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A Review On Antibiotic Stewardship In Pediatric Primary Care

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Too Much of a Good Thing:
A Scoping Review on Antibiotic Stewardship in Pediatric Primary Care

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Abstract

Background. Misuse of antibiotics for upper respiratory tract infections (URTIs) in pediatric primary care settings persists despite growing concern over antibiotic resistance. Interventions aimed at improving prescription use, coined Antibiotic Stewardship Programs (ASPs) often target clinicians for improved clinical decision-making. More recently, ASPs have begun educating patients to antibiotic needs, and for pediatric cases, parents who might pressure clinicians into prescribing unneeded antibiotics. While many reviews have targeted adult patients or emergency settings, few evaluate practices for pediatric populations. For this reason, we performed a review of the literature to summarize common strategies used to reduce antibiotic overprescribing for pediatric patients in the United States.

Methods. We searched the PubMed and Web of Science databases as well as manually reviewed abstracts of commonly cited literature. Studies were included if they had a randomized control trial design or alternative study design specifically reporting differences in before-after antibiotic use or perceptions. One independent reviewer abstracted all data. The primary outcomes were numerous across all reviewed studies, however, consistently pertained to reductions in unnecessary prescriptions for URTIs, streamlining prescribing workflow for physicians in the pediatric primary care setting, and reductions to antibiotic resistance.

Results. 11 studies met inclusion criteria with 5 studies addressing clinicians, 5 studies addressing patient parents/guardians, and 1 study addressing both clinicians and patient parents. Within the three study groupings, interventions were categorized by methodology. Clinician-focused studies included clinician-decision-support (CDS) systems, education, and both (CDS and education) categories. Patient/guardian-focused studies included ‘poster and pamphlet’ and ‘audiovisual and pamphlet’ categories. The single study targeting both clinicians and parents used education and CDS system methods. After analysis, interventions using combinations of strategies were clearly superior in affecting behavior change and reductions in antibiotic prescribing rates.

Conclusions. Though ASPs have demonstrated some efficacy, few groups have established consistent findings, methods, or outcomes. Studies show impacts on behaviors leading to antibiotic over-prescription, misuse, and subsequent development of antibiotic resistance while interventions did not lead to persistent long-term effects. Inconsistent conclusions arise from high prescribing rates among pediatric subpopulations as well as difficulties quantifying qualitative health education outcomes. Moving forward, ASP interventions must incorporate

integrated and multi-faceted interventions to achieve reductions in URTI-related antibiotic prescriptions and antimicrobial resistance.

Introduction

Knowledge of antibiotics has been and remains poor. In a 1997 survey by the National Information Program on Antibiotics, 83% of respondents did not understand or had not heard of antibiotic resistance (Finch et al, 2004; NIPA, 2016). This lack of public knowledge came despite the revolutionizing of antimicrobial agents as the second leading therapeutic category of drugs prescribed by office-based physicians in the United States (McCaig & Hughes, 1995). Over 20 years later, antimicrobial misuse is considered the largest contributing factor to antimicrobial resistance and adaptive bacterial pathogens (Maor et al, 2011). This phenomenon has been associated with the development of multi-drug-resistant organisms (MRDOs) implicated in serious diseases of children and adults, as well as the use of more toxic and expensive alternative drugs (McCaig & Hughes, 1995; Wheeler et al, 2001). Yet, despite growing concern among health professionals, public awareness surveys show nearly 70% of people have no concern over antibiotic resistance with 40% believing antibiotics are necessary for treating sort throat and runny nose (Belongia et al, 2002).

Outpatient diagnoses related to over-prescription of antibiotics are largely related to upper respiratory infections (URTIs) such as such as ear infections and bronchitis (Harris et al, 2003). Due to the generalizability of symptoms, antibiotics are prescribed frequently for these illnesses in the United States even if caused by viral pathogens. UTRIs are the single most frequent reason for seeking ambulatory medical care in the United States, accounting for approximately 75% of ambulatory antibiotic prescriptions annually (Harris et al, 2003). Children have the highest rates and use of these antibiotics, and particularly, the highest rates of inappropriate use (Adler et al, 2005). The susceptibility of this population is well documented for several reasons, including parental expectations, miscommunication between physicians and parents, dependence on antibiotics for mild illnesses, lack of parent awareness or knowledge of antibiotic resistance, diagnostic uncertainty, and physician fear of litigation after a missed or delayed diagnosis (defensive medicine), etc. (Bauchner et al, 2001; Costelloe et al, 2010; Wheeler et al, 2001).

Despite concerns over antibiotic prescription methods among children, few guidelines have been established for this population, especially for the subpopulation of neonates (Taylor et al, 2003; Taylor et al;

2005; Patel et al, 2007). Limitations are driven by variability of antibiotic needs across this age group further heightened by a lack of clear and consistent communication from pediatric patients to parents and physicians. With this in mind, a major determinant of pediatrician antimicrobial prescribing behavior is parental expectation (Wheeler et al, 2001). In a survey of a random sample of practicing pediatricians in the United States, 96% of respondents indicated that parents had requested unnecessary antibiotics for their child during the previous month; 40% reported receiving 10 or more such requests (Taylor et al, 2003). When pressured to prescribe these medications, 30% of pediatricians reported complying with this request “occasionally” or more frequently than not (Adler et al, 2005; Taylor et al, 2003).

However, recent studies have shown that satisfaction and parental pressures can be resolved by improving communications between parents and physicians (Bauchner et al). This is imperative in primary care settings where parent-physician interactions are brief and significantly dictate the outcome of the appointment, erring on the side of caution with over-prescription. While the American Academy of Pediatrics (AAP) has encouraged clarity about prescription guidelines to encourage positive parenting practices, extended explanations and follow-up questions consume considerable, already-limited, provider time (Glascoe et al, 1998). Though brevity increases diagnosis efficiency, studies have shown parents would be satisfied without physician prescription if reasons for this decision were clearly provided (Maor et al, 2011; Wheeler et al, 2001).

Although parents contribute to the problem, physicians are not blame free. Most physicians are willing to change their use of antibiotics yet still over-prescribe antibiotics out of fear for unintended consequences (Watson et al, 1999). These concerns are driven by beliefs that patients will pivot to colleagues at other practices or other settings if failing to receive antibiotics when demanding (Watson et al, 1999). Recognizing this reliance on physician practices, hospitals, medical organizations, and others have increased the surveillance of prescribing and resistance through antimicrobial stewardship programs. ASPs aim to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms, and the emergence of resistance (Delitt et al, 2007). These programs guide prescribers in the proper administration of antibiotics by instructing physicians on antibiotic use guidelines and training physicians to urge patients towards appropriate dose and duration requirements (CDC, 2013). Successful implementation of ASPs has been shown through interdisciplinary administrative teams, program innovation, and consistent information feedback loops on prescriber performance (Delitt et al, 2007). Due to their size and relative abundance of resources, entities implementing ASPs have traditionally been hospitals and skilled nursing facilities with much neglect of outpatient clinical settings.

Due to a lack of public awareness over antibiotic resistance and limited focus on pediatric populations, we present this scoping literature review on ASPs in pediatric patients within the United States. Our review assesses interventions targeting parental, physician, or combined education isolated specifically within outpatient clinical settings where little information exists of ASP efficacy. Using our summary of investigated literature, we propose an ASP clinical trial to address gaps in current practices and programs. This combined review and intervention approach progresses efforts in translational research, or "an effective translation of the new knowledge, mechanisms, and techniques generated by advances in basic science research into new approaches for prevention, diagnosis, and treatment of diseases essential for improving health (Ammentorp & Kofoed, 2011)." We hope that these resources will help to increase the efficacy of ASPs in pediatric settings and expand upon the strengths, weaknesses, outcomes, and future steps needed when designing pediatric interventions (Hersh et al, 2009).

Methods

Search Strategy. All research searches were performed using PubMed and Web of Science due to their dedication for increasing distribution of information related to biological sciences and molecular biology (Clarivate Analytics, 2019; NCBI, 2019). Studies reported in the English language were searched with no publishing date restrictions. MeSH terms were generated using the PICO method, corresponding to *Population* search terms of ("children" OR "kids" OR "adolescents" OR "child"), *Intervention* search terms of ("Respiratory tract infection*" OR "common cold" OR "flu like symptom*"), and *Comparison* search terms of ("antibiotic" OR anti-bacterial agents" OR "antibiotic" OR "drug therapy"). Primary *Outcome* search terms included "antibiotic stewardship", "antibiotic overuse", antibiotic over prescription", and "inappropriate prescribing". Additional criteria were added to limit results to studies conducted in the United States, using the following MeSH terms: "United States", "US", and "America". The first search was conducted on 03 March 2019 and continually updated for more recently published works through 05 April 2019.

Inclusion/Exclusion Criteria. We included studies on pediatric patients ≤ 18 years of age whose clinician, parent/guardian, or both underwent an antibiotic stewardship intervention for URTIs. Studies targeting multiple subpopulations were included only if intervention outcomes were isolated for each subgroup separately. Studies were included only if clinicians treated pediatric populations. Emphasis was placed on antibiotic stewardship interventions in pediatric primary care facilities with exclusion for studies in hospitals, emergency rooms, or urgent care settings. Systematic and scoping reviews were used for manual search of primary study references. Antibiotic stewardship interventions were excluded for studies where respiratory illness was not the primary outcome or where antibiotic substitutions/pharmaceutical products were tested.

Information Synthesis. A multiple pass method was used to evaluate study criteria eligibility. Both PubMed and Web of Science databases were searched with citations exported into EndNote X8 citation manager software. Studies were removed if non-English language, duplicated across databases, or full text articles were unascertainable. Titles and abstracts were screened for significance followed by a full-text review of included studies. Limitations of time and cost resulted in a single researcher reviewing all studies at each abstraction without secondary opinion. Due to the variety of ASP methods, outcomes, and study subjects, we did not conduct a meta-analysis in this review. Our PRISMA diagram is shown in Figure 1 with a log of included studies and table with reasons for excluded studies found in Tables 1 and 2.

Results

Study Abstraction. Our final literature search identified 113 citations with 65 citations (57.5%) excluded from further analysis after title and abstract screening. For these 65 studies, exclusion was predominantly due to the intervention taking place outside the United States (48), targeting an adult or mixed population (3), taking place outside of a primary care setting (3), or targeting a health outcome not related to respiratory illness (9). An additional 18 studies (15.9%) were systematic and scoping reviews. From this initial search remained 47 studies (41.6%) meeting the criteria for full-text analysis. To supplement the primary literature search, manual review was conducted of references included within 7 of 11 systematic reviews targeting pediatric populations solely within the United States (Aroll et al, 2003; Boonacker et al, 2010; Costelloe et al, 2010; Delitt et al, 2007; Glascoe et al, 1998; Patel et al, 2007; Ranji et al, 2008). From this manual search, an additional 53 papers were included by the researcher's discretion for full-text analysis. After full-text review, 11 of 113 papers were used. Results are presented according to each of three intervention populations: physicians/clinicians, parents/guardians of pediatric patients, or both.

Physicians/Clinicians. Five studies performed on physicians/clinicians utilized 3 ASP methods: clinician decision support (CDS) systems, education with informational feedback loops, and both. For CDS-related studies, clinicians underwent specific training to utilize electronic health record (EHR) databases integrated with the decision support software when treating URTI patients. This software generally involves the input of 1 or 2 simple data points such as time of year and age to trigger providers to act on influenza and colon cancer screening reminders (McGinn et al, 2013). More complex forms of CDS exist to reduce prescribing of antibiotics, assist clinicians in reducing inappropriate antibiotic prescribing, and to improve workflow for clinicians (Linder et al, 2009). The EHR-embedded CDS was provided to a variety of practitioners (e.g. physicians, residents, fellows, and nurses) for outpatient settings connected to urban, private, primary care facilities. Software was introduced for the primary purpose of more efficient diagnosis of acute respiratory infection with a secondary outcome to minimize over-prescription tendencies among practitioners. CDS software recommendations were trained by comparing clinician diagnoses to laboratory testing. Both studies were performed using a randomized control trial study design comparing primary care practices as usual for the control and practices revised by CDS software as the intervention group.

Both studies showed significant reductions in prescription rates of antibiotics between control and intervention groups. In McGinn et al (2013), significant reductions were seen for antibiotic orders overall (age-adjusted RR, 0.74; 95%CI, 0.60-0.92; p = .008), which held when stratifying their analysis between pharyngitis and pneumonia outcomes (p. 1587). Reductions were also found in rapid streptococcal test order and throat culture requests with the tendency of clinicians to delay antibiotic prescription until further symptoms progressed. Similar efficiency was found among Linder et al (2009) where clinicians reduced prescriptions by roughly 4% between intervention and control clinics (43% vs. 39%, respectively – OR=0.8; 95% confidence interval (CI), 0.6–1.2, adjusted for clustering by clinic) (p. 234). Interestingly, this paper found no significant differences between control and intervention clinics with respect to the appropriateness of antibiotic prescription (OR: 0.9 [0.6-1.4] vs. OR=0.8 [0.5-1.3], respectively) (Linder et al, 2009).

In contrast to decision-making software, 2 studies used education sessions with informational feedback loops by auditing clinicians (Gerber et al, 2013) or hosting patient focus groups (Doyne et al, 2004). Both studies targeted clinicians of pediatric patients in urban, suburban, and rural areas spanning multiple medical centers and private practices. Each study compared the antibiotic prescription tendencies prior to the intervention and effects of intervention on prescription after a 1-year follow-up. Gerber et al (2013) followed a strict protocol of 1-hour on-site clinician education sessions delivered on site by a physician member of the study team who is board-certified in pediatric infectious diseases followed by quarterly auditing of pediatric patients throughout the yearlong follow-up (p. 2346). In contrast, Doyne et al (2004) conducted educational seminars every other month followed by feedback meetings with local community members and patient parents/guardians (pg. 578). Education materials included information on over-prescription tendencies, antibiotic resistance, and the importance of clinician-parent communication (Doyne et al, 2004).

Gerber et al (2013) showed a 12.5% reduction in treatment clinician prescription tendencies (dropping from 26.8% to 14.3%) compared to control clinicians dropping 5.8% overall (28.4% to 22.6%) (p. 2349). This drop was statistically significant (differences in differences = 6.7%; P=0.01), especially when aggregated for pediatric pneumonia cases (difference in drop of 10.7%; p<0.001) with 14% difference in the drop of antibiotic prescription rates between cases (38.9% to 18.8%) and controls (40.0% to 33.9%) for acute sinusitis (Gerber et al; 2013). In contrast, Doyne et al (2004) provided results only for liquid or chewable antibiotic prescriptions rather than pill-based medications (infant population focus) (p. 578). Educational sessions also showed promising results with differential prescription rate reductions among intervention clinicians (OR=0.82 [0.71. 0.95]) compared to controls (OR=0.86 [0.77. 0.95]) (Doyne et al, 2004). This difference however, like Gerber et al (2013), showed no statistically significant differences between control and intervention groups (Doyne et al, 2004). Lower prescription tendencies were seen in the control group during both baseline and intervention periods with noted variations in the types of antibiotics prescribed but not the appropriateness of these prescription practices (Doyne et al, 2004).

Litvin et al (2013) was the only study meeting inclusion criteria that used both clinician education and CDS software to improve antibiotic prescription accuracy. The study lasted 27 months with the first 12 months dedicated to CDS adoption and antibiotic prescription education and the final 15 months evaluating quality improvements with feedback auditing (Litvin et al, 2013). In addition to monitoring prescription accuracy, education targeted communication techniques for improved parent-clinician discussion of antibiotic need. Study results showed that prescriptions were improperly diagnosed in 20% of pediatric patients with no significant changes in prescription tendencies when comparing before to after intervention (Litvin et al, 2013). Despite no significant results, antibiotic prescription did decline over the study period however delayed prescription was rarely used as an intervention method by clinicians (Litvin et al, 2013).

Parents/Guardians. Five studies were identified that targeted parent or guardian education for pediatric patients. ASP interventions differed by method of information presentation, including reading comprehension (poster and pamphlet) as compared to audiovisuals (pamphlet and video). 2 studies using reading comprehension (Roberts et al, 1983; Alder et al, 2005) targeted youths experiencing cold or flu-like symptoms that had not received antibiotics at the time of intervention. In Roberts et al (1983), educational treatment was divided between control and treatment arms, the latter receiving private face-to-face educational sessions in the 5 minutes prior to clinician visitation. In contrast, Alder et al (2005) performed a 4-pronged intervention treatment to assess differential benefits on types of parental education methods. These treatment arms included education on parent-clinician communication, information solely on antibiotic prescription, combined education integrating both prior arms, and a control group receiving information on child nutrition (Alder et al, 2005). While Roberts et al (1983) evaluated intervention success by necessity of URI visits made by parents, Alder et al (2005) used role-play between intervention researchers and parents to mock discussions with clinicians then administered post hoc questionnaires.

Both studies were designed based on "Social Cognitive Theory (SCT)," a theory that describes the influences of individual experiences, the actions of others, and environmental factors on individual health behaviors (Alder et al, 2005). SCT provides opportunities for social support through instilling expectations, behavioral capability, self-control and efficacy, and using observational learning and reinforcements to achieve behavior change (Roberts et al, 1983). Using these principles, the studies addressed if parental behavior and expectations can modify antibiotic prescription requests. These studies saw education as a tool for modifying parental antibiotic-seeking pressures. In Roberts et al (1983), necessary visits were 15% lower in the test group than the control group, which the researchers attribute to a reduction in unnecessary visits after reviewing patient charts. That being said, the study's researchers comment on the difficulty of easily defining what "necessary" means and how interpretations of this definition could have resulted in misclassification (Roberts et al, 1983). In contrast, Alder et al (2005) showed that all parental education arms, both independently or in combination, had statistically significant increases in perceived efficacy of communication with their child's provider compared to the control arm (p=0.021) (p. 135). Furthermore, a significant increase in anxiety and decreased coping capacity of parents in the control group was associated with increased rates of antibiotic prescription compared to the intervention group (OR = 1.61, p = 0.07 and OR = 1.34, p = 0.06, respectively) (Alder et al, 2005).

Audiovisual information was used in 3 ASP interventions that reinforced pamphlet information through visual graphics. All studies used randomized control trials where parents received baseline questionnaires, were randomized to a treatment or control group, underwent either educational information sessions or lack thereof, and completed an exit survey to evaluate perspective changes. For Taylor et al (2003) and Taylor et al (2005), these studies distributed the educational pamphlet "Your Child and Antibiotics" to treatment groups and "Towards Injury Protection Program" among controls, both developed by the American Academy of Pediatrics. Pamphlets were distributed 6 weeks and 6 months after enrollment with a 5-minute follow-up video used to reinforce pamphlet information just prior to clinician visitation (Taylor et al, 2003; Taylor et al, 2005). In contrast, Bauchner et al (2001) used a 20-minute video prior to clinician visitation with information discussing inappropriate prescription tendencies, common pediatric infections, differences between bacterial and viral infections, importance of prescription adherence, and the connection between over-prescription and antibiotic resistance.

Both Taylor et al (2003) and Taylor et al (2005) found no significant differences in the number of antibiotics prescribed or URTI diagnoses for the full study group or when stratified by infants (<12 months) and younger children (≥12 months). There were significant differences were found between health clinics enrolled in the study in the number of visits and antibiotic prescriptions related to URTIs that they experienced (6.9-12.6%, $p<0.001$ and 0.8-3.2%, p<0.001 respectively through analysis of variance), but no differences were seen between intervention and control groups (Taylor et al, 2005). Furthermore, the study found that antibiotics were prescribed approximately in 45.9% of the visits throughout the study, making differences in control (injury prevention pamphlet) and treatment (antibiotic education pamphlet and video) groups difficult to ascertain (Taylor et al, 2003). Similarly, Bauchner et al (2001) also showed modest effects on video intervention treatment with main significant differences in knowledge regarding discarding leftover antibiotics. Furthermore, differences in the average number of questions answered correctly between baseline (7.50) and end-of-study (7.90) questionnaires showed no significant improvements from audiovisual educational material (Bauchner et al, 2001).

Combined Interventions. Interestingly, our review found only one American-based study (Wheeler et al, 2001) that targeted ASP information towards *and* solicited feedback from both parents and clinicians. While prior studies may have incorporated both physicians and clinicians for educational sessions or feedback panels, study outcomes were not reported for both groups. The Wheeler et al (2001) intervention was performed in 5 pediatric private practices in Arkansas for a 9-month period. Under a randomized control trial study design, treatment physicians received 1-2 training sessions on antibiotic prescription followed by an 8-minute summary video while the control arm received a 20-minute video on the dangers of pediatric stimulant use (Wheeler et al, 2001). Parents consenting to the study completed an entrance survey with the intervention group receiving an antibiotic pamphlet and short video on antibiotic over-prescription while the controls watched a video on drug abuse (Wheeler et al, 2001).

Among physicians, the study showed that "unnecessary" prescription practices declined more among the treatment group than control group (no significant differences between groups). While quantitative evidence showed little effect, qualitative survey responses showed increased comfort in refusing antibiotic prescription, improved prescription practices, and confidence in discussing antibiotic resistance (Wheeler et al, 2001). Survey responses also showed that intervention educational materials were recommended to parents by clinicians throughout the intervention with all respondents believing such material should be dispersed on a seasonal basis and integrated into regular maintenance visits. Similar improvements in parental behavior were found throughout the study. Treatment groups showed an 11% lower tendency to request antibiotic prescriptions from physicians for the common cold as well as 32.5% lower expectations of receiving antibiotics upon visiting with a sick child (both measures were statistically significant at $p<0.001$) (Wheeler et al, 2001).

Discussion

This literature review shows that many gaps in ASP intervention methods and little consensus on ASP education efficacy exist for pediatric populations in the United States. While various systematic reviews have targeted ASP efficacy and performance worldwide or across a variety of clinical settings, we believe this is the first to address pediatrics in outpatient clinical settings. With few studies performed within the United States, it is evident that proactive reduction of antibiotic over-prescription has been thwarted by the tremendous difficulties in successfully instituting ASP interventions in pediatric outpatient settings. To find only 60 papers from our initial search (none meeting the search criteria within the U.S.) with 53 added from manual inspection of 7 prominent systematic reviews, more attention is needed to this topic area by the public health research community.

As outlined above, stewardship practices tend to target either parents/guardians or physicians/clinicians, with only a single study integrating both groups. Among interventions targeting parents, success appears to be driven less by the material provided and more by the translation of this knowledge into parental action. As face-to-face interaction between parents and education materials is brief, no intervention effects may have been found simply due to limited retention of materials before visitation. Though cost effective, this indirect approach limits parental internalization and applicability of knowledge to their personal circumstance. In addition, generalized information on antibiotic may fail to effectively communicate the dangers of antibiotic resistance to that parent's child. This is supported by broader educational efforts through pamphlet handouts or videos to have no differential effects between intervention and control parent groups. In contrast, interventions aimed at improving patient-clinician communications around antibiotics did show promising results in minimizing parental pressures for antibiotic prescriptions.

Among clinicians, ASP methods diverged greatly but all struggled to provide long-lasting changes in prescription practices. Decision-making portals and platforms increased clinician reflections on prescription tendencies and feedback on diagnoses. Though general decline in lab testing and antibiotic orders, few significant differences were found between intervention and control groups. Furthermore, none of the studies addressed if these reductions truly reduced "unnecessary" prescriptions as opposed to conscious, systematic reductions in prescriptions as a result of non-blinded study designs. CDS tools also require a significant amount of training data to provide successful recommendations not easily obtained by the fewer number of cases in these specific outpatient settings. Educational seminars appear to have differential reductions in prescriptions among treatment groups compared to controls but do not lead to lasting or significant overall effects.

ASP interventions not only lacked conformity in ASP methods but also failed to evaluate concrete, standardized health education outcomes. In either target group, interventions often failed to address the key underlying question of ASPs: did clinicians reduce prescription of or parents reduce demanding for antibiotic prescriptions as a result of the educational material provided? Despite intending to evaluate unnecessary antibiotic over-prescription, many reviewed studies used questionnaires whose proxies did not entirely align with this research aim. Only among parent-targeted interventions did outcome measures review the comfort of the parent to communicate with physicians or their agreement with phrases discussing antibiotic usage. Few studies identified parent's willingness to receive antibiotics when their child became ill, knowledge about antibiotic resistance, or confidence in reduced-antibiotic care. For those studies that did record these outcomes, pamphlet and audiovisual aids provided no significant differences between control and treatment groups. Similarly, clinicians guided by critical decision-making tools failed to grasp the importance of this software in an integrated electronic health record platform. In fact, both McGinn et al (2013) and Linder et al (2009) commented on the limited conclusiveness and accuracy of CDS tools as clinicians only used CDS in 10-20% of pediatric patients. Time constraints, lack of CDS software usability, and general beliefs of unimportance minimized full adoption of these tools in outpatient settings.

Though we found only a single study, the thoughtful questioning of parent and clinicians in the combined intervention of Wheeler et al offers an excellent example of how any intervention can improve antibiotic prescription tendencies. By incorporating both target populations within the same design, conducting health education interventions within each, and then evaluating their interaction, this study covered all possible mechanisms for translation of prescription knowledge into action. All studies failed to analyze (or at least failed to report on) controlling for other confounding factors impacting education retention. These include the underlying knowledge of antibiotic resistance, education level, or exposure to previous antibiotic health recommendations in the past. Differential education exposure, both in frequency and quantity of material, was noted in at least one study to influence parental decision-making. Among clinicians, comments on time intensity, impracticality of prescription report cards, insufficient study timelines, and lack of a gold standard for comparing prescription rates in a reliable, generalizable fashion also limited conclusive outcomes for interventions.

Study Limitations. This review was partially limited by the search criteria used. Firstly, search terms may not have fully exhausted the common synonyms and abbreviations used to discuss pediatric respiratory infections. In addition, narrowing our search to the United States significantly limited our search as pediatric outpatient research is more commonly conducted worldwide. As we aimed to describe intervention practices within the United States, our exclusion of papers by geographic extent sheds light on the gaps that exist in American pediatric ASP research. This lack of available or published literature also supports the need for manual investigation of systematically reviewed literature references to supplement the scarce papers identified from the initial search. Constraints of time prevented secondary review and agreement of screened papers. Additionally, inconsistent definitions of "pediatric patients" resulted in a broader window of analysis (≤ 18 years) than initially desired.

Conclusion

Overall, antibiotic over-prescription remains a pertinent concern among pediatric populations, risking the potential for antibiotic resistance among inpatient, outpatient, and hospital-based settings. Though ASPs have demonstrated efficacy among parent and physician groups, few campaigns have surfaced within the United States much less established consistent findings using standardized intervention methods or outcomes. Reviewed studies showed general impacts on behaviors towards and concern over antibiotic over-prescription while interventions took place. These short-term improvements did not persist over longer time periods. Inconclusive evidence of ASP efficacy is driven from the underlying extraordinarily high rates of current prescription among this young subpopulation as well as the difficulty in quantifying more qualitative health education measures. Moving forward, ASP resources must prioritize inclusive interventions integrating clinicians, parents/guardians, and patients towards reductions in overall URTI-related antimicrobial use and subsequent development of antimicrobial resistance (Costelloe et al, 2010). Such efforts must use a multi-faceted approach with diverse health communications (e.g. mass media, pamphlets, audiovisuals), modes of information (e.g. active and passive intervention strategies) and guidelines for post-intervention continuity (e.g. auditing, feedback loops, and integrated electronic health record platforms).

Future Recommendations

From our analysis, we recommend the following practices, methods, and strategies:

1) ***Target Both Parents and Physicians.*** Parental pressure drives antibiotic over-prescription, resulting from a lack of effective communication between parents and physicians. Targeting the intervention at a single group will limit the efficacy of overall interventions while integrated interventions can achieve a holistic outcome for the pediatric patients and clinicians.

2) ***Longer Follow-Up Period.*** Follow-up periods for prescribing practices and analyses of antimicrobial resistance are often short and scarce. Behavior change is an iterative process and requires continuous, consistent, and long-term exposure and/or recycling of health education. As summarized by Ranji et al, interventions must assess "prescribing patterns and resistance patterns over longer time periods, to evaluate if an intervention's effect can be sustained over time and if AMR is affected by reducing prescribing rates (Ranji et al, 2008)."

3) ***Increased Targeting of Urgent Care Settings***. Increased prevalence of urgent care visitations has resulted in heightened prescription of antibiotics (upwards of 50% of visitations) (Rosenberg, 2019). This stresses the need for clinician auditing or feedback systems to improve clinical decision-making assessments. Sources suggest that nurse practitioners may be effective in changing clinical behaviors in urban urgent care settings, where there is a more "anonymity" and less pressure to maintain patient-clinician relationships (Harris et al, 2003). This may be addressed using either tele-health platforms or mobile applications for parents to monitor child health to inform clinician decision-making.

4) ***Improve Health Literacy and Transparency.*** Study designs lack consistent intervention methods and outcome measures. This includes not only standardizing results for comparisons across the literature but also catering to persons with limited literacy and education when creating pamphlets, posters, and audiovisuals. Materials in English along may limit study participants to a non-generalizable sub-population or hinder study results due to reporting biases.

5) ***Exploring Cost Effectiveness of ASP Interventions***. The process of implementing interventions heavily relies on monetary benefits, especially given the costs incurred to publish and deliver educational materials (e.g., in person one-on-one education). At present, few studies have effectively quantified intervention-associated costs (e.g. publishing costs, survey costs, personal interview costs, etc.), monies saved from fewer prescriptions, or reduced consequences of antimicrobial resistance (Ranji et al, 2008).

Proposed Intervention Study

Overall Objective. This study aims to 1) identify physician barriers to proper prescribing and 2) subsequently change prescribing behaviors in the pediatric outpatient setting. To do this, both the provider and the patients' parents will be targeted through the implementation of an education-based antimicrobial stewardship program combined with an audit and feedback loop (ASP) (Suez et al, 2018).

Aims. We will first identify barriers to uptake of ASP guidelines and design a theory-informed implementation program to address these barriers. Next, we will determine how much an ASP in outpatient pediatric clinics reduces antimicrobial prescriptions for pediatric patients with viral URTIs compared to control clinics without an intervention. Finally, we will describe the fidelity of the implementation strategy at addressing the identified barriers to the uptake of ASP guidelines. From this we will provide a set of recommendations for future ASP intervention design and suggestion for a follow-up study to assess continued application of ASP practices.

Impact/Expected Outcomes. Through the implementation of this program, we expect a reduction in the prescription of antimicrobials for children with viral URTIs. Through qualitative phone interviews pre- and post-intervention conducted with enrolled PCPs, we expect to increase knowledge for ASP *implementers* as to which aspects of stewardship programs work best in pediatric outpatient settings. We will use quantitative data collected about prescribing practices after every examination to provide evidence for effective adoption and continuation of these programs in outpatient clinics. Finally, this intervention will inform current gaps in prescribing practices and establish recommendations for future mitigation of antimicrobial resistance through targeted over-prescription monitoring and maintenance.

Study Design and Recruitment Strategy. This study will follow a parallel cluster-randomized trial design. This will permit randomization of intervention clinics and simplify the enrollment process. This study will assume a null hypothesis that the prescribing rates between intervention (experimental) and non-intervention (control) clinics are equal and range approximately 1 standard deviation from the true population prescribing rate. Assuming a Type I error level of 0.05 and Type II error level of 0.20, a sample size of 1396 pediatric patients are required (split evenly 698 patients per experimental and control clinics) to detect an effect size of 15% difference between groups. To achieve this sample size, this study aims to enroll 30 experimental and 30 control clinics matched by geography (15 urban and 15 rural for both intervention and control groups), clinic size, characteristics of the population served, and ASP/antibiotic resistance knowledge among resident pediatricians. This results in a minimum of 47 pediatric patients evaluated per clinic with a goal of evaluating 60 patients per clinic to account for up to 20% loss to follow up.

Population and Setting. Inclusion criteria will be limited to outpatient clinics serving only pediatric patients. This will standardize the study population to focus conclusions on providers who specifically treat children. Excluding PCPs who treat both children and adults will limit confusion during study design and data collection. Clinics will ideally never have participated in an official ASP any time prior to our study in order to reduce reporting biases from preordained education intervention. To further emphasize this, physicians will be blinded to the intervention aims to better understand barriers to ASP adoption.

Disparities among people living in rural compared to urban areas may impact multiple aspects of the intervention. In particular, it is well documented that differences in morbidity and risk factors for chronic or infectious disease acquisition as well as patient healthcare-seeking behavior differs between these populations (Eberhardt, 2004). We will focus our intervention on different practices and practice settings throughout the United States.

Timeline. Please refer to the supplemental tables provided at the end of the document.

Pre-Intervention Procedures and Measurements. In order to have non-biased analyses, a definition for URTI was established. A diagnosis of an URTI included doctor-diagnosed flu/serious cold, throat infection, middle-ear infection, bronchitis, pneumonia, pertussis, or any other serious respiratory tract infections with confirming lab test results if done or available (Koopman et al., 2001). We must take into consideration that not all providers will have uniform diagnostic procedures, however, for our intents and purposes, our definition of URTI diagnosis will be followed as closely as possible for the review and analysis of medical charts and intervention data.

In order to evaluate provider perspectives and barriers to implementing ASPs in pediatric clinics, structured qualitative interviews will be conducted over the phone 4 weeks before the start of the study among both intervention and control group pediatricians. The questionnaire will include open ended questions covering:

i) Environmental factors (resources and recommendations for best practice);

ii) Social influences (parental pressures), professional capabilities (confidence in making diagnosis);

iii) Perceived consequences (lack of belief in personal contribution to the perpetuation of antimicrobial resistance by prescribing antibiotics; consequences from parents such as litigation based on negligence);

iv) Habitual tendencies (engrained propensity to prescribe for more situations); and

v) Barriers to the implementation of ASPs, attitudes towards said programs, and stewardship activities that may have existed prior to our project.

A phone interview was chosen over a written survey in order to facilitate open, comfortable conversation and minimize reporting bias through clearly explained survey questions, clarified clinician responses, and better ability to code answers accurately. The survey establishes a baseline for pediatrician opinions and perceived barriers.

Upon arrival for their doctor's appointment, parents will receive a survey to be filled out during check-in and prior to clinician consultation. This survey will have a set of questions pertaining to knowledge about antibiotic resistance, general health and wellness, antibiotic prescription, and injury prevention. The questionnaire will be standardized for administration among both intervention and control groups and presented as a general, anonymous survey to help improve clinic care. To minimize parent burden while not divulging the intervention's intention, survey questions will be brief, direct, and span a variety of health-related topics.

For a quantitative metric of intervention efficacy, we will compare antibiotic prescription rates (number of prescriptions/100 URTI diagnoses) per each clinic throughout the entire time period. Pediatric patient charts will be reviewed retrospectively before the intervention period begins in order to measure baseline prescription rates and match sites for intervention and control groups concludes. Throughout the intervention, prescription information from providers will be collected in real-time by maintaining an online survey platform. For each URTI appointment during the study period, a pediatrician would fill out an online form to first note that they encountered a patient with a URTI, and to then record whether an antimicrobial prescription was made (creating the numerator and denominator for our antimicrobial prescription rates per URTI). Forms will be brief, be conducted on a user-friendly platform, and will seek to minimize clinician burden for post-visit record keeping. The anonymity of this interface will minimize child privacy issues or HIPAA health violations. Formal chart reviews will be performed at 6 and 12 months following the study to observe continued efficacy of the intervention program through comparing rates of antibiotic prescribing during and after intervention completion.

Similarly, closing interviews of a comparable design will occur within the two weeks after the intervention's completion. Differences in perspectives on ASPs across these surveys will be used to measure the acceptability of our intervention among pediatricians and inform recommendations for future ASP adoption within the U.S. Finally, providers often understand the barriers to making an appropriate antimicrobial prescription (i.e., facilitators of making an inappropriate prescription), but hopefully this intervention can provide them with ways to overcome them, and these outcomes should be captured by the interviewing process.

The parental post-intervention procedure will vary slightly. Instead of evaluating prescription accuracy, surveys will be mailed out for completion and return 3 months after the intervention has taken place for both intervention and control groups. This time period was chosen in order to follow the effects of the pamphlet and video interventions on memory and information synthesis designed to reduce negative parental behaviors. The answers to the questionnaire both before and after the intervention will serve as benchmark and comparison measures to identify education impacts during appointments. These surveys will specifically recycle the questions related to antibiotic resistance, prescription, and usage from the baseline survey as well as solicit further information on additional education materials that may be helpful in a follow-up intervention. Furthermore, utilization of the phone-based application with regards to logging symptoms and clicking through the decision-making system will be tracked and matched to parents and children who do or do not show up for further consultation during intervention implementation and 1 year of follow-up. The app will additionally have a comments and evaluation section to gauge user satisfaction with the application itself.

Intervention. The implementation of the program for 12 months will determine whether physician auditing and feedback as well as education-based ASP (for both physicians and parents) aids in decreasing inappropriate prescribing rates.

Physician Intervention. This intervention provides pediatricians in intervention clinics with one 2-hour on-site educational training session delivered by accredited physicians involved in study implementation on antimicrobial stewardship and successful parent-physician communication, printed URTI treatment guidelines, and informational pamphlets to disseminate to parents upon explanation of diagnosis. The training will cover current trends and reasons for the rise in antimicrobial resistance, illnesses that necessitate antibiotics, proper prescribing guidelines of antibiotics, and ideal interactions and explanations of problematic parent-physician interactions.

Since this intervention seeks to examine the effect of modeling on prescribing and pediatricians' attitudes towards stewardship, the training will also include role-play of successful provider-parent interaction for the diagnosis of URTIs. Intervention group physicians' prescriptions will be audited monthly with study coordinators providing feedback on their prescribing measures and tendencies. This iterative surveillance cycle hopes to provide positive reinforcement for more judicious prescribing practices.

Control group physicians will receive an educational training session of equal length on general health, wellness, and injury prevention. Throughout the intervention, all PCPs, including those in control groups, will have access to digital versions of education materials pertaining to their training session. Intervention physicians will also be asked to provide antibiotic prescribing and resistance pamphlets to parents during visitations to facilitate transparent communication on antibiotic prescription at pediatric URTI appointments.

Parental Intervention. The parental portion of the intervention will be PCPs delivering a 5-7 minute explanation of antibiotic resistance, judicious prescribing, common misconceptions about prescribing for the common cold and flu-like symptoms, expected course of illness, and non-antibiotic options for relieving children's symptoms while parents followed along in the informational pamphlet. There will be both English and Spanish copies of all pamphlets and a phone-based translator service will be available in order to accommodate the most patient parents possible. These active explanations with the delivery of an informational pamphlet should result in engaged listening and internalized information by the parent.

The second part of the intervention will be the implementation of a phone-based app that allows parents to a) record their child's symptoms through a sickness log, and b) click through a decision-support system that computes what sort of illness their child is most likely experiencing, the urgency of an appointment with a physician, and a default option to schedule a call with a practice nurse to discuss the necessity of antibiotics. This intervention would utilize parent's reliance on phone-based technology as well as provide a first-line opinion without heading straight to a physician.

Outcomes. The primary outcome will be the difference in rates of antimicrobial prescriptions from URTIs in the intervention versus control groups. Supplementing this primary outcome, the more qualitative aspect of the study perception changes of PCPs interviewed will be targeted and evaluated. Secondary outcomes not measurable by our intervention will include eventual reduction in antimicrobial resistance, decrease in patient costs, fewer adverse events, and less additional clinic visits. Finally, following any stewardship protocol will increase burden on providers (e.g., more time and effort during URTI appointments), which is an important negative outcome in the outpatient setting where resources are scarce. The qualitative component of this study should identify the feasibility of future stewardship implementation strategies within the U.S. with this important burden in mind.

Challenges. While providers may know the barriers to making proper diagnoses and decisions for the need of an antibiotic or not, addressing such barriers during clinical care can be challenging. Specific barriers to proper prescription include parental pressures, doubts about proper diagnosis, and appointment time constraints. Furthermore, sustained implementation of this intervention may be compromised by providers' lack of referencing or reviewing guidelines, failure to attend the educational session or implement the lessons, fatigue in following the intervention, and incomplete survey data for URTI visits. The efforts of this study aim mitigate these challenges and constraints as much as possible.

Possible Limitations.

(1) The survey entry method for measuring antibiotic prescriptions, though excellent for efficiency and minimizing the study load placed on clinics, may still increase burden on PCPs, especially during peak cold and flu seasons when URTI appointments surge. Also, it is not a method fully integrated into their usual system which means they could forget to use it.

(2) None of the outcome measures involve direct observation of pediatricians during patient encounters. This allows for a more genuine interaction with patients, but also increases the likelihood of reporting and recall bias from PCPs.

(3) The intervention's success is defined by a reduction in antimicrobial prescriptions for URTIs, but this does not take into account providers who adopt a "wait-and-see" approach (WASP), which is promoted by many stewardship activities. Under WASP procedures, providers prescribe antibiotics for a condition, but instruct the recipients to take them only if their symptoms worsen. While this is considered an appropriate stewardship strategy, our study definitions would define this as a negative outcome.

(4) The intervention might encourage under-prescription of antibiotics in situations where they are actually needed. Through medical chart reviews and evaluating reported symptoms, study administrators/investigators will be able to determine how many prescriptions were necessary or not.

Expected Outcomes and Overall Impact. The implementation of this study hopes to provide evidence that a multi-faceted ASP, when implemented alongside behavioral interventions tailored to the outpatient pediatric setting, can be successful in minimizing the number of inappropriate antimicrobial prescriptions for URTIs in children. The key components of this intervention are simple and inexpensive. As such, these components could be included in free stewardship training modules with downloadable prescription guidelines, parent-geared pamphlets, and modeling videos that can be disseminated. This study expects to inform future implementation efforts in this setting by further revealing barriers and facilitators of evidence-based antimicrobial prescriptions for URTIs.

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Figure 1. PRIMSA flow diagram.

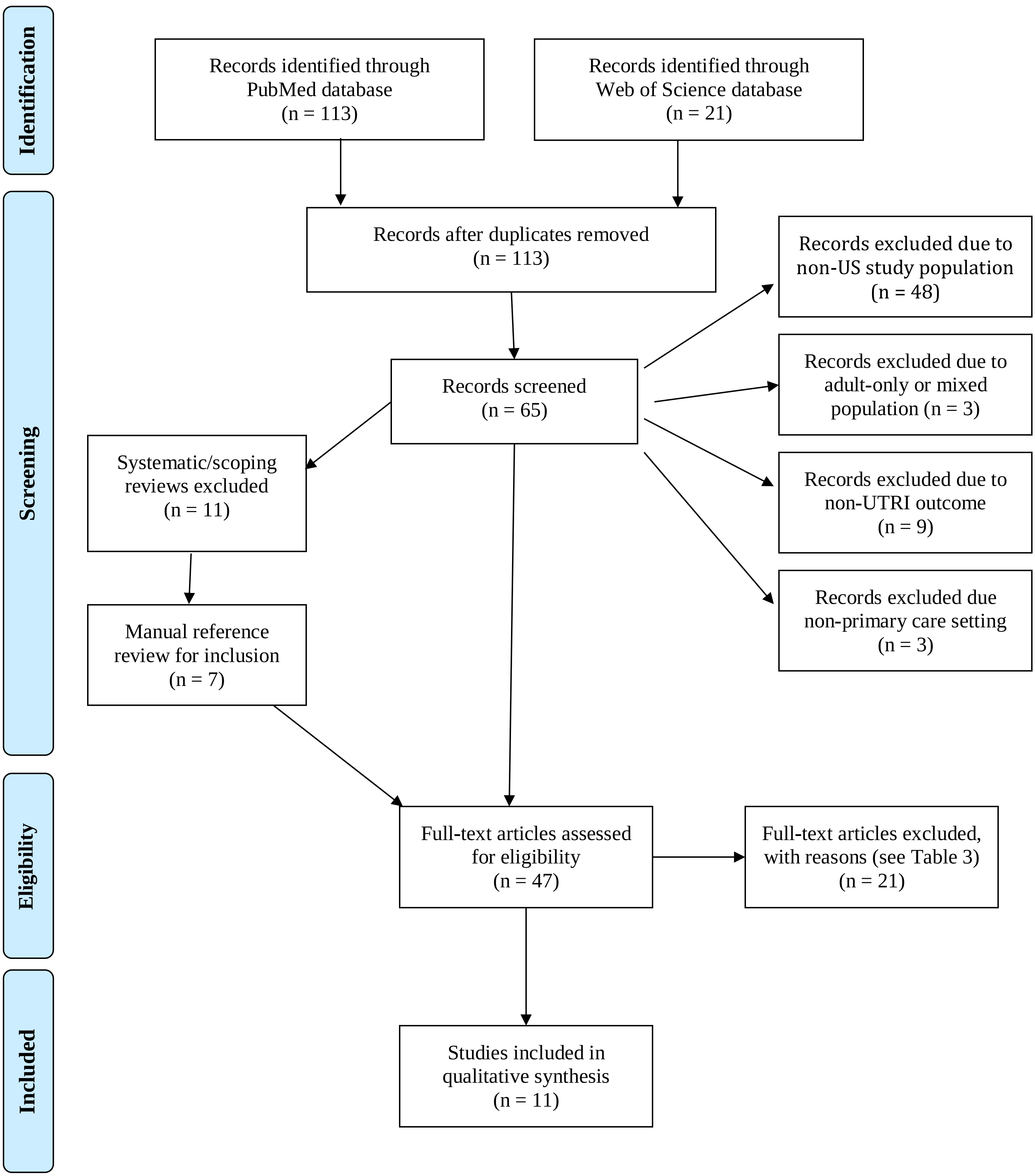

Table 2. A summary of studies meeting inclusion criteria.

Target Population	Intervention Type	Citation	Pediatric Population	Primary Outcome
Clinician	CDSS	Linder, J. et al. (2009). Documentation-based clinical decision support to improve antibiotic prescribing for acute respiratory infections in primary care: a cluster randomised controlled trial. *Journal of Innovation in Health Informatics*, *17*(4), 231-240.	Unspecified	Intervention clinicians used a CDS tool, the ARI Smart Form, in 6% of 11,954 visits. The antibiotic prescribing rate was 39% in intervention clinics vs. 43% in control clinics (OR 0.8; 95% CI, 0.6–1.2). The prescribing rate for antibiotic appropriate ARI diagnoses was 5% lower in intervention than control clinics (OR, 0.8; 95% CI, 0.5–1.3), while the prescribing rate for non-antibiotic appropriate diagnoses was 2% lower in intervention versus control clinics (OR, 0.9; 95% CI, 0.6–1.4). When the Smart Form was used, the antibiotic prescribing rate was 49% overall (88% for antibiotic appropriate, 27% for non-antibiotic appropriate diagnoses). In analyses, the ARI Smart Form was associated with a lower antibiotic prescribing rate (OR, 0.5; 95% CI, 0.3–0.8).
		McGinn et al. (2013). Efficacy of an evidence-based clinical decision support in primary care practices: a randomized clinical trial. *JAMA internal medicine*, *173*(17), 1584-1591.	Unspecified	The intervention group utilized an integrated clinical prediction rule tool in 57.5% of visits. Providers in the intervention group were significantly less likely to order antibiotics than the control group (age-adjusted RR, 0.74; 95% CI, 0.60-0.92). The intervention group was significantly less likely to order rapid streptococcal tests compared with the control group (RR 0.75; 95% CI, 0.58-0.97; p = 0.03).
	Education	Gerber, J. S. et al. (2013). Effect of an outpatient antimicrobial stewardship intervention on broad-spectrum antibiotic prescribing by primary care pediatricians: a randomized trial. *Jama*, *309*(22), 2345-2352.	18 & Under *(with adult group stratified results)*	After 1 year post-intervention, broad-spectrum antibiotic prescribing decreased by 12.5% among intervention practices and 5.8% in controls (p = 0.01). Prescribing for children with acute sinusitis decreased from 38.9% to 18.8% in intervention practices and from 40.0% to 33.9% in controls (DOD, 14.0%; p = 0.12). Prescribing changed little for streptococcal pharyngitis (intervention, from 4.4% to 3.4%; control, from 5.6% to 3.5%; DOD, 1.1%; p = 0.82) and for viral infections (intervention, from 7.9% to 7.7%; control, from 6.4% to 4.5%; DOD, 1.7%; P= 0.93).
		Doyne, E. O. et al. (2004). A randomized controlled trial to change antibiotic prescribing patterns in a community. *Archives of pediatrics & adolescent medicine*, *158*(6), 577-583.	"Young children" – No specific age range provided	The antibiotic prescription rate decreased to 0.82 (95% CI, 0.71-0.95) of the baseline rate for the intervention group and to 0.86 (95% CI, 0.77-0.95) of the baseline for the control group. Similar patterns for antibiotic prescription rates were seen for intervention and control groups both before and after the intervention and wide variations in prescription rates were observed among the practices. In general, the control practices had lower antibiotic prescribing rates during both the baseline and the intervention periods.
	CDSS + Education	Litvin, C. B. et al. (2013). Use of an electronic health record clinical decision support tool to improve antibiotic prescribing for acute respiratory infections: the ABX-TRIP study. *Journal of general internal medicine*, *28*(6), 810-816.	17 & Under	The clinical decision support software (CDSS) was used 38,592 times during the 27-month intervention. Use of antibiotics for encounters at which diagnoses for which antibiotics are rarely appropriate did not significantly change through the course of the study (27-month change, −1.89 % [95 % CI, −9.03%, 5.26%] in children). However, use of broad-spectrum antibiotics for ARI encounters improved significantly (estimated 27 month change, −16.30 [95% CI, −23.29%, −9.31%] in children). Prescribing for bronchitis did not change significantly, but use of broad-spectrum antibiotics for sinusitis declined.
Parents	Poster + Pamphlet	Alder, S. C. et al. (2005). Reducing parental demand for antibiotics by promoting communication skills. *Journal of Health Education*, *36*(3), 132-139.	1-10	Parents receiving the communication skills intervention reported higher efficacy to communicate with the physician (p = 0.021). The communication skills intervention was protective against antibiotic prescribing (p = 0.042). Satisfaction was positively associated with parents' efficacy to communicate (p = 0.002).

		Roberts, C. R. et al. (1983). Reducing physician visits for colds through consumer education. *Jama*, *250*(15), 1986-1989.	17 & Under *(with adult group stratified results)*	The intervention group made 44% fewer unnecessary visits than control families ($p < 0.002$) and 15% fewer necessary visits. Total URTI visits were 29% fewer in the intervention group ($p < 0.01$).
	Audio Visual + Pamphlet	Taylor, J. A., Kwan-Gett, T. S. C., & McMahon, E. M. (2003). Effectiveness of an educational intervention in modifying parental attitudes about antibiotic usage in children. *Pediatrics*, *111*(5), e548-e554.	> 1	6 weeks after receiving the antibiotic educational materials, parents in the intervention group had significantly different attitude scores about the antibiotic use in general and for specific conditions in children.
		Taylor, J. A., Kwan-Gett, T. S. C., & McMahon Jr, E. M. (2005). Effectiveness of a parental educational intervention in reducing antibiotic use in children: a randomized controlled trial. *The Pediatric infectious disease journal*, *24*(6), 489-493.	> 1	Overall physicians prescribed 1 or more antibiotics during 45.9% of visits for a chief complaint of URI symptoms; 92% of antibiotic usage in children presenting with URI symptoms was for a diagnosis of otitis media and/or sinusitis.
		Bauchner, H. et al. (2001). Improving parent knowledge about antibiotics: a video intervention. *Pediatrics*, *108*(4), 845-850.	6 Months – 3 Years	A total of 193 (94%) parents completed the study and no significant differences were found for adjusted posttest means between the intervention and control groups for knowledge, beliefs, or behavior. Subgroup analyses indicated that intervention group families in the urban clinic improved their knowledge score (6.03 to 6.92) and were more likely to report that there were problems with children receiving too many antibiotics (intervention 67% vs control 34%).
Both	Education + Clinical Decision Making	Wheeler, J. G. et al. (2001). Impact of a waiting room videotape message on parent attitudes toward pediatric antibiotic use. *Pediatrics-English Edition*, *108*(3), 591-596.	18 & Under	Parents who were exposed to the videotape were significantly less inclined to seek antibiotics for viral infections. Parent-focused passive education tools are effective at changing parent attitudes toward the use of antibiotics, though changes in parent attitudes in this study were not associated with changes in prescribing rates. Changes in parent attitudes may be necessary but do not seem sufficient for changes in antimicrobial prescribing patterns.

Table 3. Descriptive reasoning for paper exclusion throughout the literature review process.

Review Phase	Reason for Exclusion	Citation
Abstraction	Non-US Study Location	Alrafiaah, A. S. et al. (2017). Are the Saudi parents aware of antibiotic role in upper respiratory tract infections in children? *J Infect Public Health, 10*(5), 579-585. doi:10.1016/j.jiph.2017.01.023
		Altiner, A. et al. (2012). Converting habits of antibiotic prescribing for respiratory tract infections in German primary care--the cluster-randomized controlled CHANGE-2 trial. *BMC Fam Pract, 13*, 124. doi:10.1186/1471-2296-13-124
		Alumran, A., Hou, X. Y., & Hurst, C. (2013). Assessing the overuse of antibiotics in children with URTIs in Saudi Arabia: development of the parental perception on antibiotics scale (PAPA scale). *J Epidemiol Glob Health, 3*(1), 3-10. doi:10.1016/j.jegh.2012.11.005
		Anderson, E. C. et al. (2018). Population-based paediatric respiratory infection surveillance: a prospective inception feasibility cohort study. *Pilot Feasibility Stud, 4*, 182. doi:10.1186/s40814-018-0371-8
		Baan, E. J. et al (2018). Antibiotic use in children with asthma: cohort study in UK and Dutch primary care databases. *BMJ Open, 8*(11), e022979. doi:10.1136/bmjopen-2018-022979
		Blair, P. S. et al. (2017). Feasibility cluster randomised controlled trial of a within-consultation intervention to reduce antibiotic prescribing for children presenting to primary care with acute respiratory tract infection and cough. *BMJ Open, 7*(5), e014506. doi:10.1136/bmjopen-2016-014506
		Brink, A. J. et al. (2015). Updated recommendations for the management of upper respiratory tract infections in South Africa. *S Afr Med J, 105*(5), 344-352. doi:10.7196/samj.8716
		Butt, A. A. et al. (2017). Antibiotic prescription patterns for upper respiratory tract infections in the outpatient Qatari population in the private sector. *Int J Infect Dis, 55*, 20-23. doi:10.1016/j.ijid.2016.12.004
		De Luca, M. et al. (2016). Antibiotic Prescriptions and Prophylaxis in Italian Children. Is It Time to Change? Data from the ARPEC Project. *PLoS One, 11*(5), e0154662. doi:10.1371/journal.pone.0154662
		Dekker, A. R. J., Verheij, T. J. M., & van der Velden, A. W. (2017). Antibiotic management of children with infectious diseases in Dutch Primary Care. *Fam Pract, 34*(2), 169-174. doi:10.1093/fampra/cmw125
		Dorj, G., Hendrie, D., Parsons, R., & Sunderland, B. (2013). An evaluation of prescribing practices for community-acquired pneumonia (CAP) in Mongolia. *BMC Health Serv Res, 13*, 379. doi:10.1186/1472-6963-13-379
		Gjelstad, S. et al. (2013). Improving antibiotic prescribing in acute respiratory tract infections: cluster randomised trial from Norwegian general practice (prescription peer academic detailing (Rx-PAD) study). *Bmj, 347*, f4403.
		Gwimile, J. J. et al. (2012). Antibiotic prescribing practice in management of cough and/or diarrhoea in Moshi Municipality, Northern Tanzania: cross-sectional descriptive study. *Pan Afr Med J, 12*, 103.
		Higashi, T., & Fukuhara, S. (2009). Antibiotic prescriptions for upper respiratory tract infection in Japan. *Intern Med, 48*(16), 1369-1375.
		Horwood, J. et al. (2016). Primary care clinician antibiotic prescribing decisions in consultations for children with RTIs: a qualitative interview study. *Br J Gen Pract, 66*(644), e207-213. doi:10.3399/bjgp16X683821
		Huang, Y. H., & Huang, Y. C. (2005). Use of antimicrobial agents for upper respiratory tract infections in Taiwanese children. *Chang Gung Med J, 28*(11), 758-764.
		Ivanovska, V. et al. (2016). Antibiotic prescribing for children in primary care and adherence to treatment guidelines. *J Antimicrob Chemother, 71*(6), 1707-1714. doi:10.1093/jac/dkw030
		Juszczyk, D. et al. (2016). Electronically delivered, multicomponent intervention to reduce unnecessary antibiotic prescribing for respiratory infections in primary care: a cluster randomised trial using electronic health records—REDUCE Trial study original protocol. *BMJ open, 6*(8), e010892.
		Kirolos, A. et al. (2018). Care seeking behaviour and aspects of quality of care by caregivers for children under five with and without pneumonia in Ibadan, Nigeria. *J Glob Health, 8*(2), 020805. doi:10.7189/jogh.08.020805

		Launay, E. et al. (2016). 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, 16*(1), 126. doi:10.1186/s12887-016-0661-3
		Lucas, P. J. et al. (2015). A systematic review of parent and clinician views and perceptions that influence prescribing decisions in relation to acute childhood infections in primary care. *Scand J Prim Health Care, 33*(1), 11-20. doi:10.3109/02813432.2015.1001942
		Maina, M. et al. (2017). Inappropriate prescription of cough remedies among children hospitalised with respiratory illness over the period 2002-2015 in Kenya. *Trop Med Int Health, 22*(3), 363-369. doi:10.1111/tmi.12831
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		Maor, Y. et al. (2011). Changing parents' opinions regarding antibiotic use in primary care. *European journal of pediatrics*, *170*(3), 359-364.
		Mistik, S. et al. (2015). Sore throat in primary care project: a clinical score to diagnose viral sore throat. *Fam Pract, 32*(3), 263-268. doi:10.1093/fampra/cmv015
		Moro, M. L. et al. (2009). Why do paediatricians prescribe antibiotics? Results of an Italian regional project. *BMC Pediatr, 9*, 69. doi:10.1186/1471-2431-9-69
		Mukanga, D. et al. (2012). Integrated community case management of fever in children under five using rapid diagnostic tests and respiratory rate counting: a multi-country cluster randomized trial. *Am J Trop Med Hyg, 87*(5 Suppl), 21-29. doi:10.4269/ajtmh.2012.11-0816
		Nathwani, D. et al. (2011). Scottish antimicrobial prescribing group (SAPG): development and impact of the Scottish national antimicrobial stewardship programme. *International journal of antimicrobial agents*, *38*(1), 16-26.
		O'Brien, K. et al. (2015). Clinical predictors of antibiotic prescribing for acutely ill children in primary care: an observational study. *Br J Gen Pract, 65*(638), e585-592. doi:10.3399/bjgp15X686497
		Poulos, L. M. et al. (2013). Inappropriate prescribing of inhaled corticosteroids: are they being prescribed for respiratory tract infections? A retrospective cohort study. *Prim Care Respir J, 22*(2), 201-208. doi:10.4104/pcrj.2013.00036
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Full Text Review	Systematic or Scoping Review (Not Providing Manually-Reviewed References)	Biondi, E. et al. (2014). Treatment of mycoplasma pneumonia: a systematic review. *Pediatrics, 133*(6), 1081-1090. doi:10.1542/peds.2013-3729
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Full Text Review	Systematic or Scoping Review	Costelloe, C. et al. (2010). Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *Bmj*, *340*, c2096.

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Full Text Review	No Individual US Setting Results	Di Pietro, P. et al. (2017). Monitoring adherence to guidelines of antibiotic use in pediatric pneumonia: the MAREA study. *Ital J Pediatr*, *43*(1), 113. doi:10.1186/s13052-017-0432-2
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Table 4. Timeline of proposed epidemiological study.

Activity	Year 1												Year 2												Year 3											
	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
Pre-Intervention																																				
IRB Approval	X																																			
Enroll Clinics	X	X	X	X	X	X	X	X	X																											
Baseline Prescription Rate Analyses										X	X	X																								
Clinician Phone Interviews											X	X																								
Survey Development	X	X	X	X	X	X	X	X	X	X																										
Finalizing Parental Surveys											X	X																								
On-Site Clinician Education Session												X																								
During Intervention																																				
Parental Surveys (before appointment)													X	X	X	X	X	X	X	X	X	X	X	X												
Parental Education & Phone-based App Introduction													X	X	X	X	X	X	X	X	X	X	X	X												
Prescription Analyses (online platform)													X	X	X	X	X	X	X	X	X	X	X	X												
Post-Intervention																																				
Clinician Phone Interviews																								X	X											
Parental Survey																											X									
Formal Chart Review																														X						X
App User Follow-Up																																				X