Top 5 Outpatient Pediatric Infectious Disease Questions

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35th Annual Winter Refresher Course

Albuquerque, NM

February 11th, 2017

The Yukon: Ancient Soil Samples

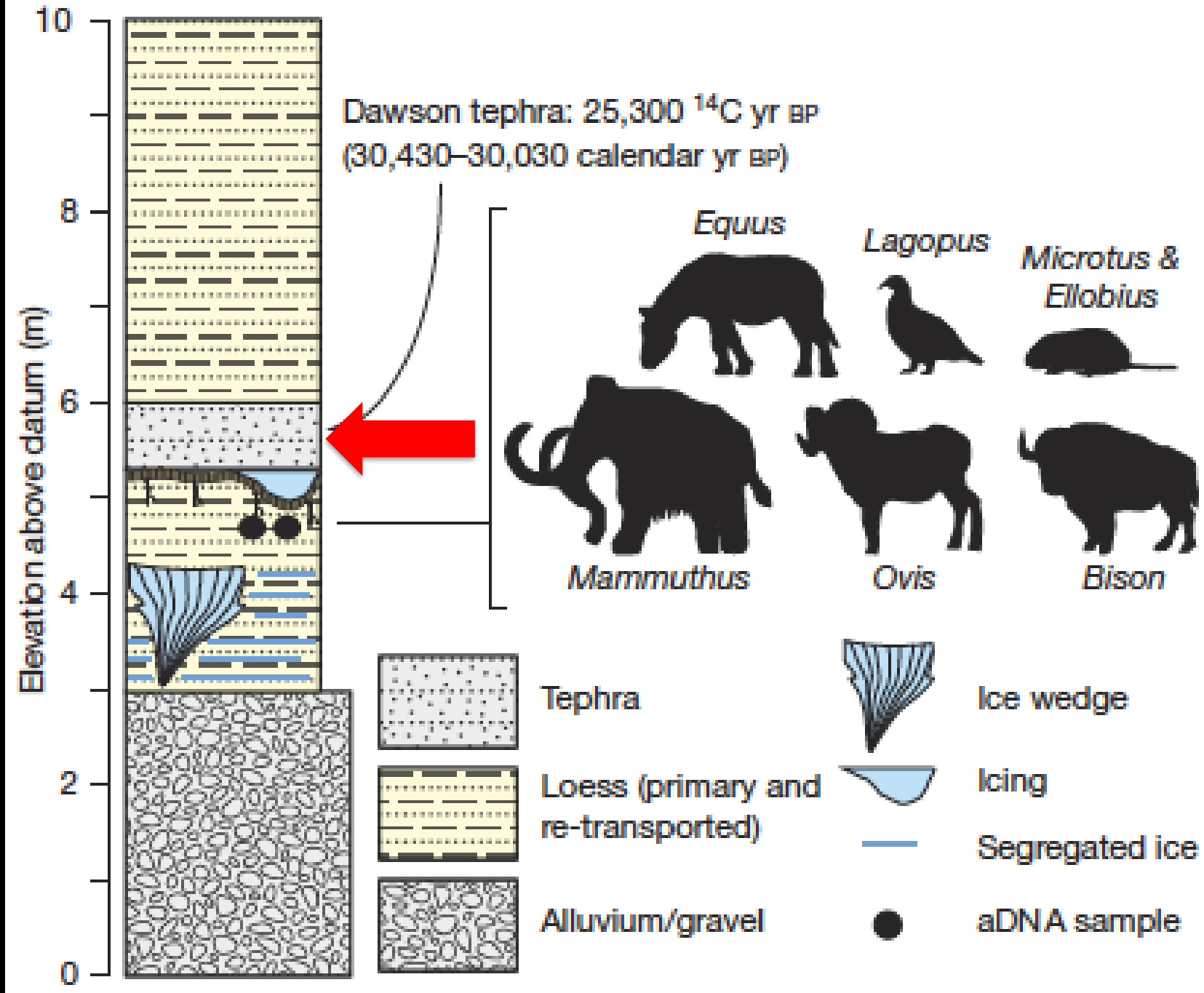
- Researchers from McMaster University collected samples from the permafrost in the Yukon
- 30,000 years old
- Had never thawed
- Ideal source of uncontaminated, ancient bacterial DNA

D'Costa VM, et al. Antibiotic Resistance is Ancient. Nature. 2011;477:457-462


145° W
135° W
65° N
60° N
ALASKA
Fairbanks
Dawson City
study site
YUKON
0
400 km

- Two 10 cm frozen core samples were collected
- The age of the sample was confirmed by PCR analysis documenting vertebrate animal DNA corresponding to the late *Pleistocene* era (e.g. ancient bison and mammoths)

D'Costa VM, et al. Antibiotic Resistance is Ancient. Nature. 2011;477:457-462


Elevation above datum (m)
10
8
6
4
2
0
Dawson tephra: 25,300 ^{14}C yr BP
(30,430–30,030 calendar yr BP)
Equus
Lagopus
Microtus &
Ellobius
Mammuthus
Ovis
Bison
Tephra
Loess (primary and
re-transported)
Alluvium/gravel
Ice wedge
Icing
Segregated ice
aDNA sample

- Researchers focused on 16s rRNA from bacteria looking for evidence of antimicrobial resistance pre-dating antibiotic use in humans

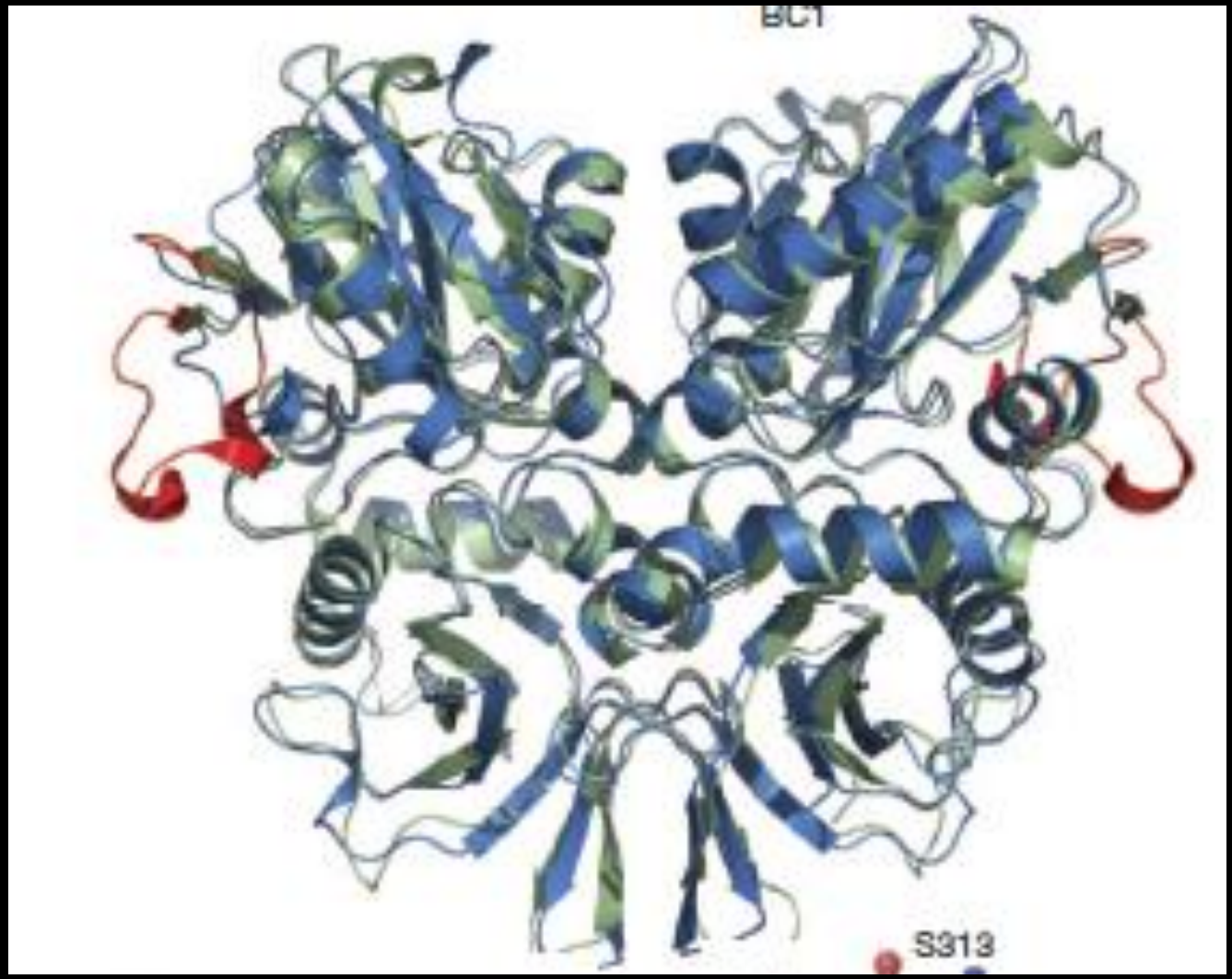
D'Costa VM, et al. Antibiotic Resistance is Ancient. Nature. 2011;477:457-462

Ancient Antimicrobial Resistance

Gene(s)	Associated Resistance
vanHAX	vancomcyin
tetM	tetracyclines
Beta-lactamases/bla	beta-lactam antibiotics

Adapted from: D'Costa VM, et al. Antibiotic Resistance is Ancient. Nature. 2011;477:457-462

Overlay of Ancient (blue) and Modern (green) Structures for the Product of the vanA Gene



An Ancient Arms Race

- Researchers concluded that antibiotic resistance predates the use of antibiotics in humans
- Likely a product of a microbiological arms race (antibiotics are produced by bacteria to compete with other bacteria/fungi in the soil, who in turn develop resistance mechanisms)
- Most of our current antibiotics derive from naturally occurring compounds (e.g. penicillins, cephalosporins)

Outline

- 1.) Prevention/management of recurrent MRSA skin and soft tissue infections
- 2.) ‘Taboo’ antibiotics in younger children: fluoroquinolones
- 3.) The child with recurrent fevers
- 4.) The child with a fever of unknown origin
- 5.) Managing vaccine hesitant parents/families

1.) Prevention/Management of Recurrent MRSA Skin and Soft Tissue Infections

Vignette

- A 6-year-old otherwise healthy boy presents to your office with a 2-day history of a 3 cm abscess over his right forearm. The lesion is drained, cultures of which grow MRSA. This is his 5th soft tissue abscess over the last 18 months, and his mother has grown frustrated. She asks you what can be done to treat this infection and to '…make sure this doesn't happen again.'

When was MRSA first reported in the literature?

- A.) 1946
- B.) 1955
- C.) 1961
- D.) 1973
- E.) 1978

When was MRSA first reported in the literature?

- A.) 1946
- B.) 1955
- C.) 1961
- D.) 1973
- E.) 1978

To-day's Drugs

Correspondence

"Celbenin"-resistant Staphylococci

SIR,—The Staphylococcus Reference Laboratory receives for phage-typing large numbers of strains of staphylococci, and it seemed that this material might usefully be examined to see whether any strains resistant to the new penicillinase-resistant penicillin (BRL 1241, "celbenin") were in circulation at about the time of introduction of the new antibiotic.

Sensitivity to Celbenin in Tube Tests with Doubling Dilutions

Strain	Date of Isolation	Source	Site	Minimal Inhibitory Concentration of Celbenin (μg. per ml.)	
13136	2/10/60	Patient A	Nephrectomy wound	Colony a	12·5
				,, c	6·5
13137	2/10/60	Nurse B	Finger infection ..	,, a	12·5
				,, c	25·0
10395	21/7/60	Patient C	Nose	,, a, ,, b	6·25
10396	5/7/60	,, C	Eczematous skin ..	,, a, ,, b	3·125
14083	28/10/60	,, C	Nose	,, a, ,, b	1·60
14668	8/11/60	,, C	,, ...	,, a, ,, b	25·0


Henry Ford Hospital

Methicillin-Resistant *Staphylococcus aureus*

Epidemiologic Observations During a Community-Acquired Outbreak

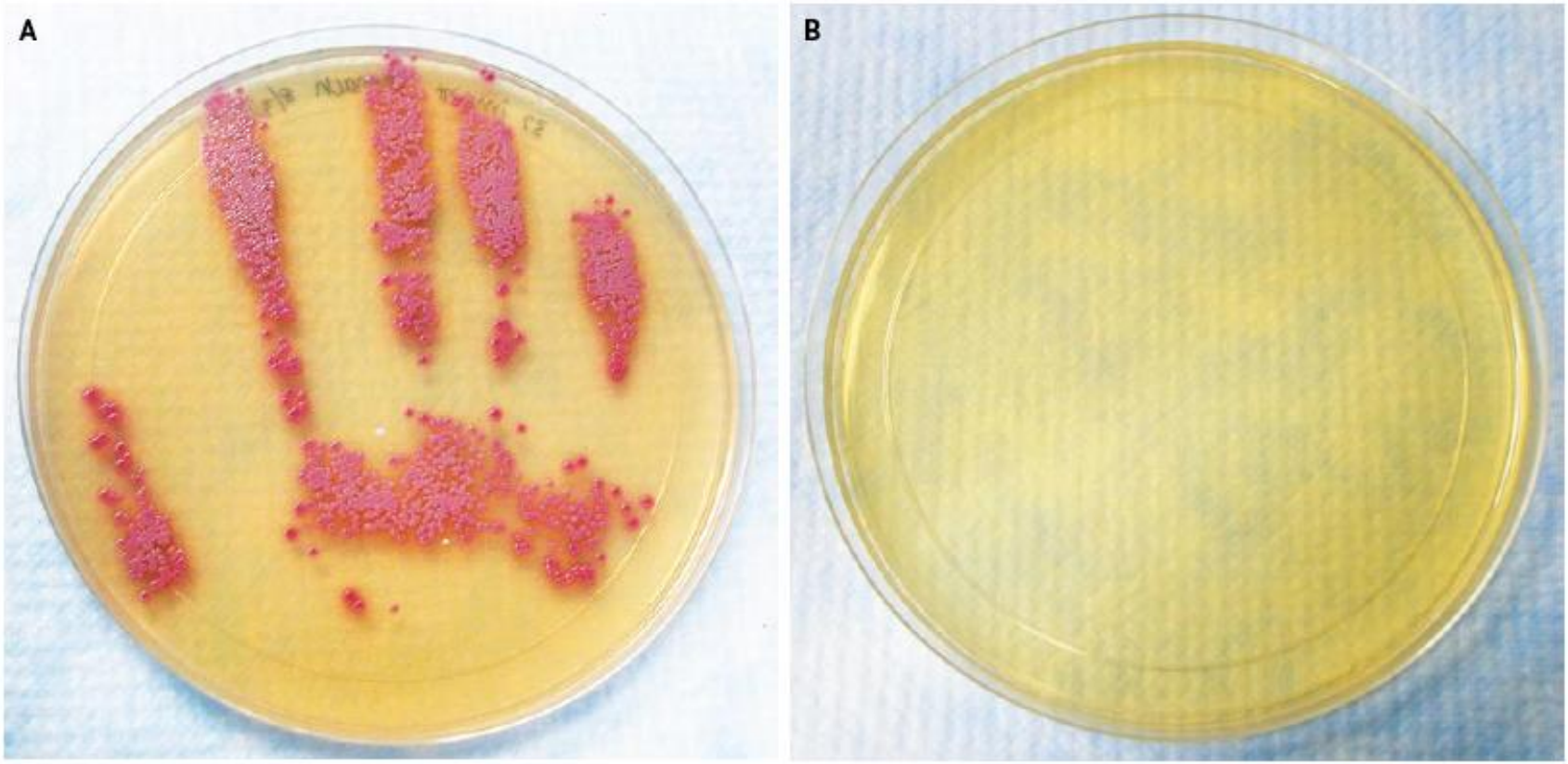
LOUIS D. SARAVOLATZ, M.D.; NORMAN MARKOWITZ, M.D.; LUCILLE ARKING, B.S.N.; DONALD POHLOD, M.S.; and EVELYN FISHER, M.D.; Detroit and Ann Arbor, Michigan

Infection with strains of methicillin-resistant *Staphylococcus aureus* occurred in 40 patients at time of admission to a large urban hospital from March to

ty-acquired cases into the hospital produced a significant increase in nosocomial methicillin-resistant *S. aureus* infections, while nosocomial methicillin sensitive *S. aureus*

1980

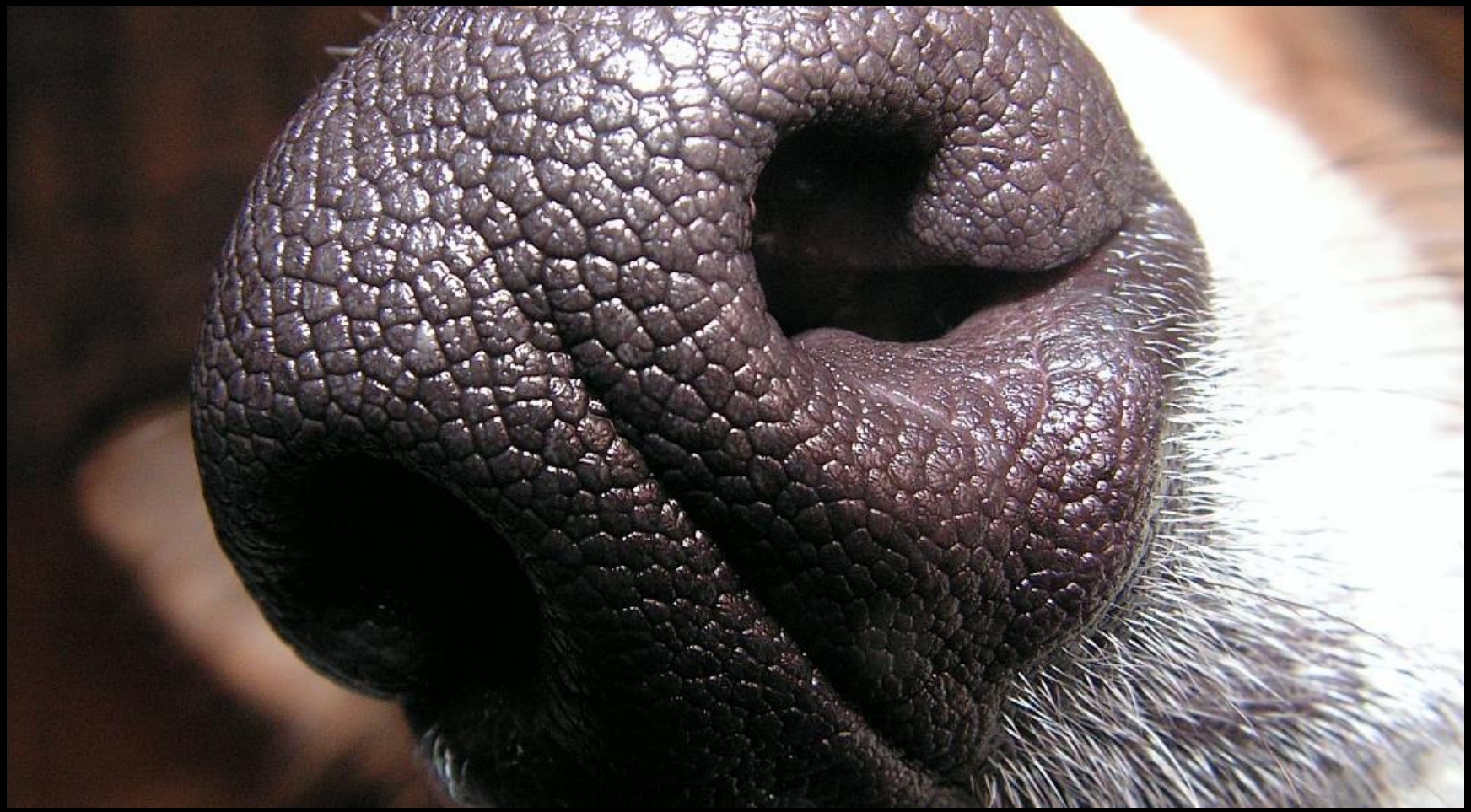
Can We Decolonize Human Skin?



N ENGL J MED 360;3 NEJM.ORG JANUARY 15, 2009

Should I 'De-colonize' My Patients, and if So, How?

a.) Nasal Colonization with *S. aureus* is Frequent



Pooled Data from the Literature--- Prevalence of *S. aureus* Nasal Colonization

Population	# Subjects	Mean Nasal Carriage %	# Studies
General	13,873	37.2	18
Health Care Workers	2,568	26.6	7
Patients on Admission	21,842	35.7	8
IDDM	454	56.4	5
Hemodialysis	454	51.5	8
HIV +	288	55.2	2
IVDU	664	35.5	5

Reproduced in part from Kluytmans, et al. 1997;10(3):505-520

Should I ‘De-colonize’ My Patients, and if So, How?

b.) Risk of Infection Appears to Increase with Colonization

Risk of Infection with Nasal Carriage of *S. aureus* in Surgical Patients

Author	Year of Publication	RR of Infection (carrier vs. non-carrier)	% Infecting Isolates Identical to Nasal Isolates
Colbeck	1959	7.0	100.0
Weinstein	1959	3.4	91.7
Williams	1959	3.3	59.6
Public Health Dept	1960	1.3	42.9
Bassett	1963	0.7	58.0
Bassett	1963	1.0	30.0
Henerson	1963	1.4	50
Howe	1963	2.4	33.3
Ketcham	1963	5.2	94.7
Calia	1969	1.8	100.0
Morales	1994	9.4	91.0
Kluytmans	1995	7.2	100.0
Saginur	1996	6.1	87.0

Reproduced in part from Kluytmans, et al. 1997;10(3):505-520

Should I 'De-colonize' My Patients, and if So, How?

b.) Risk of Infection Appears to Increase with Colonization

- **Von Eiff, et al. New England J. Medicine**
  - 219 hospitalized adults with *S. aureus* bacteremia (9.1% MRSA)
    - 82.2% were colonized intra-nasally at the time of admission with the SAME clone of *S. aureus* that was in the blood (by pulsed field gel electrophoresis)

Von Eiff, et al. NEJM. 2001;344:11

Should I 'De-colonize' My Patients, and if So, How?

b.) Risk of Infection Appears to Increase with Colonization

- **Von Eiff, et al. New England J. Medicine**
  - Second component to the study
    - 1278 adults with positive nasal cultures for *S. aureus* (5.8% MRSA) were prospectively followed for bacteremia
    - 14 developed bacteremia
    - Of these 14 infections, 12 (85.7%) were with the exact same strain/clone of *S. aureus* that was in their nose

Von Eiff, et al. NEJM. 2001;344:11

Should I 'De-colonize' My Patients, and if So, How?

- **The theory**
  - If we 'decolonize' patients, they will subsequently be at a lower risk of infection from these strains
- **The practice**
  - Mupirocin in the nose, with or without hibiclens baths, with or without rifampin/Bactrim therapy

Studies of Nasal Re-colonization after Intra-nasal Mupirocin

Author	Year	Re-colonization
Fernandez	1995	43% at 1 month 67% at 6 months
Martin	1999	40% by week 2 70% by week 10

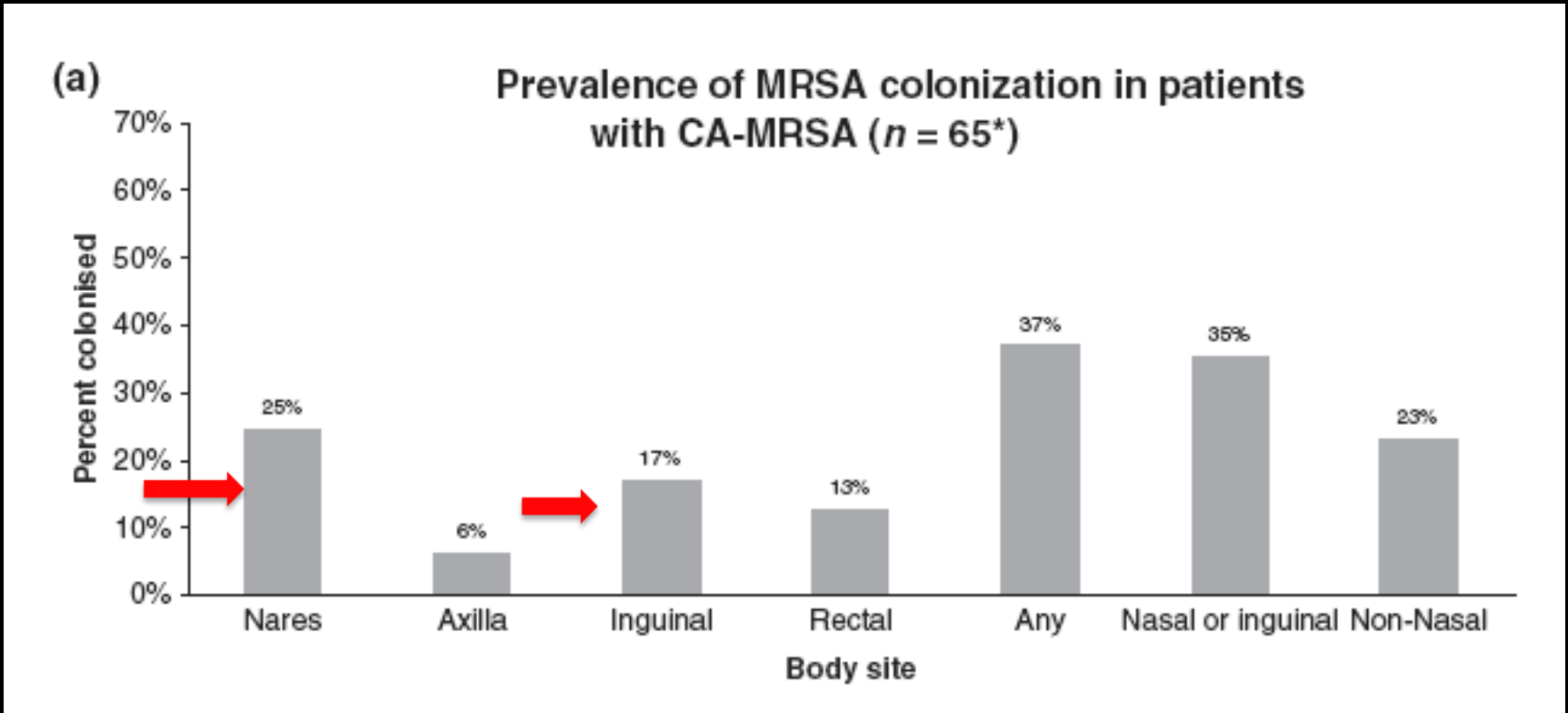
Fernandez, et al. J Antimicrob Chemother. 1995;35:399-408
Martin, et al. J Infect Dis. 1999;180(3):896-899.

Problems with Decolonization: c.) Alternative sources of infection

- MRSA has been isolated from sauna benches, stethoscopes, bars of soap, towels, razors, whirlpools, pagers
- In many of these instances, infected patients had no nasal colonization

Clinical Infectious Diseases 2008; 46:752–60

Problems with Decolonization: d.) Other Body Sites for Colonization



Clin Microbiol Infect 2010; **16:** 425–431

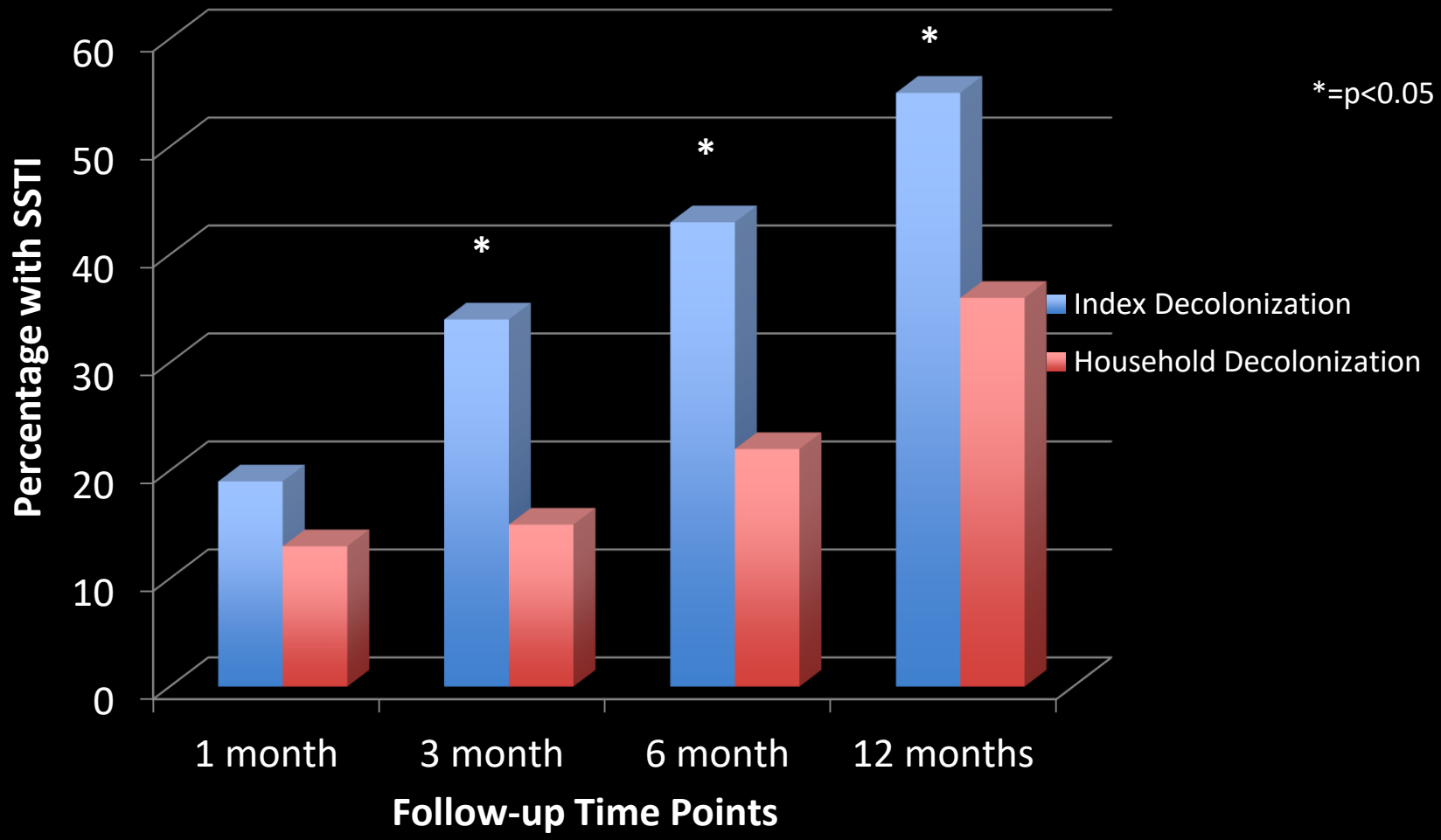
Does it Actually Work?

Summary of Controlled CA-MRSA Decolonization Studies: Index Patient Only

Author	Year	# Patients	Regime	Infection Rate
Ellis	2007	3447	Intranasal mupirocin	No effect
Rahimian	2007	19	Intranasal mupirocin	No effect
Harbath	1999	102	Intranasal mupirocin + hibiclens	No effect

Rahimian, et al. Infect Control Hosp Epidemiol. 2007;28:1415
Harbath, et al. Antimicrob Agent Chemother. 1999;43(6):1412
Ellis, et al. Animicrob Agent Chemother. 2007;51:3591

Impact of Household vs. Individual Decolonization on Recurrent SSTI's (Physician report; n=183)



Data adapted from Fritz, et al. Clin Infect Dis. 2012;54:743-752

Should I 'De-colonize' My Patients, and if So, How?

Pros and Cons

- **Why we should do it**
  - MRSA colonizes patients
  - MRSA colonized patients probably have a higher risk of infection with MRSA
  - Decolonization can remove the MRSA from patients skin in some cases

Should I 'De-colonize' My Patients, and if So, How?

Pros and Cons

- **Why we should do it**
  - Parents often feel more at ease after the intervention
  - Relatively harmless

Should I 'De-colonize' My Patients, and if So, How?

Pros and Cons

- **Why we should not do it**
  - May lead to antibiotic resistance
  - Patients tend to get re-colonized quickly
  - Not everyone is colonized (may have picked it up from fomites, contact)
  - May not be able to sterilize the multiple anatomic sites involved
  - May be re-colonized with a more aggressive strain of MRSA

Table of Recommended 'Decolonization' Interventions with Rationale

Intervention	Rationale
Mupirocin intra-nasally for 5-7 days	High frequency of nasal colonization
Hibiclens baths daily for 5-7 days	High frequency of non-nasal colonization sites
De-colonize household contacts	Data from the Washington Univ. study (Fritz, et al)
Change towels, etc	MRSA may be spread via fomites and not via colonization

Treatment Updates

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 19, 2015 VOL. 372 NO. 12

Clindamycin versus Trimethoprim–Sulfamethoxazole for Uncomplicated Skin Infections

oren G. Miller, M.D., M.P.H., Robert S. Daum, M.D., C.M., C. Buddy Creech, M.D., M.P.H., David Young
Michele D. Downing, R.N., M.S.N., Samantha J. Eells, M.P.H., Stephanie Pettibone, B.S.,
Rebecca J. Hoagland, M.S., and Henry F. Chambers, M.D., for the DMID 07-0051 Team*

Study Outline

- 524 patients from 6 months of age up with uncomplicated skin infections
  - Randomized to receive clindamycin or Bactrim
  - Double blinded

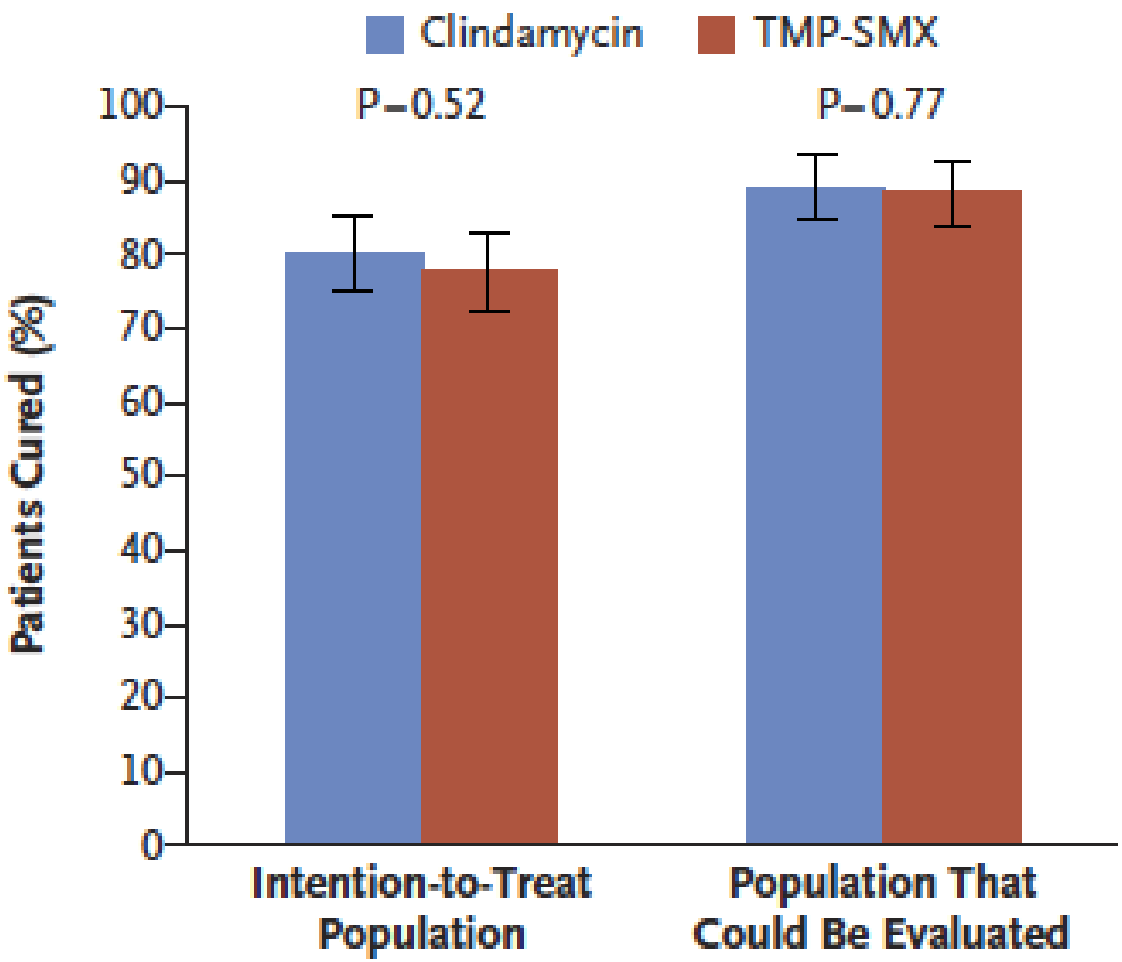


Figure 2. Comparison of the Efficacy of Clindamycin and TMP-SMX in Patients with Uncomplicated Skin Infection.

Impact of Drainage

- 44 adult patients in San Francisco underwent I and D for MRSA SSTI
- All received inappropriate therapy (β-lactam) post-procedure
- All infections resolved

Arch Surg. 2004;139:947-953

Impact of Drainage---Pediatric Data

67 Children with drained MRSA Skin abscesses

62 treated with an inactive antibiotic

37 patients did NOT have the antibiotic changed

36 patients (97.3%) cured

Pediatr Infect Dis J. 2004;23:123-127

2.) ‘Taboo’ antibiotics in younger children: fluoroquinolones

Vignette

- A 2-year-old girl with spina bifida is seen in your clinic on a Friday afternoon for fevers and supra-pubic pain. Your suspicion of a UTI is increased after her urine dip is positive, and her urine culture ultimately demonstrates growth of *Pseudomonas*. The only oral drug it is susceptible to is ciprofloxacin. Her mother is concerned about using this drug, and is worried that ‘…something bad will happen.’

Toxicology Letters, 1 (1977) 21—26

ARTHROPATHY INDUCED BY ANTIBACTERIAL FUSED *N*-ALKYL-4-PYRIDONE-3-CARBOXYLIC ACIDS

B. INGHAM, D.W. BRENTNALL, EUGENIE A. DALE and J.A. McFADZEAN

May & Baker Ltd., Dagenham, Essex, RM10 7XS (Great Britain)

(Received April 4th, 1977)
(Accepted April 21st, 1977)

SUMMARY

The antibacterial agents, nalidixic, oxolinic and pipemidic acids, induced lameness, associated with exudation of synovial fluid and blistering and ulcerative erosion of articular cartilage, in the joints of the limbs of immature, but not mature, dogs when administered daily, for periods of 1—15 days, at dose rates of 200—1000 mg/kg. Clinical recovery usually occurred within 14—21 days, even with continued medication, but the lesions had not resolved in animals autopsied up to 87 days after withdrawal of the drug. The lesions were also present at autopsy in immature dogs which had received pipemidic acid daily for 6 months, in spite of the fact that the animals had been clinically normal for all except the first 4 or 5 weeks of the study.

Microscopical examination showed that fissuring occurred in the intermediate, germinal, zone of cartilage. Hypertrophy of chondrocytes was a common finding, with some large cell nests and multinucleate cells. In a few cases, some disorganisation of epiphyseal plates was seen.

INTRODUCTION

The safety evaluation of new and 'back-log' chemicals has become a considerable industry. As a consequence, innumerable manifestations of toxicity have been recognised, and it is becoming rare to identify significant new toxic effects. In this paper we report what we believe to be an hitherto unrecognised form of drug toxicity.

Nalidixic (I), oxolinic (II) and pipemidic (III) acids are antibacterial agents with a similar spectrum of activity and appear to be of relatively low toxicity when assessed by the criteria conventionally applied to studies in laboratory animals. We have, however, found that they induce severe arthropathic changes in the major articulations of the appendicular skeleton of immature dogs.

TABLE 1. Ciprofloxacin global clinical database, Bayer AG: adverse events (as of July 2003)

All patients were <18 years old in Phase II to IV studies ($N = 2622$).*

	% of Adverse Events at Following Duration of Therapy		
	1–29 days ($N = 2292$)	30–59 days ($N = 200$)	≥60 days ($N = 130$)
Any event	19	20	20
Diarrhea	2	4	<1
Vomiting	2	<1	<1
LFT abnormal	2	2	2
Pharyngitis	2	0	<1
Rash	2	2	3
Leukopenia	1	0	0
Arthralgia	1	4	4
Nausea	1	4	2
Eosinophilia	1	<1	0
Abdominal pain	1	<1	2
Photosensitivity	<1	2	3
Arthritis	<1	1	0
Pneumonia	<1	1	0
Abnormal kidney function	<1	1	0
Injection site hypersensitivity	<1	0	2
Nervousness	<1	0	2
Bilirubinemia	<1	<1	2

* Adverse events occurring in ≥1% of patients in each duration group.

LFT, liver function test.

5-Year Follow-Up of 124 Children Receiving Fluoroquinolone Therapy

Outcome	FQ Group (n=124)	Comparator Antibiotic (n=83)
Musculoskeletal Adverse Events Possibly related to Drug	1	1

Adapted from Bradley, et al. Pediatrics. 2014;134:e146-153

Rate of Arthropathy 6 Weeks after Fluoroquinolone Therapy---Global Data

Country	FQ Group (n=335)	Comparator Antibiotic (n=349)
Argentina	10.4%	8.9%
Canada	12.5%	9.1%
Costa Rica	19.0%	0.0%
Germany	7.7%	9.1%
Mexico	0.0%	0.0%
South Africa	18.2%	11.1%

Adapted from Bradley, et al. Pediatrics. 2011:e1034-1048

Ciprofloxacin Package Insert

CIPRO®
(ciprofloxacin hydrochloride)
TABLETS

CIPRO®
(ciprofloxacin*)
ORAL SUSPENSION

Pediatric patients (1 to 17 years of age):
Complicated Urinary Tract Infections and Pyelonephritis due to *Escherichia coli.*

www.fda.gov/downloads/Drugs

- Other studies have failed to show joint abnormalities on MRI or autopsy of children on long term FQ's
- No adverse effect on height has been demonstrated

Schaad, et al. PIDJ. 1991;10:723-9
Schaad. J Med Sci. 1994;30:463-8

Pradhan, et al. Acta Pediatr. 1995;84:555-60

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Guidance for the Clinician in Rendering Pediatric Care

CLINICAL REPORT

The Use of Systemic and Topical Fluoroquinolones

John S. Bradley, MD, Mary Anne Jackson, MD, and the COMMITTEE ON INFECTIOUS DISEASES

abstract

FREE

SUMMARY

Use of a fluoroquinolone in a child or adolescent may be justified in special circumstances in which (1) infection is caused by a multidrug-resistant pathogen for which there is no safe and effective alternative and (2) the options for treatment include either parenteral nonfluoroquinolone therapy or oral fluoroquinolone therapy, and oral therapy is preferred. In other clinical

3.) The child with recurrent fevers

Vignette

- A previously healthy 3 year old girl is seen in your clinic with a febrile illness. This is her 6th febrile illness in the last 6 months. She never has viral URI symptoms with the fevers, and is otherwise well in between fevers. The episodes eventually resolve after 3-5 days. Her mother is frustrated, and is concerned you are missing '…something serious.'

- Many consequences of periodic fevers in children
  - Unnecessary antibiotics
  - Missed school
  - Missed work for parents
  - Cost of repeated medical visits
  - Parental and physician anxiety

- The presentation of febrile episodes (severity, duration, frequency, associated symptoms) may vary greatly, but most patients with such syndromes are completely well in between episodes

PFAPA Syndrome
Review of 6 Case Series and 395 Patients

- **Periodic Fevers**
  - Typically every 3-6 weeks and lasting 3-7 days at a time (mean duration 4.1 to 5.3 days)
- **Aphthous stomatitis (38-75%)**
- **Pharyngitis (75-100%)**
  - Often no exudate
- **Adenitis (61-100%)**
  - Cervical
  - No fluctuance

Marshall, et al. J Pediatr. 1987;110:43-46
Thomas, et al. J Pediatr. 1999;135:15-21
Padeh, et al. J Pediatr. 1999;135:98-101
Gattorno, et al. Pediatr. 1009;124:e721-28
Feder, et al. Acta Paediatr. 2010;99:178-184
Tasher, et al. Acta Paediatr. 2008;97:1090-1092

Presentation of PFAPA: 6 Case Series, 395 Patients

Symptom	Marshall, et al	Thomas, et al	Padeh, et al	Tasher, et al	Gattorno, et al	Feder, et al
Mean duration fever (days)	---	4.8	4.8	5.3	4.5	4.1
Pharyngitis %	75	65	100	96	84	85
Cervical LAD %	67	77	100	61	84	62
Aphthous stomatitis %	75	67	68	39	59	38
Headache %	---	65	18	46	41	44
Arthralgia %	---	---	11	---	44	---
Diarrhea %	---	30	000	13	29	---
Abdominal Pain %	---	45	18	65	53	41
Rash %	---	15	---	4	22	---

PFAPA Syndrome

- Parents often can tell when an episode is set to begin
- Periodicity may be strikingly regular, down to the day

PFAPA Syndrome

- Average age of onset around 2-3 years
- May see ‘atypical’ symptoms occasionally occurring with the fevers
  - Abdominal pain
  - Emesis
  - Diarrhea

Caorsi, et al. Curr Opin Rheum. 2010;22:579-84

PFAPA Syndrome

- Self-limited illness
  - Average duration of illness in a recent long-term follow-up study reported to be 6.3 years
  - No sequelae known
- The period between fevers typically lengthens as PFAPA begins to resolve

Wurster, et al. J Pediatr. 2011;159:958-964

Key Historical Features: Questions to Ask

- How often do the fevers occur?
  - Is there any regularity/periodicity to them?
  - e.g. every 4 weeks vs. every 4-6 weeks vs. every 3 weeks vs. no pattern

Key Historical Features: Questions to Ask

- How old was the child when the episodes began?
  - Under or over 1 year of age?
- How long do the fevers last when they occur?
  - Several days vs. weeks or more

Key Historical Features: Questions to Ask

- How high are the fevers and are they controllable with antipyresis?
- Any associated signs/symptoms
  - Particular attention to oral ulcers, cervical adenitis, pharyngitis, arthritis, abdominal pain, emesis/diarrhea, conjunctivitis
- Any concerning concurrent systemic findings?
  - e.g. weight loss, loss of developmental milestones

Key Historical Features: Questions to Ask

- Is the child otherwise well when not having a febrile episode?

Practical Approach to the Child with Periodic Fevers

- 1st---verify the presence of fever
  - How is the temperature being assessed? How frequently?
- 2nd---determine the frequency/periodicity of the episodes

Frequency/Periodicity of Various Periodic Fever Syndromes

Frequency of Episodes	PFAPA	Cyclic Neutropenia	FMF	HIDS	TRAPS
Range	q 3-6 weeks	q 2-8 weeks	q 3-4 months	q 4-8 weeks	q weeks to years
'Classic'	q 28 days	q 21 days (90%)	None	None	None

FMF=familial mediterranean fever
HIDS=Hyper IgD syndrome
TRAPS=TNF alpha receptor associated syndrome

Practical Approach to the Child with Periodic Fevers

- 3rd---Determine the length of episodes

Duration of Febrile Episodes in Various Periodic Fever Syndromes

PFAPA	Cyclic Neutropenia	FMF	HIDS	TRAPS
3-5 days	5-7 days	1-3 days	3-7 days	2 days-weeks

FMF=familial mediterranean fever
HIDS=Hyper IgD syndrome
TRAPS=TNF alpha receptor associated syndrome

Practical Approach to the Child with Periodic Fevers

- 4th---Determine if the child is well in between episodes and gaining weight
  - If not (e.g. continuing malaise, systemic symptoms, poor appetite/activity levels), more concern over a serious, systemic process (e.g. rheumatologic/oncologic disorder)

Practical Approach to the Child with Periodic Fevers

- 5th---Assess via history and examination for syndrome specific physical examination findings

Examination Findings Associated with Various Periodic Fever Syndromes

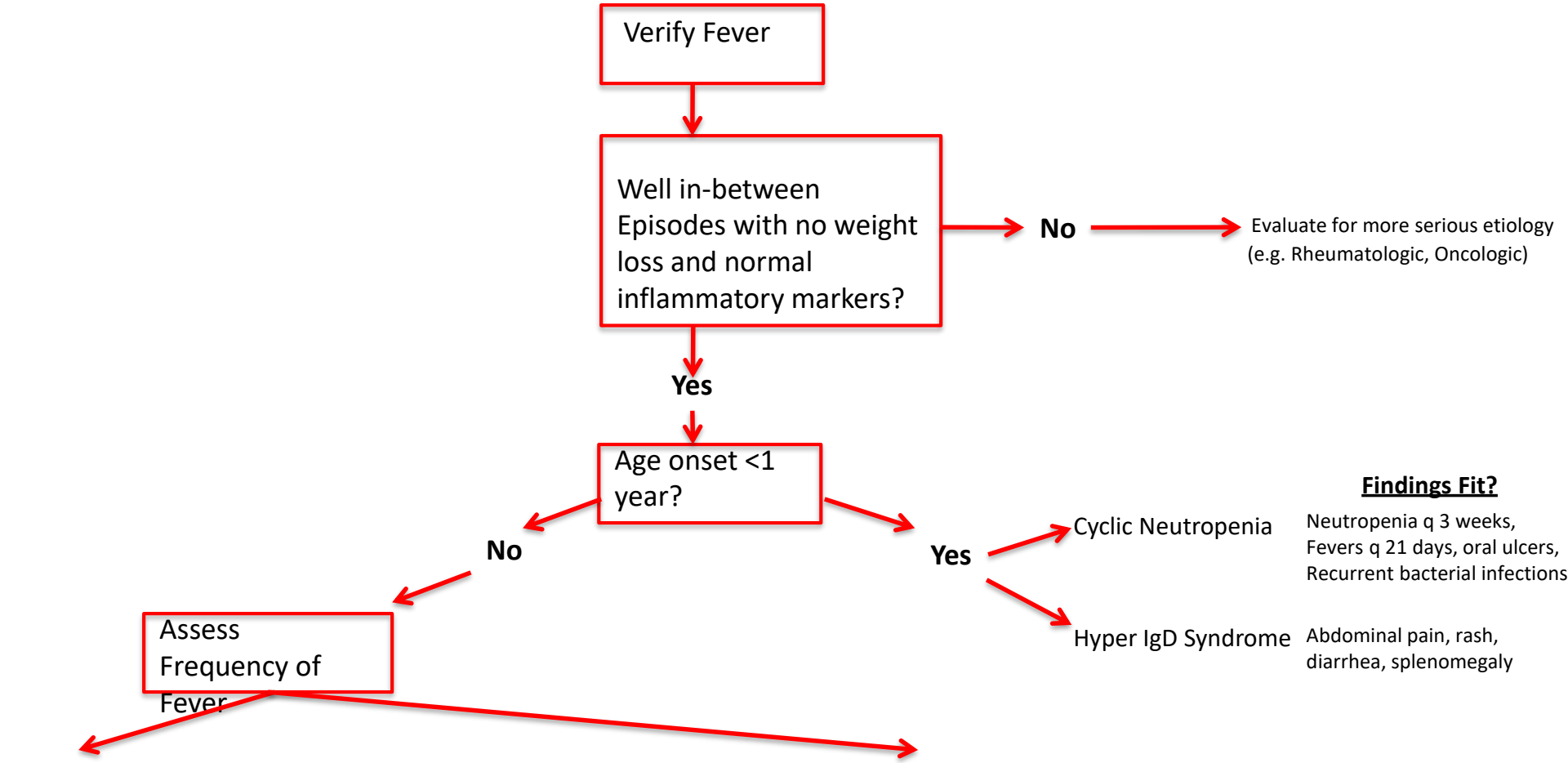
Finding	PFAPA	Cyclic Neutropenia	FMF	HIDS	TRAPS
Oral Ulcers	Yes	Yes	No	Yes	No
Pharyngitis	Yes	No	No	No	No
Cervical LAD	Yes	No	No	Yes	No
Rash	No	No	Yes	Yes	Yes
Splenomegaly	No	No	No	Yes	No
Periorbital edema	No	No	No	No	Yes
Pseudocellulitis	No	No	No	No	Yes

FMF=familial mediterranean fever
HIDS=Hyper IgD syndrome
TRAPS=TNF alpha receptor associated syndrome

Practical Approach to the Child with Periodic Fevers

- 6th---Have the family keep a fever diary
  - Record dates febrile episodes began and end
  - Record associated symptomatology (if any)

Flowchart for the Initial Evaluation of a Child with Periodic Fevers and No Suspicion of Recurrent Viral Infections



Regular		Findings Fit?
q 21 days	Cyclic Neutropenia	Neutropenia q 3 weeks, fevers q 21 days, oral ulcers, recurrent bacterial infections
q 3-6 weeks	PFAPA	Pharyngitis, cervical adenitis, oral ulcers
q 4-8 weeks	Hyper IgD Syndrome	Abdominal pain, rash, diarrhea splenomegaly

Irregular		Findings Fit?
q 4-8 weeks	Hyper IgD Syndrome	Abdominal pain, rash, diarrhea, splenomegaly
Weeks to months	FMF	Abdominal pain, rash, arthritis
Weeks to years	TRAPS	Abdominal pain, rash, periorbital edema, arthritis

Treatment of the Child with Periodic Fevers

- **PFAPA**
  - No cure
  - 1-2 mg/kg prednisone give over 1-2 doses x1 just prior to the onset of a febrile episode may abort that episode (85% or so of cases)
  - The next episode may occur sooner than expected half the time in 50% of patients
  - This may be diagnostically useful

Wurster, et al. J Pediatr. 2011;159:958-964
Padeh, et al. J Pediatr. 1999;135:98-101

Treatment of the Child with Periodic Fevers

- **PFAPA**
  - Could consider selective use of such prednisone to abort febrile episodes prior to important events a few times per year (e.g. wedding, vacation) should an episode began during or prior to the event

4.) The child with a fever of unknown origin

Vignette

- An 8-year-old boy comes to see you in clinic for a fever for 14 days. His mother denies any symptoms have been present, and his exam is unremarkable. She is worried '…something serious is going on.'

A Moving Target: The Definition of FUO in Children

Variables	Brewis, 1965	McClung 1972	Pizzo 1975	Feigin 1976	Lohr 1977	Jacobs 1998
Inclusion Criteria						
Daily Fever	**5-7 days**	21 days	14 days	14 days	**35 days**	14 days
Admitted	No	Yes---1 week	No	Yes---1 week	**Yes---1 week**	No
Total Cases	165	99	100	20	54	146
Diagnosis						
Infection	38%	28%	52%	35%	33%	44%
Rheumatologic	**5%**	11%	20%	15%	**15%**	6%
IBD	**0%**	3%	0%	5%	**13%**	3%
Cancer	**2%**	8%	6%	5%	**13%**	3%
Misc	2%	8%	6%	5%	13%	3%
No Dx	5%	11%	12%	30%	19%	42%

2016 Study of Pediatric FUO

- 69 children referred to the Univ. of Louisville over a 4-year period
- 10 patients had resolution of fevers prior to visit

Statler, et al. J Pediatr Infect Dis Soc. 2015;5(3):249-256

2016 Study of Pediatric FUO

- Of the remaining 59 patients
  - 11 had diagnosis apparent at time of visit (Cat scratch disease, EBV, sinusitis, etc)
  - Of the remaining 48 patients
    - Median of 30 days fever (IQR 21-60 days)

Statler, et al. J Pediatr Infect Dis Soc. 2015;5(3):249-256

2016 Study of Pediatric FUO

- Of these 30, only 8 had a serious diagnosis:
  - 2 with JIA, 2 with IBD, 1 with typhoid fever, 1 with hemophagocytic lymphohistiocytosis, 1 with leukemia, 1 with rheumatic fever
  - Only 1 (2%) were due to infection

Statler, et al. J Pediatr Infect Dis Soc. 2015;5(3):249-256

2016 Study of Pediatric FUO

- **Take home message:**
  - Most Pediatric FUO are not serious
  - Of those that are, most are not infectious
  - Most serious infections declare themselves, particularly after long periods of time

Statler, et al. J Pediatr Infect Dis Soc. 2015;5(3):249-256

5.) Managing vaccine hesitant parents/families

Vignette

- A first-time mother brings her 2-month old son in for a well child check. You broach the subject of immunizations---she states that she heard Donald Trump say that we ‘give too many vaccines’, and that he ‘has seen bad things happen’ to vaccinated kids. She is ‘on the fence’ about immunizing her child. What should you advise her and how?

Parental Vaccine Safety Survey

Statement	% that strongly agree or agree with statement
Some vaccines cause autism in healthy children	25%
I am concerned about serious adverse effects of vaccines	54%

Table adapted from Freed, et al. Pediatrics. 2010;125(4):654-662

July, 2016 Data

Statement	% that strongly agree or agree with statement
Concerned that vaccines cause autism	54%
Concerned that vaccines cause autism Vaccines have dangerous effects other than autism	57%

Hough-Telford, et al. Pediatrics. 2016;138(3):e20162127

National Survey---Vaccine Hesitancy, 2010

Outcome	%
Refused at least 1 vaccine	11.5%
MMR refused	17.7%
Varicella refused	32.3%
Meningococcal refused	31.8%
HPV refused	56.4%

Freed GL, et al. Pediatrics. 2010;125(4):654-660

Current Epidemiology of Vaccine Hesitancy

- **Vaccine hesitant parents more likely to be:**
  - White
  - Married
  - >30 years old
  - College educated
  - Household income >$75,000
  - ≥4 children

Siddiqui M, et al. Hum Vacc Immunother. 2013;9(12):2643-2648
Smith PJ, et al. Pediatrics. 2004;114:187-195

Rationale for Vaccine Hesitancy: Vaccinated vs. Unvaccinated Families

Group	Vaccine Aren't Safe	Vaccines Don't Work	Won't Get Sick	Don't Trust the Government
Vaccinated	15%	17%	15%	23%
Unvaccinated	61%	54%	58%	40%

Salmon DA, et al. Arch Pediatr Adolesc Med. 2005;159:470476

Sources of Trusted Information Re: Vaccines

Group	Medical Provider	Celebrities	Family/Friends	Parents of Children Allegedly Harmed by Vax
Parents	76%	26%	15%	73%

Freed GL, et al. Pediatrics. 2011;127(S1):S107-112

Timing of Vaccination Decision Making---Survey Results

Group/Population	% Decided Prior to Conception	% Decided After Conception
First-time parents	66%	34%
Experienced parents	77%	23%
Overall	72%	28%

N=171 parents

Yarnal JN, Lorh J. Development of Vaccine Preferences in Parents of Newborns. AAP National Conference and Exhibition. Abstract, Oct 26, 2015. Washington, DC.

Strategies for Engagement

- **Key Points**
  - The psychology of vaccine hesitancy is complicated and variable (one size may not fit all)
  - Poorly studied

Strategies for Engagement

- **Systematic review of published studies assessing strategies for addressing vaccine hesitancy**
  - 33,023 potential articles identified
  - 1,208 articles fit inclusion criteria
  - Only 181 evaluated the proposed intervention(s)
    - Did vaccine uptake change?
    - Did attitudes/beliefs change?

Jarrett C, et al. Vaccine. 2015;33:4180-4190

Strategies for Engagement

- **Least effective interventions (<10% increase in vaccine uptake)**
  - Passive advertising (posters, websites, billboards)
  - Extended clinic hours
  - Incentives for vaccination
  - Reminder-recall strategies

Jarrett C, et al. Vaccine. 2015;33:4180-4190

Strategies for Engagement

- **Most effective interventions (>25% increase in vaccine uptake)**
  - Aimed to increase knowledge (e.g. dialogue-based interventions)
  - Mandated vaccinations (? Increase mistrust, does not address underlying problem, not used in countries with higher vaccination rates)
  - Engaged religious or other influential community leaders

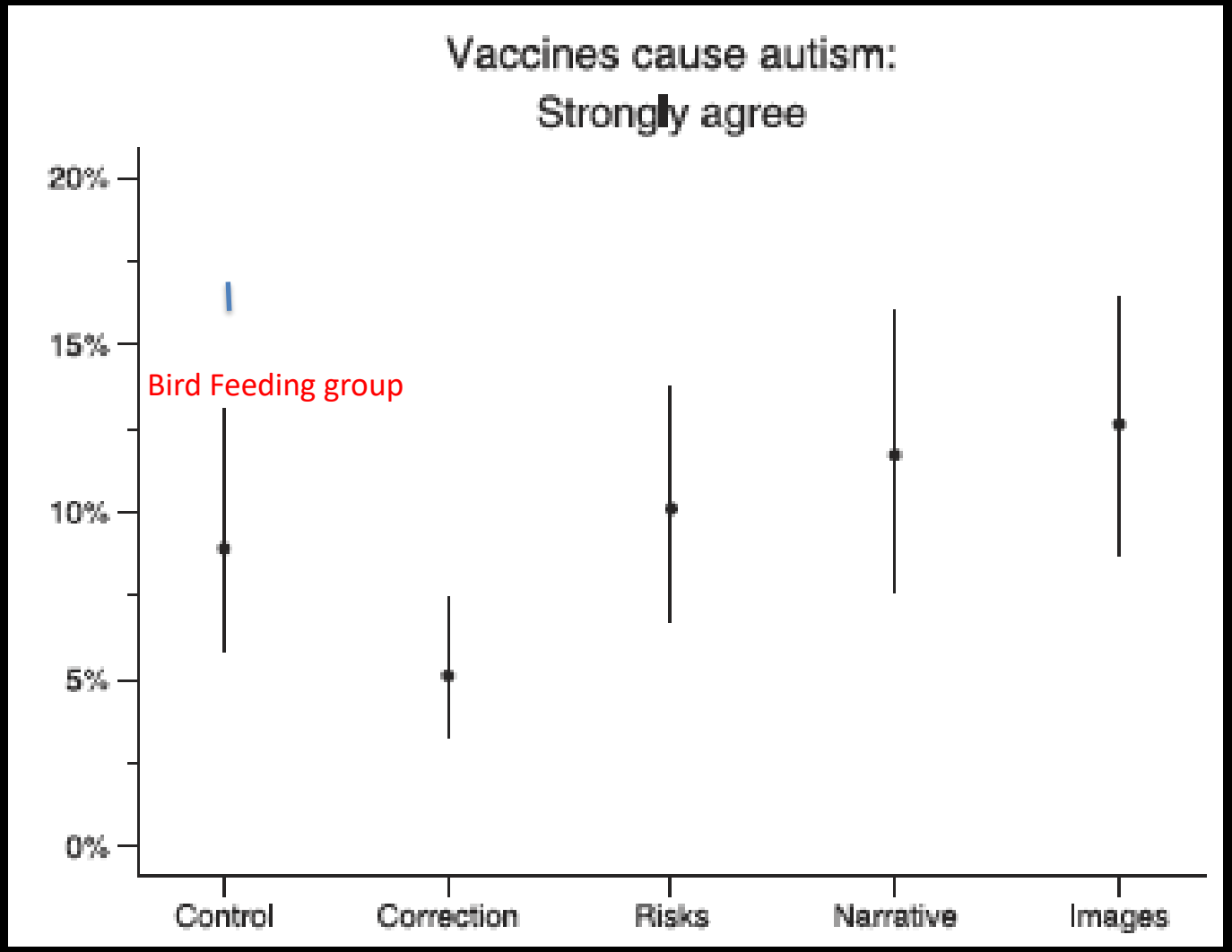
Jarrett C, et al. Vaccine. 2015;33:4180-4190

Strategies for Engagement

- **1759 parents provided with 1 of 4 narrative scripts:**
  - Information describing the lack of association with the MMR vaccine and autism
  - Discussion of the dangers of vaccine preventable diseases
  - Images of children infected with vaccine preventable diseases
  - A dramatic narrative of a child who almost died from measles
  - A control group discussing bird feeding

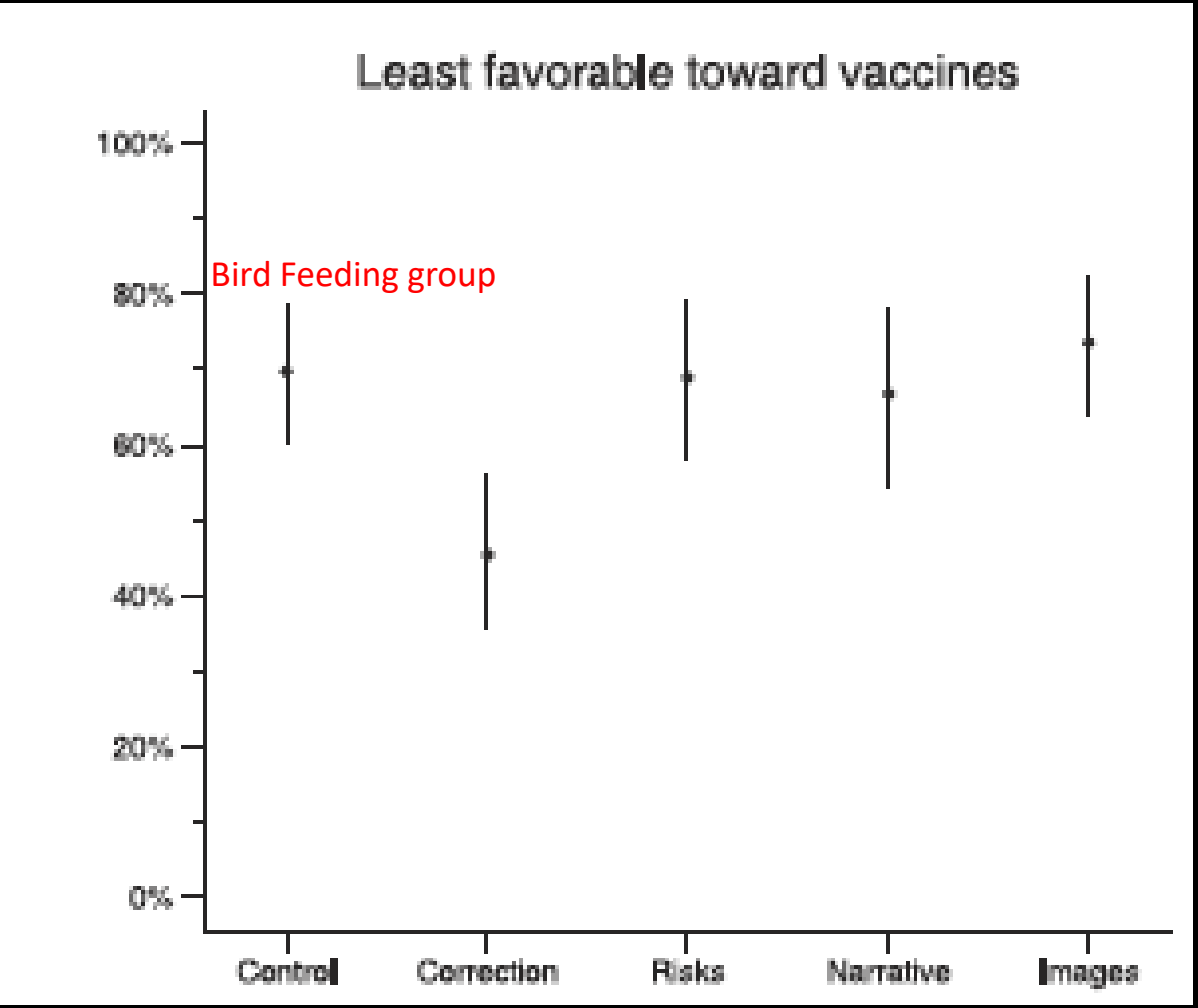
Dube, et al. Vaccine. 2015;33:4191-4203

Likelihood of Families Beliefs Changing After Interventions



Dube, et al. Vaccine. 2015;33:4191-4203

How Likely Families Are to Consent to an MMR After an Intervention



Dube, et al. Vaccine. 2015;33:4191-4203

Strategies for Engagement

- **Authors concluded:**
  - Findings similar to studies of ‘fixed-thinking’ in politics and other vaccine studies
  - ‘The 5%’ may not budge in their thought process

Dube, et al. Vaccine. 2015;33:4191-4203

Strategies for Engagement

- **So What to Do?**
  - Patience
  - Address any obvious misunderstandings
  - Provide evidence where evidence may help
  - Dialogue
  - Uncover the rationale for their hesitancy
  - Avoid ‘cheap fixes’
  - No ‘silver-bullet’, ‘one-size fits all’ approach
  - You will never convince everyone

The ‘4 C’ Model

Group	Worldview/Factors Affecting Vaccination	Engagement Approach
Complacency	Not at risk for diseases/not needed	Not opposed to vax---increase perception of risk
Convenience	Money, transportation, accessibility issues	Often open to vax---remove barriers; reminders/texting
Confidence	**Distrust in vax or the medical system**	**Hardest to deal with---firmly entrenched fears**
Calculation	Assess the pros and cons: Often those who take advantage of herd immunity	Not opposed to vax---discuss risks of contracting disease

Adapted from Betsch, et al. Policy Insights from the Behavioral and Brain Sciences. 2015;2(1):61-73

Increasing Numbers of Vaccines, 1900-2015

Year	# Vaccines	# Possible Injections by Age 2
1900	1	1
1960	5	8
1980	7	5
2000	11	20
2015	14	27

Offit PA, et al. Pediatrics. 2002;109(1):124-132
ACIP 2015 Immunization Schedule

Declining Number of Injected Antigens/Components in Vaccines, 1900-2015

Year	# Vaccines	# Possible Injections by Age 2	# Immunogenic Proteins/Sugars Injected
1900	1	1	200
1960	5	8	3,217
1980	7	5	3,041
2000	11	20	134

96% fewer antigens injected then in 1980 despite a 4-fold Increase in the # of vaccines

Offit PA, et al. Pediatrics. 2002;109(1):124-132

Take a Guess!

- In theory, children may be able to create up to 10^{11} different combinations of antibodies
- By calculating the estimated ability of the immune system to respond to antigens, a child should be able to respond to how many vaccines at one time?

Offit PA, et al. Pediatrics. 2002;109(1):124-132

10,000 vaccines at any one time

Conculsion:
The Microbial Footrace

- C


Lechuguilla Cave
Carlsbad Caverns

Lechuguilla Cave

- Discovered in 1986
- Closed off to human access without a permit
- Almost no human traffic, save for 4-6 researchers over the last quarter century

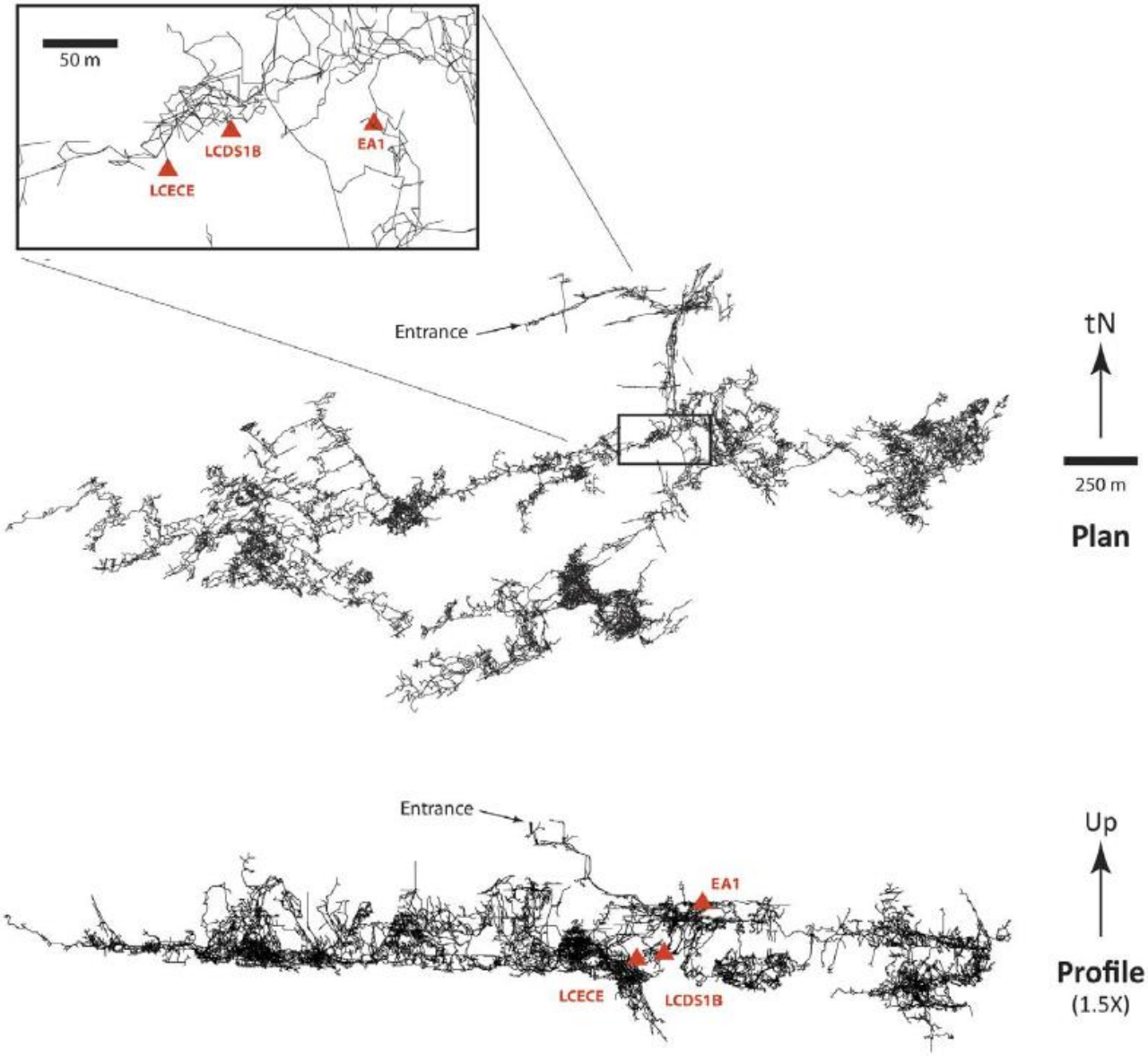


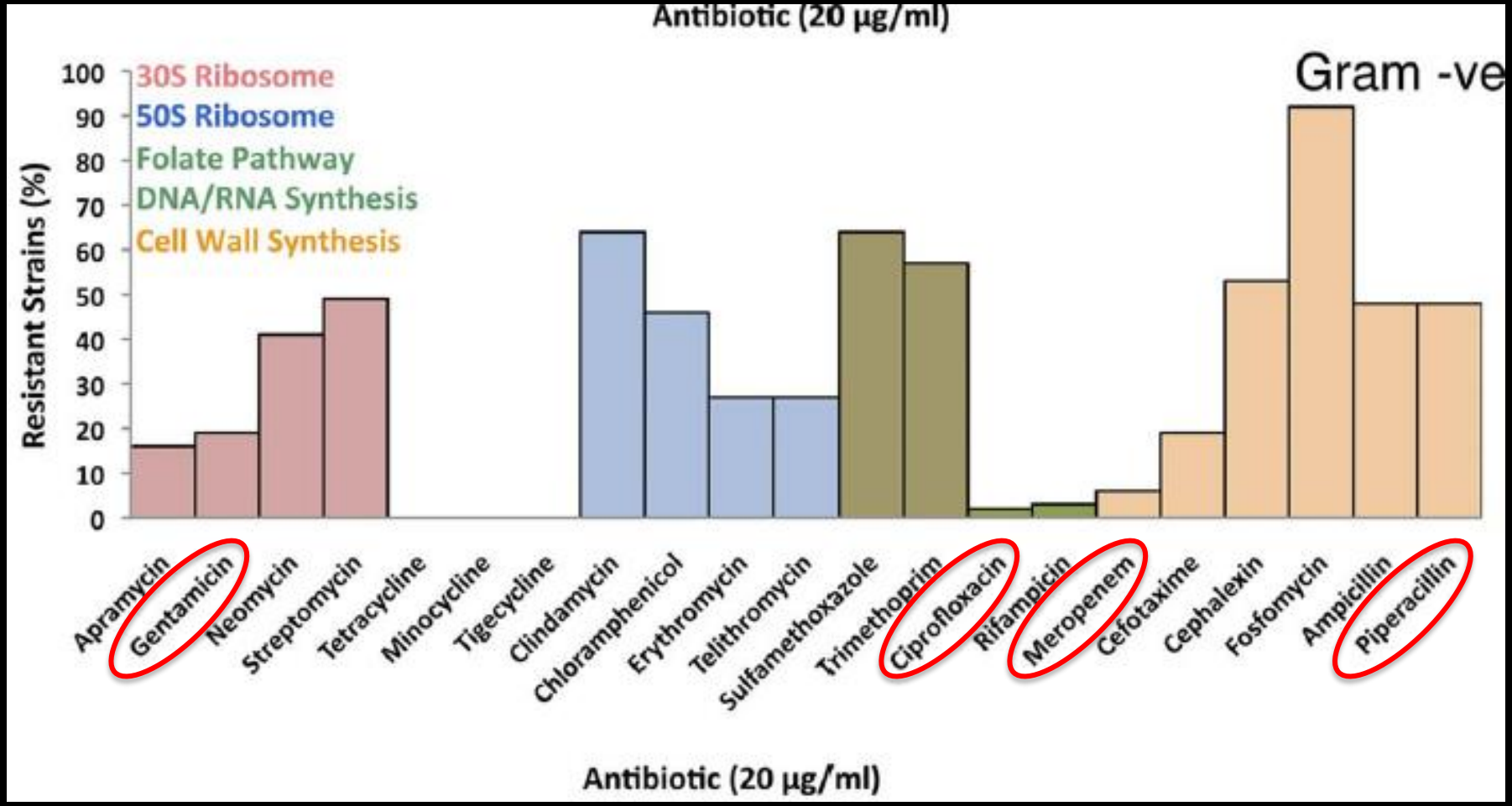
Figure 1. Plan and profile maps of Lechuguilla Cave, Carlsbad Caverns National Park, New Mexico. The sites where microbial strains were collected (LCECE, LCDS1 and LCEA1) are shown relative to the entrance and depth. tN represents true North on the plan, while the profile has an exaggerated vertical profile of 1.5×.
doi:10.1371/journal.pone.0034953.g001

DeGroot, et al. PLoS ONE. 2012;7(4)

- 3 areas of the cave were chosen to sample bacteria---each site was deep within the cave, with no evidence or knowledge of prior human contact, and no external water source

DeGroot, et al. PLoS ONE. 2012;7(4)

Antimicrobial Resistance Profile of Gram Negative Lechuguilla Cave Bacteria



DeGroot, et al. PLoS ONE. 2012;7(4)

The ecosystem of the cave was estimated to have existed for over 4 million years

It’s safe to say the bacteria have a head start on us---both in the Yukon and in New Mexico