Mark J. Kunkel,[5] Alice Baruch,[5,a] William T. McGee,[6] Arlene Reisman,[5] and Jean Chastre[7]

- Efficacy and safety of Linezolid vs Vanc vs Teicoplanin
- 1184 patients
- 57.6% (Lin) vs 46.6% (vanc) clinical success (p=0.042)
- All cause mortality 15.7% vs 17%
- **Bacteremia 5.2% vs 10.8% all = microbiologic cure**

Clinical Infectious Diseases 2012;54(5):621–9

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Clinical Infectious Diseases

MAJOR ARTICLE

Early Oral Switch to Linezolid for Low-risk Patients With *Staphylococcus aureus* Bloodstream Infections: A Propensity-matched Cohort Study

Rein Willekens,[1,2] Mireia Puig-Asensio,[1,2] Isabel Ruiz-Camps,[1,2] Maria N. Larrosa,[3] Juan J. González-López,[3] Dolors Rodríguez-Pardo,[1,2] Nuria Fernández-Hidalgo,[1,2] Carles Pigrau,[1,2] and Benito Almirante[1,2]

[1]Department of Infectious Diseases, Hospital Universitari Vall d'Hebron, [2]Department of Medicine, Universitat Autònoma de Barcelona, and [3]Department of Microbiology, Hospital Universitari Vall d'Hebron, Barcelona, Spain

- Prospective cohort, 2013-17, 152 patients in Spain
- Uncomplicated SAB, no bone/joint infections
- Standard vs Linezolid (days 3-9)

Clinical Infectious Diseases 2019;69(3):381–7

Linezolid vs SPT Outcomes

Whole Cohort				Propensity Score-matched Cohort		
Outcome	**Linezolid (n=45)**	**SPT (n=107)**	**P Value**	**Linezolid (n=45)**	**SPT (n=90)**	**P Value**
90d relapse	1 (2.2)	4 (3.7)	1	1 (2.2)	4 (4.4)	.87
14d mortality	0	10 (9.3)	.08	0	6 (6.7)	.18
30d mortality	1 (2.2)	17 (15.9)	.04	1 (2.2)	12 (13.3)	.08
LOS	8 (7-10)	19 (15-32)	<.01	8 (7-10)	19 (15-30)	<.01

Clinical Infectious Diseases 2019;69(3):381–7

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 31, 2019 VOL. 380 NO. 5

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

- Randomized, non-inferiority, multicenter trial
- 400 patients with left-sided endocarditis
- *Streptococci (49%), E.faecalis (24%),* ***S.aureus (21%)***, or CONS (6%)

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POET Results

Component	Intravenous N=199	Oral N=201	Hazard Ratio
All-cause mortality	13 (6.5)	7 (3.5)	0.53 (0.21-1.32)
Unplanned Cardiac surgery	6 (3)	6 (3)	0.99 (0.32-3.07)
Embolic event	3 (1.5)	3 (1.5)	0.97 (0.2-4.82)
Relapse bacteremia	5 (2.5)	5 (2.5)	0.97 (0.28-3.33)

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POET Regimens

PSSA	MSSA
Amox 1g x 4 + fusidic acid	Diclox 1g x 4 + fusidic acid
Amox 1gx4 + rifampicin BID	Diclox 1g x 4 + rifampicin
Linezolid BID + Fusidic acid	Linezolid BID + fusidic acid
Linezolid BID + rifampicin BID	Linezolid BID + rifampicin

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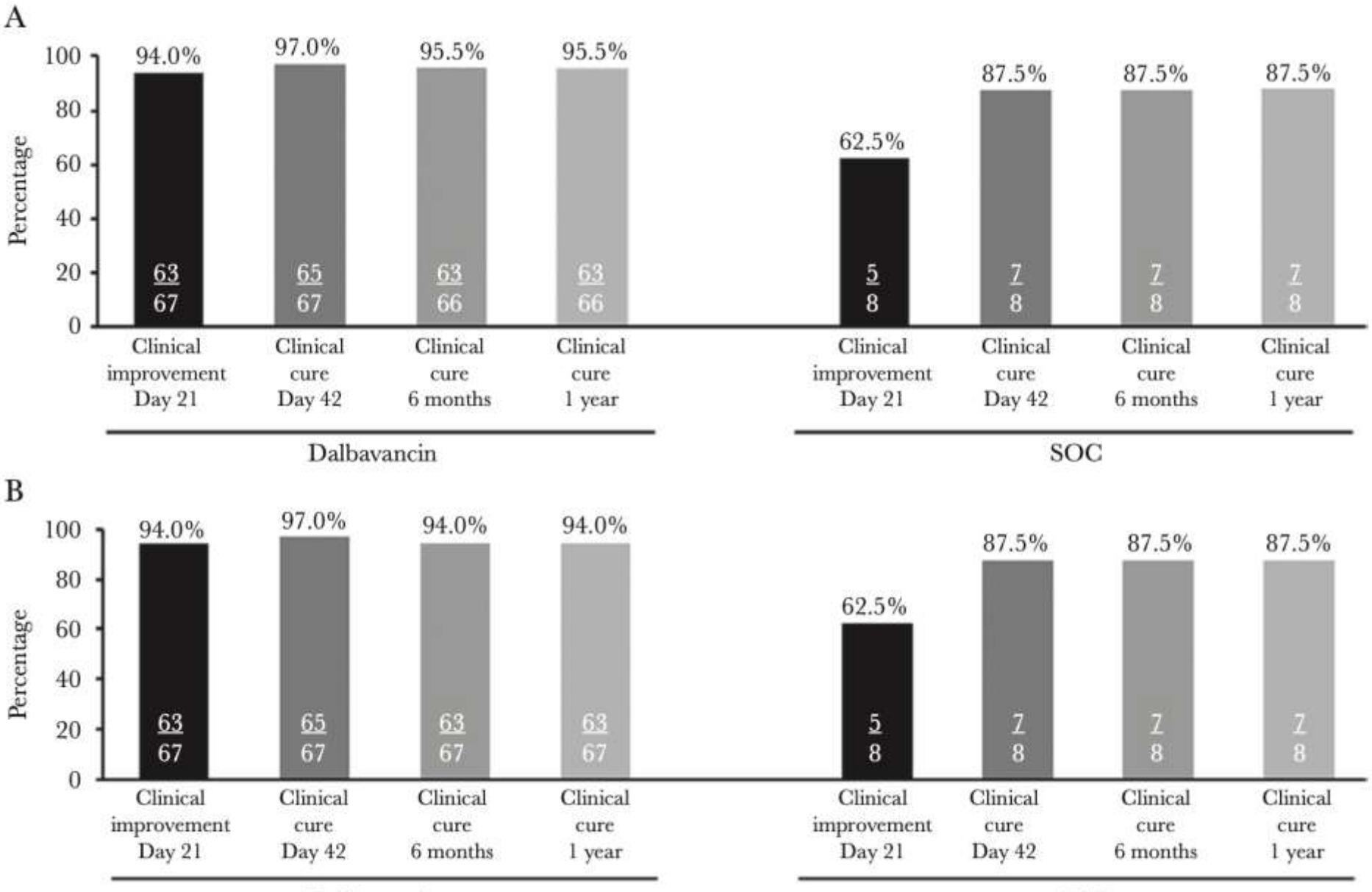
“Ok, so how about Dalbavancin”

Dalbavancin in Osteomyelitis



STUDY PROTOCOL Open Access

Dalbavancin as an option for treatment of *S. aureus* bacteremia (DOTS): study protocol for a phase 2b, multicenter, randomized, open-label clinical trial

Nicholas A. Turner[1], Smitha Zaharoff[2], Heather King[3,4], Scott Evans[5], Toshimitsu Hamasaki[5], Thomas Lodise[6], Varduhi Ghazaryan[7], Tatiana Beresnev[7], Todd Riccobene[8], Rinal Patel[8], Sarah B. Doernberg[9], Urania Rappo[10], Vance G. Fowler Jr[1], Thomas L. Holland[1*] and on behalf of the Antibacterial Resistance Leadership Group (ARLG)

- 200 adults with SAB including R sided IE!
- On effective therapy 3-10 days and CLEARANCE
- Desirability of Outcome Ranking (DOOR) at Day 70 of dalbavancin

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DOTS

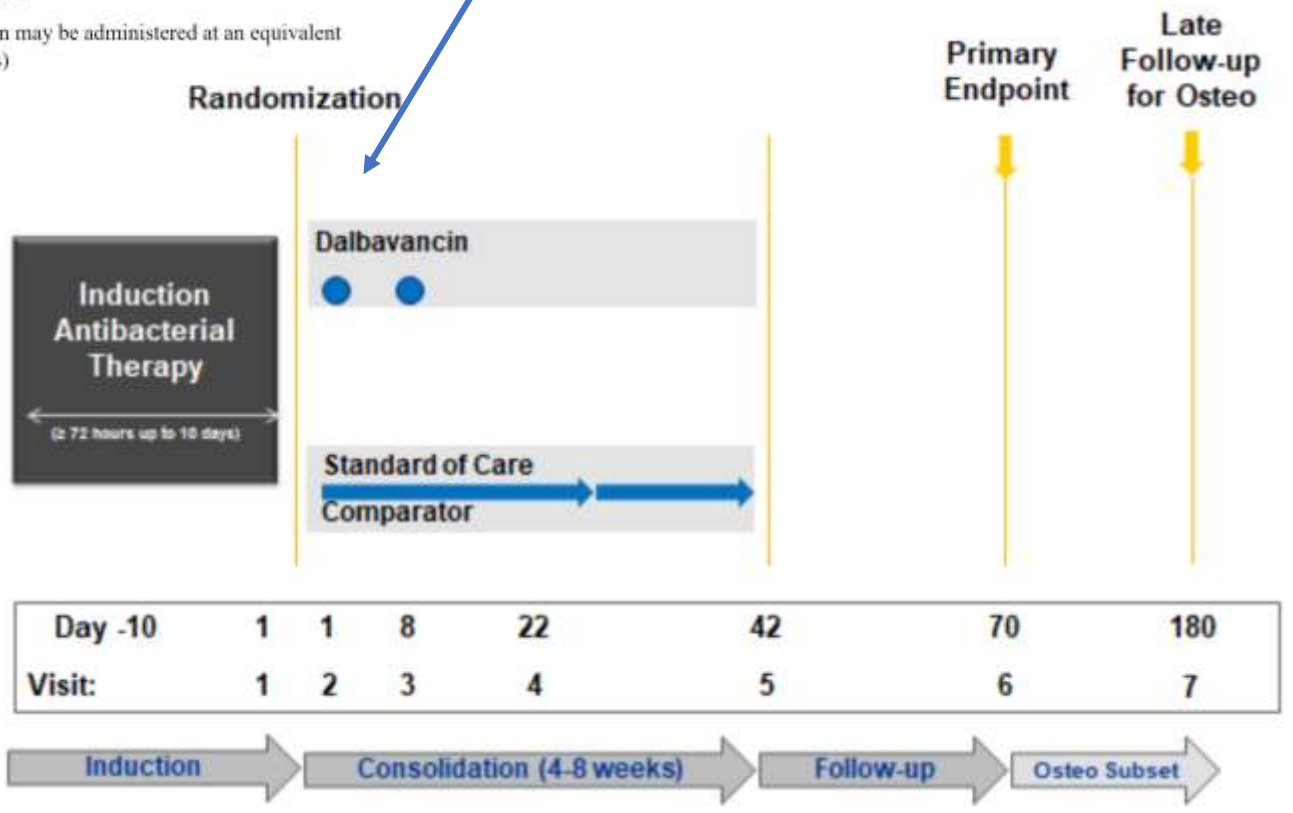
Table 1: Treatment Arms

Dalbavancin	100 subjects	Dalbavancin 1500 mg IV over 30 (± 10) minutes on Day 1 and 1500 mg IV over 30 (± 10) minutes on Day 8, renally dose-adjusted to 1125 mg for subjects with CrCl <30 and not on dialysis
Standard of Care[a]	100 subjects	• Methicillin-sensitive *Staphylococcus aureus* (MSSA): nafcillin (2 g IV q4h × 4-6 weeks)[b] OR oxacillin (2 g IV Q4h x 4-6 weeks)[b] OR cefazolin (2 g IV q8h × 4-6 weeks) • Methicillin-resistant *Staphylococcus aureus* (MRSA): vancomycin (dose per local standard of care × 4-6 weeks) OR daptomycin (6-10 mg/kg IV daily × 4-6 weeks)

[a]Renally dose-adjusted as appropriate, per local standard of care

[b]As applicable per site standard of care, nafcillin and oxacillin may be administered at an equivalent dose via continuous IV infusion (e.g., 12g/24h IV continuous)

*Whatever active abx therapy was started by primary team for 72hrs-10d prior to enrollment



Slide curtesy of Dr. Strnad PI OHSU

Do This

- Consider Linezolid for uncomplicated SAB
- Consider oral step down to complete SAB therapy
- Watch for Dalba studies

Don't Do That

- Don't treat SAB with oral beta-lactams *unless* ID input
- Don't treat SAB with dalba as first line, yet

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Question 1: Mr. Pock

"I have this patient, Mr. Pock, who is a 23 year old man with no medical history who presented to my clinic with fevers and a new vesicular rash. He said that he developed the fever about 3 days ago then the rash appeared. The rash had round patches that turned into bubbles. He is a graphic designer who works from home. His partner developed a similar condition last week. He was febrile and his skin exam was notable for vesicles concentrated on palms, buttocks, and face though dispersed throughout all in the same stage of development. No crusting. Could this be monkeypox?"

What would be an appropriate response?

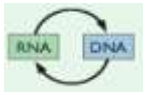
A. Possibly, he should be placed in droplet and contact isolation

B. Possibly, he should be given the vaccinia vaccine

C. Possibly but more likely he has Varicella virus and requires supportive care

D. Possibly, he should have a PCR sent for monkeypox DNA

HUMAN VIROLOGY CONCEPT MAP



Retro

DNA

SS

DS

Parvo
Parvo B19

Circo

Capsid

Icosahedral

Naked

Linear

Adeno
Adenovirus

Circular

Polyoma
JC
BK

Papilloma
HPV

Enveloped

Linear

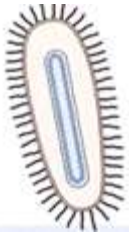
Herpes
HSV
VZV
CMV
EBV
HHV6
HHV7
HHV8

Circular

Hepadna
HBV

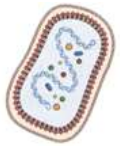
Helical

Baculo



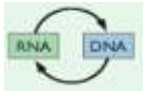
Complex

Pox
Smallpox
Monkey pox
Vaccinia



RNA

Retro



HIV
HTLV I/II

SS

(-)

Bunya
Hanta

Filo
Ebola

Rhabdo
Rabies

Arena
LCMV
Lassa

Orthomyxo
Influenza

Paramyxo
Measles
Mumps
RSV

Helical & Enveloped

(+)

Capsid

Icosahedral

Naked

Calici
Norovirus

Picorna
Polio
Rhinovirus
Hepatitis A
(HAV)

Enveloped

Flavi
DENV
WNV
HCV

Toga
CHKV
EEEV
Rubella

Helical

Corona
SARS
MERS

Enveloped

DS

Reo
Rotavirus

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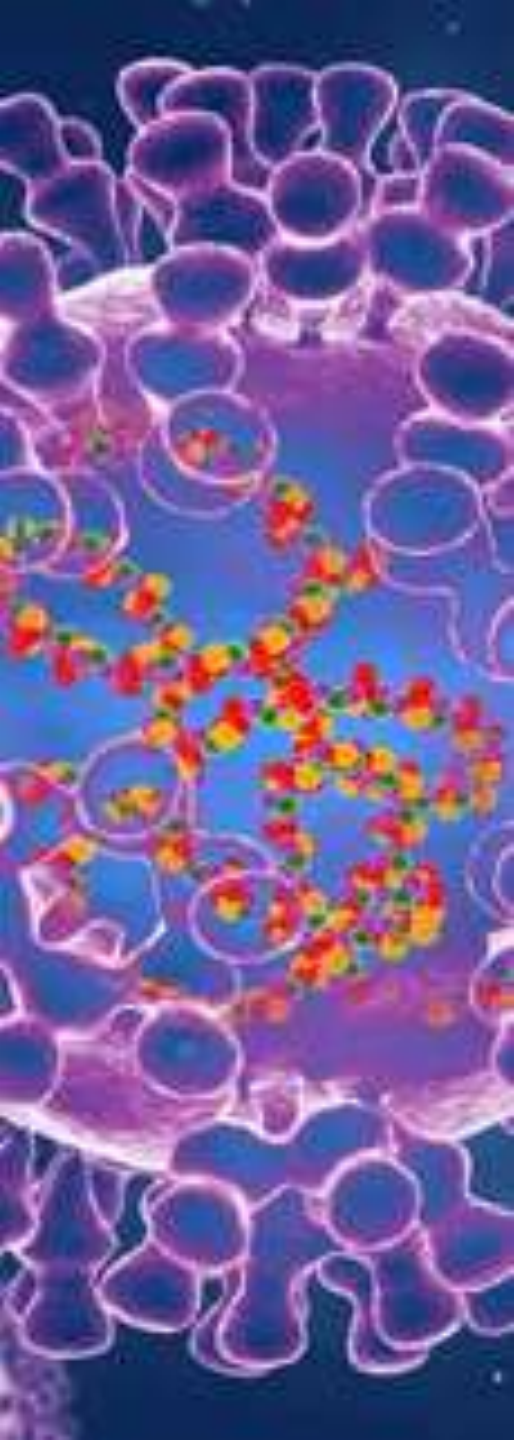

Epidemiology of Monkeypox

- 2 main strains found primarily on African continent
  - Central African strain
  - Western African strain (less virulent)
- Reservoir in rodents most likely
- Monkeys and humans are incidental hosts
- Human-Human transmission
  - Respiratory droplets
  - Contact with lesions/material
- Incubation 6-13d (5-21d range)

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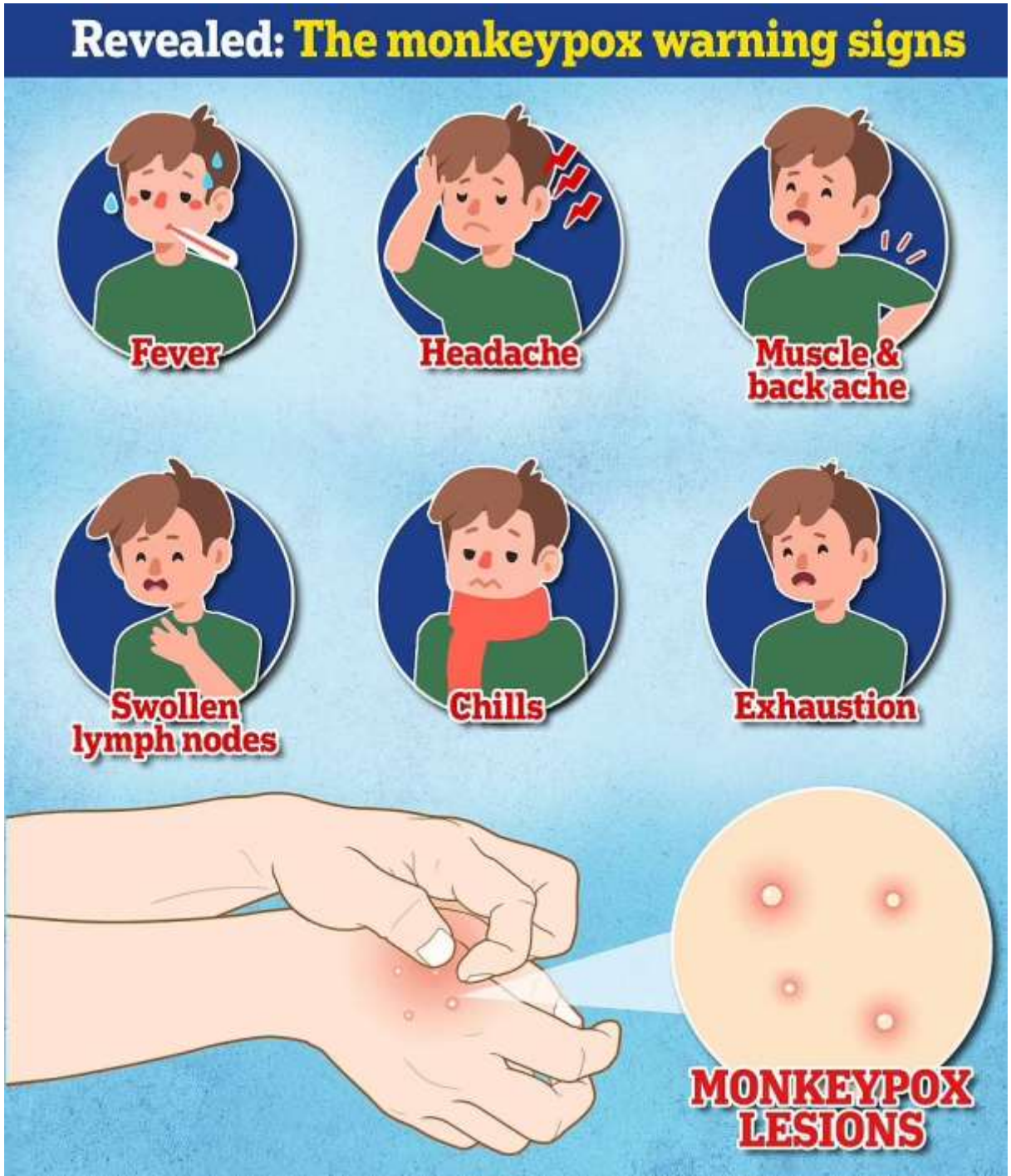
INVASION PERIOD

0-5 days

Skin Eruption

1-3 days after Fever



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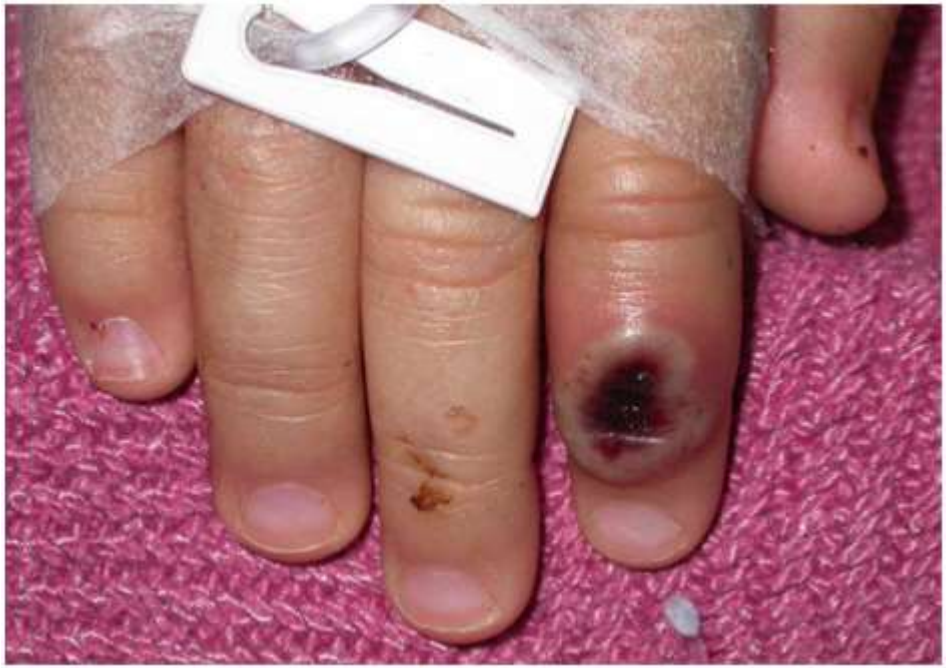
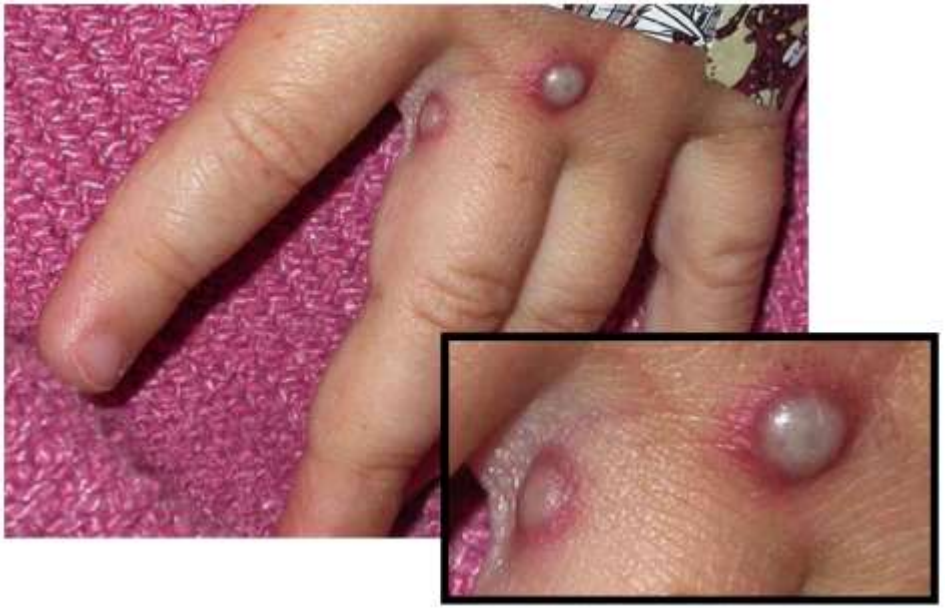
Skin Eruption





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MONKEYPOX

VISUAL EXAMPLES OF MONKEYPOX RASH


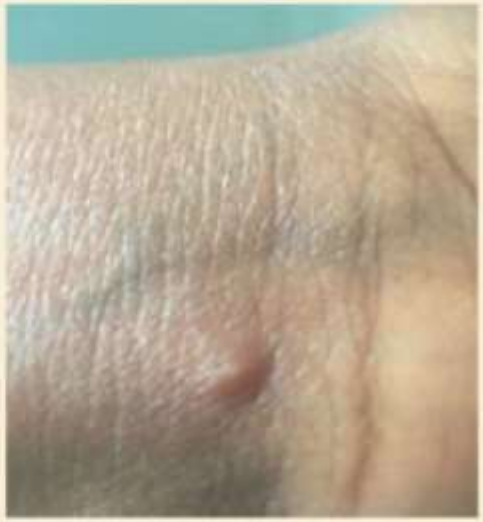
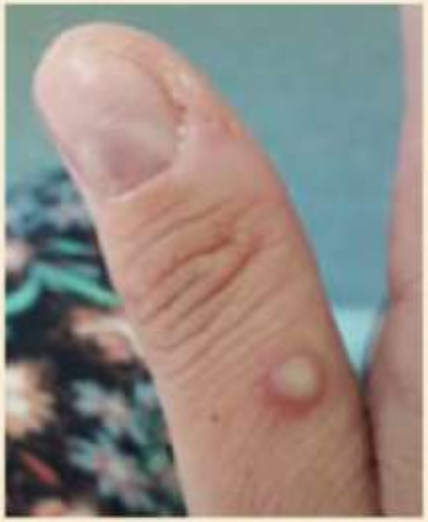
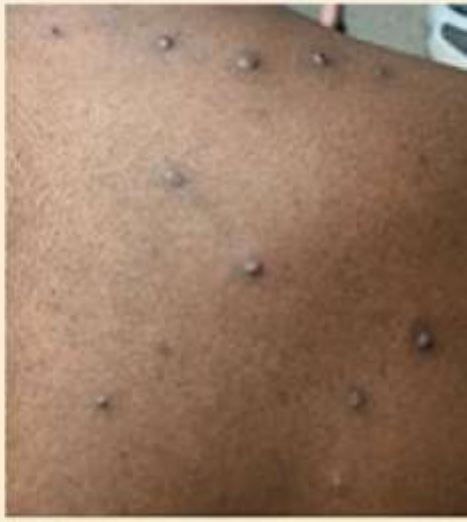

Photo Credit: NHS England High Consequence Infectious Diseases Network

CDC

CS328947-EK

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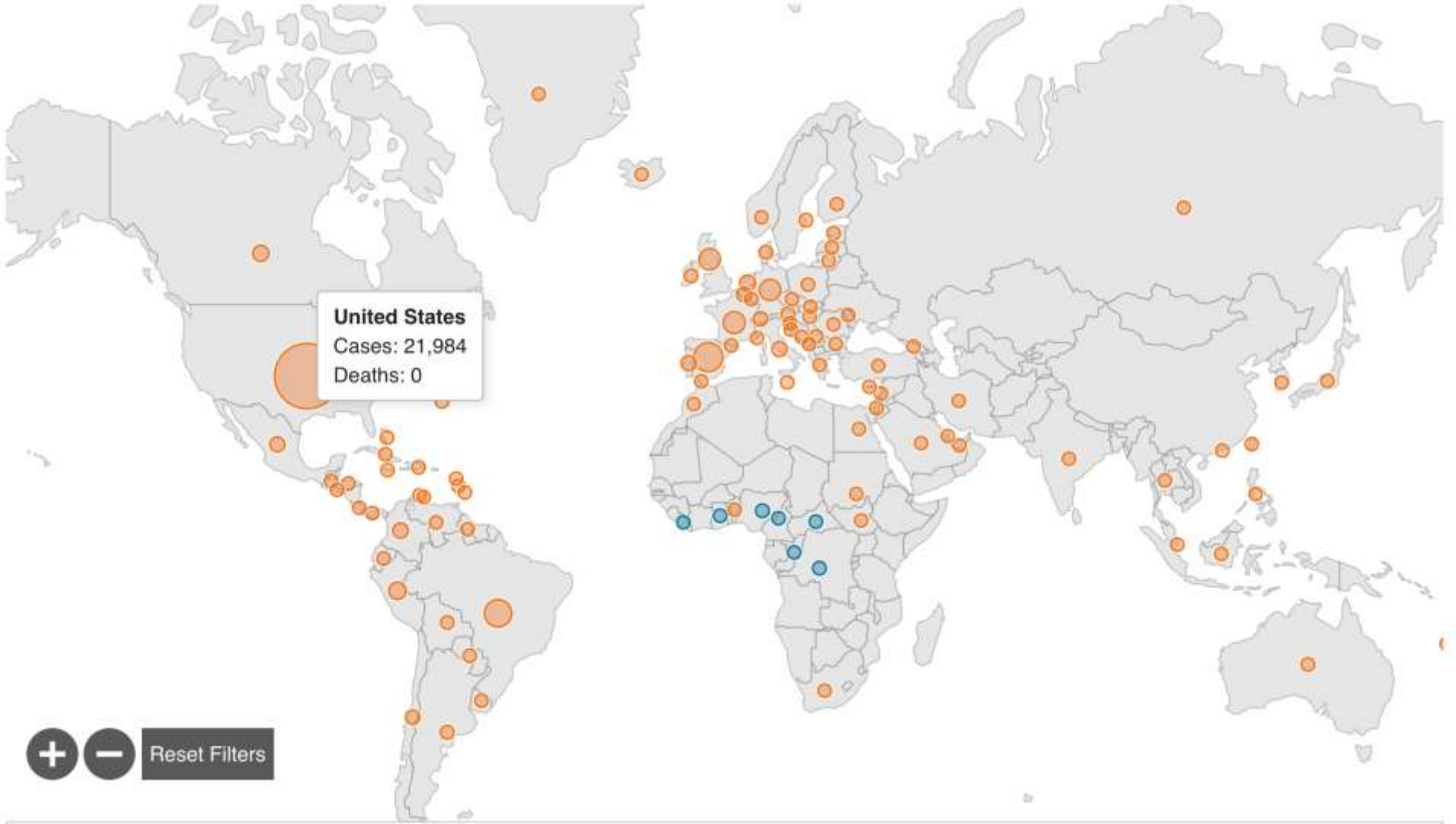
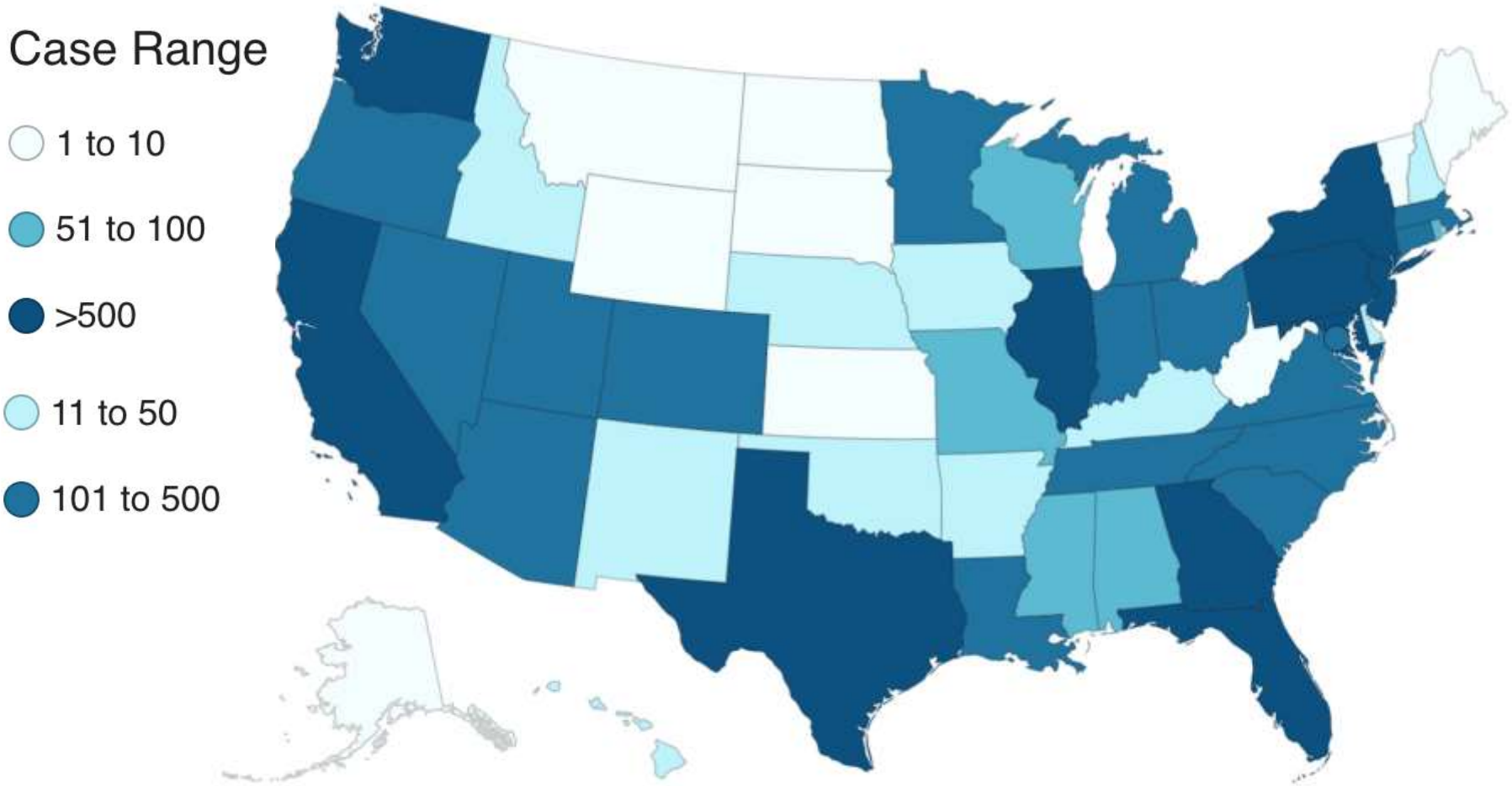
2022 Outbreak Global Map

https://www.cdc.gov/poxvirus/monkeypox/response/2022/world-map.html



21,985 Total confirmed monkeypox/orthopoxvirus cases

*One Florida case is listed here but included in the United Kingdom case counts because the individual was tested while in the UK.



What have you seen in the media?

HEALTH AND SCIENCE

CDC officials sound alarm for gay and bisexual men as monkeypox spreads in community

Gay, bisexual men at increased risk for monkeypox virus: CDC

Outbreak in Europe appears to have been caused by sexual activity at raves in Spain and Belgium: former WHO official

HEALTH

The Dangerous Parallel Between Monkeypox and AIDS

Sexually transmitted infections epidemiology

Monkeypox is spreading among gay men worldwide

Slide curtesy of Dr. Menza

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Monkeypox is not a gay virus. Haven't we been here before?

As with HIV/Aids 40 years ago, the stigma of a disease can have serious consequences for efforts to contain it.

AFRICA

As monkeypox panic spreads, doctors in Africa see a double standard

CASUAL RACISM

Stop using images of Black people to illustrate monkeypox stories

PRESS RELEASE

UNAIDS warns that stigmatizing language on Monkeypox jeopardises public health

Slide curtesy of Dr. Menza

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When to suspect…

- New characteristic rash **OR**
- Meets one epidemiologic criteria **AND**
- High clinical suspicion for monkeypox

- Contact with person w/ similar rash or + monkeypox
- Close contact within social network experiencing monkeypox activity
  - MSM who meet partners online or through social
- Traveled outside US to area with confirmed cases or where endemic
- Contact with animal or animal product known to harbor monkeypox

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Interim Guidance for Prevention and Treatment of Monkeypox in Persons with HIV Infection — United States, August 2022

Weekly / August 12, 2022 / 71(32);1023-1028

On August 5, 2022, this report was posted online as an MMWR *Early Release.*

Jesse O'Shea, MD[1,*]; Thomas D. Filardo, MD[1,2,*]; Sapna Bamrah Morris, MD[1]; John Weiser, MD[1]; Brett Petersen, MD[1]; John T. Brooks, MD[1]
(View author affiliations)

https://www.cdc.gov/mmwr/volumes/71/wr/mm7132e4.htm

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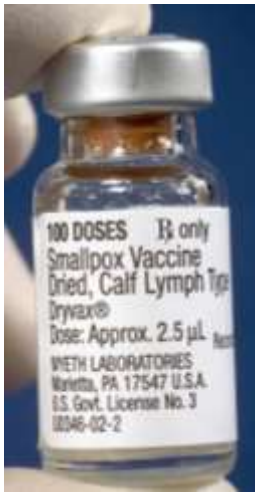
Treatment & Prevention

Tecovirimat



Vaccinia Vaccine
85% Effective

Vaccinia Immuneglobulin
Unclear effectiveness

Proc Natl Acad Sci U S A. 2010 Sep 14;107(37):16262-7.

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Do this

- Keep hMPXV on your differential
- Contact ID or TPoxx prescriber
- Call your local health dept. with any questions

Don't Do That

- Don't add to stigma

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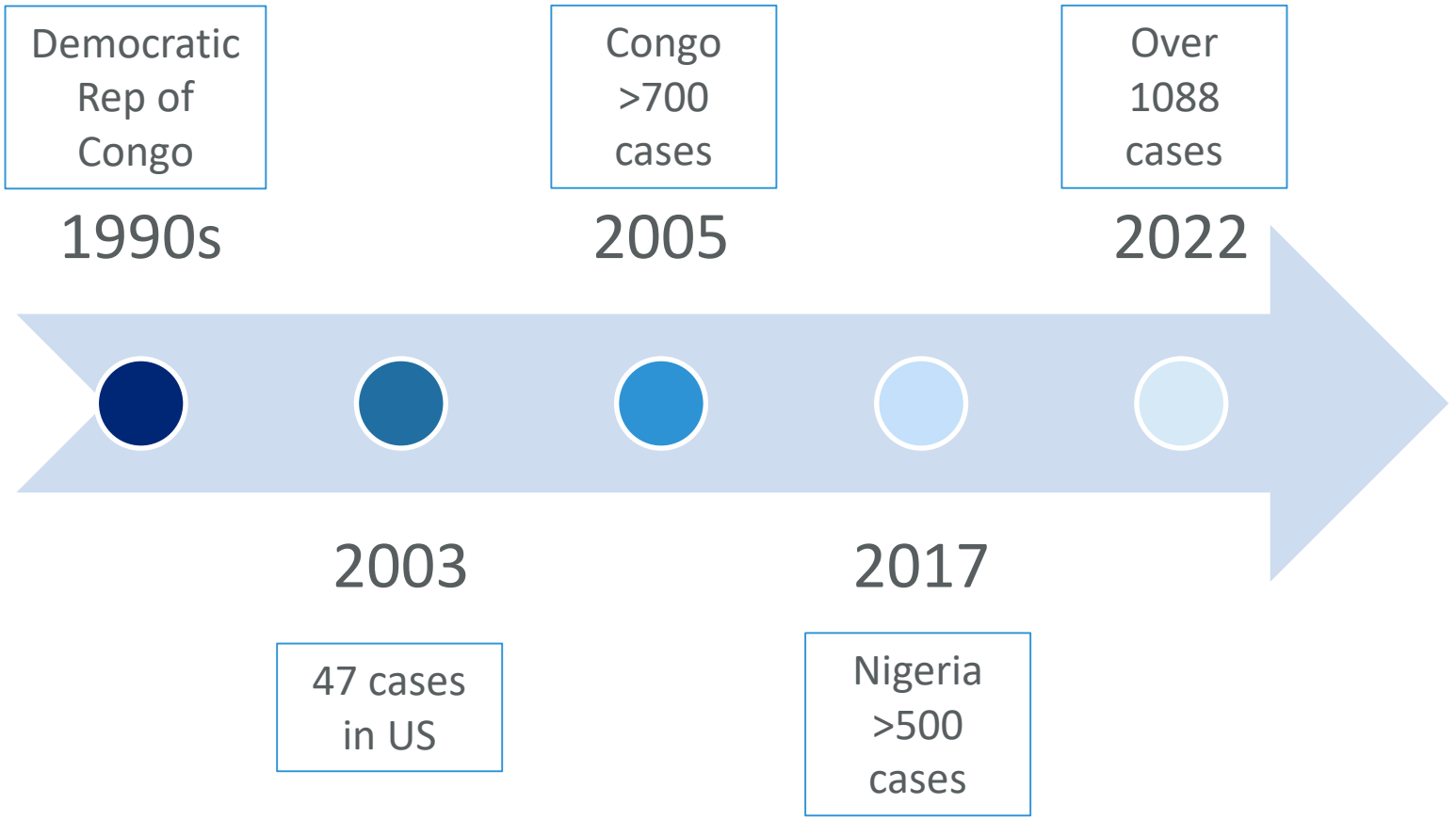
Thank You

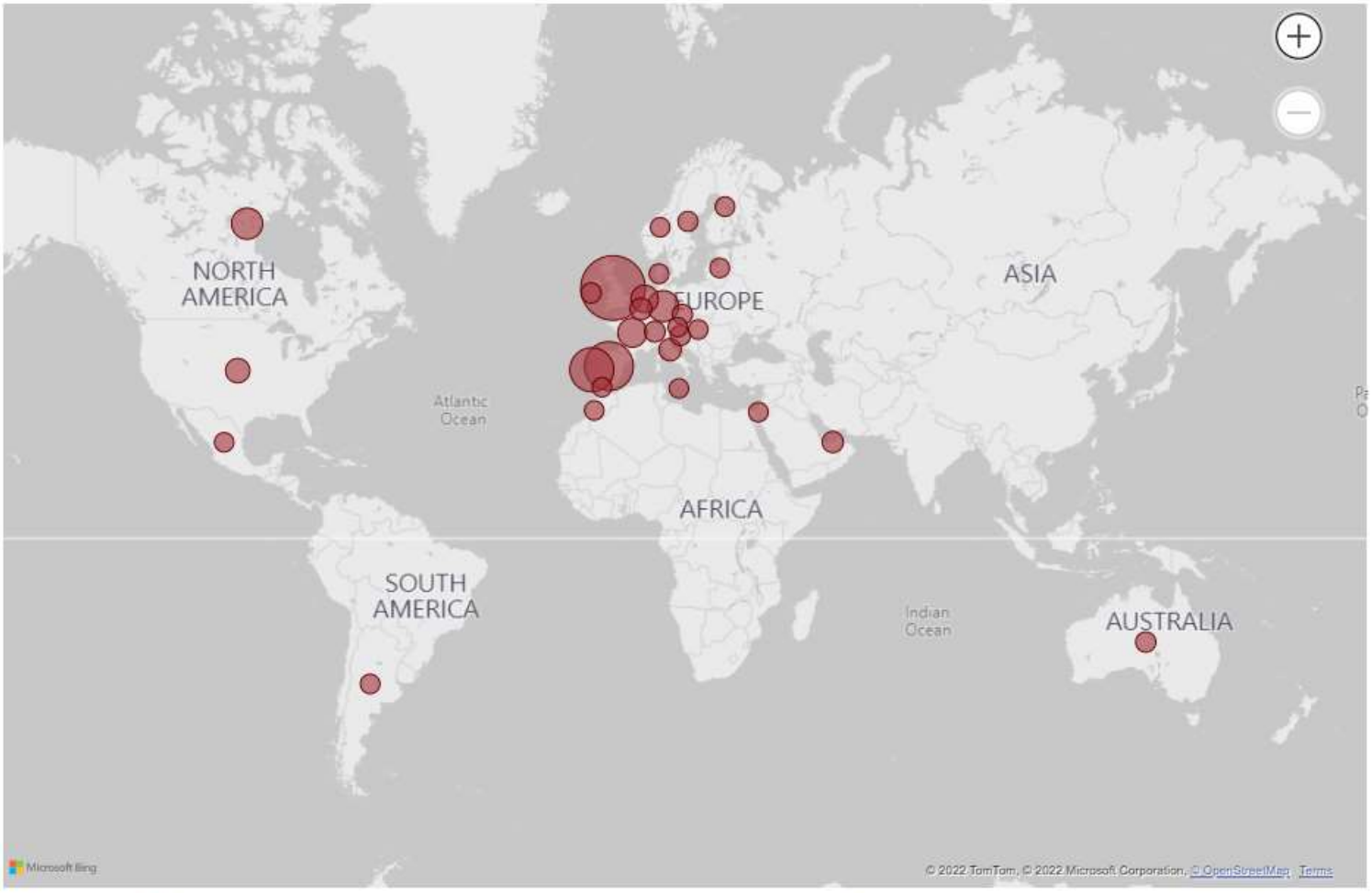
Notable Monkeypox Outbreaks



https://www.who.int/news-room/fact-sheets/detail/monkeypox

2022 Outbreak Global Map

https://www.cdc.gov/poxvirus/monkeypox/response/2022/world-map.html



Data as of 07 Jun 2022 5:00 PM EDT

Total Confirmed Cases	Number of Countries
1088	29

Country	Total Confirmed Cases
United Kingdom	302
Spain	198
Portugal	166
Canada	80
Germany	80
France	66
Netherlands	54
United States	34
Italy	20
Belgium	17
United Arab Emirates	13
Switzerland	10
Ireland	7
Australia	6
Czechia	6
Slovenia	6
Sweden	5
Denmark	3
Argentina	2
Finland	2
Total	**1088**

Notes: Numbers shown are sourced from publicly available official sources, such as the WHO, European CDC, US CDC, and Ministries of Health. Data are provided for situational awareness only and are subject to change. Confirmed cases include those confirmed as monkeypox virus and may include cases only confirmed as orthopoxvirus.

When is it probable vs confirmed?

- Recent Orthopox virus exposure AND presence of
  - Orthopox DNA by PCR
  - Orthopox using histochem or Electron microscope
  - + IgM anti-orthopox 4-56 days after rash

- Confirmed = + PCR for Monkeypox DNA