New Anti-Infectives

Ted Rosen, MD
Baylor College of Medicine
Houston, Texas

And why we need them!

BCM
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Conflict of Interest

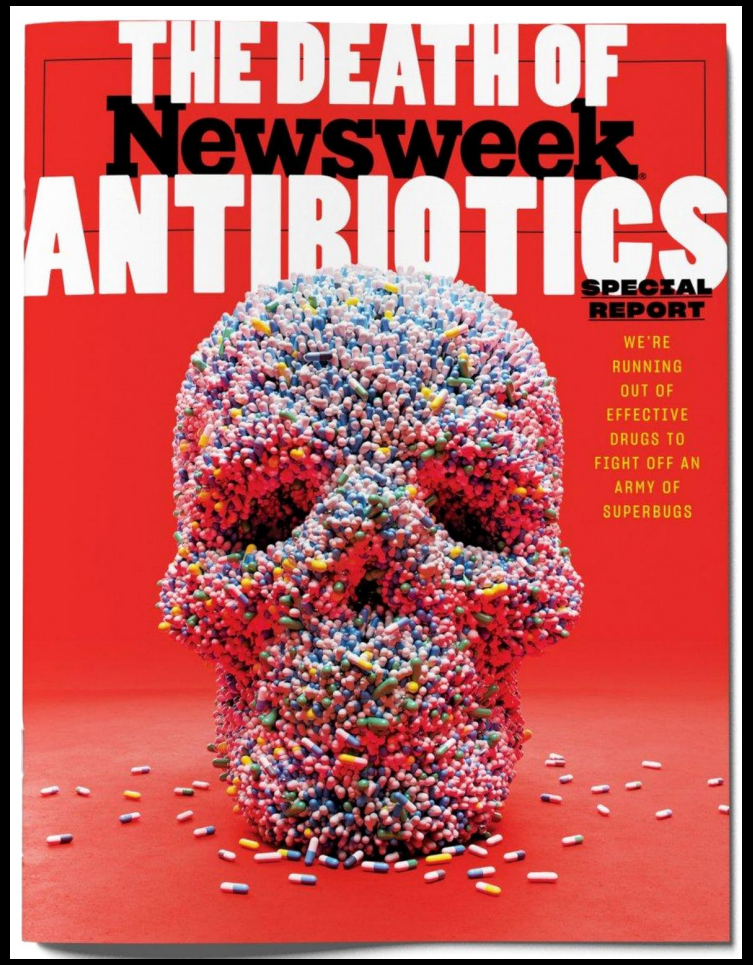
- **Advisory Board: Verrica**

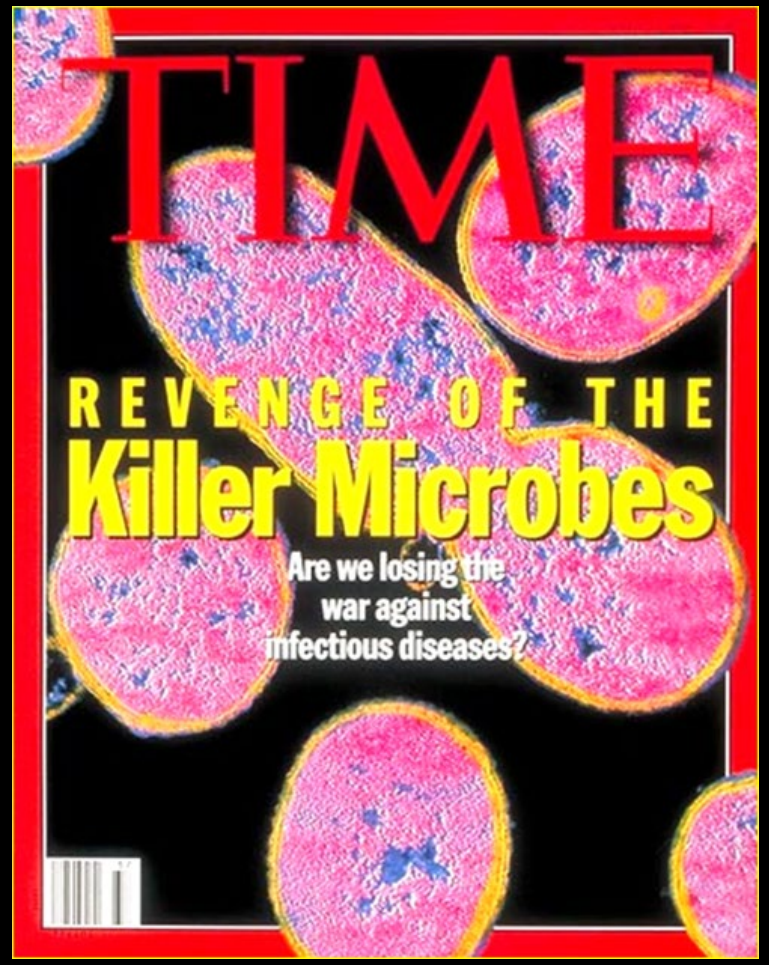
Then and Now

Infection was the #1 cause of death

Infection was the #4 cause of death

Antibiotic Resistance: Newsweek and Time

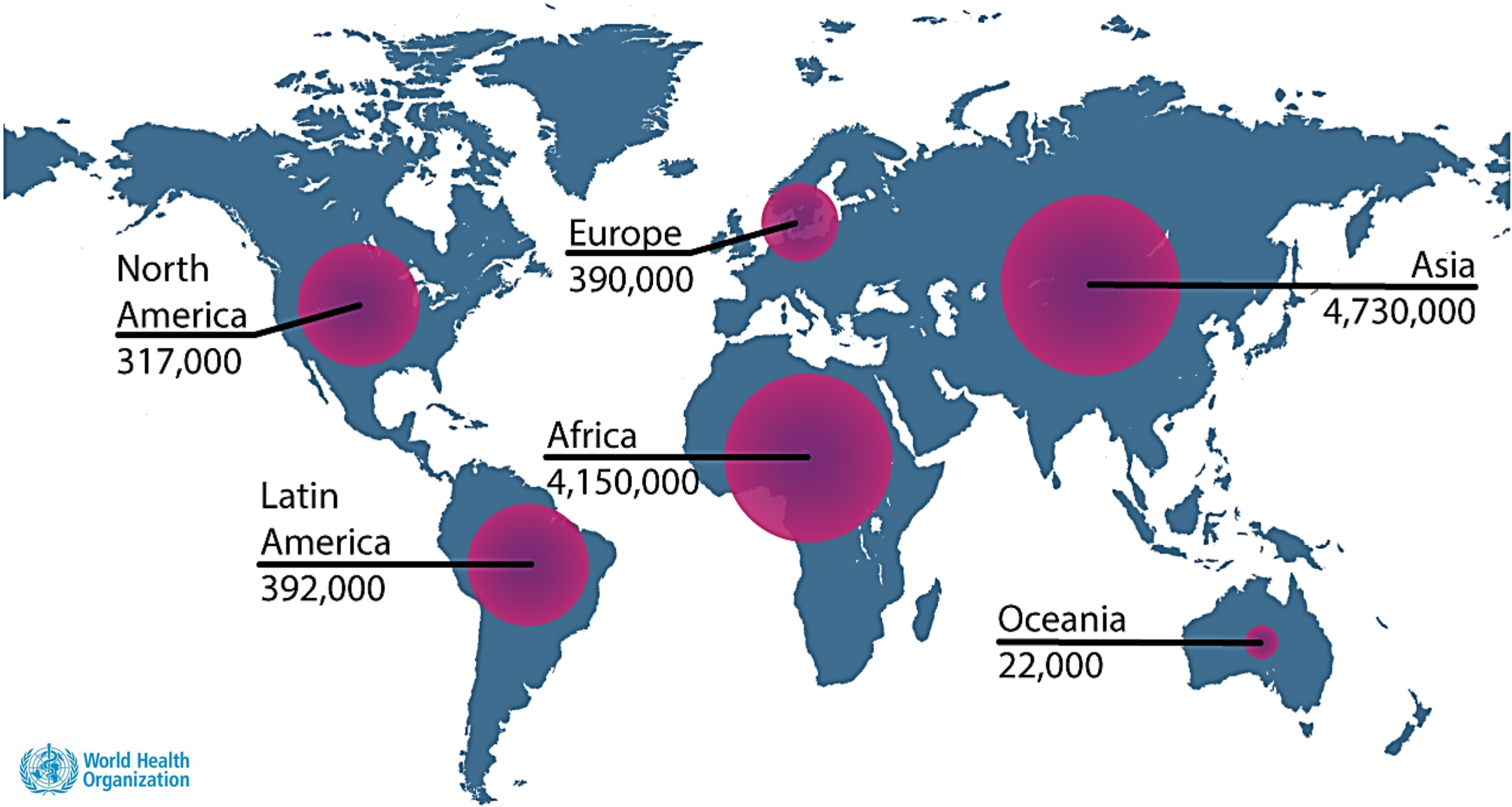




How big a problem is it?

Worldwide yearly deaths due to antibiotic-resistant microbes: ~700,000 (2019)

Estimated 10,000,000 per year by 2050 unless new drugs or techniques are developed (WHO)


North America
317,000
Europe
390,000
Asia
4,730,000
Africa
4,150,000
Latin America
392,000
Oceania
22,000
World Health Organization

By **2050**

if AMR is not tackled now.

World Health Organization

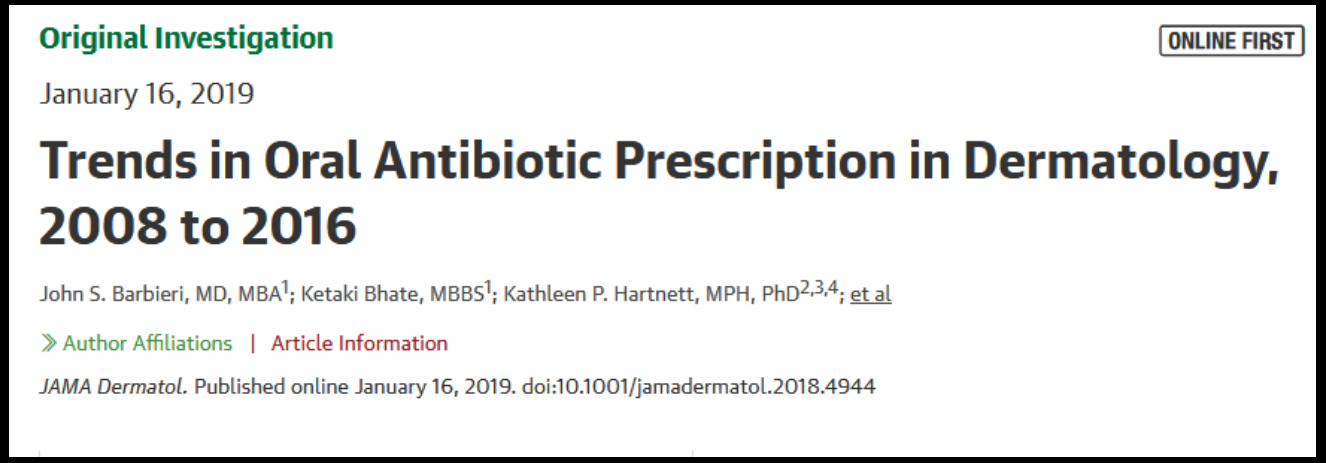
Dermatologists contribute to overuse of antibiotics

“Dermatologists comprise about 1% of all US physicians, but prescribe over 5% of all antibiotics.”

By John Jesitus

National report — Dermatologists generally know that the sensitivity of many pathogens to the antibiotics used to treat them is decreasing, experts say. But many dermatologists may

The Good News!



Original Investigation ONLINE FIRST

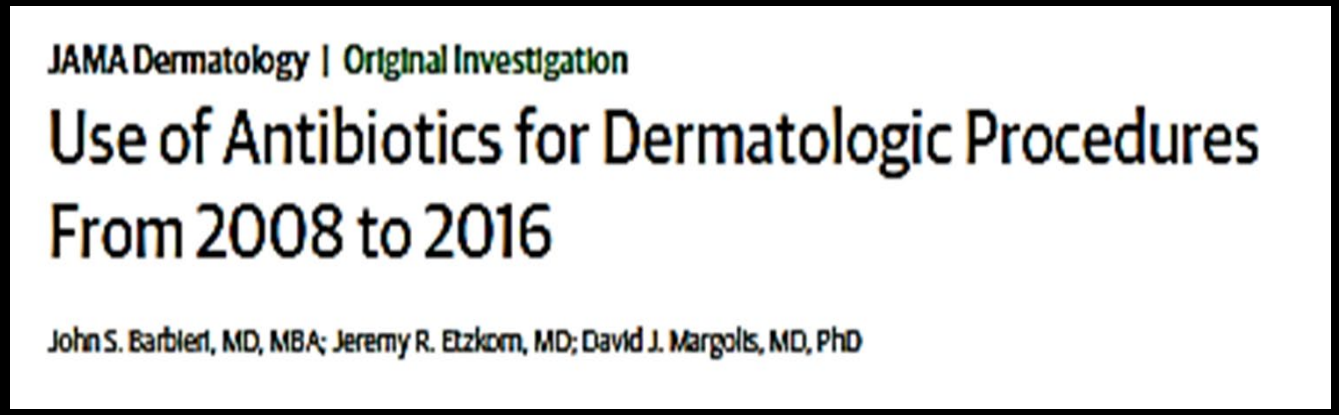
January 16, 2019

Trends in Oral Antibiotic Prescription in Dermatology, 2008 to 2016

John S. Barbieri, MD, MBA[1]; Ketaki Bhate, MBBS[1]; Kathleen P. Hartnett, MPH, PhD[2,3,4]; et al

» Author Affiliations | Article Information

JAMA Dermatol. Published online January 16, 2019. doi:10.1001/jamadermatol.2018.4944



JAMA Dermatology | Original Investigation

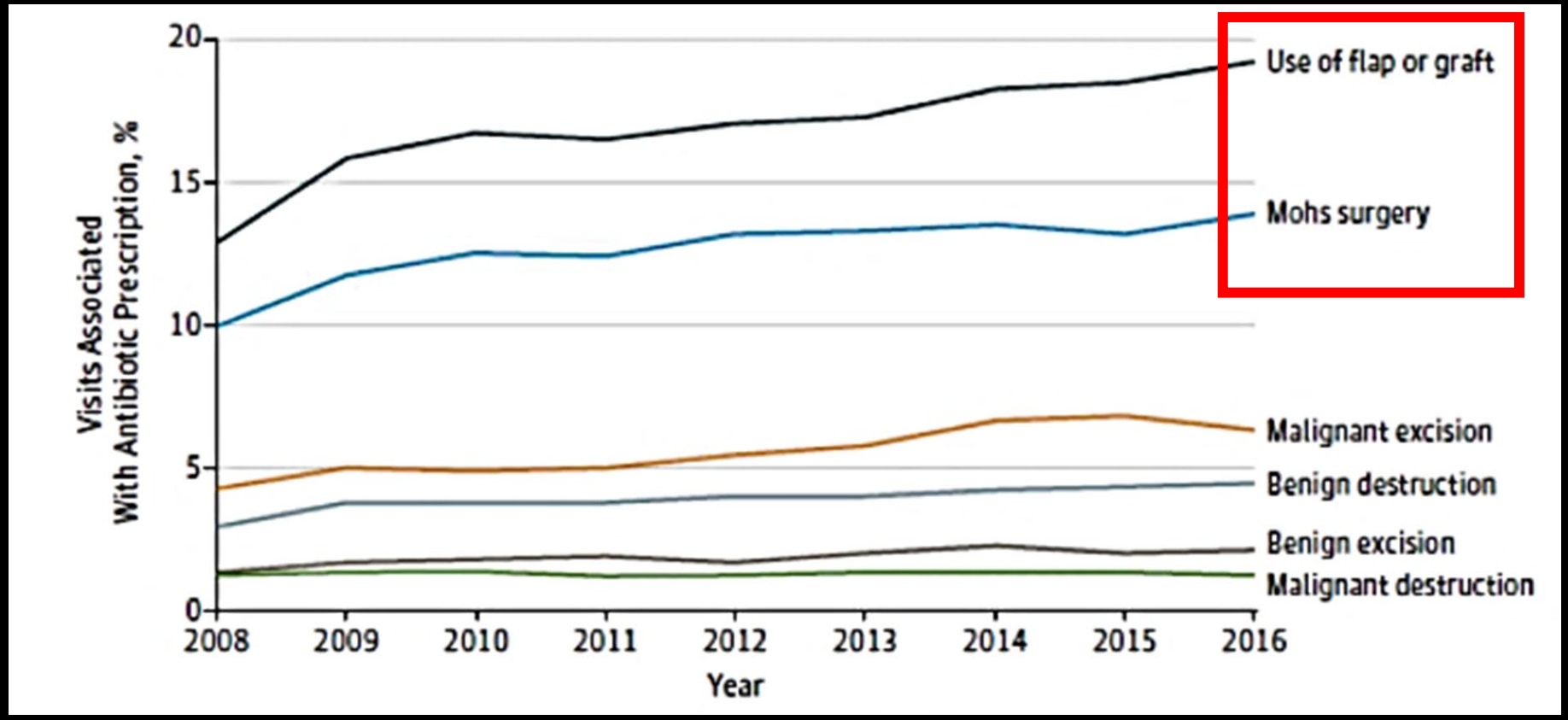
Use of Antibiotics for Dermatologic Procedures From 2008 to 2016

John S. Barbieri, MD, MBA; Jeremy R. Etzkorn, MD; David J. Margolis, MD, PhD

- Retrospective claims data (Optum)
- 2008-2016: 985,866 courses of oral antibiotics prescribed by 11,986 unique dermatologists
- DECREASE: 3.36 Abx per 100 visits to 2.13 Abx per 100 visits over time (37% decrease)
- Post-surgical use, however, rose from 2.73 to 3.92/100 visits (40%)
- May put patients at unnecessary risk of adverse events and/or develop and harbor resistant microbes
- A little closer look…..

JAMA Dermatol. 2019;155(3):290-297
JAMA Dermatol. 2019;155(4):465-470

- POST-SUGICAL INCREASED: 2.73/100 to 3.92/100 visits
- Benign excisions: 2.9% to 4.4%
- Malignant excisions: 4.2% to 6.3%
- Mohs surgery visits: 9.9% to 13.8%



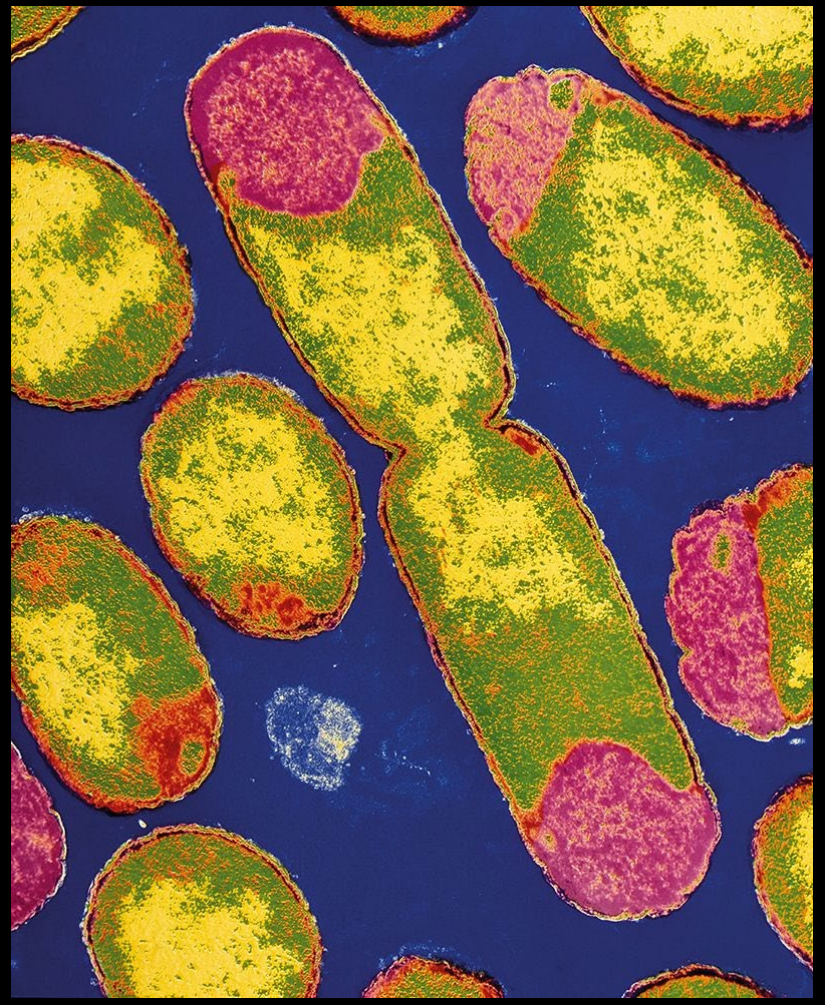
Take Home Messages…..

- **Use antibiotics wisely; When indicated!**
- **Know what you are treating**
- **Don’t use antibiotics “just in case”**
- **Proper dose and duration**
- **Have an exit strategy!**
- **Advise patients on proper antibiotic use**
  For example: Don’t “share” with family, friends

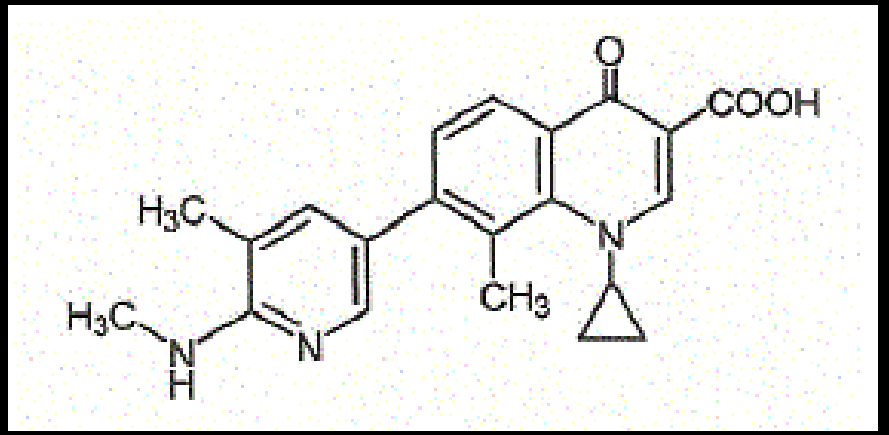
When doing surgery…

Use restraint in prescribing antibiotics!

New Antibiotics: Now



New antibiotic: Ozenoxacin



- Chemical class: Non-fluorinated quinolone
- MOA: Blocks topoisomerase II and DNA gyrase
  - Inhibits bacterial DNA replication
- **Developed as 1% cream for impetigo**
- **Dosed: BID x 5 days**
- Wide spectrum of activity against relevant Gram+ microbes, including MSSA, MRSA, mupirocin and ciprofloxacin resistant Staphylococci, Strep. pyogenes
- **Superior to placebo, and non-inferior retapamulin**
  - **Microbiological effect in as little as 2 days**
- N=875 in two international studies, age ≥ 2 months
- Status: Approved for impetigo: 12-14-2017

J Drugs Dermatol. 2018 Oct 1;17(10):1051-1057
JAMA Dermatol. 2018 Jul 1;154(7):806-813

JAMA Dermatol. 2018 Jul 1;154(7):806-813

JAMA Dermatology | Original Investigation

Efficacy and Safety of Ozenoxacin Cream for Treatment of Adult and Pediatric Patients With Impetigo
A Randomized Clinical Trial

Theodore Rosen, MD; Nuria Albareda, BS; Noah Rosenberg, MD; Fernando Garcia Alonso, MD, PhD; Sandra Roth, PharmD; Ilonka Zsolt, MD, PhD; Adelaide A. Hebert, MD

JOURNAL OF DRUGS IN DERMATOLOGY
JDD
DRUGS • DEVICES • METHODS

J Drugs Dermatol. 2018 Oct 1;17(10):1051-1057

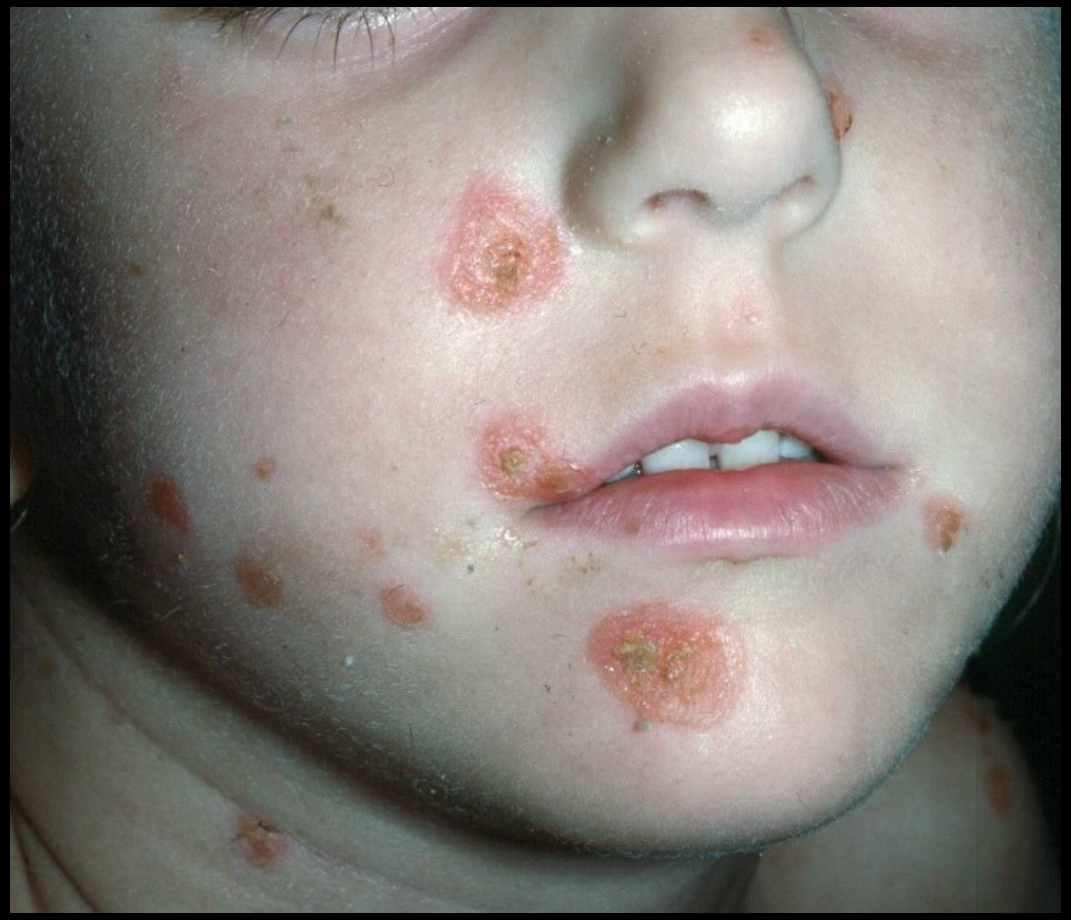
Topical Antibacterial Agent for Treatment of Adult and Pediatric Patients With Impetigo: Pooled Analysis of Phase 3 Clinical Trials

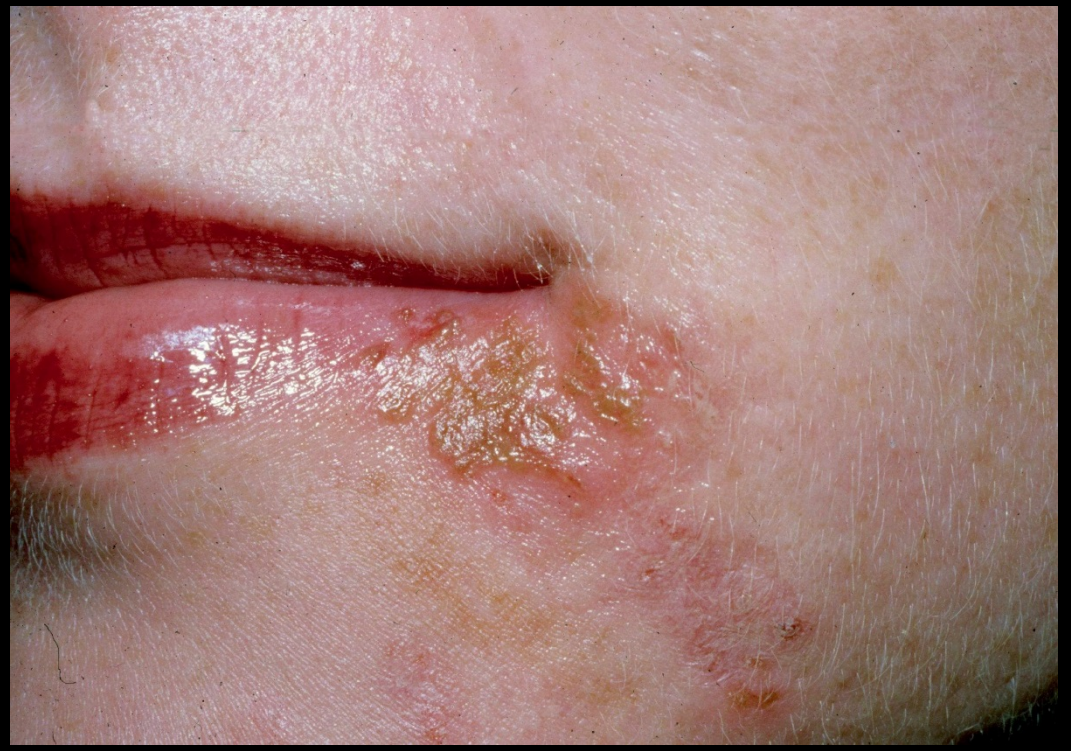
October 2018 | Volume 17 | Issue 10 | Original Article | 1051 | Copyright © 2018

Adelaide A. Hebert MD,[a] Nuria Albareda MD, Theodore Rosen MD, Antonio Torrelo MD,[d] Ramon Grimalt MD,[e] Noah Rosenberg MD,[f] Ilonka Zsolt MD,[b] Xavier Masramon MD[g]

[a]Departments of Dermatology and Pediatrics, UT Health McGovern Medical School, Houston, TX [b]Ferrer Internacional. S.A, Barcelona, Spain [c]Baylor College of Medicine, Houston, TX [d]Department of Dermatology, Children's Hospital del Niño Jesús, Madrid, Spain [e]Universitat Internacional de Catalunya, Barcelona, Spain [f]Medimetriks Pharmaceuticals Inc., Fairfield, NJ [g]SAIL S.L. Barcelona, Spain

Utility?





Do we need another agent?

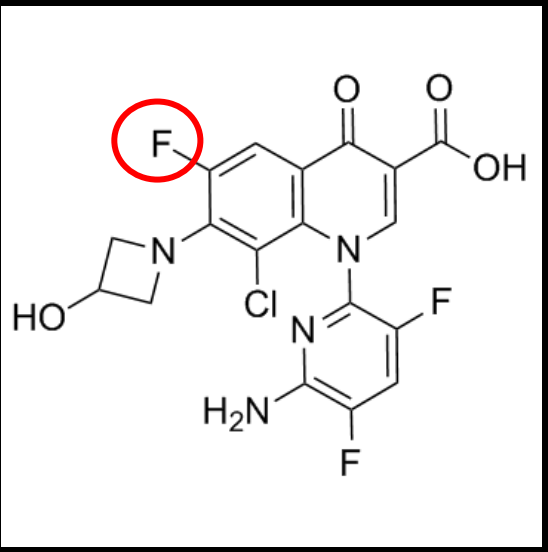
Mupirocin Resistance is Now a Global Problem

- Attempt to determine the global prevalence of MupR for MSSA and MRSA
- From among 2243 articles, chose 60 studies to analyze High Level Resistance to Mupirocin in MSSA/MRSA
- HLR = MIC ≥ 512ug/ml***

- Pooled, average prevalence:
- 10524 MSSA isolates: 8.5%
- 14843 MRSA isolates: 8.1%
- Studies done in 2006, in 2006-11, and 2011-2015, showed steadily increasing mupirocin resistance globally
- Some locales 40-60% resistance noted!

J Glob Antimicrob Resist. 2020 Mar;20:238-247

New Antibiotic: Delafloxacin



- Chemical class: Fluorinated quinolone
- MOA: Inhibits topoisomerase IV and DNA gyrase
  - Inhibits bacterial DNA replication
- **Wide spectrum activity Gr+ and Gr- organisms**
- Includes: MRSA, MSSA, Strep pyogenes, E. coli, Pseudomonas aeruginosa, Enterobacter, Klebsiella
- Available IV (unit dose 300mg) and Oral (unit dose 450mg)
- Resistance: Reported, but uncommon
- Status: Approved ABSSSI in June, 2017

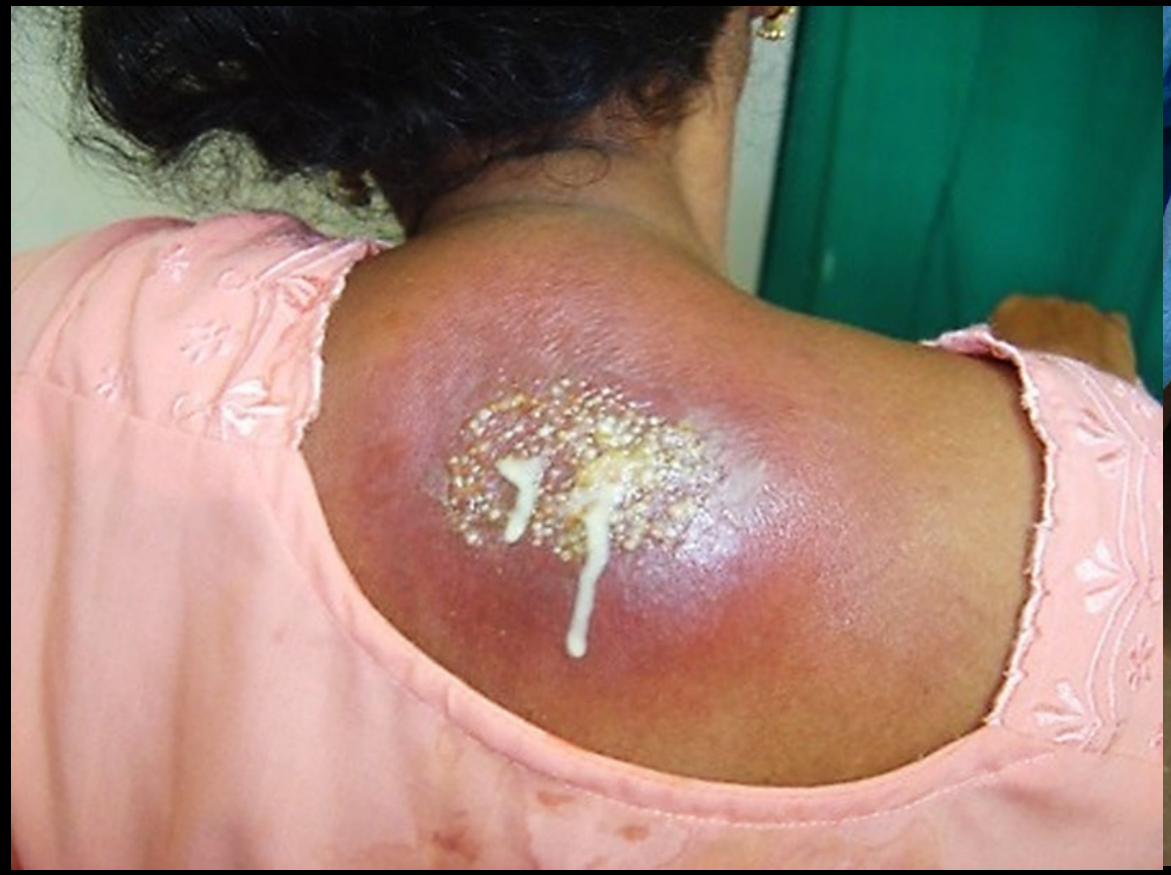
Ann Clin Microbiol Antimicrob. 2016;15(1):34-36
J Antimicrob Chemother. 2017;72:3471-3480

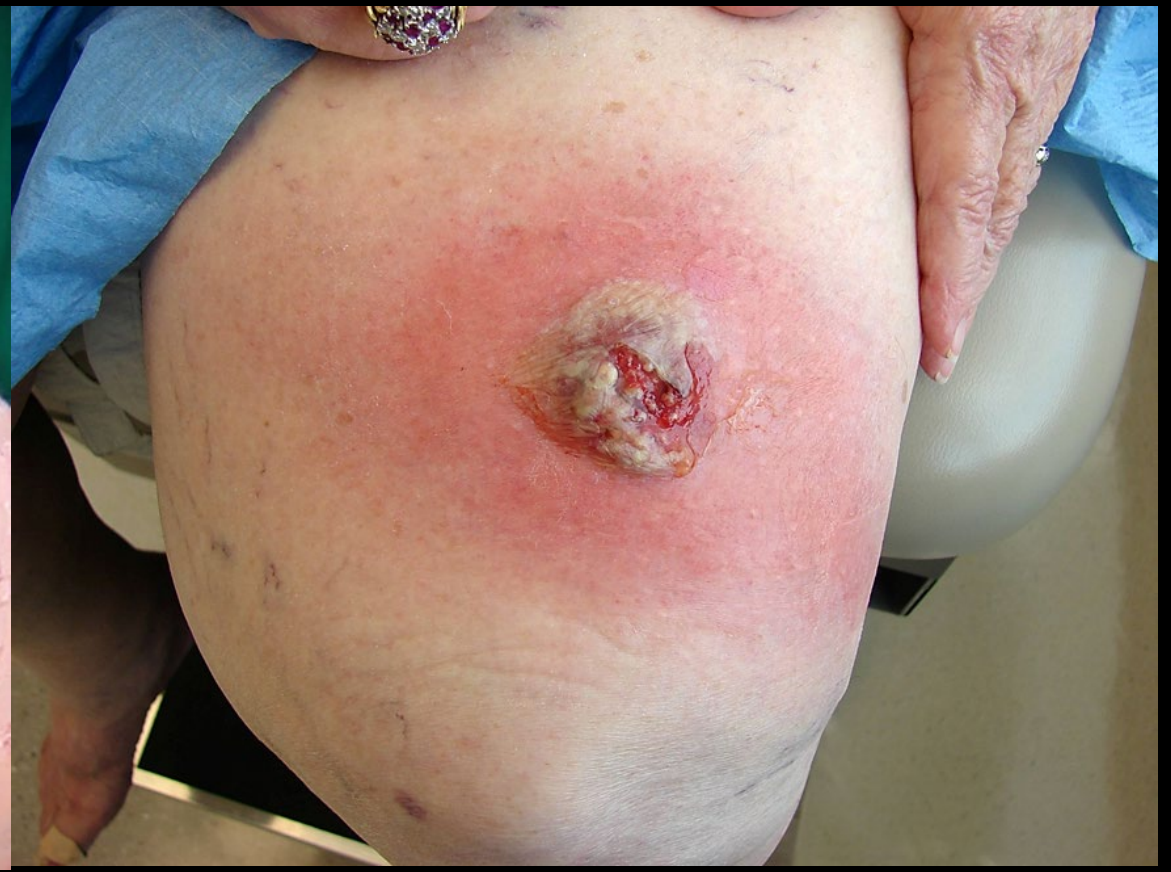
New Antibiotic: Delafloxacin

- Tested IV (300mg Q12h) or oral (450mg Q12h)
- (Oral followed 3 days IV loading dose)
- Active comparator: Vancomycin + Aztreonam
- N = 1510 in both studies combined
- Statistically non-inferior to combination
- AEs: Nausea, vomiting, diarrhea, headache, ↑LFTs
- BLACK BOX: Tendinitis and tendon rupture, Peripheral neuropathy, CNS effects (disturbed attention and memory, nervousness, agitation, delirium, disorientation, nightmares)

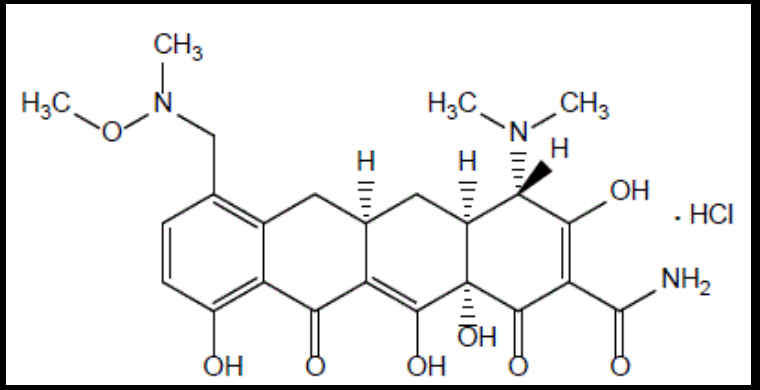
J Antimicrob Chemother. 2017 Dec 1;72(12):3471-3480

Utility?





New Antibiotic: Sarecycline



- Chemical class: tetracycline
- MOA: Binds 30S ribosomal subunit, no AA-tRNA attachment
  - Inhibits protein synthesis
  - Also anti-inflammatory in nature

Antimicrob Agents Chemother. 2018 Nov 5. pii: AAC.01297-18
J Drugs Dermatol. 2018 Mar 1;17(3):333-338.

- **Narrow spectrum activity*****
- Includes: P. acnes, S. aureus; Minimal vrs Gr- enteric bacteria
- Available: Oral only (unit doses: 60mg, 100mg, 150mg)
  - **Once daily dosing weight-based: 1.5mg/kg x 12 weeks**
- Resistance: Uncommon; Nausea, headache: 3%; Yeast <1%
- Status: Approved moderate-severe acne in October, 2018

Sarecycline

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Understanding the Complexities of Compounding

Kircik, L.H. et al.
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Once-Daily Oral Sarecycline 1.5 mg/kg/day Is Effective for Moderate to Severe Acne Vulgaris: Results from Two Identically Designed, Phase 3, Randomized, Double-Blind Clinical Trials

September 2018 | Volume 17 | Issue 9 | Original Article | 987 | Copyright © 2018

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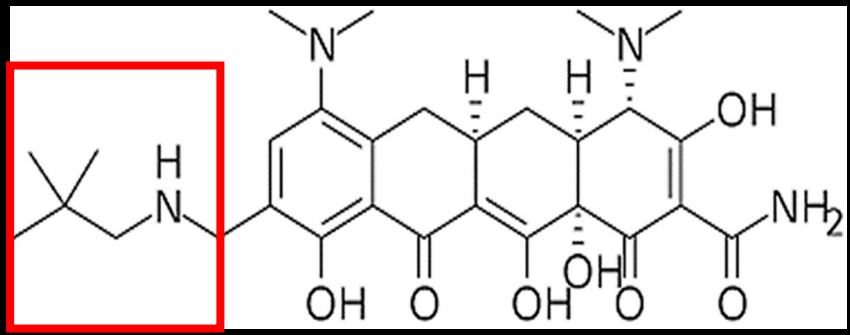
J Drugs Dermatol. 2018 Sep 1;17(9):987-996

- Two parallel Phase 3 studies
- N=1002 (saracycline) and 1000 (placebo)
- QD x 12 week
- IGA: 2 grade improvement; clear/almost
- Saracycline: 21.9% and 22.6%
- Placebo: 10.5% and 15.3%
- ~50% reduction number inflammatory lesions at therapy end (12 weeks), whereas placebo showed ~35% reduction
- Vestibular AEs <1% Photosensitivity <1%
- ER-Minocycline: Clear/AC 16-17% and mean reduction inflammatory 43-46%

New Antibiotic: Omadacycline



- Chemical class: Aminomethylcycline
- MOA: Binds 30S ribosomal subunit, no AA-tRNA attachment
  - Inhibits protein synthesis
- Wide spectrum activity Gr+ / Gr- organisms; anaerobes
- Includes: MRSA, Strep pyogenes, VRE, Legionella, Chlamydia
- Available IV (unit dose 100mg) and Oral (unit dose 150mg)
  - Once daily dosing; IV 200mg->100mg; PO 450mg x 2 d->300mg
- Resistance: <u>Uncommon</u> (evades efflux and ribosomal protection)
- Status: Approved ABSSSI in October, 2018

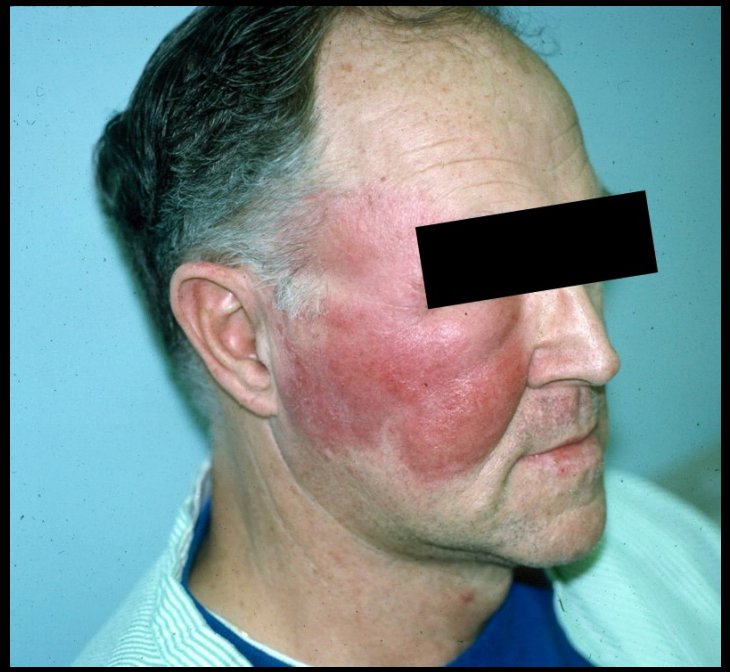
Ann Clin Microbiol Antimicrob. 2016;15(1):34-36
J Antimicrob Chemother. 2017;72:3471-3480

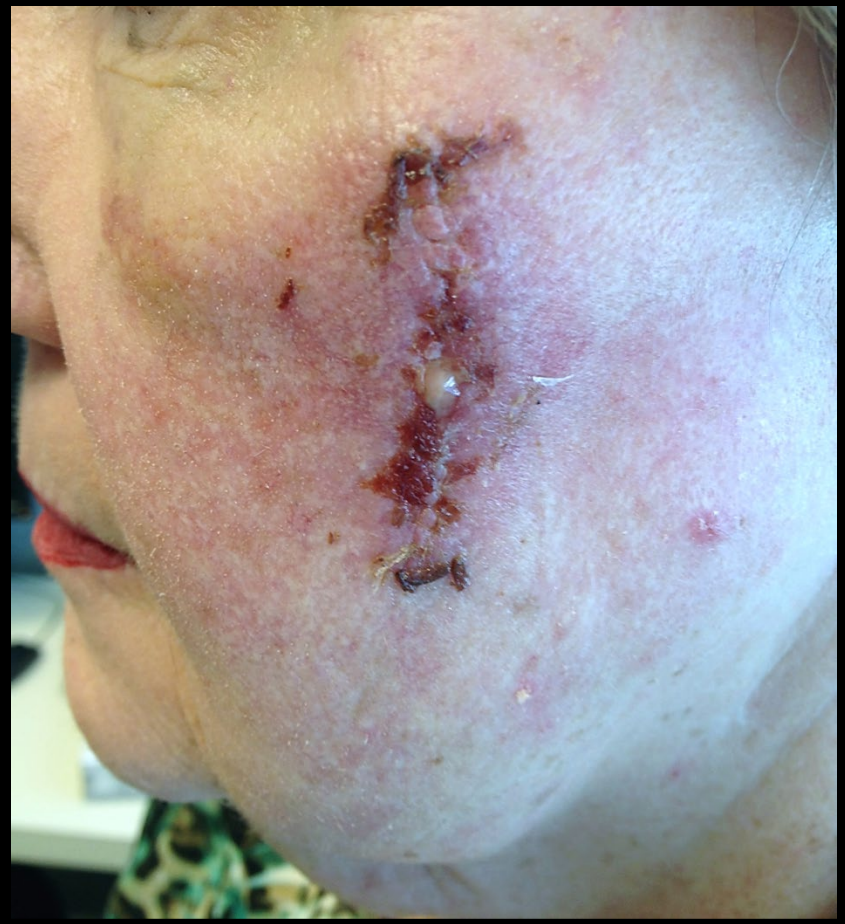
Omadacycline: O'Riordan WA, Green S, Overcash JS, et al. A phase 3 randomized, double-blind, multicentre study to compare the safety and efficacy of oral and iv omadacycline to linezolid for treating adult individuals with ABSSSI (the OASIS study). 27th European Congress of Clinical Microbiology and Infectious Diseases, Vienna, Austria; 2017

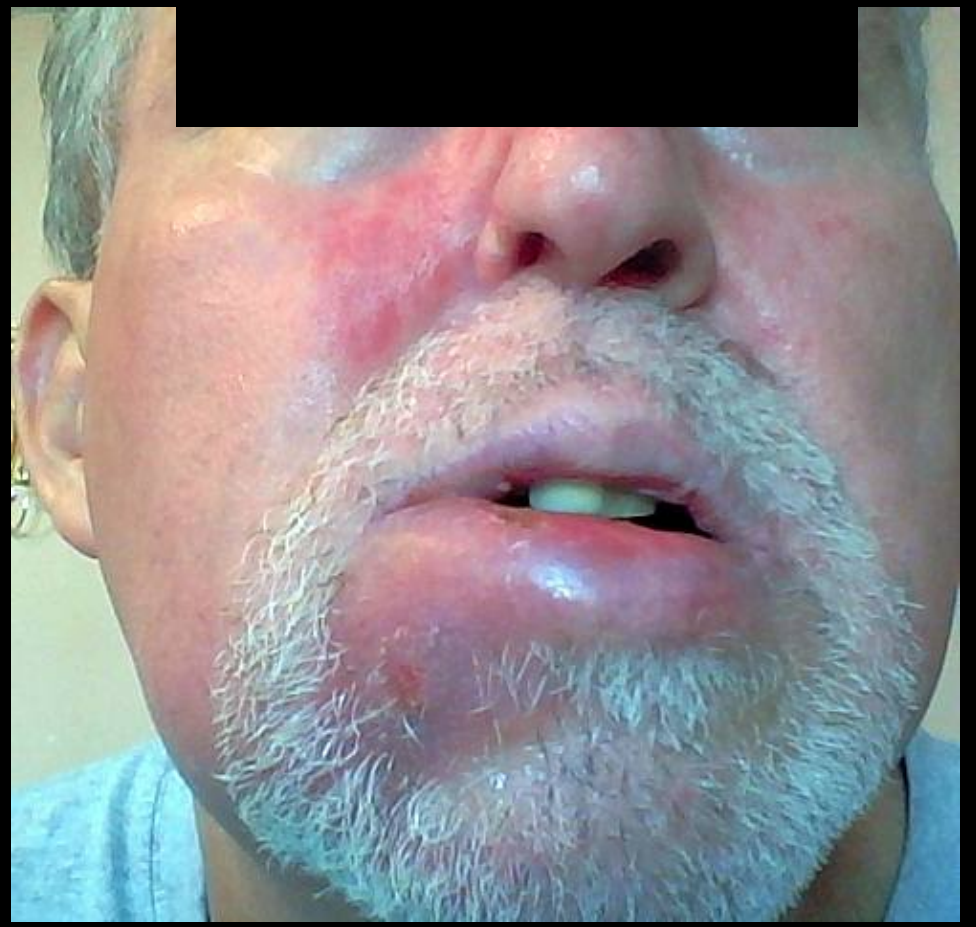
- **Once daily, broad spectrum tetracycline derivative**
  - **MRSA, Strep, most gram negative aerobes, anaerobes**
- **Oral and IV formulations; Both once daily dosing**
  - **Oral 300mg QD, IV 100mg QD (after loading doses)**
- **Tested against linezolid in ABSSSIs: Non-inferior (n=735)**
  - **No dose adjust: age, sex; hepatic or renal dysfunction**
- **Effective for: wound infection, cellulitis/erysipelas, and major abscesses with success rates >90%**
- **Minimal GI adverse events; Headache, Insomnia**
- ***Biggest issue: COST; issued specialty pharmacies***

Curr Opin Infect Dis. 2018;31(2):148-154
https://clinicaltrials.gov/ct2/show/NCT02877927

Utility?







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Antimicrob Agents Chemother. 2018 Mar 27;62(4). pii: e02551-17. doi: 10.1128/AAC.02551-17

Comparative *In Vitro* Activity of Omadacycline against Dog and Cat Bite Wound Isolates

Ellie J. C. Goldstein,[a,b] Diane M. Citron,[a] Kerin L. Tyrrell,[a] Eliza Leoncio,[a] C. Vreni Merriam[a]

[a]R. M. Alden Research Lab, Culver City, California, USA

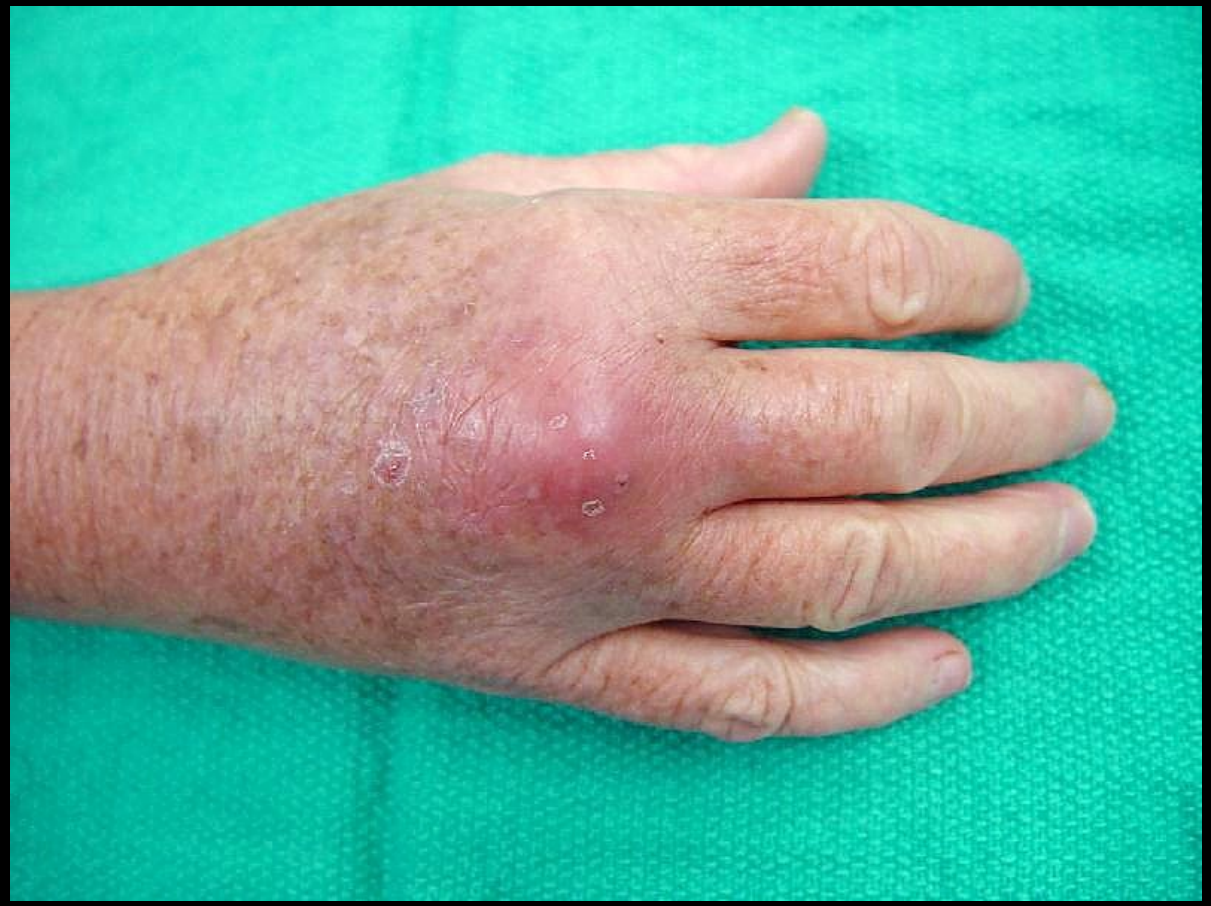
[b]David Geffen School of Medicine at UCLA, Los Angeles, California, USA

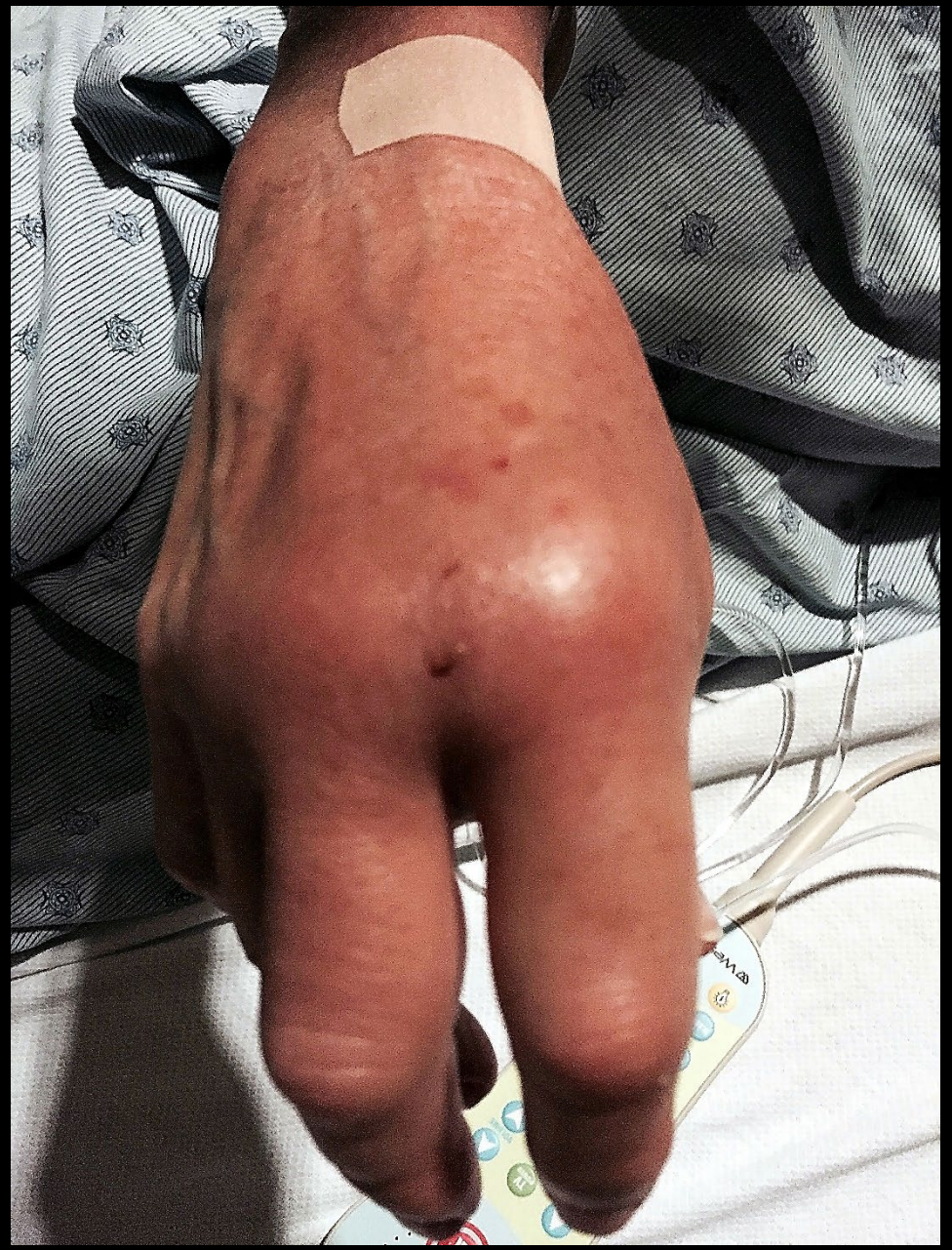
ABSTRACT Omadacycline was tested against 125 isolates recovered from infected cat and dog bites in humans. Its activity was similar to that of other compounds in the tetracycline class, and it was active against strains exhibiting tetracycline resistance. Against anaerobic isolates, resistance to tetracyclines was more prominent and omadacycline was the most active of the group. All isolates had omadacycline MICs of ≤1 μg/ml, with the exception of *Eikenella corrodens*, which showed reduced susceptibility to the entire tetracycline group.

KEYWORDS *Bacteroides pyogenes*, *Eikenella corrodens*, *Pasteurella*, *Prevotella heparinolytica*, bite wounds, cellulitis, omadacycline, tetracyclines

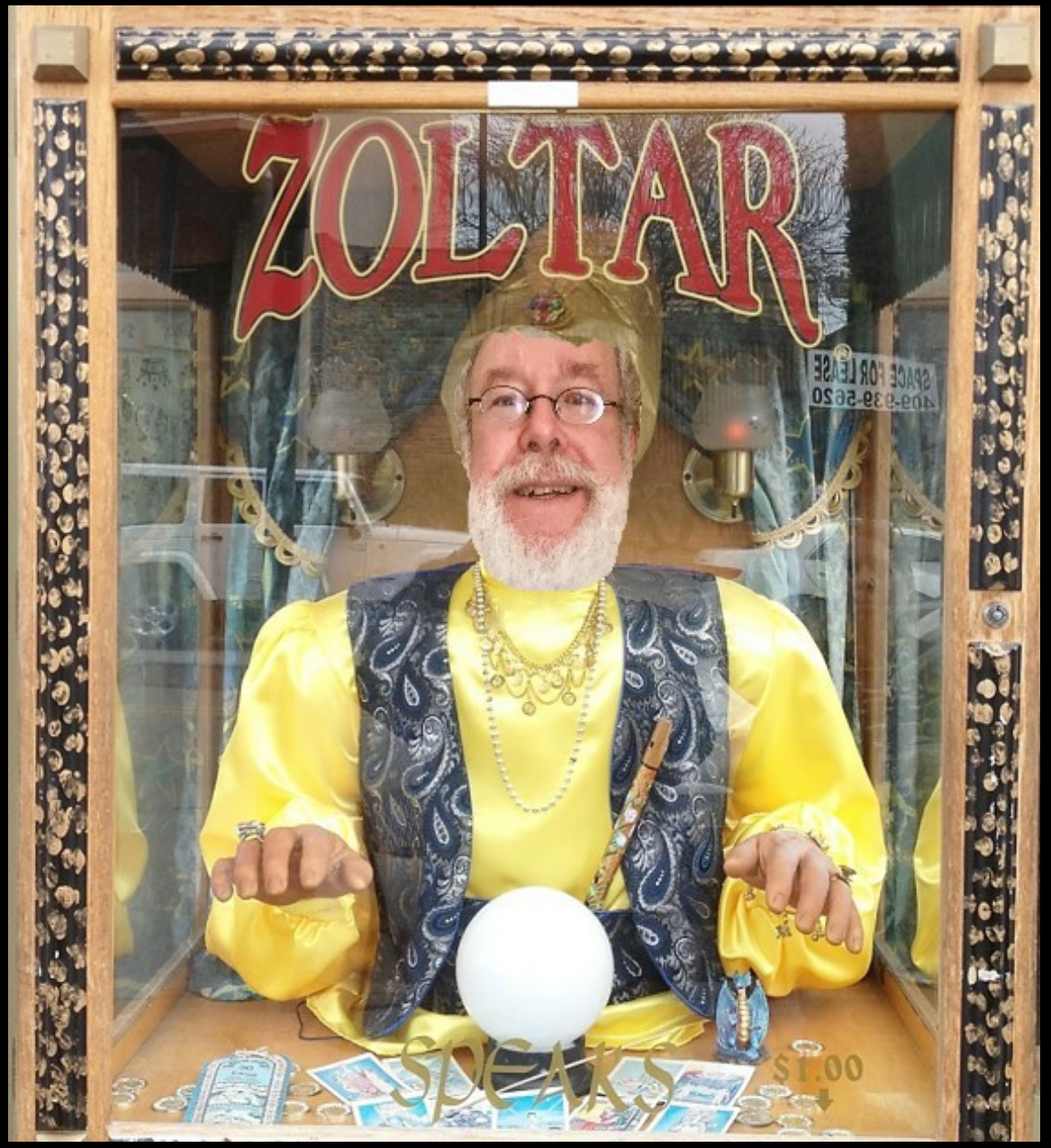
NOT effective against Eikenella (human bites) but otherwise very good

Cat bites: Omadacycline

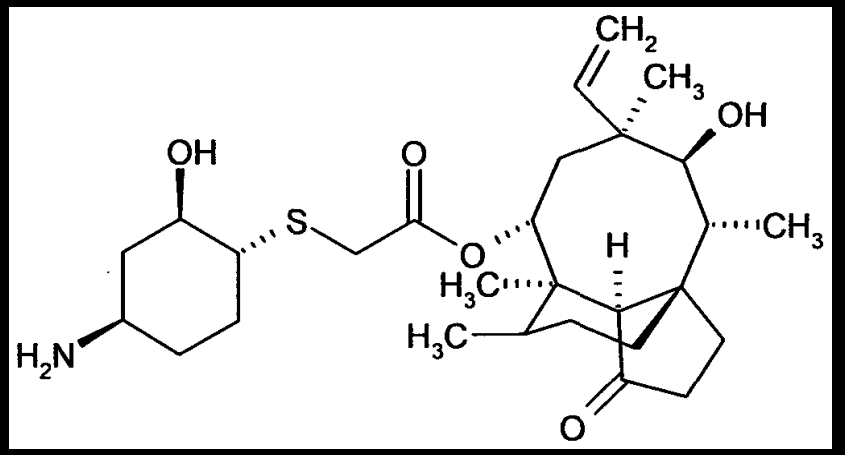




One more for the future!



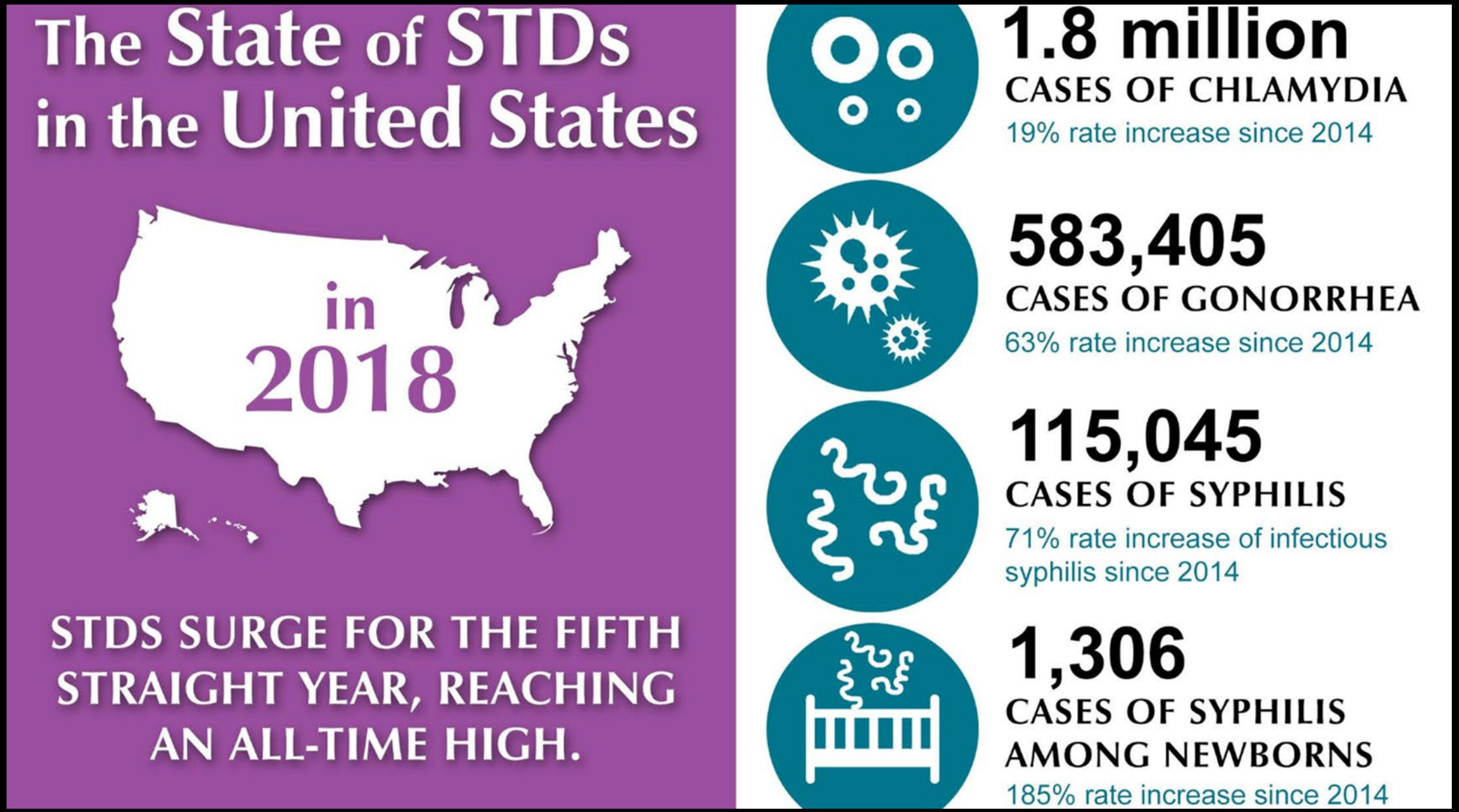
Lefamulin



- Chemical class: Heterocyclic **Pleuromutilin**
  - **Related to Retapamulin** (impetigo topical)
- MOA: Binds to peptidyl transferase site, 50S ribosome subunit
  - Inhibiting peptide transfer, and thus protein synthesis
- Active against: Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, Legionella pneumophila, Moraxella catarrhalis (CABP: first FDA approval)
- **Active against: Staphylococci (MRSA) and Neisseria gonorrhoeae**
- **Resistance: Minimal to date**; Oral 600mg and IV 150mg; BID dosing
- Status: Approved for CABP 8-19-2019

Antimicrob Agents Chemother. 2018 Apr 26;62(5). pii: e02380-17
Pharmacotherapy. 2018 Sep;38(9):935-946
J Antimicrob Chemother. 2016;71: 1022–26

Resurgent STDs


The State of STDs in the United States
in 2018
STDS SURGE FOR THE FIFTH STRAIGHT YEAR, REACHING AN ALL-TIME HIGH.
1.8 million
CASES OF CHLAMYDIA
19% rate increase since 2014
583,405
CASES OF GONORRHEA
63% rate increase since 2014
115,045
CASES OF SYPHILIS
71% rate increase of infectious syphilis since 2014
1,306
CASES OF SYPHILIS AMONG NEWBORNS
185% rate increase since 2014

CDC.gov

The State of STDs in the United States

in ~~2018~~ **2019**

STDS SURGE FOR THE FIFTH STRAIGHT YEAR, REACHING AN ALL-TIME HIGH.

1.8 million
CASES OF CHLAMYDIA
19% rate increase since 2014

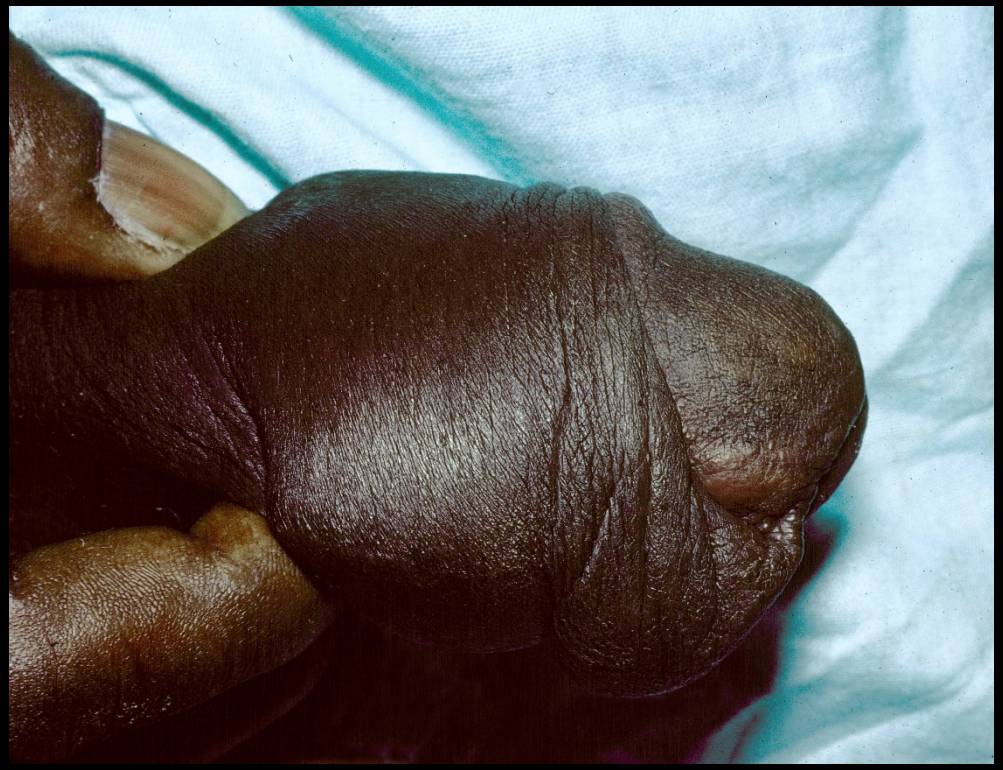
583,405 602,000
CASES OF GONORRHEA
63% rate increase since 2014

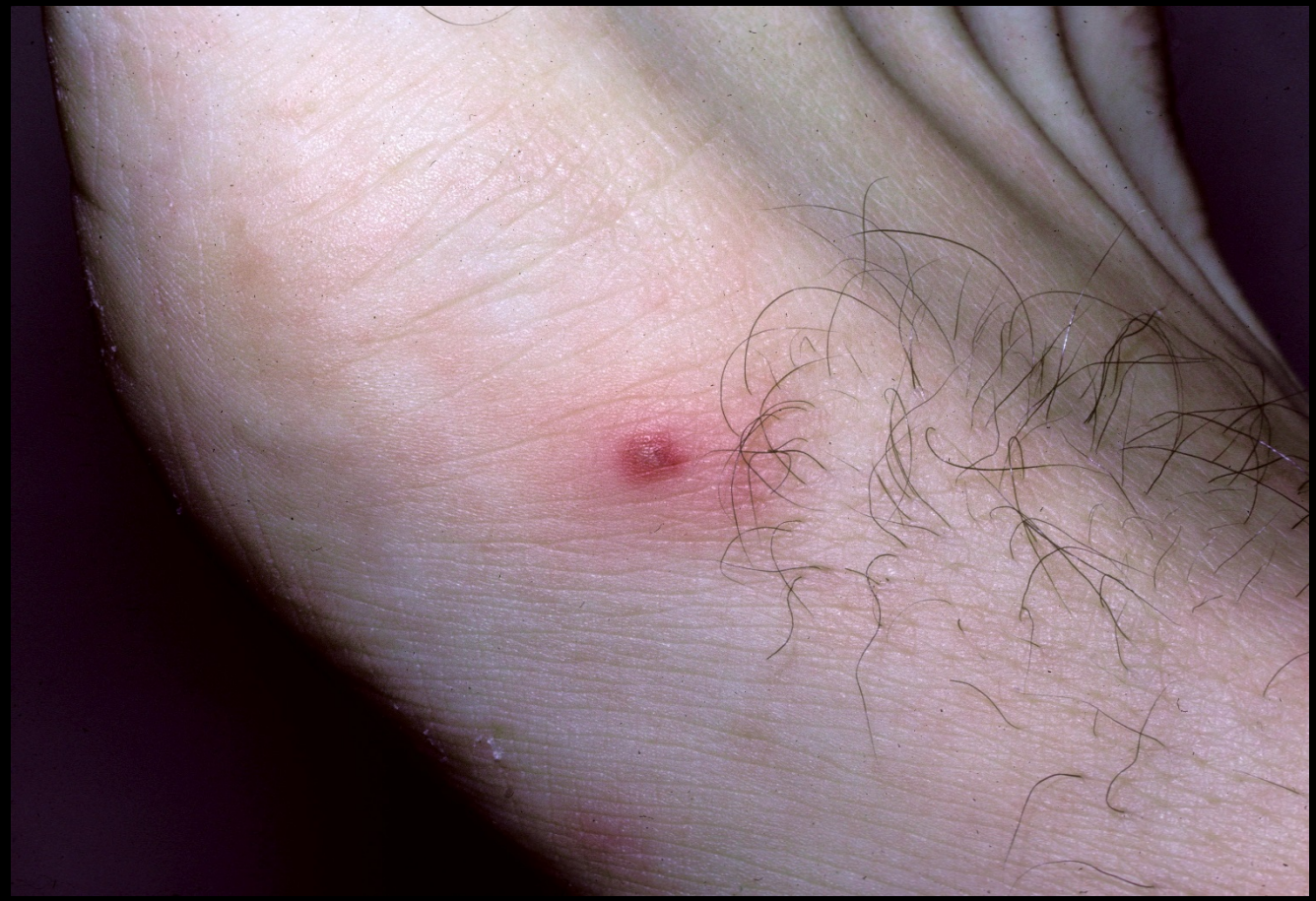
115,045 123,000
CASES OF SYPHILIS
71% rate increase of infectious syphilis since 2014

1,306 1,570
CASES OF SYPHILIS AMONG NEWBORNS
185% rate increase since 2014

CDC Roundtable, STD Prevention Conference, September, 2020

Gonorrhea





Uncomplicatd Gonorrhea

- Update to CDC's Treatment Guidelines for Gonococcal Infection, 2020

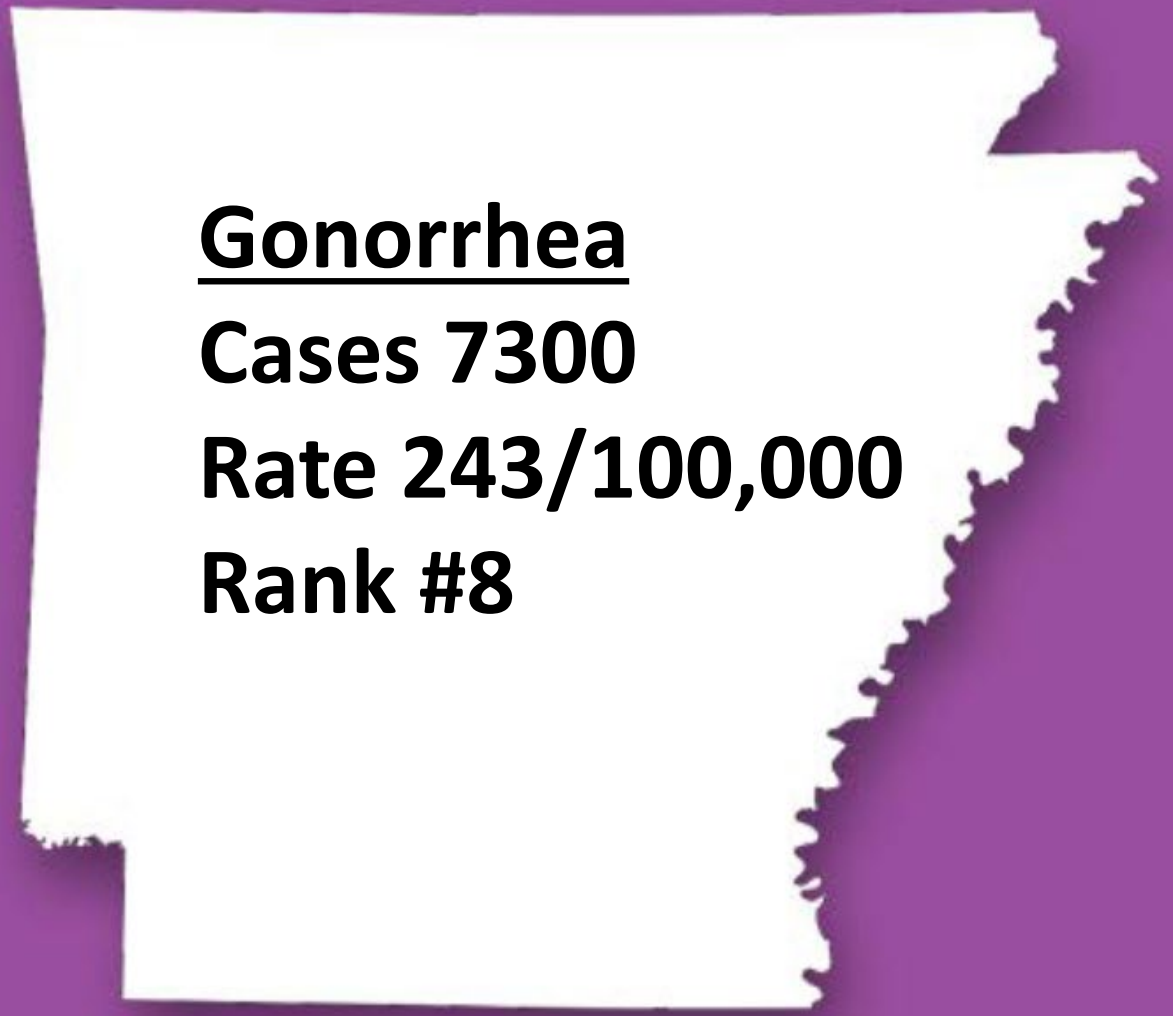
Weekly / December 18, 2020 / 69(50);1911–1916

Sancta St. Cyr, MD[1]; Lindley Barbee, MD[1,2]; Kimberly A. Workowski, MD[1,3]; Laura H. Bachmann, MD[1]; Cau Pham, PhD[1]; Karen Schlanger, PhD[1]; Elizabeth Torrone, PhD[1]; Hillard Weinstock, MD[1]; Ellen N. Kersh, PhD[1]; Phoebe Thorpe, MD[1] (View author affiliations)

- **Single dose Ceftriaxone 500mg IM**
- **No longer recommended concurrent Azithromycin therapy**

MMWR Morb Mortal Wkly Rep 2020;69:1911–1916.

ARKANSAS



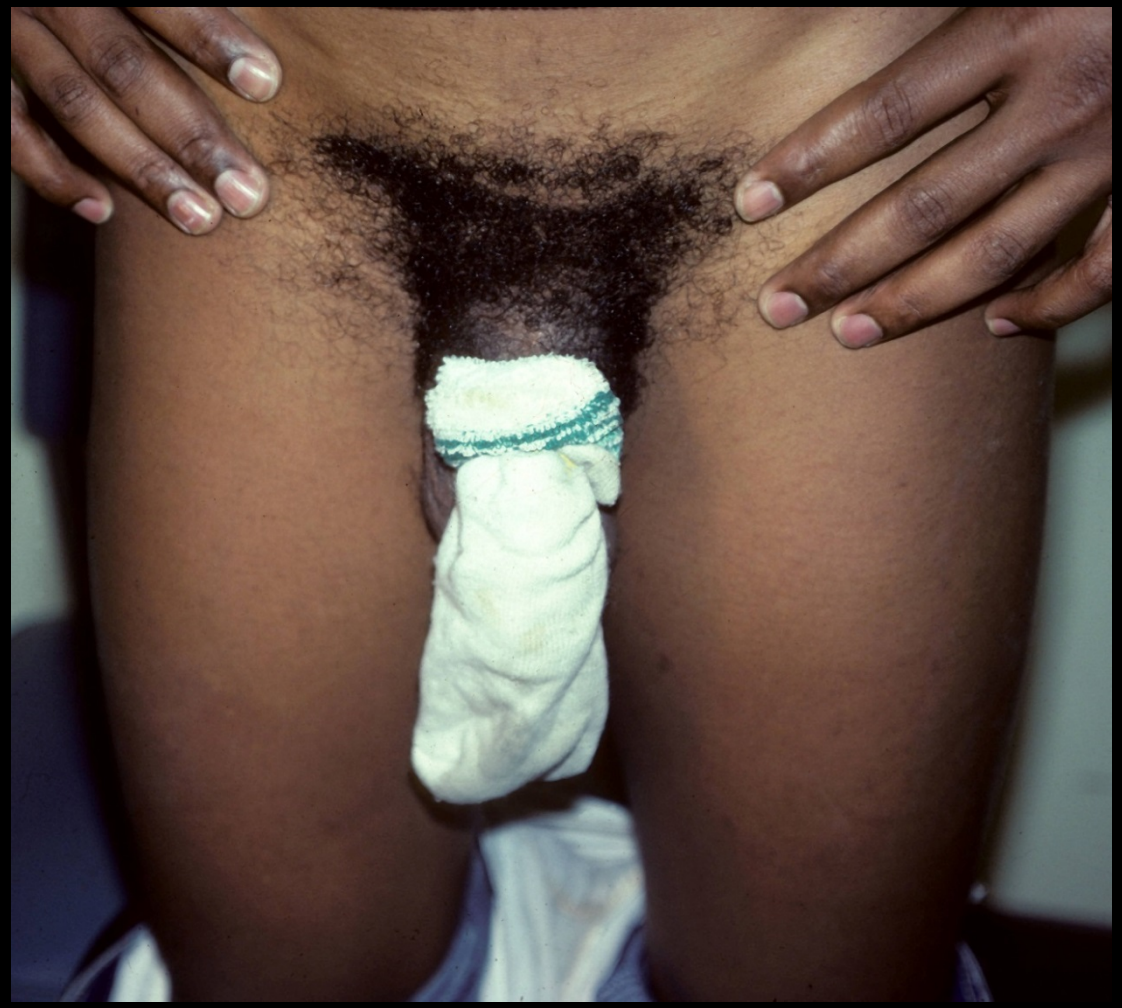
Gonorrhea

Cases 7300

Rate 243/100,000

Rank #8

Gonorrhea

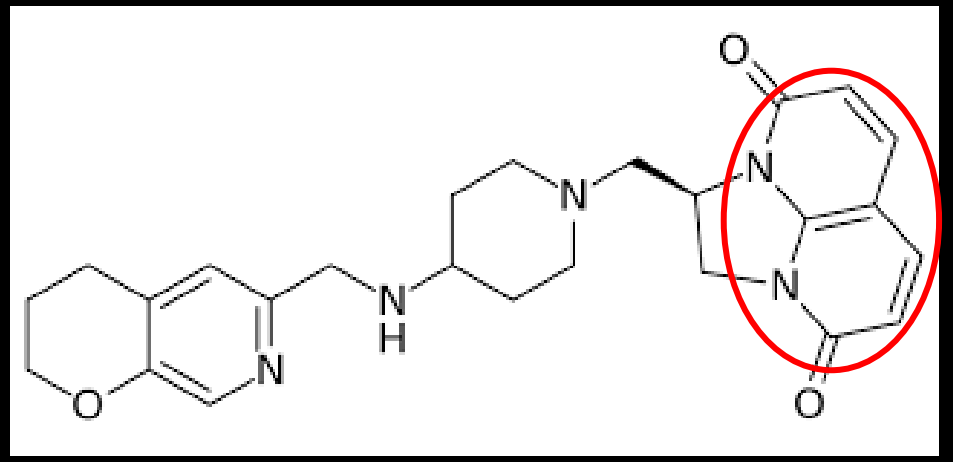


- **Treatment failure to the last resort of for gonorrhoea (third generation cephalosporins) has been confirmed in at least 11 countries:**
- **Australia, Austria, Canada, France, Japan, Norway, Slovenia, South Africa, Sweden, Great Britain and Northern Ireland**
- **Hawaii and California**

https://www.cdc.gov/std/gonorrhea/arg/default.htm

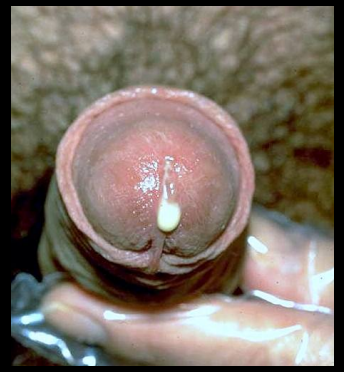
Gepotidacin

- Chemical class (new): triazaacenaphthylene
- MOA: Topoisomerase II inhibitor
  - Inhibiting DNA replication
- **Active against: Broad spectrum Gr+ and Gr-**
- **Neisseria gonorrhoeae**
  - **Including MDR-NG**
- Resistance: Reported to develop
- Single oral dose 1500-3000mg
- Status: Phase 2 done; Phase 3 enrolling GC



Antimicrob Agents Chemother. 2018 Sep 24. pii: AAC.01221-18.
Clin Infect Dis 2018;67:504–512
J Antimicrob Chemother. 2018;73:2072-2077

Phase 2 Results



Drug/Dose	% Negative Culture		
	Urethral	Rectal	Pharyngeal
Gepotidacin 1500mg x 1 dose	97	100	50
Gepotidacin 3000mg x 1 dose	96	100	50

Clin Infect Dis. 2018;67(4):504-512

plus

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

Antimicrob Agents Chemother. 2017 Jun; 61(6): e02095-16.

PMCID: PMC5444153

Published online 2017 May 24. Prepublished online 2017 Apr 3. doi: [10.1128/AAC.02095-16]

PMID: 28373199

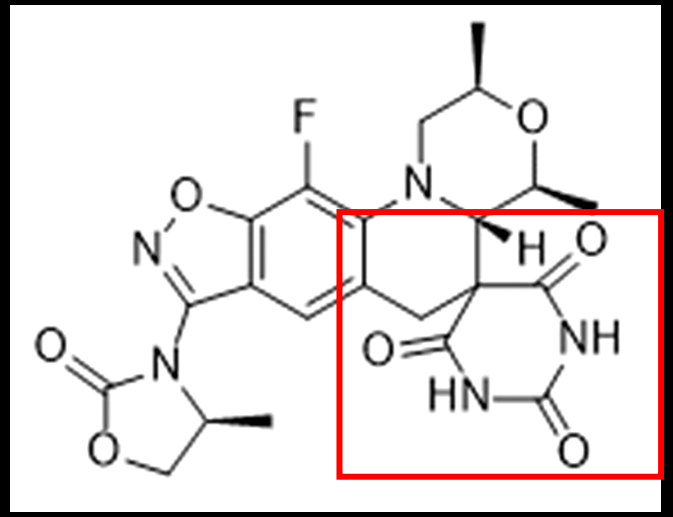
Efficacy, Safety, and Tolerability of Gepotidacin (GSK2140944) in the Treatment of Patients with Suspected or Confirmed Gram-Positive Acute Bacterial Skin and Skin Structure Infections

William O'Riordan,[a] Courtney Tiffany,[b] Nicole Scangarella-Oman,[b] Caroline Perry,[b] Mohammad Hossain,[c] Teri Ashton,[b] and Etienne Dumont[b]

Author information ▶ Article notes ▶ Copyright and License information ▶ Disclaimer

Antimicrob Agents Chemother. 2018 Sep 24. pii: AAC.01221-18.

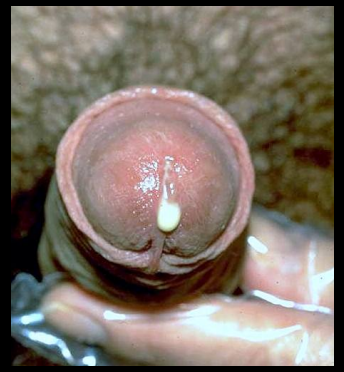
Zoliflodacin



- Chemical class (new): Spiropyrimidinetrione
- MOA: Topoisomerase & DNA gyrase inhibitor
  - Inhibiting DNA replication
- Active against: Broad spectrum Gram+ / Gram-
  - Especially effective vrs Neisseria gonorrhoeae
- Resistance: Reported to develop rarely
- Status: Phase 2 done; Phase 3 enrolling

New Engl J Med 2018;379:1835-45

Phase 2 Results

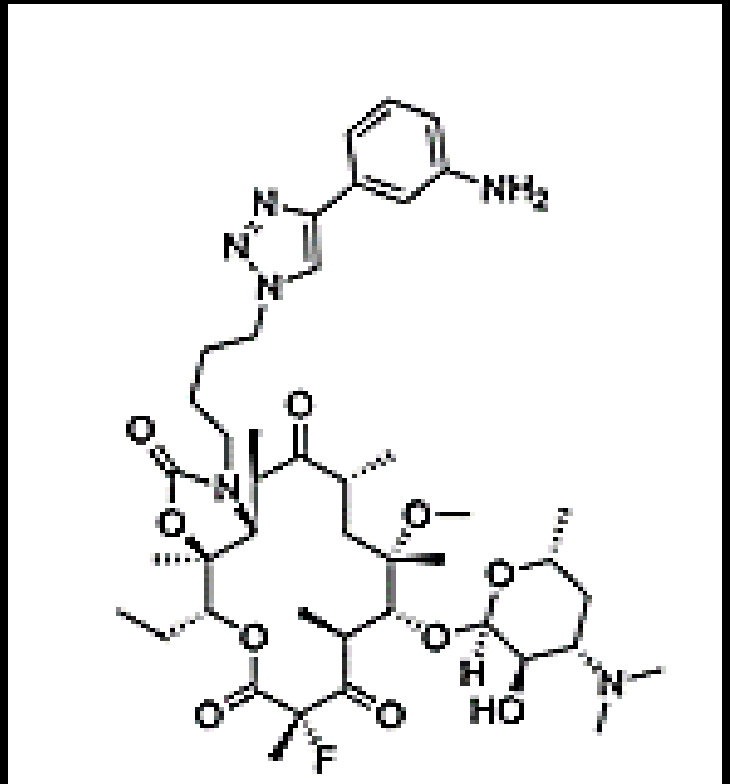


Drug/Dose	% Negative Culture			% Negative NAAT		
	Urethral	Rectal	Pharyngeal	Urethral	Rectal	Pharyngeal
Zoliflodacin 2g PO x 1 dose	96	100	82	81	100	55
Zolifoldacin 3g PO x 1 dose	96	100	50	84	100	25
Ceftriaxone 500mg IM x 1 dose	100	100	100	89	100	50

New Engl J Med 2018;379:1835-45

Solithromycin

- Chemical class: Fluoroketolide
  - Related to macrolides
- MOA: Ribosome binding at three sites
  - Inhibiting protein synthesis
- **Active against: Wide range Gr+ and Gr-**
- **Neisseria gonorrhoeae**
  - **Including MDR NG**
- Resistance: Reported
- Oral with single dose (1000mg or 1200mg)
- Status: Phase 2 =100% response (69); Phase 3 enrolling



J Pharm Pract. 2018;31:195-201
Clin Infect Dis. 2015;61:1043-8

Does ANYTHING *really* work for molluscum?

Cochrane Library

Cochrane Database of Systematic Reviews

Cochrane Database Syst Rev. 2017 May 17;5:CD004767.

Interventions for cutaneous molluscum contagiosum (Review)

van der Wouden JC, van der Sande R, Kruithof EJ, Sollie A, van Suijlekom-Smit LWA, Koning S

"No single intervention has been shown to be convincingly effective in the treatment of molluscum contagiosum. As the evidence found did not favor any one treatment, the natural resolution of molluscum contagiosum remains a strong method for dealing with the condition."

Hyperthermia and Molluscum

- **Small (n=21) Chinese prospective study**
  Patented IR heating unit (We would use heating pad)
- **44^0C (111^0F) for 30 minutes, Weekly x 12 weeks**
- **13 children, 8 sexually active adults (ages 21-28)**
- **Average # lesions = 59 (ie. Bad molluscum)**
- **12/21 complete clearance 12 weeks (children and adults)**
  Facial lesions more resistant
- **Message: Thermotherapy non-invasive MC Rx**

Br J Dermatol. 2017;176:809-812

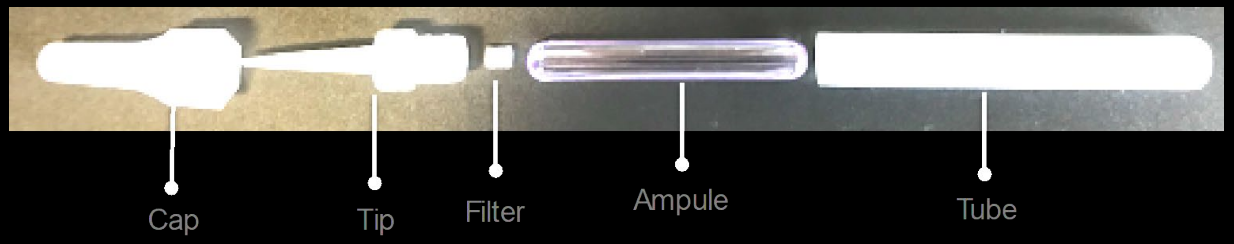
Cantharidin and Molluscum: Reinvention

- Once applied, cantharidin activates neutral serine proteases that cause degeneration of the desmosomal plaque, leading to detachment of tonofilaments from desmosomes
- This leads to **intraepidermal blistering** and nonspecific lysis of the skin, causing the tissues containing the virus to separate from the surrounding skin
- Since acantholysis is intraepidermal, healing occurs without scarring

- **Enhanced inflammatory/immune response** to viral infection?
- Leukocyte infiltration includes neutrophils, macrophages, B and T cells and eosinophils
- Release of chemokines and cytokines including TNF-a, IL-8 and CXCL-5
- Cantharidin is used in the laboratory as a model for studying leukocyte trafficking and cytokine production.

J Invest Dermatol. 1962;39:39-45
J Immunol Methods. 2001;257:213-220

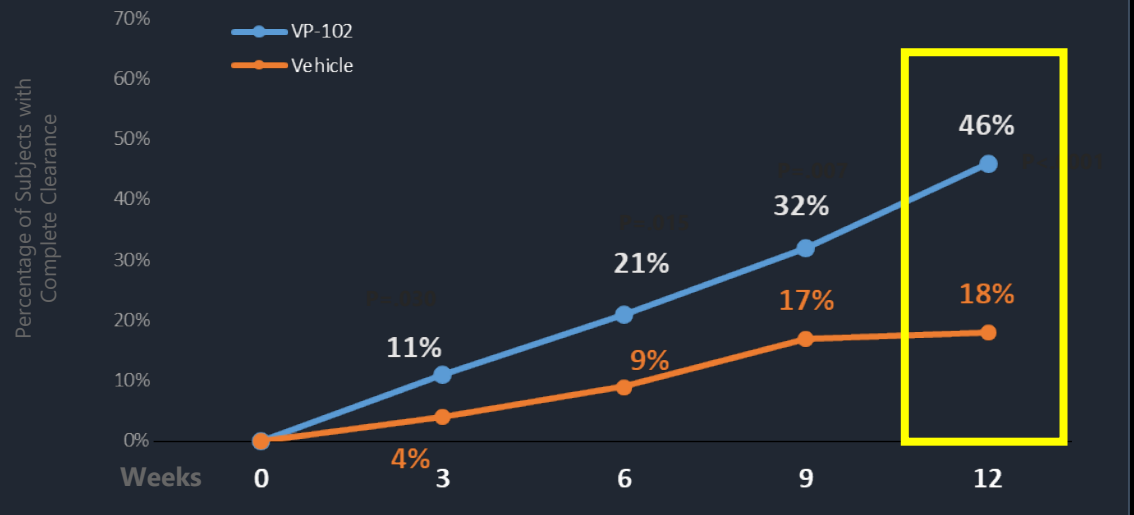
VP-102: Proprietary drug-device combination of 0.7% cantharidin administered through a single-use precision applicator



- **Cantharidin formulation with API that is greater than 99% pure and defined pharmaceutical batch process**
- **Long-term, room temperature stability**
- **Visualization agent to see which lesions have been treated**
- **Bittering agent to mitigate oral ingestion by children**

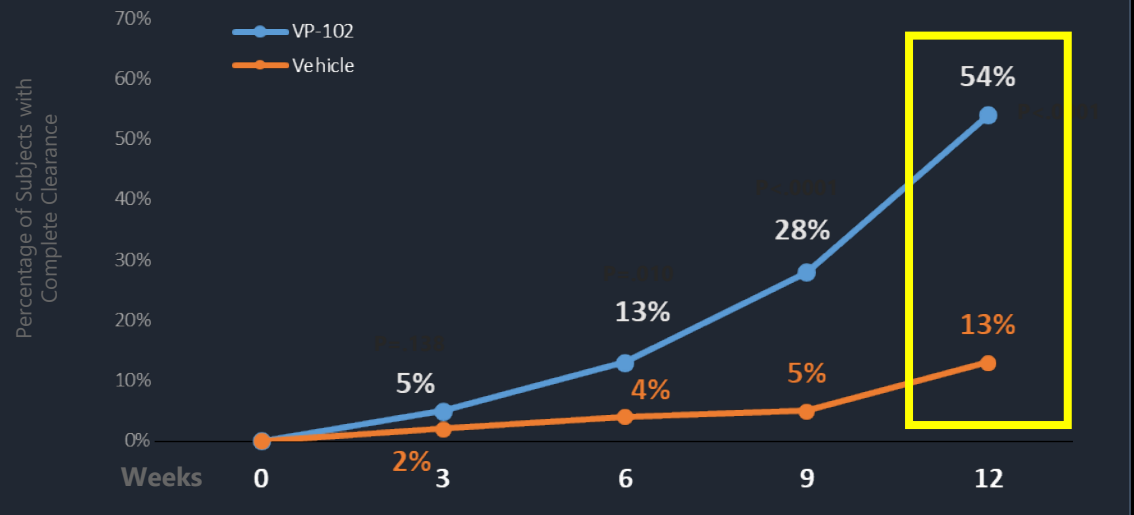
Phase 3 Studies: Statistically significant efficacy on primary endpoint of complete clearance

CAMP-1 Complete Clearance: ITT Population



	Week 3	Week 6	Week 9	Week 12
Lesion Count	↓ 38%*	↓ 45%*	↓ 51%*	↓ 69%*
% Change from Baseline	↓ 5%	↓ 5%	↓ 10%	↓ 20%

CAMP-2 Complete Clearance: ITT Population



	Week 3	Week 6	Week 9	Week 12
Lesion Count	↓ 24%*	↓ 58%*	↓ 71%*	↓ 83%*
% Change from Baseline	↑ 9%	↓ 13%	↓ 20%	↓ 19%

* Lesion count p<0.05 (pre-specified exploratory endpoint)

High Tech Mosquitoes

Dengue
Zika
Chikungunya
West Nile

EPA and Florida Dept of Health approved release of millions of GMO mosquitoes on weekly basis

Oxitec 5034 mosquitoes; Second generation

Non-biting males carry a self-destruction gene

Female offspring will die as larvae

Males will survive to mate with wild-type females and produce non-viable offspring

Home › Environment › Oxitec gets approvals to start trials with genetically modified mosquitoes

Environment | Events

OXITEC GETS APPROVALS TO START TRIALS WITH GENETICALLY MODIFIED MOSQUITOES

Keys mosquito control district will hold special workshop June 23

By **The Weekly Staff** - June 18, 2020

14,892 Fans

2,772 Followers

3,589 Followers

KEYS WEEKLY

CORONAVIR NEWS

The Aedes aegypti mosquito, which thrives in the Florida Keys, can spread disease to humans, including dengue fever, yellow fever, Zika virus and chikungunya. CONTRIBUTED

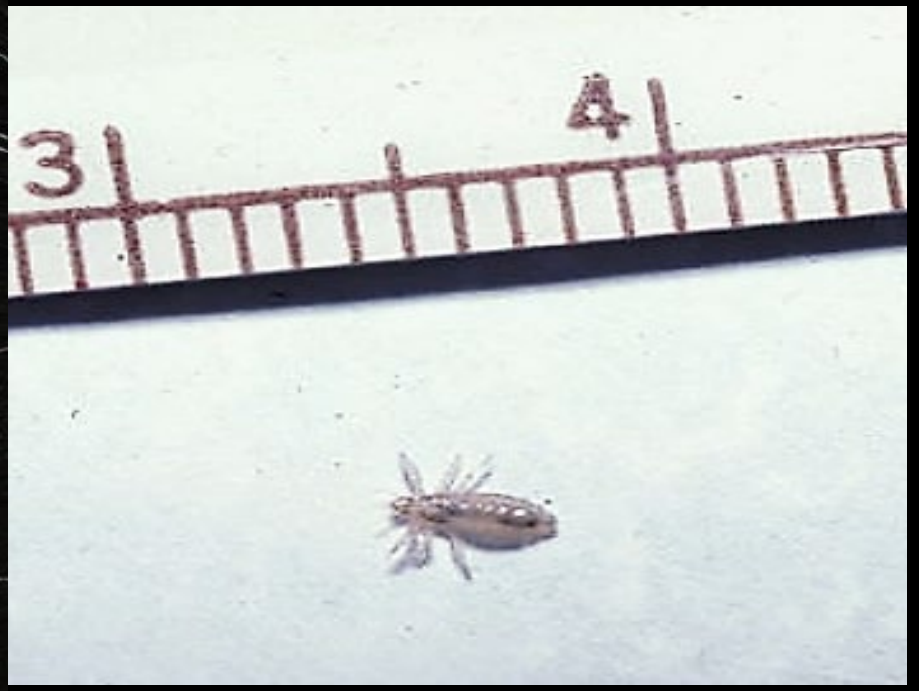
Oxitec, the company that aims to control the population of disease-carrying mosquitoes by releasing genetically modified "friendly" mosquitoes, received approval this week from seven Florida agencies and departments to begin scientific trials as part of a pilot project in the Florida Keys.

ARCIMOTO SIDEBAR

GET YOUR 10 ELECTRIC RID

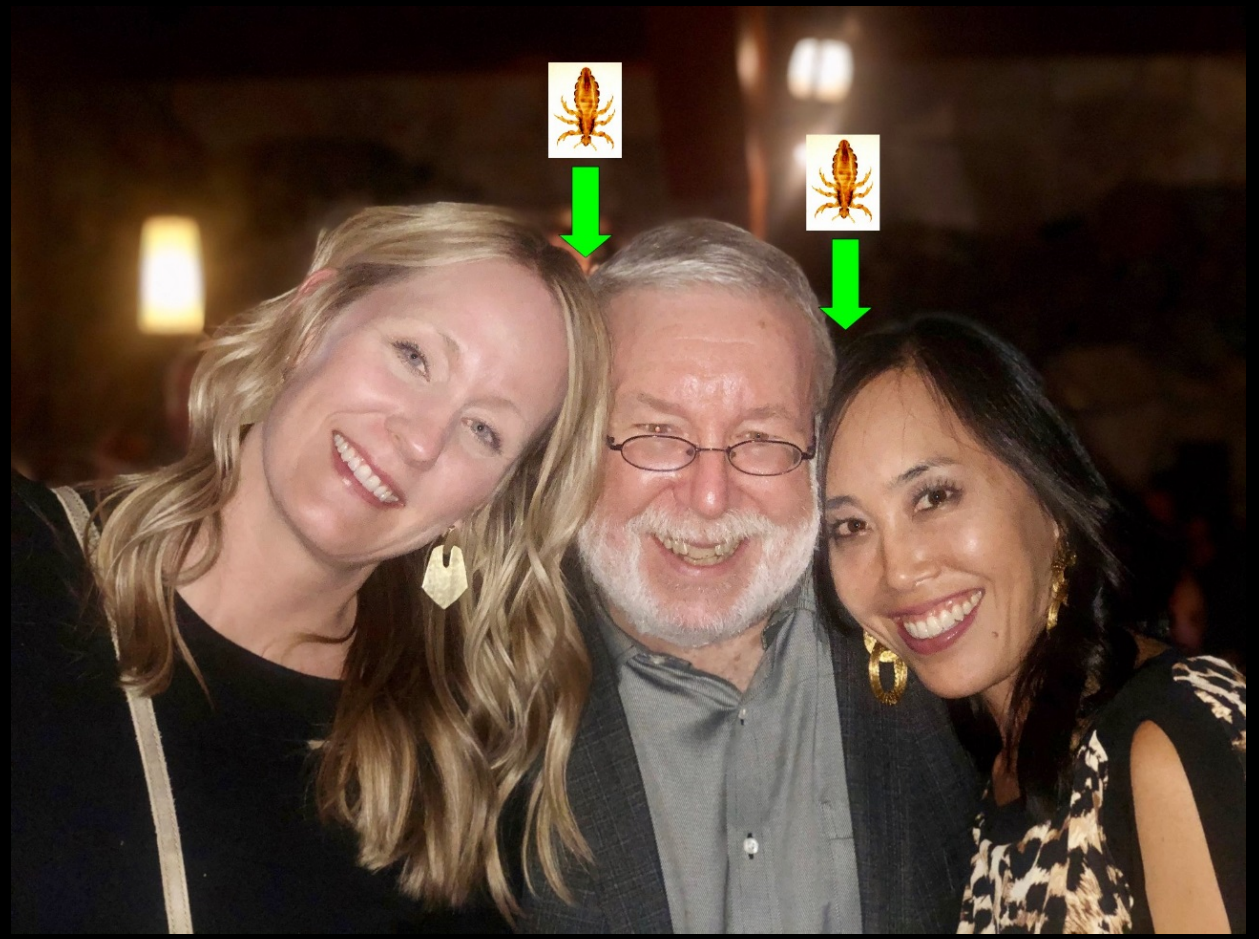
https://www.oxitec.com/en/news/oxitecs-friendly-mosquito-technology-receives-us-epa-approval-for-pilot-projects-in-us (May 1, 2020)

Pediculosis Capitis



Head Lice: Not just a pediatric disease any more!

Head Lice: Resurgence Due to Selfie Craze



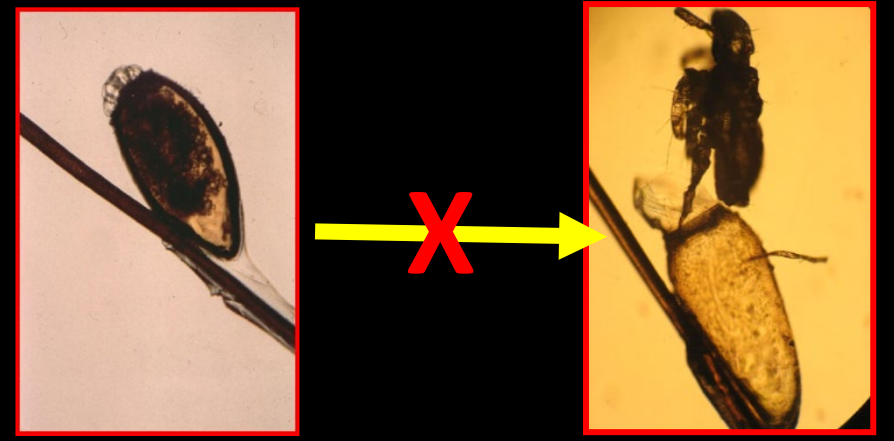
Pediculosis capitis (Head lice)

- **Collected head lice: 138 sites, 48 states**
  - **Excluded Alaska and West Virginia**
- **Summer 2013-Summer 2015**
- **96% of sites had 100% of all lice carrying resistance genes to pyrethroids**
- **42/48 states had 100% resistance of all lice collected**
- **Correlates w/ OTC pyrethroid failures**

J Med Entomol 2016;53:653-659

Abametapir = Xeglyze

- **Abametapir 0.74% : Approved 7-24-2020**
- **Blocks metalloproteinases**
- **Prevents egg from opening (no nymphs)**
- **Interferes w/ vital enzymes in adults**
- **Ovicidal and Pediculocidal**
- **Single 10 minute application**
- **USA Phase III: 14 sites, 704 patients**
- **Day 7: 88.5% complete cure**



Glob Pediatr Health. 2019 Feb 22;6:2333794X19831295
J Med Entomol. 2017;54:167-172
NCT02062060
NCT02060903

Abametapir: Safety

Adverse reactions	Abametapir lotion, 0.74%, N = 349 n (%)	Vehicle lotion N = 350 n (%)
Erythema	14 (4.0)	6 (1.7)
Rash	11 (3.2)	8 (2.3)
Skin burning sensation	9 (2.6)	0 (0.0)
Contact dermatitis	6 (1.7)	4 (1.1)
Vomiting	6 (1.7)	2 (0.6)
Eye irritation	4 (1.2)	2 (0.6)
Hair color changes	3 (1.0)	0 (0.0)

Pediatr Dermatol. 2018 Sep;35(5):616-621

Hautarzt. 2020 Jun;71(6):447-454. doi: 10.1007/s00105-020-04608-0.

[Increase of scabies and therapy resistance among German military personnel : An 8-year follow-up study in the Department of Dermatology of the Armed Forces Hospital Berlin, Germany (2012-2019)]

[Article in German]

E Elsner [1], T Uhlmann [2], S Krause [2], R Hartmann [3]

Resistant *Sarcoptes scabiei*

Hautarzt. 2020 May;71(5):374-379. doi: 10.1007/s00105-020-04561-y.

[Scabies therapy in Germany : Results of a nationwide survey with a special focus on the efficacy of first-line therapy with permethrin]

[Article in German]

B Hackenberg [1], O N Horváth [2], M Petachti [3], R Schult [4], N Yenigün [5], P Bannenberg [6]

Hautarzt. 2020 May;71(5):374-379
Hautarzt. 2020 May;71(7):447-454

Spinosad for Scabies

Spinosyns (natural) and spinosoids (synthetic)
Fermentation products soil actinomycete *Saccharopolyspora spinosa*
Most abundant: Spinosyn A and Spinosyn D (Thus: Spinosad)
Tetracyclic macrolides + two saccharides
Potent insecticides: disrupt nicotinic acetylcholine receptors
-Causes hyper-excitation of insect neurologic system
Selective; no activity against mammals, avian and aquatic animals
Spinosad 0.9% already approved for head lice
NEW DATA: USE FOR SCABIES: Single application (6-8hr)
Europe: Resistance of Sarcoptes scabiei to both permethrin & ivermectin

NCT02485717 (3-23-2020) and NCT02485704 (3-19-2020)

Review > Dan Med J. 2016 Oct;63(10):B5288.

Resistance in human pathogenic yeasts and filamentous fungi: prevalence, underlying molecular mechanisms and link to the use of antifungals in humans and the environment

Rasmus Hare Jensen [1]

Antifungal resistance is increasing and expanding in scope

Antifungal resistance is vastly underestimated***

Antifungal resistance may be due to decreased target enzyme affinity (mutation alters conformation)

Antifungal resistance may be due to upregulated production of target enzyme

Antifungal resistance may be due to multidrug efflux pumps

Antifungal resistance may be due to “work around” (alternate) pathways

BJD British Journal of Dermatology
BRITISH ASSOCIATION OF DERMATOLOGISTS CENTENARY:
THE FIRST 100 YEARS OF SUPPORTING DERMATOLOGY RESEARCH EXCELLENCE

Original Article | Full Access

Limited effectiveness of four oral antifungal drugs (fluconazole, griseofulvin, itraconazole and terbinafine) in the current epidemic of altered dermatophytosis in India: results of a randomized pragmatic trial

S. Singh ✉, U. Chandra, V.N. Anchan, P. Verma, R. Tilak

Tinea corporis, cruris, faciei: KOH verified (culture not required; T. mentagrophytes)
Rx regimens: Fluconazole 5 mg/kg/d, Griseofulvin 10 mg/kg/d, Itraconazole 5 mg/kg/d, Terbinafine 7.5mg/kg/d
Randomization; patients were treated for 8 weeks (n= 200)
Cure rates: Itraconazole 66%, Fluconazole 42%, Terbinafine 28%, Griseofulvin 14%
Cure = absence of signs/Sx and negative KOH

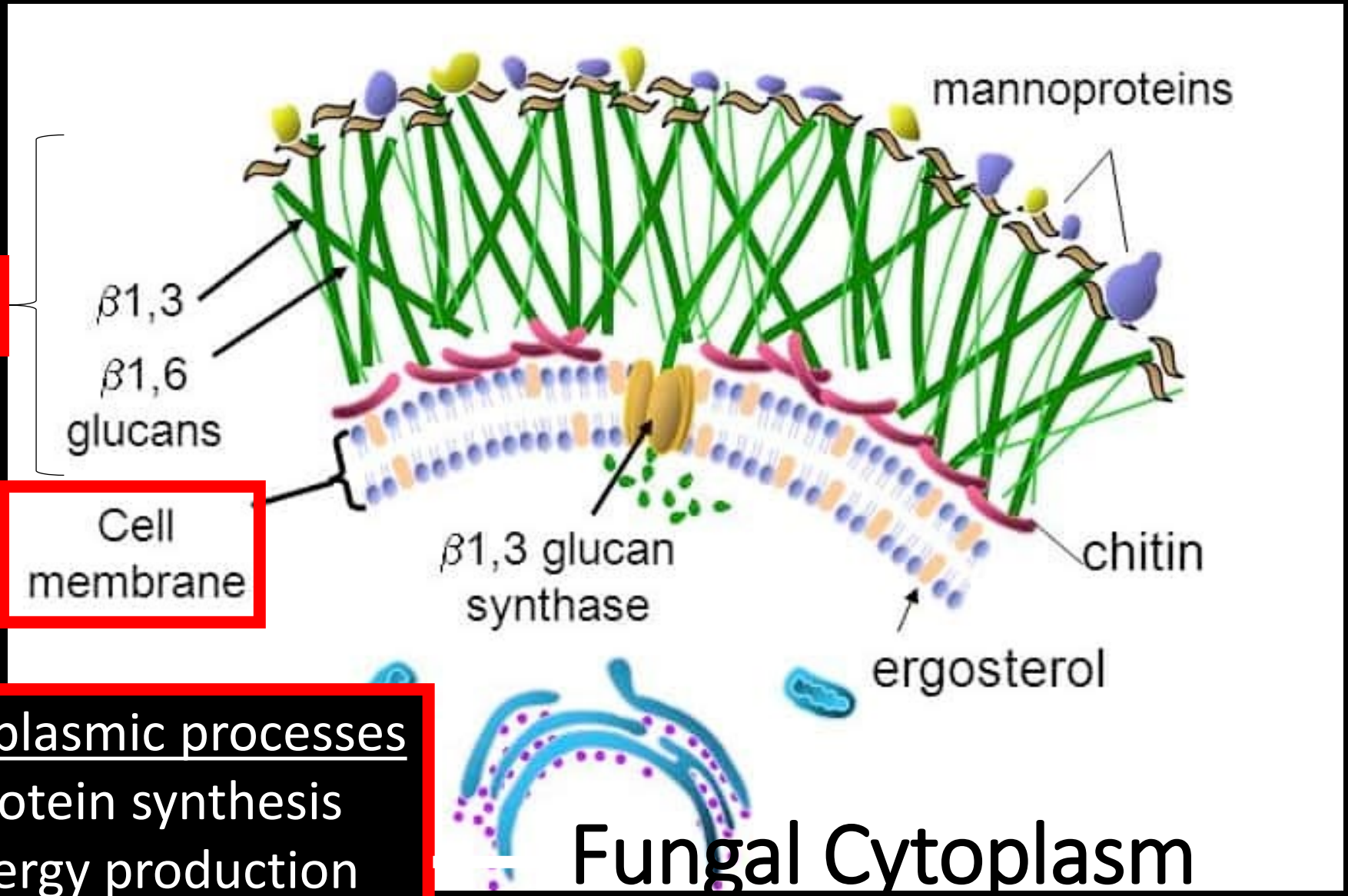
Br J Dermatol. 15 June 2020. doi: 10.1111/bjd.19146


On the horizon…

Fungal Outer Layers

Cell wall

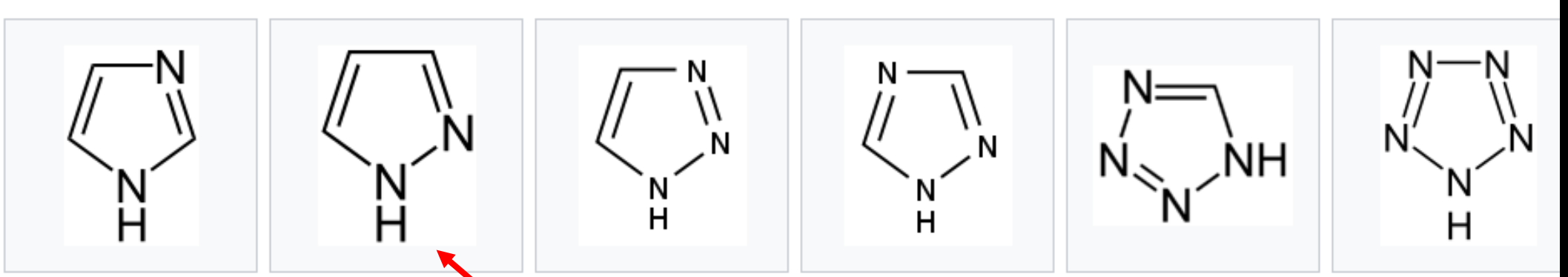
Cell membrane



Cytoplasmic processes
Protein synthesis
Energy production

Fungal Cytoplasm

Name	Class	MOA	Phase	Likely first approval
ME1111 ✅	Pyrazole	Succinate dehydrogenase	3	Onychomycosis (Topical Rx)
Rezafungin	Echinocandin	1,3-β-D-glucan synthase	3	Candidemia (IV, dosed 1x weekly)
Ibrexafungerp	Triterpenoid	1,3-β-D-glucan synthase	3	Vulvovaginal candida, Candida auris (Oral)
Olorofim	Orotimide	Dihydroorotate dehydrogenase	2b	Aspergillosis (Oral and IV)
✅ Fosmanogepix	Unique small molecule	Inositol acyltransferase	2a/b	Candida/Molds/Cocci/Crypto (Oral+IV)
MAT2203 ✅	Polyene	Cell membrane pores	2a/b	MC Candida (“Oral Amphotericin")



ME1111

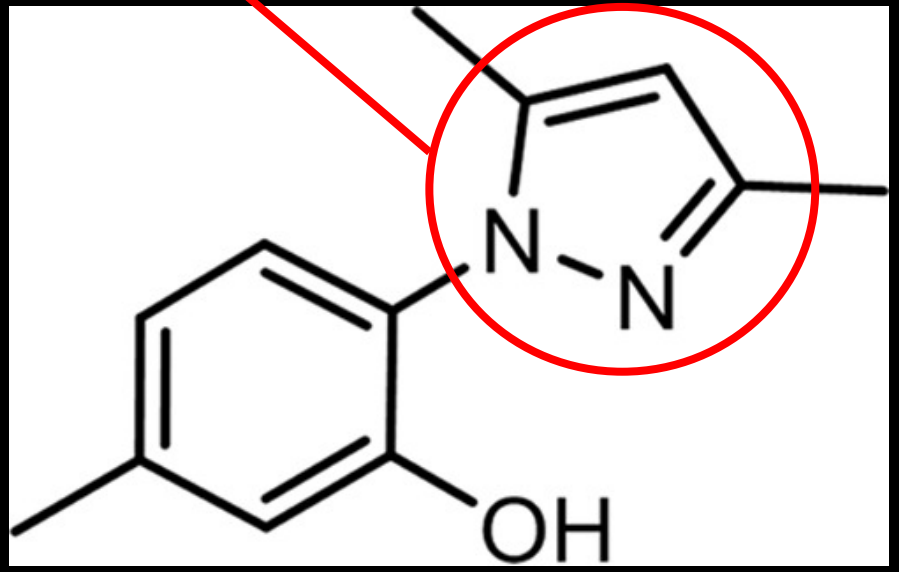
MIC90 = 0.25ug/ml

Penetrates nail

Topical use in onycho

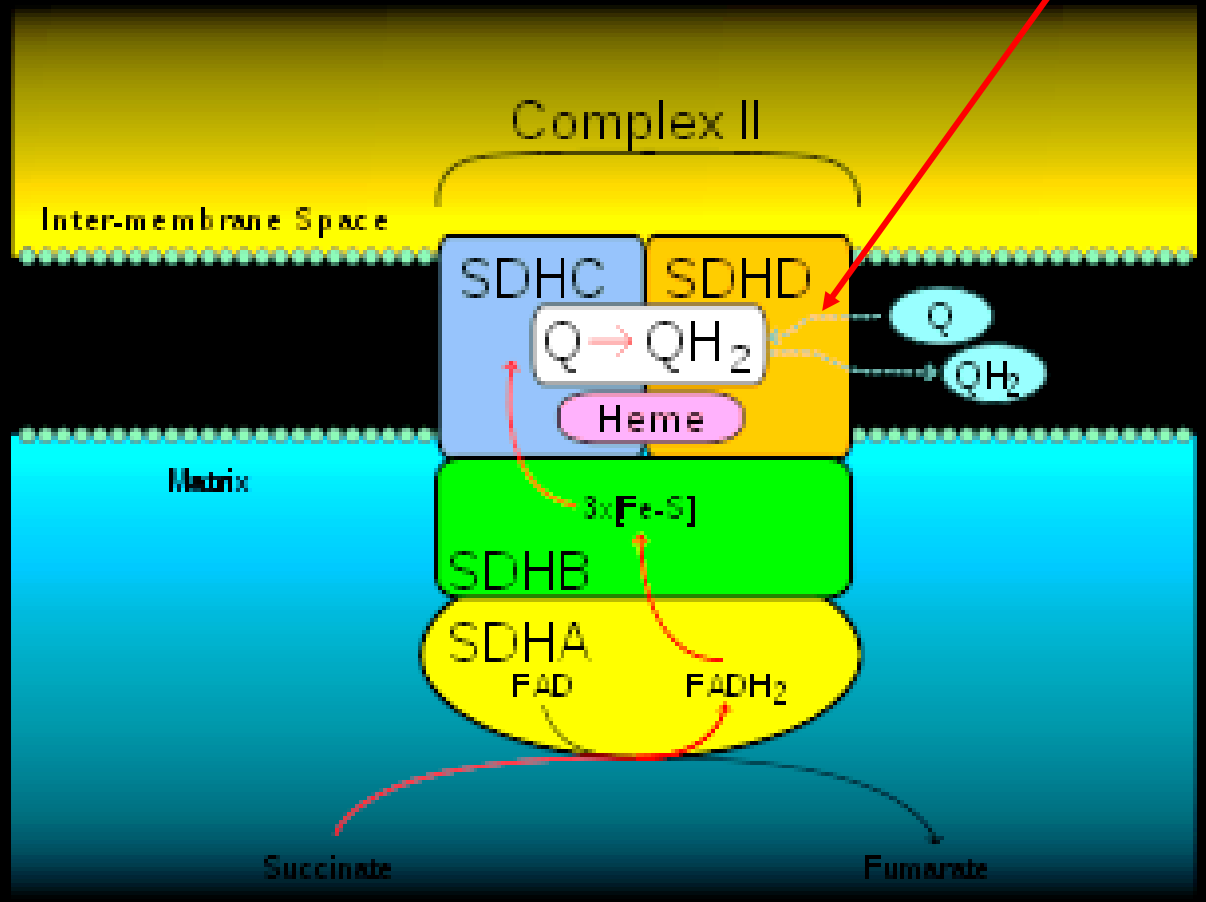
Fungal cell death

Succinate dehydrogenase



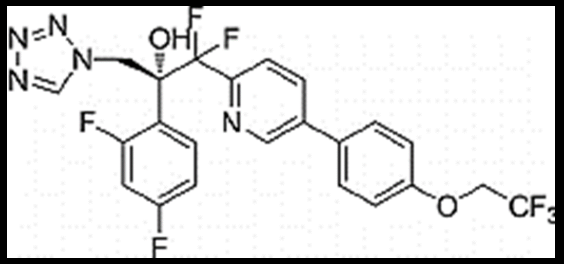
Antimicrob Agents Chemother. 2017 Dec 21;62(1). pii: e00779-17
Antimicrob Agents Chemother. 2016 Dec 27;61(1). pii: e01195-16
Antimicrob Agents Chemother. 2015 Dec 7;60(2):1035-9
Antimicrob Agents Chemother. 2015 Nov 23;60(2):873-80

ME1111 binds to and inhibits subunit D of succinate dehydrogenase complex, interfering w/ electron transport (energy generation) of the mitochondria; fungus dies



Name	Class	MOA	Phase	Likely first approval
MGCD290	HDAC Inhibitor	Hos2 Histone deacetylase inhibition	2	Adjunct to azole or echinocandin for candida/aspergillus
VT1161 ✅ (VT1598) (VT 1129)	Tetrazole	Ergosterol synthesis	3 (1) (PreClin)	Onychomycosis; other dermatophytosis for VT1161
Nikkomycin Z	Novel	Chitin syn	1/2	Coccidiodomycosis
T2307 ✅	Arylamidine	Mitochondria processes	1	Limited spectrum (Candida, Aspergillus, Malassezia, Crypto)
Aureobasidin A	Cyclic depsipeptide	Syphingolipid synthesis	1	Limited spectrum (Candida, Crypto)

VT 1161



- Tetrazole: Imidazole and triazole-like properties
- New generation inhibitor of lanosterol demethylase (CYP 51)
- Interferes w/ ergosterol synthesis: Fungal cell membrane
- Avidity: Fungal CYP51 >> human CYP51; Less inhibition cytochrome P450 in humans and thus less Drug-Drug interaction
- Potent, Broad spectrum activity against dermatophytes, Candida, molds
- Oral
- Phase 2b done for onychomycosis and vaginal Candida
- Phase 3 ongoing (Capitalism failed!) Viamet Company and VC

Int J Antimicrob Agents. 2018 Mar;51(3):333-339
Bioorg Med Chem Lett 2014;24:3455-58

VT1161

- **RENOVATE Study: Phase 2b (NCT02267356) in onychomycosis**
- **Randomized, double-blind, 4 doses plus placebo, daily 14-day loading-dose phase, then once-weekly for either 10 or 22 wks**
- **Complete cure rates at 48 weeks: 32% to 42% in the four VT-1161 dose-ranging arms compared to 0% in the placebo arm**
- **87% median reduction of nail involvement at week 48 compared to a 9% reduction in the placebo arm (even tho Rx stopped @ 22 wks)**
- **Complete cure rates continued to improve thru week 60 (no more Rx)**
- ***No patient in any VT-1161 arm discontinued the study due to a laboratory abnormality or liver dysfunction***

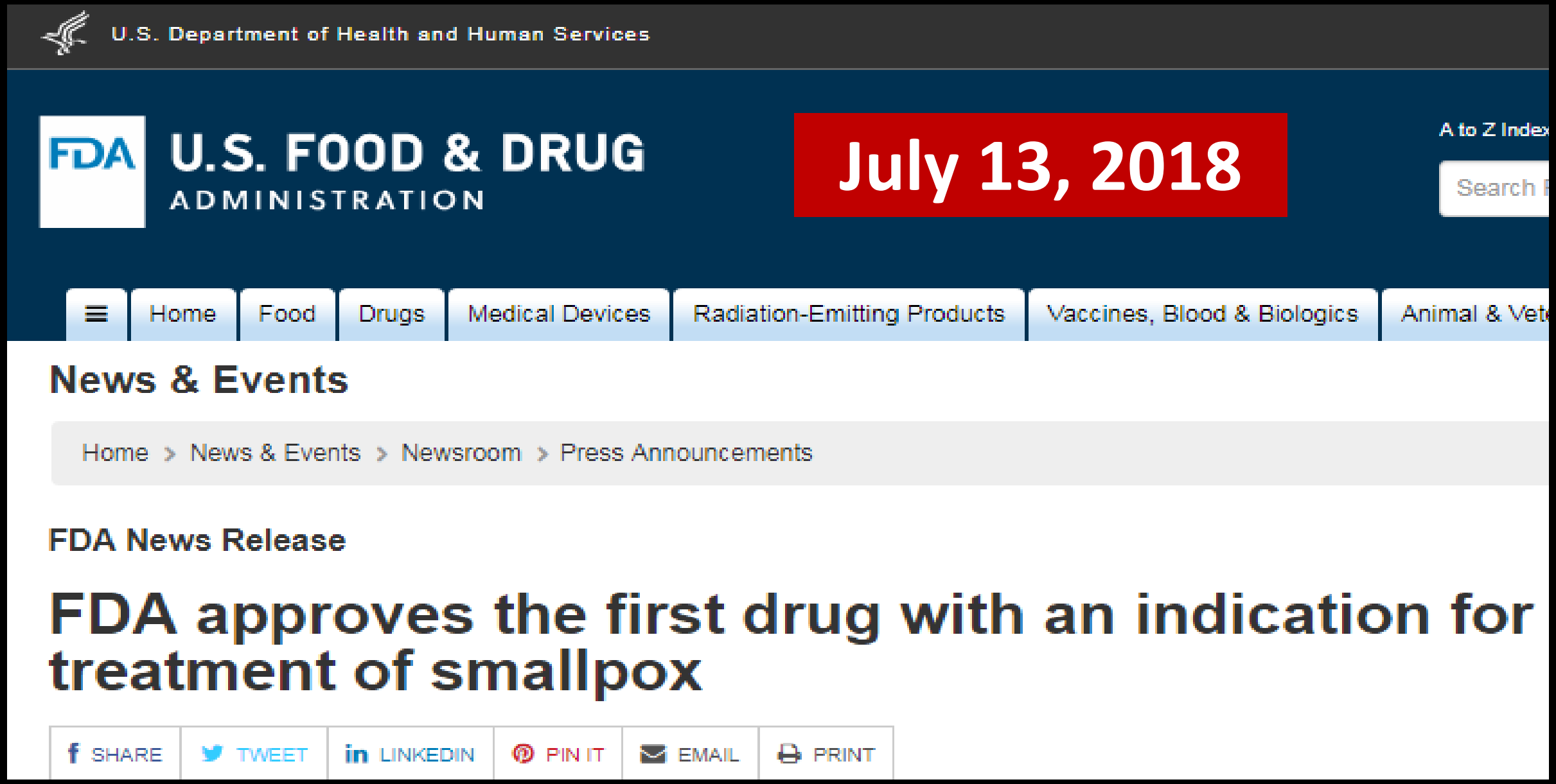
Br J Dermatol. 2020 May 18. doi: 10.1111/bjd.19224

Name	Class	MOA	Phase	Likely first approval
NP213 ✅ (Novexatin)	Synthetic Cyclic Cationic AMP	↑Plasma membrane permeability	2b-3	Onychomycosis (Aqueous topical)

Med Mycol. 2020 Mar 31;myaa015. doi: 10.1093/mmy/myaa015

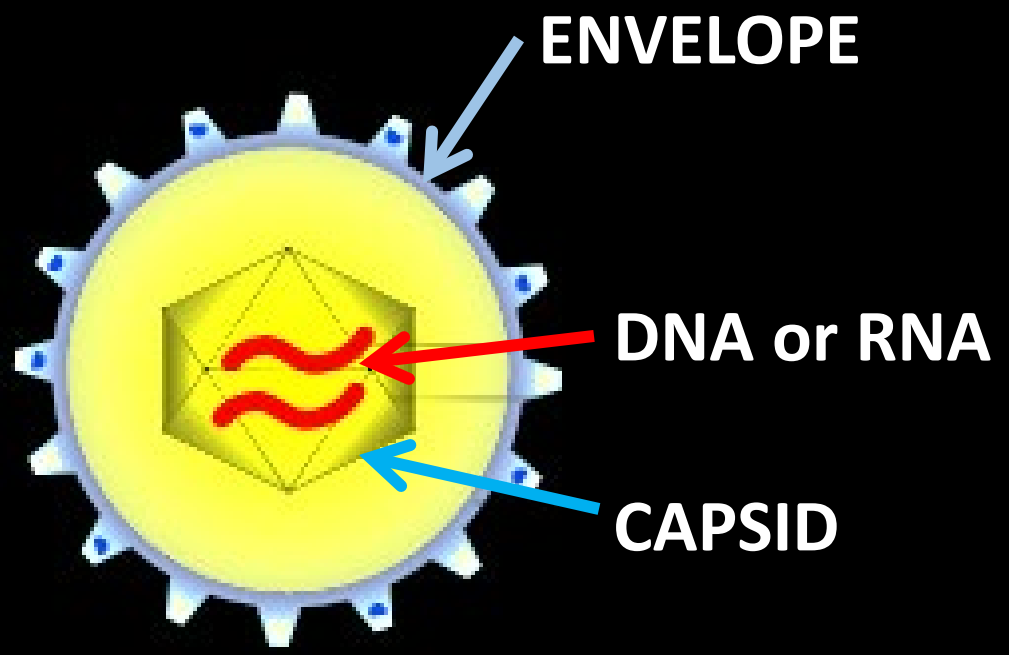

OFF
THE
WALL

Tecovirimat



Tecovirimat

- **Inhibits formation of envelope proteins required to fuse to infected cell membrane and allow smallpox virus to exit cell and infect other cells**



The OMG!

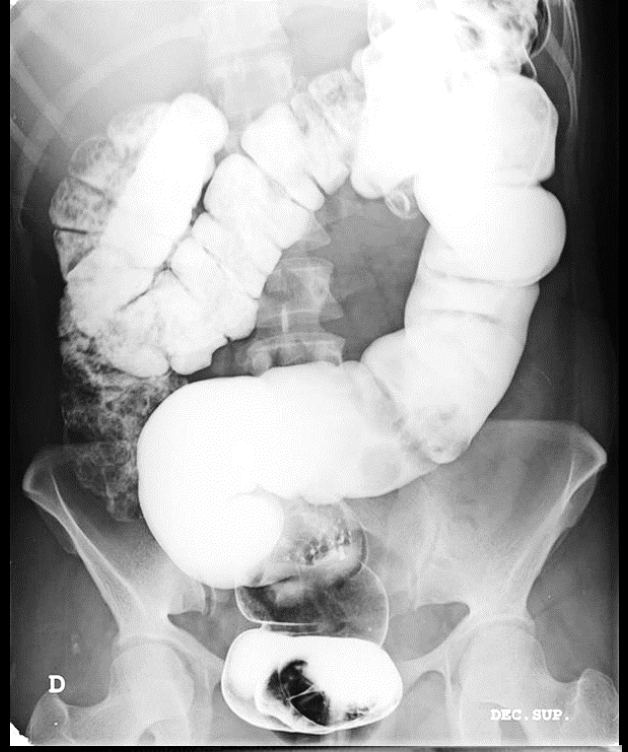
- **USA stopped administering Smallpox vaccine in 1972**
- **Smallpox deemed "eradicated" by WHO/CDC in 1980**
- **However, it is still used in biological warfare research**
- **HIGH MORTATLITY RATE ANTICIPATED IF WEAPONIZED**

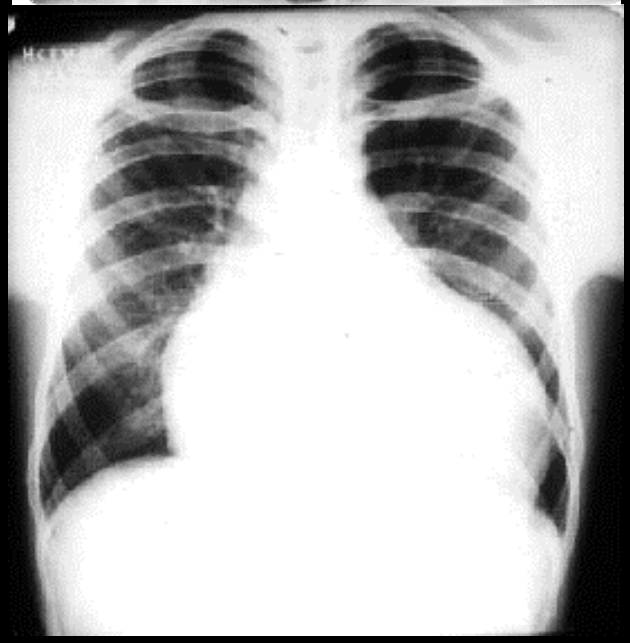
The OMG!

- USA stopped administering Smallpox vaccine in 1972
- Smallpox deemed “eradicated” by WHO/CDC in 1980
- However, it is still used in biological warfare research
- HIGH MORTATLITY RATE ANTICIPATED IF WEAPONIZED
- No therapy…..until now!
- New drug: Tecovirimat (po) [a.k.a. ST-246] TPOXX®
- Unit dose: 200mg capsules; Weight-based dosing
- 13 kg to less than 25 kg: 200 mg twice daily for 14 days
- 25 kg to less than 40 kg: 400 mg twice daily for 14 days
- 40 kg or more: 600 mg twice daily for 14 days
- Already stockpiled!!!!!

Chagas Disease

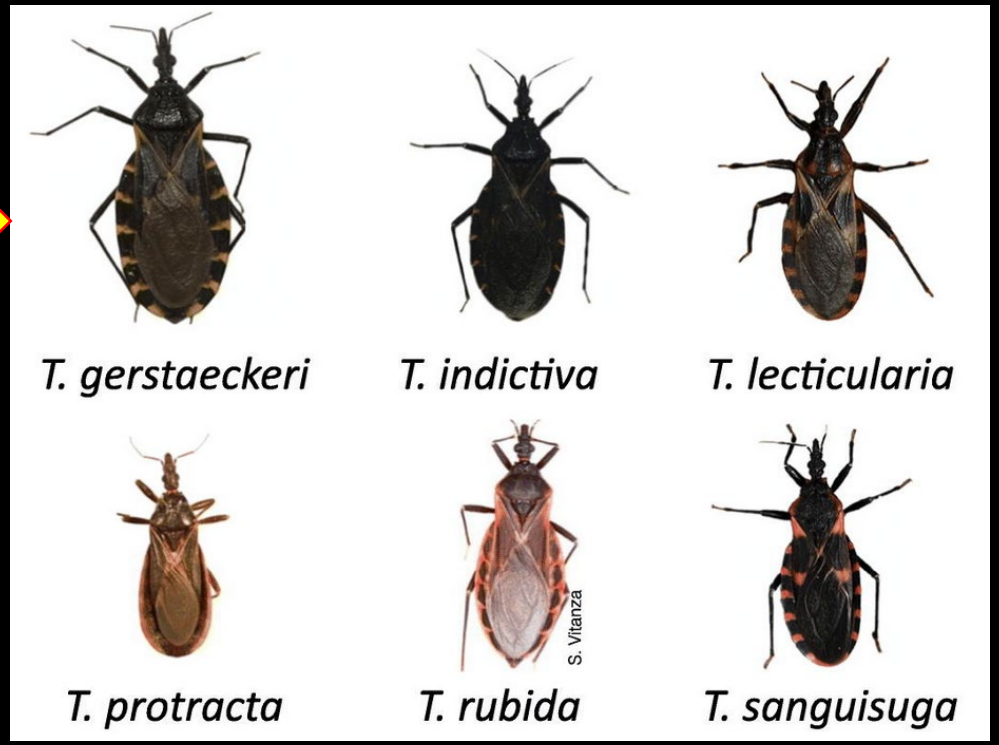
- "American trypanosomiasis"
- *T. cruzi*
- Spread by reduviid bugs
- 10-30% risk progressive dis
- **Megacolon**
- **Megaesophagus**
- **Cardiomyopathy**
- Rarely dementia
- **Should we worry?**



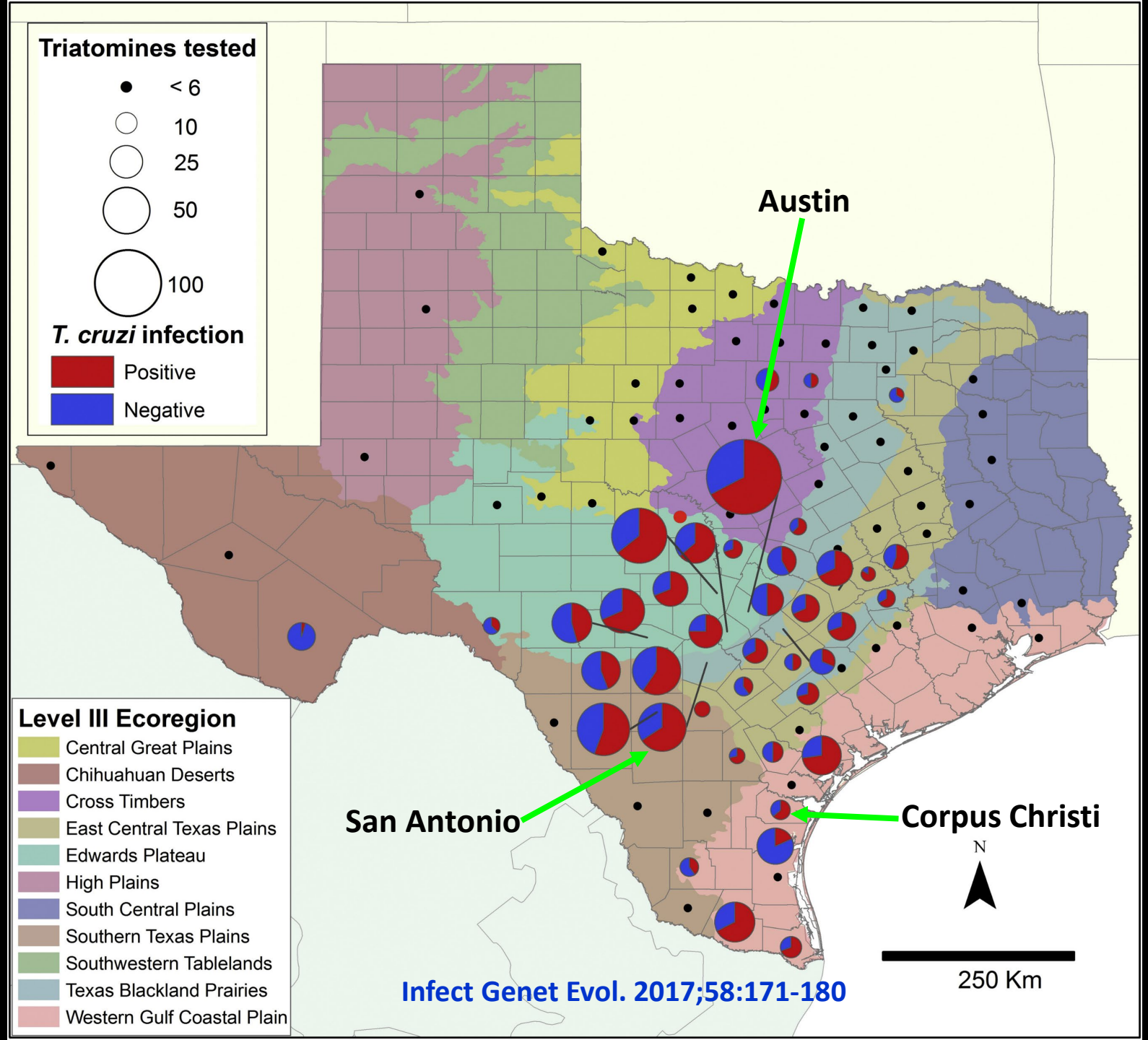


Chagas Disease in USA?

- Rare indigenous cases
- **6 US Reduviid (Triatome) species**
- T. gerstaeckeri, T. indictiva
  T. lecticularia, T. protracta
  T. rubida and T. sanguisuga
- Survey of **1510 US vectors, 54.4% harbored T. cruzi,** including subtypes known to cause Chagas disease
- **Texas, LA, FL, NM, AZ**

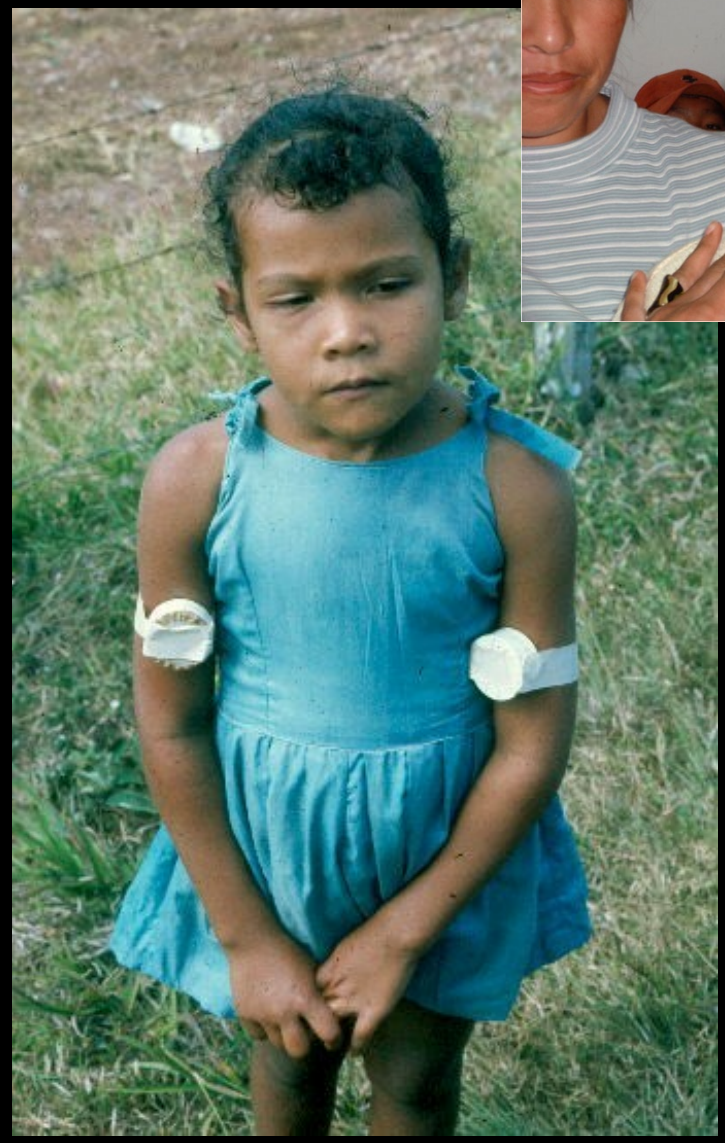


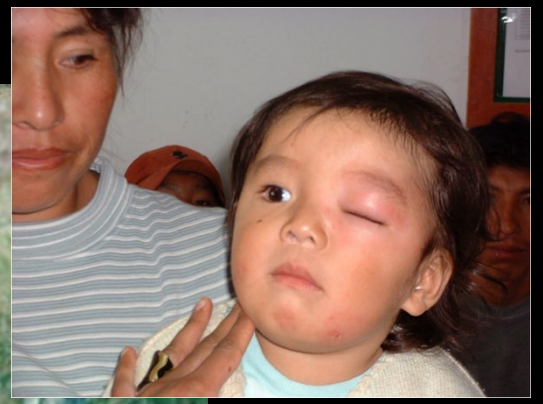
Infect Genet Evol. 2017;58:171-180


Triatomines tested
< 6
10
25
50
100
T. cruzi infection
Positive
Negative
Austin
San Antonio
Corpus Christi
Level III Ecoregion
Central Great Plains
Chihuahuan Deserts
Cross Timbers
East Central Texas Plains
Edwards Plateau
High Plains
South Central Plains
Southern Texas Plains
Southwestern Tablelands
Texas Blackland Prairies
Western Gulf Coastal Plain
N
250 Km
Infect Genet Evol. 2017;58:171-180

Benznidazole (No brand name) 8-2017

- Rx children 2-12 (and adults) w/ Chagas disease (acute or chronic)
- Parasitological cure better: younger age and acute disease (vrs chronic) 60-90%
- Destroys parasite DNA
- 5-8 mg/kg/d (divided doses) x60d
- 12.5 and 100mg tablets
- Peripheral neuropathy
- Bone marrow depression
- Hypersensitivity reactions





The Truly Obscure

Lancet 2018;392:1207

- **Onchocerciasis (River Blindness)**
- **Rx of choice: Ivermectin**
- **But repeated Q2mo….10 years!**
- **Moxidectin: longer T1/2, Better results; 8mg (4 x 2mg)**
- **Study of 1400 patients, in 3 African countries**
- **FDA Approved June, 2018**

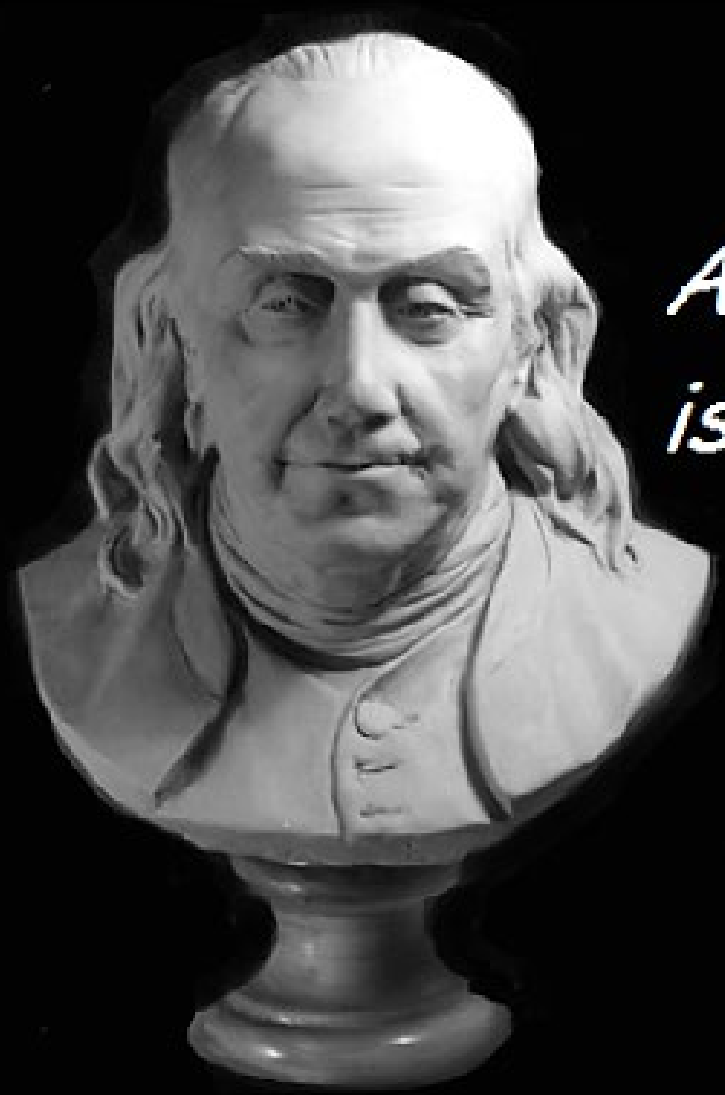
Lancet 2018;391:144

- **African Trypanosomiasis**
- **Rx of choice: Nifurtimox-Eflornithine**
- **But very toxic**
- **Fexinidazole: As effective, Few AEs 1800mg (Days 1-4) 1200mg (Days 5-10)**
- **Study of 794 patients in 2 African countries**
- **EMA approved November, 2018**
- **FDA submitted**

Prevention is better than cure.

(Desiderius Erasmus)

1466-1536



An ounce of prevention
is worth a pound of cure
- Ben Franklin

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Search MMWR Only SEARCH

Morbidity and Mortality Weekly Report (*MMWR*)

CDC > MMWR

Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines

Weekly / January 26, 2018 / 67(3);103–108

Subunit HZ vaccine is preferred over live attenuated vaccine in immunocompetent individuals, according to the US and Canadian guidelines.

Kathleen L. Dooling, MD[1]; Angela Guo, MPH[1]; Manisha Patel, MD[1]; Grace M. Lee, MD[2]; Kelly Moore, MD[3]; Edward A. Belongia, MD[4]; Rafael Harpaz, MD[1] (View author affiliations)

Form

Article Metrics

MMWR Morb Mortal Wkly Rep. 2018;67:103-108

New Recombinant Zoster Vaccine

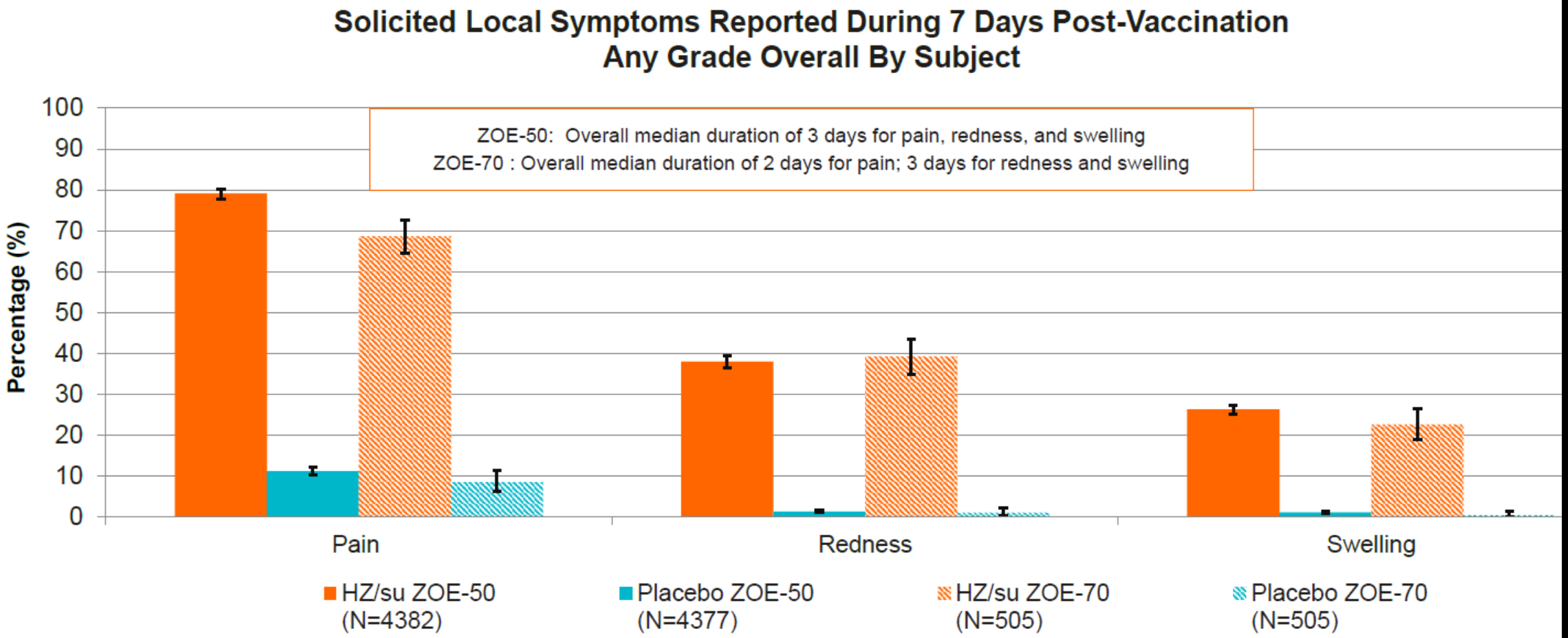
- VZV subunit vaccine for shingles (not live attenuated)
  - Glycoprotein E antigen + adjuvant; **TWO doses, IM @ 0, 2-6**
- ACIP voted to FAVOR this over existing HZ vaccine
  - Indicated for use over age 50; **EVEN if given prior vaccine**
- **90-97% effective across ALL AGES; 4 year study (9yr Ab+)**
- **88% overall effective reduction of PHN**
- Use in HIV+ inconclusive, although appears positive
- AEs: injection site reactions, systemic side effects
  - **16.5% report ANY Gr3 adverse event**
  - Myalgia, fever, headache, fatigue, shivering, GI distress

MMWR Morb Mortal Wkly Rep. 2018;67:103-108

ZOE-50 and ZOE-70

Reactogenicity Subgroups[1,2]

Duration 2-3 days

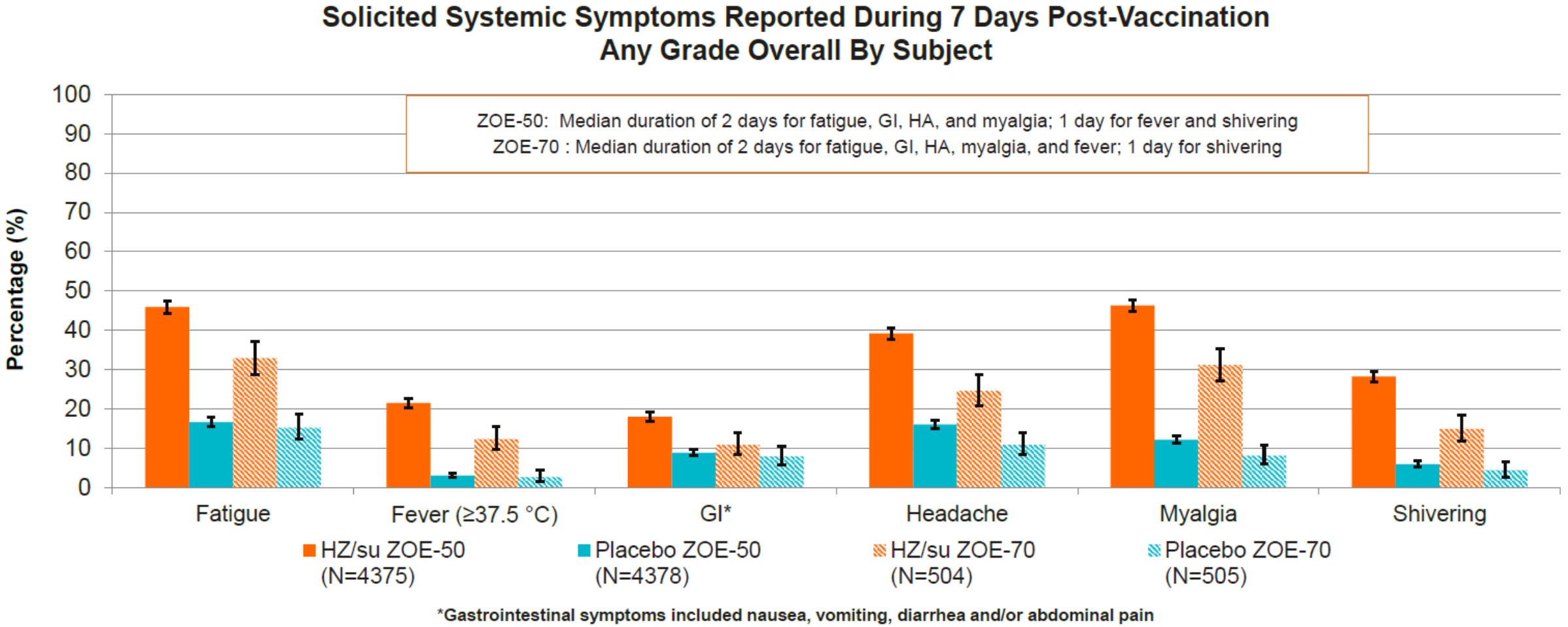


MMWR Morb Mortal Wkly Rep. 2018;67:103-108

ZOE-50 and ZOE-70

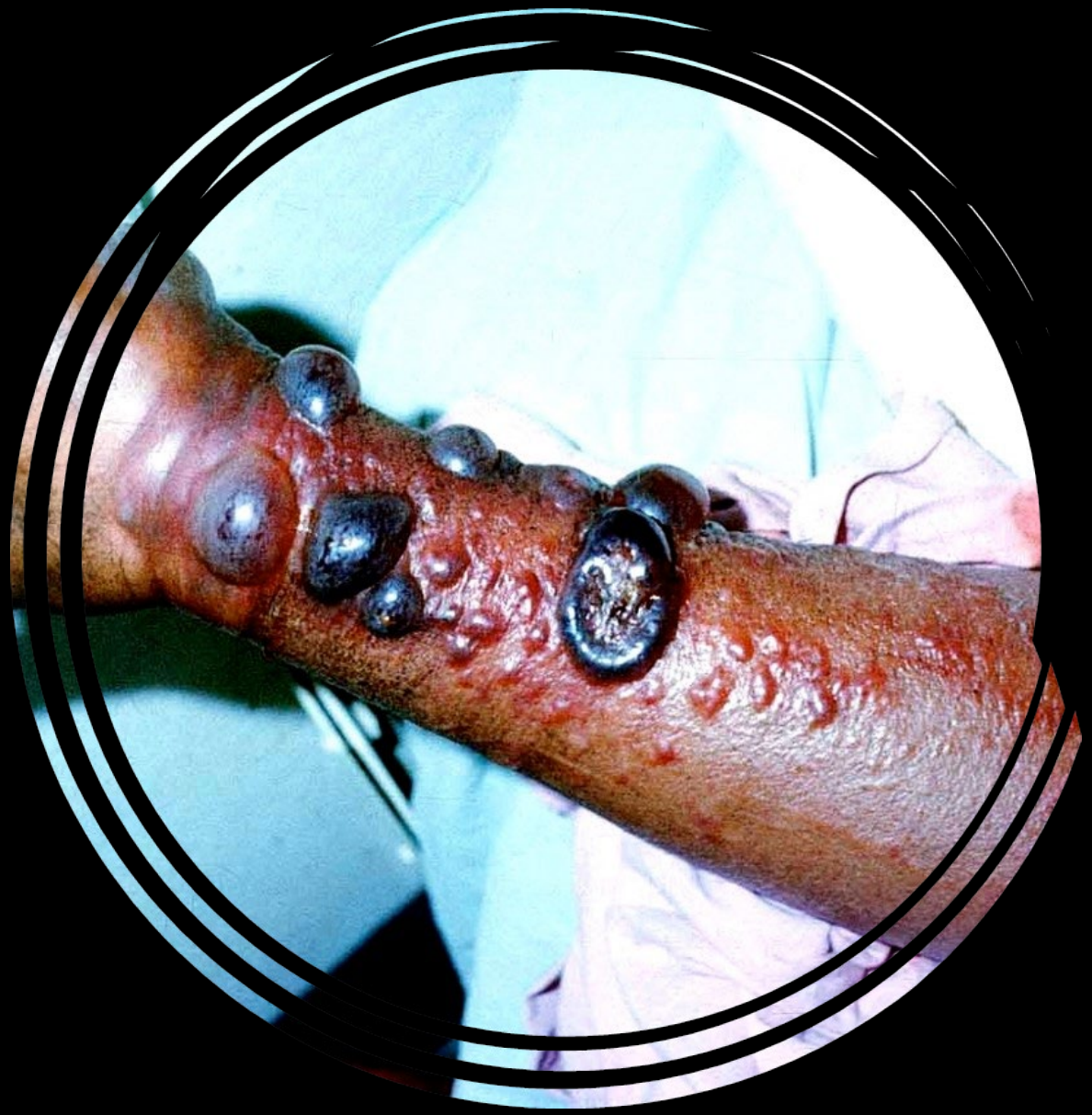
Reactogenicity Subgroups[1,2]

Duration 1-2 days



MMWR Morb Mortal Wkly Rep. 2018;67:103-108

Ebola Vaccine



- Vaccine against Zaire Strain Ebola
- **Approved in USA 12-19-2019**
- Live attenuated VS virus with Ebola protein
  - Subunit vaccine
- Tested in two African outbreaks
- Given in “ring” manner: contacts and contacts of contacts with index case(s)
- Prevents spread of disease: 100% if done immediately
- Duration of protection ???

Infect Dis Clin North Am. 2019;33:953-976

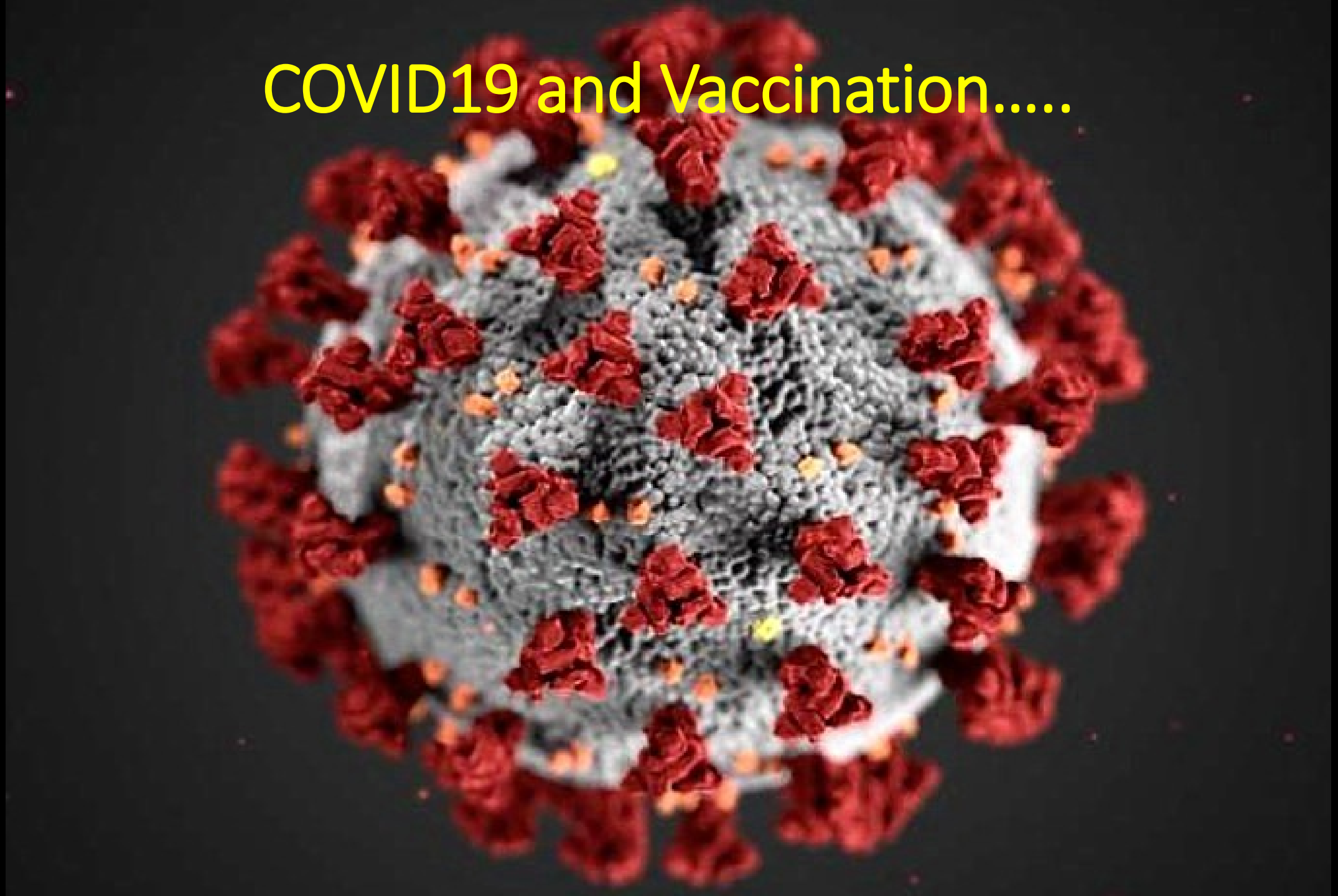
Arbovirus Vaccines

- **Entering Phase III: Zika**
- **Two DNA**
- **Two mRNA**
- **Whole inactivated virus**
- **Live attenuated virus**

- **Entering Phase III: Chikungunya**
- **VLP subunit**
- **Live attenuated virus**

Hum Vaccin Immunother. 2020 Aug 11;1-5. doi: 10.1080/21645515.2020.1796428
JAMA. 2020;323(14):1369-1377

COVID19 and Vaccination.....



LARGE TRIAL FINDS AIDS VACCINE FAILS TO STOP INFECTION

VaxGen: 2003

By ANDREW POLLACK WITH LAWRENCE K. ALTMAN
Published: February 24, 2003

E-MAIL
PRINT
SINGLE-PAGE
REPRINTS
SAVE
SHARE

The first AIDS vaccine ever to be tested in a large number of people has failed, over all, to protect them from infection with the virus that causes the disease, the company that makes it, VaxGen, said today.

The vaccine did, however, seem to significantly lower the infection rate among African-Americans and other non-Hispanic minorities participating in the trial, the company said.

AP Associated Press

Merck's Experimental AIDS Vaccine Fails

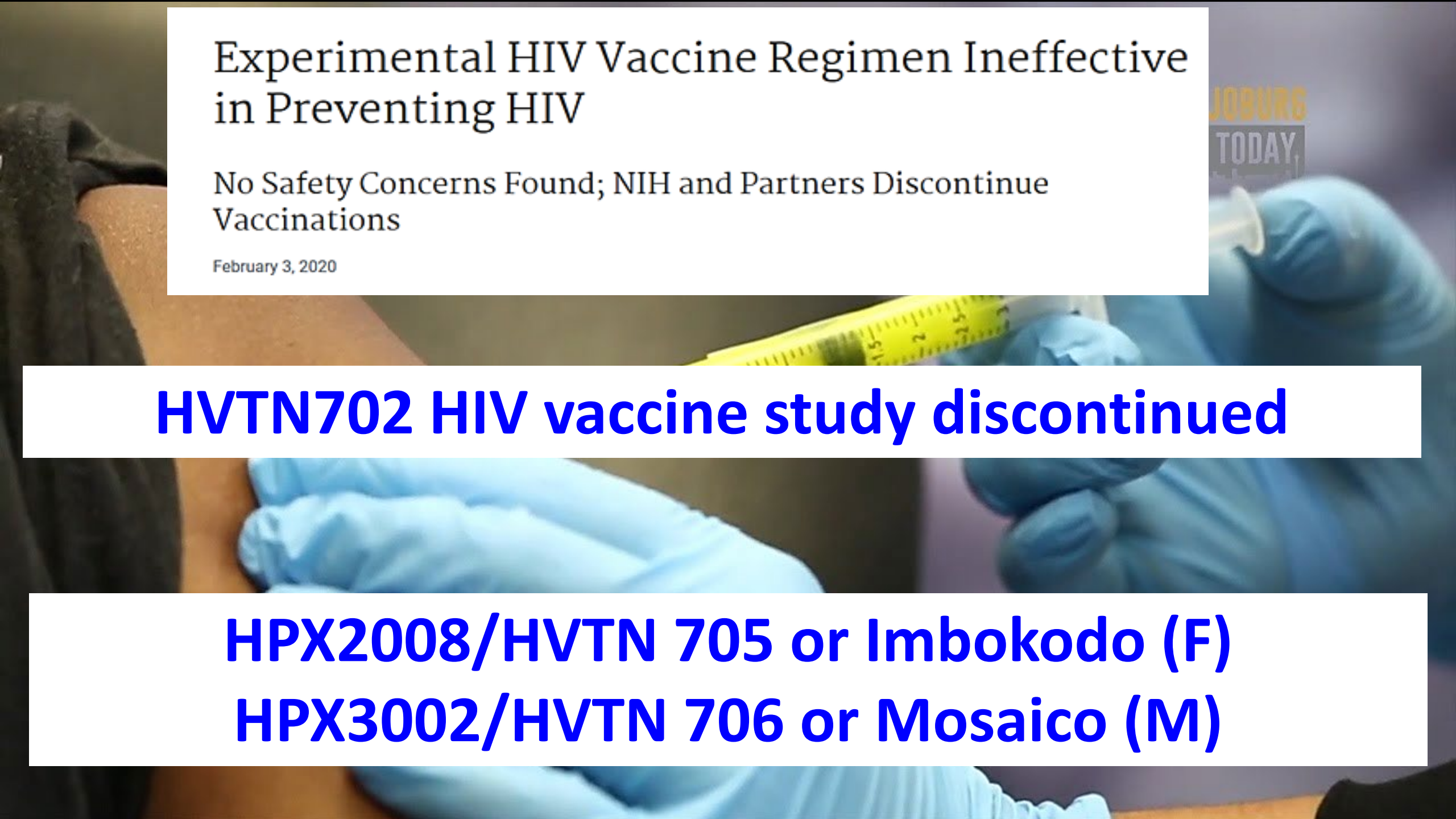
Merck: 2007

By LINDA A. JOHNSON, AP Business Writer
Saturday, September 22, 2007

PRINT E-MAIL SHARE COMMENTS (3) FONT | SIZE: TOOLS SPONSOR: verizon wireless

(09-22) 00:23 PDT Trenton, N.J. (AP) --

In a disappointing setback, a promising experimental AIDS vaccine failed to work in a large international test, leading the developer to halt the study. Merck & Co. said Friday that it is ending enrollment and vaccination of volunteers in the study, which was partly funded by the National Institutes of Health.


Experimental HIV Vaccine Regimen Ineffective in Preventing HIV
No Safety Concerns Found; NIH and Partners Discontinue Vaccinations
February 3, 2020
HVTN702 HIV vaccine study discontinued
HPX2008/HVTN 705 or Imbokodo (F)
HPX3002/HVTN 706 or Mosaico (M)


NO
Vaccines
the more you KNOW...
the more you
NO!

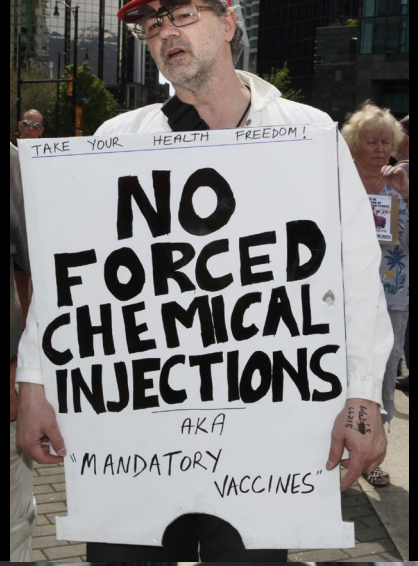

VACCINES
CAN
CAUSE
INJURY
AND
DEATH


GIVE A
VOICE
TO THE
VACCINE
INJURED


SEPARATE PHARMA & STATE
SEPARATE PHARMA & STATE
NO
on HB


IF ITS
MANDATED,
ARE WE
FREE


Merck
Pan
My Kids
My Choice
SB


TAKE YOUR HEALTH FREEDOM!
NO FORCED CHEMICAL INJECTIONS
AKA
"MANDATORY VACCINES"


VACCINE MANDATES VIOLATE BODILY AUTONOMY

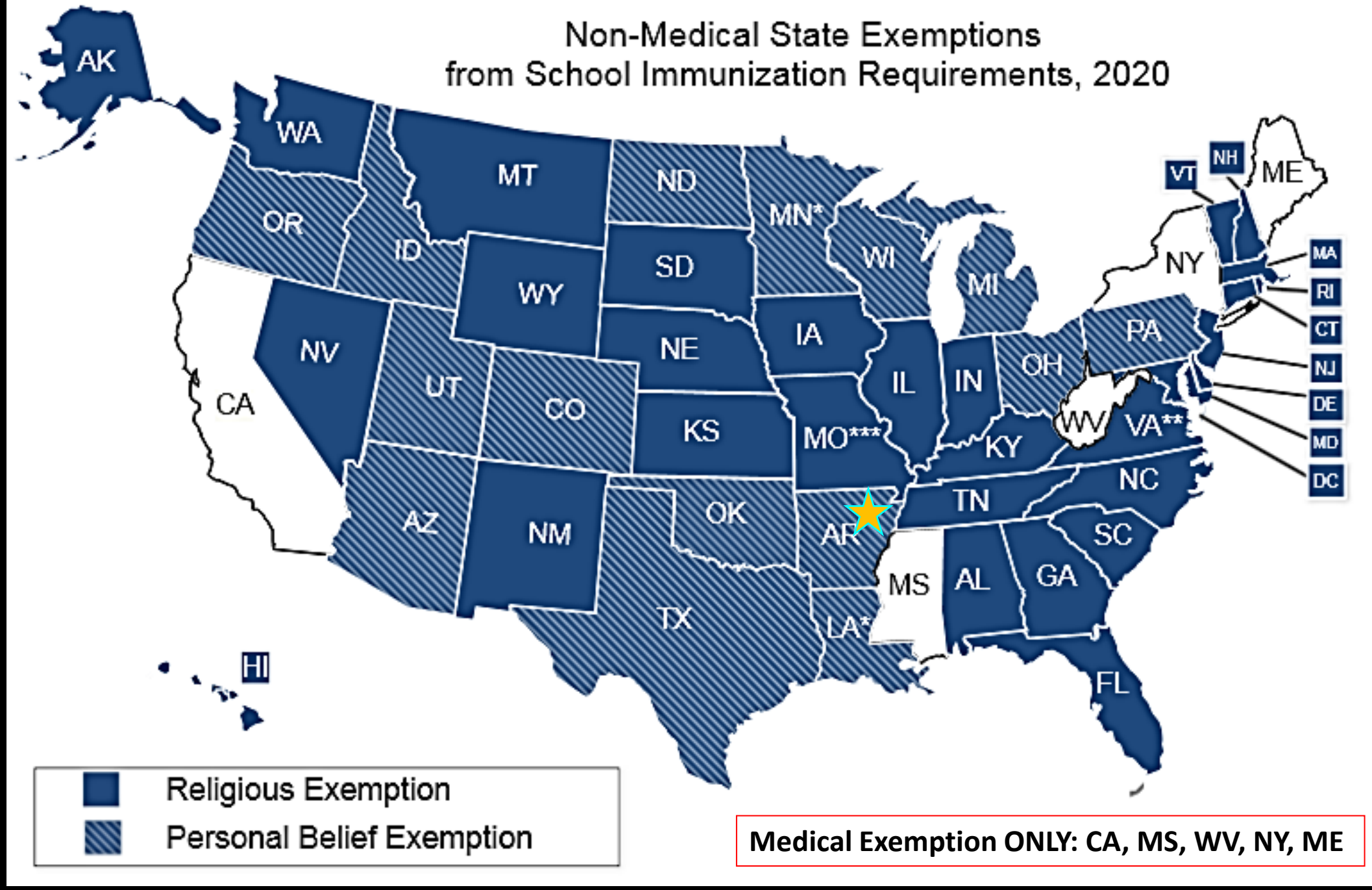

NO MEDICAL TYRANNY


U.S. LAW CLASSIFIES VACCINES AS UNAVOIDABLY UNSAFE


STOP
THE CENSORSHIP
MANDATORY VACCINES
WE WILL NOT LIVE IN FEAR
FREEDOM IS ESSENTIAL
WAKE UP, PEOPLE !!!

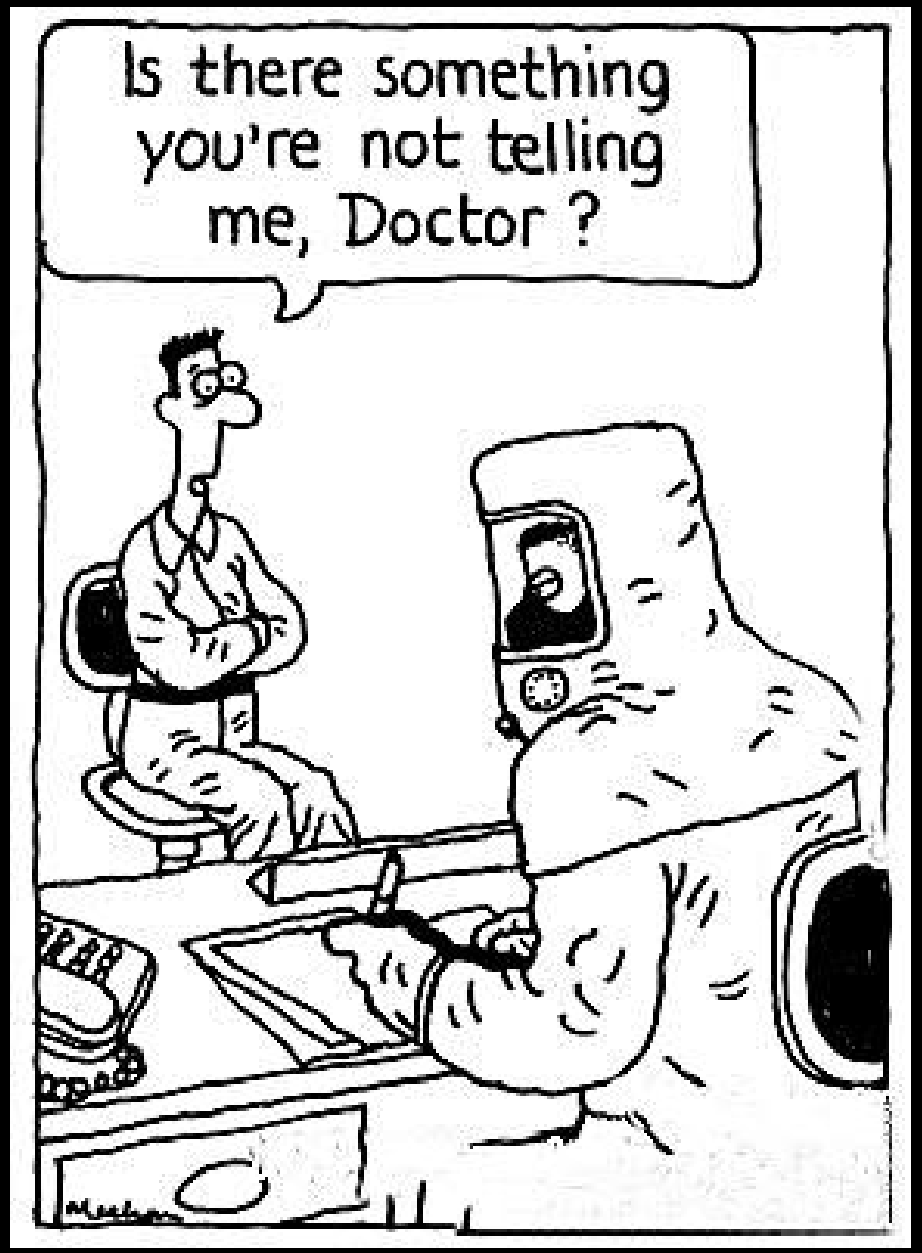
Anti-Vaccination Rationale

- **Philosophical, political, spiritual and medical concerns**
  - **Parental privilege**
  - **Religious beliefs**
  - **Bodily autonomy**
  - **Autism and other maladies**
  - **Pharma profit motive**
- **Anti-vaccination groups stem from late 19th century**
- **Spread misinformation, leading to….**
- **Vaccine hesitancy and….Vaccine refusal**


Non-Medical State Exemptions
from School Immunization Requirements, 2020
AK
WA
OR
CA
ID
NV
MT
WY
UT
AZ
CO
NM
ND
SD
NE
KS
OK
TX
MN*
IA
MO***
AR
LA*
WI
IL
MI
IN
OH
KY
TN
MS
AL
GA
FL
SC
NC
VA**
WV
PA
NY
VT
NH
ME
MA
RI
CT
NJ
DE
MD
DC
HI
Religious Exemption
Personal Belief Exemption
Medical Exemption ONLY: CA, MS, WV, NY, ME

Brothers. One received smallpox vaccine, The other did not. Can you guess which?

Drugs you will learn to love! New Anti-infectives!



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Professor of Dermatology
Vice-Chair, Dermatology
Baylor College of Medicine
Houston, Republic of Texas