Epidemiology

Sore throat in primary care project: a clinical score to diagnose viral sore throat

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Abstract

Objective. Viral agents cause the majority of sore throats. However, there is not currently a score to diagnose viral sore throat. The aims of this study were (i) to find the rate of bacterial and viral causes, (ii) to show the seasonal variations and (iii) to form a new scoring system to diagnose viral sore throat.

Methods. A throat culture for group A beta haemolytic streptococci (GABHS) and a nasopharyngeal swab to detect 16 respiratory viruses were obtained from each patient. Over a period of 52 weeks, a total of 624 throat cultures and polymerase chain reaction analyses were performed. Logistic regression analysis was performed to find the clinical score.

Results. Viral infection was found in 277 patients (44.3%), and GABHS infection was found in 116 patients (18.5%). An infectious cause was found in 356 patients (57.1%). Rhinovirus was the most commonly detected infectious agent overall (highest in November, 34.5%), and the highest GABHS rate was in November (32.7%). Analysis of data provided a scoring system, called the Mistik Score, to diagnose viral sore throat. The predictive model for positive viral analysis included the following variables: absence of headache, stuffy nose, sneezing, temperature of ≥37.5°C on physical examination, and the absence of tonsillar exudate and/or swelling. The probability of a positive viral analysis for a score of 5 was 82.1%.

Conclusion. The Mistik Score may be useful to diagnose viral sore throat. We suggest its use either alone or in combination with the Modified Centor Score.

Key words: Diagnose, sore throat, primary care, viral, score.
used as a gold standard laboratory test. New generation rapid antigen tests are better. However, they cannot be used alone or instead of throat culture (7). The clinical manifestations of GABHS and non-streptococcal pharyngitis overlap broadly (8). The Centor Score is used for the diagnosis of GABHS sore throat (9). The Modified Centor Score, which includes the evaluation of the age of patients with a sore throat, was described by McIsaac et al. (2). Although these two scores and many others are used for the diagnosis of GABHS sore throat, there is need to improve the criteria, in order to prevent the unnecessary use of antibiotics throughout the world.

The aims of this study were (i) to find the rate of bacterial and viral causes of sore throats, (ii) to show the seasonal variations and (iii) to form a new scoring system to diagnose viral sore throat which may reduce overuse of antibiotics.

Methods

Study population

Patients with a sore throat, who had applied to Bunyamin Somyurek Family Medicine Centre which is located in the centre of Kayseri province, were included in the study. Patients of any age or gender may apply to their family physicians for any medical problems. A family physician examines approximately 600 sore throat patients in a year. The family physicians were asked to include one sore throat patient for every week in the study. Sore throat patients with a history suggesting infectious causes who were between the ages of 3 and over and agreed to participate in the study were included. The patients with non-infectious causes such as postnasal drip, low humidity in the environment, irritable exposure to cigarettes or smog and malignant disease were not included in the study. Informed consents were obtained from adults and the parents of the children.

Questionnaire

The patients’ histories and clinical findings were recorded in detail. A questionnaire consisting of demographic data questions and complaints was given to the patients and the physical examination findings were also recorded. In order to minimise observer variations or discrepancies, training was given to the family physicians by an ear, nose and throat specialist.

Setting and procedure

The study was conducted in a Family Medicine Centre, in which 12 family physicians work. A throat culture for GABHS and a nasopharyngeal swab to detect 16 respiratory viruses were obtained from each patient. The study was started in the first week of June 2013 and samples were taken for 52 weeks. Throat swab cultures were collected from the patients and swab specimens were inoculated at 37°C, the plates were evaluated for the presence of GABHS. Nasopharyngeal swab specimens were collected from the patients and placed in viral transport media (Copan, Italy). The specimens were sent to the virology laboratory for respiratory virus testing.

A total of 624 throat cultures and polymerase chain reaction (PCR) analyses were performed. An Anyplex II RV16 Detection kit (Seegene, Korea) was used to detect 14 RNA viruses and two DNA viruses including human adenovirus (ADV), influenza A and B viruses (FluA, FluB), human parainfluenza viruses 1/2/3/4 (PIV1/2/3/4), human rhinovirus A/B/C (HRV A/B/C), human respiratory syncytial viruses A and B (RSV-A, RSV-B), human bocaviruses 1/2/3/4 (BoV1/2/3/4), human coronaviruses 229E, NL63 and OC43 (CoV-229E, CoV-NL63, CoV-OC43), human metapneumovirus (MPV) and human enterovirus (EV) (coxackievirus).

Statistical analysis

Univariate and multivariate binary logistic regression analyses were performed to find the factors predicting viral infection. Every factor in the history of the patient and physical examination was evaluated one by one. The statistically significant factors in univariate binary logistic regression analysis were included in the model by using multivariate binary logistic regression with the backward Wald method. In the logistic regression analysis, there was a statistically significant difference only in the analysis of viruses compared with bacteria, bacteria plus virus and no microbiological cause. There was no statistically significant difference when the no microbiological cause group was added to the virus group as presumed viral infection. The model was formed according to the equation below (9).

\[
P = \frac{e^{\beta_0 + \beta_1 X_1 + \ldots + \beta_k X_k}}{1 + e^{\beta_0 + \beta_1 X_1 + \ldots + \beta_k X_k}},
\]

where ‘P’ stands for probability. One point was given for the presence of each variable in the model (9). The probability of the presence of viral infection was calculated for each score. If the score is 0, 1 or 2 there is no virus, and if it is 4 or 5 a virus is present. When the score is 3, a decision is made by putting the score in the logistic regression model. When the coefficients are placed, \( P < 0.5 \) means there is no virus and \( P \geq 0.5 \) means a virus is present. The probability changes depending on the presence of different types of variable combinations.

Receiver operating characteristic (ROC) curve analysis was performed between the scores and the PCR analysis results. The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood and negative likelihood ratio were calculated for the scores and the signs and symptoms, which were statistically significant. Throat culture and PCR analysis were used as reference standards for the Modified Centor Score and the score to diagnose viral sore throat, respectively. The level of significance was considered at 5%.

Results

Patients’ characteristics

Over a period of 52 weeks, 624 patients were included in the study. The mean age of the patients was 25.50 ± 17.71 (range 3–85, median 21). Of the patients, 42.0% were male, and 58.0% were female. Sixty-four patients (10.3%) were preschool children, 268 (42.9%) were students, 152 (24.4%) were housewives, 32 (5.1%) were retired and the remaining 108 (17.3%) were government employees and those working in the private sector. In our study, age was not statistically significant in the logistic regression analysis for the Modified Centor Score and the Mistik Score. The distribution of viral infection versus GABHS according to age group is given in Supplementary Figure s1.

Viral analysis and throat culture

Of the 624 sore throat patients included in the study in the period June 2013–June 2014, viral infection was found in 277 patients (44.3%), and GABHS infection was found in 116 patients (18.5%). An infectious cause was found in 356 patients (57.1%), whereas no infectious cause was found in 268 patients (42.9%). Thirty-seven patients (5.9%) had both GABHS and viral infections. Viral infection only was found in 240 (38.4%) of the patients, and GABHS infection only was found in 79 patients (12.6%) (Table 1).
Detected viruses

The detected viruses are shown in Table 2. The coronavirus types were: OC43 (21), NL63 (8) and 229E (10). The parainfluenza types were: PIV1 (15), PIV 2 (1), PIV3 (11) and PIV4 (5). Four viruses were detected in one patient (rhinovirus, parainfluenza 4, bocavirus and enterovirus). In another patient, three viruses were detected (rhinovirus, coronavirus OC43 and coronavirus 229E). Sixteen patients had two virus infections including rhinovirus [six with enterovirus, three with parainfluenza (two PIV1, one PIV3), three with influenza A, two with coronavirus (OC43 and NL63), one with ADV, and one with RSV A]. There were two virus combinations of influenza A (three with influenza B, two with coronavirus 229E). Two other two-virus combinations (PIV1 plus PIV3, and coronavirus 229E plus RSV B) were also found.

Twenty-three patients had rhinovirus with GABHS. Five patients had influenza A and GABHS. Three patients had parainfluenza (PIV1) and GABHS. Two patients had RSV and GABHS (one RSV A and one RSV B). Three other patients had coronavirus (OC43), ADV, and metapneumovirus in combination with GABHS infection. One patient had rhinovirus plus enterovirus plus GABHS.

Rhinovirus was the most commonly detected infectious agent overall (highest in November at 34.5%, lowest in March at 16.6%) (Supplementary Figure s2). The highest GABHS rate was in November (32.7%) and the lowest in June (6.5%).

Evaluation with the Modified Centor Score

Of the patients, 170 (27.2%) had Modified Centor Scores of zero or less, 359 (57.5%) had scores between 1 and 3, and 95 (15.2%) had scores of 4 or more. It has been stated that empiric antibiotic treatment may be considered in patients with a score of 4 or more (10). There were 35 (5.6%) patients with a Centor Score of 4 and 95 (15.2%) patients with a Modified Centor Score of 4 or more in our study. The throat culture results were sent to the general practitioners by e-mail in approximately 48 hours. However, the design of this study did not include an intervention to reduce the antibiotic prescription rates. In general, the patients were treated based on their symptoms and the physical examination findings. In case of a GABHS positive throat culture result, the prescription of the patient was rapidly evaluated for the presence of an antibiotic. In this study, 489 (78.4%) patients were prescribed an antibiotic by their general practitioners.

Infection type and the Modified Centor Scores are given in Table 3. Viruses caused a Modified Centor Score of 4 or 5 on many occasions (HRV 23, PIV 3, coronavirus 3, FLUB 2, HEV 2, MPV 2, RSV 1, ADV 1, and two virus infections seven times).

Score to diagnose viral sore throat

The predictive model for positive viral analysis included the following variables: absence of headache, stuffy nose, sneezing, temperature of ≥37.5°C on physical examination and the absence of tonsillar exudate and/or swelling (Table 4). The logistic regression model is given in Supplementary Figure s3.

The probability of a positive viral analysis for scores of 0 to 5 was 8.3%, 14.7%–20.4%, 25.2%–36.3%, 42.2%–55.3%, 61.9%–70.7% and 82.1%, respectively. No GABHS was present in patients with a score of 5.

In order to generalise the results, we randomly split our data as 70% (training data) for ROC model building and 30% (validation data) for validation. We defined cut-off values for each variable in the training data and assessed the performances in the validation data. The performance results of each factor are given in Table 5. The sensitivity of this score, called the ‘Mistik Score’, was 60.2% and the specificity was 72.5%. The positive predictive value was 62.5% and the negative predictive value was 70.5%. The positive likelihood ratio was 2.19 and the negative likelihood ratio was 0.55. The Mistik Score was compared with the Modified Centor Score as a clinical decision rule, which is used for the diagnosis of GABHS.

Table 1. Distribution of viral and GABHS infections

<table>
<thead>
<tr>
<th>Infection</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virus</td>
<td>240</td>
<td>38.4</td>
</tr>
<tr>
<td>GABHS</td>
<td>79</td>
<td>12.6</td>
</tr>
<tr>
<td>GABHS and virus</td>
<td>37</td>
<td>5.9</td>
</tr>
<tr>
<td>None</td>
<td>268</td>
<td>42.9</td>
</tr>
<tr>
<td>Total</td>
<td>624</td>
<td>100.0</td>
</tr>
</tbody>
</table>

*Group a beta haemolytic streptococci.

Table 2. Results of viral analysis

<table>
<thead>
<tr>
<th>Virus</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinovirus</td>
<td>153</td>
<td>24.5</td>
</tr>
<tr>
<td>Coronavirus</td>
<td>39</td>
<td>6.2</td>
</tr>
<tr>
<td>Parainfluenza</td>
<td>32</td>
<td>5.1</td>
</tr>
<tr>
<td>Influenza A</td>
<td>29</td>
<td>4.6</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>15</td>
<td>2.4</td>
</tr>
<tr>
<td>RSV*</td>
<td>14</td>
<td>2.2</td>
</tr>
<tr>
<td>Influenza B</td>
<td>10</td>
<td>1.6</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>6</td>
<td>0.9</td>
</tr>
<tr>
<td>MPV*</td>
<td>6</td>
<td>0.9</td>
</tr>
<tr>
<td>Bocavirus</td>
<td>2</td>
<td>0.3</td>
</tr>
<tr>
<td>None</td>
<td>347</td>
<td>55.6</td>
</tr>
</tbody>
</table>

*Respiratory syncytial virus.

<table>
<thead>
<tr>
<th>Infection</th>
<th>Modified Centor Score</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virus</td>
<td>−1</td>
<td>0</td>
</tr>
<tr>
<td>Virus</td>
<td>19</td>
<td>60</td>
</tr>
<tr>
<td>GABHS*</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>GABHS and virus</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>None</td>
<td>27</td>
<td>54</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>122</td>
</tr>
</tbody>
</table>

*Group a beta haemolytic streptococci.
as there is no other score at present for the diagnosis of viral sore throat.

In our study, the sensitivity of the Modified Centor Score was 62.9%, the specificity was 78.5%, the positive predictive value was 40.1%, and the negative predictive value was 90.3%. The positive likelihood ratio was 2.93 and the negative likelihood ratio was 0.47.

The positive predictive values of the Mistik Score and the Modified Centor Score were found for each month, and varied between 47.8%–65.2% and 31.0%–62.5%, respectively. The diagnostic accuracy of the Mistik Score was 68%, and that of the Modified Centor Score was 75%. There was a negative correlation between the Modified Centor Score and the Mistik Score ($r = -0.357$, $P < 0.001$).

**Discussion**

**Statement of principal findings**

This study demonstrated to us, by means of laboratory findings, that viral infection was found in 44.3% of the patients and GABHS infection was found in 18.5%. An infectious cause was found in 57.1% of the patients, whereas no infectious cause was found in 42.9%. Thirty-seven (5.9%) patients had both GABHS and viral infections. Viral infection only was found in 240 (38.4%) of the patients and GABHS infection only was found in 79 patients (12.6%).

We have described herein a score to diagnose viral sore throat with the following variables: absence of headache, stuffy nose, sneezing, temperature of $\geq 37.5 ^{\circ} C$ on physical examination and the absence of tonsillar exudates and/or swelling.

**Strengths and limitations**

The strength of our study was that we worked on laboratory proven viral infections, instead of presumed viral infections, and showed the clinical association of signs and symptoms with a score which could make a major difference in the clinical approach of many family physicians and other doctors. The first variable of the score is absence of headache. It has been reported that although headache is not one of the Centor criteria, it is a commonly looked for symptom of strep throat and is associated with GABHS infection in both children and adults (11). Stuffy nose and sneezing are the most common symptoms caused by respiratory viruses. Although rhinovirus, the most common virus, is not thought to cause fever, Bellei et al. (12) reported a 50.5% incidence of fever in rhinovirus related cases in their study. This is in agreement with the Mistik Score’s fever criterion. The presence of the fever variable in both bacterial and viral scores is possible because fever is observed in both kinds of infections. Also, the difference in the temperature levels may explain how fever may be present in both scores. Exudative tonsillitis is commonly associated with ADV, EBV, and GABHS infection, although influenza virus, parainfluenza virus or enteroviruses have been reported (13–15). We had few cases of ADV and enterovirus infections or...
influenza and parainfluenza infections in our study. However, the absence of tonsillar exudates is a criterion of the Mistik Score.

The limitation of this study was that we did not ask the doctors in the study to change their routine practice and only prescribe antibiotics according to culture results. This resulted in a high antibiotic prescription rate of 74.8% in the presence of an 18.5% GABHS infection rate. Another limitation of this study was that it was designed to identify only GABHS and 16 respiratory viruses. Certain bacteria that are sometimes found in sore throat, such as group B, C and G streptococci (Streptococcus dysgalactiae spp. equisimilis, Streptococcus anginosus group), fusobacterium (F. necrophorum) and also some other viral causes like herpes simplex virus, Epstein-Barr virus and cytomegalovirus were not identified in our study (16). These might have been the cause of sore throat in cases in which no germs were identified. However, it has been stated that in 20% to 65% (average 30%) of patients with pharyngitis, no infectious pathogen can be found (16). This suggests to us that examining these microorganisms may only provide an increase of approximately 10%, or no increase in the identification rate in clinical practice. Therefore, identification of these aetiologic agents will probably not change the variables of the Mistik Score.

Comparison with existing literature

The aetiology of sore throat has been described in many textbooks and studies. Primary bacterial pathogens were stated as 30% in children aged 5- to 11-years old, 15% in adolescents and 5% in adults with pharyngitis. Viruses were identified in 15%–40% of children and in 30%–80% of adults. Rhinovirus has been stated as the most common viral agent (16). The overall GABHS rate of 18.5% and virus rate of 44.3% are in agreement with these findings. In addition, rhinovirus was the most common aetiologic agent in our study.

The spectrum of respiratory viruses stated as the causative agent in sore throat, and the rate of GABHS differ from study to study. Chi et al. reported a virus rate of 29.6% and a GABHS rate of 1.7%. Viruses mixed with bacteria were found in 11.1% of cases. They suggested that routine throat cultures and antibiotics are not indicated in children with acute pharyngitis (15). In our study, the bacterial and viral rates are higher, and mixed infection is lower. We cannot suggest not using antibiotics considering the high rates of GABHS in our study. Hashigucci and Matsunobu reported a 10.7% GABHS rate, a 33.9% rate for viruses, and no aetiologic pathogens in 28.6% of cases. ADV was the most common virus (19.6%). The rate of 42.9% for no aetiologic agent in our study is higher when compared with their study, but in agreement with other results (6,17). The rate of 42.9% for no aetiologic agent in our study is higher when compared with their study, but in agreement with other results (6,17). Laguna-Torres et al. (18) reported that the influenza A was the most common virus in influenza-like illness patients (25.1%). Our study shows that the rhinovirus was the most common virus, and this seems to be more reasonable when the ailment is a sore throat.

Many studies have been conducted in an attempt to find a score to diagnose bacterial sore throat, so that the unnecessary use of antibiotics can be prevented. In the first study by Centor et al. it was reported that knowing that a patient has a 56% chance of having GABHS on culture may be very helpful in decision making (9). In our study, we found that the chance of having a viral sore throat on PCR analysis was 82.1% by using the Mistik Score. The variables of absence of headache, stuffy nose, sneezing, temperature of ≥37.5°C on physical examination, and the absence of tonsillar exudates and/or swelling were already symptoms and signs known to be indicators of viral infection.

The increase in the diagnostic test accuracy of a score may enable its use by a large number of physicians. The Centor Score's sensitivity was reported as 49%, and the specificity as 82% (19). In our study we used the Modified Centor Score because of the presence of children. The Modified Centor Score had a sensitivity of 62.9% and a specificity of 78.5% in our study. The Mistik Score's sensitivity was higher than that of the Centor Score and similar to that of the Modified Centor Score. The specificity of the Centor Score was higher than those of the Modified Centor Score and the Mistik Score. Smeesters et al. suggested a new clinical score with a sensitivity of 41%, a specificity of 84% and a positive likelihood ratio of 2.6 for low-resource settings. They used a cut-off value and stated that the use of this score would prevent 41%–55% of unnecessary antibiotic use (20). The same calculation was performed for patients with a Mistik Score of 3–5. According to this calculation, the use of the Mistik Score could have prevented 30.7% of unnecessary antibiotic use.

The positive predictive value when using a Modified Centor Score of 4 was reported as 48% by Mazur et al. (21). In our study, a Modified Centor Score of 4 had a positive predictive value of 46.4%. However, the best cut-off point was with a score of 3, which had a positive predictive value of 40.1%. Our score had a positive predictive value of 62.5%, which seems to be better than that of the Modified Centor Score. The importance of a negative likelihood ratio has been stated as an important factor for use as a clinical criterion (6,21). A negative likelihood ratio of under 0.2 is considered useful. In our study, the negative likelihood ratios of the Modified Centor Score and the Mistik Score were 0.47 and 0.55, which were both higher than the desired level. The diagnostic accuracy of the Modified Centor Score (75%) in our study was a little higher than that of the Mistik Score (68%). This suggests to us that the Mistik Score may be used as well as the Modified Centor Score.

Implications

The use of the Mistik Score may be analysed with an example. A 5-year-old child may present to his/her general practitioner with the complaints of sore throat, runny nose and cough. The history and physical examination of the patient reveal absence of headache, stuffy nose, sneezing, cough and the absence of tonsillar exudates and/or swelling. This patient has a Centor Score of zero, and a Modified Centor Score of one. A Modified Centor Score of one indicates a 5%–10% risk of GABHS infection, and no further testing or antibiotics are suggested for this patient (7,22). In this patient, the Modified Centor Score may only suggest presumed viral infection. However, the Mistik Score has proven viral infection with PCR analysis results (61.9%–70.7%, with a score of four). If this patient had a fever of ≥38°C, this would make the Modified Centor Score two, and the Mistik Score would be five. It is possible to determine that the infection is 82.1% viral by using the Mistik Score. The use of the Modified Centor Score alone with a score of two will make further testing necessary in the case of a viral (rhinovirus) infection.

The presence of a low Modified Centor Score may suggest probable viral sore throat, but this score is not valid for showing viral infection. In addition, a low Mistik Score is not valid for showing bacterial infection. A physician may choose to use one of these scores to decide on the aetiology of sore throat. However, knowing the probabilities of both bacterial and viral sore throats may result in a better evaluation.

Conclusions

The analysis of our data allowed us to produce a scoring system to diagnose viral sore throat. Our score for diagnosing viral sore throat has slightly lower sensitivity and specificity, a higher positive predictive
value and a lower negative predictive value when compared with the Modified Centor Score. The ‘Mistik Score’ may be useful to diagnose viral sore throat either alone or in combination with the Modified Centor Score, which is used for the diagnosis of GABHS in sore throats.

Funding: this study was funded by the Scientific Research Council of Erciyes University (ERUBAP, Project No. TOA-2012–4148).

Ethical approval: Erciyes University Ethics Committee approved this study (Date: 07.08.2012, No. 2012/464).

Conflict of interest: the authors have no financial or proprietary interest in any of the instruments or products used in this study.

Supplementary material
Supplementary material is available at Family Practice online.

Acknowledgements
We presented this study as a poster at the Royal College of General Practitioners, Annual Primary Care Conference 2013, 3–5 October 2013, Harrogate, UK. The authors would like to thank Assistant Professor Ferhan Elmali for his assistance in statistical analysis, and Isabel Steel for her comments and Erciyes University Editing Office for help in editing.

References
Spectrum of bactericidal action of amylmetacresol/2,4-dichlorobenzyl alcohol lozenges against oropharyngeal organisms implicated in pharyngitis

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Adrian Shephard

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Purpose: Pharyngitis is commonly caused by a self-limiting upper respiratory tract infection (URTI) and symptoms typically include sore throat. Antibiotics are often inappropriately used for the treatment of pharyngitis, which can contribute to antimicrobial resistance, therefore non-antibiotic treatments which have broad antiseptic effects may be more appropriate. Amylmetacresol (AMC) and 2,4-dichlorobenzyl alcohol (DCBA) are present in some antiseptic lozenges and have established benefits in providing symptomatic relief and some in vitro antiviral action.

Methods: Seven bacterial species associated with pharyngitis, namely Streptococcus pyogenes, Fusobacterium necrophorum, Streptococcus dysgalactiae subspecies equisimilis, Moraxella catarrhalis, Haemophilus influenzae, Arcanobacterium haemolyticum and Staphylococcus aureus, were exposed to an AMC/DCBA lozenge dissolved in artificial saliva. In vitro bactericidal activity was measured as a log reduction in colony-forming units (CFUs).

Results: Bactericidal activity was recorded against all organisms after 1 minute. Greater than 3 log₁₀ reductions in CFUs were observed at 1 minute for S. pyogenes (log₁₀ reduction CFU/mL: ±0.9 to ±5.7), H. influenzae (6.1±0.1), A. haemolyticum (6.5±0.0) and F. necrophorum (6.5±0.0), at 5 minutes for S. dysgalactiae (6.3±0.0) and M. catarrhalis (5.0±0.9) and at 10 minutes for S. aureus (3.5±0.1).

Conclusion: An AMC/DCBA lozenge demonstrated a greater than 99.9% reduction in CFUs against all tested species within 10 minutes, which is consistent with the time a lozenge remains in the mouth. Patients with uncomplicated bacterial pharyngitis may benefit from the antibacterial action of antiseptic AMC/DCBA lozenges. Furthermore, AMC/DCBA lozenges may be more relevant and appropriate than antibiotics for pharyngitis associated with a self-limiting viral URTI.

Keywords: pharyngitis, bacterial infections, antibacterial agents, Streptococcus, sore throat

Plain language summary
Pharyngitis is a common condition. It can last several days and is usually the result of self-limiting viral infections, such as the common cold, although occasionally, pharyngitis can be caused by a bacterial infection. The most commonly reported symptom is sore throat. Antibiotics do not work against the viruses that in most cases cause pharyngitis but are often prescribed anyway. This contributes to antimicrobial resistance, where bacteria become immune to antibiotics and treatment for infections becomes difficult. Alternative treatments could help reduce inappropriate prescriptions of antibiotics for pharyngitis, and previous studies have demonstrated the antiviral and pain-relieving qualities of some antiseptic lozenges. The authors conducted a laboratory-
based study to assess the ability of antiseptic lozenges to kill a broad range of bacteria known to cause pharyngitis. They found that, when lozenges containing two antiseptic ingredients were dissolved in a solution similar to human saliva, the mixture killed 99.9% of all pharyngitis-associated bacteria that were tested within 10 minutes. These results suggest that patients with uncomplicated bacterial pharyngitis may benefit from the antibacterial and pain-relieving action of antiseptic lozenges, including those taking antibiotics. Additionally, antiseptic lozenges may be more relevant and appropriate than antibiotics for pharyngitis of a viral origin.

Introduction
Pharyngitis is associated with inflammation of the pharynx and is one of the most common reasons patients seek health care professional advice. A cute pharyngitis is predominantly caused by a viral upper respiratory tract infection such as the common cold and is usually self-limiting with symptoms, such as sore throat, lasting 3–7 days. Despite this, antibiotics are still frequently inappropriately used for the treatment of pharyngitis even though patients consulting their doctor are often primarily seeking reassurance and the treatment of pharyngitis even though patients consulting their doctor are often primarily seeking reassurance and symptomatic relief. Antibiotics are ineffective against the viruses that cause ~90% of cases, do not offer symptomatic relief and inappropriate antibiotic prescription can contribute to antimicrobial resistance, which is a serious threat to global public health. Consequently, there is a need for non-antibiotic treatments, which have broad anti-infective effects while meeting patient needs for relief of symptoms.

Antiseptics are a class of antimicrobial agent which kill via a physical action on the bacteria. In addition to bactericidal activity, some antiseptics – such as amylmetacresol (AMC) and 2,4-dichlorobenzyl alcohol (DCBA) – have been shown to have antiviral effects in vitro and anesthetic-like effects with established benefits in providing symptomatic relief of pain.

Bacterial infections contribute to 5%–15% of pharyngitis cases in adults. The most common bacterial cause of acute pharyngitis, and the reason for legitimate antibiotic prescribing to prevent complications, is group A β-hemolytic Streptococcus (GABHS or S. pyogenes) and is responsible for ~30% of cases in children and less frequent in adults at ~10% of cases, but rarely results in complications. A number of other bacteria have also been implicated in infections of the throat, which may present with a more complicated pathology or represent either opportunistic infection or an underlying medical condition.

Less common species recovered from patients presenting with symptoms of pharyngitis or with a clinical diagnosis of pharyngitis include Fusobacterium necrophorum, described in a recent study as a true pathogen rather than a colonizer of the oropharynx, and the Streptococcus dysgalactiae subspecies equi. Although there is insufficient evidence of a role for S. dysgalactiae in other adverse outcomes, M. orale and L. catarrhalis have been frequently isolated from patients with pharyngitis in combination with S. pyogenes, which may be significant considering that separate studies have demonstrated that M. catarrhalis potentiates the adhesion of S. pyogenes to the nasopharyngeal epithelium. Other bacteria cultured from patients with pharyngitis include H. influenzae, and the opportunistic pathogen, Staphylococcus aureus, although the clinical significance of S. aureus association is not known.

In patients diagnosed with tonsillitis, F. necrophorum, appears to be a clinically important species, with a prevalence significantly higher in subjects with clinical tonsillitis compared to subjects without tonsillitis. S. aureus has also been identified as a common cause of tonsillitis and was the most common pathogen isolated from patients undergoing tonsillectomy due to recurrent tonsillitis. H. influenza has similarly been recovered from patients with tonsillitis, although the clinical significance is currently unknown.

Non-antibiotic antimicrobial treatments could potentially benefit patients with bacterial pharyngitis by offering not only antimicrobial activity but also symptomatic relief. The in vitro activity of 10 lozenge formulations has previously been investigated against S. pyogenes and S. aureus. In this study, the in vitro bactericidal activity of AMC/DCBA lozenges against a broader range of potentially pathogenic oropharyngeal bacteria was assessed to evaluate the potential in vivo action of these lozenges against organisms associated with pharyngitis.

Methods and materials
Test samples
For the bactericidal assay, AMC 0.6 mg, DCBA 1.2 mg lozenges (Strepsils Honey and Lemon, Reckitt Benckiser Healthcare Ltd, Slough, UK) were dissolved into 5 mL of artificial saliva medium (0.1% meat extract [VWR International, Lutterworth, UK], 0.2% yeast extract [VWR International], 0.5% protease peptone [Oxoid, Basingstoke, UK], 0.02% potassium chloride [Fisher Scientific, Loughborough, UK], 0.02% sodium chloride [Fisher Scientific], 0.03% calcium carbonate [Fisher Scientific], 0.2% glucose [VWR International], 0.2% mucin from porcine stomach Type II [Sigma Aldrich, Gillingham, Dorset, UK], pH 6.7±0.3) at 44°C±1°C.
Test organisms and incubations
S. aureus (NCTC7445, Public Health England, Salisbury, UK) were cultured on tryptone soya agar (SGL, Corby, UK) at 32°C±2°C; S. pyogenes (NCTC12696, Public Health England) were cultured on Columbia blood agar with 5% defibrinated sheep blood (SGL) at 36°C±2°C; M. catarrhalis (NCTC3622, Public Health England) were cultured on Columbia blood agar (SGL) at 32°C±2°C; H. influenzae (NCTC4842, Public Health England) were cultured on anaerobic blood agar (FAA) with 5% horse blood (SGL) at 37°C±2°C anaerobically; A. haemolyticum (NCIMB702294, NCIMB, Aberdeen, UK) were cultured on Columbia blood agar with 5% defibrinated sheep blood at 36°C±2°C; S. dysgalactiae (ATCC12388, LGC, Teddington, UK) were cultured on Columbia blood agar with 5% defibrinated sheep blood at 36°C±2°C.

Bactericidal assay
The bactericidal assay was performed following a protocol similar to the Clinical and Laboratory Standards Institute approved guideline. Specifically, inoculum cultures were prepared for each challenge organism to give an approximate population of 10⁸ colony-forming unit (CFU)/mL in saline (0.9% sodium chloride [Fisher Scientific]). One inoculum suspension was prepared for each replicate tested. Test sample (4.9 mL) was prepared as above and inoculated with 0.1 mL of the inoculum suspension. The solution was vortexed thoroughly to mix and then tested after 1-, 5- and 10-minute contact times, consistent with the time a lozenge takes to dissolve in the mouth, by removing 1 mL of sample/inocula mixture and transferring into 9 mL of neutralizing diluent (0.1% peptone water [VWR International], 0.9% sodium chloride [Fisher Scientific], 0.3% lecithin [MP Biomedicals, Illkirch-Graffenstaden, France], 1% polysorbate 80 [Univar, Bradford, UK], pH 6.6±0.2). Neutralization validation was carried out against all test organisms. Solutions were serially diluted to 10⁻³, plated onto the appropriate agar medium and incubated for a minimum of 3 days. A positive control sample of 4.9 mL artificial saliva medium and 0.1 mL of the test inoculum for each organism was also prepared without exposure to test samples and assayed at a 30-minute time point. Test control counts were performed to confirm the total population of the culture suspensions used for each test replicate. The test controls were used to calculate the log reduction on exposure to test samples. Mean log reduction in CFUs per milliliter was calculated from three test replicates.

Results
In vitro bactericidal activity of AMC/DCBA lozenges
For all test organisms, evidence of bactericidal activity was recorded at the 1-minute time point (Table 1, Figure 1), and test control counts demonstrated that the test method and media did not affect the survival of the organisms. For S. pyogenes, H. influenzae, A. haemolyticum and F. necrophorum, the decrease in CFU/mL at 1 minute exceeded 3 log₁₀ (99.9% decrease), whereas greater than 3 log₁₀ reductions were recorded at 5 minutes for S. dysgalactiae and M. catarrhalis and at 10 minutes for S. aureus. Additionally, at all time points, the SD (Table 1) of the replicates was small (≤0.9 log₁₀ CFU/mL), indicating consistent and reproducible observations.

Discussion
This study examined the bactericidal action of an antiseptic lozenge containing AMC and DCBA. The organisms tested included gram-positive cocci (S. pyogenes, S. aureus, S. dysgalactiae) and bacilli (A. haemolyticum), as well as gram-negative cocci (M. catarrhalis) and bacilli (H. influenzae, F. necrophorum), representing a broad range of bacterial cell structures and sensitivities.

The results demonstrated that the AMC/DCBA lozenge exhibits broad bactericidal activity against a range of organisms implicated in pharyngitis and the rapid activity observed is consistent with the time taken for a lozenge to dissolve in the mouth. For all test organisms, evidence of bactericidal activity for the AMC/DCBA lozenge was recorded at the 1-minute time point. Of particular interest is the robust bactericidal activity against S. pyogenes, the most frequent cause of bacterial pharyngitis. Reductions exceeding 99.9% were achieved by 1 minute for S. pyogenes, H. influenza, A. haemolyticum and F. necrophorum, by 5 minutes for S. dysgalactiae and M. catarrhalis and by 10 minutes for S. aureus. The bactericidal activity of an AMC/DCBA lozenge within a 10-minute period is important as it is consistent with the duration that a lozenge remains in the mouth; furthermore, the active ingredients were also tested at the expected concentration achieved when a lozenge is dissolved in the mouth, assuming a volume of 5 mL of saliva. A previous in vitro evaluation of the bactericidal activity of antiseptic lozenges ([DCBA 1.2 mg, menthol 8 mg, AMC 0.6 mg] and [DCBA 1.2 mg, AMC 0.6 mg]) against S. pyogenes and S. aureus demonstrated antibacterial effectiveness. Both AMC and DCBA formulations were highly active against the
bacteria tested within 5 minutes of exposure, in contrast to the slow and weak action of the local antibiotic tyrothricin.33 The data generated in this study support and expand upon these previously published observations, providing further evidence of effectiveness against a broader range of bacterial species under in vitro conditions, including those where knowledge of their clinical pathology in pharyngitis is continuing to evolve or those that represent either an opportunistic infection or an underlying medical condition. These data likewise complement recent studies showing the in vitro viricidal effects of lozenges containing AMC/DCBA (and the active ingredients as free substances) against parainfluenza virus type 3, cytomegalovirus, respiratory syncytial virus, influenza A and severe acute respiratory syndrome coronavirus.12,13 In addition to antimicrobial activity, AMC and DCBA are proven to provide relief from the symptoms of pharyngitis, particularly sore throat, likely through their demonstrated local anesthetic-like action against voltage-gated neuronal sodium channels,14,34 and therefore may benefit patients presenting with either bacterial or viral pharyngitis. Furthermore, by relieving symptoms and managing patient expectations, the number of instances of inappropriate antibiotic prescribing for viral pharyngitis may be reduced.

A limitation of this study is that these observations were performed in vitro and therefore do not fully reflect the environment of the throat. For example, the throat may...
contain multiple microorganisms whereas this study tested the bactericidal activity against organisms in isolation. The role of the patient's immune system and swallowing action on the antimicrobial activity of the lozenge or active ingredients can also not be determined using in vitro methodology. However, the incidence of these bacteria is relevantly low in the general population; therefore, studying the bactericidal activity of AMC/DCBA in vivo can be challenging. Consequently, an in vitro approach is advantageous allowing the rapid generation of robust data, for multiple organisms simultaneously, that can be used to evaluate the potential of AMC/DCBA for efficacy in vivo.

Conclusion
These data show that an AMC/DCBA lozenge demonstrates bactericidal activity against all test organisms, representing a broad range of bacterial cell structures, from 1 minute and achieves greater than 99.9% kill for all test organisms within 10 minutes, which is consistent with the duration that a lozenge remains in the mouth. Therefore, patients with uncomplicated bacterial pharyngitis, including those taking antibiotics, from low-risk populations and without additional risk factors, may benefit from the antiseptic action of AMC/DCBA against a range of bacterial species associated with pharyngitis. Most cases of pharyngitis should not require antibiotics as they are typically self-limiting and often viral in origin. Therefore, over-the-counter antiseptics like AMC/DCBA may be more appropriate, unless the condition deteriorates or a streptococcal infection is diagnosed.

Data sharing statement
All data generated or analyzed during this study are included in this manuscript.

Acknowledgments
The authors would like to thank Aisat Fatade Ogunpola (a former employee of Reckitt Benckiser Healthcare Ltd, UK) for laboratory support. Medical writing assistance was provided by Daniel East at Elements Communications Ltd, Westerham, UK and was funded by Reckitt Benckiser Healthcare Ltd, UK. This work was supported by Reckitt Benckiser Healthcare Ltd, UK.

Author contributions
All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure
Derek Matthews, Robert Atkinson and Adrian Shephard are employees of Reckitt Benckiser Healthcare Ltd, UK. The authors report no other conflicts of interest in this work.

References
META-ANALYSIS

Efficacy of AMC/DCBA lozenges for sore throat: A systematic review and meta-analysis

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Summary

Background: Lozenges containing Amylmetacresol and 2,4-Dichlorobenzylalcohol (AMC/DCBA, e.g. Strepsils®) are marketed as a remedy for acute sore throat. This over-the-counter formulation has antiseptic and local anaesthetic qualities.

Objectives: The objective of this systematic review and meta-analysis is to evaluate the efficacy and safety of AMC/DCBA for the relief of pain associated with acute uncomplicated sore throat.

Methods: A systematic review of Literature was conducted using databases Medline, Embase and Cochrane to identify randomised controlled trials comparing AMC/DCBA against placebo or alternative local treatment options for acute uncomplicated sore throat. An additional hand search was performed. Two reviewers independently assessed citations for relevance, inclusion criteria and risk of bias. Meta-analysis was performed on included trials and standardised mean differences (SMD; $d_{Cohen}$) with 95% confidence intervals (CIs) were calculated.

Results: The literature search yielded 77 citations, 3 of which met the inclusion criteria. AMC/DCBA lozenges (0.6 mg Amylmetacresol, 1.2 mg 2, 4-Dichlorobenzylalcohol) were compared with unflavoured, non-medicated lozenges. The AMC/DCBA formulation additionally contained lidocaine in one and flavouring additives in another trial. A total of 660 adults participated in the included trials. Primary outcome was reduction in pain intensity against baseline, 2 hours after intervention compared with placebo group. Fixed effects meta-analysis resulted in a standardised mean difference in pain intensity of −0.6 (−0.75; −0.45) on an 11-point ordinal rating scale, favouring the AMC/DCBA lozenges. Secondary outcomes were sore throat relief, difficulty swallowing and throat numbness. No serious side effects were reported, whereas mild side effects like headache, cough, nasal congestion and irritation of the oral cavity, were reported in up to 16% of subjects in both groups. All included trials were sponsored by a manufacturer of AMC/DCBA containing lozenges.

Conclusions: Lozenges with AMC/DCBA can be a safe treatment option to relieve pain in patients with uncomplicated sore throat looking for local treatment options and valuing the modest additional effect compared with non-medicated lozenges.

Registration: PROSPERO CRD42015008826.
INTRODUCTION

Over the course of one year, approximately 30% of the general population will experience at least one episode of sore throat mostly caused by viral infection. The majority of affected individuals do not seek medical attention and the natural course is usually self-limiting. Although treatment with antibiotics may shorten the duration of symptoms in the small subgroup of patients with bacterial infections, antibiotic stewardship and the relatively high prevalence of side effects warrant careful consideration.2,3 Patient history, clinical examination, and the use of scoring systems to predict bacterial infections, have a limited reliability in identifying the small proportion of patients who will develop complications.4 Because of decrease in the incidence of complications like rheumatic fever or post-streptococcal glomerulonephritis, most industrialised countries do not recommend preventive antibiotics.4,6

Perceived patient pressure is an important factor for antibiotic prescriptions.7 Physicians tend to overestimate patients’ preferences for treatment with antibiotics and patients desire antibiotics mainly because they expect pain relief.8,9 Gargling with emollient fluids, drinking warm liquids and analgesic medications, are commonly used symptomatic treatment options.10 Lozenges containing a combination of Amylmetacresol and 2, 4-Dichlorobenzylalcohol (AMC/DCB A) are marketed worldwide as over-the counter drug (OTC) for pain relief for sore throat.11 Proposed mechanisms of action of AMC/DCB are antiseptic (virucidal) as well as anaesthetic qualities, which have been demonstrated in in vitro studies.12-14 Therefore, AMC/DCB lozenges might be a useful option for symptom relief in patients with sore throat and might contribute to the reduction in antibiotic prescription for sore throat.

We have performed a systematic review and meta-analysis of randomised controlled trials (RCTs) to assess the efficacy and safety of AMC/DCB lozenges vs placebo lozenges for the treatment of acute uncomplicated sore throat pain in ambulatory patients. We will discuss the implications of our findings for current treatment practice in this group of patients.

1.1 | Review questions

- Are AMC/DCB lozenges more effective than placebo in reducing throat pain in patients consulting for acute sore throat in ambulatory settings?
- How frequent and severe are side effects of AMC/DCB lozenges?

METHODS

This systematic review has been conducted according to the guidelines of the PRISMA statement(S1) and AMSTAR.15,16 The review has been prospectively registered with the international prospective register of systematic reviews (PROSPERO) CRD42015008826.17

What’s known

Non medicated Lozenges are a popular home remedy for sore throat. The emollient effects of lozenges are probably mediated by increased salivation. Various lozenges with pharmaceutically active substances with local anaesthetic effects or vitro antimicrobials and antiviral effects are marketed for symptom relief in sore throat.

What’s new

This is the first quantitative summary of evidence from randomised clinical trials for effectiveness of local treatment of acute uncomplicated sore throat with AMC/DCB lozenges. AMC/DCB provided a modest additional effect compared with non-medicated lozenges and can be a safe treatment option to relieve pain in patients with uncomplicated sore throat.

2.1 | Data sources

We searched three electronic bibliographic databases for relevant publications: MEDLINE (PubMed), EMBASE and Cochrane (CENTRAL). We included studies published between 1966 and 20 September 2016. The search algorithm contained the following keywords and MeSH-terms: (Dichlorobenzylalcohol* OR AMC DCBA OR cresol* OR Neo Angin OR Strepsils) AND (pharyngitis OR tonsillitis OR rhinopharyngitis OR tonsillopharyngitis OR pharyngotonsillitis OR sore throat) NOT (tonsillectomy OR intubation OR postoperative OR autoimmune). Additionally, we performed a manual search in the reference lists of eligible papers and searched for unpublished trials in trial registries www.clinicaltrials.gov, ISRCTN and EURLACT.18-20

If necessary, investigators of included or unpublished trials were contacted by telephone or by e-mail to obtain additional information.

2.2 | Study selection

Our search strategy included all relevant published randomised controlled trials and reviews about the treatment of acute sore throat. We excluded articles that focused on sore throat caused by intubation or autoimmune diseases, pregnancy or chronic sore throat. Inclusion criteria were:

- randomised controlled trials
- patients with acute sore throat
- topical treatment with AMC/DCB
- ambulatory setting
- sore throat probably caused by upper respiratory tract infection (URTI)

Exclusion criteria were:

- non-randomised, observational study designs
- postoperative patients
probable causes of sore throat other than URTI
- allergy
- chronic respiratory diseases like asthma
- malignant disease
- pregnancy

We did not place restrictions on duration of application, duration of follow-up, publication language, year of publication, or study population characteristics.

Two independent reviewers (AHV, GW) screened titles and abstracts of publications using a standardised form. We excluded titles and abstracts that clearly did not meet the inclusion criteria. For those titles fulfilling inclusion criteria full-text articles were obtained. The reviewers resolved disagreements by consensus.

2.3 Data extraction and analysis

We extracted information from the original reports into standardised forms. We did not have access to individual data and used summary data provided in the included publications. For all trials, the following data were extracted:

- Study characteristics: first author; year of publication; country of origin; funding source; study design and setting; duration of follow-up; number of randomised patients; number of patients analysed for each outcome; number of drop-outs with reason for discontinuation, registration in a public clinical trial registry.
- Population characteristics: inclusion and exclusion criteria; patient characteristics (eg, age, gender, race) underlying disease or condition; co-morbidities (eg, sleep apnea).
- Intervention characteristics: description of intervention, duration of treatment.
- Outcomes: Primary outcome sore throat pain intensity and secondary outcomes: sore throat pain relief, difficulty swallowing and throat numbness were recorded, including assessment methods and measurement characteristics. We collected quantitative data for each of the outcomes, details of their definitions and cut-offs for categorisations. We extracted data on any reported adverse events.

Standardised mean differences with confidence intervals were calculated, assuming fixed effects. All confidence intervals reported in this paper are 95% confidence intervals unless stated otherwise. Heterogeneity was quantified by calculating the I² statistic. Risk of selection, performance, detection, attrition, reporting and other bias of all included trials was assessed with the Cochrane bias assessment tool. Publication bias was assessed by calculating funnel plots and identification of unpublished trials. Rigor of reporting was assessed according to the CONSORT statement for reporting randomised controlled trials. Quality of evidence was appraised with GRADE.

All data were entered in and analysed with Review manager (RevMan) version 5.3.

3 RESULTS

3.1 Search results and study selection

We identified 84 potentially relevant publications through database and hand search. A list of all citations is available on request. After screening of titles and abstracts, 8 publications were evaluated according to the eligibility criteria and included in our final analysis (Figure 1). All included trials were financed by Reckitt Benckiser.
Healthcare International (RB), manufacturer of AMC/DCBA containing lozenges.\textsuperscript{25–27} The search and selection process is displayed in Figure 1.

We conducted a separate search of trial registries, using the key words “Amylmetraceros AND adults” or “Dichlorobenzylalcohol AND adults.” We identified 6 RCTs from the EURACT and 1 RCT from the ISRCTN clinical trial registry.\textsuperscript{19,20} The trial identified from the ISRCTN registry, was explicitly labelled as published by Wade 2011. Of the remaining 6 trials, 3 trials were probably identical with McNally 2010, Wade 2011 and McNally 2012, which suggests that Wade 2011 was registered in both the ISRCTN and EURACT registries\textsuperscript{(S2)}.

3 trials were unpublished and no results of these trials were documented in the registries\textsuperscript{26}. One of these 3 unpublished trials was conducted between 2012 and 2015 sponsored by Cassella-med GmbH & Co. KG (Gereonsmühlengasse, Cologne, Germany), of Klosterfrau Healthcare Group, a German pharmaceutical manufacturer and marketing partner of RB until 2014.\textsuperscript{28} We contacted the trial contact person in January 2015 to inquire if the trial had been published and to ask for detailed information to include the trial in out meta-analysis.

We received information that the results of the trial were being analysed and publication was expected in 2016.\textsuperscript{29} No further information on the results of the trial was provided, so that we could not include this unpublished trial in out meta-analysis.

We have no information on the results of the other 2 unpublished trials. All unpublished randomised controlled trials were sponsored by RB except for the aforementioned trial sponsored by Cassella.

### 3.2 Study characteristics and assessment of reporting

The characteristics of the included trials are summarised in Table 1. A total of 661 patients were included in the 3 eligible RCTs. In all RCTs, lozenges containing 0.6 mg AMC and 1.2 mg DCBA were applied in the intervention group, whereas the control group was treated with placebo lozenges without AMC/DCBA or other active substances. In one of the trials (Wade 2011) cooling or warming flavours were added to the treatment lozenges, while no flavour was added to the placebo lozenges.\textsuperscript{26} The study medication in the intervention group of one of the trials (McNally 2012), contained lidocaine in addition to AMC/DCBA while the placebo lozenges contained neither AMC/DCBA nor Lidocaine.\textsuperscript{27} This McNally 2012 study had a smaller number of subjects than the other studies, while the results of this study tended to be similar in magnitude and direction to the results of the other included studies (Figures 2C and A, TableS3, TableS4a, S4b, S4c, S4d).

We conducted a sensitivity analysis by calculating the results of the meta-analysis without inclusion of the McNally 2012 study with lidocaine-containing intervention medication. This sensitivity analysis indicated no significant differences in magnitude or direction of the meta-analysis results when omitting the results of this trial (TableS4a, S4b, S4c, S4d).

All studies included had similar inclusion and exclusion criteria.\textsuperscript{25–27} Main inclusion criteria were sore throat with confirmed tonsillitis with duration of ≤ 4 days before inclusion, probably caused by URTI and with sore throat pain intensity ≥ 6 on the 11-point throat soreness scale (TS).\textsuperscript{30} Main exclusion criteria were known allergy to the study medication, chronic respiratory diseases and recent use of analgesics. The Wade 2011 trial did not describe exclusion criteria.

The reporting did not fully adhere to stipulations of the CONSORT statement.\textsuperscript{23} Setting, study population, data allowing assessment of selection bias and limitations of the trials were not sufficiently reported.\textsuperscript{23,25–27} Patients were recruited in ambulatory care settings and by advertisements in the United Kingdom, but it remains unclear if these “primary care investigational sites” were general practice surgeries, or linked to a commercial clinical trials company. Additionally, it is not reported whether patients received an incentive for participation and completion of the study. Limitations of the trials were not discussed at all or only incompletely in 2 of the 3 included trials. A patient flow chart as stipulated by the CONSORT statement was available for 2 of the 3 trials (McNally 2010, Wade 2011).\textsuperscript{23,25,26} In 2 of the trials (Wade 2011, McNally 2012) no screening failures were reported, but a several patients who did not meet the inclusion criteria were randomised and included in the intention-to-treat analysis of these trials (Table 1).\textsuperscript{26,27} As McNally 2010 only reported treatment effects calculated with per-protocol data, we asked for additional information, but this request remained unanswered. All included trials reported patient characteristics (age, sex) of eligible patients, but not of drop-outs.\textsuperscript{25–27} Patient characteristics including throat soreness at baseline and medical history were similar in intervention and control groups of the trials, but Wade 2011 did not report on baseline symptom severity for any symptom or group and the other two trials reported incompletely.

There was some imbalance of male trial participants in the McNally 2012 trial, with 33% males in the intervention vs 58% in the control group.\textsuperscript{27} Concomitant disease was not reported by Wade 2011 and McNally 2012.\textsuperscript{26,27}

McNally 2010 reported concomitant medication in 52% of the treatment and 60% of the placebo group, including anti-histamines and 1 patient (0.6%) in each group taking systemic antibiotics.\textsuperscript{25} McNally 2012 reported that 56% of the treatment group vs 42% placebo group used concomitant non-analgesic medication, including one patient in the treatment group taking the NSAID etodolac for rheumatoid arthritis.\textsuperscript{27} Acetaminophen was allowed as rescue medication in one of the trials (McNally 2010). The average consumption of rescue medication was 2 doses within 24 hours after the start of intervention and 5 doses within 96 hours after treatment begin and no significant difference in consumption was found between intervention and placebo groups. Wade 2011 provided no information on rescue or concomitant medication.\textsuperscript{26}

Risk of bias of all included trials was assessed with the Cochrane bias assessment tool and is reported in Table 2.\textsuperscript{22} Risk of bias was generally low in all trials, but an unclear risk of bias was found for allocation concealment in the McNally 2010 and 2012 trials and for blinding of participants in all trials. Incomplete outcome data and selective reporting bias were high in the Wade 2011 trial and unclear in McNally 2012. An unclear risk of “other bias” was found in all included trials because of possible publication bias based on funding by the manufacturer of AMC/DCBA lozenges in combination with the unpublished trials identified through literature search.
<table>
<thead>
<tr>
<th>References</th>
<th>Number of Participants</th>
<th>Age mean (inclusion criteria)</th>
<th>Sex(%) male</th>
<th>Ethnic back-ground(%) caucasian</th>
<th>Setting (Country)</th>
<th>Treatment</th>
<th>Comparison</th>
<th>Follow up</th>
<th>Dropouts</th>
</tr>
</thead>
<tbody>
<tr>
<td>McNally 2010</td>
<td>310</td>
<td>36 (18-76)</td>
<td>32%</td>
<td>98%</td>
<td>United Kingdom</td>
<td>AMC 0.6 mg/DCBA 1.2 mg lozenge</td>
<td>unflavoured sugar based lozenge</td>
<td>2 h, 24 h, 3 d</td>
<td>Intervention group (n = 3): mouth ulcer (n = 1) lost to follow-up (n = 1) withdrew, lack of time after 1h (n = 1) Placebo group (n = 2): vomiting (n = 1) throat pain increase (n = 1)</td>
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<td>Wade 2011</td>
<td>225</td>
<td>32 (16-75)</td>
<td>42%</td>
<td>97%</td>
<td>United Kingdom</td>
<td>AMC 0.6 mg/DCBA 1.2 mg cool (1) or warm (2) lozenge</td>
<td>unflavoured sugar based lozenge</td>
<td>120 min</td>
<td>Excluded from per protocol analysis: intervention group cool (n = 10) throat soreness &lt; 6 (n = 8) Missing assessment (n = 2) intervention group warm (n = 2): throat soreness &lt; 6 (n = 1) wrong assessment time (n = 1) placebo group (n = 10) throat soreness &lt; 6 (n = 10)</td>
</tr>
<tr>
<td>McNally 2012</td>
<td>126</td>
<td>32 (18-75)</td>
<td>41%</td>
<td>98%</td>
<td>United Kingdom</td>
<td>AMC 0.6 mg/DCBA 1.2 mg + lidocaine 10 mg lozenge</td>
<td>unflavoured sugar based lozenge</td>
<td>2 h, 1-3 d</td>
<td>Drop-outs reported: intervention group (n = 0) placebo group (n = 0) Excluded from per protocol analysis (n = 16): no differentiation between intervention and placebo groups: throat soreness &lt; 6 (n = 4) wrong assessment time (n = 1) no URTI (n = 5) difficulty swallowing ≤ 50 mm (VAS100) at screening (n = 6) swollen throat ≤ 33 mm (VAS100) at screening (n = 5)</td>
</tr>
</tbody>
</table>
**FIGURE 2** Forest plots for primary and secondary outcomes (A) sore throat pain intensity as measured with the 11-pt Throat Soreness Scale (TSS); (B) sore throat pain relief on the 7-pt sore throat relief scale; (C) difficulty swallowing on a 100 mm visual analogue scale (VAS)

**TABLE 2** Risk of bias of included trials

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<tr>
<th>Reference</th>
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<th>blinding of outcome assessment</th>
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<td>low</td>
<td>unclear</td>
<td>unclear</td>
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<td>low</td>
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<td>Wade et al 2011</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>unclear</td>
<td>high</td>
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<td>unclear</td>
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<tr>
<td>McNally et al 2012</td>
<td>low</td>
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<td>unclear</td>
<td>low</td>
<td>unclear</td>
<td>unclear</td>
<td>high</td>
</tr>
</tbody>
</table>
No indication for publication bias was detected in the funnel plot (Table S5).

4 | META-ANALYSIS

4.1 | Primary outcome

All included trials included sore throat pain intensity as a primary outcome. We pooled the results of the included trials for the primary outcome of sore throat after 2 hours as measured with the 11-point ordinal TSS, with 0 meaning no sore throat and 10 meaning maximum sore throat. One of the trials (Wade 2011) did not report baseline values of the outcomes. The reported mean sore throat pain intensity calculated from the other trials was 7.15 points before the start of treatment.25-27,28 120 minutes after start of treatment, the weighted mean sore throat pain reduction on this scale was −1.92 (−1.78 to −2.06) in the treatment group and −0.95 (−0.85 to −1.03) in the placebo group respectively. Meta-analysis showed a standardised mean difference of −0.60 (−0.75 to −0.45) in the treatment group compared with the placebo group and this difference was statistically significant (P < .00001) (Figure 2A). We did not find indication of heterogeneity in effect estimates (I²=0%).

4.2 | Secondary outcomes

4.2.1 | Sore throat relief

All included trials reported about sore throat relief after 2 hours. Sore throat relief was measured with a 7-point categorical sore throat relief scale,30 where 0 signifies no sore throat relief and 6 complete sore throat relief. By default, the initial measurement was deemed 0. Mean absolute sore throat relief scores were 1.90 and 0.87 in treatment and placebo groups, respectively. This is equivalent with mild relief on the scale in the treatment group and slight relief in the placebo group.

Standardised mean difference in sore throat pain relief at 120 minutes was with 0.89 (1.04, 0.73; P < .00001) points significantly higher in the treatment group compared with the placebo group, as depicted in Figure 2B. Calculated heterogeneity was low.

4.2.2 | Difficulty swallowing

Difficulty swallowing after 2 hours was measured with a visual analogue scale (VAS 100) in all included trials with 0 representing swallowing not difficult and 100 very difficult. Baseline characteristics were not reported in one of the publications (Wade 2011). Before treatment, difficulty swallowing was measured as 67.1 and 66.0 at baseline in intervention and control groups, respectively as calculated from the other trials. 120 minutes after the start of treatment, mean difficulty swallowing in the treatment and placebo group had decreased with −16.2 and −6.1, respectively on the VAS 100 scale with a standardised mean difference of −0.90 (−1.06, −0.75; P < .00001), favouring the treatment group. A forest plot with comparison of results for change in difficulty swallowing is represented in Figure 2C. The heterogeneity was high for this outcome (I² 87%), but needs to be interpreted with caution.

4.2.3 | Throat numbness

Wade 2011 and McNally 2012 reported on throat numbness, measured with a 5-pt. categorical scale from 1 representing none to 5 representing complete numbness. Baseline throat numbness was not reported in both publications, so that only relative improvement could be evaluated. Mean increase in throat numbness was 2.05 in the treatment and 1.59 in the placebo group at 2 hours after start of treatment. Standardised mean difference was 0.59 (0.39, 0.78; P < .00001) in favour of AMC/DCBA at 2 hours after the start of treatment (Table S3). A summary of findings table for the meta-analysis is available in Table S6.

4.2.4 | Other reported outcomes

2 trials reported on onset of anaesthesia with a median onset after 45 minutes (15 to 780 ns) in McNally 2010 and 30 minutes in McNally 2012. Meta-analysis was not possible because of incomplete reporting. For the outcomes throat numbness and sore throat relief, McNally 2012 reports maximum results at 15 minutes after treatment begin. All trials reported on significant subjective improvement of the general condition in patients in the treatment group compared with the placebo group on different dimensions of consumer questionnaires.25,26 Aggregation of these data for these outcomes was not attempted, because of lack of comparable measurement methods and incomplete reporting of data where there was overlap (Wade 2011).25-27 In the McNally 2010 trial, the subjects were questioned for freedom of symptoms after 24, 48 and 72 hours. After 24 hours, the difference between placebo and treatment groups was not significant. After 48 and 96 hours, 16% and 35% of subjects in the treatment group vs 6% and 10% in the placebo group were free from symptoms and these differences were statistically significant.25 McNally (2012) found a significant improvement of throat swelling of −8.8 (−15.3 to −2.2; P < .0001) on a VAS 100 swollen throat scale, with 0 meaning not swollen and 100 very swollen.27 Additionally, McNally (2010) found a significant improvement in eating and speaking in the treatment vs placebo group.25 Wade reported on the emotional benefit as reported in a questionnaire with of 52 and 58% of subjects in cold and warm treatment groups reporting benefit compared with 19% in the placebo group (p < .00001).26

5 | ADVERSE EFFECTS

All included trials reported adverse events, which varied from 2%-16%, and did not differ significantly between intervention and control group in any of these trials. Most reported side effects were mild and could be attributed to the URTI.31 Examples are headache, earache, cough, chills, pyrexia and nasal congestion.25-27 However, 3 events of mouth ulceration were reported in the treatment group by McNally
(2010), one of which severe and probably related to the study medication, one mild and possibly related, and a possibly related case of tongue ulceration in the control group. Apart from this, no clinically significant related side effects or serious adverse events were reported in the intervention group of any of the trials.

6 | DISCUSSION

6.1 | Summary of main results

This meta-analysis summarises 3 RCTs with 660 subjects, comparing AMC/DCBA with non-medicated lozenges for treatment of sore throat. A standardised mean difference on the main outcome of reduction in sore throat pain on an 11-pt. pain scale after two hours of −0.60 (−0.75 to −0.45; P < .00001) was observed. For the secondary outcomes sore throat relief on a 7-pt. scale SMDS of 0.89 (1.04, 0.73; P < .00001) and difficulty swallowing on an 11-pt. scale a SMD of −0.90 (−1.06, −0.75; P < .00001) was observed after 2 hours. In both groups 2-16% of subjects reported adverse events, which were mostly mild and could be attributed to the underlying URTI, but in 2 patients with mouth ulcers a relation with the study medication could not be ruled out.

6.2 | Meaning of the results and comparison with other topical treatments

The reported SMD of 0.60 for throat soreness corresponds to an average pain reduction in 1.9 pt. on the 11-pt. pain scale in the intervention group after 2 hours. This is slightly below the estimated minimum value considered as clinically important pain reduction in acute pain of ≥ 2 pt. on an 11-pt. pain scale. The control group also showed an average reduction in 0.95 pt. on the 11-pt. pain scale. Albeit this is statistically significant lower than in the intervention group this is less than the 2 pt. considered clinically important. The difference in pain reduction between AMC/DCBA and non-medicated lozenges might be imperceptible for most people suffering from sore throat. The effect sizes of the favourable effects of AMC/DCBA compared with placebo for the other outcomes were 1.90 and 0.87 (SMD 0.89) on the 7-pt throat pain relief scale and −11% reduction in difficulty swallowing on the VAS100. This is lower, than the threshold of 33% or ca. 30 mm considered significant in postoperative pain. Although no studies on the threshold of clinically significant pain reduction pain in acute sore throat have been conducted, it is unlikely that the effect size in acute sore throat is smaller than for other kinds of acute pain.

For some of the other reported outcomes not evaluated in all studies, a significant subjective benefit was reported compared with placebo. Since this is not a standard outcome in trials evaluating the effectiveness of sore throat relief, the meaning of this finding remains unclear given the small benefit observed with established outcomes. Additionally, the single question assessing betterment is not validated and could be interpreted as suggestive (“At 2 hours post dose, do you feel any better than before you took the throat lozenge?”). All included trials measured pain relief for up to 2 hours after treatment begin. Only McNally 2010 reported about subjective freedom from symptoms at 24, 48 and 72 hours after treatment begin and found a significant difference between treatment and placebo groups at 48 and 72 hours with 16 and 35% of the treatment vs 6 and 10% of the placebo group reporting no symptoms.

The included trials reported 2-16% mostly mild adverse effects. The incidence of adverse effects did not differ significantly between intervention and control groups. No clinically significant related side effects or serious adverse effects were reported.

Several other topical treatment options for sore throat are available and have similar effect on pain reduction. Ambroxol is a substance with local anaesthetic properties, available as lozenge. A meta-analysis on the efficacy of ambroxol as a topical treatment of sore throat vs placebo lozenges showed a difference in pain reduction in SMD = −0.11 (CI −0.15; −0.07) for 20 mg ambroxol after 3 hours. At the end of the first day 69% in the ambroxol group and 53% in the Placebo group reported a good or very good efficacy. Another option for local treatment of sore throat is flurbiprofen, a non-steroidal anti-inflammatory drug, available as spray or lozenge. A trial on the efficacy of lozenges containing the local anaesthetic lidocaine, found a significant difference in sore throat pain relief compared with placebo with 38% in the treatment group against 12% in the placebo group showing a ≥50% improvement in pain relief. One study assessing the effectiveness of a flurbiprofen spray compared with non-medicated spray, reported a statistically significant average pain reduction (intervention −1.82, control −1.13 points on the STIS) in a similar range as in our review of AMC/DCBA in both groups. 5 other trials reported statistically significant benefit for flurbiprofen lozenges compared with placebo lozenges. The reported efficacy on the 11-pt- ordinal sore throat scale, was −1.01 and −2.14 for flurbiprofen vs −0.45 and −1.65 for placebo lozenges.

All these RCTs of different topical treatments report a statistically significant small effect size of pain relief compared with placebo. Consistently, a significant proportion of patients in the placebo group also reported improvement. The non-medicated lozenges serving as comparisons for lozenges containing a pharmaceutically active substance cannot be regarded as an inert placebo intervention. The emollient effects of lozenges are probably mediated by increased salivation. There sucking lozenges in general might be beneficial to soothe sore throat and the benefits of medicated lozenges are underestimated.

6.3 | Strengths and limitations

6.3.1 | Limitations of the trials

Recruitment setting was described incompletely and some of the patients were recruited via advertisements, so that selection bias cannot be ruled out. This is a possible limitation for generalising the finding to patients seen in general practice which might be sicker than those included in the trials. A patient flowchart was missing in McNally 2012 and not all trials report on number of patients screened for inclusion and on drop-outs. One trial (Wade 2011) did not report absolute baseline values for any of the outcomes and only reported relative changes to the unreported baseline values. The control group in this
trial had less smokers, than the treatment group, with 15% and 26%, respectively but this is unlikely to have changed the direction of the results. Additionally, the mean duration of sore throat in the control group was reported to be 3.6 ± 7.1 days, which is implausible, since one of the inclusion criteria was sore throat with duration of less than four days. Reporting on disease severity was incomplete and Wade 2011 and McNally 2012 included patients who did not meet inclusion criteria in their ITT analyses. Exclusion of patients using antibiotic or antihistaminic co-medication was incomplete. In one of the trials acetaminophen was allowed as rescue medication, but failed to report on the differences in use of this rescue medication in both treatment and placebo groups.24 It is therefore possible that analgesic co-medication might have influenced results.

In one of the trials AMC/DCBA was combined with lidocaine in the treatment lozenges, whereas the placebo lozenge contained no active ingredient.27 The positive effects of the intervention treatment were not as strong as in the other 2 trials, where no co-medication was included in the AMC/DCBA lozenge. Inhibition of the effects of AMC/DCBA by concurrent application of lidocaine cannot be ruled out, especially as the analgesic effect of AMC/DCBA is at least partly mediated by blockade of voltage gated sodium channels, which parallels the mechanism of action of lidocaine, which also targets these channels.12,24 All of the included trials used non-medicated unflavoured lozenges were used in the control group, while the lozenges in the some of the treatment groups (Wade 2011) were flavoured.26 AMC/DCBA has a distinct taste, so that blinding was impaired in this respect and it cannot be ruled out that the taste difference had an influence on patients’ evaluation of the treatment effect.26,46-48 This is especially important as subjective measures were used for the evaluation of the treatment effect. Furthermore, all included RCTs were sponsored by the manufacturer of AMC/DCBA. The included trials focused on pain relief after 2 hours and two of the trials extended their follow-up to 72 hours, whereas the average duration of acute sore throat is 6 to 8 days.49 The effect of local treatment with lozenges is expected to wear off after a few hours, so that repeated sucking of lozenges is needed for sustained pain relief. Interestingly, McNally 2012 reported maximum throat numbness and sore throat relief at 15 minutes post-dose and the median onset of anaesthesia was reported at 30 minutes in this trial. Therefore, treatment with oral analgesics might be a better option for patients with systemic symptoms like fever and headache, because of the longer lasting analgesic effect and systemic symptom relief.28 It is noteworthy that the package insert limits the use of AMC/DCBA to 3 days without consulting a physician.21

6.3.2 | Limitations of the review

The results of our analysis are limited by several factors. We had to rely on published aggregated data and had no access to individual patient data for the analysis. For one of the trials (McNally 2010), only treatment effects calculated with per-protocol data were reported. Intention-to-treat analysis base on the reported data resulted in a slightly less favourable difference for the treatment group, but the result was still statistically significant. Our request for more data was not successful. The treatment lozenge in one trial contained lidocaine and indirect comparison or correction for this effect was not attempted.27 Although the funnel plot is not suggestive for publication bias, this result should be interpreted with caution because of the small number of trials included in the analysis. We identified 3 unpublished trials in public study registries from which we have no information on the results. All identified published and unpublished randomised controlled trials have been sponsored by manufacturers of AMC/DCBA containing lozenges.

7 | CONCLUSIONS

Lozenges with AMC/DCBA can be a safe treatment option to relieve pain in patients with uncomplicated sore throat valuing the modest additional effect compared with non-medicated lozenges.

8 | IMPLICATIONS FOR RESEARCH

Because of the small, but robust effects found in the meta-analysis and because of several completed, yet unpublished RCTs, we do not expect further research on short term effectiveness of AMC/DCBA to yield significantly different results with major relevance for treatment of patients with uncomplicated sore throat. Future trials on the effectiveness of topical treatments for sore throat should avoid the uncontrolled addition of pharmaceutically active ingredients in the study medication. In planning follow-up time, the average duration of the underlying condition should be taken into account. Future trials should adhere better to standards of reporting.

AUTHOR CONTRIBUTION

AHV, GW and JFC were responsible for the study design. Literature search and data extraction have been performed by AHV, GW and CK. Statistical analysis was done by SB, AHV and GW. All authors drafted and reviewed the manuscript.

DISCLOSURES

The authors declare that they have no proprietary, financial, professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in this paper.

ACKNOWLEDGEMENTS

The authors thank Ms Annekathrin Haase for reviewing the manuscript.

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SUPPORTING INFORMATION

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