Window of Susceptibility to Acute Otitis Media Infection

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abstract

BACKGROUND: Contemporary, quantitative data are needed to inform recommendations and decision-making regarding referral and surgeon endorsement of tympanostomy tube placement in young children with recurrent acute otitis media (AOM).

METHODS: A prospective, observational cohort study of 286 children in a primary care pediatric practice setting, who had at least 1 AOM (range 1–8). Children were followed longitudinally from 6 to 36 months old. AOMs were microbiologically confirmed by tympanocentesis for diagnostic accuracy. A window of susceptibility (WOS) was defined as AOMs closely spaced in time with no gap in occurrence >6 months. For prediction of total number of AOMs, we used a quasi-poisson generalized linear model.

RESULTS: Eighty percent of AOMs occurred during child age 6 to 21 months old. Seventy two percent of WOS intervals were <5 months and 97% were <10 months. Clinically applicable models were developed to predict which children would benefit most from tympanostomy tubes. Significant predictors were child age at the first AOM ($P < .001$) and daycare attendance ($P = .03$). The age of a child when 2, 3, or 4 AOMs had occurred allowed prediction of the number of additional AOMs that might occur. After insertion of tympanostomy tubes, 16 (52%) of 31 children had no additional AOMs.

CONCLUSIONS: Recurrent AOM occurs in a narrow WOS and number of AOMs can be predicted at time of AOM based on child age and daycare attendance. Insertion of tympanostomy tubes likely occurs in many children after the WOS to recurrent AOM has passed or only 1 more AOM may be prevented at most.

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Dr Bajorski directly accessed and verified the underlying data reported in the manuscript, performed statistical analysis, developed statistical models, and contributed to manuscript writing; Dr Fuji directly accessed and verified the underlying data reported in the manuscript performed statistical analysis and contributed to manuscript writing; Dr Kaur supervised microbiology, all data capture and data management, directly accessed and verified the underlying data reported in the manuscript, and contributed to manuscript writing; Dr Pichichero conceived the study, enrolled and followed children in the study, performed tympanocentesis, oversaw data collection from child subjects, prepared the first and final version of the manuscript, and secured funding for the project; and all authors had full access to all the data in the study, approved the final manuscript, and accept responsibility to submit for publication.

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WHAT'S KNOWN ON THIS SUBJECT: Recurrent acute otitis media (AOM) occurs most frequently in the first 2 years of life and leads to tympanostomy tube surgery.

WHAT THIS STUDY ADDS: This study provides contemporary, quantitative data on recurrent AOM and models to predict future AOM frequency. The notion that children with several AOMs in closely spaced time are destined to experience similar AOM frequency in the near future needs to be reassessed.

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About 60% of children will suffer at least 1 acute otitis media (AOM) infection[1] and a subset of about 10% to 15% of children are particularly vulnerable to recurrent AOMs.[1] These children are most often referred to an otolaryngologist for tympanostomy tube insertion surgery[2,3] and their overall care incurs the greatest financial and health burden associated with AOM. Although there are risks associated with untreated recurrent AOM[2] and use of antibiotics to treat AOM,[4,5] the benefits of tube insertion for recurrent AOM are limited and not clearly defined.[2,6] Whereas some studies suggest increased quality of life scores and less recurrent AOM after tube insertion,[7,8] aggregate data suggests tube insertion may prevent up to 1 AOM event within 6 months of the surgery,[2,9,10] a benefit not clearly evident by 12 months postsurgery. In addition, tube insertion can cause tympanic membrane abnormalities and complications, such as focal atrophy, chronic perforation, and chronic otorrhea.[3,11]

In the last 15 years, our group has prospectively studied AOM susceptibility in cohorts of children followed from about 6 months to 5 years of age.[12,13] In these cohorts, otitis prone children were defined according to the American Academy of Pediatrics (AAP) guideline – 3 AOM episodes within 6 months or 4 AOM within 12 months.[14] We applied the term stringently-defined otitis prone because our unique study design requires the detection of the instigating bacterial pathogen by tympanocentesis in virtually all cases, thus unambiguously identifying AOM cases. These children are more often male, in daycare, and have siblings in the home,[1] covariates that increase the likelihood of pathogen exposure associated with occurrence of AOM.

The primary objective of the current study was to quantitatively examine recurrent AOM incidence with respect to age of occurrence, the influence of day care attendance, and other risk factors in individual children. Here we introduce the concept of a window of susceptibility (WOS) to AOM as new terminology, referring to a child who has 2 or more closely spaced AOM occurrences during a window of time. Prior literature may be misunderstood to imply that AOM occurs in a broad WOS of age 6 months to 5 years old[15,16] or an age range of 6 months to 12 years old.[14] Considering the circumstance where a practicing clinician confronts the situation with a child who has closely spaced AOMs, we sought to know what to expect and advise the parent.

A secondary objective was to develop models to predict the risk and timing of AOM recurrences based on the natural history of disease in young children who do not get tympanostomy tubes. The prediction models were developed to assist clinicians in understanding and explaining to parents benefit to expect if tympanostomy tubes were to be inserted based on the child's age and number of AOMs. A tertiary objective was to assess the natural history of recurrent AOM after tympanostomy tube placement in accord with current guideline thresholds.

METHODS

Study Population

As previously described,[12] children were prospectively enrolled at about 6 months of age and followed to 60 months of age from June 2006 to August 2017. The children were all from a primary care pediatric practice in Rochester, NY comprised of a typical mixed demographic of largely middle class, health care-insured families but including both wealthy and below poverty line families on public assistance, and broadly representative of the racial and ethnic diversity in the community. The diagnosis of AOM was made based on the AAP guidance wherein a presumed middle ear effusion and a full or bulging tympanic membrane were required.[14]

Almost all episodes (estimate >85%) of clinically diagnosed AOM were confirmed by culture of middle ear fluid collected by tympanocentesis up to 36 months of age. Children experiencing 3 AOM episodes within a 6 month time span or 4 episodes within a 12-month time span, virtually all confirmed by tympanocentesis, were termed otitis prone.[2,14] Multiple risk factors known to impact the occurrence of AOM were recorded. The electronic medical record of all children was accessed for details of demographic and epidemiologic risk, vaccinations, AOM diagnoses from birth to child age 5 years old. We have previously reported that AOM is infrequent after 36 months old in our study population[17] and data from those children were so sparse that they were not included in the current study. Infrequently AOM diagnosis was made at Urgent Care centers and when that occurred, typically (estimate >85%) parents brought the child to the study practice and AOM clinical diagnosis was confirmed the following day by reexamination by 1 of the study clinicians and tympanocentesis performed. The details of the methods and culture results from the middle ear fluid from the study children have been reported previously.[1,18,19] Tympanocentesis cultures collected from the study cohort yields Streptococcus pneumoniae, Haemophilus influenzae or Moraxella catarrhalis by culture or polymerase chain

reaction in ~90% of middle ear fluid (MEF) sample.[1] The Rochester General Hospital IRB approved the study and written informed consent was obtained from parents before enrollment in the study.

WOS Definition

To explore the WOS concept, we needed to define more precisely what the WOS is. When AOMs are spaced within a relatively short period of time, this has been used in the past to define the otitis prone child.[14] Here we evaluated the occurrence of AOMs over time in individual children to ascertain the best definition that fit the data; a cumulative distribution curve of AOM occurrences in the cohort identified patterns of AOMs closely spaced in time and gaps between consecutive AOMs. The data identified AOMs spaced more than 6 months apart as separate AOM infections or a separate WOS. Hence, our definition of WOS in this report is an AOM sequence of 2 or more with no gap longer than 6 months. A gap of 6 months followed by 1or more AOMs is an isolated event or a different WOS for an individual child.

Statistical Analysis

Analysis of demographic and risk factor covariates was based on the 2-sample test of Poisson rates. For the prediction of the total number of AOMs, we used a quasi-poisson generalized linear model. Mild under-dispersion (variance smaller than expected) occurred in a Poisson model,[20] likely caused by some correlation among children, especially those attending the same daycare, but we do not have specific data that would allow us to include this in the model. Natural logarithm as the link function was used. The model fit was confirmed by plots of a given functional relationship with respect to a continuous predictor, such as the age at AOM 1 through AOM 4, respectively, and the averages in a +/− 1-month window around the age specified. The distributional assumptions of the models were verified with residual analysis. The reported *P* values for the significance of predictors were based on the t-statistics for the discussed predictor in the model. Based on the quasi-poisson generalized linear model, a pseudo-R^2 was determined based on the method of Cohen.[21]

RESULTS

Analysis of demographic and risk factor covariates: sex, race and ethnicity, daycare attendance, breastfeeding siblings in the home,

TABLE 1 Demography and Risk Factors

# of AOMs	1	2	3	4	5	6	7	8	Overall
Sex									
Male	61 (56)	35 (51)	26 (60)	17 (63)	15 (68)	8 (73)	3 (100)	2 (67)	167 (58)
Female	48 (48)	33 (49)	17 (40)	10 (37)	7 (32)	3 (27)	0	1 (33)	119 (42)
Not reported	0	0	0	0	0	0	0	0	0
Race									
White	86 (79)	55 (81)	31 (72)	25 (93)	20 (91)	10 (91)	3 (100)	3 (100)	233 (81)
African-American	4 (4)	6 (9)	3 (7)	1 (4)	0	1 (9)	0	0	15 (5)
More than 1 race	10 (9)	6 (9)	4 (9)	1 (4)	0	0	0	0	21 (7)
Other	9 (8)	1 (1)	5 (12)	0	2 (9)	0	0	0	17 (6)
Not reported	0	0	0	0	0	0	0	0	0
Day care									
Yes	53 (49)	36 (53)	23 (53)	21 (78)	19 (86)	8 (73)	2 (67)	1 (33)	163 (57)
No	51 (47)	29 (43)	17 (40)	6 (22)	3 (14)	3 (27)	0	2 (67)	111 (39)
Not reported	5 (5)	3 (4)	3 (7)	0	0	0	1 (33)	0	12 (4)
Feeding									
Breastfed	29 (27)	15 (22)	9 (21)	7 (26)	3 (14)	3 (27)	0	0	66 (23)
Formula-fed	51 (47)	37 (54)	21 (49)	15 (5)	17 (77)	6 (55)	2 (67)	2 (67)	151 (53)
Both	19 (17)	7 (10)	6 (14)	4 (15)	2 (9)	1 (9)	0	0	39 (14)
Not reported	10 (9)	9 (13)	7 (16)	1 (4)	0	1 (9)	1 (33)	1 (33)	30 (10)
Smoking in home									
Yes	10 (9)	3 (4)	6 (14)	2 (7)	0	2 (18)	0	0	23 (8)
No	95 (87)	62 (91)	37 (86)	25 (93)	22 (100)	9 (82)	3 (100)	3 (100)	256 (90)
Not reported	4 (4)	3 (4)	0	0	0	0	0	0	7 (2)
Atopy									
Yes	33 (30)	23 (34)	13 (30)	8 (30)	4 (18)	4 (36)	1 (33)	1 (33)	87 (30)
No	72 (66)	40 (59)	26 (60)	18 (67)	15 (68)	5 (45)	2 (67)	1 (33)	179 (63)
Not reported	4 (4)	5 (7)	4 (9)	1 (4)	3 (14)	2 (18)	0	1 (33)	20 (7)
Family Hx AOM									
Yes	43 (39)	38 (56)	21 (49)	19 (70)	10 (45)	8 (73)	3 (100)	2 (67)	144 (50)
No	64 (64)	27 (40)	20 (47)	7 (26)	12 (55)	3 (27)	0	1 (33)	134 (47)
Not reported	2 (2)	3 (4)	2 (5)	1 (4)	0	0	0	0	8 (3)

Data presented as *n* (%) unless specified otherwise.

smoking in the home, atopy, and family history of otitis media, identified daycare attendance as a significant factor ($P < .001$) associated with number of AOMs in the child population (Table 1). Children attending daycare had an average of 2.7 AOMs, whereas those not attending had an average of 2.0 AOMs.

AOMs were infrequent among children before 6 months old ($n = 23$ [8%] of 286, see Supplemental Table 3), but then AOMs increased sharply and had a broad peak from child age 6 to 21 months old, accounting for 80% of AOMs, when they decreased in frequency through the remainder of the observation time interval. The number of AOMs per child per 2-month period is shown in Supplemental Fig 6.

Defining the WOS to AOM

Figure 1 shows the cumulative distribution function of the gaps between sequential AOMs. The line in Figure 1 becomes less steep beyond the threshold of 6 months, suggesting that sequential AOMs spaced more than 6 months apart should not be included within the same WOS. The rate of change in the fraction of AOMs as shown in Figure 1 versus the gap between AOMs is illustrated in Supplemental Fig 7, further illustrating that the rate of change is high up until the 6-month gap threshold.

Figure 2A shows 67 children with 2 AOMs. Of those, 49 had closely spaced AOMs that was a WOS with the mean length of 1.9 month (95% confidence interval [CI] [1.5–2.3]). In the remaining 18 children, isolated cases of AOM occurred with gaps wider than 6 months. Figure 2B shows 41 children with 3 AOMs. Of those, 38 children had closely spaced AOMs that was a WOS with the mean length of 3.6 months (CI 2.9–4.4). In the remaining 3 children, isolated cases of AOM occurred with gaps wider than 6 months. Figure 2C shows 28 children with 4 AOMs. All of them had at least 1 WOS, and 5 of them had 2 WOS. The mean WOS was 3.9 (CI 3.0–4.7). Figure 2D shows children with more than 4 AOMs. The mean WOS among the 35 children with more than 4 AOMs was 7.0 CI 6.0–8.0). Of note, 4 children in Fig 2D had 2 WOS periods separated by more than 6 months without any intercurrent AOMs. For 8 out of 9 children who had 2 episodes of WOS (Fig 2 C and D), we found that the child changed rooms in the day care setting between their separated WOS times, moving from the infant room to the toddler room. Details are provided in Supplemental Table 4.

Figure 3 shows the overall cumulative distribution of WOS length. In our cohort, 72% of the WOS intervals were shorter than 5 months and 97% were shorter than 10 months.

Prediction Models for AOM

We have published previously on risk factors associated with recurrent AOM in this child cohort[22]; however, those analyses used the- specific definition of the AAP and American Academy of Otolaryngology Head and Neck Surgery of 3 AOM within 6 months or 4 AOM within 12 months. Here we undertook a novel analysis of risk factors associated with 2, 3, 4, or 5 AOMs in a newly defined WOS terminology. We explored the factors shown in Table 1 and sought to predict the expected total number of AOMs in the first 3 years of the child's life. The only significant predictors were the child's age at the first AOM (age at AOM1) ($P < .001$) and daycare attendance ($P = .03$), $R^2 = 0.3$. Different models were suitable for the children who attended daycare versus those who did not. Figure 4A shows the model for children at the time of their first AOM who attended daycare. There was more variability when age was older than 15 months because of fewer observations in that range. Figure 4B shows the model for children who did not attend daycare. For children who did not attend daycare, the model predicts that only approximately 1 additional AOM after

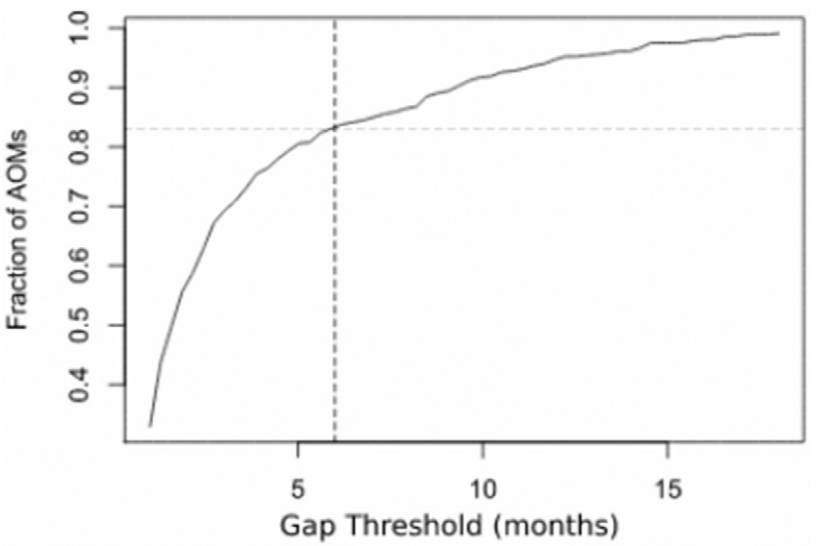

FIGURE 1
The cumulative distribution function of the gaps between the consecutive AOMs. The vertical dashed line shows the threshold of 6 months and the horizontal one shows 83% of all AOMs accumulated up until that threshold.

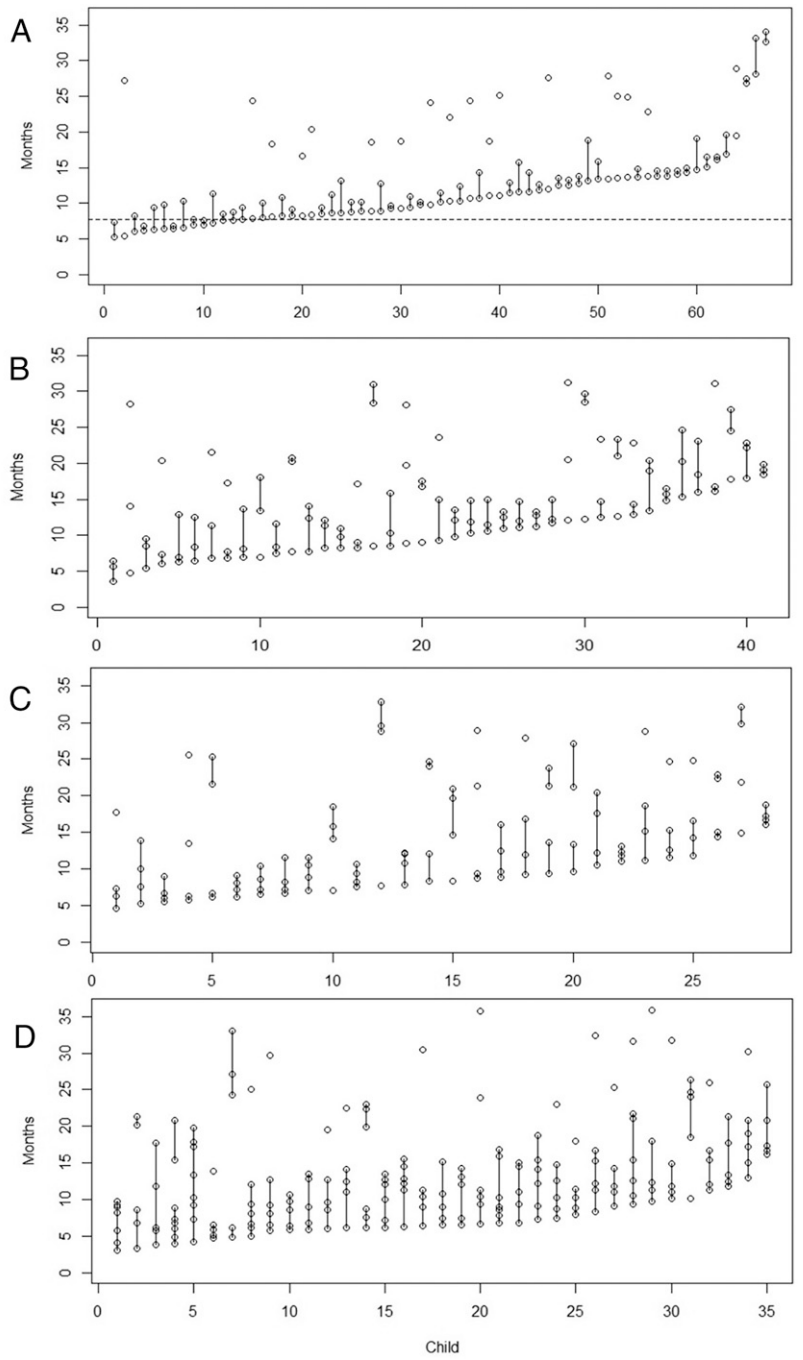

FIGURE 2

Children with 2 AOMs (2A), 3 AOMs (2B), 4 AOMs (2C), and with more than 4 AOMs (2D). The small circles represent the time of the AOMs, and the lines show the WOS. In each subfigure the mean and (95% CIs) are shown for the WOS among children with 2 AOMs (2A), 3 AOMs (2B), 4 AOMs (2C), and with more than 4 AOMs (2D). When there was a gap in time of >6 months between an AOM, this was considered an isolated event and shown as a single dot without connecting line. Figure 2A includes 67 children with 2 AOMs. Of those, 49 had closely spaced AOMs that was a WOS. In the remaining 18 children, isolated cases of AOM occurred with gaps wider than 6 months. Figure 2B includes 41 children with 3 AOMs. Of those, 38 children had closely spaced AOMs that was a WOS. In the remaining 3 children, isolated cases of AOM occurred with gaps wider than 6 months. Figure 2C includes 28 children with 4 AOMs. All of them had at least 1 WOS, and 5 of them had 2 WOS. Figure 2D includes 35 children with more than 4 AOMs.

the first one happened at any age. Figure 4 C, D, and E shows a model for children who have experienced a second, third, and fourth AOM, respectively. For second, third, and fourth AOMs, the model was not influenced by daycare. Details for Fig 4 B, C, D and E are in Supplemental Information (Supplemental Figs 8–12, Supplemental Tables 5–9). Supplemental text provides the formula for input of child age, and AOM1, AOM2, AOM3, or AOM4, and daycare to derive a prediction for individual children regarding likelihood of future AOM frequency.

Table 2 provides finite predictions for future AOMs. For example, for children who experienced their first AOM before the age of 6 months, as many as 2.7 additional AOMs on average (with a 95% CI [2.2–3.1]), can be expected. On the other hand, when the first AOM occurs after 15 months of age, only up to 1 additional AOM, on average, can be expected. For children who experienced their second AOM before the age of 6 months, as many as 2.9 additional AOMs, on average (with a 95% CI [2.2–3.6]), can be expected.

Tympanostomy Tubes

In the study cohort, all of whom had at least 1 AOM, 69 (23.8%) children met the commonly employed definition of otitis prone of 3 AOMs within 6 months or 4 AOMs within 12 months window.[14] Among those attending or not attending day care or daycare status not reported (only 12 cases), 23.9%, 20.7% and 50.0%, respectively, met the definition. Parents of 31 children requested and had their child receive pressure equalizing tympanostomy tubes (PETs) after experiencing 3 AOMs ($n = 15$) or >3 ($n = 16$). After insertion of PETs, 16 (52%) children had no additional AOMs, 9 (29%)

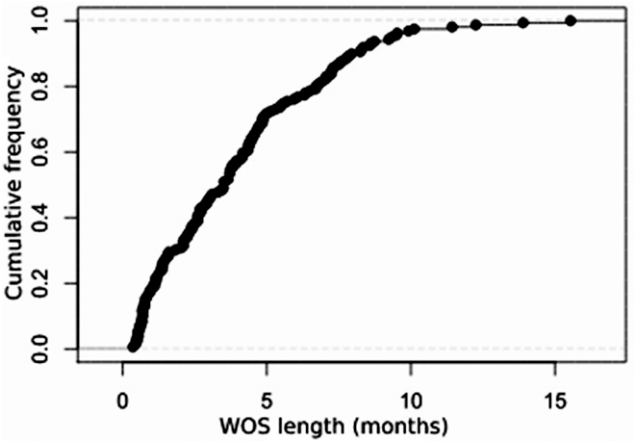

FIGURE 3
The cumulative distribution function of the WOS length.

children had 1 AOM for a total of 81% (Fig 5). Three (10%) children had 2 AOMs and 3 (10%) children had 3 AOMs after tubes were placed and they tended to have had recurrent AOM at a younger age, consistent with results described above. For 10 (67%) out of 15 children that had any AOMs, they occurred within 6 months of PET insertion and for the remaining 5 (33%) children, an AOM occurred 10 to 16 months later (Supplemental Fig 13).

DISCUSSION

In the past decade major changes have occurred in the incidence of AOM and recurrent AOM caused by updated recommendations on diagnostic criteria and treatment[14] and introduction of pneumococcal conjugate vaccines. Here, for the first time, we report recurrent AOM incidence with respect to age of occurrence, the influence of day care attendance, and other risk factors in individual children to identify the length in time of the WOS to AOM in early life. We developed prediction models to assist clinicians in understanding and explaining to parents what benefit to expect if tympanostomy tubes are inserted based on the child's age, number of AOMs, and daycare attendance. Thirdly, we assessed what happens to children after tubes are inserted.

AOMs are infrequent among children before 6 months old but when they occur and the child is in daycare, our results suggest that the child is destined to recurrent AOM with 3 to 4 future episodes yet to come. This possibility should be considered in the context of possible adverse effects of

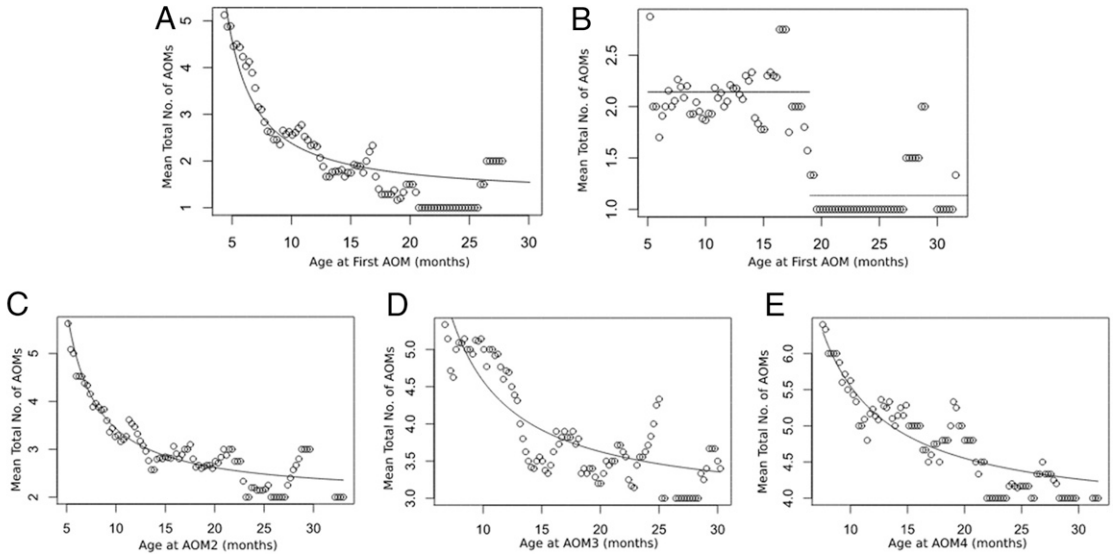

FIGURE 4
The model for predicting Total AOMs as a function of age of AOM. The model for predicting total AOMs as a function of age at first AOM (age AOM1) for children who attended (4A) and did not attend (4B) daycare. The dots represent the averages in a +/− 1-month window around the age specified on the horizontal axis. A very good fit between the averages and the line shows the functional relationship in the model. In 4B, for age at time of AOM 1 up until 19 months, the trend is flat as shown by the solid flat line at the level of 2.14 average total AOMs. For age AOM1 above 19 months, the trend is again flat, but at a lower level of 1.1 average total AOMs (again shown by the lower solid flat line). The model for predicting total AOMs as a function of age at AOM2 (4C), Age at AOM3 (4D), and Age at AOM4 (4E) are also shown. The dots represent the averages in a +/− 1-month window around the age specified on the horizontal axis.

TABLE 2 Predicted Additional AOMs Based on Child Age at Occurrence of AOM 1, 2, 3, or 4

	Number of Predicted Additional AOMs (95% CI)				
Child age in months	6	9	12	15	18
AOM 1 occurs and in cay care, predicted future AOMs	2.7 (2.2–3.1)	1.6 (1.3–1.8)	1.1 (0.9–1.4)	0.9 (0.6–1.2)	0.8 (0.5–1.1)
AOM 1 occurs and no daycare, predicted future AOMs	1.1 (0–3.8)	1.1 (0–3.8)	1.1 (0–3.8)	1.1 (0–3.8)	1.1 (0–3.8)
AOM 2 occurs, predicted future AOMs	2.9 (2.2–3.6)	1.6 (1.3–1.9)	1.1 (0.9–1.4)	0.9 (0.6–1.2)	0.7 (0.4–1)
AOM 3 occurs, predicted future AOMs	3.2 (1.8–4.7)	1.8 (1.3–2.4)	1.2 (0.8–1.6)	0.9 (0.5–1.3)	0.7 (0.3–1.2)
AOM 4 occurs, predicted future AOMs	NA	1.8 (0.8–2.8)	1.2 (0.6–1.8)	0.9 (0.3–1.4)	0.7 (0–1.3)

CI, confidence intervals; NA, Not applicable because no observations for 4 AOMs by child age 6 mo old.

systemic antibiotics on vaccine-induced antibody levels,[5] contribution to antibiotic resistance from exposure,[23,24] and side effects from antibiotic consumption.

AOMs are most frequent in children from 6 to 14 months of age at the rate of at least 0.3 AOMs per 2-month interval, but then the occurrence of AOM is significantly reduced (Supplemental Fig 6). We found that the WOS of AOM is very short for most children and depending on the age of the child at that moment and if in daycare or not, the likelihood of further future AOMs can be reasonably predicted with good accuracy. Of course, there will be exceptions, and we provide the percentages to help the clinician set expectations. Importantly, the widely held notion that the child with 2, 3, or 4 AOMs in closely spaced time is destined to experience at least the same number going forward needs to be reassessed based on the findings of our report. Faced with such children, following current AAP and American Academy of Otolaryngology Head and Neck Surgery guidelines, many receive tubes and the cessation of AOM is attributed to the surgery when, in fact, our data suggests the WOS may have ended and the child would have experienced an end to AOMs with patience and watchful waiting.

Children in daycare were identified as at higher risk for recurrent AOM, consistent with prior reports.[1,25] The quantitative difference in likelihood of recurrent AOM among children attending daycare versus those not in daycare was clinically and statistically significant (Table 2). Mingling with a new group of children and greater freedom to move about may explain exposure to new pathogens that triggers second episodes of WOS in children who attend daycare. For children not in daycare, occurrence of AOM is not only less frequent but rarely is followed by recurrent AOM sufficient in number to lead to a recommendation for tympanostomy tubes.

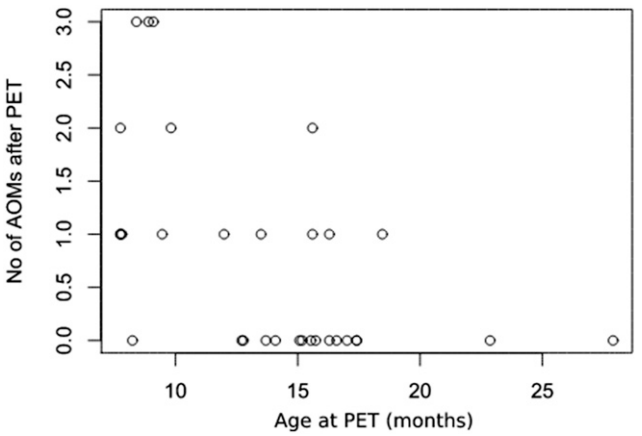

FIGURE 5
The number of AOMs experienced after pressure equalizing tubes (PETs) shown versus the age at the time of PET insertion (horizontal axis).

Clinicians dealing with children who experience recurrent AOM, especially when AOMs occur in rapid succession in a short time interval, would benefit from data to inform their decisions and discussions with parents regarding options of management. The predictive models described in this report should prove useful in that regard. Using input of child age, daycare attendance, and AOM number in a sequence of AOMs, tabulation and simple mathematical formulas are provided to allow clinicians to be more precise in predicting likely further numbers of AOMs (see imbedded macro in Supplemental Information of this report).

After tympanostomy tubes are inserted, some children experience no further AOMs and others subsequently have additional AOMs manifest as otorrhea from the tube. If the child has experienced 3 or 4 AOMs in rapid succession, the expectation is that 3 or 4 more AOMs are on the horizon. In our cohort, half the children had no further AOMs and 81% had none or 1. If AOM occurs frequently after tube surgery, our data suggests that most likely (83%) the child had at least 3 AOMs before 9 months of age.

Our study has limitations. The study cohort was derived from a single

community in upstate New York, and approximately three-fourths of the children were reported as non-Hispanic white. To confirm the clinical diagnosis of AOM, the children had tympanocentesis completed, which is not standard practice.

The performance of tympanocentesis to confirm the clinical diagnosis of AOM is a strength since it removes diagnostic uncertainty in a setting where AOM may be over-diagnosed. Drainage of MEF using tympanocentesis may have a therapeutic benefit, as previously reported.[26] The children who underwent tympanocentesis did not exhibit a different pattern in our models predicting the total number of AOMs based on the age at which the first, second, third, or fourth AOM was observed. Also, Figure 5 shows that tympanocentesis at an early age (thus coinciding with early AOMs) tends to be followed by more AOMs versus tympanocentesis at later age. These strengths and limitations of our study should be considered by clinicians in interpreting our results.

In conclusion, recurrent AOM occurs in a narrow WOS and number of AOMs can be predicted at time of AOM based on child age and daycare attendance. Insertion of tympanostomy tubes likely occurs in many children after the WOS to recurrent AOM has passed or only 1 more AOM may be prevented at most. Multiple courses of antibiotics have consequences as do tympanostomy tubes[2,27,28] and assessment of risk and benefit should be individualized.

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ABBREVIATIONS

AAP: American Academy of Pediatrics
AOM: acute otitis media
WOS: window of susceptibility

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REFERENCES

1. Kaur R, Morris M, Pichichero ME. Epidemiology of acute otitis media in the postpneumococcal conjugate vaccine era. *Pediatrics*. 2017;140(3):e20170181
2. Rosenfeld RM, Tunkel DE, Schwartz SR, et al. Clinical practice guideline: tympanostomy tubes in children (update). *Otolaryngol Head Neck Surg*. 2022;166(1_suppl suppl):S1–S55
3. Gaddey HL, Wright MT, Nelson TN. Otitis media: rapid evidence review. *Am Fam Physician*. 2019;100(6):350–356
4. Poole NM, Shapiro DJ, Fleming-Dutra KE, Hicks LA, Hersh AL, Kronman MP. Antibiotic prescribing for children in United States emergency departments: 2009-2014. *Pediatrics*. 2019;143(2):e20181056
5. Chapman TJ, Pham M, Bajorski P, Pichichero ME. Antibiotic use and vaccine antibody levels. *Pediatrics*. 2022;149(5):e2021052061
6. Steele DW, Adam GP, Di M, Halladay CH, Balk EM, Trikalinos TA. Effectiveness of tympanostomy tubes for otitis media: a meta-analysis. *Pediatrics*. 2017;139(6):e20170125
7. Kujala T, Alho OP, Luotonen J, et al. Tympanostomy with and without adenoidectomy for the prevention of recurrences of acute otitis media: a randomized controlled trial. *Pediatr Infect Dis J*. 2012;31(6):565–569
8. Chow Y, Wabnitz DA, Ling J. Quality of life outcomes after ventilating tube insertion for otitis media in an Australian population. *Int J Pediatr Otorhinolaryngol*. 2007;71(10):1543–1547
9. Lous J, Ryborg CT, Thomsen JL. A systematic review of the effect of tympanostomy tubes in children with recurrent acute otitis media. *Int J Pediatr Otorhinolaryngol*. 2011;75(9):1058–1061
10. Venekamp RP, Mick P, Schilder AG, Nunez DA. Grommets (ventilation tubes) for recurrent acute otitis media in children. *Cochrane Database Syst Rev*. 2018;5(5):CD012017
11. Johnston LC, Feldman HM, Paradise JL, et al. Tympanic membrane abnormalities and hearing levels at the ages of 5 and 6 years in relation to persistent otitis media and tympanostomy tube

insertion in the first 3 years of life: a prospective study incorporating a randomized clinical trial. *Pediatrics*. 2004;114(1):e58–e67

12. Pichichero ME. Ten-year study of the stringently defined otitis-prone child in Rochester, NY. *Pediatr Infect Dis J*. 2016;35(9):1033–1039
13. Pichichero ME. Ten-year study of acute otitis media in Rochester, NY. *Pediatr Infect Dis J*. 2016;35(9): 1027–1032
14. Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. *Pediatrics*. 2013;131(3):e964–e999
15. Heidemann CH, Lous J, Berg J, et al. Danish guidelines on management of otitis media in preschool children. *Int J Pediatr Otorhinolaryngol*. 2016;87: 154–163
16. Le Saux N, Robinson JL; Canadian Paediatric Society, Infectious Diseases and Immunization Committee. Management of acute otitis media in children six months of age and older. *Paediatr Child Health*. 2016;21(1):39–50
17. Chapman TJ, Morris MC, Xu L, Pichichero ME. Nasopharyngeal colonization with pathobionts is associated with susceptibility to respiratory illnesses in young children. *PLoS One*. 2020;15(12):e0243942
18. Casey JR, Kaur R, Friedel VC, Pichichero ME. Acute otitis media otopathogens during 2008 to 2010 in Rochester, New York. *Pediatr Infect Dis J*. 2013;32(8): 805–809
19. Kaur R, Fuji N, Pichichero ME. Dynamic changes in otopathogens colonizing the nasopharynx and causing acute otitis media in children after 13-valent (PCV13) pneumococcal conjugate vaccination during 2015-2019. *Eur J Clin Microbiol Infect Dis*. 2022;41(1): 37–44
20. Cameron ACTP. *Regression Analysis of Count Data*. Cambridge UK; New York: NY Cambridge University Press; 1998
21. Cohen J, Cohen P, West SG, Aiken LS. *Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences*, 3rd ed. New York, NY: Routledge; 2002
22. Kaur R, Morris M, Pichichero ME, Kaur R, Morris M, Pichichero ME. Epidemiology of acute otitis media in the post-pneumococcal conjugate vaccine era. *Pediatrics*. 2018;141(3):e20174067
23. Llor C, Bjerrum L. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. *Ther Adv Drug Saf*. 2014;5(6): 229–241
24. Wall S. Prevention of antibiotic resistance - an epidemiological scoping review to identify research categories and knowledge gaps. *Glob Health Action*. 2019;12(1):1756191
25. Paradise JL, Rockette HE, Colborn DK, et al. Otitis media in 2253 Pittsburgh-area infants: prevalence and risk factors during the first two years of life. *Pediatrics*. 1997;99(3): 318–333
26. Pichichero ME, Casey JR, Almudevar A. Reducing the frequency of acute otitis media by individualized care. *Pediatr Infect Dis J*. 2013;32(5): 473–478
27. Hoberman A, Preciado D, Paradise JL, et al. Tympanostomy tubes or medical management for recurrent acute otitis media. *N Engl J Med*. 2021;384(19): 1789–1799
28. Wald ER. Management of recurrent acute otitis media. *N Engl J Med*. 2021;384(19):1859–1860