Otitis Media Pathophysiology

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ESPO

Children's National Health System

- ***No financial disclosures...***

Objectives

- Review advances in our understanding of OM pathophysiology
- Describe recent innovations in OM diagnosis
- Discuss recent updated guidelines for optimal OM treatment
- Predict the future of OM evaluation and management, focusing on impact of artificial intelligence and automation

Question #1

The incidence of Acute Otitis Media in children is:

1) Increasing (excluding C-19 related 2020 year)
2) Decreasing
3) Stable
4) Variable

Question #1

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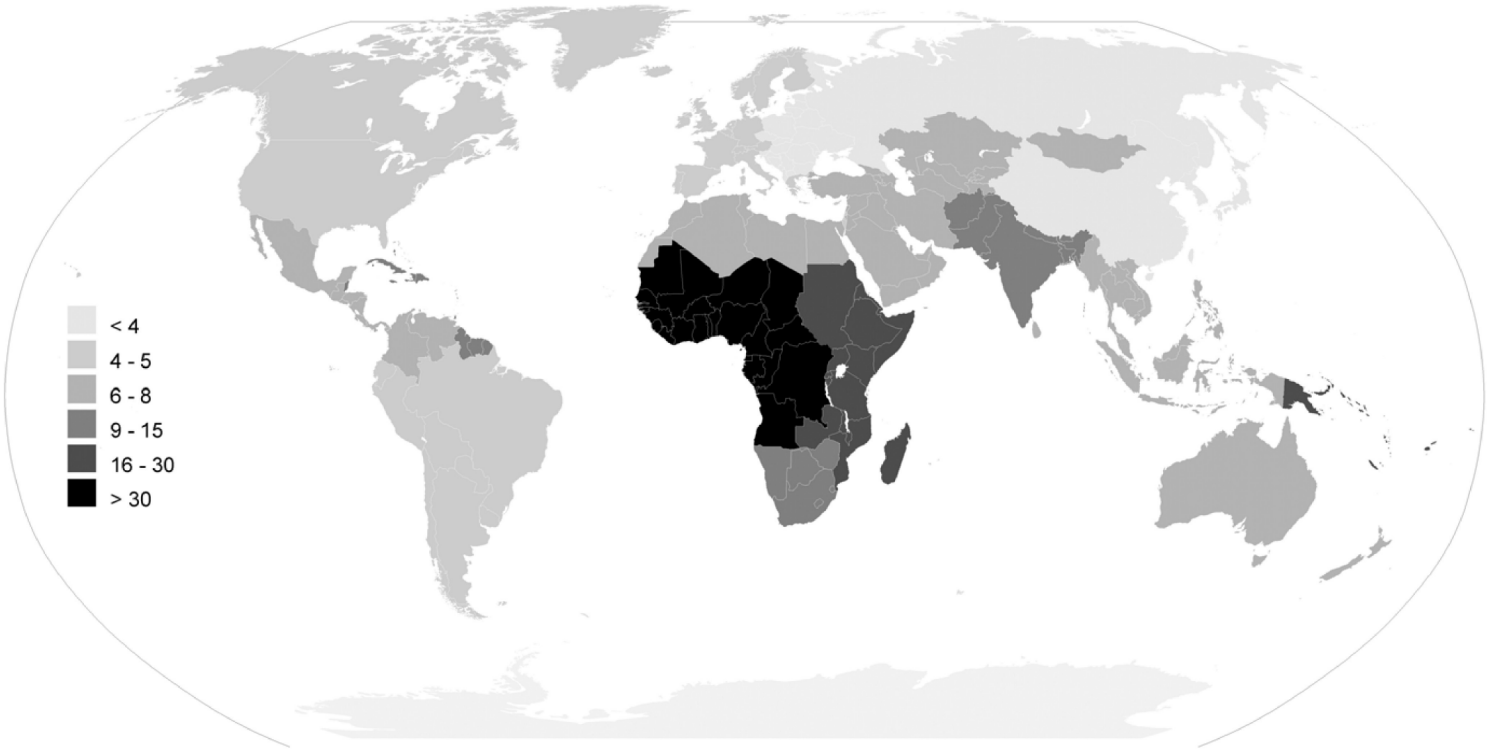


Figure 3. AOM incidence rate estimates for the year 2005 per hundred people, by the 21 WHO regions.
doi:10.1371/journal.pone.0036226.g003

Monasta, Lorenzo, et al. PloS one, 2012, Vol.7 (4), p.e36226-e36226

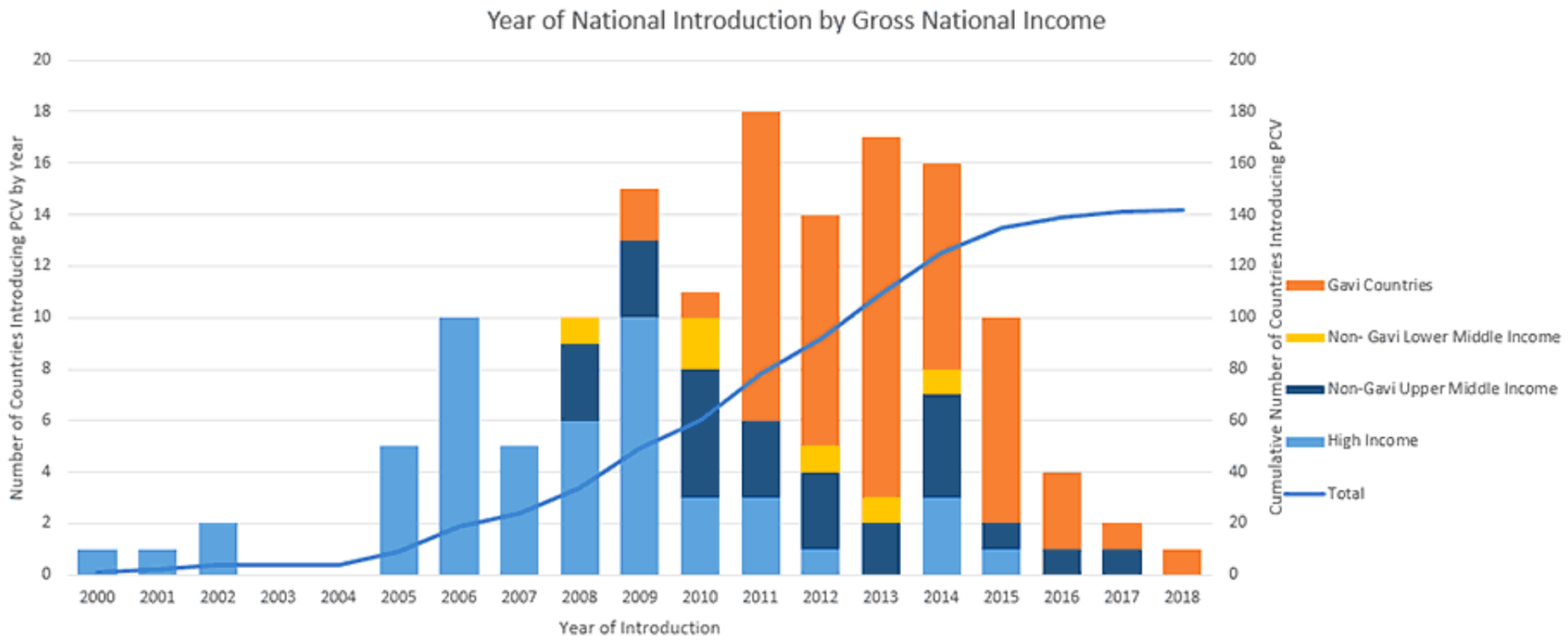


Figure. A total of 142 countries have introduced PCV from 2000 through 2018. Of the 73 Gavi-eligible countries, 59 (81%) introduced PCV. Among non-Gavi eligible countries, PCV has been introduced in 6 (50%) of 12 lower middle-income countries, 26 (51%) of 51 upper middle-income countries, and 51 (88%) of 58 high-income countries. Figure courtesy of the International Vaccine Access Center (IVAC).

Bacteriology of OM

EARLY PCV7		LATE PCV7		EARLY PCV13	
S. Pneumo	30%	S. Pneumo	45%	S. Pneumo	25%
NTHi	50 %	NTHi	25%	NTHi	55%

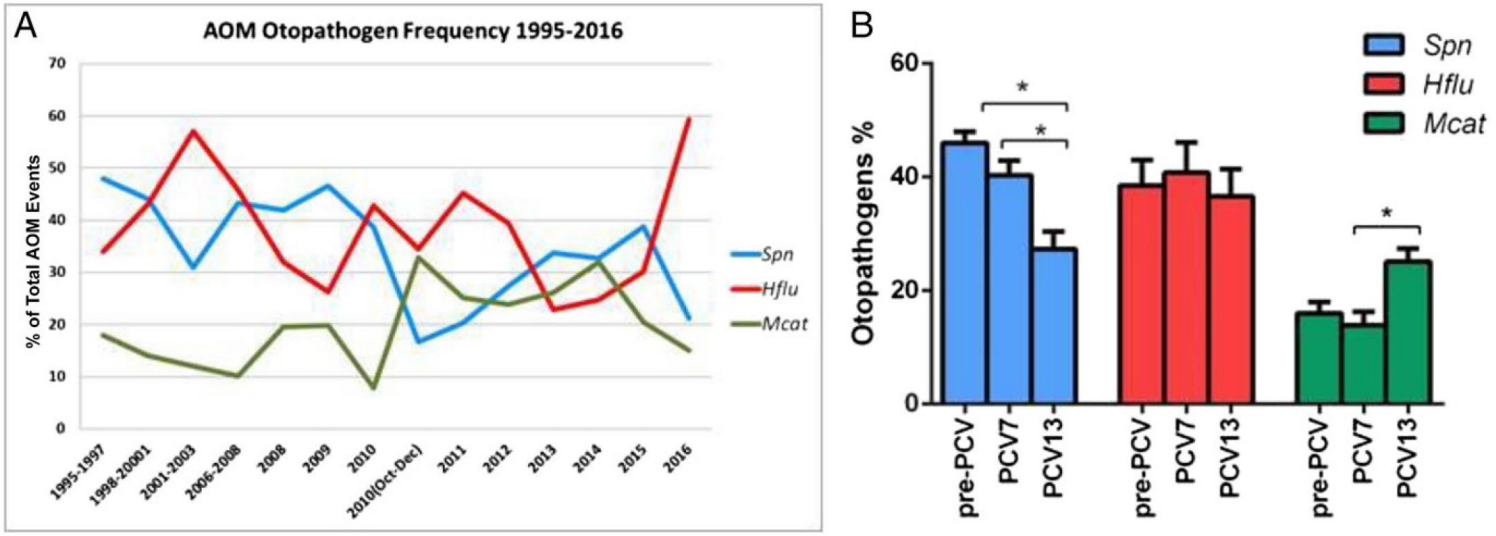


FIGURE 2
(A) The frequency of otopathogens isolated from MEF during AOM from 1995 to 2016. (B) The changes in otopathogen prevalence in different vaccine eras (* $P < .05$). Spn, *S pneumonia*; Hflu, *H influenzae*; and Mcat, *M catarrhalis*.

Kaur, R; Morris, M; Pichichero, M. Pediatrics (Evanston), 2017-09-01, Vol.140 (3)

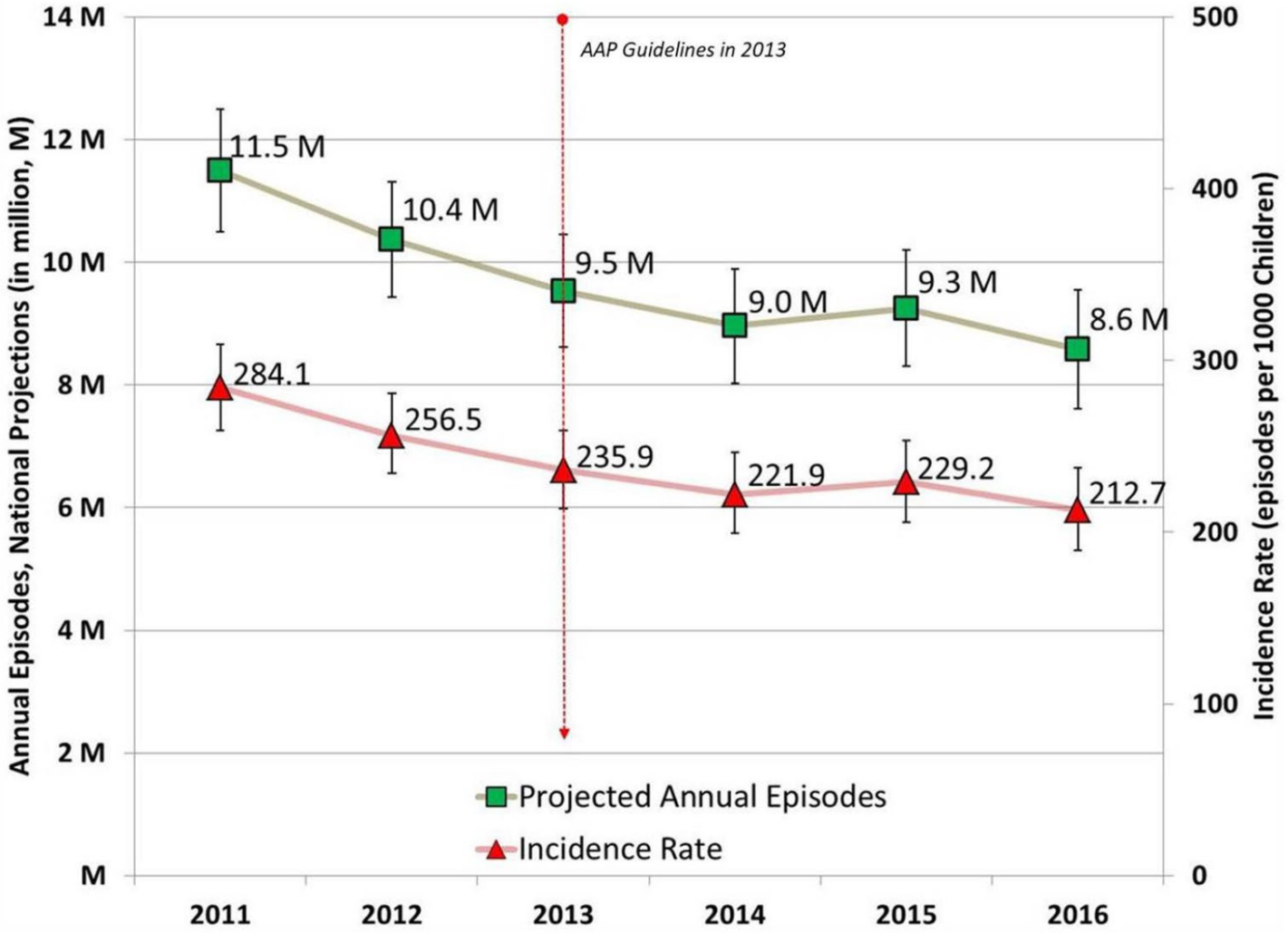


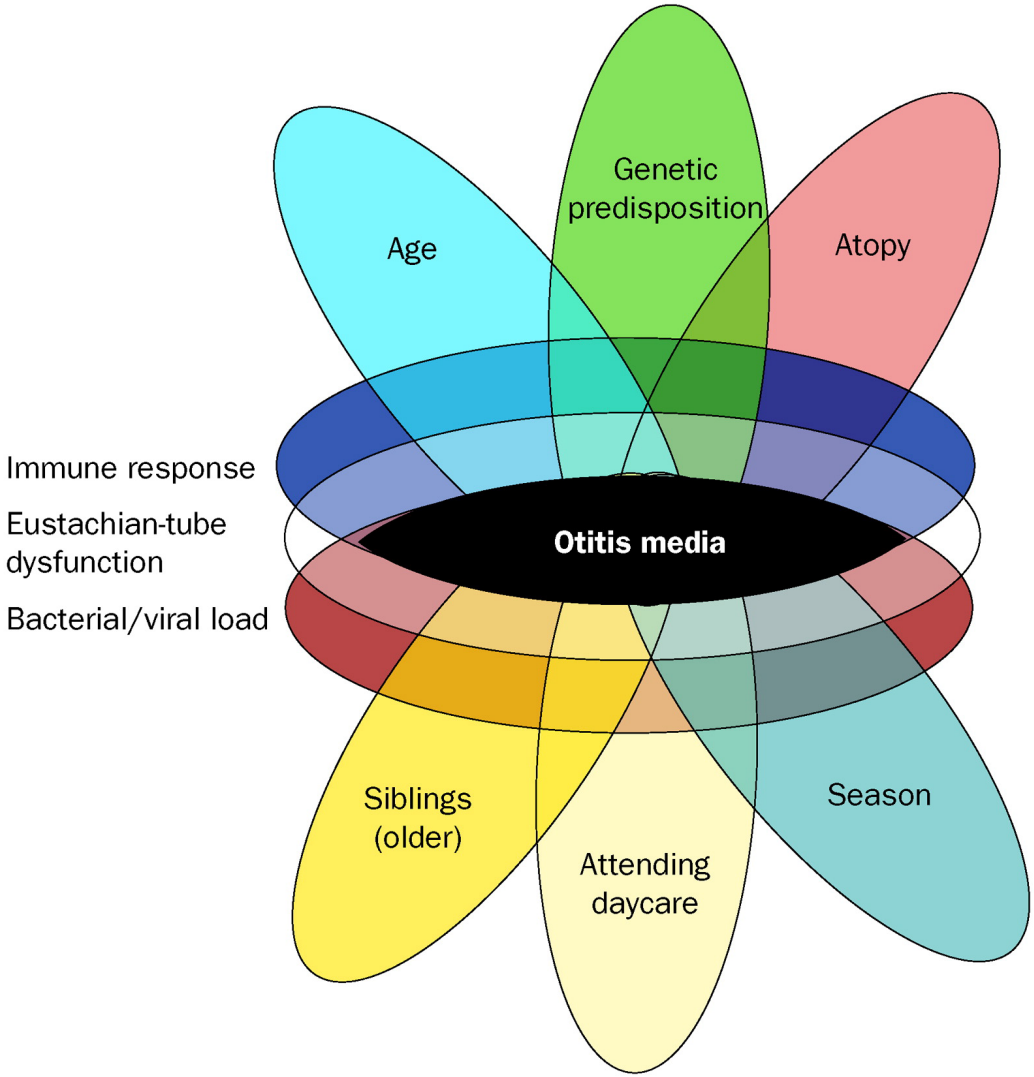
Fig. 1. Annual projections of acute otitis media episodes and incidence rates in children age 0–9 years in the US.

Suaya, José A, et al. Vaccine, 2018-11-26, Vol.36 (49), p.7479-7486

Question #2

The main factor contributing to Otitis Media susceptibility in children is:

1) Eustachian Tube dysfunction
2) Adenoidal disease
3) Immune system
4) Pathogen



Rovers, M; Schilder, A; Zielhuis, G; Rosenfeld, R. The Lancet (British edition), 2004, Vol.363 (9407), p.465-473

Question #2

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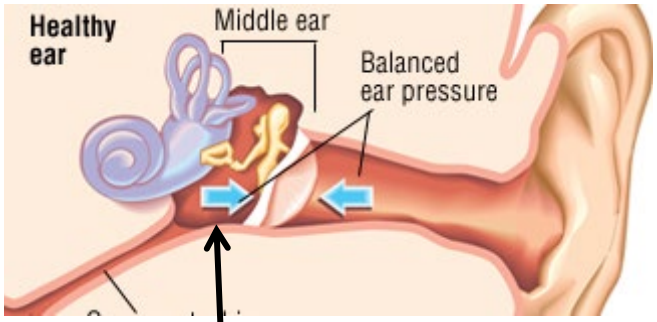
2) Adenoidal disease

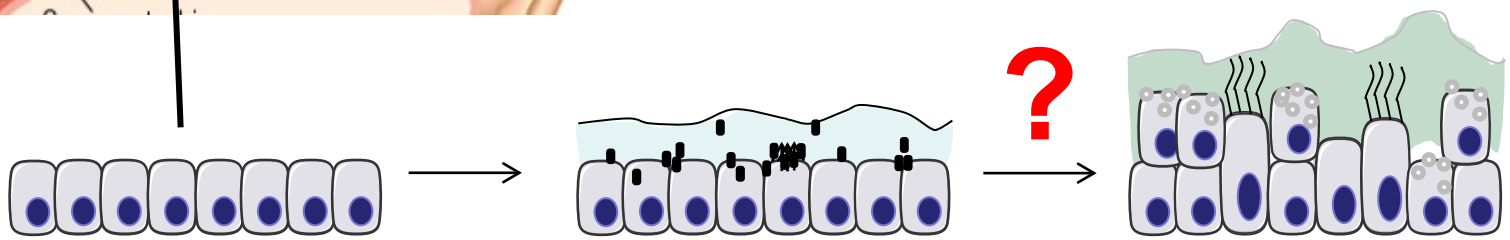
3) **Immune system**

4) Pathogen

Otitis Media: a Continuum of Disease



Ubiquitous condition of early childhood with up to 15 million office visits and national cost of 3 to 6 billion dollars (+ hearing loss, speech delay, family burden)



Healthy
- No fluid

Acute OM
- High bacteria count
- Purulent fluid
- Immune cells

NTHi

Chronic OM
- Remodeling of epithelium
- Production of **mucus** – **COME**

Low bacteria 'count'

- May be suppurative - **CSOM**

High bacteria 'count'

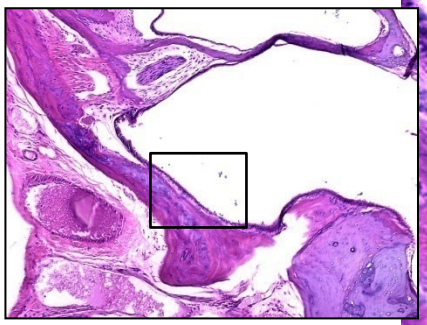
The Laryngoscope

NTHi Induction of Cxcl2 and Middle Ear Mucosal Metaplasia in Mice

Diego Preciado, MD, PhD; Katelyn Burgett, BS; Svetlana Ghimbovschi, PhD; Mary Rose, PhD

Saline

10x



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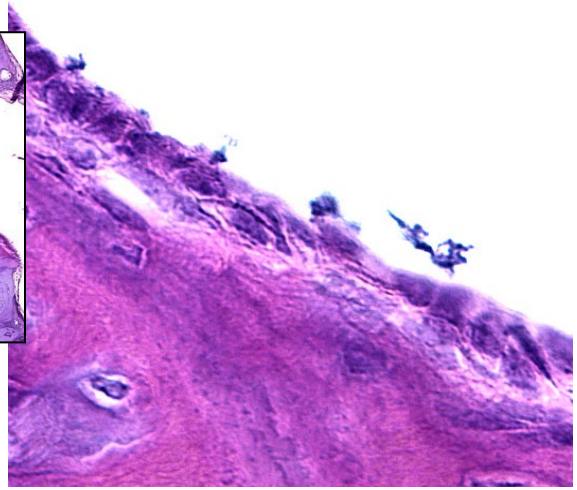

NTHI

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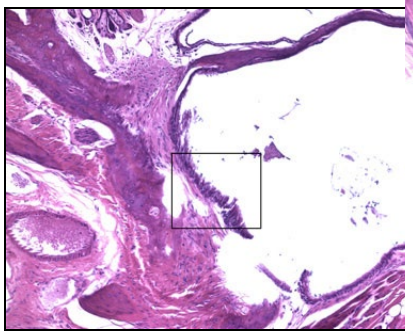

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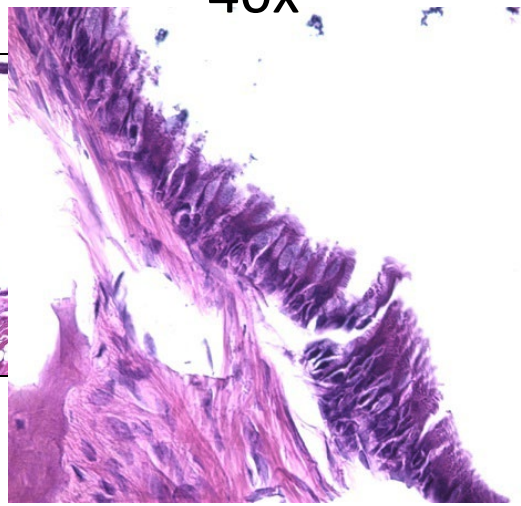

***In vivo* chronic effect of Non-typeable *Haemophilus influenza* on mouse ear**

Question #3

Acute Otitis Media inflammatory response is primarily mediated by:

1) Neutrophils
2) Natural Killer cells
3) Eosinophils
4) Memory T-cell and B-cell activation

Question #3

Acute Otitis Media inflammatory response is primarily mediated by:

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The Laryngoscope

NTHi Induction of Cxcl2 and Middle Ear Mucosal Metaplasia in Mice

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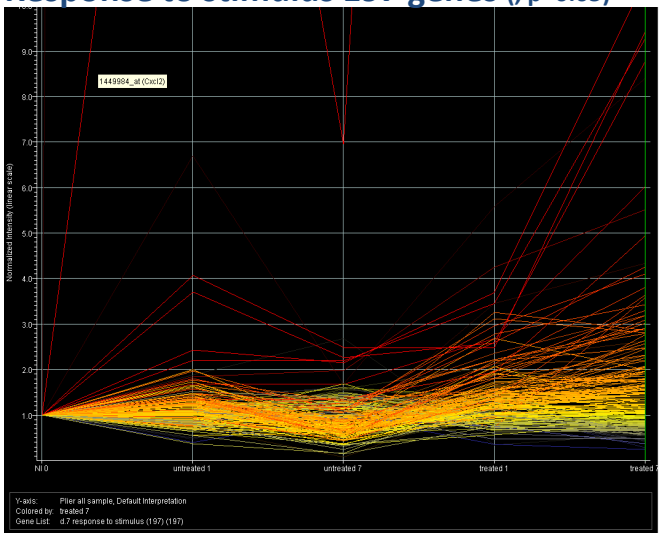
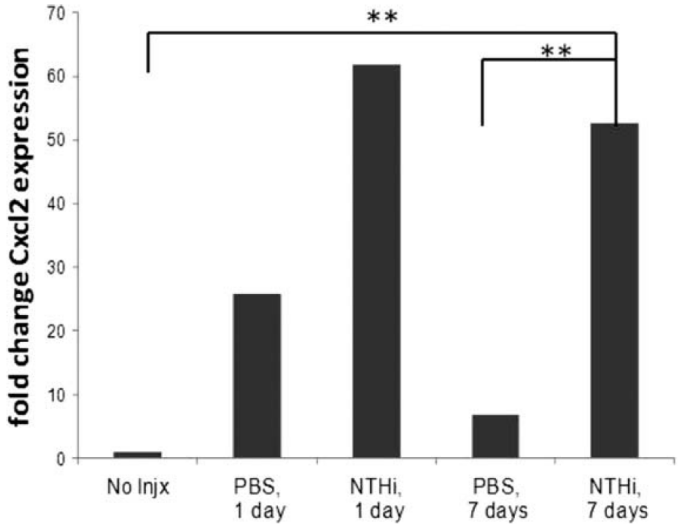
TABLE I.
Fold Changes of Top 5 Inflammatory Genes Significantly Changed With Middle Ear NTHi Innoculation ($p < 0.01$).

ID No.	Gene	PBS,1d	NTHi,1d	PBS,7d	NTHi,7d	*P*-value	Gene Name
1449984_at	Cxcl2	25.888	61.880	6.951	52.706	0.00205	C-X-C motif liga nd 2
1451713_a_at	Fcer2a	6.699	5.582	1.676	8.397	0.00614	Fc receptor, IgE
1418747_at	Sfpi1	1.676	2.682	1.668	6.015	0.0095	SFFV proviral int 1
1442233_at	Fyb	1.841	4.243	1.978	5.505	0.0105	FYN binding protein
14422579_at	Hspe1	1.787	2.593	1.118	4.249	0.0102	Heat shock protein 1

Response to stimulus 197 genes (, p<0.05)





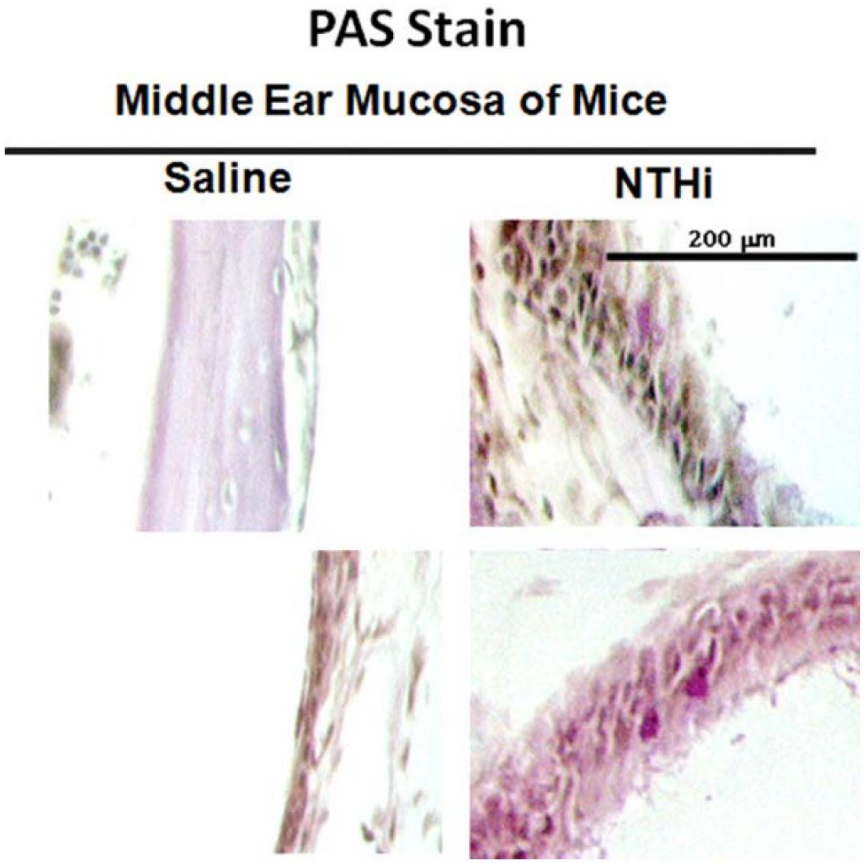


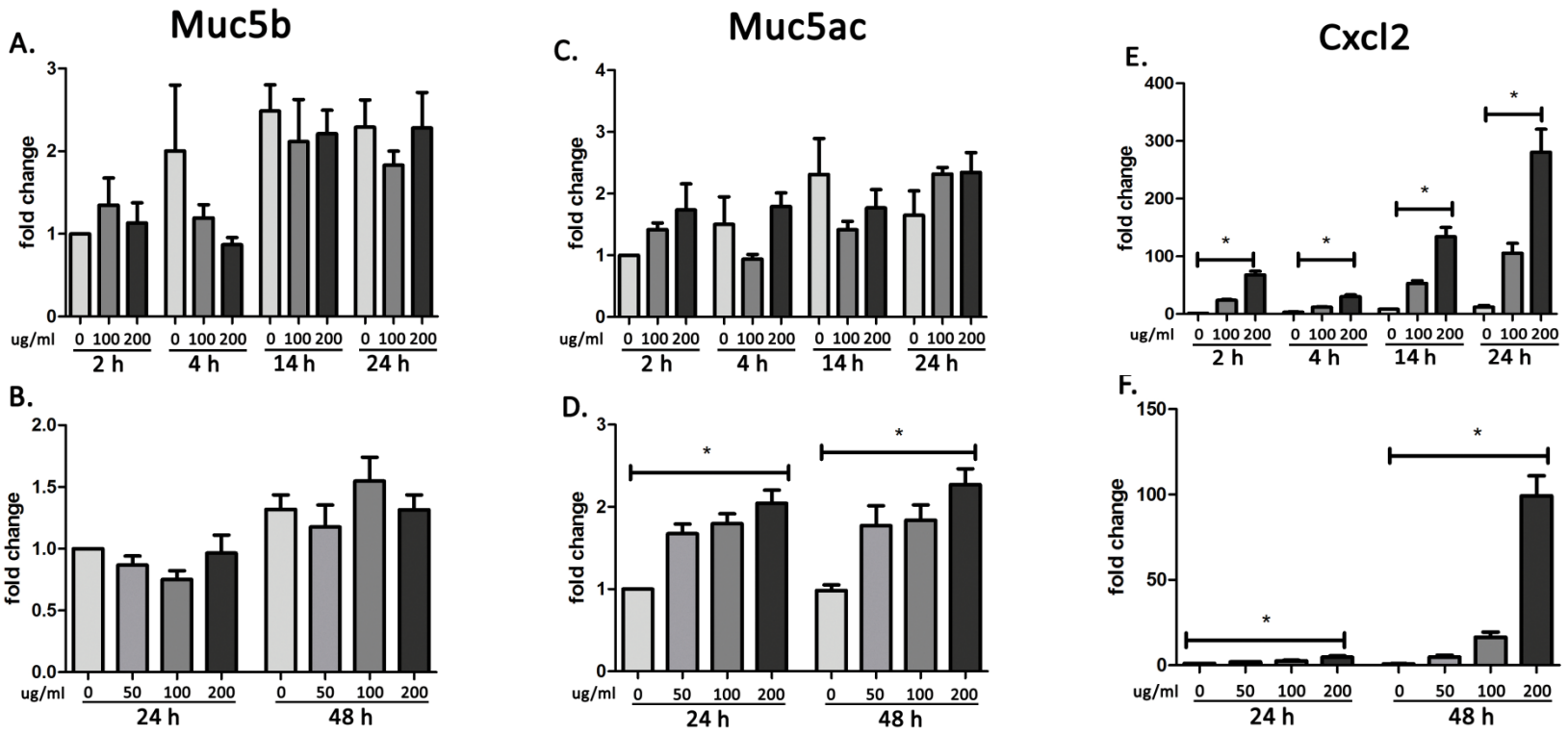
Fig. 2. PAS staining of mouse middle ear mucosa following NTHi exposure. Representative images of mouse middle ear mucosa after weekly exposure to 300 ug/ml NTHi lysates versus 1X PBS at 4 weeks. Sporadic and modest, but statistically significant increase in PAS positive cells (black arrows) was noted with NTHi.

JAMA Otolaryngol Head Neck Surg. 2015;141(11):997-1005. doi:10.1001/jamaoto.2015.2338
Published online October 29, 2015.

Original Investigation

Middle Ear Response of *Muc5ac* and *Muc5b* Mucins to Nontypeable *Haemophilus influenzae*

Stéphanie Val, PhD; Hyung-Joo Kwon, PhD; Mary C. Rose, PhD; Diego Preciado, MD, PhD



1) Mucins genes not upregulated with NTHi stimulation in mMEEC at early time points.

2) Robust Cxcl2 upregulation with NTHi for mMEEC in culture.

JAMA Otolaryngol Head Neck Surg. 2015;141(11):997-1005. doi:10.1001/jamaoto.2015.2338
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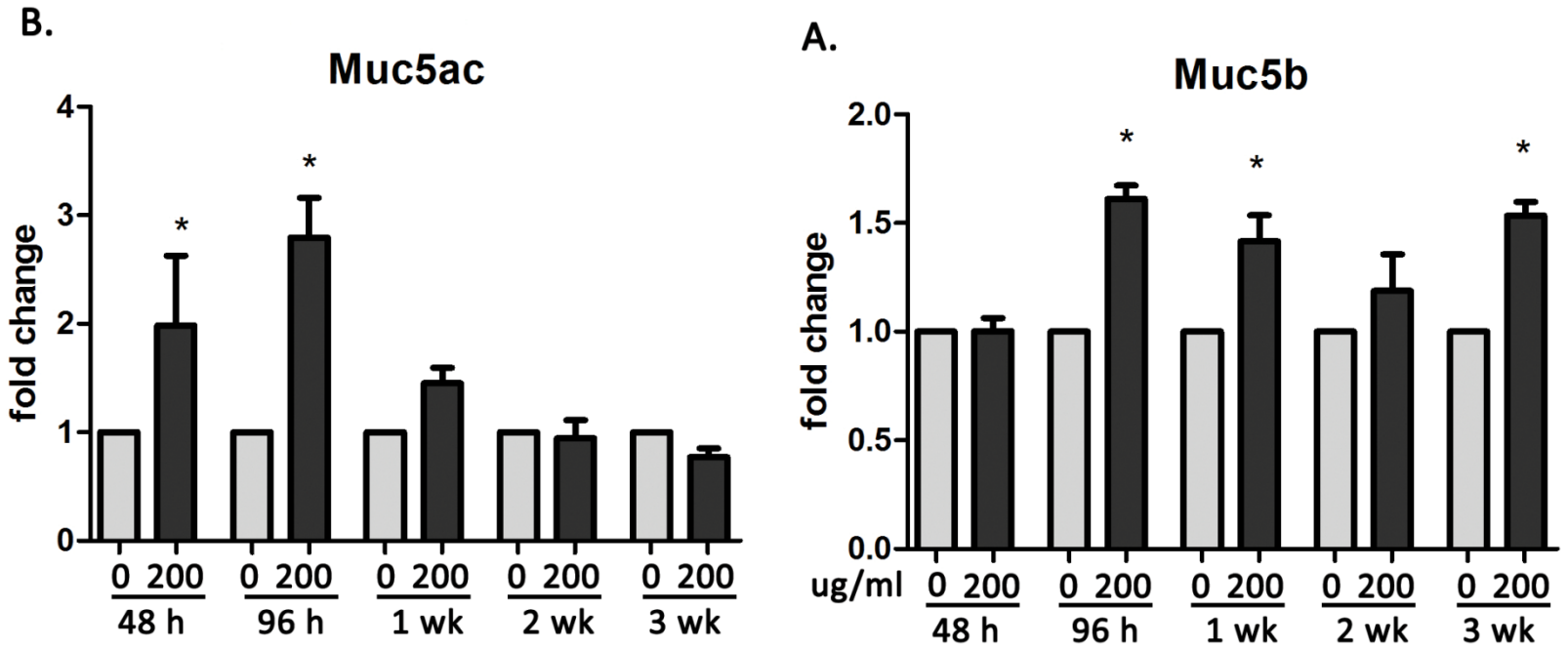


1) Muc5ac upregulated at 48-96 hours.

2) Muc5b upregulation occurs later and is more attenuated, from 96 hours to 3 weeks.

Respiratory Tract Mucin Genes and Mucin Glycoproteins in Health and Disease

MARY CALLAGHAN ROSE AND JUDITH A. VOYNOW

Physiol Rev 86: 245–278, 2006;
doi:10.1152/physrev.00010.2005.

Regulation of Mucin Genes in Chronic Inflammatory Airway Diseases

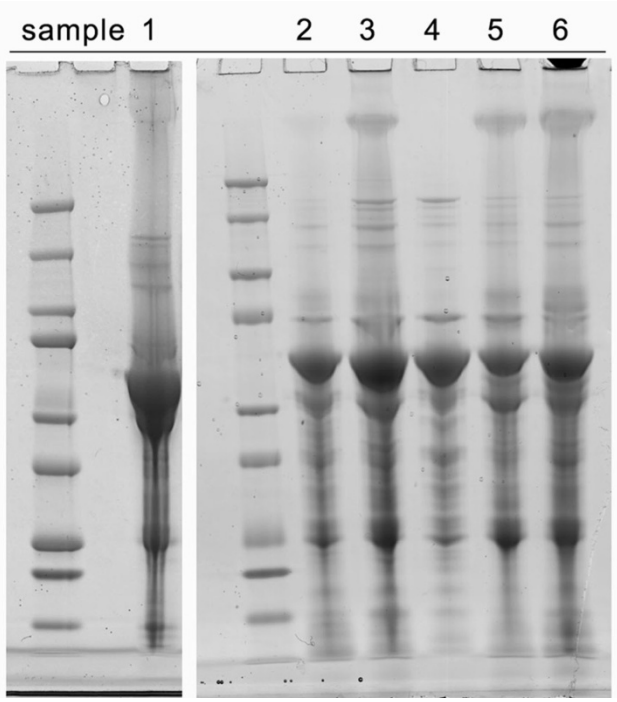
Judith A. Voynow, Sandra J. Gendler, and Mary C. Rose

Department of Pediatrics, Duke University Medical Center, Durham, North Carolina; Department of Biochemistry/Molecular Biology and Tumor Biology Program, Mayo Clinic College of Medicine, Scottsdale, Arizona; and Research Center for Genetic Medicine, Children's National Medical Center and Departments of Pediatrics and Biochemistry/Molecular Biology, George Washington University, Washington, D.C.

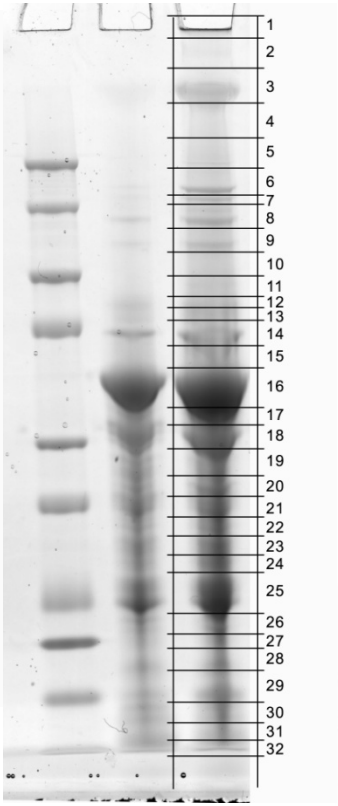
Am J Respir Cell Mol Biol Vol 34. pp 661–665, 2006

Human COM Effusion Proteomics

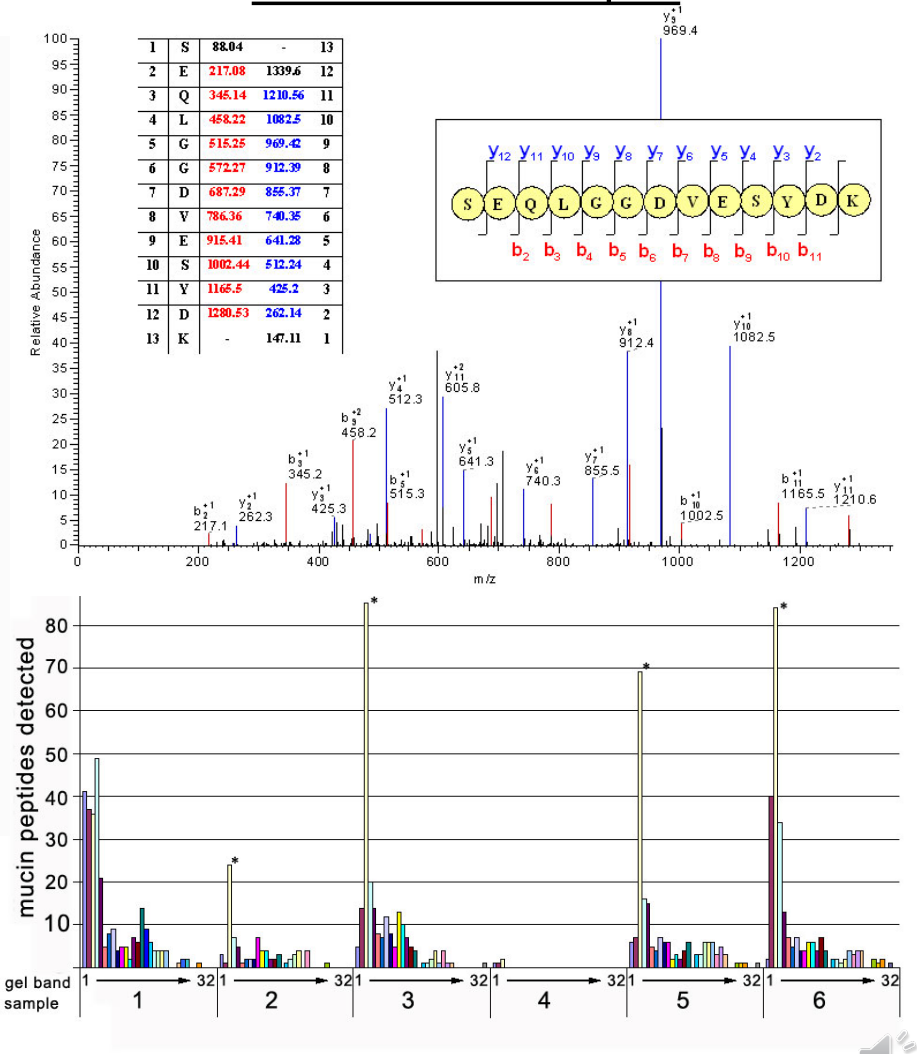
1. SDS PAGE gel



2. Fractionation



3. LC-MS Mass Spec



MUC5B Is the Predominant Mucin Glycoprotein in Chronic Otitis Media Fluid

DIEGO PRECIADO, SAMITA GOYAL, MICHAEL RAHIMI, ALAN M. WATSON, KRISTY J. BROWN, YETRIB HATHOUT, AND MARY C. ROSE

0031-3998/10/6803-0231
PEDIATRIC RESEARCH

Table 3. *Unique MUC5B peptides identified*

Peptide	Amino acid	Frequency	Bin (1-32)
AAGGAVCEQPLGLECR	2874–2890	2	1
AAYEDFNVQLR	108–119	15	3,9,10,11,14,18,20,21,22
AFGQFFSPGEVIYNK	4162–4177	2	3
ALSIHYK	5076–5082	9	1,3,4,5,7,14
AQAQPGVPLR	2362–2371	198	1,2,3,4,5,6,7
AVTLSLDGGDTAIR	489–503	36	1,3,4,8,11,12,13,15,18,19,20,21,22,23,24,29
DGNYYDVGAR	1225–1234	40	2,3,4,5,6,8,9,10,11,12,13,15
EEGLILFDQIPVSSGFSK	5159–5176	19	1,3,5,6,8,9,10,11,12,13,14,15,19
GATGGLCDLTCPPTK	5290–5304	2	1
GPGGDPPYK	976–985	29	1,3,4,5,6,7,8,9,10,11,15,20,21,22
IVTENIPCGTTGTTCSK	938–954	1	3
LCLGTCVAYGDGHFITFDGDR	898–918	2	23,24
LFVESYELILQEGTFK	958–973	1	16
LTDPNSAFSR	626–635	118	1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,20,21,22,23,27,28,29
LTPLQFGNLQK	225–236	62	1,3,4,5,7,8,9,10,11,12,13,14,15,17,18,19,20,21,24,25
NGVLVSVLGTTTMR	5114–5127	7	3
NWEQEGVFK	1576–1585	18	2,3,4,5,7,8,9,10,11
PGFVTVTRPR	5403–5412	3	7,8,12
SEQLGGDVESYDK	1521–1532	69	1,2,3,4,5,6,7,8,9,10,11
SMDIVLTVTMVHGK	5082–5095	6	3,3,8
SVVGDALEFGNSWK	1043–1056	27	1,3,4,5,8,10,11,12,13,14,15,20,21,23,24,29,31
TGLLVEQSGDYIK	162–174	62	3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,19,20,21,24,26,27,29
VCGLCGNFDDNAINDFATR	1047–1062	20	3,4,5,11,12,15,19,20,21,23,24,28
VYKPCGPIQPATCNSR	5302–5317	1	3
YAYVVDACQPTCR	699–714	2	8,9

Table 4. *Unique MUC5AC peptides identified*

Peptide	Amino acid	Frequency	Bin (1-32)
AEDAPGVPLR	1431–1440	1	3
GTDSGDFDTLENLR	1399–1413	2	3,5
HQDGLVVVTTK	4860–4870	2	8,9
NQDQQGPFK	2723–2732	1	3
RPEEITR	4045–4051	8	3,4
SYRPGAVVPSDK	1243–1254	1	3

MUC5B Is the Predominant Mucin Glycoprotein in Chronic Otitis Media Fluid

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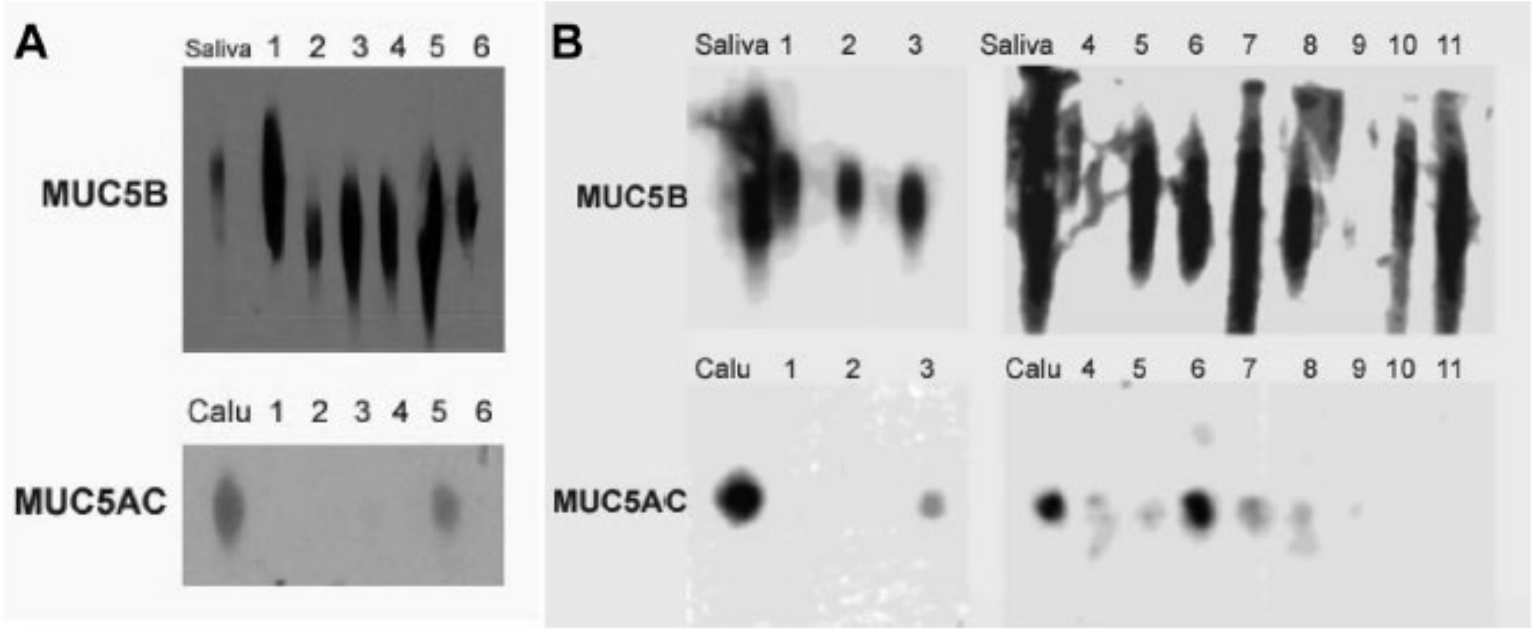
0031-3998/10/6803-0231
PEDIATRIC RESEARCH

MUC5B IN MIDDLE EAR EFFUSIONS



International Journal of Pediatric Otorhinolaryngology 90 (2016) 133–137

Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: http://www.ijporlonline.com/

Younger patients with COME are more likely to have mucoid middle ear fluid containing mucin MUC5B☆

Vanessa Duah [a], Zhen Huang [b], Stephanie Val [b, c], Christie DeMason [b], Marain Poley [b], Diego Preciado [b, c, *]

	MUC5AC	MUC5B
Mucoid	30/42 (71.4%)	42/42 (100%)
Serous	2/6 (33%)	5/6 (83%)
Total	32/48 (66.7%)	47/48 (97%)

p<0.05

Duah et al., *IJPORL*, 2016 Nov;90:133-137

What else is going on in the human chronic middle ear fluid proteome?

“One finds what one seeks, and one seeks what one knows…”

- Claude Bernard (1813-1878)

30 most abundant proteins in mucoid OM secretions

	HIGH PEPTIDE COUNT
Q8TDL5	Long palate, lung and nasal epithelium carcinoma-associated protein 1 (LPLUNC1)
P02788	Lactotransferrin (LTF)
Q9HC84	Mucin-5B (MUC5B)
P62736	Actin, aortic smooth muscle (ACTA2)
P62805	Histone H4 (HIST1H4A)
P05109	Protein S100-A8 (S100A8)
P06702	Protein S100-A9 (S100A9)
	INTERMEDIATE PEPTIDE COUNT
P60709	Actin, cytoplasmic 1 (ACTB)
P02679	Fibrinogen gamma chain (FGG)
Q9NP55	Protein Plunc (PLUNC)
P05164	Myeloperoxidase (MPO)
P02675	Fibrinogen beta chain (FGB)
P08311	Cathepsin G (CTSG)
Q96QV6	Histone H2A type 1-A (HIST1H2AA)
P04406	Glyceraldehyde-3-phosphate dehydrogenase (GAPDH)
P08246	Leukocyte elastase (ELA2)
P01833	Polymeric immunoglobulin receptor (PIGR)
Q9UGM3	Deleted in malignant brain tumors 1 protein (DMBT1)
P06733	Alpha-enolase (ENO1)
P33778	Histone H2B type 1-B (HIST1H2BB)
Q562R1	Beta-actin-like protein 2 (ACTBL2)
P80188	Neutrophil gelatinase-associated lipocalin (LCN2)
P12814	Alpha-actinin-1 (ACTN1)
P04083	Annexin A1 (ANXA1)
P08670	Vimentin (VIM)
P30740	Leukocyte elastase inhibitor (SERPINB1)
Q9BYX7	Beta-actin-like protein 3 (ACTBL3)
P02671	Fibrinogen alpha chain (FGA)
P61626	Lysozyme C (LYZ)
P02790	Hemopexin (HPX)

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P62805	Histone H4 (HIST1H4A)
P05109	**Protein S100-A8 (S100A8)**
P06702	**Protein S100-A9 (S100A9)**
	INTERMEDIATE PEPTIDE COUNT
P60709	Actin, cytoplasmic 1 (ACTB)
P02679	Fibrinogen gamma chain (FGG)
Q9NP55	**Protein Plunc (PLUNC)**
P05164	Myeloperoxidase (MPO)
P02675	Fibrinogen beta chain (FGB)
P08311	Cathepsin G (CTSG)
Q96QV6	Histone H2A type 1-A (HIST1H2AA)
P04406	Glyceraldehyde-3-phosphate dehydrogenase (GAPDH)
P08246	Leukocyte elastase (ELA2)
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P04083	Annexin A1 (ANXA1)
P08670	Vimentin (VIM)
P30740	Leukocyte elastase inhibitor (SERPINB1)
Q9BYX7	Beta-actin-like protein 3 (ACTBL3)
P02671	Fibrinogen alpha chain (FGA)
P61626	Lysozyme C (LYZ)
P02790	Hemopexin (HPX)

→Proteins implicated in innate mucosal immunity

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P62736	Actin, aortic smooth muscle (ACTA2)
P62805	**Histone H4 (HIST1H4A)**
P05109	Protein S100-A8 (S100A8)
P06702	Protein S100-A9 (S100A9)
	INTERMEDIATE PEPTIDE COUNT
P60709	Actin, cytoplasmic 1 (ACTB)
P02679	Fibrinogen gamma chain (FGG)
Q9NP55	Protein Plunc (PLUNC)
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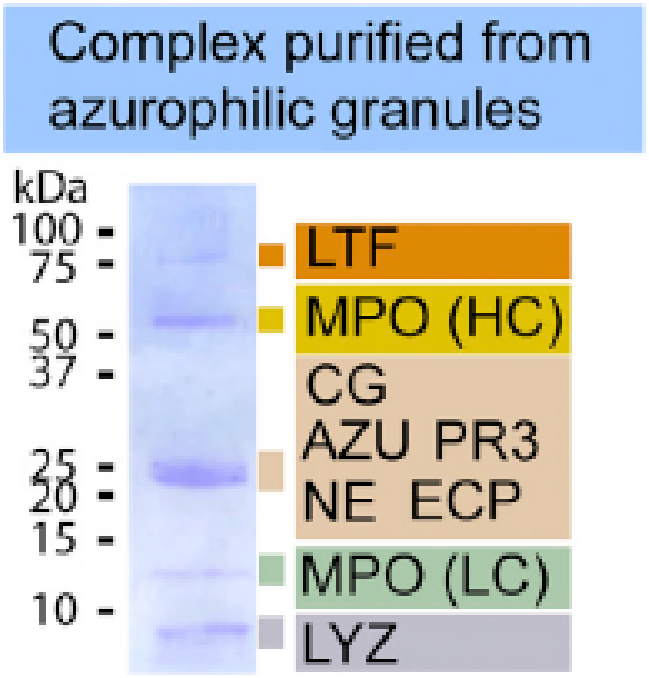
P12814	Alpha-actinin-1 (ACTN1)
P04083	Annexin A1 (ANXA1)
P08670	Vimentin (VIM)
P30740	**Leukocyte elastase inhibitor (SERPINB1)**
Q9BYX7	Beta-actin-like protein 3 (ACTBL3)
P02671	Fibrinogen alpha chain (FGA)
P61626	**Lysozyme C (LYZ)**
P02790	Hemopexin (HPX)

“Neutrophil” proteins:



Metzler et al., 2014, Cell Report

Our MEEs: average/sample

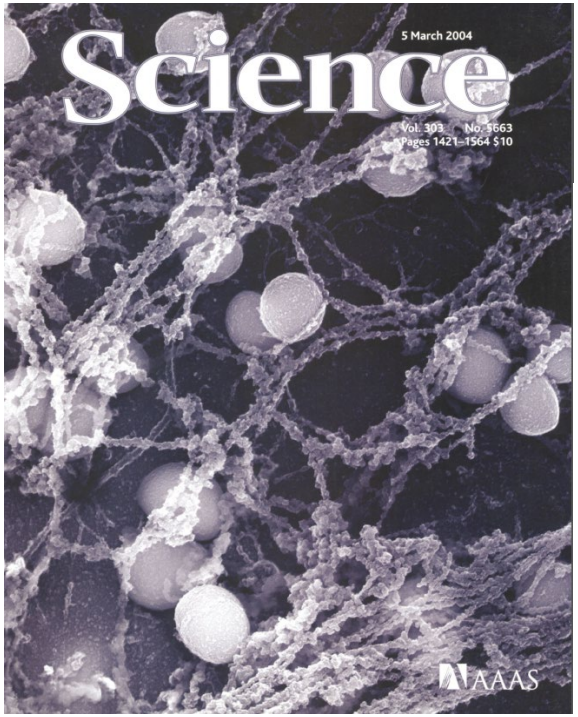
LTF	211
MPO	53
CG	28
AZU3	4
PR3	12
NE	79
ECP	2
LYZ	63

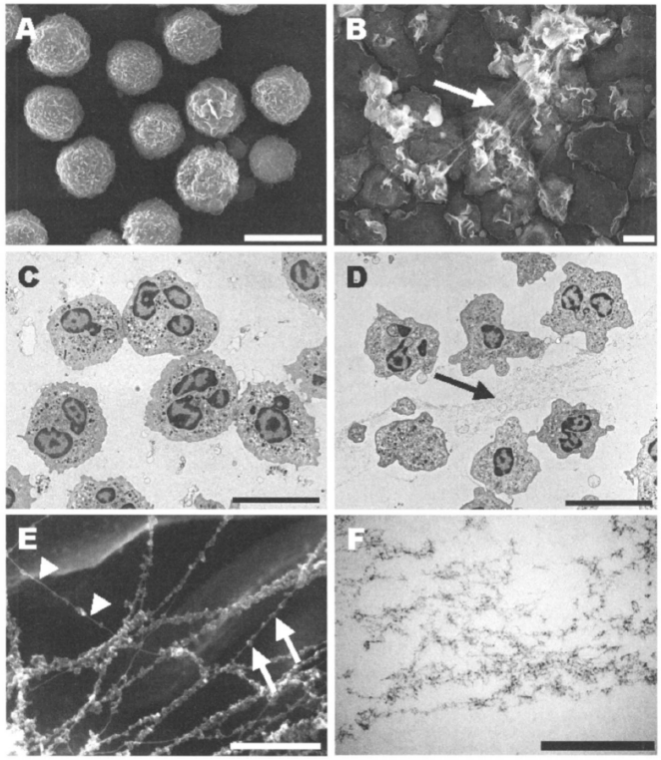
Total average: 452

Total peptide count/sample 2323

→ *These proteins represent 19.5% of peptide count in samples*

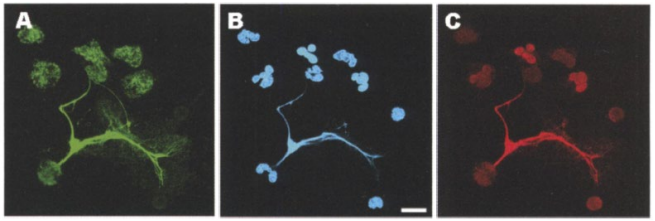
Neutrophil extracellular traps





Induction with
PMA (B, D, E, F)

NETs



Neutrophil elastase | DNA | H2A+H2B

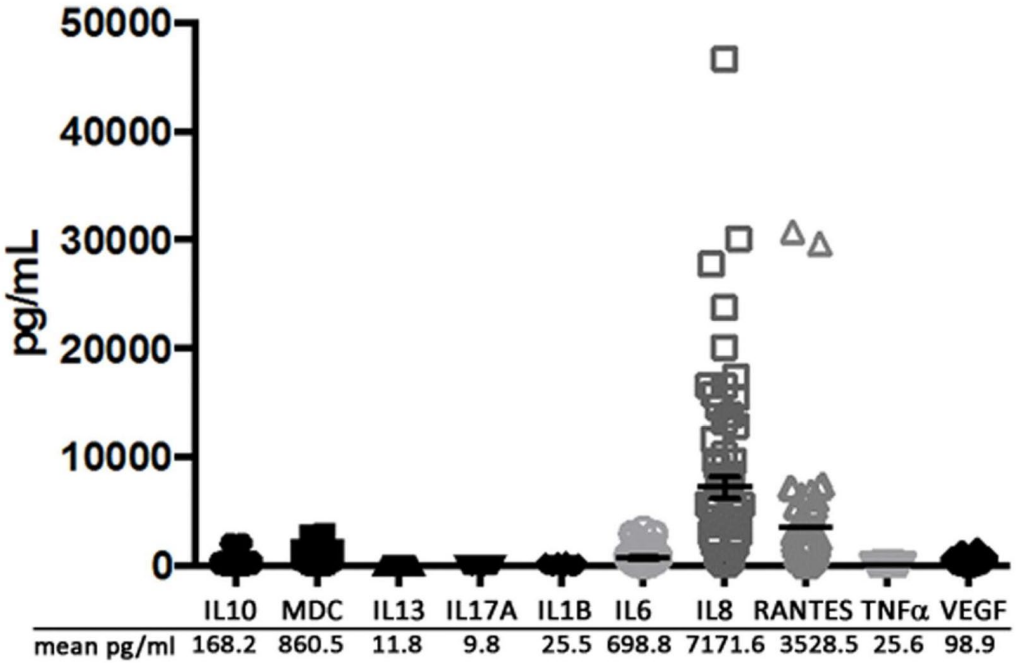
Brinkmann et al., 2004, Science
Max Plank Institute (Berlin)

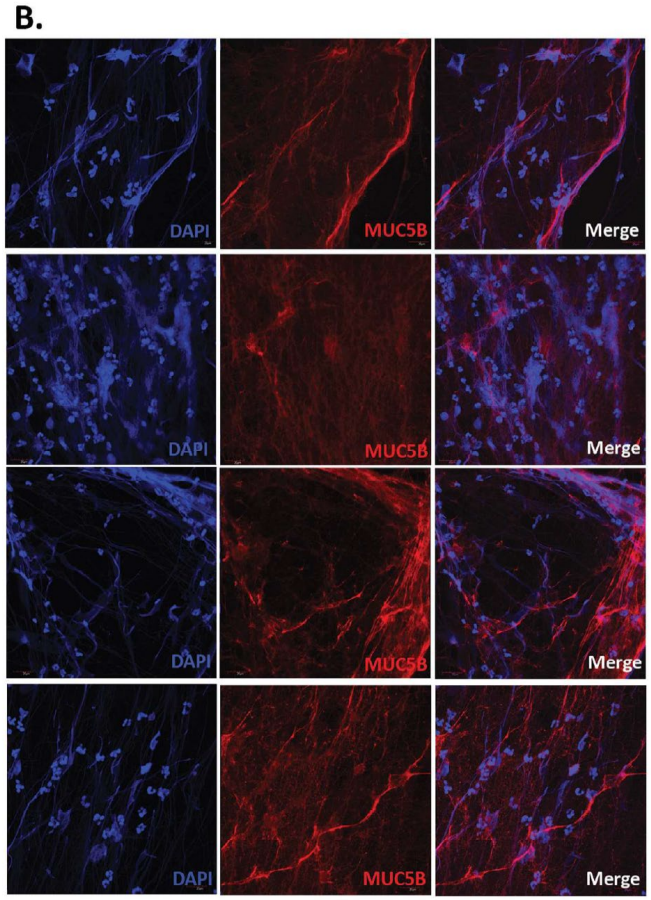
PLOS ONE | DOI:10.1371/journal.pone.0152865 April 14, 2016

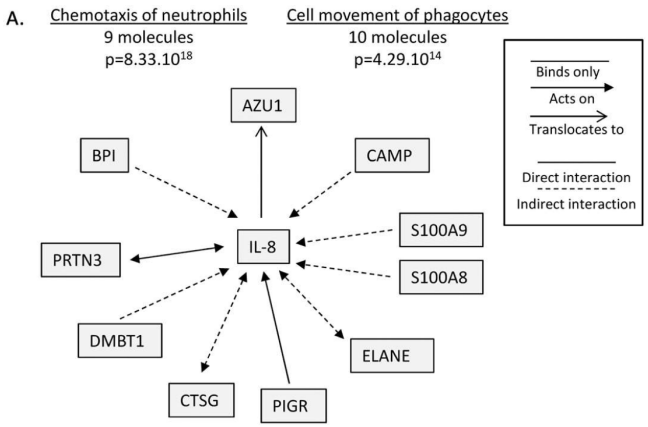
RESEARCH ARTICLE

Proteomic Characterization of Middle Ear Fluid Confirms Neutrophil Extracellular Traps as a Predominant Innate Immune Response in Chronic Otitis Media

Stephanie Val[1], Marian Poley[1], Kristy Brown[2], Rachel Choi[1], Stephanie Jeong[1], Annie Colberg-Poley[2], Mary C. Rose[2], Karuna C. Panchapakesan[2], Joe C. Devaney[2], Marcos Perez-Losada[2], Diego Preciado[1,3]*







Relationship of the Middle Ear Effusion Microbiome to Secretory Mucin Production in Pediatric Patients With Chronic Otitis Media

Anna Krueger, MS, Stéphanie Val, PhD,* Marcos Pérez-Losada, PhD,†‡ Karuna Panchapakesan, PhD,§ Joe Devaney, PhD,§ Vanessa Duah, BS,* Christine DeMason, MD,* Marian Poley, BS, BA,* Mary Rose, PhD,§¶ and Diego Preciado, MD, PhD*¶*

The Pediatric Infectious Disease Journal • Volume 36, Number 7, July 2017

Relationship of the Middle Ear Effusion Microbiome to Secretory Mucin Production in Pediatric Patients With Chronic Otitis Media

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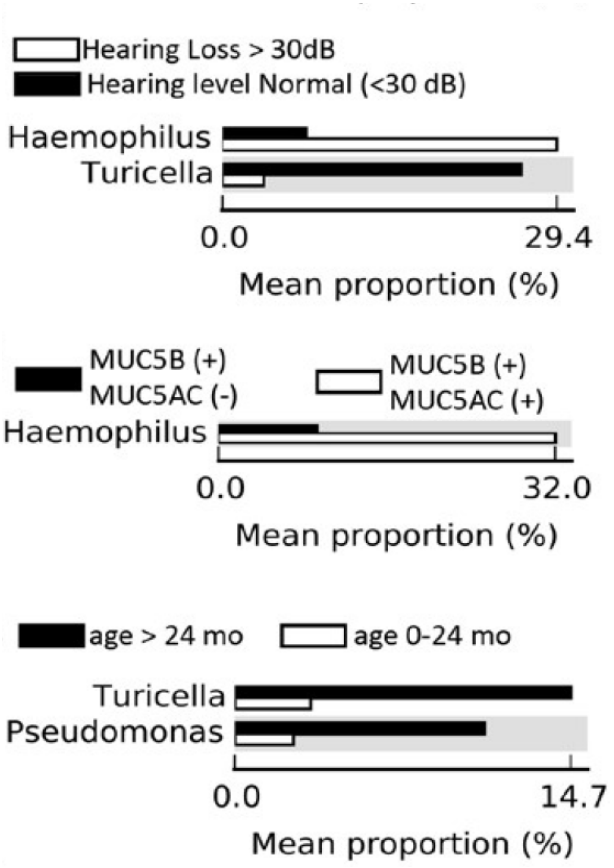
The Pediatric Infectious Disease Journal • Volume 36, Number 7, July 2017

TABLE 3. The 10 most relatively abundant genera in 50 middle ear effusions from children with chronic otitis media

Operational Taxonomic Unit	Relative Abundance (%)
Haemophilus	22.54
Moraxella	11.11
Turicella	7.84
Alcaligenaceae; unclassified	5.84
Pseudomonas	5.40
Alloiococcus	5.08
Chitinophagaceae; unclassified	4.57
Streptococcus	4.21
Stenotrophomonas	4.12
Staphylococcus	3.39



Received: 12 March 2020 | Revised: 21 April 2020 | Accepted: 29 April 2020

DOI: 10.1002/lio2.396

ORIGINAL RESEARCH

Laryngoscope Investigative Otolaryngology

MUC5B induces in vitro neutrophil extracellular trap formation: Implication in otitis media

Stéphanie Val PhD[1] | Anna Krueger MS[1] | Arman Hussain MD[1] | Amarel Tomney MS[1] | Yajun Chen PhD[1] | Christopher Lazarski PhD[2] | Diego Preciado MD, PhD[1,3]

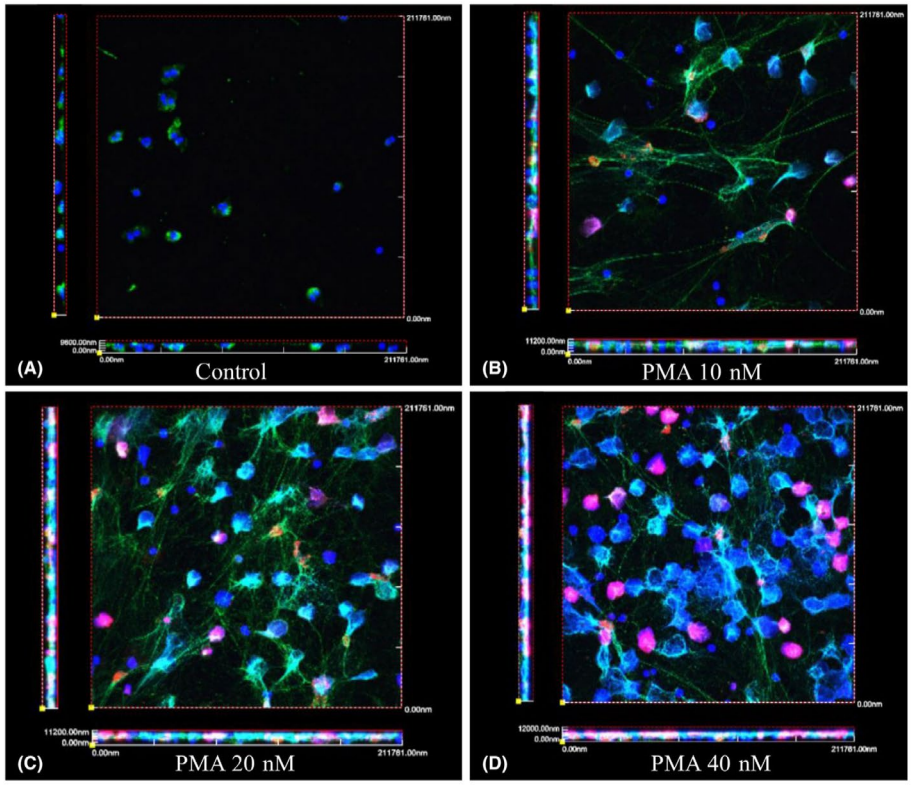


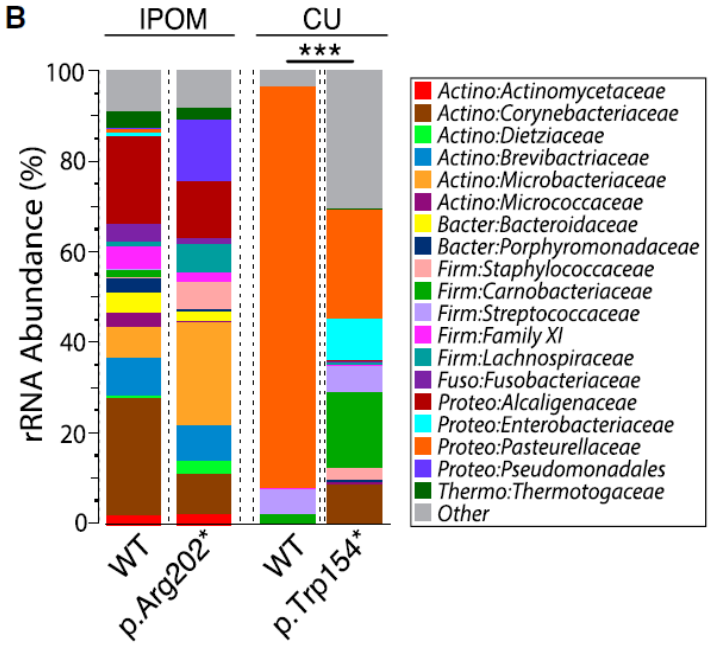
TABLE 1 NETosis scores to compare the effect of different OM mediators

	Average	SE	n	*P*-value
Control	1.00	0.00	11	
PMA 10 nM	**19.00**	**3.73**	**5**	**.001**
PMA 20 nM	**14.39**	**5.39**	**5**	**.03**
PMA 40 nM	**13.56**	**4.04**	**5**	**.03**
IL-8 10 ng/mL	**3.27**	**0.89**	**4**	**.02**
IL-8 20 ng/mL	**5.44**	**2.63**	**4**	**.03**
IL-8100 ng/mL	**5.36**	**3.43**	**3**	**.02**
TNF-α 0.5 ng/mL	2.31	1.17	3	.21
TNF-α 1 ng/mL	2.95	0.98	5	.17
TNF-α 5 ng/mL	2.20	1.23	3	.56
MUC5B 10 µg/mL	**16.27**	**1.52**	**6**	**.001**
MUC5B 20 µg/mL	**15.39**	**1.59**	**6**	**.001**
MUC5B 40 µg/mL	**8.75**	**1.24**	**6**	**.001**

Note: In order to compare conditions, a NETosis score was calculated as DAPI, MPO, and CitH3 IF staining intensity summed fold inductions for PMA, IL-8, TNF-α, and MUC5B treatments analyzed by confocal microscopy. Bold lines indicate *P*-value <.05.

FUT2 Variants Confer Susceptibility to Familial Otitis Media

Regie Lyn P. Santos-Cortez,[1,2,3,*] Charlotte M. Chiong,[3,4,5] Daniel N. Frank,[6] Allen F. Ryan,[7] Arnaud P.J. Giese,[8] Tori Bootpetch Roberts,[1] Kathleen A. Daly,[9] Matthew J. Steritz,[1] Wasyl Szeremeta,[10] Melquiadesa Pedro,[3] Harold Pine,[10] Talitha Karisse L. Yarza,[3,4] Melissa A. Scholes,[1,11] Erasmo Gonzalo d.V. Llanes,[3,5] Saira Yousaf,[8] Norman Friedman,[1,11] Ma. Leah C. Tantoco,[3,5] Todd M. Wine,[1,11] Patrick John Labra,[5] Jeanne Benoit,[6] Amanda G. Ruiz,[1,11] Rhodieleen Anne R. de la Cruz,[5] Christopher Greenlee,[1,11] Ayesha Yousaf,[12] Jonathan Cardwell,[13] Rachelle Marie A. Nonato,[5] Dylan Ray,[1] Kimberly Mae C. Ong,[5] Edward So,[8] Charles E. Robertson,[6] Jordyn Dinwiddie,[1,11] Sheryl Mae Lagrana-Villagracia,[3] University of Washington Center for Mendelian Genomics (UWCMG), Samuel P. Gubbels,[1] Rehan S. Shaikh,[12] Stephen P. Cass,[1] Elisabet Einarsdottir,[14,15] Nanette R. Lee,[16] David A. Schwartz,[13] Teresa Luisa I. Gloria-Cruz,[3,5] Michael J. Bamshad,[17] Ivana V. Yang,[13] Juha Kere,[14,15,18] Generoso T. Abes,[3,5] Jeremy D. Prager,[1,11] Saima Riazuddin,[8] Abner L. Chan,[3,5] Patricia J. Yoon,[1,11] Deborah A. Nickerson,[17] Eva Maria Cutiongco-de la Paz,[19,20] Sven-Olrik Streubel,[1,11] Maria Rina T. Reyes-Quintos,[3,4,5,19] Herman A. Jenkins,[1] Petri Mattila,[21] Kenny H. Chan,[1,11] Karen L. Mohlke,[22] Suzanne M. Leal,[23] Lena Hafrén,[21] Tasnee Chonmaitree,[24] Michele M. Sale,[25,26,27] and Zubair M. Ahmed[8]



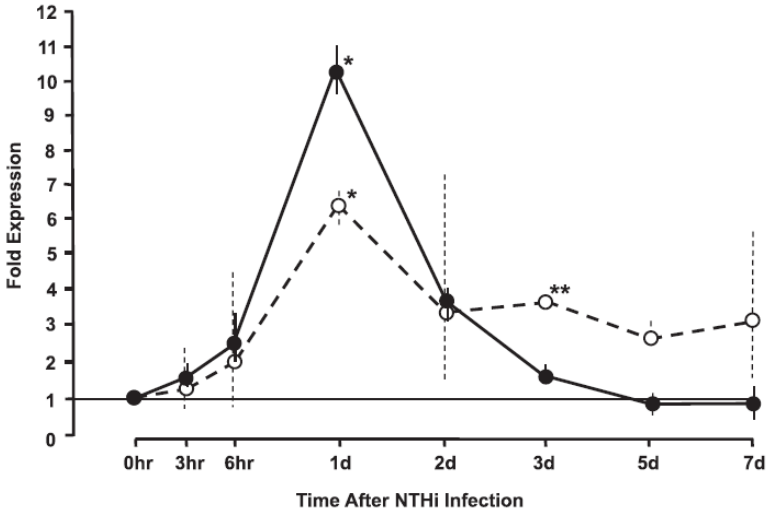
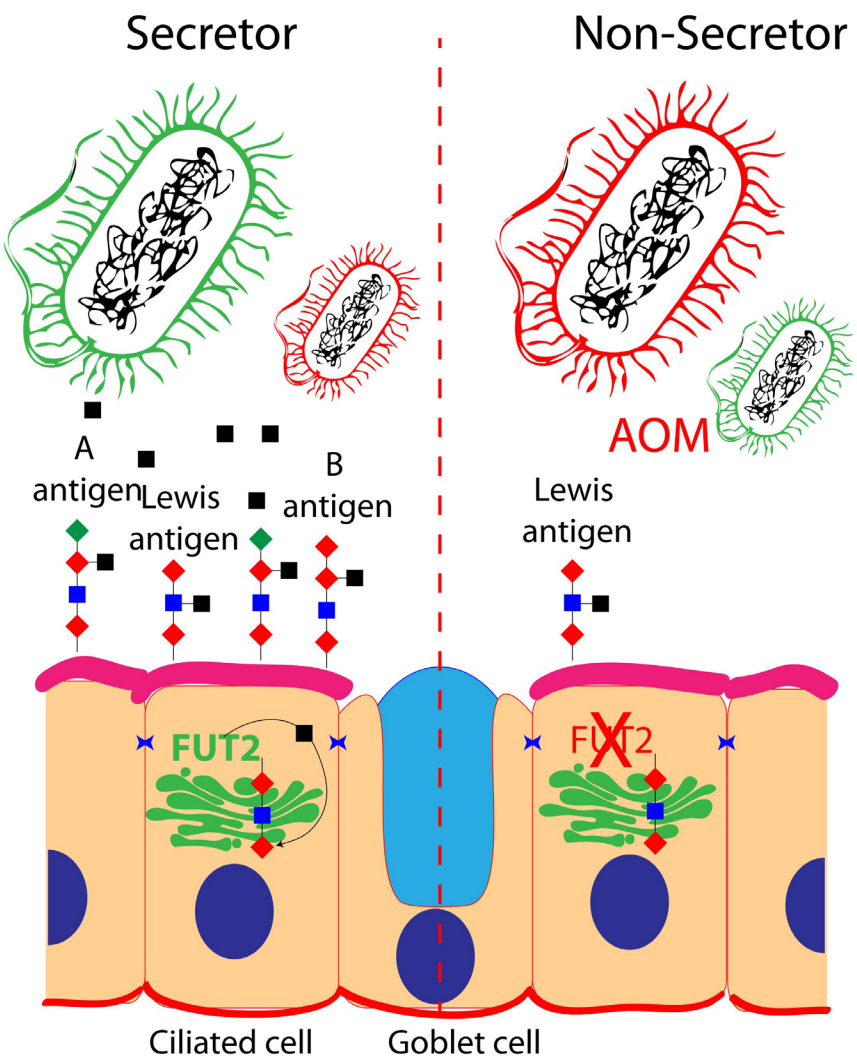
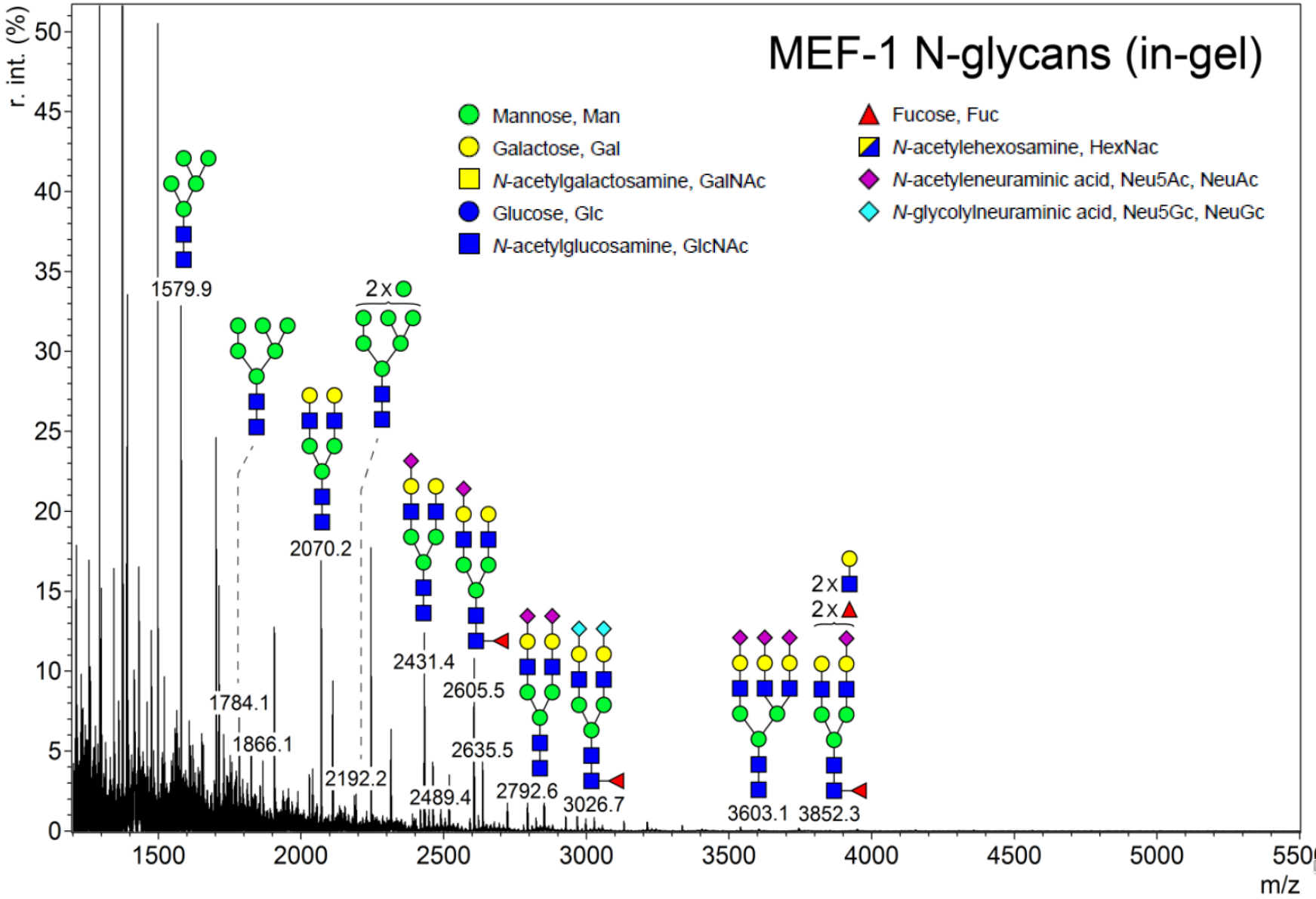


Figure 3. Fold Expression of *Fut2* across Different Time Points after Inoculation of Non-typeable *Haemophilus influenzae* into the Mouse Middle Ear



Giese, A; et al. Front. Genet., 23 April 2020 | https://doi.org/10.3389/fgene.2020.00313

Middle ear MUC5B



“every generalization is wrong, including this one…”

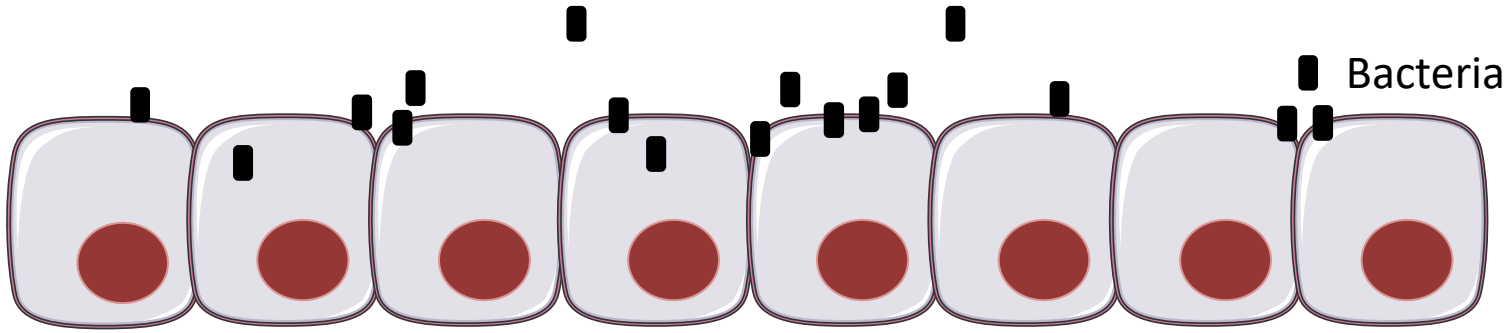
- Mark Twain

“all you need in this life is ignorance and confidence, and then success is sure…”

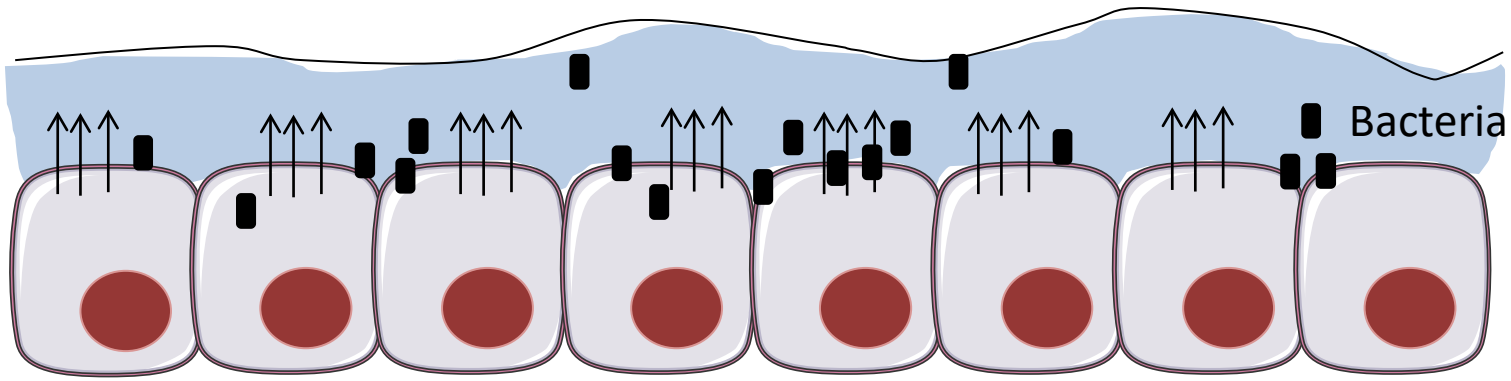
- Mark Twain

Putting it all together:
OM MODEL

Middle ear infection



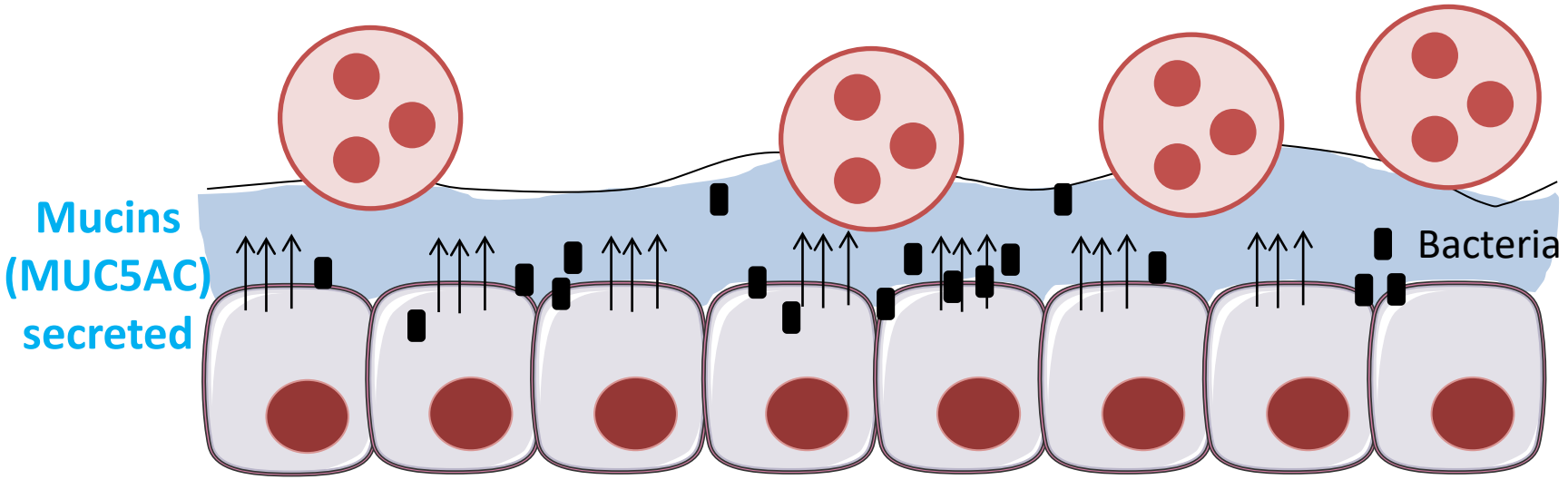
Secretion of pro-inflammatory mediators (IL8)/exosomes



Acute Otitis Media

Children's National
Sheikh Zayed Institute
for Pediatric Surgical Innovation
Part of the Children's National Health System

Neutrophil chemotaxis

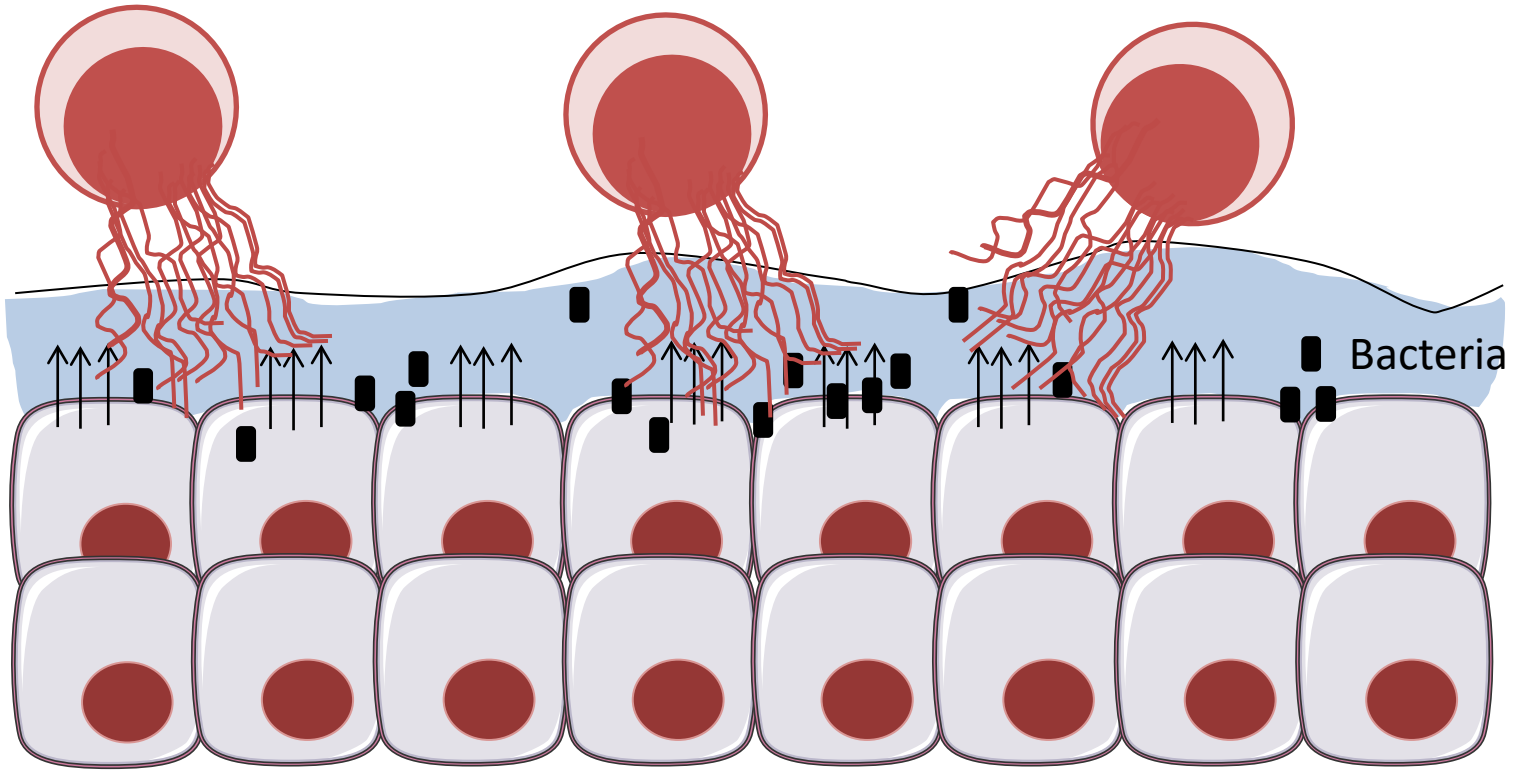


Children's National

Sheikh Zayed Institute
for Pediatric Surgical Innovation

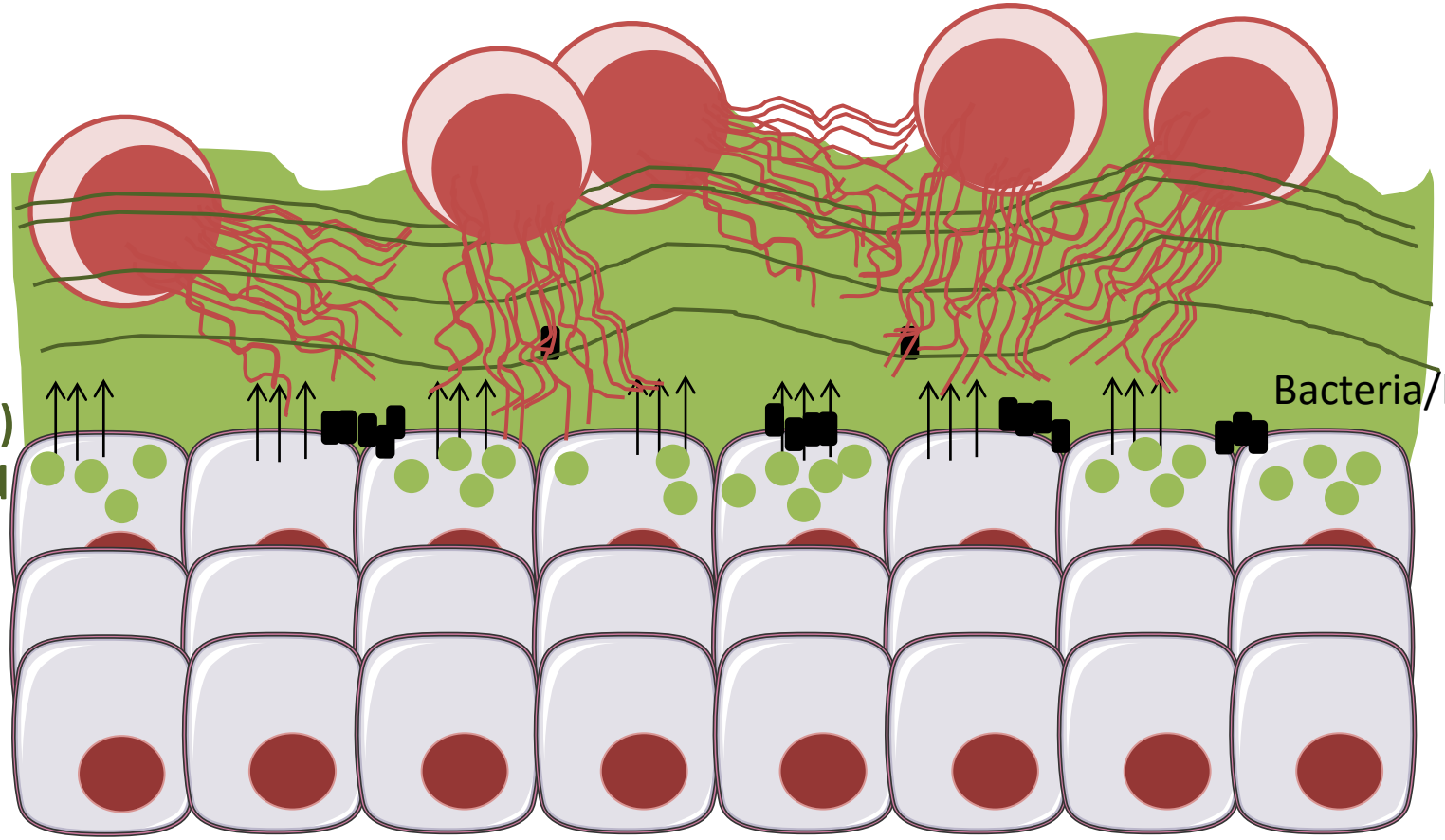
Part of the Children's National Health System

NETosis



Chronic Otitis Media

High viscosity of the MEEs: NETs trapped in the mucus, NET DNA increases MEE viscosity



Summary

- **Holisitic** understanding of OM reveals**:**
  - **Temporal** regulation of inflammation
  - **Proteome** profile of **neutrophilic activation**
  - **Microbiome** is correlated to **mucins, age, resp disease**

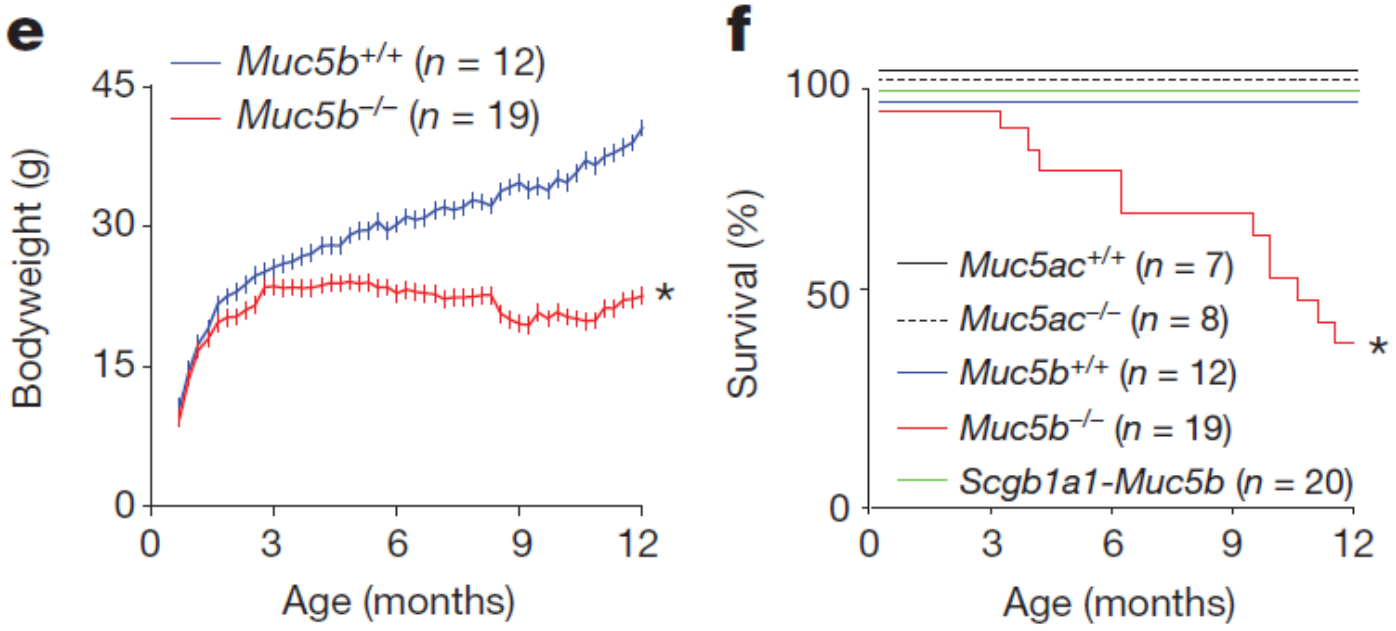
- **Reductionist** understanding of OM**:**
  - **MUC5B** is predominant macromolecular component
  - **NETs/Biofilms**

LETTER

doi:10.1038/nature12807

Muc5b is required for airway defence

Michelle G. Roy[1]*, Alessandra Livraghi-Butrico[2]*, Ashley A. Fletcher[3]*, Melissa M. McElwee[1], Scott E. Evans[1], Ryan M. Boerner[4], Samantha N. Alexander[1], Lindsey K. Bellinghausen[1], Alfred S. Song[1], Youlia M. Petrova[1], Michael J. Tuvim[1], Roberto Adachi[1], Irlanda Romo[1,5], Andrea S. Bordt[6], M. Gabriela Bowden[6,7], Joseph H. Sisson[8], Prescott G. Woodruff[9], David J. Thornton[10], Karine Rousseau[10], Maria M. De la Garza[1], Seyed J. Moghaddam[1], Harry Karmouty-Quintana[4], Michael R. Blackburn[4], Scott M. Drouin[4], C. William Davis[2], Kristy A. Terrell[2], Barbara R. Grubb[2], Wanda K. O'Neal[2], Sonia C. Flores[3], Adela Cota-Gomez[3], Catherine A. Lozupone[3], Jody M. Donnelly[3], Alan M. Watson[3], Corinne E. Hennessy[3], Rebecca C. Keith[3], Ivana V. Yang[3], Lea Barthel[3,11], Peter M. Henson[3,11], William J. Janssen[3,11], David A. Schwartz[3], Richard C. Boucher[2], Burton F. Dickey[1] & Christopher M. Evans[1,3]



LETTER

doi:10.1038/nature12807

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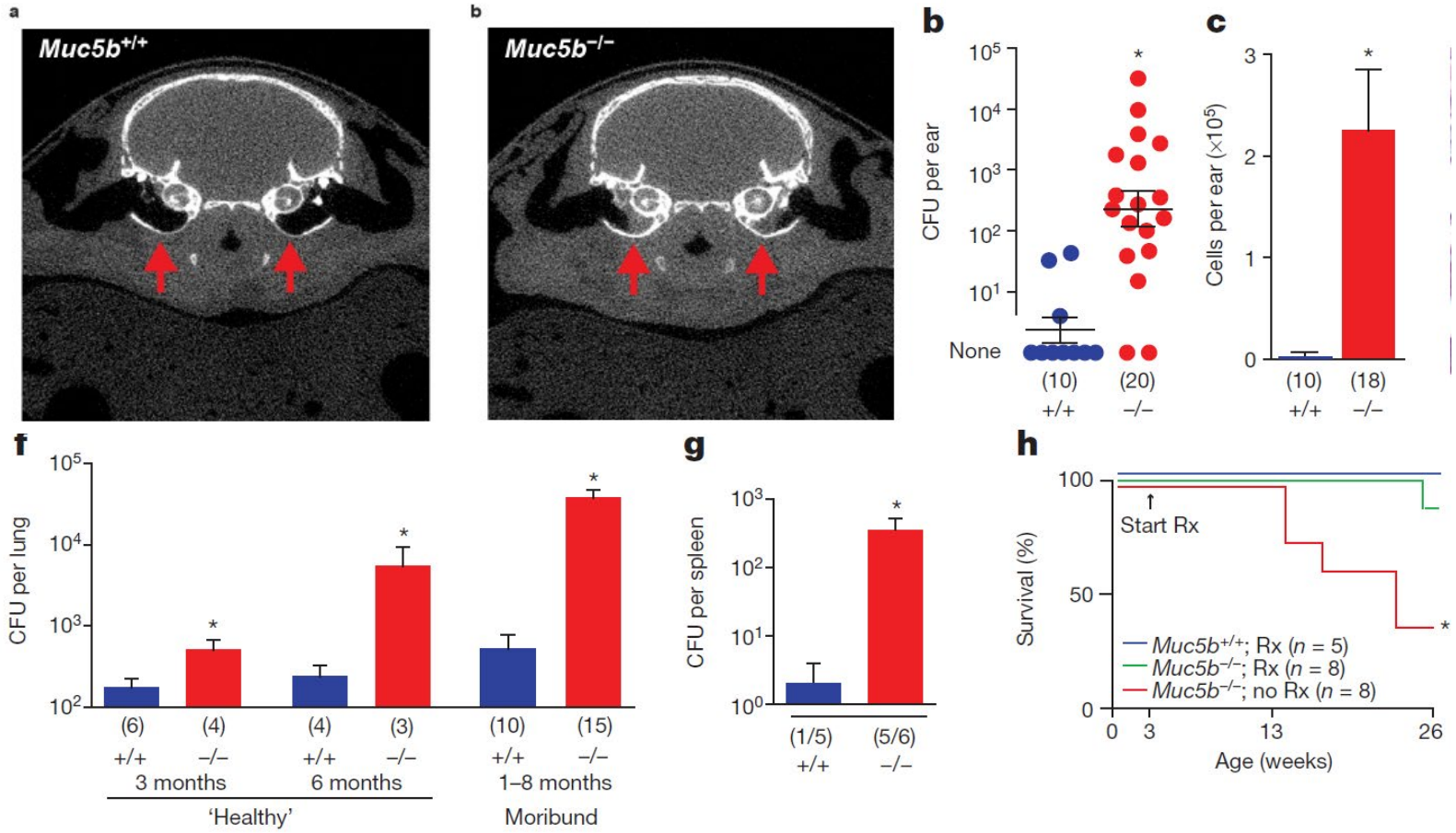
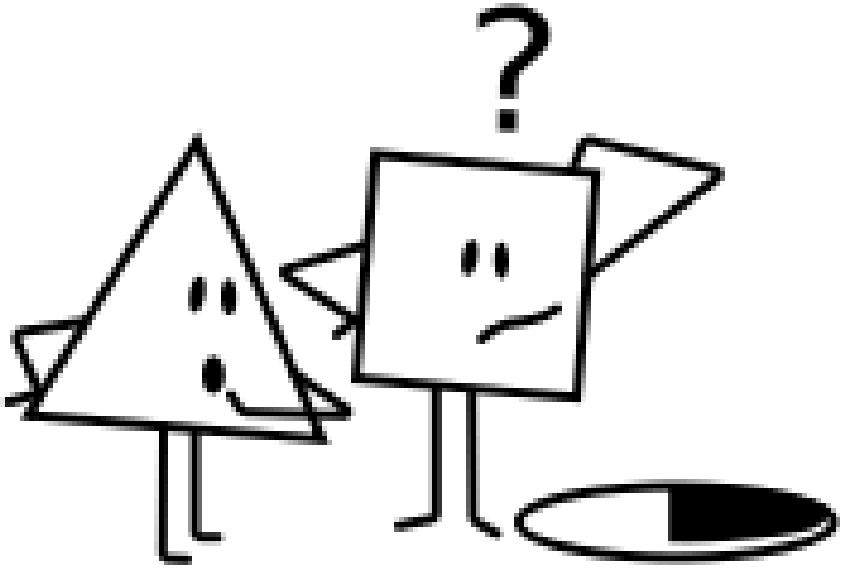


MUC5B is required for the middle ear innate immunity: not the bad guy ?

Summary – Human studies

- MUC5B is predominant mucin in COM
- Glue ear comprised by NETosis and mucin
- MUC5B glycosylation pattern contributes to neutrophil activation and OM susceptibility
- A traditional respiratory microbiome profile correlates to young age, respiratory disease, hearing loss and mucin content



How is Otitis Media managed?

ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES

2019

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Despite these gains, CDC's 2019 AR Threats Report shows additional actions are needed to protect people.

2.8M+ antibiotic-resistant infections each year

35k+ deaths from antibiotic resistance each year

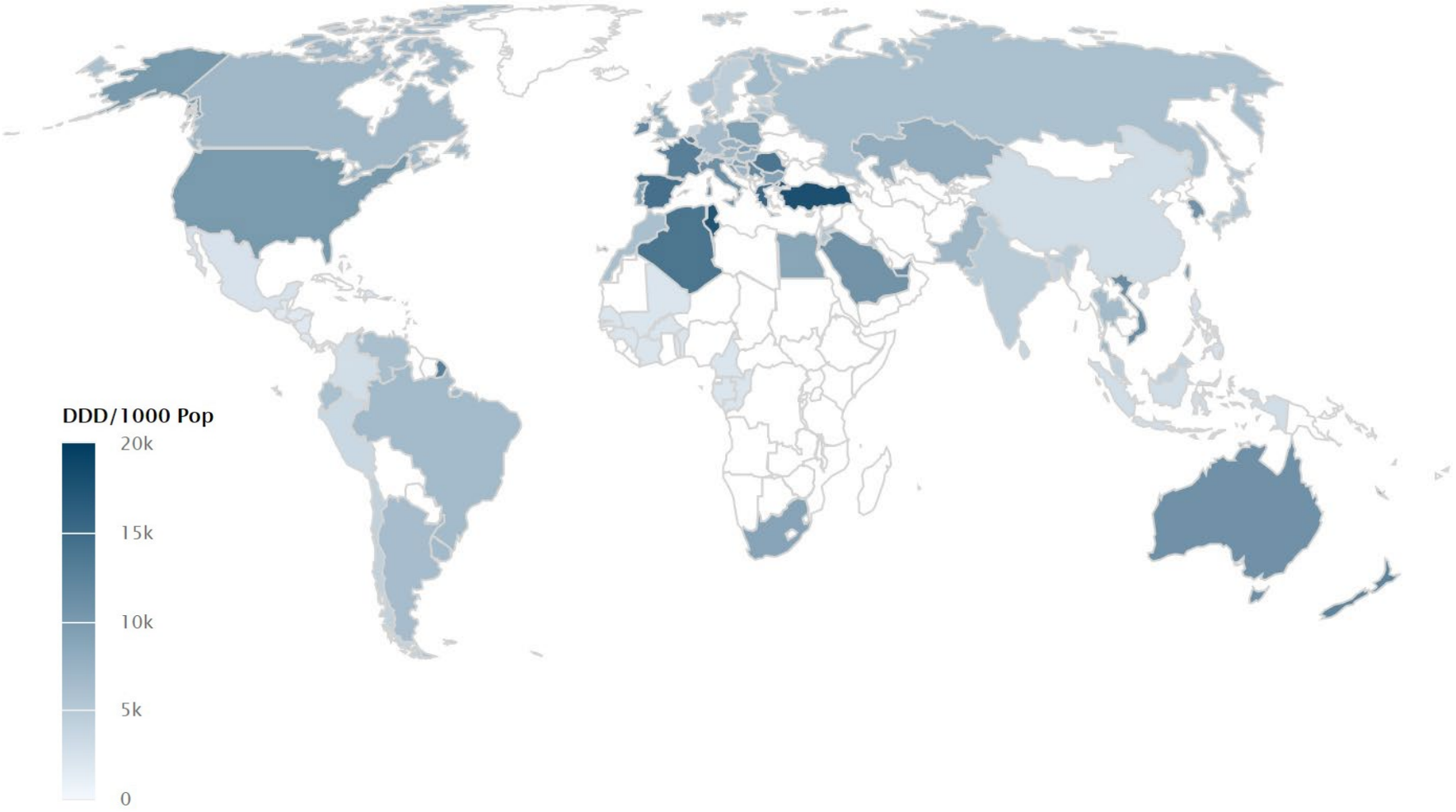
Plus: 223,900 cases and 12,800 deaths from *Clostridioides difficile*

AND INCREASES IN INFECTIONS CAUSED BY:

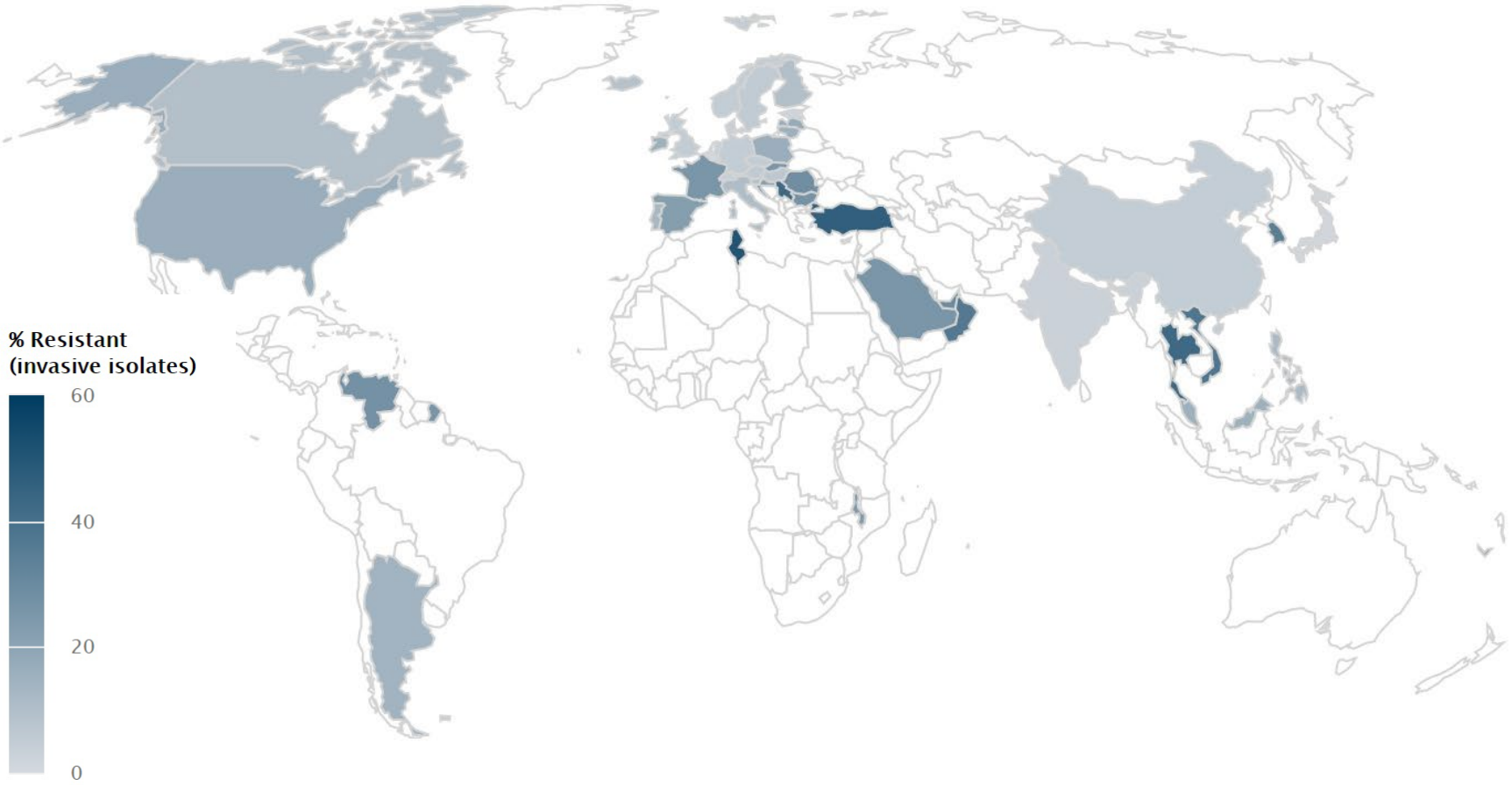
- ↑ **315%** Erythromycin-resistant invasive group A strep
- ↑ **124%** Drug-resistant *Neisseria gonorrhoeae*
- ↑ **50%** ESBL-producing Enterobacteriaceae

Use of All Antibiotics in 2015

Source: IQVIA



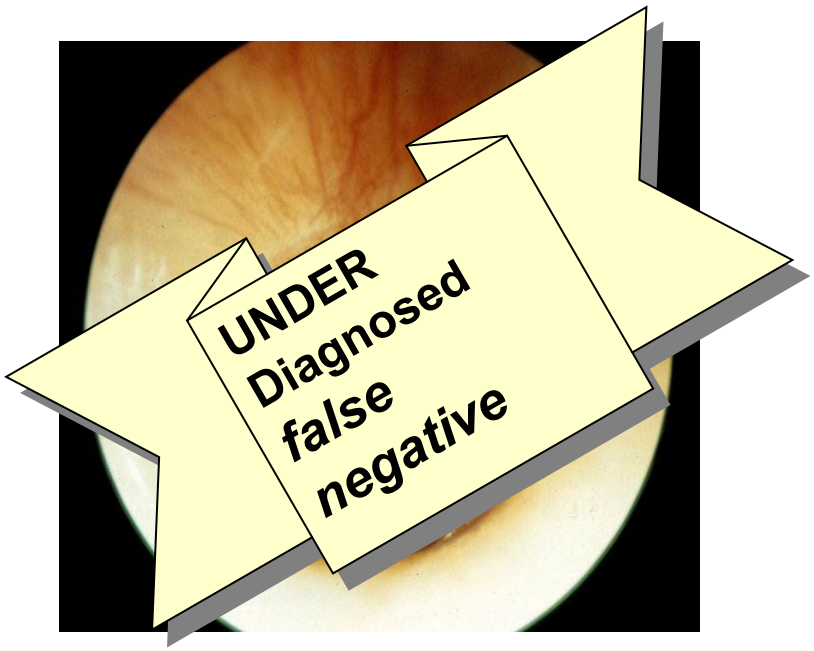
Resistance of *Streptococcus pneumoniae* to Penicillins



Acute Otitis Media

Rapid onset of signs and symptoms of inflammation in the middle ear

Otitis Media with Effusion



Middle ear effusion without signs or symptoms of acute infection

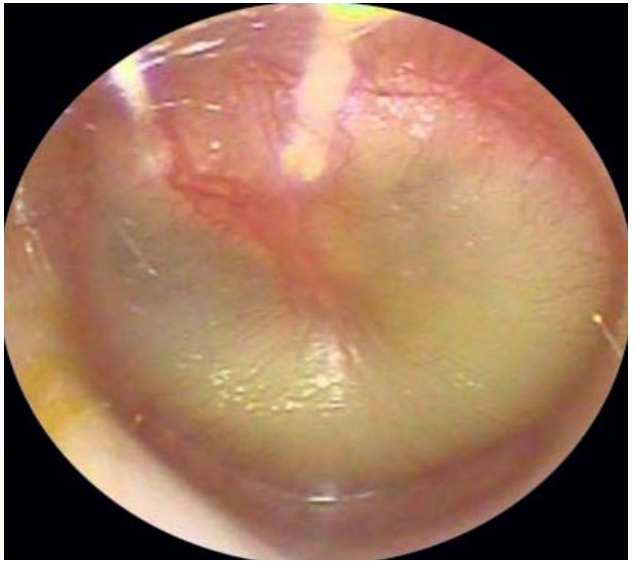
"A specialist is someone who learns more and more about less and less until he/she knows everything about nothing….

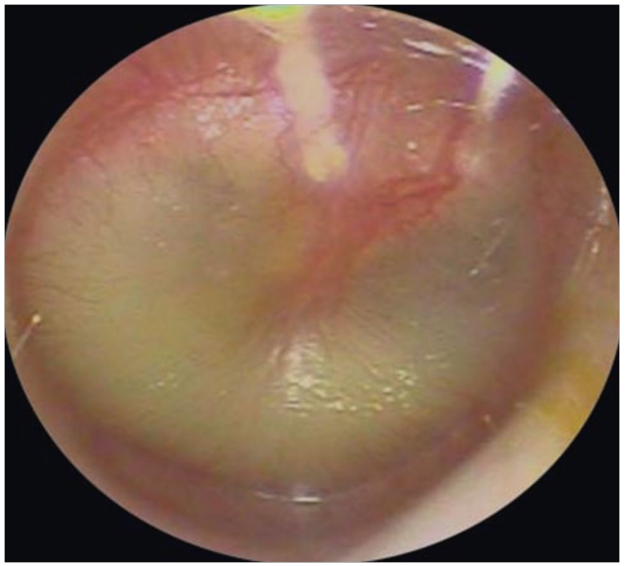
A generalist is someone who learns less and less about more and more until he/she knows nothing about everything."


HELLO
I AM...
AN EXPERT

Case 1

- 18 mo old, otherwise healthy
- 2 days of 38°C, fussy
- Pulling on ears
- Crying during the night time
- First episode
- Flat tymps





Case 1

- **Antibiotics are indicated for this child**
  - **TRUE**
  - **FALSE**

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

The Diagnosis and Management of Acute Otitis Media

Allan S. Lieberthal, Aaron E. Carroll, Tasnee Chonmaitree, Theodore G. Ganiats, Alejandro Hoberman, Mary Anne Jackson, Mark D. Joffe, Donald T. Miller, Richard M. Rosenfeld, Xavier D. Sevilla, Richard H. Schwartz, Pauline A. Thomas and David E. Tunkel

Pediatrics 2013;131;e964; originally published online February 25, 2013;
DOI: 10.1542/peds.2012-3488

The clinician should prescribe antibiotic therapy for bilateral AOM in children younger than 24 months without severe signs or symptoms (ie, mild otalgia for less than 48 hours, temperature less than 39°C [102.2°F]). (Evidence Quality: Grade B, Rec. Strength: Recommendation)

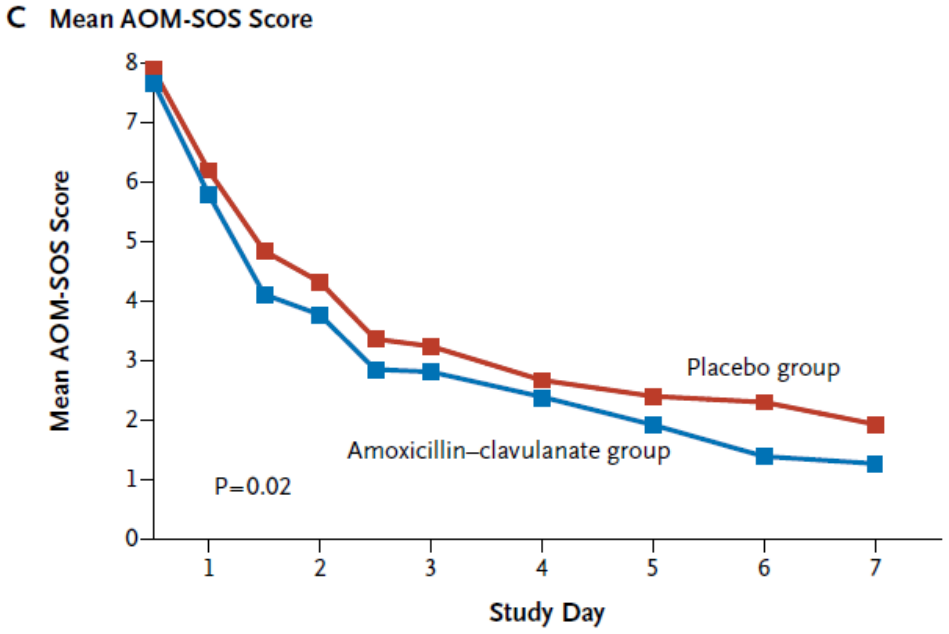
TABLE 4 Recommendations for Initial Management for Uncomplicated AOM[a]

Age	Otorrhea With AOM[a]	Unilateral or Bilateral AOM[a] With Severe Symptoms[b]	Bilateral AOM[a] Without Otorrhea	Unilateral AOM[a] Without Otorrhea
6 mo to 2 y	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy or additional observation
≥2 y	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy or additional observation	Antibiotic therapy or additional observation[c]

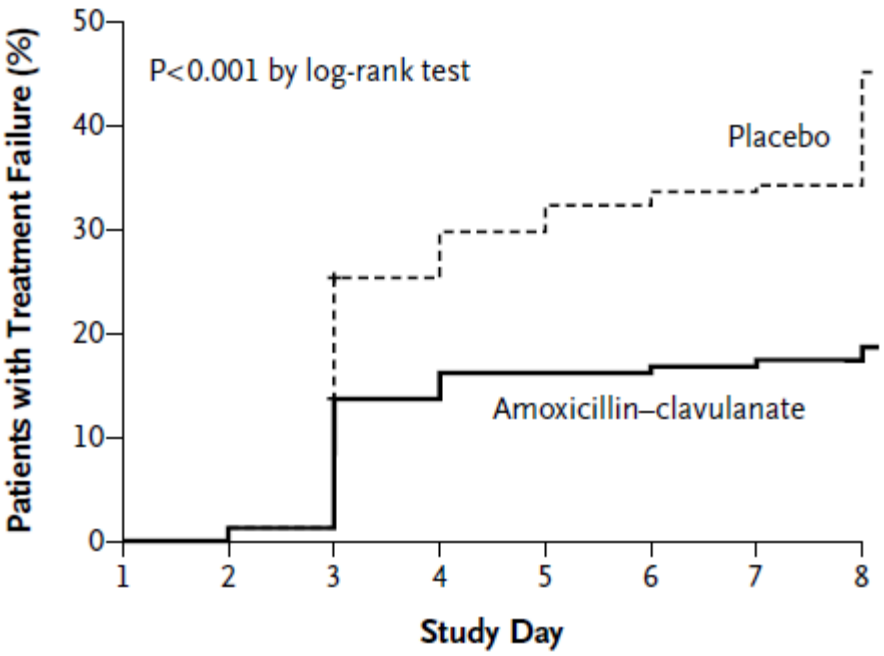
"Although it's nothing serious, let's keep an eye on it to make sure it doesn't turn into a major lawsuit."

NEJM 2011 Randomized Trials

Hoberman A, et al. *NEJM.* 2011;364



Tahtinen P, et al. *NEJM.* 2011;364



Persistence of Clinical Infection Signs Hoberman A, et al.

- **Day 10-12**
  - **Amoxicillin–clavulanate – 16%**
  - **Placebo– 51%**

  P<0.001
- ***"In 6-23 month old pts amoxicillin–clavulanate for 10 days affords a measurable short-term benefit, irrespective of the apparent severity of the illness"***

Adapted from:
Hoberman A, et al. *N Engl J Med* 2011;364:105-15.

Duration of Treatment
Hoberman A, et al. NEJM 2018

Table 3. Symptomatic Response in Index Episode of Acute Otitis Media as Measured by AOM-SOS Score.*

Measure of Symptomatic Response	10-Day Group (N=242)	5-Day Group (N=238)	All Children (N=480)	P Value
AOM-SOS score over period from day 6 to 14†				
All children				
No. of children	232	228	460	
Mean score	1.34 ±1.76	1.61±1.96	1.47±1.86	0.07‡
Children with clinical success§				
No. of children	193	145	338	
Mean score	1.32 ±1.81	1.34±1.69	1.33±1.76	0.02¶
Children with clinical failure				
No. of children	33	73	106	
Mean score	1.63±1.53	1.99±2.20	1.88±2.02	
AOM-SOS score at the day-12-to-14 assessment				
All children				
No. of children	233	227	460	
Mean score	1.20±2.06	1.89±2.73	1.54±2.44	0.001‡
Children with clinical success§				
No. of children	199	151	350	
Mean score	1.04±2.02	1.27±2.02	1.14±2.02	<0.001¶
Children with clinical failure				
No. of children	34	76	110	
Mean score	2.15±2.06	3.13±3.45	2.83±3.11	
Decrease of >50% in AOM-SOS score from baseline to the day-12-to-14 assessment — no./total no. (%)‖				
All children	211/233 (91)	181/227 (80)	392/460 (85)	0.003‡
Children with clinical success§	182/199 (91)	133/151 (88)	315/350 (90)	<0.001¶
Children with clinical failure	29/34 (85)	48/76 (63)	77/110 (70)	

First line Abx for AOM

- **Amoxicillin 40 mg/kg BID**
- **Amoxicillin/clavulonic acid 40 mg/kg BID**
- **Amoxicillin 90 mg/kg BID**
- **Amoxicillin/clavulonic acid 90 mg/kg BID**

Initial Immediate or Delayed Antibiotic Treatment	
Recommended First-line Treatment	Alternative Treatment (if Penicillin Allergy)
Amoxicillin (80–90 mg/ kg per day in 2 divided doses)	Cefdinir (14 mg/kg per day in 1 or 2 doses)
or	Cefuroxime (30 mg/kg per day in 2 divided doses)
Amoxicillin-clavulanate[a] (90 mg/kg per day of amoxicillin, with 6.4 mg/kg per day of clavulanate [amoxicillin to clavulanate ratio, 14:1] in 2 divided doses)	Cefpodoxime (10 mg/kg per day in 2 divided doses)
	Ceftriaxone (50 mg IM or IV per day for 1 or 3 d)

Alternative Treatment
Ceftriaxone, 3 d
Clindamycin (30–40 mg/kg per day in 3 divided doses), with or without third-generation cephalosporin
Failure of second antibiotic
Clindamycin (30–40 mg/kg per day in 3 divided doses) plus third-generation cephalosporin
Tympanocentesis[b]
Consult specialist[b]

Schilder A, et al. OtoHNS, 2017

Otolaryngology–Head and Neck Surgery 156(4S)

AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

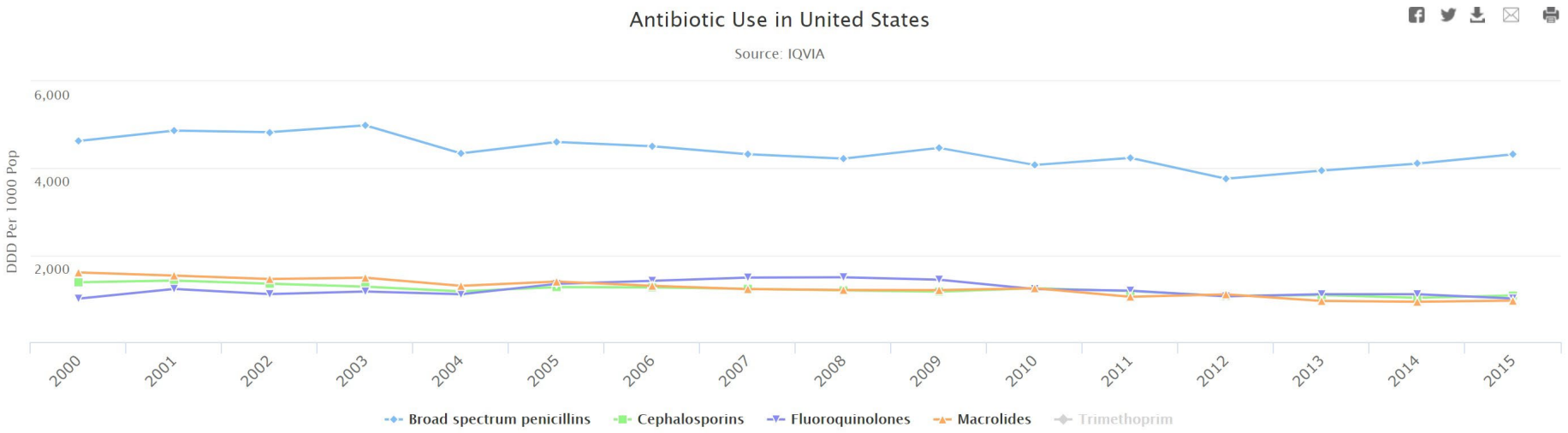
Table 6. Selected National Guidelines for AOM.

Country	Age	Diagnosis/Instruments	Management	First-Line Antibiotics[a]
United States, 2013[66]	6 mo to 12 y	Stringent criteria Key factors: TM bulging or new-onset otorrhea, use of pneumatic otoscopy and tympanometry, treat pain	ABx: children ≥6 mo with severe AOM, nonsevere bilateral AOM in children 6 to 23 mo WW: nonsevere unilateral AOM in children <23 mo, nonsevere AOM in children >24 mo	High-dose amox; high-dose amox-clav in children receiving amoxicillin in the previous 30 d or with otitis-conjunctivitis
Japan, 2013[68]	0-15 y	Accurate diagnosis Otomicroscopy or otoscopic observation, pneumatic otoscopy acceptable	Mild AOM: 3 d WW, otherwise ABx Moderate AOM: immediate ABx Severe AOM: myringotomy and ABx	Low dose amox → high dose amox → amox-clav or ceftidoren pivoxil
South Korea[69] 2012	0-15 y	Definitive (Sx and TM findings) vs suspicious (Sx without objective findings) diagnosis	WW: possible, FU visit after 2 to 3 d ABx: severe AOM, <6 mo, 6 to 24 mo with definite AOM, when FU is impossible, comorbidities	High-dose amox Severe AOM: high-dose amox-clav
The Netherlands, 2014[70]	0-18 y	Patient's history, Sx, and otoscopy findings; treat pain	Immediate ABx: infants <6 mo, severe AOM Consider ABx: children <2 years and bilateral AOM, otorrhea, persisting Sx	Low-dose amox Amox-clav if no improvement after 48 h

Antibiotic Use

Map | Trend | Chart

? Help



Case 2

- 18 mo old, otherwise healthy
- Afebrile
- Pulling on ears
- Crying during the night time for 2 months
- First episode
- Flat tymps, 30 dB CHL

Tympanostomy Tube CPG

AAO-HNS

STATEMENT 1. OME OF SHORT DURATION: Clinicians should <u>not</u> perform tympanostomy tube insertion in children with a single episode of otitis media with effusion (OME) of less than 3 months duration, from the date of onset (if known) or from the date of diagnosis (if onset is unknown).

<u>Recommendation against</u> based on systematic review of observational studies of natural history and an absence of any RCTs on efficacy of tubes for children with OME less than 2-3 months duration with a preponderance of benefit over harm.

- <u>Benefits</u>: Avoid unnecessary surgery in children for whom benefits are uncertain and have not been studied, avoid surgery in children with OME and good spontaneous resolution
- <u>Value judgments</u>: Exclusion of children with OME <2m duration from all RCTs of tube efficacy was compelling evidence to question the value of surgery given the know risks of the procedure

Otolaryngol Head Neck Surg 2013; 149(Suppl):S1-35

Case 3

- 18 mo old, otherwise healthy
- Recurrent AOM, 5 times in 6 months
- Pulling on ears
- Currently afebrile
- Crying during the night time
- Normal Tymps, Normal Audio

Case 3

- **Prophylactic antibiotics- they are indicated**
  - **TRUE**
  - **FALSE**
- **PE tubes – they are indicated**
  - **TRUE**
  - **FALSE**

Clinical Practice Guideline: Tympanostomy Tubes in Children (Update)

Richard M. Rosenfeld, MD, MPH, MBA[1], David E. Tunkel, MD[2], Seth R. Schwartz, MD, MPH[3], Samantha Anne, MD, MS[4], Charles E. Bishop, AuD, PhD, CCC-A[5], Daniel C. Chelius, MD[6], Jesse Hackell, MD[7,8], Lisa L. Hunter, PhD[9], Kristina L. Keppel, DNP, APNP, CPNP[10], Ana H. Kim, MD[11], Tae W. Kim, MD, MEHP[12], Jack M. Levine, MD[13], Matthew T. Maksimoski, MD[14], Denee J. Moore, MD[15], Diego A. Preciado, MD, PhD[16], Nikhila P. Raol, MD, MPH[17], William K. Vaughan[18], Elizabeth A. Walker, PhD, CCC-A/SLP[19], and Taskin M. Monjur[20]

Otolaryngology–
Head and Neck Surgery
2022, Vol. 166(1S) S1–S55

DOI: 10.1177/01945998211065662
http://otojournal.org
SAGE

Clinicians should *NOT* prescribe prophylactic antibiotics to reduce the frequency of episodes of AOM in children with recurrent AOM. (Evidence Quality: Grade B, Rec. Strength: Recommendation)

STATEMENT 6. RECURRENT AOM WITHOUT MEE: **Clinicians should *not* perform tympanostomy tube insertion in children with recurrent acute otitis media who *do not* have MEE in either ear at the time of assessment for tube candidacy.** *Recommendation against based on systematic reviews and randomized controlled trials with a preponderance of benefit over harm.*

Tympanostomy Tubes or Medical Management for Recurrent Acute Otitis Media

Hoberman A et al. DOI: 10.1056/NEJMoa2027278

CLINICAL PROBLEM

In the United States, acute otitis media is the leading indication for pediatric antimicrobial treatment, and tympanostomy-tube placement for recurrent acute otitis media is the most frequently performed operation in children after the neonatal period. However, studies of this treatment have yielded mixed results, and official recommendations for tube placement differ.

CLINICAL TRIAL

Design: A randomized, unblinded trial comparing tympanostomy-tube placement with medical management in children with recurrent acute otitis media.

Intervention: 250 children 6 to 35 months of age who had recurrent acute otitis media (≥3 episodes in 6 months, or ≥4 episodes in 12 months with ≥1 episode within the preceding 6 months) were assigned to tympanostomy-tube placement or episodic antimicrobial treatment (amoxicillin [90 mg/kg of body weight/day] with clavulanate [6.4 mg/kg/day] for 10 days; for inadequate response, ceftriaxone at 75 mg/kg intramuscularly, repeated in 48 hours). The primary outcome was the incidence of episodes during 2-year follow-up.

RESULTS

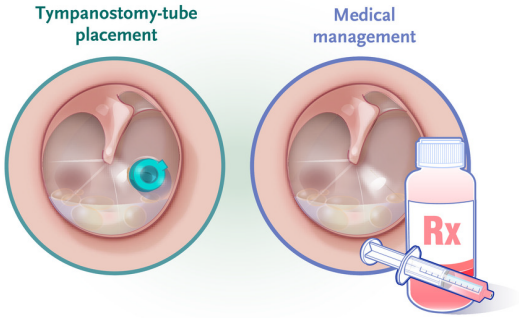
Efficacy: The incidence of acute otitis media per child-year did not differ significantly between the groups.

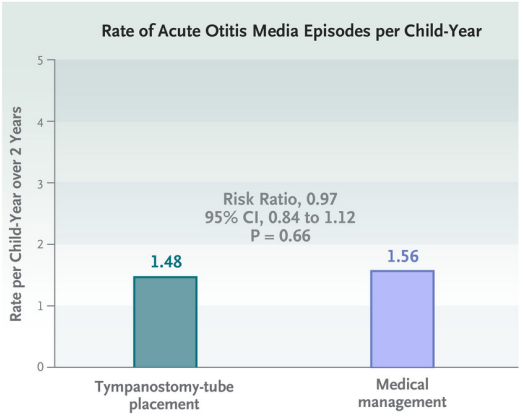
Safety: Serious adverse events did not differ substantially between groups (3 events in the tympanostomy-tube group and 8 in the medical-management group). Children receiving medical management did not have evidence of increased antimicrobial resistance.

LIMITATIONS AND REMAINING QUESTIONS

Because 54 of 121 children assigned to medical management underwent tympanostomy-tube placement during the follow-up period, interpretation of the findings is more difficult; tympanostomy tubes already in place may affect the symptoms of subsequent infections.

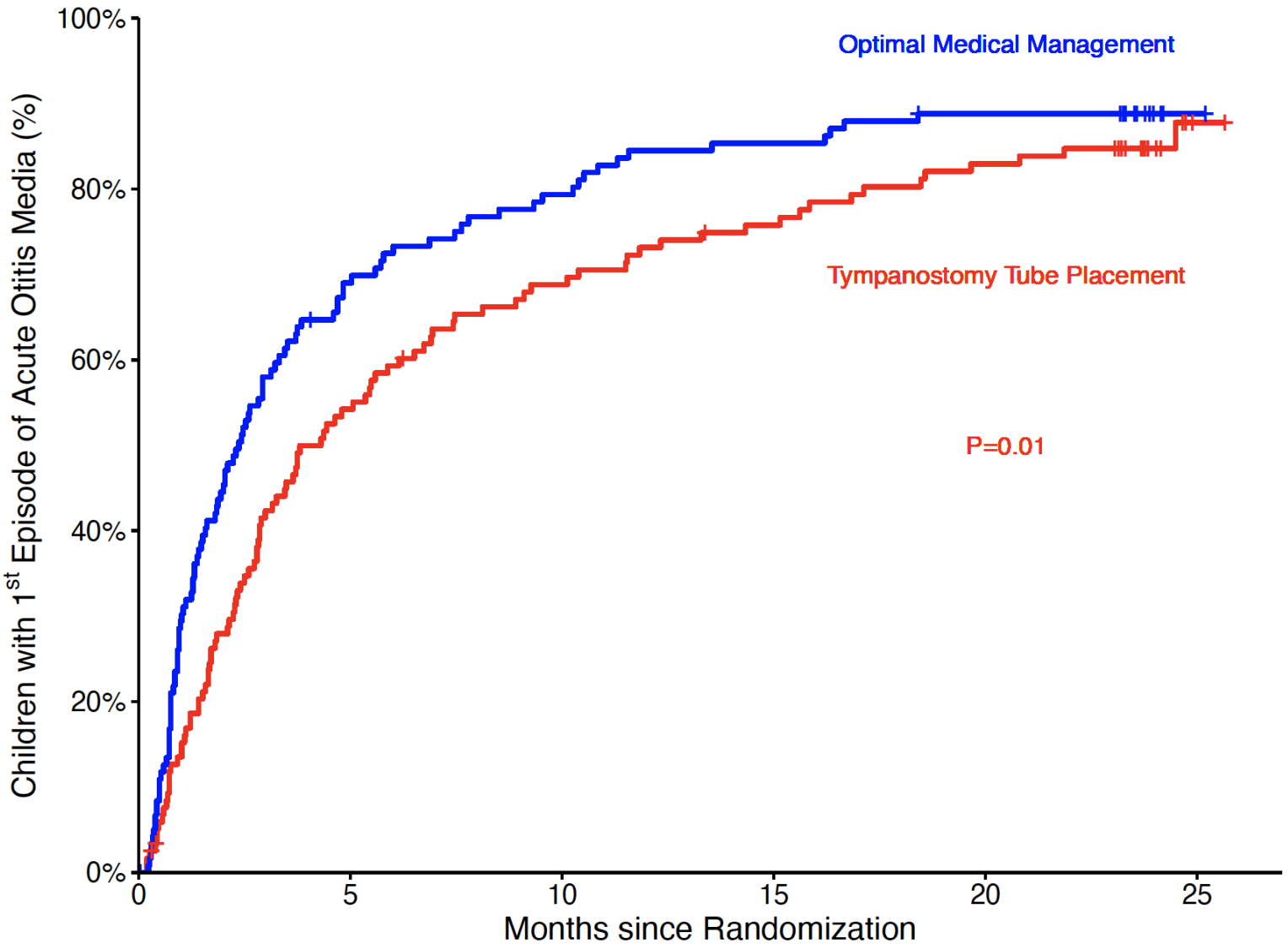
Links: Full article | NEJM Quick Take | Editorial





CONCLUSIONS

In children with recurrent acute otitis media, placement of tympanostomy tubes was not superior to medical management in reducing the rate of acute otitis media episodes during the subsequent 2 years.


100%
80%
60%
40%
20%
0%
Children with 1st Episode of Acute Otitis Media (%)
0
5
10
15
20
25
Months since Randomization
Optimal Medical Management
Tympanostomy Tube Placement
P=0.01

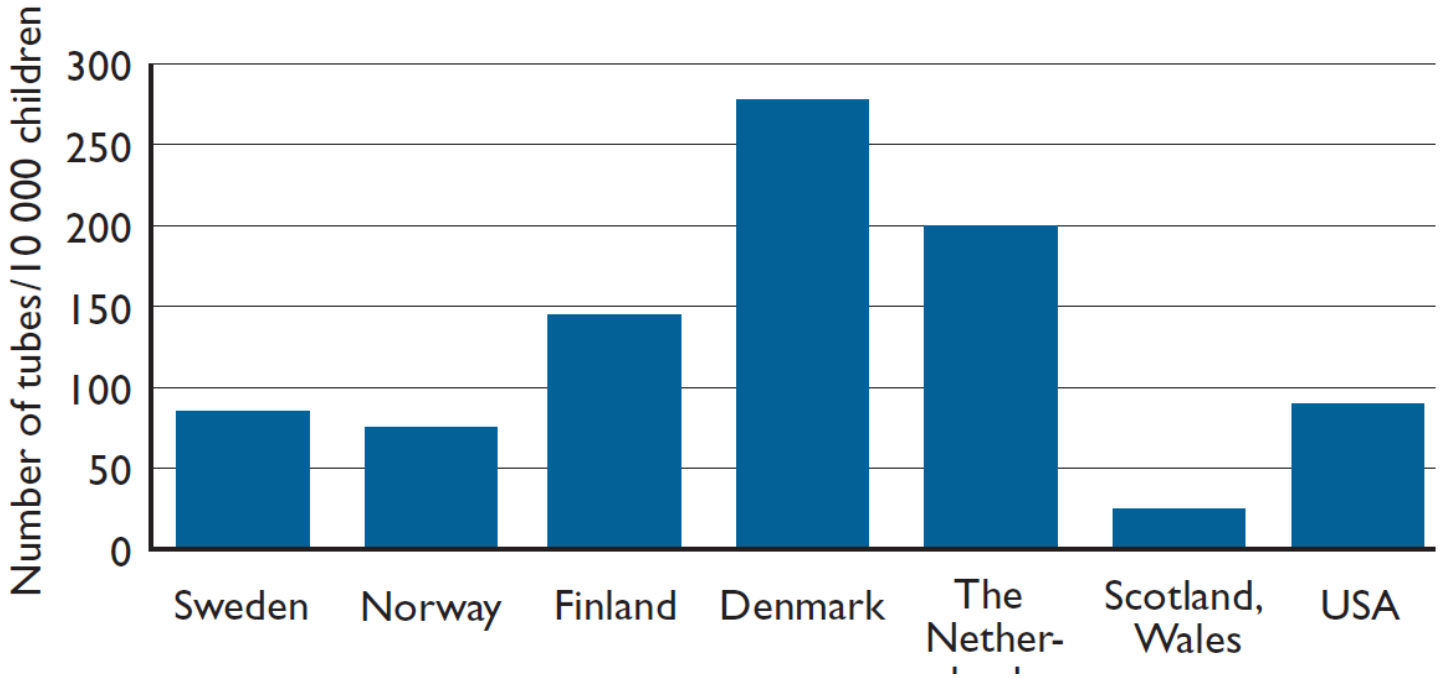
Secondary Outcomes

- **50% of medical management group crossed over to TTP**
- ***Tubes associated with less severe OM symptoms scores***
- ***Less usage of oral antibiotics in TTP group***
- ***Less days with diarrhea in TTP group***
- ***More days with otorrhea in TTP group***

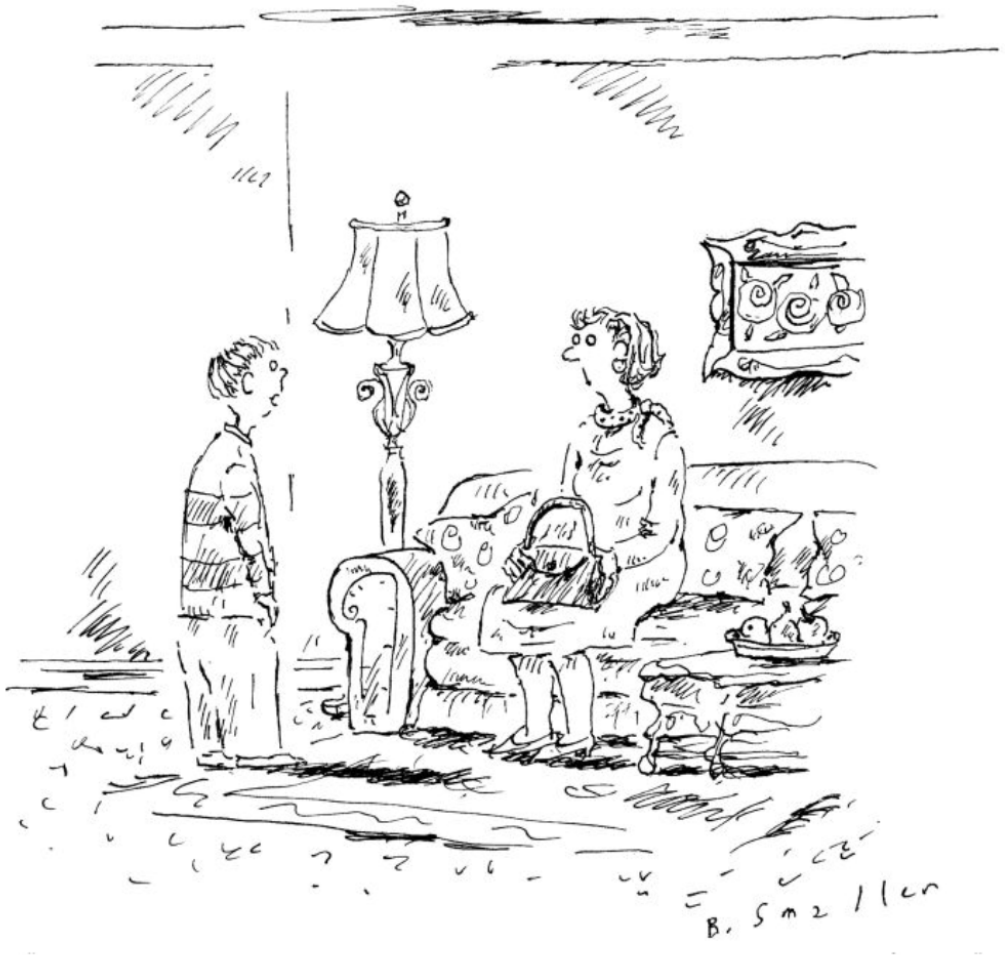
"Although it's nothing serious, let's keep an eye on it to make sure it doesn't turn into a major lawsuit."

Tympanostomy tube insertion for otitis media in children

SBU Report, 2008



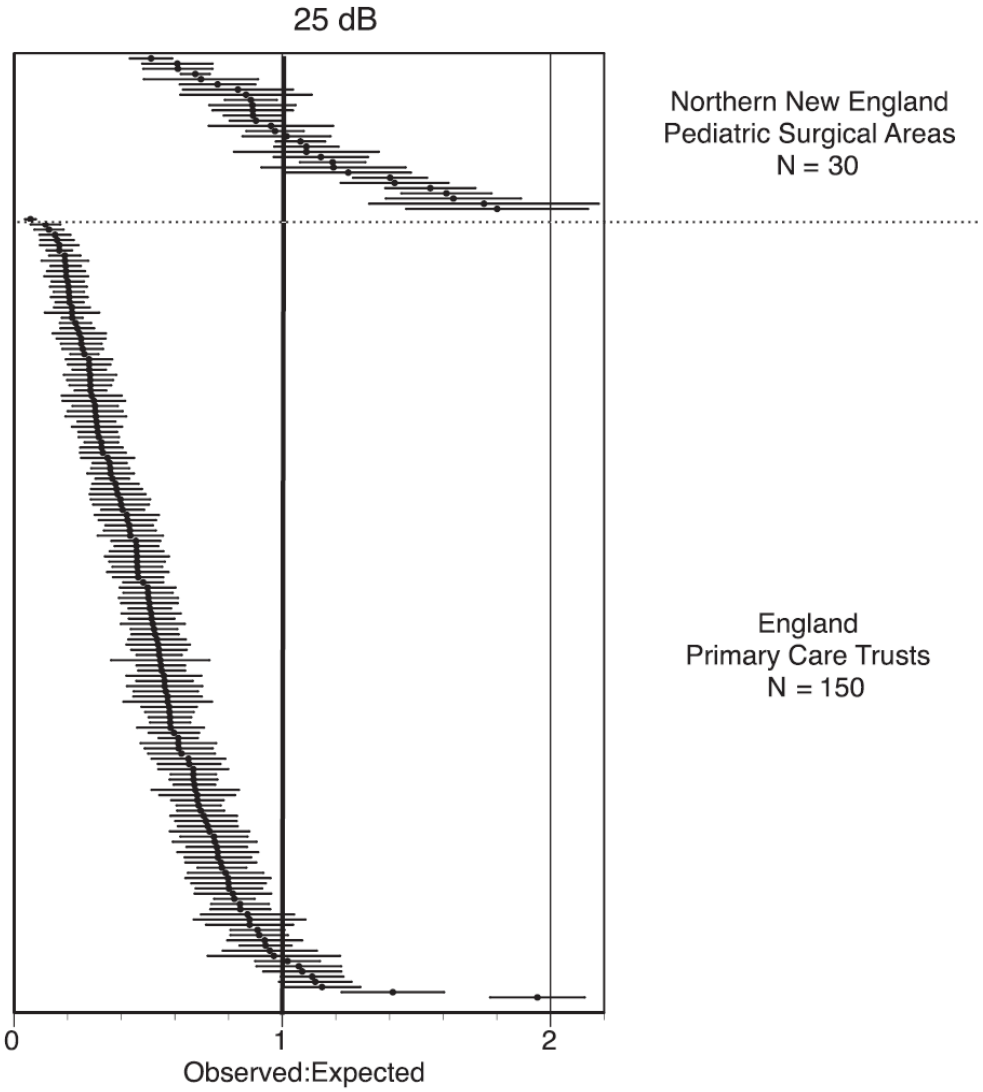
Type: Systematic Review • ISBN: 978-91-85413-22-5 • ISSN: 1400-1403
Report no: 189 • Publishing year: 2008



"When I grow up, I want to go into medicine and help people who can pay out of pocket."

Parker, DM et al. Variation in Utilization and Need for Tympanostomy Tubes across England and New England

(J Pediatr 2016;179:178-84).



Variation in Use of Tympanostomy Tubes: Impact of Privately Owned Ambulatory Surgery Centers

(J Pediatr 2019;204:183-90).

Jennifer N. Cooper, PhD[1,2], and Charles A. Elmaraghy, MD[3,4]

Table II. Predictors of the zip code–level rate of outpatient pediatric tympanostomy tube placement in Florida

Characteristics	Percent difference (SE)	*P*
Urban/rural classification		
Large central metro	ref	
Large fringe metro	–9.9 (3.7)	.007
Medium and small metro	–12.0 (4.9)	.01
Micropolitan and noncore	–3.6 (5.9)	.55
Percentage of residents who are non-Hispanic white		
Lowest tertile	ref	
Middle tertile	17.9 (4.5)	<.001
Highest tertile	–4.2 (5.8)	.47
Index of SES		
Lowest tertile	ref	
Middle tertile	15.0 (3.5)	<.001
Highest tertile	13.6 (4.3)	.002
Percentage of procedures performed at privately owned ASCs		
Lowest tertile (<22.3%)	ref	
Middle tertile (22.3%-58.6%)	27.0 (3.7)	<.001
Highest tertile (>58.6%)	51.9 (4.8)	<.001

Adjusted estimated percent increases in the rate of tympanostomy tube placement in each group in comparison to the reference group are shown.

Future in Otitis Media

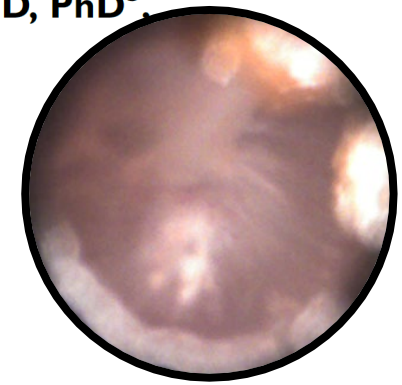
AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

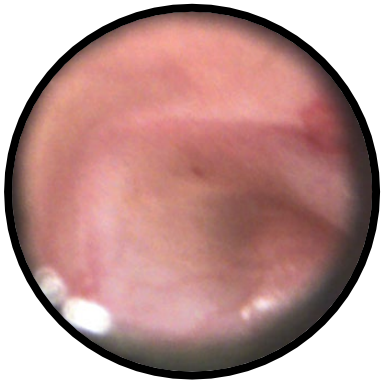
Otolaryngology–Head and Neck Surgery
1–8

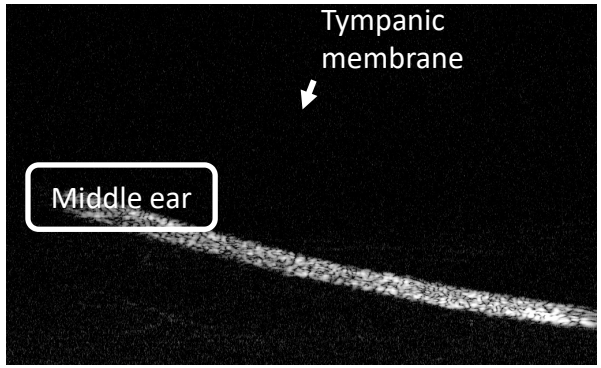
DOI: 10.1177/0194599819900762
http://otojournal.org
SAGE

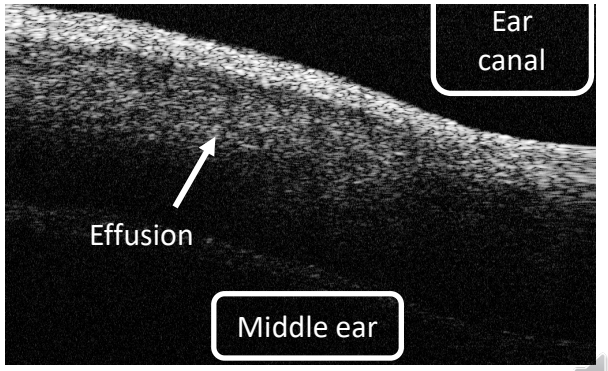
Otitis Media Middle Ear Effusion Identification and Characterization Using an Optical Coherence Tomography Otoscope

Diego Preciado, MD, PhD[1,2], Ryan M. Nolan, MEng, CCRP[3], Radhika Joshi, CCRP[1,2], Gina M. Krakovsky, APRN[1], Anqi Zhang, PhD[3], Nickolas A. Pudik[3], Nankee K. Kumar[2], Ryan L. Shelton, PhD[3], Stephen A. Boppart, MD, PhD[3], and Nancy M. Bauman, MD[1]









American Journal of Emergency Medicine 36 (2018) 1796–1801

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

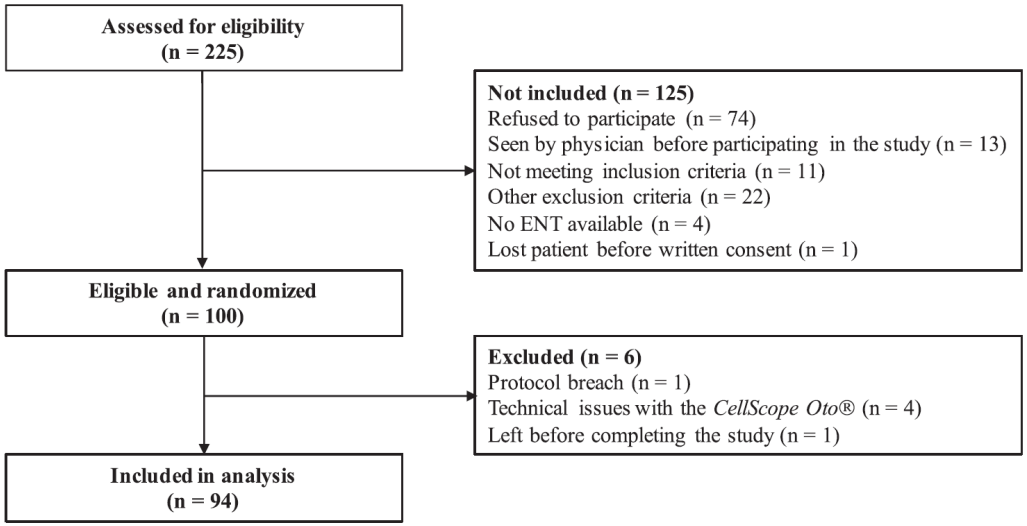
journal homepage: www.elsevier.com/locate/ajem

Original Contribution

Diagnosing acute otitis media using a smartphone otoscope; a randomized controlled trial

Sarah Mousseau, MD [a], Annie Lapointe, MD, MPH [b], Jocelyn Gravel, MD, MSc [a,*]

© CellScope Inc.



Smartphone app that chirps in your ear could diagnose ear infections

TECHNOLOGY 15 May 2019

Otology & Neurotology
39:1060–1065 © 2018, Otology & Neurotology, Inc.

Development of an Automatic Diagnostic Algorithm for Pediatric Otitis Media

*†Thi-Thao Tran, ‡§Te-Yung Fang, *||¶Van-Truong Pham, *Chen Lin, ‡§Pa-Chun Wang, and *Men-Tzung Lo

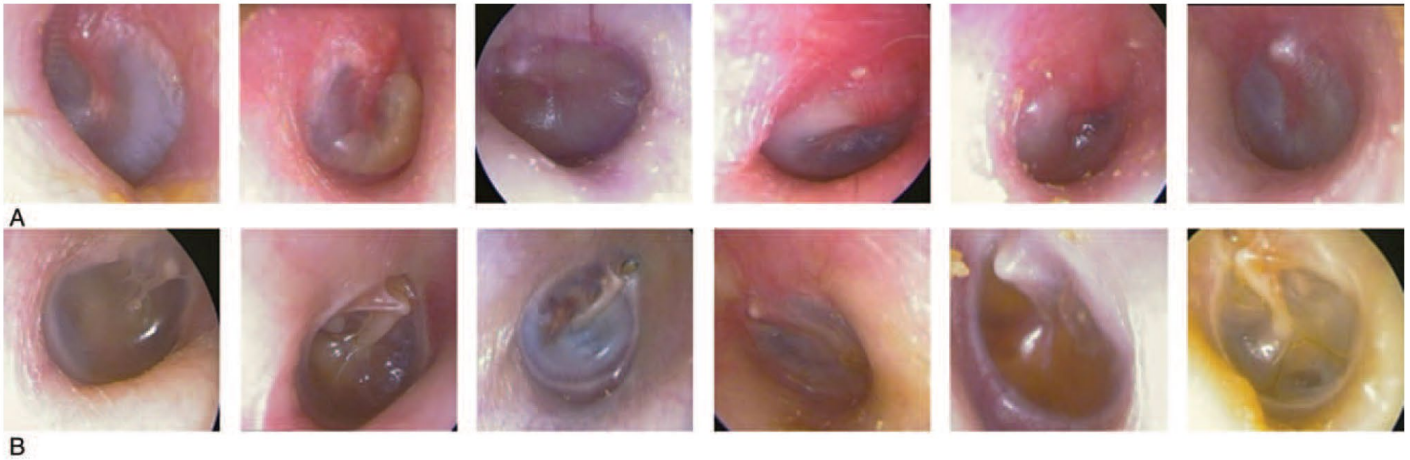


TABLE 2. *The overall results by the OM image classification approach*

	Measures		
OM Types	Sensitivity	Specificity	Accuracy
AOM	89.48%	93.33%	91.89%
OME	93.33%	89.48%	91.31%

AOM indicates acute otitis media; OME, otitis media with effusion.

Shaping Magnetic Fields to Direct Therapy to Ears and Eyes

Annu. Rev. Biomed. Eng. 2014. 16:455–81

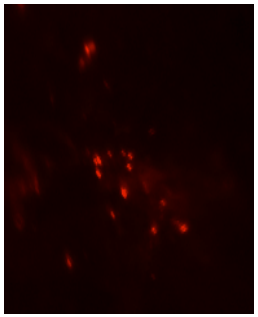
B. Shapiro,[1,2] S. Kulkarni,[1] A. Nacev,[1] A. Sarwar,[1] D. Preciado,[3] and D.A. Depireux[2]

[1]Fischell Department of Bioengineering, [2]The Institute for Systems Research (ISR), University of Maryland, College Park, Maryland 20742; email: benshap@umd.edu

[3]Otolaryngology, Sheikh Zayed Institute for Pediatric Surgical Innovation, Children's National Medical Center, Washington, DC 20010

Control
no push
no particles
in middle ear

Push: Red
particles in
middle ear
scrape



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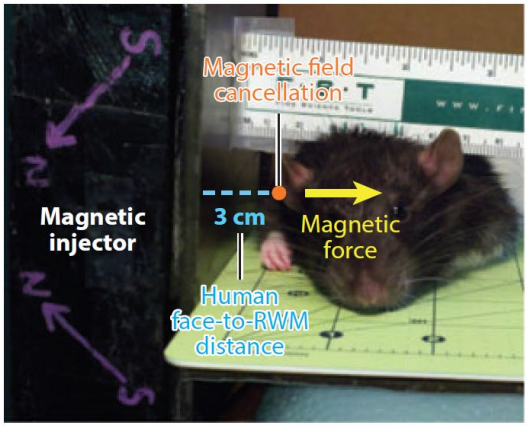

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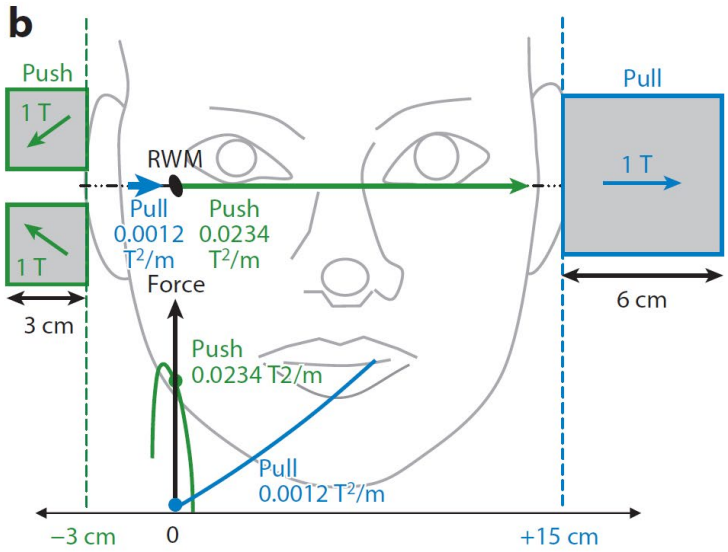
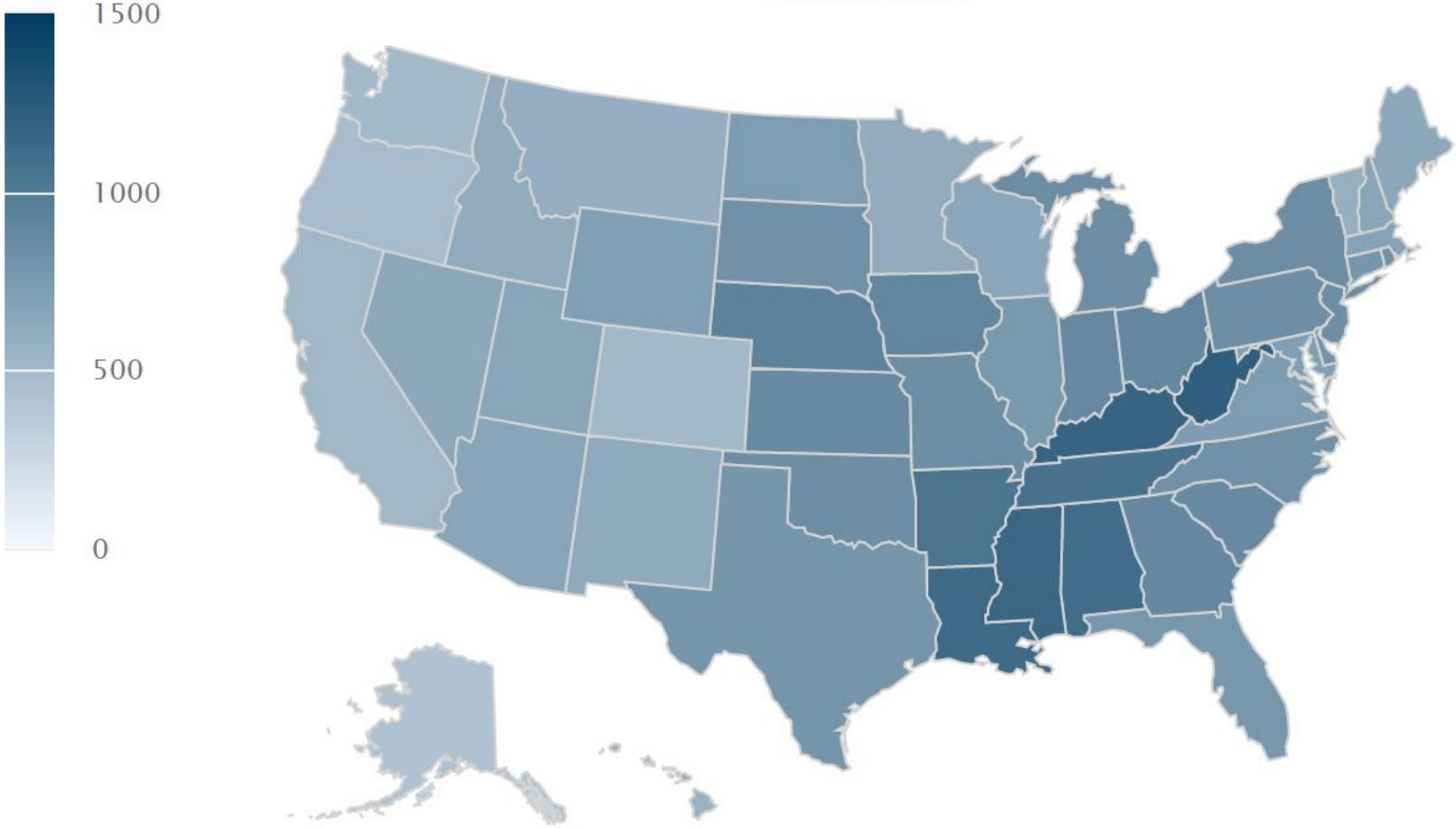
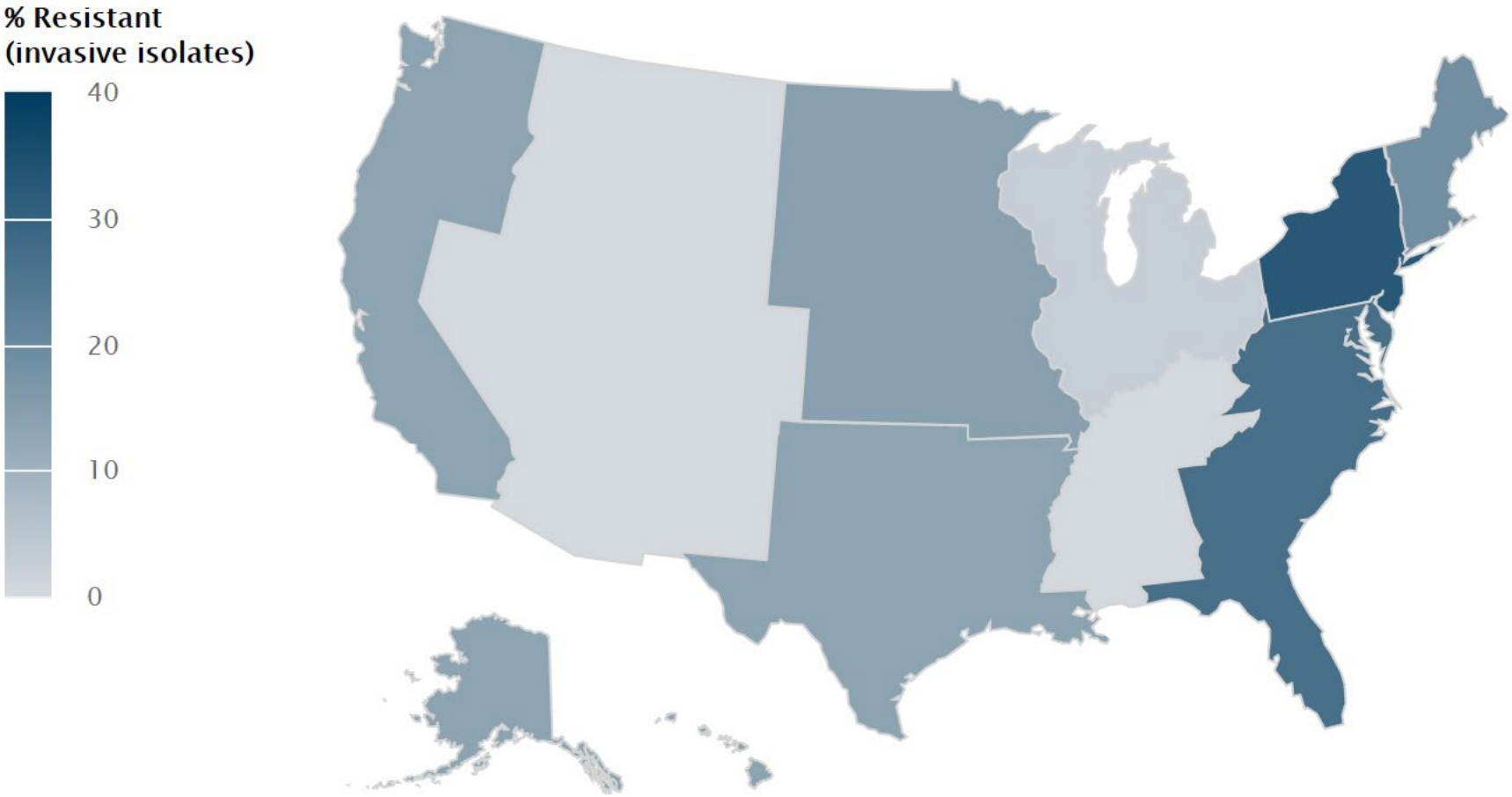


Use of All Antibiotics in 2017

Source: IQVIA



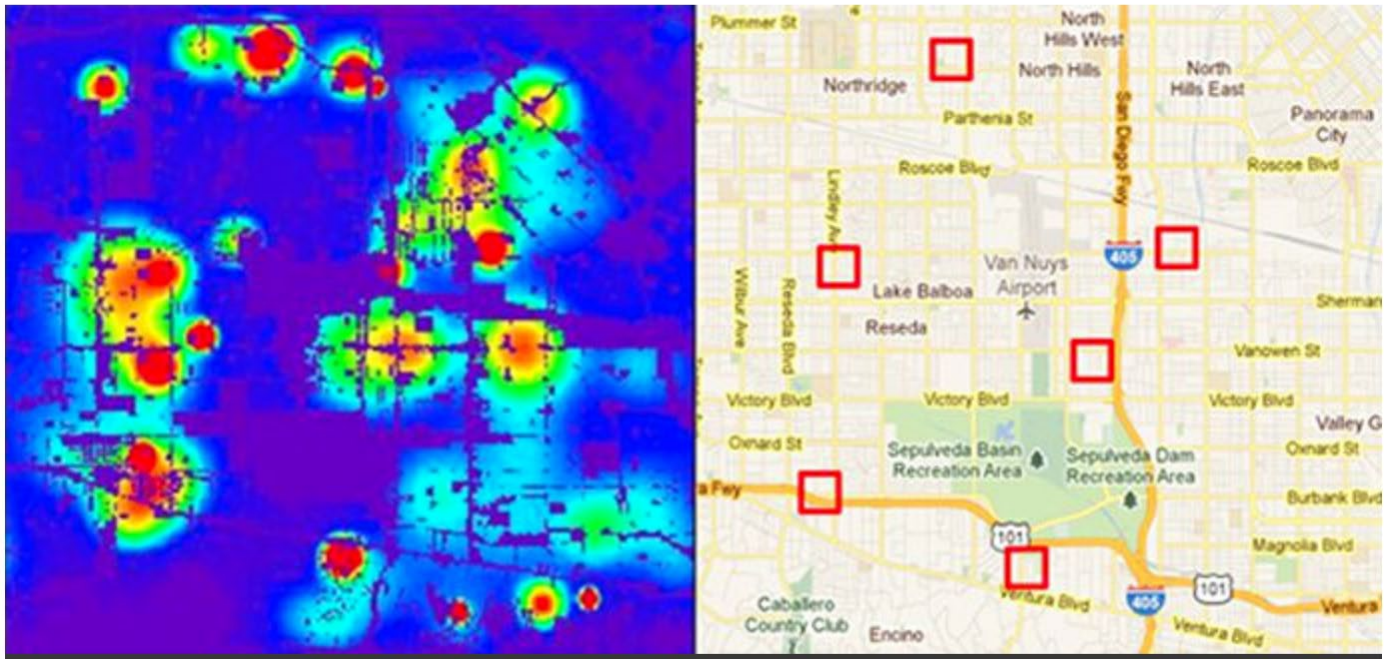
Resistance of *Streptococcus pneumoniae* to Penicillins



Smithsonian.com

Artificial Intelligence Is Now Used to Predict Crime. But Is It Biased?

The software is supposed to make policing more fair and accountable. But critics say it still has a way to go.

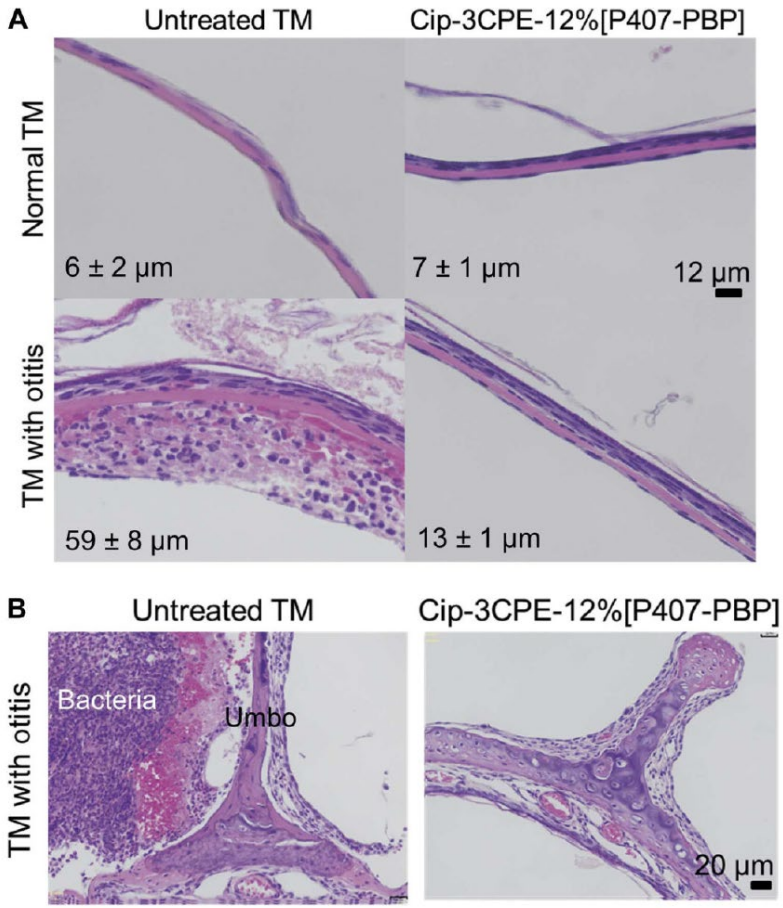


Predictive policing is built around algorithms that identify potential crime hotspots.. (PredPol)

Treatment of otitis media by transtympanic delivery of antibiotics

Rong Yang[1], **Vishakha Sabharwal**[2], **Obiajulu S. Okonkwo**[1], **Nadya Shlykova**[2], **Rong Tong**[1,*], **Lily Yun Lin**[1], **Weiping Wang**[1], **Shutao Guo**[1], **John J. Rosowski**[3], **Stephen I. Pelton**[2], and **Daniel S. Kohane**[1,†]

[1]Laboratory for Biomaterials and Drug Delivery, Department of Anesthesiology, Division of Critical Care Medicine, Boston Childrens Hospital, Harvard Medical School, Boston, MA 02115, USA



Sci Transl Med. 2016 September 14; 8(356): 356ra120. doi:10.1126/scitranslmed.aaf4363.

Conclusions

- OM is an immunological disease –
  - NTHi is dominant pathogen in 2022
  - MUC5B is predominant mucin
- We need to improve diagnostic methods
- Tubes do not reduce number of infections, but improve disease severity
- Transtympanic drug delivery will be a game changer

Acknowledgements

Collaborators:

- **Dr. Stephanie Val**
- **Dr. Yajun Chen**
- Dr Mary Rose Dr Kristy Brown
- Dr XX Gu (NIH)
- Dr Jinzhen Lin (UMN)

And others that participated:

- Katelyn Burgett (RA)
- Amarel Tomney (RA)
- Marian Poley (RA)
- Anna Kreuger (RA)
- Dr Colberg-Poley
- Dr Gustavo Nino

Students:

- Elisabeth Stanley, Ariella Cohen, Stephanie Jeong, Rachel Choi, Morgan Wright, Vanessa Duah, McKenzie Tolan, Gabriel Nahas

NIH National Institute on Deafness and Other Communication Disorders (NIDCD)

NIH National Heart, Lung, and Blood Institute

The Triological Society
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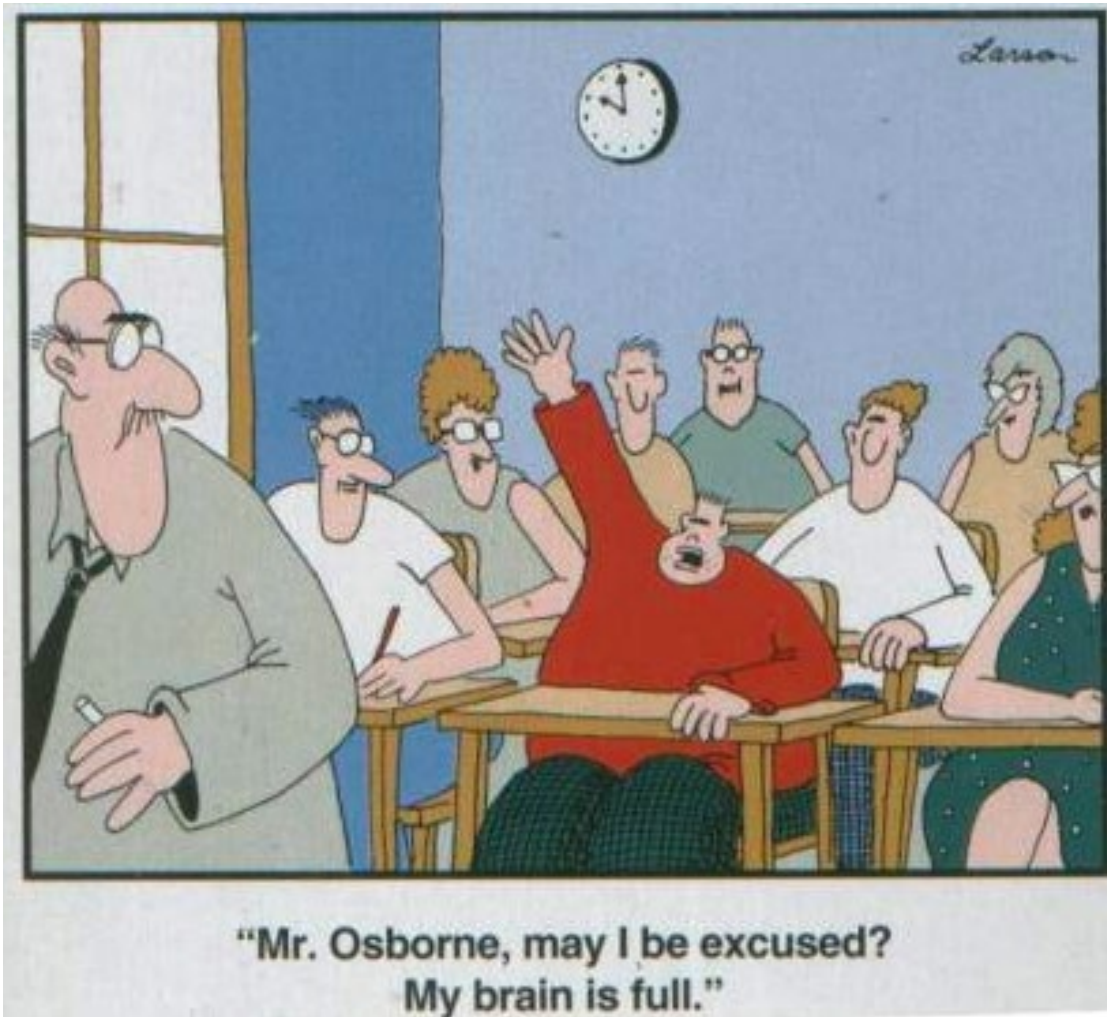
University of Maryland A. James Clark School of Engineering

Thank-you!



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