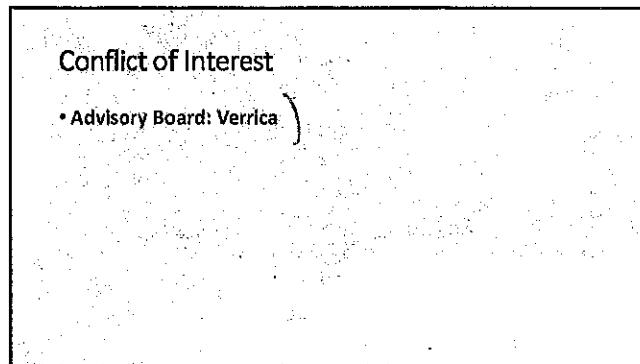
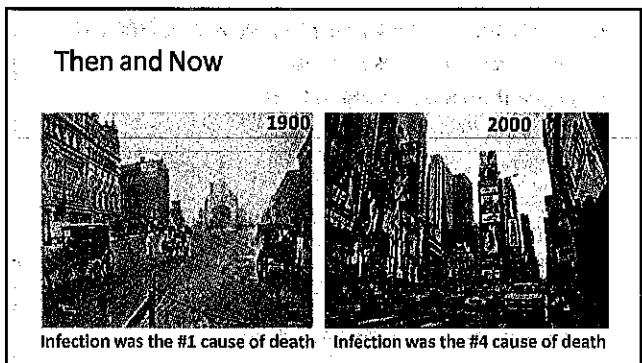


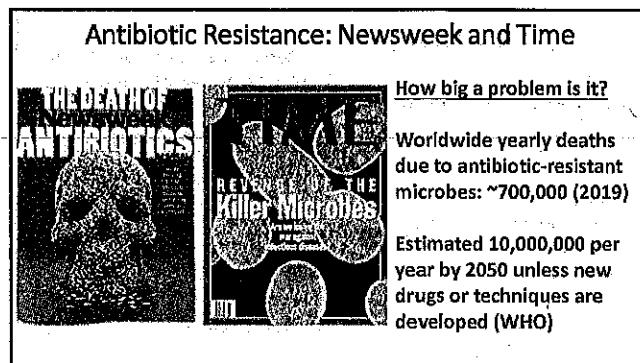
1



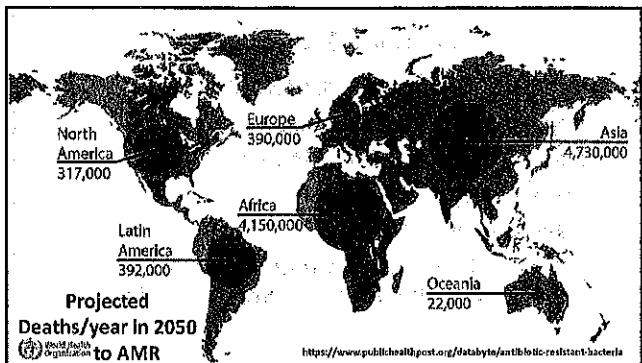
2



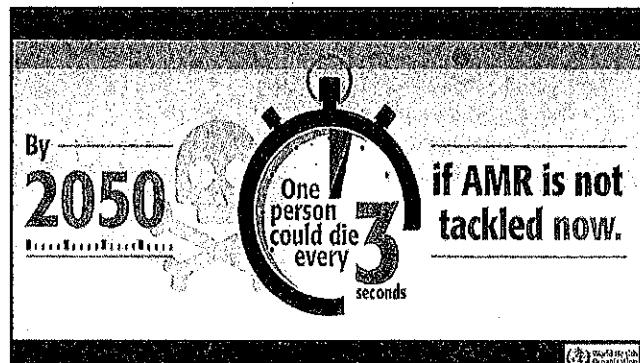
3



4



5



6

The emergence and spread of antimicrobial-resistant pathogens has accelerated
Antimicrobial-resistant pathogens are the single worst threat to global health
Essential anti-infective drugs now routinely fail
The speed at which drugs fail far outpaces the development of replacement medications
Thus, the therapeutic arsenal is shrinking
In the absence of urgent corrective and protective actions, the world is heading toward
a post-antibiotic era where infections will once again kill unabated
Without effective antibiotics, the success of major surgery, solid organ transplantation,
cancer chemotherapy would be compromised. (Perhaps the most significant point)
Human practices, behaviors and policy failures have led to this condition
We, the human race, have failed to handle antibiotics with care

 World Health Organization

Dr. Tedros Adhanom Ghebreyesus

7

Dermatologists contribute to overuse of antibiotics



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

Attributed to: Dermatologists probably know better the sensitivity of their patients to antibiotics than do most other physicians, experts say. But many physicians may

8

The Good News!

Original Investigation
JAMA Dermatol 2019;156:106-110
DOI:10.1001/jamadermatol.2018.4200
Copyright © 2019 American Medical Association. All rights reserved.
Reprinted with permission from JAMA Dermatology. All rights reserved.
This article is available online at jamanetwork.com/journals/jamadermatology.

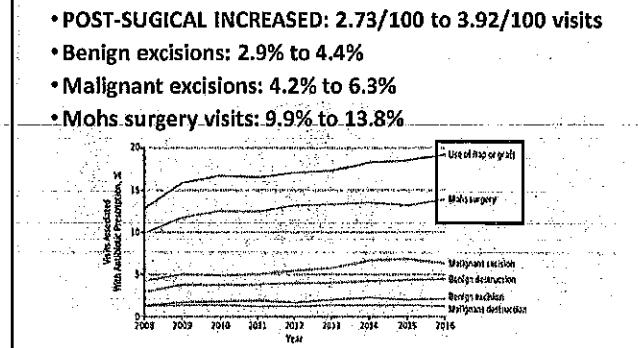
Trends In Oral Antibiotic Prescription in Dermatology, 2008 to 2016

JAMA Dermatology Original Investigation
Use of Antibiotics for Dermatologic Procedures From 2008 to 2016
Mohs surgery, IQ, Wound, Biopsy, Reconstructive surgery, etc.

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

- 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.....

9



10

Antibiotic Use in Derm Surgery

- Usually used: cephalaxin and doxycycline
- 5-10 days typical course
- Major regional differences
- EG: Mohs surgery 2014-16



11

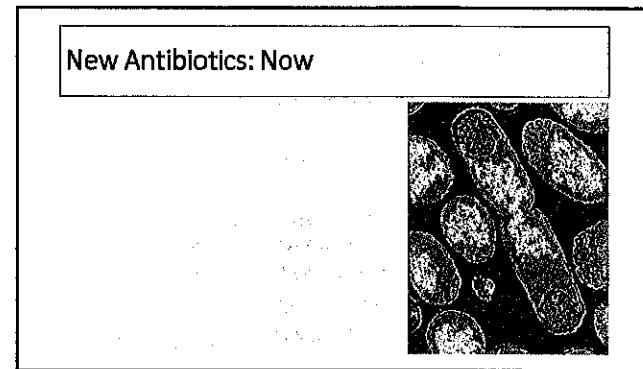
Take Home Messages....

- 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

12



13



14

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 \geq 2 months
- Status: Approved for impetigo: 12-14-2017

J Drugs Dermatol. 2018 Oct;15(10):1051-1057
JAMA Dermatol. 2019 Jul 1;154(7):806-819

15

JAMA Dermatol. 2018 Jul 1;154(7):806-819

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

J Drugs Dermatol. 2018 Oct 1;15(10):1051-1057

JDD

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

J Drugs Dermatol. 2018 Oct 1;15(10):1051-1057

16

Utility?

Do we need another agent?

17

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***

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

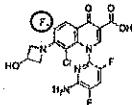
Pooled, average prevalence:

- 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!

18

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;14(1):34-35
J Antimicrob Chemother. 2017;72:3473-3480

19

New Antibiotic: Delafloxacin (Baxdela®)

- 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):3473-3480

20

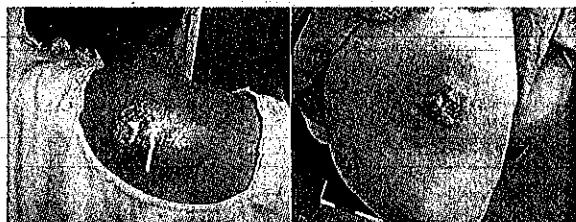
New Antibiotic: Delafloxacin

- Tested IV (300mg Q12h) or oral (450mg Q12h)
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J Antimicrob Chemother. 2017 Dec 1;72(12):3473-3480

21

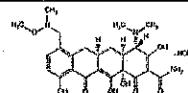
Utility?



22

New Antibiotic: Sarecycline

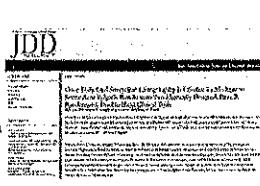
- Chemical class: tetracycline
- MOA: Binds 30S ribosomal subunit, no AA-tRNA attachment
 - Inhibits protein synthesis
 - Also anti-inflammatory in nature
- Narrow spectrum activity***
- Includes: *P. acnes*, *S. aureus*; Minimal vrs Gr- enteric bacteria
- Available: Oral only (unit doses: 60mg, 100mg, 150mg)
 - Once daily dosing weight-based: 1.5mg/kg × 12 weeks
- Resistance: Uncommon; Nausea, headache: 3%; Yeast <1%
- Status: Approved moderate-severe acne in October, 2018



Antimicrob Agents Chemother. 2018 Nov 5; pii: AACD1297-18.
J Drugs Dermatol. 2018 Mar 1;17(3):333-338.

23

Sarecycline

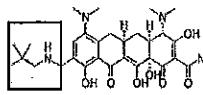


- Two parallel Phase 3 studies
- N=1002 (sarecycline) and 1000 (placebo)
- QD × 12 week
- IGA: 2 grade improvement; clear/almost clear
- Saracycline: 21.9% and 22.6%
- Placebo: 10.5% and 15.3%
- ~50% reduction number inflammatory lesions at therapy end (12 weeks), whereas placebo showed ~35% reduction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

24

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: **Uncommon** (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(3):473-480

25

Omadacycline: O'Brianhan WA, Green S, Overcash J, 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 QASIS 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):149-154
<https://clinicaltrials.gov/ct2/show/NCT02877927>

26

Utility?



27

Antimicrobial Agents and Chemotherapy

Antimicrob Agents Chemother. 2018 Mar;72(4): pii: e02551-17. doi: 10.1128/AAC.02551-17



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

Elli Z, C. Goldstein,¹* Diana M. Citron,²* Karla L. Tyndall,³ Aliza Leibowitz,³ C. Veni Menardo³

¹Los Angeles Biomedical Research Institute, California, USA

²University of Southern California, 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 *Staphylococcus aureus*, its sensitivity to tetracycline 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 *Stenotrophomonas maltophilia*, which showed reduced susceptibility to the entire tetracycline group.

KEYWORDS: bacterioides fragilis, *Escherichia coli*, *Pseudomonas aeruginosa*, *Prevotella hepatis*, *Stenotrophomonas maltophilia*, tetracyclines

**NOT effective against Elkenella (human bites)
but otherwise very good**

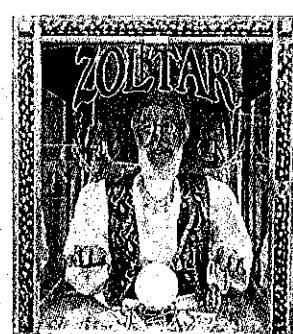
28

Cat bites: Omadacycline



29

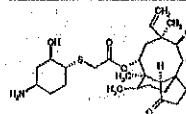
One more for the future!



30

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;62(5): pii: e02380-17
Pharmacoepiogr. 2018 Sep;34(9):931-946
J Antimicrob Chemother. 2016;71: 1022-26

31

Resurgent STDs

32

The State of STDs in the United Statesin
2018

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

CDC.gov

1.8 million
CASES OF CHLAMYDIA
10% 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

Gonorrhea**The State of STDs in the United States**in
2019

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

1.8 million
CASES OF CHLAMYDIA
10% 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

33

34

Uncomplicated Gonorrhea**Update to CDC's Treatment Guidelines for Gonococcal Infection, 2020**

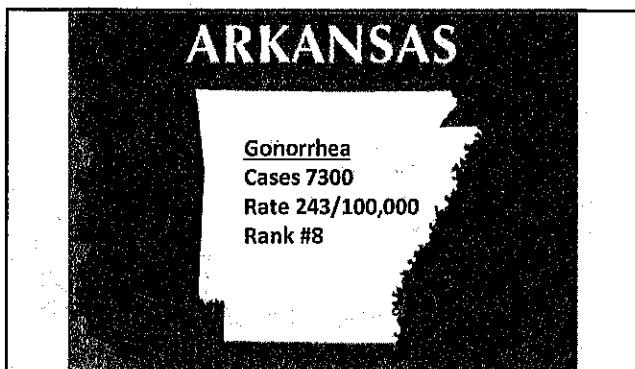
Revised December 18, 2020 / CDC-19-011-014
 Sam Lutfi, MPH, Emily Farber, MS, MPH, Courtney A. Winkler, PhD, Alisa M. Rabinowitz, PhD, Carol Morris, PhD, Karen Schrag, PhD, Daniel T. Tietz, PhD, Michael J. Pyle, PhD, Jennifer C. Thompson, PhD, Other editor(s): Michael C. Lamm

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

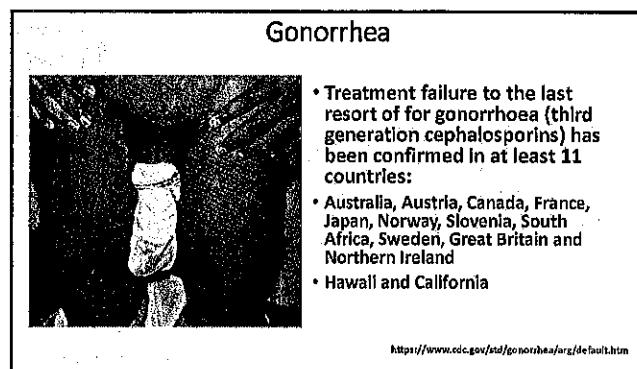
MMWR Morb Mortal Wkly Rep 2020;69:1911-1916.

35

36



37



38

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(4):504-512.
J Antimicrob Chemother. 2018;73:2072-2077.

39

Phase 2 Results

Drug/Dose	97%	100%	50%
Gepotidacin 1500mg x 1 dose	97	100	50
Gepotidacin 3000mg x 1 dose	96	100	50

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

40

plus

Antimicrobial Agents and Chemotherapy®

Accepted Article
Published online 2017 May 23. Prepublished online 2017 Apr 3. doi: 10.1128/AAC.00254-16
PMCID: PLUG141153
PMID: 28513222

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'Farrell,¹ Courtney Tiffey,¹ Nicole Scampatti-Osuna,¹ Christine Petty,¹ Muhammad Hussain,¹ Trish Adcock,¹ and Elenore Dumont²

1Merck Research Laboratories, Kenilworth, New Jersey, United States; 2Merck Research Laboratories, West Point, Pennsylvania, United States

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

41

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

42

Phase 2 Results

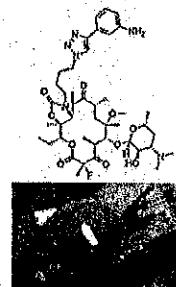
Drug/Dose	Urticaria	% Negative Culture	Mental Status	Physical Exam	Normal	Unusual	Negative MAC	Positive MAC	Unusual MAC
Zollfotadolin 2g PO x 1 dose	96	100	92	81	100	55			
Zollfotadolin 3g PO x 1 dose	96	100	50	84	100	25			
Ceftriaxone 500mg IM X 1 dose	100	100	100	89	100	50			

New Engl J Med 2018;379:1835-45

43

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;63:1043-8

44

Does ANYTHING really work for molluscum?



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



"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."

45

Hyperthermia and Molluscum

- Small (n=21) Chinese prospective study
- Patented IR heating unit (We would use heating pad)
- 44°C (111°F) 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

46

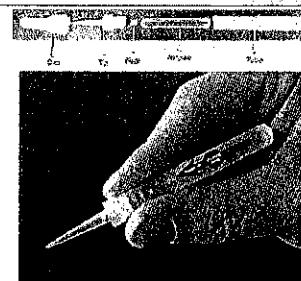
Cantharidin and Molluscum: Reinvention

- 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- α , IL-8 and CXCL-5
- Cantharidin is used in the laboratory as a model for studying leukocyte trafficking and cytokine production.

J Invest Dermatol. 196;39:39-45
J Immunol Methods. 2003;287:213-220

47

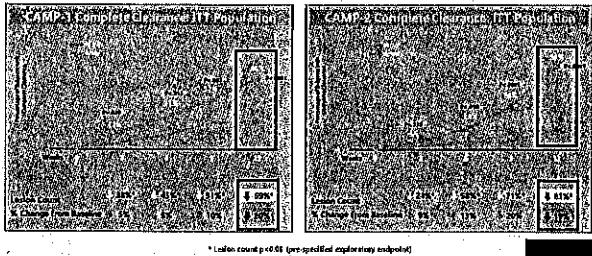
VP-102: Proprietary drug-device combination of 0.7% cantharidin administered through a single-use precision applicator



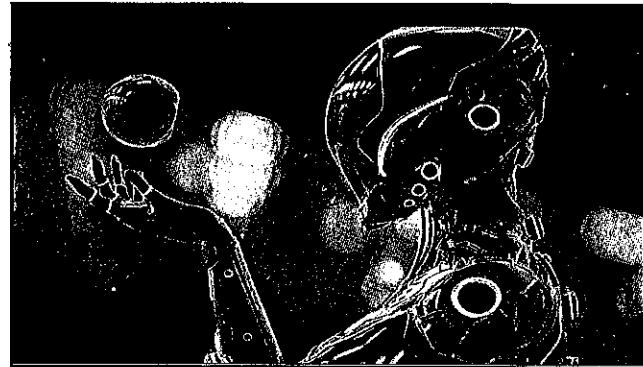
- Cantharidin formulation with API that is greater than 99% pure and defined pharmaceutical batch process
- Long-term, room temperature stability
- Visualization agent to see which lesions have been treated
- Bittering agent to mitigate oral ingestion by children

48

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



49



50

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

Oxitec 5034 mosquitoes; Second generation

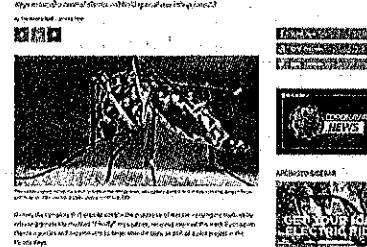
Non-biting males carry a self-destruction gene

Female offspring will die as larvae

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

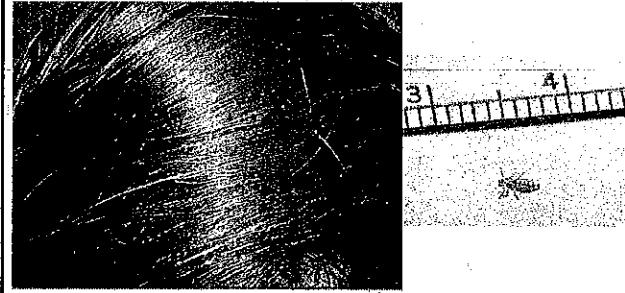
<https://www.oxitec.com/en/news/oxitecs-friendly-mosquito-technology-receives-us-epa-approval-for-pilot-projects-in-us> (May 1, 2020)

OXITEC GETS APPROVALS TO START TRIALS WITH GENETICALLY MODIFIED MOSQUITOES



51

Pediculosis Capitis



52

Head Lice: Not just a pediatric disease any more!



53

Head Lice: Resurgence Due to Selfie Craze



54

Pediculosis capitis (Head lice)

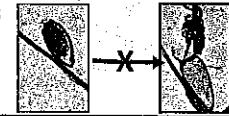
- Collected head lice: 138 sites, 48 states
- Excluded Alaska and West Virginia
- Summer 2013-Summer 2015
- 96% of sites had 100% of all lice carrying resistance genes to pyrethroids
- 42/48 states had 100% resistance of all lice collected
- Correlates w/ OTC pyrethroid failures

J Med Entomol 2016;53:653-659

55

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



56

Abametapir: Safety

Adverse reactions	Abametapir lotion, 0.74%, N=349 n (%)	Vehicle lotion N=350 n (%)
Eruptions	14 (4.0)	6 (1.7)
Pain	11 (3.2)	9 (2.3)
Skin burning sensations	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

57

> Hautarzt. 2020 Jun;71(6):447-454. doi: 10.1007/s00108-020-01620-0.

[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)]

[Ardele in Germany]
E Klöse¹, T Uhlmann², S Krause³, R Hartmann³

> Hautarzt. 2020 May;71(5):374-379. doi: 10.1007/s00108-020-01681-y.

Resistant *Sarcoptes scabiei*

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

[Ardele in Germany]
B Rückenberg¹, O N Hövener², M Petzelt³, R Schulz⁴, J Verkijen⁵, P Bantenberg⁶

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

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

58

Spinosad for Scabies

Spinosyns (natural) and spinosols (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)

59

> Dan Med J. 2016 Oct;63(10):B528.

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 Haro Jensen¹

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

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BJD British Journal of Dermatology
ESTABLISHED 1864
THE LEAD JOURNAL OF DERMATOLOGICAL RESEARCH & RESEARCH RESULTS

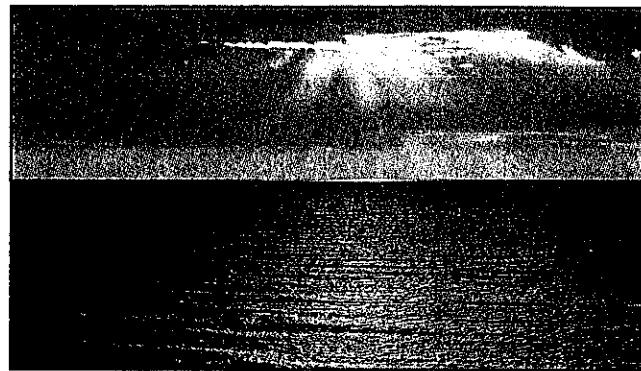
Original Article | © Full Access |
Limited effectiveness of four oral antifungal drugs (fluconazole, griseofulvin, itraconazole and terbinafine) in the current epidemic of altered dermatophytosis in India: results of a randomized pragmatic trial

S. Singh, S. U. Chandra, V.H. Anchan, P. Verma, R. Tatak

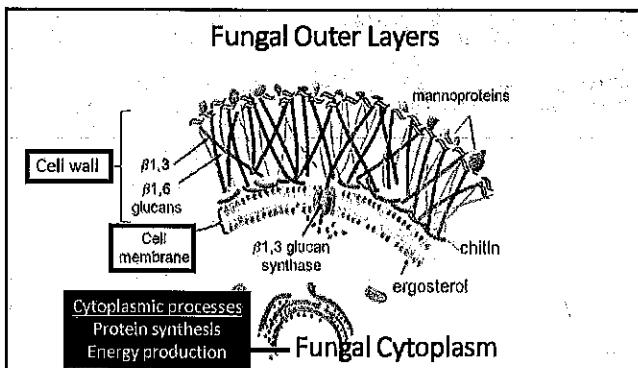
Tinea corporis, cruris, faciei: KOH verified (culture not required; *T. mentagrophytes*)
Rx regimens: Fluconazole 5 mg/kg/d, Griseofulvin 10 mg/kg/d, Itraconazole 5 mg/kg/d, Terbinafine 7.5 mg/kg/d
Randomization: patients were treated for 8 weeks (n= 200)
Cure rates: Itraconazole 65%, Fluconazole 42%, Terbinafine 28%, Griseofulvin 14%
Cure = absence of signs/Sx and negative KOH

BjD Dermatol, 15 June 2020. doi:10.1111/bjd.13146

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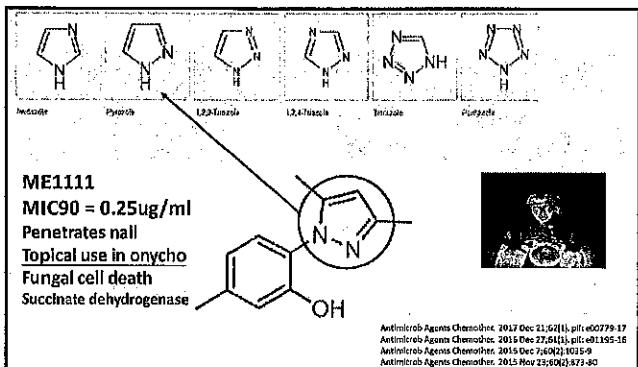
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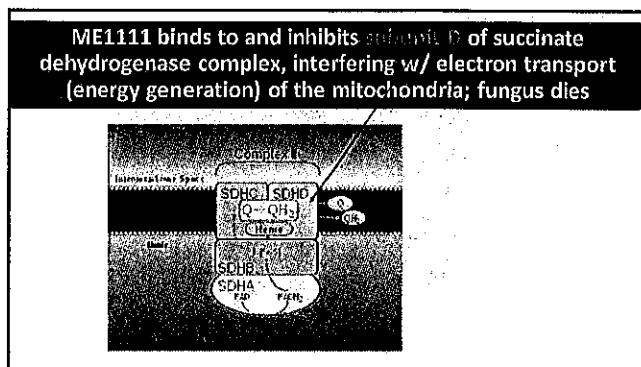
63

Name	Class	MoA	Phase	Atkin/USA 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)
Dlorofim	Orotimide	Dihydroorotate dehydrogenase	2b	Aspergillosis (Oral and IV)
Fosmanogepix	Unique small molecule	Inositol acyltransferase	2a/b	Candida/Mold/Cocc/Crypto (Oral+IV)
MAT2203	Polyene	Cell membrane pores	2a/b	MC Candida ("Oral Amphotericin")

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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) (VT1129)	Tetrazole	Ergosterol synthesis	3 (1) (PreClin)	Onychomycosis; other dermatophytosis for VT1161
Nikkomycin Z	Novel	Chitin syn	1/2	Coccidioidomycosis
T2307	Arylamidine	Mitochondria processes	1	Limited spectrum (Candida, Aspergillus, Malassezia, Crypto)
Aureobasidin A	Cyclic depsipeptide	Syphingolipid synthesis	1	Limited spectrum (Candida, Crypto)

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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):339-339
Bioorg Med Chem Lett. 2014;24:3455-58

68

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

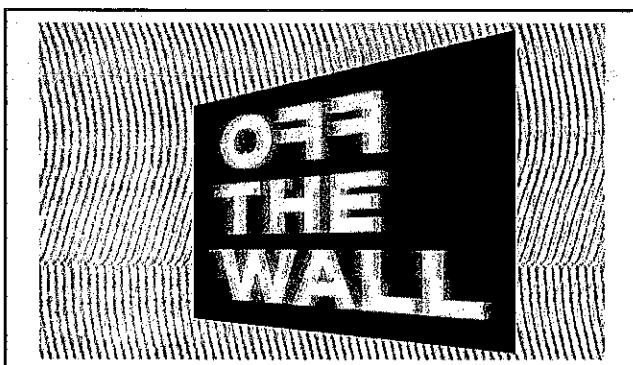
Br J Dermatol. 2020 May 18. doi: 10.1111/bjd.19224

69

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;mya015. doi: 10.1089/myc/mya015

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Tecovirimat

U.S. Department of Health and Human Services

FDA U.S. FOOD & DRUG ADMINISTRATION July 13, 2018

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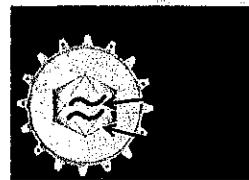
FDA approves the first drug with an indication for treatment of smallpox

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72

Tecovirimat

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



73

The OMGI

- 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 MORTALITY RATE ANTICIPATED IF WEAPONIZED**



74

The OMGI

- 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 MORTALITY 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!!!!

75

Chagas Disease

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

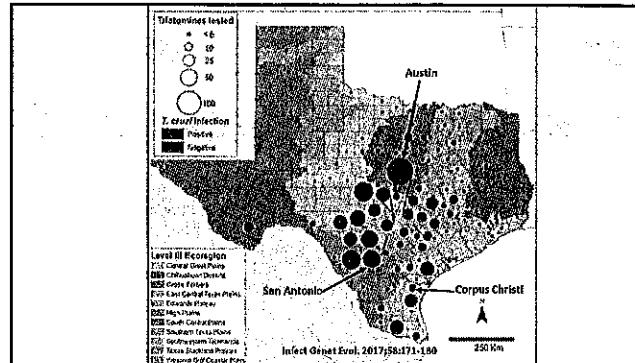


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Chagas Disease in USA?

- Rare indigenous cases
 - 6 US Reduviid (Triatomine) 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

77



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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



79

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

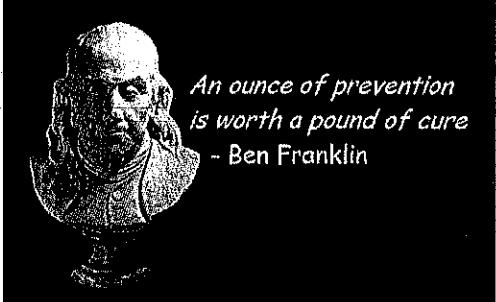
- **African Trypanosomiasis**
- Rx of choice: Nifurtimox-Eflornithine
- But very toxic
- Fexinidazole: As effective, Few AEs
1800mg (Days 1-4) 1200mg (Days 5-10)
- Study of 794 patients in 2 African
countries
- EMA approved November, 2018
- FDA submitted

80



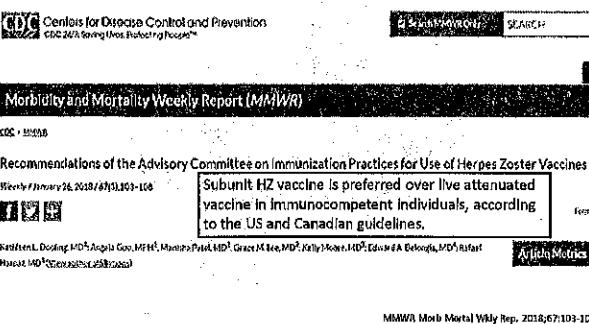
Prevention is better than cure.
(Desiderius Erasmus)

81



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

82



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

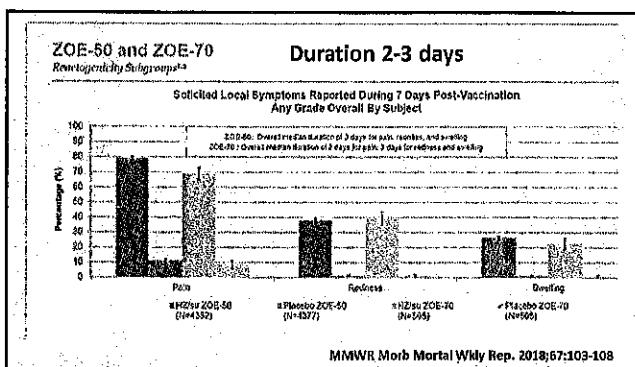
83

New Recombinant Zoster Vaccine

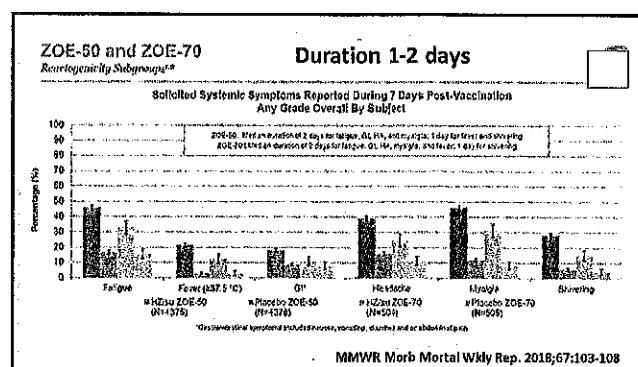
- VZV subunit vaccine for shingles (not live attenuated)
 - Glycoprotein E antigen + adjuvant; TWO doses, IM @ 0, 2-6
- ACIP voted to FAVOR this over existing HZ vaccine
 - Indicated for use over age 50; EVEN if given prior vaccine
 - 90-97% effective across ALL AGES; 4 year study (9yr Ab+)
 - 88% overall 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

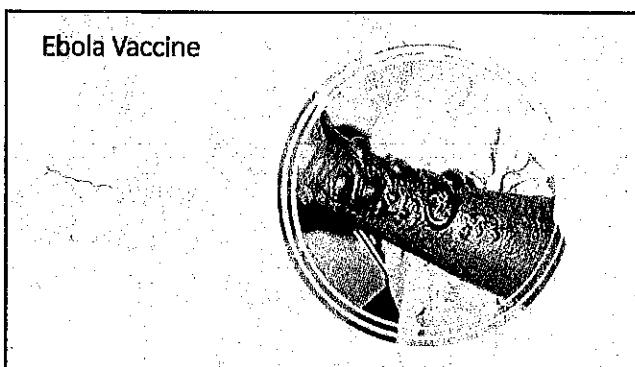
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85



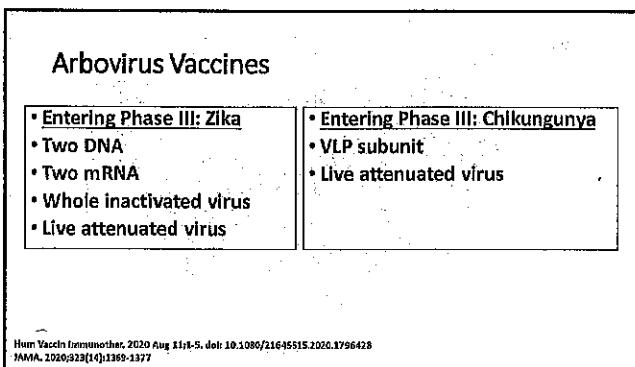
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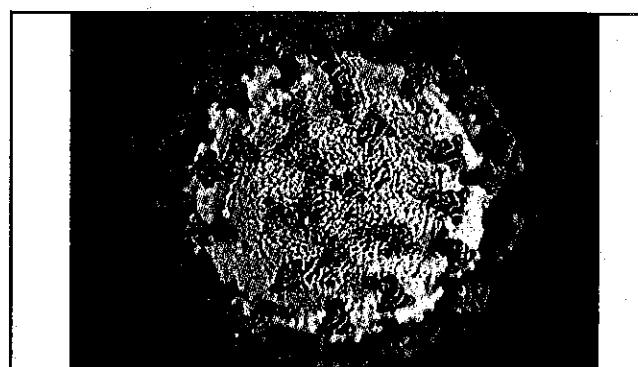
87

- 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;33:951-976

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LARGE TRIAL FINDS AIDS VACCINE FAILS TO STOP INFECTION

VaxGen: 2003

The first AIDS vaccine ever to be tested in a large number of people has failed, after 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.

Merck's Experimental AIDS Vaccine Fails

By LINDA A. PELLEGRINO, AP Business Writer
Published: September 23, 2007

(09-24) 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.

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Experimental HIV Vaccine Regimen Ineffective in Preventing HIV

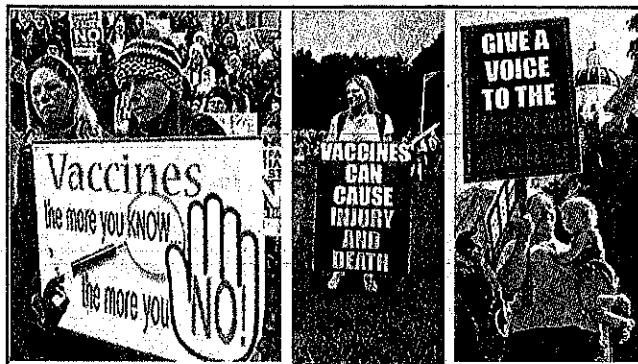
No Safety Concerns Found; NIH and Partners Discontinue Vaccinations

February 3, 2009

HVTN702 HIV vaccine study discontinued

**HPX2008/HVTN 705 or Imbokodo (F)
HPX3002/HVTN 706 or Mosaico (M)**

92



93

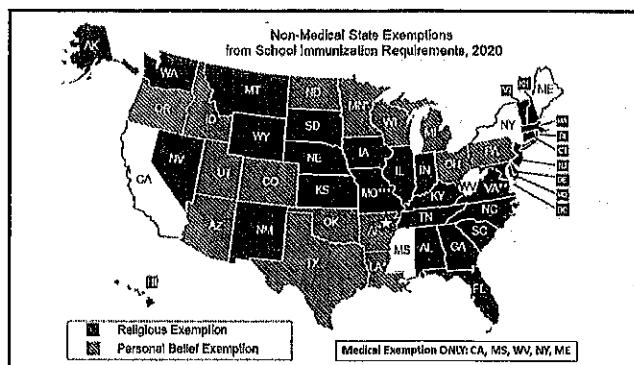


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Anti-Vaccination Rationale

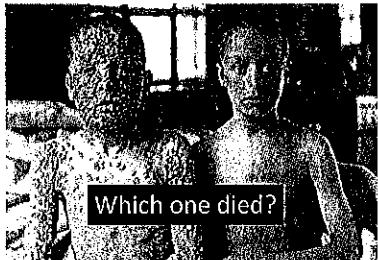
- Philosophical, political, spiritual and medical concerns
- Parental privilege
- Religious beliefs
- Bodily autonomy
- Autism and other maladies
- Pharma profit motive
- Anti-vaccination groups stem from late 19th century
- Spread misinformation, leading to....
- Vaccine hesitancy and...Vaccine refusal

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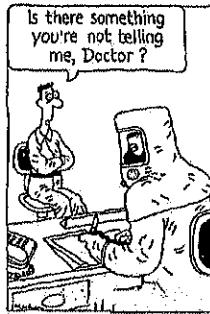
96

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



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



98

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

