

# Antimicrobial Prophylaxis: Yes? No? or We Don't Know!

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# Learning Objectives

- Recognize historical basis for prior recommendations regarding antimicrobial prophylaxis for children who have had a urinary tract infection (UTI)
- Synthesize recent evidence regarding antimicrobial prophylaxis after UTI to challenge prior paradigm and inform new recommendations.
- Repeat above objectives for Otitis Media (OM).

# History of Antimicrobial Prophylaxis

- Most of the evidence for the effectiveness of prophylaxis comes from children with congenital or acquired immunodeficiencies
  - Oncology
  - Chronic granulomatous disease
  - Transplant, both stem cell and solid organ
  - Asplenia
- Secondary prophylaxis (meningococcal disease, pertussis, etc)

# What about antibiotic prophylaxis for common childhood infections?

- UTI
- OM

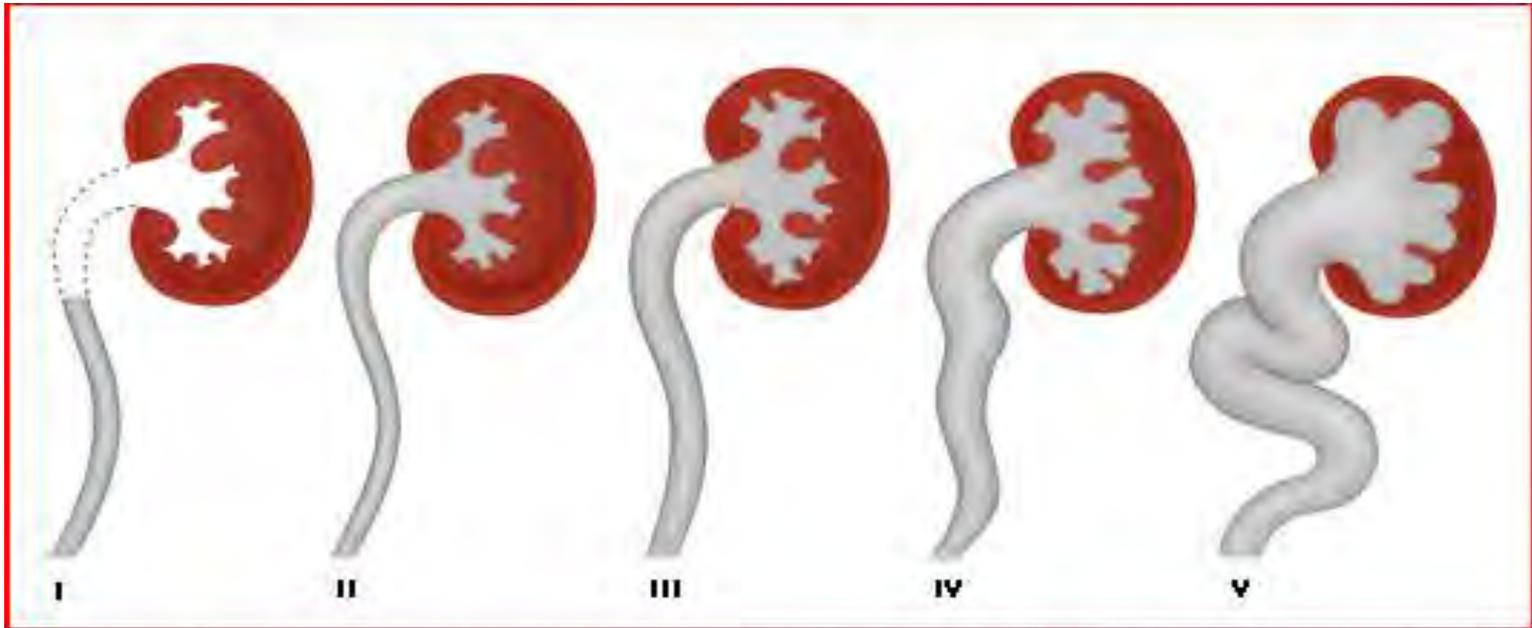
# What about antibiotic prophylaxis for common childhood infections?

- UTI
- OM

# Vesicoureteral Reflux (VUR)

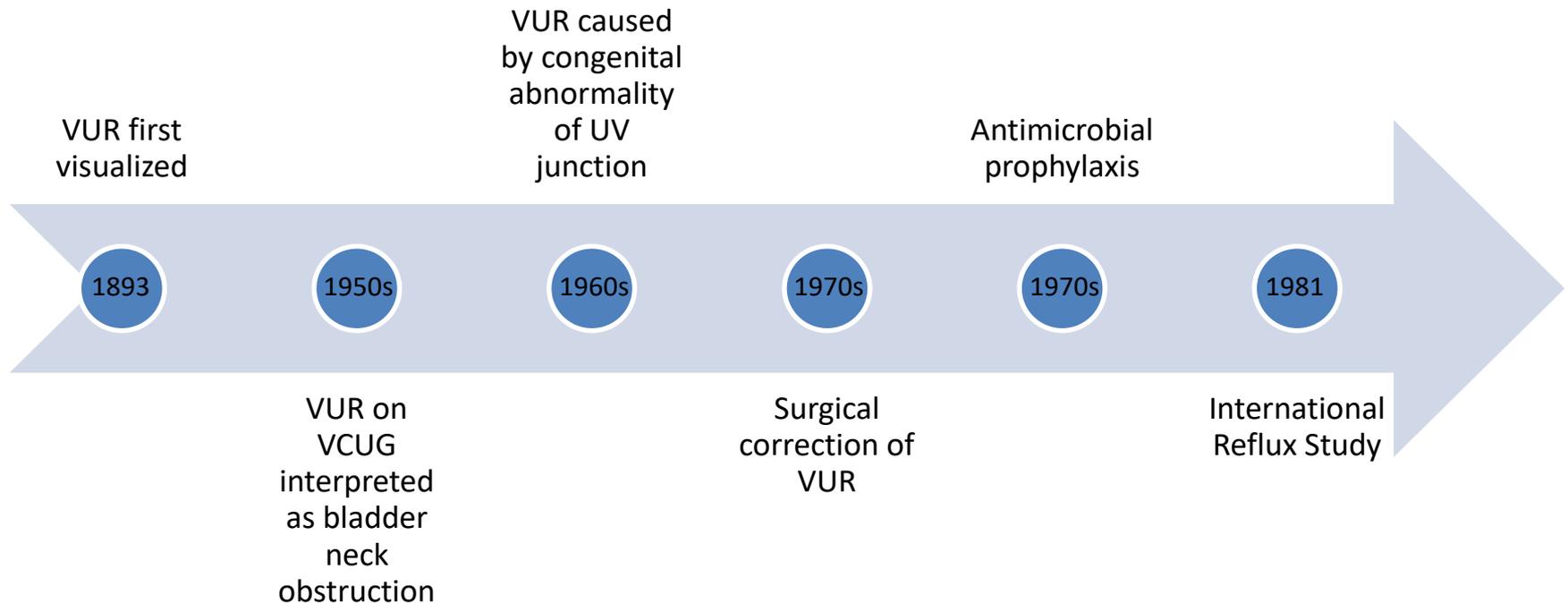
- Retrograde flow of urine from bladder into upper urinary tract
- Primary: Incompetent ureterovesical junction
- Secondary: Consequence of other anatomical or functional bladder pathology

# International Classification of VUR

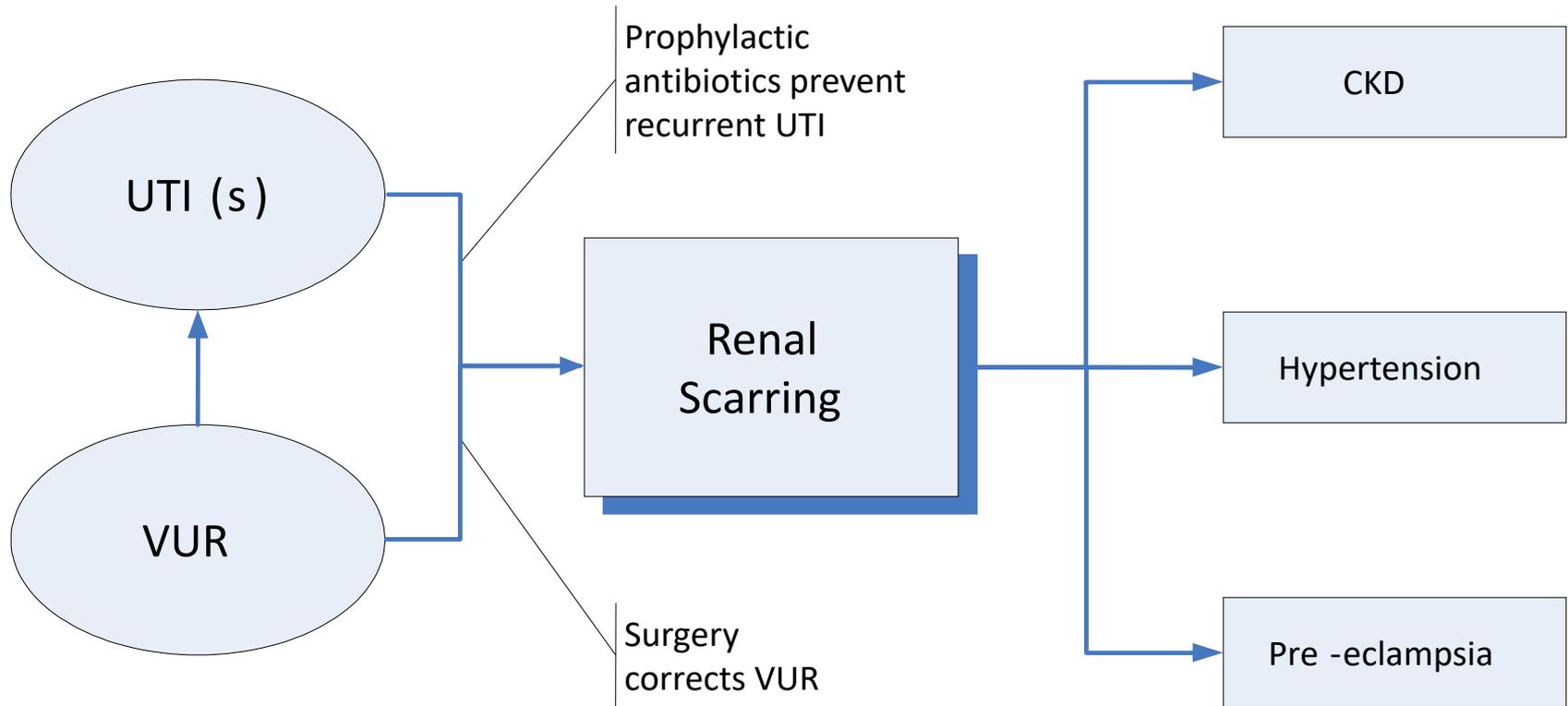


**International classification of vesicoureteral reflux (VUR)** Modified from International Reflux Committee. Medical versus surgical treatment of primary vesicoureteral reflux. *Pediatrics* 1981; 67:392.

# History of Diagnosis and Management of VUR



# Conceptual Model



## SPECIAL ARTICLE

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# Routine diagnostic imaging for childhood urinary tract infections: A systematic overview

Paul Thomas Dick, MDCM, FRCPC, and William Feldman, MD, FRCPC

From the Paediatric Outcomes Research Team, Division of General Paediatrics, Hospital for Sick Children and University of Toronto, Toronto, Ontario, Canada

*The Journal of Pediatrics*  
January 1996

“The objective of this study was to answer the question, What is the evidence that routine diagnostic imaging of children after their first UTI results in prevention of renal scarring, hypertension, or renal failure?”

# Results

- No controlled trials or analytic studies evaluating or comparing management strategies
- All studies descriptive
- Majority sampled children through referral for consultation, radiologic investigation, hospitalization or recurrent UTI.
- No studies described exclusively first UTIs in a primary care setting.
- No direct evidence (linking routine imaging to reduced renal scarring, HTN, renal failure) to support effectiveness of routine diagnostic imaging.

# Where to begin?

- Are our interventions for children diagnosed with VUR effective?
- (Because if they're not, then maybe it's not worth screening for VUR)

# Outcomes to Evaluate Pros and Cons of Antimicrobial Prophylaxis

- Likelihood of reinfections
  - Proportion of children with reinfections
  - Time to first reinfection
- Likelihood of renal scarring
  - Proportion of children with renal scarring
  - Extent of renal scarring
- Impact on the emergence of antimicrobial resistance
  - Urinary tract (gastrointestinal tract)
  - Elsewhere

# Antimicrobial Prophylaxis for UTI

**Table 1. Recent Studies Evaluating the Efficacy of Antimicrobial Prophylaxis in the Prevention of Recurrent Urinary Tract Infection, According to Grade of Vesicoureteral Reflux.\***

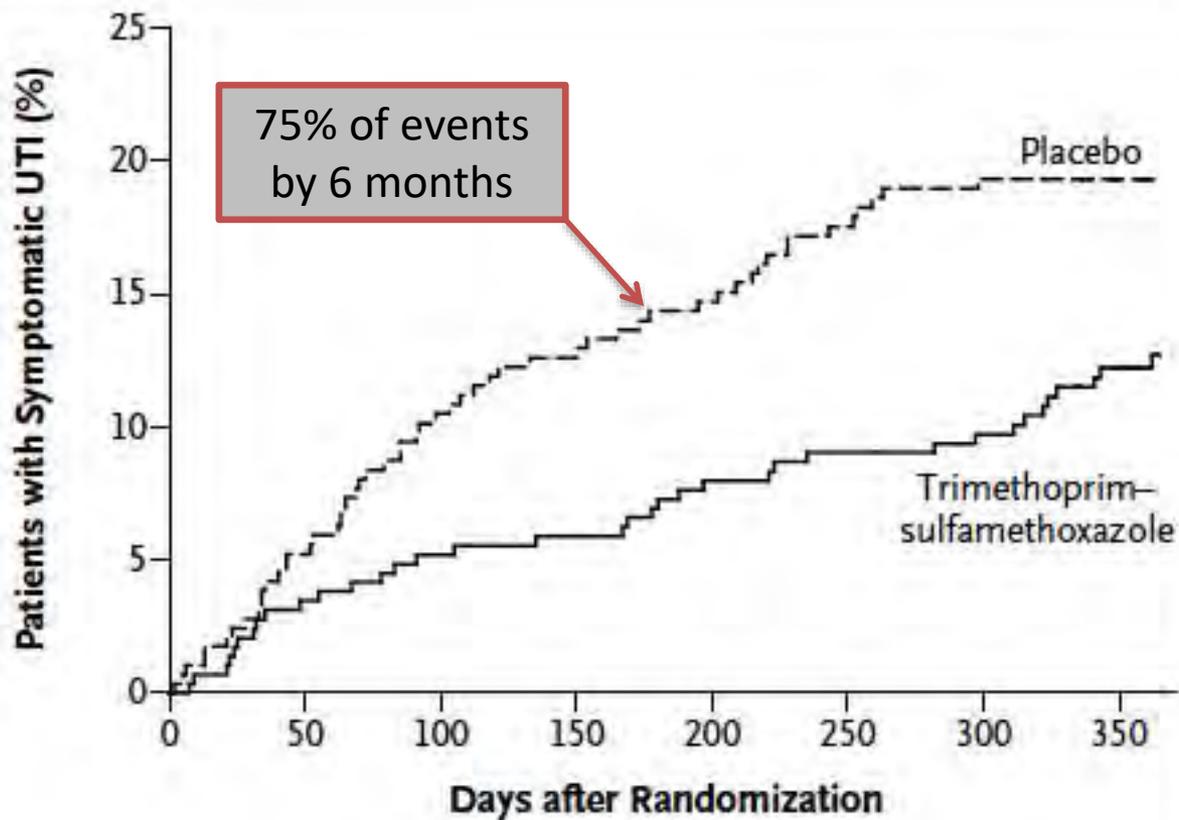
Study Reference and Subjects' Grade of Vesicoureteral Reflux	Number of Subjects	Blinded Study	Age of Subjects	Method of Diagnosis	Duration of Follow-up	Receipt of Antimicrobial Agent		Relative Risk % (95% CI)	Difference in Absolute Risk
						Yes no. of infections/total no. (%)	No no. of infections/total no. (%)		
Garin et al. <sup>6</sup>	218	No	1 mo–18 yr	Bladder catheterization or clean voided collection	12 mo				
None						4/45 (9)	14/60 (23)	0.4 (0.1 to 1.1)	14 (-28 to -1)
Grades I through III						13/55 (24)	13/58 (22)	1.1 (0.5 to 2.1)	1 (-14 to 17)
Roussey-Kesler et al. <sup>7</sup>	225	No	1–36 mo	Bag collection	18 mo				
Grades I through III						18/103 (17)	32/122 (26)	0.7 (0.4 to 1.1)	-9 (-19 to 2)
Pennesi et al. <sup>8</sup>	100	No	0–30 mo	Bag collection	24 mo				
Grades II through IV						18/50 (36)	15/50 (30)	1.2 (0.7 to 2.1)	6 (-12 to 24)
Montini et al. <sup>9</sup>	338	No	2–84 mo	Bag collection	12 mo				
None						5/129 (4)	3/81 (4)	1.1 (0.3 to 4.6)	0 (-5 to 6)
Grades I through III						10/82 (12)	9/46 (20)	0.6 (0.3 to 1.4)	-7 (-21 to 6)
Craig et al. <sup>10</sup>	576	Yes	0–18 yr	Suprapubic aspiration, bladder catheterization, or clean voided collection	12 mo				
None						15/119 (13)	17/115 (15)	0.9 (0.4 to 1.6)	-2 (-11 to 7)
Grades I through V						14/122 (11)	21/121 (17)	0.7 (0.4 to 1.2)	-6 (-14 to 3)
Unknown						7/47 (15)	17/52 (33)	0.5 (0.2 to 1.0)	-18 (-34 to -1)

\* A relative risk of less than 1.0 and a negative difference in absolute risk indicate a decreased risk of urinary tract infection among subjects who received an antimicrobial agent. Values for the difference in absolute risk may not equal the numerical between-group difference because of rounding. Risk values and 95% confidence intervals were calculated with the use of Fisher's exact test (Intercooled Stata software, version 8.0).

ORIGINAL ARTICLE

# Antibiotic Prophylaxis and Recurrent Urinary Tract Infection in Children

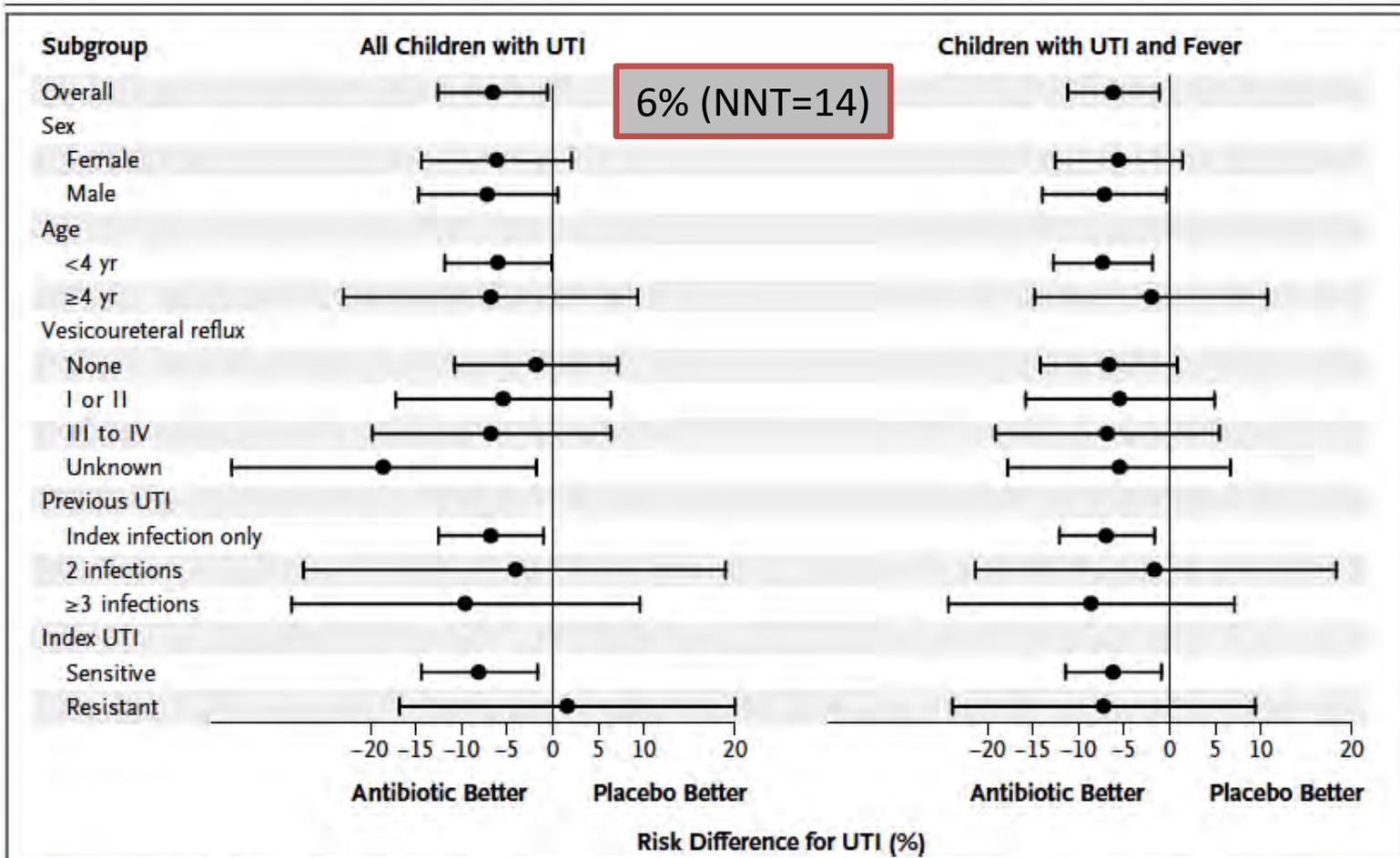
Jonathan C. Craig, M.B., Ch.B., Ph.D., Judy M. Simpson, Ph.D.,  
Gabrielle J. Williams, Ph.D., M.P.H., Alison Lowe, B.Sc., Graham J. Reynolds, M.B., B.S.,  
Steven J. McTaggart, M.B., B.S., Ph.D., Elisabeth M. Hodson, M.B., B.S.,  
Jonathan R. Carapetis, M.B., B.S., Ph.D., Noel E. Cranswick, M.B., B.S.,  
Grahame Smith, M.B., B.S., Les M. Irwig, M.B., B.Ch., Ph.D.,  
Patrina H.Y. Caldwell, Ph.D., Sana Hamilton, M.P.H., and Leslie P. Roy, M.B., B.S.,  
for the Prevention of Recurrent Urinary Tract Infection in Children with  
Vesicoureteric Reflux and Normal Renal Tracts (PRIVENT) Investigators



**No. at Risk**

Antibiotic	288	278	273	271	264	261	257	216
Placebo	288	271	254	248	242	232	225	208

**Figure 2. Time to Symptomatic Urinary Tract Infection (UTI) (Primary Outcome).**



**Figure 3. Effect of Trimethoprim–Sulfamethoxazole on the Risk of Symptomatic Urinary Tract Infection (UTI) with and without Fever.**

The differences in risk rather than hazard ratios are shown for subgroups of patients receiving either trimethoprim–sulfamethoxazole (antibiotic group) or placebo because the risk difference appeared to be a more consistent measure and more clinically applicable. No significant interactions were identified among the various subgroups of patients. The horizontal bars represent 95% confidence intervals.

# Limitations

- Different population (e.g. 35% boys, uncirc'd)
- Half had no VUR
- F/u for only 12 months
- Only 27% had DMSA scan at 1 year, so limited info on scarring

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Antimicrobial Prophylaxis for Children with Vesicoureteral Reflux

The RIVUR Trial Investigators\*

This article was published on May 4, 2014,  
at [NEJM.org](http://NEJM.org).

DOI: [10.1056/NEJMoa1401811](https://doi.org/10.1056/NEJMoa1401811)

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# Study Design

- Sponsored by NIDDK
- Multicenter, randomized, placebo-controlled
  - 5 core sites (Pittsburgh, Philadelphia, Detroit, Buffalo, and Baltimore)
  - 19 clinical sites (primary care, urology, nephrology, ED, inpatient)
  - Data coordinating center at UNC Chapel Hill



# Study Design

## **Inclusion**

- 2 mo – 5 yr at randomization
- 1<sup>st</sup> or 2<sup>nd</sup> F/S UTI
  - Pyuria, positive urine culture (catheterized, SPA or clean voided specimens; bag specimens not permitted)
- Grade I-IV VUR

## **Exclusion**

- UTI diagnosed >112 d prior to randomization
- Co-morbid urologic anomalies
- Contraindications to use of TMP-SMZ
- Selected other medical conditions

## **Follow-up**

- Phone calls q 2 mo, visits q 6 mo, unscheduled to rule out UTI
- DMSA scan at entry, 12 mo, 4 mo after Tx. failure, and 24 mo

# Definition of UTI

- **Pyuria**
  - $\geq 10$  WBC/mm<sup>3</sup> (uncentrifuged) or
  - $\geq 5$  WBC/hpf (centrifuged), or
  - + LE (dipstick)
- **Culture proven infection**
  - $\geq 50,000$  CFU/mL (catheterized, SPA) or
  - $\geq 100,000$  CFU/mL (clean voided specimen)
- **Fever**
  - $\geq 38^{\circ}$  C documented at home or office
- **Symptoms**
  - Suprapubic, abdominal, flank pain or tenderness
  - Urgency, frequency, hesitancy, dysuria, foul smelling urine
  - Infants <4 mo: failure to thrive, dehydration, or hypothermia

# Endpoints

## Primary

- Recurrence of  $F/S$  UTI

## Secondary

- Renal scarring
  - Prevalence, extent, new renal scars on outcome scan
- Treatment failure
  - 2  $F$  UTI, 1  $F$  UTI and 3  $S$  UTI, 4  $S$  UTI, new or worse renal scar at 12 mo
- Bacterial resistance
  - Stool colonization with *E. coli* resistant to TMP-SMZ
  - Recurrent  $F/S$  UTI caused by TMP-SMZ-resistant pathogens

## Covariates

- VUR grade
- Bladder and bowel dysfunction
- Constipation
- Adherence

10,871 Children assessed for eligibility

9,445 Not eligible  
6,374 No UTI criteria  
807 No VCUG  
1,646 No VUR  
61 Grade V VUR  
557 Failed other criteria

1426 Eligible

819 Did not participate

607 Randomized

302 Assigned to TMP-SMZ

305 Assigned to placebo

247 Assessed at 1-year visit  
261 Assessed at 2-year visit

262 Assessed at 1-year visit  
259 Assessed at 2-year visit

302 Included in analysis

305 Included in analysis

# Selected Baseline Clinical Characteristics

Characteristics	TMP-SMZ (N=302)	Placebo (N=305)
<b>Index UTI</b>		
<b>First</b>	275 (91)	279 (91)
<b>Febrile</b>	253 (84)	268 (88)
<b>Pathogen resistant to TMP-SMZ</b>	55 (20)	65 (22)
<b>Bladder and bowel dysfunction</b>	34 (54)	37 (59)
<b>Hydronephrosis (renal US)</b>	19 (6)	13 (4)
<b>VUR</b>		
<b>Grade I</b>	35 (12)	33 (11)
<b>Grade II</b>	123 (41)	131 (44)
<b>Grade III</b>	118 (39)	112 (37)
<b>Grade IV</b>	25 (8)	25 (8)
<b>Bilateral</b>	146 (49)	141 (47)
<b>Renal scarring</b>	12 (3)	9 (4)

# Clinical Outcomes by Treatment Group

Outcome	TMP-SMZ n/N (%)	Placebo n/N (%)	Absolute Risk Difference (95% CI)
Recurrent <i>F/S</i> UTI***	39/302 (12.8)	72/305 (25.4)	12.6 (6.1 to 19.0)
Treatment failure*	14/302 (5.0)	27/305 (9.6)	4.5 (0.2 to 8.8)
Renal scarring			
Overall	27/227 (11.9)	24/235 (10.2)	-1.7 (-7.4 to 4.0)
Severe	9/227 (4.0)	6/235 (2.6)	-1.4 (-4.7 to 1.8)
New	18/220 (8.2)	19/227 (8.4)	0.19 (-4.9 to 5.3)
Resistance			
Resistant <i>E. coli</i> in stool	56/203 (27.6)	41/210 (19.5)	-8.1 (-16.2 to 0.1)
First recurrent <i>F/S</i> UTI with resistant <i>E. coli</i> ***	19/30 (63.3)	11/57 (19.3)	-44.0 (-64.1 to -24.0)

\* For p-value < 0.05, \*\* for p-value <0.01, \*\*\* for p-value <0.001



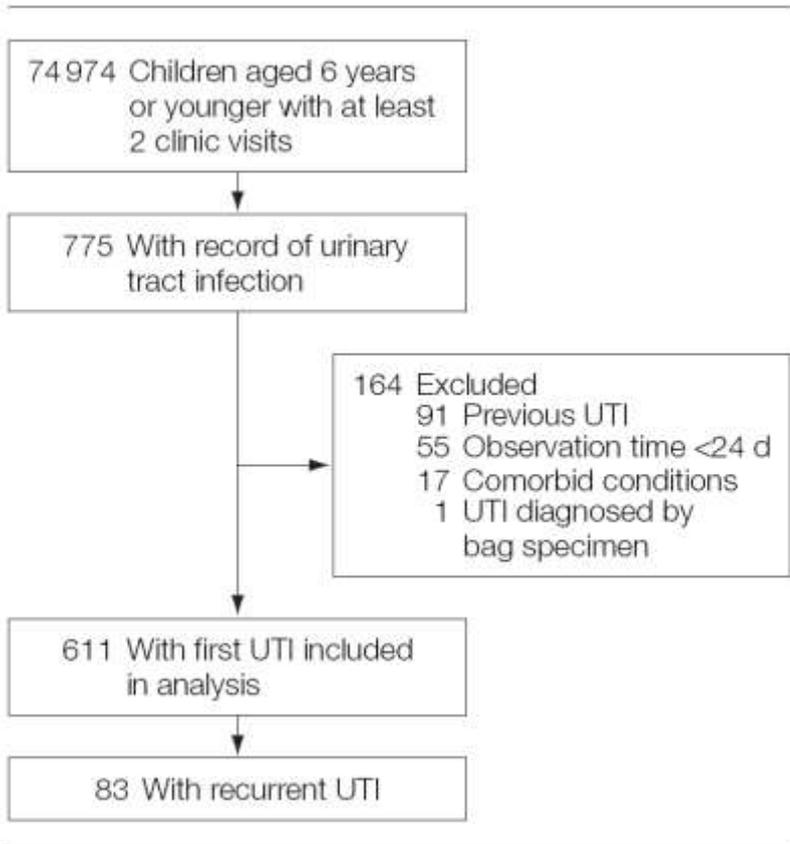
# Summary

- Prophylaxis cut recurrent infections in half.
- Breakthrough infections more likely to be TMP/SMZ resistant (2/3).
- No effect on new or total renal scarring
- GFR unchanged in both groups (based on cystatin-C measurements)

# Recurrent UTIs in Children

## Risk Factors and Association with Prophylactic Antimicrobials

**Figure.** Primary Care Cohort



- EHR data from network of 27 primary care practices with at least 2 clinic visits (2001-2006)
- $\geq 50,000$  CFU/mL, single organism
- Recurrent UTI, 2<sup>nd</sup> positive culture  $\geq 2$  wk after completion of therapy
- 58% children <2 yr had VCUG
- White race, age 3-5 yr and grade 4-5 VUR increased risk of recurrence
- Gender, grade 1-3 VUR no increased risk of recurrence
- **Antimicrobial prophylaxis**
  - **No decreased risk of recurrent UTI**
  - **Increased risk of resistant infections**

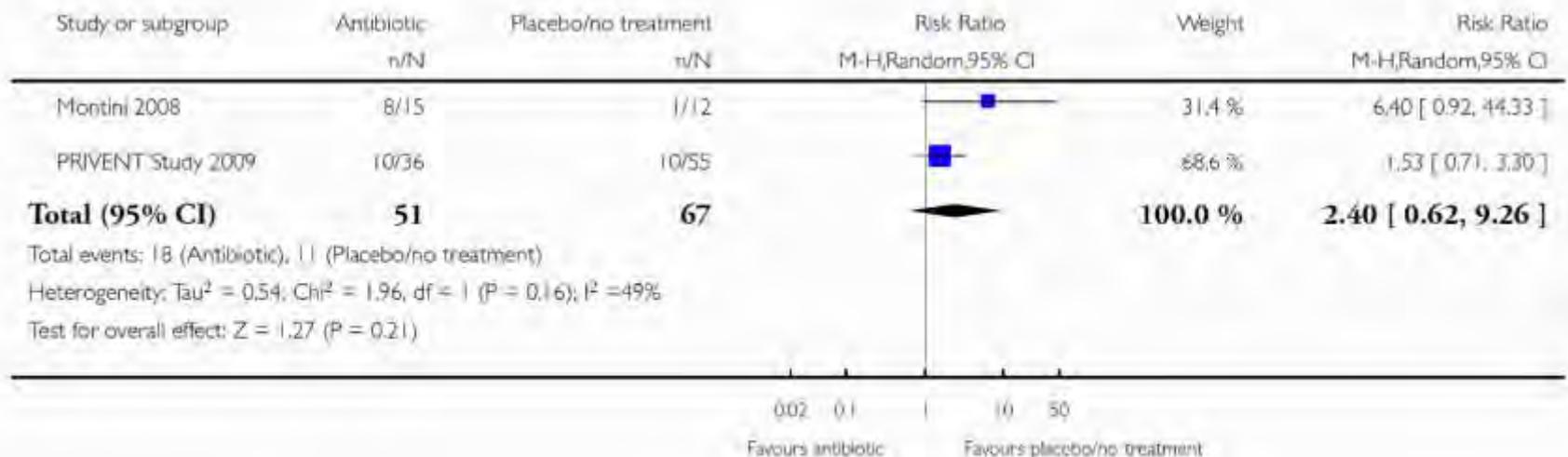
# Long-Term Antimicrobial Prophylaxis and Resistance

## Analysis 1.7. Comparison 1 Antibiotic treatment versus placebo/no treatment, Outcome 7 Microbial resistance to prophylactic drug.

Review: Long-term antibiotics for preventing recurrent urinary tract infection in children

Comparison: 1 Antibiotic treatment versus placebo/no treatment

Outcome: 7 Microbial resistance to prophylactic drug



Williams G, Craig JC. *Cochrane Database of Systematic Reviews* 2011, Issue 3. Art. No.: CD001534. DOI: 10.1002/14651858.CD001534.pub3.



## CLINICAL PRACTICE GUIDELINE

# Urinary Tract Infection: Clinical Practice Guideline for the Diagnosis and Management of the Initial UTI in Febrile Infants and Children 2 to 24 Months

SUBCOMMITTEE ON URINARY TRACT INFECTION, STEERING  
COMMITTEE ON QUALITY IMPROVEMENT AND MANAGEMENT

### KEY WORDS

urinary tract infection, infants, children, vesicoureteral reflux,  
voiding cystourethrography

### ABBREVIATIONS

## abstract



**OBJECTIVE:** To revise the American Academy of Pediatrics practice parameter regarding the diagnosis and management of initial urinary tract infections (UTIs) in febrile infants and young children.

treatment of a febrile UTI recurrence may be of greater importance regardless of whether VUR is present or the child is receiving antimicrobial prophylaxis. A national study (the Randomized Intervention for Children With Vesicoureteral Reflux study) is currently in progress to identify the effects of a prophylactic antimicrobial regimen for children 2 months to 6 years of age who have experienced a UTI, and it is anticipated to provide additional important data<sup>58</sup> (see Areas for Research).

### ***Action Statement 6a***

- Aggregate quality of evidence: B (RCTs).

exposure. In some cases, parents may prefer to subject their children to the procedure even when the chance of benefit is both small and uncertain. Antimicrobial prophylaxis seems to be ineffective in preventing recurrence of febrile UTI/pyelonephritis for the vast majority of infants. Some parents may want to avoid VCUG even after the second UTI. Because the benefit of identifying high-grade reflux is still in some doubt, these preferences should be considered. It is the judgment of the committee that VCUG is indicated after the second UTI.

- Exclusions: None.

# Urinary tract infection in infants and children: Diagnosis and management

Joan L Robinson, Jane C Finlay, Mia Eileen Lang, Robert Bortolussi; Canadian Paediatric Society  
Community Paediatrics Committee, Infectious Diseases and Immunization Committee  
Paediatr Child Health 2014;19(6):315-19  
**Posted:** Jun 13 2014

- Antibiotic prophylaxis is no longer recommended for grades I through III VUR or pending results of the initial RBUS.

**JAMA Pediatrics | Review**

# 2018 Update on Pediatric Medical Overuse A Review

Eric R. Coon, MD, MS; Ricardo A. Quinonez, MD; Daniel J. Morgan, MD, MS; Sanket S. Dhruva, MD, MHS;  
Timmy Ho, MD, MPH; Nathan Money, DO; Alan R. Schroeder, MD

## Prophylactic Antibiotics for Urinary Tract Infection and Risk of Renal Scarring

### Background

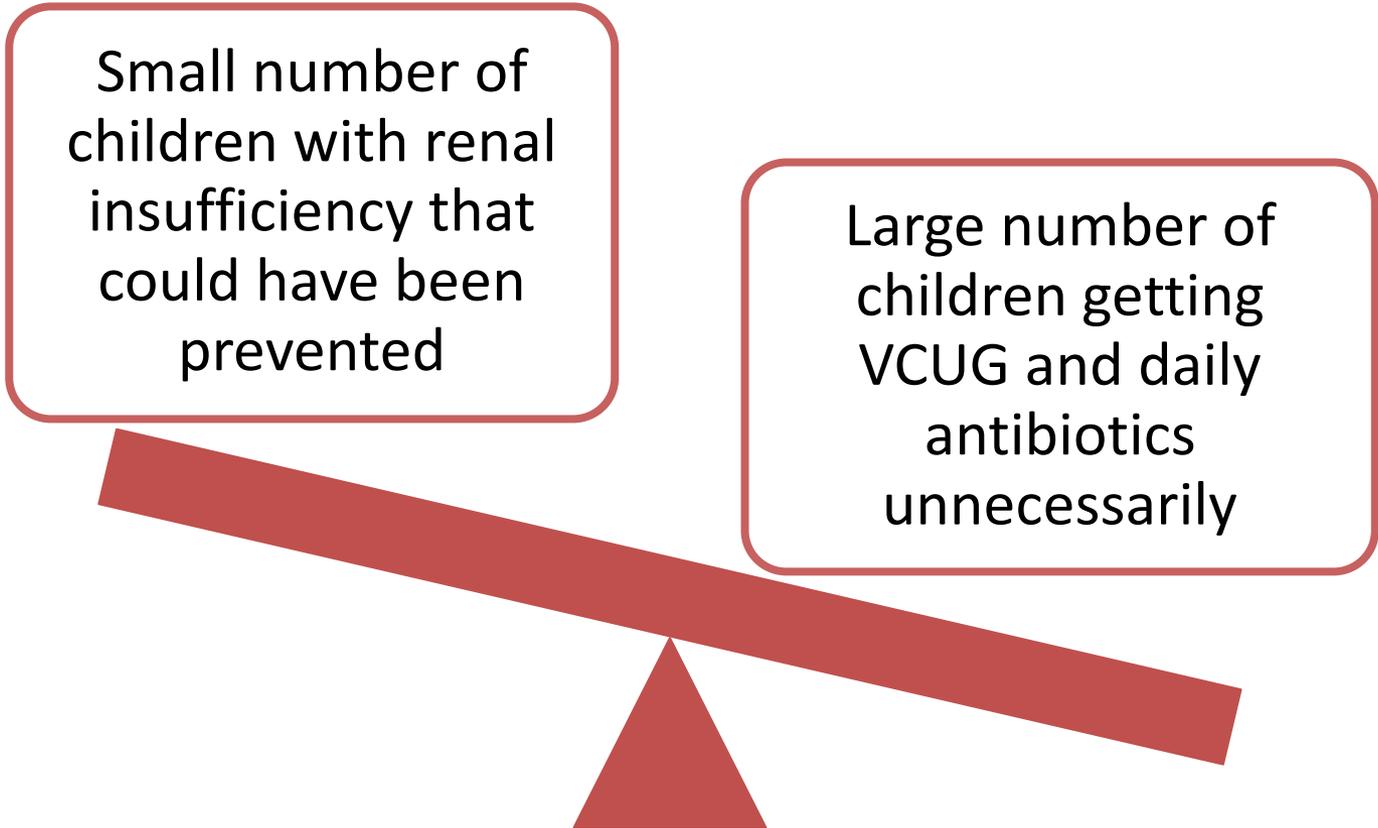
Because childhood urinary tract infection (UTI) is associated with renal scarring, prophylactic antibiotics have been advocated to decrease risk of recurrent UTI, with the hope of preventing long-term kidney damage. Individual RCTs have not been powered to detect differences in renal scarring.

### Findings

A meta-analysis of 7 RCTs of prophylactic antibiotics vs placebo involving 1427 patients demonstrated no significant impact on the development of renal scarring by dimercaptosuccinic acid scan (pooled risk ratio, 0.83; 95% CI, 0.55-1.26).<sup>21</sup> A subgroup analysis involving only patients with vesicoureteral reflux yielded similar findings (pooled risk ratio, 0.79; 95% CI, 0.51-1.24). Approximately half of patients included in this meta-analysis had no or low grade (<grade III) vesicoureteral reflux at the time of study enrollment, and renal scarring was a secondary outcome in all of the included trials. The evidence quality is 1a (systematic review of RCTs).

### Implications

Although prophylactic antibiotics are modestly effective in preventing recurrent UTIs, the goal of preventing renal scarring is not supported by the summary data from this meta-analysis. Given the high number needed to treat to prevent 1 infection (daily antibiotics for 8 patients for 2 years, or 5840 total doses of antibiotics per the most recent RCT),<sup>22</sup> and the concerns about promotion of antimicrobial resistance and other drug-related adverse effects, routine prophylactic antibiotics following UTI should be discouraged. Additionally, the findings bring into question whether the link between UTI and renal scarring is causal.<sup>23</sup>



Small number of children with renal insufficiency that could have been prevented

Large number of children getting VCUG and daily antibiotics unnecessarily

# What about antibiotic prophylaxis for common childhood infections?

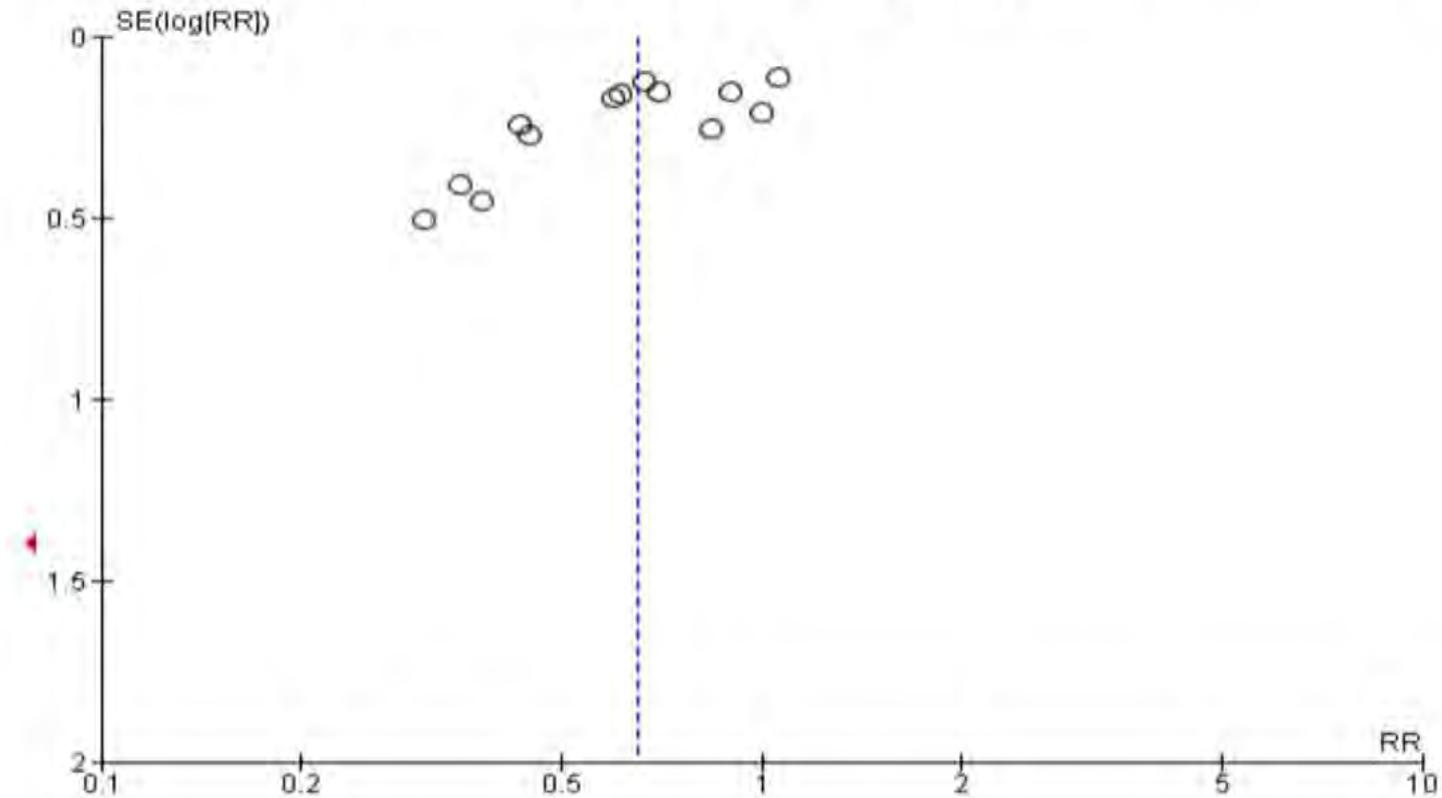
- UTI
- OM

# Prophylaxis for OM

- Long-term, low-dose antibiotic use, referred to as antibiotic prophylaxis or chemoprophylaxis, has been used to treat children with recurrent AOM to prevent subsequent episodes.
- Antibiotics given once or twice daily

# Cochrane Review

Figure 1. Funnel plot of comparison: 1 Antibiotic versus control - primary outcomes, outcome: 1.1 Prevention - any AOM or CSOM during intervention.



# Cochrane Review

- Reduced any episode of AOM (risk ratio (RR) 0.65, 95% CI 0.53 to 0.79)
- Number of episodes of AOM (incidence rate ratio (IRR) 0.51, 95% CI 0.39 to 0.66)
- Approximately five children would need to be treated long-term to prevent one child experiencing AOM whilst on treatment.
- Antibiotics prevented 1.5 episodes of AOM for every 12 months of treatment per child.

# Cochrane Review

Antibiotic versus control - secondary outcomes for the prevention of acute and chronic suppurative otitis media in children						
Patient or population: patients with the prevention of acute and chronic suppurative otitis media in children						
Settings:						
Intervention: Antibiotic versus control - secondary outcomes						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Antibiotic versus control - secondary outcomes				
Side effects - any clinical side effects during intervention	8 per 1000	16 per 1000 (2 to 127)	RR 1.99 (0.25 to 15.89)	817 (12 studies)	⊕⊕⊕○ moderate <sup>1</sup>	

# Randomized placebo-controlled trials of prophylaxis

- Reported a decrease of 0.09 episodes per month in the frequency of AOM attributable to therapy (approximately 0.5 to 1.5 AOM episodes per year for 95% of children).
- An estimated 5 children would need to be treated for 1 year to prevent 1 episode of OM.
- The effect may be more substantial for children with 6 or more AOM episodes in the preceding year.

# Durability of Benefit

- This decrease in episodes of AOM occurred only while the prophylactic antibiotic was being given.
- The modest benefit afforded by a 6-month course of antibiotic prophylaxis does not have longer-lasting benefit after cessation of therapy.



## CLINICAL PRACTICE GUIDELINE

# The Diagnosis and Management of Acute Otitis Media

## abstract



This evidence-based clinical practice guideline is a revision of the 2004 acute otitis media (AOM) guideline from the American Academy of Pediatrics (AAP) and American Academy of Family Physicians. It provides recommendations to primary care clinicians for the management of children from 6 months through 12 years of age with uncomplicated AOM.

In 2009, the AAP convened a committee composed of primary care physicians and experts in the fields of pediatrics, family practice, otolaryngology, epidemiology, infectious disease, emergency medicine, and guideline methodology. The subcommittee partnered with the Agency for Healthcare Research and Quality and the Southern California Evidence-Based Practice Center to develop a comprehensive review

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

### KEY WORDS

acute otitis media, otitis media, otoscopy, otitis media with effusion, watchful waiting, antibiotics, antibiotic prophylaxis, tympanostomy tube insertion, immunization, breastfeeding

### ABBREVIATIONS

AAFP—American Academy of Family Physicians  
AAP—American Academy of Pediatrics  
AHRQ—Agency for Healthcare Research and Quality  
ADM—acute otitis media

## **Key Action Statement 5A**

**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)**

Antimicrobial Prophylaxis: Yes?  
No? or We Don't Know!

NO