
Chapter 9

General discussion

Doctor and parent: consensus in dealing with upper respiratory infections in children?

Case history

On a busy Monday morning consulting hour 4-year-old Kevin visits your family practice, accompanied by his mother. You have known the family for quite some years. Their family includes father Ron, mother Annabel, Kevin and his 2-year-old sister Lisette. You have seen Kevin 3 times this year for an aspecific upper respiratory infection and 2 times for a throat infection. Most of these episodes were treated symptomatically with analgesics or a cough mixture. Kevin is a heavy snorer, but otherwise sleeps well. Six weeks ago you prescribed Kevin antibiotics because his mother felt that at that time the symptoms were not resolving spontaneously. Kevin is now again suffering from a sore throat with fever and has been absent from school for the last 3 days. Friends told the mother that their child had had the same problems as Kevin and that adenotonsillectomy (T&Ads) “made him a different child”. She wants your opinion. On examination you see an otherwise healthy 4-year-old boy, who is suffering from an acute throat infection. No alarming signs are present. You decide to treat this episode with penicillin for 7 days. You have just read the results of a recent trial on adenotonsillectomy in children and tell the mother that adenotonsillectomy in children with recurrent upper respiratory infections is unlikely to reduce the number of throat infections or other upper respiratory infections materially and that you do not think referral is appropriate. You advice her on how to deal with these upper respiratory infections and when to contact you. She tells you she is glad an operation is not needed (yet) and leaves your practice. Six weeks later you see her again with Kevin, who is again suffering from an aspecific upper respiratory infection. She, as well as her family and friends, believe a referral to the ENT-surgeon is now necessary.

State of the art on the effectiveness of adenotonsillectomy in children

Children with very frequent throat infections

For children with very frequent throat infections (i.e. 7 or more in the preceding year; 5 or more in each of the 2 preceding years; or 3 or more in each of the 3 preceding years) (adeno)tonsillectomy compared to a non-surgical management reduces the number of throat infections by 1.2 (95% CI 0,8 tot 1.7) episodes per person year.^{1,2} Most doctors agree that (adeno)tonsillectomy is beneficial for this very selective group of children with very frequent throat infections. However, even in these children a spontaneous reduction of the incidence of throat infections can be expected.

Children with obstructive sleep apnoea

Children with obstructive sleep apnoea (OSA) due to adenotonsillar hypertrophy generally benefit from T&Ads. The effectiveness of adenotonsillectomy for obstructive sleep apnoea has not been ascertained in a randomised trial, but several uncontrolled studies have shown considerable postoperative improvement of objective sleep parameters and obstructive complaints.³⁻⁵

Children with relatively mild symptoms of throat infections or adenotonsillar hypertrophy.

Children with very frequent throat infections or a high suspicion of OSA constitute approximately 35% of the children currently undergoing T&Ads in The Netherlands, whereas 65% are operated for non-evidence based indications like less frequent throat infections and milder symptoms of adenotonsillar hypertrophy, or for other indications such as upper respiratory infections. To assess the effectiveness of adenotonsillectomy in these children, we performed our randomised trial. Its results show that many of the children with relatively mild symptoms of throat infections or adenotonsillar hypertrophy will derive only modest benefits from an operation over watchful waiting.

Since Kevin, the boy in our case history, is suffering from relatively mild symptoms of throat infections and recurrent upper respiratory infections, the results of our trial are applicable to him. You therefore decide that referral is, at this moment, not indicated.

The doctor

In the Netherlands, throat infections and other upper respiratory infections are primarily managed by the general practitioner. If our trial results are to be implemented in daily practice, the GP - and ENT surgeon - should be familiar with the trial results and agree with its conclusions.⁶ Currently, many general practitioners and ENT surgeons believe that adenotonsillectomy is not only effective in children with very frequent throat infections and OSA but also in children with less severe throat infections or other indications such as recurrent upper respiratory infections and milder symptoms of adenotonsillar hypertrophy.⁷⁻¹⁰ The question is whether our trial results will change these beliefs.

The parents

When consulting a doctor, parents of children with recurrent upper respiratory infections have certain views about the problem and expectations for treatment, such as effectiveness of antibiotics or surgery.¹¹⁻¹⁴ Prior expectations of parents in the beneficial effect of adenotonsillectomy are usually strong. However, the available trial results are not in agreement with these common expectations and it may be difficult to change them.

Given the growing evidence that patients wish to be involved in decision-making, particularly when the condition is not life threatening, it is important to be aware of patients' (in this case parents') views and expectations.^{15,16} It is also important to realise that the expectations of parents of children with upper respiratory infections influence the doctor's decision.^{9,12,17}

It is obvious that the help-seeking behaviour in the presented case history did not begin in the general practitioners office, but started much earlier in parents' conversations with friends and relatives. The factors that influence patients help-seeking behaviour include 1) signs and symptoms; 2) social interference; 3) medical beliefs; and 4) lay referral network.

Signs and symptoms

The interpretation of the symptoms by the parents affects help-seeking behaviour and is influenced by previous experiences, the perceived seriousness of the symptoms and their duration and/or frequency. As Howel et al.¹⁸ have shown, parental worry and eagerness for surgery were significantly associated with the duration of episodes of throat infections and the number of episodes in the previous year.

Social interference

When valued activities or social demands, such as school or work, are affected by a condition, parents are more likely to seek prompt medical attention. Also if the illness of the child leads to disagreements between the parents regarding the need for therapeutic interventions, medical professionals are often consulted.¹⁹ Two recent studies have shown that recurrent throat infections have a considerable impact on children and their families, especially if a child misses school, or if parents have to take time off work.^{18,20}

Medical beliefs

People have concepts of health and illness that influence how they react to physical symptoms. These medical beliefs are acquired through personal previous experiences, from family and friends, and through the media.¹⁹ In families where parents or siblings have undergone adenotonsillectomy, a higher proportion of parents preferred adenotonsillectomy,¹⁸ and similarly, the probability of a child having a tonsillectomy increased significantly, compared with families where no family members had been treated surgically.^{21,22}

Lay referral network

The lay referral network has an important influence on the help-seeking behaviour for upper respiratory infections.²³ Most people have an informal network of family and friends who offer their own interpretation of the symptoms and ideas about how they should be treated well before any professional medical help is sought. As Burton recently stated, “The word on the street is still this – if you are having trouble with your throat, you should have your tonsils out”.²³

Interaction between doctor and parents

According to current best evidence a referral of Kevin to an ENT-surgeon is not yet indicated. Which tools does the general practitioner have to provide care to such children and to inform the parents so that they agree on evidence-based management of his symptoms?

Education

- *health education*

In the Netherlands the general practitioner is an important source of medical information for many families. As such, he/she should be aware that patients' knowledge of the usual presentation of upper respiratory infections, their natural course, and appropriate treatment is incomplete or inaccurate.²⁴ In particular, the self-limiting character of upper respiratory tract symptoms is often not recognised by patients.^{13,25} Many patients consider antibiotics as necessary treatment for upper respiratory symptoms,²⁴⁻²⁶ 54% believes that bacteria are the cause of upper respiratory infections, only 28% knows that upper respiratory infections are usually caused by viruses and the majority of lay public does not know the difference between bacteria and viruses.^{13,27}

General practitioners therefore have an important task to inform the parents that the natural history of the disease is favourable and that with growing age the incidence of upper respiratory infections will decrease. The latter is probably attributable to maturation of the immune system with growing age. Furthermore, children are often referred for adenotonsillectomy when their complaints are most severe and these are likely to become less severe in time, whether surgery is being performed or not (regression to the mean). This expected reduction in complaints might explain the high parental satisfaction with the surgical procedure.²⁸⁻³⁰ These phenomena emphasise the need for a control group in effectiveness studies. In our randomised trial -including a non-surgical control group- children allocated to the adenotonsillectomy group experienced fewer fever episodes and more improvement of sleeping and eating patterns in the first 6 months after surgery than those in the watchful waiting group. During the remaining follow-up of the trial, however, these differences gradually disappeared. The early difference regarding the objective outcome fever between the surgical and non-surgical group can only be explained by the effectiveness of adenotonsillectomy; the early difference regarding the subjective parameters might also be explained by the parental satisfaction with the surgical strategy (or dissatisfaction with the watchful waiting strategy).

- *encouragement of self management by e.g. supplying leaflets*

Several studies showed that interventions such as distribution of a leaflet with information on a medical condition may have a favourable, but small, impact on health care utilization.^{31,32} Such educational material is usually appreciated by both patients and doctors.³³

Management

- *shared-decision making*

In consultations in which disagreement might occur between parents and clinicians about the necessity of adenotonsillectomy (or antibiotics) a “shared-decision making” model could be applied.^{34,35} This implies explicit exploration of expectations and explanation of possible options and risks. Applying such models improve satisfaction of parents with a non-surgical approach. In current practice, time constraints seriously hampers shared-decision making.

- *management guidelines*

Clinical practice guidelines that are based on valid evidence may facilitate evidence-based care. However, most studies evaluating the effect of clinical guidelines have shown that they lead to only limited changes in physician behaviour.³⁶⁻³⁹ Several barriers are known to influence the implementation of trial results, notably lack of

awareness and of agreement, and external barriers such as lack of time and of other treatment options.⁶ For example, a study by Rovers et al.³⁷ on the effect of tympanostomy tubes in children with bilateral otitis media with effusion showed that dissemination of their trial results did not change the prior beliefs of otorhinolaryngologists. If the expectations as to the effects of adenotonsillectomy on reducing upper respiratory infections remain high, even though trial results do not confirm these beliefs, daily practice is unlikely to change. Therefore, simple dissemination of a guideline is not sufficient. For successful implementation in daily practice, it is important to design implementation strategies.⁴⁰⁻⁴²

In 1999 the Dutch College of General Practitioners (NHG) has issued a guideline for the treatment of sore throat in general practice (NHG-Standaard Acute Keelpijn 1999, revised version from 1990).⁴³ Importantly, this guideline is inconclusive about the indications for (adeno)tonsillectomy. If such a guideline would be developed on the indications for adenotonsillectomy in children, and both individual general practitioners and ENT-surgeons would support this guideline, the chance of implementation of our trial results would increase.

- *other treatment options*

Upper respiratory infections are inevitable when growing up and young children experience on average 6 upper respiratory infections per year.^{44,45} Cultural and social differences play a role in how these upper respiratory infections are managed internationally, such as a preference for antibiotics (e.g. US and UK) or for surgical management of upper respiratory infections (e.g. the Netherlands).⁴⁶ Regarding antibiotics for acute sore throat, recent studies have shown that antibiotics confer only relative benefits in the treatment of acute sore throat and that the absolute benefits are modest.^{47,48} Protecting sore throat sufferers against suppurative and non-suppurative complications in modern western society can only be achieved by treating many children with antibiotics of whom most will derive no benefits from it.^{47,48}

However, children like Kevin have serious complaints and need care. At present, the best available treatment for these children is watchful waiting with careful monitoring of the child and reassurance of parents. During sore throat episodes children should receive adequate symptomatic relief, in particular by sufficient administration of analgesics.^{49,50} It is known that, especially in children, analgesics are often given “on demand” and that both the frequency and dosage are usually not optimal.^{49,51}

Future research

Future research could focus on 3 issues:

1) Individual targeting of the available treatment options.

It is important to individualise the currently available treatment options on an individual basis, as there is no doubt that subgroup(s) exist in which an operation and/or antibiotics and/or watchful waiting are more effective. Unfortunately, these subgroups can not be identified as yet.^{48,52}

- *IPD-meta-analyses.* The power of the available individual trials on adenotonsillectomy is too limited to identify subgroups of children that might benefit from the operation. To identify such subgroups larger numbers or specific groups of children should be studied. However, a more efficient approach to detect subgroups with differences in treatment effect might be to perform individual patient data (IPD) meta-analyses including the original data from all adenotonsillectomy trials performed so far.^{53,54}

- *Prognostic research.* If it were possible to identify children at high-risk of developing frequent upper respiratory infections or complications, we could target our medical interventions, such as adenotonsillectomy, at these children. The prognostic study presented in this thesis is the only available study so far attempting to identify these children,⁵² and showed that it is not possible to predict the development of chronic recurrent upper respiratory infections satisfactorily. Our study might be hampered by a limited sample size, and much larger studies, perhaps also combining individual study data, are necessary to assess whether it is possible –or simply impossible- to predict chronic recurrent upper respiratory infections.

2) Etiological research

Upper respiratory infections are known to be a complex, multifactorial disease resulting from interplay between host factors such as age, genetic predisposition, immunological response, and the microbial load (viral and bacterial), which is influenced by environmental factors such as siblings, group day care and season.^{55,56}

The relative importance of, and interactions between the various known etiological factors is still poorly understood. More insight into the pathogenesis of upper respiratory infections is urgently needed to answer the question why some children are more susceptible to infections of Waldeyer's ring than others and to develop more effective preventive and therapeutic approaches.

3) Preventive measurements and novel therapies

Research in the past decade has focused on the development of preventive strategies for upper respiratory infections, such as immunization with pneumococcal⁵⁷⁻⁵⁹ and viral vaccines,⁶⁰ intranasally administered immunoglobulins,⁶¹ probiotics,^{62,63} α streptococci spray^{46,64} and intranasal steroids.^{65,66} Most of these studies, however, have shown limited benefits of these interventions. Future research should focus on new and more effective therapies that reduce the frequency and/or severity of upper respiratory infections. Most success is expected if such therapies focus on interactions between pathogenic factors.

References

1. Paradise JL, Bluestone CD, Bachman RZ, Colborn DK, Bernard BS, Taylor FH, et al. Efficacy of tonsillectomy for recurrent throat infection in severely affected children. Results of parallel randomized and nonrandomized clinical trials. *N Engl J Med* 1984;**310**:674-83.
2. van Staaik BK, van den Akker EH, van der Heijden GJMG, Schilder AG, Hoes AW. Adenotonsillectomy for upper respiratory infections. Evidence based? *Arch Dis Child* 2004. Accepted for publication.
3. Nieminen P, Tolonen U, Lopponen H. Snoring and obstructive sleep apnea in children: a 6-month follow-up study. *Arch Otolaryngol Head Neck Surg* 2000;**126**:481-6.
4. de Serres LM, Derkay C, Sie K, Biavati M, Jones J, Tunkel D et al., Impact of adenotonsillectomy on quality of life in children with obstructive sleep disorders. *Arch Otolaryngol Head Neck Surg* 2002;**128**:489-96.
5. Flanary VA. Long-term effect of adenotonsillectomy on quality of life in pediatric patients. *Laryngoscope* 2003;**113**:1639-44.
6. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999;**282**:1458-65.
7. Blair RL, McKerrow WS, Carter NW, Fenton A. The Scottish tonsillectomy audit. Audit Sub-Committee of the Scottish Otolaryngological Society. *J Laryngol Otol* 1996;**110 Suppl 20**:1-25.
8. Donnelly MJ, Quraishi MS, McShane DP. Indications for paediatric tonsillectomy GP versus Consultant perspective. *J Laryngol Otol* 1994;**108**:131-4.
9. Capper R, Canter RJ. Is there agreement among general practitioners, paediatricians and otolaryngologists about the management of children with recurrent tonsillitis? *Clin Otolaryngol* 2001;**26**:371-8.
10. van den Akker EH, Schilder AG, Kempes YJ, van Balen FA, Hordijk GJ, Hoes AW. Current indications for (adeno)tonsillectomy in children: a survey in The Netherlands. *Int J Pediatr Otorhinolaryngol* 2003;**67**:603-7.
11. Macfarlane J, Holmes W, Macfarlane R, Britten N. Influence of patients' expectations on antibiotic management of acute lower respiratory tract illness in general practice: questionnaire study. *BMJ* 1997;**315**:1211-4.
12. Vinson DC, Lutz LJ. The effect of parental expectations on treatment of children with a cough: a report from ASPN. *J Fam Pract* 1993;**37**:23-7.
13. Chan CS. What do patients expect from consultations for upper respiratory tract infections? *Fam Pract* 1996;**13**:229-35.
14. Harbarth S, Albrich W, Brun-Buisson C. Outpatient antibiotic use and prevalence of antibiotic-resistant pneumococci in France and Germany: a sociocultural perspective. *Emerg Infect Dis* 2002;**8**:1460-7.
15. Rollnick S, Seale C, Kinnersley P, Rees M, Butler C, Hood K. Developing a new line of patter: can doctors change their consultations for sore throat? *Med Educ* 2002;**36**:678-81.
16. Coulter A. Managing demand at the interface between primary and secondary care. *BMJ* 1998;**316**:1974-6.
17. Webb S, Lloyd M. Prescribing and referral in general practice: a study of patients' expectations and doctors' actions. *Br J Gen Pract* 1994;**44**:165-9.
18. Howel D, Webster S, Hayes J, Barton A, Donaldson L. The impact of recurrent throat infection on children and their families. *Fam Pract* 2002;**19**:242-6.
19. Taylor SE. Health psychology; fourth edition. McGraw-Hill International editions 1999.
20. Stewart MG, Friedman EM, Sulek M, Hulka GF, Kuppersmith RB, Harrill WC et al. Quality of life and health status in pediatric tonsil and adenoid disease. *Arch Otolaryngol Head Neck Surg* 2000;**126**:45-8.

21. Katznelson D, Gross S. Familial clustering of tonsillectomies and adenoidectomies. *Clin Pediatr (Phila)* 1980;**19**:276-83.
22. Domenighetti G, Bisig BE. Tonsillectomy: a family-transmissible surgical procedure. *Lancet* 1995;**346**:1376.
23. Burton M. Tonsillectomy. *Arch Dis Child* 2003;**88**:95-6.
24. Mainous AGI, Zoorob RJ, Oler MJ, Haynes DM. Patient knowledge of upper respiratory infections: implications for antibiotic expectations and unnecessary utilization. *J Fam Pract* 1997;**45**:75-83.
25. van Duijn H, Kuyvenhoven M, Welschen I, den Ouden H, Slootweg A, Verheij T. Patients' and doctors' views on respiratory tract symptoms. *Scand J Prim Health Care* 2002;**20**:201-2.
26. Delbanco TL. Enriching the doctor-patient relationship by inviting the patient's perspective. *Ann Intern Med* 1992;**116**:414-8.
27. Butler CC, Rollnick S, Pill R, Maggs-Rapport F, Stott N. Understanding the culture of prescribing: qualitative study of general practitioners' and patients' perceptions of antibiotics for sore throats. *BMJ* 1998;**317**:637-42.
28. Wolfensberger M, Haury JA, Linder T. Parent satisfaction 1 year after adenotonsillectomy of their children. *Int J Pediatr Otorhinolaryngol* 2000;**56**:199-205.
29. Conlon BJ, Donnelly MJ, McShane DP. Improvements in health and behaviour following childhood tonsillectomy: a parental perspective at 1 year. *Int J Pediatr Otorhinolaryngol* 1997;**41**:155-61.
30. Faulconbridge RV, Fowler S, Horrocks J, Topham JH. Comparative audit of tonsillectomy. *Clin Otolaryngol* 2000;**25**:110-7.
31. Macfarlane JT, Holmes WF, Macfarlane RM. Reducing reconsultations for acute lower respiratory tract illness with an information leaflet: a randomized controlled study of patients in primary care. *Br J Gen Pract* 1997;**47**:719-22.
32. Macfarlane J, Holmes W, Gard P, Thornhill D, Macfarlane R, Hubbard R. Reducing antibiotic use for acute bronchitis in primary care: blinded, randomised controlled trial of patient information leaflet. *BMJ* 2002;**324**:91-4.
33. Roland M, Dixon M. Randomized controlled trial of an educational booklet for patients presenting with back pain in general practice. *J R Coll Gen Pract* 1989;**39**:244-6.
34. Elwyn G, Gwyn R, Edwards A, Grol R. Is 'shared decision-making' feasible in consultations for upper respiratory tract infections? Assessing the influence of antibiotic expectations using discourse analysis. *Health Expect* 1999;**2**:105-17.
35. Butler CC, Kinnersley P, Prout H, Rollnick S, Edwards A, Elwyn G. Antibiotics and shared decision-making in primary care. *J Antimicrob Chemother.* 2001;**48**:435-40.
36. Donaldson LJ, Hayes JH, Barton AG, Howel D, Hawthorne M. Impact of clinical practice guidelines on clinicians' behaviour: tonsillectomy in children. *J Otolaryngol* 1999;**28**:24-30.
37. Rovers MM, Van Der BS, Ingels K, van der Wilt GJ, Zielhuis GA. Does a trial on the effects of ventilation tubes influence clinical practice? *Clin Otolaryngol* 2003;**28**:355-9.
38. Andrew Clement W, Dempster JH. Implementation by Scottish otolaryngologists of the Schottisch Intercollegiate Guideline Network document *Management of Sore Throats and the Indications for Tonsillectomy*: four years on. *J Laryngol Otol* 2004;**118**:357-61
39. O'Connor PJ, Amundson G, Christianson J. Performance failure of an evidence-based upper respiratory infection clinical guideline. *J Fam Pract* 1999;**48**:690-7.
40. Moulding NT, Silagy CA, Weller DP. A framework for effective management of change in clinical practice: dissemination and implementation of clinical practice guidelines. *Qual Health Care* 1999;**8**:177-83.
41. Wensing M, van der WT, Grol R. Implementing guidelines and innovations in general practice: which interventions are effective? *Br J Gen Pract* 1998;**48**:991-7.
42. Cohen SJ, Halvorson HW, Gosselink CA. Changing physician behavior to improve disease prevention. *Prev Med* 1994;**23**:284-91.
43. NHG-standaard acute keelpijn. *Huisarts Wet* 1999;**42**:271-278.

44. Monto AS, Ullman BM. Acute respiratory illness in an American community. The Tecumseh study. *JAMA* 1974;**227**:164-9.
45. Kvaerner KJ, Nafstad P, Jaakkola JJ. Upper respiratory morbidity in preschool children: a cross-sectional study. *Arch Otolaryngol Head Neck Surg* 2000;**126**:1201-6.
46. Schilder AG, Lok W, Rovers MM. International perspectives on management of acute otitis media: a qualitative review. *Int J Pediatr Otorhinolaryngol* 2004;**68**:29-36.
47. Del Mar CB, Glasziou PP, Spinks AB. Antibiotics for sore throat. *Cochrane Database Syst Rev* 2000;CD000023.
48. Zwart S, Rovers MM, de Melker RA, Hoes AW. Penicillin for acute sore throat in children: randomised, double blind trial. *BMJ* 2003;**327**:1324.
49. Bertin L, Pons G, d'Athis P, Lasfargues G, Maudelonde C, Duhamel JF, et al. Randomized, double-blind, multicenter, controlled trial of ibuprofen versus acetaminophen (paracetamol) and placebo for treatment of symptoms of tonsillitis and pharyngitis in children. *J Pediatr* 1991;**119**:811-4.
50. Schachtel BP, Thoden WR. A placebo-controlled model for assaying systemic analgesics in children. *Clin Pharmacol Ther* 1993;**53**:593-601.
51. Medisch-farmaceutische mededelingen 1992;**7**:703-704.
52. van Staaïj BK, Rovers MM, van den Akker EH, Schilder AG, Hoes AW. Is it possible to predict chronic recurrent upper respiratory infections in children? submitted 2004.
53. Stewart, LA, Palmer MKB. Meta-analysis of the literature or of individual patient data: is there a difference? *Lancet* 1993;**341**, 418-422.
54. Oxman AD, Clarke MJ, Stewart LA From science to practice. meta-analysis using individual patient data are needed. *JAMA* 1995;**274**:845-846.
55. Kvaerner KJ, Nafstad P, Jaakkola JJK. Upper respiratory morbidity in preschool children - A cross-sectional study. *Archives of Otolaryngology-Head & Neck Surgery* 2000;**126**:1201-6.
56. Selwyn BJ. The Epidemiology of Acute Respiratory-Tract Infection in Young-Children - Comparison of Findings from Several Developing-Countries. *Reviews of Infectious Diseases* 1990;**12**:S870-S888.
57. Straetemans M, Sanders EA, Veenhoven RH, Schilder AG, Damoiseaux RA, Zielhuis GA. Pneumococcal vaccines for preventing otitis media. *Cochrane Database Syst Rev* 2002;CD001480.
58. Dagan R, Sikuler-Cohen M, Zamir O, Janco J, Givon-Lavi N, Fraser D. Effect of a conjugate pneumococcal vaccine on the occurrence of respiratory infections and antibiotic use in day-care center attendees. *Pediatr Infect Dis J* 2001;**20**:951-8
59. Eskola J, Kilpi T, Palmu A, Jokinen J, Haapakoski J, Herva E, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. *N Engl J Med* 2001;**344**:403-9.
60. Hoberman A, Greenberg DP, Paradise JL, Rockette HE, Lave JR, Kearney DH, et al. Effectiveness of inactivated influenza vaccine in preventing acute otitis media in young children: a randomized controlled trial. *JAMA* 2003;**290**:1608-16.
61. Heikkinen T, Ruohola A, Ruuskanen O, Waris M, Uhari M, Hammarstrom L. Intranasally administered immunoglobulin for the prevention of rhinitis in children. *Pediatr Infect Dis J* 1998;**17**:367-72.
62. Hatakka K, Savilahti E, Ponka A, Meurman JH, Poussa T, Nase L, et al. Effect of long term consumption of probiotic milk on infections in children attending day care centres: double blind, randomised trial. *BMJ* 2001;**322**:1327.
63. Lodinova-Zadnikova R, Cukrowska B, Tlaskalova-Hogenova H. Oral administration of probiotic *Escherichia coli* after birth reduces frequency of allergies and repeated infections later in life (after 10 and 20 years). *Int Arch Allergy Immunol* 2003;**131**:209-11.
64. Falck G, Grahn-Hakansson E, Holm SE, Roos K, Lagergren L. Tolerance and efficacy of interfering alpha-streptococci in recurrence of streptococcal pharyngotonsillitis: a placebo-controlled study. *Acta Otolaryngol* 1999;**119**:944-8.

65. Ruohola A, Heikkinen T, Waris M, Puhakka T, Ruuskanen O. Intranasal fluticasone propionate does not prevent acute otitis media during viral upper respiratory infection in children. *J Allergy Clin Immunol* 2000;**106**:467-71.
66. Puhakka T, Makela MJ, Malmstrom K, Uhari M, Savolainen J, Terho EO, et al. The common cold: effects of intranasal fluticasone propionate treatment. *J Allergy Clin Immunol* 1998;**101**:726-31.

