Effects of Delayed Antibiotic Prescribing Vs. Immediate or No Antibiotic for URI's in Primary Care: A Systematic Review

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Abstract

Introduction: Delayed antibiotic prescription (DAP) is an evidence-based intervention to fight the global issue of antibiotic resistance. Evidence of its benefits for treating respiratory tract infections (RTIs) have long existed in literature but never fully accepted. This paper's purpose is to evaluate new evidence and the overall effects of DAP on patients with upper respiratory infections in the primary care practice.

Methods: This systematic review of the literature was guided by the PARIHS model to investigate patient outcomes and satisfaction rates with delayed antibiotic prescription compared to immediate and no prescription when treating RTI symptoms. JSTOR Journals, Health Source, OVID, CINAHL, Cochrane, PubMed, and MEDLINE were databases used in gathering the literature. Articles were screened with an inclusion criterion. A Rapid Critical Appraisal Tool was used to score articles on its relevance and validity to answer the PICOT question. Articles' quality appraisal score of less than four were excluded from this review. Scores are illustrated in the Evidence Synthesis Table.

Results: Five randomized controlled trials and three cohort studies were analyzed. Study findings overall revealed that DAP reduces antibiotic use, and no significant difference was seen in symptom severity through all prescribing approaches. Interestingly, only two of the three studies found that DAP is related to higher patient satisfaction.

Discussion: DAP can be used safely in most patients with acute RTIs. However, more research is needed in the United States to give a better generalizability to the population.

Keywords: delayed antibiotic prescribing, no antibiotics, upper respiratory infections, treatment, primary care, and patient satisfaction

Introduction

Across the country, upper respiratory infections account for 10 million office visits per year with over $22 billion in patient costs (Thomas & Bomar, 2022). Antibiotic resistance is a global challenge for health care providers who face an everyday battle when seeing patients for viral upper respiratory infection symptoms who expect and often, demand antibiotics. This trend contributes to the increasing evolution of antimicrobial resistance within the United States. Agency for Healthcare Research and Quality (2016) found that at least 2 million people are affected by antibiotic-resistant bacteria, causing 23,000 deaths each year. Inappropriate antibiotic prescribing increases patient risk of drug side effects, drug resistance, and unnecessary cost. At the same time, antibiotic avoidance can increase risk of potential serious bacterial infections that could have been avoided through earlier treatment. Primary care providers prescribe about 64% of all antibiotics and shoulder the burden of this challenge (Shuldiner et al., 2022). A strategy to lessen antibiotic overuse while also lessening risk of serous bacterial infection is the delayed antibiotic prescribing method. “Delayed prescribing, also called “wait-and-see prescribing”, is the process whereby a GP makes an antibiotic prescription available during the consultation but asks the patient to delay its use to see if symptoms will resolve first” (Sargent et al., 2016). Studies provide evidence to support prescribing, not prescribing, and delaying the prescription of antibiotics for viral URI (upper respiratory infection) symptoms. This review of the literature will examine the most recent evidence addressing antibiotic prescribing for viral URI symptoms from the perspective of a primary care provider considering patient outcomes and patient satisfaction.

The most significant cause of antimicrobial resistance is the excessive and inappropriate use of antibiotics (Spurling et al., 2017). Inappropriate use of antibiotics not only increases

antibiotic-resistant infections but also strains valuable resources, places patients at an increased risk of developing adverse reactions, and increases re-consultation rates (De La Poza et al., 2016). The estimated mortality rate from drug-resistant bacteria may surpass 10 million by 2050 (O'Neill, 2013). In 2016, there was a budget of over 1.2 billion dollars to address antibiotic resistance throughout the U.S. This led to President Biden's request for more funds to the CDC's Antibiotic Resistance Solutions Initiative, which invests in national infrastructure to prevent antimicrobial resistance, improve surveillance and promote stewardship (Williams, 2022).

Delayed antibiotic prescribing (DAP) occurs when the provider prescribes the antibiotic but advises the patient to start the antibiotic only if symptoms worsen. It has also been called the "just in case prescribing" because to some providers, it can provide reassurance that a delay in care is avoided. This type of prescribing can decrease re-consultation rates, increase patient satisfaction, and prevent potential health complications while decreasing the duration of the infection course (Stuart et al., 2021). Over the years, this strategy has been advocated as a safety net for avoiding complications of RTIs, and reducing antibiotic use, while maintaining control of symptoms and providing high levels of patient satisfaction (Spurling et al., 2017). Inconsistent support of delayed antibiotic prescribing has been found in previous studies and within the United States' medical providers, but recommendations for DAP persist in international guidelines and continue to be discussed in literature (Spurling et al., 2021).

Upper respiratory tract infections are the bread and butter of healthcare providers' clinical management in all ages. The literature surrounding this topic reveals conflicting findings regarding patient outcomes and patient satisfaction associated with delayed antibiotic prescription compared to immediate prescription and no antibiotic prescription when treating RTI symptoms. In a meta-analysis examining complications resulting in hospital admission or

death following no antibiotic prescription compared to delayed prescription and immediate prescription, both hospital admission and death were lower with delayed versus no antibiotics (OR=.62, 95% CI:.30-1.27) and delayed versus immediate antibiotics (OR=.78, CI:.53-1.13) (Stuart et al., 2021). Stuart et al. (2021) also found a significant reduction in re-consultation rates (OR=.72, 95% CI: .60 -.87) and an increase in patient satisfaction (adjusted mean difference 0.09, 0.06 to 0.11) comparing delayed prescription versus no antibiotics. On the other hand, another meta-analysis found no difference in complication rates and clinical outcomes between delayed antibiotic prescribing, immediate, and no prescription in cough and common cold (Spurling et al., 2017). Interestingly, the same study found that delayed antibiotics revealed lower antibiotic use than immediate antibiotics (Spurling et al., 2017). Stuart et al. (2021) further recognize DAP strategy to be safe for most patients and unlikely to lead to poorer symptom control and duration. However, in one cohort study, there was concerns that reducing antibiotic prescribing or not prescribing antibiotics at all led to increased incidence of certain respiratory infections (Gulliford et al., 2016).

A clinical guideline from the American College of Physicians (2016) advised that providers should not prescribe antibiotics for patients with the common cold, acute uncomplicated bronchitis, and acute rhinosinusitis, unless symptom persists more than 10 days, has purulent nasal discharge or facial pain for at least 3 days, high fever greater than 39 degrees Celsius, or worsening symptoms lasting greater than 5 days. It further listed other specific RTIs with antibiotic prescribing strategies and recommendations. DAP was only mentioned twice in the guideline as an appropriate approach to overcome inappropriate antibiotic prescription. Even with the publication of this guideline and other evidence, the CDC (2021) estimated that over 28% of antibiotic prescriptions from doctors' offices and emergency rooms each year were

unnecessary. Since the overall goal of antibiotic stewardship is to decrease antibiotic resistance and further misuse, it is important for providers to consider the clinical guideline and recent studies that regard delayed antibiotics as a safe strategy to reduce antibiotic usage and increase patient satisfaction when compared to no antibiotics with RTI therapy.

Purpose

Antibiotic resistance has been a major concern when treating URI's. It has been a controversial topic among providers who must decide whether to prescribe antibiotics or not, where not prescribing often goes against patients' wishes and expectations. Since the evolution of health insurance, patient satisfaction rates make up about 10 % of a providers' salary in some states. This systematic review aims to evaluate new evidence and the overall effects of delayed antibiotic prescribing on patients with URI's in the community. *The clinical practice question guiding this review was: In primary care, how does providing a "delayed antibiotic prescription," compared to an "immediate antibiotic prescription" or "no antibiotic prescription," affect antibiotic prescription and use, patient outcomes, and satisfaction rates when managing upper respiratory tract infections?*

Conceptual Framework

The Promoting Action on Research Implementation in Health Services (PARIHS) model guided this literature review. This framework, developed by Kitson and colleagues (2008), was created to evaluate integration of evidence in a health care setting. The concepts of successful integration are based on strength of the evidence, clinical experience, and patient choice. These concepts are central to the decision of whether to prescribe or not prescribe antibiotics for URI symptoms and helped to guide this review.

Methods

Project Design

This systematic review of the literature was guided by the PARIHS model and presents the latest evidence comparing patient outcomes and patient satisfaction rates associated with delayed antibiotic prescription compared to immediate and no prescription when treating upper respiratory infection symptoms. Due to conflicting findings among studies and new findings supporting delayed prescription, a review of the current evidence is needed.

Search Strategy

Terms used to conduct this research included *delayed antibiotic prescribing*, *no antibiotics*, upper *respiratory infections, treatment*, *primary care*, and *patient satisfaction*. The Boolean feature was used in the search to eliminate inappropriate articles. This linked different concepts or terms together, allowing the search to be more precise (Melnyk et al., p. 105). Articles were screened by the inclusion criteria: articles had to be primary research, peer reviewed, published in English within ten years, and addressing the prescription of antibiotics for management of URI symptoms in primary care. Seven databases including JSTOR Journals, Health Source, OVID, CINAHL, Cochrane, PubMed, and MEDLINE were searched. Further pertinent articles were obtained through ancestry search method. Lastly, rapid critical appraisal tools from a reference textbook (Melnyk & Fineout-Overholt, 2019) were utilized to evaluate for their validity, reliability, and applicability to answer the PICOT question. Scores were recorded and gathered to be included in the evidence synthesis table.

Selection Process

Using a flow diagram, see Figure 1, the selection process included screening out studies based on title, then abstract, then full-text review using the inclusion criteria. Duplicate articles were removed. All articles were reviewed for their relevance and strength of evidence by

utilizing the Rapid Critical Appraisal Tools as mentioned earlier. It was important that the appraisal tool matched the article's study design, which was either RCTs or cohort studies, see Appendix A and B. Articles with a cutoff score of 4 were deemed adequate. Randomized, controlled designs and cohort studies were given preference because they provide the highest quality level of evidence with the least biases. The search and screening process was completed solely by this author.

Synthesis Method

For this review, an Evidence Synthesis Table, see Table 1, was used to organize and summarize the relevant information from the individual studies. From there, the information was easily compared and reviewed in a time efficient manner. Synthesis of the findings across studies was accomplished using the Evidence Synthesis Table to find common themes across studies addressing the research question. Articles' appraisal scores were included in the evidence synthesis table.

Results

Search Results

A flow diagram using the PRISMA template (Page et. al, 2021) was used to organize the literature search process. After inserting the keywords in the databases, the search populated a total of 641 articles. When duplications were removed, 603 articles were left to be screened first by title, then abstract, then full-text, followed by the inclusion criteria, and finally the quality appraisal scores. See Flow Chart, Figure 1, for screening process. After the identification and screening process, seven articles were selected to include in this systematic review.

Characteristics of Studies

An evidence synthesis table, see Table 1, was utilized to collect and organize pertinent evidence. The final sample of studies included a total of five randomized controlled trials (RCTs) (de la Poza Abad et al., 2016; Mas-Dalmau et al., 2021; Hoye et al., 2013; Little et al., 2014; Moore et al., 2017) and three cohort studies (Francis et al., 2012; Moore et al., 2017; Staa et al., 2021) conducted to evaluate the outcomes of utilizing delayed antibiotic prescription (DAP) for acute respiratory tract infections (RTIs) in a primary care setting.

All the RCTs focused on examining the effectiveness of DAP compared to immediate antibiotic prescription (IAP) or no antibiotic prescription (NAP) in patients with RTI symptoms. Their sample sizes ranged from 398 (de la Poza Abad et. al, 2016) to 889 (Little et. al, 2014) with a total sample size across studies of 2,999. The studies were conducted on patients of all ages who reported to a primary care clinic, but Little et al. (2014) and Mas-Dalmau et al. (2021) included only children with RTIs. Surprisingly, all five RCTs were conducted outside of the United States. Using the Rapid Critical Appraisal Tool, Appendix A, for scoring, they all had a score of eight or greater out of a possible eleven, which showcased their reliability and validity to answer the PICOT question.

The cohort studies' sample sizes were significantly larger than the RCTs'. Their sample sizes ranged from 1107 participants (Moore et al., 2017) to 1.96 million (Staa et al., 2021), totaling 1,964,475 participants across the three studies. Only one study (Staa et al., 2021) targeted children and adults within the community while the others focused on adults only. This same study also was the only one to meet all criteria on the Rapid Critical Appraisal Tool, Appendix B, with a score of seven out of seven. Moore et al.'s (2017) study received a score of four out of seven while the other cohort study (Francis et al., 2012) received a five. Like the RCTs, all cohort studies were set in European countries.

Synthesis of Findings Across Studies

Study findings overall revealed two major themes: *Delayed antibiotic prescribing lessens antibiotic use* and *antibiotic prescribing type has minimal effect on symptom severity*. Regarding the first theme, all studies in this review found that DAP reduced antibiotic prescription and use in children and adults with RTI symptoms. Four articles (de la Poza Abad et. al, 2016; Little et. al, 2014; Mas-Dalmau et. al, 2021; Moore et. al, 2017) compared antibiotic use and prescription between DAP, IAP, and NAP. When compared to IAP, findings supported that DAP significantly reduced antibiotic use but not better than NAP (IAP: 96% (142), DAP: 25.3% (37), NAP:12% (17); $P < .001$) (de la Poza Abad et. al, 2016; Mas-Dalmau et al., 2021). More specifically, in one study (Francis et al., 2013), patients who were given IAP were two times more likely to consume an antibiotic during a given period than those whose providers used DAP.

The second theme, *antibiotic prescribing type has minimal to no effect on symptom severity*, was also found throughout the studies. One article (de la Poza Abad et. al, 2016) found no significant difference between symptom duration or severity between DAP, IAP, and NAP. Although Moore et. al (2017) had similar findings, they also found that DAP and IAP reduced the risk of poorer symptomatic outcomes when compared to NAP (DAP: 58% of 197, *RR*=.88 (95% *CI*=.78 - 1.00), *p*=.04; IAP: 60% of 728, *RR*=.87 (95% *CI* = .70 - .96), *p* =.006; NAP: 67% of 587). Another article (Little et al., 2014) also found no significant difference in symptom severity between the prescribing (*p*=.29)) or secondary outcomes. They did find that adverse effects were slightly higher in the NAP group (2.5%) when compared to the other two prescribing types. The study done by Mas-Dalmau et al. (2021) found similar results as well, but with a greater risk of gastrointestinal adverse effects with IAP.

Patient satisfaction and re-consultation rates were also examined by several studies. Three articles (de la Poza Abad et. al, 2016; Little et. al, 2014; Mas-Dalmau et. al, 2021) measured patients' satisfaction with DAP. With children, Mas-Dalmau et al. (2021) concluded that parental satisfaction was similar across all antibiotic prescription methods. De la Poza Abad et al. (2016) and Little et al. (2014) found higher levels of patient satisfaction with DAP, but there was no significant difference (p=.667). Mas-Dalmau et al. (2021) measured the re-consultation rate between the three antibiotic methods finding no significant differences.

Several other types of patient outcomes were measured in these articles, when antibiotic prescribing types were compared. Staa et al. (2021) measured the mean risk of hospital admission when using DAP compared to NAP. With its low utilization rate (8.3-9.2%), they concluded that DAP had 52% increased risk of infection-related hospitalization, but the cause was unrelatable to the approach itself. Hoye et al. (2013) found patients in rural areas with the DAP approach were more likely to fill the prescription and use it versus patients in urban areas (rural: 13,560 (92.9%), urban 18,787 (91.5%); p =.020). They also found that older adults had twice the odds of filling the prescription compared to younger groups (Hoye et. al, 2013). Additionally, Mas-Dalmau et al. (2021) found that when DAP was provided to children, they were less likely to take the medication (25.3%) when compared to adults (32.6%). There was also a noticeable difference on prescription practices by the gender of the provider. Female providers were found to use the DAP option twice as often in treating RTIs than male providers (female: 15.5%, male: 8.8%) (Hoye et. al, 2013).

Discussion

This study supports that delayed antibiotic prescription decreases antibiotic overuse, when compared to immediate antibiotic prescribing, without significant risks to symptom

severity in children and adults. This review also has evidence that DAP can also decrease re-consultation rates, symptoms, and risk of complications (de la Poza Abad et al., 2016, Moore et al., 2017). Although no significant difference in patient satisfaction was found between prescribing types across the studies, there was evidence to support that delayed prescribing did result in higher patient satisfaction compared to no antibiotic prescription (Little et al., 2014). In a 2016 systematic review, McDonagh et al. found that DAP reduces antibiotic prescription by 76 % without a decrease in patient satisfaction or an increase in re-consultation rates with RTIs in adults and children. Additionally, Hoye et al. (2013) concluded in their study that the living environment affects antibiotic prescription and patient's use. Patients from rural practices are more likely to fill the prescription than urban. In a recent Cochrane review, it recommended that a delayed antibiotic strategy could be used when it is clinically safe not to prescribe immediately (Spurling et. al, 2017). It also found, when comparing all three prescription strategies in children and adult, there was no difference in symptoms or complications, but antibiotic intakes was noted to be lower for DAP compared to IAP. Unlike the UK, the United States lacks the defined guidelines to know when to implement DAP.

Future studies should be well designed and include adequate description, instructions, and expectations of participants' roles. Not all articles included in this study measured all clinically important outcomes (i.e., patient satisfaction, antibiotic use, adverse effects, symptom severity, re-consultation rate). There was a lack of certain outcome's consistency in the findings throughout this review. Some of the articles met resistance with limited data collection compared to the number of participants. Bottom line is there is an abundance of research on the benefits of using DAP on uncomplicated RTIs for children and adults in primary care practice. Healthcare providers should inquire on how they can implement antibiotic stewardship in their practices.

Kitson et al. (2008) conceptual framework of integration guided this study. It is based on strong evidence, clinical experience, and patient's choice. It did not consider the provider's choice on whether to use the information or not. While there is strong evidence that supports DAP in the management of RTIs, some providers are not implementing it in their practices. It is often more common for Nurse Practitioners and Physician Assistants to adopt this approach in their practices versus primary physicians. Most RTIs do not need antibiotics, but all need a clearly communicated plan (Gerber & Offit, 2021). One factor that may be limiting improvements in the appropriate use of antibiotics in acute RTI is the lack of diagnostic certainty in some cases (AHRQ, 2016).

Recommendations from Findings

Currently, it appears that the understanding and use of DAP for RTIs in primary practice are inconsistent throughout the studies. Reasons of the inconsistencies are not clear. In one study, the outcome was greatly affected by the providers' failure to utilize DAP even when the patients were eligible for this type of treatment (Hoye et. al, 2013). Delayed antibiotic prescription is a strategy to lessen the global antimicrobial resistance problem without delaying patient care if symptoms do worsen. Several findings of the studies reviewed found that DAP reduces reduced antibiotic use without any significant harm or complications to the patients. In 2008, the United Kingdom's National Institute for Health and Clinical Excellence (NICE) released a guideline recommending DAP and patient education on the expected duration and treatment of some common RTI symptoms. For children, the United States' Centers for Disease Control and Prevention (CDC) recommends that clinicians educate parents about the ineffectiveness of treating most upper respiratory infections with antibiotics (AHRQ, 2016). Recently, Mangione-Smith et al. (2015) found an 85% decrease in antibiotic prescribing and increased patient

satisfaction when providers took their time to explain why antibiotics are not needed and give recommendations on symptomatic management.

These studies found that less than the desirable number of providers used DAP in their practices, and although this finding was not unexpected, it highlighted a gap in the providers' support of the antibiotic stewardship (Hoye et al., 2013). Being a good antibiotic steward means appropriately prescribing the antibiotics for the right clinical judgement, the right duration, and at the right dosage to protect the patients and public from antibiotic resistance and unwanted harm. Additionally, there is a need in continual education for the providers to stay current on treatment guidelines. Using DAP is an evidence-based intervention (Meeker et al., 2014). In one study, Meeker et al. (2014) found a 20% reduction in inappropriate prescribing for acute respiratory tract infections from displaying posters in the examination rooms with the provider's photo, signature, and the commitment to use antibiotics appropriately. Providers must also spend the time to properly educate the patients that symptoms of viral agents do not require antibiotics. There are printable educational materials available over the internet that can be supplied to the patients as reference.

Interestingly, all of the studies found for this review were conducted outside of the United States. Studies in the U.S. may yield different results. Therefore, future studies should be conducted in the U.S. to explore barriers and opportunities for improving uptake of DAP. Another recommendation for future studies would be to have clear instructions and expectations for the participants. Some studies met resistance with limited data collection compared to the number of participants. Those wanting to conduct future research should strive to formulate an experimental design to provide the highest level of evidence. Furthermore, no significant difference was found in symptom severity between different approaches in both children and

adults, which was a common theme with most of the studies. However, not all important clinical outcomes were considered throughout the studies, which highlights further gaps in recent studies.

Limitations

Few limitations were identified in this literature. A major limitation to this review was that few recent studies were conducted in the U.S, which really limits our recommendation from this project. As stated earlier, results may differ if the studies had taken place in the U.S. Also, there seemed to be a lack of interest in the patients and providers to participate in the studies. In one study, only 57% of the participants returned the necessary data from the antibiotic strategy (Moore et al., 2017). Patients' understanding of the antibiotic strategies and how to record data accurately along with providers' participation played a major role in the gaps and inconsistency of the studies. Several studies could not avoid certain biases. Furthermore, only four out of the seven studies included in this project were experimental. The rest were observational.

Conclusions and Implications

This study supports that delayed antibiotic prescription can be used safely in most uncomplicated RTI cases with more benefits and few risks in both adults and children. DAP used on patients in a primary care setting was consistently found to be associated with decreased antibiotic use. Overall, providers should feel confident that the use of delayed antibiotic prescription does not cause patient additional harm and may even increase patient satisfaction. Healthcare providers should inquire more about how they can implement antibiotic stewardship in their practice and help address the growing antibiotic resistance issue.

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Table 1

Evidence Synthesis Table

Author	Purpose	Design / Framework	Sample/ Setting	Methods	Findings	Quality Appraisal/ Limitations	Conclusions/ Application
De la Poza Abad et al., 2016	To compare the outcome and safety of 2 DAP strategies in acute, uncomplicated respiratory infections.	Pragmatic, open-label, randomized, multicenter, clinical trial n/a	n= 398 (adults), mean age 45, 34.2% male, 54.8% nonsmokers 23 primary care centers in Spain	Pts randomized to 1 of 4 prescription strategy: (1) DAP-pt led, (2) DAP-collect, (3) IAP, (4) NAP; data collected included: symptom duration & severity (1.8-3.5 points on Likert scale), satisfaction, and pts' belief in effectiveness; follow-up telephone interview after 48 hours, day 7, day 15, day 22, & 1 year.	MD of severe symptom= 3.6 days ($p < .05$) (IAP), 4.7 (NAP), 3 (prescription collection, P = .003), 3 P = .05 (pt led); IAP vs DAP: 0.4 days less than prescription collection, 1.5 days less in pt led; moderate symptom (p<.001): MD= 4.7 (IAP), 5.2 prescription collection, 6 (pt-led), 6.5 (NAP); Pt satisfaction: (P = .14) in 4 groups. Abx use: 91.1% (IAP), 12.1 (NAP), 23% (prescription collection), 32.6% (pt-led);	8/11 absence of unique consensus definition of RTIs; smaller than target sample size.	DAP vs IAP: greater symptom burden and duration but reduced ABX use and re-consultation; no difference in complications, adverse effects, perception of general health statuses. Satisfaction: similar across groups.
Francis et al., 2012	To measure DAP in adults with acute cough for duration, numbers of consumption, and factors associated with consumption.	Prospective observational cohort study. N/a	N= 3368 Ages 18 and older "in general practices in 14 primary care networks in 13 European countries"	Physicians record pts' symptoms and ABX prescribing while pts record their consumption of ABX from any source during 28-day follow up; NAP=1226, IAP= 1294, DAP=170.	6.3% were prescribed DAP- 44.4% took the ABX & 10.7% took another ABX during follow up period; IAP 71.5% took ABX &29.6% took ABX same day	5/7 No prognostic risk factors; broad pt eligibility criteria; pts were not randomized; data obtained through observation;	DAP - effective in reducing ABX prescribing but used infrequently. Pts with viral ARTIs- less likely to consume ABX.

Author	Purpose	Design / Framework	Sample/ Setting	Methods	Findings	Quality Appraisal/ Limitations	Conclusions/ Application
						variable physicians cooperation; small sample size in comparison to IAP & NAP.	
Høye et al., 2013	"To measure the effects of a GP educational intervention and a computer delayed-prescribing pop-up reminder on antibiotic-dispensing rates & to identify factors influencing GPs' decisions to issue delayed prescriptions and patients' decisions to fill their prescriptions"	Controlled & RCTs N/a	n=80 groups, 495 GPs Urban and rural practices in 11 southern Norway counties	41 groups/ randomized control (prescribing for pts > 70 years old) vs 39 groups to interventions (DAP pop-up vs no pop-up); DV= dispensing/not dispensing of prescribed ABX at pharmacy and GPs' DAP; collected data 1 year prior and after to intervention (2004-2007) from GPs' EMR system and compared with NorPD to verify dispensation; "multilevel logistic regression analysis".	328 GPs completed: 107 DAP pop-up, 49 no pop-up, 172 control group; 92% of control dispensed ABX- 4428 acute tonsillitis (93.8%/OR 1.75), 5911 acute sinusitis (91.3%/OR 1.04), 5391 acute bronchitis (93.8%/OR 1.45), 3604 PNA (95.8%/OR 2.03), 3179 AOM (88%/OR 0.85), 1942 other RTIs (93.9%/OR 1.35); pop-up intervention dispensing rate decrease to 90.2% vs no pop-up 91.8%, control increase 92.4%; risk of prescription by GP in pop-up= 0.96 (95%CI= 0.94-0.98); pop-up & educational group prescribed 29.3% of RTIs, 1194/10,860 pop-up response (11%)= DAP.	10/11 selection bias, no record of pts' actual ABX consumption, findings contradict concerns to advocate DAP to lower unnecessary ABX use	Rural practices fill more than urban; older adults had twice the odd of filling compared to younger groups; URTIs & acute sinusitis & AOM had half the odds of filling; female GPs practiced twice as much of DAP; educational DAP intervention with pop-up reminder decreased ABX dispense (RR 0.96) vs without.
Little et al., 2014	"To estimate the effectiveness of different	RCT n/a	n=889 pts -3 years old and	333/889- IAP; rest-randomly assigned to 1 of 4 DAP categories:	DAP vs NAP= no difference recontact (aRR 1.41; 95% CI,	8/11	All strategies= equally effective. No difference in

Author	Purpose	Design / Framework	Sample/ Setting	Methods	Findings	Quality Appraisal/ Limitations	Conclusions/ Application
	strategies involving DAP for acute respiratory tract infections."		older in primary care of UK	- recontact for prescription - postdated prescription - collection (pts return to collect a prescription from the clinic) - pt led (pt "given a physical prescription and asked to wait before filling it") 1 group given no prescription mean symptom severity (0-6 scale; 0=no problem" , 6 = "as bad as it could be) at days 2-4, ABX use, pts' beliefs ineffectiveness of ABX use; follow up at 14 day compared to IAP use of ABX.	0.95-2.03), postdate (aRR 1.41; 95% CI, 0.92-1.98), collect in clinic (aRR 1.28; 95% CI, 0.80-1.87), or wait (aRR 1.52; 95% CI, 1.00-2.10); ABX higher in IAP group (97% vs 37%, adjusted risk ratio 3.70; 95% CI, 3.57–3.76); no difference noted between DAP categories, 32% to 39% (*P*=.29) or secondary outcomes; adverse effects (2.5%) higher in NAP group; satisfaction: DAP (2.38, P=0.667); re-consultation rate: DAP -similar (2.97, P=0.563).	limited sample size; control group- more severe symptoms at baseline.	mean symptom severity or duration, ABX use. Higher levels of satisfaction and belief about effectiveness of antibiotic in DAP: no significant difference.
Mas-Dalmau et al., 2021	"To assess the effectiveness and safety of DAP compared to IAP and NAP in children with uncomplicated respiratory infections".	Quantitative RCTs n/a	N= 436 Children ages 2-14 from 39 primary care clinic in Spain.	RCTs comparing 3 antibiotic prescribing strategies for ARTIs in children; randomly assigned; measured symptom duration/severity, ABX use, pt satisfaction, parental beliefs, re-consultation, and complications at 30 days.	MD of severe symptom: 10.1 (6.3) -IAP, 10.9 (8.5)-NAP, 12.4 (8.4)-DAP; ABX use: IAP-96% (142), DAP-25.3% (37), NAP-12% (17); satisfaction-similarly high for the 3 arms (*P* = .389); similar re-consultation.	9/12 Did not consider ER admission or chances of recurrence of symptoms; No specific patient criteria; No disclosure of	DAP-Reduces ABX use without harm but not shown to be better than NAP; no significant difference in symptoms or duration, complications, pt satisfaction, re-consultation with

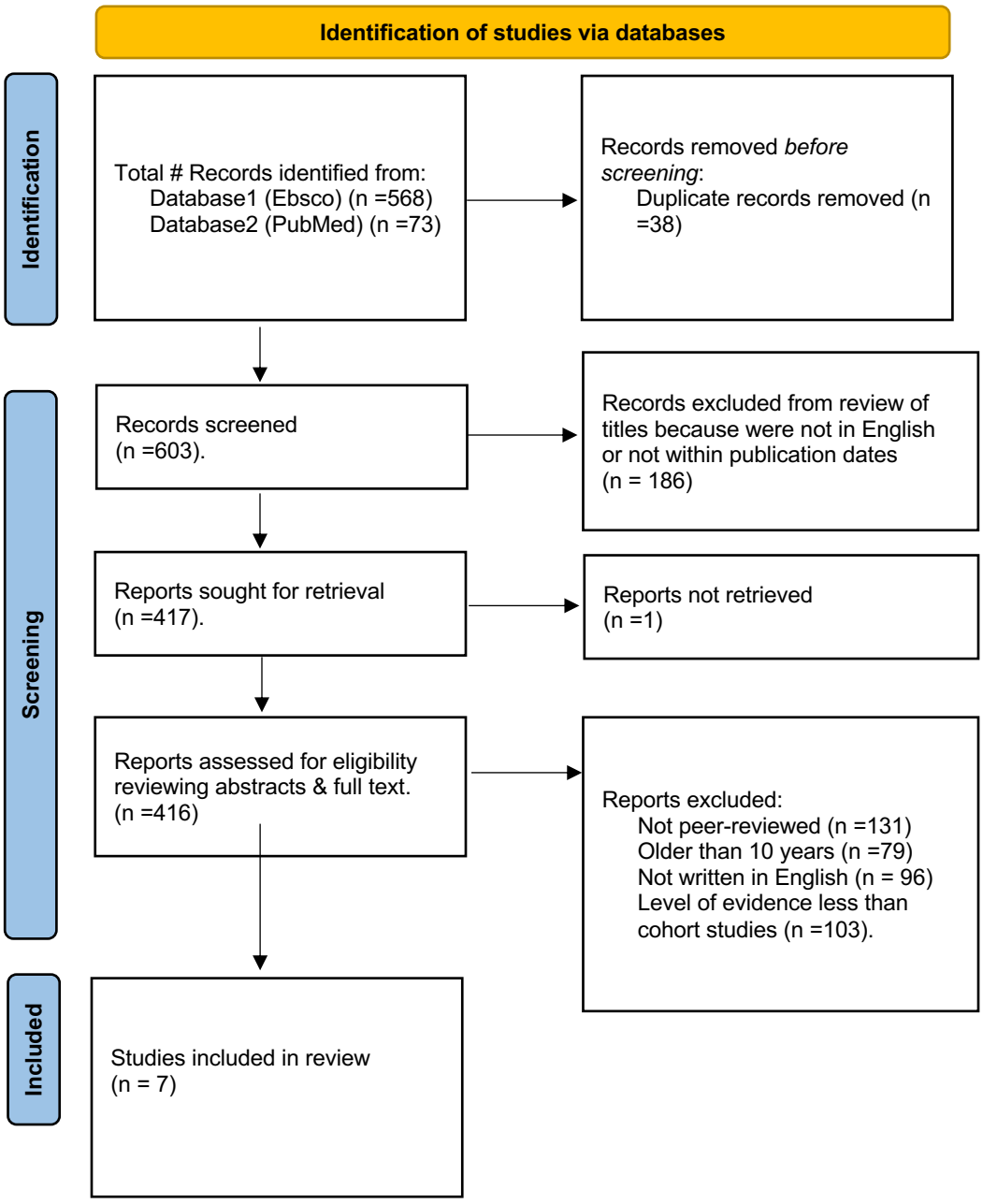
Author	Purpose	Design / Framework	Sample/ Setting	Methods	Findings	Quality Appraisal/ Limitations	Conclusions/ Application
						statistical analysis.	DAP, NAP, and IAP; gastrointestinal adverse effects higher in IAP.
Moore et al., 2017	"To determine the symptomatic outcome of acute sore throat in adults according to antibiotic prescription strategy in routine care".	Cohort studies & RCT N/a	2 cohort (n=1107), 1 RCT (n= 781) Adults in UK general practice.	Random sample (n=2976) filled symptom diary; brief clinical performa-symptom severity & findings during exam; outcome collected: diary & note review; measured outcome: poorer global symptom control.	38,39%= NAP; 48%= IAP; 13%,14%= DAP; 58% of DAP took ABX; NAP vs IAP & DAP on reported poorer symptom: IAP (60% of 728) RR 0.87 (95% CI = 0.70 - 0.96), P = 0.006; DAP (58% of 197) 0.88 (5% CI = 0.78 to 1.00), P = 0.042; NAP 67% of 587; no difference in symptom severity seen in IAP & DAP.	4/7 Less than half diary returned, no definition of severity, unequal severity of symptoms in sample, potential misclassification bias, no clear protocol to use DAP strategy	DAP reduces ABX prescribing, same in symptom benefit as IAP, decrease symptoms compared to NAP, reduces re-consultation & risk of septic complications.
Staa et al., 2021	"To evaluate the clinical safety of DAP for upper respiratory tract infections (URTIs), which is recommended in treatment guidelines for less severe cases".	Cohort Studies N/a	n=1.96 million 2 cohort studies- 1 from UK population vs 1 from Wales general practice	2 large population-based cohort studies were taken from 2 databases: CPRD, SAIL. Data from CPRD obtained 2000-2015; SAIL: 2000-2017. Outcome of interest: hospital admission for infection-related complications that occurred 30 days after ABX prescription,	CPRD: 1.45 million out of 1.54 million pts were given ABX over 3 month period; SAIL: 0.69 million prescriptions were given out of 0.42 million; mean predicted risk of infection-related hospital admission= 0.16% (both groups); incidence of infection-related hospitalization: 0.15 per 100 person/ 3247 cases (CPRD); 0.67/ 4242 (SAIL); frequency of DAP was	7/7 "No external validation of risk prediction model was conducted"; risk factors did not higher underlying risks of hospitalization with DAP; DAP prescribing "irrespective of whether this was intended or not	DAP is probably safe for patients. Risk of complications from URTIs was unrelated to DAP. More research is needed.

Author	Purpose	Design / Framework	Sample/ Setting	Methods	Findings	Quality Appraisal/ Limitations	Conclusions/ Application
				death, and repeated ABx prescribing. Time-to-event COX proportional hazard regression models to estimate hazard ratios and CI with DAP; negative binomial regression models to estimate incidence rate ratios with IAP.	8.3% (CPRD) & 9.2% (SAIL). DAP- 52% increased risk of infection-related hospitalization from both databases (adjusted HR, 1.52; 95%CI,1.43-1.62); effects lowest in children (HR, 1.61;95%CI,1.25-1.47) vs adults 19-59 years (HR, 1.61;95%CI, 1.42-1.84)	by the clinicians at the initial URTI diagnosis"; "incidence rates of the clinical outcomes were different"; little "targeting of delayed to provide more specific guidance when and when not to use DAP prescribing".	

Abbreviations (*in alphabetical order*): ABX= antibiotic, aRR=adjusted risk ratio, ARTI= acute respiratory tract infection, BMI=body mass index, CI=confidence interval, CPRD=Clinical Practice Research Datalink, DAP= delayed antibiotic prescription, DV=dependent variable, EMR=electronic medical record, GP=General Physician, IAP= immediate antibiotic prescription, MD=mean difference, NAP= no antibiotic prescription, NorPD=Norwegian Prescription Database, OR= odds ratio, pt= patient, PRN=as needed; RCT=randomized controlled trial, , RR= relative risk, RTI= respiratory tract infection, SAIL=Secure Anonymized Information Linkage, URTI=upper respiratory tract infection, vs= versus

Figure 1

Screening Flow Diagram



Appendix A
Rapid Critical Appraisal Questions for Randomized Clinical Trials (RCT)

VALIDITY			
1. Are the results of the study valid?			
a. Were the participants randomly assigned to the experimental and control groups?	Yes	No	Unknown
b. Was random assignment concealed from the individuals who were first enrolling participants into the study?	Yes	No	Unknown
c. Were the participants and providers blind to the study group?	Yes	No	Unknown
d. Were reasons given to explain why participants did not complete the study?	Yes	No	Unknown
e. Were the follow-up assessments conducted long enough to fully study the effects of the intervention?	Yes	No	Unknown
f. Were the participants analyzed in the group to which they were randomly assigned?	Yes	No	Unknown
g. Was the control group appropriate?	Yes	No	Unknown
h. Were the instruments used to measure the outcomes valid and reliable?	Yes	No	Unknown
i. Were the participants in each of the groups similar on demographic and baseline clinical variables?	Yes	No	Unknown
RELIABILITY			
2. What are the results?			
a. How large is the intervention or treatment effect (NNT, NNH, effect size, level of significance)?	___	___	___
b. How precise is the intervention or treatment (CI)?	___	___	___
APPLICABILITY			
3. Will the results help me in caring for my patients?			
a. Were all clinically important outcomes measured?	Yes	No	Unknown
b. What are the risks and benefits of the treatment?			
c. Is the treatment feasible in my clinical setting?	Yes	No	Unknown
d. What are my patient's/family's values and expectations for the outcome that is trying to be prevented and the treatment itself?			

Source: Melnyk, B., & Fineout-Overholt, E. (2019). *Evidence-based practice in nursing & healthcare (4th ed*.). Wolters Kluwer.

Appendix B
Rapid Critical Appraisal Questions for Cohort Studies

VALIDITY

1. Are the results of the study valid?

a. Was there a representative and well-defined sample of patients at a similar point in the course of the disease?	**Yes**	**No**	**Unknown**
b. Was follow up sufficiently long and complete?	Yes	No	Unknown
c. Were objective and unbiased outcome criteria used?	Yes	No	Unknown
d. Did the analysis adjust for important prognostic risk factors and confounding variables?	Yes	No	Unknown

APPLICABILITY

1. Will the results help me in caring for my patients?

a. Were the study patients similar to my own?	**Yes**	**No**	**Unknown**
b. Will the results lead directly to selecting or avoiding therapy?	Yes	No	Unknown
c. Are the results useful for reassuring or counseling patients?	Yes	No	Unknown

Source: Melnyk, B., & Fineout-Overholt, E. (2019). *Evidence-based practice in nursing & healthcare (4th ed*.). Wolters Kluwer.