Updates on *H. pylori* Research in Alaska

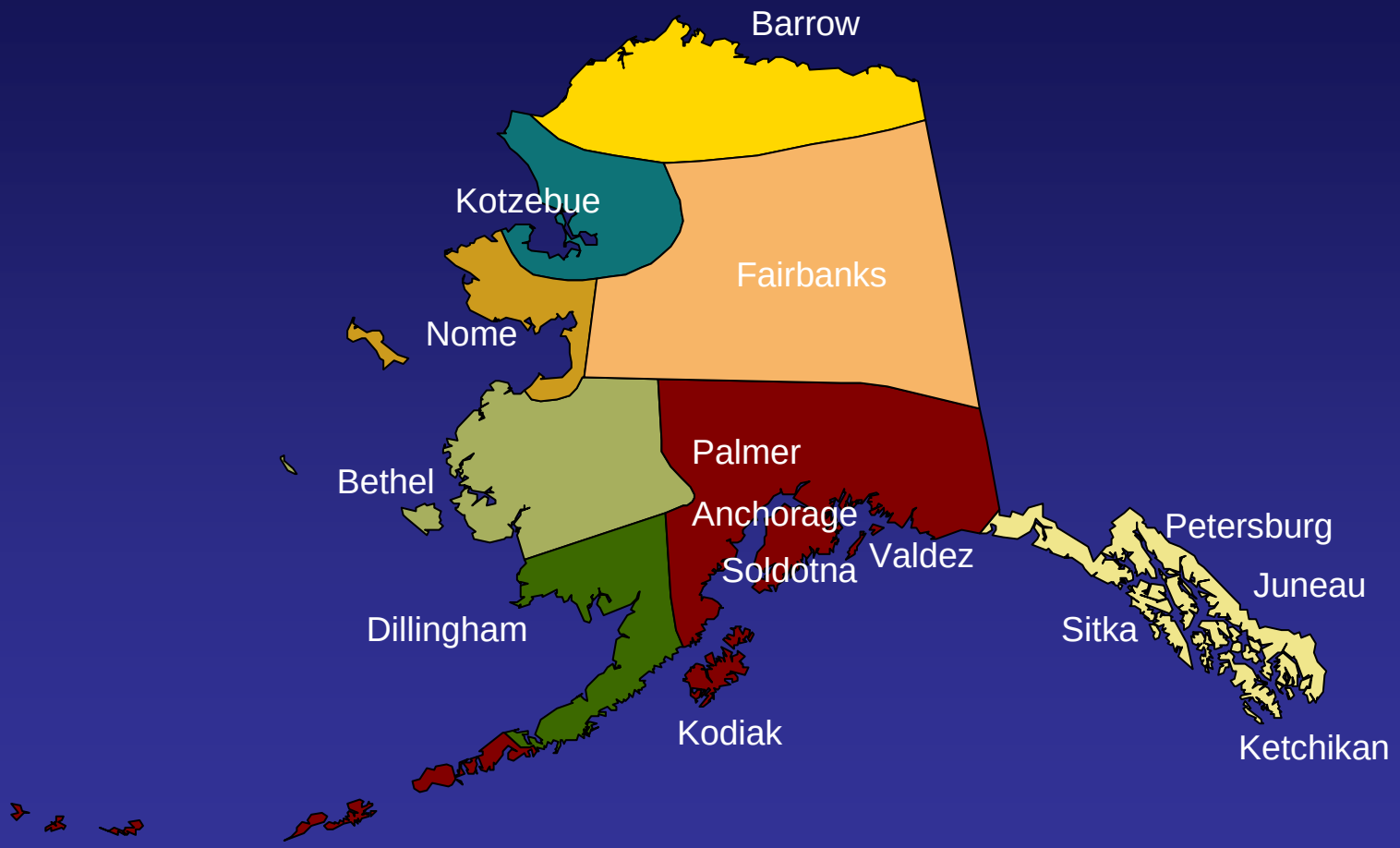
Copenhagen, Denmark, September 21, 2011

Michael G. Bruce MD, MPH
Arctic Investigations Program, CDC
Anchorage, Alaska

Topics
Alaska

- Background
- Update on antimicrobial resistance
- Update on diagnostic testing (5 tests)
- Update on virulence factors/pathology

Alaska


Barrow
Kotzebue
Fairbanks
Nome
Palmer
Bethel
Anchorage
Petersburg
Valdez
Soldotna
Juneau
Dillingham
Sitka
Kodiak
Ketchikan


CDC
Centers for Disease Control and Prevention

Alaska

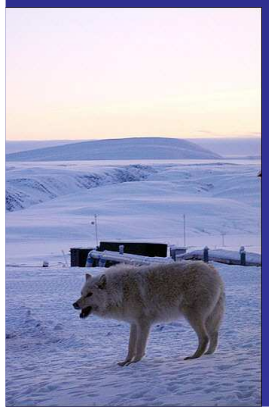
- Population: 710,000
  - Anchorage 280,000
- Statehood in 1959
  - Infrastructure and services not well developed
- “The Last Frontier”
  - “Boom and bust” economy
    - Fishing, logging, mining
    - Oil and Gas

Alaska Natives

- The indigenous people of Alaska
  - Eskimos: Inuit, Yupik, Siberian Yupik
  - Aleuts
  - Athabaskan
  - Coastal Tribes: Haida, Tlingit, Tsimshian
- 20 Languages
- 2010 Census: 105,000 persons
  - 15% of State population
    - AI/AN in US: 0.9%

Alaska Native Demographics

- 60% live in rural areas
- 45% under age 19
  - vs. 30% of US
- Median income ½ that of non-Natives
  - Unemployment high
  - Housing older, more crowded
  - 25% of villages without running water, flush toilets

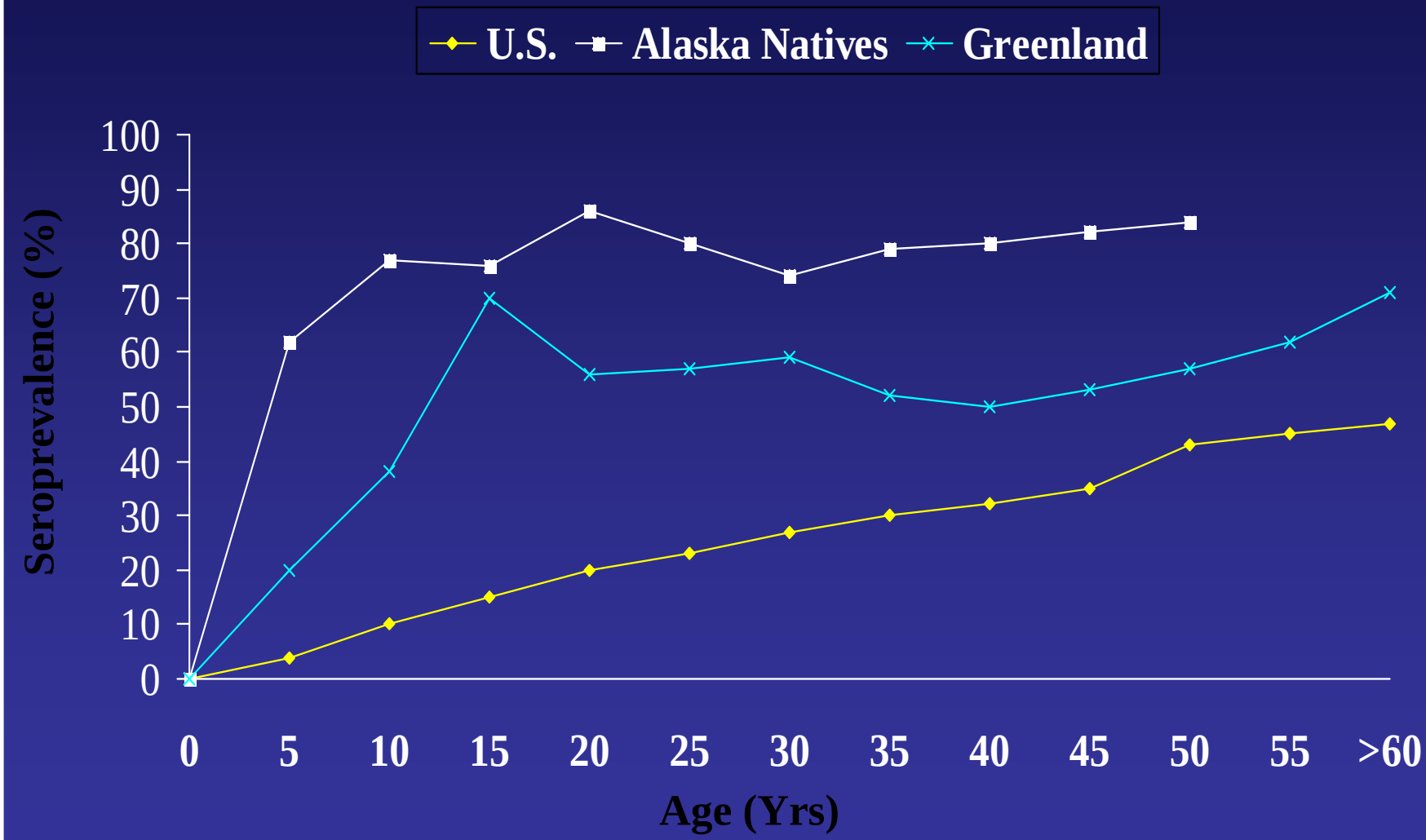


What we have learned from previous studies in Alaska

- Seroprevalence among Alaska Native people is high: 75% overall*

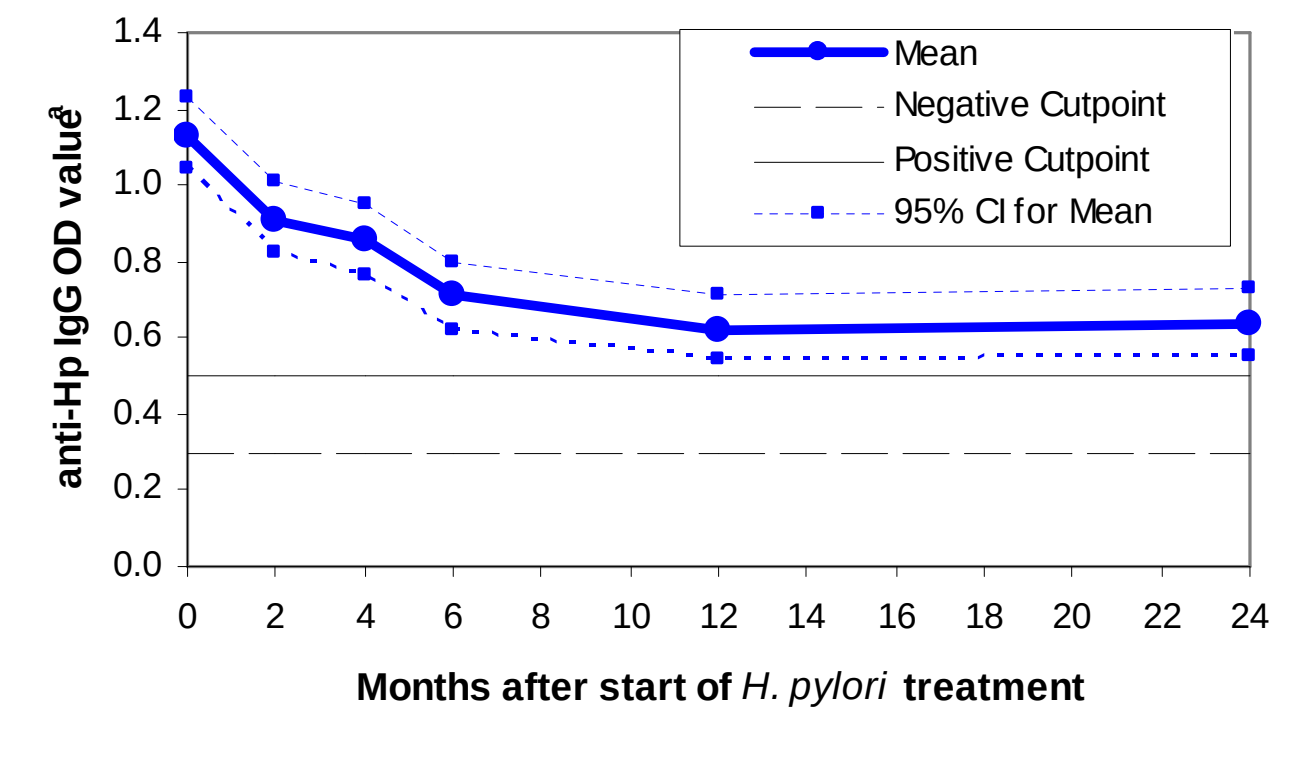
* Parkinson et al.

Seroprevalence of *H. pylori* in Alaska & Greenland compared to the US



Taylor et al *Epi Rev* 1991, Parkinson et al *Clin Diag Lab Immun* 2000, Koch et al *Helicobacter* 2005

H. pylori-specific IgG for 24 months after eradication



71% of persons remained seropositive after 24 months

What we have learned from previous studies in Alaska

- Seroprevalence among Alaska Native people is high: 75% overall*
- Reinfection rate at 2 years is high: 16%**
- The proportion of isolates demonstrating antimicrobial resistance is high○
- Treatment failure rate: 35%**
- *H. pylori* IgG antibody positivity is associated with gastric cancer in a case-control study╪

* Parkinson et al., **McMahon et al., ○Bruce et al., ╪Keck et al.

State of Alaska Epidemiology **Bulletin**

Department of Health and Social Services
William J Streur, Commissioner

3601 C Street, Suite 540
Anchorage, AK 99503 http://www.epi.Alaska.gov

Division of Public Health
Ward B Hurlburt, MD, MPH, CMO/Director

Local (907) 269-8000
24 Hour Emergency 1-800-478-0084

Editor:
Joe McLaughlin, MD, MPH
Louisa Castrodale, DVM, MPH

Bulletin No. 16 June 1, 2011

Helicobacter pylori Antimicrobial Resistance and Treatment for Alaska Native People

Background

Helicobacter pylori bacterial infection predisposes individuals to gastric and duodenal ulcers, chronic active gastritis, mucosal-associated lymphoid tissue (MALT) lymphoma, and gastric adenocarcinoma.[1] Infection usually occurs during childhood, presumably by direct person-to-person transmission, more commonly in crowded household settings.[1] With a seroprevalence of 75% (range: 61–84%, by region), Alaska Native people experience higher rates of *H. pylori* infection and stomach cancer than non-Native Alaskans.[2,3] Antimicrobial resistance is more common in *H. pylori* isolates from Alaska Native people than in other U.S. populations,[4] and contributes to relatively high treatment failure rates (26% in one study).[5] Understanding antimicrobial resistance patterns can guide therapy and increase *H. pylori* treatment success in Alaska Native patients.

Methods

The Arctic Investigations Program (AIP), Centers for Disease Control and Prevention (CDC) *H. pylori* Sentinel Surveillance System cultures *H. pylori* from endoscopic biopsy tissue submitted from five hospitals that provide care to Alaska Native people across five regions of Alaska. The AIP laboratory conducts minimum inhibitory concentration testing of isolates for antibiotics commonly used to treat *H. pylori* infection (i.e., metronidazole, clarithromycin, levofloxacin, amoxicillin, and tetracycline).[4]

Results

Of the 1,256 Alaska Native stomach biopsy samples received from January 2000 through December 2009, 45.1% (566/1,256) were culture-positive for *H. pylori*. Among patients with *H. pylori*-positive cultures, the proportions of isolates demonstrating resistance to metronidazole, clarithromycin, levofloxacin, and amoxicillin were 41.7% (235/564), 29.3% (165/564), 19.7% (37/188) and 1.8% (10/564), respectively. We found no tetracycline-resistant isolates or statistically significant trends in antimicrobial resistance over time. Levofloxacin resistance was more common in patients living in Anchorage/Mat-Su than other regions (29.1% vs. 15.8%, P=0.04; Table). Clarithromycin and metronidazole resistance were more frequent in females than males (36.4% vs. 22.6%, P=0.003 and 52.2% vs. 31.9%, P<0.001, respectively).

Discussion

high prevalence of infection, reinfection, and treatment failure of *H. pylori* in Alaska Native people warrants *H. pylori* screening and treatment guidelines specific to this population (Box).

Box. *H. pylori* Screening and Treatment Guidelines for Alaska Native Patients

- Test and treat *H. pylori* infection in persons with: 1) duodenal or gastric ulcers;[6] 2) MALT lymphoma; 3) severe gastritis (not NSAID or alcohol-related), especially in those patients with unexplained anemia.
- Do **not** test for *H. pylori* in routine dyspepsia evaluations because most patients will have positive serologic results regardless of their symptoms.
- Treat *H. pylori* infection with an FDA-approved regimen accounting for local antimicrobial resistance patterns. In Alaska Native patients, metronidazole-based quadruple therapy regimens (usually containing tetracycline, bismuth, and a proton pump inhibitor [PPI]) have shown superior cure rates.[5]
- Test individuals treated for *H. pylori* infection 2 months after completion of therapy.
- Consider other therapies (e.g., PPI, H2 blockers, or pro-kinetic drugs) instead of *H. pylori* treatment in people with: 1) dyspepsia without anemia; 2) mild to moderate gastritis, esophagitis, or clear reflux symptoms; 3) poor gastric motility.

(Abbreviations: NSAID=nonsteroidal anti-inflammatory drug; FDA=Food and Drug Administration)

Recommendations:

1. Providers should follow the *H. pylori* screening and treatment guidelines for Alaska Native patients (Box).
2. Test for *H. pylori* cure with urea breath, fecal antigen, or endoscopic tests 2 months after completion of therapy.
3. If at a participating hospital, send endoscopic gastric biopsy specimens to the AIP laboratory for *H. pylori* and antimicrobial resistance surveillance.

References:

1. Kusters JG, van Vliet AH, Kuipers EJ. Pathogenesis of *Helicobacter pylori* infection. *Clin Microbiol Rev* 2006;19:449-90.
2. Parkinson AJ, Gold BD, Bulkow L, et al. High prevalence of *Helicobacter pylori* in the Alaska Native population and association with low serum ferritin levels in young adults. *Clin Diagn Lab Immunol* 2000;7(6):885-8.
3. Wiggins CL, Perdue DG, Henderson JA, et al. Gastric cancer among

JCM Accepts, published online ahead of print on 3 August 2011
J. Clin. Microbiol. doi:10.1128/JCM.01067-11

Alaska Sentinel Surveillance Study of *Helicobacter pylori* Isolates in Alaska Native Persons from 2000-2008.

H. pylori Isolate Surveillance Study in Alaska Natives

Adrienne H Tveit, PharmD[1]; Michael G Bruce, MD, MPH[2]; Dana L Bruden, MS[2]; Julie Morris, BS[2]; Debby A Hurlburt, BS[2]; Thomas W Hennessy, MD, MPH[2]; Brian McMahon, MD[1]

[1] Alaska Native Medical Center, Anchorage, Alaska
[2] Arctic Investigations Program, Center for Disease Control and Prevention, Alaska Native Medical Center, Anchorage, Alaska

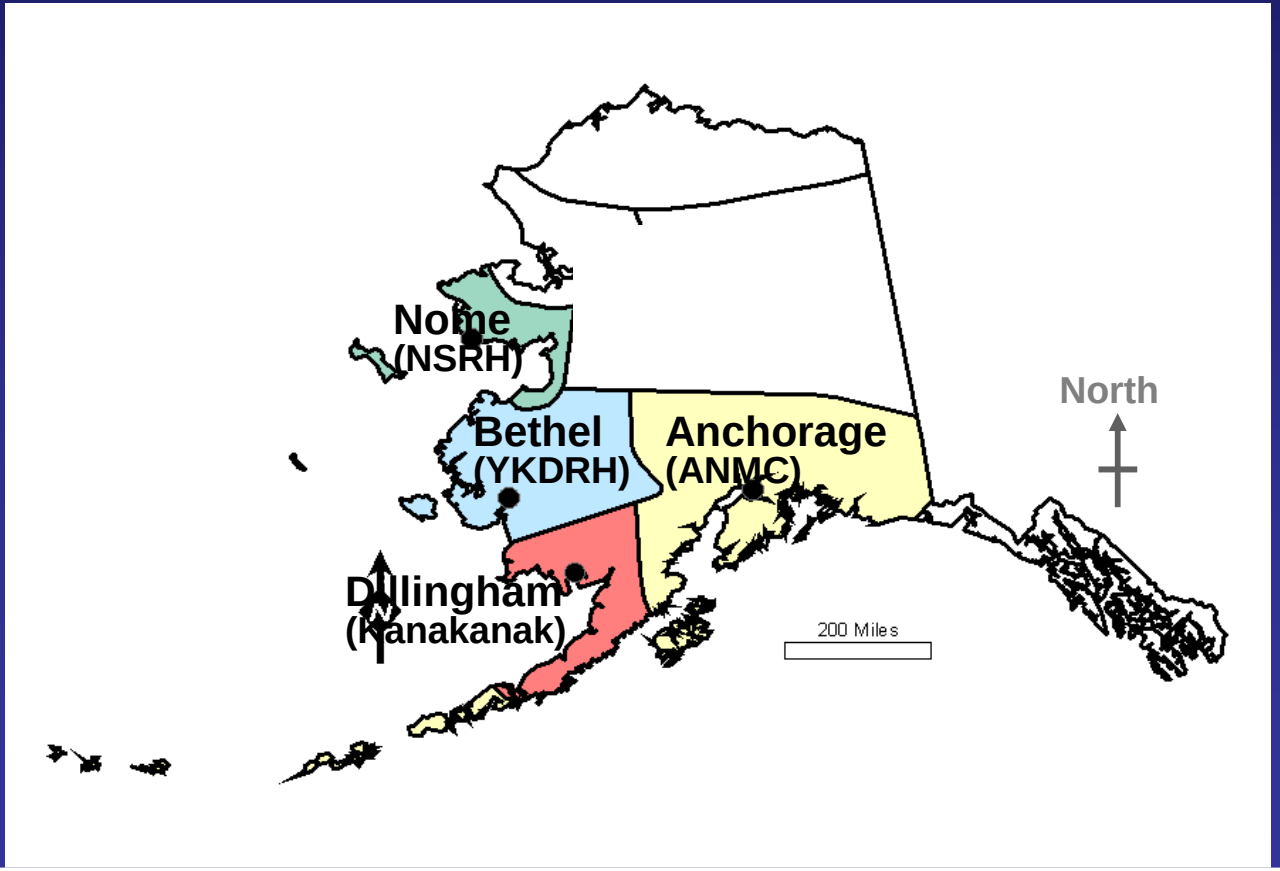
Arctic Investigations Program
Centers for Disease Control and Prevention
4055 Tudor Centre Drive
Anchorage, AK 99508 USA
email: zwa8@cdc.gov
phone: 907-729-3400
fax: 907-729-3429

Alaska Native Medical Center
4315 Diplomacy Drive
Anchorage, AK 99508 USA

Adrienne H Tveit-Data Interpretation; Manuscript drafting
Michael G Bruce-Planning, Data Interpretation; Manuscript drafting

Alaska Sentinel Surveillance for Antimicrobial Resistance

- Norton Sound Regional Hospital (NSRH)
- Yukon Kuskokwim Delta Regional Hospital (YKDRH)
- Kanakanak Hospital
- Alaska Native Medical Center (ANMC)



Alaska Sentinel Surveillance Methods

- Upper endoscopy biopsies obtained from January 2000 to December 2008
  - Patients presenting for routine endoscopies for clinical indications
- *H. pylori* identified by culture at CDC in Anchorage
- Susceptibility profile determined by agar dilution
  - Metronidazole (MIC > 8 µg/ml)
  - Clarithromycin (MIC ≥ 1 µg/ml)
  - Amoxicillin (MIC ≥ 1 µg/ml)
  - Levofloxacin* (MIC ≥ 2 µg/ml)
  - Tetracycline (MIC ≥ 2 µg/ml)

*Susceptibility testing by etest, initiated in 2003, no prior data available

CDC
Centers for Disease Control and Prevention

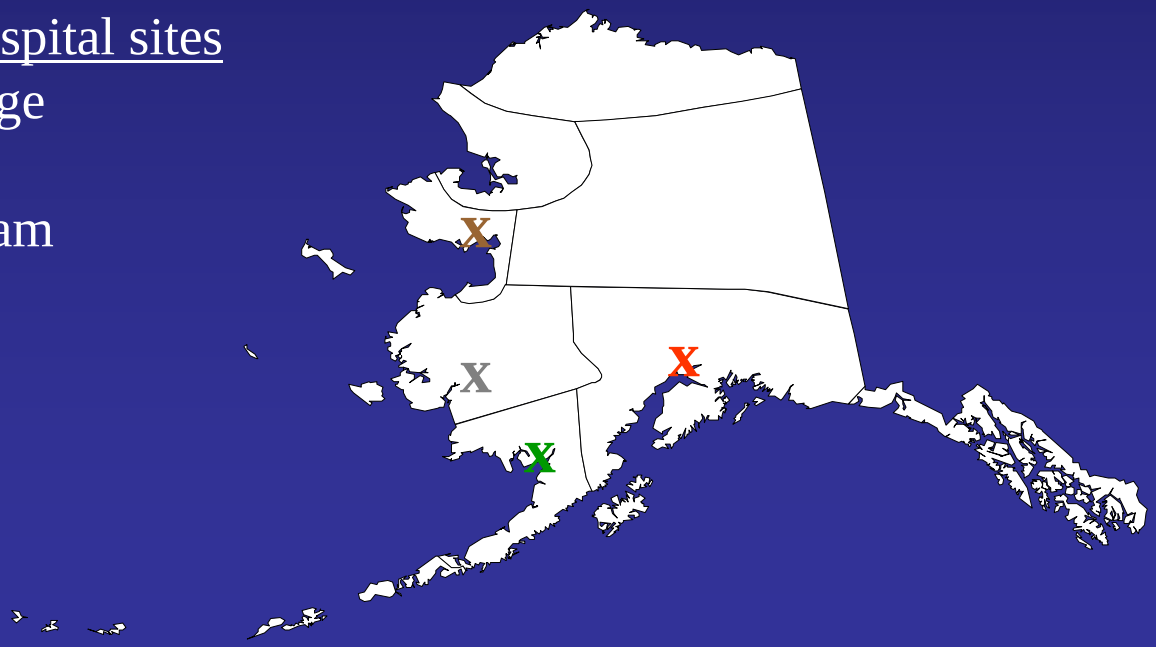
Descriptive Epidemiology

- 1,181 upper endoscopies performed from 2000-2008
- Proportion of EGD's by hospital:
  - 58% at ANMC in Anchorage
  - 20% at YKDRH in Bethel
  - 15% at Kanakanak hospital in Dillingham
  - 7% at NSRH in Nome
- Mean age of participants: 51 years
- Gender: 52% male

H. pylori Positivity

- 532 (45%) persons culture-positive for *H. pylori*

Sentinel hospital sites
X Anchorage
X Bethel
X Dillingham
X Nome



Antimicrobial Resistance 2000-2008

Antibiotic	n/N	% Resistant
Metronidazole	222/531	**42%**
Clarithromycin	159/531	**30%**
Amoxicillin	10/531	**2%**
Metronidazole & Clarithromycin	82/531	**15%**
Levofloxacin*	30/155	**19%**
Metronidazole & Clarithromycin & Levofloxacin	10/155	**6%**
Tetracycline	0/523	**0%**

*Data for 2003-2008

CDC
Centers for Disease Control and Prevention

Antimicrobial Resistance 2000-2008

Antibiotic	n/N	% Resistant
Metronidazole	222/531	**42%**
Clarithromycin	159/531	**30%**
Amoxicillin	10/531	**2%**
Metronidazole & Clarithromycin	82/531	**15%**
Levofloxacin*	30/155	**19%**
Metronidazole & Clarithromycin & Levofloxacin	10/155	**6%**
Tetracycline	0/523	**0%**

*Data for 2003-2008

CDC
Centers for Disease Control and Prevention

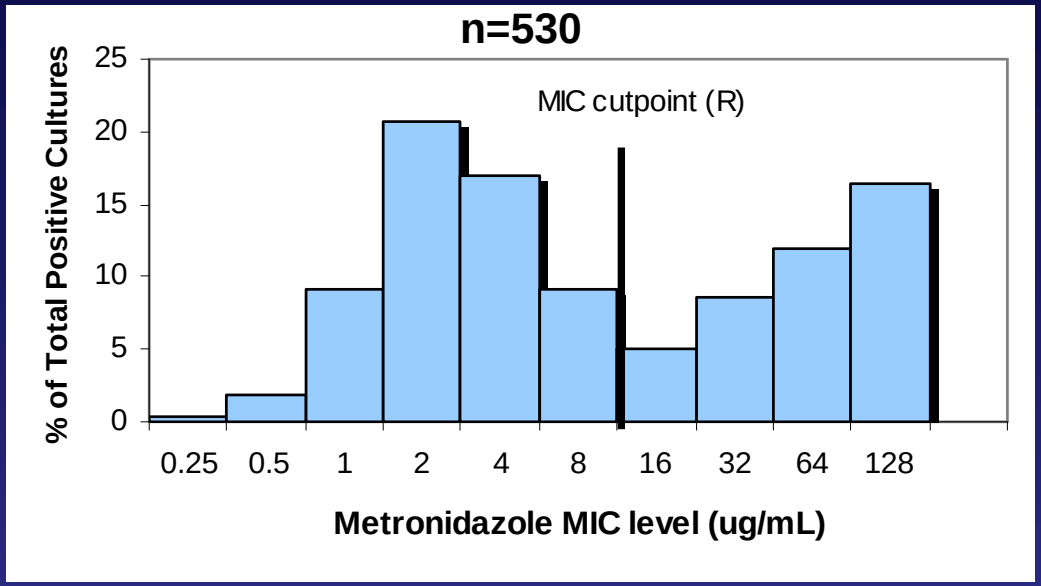
Antimicrobial Resistance 2000-2008

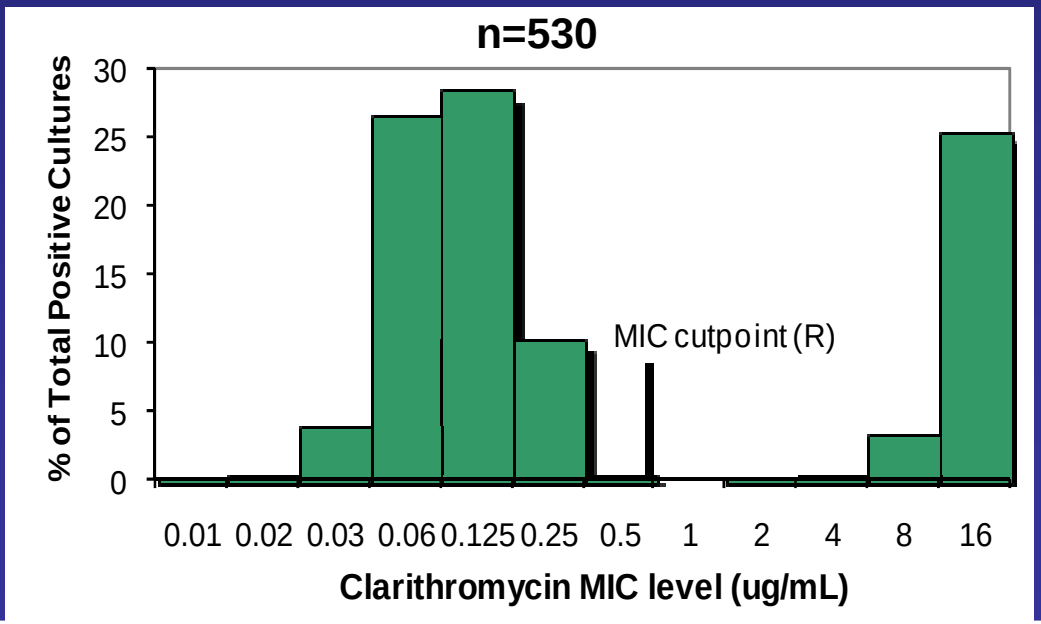
Antibiotic	n/N	% Resistant
Metronidazole	222/531	**42%**
Clarithromycin	159/531	**30%**
Amoxicillin	10/531	**2%**
Metronidazole & Clarithromycin	82/531	**15%**
Levofloxacin*	30/155	**19%**
Metronidazole & Clarithromycin & Levofloxacin	10/155	**6%**
Tetracycline	0/523	**0%**

*Data for 2003-2008

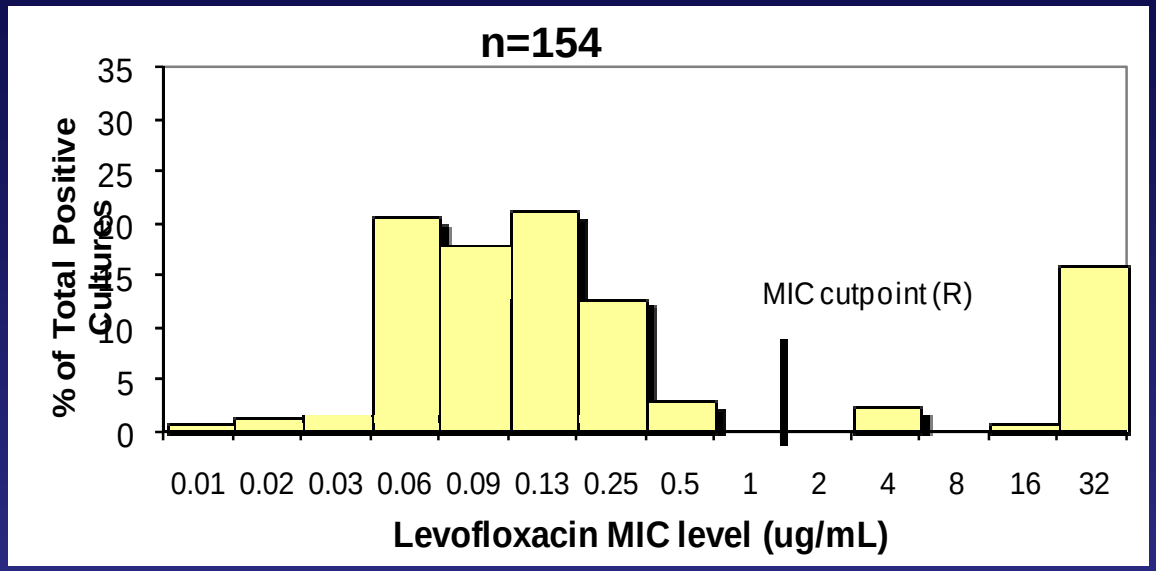
CDC
Centers for Disease Control and Prevention

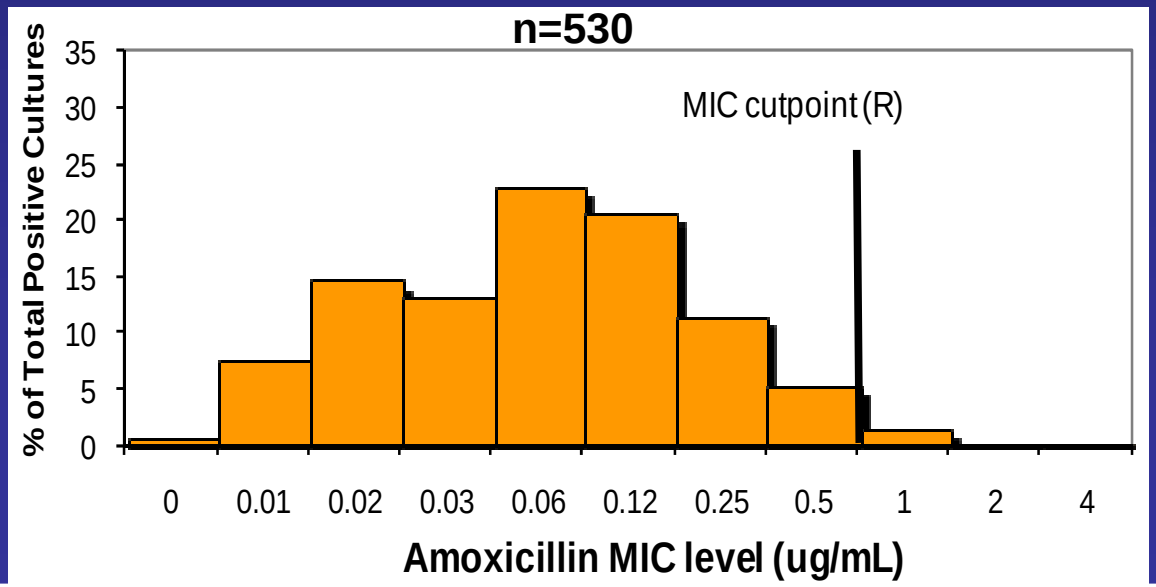
Antibiotic MIC Data



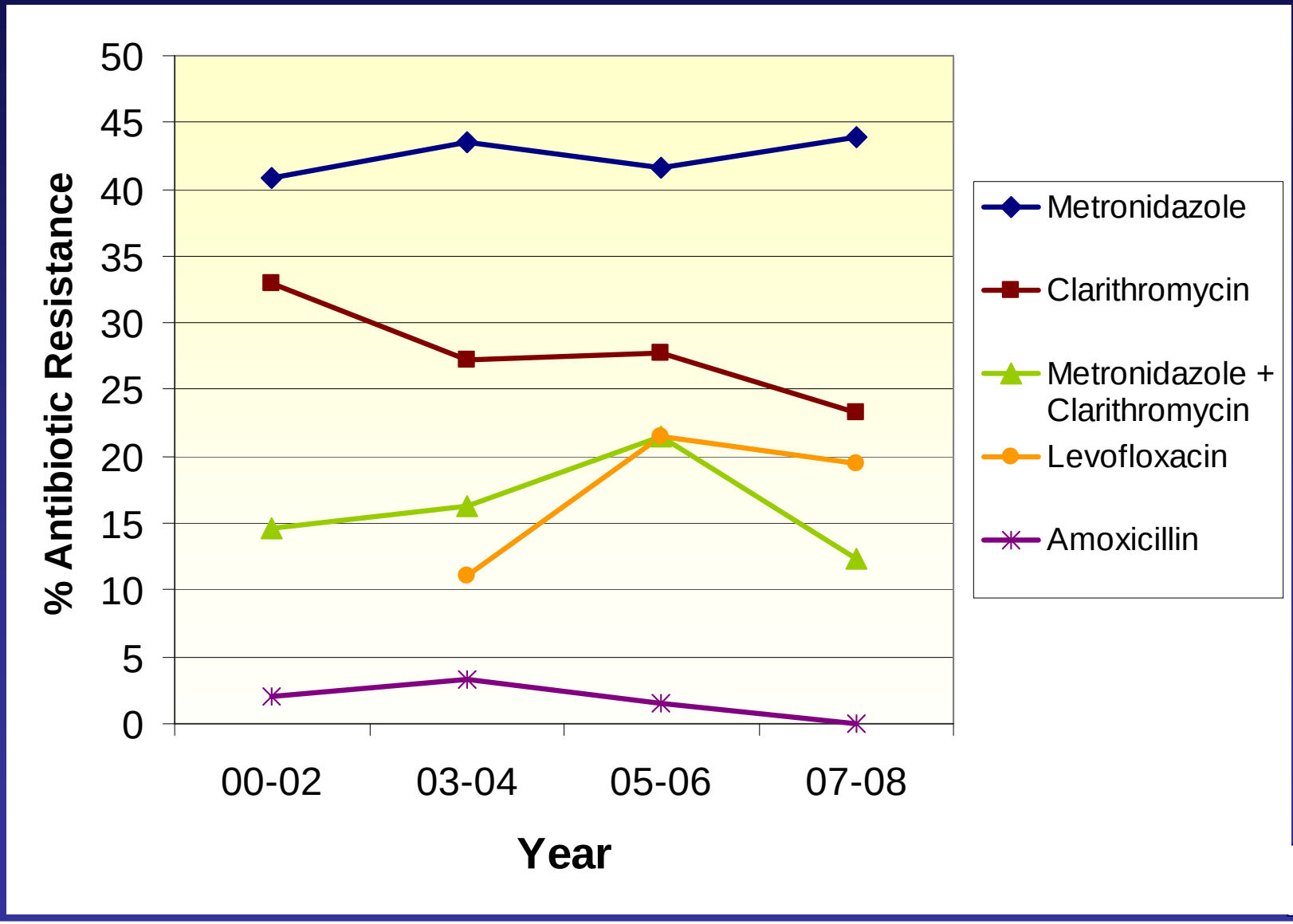


Antibiotic MIC Data

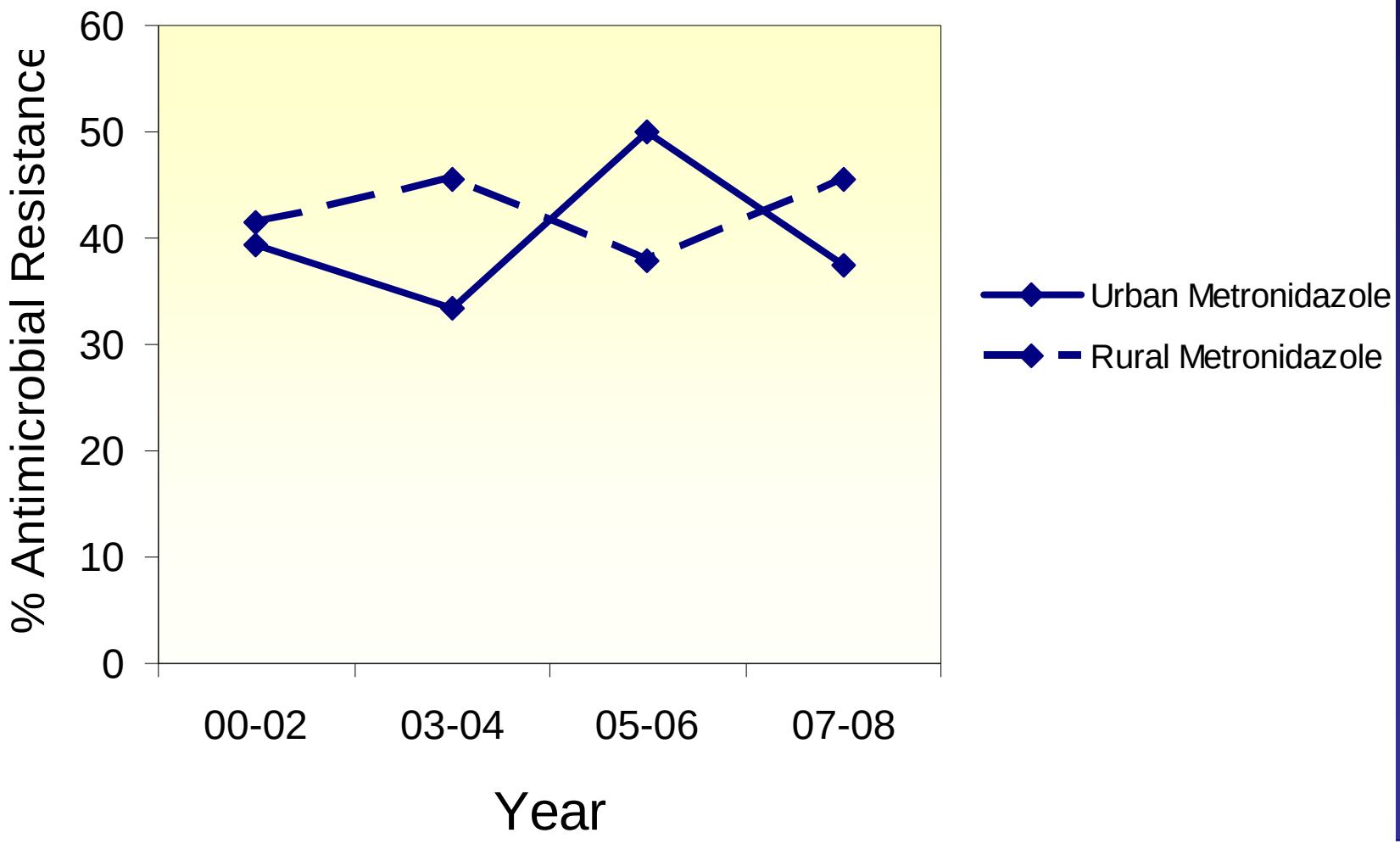




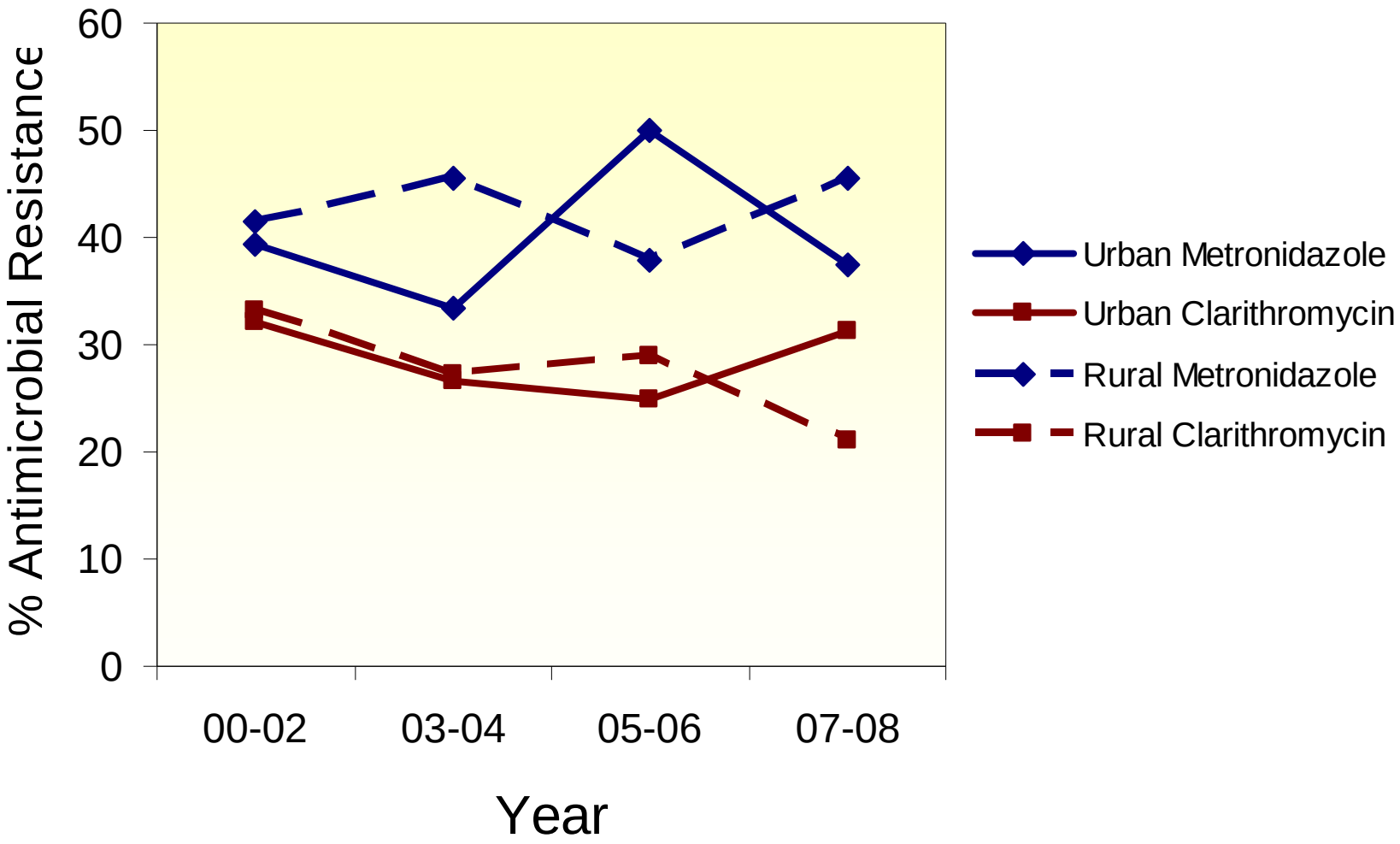
Trends in Antimicrobial Resistance 2000-2008



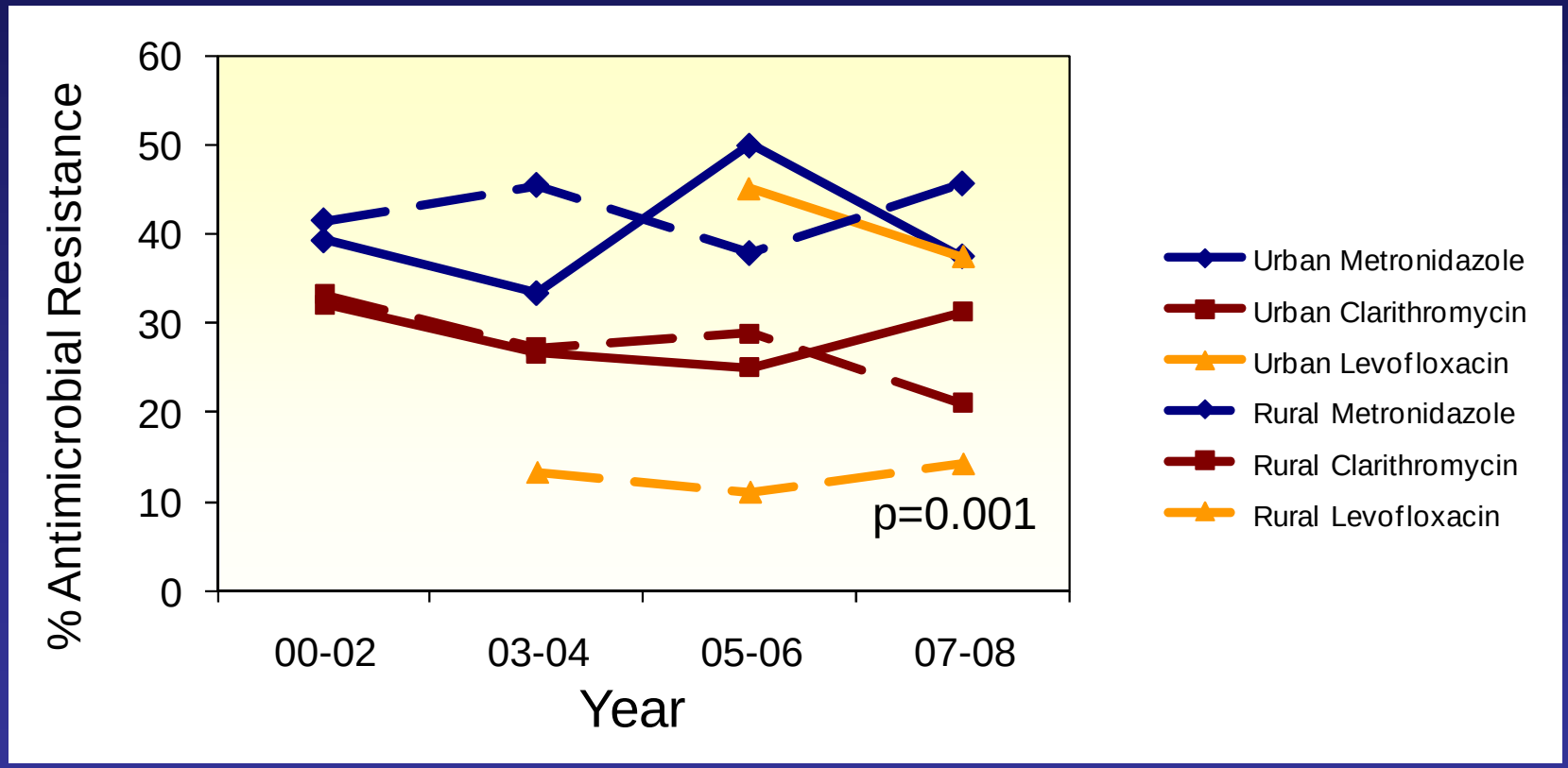
Urban vs. Rural Resistance Patterns



Urban vs. Rural Resistance Patterns



Urban vs. Rural Resistance Patterns



Univariate Risk Factors

Factor	Level	Metronidazole		Clarithromycin		Levofloxacin	
		% Resistant	OR (95% CI)	% Resistant	OR (95% CI)	% Resistant	OR (95% CI)
Residence	Urban Rural	40% 42%	0.9 (0.6-1.3)	30% 30%	1.0 (0.7-1.6)	38% 13%	**4.2** (1.8-9.8)
Referral Hospital	Urban Rural	44% 39%	1.2 (0.9-1.7)	31% 29%	1.1 (0.8-1.4)	24% 12%	2.3 (0.9-5.7)
Sex	Female Male	52% 32%	**2.2** (1.6-3.1)	37% 24%	**1.9** (1.3-2.7)	24% 16%	1.6 (0.7-3.6)

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Univariate Risk Factors

Factor	Level	Metronidazole		Clarithromycin		Levofloxacin	
		% Resistant	OR (95% CI)	% Resistant	OR (95% CI)	% Resistant	OR (95% CI)
Residence	Urban Rural	40% 42%	0.9 (0.6-1.3)	30% 30%	1.0 (0.7-1.6)	38% 13%	**4.2** (1.8-9.8)
Referral Hospital	Urban Rural	44% 39%	1.2 (0.9-1.7)	31% 29%	1.1 (0.8-1.4)	24% 12%	2.3 (0.9-5.7)
Sex	Female Male	52% 32%	**2.2** (1.6-3.1)	37% 24%	**1.9** (1.3-2.7)	24% 16%	1.6 (0.7-3.6)

CDC
Centers for Disease Control and Prevention

Risk Factors

Factor	Level	Metronidazole		Clarithromycin		Levofloxacin	
		% Resistant	OR (95% CI)	% Resistant	OR (95% CI)	% Resistant	OR (95% CI)
Residence	Urban Rural	40% 42%	0.9 (0.6-1.3)	30% 30%	1.0 (0.7-1.6)	38% 13%	**4.2** (1.8-9.8)
Referral Hospital	Urban Rural	44% 39%	1.2 (0.9-1.7)	31% 29%	1.1 (0.8-1.4)	24% 12%	2.3 (0.9-5.7)
Sex	Female Male	52% 32%	**2.2** (1.6-3.1)	37% 24%	**1.9** (1.3-2.7)	24% 16%	1.6 (0.7-3.6)

Limitations

- Surveillance sites voluntarily send in routine upper endoscopy biopsy specimens to CDC for testing
- Prior treatment for *H. pylori* and treatment failures were unknown
- Patients previous antibiotic use was unknown
- Study may not represent the entire state of Alaska
  - May not represent all AN/AI

Summary/Conclusions

- High proportion of *H. pylori* isolates are resistant to antibiotics in Alaska
- 1 of 5 persons demonstrate levofloxacin resistance
- No trends over time with *H. pylori* resistance
- Continued surveillance may help guide future antimicrobial therapy recommendations to medical providers for treatment of *H. pylori* infections in the AN/AI population

CDC
Centers for Disease Control and Prevention

Diagnostic Accuracy of Hp Tests Alaska

- **Diagnostic Accuracy of Tests for *Helicobacter Pylori* in an Alaska Native Population**
-

- Dana L Bruden, MS [1]
- Michael G Bruce, MD, MPH [1]
- Karen M Miernyk, BS [1, 2]
- Julie Morris, BS [1]
- Debby Hurlburt, RN [1]
- Thomas W Hennessy, MD, MPH [1]
- Helen Peters, RN [1]
- Frank Sacco, MD [2]
- Alan J Parkinson, PhD [1]
- Brian J McMahon, MD[1, 2]
-
- [1]Arctic Investigations Program, Division of Preparedness and Emerging Infections, National Center for Emerging Zoonoses and Infectious Diseases, Centers for Disease Control and Prevention, Anchorage, Alaska
- [2] Alaska Native Tribal Health Consortium, Anchorage Alaska.
-
- Corresponding Author:
- Dana Bruden, MS

Diagnostic Accuracy of Hp Tests Alaska

- **The cohort**: persons ≥ 18 years of age undergoing EGD for clinical indications at ANMC in Anchorage, Alaska were consented into the *H. pylori* reinfection study 9/98 – 12/00
- **The study**: a cross-sectional analysis to determine the sensitivity and specificity of five tests for *H. pylori*:
  - Serology
  - Culture
  - CLO test®
  - Histology
  - ^{13}C urea breath test

Diagnostic Accuracy of Hp Tests Alaska

- Since participants were recruited prior to EGD, the cohort consisted of persons both positive and negative for *H. pylori.*
- Upon enrollment, a medical chart review was performed at ANMC to determine the participants' history of: peptic ulcer disease, previous EGD procedures, and previous treatment for an *H. pylori* infection.
- Endoscopic findings documented during EGD included location and type of ulcer and presence of antral and fundal gastritis.

Characteristics of 280 patients enrolled in Anchorage, Alaska undergoing EGD, 1999 - 2000

Characteristic	% (n)
Mean Age (min, max)	48 years (19, 88)
Sex (Female)	66% (184)
Medical Chart Review	
History of Peptic Ulcer Disease	19% (53)
Previous EGD	32% (90)
Previously Treated for *H. pylori*	23% (63)
Endoscopist Evaluation during EGD	
Moderate-Severe Gastritis	41% (115)
Mild-No Gastritis	59% (165)
Ulcer	9% (25)

Percent positive for *H. pylori* by test type among 280 patients enrolled in Anchorage, Alaska for an *H. pylori* reinfection study, 1999-2000

Test Type	% *H. pylori* Positive (n/N)
Histology	50% (140/280)
Culture	51% (144/280)
CLO test® [a]	49% (138/280)
Gold Standard [b]	53% (149/280)
^{13}C-UBT [c]	55% (155/280)
anti-HP IgG	67% (188/280)

[a]– rapid urease test, Ballard Medical Products.
[b]– a positive culture or in the case of a negative culture, a positive histology result and a positive CLO test®.
[b]– ^{13}C urea breath test, BreathTek ™, Meretek Diagnostics Inc.

Sensitivity and specificity of non-invasive tests in relation to invasive tests and a gold standard in 280 patients from Anchorage, Alaska, 1999-2000

Test type 1	Test type 2	Sensitivity	Specificity	NPV [a]	PPV [a]	Accuracy
^{13}C-UBT [b] vs.	Histology	93.6% (131/140)	82.9% (116/140)	92.8% (116/125)	84.5% (131/155)	88.2% (247/280)
	Histology and CLO test® [c]	96.8% (121/125)	78.1% (121/155)	96.8% (121/125)	78.1% (121/155)	86.4% (242/280)
	Culture	93.1% (134/144)	84.6% (115/136)	92.0% (115/125)	86.5% (134/155)	89.0% (249/280)
	Culture and CLO test®	94.6% (123/130)	78.7% (118/150)	94.4% (118/125)	79.4% (123/155)	86.1% (241/280)
	Gold Standard	93.3% (139/149)	87.8% (115/131)	92.0% (115/125)	89.7% (139/155)	90.7% (254/280)

[a] – Negative and positive predictive value.
[b] – ^{13}C urea breath test, BreathTek ™, Meretek Diagnostics Inc.
[c] – rapid urease test, Ballard Medical Products.
Gold standard was a positive *H. pylori* test by culture or, in the case of a negative culture result, a positive histology result and a positive CLO test

Sensitivity and specificity of non-invasive tests in relation to invasive tests and a gold standard in 280 patients from Anchorage, Alaska, 1999-2000

Test type 1	Test type 2	Sensitivity	Specificity	NPV [a]	PPV [a]	Accuracy
^{13}C-UBT [b] vs.	Histology	93.6% (131/140)	82.9% (116/140)	92.8% (116/125)	84.5% (131/155)	88.2% (247/280)
	Histology and CLO test® [c]	96.8% (121/125)	78.1% (121/155)	96.8% (121/125)	78.1% (121/155)	86.4% (242/280)
	Culture	93.1% (134/144)	84.6% (115/136)	92.0% (115/125)	86.5% (134/155)	89.0% (249/280)
	Culture and CLO test®	94.6% (123/130)	78.7% (118/150)	94.4% (118/125)	79.4% (123/155)	86.1% (241/280)
	Gold Standard	93.3% (139/149)	87.8% (115/131)	92.0% (115/125)	89.7% (139/155)	90.7% (254/280)

[a] – Negative and positive predictive value.
[b] – ^{13}C urea breath test, BreathTek ™, Meretek Diagnostics Inc.
[c] – rapid urease test, Ballard Medical Products.
Gold standard was a positive *H. pylori* test by culture or, in the case of a negative culture result, a positive histology result and a positive CLO test

[a] – Negative and positive predictive value.
[b] – ^{13}C urea breath test, BreathTek ™, Meretek Diagnostics Inc.
[c] – rapid urease test, Ballard Medical Products.

Sensitivity and specificity of non-invasive tests in relation to invasive tests and a gold standard in 280 patients from Anchorage, Alaska, 1999-2000

Test type 1	Test type 2	Sensitivity	Specificity	NPV [a]	PPV [a]	Accuracy
Anti-HP IgG vs.	Histology	91.5% (118/129)	61.8% (81/131)	88.0% (81/92)	70.2% (118/168)	76.5% (199/260)
	Histology and CLO test®	93.1% (108/116)	58.3% (84/144)	91.3% (84/92)	64.3% (108/168)	73.8% (192/260)
	Culture	93.3% (126/135)	66.4% (83/125)	90.2% (83/92)	75.0% (126/168)	80.3% (209/260)
	Culture and CLO test®	93.4% (113/121)	60.4% (84/139)	91.3% (84/92)	67.3% (113/168)	75.8% (197/260)
	Gold Standard	92.9% (130/140)	68.3% (82/120)	89.1% (82/92)	77.4% (130/168)	81.5% (212/260)

Sensitivity and specificity of non-invasive tests in relation to invasive tests and a gold standard in 280 patients from Anchorage, Alaska, 1999-2000

Test type 1	Test type 2	Sensitivity	Specificity	NPV [a]	PPV [a]	Accuracy
Anti-HP IgG vs.	Histology	91.5% (118/129)	61.8% (81/131)	88.0% (81/92)	70.2% (118/168)	76.5% (199/260)
	Histology and CLO test®	93.1% (108/116)	58.3% (84/144)	91.3% (84/92)	64.3% (108/168)	73.8% (192/260)
	Culture	93.3% (126/135)	66.4% (83/125)	90.2% (83/92)	75.0% (126/168)	80.3% (209/260)
	Culture and CLO test®	93.4% (113/121)	60.4% (84/139)	91.3% (84/92)	67.3% (113/168)	75.8% (197/260)
	Gold Standard	92.9% (130/140)	68.3% (82/120)	89.1% (82/92)	77.4% (130/168)	81.5% (212/260)

Among *H. pylori* positive persons (according to gold standard, n = 149), the relationship between anti-HP IgG OD and Delta Over Baseline (DOB) for the ^{13}C-UBT test

		Anti-HP IgG OD [a]			^{13}C-UBT DOB [b]	
Factors	High OD ≥ 1.1 (n = 76)	Low OD < 1.1 (n = 73)	P-value	High ≥ 10% (n = 71)	Low < 10% (n = 78)	P-value
			Demographics			
% Male	54% (41)	19% (14)	<0.0001	31% (22)	42% (33)	0.15
% ≥ 50 Yrs	33% (25)	40% (29)	0.39	53% (27)	29% (27)	0.002
			Histo Exam			
% Intestinal Metaplasia	11% (8)	12% (9)	0.73	8% (6)	14% (11)	0.27
% Acute Gastritis	55% (42)	49% (36)	0.47	49% (35)	55% (43)	0.48
% Chronic Gastritis	93% (71)	77% (56)	0.003	86% (61)	85% (66)	0.82
% Numerous *H. pylori*	42% (32)	36% (26)	0.42	54% (38)	26% (20)	0.0005
			Endoscopic Factors			
% Ulcer	10% (7)	11% (8)	0.76	9% (6)	12% (9)	0.57
% Gastritis	58% (42)	40% (29)	0.03	49% (34)	48% (37)	0.88

[a] – anti-HP IgG OD was associated with male gender (p < 0.0001, OR = 6.2) and chronic gastritis (p = 0.003, OR = 5.8) on multivariate analysis

[b] – DOB from ^{13}C-UBT test was associated with numerous *H. pylori* (p = 0.0005, OR = 3.6) and older age (p = 0.01, OR = 2.5) on multivariate analysis

Among *H. pylori* positive persons (according to gold standard, n = 149), the relationship between anti-HP IgG OD and Delta Over Baseline (DOB) for the ^{13}C-UBT test

		Anti-HP IgG OD [a]			^{13}C-UBT DOB [b]	
Factors	High OD ≥ 1.1 (n = 76)	Low OD < 1.1 (n = 73)	P-value	High ≥ 10% (n = 71)	Low < 10% (n = 78)	P-value
			Demographics			
% Male	54% (41)	19% (14)	<0.0001	31% (22)	42% (33)	0.15
% ≥ 50 Yrs	33% (25)	40% (29)	0.39	53% (27)	29% (27)	0.002
			Histo Exam			
% Intestinal Metaplasia	11% (8)	12% (9)	0.73	8% (6)	14% (11)	0.27
% Acute Gastritis	55% (42)	49% (36)	0.47	49% (35)	55% (43)	0.48
% Chronic Gastritis	93% (71)	77% (56)	0.003	86% (61)	85% (66)	0.82
% Numerous *H. pylori*	42% (32)	36% (26)	0.42	54% (38)	26% (20)	0.0005
			Endoscopic Factors			
% Ulcer	10% (7)	11% (8)	0.76	9% (6)	12% (9)	0.57
% Gastritis	58% (42)	40% (29)	0.03	49% (34)	48% (37)	0.88

[a] – anti-HP IgG OD was associated with male gender (p < 0.0001, OR = 6.2) and chronic gastritis (p = 0.003, OR = 5.8) on multivariate analysis

[b] – DOB from ^{13}C-UBT test was associated with numerous *H. pylori* (p = 0.0005, OR = 3.6) and older age (p = 0.01, OR = 2.5) on multivariate analysis

Diagnostic Accuracy of Hp Tests
Alaska
Summary

- The sensitivity and specificity of the ^{13}C-UBT was 93% and 88%, respectively, relative to the gold standard.
- The antibody test had an equivalent sensitivity of 93% with a reduced specificity of 68%.
  - The false positive results for the antibody test were associated with previous treatment for an *H. pylori* infection (RR = 2.8).
- High levels of antibody to *H. pylori* were associated with chronic gastritis and male gender while high levels of a ^{13}C-UBT test were associated with older age and the *H. pylori* bacteria load on histological examination (RR = 4.4).

J Clin Microbiol. 2011 Sep;49(9):3114-21. Epub 2011 Jul 13.

Characterization of Helicobacter pylori cagA and vacA Genotypes among Alaskans and Their Correlation with Clinical Disease.

Miernyk K, Morris J, Bruden D, McMahon B, Hurlburt D, Sacco F, Parkinson A, Hennessy T, Bruce M.

Arctic Investigations Program, Centers for Disease Control and Prevention, 4055 Tudor Centre Dr., Anchorage, AK 99517. kmiernyk@cdc.gov.

Abstract

Helicobacter pylori infection is common in Alaska. The development of severe H. pylori disease is partially determined by the virulence of the infecting strain. Here we present vacA and cagA genotype data for H. pylori strains isolated from Alaskans and their correlation with clinical disease. We enrolled patients scheduled for esophagogastroduodenoscopy and positive for H. pylori infection. Gastric biopsy specimens from the stomach antrum and fundus were cultured. We performed PCR analysis of the H. pylori vacA gene and for the presence of the cagA gene and cagA empty site. We genotyped 515 H. pylori samples from 220 Native and 66 non-Native Alaskans. We detected the cagA gene in 242/286 (85%) persons; of 222 strains that could be subtyped, 95% (212) were non-Asian cagA and 3% (6) were East Asian cagA. After removing mixed infections (n = 17), 83% of H. pylori strains had either the vacA s1m1 (120/269) or s2m2 (103/269) genotype. Sixty-six percent (68/103) of H. pylori strains with the vacA s2m2 genotype also contained the cagA gene. Infection with an H. pylori strain having the cagA gene or vacA s1m1 genotype (compared with s1m2 and s2m2) was associated with a decreased risk of esophagitis (P = 0.003 and 0.0003, respectively). Infection with an H. pylori strain having the vacA s1m1 genotype (compared with s1m2 and s2m2) was associated with an increased risk of peptic ulcer disease (PUD) (P = 0.003). The majority of H. pylori strains in this study carried the non-Asian cagA gene and either the vacA s1m1 or s2m2 genotype. A majority of H. pylori strains with the vacA s2m2 genotype also contained the cagA gene. There was an association of H. pylori genotype with esophagitis and PUD.

PMID: 21752979 [PubMed - in process]

Virulence Testing

- The majority of *H. pylori* strains from persons in our reinfection study contain the *CagA* gene
  - AN/AI persons more likely than non-Native persons to have a *CagA* positive strain
- The majority of *CagA* genes are non-Asian (type 2a)
- Infection with a *CagA* positive strain is associated with acute gastritis in the fundus

Genotyping of *CagA* & *VacA*, Alaska Background

- The vacuolating cytotoxin gene *(vacA*) and cytotoxin associated gene A (c*agA*) are *H. pylori* virulence factors
- The variation of alleles in the signal (s1, s2) and mid (m1, m2) regions of the *vacA* gene confer different degrees of cytotoxin production (s1/m1 high & s2/m2 low)
- S1 strain subtypes: s1a, s1b, and s1c
- M1 strain subtypes: m1a and m1b
- The *vacA* s1/m1 genotype is related to severe clinical outcomes in some populations

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

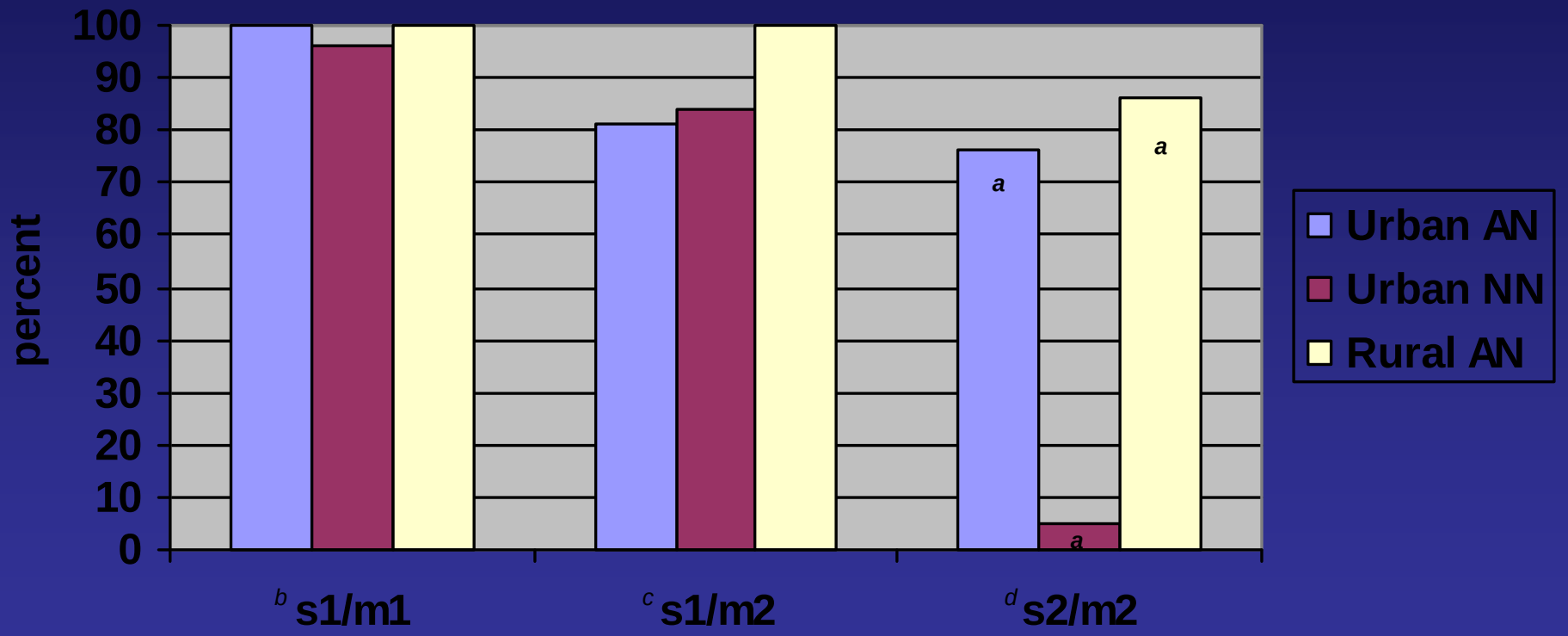
Genotyping of *CagA* & *VacA*, Alaska Background

- The presence of the *cagA* is related to severe clinical outcomes in some populations
- *VacA* and *cagA* genotypes vary geographically and associations with clinical outcome are not consistent among all regions of the world
- There is very little data on *vacA* and *cagA* genotypes in *H. pylori* strains from Alaska

Genotyping of *CagA* & *VacA*, Alaska Background

- **Group 1 -** Urban Alaska Natives living in Anchorage
  - Population: 22,889
  - Patients recruited at the Alaska Native Medical Center (ANMC)
- **Group 2 -** Rural Alaska Natives living in 3 rural Alaska regions
  - 3 cities and 35 villages, population 30,000
  - Patients recruited from 3 regional hospitals
- **Group 3 -** Urban Alaska non-Natives living in Anchorage
  - Anchorage, population 237,394
  - Patients recruited from 2 Private Gastroenterology groups

Percentage of *vacA* genotypes that were *cagA* positive



[a]AN persons were more likely than NN persons to have a v*acA* s2/m2, *cagA* positive genotype (80% vs 5%, p<0.0001).
[b] sample sizes: urban AN 67/67; urban NN 25/26; rural AN 26/26
[c] sample sizes: urban AN 17/21; urban NN 16/19; rural AN 4/4
[d] sample sizes: urban AN 37/49; urban NN 1/19; rural AN 30/35

Genotyping of *CagA* & *VacA*, Alaska

- Significant difference in the vacA s2m2, *cagA*-positive genotype between Alaska Natives and non-Natives
  - 80% (67/84) of our s2m2 genotypes in Alaska Natives were cagA-positive and only 5% of our non-Native s2m2 isolates (1/19) were cagA-positive.
    - The clinical significance of this finding is unknown

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

VacA Genotypes and Clinical Findings

Clinical Feature	VacA Genotype			P value
	s1/m1	s1m2	s2m2	
Gastric Ulcer	11% (12)	3% (1)	4% (4)	0.06
Esophagitis	15% (16)	32% (12)	36% (39)	0.002
Acute Gastritis mod-severe	56% (50)	59% (16)	30% (26)	0.0004
PUD	25% (30)	11% (5)	12% (14)	0.01

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

VacA Genotypes and Clinical Findings

Clinical Feature	VacA Genotype			P value
	s1/m1	s1m2	s2m2	
Gastric Ulcer	11% (12)	3% (1)	4% (4)	0.06
Esophagitis	15% (16)	32% (12)	36% (39)	0.002
Acute Gastritis mod-severe	56% (50)	59% (16)	30% (26)	0.0004
PUD	25% (30)	11% (5)	12% (14)	0.01