

Cost-Effectiveness of Treatment of Acute Otorrhea in Children With Tympanostomy Tubes

Thijs M.A. van Dongen, MD, PhD^a, Anne G.M. Schilder, MD, PhD^{a,b,c}, Roderick P. Venekamp, MD, PhD^{a,b}, G. Ardine de Wit, PhD^{d,e}, Geert J.M.G. van der Heijden, PhD^{a,b,f}

abstract

BACKGROUND: Acute otorrhea is a common problem in children with tympanostomy tubes. We recently demonstrated that treatment with antibiotic-glucocorticoid eardrops is clinically superior to oral antibiotics and initial observation. The aim of this study was to assess the cost-effectiveness of these three common treatment strategies for this condition.

METHODS: We performed an open-label pragmatic trial in which 230 children with acute uncomplicated tympanostomy-tube otorrhea were randomly allocated to receive 1 of 3 treatments: hydrocortisone-bacitracin-colistin eardrops, oral amoxicillin-clavulanate suspension, and initial observation (no assigned medication prescription to fill). Parents kept a daily diary capturing ear-related symptoms, health care resource use, and non-health care costs for 6 months. At 2 weeks and 6 months, the study doctor visited the children at home performing otoscopy. Using a societal perspective, treatment failure (otoscopic presence of otorrhea at 2 weeks) and number of days with otorrhea as reported in the daily diary were balanced against the costs.

RESULTS: Antibiotic-glucocorticoid eardrops were clinically superior to oral antibiotics and initial observation both at 2 weeks and 6 months. At 2 weeks, mean total cost per patient was US \$42.43 for antibiotic-glucocorticoid eardrops, US\$70.60 for oral antibiotics, and US\$82.03 for initial observation. At 6 months, mean total cost per patient was US\$368.20, US\$420.73, and US\$640.44, respectively. Because of the dominance of eardrops, calculating incremental cost-effectiveness ratios was redundant.

CONCLUSIONS: Antibiotic-glucocorticoid eardrops are clinically superior and cost less than oral antibiotics and initial observation in children with tympanostomy tubes who develop otorrhea.



WHAT'S KNOWN ON THIS SUBJECT: Otorrhea is common in children with tympanostomy tubes: annually, 2 of 3 children develop 1 or more episodes. Antibiotic-glucocorticoid eardrops are the most effective treatment in both the short- and long-term.

WHAT THIS STUDY ADDS: Treatment with antibiotic-glucocorticoid eardrops costs less than oral antibiotics and initial observation in children with tympanostomy tubes who develop otorrhea. Non-health care costs constitute a substantial proportion of the total costs of this condition.

Departments of ^aEpidemiology, ^dPublic Health, Health Technology Assessment and Medical Humanities, Julius Center for Health Sciences and Primary Care, and ^bOtorhinolaryngology, Division of Surgical Specialties, University Medical Center Utrecht, Utrecht, Netherlands; ^cUCL ENT Clinical Trials Programme, Ear Institute, Faculty of Brain Sciences, University College London, London, United Kingdom; ^eDepartment of Nutrition, Prevention and Care, National Institute of Public Health and the Environment, Bilthoven, Netherlands; and ^fDepartment of Social Dentistry, Academic Centre for Dentistry Amsterdam (ACTA), University of Amsterdam and VU University Amsterdam, Amsterdam, Netherlands

Dr van Dongen collected, analyzed, and interpreted the data, and drafted the initial manuscript; Dr Schilder designed, planned, and supervised the study and interpreted the data, reviewed and revised the manuscript, and was guarantor of the study; Drs Venekamp, de Wit, and van der Heijden supervised the analyses, interpreted the data, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

This trial has been registered with the Netherlands Trial Register (www.trialregister.nl) (identifier NTR1481).

www.pediatrics.org/cgi/doi/10.1542/peds.2014-3141

DOI: 10.1542/peds.2014-3141

Accepted for publication Feb 11, 2015

With ~50 000 procedures in the Netherlands, >20 000 in the United Kingdom, and almost 700 000 in the United States each year, insertion of tympanostomy tubes (also known as grommets or ventilation tubes) is one of the most frequently performed surgical procedures in children (Dutch Hospital Database [Landelijke medische registratie], 2010).¹⁻² Annually, 2 of 3 children with tympanostomy tubes develop 1 or more episodes of otorrhea: this is caused by an acute middle ear infection, whereby middle ear fluid drains through the tube.³ As parents generally hope that tympanostomy tubes will solve their child's middle ear problems, they may be disappointed, or anxious, when their child develops otorrhea.

The societal costs of middle ear infections are considerable.⁴⁻⁶ Previously, Roland et al⁷ showed, by using decision-analytic modeling, that the direct health care costs of a single episode of otorrhea in children with tubes approximated US \$250 in 2004. In addition, parents often have to stay home from work when their child is unable to go to day care or school, leading to high non-health care costs.⁸⁻¹⁰

We recently demonstrated that topical treatment with antibiotic-glucocorticoid eardrops is more effective than oral antibiotics and initial observation in children with tube discharge.¹¹ The objective of this article was to establish for the first time the cost-effectiveness of these treatment strategies.

METHODS

Design and Participants

This cost-effectiveness study was performed alongside an open-label pragmatic randomized trial in the Netherlands. Its design, methods, and clinical outcomes are reported in more detail elsewhere.¹¹ The study was approved by the medical ethics committee of the University Medical

Centre Utrecht and was monitored according to the Good Clinical Practice quality standard.

Family physicians and ear, nose, and throat (ENT) surgeons approached parents of children with tympanostomy tubes for trial participation. Parents interested in trial participation contacted our research team when their child developed otorrhea. Children aged between 1 and 10 years with discharge for up to 7 days were eligible for trial participation. We excluded children with a body temperature >38.5°C, those who had used antibiotics in the previous 14 days, those who had tubes inserted within the previous 14 days, and those who had experienced another episode of otorrhea in the previous 28 days, had ≥3 episodes of otorrhea in the previous 6 months, or had ≥4 episodes in the previous year. We also excluded children with Down syndrome, craniofacial anomalies, a known immunodeficiency, and children with a known allergy to the medications used in this study.

Randomization and Interventions

After obtaining informed consent, children were randomized to 1 of 3 treatment strategies: hydrocortisone-bacitracin-colistin eardrops (5 drops, 3 times daily in the discharging ear[s] for 7 days), oral amoxicillin-clavulanate suspension (30 mg amoxicillin and 7.5 mg clavulanate per kilogram of body weight per day, divided into 3 daily doses taken orally for 7 days), or initial observation for 14 days. After the first follow-up visit, further management of otorrhea was left to the discretion of the child's family physician or ENT surgeon.

Follow-up Measurements

Parents kept a daily diary capturing ear-related symptoms, direct health care resource use (prescriptions, health care visits, surgical procedures, and hospitalizations) and direct (over-the-counter drugs, travel costs, costs for child care) and

indirect non-health care costs (parental time of work) for 6 months. We used monthly telephone reminders to optimize compliance with completing the daily diary.

At 2 weeks and 6 months, the study doctor visited the children at home, performed otoscopy, and checked diaries for completeness. Data quality was monitored by an independent third party, including close-in and close-out visits and regular on-site visits for source data verification.

Clinical Outcomes

Clinical effectiveness of antibiotic-glucocorticoid eardrops, oral antibiotics, and initial observation was assessed by the following:

1. otoscopy by the study doctor at 2 weeks (ie, treatment failure defined as presence of otorrhea); and
2. parental diaries at 6 months (ie, mean number of days with otorrhea).

Resource Use and Valuation

All costs were estimated at the patient level for 2009, when the trial started. If only cost estimates from before 2009 were available, these were adjusted to the price level of 2009, by using the Dutch consumer price index published by Statistics Netherlands.¹²

Costs of medication were retrieved from the Dutch formulary, a pharmacist's fee was added for every prescription.^{13,14} We used the cost estimates as presented in the Dutch Formulary, which are based on the defined daily dose system. Use of oral and topical antibiotics with or without glucocorticoids was calculated per course of 3, 5, or 7 days, unless stated otherwise. We used the current cost estimate if medication prices for 2009 were not available. Costs of over-the-counter and complementary medicines were calculated per day, based on current average retail prices. Health care visits, telephone consultations, and hospitalizations (per day) were

TABLE 1 Cost Estimates Used in This Study, in Euros, Pounds Sterling and US Dollars for 2009

| Resources | Cost Estimate | | | Source |
|--|------------------------------|----------------|-------------------|-----------------|
| | € | £ ^a | US\$ ^a | |
| Tube removal/reinsertion | 380.47 | 337.90 | 548.11 | Cost study |
| Tube insertion and adenoidectomy | 717.02 | 636.79 | 1032.94 | Cost study |
| Tube insertion and tonsillectomy | 738.25 | 655.64 | 1063.52 | Cost study |
| Adenotonsillectomy | 379.01 | 336.60 | 546.00 | Cost study |
| Hospitalization, per d | | | | Guideline |
| Short stay (1 d) | 251.00 | 222.91 | 361.59 | |
| Long stay (>1 d) | 457.00 | 405.86 | 658.35 | |
| Health care visit | | | | Guideline |
| ENT surgeon | 72.00 | 63.94 | 103.72 | |
| Family physicians | 28.00 | 24.87 | 40.34 | |
| Other medical professional | See Supplemental Information | | | |
| Health care telephone consultation | | | | Guideline |
| ENT surgeon | 36.00 | 31.97 | 51.86 | |
| Family physicians | 14.00 | 12.43 | 20.17 | |
| Other health care professional | See Supplemental Information | | | |
| Medication | | | | Dutch formulary |
| Hydrocortisone-bacitracin-colistin eardrops | 9.88 | 8.77 | 14.23 | |
| Oral amoxicillin-clavulanate suspension | 2.47 | 2.19 | 3.56 | |
| Other medication | See Supplemental Information | | | |
| Pharmacist fee, per prescription | 5.50 | 4.88 | 7.92 | Guideline |
| Over-the-counter and complementary and alternative medicines | See Supplemental Information | | | Retail prices |
| Travel expenses, per hospital visit | 5.80 | 5.15 | 8.36 | Guideline |
| Parental time off work, per h ^b | 26.37 | 23.42 | 37.99 | Guideline |
| Child care, per h | 5.00 | 4.44 | 7.20 | NIBUD |

^a The exchange rate of December 31, 2009, was used to convert cost estimates in Euros to Pounds Sterling (€1 = £0.8881) and US Dollars (€1 = US\$1.4406).²¹

^b Mean productivity loss employee aged 25–35 y.

valued according to the Dutch guideline for pharmacoeconomic evaluation.¹³ We did not include home visits or phone calls by the trial team in resource use and cost estimates. Costs of surgical procedures were retrieved from a previous Dutch costing study that calculated costs for the different components of surgical procedures,

which were then added to reach a reliable cost estimate.¹⁵

Parental time off work was calculated per hour, averaging hourly production losses for men and women, assuming parents to be between 25 and 35 years of age. Hourly estimates were derived from the Dutch guideline for pharmacoeconomic evaluation and are corrected for the elasticity of

labor productivity.¹³ The hourly cost estimate for child care was derived from the Dutch National Institute for Family Finance Information (NIBUD).¹⁶ Travel expenses were calculated for health care visits, surgical procedures, and hospitalizations following the Dutch guideline for pharmacoeconomic evaluation.¹³

The most relevant cost estimates are given in Table 1; a comprehensive overview can be found in Supplemental Table 5.

Statistical Analysis

We used a short time horizon for all analyses and therefore took no discount rate into account. First, we compared the clinical effectiveness of the treatment strategies by the following:

1. calculating the risk differences (RD), with 95% confidence intervals (CI) and numbers needed to treat (NNT), for treatment failure, defined as otoscopic presence of otorrhea at 2 weeks (short-term clinical outcome); and
2. calculating the differences in mean number of days with otorrhea during 6 months of follow-up, with 95% CIs (long-term clinical outcome).

Second, by using a societal perspective, we compared the costs within the 3 treatment groups by calculating mean costs per patient,

TABLE 2 Clinical Effectiveness of Treatment Strategies

| Clinical Outcome Measures | Antibiotic-Glucocorticoid Eardrops, n = 76 | Oral Antibiotics, n = 77 | Initial Observation, n = 77 | Antibiotic-Glucocorticoid Eardrops | | Oral Antibiotics |
|--|--|--------------------------|-----------------------------|------------------------------------|-------------------------|----------------------------|
| | | | | Versus Initial Observation | Versus Oral Antibiotics | Versus Initial Observation |
| At 2-wk follow-up ^a | n = 75 | n = 77 | n = 75 | | | |
| Children with otorrhea, n/total (%) | 4 (5) | 34 (44) | 41 (55) | | | |
| Risk difference, % (95% CI) | | | | 49 (37 to 62) | 39 (26 to 51) | 11 (–6 to 27) ^b |
| NNT | | | | 2 | 3 | 10 |
| During 6-mo follow-up ^c | n = 74 | n = 74 | n = 73 | | | |
| Total no. of days with otorrhea, mean (95% CI) | 9.9 (7.4 to 12.3) | 16.4 (13.3 to 19.4) | 24.1 (18.4 to 29.8) | | | |
| Differences in mean (95% CI) | | | | 14.2 (8.1 to 20.4) | 6.5 (2.6 to 10.4) | 7.7 (1.3 to 14.2) |

^a Assessed by doctor.

^b Short-term diary of 1 child was missing for whom we did have a primary outcome assessment (this child was excluded), so results are slightly different from our previous publication.¹¹

^c As reported in parental diary.

TABLE 3 Use of Resources and Mean Costs (in US Dollars) per Child During 2-Week Follow-up

| Resources | Treatment | | | | | |
|---|---|-----------------------|---------------------------------|-----------------------|------------------------------------|-----------------------|
| | Antibiotic-Glucocorticoid Eardrops, <i>n</i> = 75 | | Oral Antibiotics, <i>n</i> = 77 | | Initial Observation, <i>n</i> = 76 | |
| | Mean No. Used (SE) | Mean Costs, US\$ (SE) | Mean No. Used (SE) | Mean Costs, US\$ (SE) | Mean No. Used (SE) | Mean Costs, US\$ (SE) |
| Intervention costs | — | 22.15 (0) | — | 11.48 (0) | — | 0.00 (0) |
| Study medication | 1.0 (0) | 14.23 (0) | 1.0 (0) | 3.56 (0) | 0.00 (0) | 0.00 (0) |
| Pharmacist fee | 1.0 (0) | 7.92 (0) | 1.0 (0) | 7.92 (0) | 0.00 (0) | 0.00 (0) |
| Direct health care costs | — | 14.68 (4.27) | — | 21.34 (5.18) | — | 43.82 (6.64) |
| Tube removal/reinsertion | 0.00 (0) | 0.00 (0) | 0.00 (0) | 0.00 (0) | 0.00 (0) | 0.00 (0) |
| Tube insertion and adenoideotomy | 0.00 (0) | 0.00 (0) | 0.00 (0) | 0.00 (0) | 0.00 (0) | 0.00 (0) |
| Tube insertion and tonsillectomy | 0.00 (0) | 0.00 (0) | 0.00 (0) | 0.00 (0) | 0.00 (0) | 0.00 (0) |
| Adenotonsillectomy | 0.00 (0) | 0.00 (0) | 0.00 (0) | 0.00 (0) | 0.00 (0) | 0.00 (0) |
| Hospitalization, d | 0.00 (0) | 0.00 (0) | 0.00 (0) | 0.00 (0) | 0.00 (0) | 0.00 (0) |
| Health care visit | | | | | | |
| ENT surgeon | 0.04 (0.02) | 4.15 (2.36) | 0.04 (0.02) | 4.04 (2.30) | 0.13 (0.04) | 13.65 (4.05) |
| Family physicians | 0.11 (0.04) | 5.54 (2.07) | 0.14 (0.04) | 7.81 (2.63) | 0.34 (0.07) | 15.30 (3.09) |
| Other health care professional | 0.01 (0.01) | 2.90 (2.90) | 0.03 (0.03) | 2.69 (2.69) | 0.00 (0) | 0.00 (0) |
| Health care telephone consultation | | | | | | |
| ENT surgeon | 0.00 (0) | 0.00 (0) | 0.05 (0.03) | 2.69 (1.63) | 0.16 (0.05) | 8.19 (2.58) |
| Family physicians | 0.03 (0.02) | 0.54 (0.38) | 0.08 (0.03) | 1.57 (0.62) | 0.13 (0.04) | 2.65 (0.79) |
| Other health care professional | 0.01 (0.01) | 0.35 (0.35) | 0.00 (0) | 0.00 (0) | 0.00 (0) | 0.00 (0) |
| Medication | | | | | | |
| Antibiotic-(glucocorticoid) eardrops, wk prescribed | 0.00 (0) | 0.00 (0) | 0.08 (0.03) | 0.92 (0.38) | 0.12 (0.04) | 1.48 (0.47) |
| Oral antibiotics, wk prescribed | 0.03 (0.02) | 0.07 (0.05) | 0.00 (0) | 0.00 (0) | 0.12 (0.04) | 0.29 (0.10) |
| Other medication | — | 0.72 (0.72) | — | 0.69 (0.54) | — | 0.17 (0.09) |
| Pharmacist fee | 0.05 (0.03) | 0.42 (0.26) | 0.12 (0.04) | 0.93 (0.33) | 0.26 (0.06) | 2.09 (0.48) |
| Direct non-health care costs | — | 1.03 (0.28) | — | 4.22 (1.54) | — | 9.72 (3.90) |
| Over-the-counter medicines | | | | | | |
| Analgesics, d used | 0.61 (0.15) | 0.12 (0.03) | 1.05 (0.20) | 0.27 (0.07) | 1.59 (0.33) | 0.29 (0.06) |
| Nasal sprays, bottles | 0.13 (0.04) | 0.38 (0.13) | 0.25 (0.06) | 0.81 (0.19) | 0.26 (0.06) | 0.82 (0.19) |
| Cough medicines, d used | 0.21 (0.09) | 0.08 (0.04) | 0.26 (0.10) | 0.08 (0.03) | 0.63 (0.23) | 0.17 (0.06) |
| Complementary and alternative medicines, d used | 0.00 (0) | 0.00 (0) | 0.00 (0) | 0.00 (0) | 0.16 (0.10) | 0.04 (0.03) |
| Child care, h | 0.00 (0) | 0.00 (0) | 0.35 (0.21) | 2.53 (1.49) | 1.01 (0.54) | 7.30 (3.90) |
| Travel expenses, hospital visits | 0.05 (0.03) | 0.45 (0.22) | 0.06 (0.03) | 0.54 (0.28) | 0.13 (0.04) | 1.10 (0.33) |
| Indirect non-health care costs | — | 4.56 (2.49) | — | 33.55 (17.81) | — | 28.49 (13.60) |
| Parental time off work, h | 0.12 (0.07) | 4.56 (2.49) | 0.88 (0.47) | 33.55 (17.81) | 0.75 (0.36) | 28.49 (13.60) |
| Total costs | — | 42.43 (4.92) | — | 70.60 (19.27) | — | 82.03 (18.62) |
| Total health care costs | — | 36.83 (4.27) | — | 32.83 (5.18) | — | 43.82 (6.64) |
| Total non-health care costs | — | 5.59 (2.50) | — | 37.77 (18.36) | — | 38.21 (15.04) |

—, not applicable.

with SEs, in both the short (2 weeks) and long term (6 months).

Third, we compared differences in costs between groups to differences in clinical effects between groups, by calculating incremental cost-effectiveness ratios. Short-term cost-effectiveness was expressed as the costs to treat the number of patients needed to prevent 1 treatment failure at 2 weeks. Long-term cost-effectiveness was expressed as cost per day with otorrhea avoided at 6 months of follow-up. Uncertainty

for long-term costs and effects was addressed in probabilistic sensitivity analysis by using bootstrapping techniques with 2000 replicates. Results of this analysis were plotted in a cost-effectiveness plane. All analyses were performed on an intention-to-treat basis, for which we used SPSS version 20 (IBM SPSS Statistics, IBM Corporation, Chicago, IL) and R: A Language and Environment for Statistical Computing (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Participants

Between June 2009 and May 2012, 230 children with tympanostomy tubes and acute otorrhea were randomly allocated to receive either antibiotic-glucocorticoid eardrops (76 children), oral antibiotics (77 children), or initial observation (77 children); 71 (93%), 68 (88%), and 61 (79%) children in the 3 groups, respectively, fully adhered to the assigned management

strategy.¹¹ Their mean age was 4.5 years (SD 2.0). Demographic and clinical characteristics of the 3 groups at baseline were comparable and are described in more detail elsewhere.¹¹

Completeness of Data

At 2 weeks, clinical outcomes and parental diaries, including resource use data were available for 227 (99%) of the 230 children (Supplemental Fig 2). At 6 months, 221 (96%) parental diaries were available.

Clinical Outcomes

Antibiotic-glucocorticoid eardrops were superior to oral antibiotics and initial observation both at 2 weeks and 6 months (Table 2). At 2 weeks, 5% of children treated with eardrops had otorrhea versus 44% of those treated with oral antibiotics (RD -39%, 95% CI -51% to -26%, NNT 3) and 55% of those allocated to initial observation (RD -49%, 95% CI -62% to -37%, NNT 2). At 6 months, the mean number of days with otorrhea was 10 in children treated with eardrops versus 16 in those treated

with oral antibiotics (mean difference -6.5, 95% CI -10.4 to -2.6) and 24 in those allocated to initial observation (mean difference -14.2, 95% CI -20.4 to -8.1).

Costs

Mean costs per patient were lower in children treated with antibiotic-glucocorticoid eardrops than in those receiving oral antibiotics or initial observation in both the short and long term (Tables 3 and 4). At 2 weeks, the mean total costs per patient were US \$42.43 (SE 4.92) for

TABLE 4 Use of Resources and Mean Costs (in US Dollars) per Child During 6-Month Follow-up

| Resources | Treatment | | | | | |
|---|--|-----------------------|--------------------------|-----------------------|-----------------------------|-----------------------|
| | Antibiotic-Glucocorticoid Eardrops, n = 74 | | Oral Antibiotics, n = 74 | | Initial Observation, n = 73 | |
| | Mean No. Used (SE) | Mean Costs, US\$ (SE) | Mean No. Used (SE) | Mean Costs, US\$ (SE) | Mean No. Used (SE) | Mean Costs, US\$ (SE) |
| Intervention costs | — | 22.15 (0) | — | 11.48 (0) | — | 0.00 (0) |
| Study medication | 1.0 (0) | 14.23 (0) | 1.0 (0) | 3.56 (0) | 0.00 (0) | 0.00 (0) |
| Pharmacist fee | 1.0 (0) | 7.92 (0) | 1.0 (0) | 7.92 (0) | 0.00 (0) | 0.00 (0) |
| Direct health care costs | — | 270.51 (396.50) | — | 283.35 (427.26) | — | 504.11 (844.32) |
| Tube removal/reinsertion | 0.11 (0.04) | 59.25 (171.36) | 0.09 (0.04) | 51.85 (185.24) | 0.15 (0.05) | 82.59 (217.55) |
| Tube insertion and adenoidectomy | 0.03 (0.02) | 27.92 (168.65) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Tube insertion and tonsillectomy | 0.01 (0.01) | 14.37 (126.63) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Adenotonsillectomy | 0.01 (0.01) | 7.38 (63.47) | 0 (0) | 0 (0) | 0.01 (0.01) | 7.48 (63.90) |
| Hospitalization, d | 0.04 (0.04) | 26.69 (229.60) | 0.07 (0.05) | 44.48 (274.19) | 0.18 (0.13) | 100.98 (703.87) |
| Health care visit | | | | | | |
| ENT surgeon | 0.55 (0.09) | 57.47 (78.94) | 0.80 (0.12) | 82.70 (104.40) | 1.11 (0.15) | 115.09 (128.86) |
| Family physicians | 0.64 (0.12) | 32.14 (51.12) | 0.81 (0.12) | 41.52 (68.69) | 1.55 (0.23) | 79.90 (111.00) |
| Other health care professional | 0.16 (0.05) | 14.99 (47.80) | 0.22 (0.08) | 16.06 (49.71) | 0.44 (0.18) | 34.08 (120.04) |
| Health care telephone consultation | | | | | | |
| ENT surgeon | 0.16 (0.06) | 8.41 (25.79) | 0.31 (0.07) | 16.12 (30.86) | 0.62 (0.11) | 31.97 (48.61) |
| Family physicians | 0.26 (0.06) | 5.82 (13.31) | 0.43 (0.08) | 9.15 (15.93) | 0.53 (0.11) | 11.86 (19.80) |
| Other health care professional | 0.01 (0.01) | 0.35 (3.01) | 0 (0) | 0 (0) | 0.04 (0.03) | 1.38 (8.29) |
| Medication | | | | | | |
| Antibiotic-(glucocorticoid) eardrops, wk prescribed | 0.50 (0.10) | 5.67 (10.76) | 0.99 (0.16) | 10.20 (13.47) | 1.37 (0.18) | 16.87 (20.04) |
| Oral antibiotics, wk prescribed | 0.45 (0.26) | 0.95 (3.87) | 0.27 (0.12) | 0.66 (2.36) | 1.15 (0.31) | 2.67 (4.79) |
| Other medication | — | 1.82 (7.02) | — | 0.65 (2.11) | — | 1.55 (7.21) |
| Pharmacist fee | 0.92 (0.15) | 7.28 (10.05) | 1.26 (0.18) | 9.96 (12.10) | 2.23 (0.25) | 17.69 (16.73) |
| Direct non-health care costs | — | 14.45 (28.07) | — | 24.77 (48.10) | — | 36.93 (54.82) |
| Over-the-counter medicines | | | | | | |
| Analgesics, d used | 3.19 (0.57) | 0.67 (0.94) | 4.12 (0.88) | 0.74 (1.23) | 5.74 (1.10) | 1.16 (1.98) |
| Nasal sprays, bottles | 0.68 (0.17) | 2.07 (4.33) | 0.82 (0.17) | 2.68 (4.99) | 1.55 (0.39) | 4.78 (10.34) |
| Cough medicines, d used | 1.77 (0.41) | 0.41 (0.87) | 0.84 (0.27) | 0.20 (0.56) | 2.49 (0.65) | 0.78 (1.94) |
| Complementary and alternative medicines, d used | 0.24 (0.13) | 0.04 (0.28) | 0.15 (0.09) | 0.03 (0.18) | 0.82 (0.34) | 0.21 (0.83) |
| Child care, h | 0.53 (0.35) | 3.80 (21.60) | 1.57 (0.66) | 11.29 (40.64) | 1.97 (0.79) | 14.21 (48.59) |
| Travel expenses, hospital visits | 0.89 (0.13) | 7.45 (9.44) | 1.18 (0.20) | 9.82 (14.26) | 1.89 (0.32) | 15.80 (23.03) |
| Indirect non-health care costs | — | 61.09 (202.96) | — | 101.13 (328.38) | — | 99.39 (258.48) |
| Parental time off work, h | 1.61 (0.62) | 61.09 (202.96) | 2.66 (1.00) | 101.13 (328.38) | 2.62 (0.80) | 99.39 (258.48) |
| Total costs | — | 368.20 (510.07) | — | 420.73 (677.29) | — | 640.44 (929.06) |
| Total health care costs | — | 292.67 (396.50) | — | 294.83 (427.26) | — | 504.11 (844.32) |
| Total non-health care costs | — | 75.54 (220.00) | — | 125.90 (359.29) | — | 136.33 (271.43) |

antibiotic-glucocorticoid eardrops, US \$70.60 (SE 19.27) for oral antibiotics, and US \$82.03 (SE 18.62) for initial observation (Table 3). Mean total health care costs were US \$36.83 (SE 4.27), US \$32.83 (SE 5.18) and US \$43.82 (SE 6.64), respectively. Non-health care costs constituted almost half of the total costs in children treated with oral antibiotics and initial observation.

At 6 months, the mean total costs per patient were US \$368.20 (SE 510.07) for antibiotic-glucocorticoid eardrops, US \$420.73 (SE 677.29) for oral antibiotics, and US \$640.44 (SE 929.06) for initial observation (Table 4). Mean total health care costs were US \$292.67 (SE 396.50), US \$294.83 (SE 427.26) and US \$504.11 (SE 844.32), respectively. Non-health care costs contributed up to 30% of the total costs.

Balancing Effects and Costs

Treatment with antibiotic-glucocorticoid eardrops is both clinically superior and has economic benefits over oral antibiotics and initial observation. Because of this dominance, calculating incremental cost-effectiveness ratios is redundant. The cost-effectiveness plane resulting from the probabilistic sensitivity analyses over 6 months show eardrops

to be superior in terms of clinical effectiveness in 100% of the bootstrap samples, with lower costs as compared with oral antibiotics and initial observation in 71% and 99% of the bootstrap samples, respectively (Fig 1).

DISCUSSION

Antibiotic-glucocorticoid eardrops are clinically superior and cost less than oral antibiotics and initial observation in children with tympanostomy tubes who develop otorrhea. Non-health care costs constitute a substantial proportion of the total costs of this condition.

We are the first to present cost-effectiveness of the most common treatment strategies in children with tubes and otorrhea. This economic evaluation was conducted alongside a pragmatic randomized trial, which is considered the best approach for economic evaluations.¹⁷ Adherence to the allocated treatment strategies in the first 2 weeks was high and we were able to include almost all (99% of randomized children in the short term and 97% in the long term) of included children in the cost-effectiveness analysis.

Some aspects of our study deserve further attention. First, we used a pragmatic, nonblinded trial design to enhance the applicability of our

findings to daily practice. Observer and reporting bias were reduced by using 2 different clinical and objective outcomes, 1 reported by a physician and 1 reported by parents, which were consistent in favoring eardrops, while strictly adhering to our predefined outcomes and statistical analyses plan as listed in our study protocol.¹¹ Second, hydrocortisone-bacitracin-colistin eardrops are not routinely available in most countries. We believe that the clinical effectiveness of any combination of antibiotic-glucocorticoid eardrops with a similar antimicrobial activity profile will be the same.¹¹ Third, the health care costs of all 3 treatment strategies may be somewhat higher than we have reported because we did not include data on diagnostic procedures (eg, sampling for microbiological analysis, audiometry) during follow-up. Because the number of diagnostic procedures will be related to persistence of symptoms, the true difference in costs between the groups may be even larger than reported. Fourth, the large SEs reflect the generally skewed distribution of costing data. Although one would use the median to present skewed clinical data, it is common to use the mean in cost-effectiveness analyses to assess the actual impact of interventions on health care budgets. The cost-effectiveness plane, based on bootstrapping techniques, provides a more reliable visualization of the sampling distribution. It shows that eardrops were more effective and less costly as compared with oral antibiotics and initial observation in the vast majority of the samples. Fifth, we chose to balance the societal costs with clinical outcomes instead of quality-adjusted life years. When our trial started, no suitable questionnaire was available for children to self-report their generic health-related quality of life. The most commonly used instrument in economic evaluations, the EQ5D (Youth) requires collection by proxy in children (<8 years of age) and

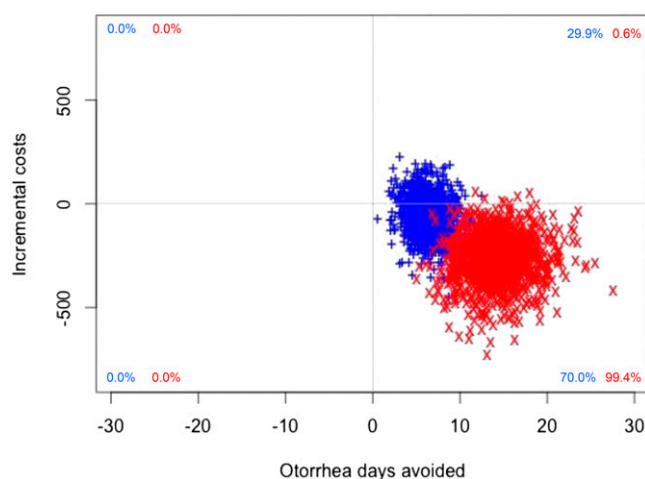


FIGURE 1 Cost-effectiveness plane, showing incremental costs (in US Dollars) and effects of antibiotic-glucocorticoid eardrops as compared with oral antibiotics (blue +) and initial observation (red x) during 6 months of follow-up, with percentages of bootstrap samples per quadrant.

therefore does not provide direct health-related quality of life outcomes, but observational assessment of a child's functioning.^{18–20} In our trial, as previously reported, the generic and disease-specific health-related quality-of-life scores at baseline indicated good quality of life and were similar across the groups.¹¹ The change in generic health-related quality-of-life scores at 2 weeks of follow-up did not differ significantly among the study groups. The changes in disease-specific health-related quality-of-life scores at 2 weeks were small but consistently favored

eardrops. As such, we believe that use of health-related quality-of-life outcomes would not have changed our conclusions. Last, as recommended in economic evaluations, we included all health care resource use during follow-up in our analyses, although not all health care use may be directly related to the initial treatment strategies. Because the most expensive resources (ie, surgery and hospitalization) were higher in the children treated with eardrops than in those treated with oral antibiotics, and comparable to those allocated to initial observation, we believe that

a different approach would not have altered our conclusions.

CONCLUSIONS

Antibiotic-glucocorticoid eardrops are clinically superior and cost less than oral antibiotics and initial observation in children with tympanostomy tubes who develop otorrhea, both in the short and long term.

ACKNOWLEDGMENT

Mart Janssen provided the R syntax that was used to create the cost-effectiveness plane.

Address correspondence to Thijs M.A. van Dongen, MD, PhD, Julius Center for Health Sciences and Primary Care, STR 6.131, University Medical Center Utrecht, PO Box 85500, 3508 GA Utrecht, The Netherlands. E-mail: t.m.a.vandongen@umcutrecht.nl.

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2015 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: Microbiological analyses of samples taken as part of the trial were supported by GlaxoSmithKline through the University Medical Center Utrecht. The authors have no other financial relationships relevant to this article to disclose.

FUNDING: Supported by a grant from the Netherlands Organization for Health Research and Development, Healthcare Efficiency Research Program (ZonMw, grant 170992502). This organization did not participate in the design and conduct of the trial, or the collection, management, analysis, and interpretation of the data, nor did it have a role in the preparation, review, or approval of the manuscript. All authors were independent from the funder and had access to all the data.

POTENTIAL CONFLICT OF INTEREST: Microbiological analyses of samples taken as part of the trial were supported by GlaxoSmithKline through the University Medical Center Utrecht. The authors have no other potential conflicts of interest relevant to this article to disclose.

REFERENCES

1. Health and Social Care Information Centre. United Kingdom. Available at: www.hscic.gov.uk. Accessed February 1, 2013
2. Cullen K, Hall M, Golosinskiy A. *Ambulatory Surgery in the United States, 2006. National Health Statistics Reports; No. 11. Revised.* Hyattsville, MD: National Center for Health Statistics; 2009
3. van Dongen TM, van der Heijden GJ, Freling HG, Venekamp RP, Schilder AG. Parent-reported otorrhea in children with tympanostomy tubes: incidence and predictors. *PLoS ONE*. 2013;8(7):e69062
4. Gates GA. Cost-effectiveness considerations in otitis media treatment. *Otolaryngol Head Neck Surg*. 1996; 114(4):525–530
5. Bondy J, Berman S, Glazner J, Lezotte D. Direct expenditures related to otitis media diagnoses: extrapolations from a pediatric medicaid cohort. *Pediatrics*. 2000;105(6). Available at: www.pediatrics.org/cgi/content/full/105/6/E72
6. Ahmed S, Shapiro NL, Bhattacharyya N. Incremental health care utilization and costs for acute otitis media in children. *Laryngoscope*. 2014;124(1):301–305
7. Roland PS, Waycaster CR, Wall GM, Glass JD. An economic evaluation of two otological treatments for acute otitis media in tympanostomy tube patients. *Value Health*. 2006;9(4):219–226
8. Alsarraf R, Jung CJ, Perkins J, Crowley C, Alsarraf NW, Gates GA. Measuring the indirect and direct costs of acute otitis media. *Arch Otolaryngol Head Neck Surg*. 1999;125(1):12–18
9. Capra AM, Lieu TA, Black SB, Shinefield HR, Martin KE, Klein JO. Costs of otitis media in a managed care population. *Pediatr Infect Dis J*. 2000;19(4): 354–355
10. Niemelä M, Uhari M, Möttönen M, Pokka T. Costs arising from otitis media. *Acta Paediatr*. 1999;88(5):553–556
11. van Dongen TM, van der Heijden GJ, Venekamp RP, Rovers MM, Schilder AG. A trial of treatment for acute otorrhea in children with tympanostomy tubes. *N Engl J Med*. 2014;370(8):723–733
12. Statistics Netherlands. Available at: <http://statline.cbs.nl>. Accessed February 1, 2013
13. Hakkaart-van Roijen L, Tan SS, Bouwmans CAM. Handleiding voor kostenonderzoek, methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg. Diemen, Netherlands: College voor zorgverzekeringen; 2010.
14. College voor Zorgverzekeringen. Independent drug information for healthcare professionals [in Dutch]. 2009. Available at: www.farmacotherapeutischkompas.nl. Accessed February 1, 2013

15. Buskens E, van Staaij B, van den Akker J, Hoes AW, Schilder AG. Adenotonsillectomy or watchful waiting in patients with mild to moderate symptoms of throat infections or adenotonsillar hypertrophy: a randomized comparison of costs and effects. *Arch Otolaryngol Head Neck Surg.* 2007;133(11):1083–1088
16. National Institute for Family Finance Information (NIBUD) Web site [in Dutch]. Available at: www.nibud.nl/uitgaven/kinderen/oppas.html. Accessed February 1, 2013
17. Ramsey S, Willke R, Briggs A, et al. Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA Task Force report. *Value Health.* 2005;8(5):521–533
18. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med.* 2001;33(5):337–343
19. Wille N, Badia X, Bonsel G, et al. Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. *Qual Life Res.* 2010;19(6):875–886
20. Brouwer CN, Maillé AR, Rovers MM, Grobbee DE, Sanders EA, Schilder AG. Health-related quality of life in children with otitis media. *Int J Pediatr Otorhinolaryngol.* 2005;69(8):1031–1041
21. European Central Bank. Euro Exchange Rates USD. Available at: www.ecb.int/stats/exchange/eurofxref/html/index.en.html. Accessed February 1, 2013

Cost-Effectiveness of Treatment of Acute Otorrhea in Children With Tympanostomy Tubes

Thijs M.A. van Dongen, Anne G.M. Schilder, Roderick P. Venekamp, G. Ardine de Wit and Geert J.M.G. van der Heijden

Pediatrics 2015;135:e1182

DOI: 10.1542/peds.2014-3141 originally published online April 20, 2015;

Updated Information & Services

including high resolution figures, can be found at:
<http://pediatrics.aappublications.org/content/135/5/e1182>

References

This article cites 14 articles, 1 of which you can access for free at:
<http://pediatrics.aappublications.org/content/135/5/e1182#BIBL>

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):
Ear, Nose & Throat Disorders
http://www.aappublications.org/cgi/collection/ear_nose_-_throat_disorders_sub
Otitis Media
http://www.aappublications.org/cgi/collection/otitis_media_sub
Infectious Disease
http://www.aappublications.org/cgi/collection/infectious_diseases_sub
Epidemiology
http://www.aappublications.org/cgi/collection/epidemiology_sub

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
<http://www.aappublications.org/site/misc/Permissions.xhtml>

Reprints

Information about ordering reprints can be found online:
<http://www.aappublications.org/site/misc/reprints.xhtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Cost-Effectiveness of Treatment of Acute Otorrhea in Children With Tympanostomy Tubes

Thijs M.A. van Dongen, Anne G.M. Schilder, Roderick P. Venekamp, G. Ardine de Wit and Geert J.M.G. van der Heijden

Pediatrics 2015;135:e1182

DOI: 10.1542/peds.2014-3141 originally published online April 20, 2015;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/135/5/e1182>

Data Supplement at:

<http://pediatrics.aappublications.org/content/suppl/2015/04/14/peds.2014-3141.DCSupplemental>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2015 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

