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Antibiotic prescriptions for children`s lower respiratory tract infections fell from 2014-2020 but misuse was seen

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Antibiotic prescriptions for children with lower respiratory tract infections fell from 2014-2020 but misuse was still an issue

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

Abbreviations

CAP, community-acquired pneumonia; CI, confidence interval; ENT, ear, nose and throat specialist; GP, general practitioner; LRTI, lower respiratory tract infection.

ABSTRACT (200/200 words)

Aim

We evaluated main trends in antibiotic prescriptions for children with lower respiratory tract infection (LRTI) by Terveystalo, Finland's largest private healthcare company.

Methods

The study comprised 89,359 children aged 0-17 years (57.2% boys) who visited Terveystalo primary care clinics from 2014-2020 with LRTI. The data were assessed by age, study year, location, the doctor's speciality and whether the diagnosis was bronchitis or community-acquired pneumonia (CAP).

Results

There were gradual decreases in overall antibiotic prescription rates during the study period (37.0% in 2014 vs 20.1% in 2020) and in prescribed macrolides (16.8% vs 7.5%). Altogether, 31.3% of 72,737 children with bronchitis and 22.5% of those 16,622 with CAP received antibiotics. Macrolides were the most frequently prescribed antibiotics for bronchitis, at more than 40%, without any substantial relative decrease during the study. Costs of antibiotics increased from 2014 to 2016, and then decreased in line with the reduction in prescriptions. However, there was still a marked overuse of antibiotics, especially macrolides, for children with bronchitis. The relative use of amoxicillin for CAP increased from 41.4% to 65.4% between 2016-2020, in line with current guidelines.

Conclusion: Despite an overall reduction in prescribed antibiotics, some antibiotics were still overused, particularly macrolides for bronchitis.

Keywords: Antibiotics, bronchitis, community-acquired pneumonia, lower respiratory tract infections, macrolides

Key Notes

- This nationwide study evaluated antibiotics prescribed for nearly 90,000 children with lower respiratory tract infections by the largest private healthcare company in Finland.
- Despite an overall reduction in prescriptions from 37.0% in 2014 to 21.1% in 2020, macrolides were still overused for bronchitis.
- Antibiotics were prescribed only for 22.5% community-acquired pneumonias, which is against the guidelines, whereas amoxicillin prescriptions increased during the study years in line with the guidelines.

INTRODUCTION

Lower respiratory tract infection (LRTI) is an umbrella term that is used for infections in the lower airways, such as bronchitis, influenza and community-acquired pneumonia (CAP). However, LRTI has also been used as a synonym for CAP. Bronchitis presents with symptoms and signs that affect both upper and lower airways, and it is primarily caused by viruses, irrespective of the presence or absence of wheezing.[1,2] Symptoms of influenza vary in children, and influenza cannot be clinically separated from LRTIs caused by other viruses.[3]

CAP diagnosis is clinical, and this means that radiological or laboratory studies are not needed in uncomplicated cases, according to the national[1] and international huidelines.[4,5] However, similar symptoms and signs, such as cough, fever, tachypnoea, fatigue, and crackles on auscultation, may occur in children with other LRTIs.[2] That is why the boundaries between different LRTI syndromes are blurred. Substantial variations can occur in how doctors interpret clinical findings and reach specific diagnoses.[6,7]

Current evidence-based guidelines recommend that children with CAP should be treated with amoxicillin or narrow-spectrum antibiotics which are effective against *Streptococcus pneumoniae.*[1,4,5] However, there are two exceptions when it comes to children with full pneumococcal vaccinations. The British Thoracic Society guidelines[4] state that children under the age of 2 years need not be treated with antibiotics if they have CAP with mild symptoms. The guidelines from the Infectious Diseases Society of America[5] provide the same advice for children under the age of 5 years. Macrolides are not recommended for monotherapy, because *Streptococcus pneumoniae* is not sufficiently susceptible to macrolides in many countries.[1,4,5] The Finnish

evidence-based Current Care Guidelines for LRTIs in children were published in 2014[1,2] and are consistent with the British and American guidelines.

A task force set up by the European Paediatric Association concluded that over-consumption of antibiotics by children with spontaneously recovering respiratory tract infections was one of the important healthcare problems in Europe.[8] Reduced consumption and more targeted primary care prescriptions are necessary to decrease the emergence of resistant bacteria and to increase the stewardship of the antibiotics that are available.[8,9]

This study aimed to evaluate antibiotics prescribed for Finnish children with LRTIs from 2014-2020 by a nationwide private outpatient network. Special attention was paid to how well the doctors complied with the 2014 Finnish Current Care Guidelines for children's LRTIs[1,2], specifically regarding prescribing of macrolides. In addition, we estimated the costs of the prescribed antibiotics, in relation to patients' age, hospital districts and the doctors' speciality.

MATERIAL AND METHODS

The study was conducted using data from the electronic health records of Terveystalo, the largest private healthcare company in Finland. Terveystalo has more than 300 clinics, which cover all 20 hospital districts across the country, and these receive about 250,000 paediatric visits a year. Finland provides comprehensive, high-quality health services for children, including child health clinics and school health care. Parents can also choose from a range of private health care services, and about 45% of children are covered by these policies. Prescriptions issued by all public and private healthcare providers are entered into the same electronic system and can be viewed online

by any pharmacy. This medication is then dispensed at nationally set rates. The Government pays 40% of the costs of children's antibiotics and their parents, or the insurance company, pay the rest.

The study population comprised children aged 0-17 who visited Terveystalo private primary care clinics from January 2014 to 31 December 2020 (Table S1). The children were divided into 3 age groups: under 5, 5-9 and 10-17 years. We excluded patients with a concomitant bacterial diagnosis, such as a urinary tract infection or streptococcal pharyngitis, and LRTIs complicated by acute otitis media or sinusitis (Table S2). The antibiotics that were prescribed were identified by the Anatomical Therapeutic Chemical Classification system (Table S3).

Terveystalo uses the Dynamic Health tool (TietoEVRY, Espoo, Finland) to handle the electronic health record data. Mandatory fields include certain codes, such as the International Classification of Diseases, Tenth Revision, codes. The records are inputted online by the practitioners and stored online in Microsoft Structured Query Language server database (Microsoft Corp, Washington, USA).

The data extracted from the database for this study included the patient's age and sex, information on their visits, and diagnoses and medications registered by the practitioners. The ages were calculated from birth dates and presented as the actual ages during the visits. Doctors were classified as paediatricians, general practitioners (GP), ear, nose and throat (ENT) doctors, and others. All the patient data were actively managed and conformed to the European Union's General Data Protection Regulation and Finland's data security legislation.

Cost data

Antibiotic-related costs were estimated using the June 2021 reference price for each product in Euros. The Finnish Pharmaceutical Pricing Board sets the national reference prices that all pharmacies charge for medication, such as antibiotics, and these are reimbursed under the Health Insurance Act. The data that were collected, included the name of the drug that was prescribed to each patient, but this did not include detailed information about the dose, the amount of the drug in the tablet, its concentration in the mixture or the size of the prescribed packet. Therefore, the costs were estimated as the lowest and highest prices for each antibiotic, using the smallest and largest packet that could be dispensed. This meant that the variations in costs could be compared by study years. The annual costs and the cost per patient were estimated on the assumption that every prescribed antibiotic was purchased.

Statistical analysis

All the LRTI visits made by the eligible children during the study period were included in the analyses. We used SPSS for Windows, version 26 (IBM Corp, New York, USA) for the data management. In addition, we used the Wald test of Stata, version 16.1 (StataCorp, Texas, USA), to calculate the 95% confidence intervals (95% CI) for the proportions. The statistical analyses focused on percentages to take account of the fact that respiratory infections were reduced by lockdown measures throughout 2020.[10,11] These measures followed the World Health Organization announcement on 11 March 2020 that COVID-19 was officially a pandemic.

Ethics

This was a register-based study and patients were not contacted, which meant that informed consent was not required from patients or their parents or guardians under Finnish law. The study was approved by the Chief Medical Officer of Terveystalo.

RESULTS

Between 2014 and 2020, children aged 0-17 made 117,878 visits (57.5% boys) to Terveystalo primary care clinics with LRTI. We excluded 28,519 (24.2%) of the total visits from the analyses due to non-respiratory bacterial infections or LRTI complications that required antibiotic treatment. These exclusions were 23,923 (83.9%) cases of acute otitis media, 3,881 (13.6%) cases of sinusitis and 715 (2.5%) cases of LRTI with another bacterial infection. The remaining 89,359 (75.8%) visits for uncomplicated LRTI (57.2% boys) were included in the analyses on antibiotic prescriptions and comprised 81.4% of patients with bronchitis and 18.6% with CAP (Table 1). Nearly half (46.8%) of the visits that we studied were in children under 5 years and a fifth (19.9%) under 2 years of age.

The overall numbers of LRTIs peaked in 2017-2018, decreased in 2019 and then fell further in 2020 due to the COVID-19 pandemic (Table 2). Compared to bronchitis, there were relatively more CAP visits in 2020 than in 2014-2019 (Table 2). This was because fewer children visited the outpatient clinics in 2020, the first year of the COVID-19 pandemic, but they presented with more severe infections.

Overall antibiotic prescriptions for LTRIs and specifically macrolide prescriptions gradually decreased in all age groups during the study years (Figure 1). The highest rate of antibiotic prescriptions was for children who were over 10 years old: 41.0% in 2014 and 23.9% in 2020. The figures for macrolides were 18.2% and 10.3%, respectively. The largest decrease in the macrolide prescription rates was in children under age 5 years, from 14.3% in 2014 to 4.6% in 2020, meaning a relative reduction of 67.8%. Prescribing macrolides for children under age 2 years fell from 12.5% to 1.6%, respectively, meaning a relative reduction of 87.2%.

When we included only those children who were treated with antibiotics in the analyses, macrolides were the most frequently prescribed antibiotics for bronchitis. These accounted for a minimum of 44.8% when all study years were individually examined (Figure 2A). We observed rather stable prescription rates for other antibiotics, except a marginal increase in amoxicillin-clavulanic acid prescriptions in 2019 and 2020.

Antibiotics were prescribed only for 22.5% of children with CAP, compared to 31.3% of those with bronchitis. Amoxicillin was the first-line antibiotic chosen for CAP (Figure 2B). The numbers of amoxicillin prescriptions remained constant between 2014-2020, but the amoxicillin prescription rate for CAP increased because the overall antibiotic prescriptions decreased. The consumption of amoxicillin for CAP in relation to other antibiotics increased from 41.4% in 2016 to 65.4% in 2020. Concomitantly, the relative use of macrolides decreased from 37.0% in 2016, when prescribing rates were highest, to 20.5% in 2020 (Figure 2B).

The costs of the antibiotics increased from 2014 to 2016, and then decreased. The highest annual costs in 2016 were estimated to be €52,000 to €104,200 if the lowest and highest reference prices were used (Figure 3). In 2019, the figures were €27,900 to €55,400, respectively. The annual costs were lowest in 2020, probably due to the pandemic, and these were €9,300 if the lowest and €18,600 if the highest reference prices were used. During the total 2014-2020 study period, 80% to 91% of the costs were due to antibiotics prescribed for bronchitis, with a slightly decreasing trend over time. The mean cost per antibiotic prescription from 2014-2020 was €9.20 (95% CI €9.17–9.23) at the lowest and €18.55 (95% CI €18.45–18.64) at the highest reference price. When both treated and non-treated patients were included in the analysis, the mean antibiotic-related cost per patient ranged from €3.45 to €6.96 in 2014 to and from €1.84 to €3.67 in 2020, when the lowest and

highest reference prices were used, respectively. The decreasing cost trends were similar for prescriptions for bronchitis and CAP (data not shown).

Paediatricians prescribed antibiotics less often than GPs and ENT doctors (Figure 4). For example, macrolide prescription rates were highest amongst ENT doctors each year, with some reductions between 2017 and 2020 (Figure 4). There were notable regional variations in overall antibiotic use (21.9–46.7%) and macrolide use (5.8–27.1%) from 2014 to 2020 (Figure S1).

DISCUSSION

This real-life register-based study on antibiotic prescriptions in the private sector issued to nearly 90,000 paediatric patients aged 0-17 years with LRTI found that bronchitis accounted for 81.4% of the diagnoses and CAP accounted for 18.6% in 2014-2020. The overall antibiotic prescription rate was 31.3% for bronchitis and 22.5% for CAP. Our antibiotic prescription rate for bronchitis is in line with the international reports[7,12,13], but our prescription rate for CAP was exceptionally low compared to the rates over 80% in other studies[13-15].

The present study produced two key findings. First, prescriptions of antibiotics for children with LRTI gradually decreased from 37.0% in 2014 to 20.1% in 2020. This result suggests that the national 2014 guidelines[1,2] had some but slow impact on prescribing practices. The reduction is in line with observations made in children treated in the 2010`s in paediatric emergency departments in France[13,14]. The use of broad-spectrum antibiotics such as amoxicillin-clavulanic acid decreased in the primary care clinics in USA[7,12], and in the national antibiotic prescription data from France[15]. The use of broad-spectrum antibiotics was not any notable problem in our data, although a marginal increase for amoxicillin-clavulanic avid was seen in 2019-2020.

Contrary to our expectations, there were more antibiotic prescriptions for bronchitis, which is mainly considered a viral self-improving infection,[2,8,9] than for CAP, which needs to be treated with antibiotics that tackle *Streptococcus pneumoniae.*[1,4,5] The newest evidence on the futility of antibiotics in presumably viral respiratory tract infections comes from England[16]. A prospective randomised controlled trial allocated 432 children aged 6 months to 12 years with uncomplicated respiratory tract infection to amoxicillin or placebo treatment arms, and disease courses and durations of the symptoms did not differ between the arms[16].

The second key finding was that macrolide prescriptions reduced from 16.8% in 2014 to 7.5% in 2020, which means that the use of macrolides more than halved. This reduction was mostly due to fewer prescriptions of macrolides for children with CAP that is in line with the current guidelines[1,4,5]. Macrolides were the first choices for treating bronchitis by all doctors, including paediatricians, and for children at all ages. Like viral bronchitis, *Mycoplasma pneunoniae* or *Clamydophila pneumoniae* infections usually improve spontaneously, even in the case of pneumonia without severe symptoms[17,18], and microbe-specific diagnosis and antibiotics are not needed.

Some decrease in macrolide use has been documented in other paediatric studies, but macrolides are still overused in many countries[18-20] A retrospective American register study of 252,177 paediatric outpatients with CAP found that macrolide monotherapy was used in 43.2% of cases, narrow-spectrum well-targeted antibiotics in 26.1% and broad-spectrum antibiotics in 24.7%[19]. The figures mean that only one-fourth of children with CAP were treated according to the recommendations. The overall risks of subsequent hospitalisation (0.59%) or the development of severe pneumonia (0.05%) were low, but interestingly, the risks were highest in children who received broad-spectrum

antibiotics.

The latest study year, 2020, was during the COVID-19 pandemic. Many studies have concluded that social distancing, quarantines and hygiene measures reduced the circulation of all respiratory viruses[10,11]. Less frequent virus contacts, coupled with decreased access to medical facilities, have reduced visits to doctors[10,11], which was seen also in the present study. We found evidence that children, who visited primary care clinics in 2020, presented with more severe infections than in 2014-2019. Despite this, antibiotic prescription rates reduced. Because the data are presented as ratios, we feel confident that we have presented an accurate picture of the ongoing trends in antibiotic prescriptions from 2014 to 2020.

There were only minor differences by age, with fewer prescriptions for younger children, and these can be partly explained by the currently available guidelines. The British and American CAP guidelines, for example, suggest that children with mild disease under the ages of 2 years and 5 years, respectively, can be treated without antibiotics[4,5]. Our findings suggest that those recommendations were followed, but however, this does not explain the overall low antibiotic prescription rate for CAP. Young children visited more often paediatricians than other doctors, and paediatricians are known to be more adherent with guidelines[15,21,22] and accordingly, prescribed antibiotics less often than GPs and ENT doctors.

The finding that less than one-fourth of children with CAP were treated with antibiotics in the present study needs special attention. We did not find any explanation for this unexpected observation. One simple reason may be that some doctors do not divide LRTIs into separate diagnosis-specific groups, such as bronchitis and pneumonia, and they describe antibiotics based on severity of the clinical picture[6,9,23]. A study from France focused on 680 GPs and 70 community

paediatricians and found substantial inconsistency in relation to diagnoses in antibiotic prescribing[15]. Paediatricians prescribed antibiotics for nearly all children with CAP (99.2%), which was in accordance with the guidelines, and GPs prescribed antibiotics for two-thirds (65.2%) and paediatricans for half (47.2%) of bronchitis cases, which is against the guidelines.

Although many guidelines have been published on how to treat LRTIs in children, very few studies have looked at how successfully the guidelines have been implemented[7,12,20]. One American study evaluated the impact of a 6-month personalised audit and feedback programme on how primary care providers issued prescriptions for antibiotics for paediatric CAP[20]. The participants diagnosed CAP in 301 children who were treated with antibiotics, and 94.1% of patients over age 5 years received antibiotics in accordance with the guidelines, compared to 78.6% in controls. The nation-wide electronic health record system used by all doctors of the present study provides a suitable template for doctor-specific education and feedbacks containing real-time clinical data, including data on prescriptions, as was successfully used to reduce cough medicine prescriptions for children[24,25]. Based on our results, active interventions should not only target the use of appropriate therapy but also improving differential diagnosis of LRTIs in children.

An observational study on costs in 14 primary care networks across 13 European countries comprised 2,690 children with LRTI. The mean total cost for treating each patient was €24 to €116, depending on the country[26]. In Finland, such cost was €84. The medication costs formed 11% to 22% of the total costs. A time-series analysis in South Korea showed a decreasing trend in antibiotic-related costs for children with LRTI, after a national programme targeted at GPs, was introduced to reduce medication costs. However, the costs increased after the intervention, which confirms that repeated or continuous efforts are needed[27].

The main strength of this study was that the data came from outpatient clinics across Finland and included nearly 90,000 children aged 0-17 with LRTIs. The information was electronically collected online and obtained for this study from the centralised and uniformly coded health records. The main limitation was that the data only covered the private sector, and so, the findings may not fully reflect cases treated by the public sector. In addition, the diagnoses were obtained directly, without any checking, from the electronic records.

CONCLUSION

This study showed an overall reduction in the number for antibiotics dispensed to children aged 0-17 with LRTIs from 2014-2020 by a large private healthcare provider. However, there was still a marked overuse of antibiotics, especially macrolides for bronchitis, despite a decreasing trend over time. Instead, antibiotics were prescribed for CAP less than recommended by the guidelines, The relative use of amoxicillin for CAP cases increased between 2016 (41.4%) and 2020 (65.4%), which was in line with recommendations. Our results suggest that compliance with the Finnish Current Care Guidelines for children`s LRTIs, which were published in July 2014, remained inappropriate until 2020.

REFERENCES

1. Tapiainen T, Aittoniemi J, Immonen J, et al. Finnish guidelines for the treatment of community-acquired pneumonia and pertussis in children. *Acta Paediatr.* 2016;105:39–43.
2. Tapiainen T, Aittoniemi J, Immonen J, et al. Finnish guidelines for the treatment of laryngitis, wheezing bronchitis and bronchiolitis in children. *Acta Paediatr*. 2016;105:44–9.
3. Heikkinen T. Influenza in children. *Acta Paediatr*. 2006;95:778–84.

4. Harris M, Clark J, Coote N, et al. British Thoracic Society guidelines for the management of community acquired pneumonia in children: update 2011. *Thorax*. 2011;66:ii1–23.
5. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: Clinical Practice Guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis.* 2011;53:e25–76.
6. Mansbach JM, Espinola JA, Macias CG, Ruhlen ME, Sullivan AF, Camargo CA. Variability in the diagnostic labeling of nonbacterial lower respiratory tract infections: A multicenter study of children who presented to the emergency department. *Pediatrics.* 2009;123:e573–81.
7. Gerber JS, Prasad PA, Russell Localio A, et al. Variation in antibiotic prescribing across a pediatric primary care network. *J Pediatric Infect Dis Soc*. 2015;4:297–304.
8. Størdal K, Wyder C, Trobisch A, Grossman Z, Hadjipanayis A. Overtesting and overtreatment—statement from the European Academy of Paediatrics (EAP). *Eur J Pediatr.* 2019;178:1923–7.
9. Esposito S, Bianchini S, Argentiero A, Neglia C, Principi N. How does one choose the appropriate pharmacotherapy for children with lower respiratory tract infections? *Expert Opin Pharmacother*. 2020;21:1739–47.
10. Isba R, Edge R, Auerbach M, et al. COVID-19: Transatlantic declines in pediatric emergency admissions. *Pediatr Emerg Care*. 2020;36:551–3.
11. Kuitunen I, Artama M, Mäkelä L, Backman K, Heiskanen-Kosma T, Renko M. Effect of social distancing due to the COVID-19 pandemic on the incidence of viral respiratory tract infections in children in Finland during early 2020. *Pediatr Infect Dis J*. 2020;39:E423–7.
12. Mainous A. Lambourne CA, Nietert PJ. Impact of a clinical decision support system on antibiotic prescribing for acute respiratory infections in primary care: quasi-experimental

trial. *J Am Med Inform Assoc.* 2013;2):317-24.

13. Angoulvant F, Skurnik D, Bellanger H, et al. Impact of implementing French antibiotic guidelines for acute respiratory-tract infections in a paediatric emergency department. *Eur J Clin Microbiol Infect Dis.* 2012;31:1295-303.
14. Launay E, Levieux K, Levy C, et al. Compliance with the current recommendations for prescribing antibiotics for paediatric community-acquired pneumonia is improving: data from a prospective study in a French network. BMC Pediatr. 2016;16:126.
15. Trinh NTH, Cohen R, Lemaitre M, et al. Community antibiotic prescribing for children in France from 2015 to 2017: a cross-sectional national study. *J Antimicrob Chemother*. 2420;75:2344–52.
16. Little P, Francis NA, Beth Stuart B, et al. Antibiotics for lower respiratory tract infection in children presenting in primary care in England (ARTIC PC): a double-blind, randomised, placebo-controlled trial. *Lancet.* 2021 Sep;S0140-6736(21)01431-8.
17. Meyer Sauteur PM, Unger WWJ, Van Rossum AMC, Berger C. The art and science of diagnosing Mycoplasma pneumoniae infection. *Pediatr Infect Dis J.* 2018;37:1192–5.
18. Principi N, Esposito S. Emerging role of Mycoplasma pneumoniae and Chlamydia pneumoniae in paediatric respiratorytract infections. *Lancet Infect Dis.* 2001;1:334–44.
19. Lipsett SC, Hall M, Ambroggio L, et al. Antibiotic choice and clinical outcomes in ambulatory children with community-acquired pneumonia. J Pediatr. 2021;229:207-215.e1.
20. Diaz MCG, Handy LK, Crutchfield JH, Cadilla A, Hossain J, Werk LN. Impact of a personalized audit and feedback intervention on antibiotic prescribing practices for outpatient pediatric community-acquired pneumonia. Clin Pediatr (Phila). 2020;59:988–94.
21. Frost HM HM, McLean HQ, Chow BDW. Variability in antibiotic prescribing for upper respiratory illnesses by provider specialty. *J Pediatr.* 2018;203:76-85.e8.
22. Saleh EA, Schroeder DR, Hanson AC, Banerjee R. Guideline-concordant antibiotic

prescribing for pediatric outpatients with otitis media, community-acquired pneumonia, and skin and soft tissue infections in a large multispecialty healthcare system. *Clin Res Infect Dis*. 2015;2:1010.

23. Shah SN, Bachur RG, Simel DL, Neuman MI. Does this child have pneumonia? The rational clinical examination systematic review. *JAMA*. 2017;318:462–71.

24. Csonka P, Heikkilä P, Koskela S, et al. Cough and cold medicine prescription rates can be significantly reduced by active intervention. *Eur J Pediatr*. 2021 Dec [Online ahead of print].

25. Palmu S, Heikkilä P, Kivistö JE, et al. Cough medicine prescriptions for children were significantly reduced by a systematic intervention that reinforced national recommendations. *Acta Paediatr.* 2022 Feb 10 [Online ahead of print].

26. Oppong R, Coast J, Hood K, Nuttall J, Smith RD, Butler CC. Resource use and costs of treating acute cough/lower respiratory tract infections in 13 European countries: results and challenges. *Eur J Heal Econ*. 2011;12:319–29.

27. Han E, Chae SM, Kim NS, Park S. Effects of pharmaceutical cost containment policies on doctors' prescribing behavior: Focus on antibiotics. *Health Policy.* 2015;119:1245–54.

LEGENDS

Table 1. Characteristics of the 89,359 cases aged 0-17 with lower respiratory tract infections

Table 2. Numbers of children with lower respiratory tract infection (LRTI), divided into uncomplicated and complicated (acute otitis, sinusitis and other bacterial infections) cases, and into bronchitis and pneumonia (CAP) cases, in relation to all acute respiratory infections.

Figure 1. Antibiotic prescription rates for lower respiratory tract infection (LRTI), namely bronchitis and community-acquired pneumonia (CAP), in three age groups from 2014 to 2020. Error bars indicate 95% confidence intervals (95% CI). N = 89,359. The grey background demonstrates the COVID-19 pandemic.

Figure 2. Antibiotic prescription rates for bronchitis (Panel A, n = 22,733) and community-acquired pneumonia (Panel B, n = 3,740) among those children who received antibiotics. Children not prescribed antibiotics were excluded. Error bars indicate 95% confidence intervals (95% CI). The grey background demonstrates the COVID-19 pandemic.

Figure 3. Annual antibiotic costs estimated with the lowest (min €) and highest (max €) reference prices in Euros and the proportion of the costs for those with bronchitis or community-acquired pneumonia. The grey background demonstrates the COVID-19 pandemic.

Figure 4. Macrolide prescription rates by provider speciality for children with lower respiratory tract infection, namely bronchitis or community-acquired pneumonia. PED, paediatrics. GP, general practitioner. ENT, ear, nose and throat specialist. Error bars indicate 95% confidence intervals (95% CI). N = 89,359. The grey background demonstrates the COVID-19 pandemic.

Table 1. Characteristics of the 89,359 cases aged 0-17 with lower respiratory tract infections

	n (%)
Age groups (years)	
<2	17,741 (19.9)
<5	41,864 (46.8)
5.00–9.99	22,013 (24.6)
10.00–17.99	25,482 (28.5)
Gender (boys)	51,123 (57.2)
Community-acquired pneumonia	16,622 (18.6)
Bronchitis	73,566 (82.3)
Specialist visit to	
Paediatrician	32,023 (35.8)
General practitioner	43,792 (49.5)
Ear nose and throat	7,146 (8.0)
Other specialities	6,398 (7.2)

Uncomplicated LRTIs which were included in the analyses on antibiotic prescriptions

Table 2. Numbers of children with lower respiratory tract infection (LRTI), divided into uncomplicated and complicated (acute otitis, sinusitis and other bacterial infections) cases, and into bronchitis and pneumonia (CAP) cases, in relation to all acute respiratory infections.

Visits for respiratory infection	**Year 2014 n (%)**	**Year 2015 n (%)**	**Year2016 n (%)**	**Year 2017 n (%)**	**Year 2018 n (%)**	**Year 2019 n (%)**	**Year 2020 n (%)**
All visits	94,560	98,700	122,811	134,517	134,206	130,733	78,655
Uncomplicated LRTI (% of all visits)	10,719 (11.4)	12,661 (12.8)	18,258 (14.9)	15,675 (11.7)	14,744 (11.0)	12,247 (9.4)	5,055 (6.4)
Complicated LRTI (% of all visits)	3,917 * (4.1)	3,791 * (3.8)	5041 * (4.1)	4,646 * (3.5)	4,824 * (3.2)	4,244* (3.2)	2,056 (2.6)
Bronchitis (% of uncomplicated LRTI)	9,702 (90.5)	10,630 (84.0)	14,136 (77.4)	13,595 (86.7)	11,252 (76.3)	9,683 (79.1)	3,739 (74.0)
CAP (% of uncomplicated LRTI)	1,017 # (9.5)	2,031 # (16.0)	4,122 & (22.6)	2,080 # (13.3)	3,492 & (23.7)	2,564 # (20.9)	1,316 (26.0)

Statistical significance compared to the year 2020: * $p < 0.001$ between visits for complicated and uncomplicated LRTI cases; # $p < 0.001$ between visits for CAP and bronchitis cases; & $p < 0.01$ between visits for CAP and bronchitis cases. Complicated LRTIs were not included on the analyses on antibiotic prescriptions.

Figure 1. Antibiotic prescription rates for lower respiratory tract infection (LRTI), namely bronchitis and community-acquired pneumonia (CAP), in three age groups from 2014 to 2020. Error bars indicate 95% confidence intervals (95% CI). N = 89,359. The grey background demonstrates the COVID-19 pandemic.

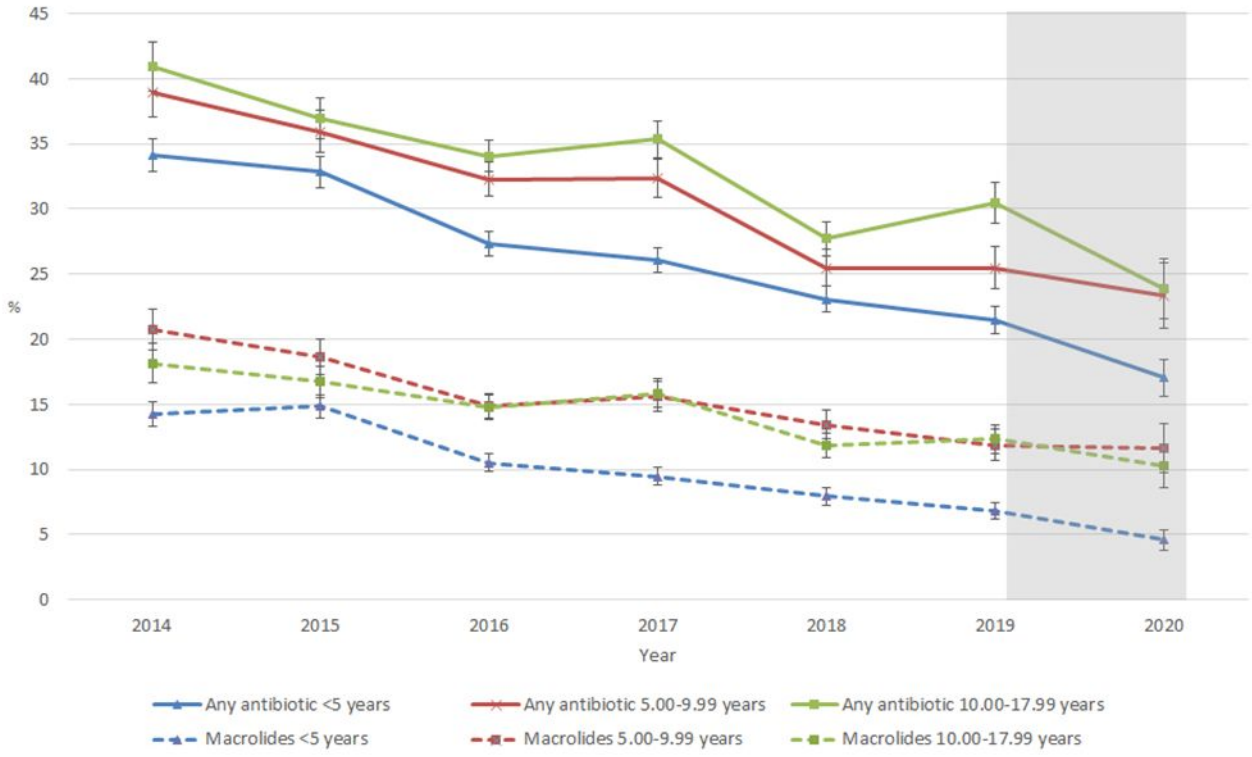


Figure 2. Antibiotic prescription rates for bronchitis (Panel A, n = 22,733) and community-acquired pneumonia (Panel B, n = 3,740) among those children who received antibiotics. Children not prescribed antibiotics were excluded. Error bars indicate 95% confidence intervals (95% CI). The grey background demonstrates the COVID-19 pandemic.

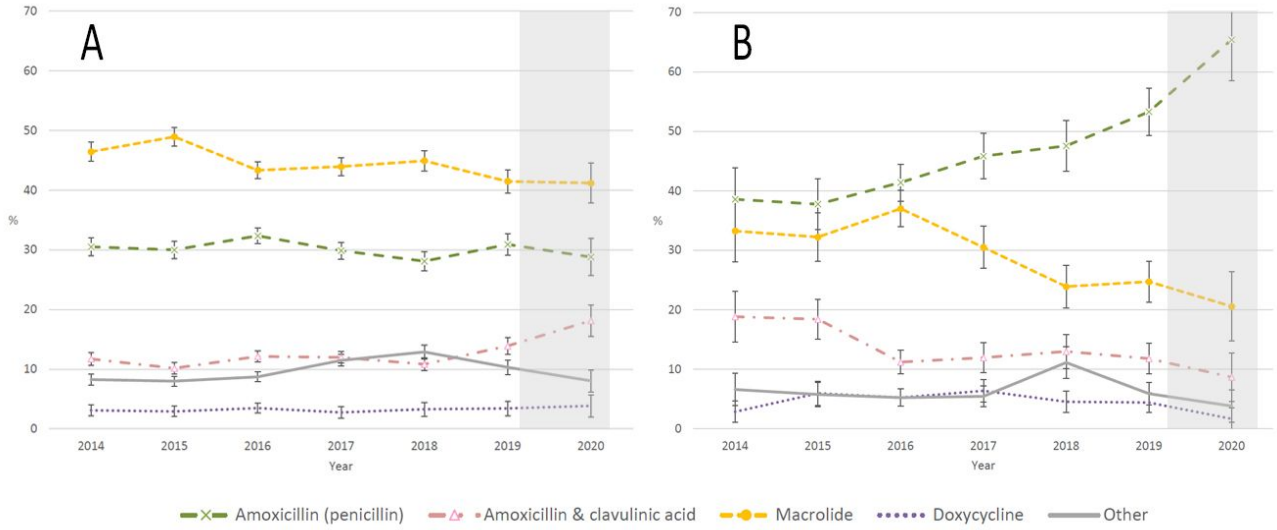


Figure 3. Annual antibiotic costs estimated with the lowest (min €) and highest (max €) reference prices in Euros and the proportion of the costs for those with bronchitis or community-acquired pneumonia. The grey background demonstrates the COVID-19 pandemic.

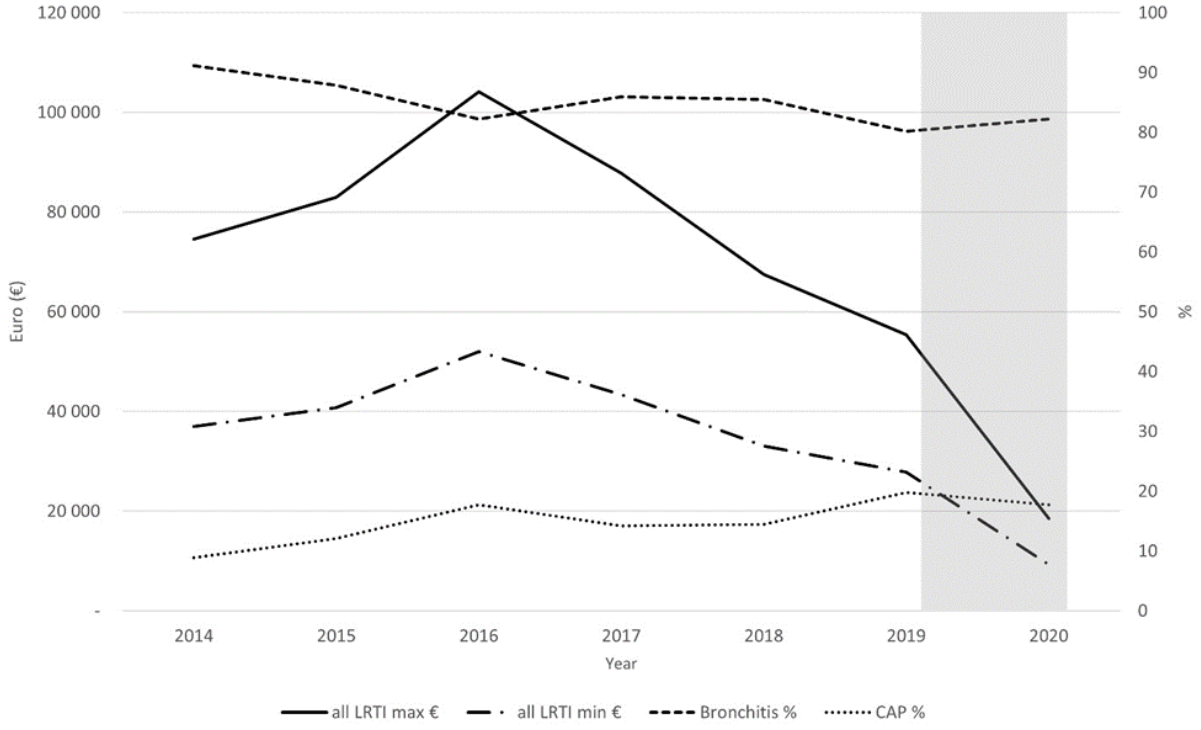
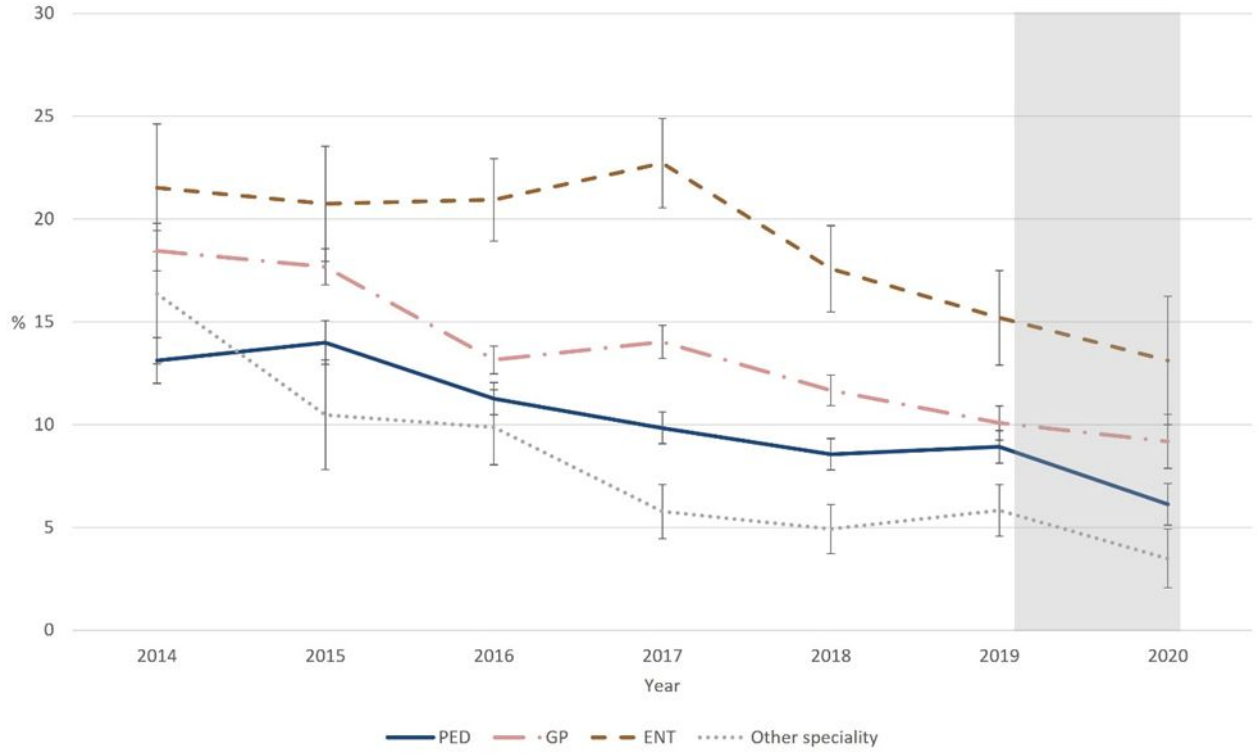


Figure 4. Macrolide prescription rates by provider speciality for children with lower respiratory tract infection, namely bronchitis or community-acquired pneumonia. PED, paediatrics. GP, general practitioner. ENT, ear, nose and throat specialist. Error bars indicate 95% confidence intervals (95% CI). N = 89,359. The grey background demonstrates the COVID-19 pandemic.



Supplementary material

Figure S1. Antibiotic prescription rates in children with lower respiratory tract infections (LRTI), namely bronchitis or pneumonia, in relation to the 20 hospital districts in Finland. Total number of visits from 2014 to 2020 (n=89,141). Missing cases (n=218, 0.2%). Visits for LRTIs in brackets.

Table S1 Diagnostic categories for lower respiratory tract infection included in the study. International Classification of Diseases, Tenth Revision.

Table S2 Competing diagnosis codes. International Classification of Diseases, Tenth Revision

Table S3 Antibiotic groups. Anatomical Therapeutic Chemical classification.

Antibiotic prescriptions for children with lower respiratory tract infections fell from 2014-2020 but misuse was still an issue.

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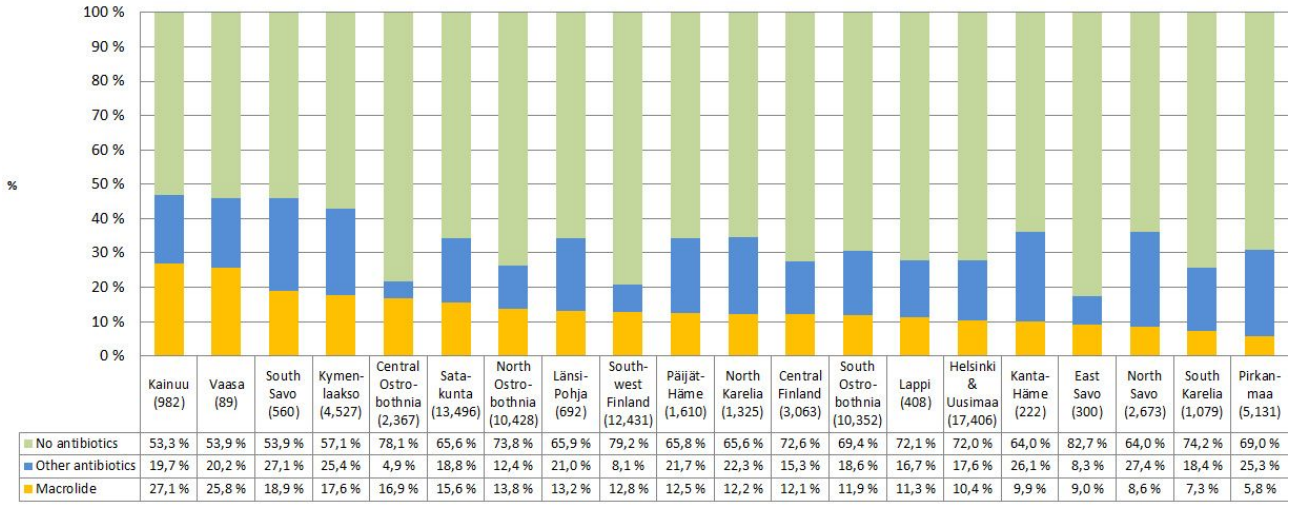
Supplementary Figure and Tables

Figure S1 Antibiotic prescription rates in children with lower respiratory tract infection (LRTI, bronchitis or community-acquired pneumonia) in relation to the 20 hospital districts in Finland. The number in parenthesis indicates the visits for LRTI in the district. The total number of visits from 2014 to 2020, n = 89,141. Missing cases, n = 218 (0.2%)



	Kainuu (982)	Vaasa (89)	South Savo (560)	Kymen-laakso (4,527)	Central Ostro-bothnia (2,367)	Sata-kunta (13,496)	North Ostro-bothnia (10,428)	Länsi-Pohja (692)	South-west Finland (12,431)	Päijät-Häme (1,610)	North Karelia (1,325)	Central Finland (3,063)	South Ostro-bothnia (10,352)	Lappi (408)	Helsinki & Uusimaa (17,406)	Kanta-Häme (222)	East Savo (300)	North Savo (2,673)	South Karelia (1,079)	Pirkan-maa (5,131)
No antibiotics	53,3 %	53,9 %	53,9 %	57,1 %	78,1 %	65,6 %	73,8 %	65,9 %	79,2 %	65,8 %	65,6 %	72,6 %	69,4 %	72,1 %	72,0 %	64,0 %	82,7 %	64,0 %	74,2 %	69,0 %
Other antibiotics	19,7 %	20,2 %	27,1 %	25,4 %	4,9 %	18,8 %	12,4 %	21,0 %	8,1 %	21,7 %	22,3 %	15,3 %	18,6 %	16,7 %	17,6 %	26,1 %	8,3 %	27,4 %	18,4 %	25,3 %
Macrolide	27,1 %	25,8 %	18,9 %	17,6 %	16,9 %	15,6 %	13,8 %	13,2 %	12,8 %	12,5 %	12,2 %	12,1 %	11,9 %	11,3 %	10,4 %	9,9 %	9,0 %	8,6 %	7,3 %	5,8 %

Table S1 Diagnostic categories for lower respiratory tract infection included in the study. International Classification of Diseases, Tenth Edition.

Bronchitis: J20, J20.0, J20.1, J20.2, J20.3, J20.4, J20.5, J20.6, J20.7, J20.8, J20.9, J21.0, J21.8, J21.9, J21.99, J22
Community-acquired pneumonia: J13, J14, J15, J15.0, J15.1, J15.2, J15.3, J15.4, J15.5, J15.6, J15.7, J15.8, J15.9, J16, J16.0, J16.8, J18.9, J09, J10.0, J10.1, J10.8, J11, J11.0, J11.1, J11.8, J12, J12.0, J12.1, J12.2, J12.18, J12.19

Table S2 Competing diagnosis codes. International Classification of Diseases, Tenth Edition.

Otitis media: H65.0, H65.1, H65.2, H65.3, H65.4, H65.9, H66.0, H66.1, H66.2, H66.3, H66.4, H66.9, H67.0.
Sinusitis: J01.0, J01.1, J01.2, J01.3, J01.4, J01.8, J01.9.
Mycobacterial infection: A31, A31.0, A31.9.
Clamydial infection: A70, A71.0, A71.1, A71.9.
Pharyngeal infection: J02.8, J02.9, J03.0, J03.8, J03.9, J39.0, J39.1.
Sialoadenitis: K11.2, K11.3.
Appendicitis: K35.0, K35.1, K35.9, K36.
Skin infection: L00, L01, L01.0, L01.1, L02, L02.1, L02.2, L02.3, L02.4, L02.8, L02.9, L03, L03.0, L03.1, L03.2, L03.3, L05.0.
Pyelonephritis: N10.
Cystitis: N30, N30.0, N30.9.

Table S3 Antibiotic groups. Anatomical Therapeutic Chemical (ATC) classification system

Amoxicillin (penicillin)	
J01CA04	Amoxicillin
J01CE02	Phenoxymethylpenicillin
Amoxicillin-clavulinic acid	
J01CR02	Amoxicillin/Clavulanic acid
First-generation cephalosporin	
J01DB01	Cefalexin
Macrolide	
J01FA01	Erythromycin
J01FA06	Roxithromycin
J01FA09	Clarithromycin
J01FA10	Azithromycin
J01FA15	Telithromycin
Doxycycline	
J01AA02	Doxycycline
Other	
J01DC02	Cefuroxime
J01CA08	Pivmecillinam
J01DD04	Ceftriaxone
J01EA01	Trimethoprim
J01EE01	Sulfamethoxazole/Trimethoprim
J01EE02	Sulfasalazine/Trimethoprim
J01MA01	Ofloxacin
J01MA02	Ciprofloxacin
J01MA06	Norfloxacin
J01MA12	Levofloxacin
J01XA01	Vancomycin
J01AA07	Tetracycline