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La prescripció antibiòtica diferida en infeccions respiratòries a l'atenció primària: assaig clínic, anàlisi cost-efectivitat i estudi qualitatiu

Gemma Mas Dalmau

LA PRESCRIPCIÓ ANTIBIÒTICA DIFERIDA EN INFECCIONS RESPIRATÒRIES A L'ATENCIÓ PRIMÀRIA: ASSAIG CLÍNIC, ANÀLISI COST-EFECTIVITAT I ESTUDI QUALITATIU

Gemma Mas Dalmau, 2023

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Departament de Pediatria, d'Obstetricia i Ginecologia, i de Medicina Preventiva i Salut Pública.
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1. RESUM

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RESUM

Antecedents

Els antibiòtics es prescriuen en excés en les infeccions respiratòries agudes (IRA) en l'àmbit de l'atenció primària (AP). La prescripció diferida d'antibiòtics (PDA) és una estratègia dissenyada per promoure un ús més racional dels antibiòtics. L'evidència sobre l'eficàcia de la PDA en nens amb IRAs atesos a l'AP és escassa i encara més, en estudis que hagin avaluat el seu cost-efectivitat. La PDA encara no és àmpliament implementada pels professionals i hi ha una manca d'estudis qualitatius d'aquesta estratègia en el nostre entorn.

Objectius

Els objectius d'aquesta tesi van ser els següents: (1) determinar l'eficàcia i seguretat de la PDA comparada amb la prescripció antibiòtica immediata (PIA) i la no prescripció antibiòtica (NPA) en nens amb IRAs tractats a l'AP; (2) comparar el cost-efectivitat de les tres estratègies de prescripció i; (3) explorar les percepcions i actituds dels professionals en relació a l'ús dels antibiòtics i de les estratègies de PDA en el tractament de les IRAs en adults atesos a l'AP.

Mètodes

La tesi es presenta com a compendi de 3 articles corresponents a estudis publicats en revistes biomèdiques revisades per parells, que són els següents: (1) un assaig clínic aleatoritzat que va avaluar l'eficàcia de la PDA en comparació amb la PIA i la NPA en nens amb IRAs, atesos en 39 centres d'AP pertanyents a 9 comunitats autònomes d'Espanya; (2) una anàlisi cost-efectivitat, des d'una perspectiva social, de tres estratègies de prescripció en el context de l' assaig clínic previ; i (3) un estudi qualitatiu en el qual es van incloure professionals de 6 centres d'AP de l'àrea metropolitana de Barcelona, basat en 4 grups de discussió i posteriorment, 3 entrevistes individuals semiestructurades.

Resultats

L'assaig clínic va incloure 436 nens. La durada mitjana dels símptomes severs va ser lleugerament major en la PDA en comparació amb la PIA i la NPA. El valor mitjà per la major severitat de qualsevol símptoma va ser similar per a les 3 estratègies. L'ús d'antibiòtics i els

efectes adversos gastrointestinals van ser significativament més freqüents per a la PIA. Les complicacions, les visites addicionals a l'AP i la satisfacció van ser similars per a les 3 estratègies.

En termes de cost-efectivitat, inclús quan es va incloure el cost de les resistències antimicrobianes (RAM), la PDA va ser la més cost-efectiva de les 3 estratègies. Els valors de dies de vida ajustats per la qualitat (QALD) per a les tres estratègies van ser molt similars. L'anàlisi de sensibilitat determinista va indicar que els costos indirectes no sanitaris van tenir el major impacte en la relació incremental cost-efectivitat (ICER).

L'estudi qualitatiu, el qual va incloure 25 metges de família i 1 infermera, va destacar que la consulta per IRAs en adults estava associada amb una pobre educació en salut, i que l'ús inadequat d'antibiòtics estava relacionat principalment amb una estratègia de medicina defensiva. La PDA s'utilitzava quan hi havia dubtes sobre l'etiologia i tenint en compte el context de la visita i el perfil del pacient.

Conclusions

En nens amb IRAs no complicades atesos a l'AP, per a la PDA en comparació amb la PIA i la NPA, els resultats d'eficàcia i seguretat van ser similars i els resultats cost-efectivitat van ser lleugerament millors. Les pressions de temps sobre els professionals, la pobre educació en salut dels pacients i la falta de relació metge-pacient en alguns escenaris van ser debilitats que afectaven tant l'ús adequat d'antibiòtics com de la PDA en població adulta.

RESUMEN

Antecedentes

Los antibióticos se prescriben en exceso en las infecciones respiratorias agudas (IRA) en el ámbito de la atención primaria (AP). La prescripción diferida de antibióticos (PDA) es una estrategia diseñada para promover un uso más racional de los antibióticos. La evidencia sobre la eficacia de la PDA en niños con IRAs atendidos en la AP es escasa y aún más, en estudios que hayan evaluado su coste-efectividad. La PDA todavía no es ampliamente implementada por los profesionales y hay una falta de estudios cualitativos de esta estrategia en nuestro entorno.

Objetivos

Los objetivos de esta tesis fueron los siguientes: (1) determinar la eficacia y seguridad de la PDA comparada con la prescripción antibiótica inmediata (PIA) y la no prescripción antibiótica (NPA) en niños con IRAs tratados en AP; (2) comparar el coste-efectividad de las tres estrategias de prescripción y; (3) explorar las percepciones y actitudes de los profesionales en relación al uso de los antibióticos y de las estrategias de PDA en el tratamiento de las IRAs en adultos atendidos en AP.

Métodos

La tesis se presenta como compendio de 3 artículos correspondientes a estudios publicados en revistas biomédicas revisadas por pares, que son los siguientes: (1) un ensayo clínico aleatorizado que evaluó la eficacia de la PDA en comparación con la PIA y la NPA en niños con IRAs, atendidos en 39 centros de AP pertenecientes a 9 comunidades autónomas de España; (2) un análisis coste-efectividad, desde una perspectiva social, de tres estrategias de prescripción en el contexto del ensayo clínico previo; y (3) estudio cualitativo en el que se incluyeron profesionales de 6 centros de AP del área metropolitana de Barcelona, basado en 4 grupos de discusión y posteriormente, 3 entrevistas individuales semiestructuradas.

Resultados

El ensayo clínico incluyó a 436 niños. La duración media de los síntomas severos fue ligeramente mayor en la PDA en comparación con la PIA y la NPA. El valor medio por la mayor severidad de cualquier síntoma fue similar para las 3 estrategias. El uso de antibióticos y los efectos adversos

gastrointestinales fueron significativamente más frecuentes para la PIA. Las complicaciones, las visitas adicionales en AP y la satisfacción fueron similares para las 3 estrategias.

En términos de coste-efectividad, incluso cuando se incluyó el costo de las resistencias antimicrobianas (RAM), la PDA fue la más coste-efectiva de las 3 estrategias. Los valores de días de vida ajustados por la calidad (QALD) para las 3 estrategias fueron muy similares. El análisis de sensibilidad determinista indicó que los costes indirectos no sanitarios tuvieron el mayor impacto en la relación incremental coste-efectividad (ICER).

El estudio cualitativo, el cual incluyó a 25 médicos de familia y 1 enfermera, destacó que la consulta por IRAs en adultos estaba asociada con una pobre educación en salud, y que el uso inadecuado de antibióticos estaba relacionado principalmente con una estrategia de medicina defensiva. La PDA se utilizaba cuando había dudas sobre la etiología y teniendo en cuenta el contexto de la visita y el perfil del paciente.

Conclusiones

En niños con IRAs no complicadas atendidos en AP, para la PDA en comparación con la PIA y la NPA, los resultados de eficacia y seguridad fueron similares y los resultados coste-efectividad fueron ligeramente mejores. Las presiones de tiempo sobre los profesionales, la pobre educación en salud de los pacientes y la falta de relación médico-paciente en algunos escenarios fueron debilidades que afectaban tanto al uso adecuado de antibióticos como de la PDA en población adulta.

ABSTRACT

Background

Antibiotics are overprescribed in acute respiratory tract infections (RTIs) in the primary care (PC) setting. Delayed antibiotic prescription (DAP) is a strategy designed to promote more rational use of antibiotics. Evidence on the efficacy of DAP in children with RTIs attended to in PC is scarce, and especially so in studies that have evaluated its cost-effectiveness. DAP is not yet widely implemented by professionals and there is a lack of qualitative studies of this strategy in our setting.

Objectives

The objectives of this thesis were as follows: (1) to determine the efficacy and safety of DAP compared to immediate antibiotic prescription (IAP) and no antibiotic prescription (NAP) in children with RTIs treated in PC; (2) to compare the cost-effectiveness of the 3 prescribing strategies; and (3) to explore professional's perceptions and attitudes regarding antibiotic use and DAP strategies in the treatment of RTIs in adults attended to in PC.

Methods

The thesis is presented as a compendium of 3 articles corresponding to studies published in peer-reviewed biomedical journals, as follows: (1) a randomized clinical trial that evaluated DAP efficacy compared to IAP and NAP in children with RTIs attended in 39 PC centres located in 9 Spanish autonomous communities.; (2) a cost-effectiveness analysis, from a social perspective, of the 3 prescribing strategies in the context of the previous clinical trial; and (3) a qualitative study involving professionals from 6 centres in the metropolitan area of Barcelona, based on 4 focus group were carried out and subsequently, 3 individual semi-structured interviews.

Results

The clinical trial included 436 children. Mean duration of severe symptoms was slightly greater in DAP compared to IAP and NAP. The median value for the greatest severity of any symptom was similar for the 3 strategies. Antibiotic use and gastrointestinal adverse effects were significantly more frequent for IAP. Complications, additional PC visits, and satisfaction were similar for the 3 strategies.

In cost-effectiveness terms, and even when the cost of antimicrobial resistance (AMR) was considered, DAP was the most cost-effective of the 3 strategies. The quality-adjusted life-days (QALD) values for the 3 strategies were very similar. Deterministic sensitivity analysis indicated that non-healthcare indirect costs had the greatest impact on the incremental cost-effectiveness ratio (ICER).

Finally, the qualitative study, which included 25 family physicians and 1 nurse from 6 PC centres, highlighted that adult consultation for RTIs were associated with poor health education, and that inappropriate antibiotic use was mainly related to a defensive medicine strategy. DAP was deployed when there were doubts about the aetiology and taking into account the visit context and the patient's profile.

Conclusions

In children with uncomplicated RTIs attended to in PC, for DAP compared to IAP and NAP, efficacy and safety results were similar and cost-effectiveness results were slightly better. Time pressures on professionals, poor health education of patients, and an absent doctor-patient relationship in some scenarios were weaknesses that affected both the appropriate use of antibiotics and of DAP in adult population.

2. INTRODUCCIÓ

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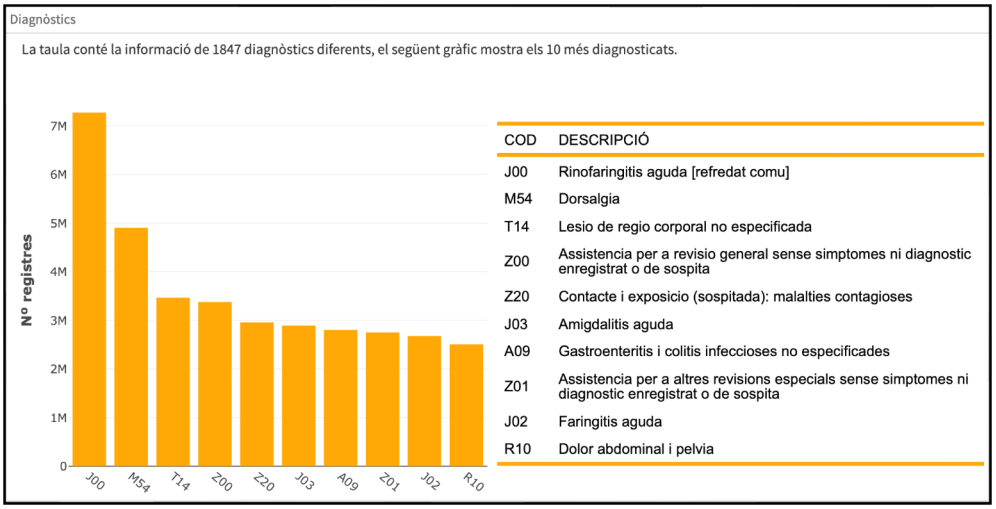
2.1. LES INFECCIONS RESPIRATÒRIES A L'ATENCIÓ PRIMÀRIA

Els processos infecciosos representen aproximadament un terç de les visites a l'atenció primària (AP) (1), sent el 57.7% d'aquests per infeccions respiratòries, segons la *Base de Datos Clínicos de la AP de España* (BDCAP)(2)

A Catalunya, diferents tipus d'infeccions respiratòries es troben entre els deu diagnòstics més freqüents realitzats a l'AP, segons dades del Sistema d'Informació per al Desenvolupament de la Recerca en l'Atenció Primària (SIDIAP). El SIDIAP (3) és una plataforma d'informació que recopila dades procedents del sistema de salut català **(Figura1)**.

Figura 1: Els diagnòstics més habituals a l'atenció primària de Catalunya



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Les principals infeccions respiratòries consultades són processos aguts, no complicats i la majoria de les vies altes. Les infeccions respiratòries de vies altes afecten la cavitat nasal, laringe i oïda com ho són el constipat comú, la rinitis, la faringitis aguda, la faringoamigdalitis, la laringitis aguda i l'otitis mitjana aguda. Les infeccions respiratòries de vies baixes en canvi, afecten la tràquea i els bronquis com ho són la traqueïtis o la bronquitis aguda i la pneumònia. Les infeccions respiratòries més freqüentment consultades en AP són: la faringoamigdalitis aguda, el refredat comú, la bronquitis aguda (1,2), i en nens també, l'otitis mitjana aguda (4). Així mateix, la freqüència de les infeccions respiratòries presenta variabilitat segons l'edat de la població i

l'estació de l'any, sent major entre la població pediàtrica, sobretot entre 0 i 4 anys, i la gent gran, així com més elevada durant l'hivern.

La majoria d'aquestes infeccions són d'origen viral i són processos autolimitats en el temps (curació sense necessitat de tractament). Tot i això, els antibiòtics es prescriuen en molts d'aquests episodis en l'àmbit de l'AP (5).

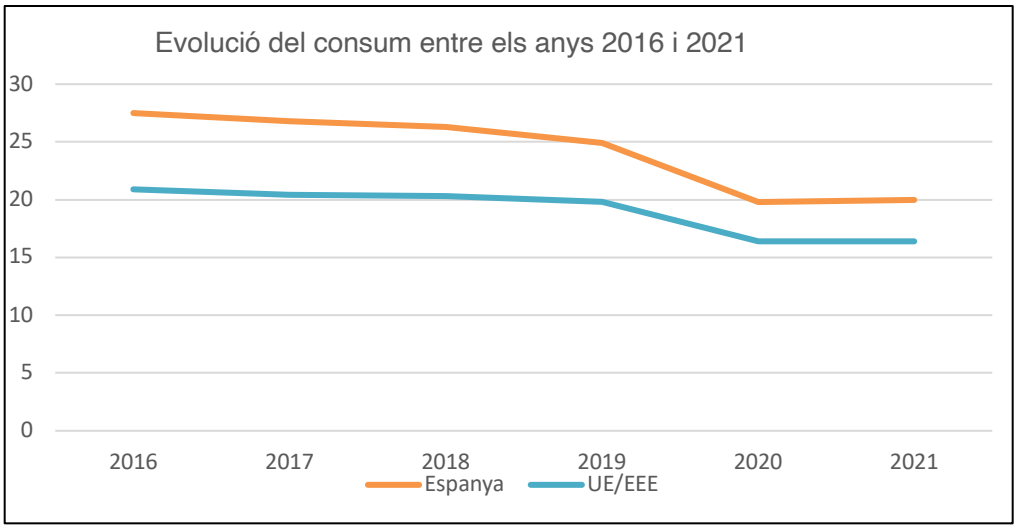
2.2. EL CONSUM D'ANTIBIÒTICS EN LES INFECCIONS RESPIRATÒRIES AGUDES A L'ATENCIÓ PRIMÀRIA

2.2.1. El consum d' antibiòtic en l'atenció primària a Europa i Espanya.

El consum d'antibiòtic varia considerablement entre els països d'Europa. El consum d'antibiòtics total (AP i hospitalària) és més gran al sud i est d'Europa i menor, al nord. El país amb el consum relatiu d'antibiòtic menor el 2021 va ser Holanda i major, Romania. La majoria dels països mostren una disminució del consum en els últims anys, especialment, a partir de la pandèmia COVID i entre els països amb consums més alts (6,7) com Espanya (7).

Espanya és un dels països d'Europa amb una taxa de consum d'antibiòtics més elevada. El consum total (AP i hospitalària) d'antimicrobians d'ús sistèmic (grup J01) el 2021 va ser a Espanya de 20.0 dosi diària definida (DDD), superior a la mitjana de la Unió Europea (UE)/Espai Econòmic Europeu (EEE), que va ser 16.4 DDD **(Figura 2).** Només França, Grècia, Bulgària, Xipre, Romania i Polònia van presentar un consum antibiòtic superior a Espanya (6)**.**

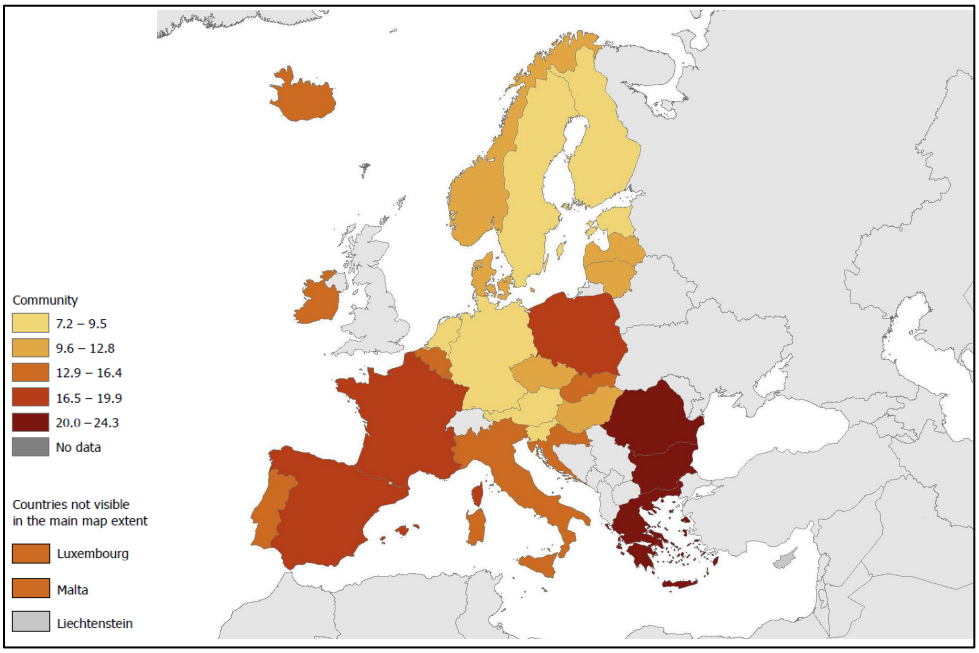
Figura 2: Evolució del consum (atenció primària i hospitalària) d'antimicrobians d'ús sistèmic (grup J01), Espanya i UE/EEE 2016-2021 (expressat com a DDD/1000 habitants/dia).



Font: *Surveillance report. European Centre for Desease prevention and control* (6).

Les dades de consum no canvien quan ens centrem en el consum antibiòtic dels antimicrobians d'ús sistèmic (grup J01) únicament en AP. Espanya té un consum superior a la mitjana de la UE/EEE i manté la mateixa posició respecte als altres països **(Figura 3).**

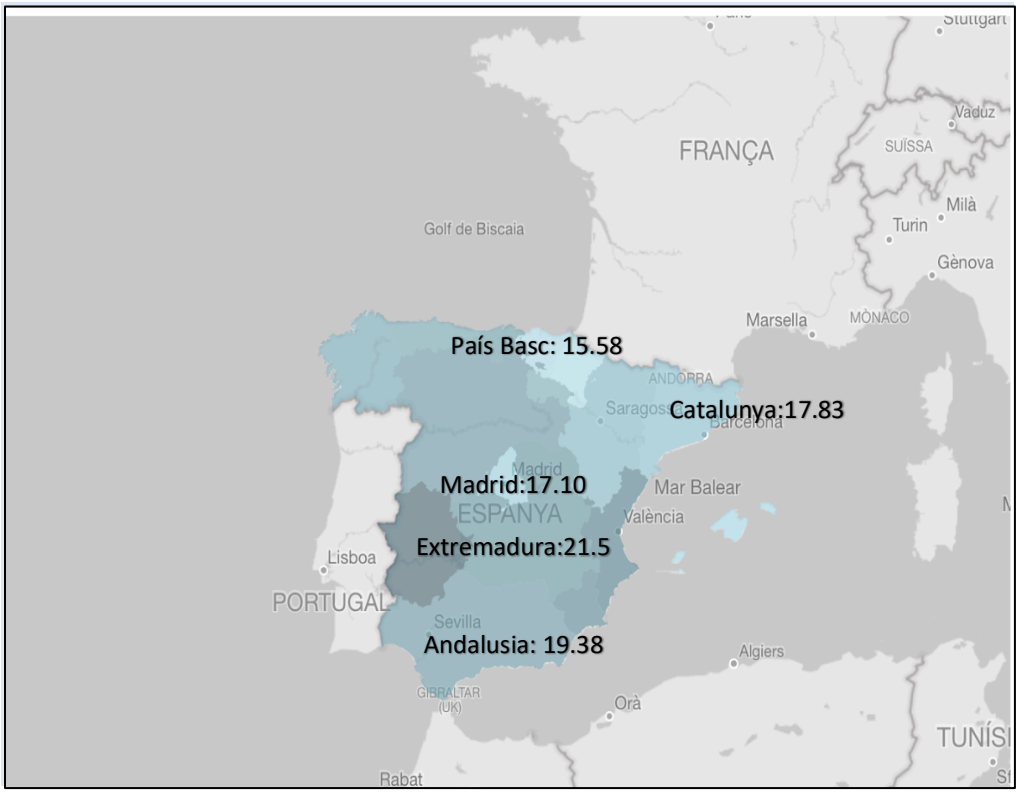
Figura 3: Community consumption of antibacterials for systemic use (ATC group J01), EU/EEA countries, 2021 (expressed as DDD/1.000 habitants/day)



Font: *Surveillance report. European Centre for Desease prevention and control* (6).

El consum d'antibiòtics entre els anys 2014 i 2020 va disminuir el 32.4% (8). El consum d'antibiòtics d'ús sistèmic (grup J01) a l'AP per comunitats autònomes va ser menor en les comunitats del nord-est d'Espanya i Madrid i major, a la Comunitat Valenciana, Regió de Múrcia i Extremadura (9) (**Figura 4**).

Figura 4: Consum d'antibacterians d'ús sistèmic a l'atenció primària a Espanya, per comunitats autònomes l'any 2021 (expressat com a DDD/1000 habitants/dia).



Font: *Plan Nacional de Resistencias frente a la Resistencia a los Antibióticos* (9)

2.2.2. La sobreprescripció dels antibiòtics en infeccions respiratòries

Entre el 80-90% dels antibiòtics són prescrits a l'AP i en format via oral. A més, aproximadament el 50% d'aquestes prescripcions són per infeccions respiratòries tot i ser majoritàriament autolimitades (10).

Un estudi dut a terme al Regne Unit en AP amb població tant adulta com pediàtrica va concloure que en la meitat dels episodis consultats per infeccions respiratòries agudes (IRA), se'ls va prescriure antibiòtics (11). Un altre estudi dut a terme a l'AP a Austràlia també amb població

adulta i pediàtrica va demostrar que les taxes de prescripció d'antibiòtics per IRAs eren entre 4-9 vegades més elevades que les recomanades per les guies de pràctica clínica (12). Estudis realitzats només amb població pediàtrica a l'AP també van concloure que la prescripció en nens per IRA era alta (13,14). Un estudi dut a terme als Estats Units amb nens va determinar que la prescripció antibiòtica per IRAs va ser del 56.9%, quan l'estimació d'origen bacterià era del 27.4% dels casos, així que pràcticament el doble de l'esperat (14).

Així mateix, diversos estudis demostren que els casos d'incertesa en infeccions respiratòries estan relacionats amb nivells més alts d'antibiòtics (15–17). En el camp de la incertesa, la de tipus diagnòstica és la més freqüent en l'àmbit de l'AP.

2.2.3. Efectes dels antibiòtics en els individus i en la comunitat.

Els antibiòtics poden ocasionar efectes adversos, especialment en nens. Els efectes adversos més comuns dels antibiòtics utilitzats en AP tant en adults com en nens són gastroentestinals com la diarrea o les nàusees per alteració de la flora, cutanis com les erupcions o la urticària, per reaccions al·lèrgiques (18,19), i la candidiasis vaginal també per alteració de la flora (19). Concretament en població pediàtrica, els antibiòtics són els fàrmacs que ocasionen més freqüentment efectes adversos (18).

Entre els efectes adversos rars però molt greus, trobem a més de l'anafilaxi, la infecció per *Clostridium difficile.* Els antibiòtics no només poden comportar efectes adversos sinó que també la seva prescripció incrementa la creença de l'eficàcia dels antibiòtics i la seva demanda en futurs episodis (20–22). Així mateix, el consum d'antibiòtics està estretament relacionat amb les resistències antimicrobianes (RAM) (23–25). Les RAM són un fenomen en què els microorganismes com els bacteris es tornen resistents als medicaments antimicrobians com els antibiòtics, comportant el risc d'episodis més greus i de més difícil tractament així com, incrementant el risc de contagi i la càrrega econòmica dels sistemes de salut (26).

L'estudi de Goossens et al. (24) va avaluar l'associació entre el consum d'antibiòtics d'ús sistèmic utilitzats en AP i les taxes de RAM en 26 països d'Europa entre els anys 1997 i 2002. Els autors van determinar la correlació entre les RAM i el consum antibiòtic, a major consum antibiòtic, les

RAM eren més elevades. Així doncs, les taxes més elevades de RAM es van donar en països amb consums més elevats d'antibiòtic, situats al sud i est d'Europa, entre els quals hi ha Espanya.

Costelloe et al. (25) va dur a terme una revisió sistemàtica de 24 estudis i és d'especial interès perquè va avaluar l'efecte del consum d'antibiòtics per a les infeccions respiratòries i urinàries en AP, en el sorgiment de les RAM en els individus, en comptes de amb dades de RAM poblacionals. L'estudi va concloure que als pacients que se'ls prescrivia un antibiòtic desenvolupaven resistència bacteriana a l'antibiòtic prescrit. Aquest efecte podia durar fins a un any després de la prescripció.

Per tant, l' ús indegut i excessiu dels antibiòtics ha estat el principal factor que ha afavorit la ràpida propagació de les RAM (26), fenomen natural i conegut des de fa més de 70 anys amb la implementació de la mateixa penicil·lina(27). Paral·lelament a la ràpida propagació de les RAM, els avenços en la investigació de nous antibiòtics han estat molt escassos (27). Aquesta realitat porta a la població mundial a una situació d'especial vulnerabilitat per la pèrdua de l'eficàcia dels antibiòtics, fàrmacs capaços de destruir micoorganismes bacterians, quan aquest tipus de microorganismes han estat la principal causa de morbiditat i mortalitat per a l'ésser humà (28).

En aquest context, a l' Assemblea Mundial de la Salut de 2014 es va concloure que la situació de les RAM representava una "*greu amenaça per a la salut humana"* i esdevé un dels principals reptes de salut pública a nivell mundial. Per aquest motiu, en l'Assemblea Mundial de la Salut del 2015, els països acorden un Pla d'Acció Mundial sobre les RAM. Aquest pla requereix la implicació a nivell internacional de tots els sectors, no només de la medicina sinó també, de la veterinària, l'agricultura, les finances i el medi ambient. Les mesures que es fan constar en aquest Pla s'han d' implementar en un termini de 10 anys.

Els cinc objectius d' aquest Pla d' Acció Mundial són: *1) millorar la conscienciació i la comprensió pel que fa a la resistència als antimicrobians; 2) reforçar els coneixements a través de la vigilància i la investigació; 3) reduir la incidència de les infeccions; 4) utilitzar de forma òptima els agents antimicrobians; i 5) assegurar una inversió sostenible per combatre la resistència als antimicrobians.* El Pla inclou mesures per a cada objectiu per als Estats Membres de l'Organització Mundial de la Salut i associats (29).

En l'àmbit Espanyol, el 2014 es va crear el *Plan Nacional frente a la resistencia de los antibióticos* (PRAN). Aquest és un pla estratègic creat per requeriment de la Comissió Europea als Estats membres de la UE i inclou tant la salut humana com animal i veterinària. Entre les seves línies de treball es troba la reducció de l'ús d'antibiòtics (8).

2.3. LA PRESCRIPCIÓ DIFERIDA D'ANTIBIÒTICS

Diferents estratègies s'han desenvolupat per disminuir el consum d'antibiòtics com ho són: les intervencions educatives a pacients i/o metges, intervencions per a la millora de les habilitats comunicatives dels metges, millorar l'accés al test de diagnòstic ràpid, auditories i comunicació de feedbacks als metges per al seguiment de prescripcions així com també, l'estratègia de l'espera vigilant i la prescripció diferida d'antibiòtics (PDA). En l'estratègia espera vigilant, s'espera un període d'observació abans de realitzar la prescripció antibiòtica i en la PDA, en canvi, es prescriu l'antibiòtic però es recomana utilitzar en cas d'empitjorament o no millora (30). També hi ha diferents tipus de PDA, la PDA en mà o la PDA en recepció. En la PDA en mà, es dona la prescripció antibiòtica al pacient en la consulta inicial i en la PDA en recepció, els pacients poden recollir l'antibiòtic a la recepció del seu centre d'AP al cap d'un dies després de la consulta inicial.

La PDA és una estratègia dissenyada per fomentar un ús més racional dels antibiòtics per a les IRAs, especialment per als casos d'incertesa diagnòstica. La PDA s'ha utilitzat per a casos en què diferenciar les etiologies virals de les bacterianes pot ser difícil, com succeeix amb les infeccions respiratòries, i també en la conjuntivitis (31) i les del tracte urinari (32).

Eficàcia de la PDA

La recerca sobre l'eficàcia de la PDA en les IRAs ha estat realitzada a nivell internacional, principalment a l'àrea anglosaxona. Una revisió sistemàtica (33) que va comparar la PDA amb la prescripció immediata d'antibiòtics (PIA) i la no prescripció d'antibiòtics (NPA) en les IRAs tant en adults com en nens, no va trobar diferències en la majoria dels símptomes i en les complicacions. El nombre de reconsultes (a l'AP i hospitalària) va ser similar per a la PDA i la PIA. El consum d'antibiòtics va ser del 93%, 31% i 14% per a les estratègies PIA, PDA i NPA, respectivament.

La satisfacció entre els pacients assignats a la PDA va ser similar a la dels pacients assignats a la PIA i superior que aquells assignats a la NPA.

En l'àmbit espanyol i amb població adulta, Llor et al. (34) va realitzar un estudi observacional en el qual l'estratègia PDA va mostrar la disminució en el consum d'antibiòtic. Així mateix, el nostre grup de recerca va publicar els resultats d'un assaig clínic que va avaluar l'ús de dos tipus de PDA en comparació amb la PIA i la NPA en les IRAs no complicades en adults (22). L'estudi va mostrar que les estratègies de PDA van tenir lleument més severitat i durada dels símptomes en comparació amb la PIA. En canvi, el consum va ser considerablement menor per a les estratègies de PDA en comparació amb la PIA, sense diferències en els efectes adversos, complicacions, reconsultes a l'AP i satisfacció.

Alguns assajos clínics a nivell internacional han avaluat l'eficàcia de la PDA per a les IRAs només en població pediàtrica, concretament ho han fet en otitis mitjana aguda (35–37) i faringitis (38,39). En nens amb otitis mitjana aguda que van ser assignats a la PDA en comparació amb la PIA, no es va detectar cap diferència en la freqüència d'otàlgia (36). No obstant això, la durada de la malaltia va ser lleugerament més curta (35) i l'ús d'antibiòtics va ser més elevat per a la PIA en comparació amb l'estratègia PDA (35,36). El curs clínic va ser millor per als nens amb faringitis aleatoritzats a la PIA en lloc de la PDA, però també van tenir un nombre major d'episodis posteriors per a la mateixa infecció (38,39). Els efectes adversos van ser més freqüents entre els nens amb faringitis (39) i amb otitis (35) aleatoritzats a l'estratègia PIA que a la PDA.

Cost-efectivitat de la PDA

Pel que fa a l'anàlisi econòmica dels diferents tipus de prescripció antibiòtica en IRAs, escassos estudis l'han avaluat (40–43). Els estudis de Coco et al.(40) i Shaikh et al.(41) que van incloure l'estratègia PDA en la seva anàlisi econòmica, coincideixen que l'estratègia de PIA amb amoxicil·lina va ser la més efectiva. Concretament, Coco et al. (40), van concloure que l'estratègia de PIA amb amoxicil·lina durant 7-10 dies, entre les 4 estratègies de prescripció avaluades (espera vigilant, PDA, PIA amb amoxicil·lina durant 5 dies, i PIA amb amoxicil·lina durant 7-10 dies), va ser l'estratègia més efectiva amb un guany de 3.5 hores de qualitat de vida ajustada a un cost addicional de 22.90 dòlars estatunidencs (USD) en comparació amb l'estratègia PDA. La PDA va ser l'estratègia menys costosa. El menor cost de la PDA es va atribuir a la reducció tant

en l'ús d'antibiòtics com en les reconsultes. L'estudi de Shaikh et al. (41) van concloure que la PIA amb amoxicil·lina, entre 5 estratègies de prescripció (espera vigilant, la PDA, la PIA amb amoxicil·lina/clavulànic, la PIA amb amoxicil·lina i la PIA amb cefdinir), va ser l'estratègia més cost-efectiva amb un guany incremental de 0.36 dies en dies de vida ajustats per qualitat (QALD) i 36.37 USD en comparació amb la PDA.

Gaboury et al. (42) y Sun et al. (43) van avaluar el cost-efectivitat de diferents estratègies de prescripció des d'una perspectiva social, tot i que no van incloure l'estratègia PDA. Els resultats de Gaboury et al. van suggerir que l'estratègia PIA amb amoxicil·lina pot ser cost-efectiva en comparació amb l'estratègia espera vigilant en nens de dos anys d'edat o més. En canvi, els resultats de Sun et al. (43) van mostrar que l'estratègia d'espera vigilant era cost-efectiva en termes d'USD per anys de vida ajustats per discapacitat (DALY) evitat, en comparació amb la PIA i la NPA. No obstant, una limitació important d'aquests estudis va ser que no van tenir en compte el cost de les RAM (40–43).

Percepcions i actituds dels professionals vers la PDA

Des de la investigació qualitativa, la PDA també ha estat poc estudiada. Una revisió sistemàtica (44) sobre les percepcions i experiències dels metges de família en la prescripció d'antibiòtics i estratègies per a un ús més racional d'aquest tipus de fàrmacs, mostra que els metges perceben la PDA com una possible eina d'utilitat en casos d'incertesa ja que se li pot donar al pacient un accés ràpid a l'antibiòtic, podria complir les seves expectatives en rebre una cosa tangible i a més, proporcionar-li seguretat, en donar-li control sobre la seva malaltia.

L'estudi d'Arroll et al. (45) i el de Høye et al. (46) van ser els dos inclosos en aquesta revisió sistemàtica que van estudiar la PDA. Arroll et al. (45) va entrevistar metges de família i pacients que havien participat en la PDA en un assaig clínic sobre infeccions respiratòries i va fer aflorar algunes idees d'interès destacat, com les expectatives del pacient quan consulta al metge per una infecció. També es mostra en aquest estudi com les característiques sociodemogràfiques del pacient (baix nivell educatiu, mal domini de la llengua del país o l'edat) podrien determinar la utilització de la PDA. Entre els resultats de l'estudi de Høye (46) sorgeix també la importància de l'elecció del pacient ja que ha de ser un pacient que comprengui les instruccions i també, se l'ha d'informar molt bé quan se li ofereix la PDA. En el nostre àmbit, un estudi transversal conduït

pel nostre grup de recerca en 23 centres d'AP pertanyents a quatre comunitats autònomes d'Espanya va concloure que menys del 50% dels professionals de primària utilitzaven l'estratègia PDA (47).

2.4. JUSTIFICACIÓ

Els antibiòtics es prescriuen en excés en les IRAs en l'àmbit de l'AP. Tanmateix, la decisió de prescriure és sovint complexa. La PDA és una estratègia dissenyada per promoure un ús més racional d'aquest tipus de fàrmacs. Des de fa anys s'ha estudiat des de diferents aproximacions i entorns. No obstant això, encara persisteixen alguns buits importants per a la seva adequada implementació.

Alguns estudis han avaluat l'eficàcia de la PDA però l'evidència és escassa sobre l'ús de la PDA en nens, amb estudis realitzats només als Estats Units d'Amèrica (36,37,39), Regne Unit (35) i Jordania (38). Els efectes de l'estratègia PDA en països d'economies d'alts ingressos amb taxes elevades d'ús d'antibiòtics, com els del sud d'Europa (48) són encara desconeguts.

L'evidència és encara més escassa en estudis cost-efectivitat que hagin avaluat les estratègies de PDA (40–43) en població pediàtrica. Així mateix, els estudis realitzats han estat centrats en l'otitis mitjana aguda i la faringitis i conduits als Estats Units d'Amèrica (40,41,43) i Canadà (42). Així mateix, cap d' ells va incloure en la seva anàlisi el cost de les RAM (40–43).

La PDA encara no és àmpliament implementada pels professionals, segons diversos estudis qualitatius que han investigat les opinions i experiències de la PDA per a les IRAs entre els professionals del nord d'Europa (46) i Nova Zelanda (45). Així mateix, segons el nostre coneixement, no hi ha evidència d'estudis qualitatius focalitzats en la PDA en el sud d'Europa.

En el nostre entorn, l'eficàcia de la PDA ha estat estudiada pel nostre grup de recerca a través d'un assaig clínic aleatoritzat (ACA) multicèntric en pacients adults amb IRAs atesos a AP (ACA-adults) (22). En aquest estudi, la PDA en comparació amb la PIA va mostrar lleugerament major duració i severitat dels símptomes però a la vegada, la disminució significativa del consum d'antibiòtics, sense diferències en les complicacions. Així mateix, també el nostre grup va dur a

terme un estudi transversal el qual va mostrar que menys de la meitat dels professionals utilitzaven la PDA a Espanya (47).

Per tant, la present tesi conformada per un ACA multicèntric sobre l'eficàcia de la PDA en nens amb IRAs atesos a AP, un estudi cost-efectivitat i un estudi qualitatiu amb professionals de la salut sobre els antibiòtics i la PDA, dona continuïtat a una línia de recerca sobre la PDA i l'ús racional dels antibiòtics en IRAs a l'AP, liderada pel mateix grup d'investigadors.

L'assaig clínic d'aquesta tesi ha comparat la PDA amb la PIA i la NPA, en població pediàtrica amb IRAs atesos en centres d'AP d' Espanya. En el marc d' aquest assaig, s'ha realitzat una avaluació de cost-efectivitat, comparant les tres estratègies de prescripció. Finalment, l'estudi qualitatiu amb professionals de la salut d'AP ha permès conèixer les seves percepcions i actituds sobre l'ús dels antibiòtics i la PDA en aquest tipus d'infeccions en població adulta.

3. OBJECTIUS

3. OBJECTIUS

3.1. OBJECTIUS GENERALS

I) Determinar l'eficàcia i la seguretat de la PDA en les IRAs no complicades en pacients pediàtrics.

II) Avaluar el cost-efectivitat de la PDA en les IRAs no complicades en pacients pediàtrics.

III) Explorar les percepcions, actituds i satisfacció dels professionals de la salut sobre la utilització d'antibiòtics i les diferents estratègies de PDA en el tractament de les IRAs no complicades en pacients adults.

3.2. OBJECTIUS ESPECÍFICS

OBJECTIUS ESPECÍFICS RELACIONATS AMB L'OBJECTIU GENERAL I

- Determinar l'eficàcia en la durada i severitat dels símptomes de la PDA comparada amb la PIA i la NPA en població pediàtrica.
- Determinar l'impacte de la PDA comparada amb la PIA i la NPA en el consum d' antibiòtics en les IRAs no complicades en 30 dies, en població pediàtrica.
- Determinar l'impacte de la PDA comparada amb la PIA i la NPA en la satisfacció dels pares en l'efectivitat dels antibiòtics en les IRAs.
- Determinar les creences dels pares en l'efectivitat dels antibiòtics, en les IRAs.
- Avaluar l'impacte de la PDA sobre la reconsulta a l'AP en 30 dies, en població pediàtrica.
- Avaluar les complicacions relacionades amb el procés infecciós durant 30 dies.

OBJECTIUS ESPECÍFICS RELACIONATS AMB L'OBJECTIU GENERAL II

- Avaluar el cost-efectivitat de la PDA comparada amb la PIA i la NPA en les IRAs no complicades en pacients pediàtrics.

OBJECTIUS ESPECÍFICS RELACIONATS AMB L'OBJECTIU GENERAL III

- Explorar les percepcions dels professionals de la salut sobre les IRAs i la utilització d'antibiòtics en població adulta.
- Identificar les percepcions, les preferències i les actituds dels professionals de la salut en relació a les diferents estratègies de PDA, en el tractament de les IRAs en població adulta.

- Conèixer les possibles diferències en les percepcions i actituds sobre els antibiòtics i les estratègies de PDA dels professionals de la salut, en funció de la seva participació o no participació en l'ACA-adults.
- Examinar les valoracions dels professionals sanitaris participants en l'ACA-adults sobre l'experiència i el desenvolupament de l'estudi.

4. MÈTODES

4. MÈTODES

4.1. ESTUDI 1. ASSAIG CLÍNIC ALEATORITZAT SOBRE LA PRESCRIPCIÓ DIFERIDA D'ANTIBIÒTICS EN COMPARACIÓ AMB LA PRESCRIPCIÓ IMMEDIATA I LA NO PRESCRIPCIÓ EN NENS AMB INFECCIONS RESPIRATÒRIES

4.1.1. DISSENY

Assaig clínic fase IV, aleatoritzat, prospectiu, multicèntric i paral·lel que va comparar la PDA (que va ser PDA en mà) amb la PIA i la NPA. Aquest estudi aborda l'objectiu general I així com, els específics relacionats amb aquest.

4.1.2. POBLACIÓ D'ESTUDI

La població d'estudi van ser nens en edats compreses entre els 2 i 14 anys, amb IRAs no complicades, incloent-hi l'otitis mitjana aguda, la rinosinusitis, la faringitis i la bronquitis aguda. Els nens eren inclosos si els seus pediatres tenien dubtes raonables de si havien de prescriure o no antibiòtics.

4.1.3. MOSTRA I RECLUTAMENT

Es va estimar una mostra de 450 pacients pediàtrics (150 per braç de tractament). El reclutament va ser dut a terme entre juny de 2012 i juny de 2016 en 39 centres d'AP d'Espanya, pertanyents a 9 comunitats autònomes (Catalunya, País Basc, Astúries, Madrid, Castella la Manxa, Castella i Lleó, Galícia, Aragó i València).

4.1.4. INTERVENCIONS

Els pacients van ser aleatoritzats en un dels tres braços d'estudi: la PDA, la PIA o la NPA. L'aleatorització es va estratificar per patologia i en blocs. L'assignació es va realitzar de forma centralitzada mitjançant una plataforma via online. Els nens, pares i pediatres no estaven cegats. Els pediatres en la visita inicial explicaven als pares l'evolució natural de la malaltia del seu fill. Per als nens assignats a la PDA, els pediatres van entregar la recepta d'antibiòtics als pares, recomanant-los les circumstàncies en què havien de considerar usar l'antibiòtic o tornar al metge. Per als nens assignats a la NPA, els pediatres no van receptar antibiòtics. Per als nens assignats a la PIA, els pediatres van prescriure antibiòtics per ser presos des del dia de la visita inicial. En

totes dues estratègies (NPA i PIA), els pediatres van explicar als pares les circumstàncies en què havien de considerar tornar al metge. Cada pediatre va decidir el tipus d'antibiòtic a prescriure per a les estratègies PDA i PIA.

4.1.5. VARIABLES

La variable principal va ser l'eficàcia en la severitat i la durada dels símptomes de les IRAs durant 30 dies. La severitat dels símptomes va ser puntuada pels pares en una escala Likert de 7 punts (49,50).

Les variables secundàries d'eficàcia van ser l'ús d'antibiòtics durant 30 dies, la satisfacció dels pares i les creences respecte a l'eficàcia dels antibiòtics, i les visites addicionals no programades a l'AP durant 30 dies. La satisfacció dels pares (48,49) i les creences sobre l'eficàcia dels antibiòtics es van avaluar amb una escala Likert de 6 punts (22,51). Es van registrar també les complicacions relacionades amb la infecció durant els primers 30 dies.

4.1.6. RECOLLIDA DE DADES

En la visita inicial, els pediatres van recollir les dades sobre l'estat de salut dels infants. El centre coordinador (Servei d'Epidemiologia de l'Hospital de la Santa Creu i Sant Pau-Centre Cochrane iberoamericà) va fer un seguiment dels nens, trucant per telèfon als pares els dies 2 i 30 després de la inclusió, així com els dies 7, 15 i 22, si els pares van indicar en la trucada anterior que els símptomes continuaven. Les variables de satisfacció i creences sobre l'efectivitat dels antibiòtics eren les úniques que només es registraven una vegada, en la trucada del dia 30.

4.1.7. ANÀLISI

Les característiques poblacionals es van descriure mitjançant l'ús de freqüències i percentatges per a variables categòriques i, mitjanes i desviació estàndard (DE) per a les variables quantitatives. La durada dels símptomes i la gravetat dels símptomes després de la primera visita es van descriure mitjançant l'ús de mitjanes (DE) i medianes i del rang interquartil (IQR), respectivament. La regressió negativa binomial i regressió logística van ser utilitzades per comprar entre les 3 branques la durada i severitat respectivament per a cada símptoma. Es va utilitzar la prova de Pearson x^2 per comparar les variables secundàries (freqüències i percentatges) per als 3 braços, considerant la PIA com a categoria de referència. Totes les anàlisis es van guiar per un enfocament d'intenció de tractar. La significança es va fixar en 5%

(α = 0.05). Totes les anàlisis estadístiques es van realitzar utilitzant el programari Stata versió 13.1 (Stata Corp, College Station, TX).

4.1.8. ASPECTES ÈTICS

L'estudi va ser aprovat pel Comitè Ètic d'Investigació Clínica de l'Institut d'atenció Primària IDIAP Jol i Gurina, per tots els comitès d'ètica implicats i per l'Agència Espanyola del Medicament i productes Sanitaris.

4.1.8. FINANÇAMENT

Finançat per l'Instituto de Salud Carlos III en el marc d'una convocatòria de 2016 (*Acción Estratégica en Salud 2013-2016: Programa de Investigación Orientada a los Retos de la Sociedad*) en el marc del *Plan Nacional de Investigación Científica e Investigación Técnica e Innovación* 2013-2016 (expediente PI11/02192), cofinançat per la Unió Europea a través del Fons Europeu de Desenvolupament Regional i amb el suport del Ministeri de Sanitat Espanyol, Serveis Socials i Igualtat (referencia EC11-339).

4.2. ESTUDI 2. ANÀLISI COST-EFECTIVITAT SOBRE LA PRESCRIPCIÓ ANTIBIÒTICA DIFERIDA EN COMPARACIÓ AMB LA PRESCRIPCIÓ IMMEDIATA I LA NO PRESCRIPCIÓ EN NENS AMB INFECCIONS RESPIRATÒRIES

4.2.1 DISSENY

Anàlisi cost-efectivitat dut a terme en el context de l'ACA sobre la PDA en població pediàtrica (Estudi 1). Aquest estudi 2 aborda l'objectiu general II així com, els específics relacionats amb aquest.

4.2.2. MODEL DE DECISIÓ DE COST-EFECTIVITAT

Es va desenvolupar un arbre de decisió per comparar les tres estratègies per a un període de temps de 30 dies. Es va adoptar una perspectiva social que incloïa els costos directes de l'atenció mèdica i els costos directes i indirectes no relacionats amb l'atenció mèdica.

4.2.3. RECURSOS UTILITZATS I COSTOS

Els costos totals, en euros per a l'any 2022, es van calcular utilitzant un enfocament de costos ascendent**.** Les dades de mesurament es van recopilar durant l'ACA.

Costos sanitaris directes

Els costos van ser per les visites a l'AP i les emergències hospitalàries, l'ús de medicaments antibiòtics i no antibiòtics durant el seguiment de 30 dies, el temps del metge i les visites i fàrmacs addicionals per efectes adversos i complicacions (visites al servei d'urgències i ingressos hospitalaris).

Costos directes i indirectes no sanitaris

Els costos no sanitaris van ser els desplaçaments a les institucions sanitàries, l'estacionament i el temps de consulta ambulatòria per als pares. El cost indirecte va ser el temps perdut de feina pels pares. Les dades es van calcular utilitzant fonts d'informació secundàries excepte el temps perdut a la feina que es va recopilar durant l'ACA (52).

Costos de les RAM

El cost de les RAM es va calcular per prescripció i per dia, utilitzant dades publicades pel *European Centre for Disease Prevention and Control* (25) i la metodologia d'Oppong et al. (53).

Tots els costos es van incloure en una anàlisi de sensibilitat determinista (diagrama tornado), el rang de la qual va ser baix-alt.

4.2.4. ESTIMACIONS D'EFECTIVITAT

Les estimacions d'efectivitat es van calcular a partir de dies de vida ajustats per qualitat (QALD). Els QALD es van calcular multiplicant els dies en cada estat de salut (39) recopilats durant l'ACA pel valor d' utilitat de la qualitat de vida del nen en un moment donat. Els valors d' utilitat utilitzats es van basar en puntuacions d'una escala visual analògica (EVA) del 0 al 100 (40,41,43). El valor de QALD per a un període de 30 dies per a un nen en perfecte estat de salut va ser de 30. Els dies de símptomes específics moderats o greus i efectes adversos van indicar disutilitat, que es va calcular com la diferència entre 1 i la puntuació mitjana de l'EVA per a cada estratègia. Per als nens que van presentar efectes adversos es va calcular el nombre de dies d'efectes adversos segons l'estudi de Coco et al. (40).

4.2.5. ANÀLISI

Els tres braços de l'arbre de decisió es van comparar en termes de cost per QALD utilitzant la relació cost-efectivitat incremental (ICER), entre alternatives no dominades. Els resultats de l'anàlisi de cost-efectivitat es van generar mitjançant la recopilació del cost total (costos sanitaris directes, costos directes i indirectes en l'atenció sanitària i costos de les RAM) en euros per pacient tractat i l'efectivitat mesurada en QALD també, per pacient tractat. També es va calcular el benefici monetari net (BNM).

Es va realitzar una anàlisi de sensibilitat determinista per a tots els costos a través de l'anàlisi de tornado. També vam realitzar una anàlisi de sensibilitat probabilística a través de 10.000 iteracions de Monte Carlo. Així com també, es va traçar un plànol de cost-efectivitat incremental i una corba d' acceptabilitat de cost-efectivitat per calcular la probabilitat que una alternativa pugui ser cost-efectiva, atès un rang llindar de valors de disposició a pagar. Vam considerar un valor de disposició a pagar de 82.2 euros per dia (41,52). Per a les anàlisis es va utilitzar el programari estadístic TreeAge Pro-2021.

4.3. ESTUDI 3. ESTUDI QUALITATIU SOBRE LES PERCEPCIONS, ACTITUDS I SATISFACCIÓ DELS PROFESSIONALS SANITARIS SOBRE LA UTILITZACIÓ D'ANTIBIÒTICS I LES DIFERENTS ESTRATÈGIES DE PRESCRIPCIÓ ANTIBIÒTICA DIFERIDA EN EL TRACTAMENT D'ADULTS AMB INFECCIONS RESPIRATÒRIES

4.3.1. DISSENY

Estudi qualitatiu en el què es van dur a terme grups de discussió (GD) i entrevistes semiestructurades (54–56) amb professionals sanitaris de 6 centres d'AP de l'àrea metropolitana de Barcelona (Espanya). Aquest estudi aborda l'objectiu general III així com, els específics relacionats amb aquest.

4.3.2. POBLACIÓ D'ESTUDI

Metges de família de 6 centres d'AP de l'àrea metropolitana de Barcelona, 5 dels quals havien participat prèviament en l'ACA-adults (22).

4.3.3. MOSTRA I RECLUTAMENT

El mostreig va ser intencionat i per representativitat teòrica (54,56). Els criteris per definir els perfils professionals que reflectissin discursos possiblement diferents van ser els següents: (a) la participació prèvia del professional a l'ACA-adults (si/no); i (b) el nivell socioeconòmic de la població del centre d'AP del professional (mitjà-baix/mitjà-alt). Inicialment es va considerar una mostra entre 24 i 36 participants, distribuïts a raó d'entre 6 i 9 participants per grup, en un total de 4 grups.

4.3.4. RECOLLIDA DE DADES

L'estudi es va realitzar en dues fases: primer, GDs i posteriorment, entrevistes individuals semiestructurades (54–56).

Grups de discussió

Els GDs es van dissenyar d'acord amb els criteris de mostreig de la següent manera: GD1, participants en l'ACA-adults i àrea socioeconòmica mitjana-baixa; GD2, participants en l'ACA-adults i àrea socioeconòmica mitjana-alta; GD3, no participants en l'ACA-adults i àrea socioeconòmica mitjana-baixa; GD4, no participants en l'ACA-adults i àrea socioeconòmica

mitjana-alta. En relació al GD2, no es van poder reclutar prou metges de família i es va incloure una infermera. Es va utilitzar un guió. Els GDs, organitzats amb un moderador i un observador, es van dur a terme en una sala de reunions del centre coordinador (Servei d'Epidemiologia de l'Hospital de la Santa Creu i Sant Pau-Centre Cochrane iberoamericà). Tots els GDs van ser gravats digitalment en àudio i posteriorment, transcrits textualment.

Entrevistes individuals semiestructurades

Es van realitzar entrevistes semiestructurades, en les quals es va utilitzar un guió per tal d'explorar més a fons les qüestions clau sorgides en els GDs. Tots els entrevistats havien participat prèviament en els GDs. Les entrevistes es van realitzar als centres d'AP on treballaven els participants.

4.3.5. ANÀLISI

Es va realitzar una anàlisi temàtica inductiva com ho descriuen Braun i Clarke (57). Es va utilitzar el programari Atlas.ti (versió 8) per a la codificació i l'anàlisi de les dades. Les discrepàncies sobre temes i codis emergents es van resoldre per consens entre els investigadors.

4.3.6. ASPECTES ÈTICS

L'estudi va ser aprovat pel Comitè Ètic d'Investigació Clínica de l'Institut d'Investigació d'atenció Primària IDIAP Jordi Gol i Gurina.

4.3.7. FINANÇAMENT

Finançat per l'*Instituto de Salud Carlos III* en el marc d' una convocatòria de 2012 (*Acción Estratégica en Salud: Programa de Investigación Orientada a los Retos de la Sociedad*) en el marc del Plan Nacional de Investigación Científica y Técnica y de Innovación 2008-2011 (PI12/03043), cofinançat per a la Unió Europea a través del Fons Europeu de Desenvolupament Regional.

5. RESULTATS

5. RESULTATS

5.1. ESTUDI 1. ASSAIG CLÍNIC ALEATORITZAT SOBRE LA PRESCRIPCIÓ DIFERIDA D'ANTIBIÒTICS EN COMPARACIÓ AMB LA PRESCRIPCIÓ IMMEDIATA I LA NO PRESCRIPCIÓ EN NENS AMB INFECCIONS RESPIRATÒRIES

5.1.1. RESUM DELS RESULTATS DE L'ESTUDI 1

Població

Un total de 436 nens, amb edat mitjana (DE) 6.3 (3.0) anys, van ser inclosos en l'estudi i l'anàlisi, 226 (51.8%) dels quals eren nenes; 224 (51.4%) tenien otitis mitjana aguda, 146 (33,5%) tenien faringitis, 40 (9.2%) tenien bronquitis aguda i 26 (6.0%) tenien rinosinusitis.

Variables principals

La durada en dies de qualsevol símptoma fins a la desaparició va ser similar per als 3 braços. La durada mitjana (DE) en dies de qualsevol símptoma fins a la desaparició va ser per la PDA 8.3 (7.7) versus la PIA 8.3 (7.8) (p=0.968), i la NPA 7.9 (9.3) versus la PIA 8.3 (7.8) (p=0.593) (p_{global}=0.888). La durada mitjana (DE) en dies de símptomes greus va ser per la PDA 12.4 (8.4) versus la PIA 10.1 (6.3) (p=0.247), i la NPA 10.9 (8.5) versus la PIA 10.1 (6.3) (p=0.682) (p_{global}=0.539). La durada mitjana (DE) en dies de símptomes moderats va ser per la PDA 11.7 (8.7) versus la PIA 10.2 (7,5) (p=0.257), i la NPA 10.0 (8.4) versus PIA 10.2 (7.5) (p=0.869) (p_{global}=0.435). La major gravetat per a qualsevol símptoma en l'escala Likert de 7 punts va ser similar per als 3 braços, amb una puntuació mitjana (IQR) de 3 (2-4).

Variables secundàries

Els antibiòtics van ser consumits al braç de PIA per 142 (96.0%) nens en comparació amb 37 (25.3%) nens al braç PDA (p<0.001) i 17 (12.0%) nens al braç NPA (p<0.001). L'ús de medicaments no antibiòtics va ser similar entre la PDA (n = 136; 93,2%) i la NPA (n=136; 95,8%), i major que per a la PIA (n=108; 73.0%) (p<0.001). La creença que els antibiòtics van ser molt o extremadament efectius va ser més elevada per als pares de nens del braç de la PIA que els dels altres braços (PIA n=106 [81.6%] versus PDA n = 38 [42.2%] versus NPA n=23 [29.1%]; P < 0.001). Els efectes adversos gastrointestinals van ser menors als braços de la PDA i la NPA en comparació amb el braç de la PIA (p = 0.037). No hi va haver diferències entre els braços en les complicacions (p=0.813) o les visites no programades a l'AP (p = 0.895), mentre que la satisfacció va ser igualment alta per als 3 braços (p = 0.389).

5.1.2. PUBLICACIÓ DE L'ESTUDI 1

Mas-Dalmau G, Villanueva López C, Gorrotxategi Gorrotxategi P, Argüelles Prendes E, Espinazo Ramos O, Valls Duran T, Gonzalo Alonso ME, Cortés Viana MP, Menéndez Bada T, Vázquez Fernández ME, Pérez Hernández AI, Muñoz Ortiz L, Little P, de la Poza Abad M, Alonso-Coello P; DAP PEDIATRICS GROUP*. Delayed Antibiotic Prescription for Children With Respiratory Infections: A Randomized Trial. Pediatrics. 2021 Mar;147(3):e20201323. Doi: 10.1542/peds.2020-1323. Journal Impact Factor (2021): 9.703

Aquest estudi va ser posteriorment inclòs en el metanàlisi de Stuart et al. (58) sobre la PDA en IRAs tant en població adulta com en pediàtrica. Així mateix, aquest manuscrit va ser considerat per la *Canadian Family Physician*, revista oficial del Col·legi de metges de família del Canadà, entre els 10 estudis publicats durant el 2021 amb més rellevància per als metges de família (59).

Delayed Antibiotic Prescription for Children With Respiratory Infections: A Randomized Trial

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abstract

OBJECTIVES: To assess the effectiveness and safety of delayed antibiotic prescription (DAP) compared to immediate antibiotic prescription (IAP) and no antibiotic prescription (NAP) in children with uncomplicated respiratory infections.

METHODS: Randomized clinical trial comparing 3 antibiotic prescription strategies. The participants were children with acute uncomplicated respiratory infections attended to in 39 primary care centers. Children were randomly assigned into prescription arms as follows: (1) DAP, (2) IAP, or (3) NAP. Primary outcomes were symptom duration and severity. Secondary outcomes were antibiotic use, parental satisfaction, parental beliefs, additional primary care visits, and complications at 30 days.

RESULTS: In total, 436 children were included in the analysis. The mean (SD) duration of severe symptoms was 10.1 (6.3) for IAP, 10.9 (8.5) for NAP, and 12.4 (8.4) for DAP (P = .539), although the differences were not statistically significant. The median (interquartile range) of the greatest severity for any symptom was similar for the 3 arms (median [interquartile range] score of 3 [2–4]; P = .619). Antibiotic use was significantly higher for IAP (n = 142 [96%]) compared to DAP (n = 37 [25.3%]) and NAP (n = 17 [12.0%]) ($P < .001$). Complications, additional visits to primary care, and satisfaction were similar for all strategies. Gastrointestinal adverse effects were higher for IAP.

CONCLUSIONS: There was no statistically significant difference in symptom duration or severity in children with uncomplicated respiratory infections who received DAP compared to NAP or IAP strategies; however, DAP reduced antibiotic use and gastrointestinal adverse effects.

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Deidentified individual participant data, the study protocol, the statistical analysis plan, and the informed consent form will be made available after publication. The data will be made available to researchers who provide a methodologically sound proposal for use. Proposals should be submitted to the corresponding author.

WHAT'S KNOWN ON THIS SUBJECT: Delayed antibiotic prescription (DAP) in primary care settings optimizes antibiotic use in adults with acute uncomplicated respiratory infections in high-income–economy countries, such as those in southern Europe, with higher rates of antibiotic use.

WHAT THIS STUDY ADDS: The current study is the largest ever conducted on DAP for children and is the first study of DAP in a pediatric population in a southern Europe country with a high rate of antibiotic use.

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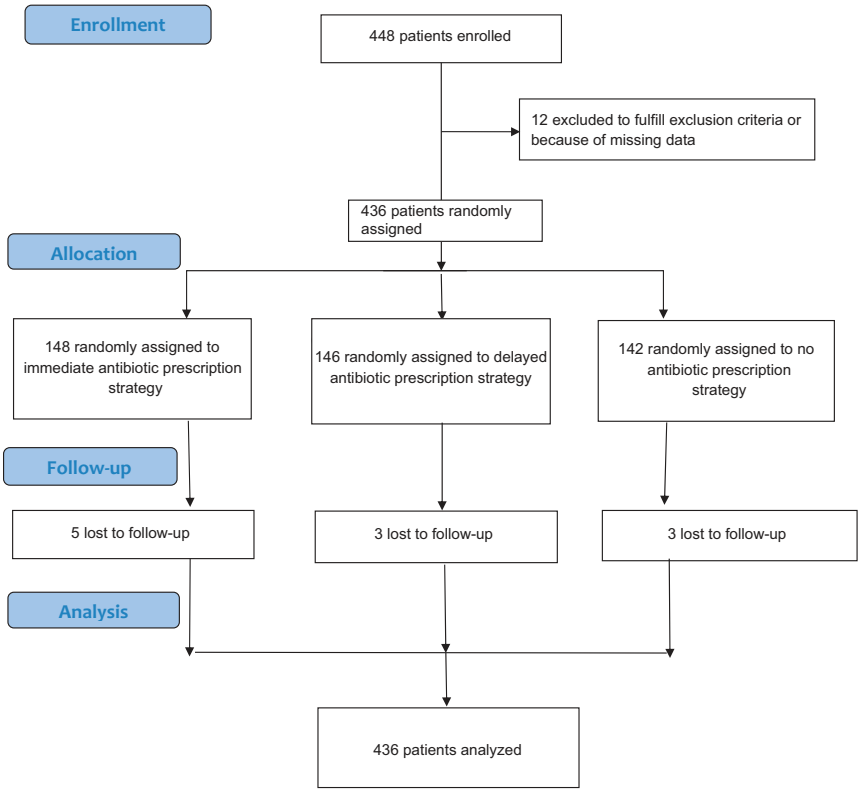

FIGURE 1
Flow diagram. The number of participants enrolled, randomly assigned, followed-up, and included in the analysis are shown in the figure.

Respiratory tract infections (RTIs) are a major reason for medical visits in pediatrics.[1] Most RTIs are self-limiting, and antibiotics hardly alter the course of the condition,[2–4] yet antibiotics are frequently prescribed for these conditions.[5,6] Antibiotic prescription for RTIs in children is especially considered to be inappropriately high.[7,8] The fact that antibiotics are overused is the main reason why resistance to antimicrobial agents has developed[9] to the point of becoming a threat to public health.[10] Use of antibiotics places patients at risk for adverse effects[11] and enhances beliefs to consult for similar episodes.[12]

In primary care, diagnostic methods are often limited, leading to uncertain diagnoses and unclear cases of antibiotic prescription. Antibiotics are also prescribed because of the concern to avoid complications[13] or to meet parental expectations when symptoms persist.[14] Delayed antibiotic prescription (DAP) has been used in primary care when there are reasonable doubts about the need for immediate antibiotic prescription (IAP), which is what happens with some RTIs, conjunctivitis,[15] and urinary tract infections.[16] Some clinical practice guidelines recommend DAP when in doubt that antibiotics may be necessary.[17]

DAP consists of prescribing an antibiotic to take only if the patient's condition worsens or fails to improve a few days after a medical visit. The latest Cochrane systematic review comparing DAP, IAP, and no antibiotic prescription (NAP) in adults and children reported no differences in most symptoms or in complications, whereas antibiotic intake was considerably lower for DAP compared to IAP for similar patient satisfaction levels. Reconsultation rates were also similar for the DAP and IAP strategies.[18]

Randomized clinical trials used to assess DAP for RTIs in children have been conducted for acute otitis media[19–21] and pharyngitis.[22,23] For the otitis media trials, duration of otalgia was slightly shorter[19] and antibiotic use was lower for DAP compared to IAP.[19,20] No differences were observed in otalgia frequency,[20] pain severity, distress, or school absenteeism.[19] As for the pharyngitis trials, only in a single study[22] was the severity of symptoms significantly higher in children allocated to DAP compared to IAP. In both the otitis[19–21] and pharyngitis[22,23] studies, children randomly assigned to IAP experienced more adverse effects.

There is scant evidence about the use of DAP in children, with studies conducted only in the United States,[20,21,23] England,[19] and Jordan.[22] The effects of a DAP strategy in high-income–economy countries with higher rates of antibiotic use, such as those in southern Europe,[24] are still unknown. We therefore conducted a randomized clinical trial to assess the effectiveness of DAP compared to IAP and NAP.

METHODS

Design

We used a multicenter randomized clinical trial to compare 3 treatment strategies for children with acute uncomplicated RTIs: DAP, IAP, and NAP.

Participants

Patients eligible for inclusion were children aged 2 to 14 years who, with their parent(s), attended a primary care pediatrician's office with the following conditions: pharyngitis,

TABLE 1 Patient Baseline Characteristics

	Prescription Strategy			Total (N = 436)
	IAP (n = 148)	DAP (n = 146)	NAP (n = 142)	
Girls	79 (53.4)	68 (46.6)	79 (55.6)	226 (51.8)
Age, y, mean (SD)	6.4 (3.1)	6.4 (3.2)	6.1 (2.8)	6.3 (3.0)
2–5	67 (45.2)	71 (48.6)	73 (51.4)	211 (48.4)
6–10	59 (39.9)	58 (39.7)	57 (40.1)	174 (39.9)
11–14	22 (14.9)	17 (11.7)	12 (8.4)	51 (11.7)
Wt, kg, mean (SD)	25.8 (11.6)	26.1 (12.1)	24.0 (10.0)	25.3 (11.3)
Parental education				
Primary or less	7 (4.7)	3 (2.1)	7 (4.9)	17 (3.9)
Secondary	66 (44.6)	65 (44.5)	61 (43.0)	192 (44.0)
Tertiary	75 (50.7)	78 (53.4)	74 (52.1)	227 (52.1)
Respiratory comorbidity	16 (10.8)	14 (9.6)	11 (7.8)	41 (9.4)
Pulmonary disease	13 (8.8)	13 (8.9)	7 (4.9)	33 (7.6)
Smoker parents	60 (40.5)	57 (39.0)	56 (39.4)	173 (39.7)
Respiratory tract infection				
Rhinosinusitis	9 (6.1)	9 (6.1)	8 (5.6)	26 (6.0)
Pharyngitis	48 (32.4)	49 (33.6)	49 (34.5)	146 (33.5)
Acute bronchitis	14 (9.5)	13 (8.9)	13 (9.2)	40 (9.2)
Acute otitis media	77 (52.0)	75 (51.4)	72 (50.7)	224 (51.4)
Symptom severity score, mean (SD)[a]				
Fever	3.7 (2.0)	3.7 (1.6)	4.1 (1.7)	3.8 (1.8)
Discomfort and/or general pain	3.1 (1.3)	3.0 (1.1)	3.0 (1.3)	3.0 (1.2)
Cough	2.1 (1.9)	2.4 (1.9)	2.5 (2.1)	2.3 (1.9)
Difficulty sleeping	2.6 (1.8)	2.8 (1.8)	3.1 (1.8)	2.8 (1.8)
Everyday routine disruptions	2.8 (1.4)	2.7 (1.3)	2.9 (1.3)	2.8 (1.4)
Irritability	2.6 (1.6)	2.6 (1.5)	2.6 (1.6)	2.6 (1.6)
Symptom duration previsit, d, mean (SD)	2.5 (3.1)	2.8 (5.8)	2.2 (3.2)	2.5 (4.2)
General health status score, mean (SD)[b]	66 (19)	65 (17)	64 (19)	65 (18)
Feverish	32 (36.8)	28 (33.3)	19 (26.0)	79 (32.4)
Fever ≥38°C lasting ≥24 h	51 (34.5)	54 (37.0)	62 (43.7)	167 (38.3)
Parental worry level				
Not at all or only slightly worried	17 (11.5)	25 (17.1)	17 (12.0)	59 (13.5)
A little worried	52 (35.1)	46 (31.5)	47 (33.1)	145 (33.3)
Moderately worried	69 (46.6)	71 (48.6)	73 (51.4)	213 (48.9)
Very or extremely worried	10 (6.8)	4 (2.7)	5 (3.5)	19 (4.4)

Data are reported as frequencies and percentages except where otherwise indicated.

[a] Symptoms, scored on a Likert scale from 0 (no problems) to 6 (as bad as it could be), are those common to the 4 studied pathologies.

[b] Scored at first visit on a visual analog scale from 0 (worst health status) to 100 (best health status).

rhinosinusitis, acute bronchitis, or acute otitis media (Supplemental Information). Children were included if pediatricians had reasonable doubts about the need to prescribe an antibiotic. Pediatricians that had access to rapid streptococcal testing did not include children with pharyngitis but included children with the other 3 infections. Recruitment was conducted in 39 primary care centers in Spain between June 2012 and June 2016. The study was approved by the Clinical Research Ethics Committee of the Institute for Primary Health Care Research Jordi Gol i Gurina, by all other ethics committees involved, and by the Spanish Agency of Medicines and Medical Devices.

Interventions

Children were randomly allocated to one of the DAP, IAP, or NAP arms. Randomization was stratified by pathology and in blocks. Allocation was performed centrally by using an online platform. Children, parents, and health professionals were not blinded.

Parents were advised that regardless of the arm and counting days from the onset of symptoms, their child was likely to feel more or less the same for up to 4 days for acute otitis media, 7 days for pharyngitis, 15 days for rhinosinusitis, and 20 days for acute bronchitis.

For children allocated to DAP, pediatricians handed the antibiotic prescription to parents, recommending them to only consider administering the antibiotic if (1) the child did not start to feel better after 4, 7, 15, or 20 days from symptom onset for acute otitis media, pharyngitis, rhinosinusitis, or acute bronchitis, respectively; (2) the child had a temperature of ≥39°C after 24 hours or a temperature of ≥38°C but <39°C after 48 hours; or (3) the child

TABLE 2 Patient Symptoms at the First Visit

	Prescription Strategy			Total (N = 436), n (%)
	IAP (n = 148), n (%)	DAP (n = 146), n (%)	NAP (n = 142), n (%)	
Moderate symptoms (3 or 4)[a]	120 (81.1)	115 (78.8)	117 (82.4)	352 (80.7)
Severe symptoms (5 or 6)[a]	71 (48.0)	70 (48.0)	75 (52.8)	216 (49.5)
Common symptoms[b]				
Everyday routine disruptions	128 (96.2)	126 (98.4)	125 (98.4)	379 (97.7)
Irritability	100 (91.7)	98 (92.5)	97 (91.5)	295 (91.9)
Pharyngitis symptoms				
Fever	41 (89.1)	45 (100.0)	42 (97.7)	128 (95.5)
Headache	33 (86.8)	29 (96.7)	23 (74.2)	85 (85.9)
Sore throat	46 (95.8)	47 (97.9)	47 (100.0)	140 (97.9)
Difficulty swallowing	43 (91.5)	43 (93.5)	43 (95.6)	129 (93.5)
Acute otitis media symptoms				
Earache	76 (100.0)	70 (97.2)	71 (100.0)	217 (99.1)
Rhinosinusitis and acute bronchitis symptoms				
Breathlessness	16 (80.0)	16 (88.9)	14 (77.8)	46 (82.1)
Chest noises breathing	15 (93.8)	10 (83.3)	14 (93.3)	39 (90.7)
Pharyngitis and acute bronchitis symptoms				
Cough	38 (74.5)	35 (79.6)	31 (75.6)	104 (76.5)
Rhinosinusitis, pharyngitis, and acute bronchitis symptoms				
Discomfort and/or general pain	68 (98.6)	69 (100.0)	66 (100.0)	203 (99.5)
Nasal mucus	46 (82.1)	51 (89.5)	46 (86.8)	143 (86.1)
Difficulty sleeping	45 (90.0)	47 (87.0)	42 (87.5)	134 (88.2)

Statistical significance was calculated per symptom by using Pearson's χ^2 test.

[a] Symptoms are scored on a Likert scale from 0 (no problems) to 6 (as bad as it could be).

[b] Symptoms common to the 4 studied pathologies.

felt much worse. Parents were told to consider returning to the doctor if they felt it was necessary or if the child felt worse even after taking the antibiotic.

For children allocated to NAP, pediatricians did not prescribe antibiotics. For children allocated to IAP, pediatricians prescribed antibiotics to be taken from the day of the consultation. In both strategies, pediatricians recommended that parents consider returning to the doctor if (1) the child did not start to feel better after 4, 7, 15, or 20 days from symptom onset for acute otitis media, pharyngitis, rhinosinusitis, or acute bronchitis, respectively; (2) the child had a temperature of ≥39°C after 24 hours or a temperature of ≥38°C but <39°C after 48 hours; or (3) the child felt much worse, their condition worsened, or the parent(s) deemed it necessary.

All parents were informed that it was normal for a child to feel slightly worse in the first days after the visit. Each pediatrician decided the antibiotic type to be prescribed for both the DAP and IAP strategies.

Outcomes

Primary efficacy outcomes were severity and duration of acute uncomplicated RTI symptoms over 30 days. Symptom severity was scored by parents on a 7-point Likert scale (0 = no problem to 6 = as bad as it could be). Scoring was as follows: 0 = absence of symptoms, 1 to 2 = mild symptoms, 3 to 4 = moderate symptoms, and 5 to 6 = severe symptoms. Symptom duration was calculated to the point when symptoms disappeared.

Secondary efficacy outcomes were antibiotic use over 30 days, parental satisfaction and beliefs regarding antibiotic efficacy, and additional unscheduled visits to primary care over 30 days. Parental satisfaction was scored according to a 6-point Likert scale ("extremely satisfied" to "not at all satisfied"). Both the severity and satisfaction scales have been previously validated[14,25] and used in other studies.[13,14] Beliefs on antibiotic efficacy were evaluated with a 6-point Likert scale ("extremely effective" to "not at all effective").[13,26] Infection-related complications were recorded for the first 30 days (pneumonia, abscesses, cellulitis, visits to the hospital emergency department, and hospital admissions).

Procedures

Previously trained pediatricians informed parents in a structured manner regarding the condition's natural course, self-limiting processes, adverse effects, and marginal benefits of antibiotics. Included children ≥12 years of age and all parents signed an informed consent form. Eligible children were randomly assigned into the different arms, and parents were given the corresponding DAP, NAP, or IAP recommendations. In the baseline

TABLE 3 Duration in Days of Patient Symptoms After the First Visit

	Prescription Strategy					Total (N = 436)	
	IAP (n = 148)	DAP (n = 146)		NAP (n = 142)			
	Mean (SD)	Mean (SD)	P[a]	Mean (SD)	P[a]	Mean (SD)	Overall P
Any symptom to disappearance	8.3 (7.8)	8.3 (7.7)	.968	7.9 (9.3)	.593	8.1 (8.2)	.888
Moderate symptoms (3 or 4)[b]	10.2 (7.5)	11.7 (8.7)	.257	10.0 (8.4)	.869	10.7 (8.2)	.435
Severe symptoms (5 or 6)[b]	10.1 (6.3)	12.4 (8.4)	.247	10.9 (8.5)	.682	11.3 (7.9)	.539
Common symptoms[c]							
Everyday routine disruptions	4.2 (3.8)	4.5 (4.0)	.848	4.8 (5.1)	.488	4.6 (4.4)	.837
Irritability	4.6 (4.3)	4.7 (4.1)	.767	4.9 (5.6)	.794	4.9 (4.7)	.965
Pharyngitis symptoms							
Fever	3.6 (2.2)	4.0 (5.2)	.534	4.2 (5.3)	.400	3.9 (4.5)	.824
Headache	5.8 (8.7)	5.5 (7.0)	.867	3.3 (3.0)[d,e]	.052	5.1 (7.0)	.080
Sore throat	5.2 (4.7)	5.0 (4.1)	.824	5.5 (6.2)	.741	5.2 (5.0)	.907
Difficulty swallowing	4.9 (4.8)	4.7 (3.8)	.812	5.0 (5.2)	.952	4.9 (4.6)	.970
Acute otitis media symptoms							
Earache	5.1 (5.3)	4.4 (3.9)	.239	5.2 (6.3)	.893	4.9 (5.2)	.567
Rhinosinusitis and acute bronchitis symptoms							
Breathlessness	7.5 (6.5)	10.2 (9.8)	.321	11.6 (11.1)	.169	9.7 (9.3)	.175
Chest noises breathing	6.2 (4.1)	5.3 (5.2)	.694	10.6 (16.0)[e]	.111	7.6 (10.5)	.101
Pharyngitis and acute bronchitis symptoms							
Cough	7.9 (4.4)	9.5 (7.1)	.295	8.0 (6.6)	.948	8.5 (6.0)	.527
Rhinosinusitis, pharyngitis, and acute bronchitis symptoms							
Discomfort and/or general pain	7.9 (8.2)	6.6 (6.7)	.222	5.6 (5.2)[d]	.023	6.7 (6.8)	.022
Nasal mucus	10.3 (9.0)	10.5 (8.9)	.811	8.3 (7.5)	.260	9.6 (8.5)	.444
Difficulty sleeping	5.8 (7.4)	5.2 (5.2)	.546	5.5 (5.6)	.745	5.5 (6.1)	.890

Only patients who had symptoms for 1 d or more were included. Statistical significance was calculated by adjusting a negative binomial regression model per symptom, with the number of days with the symptom as the dependent variable and prescription strategy and antibiotic use as independent variables.

[a] IAP is the reference category.

[b] Symptoms are scored on a Likert scale from 0 (no problems) to 6 (as bad as it could be).

[c] Symptoms common to the 4 studied pathologies.

[d] $P < .05$ compared to IAP.

[e] $P < .10$ compared to DAP.

visit, pediatricians collected data on the children's health status using a visual analog scale scored from 0 to 100 (0 = worst and 100 = best) and on the severity of their symptoms.

The coordinating center followed-up children by telephoning parents on days 2 and 30 after inclusion, as well as on days 7, 15, and 22 if parents indicated in the previous call that symptoms continued. Data collected in the telephone follow-up were health status, severity and duration of symptoms, use of antibiotics and nonantibiotic medication, and in addition, additional visits to primary care, adverse events, and complications, crosschecked against medical records. Parental satisfaction and belief data were collected only on day 30.

Statistical Analysis

The calculated sample size was 450 children (150 per arm), considering a mean (SD) duration of untreated acute uncomplicated RTI of 12 days.[14] A 2-day reduction in duration was considered a clinically relevant outcome adopting a bilateral approach. The sample size of 450 children was calculated to identify this difference with a type I error of 5% (α = .05) and power of 80% (β = .2). GRANMO sample size calculator software was used.[27] Although the parents and children could interrupt medication at any point in the study, they were still included in follow-up.

Population characteristics were described by using frequencies and percentages for categorical variables and means and SD for quantitative variables. Pearson's χ^2 test was used to compare patient symptoms at the first visit (frequencies and percentages) for the 3 arms. Symptom duration and symptom severity after the first visit were described by using means (SD) and medians and interquartile range (IQR), respectively. For the 3 arms, for each symptom after the first visit, negative binomial regression was used to compare symptom duration, and logistic regression was used to compare symptom severity. Both regression models were adjusted for prescription strategy and informed antibiotic use, and only children with symptoms lasting a day or more were included. Pearson's χ^2 test was used to compare secondary outcomes (frequencies and percentages) for the 3 arms, considering IAP as the reference category. All analyses were guided

TABLE 4 Severity Scores for Patient Symptoms After the First Visit

	Prescription Strategy			Total	
	IAP, median (IQR)	DAP, median (IQR)	NAP, median (IQR)	Total, median (IQR)	Overall *P*
Maximum severity of any symptom[a]	3 (2–4)	3 (2–4)	3 (2–4)	3 (2–4)	.619
Common symptoms[b]					
Everyday routine disruptions	2 (1–3)	2 (2–3)	2 (2–3)	2 (2–3)	.740
Irritability	2 (1–3)	2 (2–3)	2 (1–3)	2 (2–3)	.556
Pharyngitis symptoms					
Fever	2 (1–3)	2 (2–3)	3 (2–4)[c,d]	2 (2–3)	.090
Headache	2 (1–4)	3 (2–3)	3 (3–4)	3 (2–4)	.926
Sore throat	3 (2–3)	3 (2–5)[c]	3 (2–4)	3 (2–4)	.044
Difficulty swallowing	2 (2–3)	3 (2–4)	2 (2–4)	3 (2–4)	.141
Acute otitis media symptoms					
Earache	2 (1–3)	2 (1–3)	2 (2–3)	2 (1–3)	.543
Rhinosinusitis and acute bronchitis symptoms					
Breathlessness	3 (2–3)	3 (2–3)	2 (2–3)	3 (2–3)	.822
Chest noises on breathing	2 (1–2)	2 (2–3)	2 (2–3)	2 (1–2)	.113
Pharyngitis and acute bronchitis symptoms					
Cough	2 (2–3)	3 (2–3)[c]	2 (1–3)	2 (2–3)	.097
Rhinosinusitis, pharyngitis, and acute bronchitis					
Discomfort and/or general pain	2 (1–3)	2 (2–3)	3 (2–3)[c]	2 (2–3)	.145
Nasal mucus	2 (1–3)	2 (2–3)	3 (2–3)	3 (2–3)	.682
Difficulty sleeping	2 (1–3)	2 (2–3)	2 (2–4)	2 (2–3)	.769

The medians and IQRs for symptom severity were calculated for symptoms lasting >1 consecutive day during the 30-d follow-up. Statistical significance was calculated by adjusting an ordered logistic regression model per symptom, with severity as the dependent variable and prescription strategy and antibiotic use as independent variables.

[a] Symptoms are scored on a Likert scale from 0 (no problems) to 6 (as bad as it could be).

[b] Symptoms common to the 4 studied pathologies.

[c] $P < .05$ compared to IAP.

[d] $P < .10$ compared to DAP.

by an intention-to-treat approach (children randomly allocated to each prescription strategy were included). Children who were lost to follow-up were assigned the average duration and severity of symptoms of the other children included in the same strategy. Significance was set to 5% ($\alpha = .05$). All statistical analyses were performed by using Stata software version 13.1 (Stata Corp, College Station, TX).

RESULTS

Trial Population

A total of 436 children, with mean (SD) age 6.3 (3.0) years, were included in the study and the analysis (Fig 1), 226 (51.8%) of whom were girls; 224 (51.4%) had acute otitis media, 146 (33.5%) had pharyngitis, 40 (9.2%) had acute bronchitis, and 26 (6.0%) had rhinosinusitis. Fever and discomfort and/or general pain were the most frequent symptoms for all 4 conditions and were also the severest symptoms at the first visit (mean scores of 3.8 and 3.0, respectively, on the 7-point Likert scale [0–6]). At the first visit, mean (SD) duration of symptoms was reported as 2.5 (4.2) days, whereas mean (SD) health status was scored as 65 (18) (0–100). Most children (n = 395 [90.6%]) had no respiratory comorbidity. One or both parents of 173 (39.7%) children were smokers, and the parents of 227 (52.1%) children had finished tertiary education. Parents mainly indicated that they were moderately worried (n = 213 [48.9%]) or a little worried (n = 145 [33.3%]) at the first visit (Table 1). Symptoms at the first visit were similar for the 3 arms (Table 2).

Primary Outcomes

Duration in days of any symptom until disappearance was similar for the 3 arms. Mean (SD) duration in days of any symptom until disappearance was DAP 8.3 (7.7) versus IAP 8.3 (7.8) (P = .968) and NAP 7.9 (9.3) versus IAP 8.3 (7.8) (P = .593) ($P_{overall}$ = 0.888). Mean (SD) duration in days of severe symptoms was DAP 12.4 (8.4) versus IAP 10.1 (6.3) (P = .247) and NAP 10.9 (8.5) versus IAP 10.1 (6.3) (P = .682) ($P_{overall}$ = 0.539). Mean (SD) duration in days of moderate symptoms was DAP 11.7 (8.7) versus IAP 10.2 (7.5) (P = .257) and NAP 10.0 (8.4) versus IAP 10.2 (7.5) (P = .869) ($P_{overall}$ = 0.435). Regarding the symptoms common to all 4 conditions, namely, everyday routine disruptions and irritability, mean (SD) duration was similar for the 3 arms (P = .837 and P = .965, respectively) (Table 3).

The greatest severity for any symptom on the 7-point Likert scale was similar for the 3 arms, for a median (IQR) score of 3 (2–4). Severity of both common symptoms and specific symptoms was broadly similar for all 3 arms, with significant differences only between DAP and IAP in 2 of 13 symptoms (sore throat and cough), between IAP and NAP in 2 of 13 symptoms (fever and

TABLE 5 Secondary Outcomes

	Prescription Strategy					Total	
	IAP	DAP		NAP			
	n = 148	*n* = 146	*P*[a]	*n* = 142	*P*[a]	*N* = 436	Overall *P*
Antibiotic used	142 (96.0)	37 (25.3)	<.001	17 (12.0)	<.001	196 (45.0)	<.001
Antibiotic duration, d, mean (SD)	7.9 (2.0)	8.4 (2.3)	.181	7.5 (2.7)	.613	7.9 (2.1)	.316
Type of antibiotic			.475		.092		.108
Amoxicillin	106 (74.7)	30 (81.1)		9 (52.9)		145 (74.0)	
Azithromycin	11 (7.8)	2 (5.4)		2 (11.8)		15 (7.7)	
Amoxicillin-clavulanate	9 (6.3)	4 (10.8)		1 (5.9)		14 (7.1)	
Phenoxymethylpenicillin (penicillin V)	7 (4.9)	1 (2.7)		1 (5.9)		9 (4.6)	
Other[b]	9 (6.3)	0 (0.0)		4 (23.5)		13 (6.6)	
Nonantibiotic medication	108 (73.0)	136 (93.2)	<.001	136 (95.8)	<.001	380 (87.2)	<.001
Unscheduled primary care visits	16 (10.8)	15 (10.3)	.881	17 (12.0)	.756	48 (11.0)	.895
Health status score, mean (SD)[c]	97 (8)	97 (8)	.555	97 (9)	.929	97 (8)	.762
Gastrointestinal adverse effects	13 (8.8)	5 (3.4)	.064	4 (2.8)	.040	22 (5.1)	.037
Complications	2 (1.4)	1 (0.7)	.577	2 (1.4)	.967	5 (1.2)	.813
Parental satisfaction			.352		.373		.389
Not at all or slightly satisfied	2 (1.4)	1 (0.7)		0 (0.0)		3 (0.7)	
Little or moderately satisfied	10 (7.0)	5 (3.6)		10 (7.2)		25 (5.9)	
Very or extremely satisfied	130 (91.2)	135 (95.7)		129 (92.8)		394 (93.4)	
Belief in antibiotic effectiveness			<.001		<.001		<.001
Not at all or slightly effective	3 (2.3)	8 (8.9)		9 (11.4)		20 (6.7)	
Little or moderately effective	21 (16.1)	44 (48.9)		47 (59.5)		112 (37.4)	
Very or extremely effective	106 (81.6)	38 (42.2)		23 (29.1)		167 (55.9)	

Data are reported as frequencies and percentages except where otherwise indicated.

[a] IAP is the reference category.

[b] Antibiotics prescribed to <5 patients: cefuroxime, benzathine benzylpenicillin (benzathine penicillin G), and combinations (amoxicillin with cefuroxime, amoxicillin with phenoxymethylpenicillin [penicillin V]).

[c] Scored on a visual analog scale from 0 (worst health status) to 100 (best health status).

discomfort and/or general pain), and between DAP and NAP in 1 of 13 symptoms (fever) (Table 4).

Secondary Outcomes

Antibiotics were taken in the IAP arm by 142 (96.0%) children compared with 17 (12.0%) children in the NAP arm ($P < .001$) and 37 (25.3%) children in the DAP arm ($P < .001$). Of the 17 children in the NAP arm who took antibiotics, only 7 of these attended an unscheduled visit to primary care, and the mean duration between randomization and antibiotic prescription was 2 days. There were no significant differences in antibiotic treatment duration ($P = .316$) nor in the type of antibiotic ($P = .108$) for the 3 arms. Nonantibiotic medication use was similar for DAP ($n = 136$ [93.2%]) and NAP ($n = 136$ [95.8%]) and higher than for IAP ($n = 108$ [73.0%]) ($P < .001$). Belief that antibiotics were very or extremely effective was higher for parents of children in the IAP arm than in the other arms (IAP $n = 106$ [81.6%] versus DAP $n = 38$ [42.2%] versus NAP $n = 23$ [29.1%]; $P < .001$). Gastrointestinal adverse effects were lower in the DAP and NAP arms compared to the IAP arm ($P = .037$). There were no differences between arms in complications ($P = .813$) or unscheduled visits to primary care ($P = .895$), and satisfaction was similarly high for the 3 arms ($P = .389$). There were 5 complications: perforated eardrum and hospitalization due to dehydration (1 child each) and 3 unscheduled visits to the hospital (Table 5).

DISCUSSION

We report findings for DAP compared to IAP and NAP strategies for children with uncomplicated RTIs as explored in this trial of DAP in children. To our knowledge, this is the largest such study conducted to date. Moderate and severe symptom durations for DAP were slightly greater than for IAP and NAP, although differences were not statistically significant. The greatest severity for any symptom was similar for the 3 arms. Antibiotic use was significantly lower in the DAP and NAP arms than in the IAP arm, and nonantibiotic medication was significantly higher in the DAP and NAP arms. Complications, unscheduled visits to primary care, and emergency hospital visits were similar for all 3 strategies, and likewise, satisfaction was high for all 3 strategies. The IAP arm experienced more gastrointestinal adverse effects than the DAP and NAP arms.

Our findings coincide for the most part with the findings of the 2017 Cochrane review[18] on DAP for RTIs, which reported similar symptom durations and no difference in complications for the 3 strategies and lower antibiotic use for DAP and NAP strategies. However, low use of antibiotics observed in clinical trials should be viewed with caution

because the study participants receive structured advice and so are more motivated.[28] In terms of satisfaction, this was high and similar for the 3 arms in our study, contrasting with the Cochrane review,[18] which reported higher satisfaction for IAP than for DAP and NAP. In our study, we found a significant reduction in gastrointestinal adverse events for DAP and NAP compared to IAP, corroborating previous studies in which authors have evaluated DAP for RTIs in children.[19,20]

Our findings are broadly similar to those of a previous trial in an adult population in Spain conducted by our group.[26] In that study, moderate and severe symptom durations were higher for DAP than for IAP but lower than for NAP, whereas in our study in children, symptom duration was slightly greater for DAP than for either IAP or NAP. As for antibiotic use, findings for DAP in children were more favorable than in adults: 32.6% of adults compared with 25.3% of children allocated to DAP took antibiotics. The lower use of antibiotics in our pediatrics study compared to our adult study may be related to 2 factors: greater concern of parents about the adverse effects of antibiotics and more medical consultations for milder episodes. Parents have been reported to be cautious about using antibiotics for RTIs in children on the basis of concerns about adverse effects[29] and past experiences,[30] whereas adults tended not to recall serious consequences of antibiotic treatment.[30] As for medical consultations, parents visited the doctor on behalf of children 3.5 days sooner than adults, and milder episodes led to a higher proportion of doctor visits on behalf of children (the median value of the highest severity score [any symptom] was 2 points lower for children than for adults). The reasons for an earlier medical visit may be fears of the condition worsening or major complications in children or differences in perceptions of the antibiotic risk/benefit equation.[30]

Our findings need to be considered in relation to some limitations. A first main limitation was the open-label design of the study, with outcomes reported by children.[31] However, to reduce the possible placebo effect caused by the open-label nature of the study, all the children received structured information about respiratory diseases and the use of nonantibiotic medication. The second limitation was related to the inferred results for acute bronchitis and rhinosinusitis, as 85% of the included children had acute media otitis or pharyngitis. Nevertheless, strengths of the study are its pragmatic design and the fact that it is the largest ever conducted on DAP for children in southern Europe, in a country with a high rate of antibiotic use.

DAP is an efficacious and safe strategy for reducing inappropriate antibiotic treatment of uncomplicated RTIs in children when the doctor has reasonable doubts regarding the indication. DAP is therefore a useful tool for addressing the public health issue of bacterial resistance.[10] However, NAP remains the recommended strategy when it is clear that antibiotics are not indicated like in most cases of acute bronchitis.[32]

We suggest that the results of this study will enable recommendations to be made for DAP for specific RTIs in children given that as yet there are no guidelines that draw distinctions according to age groups.[33] There is a need, however, for further studies in which authors explore patient profiles for which DAP would be not appropriate, as well as studies in which authors assess DAP-related educational interventions for physicians and parents and children with acute uncomplicated RTIs.[34]

CONCLUSIONS

In this randomized clinical trial of antibiotic treatment strategies for acute, uncomplicated RTIs in children, there was no statistically significant difference in symptom duration or severity who received DAP compared to NAP and IAP strategies. DAP compared to IAP led to greatly reduced antibiotic use and fewer gastrointestinal adverse effects associated with antibiotic intake.

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ABBREVIATIONS

DAP: delayed antibiotic prescription
IAP: immediate antibiotic prescription
IQR: interquartile range
NAP: no antibiotic prescription
RTI: respiratory tract infection

Dr Alonso-Coello conceptualized and designed the study, contributed to drafting of the manuscript, obtained funding, made administrative, technical, and material support, conducted study supervision and had full access to all the data in the study, and assumed responsibility for the integrity of the data and the accuracy of the data analysis; Ms Mas-Dalmau conceptualized and designed the study, contributed to drafting of the manuscript, made administrative, technical, and material support, and conducted study supervision; Drs Villanueva López and Gorrotxategi Gorrotxategi conceptualized and designed the study, conducted the acquisition and interpretation of data, and critically reviewed the manuscript for important intellectual content; Ms Argüelles Prendes, Mr Espinazo Ramos, Ms Valls Duran, Ms Gonzalo Alonso, Dr Cortés Viana, Ms Menéndez Bada, Dr Vázquez Fernández, and Ms Pérez Hernández conducted the acquisition and interpretation of data and critically reviewed the manuscript for important intellectual content; Dr de la Poza Abad conceptualized and designed the study, obtained funding, conducted the interpretation of data, and critically reviewed the manuscript for important intellectual content; Ms Muñoz Ortiz conducted the statistical analysis and critically reviewed the manuscript for important intellectual content; Dr Little conceptualized and designed the study and critically reviewed the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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5.2. ESTUDI 2. ANÀLISI COST-EFECTIVITAT SOBRE LA PRESCRIPCIÓ ANTIBIÒTICA DIFERIDA EN COMPARACIÓ AMB LA PRESCRIPCIÓ IMMEDIATA I LA NO PRESCRIPCIÓ EN NENS AMB INFECCIONS RESPIRATÒRIES

5.2.1. RESUM DELS RESULTATS DE L'ESTUDI 2

Un total de 422 pacients pediàtrics van ser inclosos en l'anàlisi.

Cost-efectivitat

Els costos totals en euros van ser 109.68 per la PIA, 100.90 per la PDA i 97.48 per la NPA. L'efectivitat en QALDs va ser 27.94 per a la PDA, 27. 88 per a la PIA i 27.82 per a la NPA. La PDA va ser l'estratègia més cost-efectiva en general. La PIA va ser més costosa i similar en efectivitat a la PDA, sent així l'estratègia dominada. La NPA va ser menys costosa i efectiva que la PDA per 0.12 QALDs. L'ICER comparant la PDA amb la NPA va ser de 28.84 euros per QALD guanyat. Els resultats del BNM van confirmar que la PDA hauria de ser l'estratègia preferida, tot i que la diferència entre PDA i NPA va ser molt petita (6.33 euros).

Anàlisi de sensibilitat determinista

El cost del temps perdut en el treball i, en segon lloc, el cost de les visites a l'AP van ser les variables amb major impacte en l'ICER. Un augment en el temps perdut en el treball per part dels pares va augmentar el valor d'ICER, mentre que qualsevol augment en les visites a l'AP va reduir el valor d'ICER. Això s'explica pel fet que el temps perdut a la feina va afectar a la PDA més que en la NPA, mentre que les visites a l'AP van afectar a la NPA més que a la PDA.

Anàlisi probabilística de sensibilitat

La PDA és més efectiva i més costosa que la NPA, com ho indica el 79.10% de les iteracions al quadrant I; però, el fet que l'ICER estigui per sota del valor disposat a pagar (82.2 euros) per al 61.34% de les iteracions al quadrant I indica que la PDA és l'estratègia socialment elegible. A més, la PDA podria ser una opció dominant en el 20.77% de les iteracions (representades en el quadrant IV).

Quan augmenta el valor de la disposició a pagar, la PDA es torna més elegible; és a dir, la probabilitat d'iteracions rendibles augmenta per a l'estratègia PDA. Per un valor de disposició a

pagar de 82.2 euros, la PDA en comparació amb la NPA representa al voltant del 81.75% de les iteracions de rendibilitat. Per a qualsevol valor disposat a pagar, la PIA està dominada per una o ambdues de les altres alternatives.

5.2.2. PUBLICACIÓ DE L'ESTUDI 2

Mas-Dalmau G, Pérez Lacasta MJ, Alonso-Coello P, Gorrotxategi Gorrotxategi P, Argüelles Prendes E, Espinazo Ramos O, Valls Duran T, Gonzalo Alonso ME, Cortés Viana MP, Menéndez Bada T, Vázquez Fernández ME, Pérez Hernández AI, Muñoz Ortiz L, Villanueva López C, Little P, de la Poza Abad M, Carles Lavila M; DAP PEDIATRICS GROUP. A trial-based cost-effectiveness analysis of antibiotic prescription strategies for non-complicated respiratory tract infections in children. BMC Pediatrics. 2023. Doi: 10.1186/s12887-023-04235-3. In press Journal Impact Factor (2022): 2.4

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A trial-based cost-effectiveness analysis of antibiotic prescription strategies for non-complicated respiratory tract infections in children

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Abstract

Background Antibiotic prescription for respiratory tract infections (RTIs) in children attending primary care centres is almost double that predicted according to bacterial prevalence. Delayed antibiotic prescription (DAP) is designed to deploy a more rational use of antibiotics. While studies have evaluated DAP efficacy and safety for children with RTIs, little research has been conducted on the economic implications.

Methods Our trial compared cost-effectiveness for DAP, immediate antibiotic prescription (IAP), and no antibiotic prescription (NAP) for children aged 2–14 years with acute uncomplicated RTIs attended to in 39 primary care centres in Spain. The main outcome was the incremental cost-effectiveness ratio (ICER), measured in euros per gained quality-adjusted life days (QALDs). Net monetary benefit (NMB) was also calculated as a tool for decision making. The analysis was performed from a societal perspective for a time horizon of 30 days, and included healthcare direct costs, non-healthcare direct and indirect costs, and the antimicrobial resistance (AMR) cost.

Results DAP was the most cost-effective strategy, even when the cost of AMR was included. QALD values for the three strategies were very similar. IAP compared to DAP was more costly (109.68 vs 100.90 euros) and similarly effective (27.88 vs 27.94 QALDs). DAP compared to NAP was more costly (100.90 vs 97.48 euros) and more effective (27.94 vs. 27.82 QALDs). The ICER for DAP compared to NAP was 28.84 euros per QALD. The deterministic sensitivity analysis indicated that non-healthcare indirect costs had the greatest impact on the ICER. The cost-effectiveness acceptability curve showed that DAP was the preferred option in approximately 81.75% of Monte Carlo iterations, assuming a willingness-to-pay value of 82.2 euros per gained QALD.

AQ1 AQ2 AQ3 AQ4

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Conclusions When clinicians are in doubt about whether an antibiotic is needed for children with RTIs attending PC centres, those treated with the DAP strategy will have slightly better efficiency outcomes than those treated with IAP because its costs are lower than those of IAP. DAP is also the most cost-effective strategy over a time horizon of 30 days if AMR is considered, despite higher short-term costs than NAP. However, if in the long term the costs of AMR are larger than estimated, NAP could also be an alternative strategy.

Trial registration This trial has been registered at www.clinicaltrials.gov (identifier NCT01800747; Date: 28/02/2013 (retrospectively registered).

Keywords Cost effectiveness, Delayed antibiotic prescription, Respiratory tract infections, Primary care, Paediatrics

Background

One of the most frequent reasons for antibiotic prescription to children in primary care (PC) is a respiratory tract infection (RTI), [1] representing a significant economic burden for the health system [2]. The rate of outpatient antibiotic prescription for RTIs in children is high, [3–5] at almost double the rate predicted according to bacterial prevalence [3]. Most RTIs have a viral aetiology and are self-limiting, but antibiotics are indicated if a bacterial infection is suspected. Antibiotic prescription is typically associated with cases of diagnostic uncertainty [6–8] but is also the outcome of other factors, such as patient pressure for antibiotic prescription [9, 10]. Antibiotic prescription increases belief in efficacy and the demand for new consultations, [11, 12] although antibiotics are the most frequent cause of adverse effects in children, e.g., gastrointestinal and skin problems [6–8, 13].

Over the long term, overuse of antibiotics is associated with bacterial resistance, [14] and reducing this resistance is a major global public health challenge [15]. According to the European Centre for Disease Prevention and Control (ECDPC), antimicrobial resistance (AMR) is responsible for approximately 33 110 deaths and 874 541 disability-adjusted life-years in the European Union/European Economic Area (EU/EEA) [16]. While this impact is recognized, relatively few countries have specific actions in place to reduce antibiotic intake.

Delayed antibiotic prescription (DAP) for RTIs, a strategy designed to foster more rational use of antibiotics, is recommended by clinical practice guidelines when there is uncertainty regarding immediate antibiotic prescription (IAP) [17, 18]. DAP is defined as a prescription issued for an antibiotic to be taken only if the condition has not improved or has worsened some days after the visit. A recent individual-patient-data meta-analysis comparing DAP, IAP, and no antibiotic prescription (NAP) reported that RTI symptom severity was similar for DAP and IAP, symptom duration was around the same for DAP and NAP and slightly shorter for IAP, re-consultations and complication rates were lower for DAP versus NAP, and patient satisfaction was higher for DAP [19].

While several randomized clinical trials (RCTs) have evaluated the efficacy and safety of DAP in children with RTIs, [19] there is a lack of cost-effectiveness studies evaluating antibiotic prescription strategies [20–23] in paediatric populations. Studies that do exist have focused on otitis media and have been carried out in the USA [20, 21, 23] and Canada [22]. Those studies have one important limitation: the cost of AMR was not taken into account [20–23].

Although IAP, the current form of treatment, is slightly more effective than DAP, according to a recent meta-analysis [19], previous economic analyses also conclude that DAP is the least costly strategy [20, 21], because it implies less antibiotic consumption, and fewer adverse effects. Therefore, DAP will likely be more cost-effective than IAP. The differences between DAP and NAP, however, are not easy to determine, since the results may depend on the complications derived from the non-use of antibiotics, and/or on the adverse effects derived from antibiotic use. Finally, it should be noted that the impact of DAP in reducing AMR cannot be appreciated over the short term. For children with RTIs, therefore, our aim was to analyse the overall cost-effectiveness of the DAP, IAP, and NAP strategies, including, in addition, an estimate of the AMR cost. This study was conducted in the context of a RCT [24].

Methods

Design

Trial-based cost-effectiveness analysis.

Randomized clinical trial

The RCT [24] compared three antibiotic treatment strategies (DAP, IAP, and NAP), deployed in children with acute uncomplicated RTIs. Recruitment took place between June 2012 and June 2016 in 39 centres in Spain. Participants were children aged 2–14 years who attended with one of the following conditions: pharyngitis, rhinosinusitis, acute bronchitis, or acute otitis media. Children were included if paediatricians had a reasonable

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doubt about the need to prescribe an antibiotic. Children with pharyngitis were excluded when paediatricians had access to rapid streptococcal testing.

Prescription strategies were as follows:

Immediate antibiotic prescription: an antibiotic was prescribed to be started immediately on the day of the visit.

Delayed antibiotic prescription: an antibiotic was prescribed, but not to be started immediately; rather, parents were given structured recommendations about when to administer the antibiotic and when to consider returning to the paediatrician.

No antibiotic prescription: no antibiotic was prescribed, but parents were given structured recommendations about when to consider returning to the paediatrician.

For both the DAP and IAP strategies, each paediatrician decided the type of antibiotic to prescribe.

Primary outcomes were symptom duration and symptom severity. Symptom duration was measured as days until symptoms disappeared. Symptom severity was collected by parents using a 7-point Likert scale (0=absence of symptoms, 1–2=mild symptoms, 3–4=moderate symptoms, and 5–6=severe symptoms). Secondary outcomes were antibiotic use, additional visits, complications at 30 days, and beliefs and satisfaction of the parents.

Data were collected by paediatricians at the initial visit. Follow-up data were collected by telephone on days 2 and 30 after inclusion, and additionally, on days 7,15 and 22 when parents stated in the previous telephone call that symptoms persisted.

Cost-effectiveness decision model

A decision tree (Fig. 1) was created to compare the three strategies for a time frame of 30 days. A societal perspective was adopted that included healthcare direct costs, and non-healthcare direct and indirect costs. The three antibiotic strategies were deployed starting with a baseline visit (V0) in which, as the initial treatment, antibiotics were prescribed for the IAP and DAP arms, and no antibiotics were prescribed for the NAP arm. Two outcomes resulted following V0: (1) symptoms resolved; or (2) symptoms persisted. The response to those outcomes then depended on the original strategy assigned to each patient.

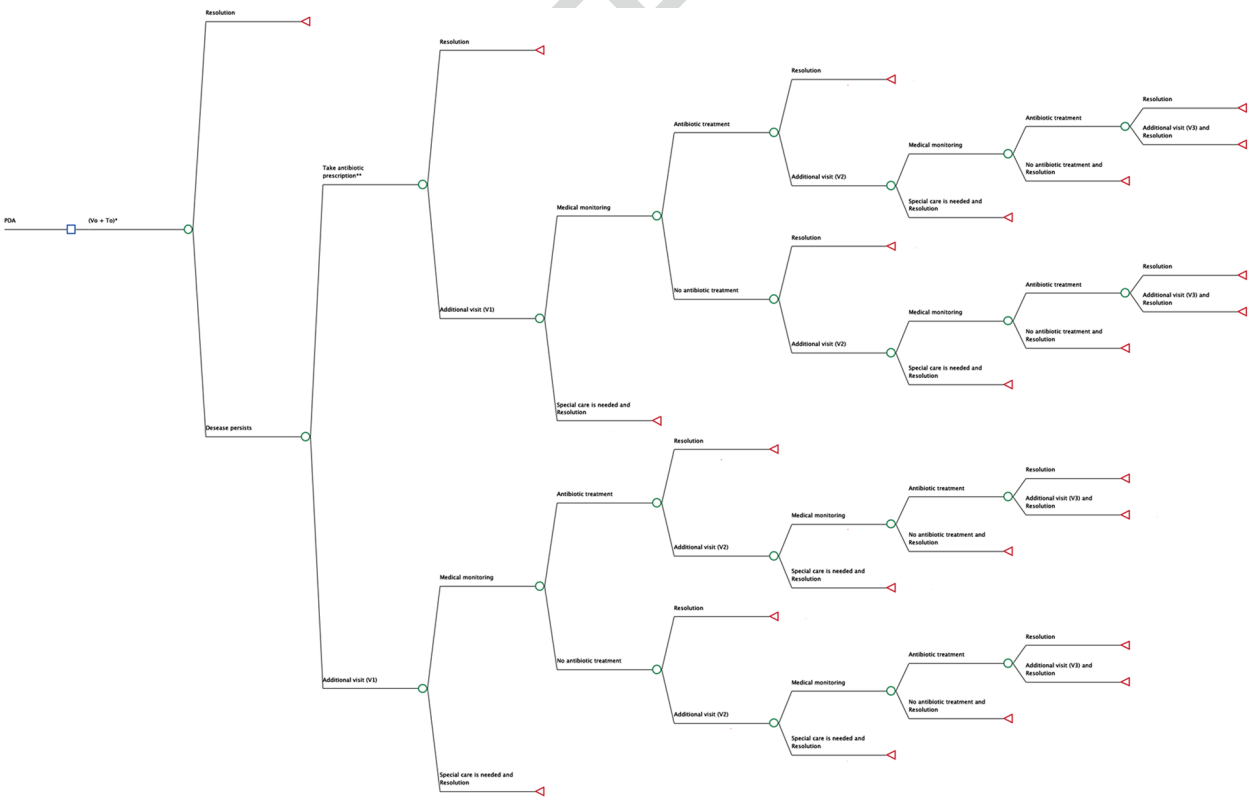

Fig. 1 Decision tree. *V0 represents the baseline visit for the three strategies, each of which has a different initial treatment value (T0). DAP: delayed antibiotic prescription; IAP: antibiotic treatment; and NAP: no antibiotic. **If symptoms persist, the DAP alternatives are antibiotic prescription or a first additional primary care visit (V1). The only alternative for NAP and IAP is V1

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IAP and NAP

If symptoms persisted, the patient returned to the PC centre (V1). Two possible outcomes resulted following V1: (1) antibiotic treatment, either continuation (with the same or a different antibiotic) for the IAP arm, or prescription of an antibiotic to be started immediately for the NAP arm, or further waiting while continuing with the previous treatment; or (2) diagnosis and treatment of possible complications, specifically, pneumonia, abscesses, cellulitis, emergency department (ED) visits, and hospital admissions. The same procedure was applied to successive visits.

DAP If symptoms failed to resolve after V0, parents could decide to either administer the prescribed antibiotic or return to the PC centre (V1). Following V1, the procedure was the same as for the IAP and NAP strategies.

The observed cases for each subtree and for each strategy, as represented in the decision tree (Fig. 1), were extracted from the RCT and are reported in Table 1.

Resource use and costs

Total costs, in euros for the year 2022, were calculated using a bottom-up costing approach (Table 2). Measurement data were collected during the RCT.

Healthcare direct costs

Costed were PC visits and ED visits, antibiotic and non-antibiotic medication use during the 30-day follow-up, doctor time (to explain recommendations for the assigned antibiotic strategy), and additional visits and drugs for adverse effects and complications (ED visits and hospital admissions). ED visits were evaluated by level of urgency as either non-urgent or a minor emergency. PC and ED visits were costed using data sourced from the Department of Health (Generalitat de Catalunya) [26]. Antibiotic and non-antibiotic medication costs were based on Spanish official prices. Considered were several classes of drugs currently in use: amoxicillin, amoxicillin-clavulanate, phenoxymethylpenicillin, and cefuroxime as antibiotics, and paracetamol and ibuprofen as non-antibiotic medication. Antibiotic and non-antibiotic medication costs were calculated from the number of packages needed to dose a 6-year-old child (the mean age of the included children). Doctor time to explain DAP and NAP strategy recommendations was calculated as equivalent to an additional 10% of the standard consultation time (i.e., 1 min per mean 10-min visit). No doctor time was counted for IAP as this strategy was considered the usual option.

In relation to adverse effects, we assumed that a rate of 10% in children treated with antibiotics, similar to

Table 1 Model inputs: observed cases for each strategy

Strategy					Cases (%)
DAP	Resolution				70.71
	Disease persists	Take prescribed antibiotic	Resolution		20.00
			Additional visit (V1) / No antibiotic treatment / Resolution		1.43
		Additional visit (V1)	Antibiotic treatment / Resolution		3.57
			No antibiotic treatment	Resolution	2.14
				Additional visit (V2) / No antibiotic treatment / Resolution	1.43
			Special care is needed / Resolution		0.71
IAP	Resolution				91.61
	Disease persists, additional visit (V1)	No antibiotic treatment	Resolution		5,59
			Special care is needed / Resolution		0,70
			Additional visit (V2) / Antibiotic treatment	Resolution	0.70
				Special care is needed / Resolution	0.70
				Additional visit (V3) / No antibiotic treatment / Resolution	0.70
NAP	Resolution				87.77
	Disease persists, additional visit (V1)	Antibiotic treatment / Resolution			5.04
		Special care is needed / Resolution			1.44
		No antibiotic treatment	Resolution		5.04
			Additional visit (V2) / No antibiotic treatment / Resolution		0.72

DAP delayed antibiotic prescription, *IAP* immediate antibiotic prescription, *NAP* no antibiotic prescription

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Table 2 Healthcare and non-healthcare costs

Cost category	Measure	Data source	€ (2022)	Tornado diagram	
				Variable	
				Low	High
Healthcare direct costs					
Antibiotic medication	mean standard treatment cost	Official prices [25]	5.20	4.42	5.98
Amoxicillin			4.58		
Amoxicillin-clavulanate			6.24		
Phenoxymethylpenicillin (penicillin V)			5.89		
Cefuroxime			11.62		
Non-antibiotic medication	mean standard treatment cost	Official prices [25]	2.50	2.13	2.88
ED visits	complications (minor emergency)	Rates 2020 [26]	215	182.75	247.25
	complications (non-urgent)	Rates 2020 [26]	130	110.50	149.50
PC visits	initial, additional, and adverse effects visits	Rates 2020 [26]	50	42.50	57.50
Doctor time (NAP and DAP)	mean 1 min	Research team consensus	5	4.25	5.75
Non-healthcare direct and indirect costs					
Expenditure per visit	no. of visits x (travel/visit time + transport + parking)		16.50	14.03	18.98
Time per visit	mean 40 min (travel/visit)	Research team consensus	10.50		
Transport per km	mean 0.20 €	Captio report [27]	1		
Parking per visit	mean cost	Rates 2022 [28]	5		
Time lost to work	hourly wage	INE [29]	15.85	13.47	18.23
AMR cost					
AMR	expected antibiotic cost, 30 days	Oppong et al. [30] Holmes et al. [31]	0.20	0.17	0.23

AMR antimicrobial resistance, *DAP* delayed antibiotic prescription, *ED* emergency department, *NAP* no antibiotic prescription, *PC* primary care

the rate reported in the analysis by Coco et al. [20] and reflecting our RCT. We also assumed that adverse effects would always involve an additional visit and sometimes the prescription of non-antibiotic medication.

Non-healthcare direct and indirect costs

Direct costs calculated, using secondary information sources, were travel to healthcare institutions, parking, and outpatient consultation time for parents, while an indirect cost was time lost to work by parents (measured using a human capital approach), calculated from hourly wage data obtained from the Spanish National Statistics Institute (INE) [29]. Data on time lost to work were collected during the RCT. This cost was included, irrespective of who finally assumed it (the employer or the individual).

AMR cost

AMR was costed per prescription and per day using data published by the ECDPC [32] and the methodology of Oppong et al. [30]. Assuming that the Spanish population represents approximately 9% of the EU/EEA population and that prescriptions are made for seven days, we estimated 0.20 euros (2022) as the AMR cost per prescription over 30 days. The European average is similar to this value (0.15 pounds sterling, equivalent to 0.18 euros) according to Holmes et al. [31].

While AMR was included in our model as a cost, the cost of the reduction in antibiotic effectiveness assumed by society was not included, as is the usual practice in economic evaluations, due to the complexity of calculating this cost [30].

All costs were included in a deterministic sensitivity analysis (tornado diagram) whose low–high range is shown in Table 2.

Effectiveness estimates

Effectiveness estimates were calculated from quality-adjusted life-days (QALDs). QALD was used rather than quality-adjusted life year (QALY) because our time horizon was 30 days [20]. QALDs were calculated

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by multiplying days in each health state (moderate or severe specific symptoms, adverse effects, and days without symptoms), as collected during the RCT, by the associated utility value reflecting the child's health-related quality of life at a given point in time.

Utility is normally scaled from 0 (= death) to 1 (= perfect health) and utility values for different health states in children with non-complicated RTIs are reported in the literature [20, 21, 23]. However, since, in our RCT, parents reported their children's health state using a visual analogue scale (VAS), scored from 0 (= worst state) to 100 (= best state), the utility values used were based on those VAS scores.

The QALD value for a 30-day period for a child in perfect health is 30. Days of main moderate or severe specific symptoms and adverse effects indicated disutility, which we calculated as the difference between 1 and the average VAS score for each strategy. Data were collected to calculate utility as follows: on day 2, in relation to main severe specific symptoms, on day 7 in relation to main moderate specific symptoms, and on day 30 for no specific symptoms. Those days were chosen based on the mean duration in days for the main severe specific symptoms of 2.4 for DAP, 2.6 for IAP, and 2.6 for NAP, and for main moderate specific symptoms of 7 for DAP, 6.9 for IAP, and 6.9 for NAP.

For adverse effects, we calculated the number of days of adverse effects according to Coco et al. [20], and the associated disutility as reported by Shaikn et al. [21]. The disutility value for gastrointestinal adverse effects was 0.12, assuming that diarrhoea is a common, 2-day adverse effect, in 10% of children that used antibiotics. In the case of hospitalization, disutility was rated as equivalent to the main severe symptoms and main moderate symptoms by consensus of the research team [21]. Utility values and average days in each health state are reported in Table 3. A probabilistic sensitivity analysis was performed for these values.

Analyses

The three arms of the decision tree were compared in terms of cost per QALD using the ICER for the non-dominated alternatives. Cost-effectiveness analysis results were generated by summing direct health costs, non-healthcare direct and indirect costs, and AMR cost in euros per patient treated to obtain a total cost. Effectiveness was measured in gained QALDs, also per patient treated. The options, presented in order of costs (lowest to highest) were assumed to be mutually exclusive (a patient can only receive one intervention at a time). Dominated alternatives were excluded. Of the two dominance types, strict and extended, an alternative had strict dominance if it was less costly and yet more effective, and had extended dominance if its ICER was greater than the ICER of the next most effective alternative. We also calculated the net monetary benefit (NMB) [33] was also calculated as a better tool for decision making. Since the time horizon of the model was short (30 days), no discount rate over time was calculated.

We conducted a deterministic sensitivity analysis for all costs as listed in Table 2. The tornado analysis tested multi-way effects on the results of the model, reflecting the impact of variations in the ICER, which oscillated between low and high in a range from minus 15% to plus 15%.

We also conducted a probabilistic sensitivity analysis, in which all parameters were simultaneously and randomly varied across 10 000 Monte Carlo iterations in order to calculate cost-effectiveness probabilities for the three strategies. Distributions used were a beta distribution for utilities and probabilities, and a gamma distribution for costs [33].

An incremental cost-effectiveness plane and a cost-effectiveness acceptability curve were plotted to calculate the probability that an alternative may be cost-effective, given a threshold range of values (0–164.4 euros) for willingness-to-pay. The willingness-to-pay value was defined as the maximum cost that a society is willing to pay for one QALD gained in health. We considered a willingness-to-pay value of 82.2 euros per day, in accordance with the recommended 30 000 euros/QALY [21, 29].

TreeAge Pro 2021 (TreeAge, Williamstown, Massachusetts) statistical software was used for the analyses.

Table 3 Health state: utilities and average days

Health state	Utility value (days on average)			Reference
	DAP	IAP	NAP	
Zero symptoms	0.969 (20.57)	0.96 (20.50)	0.963 (20.58)	Mas-Dalmau et al. [24]
Severe symptoms	0.776 (2.39)	0.782 (2.57)	0.773 (2.57)	Mas-Dalmau et al. [24]
Moderate symptoms	0.875 (7.04)	0.897 (6.94)	0.879 (6.86)	Mas-Dalmau et al. [24]
Adverse effect disutility	0.12 (0.05)	0.12 (0.20)	0.12 (0.02)	Shaikn et al. [21] / Coco [18]

DAP delayed antibiotic prescription, *IAP* immediate antibiotic prescription, *NAP* no antibiotic prescription

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Results

Patients and clinical outcomes

A total of 422 paediatric patients were included in the trial. Mean (SD) age was 6.3 (3.0) years, and 216 (51.2%) were girls. Diagnoses were acute otitis media ($n=217$; 51.4%), pharyngitis ($n=141$; 33.4%), bronchitis ($n=39$; 9.2%), and rhinosinusitis ($n=25$, 5.9%). Most children ($n=382$; 90.5%) had no respiratory comorbidities. Table 4 summarizes patient sociodemographic and clinical characteristics.

Note that of five ED visits, three were non-urgent and two were minor emergencies. A single DAP case of hospitalization for dehydration due to fever was considered an outlier because of its undue impact on the overall results (given its very high cost), and also because it had the same probability of occurring in any of three arms and mainly depended on risk factors such as the age of child. This case was therefore costed as a minor emergency.

Cost-effectiveness

The cost-effectiveness of each antibiotic strategy is shown in Table 5, ordered from least to most costly. The ICER calculation allowed us to determine which strategies were dominated or excluded.

Total costs in euros were 109.68 for IAP, 100.90 for DAP, and 97.48 for NAP. QALDs were 27.94 for DAP, 27.88 for IAP, and 27.82 for NAP. DAP was the most cost-effective strategy overall. IAP was more costly but equally as effective as DAP. NAP was both less costly and less effective than DAP (by 0.12 QALDs). Comparing DAP with NAP, the ICER was 28.84 euros per gained QALD for DAP. The NMB results confirmed that DAP should be the preferred strategy, although the difference between DAP and NAP was very small (6.33 euros). The very similar QALD results for the three strategies approximate our analysis to a cost minimization analysis (Table 5).

Deterministic sensitivity analysis

The cost of parental time lost to work, followed by the cost of PC visits, were the variables with the greatest impact on the ICER (Fig. 2). The relationship between time lost to work and impact on ICER was positive (in red to the right of the ICER value), while the relationship between PC visits and impact on ICER was negative (in blue to the right of the ICER value). Thus, any increase in time lost to work by parents increased the ICER value, while any increase in PC visits reduced the ICER value. This is explained by the fact that time lost to work affected DAP more than NAP, while PC visits affected NAP more than DAP.

The impact on the ICER was greater than the variation in the baseline value only in the case of time lost to work,

Table 4 Patient sociodemographic and clinical characteristics

	Measure	IAP ($n=143$)	DAP ($n=140$)	NAP ($n=139$)	Total ($n=422$)
Age	mean (SD), years	6.4 (3.1)	6.4 (3.2)	6.1 (2.8)	6.3 (3.0)
Girls	cases (%)	75 (52.5)	64 (45.7)	77 (55.4)	216 (51.2)
Respiratory comorbidity	number (%)	15 (10.5)	14 (10.0)	11 (7.9)	40 (9.5)
Respiratory infection	cases (%)				
Rhinosinusitis		8 (5.6)	9 (6.4)	8 (5.8)	25 (5.9)
Pharyngitis		46 (32.2)	46 (32.9)	49 (35.3)	141 (33.4)
Acute bronchitis		14 (9.8)	12 (8.6)	13 (9.4)	39 (9.2)
Acute otitis media		75 (52.5)	73 (52.1)	69 (49.6)	217 (51.4)
Main specific symptoms[a]	mean (SD)				
Severe (5–6)	days	2.6 (5.4)	2.4 (6)	2.6 (6.5)	3 (6)
Moderate (3–4)		6.9 (5.8)	7 (6.3)	6.9 (7.9)	6.95(6.7)
Complications[b]	cases	2	1	2	5
Antibiotics[c]	prescriptions used	146	35	17	198
Non-antibiotic medication[c]	prescriptions used	173	200	231	604
Additional PC visits[c]	visits, number	16	15	18	49

Data are reported as frequencies and percentages except otherwise indicated

DAP delayed antibiotic prescription, *IAP* immediate antibiotic prescription, *NAP*: no antibiotic prescription

[a] Fever or difficulty swallowing for pharyngitis, earache for acute otitis media, breathlessness for rhinosinusitis, and breathlessness or chest breathing noise for acute bronchitis

[b] Perforated eardrum ($n=1$); hospitalization for dehydration ($n=1$); ED visits ($n=3$)

[c] Data are reported in terms of frequency, as a patient may have used more than one antibiotic or non-antibiotic drugs or may have visited more than once

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Table 5 Cost-effectiveness ranking

	Strategy	Cost (euros, 2022)	Incremental cost (euros)	Effectiveness (QALDs)	Incremental effectiveness (QALDs)	ICER (euros/ QALDs)	NMB
Category (excluding dominated)	NAP	97.48		27.82			2189.58
	DAP	100.90	3.42	27.94	0.12	28.84	2195.91
Category (all)	NAP	97.48		27.82			2189.58
	DAP	100.90	3.42	27.94	0.12	28.84	2195.91
	IAP	109.68	8.78	27.88	-0.06	-148.11	2182.26

DAP delayed antibiotic prescription, *IAP* immediate antibiotic prescription, *ICER* incremental cost-effectiveness ratio, *NAP* no antibiotic prescription, *NMB* net monetary benefit, *QALD* quality-adjusted life days

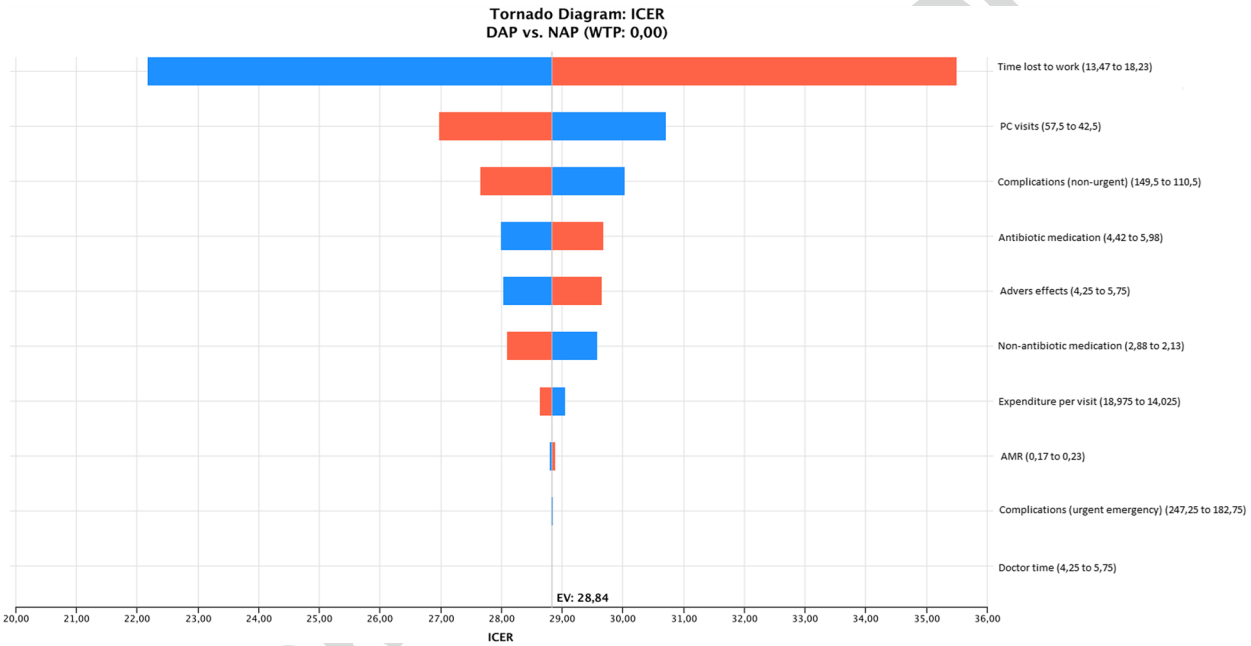

Fig. 2 Deterministic sensitivity analysis: tornado diagram. ICER: incremental cost-effectiveness ratio. DAP: delayed antibiotic prescription; NAP: no antibiotic prescription

with a variation of 15% in time lost to work having a 23% impact on the ICER (Table 6).

Probabilistic sensitivity analysis

Figure 3 shows the incremental cost-effectiveness scatterplot with 10 000 Monte Carlo iterations of the probabilistic model. DAP was more effective and more costly than NAP, as indicated by the 79.10% of iterations in quadrant I; however, the fact that ICER was below the willingness-to-pay value (82.2 euros) for 61.34% of the iterations in quadrant I indicates that DAP was the societally eligible strategy. Furthermore, DAP could be a dominated option in 20.77% of the iterations (represented in quadrant IV).

Figure 4 depicts the cost-effectiveness acceptability curve for the probabilistic sensitivity analysis. As the willingness-to-pay value increased, DAP became more eligible, i.e., the probability of cost-effective iterations increased for the DAP strategy. For a willingness-to-pay value of 82.2 euros, DAP compared to NAP accounted for around 81.75% of cost-effectiveness iterations. For any willingness-to-pay value, IAP was dominated by one or both of the other alternatives.

Discussion

Main findings

DAP was the most cost-effective strategy for children aged 2–14 years attending PC centres with RTIs, whose paediatricians had reasonable doubt about the need

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Table 6 Tornado results

Variable	Impact	Low ICER	High ICER	Cum Risk %
Time lost to work	Increase	22.18	35.50	0.87
PC visits	Decrease	26.97	30.71	0.93
Complications (non-urgent)	Decrease	27.66	30.02	0.96
Antibiotic medication	Increase	28.00	29.68	0.98
Adverse effects	Increase	28.03	29.65	0.99
Non-antibiotic medication	Decrease	28.09	29.57	1.00
Expenditure per visit	Decrease	28.64	29.04	1.00
AMR	Increase	28.81	28.87	1.00
Complications (minor emergency)	Decrease	28.83	28.85	1.00
Doctor time (for DAP and NAP)	Increase	28.84	28.84	1.00

AMR antimicrobial resistance, *DAP* delayed antibiotic prescription, *ICER* incremental cost-effectiveness ratio, *NAP* no antibiotic prescription, *PC* primary care

to prescribe an antibiotic. NAP was less costly but less effective than DAP, although the difference was very small (0.12 QALDs). The ICER of DAP compared to NAP was 28.84 euros per gained QALD. The probabilistic sensitivity analysis showed that DAP was more cost-effective than NAP in 81.75% of the Monte Carlo iterations, with 82.2 euros as the willingness-to-pay value based on the recommended 30 000 euros/QALY. IAP was the dominated strategy, as it cost more and was equally as effective as DAP. The deterministic sensitivity analysis showed that time lost to work and PC visits were the costs with most impact on ICER values. Inclusion of the AMR cost in the analysis, referring to an interval of 30 days, did not change the results.

Results in context

Two previous studies [20, 21] have evaluated the cost-effectiveness of different antibiotic prescription strategies, including DAP. IAP in our study was more costly than DAP, as in the studies by Coco et al. [20] and Shaikh et al. [21] both of which also adopted a societal perspective. However, in our study, the cost difference between IAP and DAP (8.78 euros) was less than the 22.9 US dollars (DAP compared to IAP with 7–10 days of amoxicillin) for the Coco et al. study, and 36.37 US dollars (DAP compared to IAP with amoxicillin) for the Shaikh et al. study. The incremental gain in QALDs between strategies was very small in our study, as was the case in the above-mentioned two studies. Nevertheless, in those studies, IAP was the most cost-effective strategy, whereas in our study, DAP was the most cost-effective strategy. Our incremental gain in QALDs for DAP compared to IAP was 1.44 h, compared to the incremental gain in QALDs for IAP compared to DAP of 8.6 h in the Shaikh et al. study (IAP with amoxicillin), and 3.5 h in the Coco et al. study (IAP with 7–10 days of amoxicillin). Once the lower use of antibiotics and the lower adverse effects that can occur in DAP are considered, a possible explanation for the differences could be that our disutility values for the health status of children randomized to DAP, based on parent-reported VAS values, were lower than in previous studies.

Two other studies have evaluated the cost-effectiveness of different antibiotic prescription strategies but without including the DAP option. Sun et al., [23] in a study which was also based on a societal perspective, applied a watchful waiting approach as recommended in American Academy of Pediatrics guidelines, i.e., an antibiotic is considered for prescription only after waiting to see if symptoms would self-resolve. On the basis that watchful waiting could be considered a similar strategy to DAP, our finding that DAP was the most cost-effective strategy corroborates that Sun et al. [23] finding that watchful waiting was the most cost-effective strategy. Gaboury et al. [22] evaluated the cost-effectiveness of different antibiotic prescription strategies, not including DAP; they reported a result that coincides with Coco et al. [20] and Shaikh et al. [21], namely, that IAP was more cost-effective than watchful waiting. However, in the Gaboury et al. study, and contrasting with our study and those by Coco et al. and Shaikh et al. (adopting a societal perspective), watchful waiting compared to IAP with amoxicillin cost 9.48 Canadian dollars more.

Accounting for the AMR cost, to some extent our results coincide with the Oppong et al. [30] study that evaluated the cost-effectiveness of amoxicillin compared to placebo for adults with lower-RTIs attending PC centres. That study found that the dominant strategy did not change when AMR cost was included, but only for European data, i.e., not for data from other regions. Amoxicillin was the dominant strategy for those European data, while DAP was the cost-effective strategy in our study.

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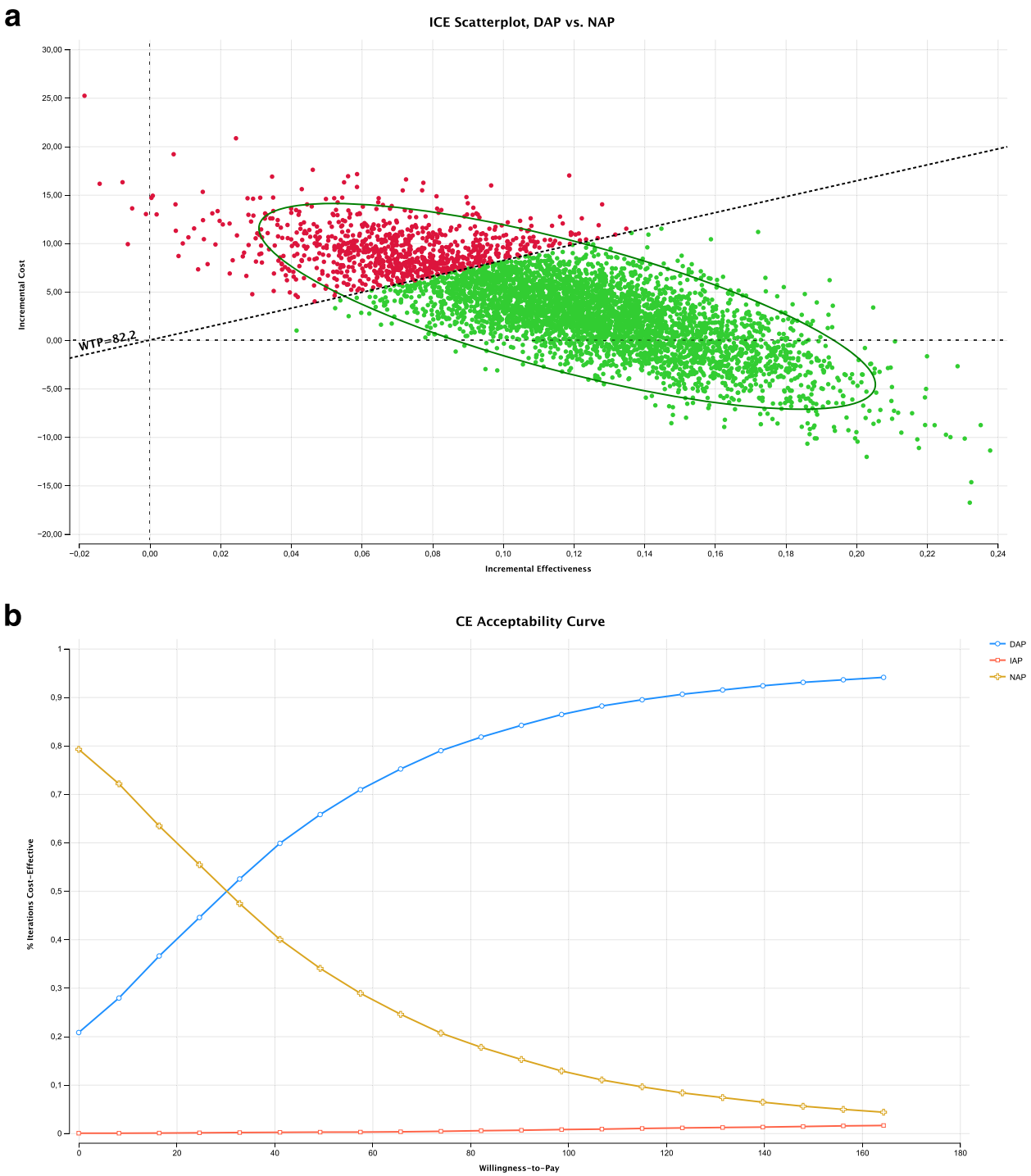

Fig. 3 Probabilistic sensitivity analysis: cost-effectiveness plane. DAP: delayed antibiotic prescription; NAP: no antibiotic prescription; WTP: willingness-to-pay

Note, however, that the Oppong et al. study did not adopt, as we did, a societal perspective.

However, in comparisons between our findings and those of the above-cited studies, similarities and differences must be interpreted with care, both because of the variety of methods used and because those studies were carried out in the USA or Canada with their different health system models and healthcare costs.

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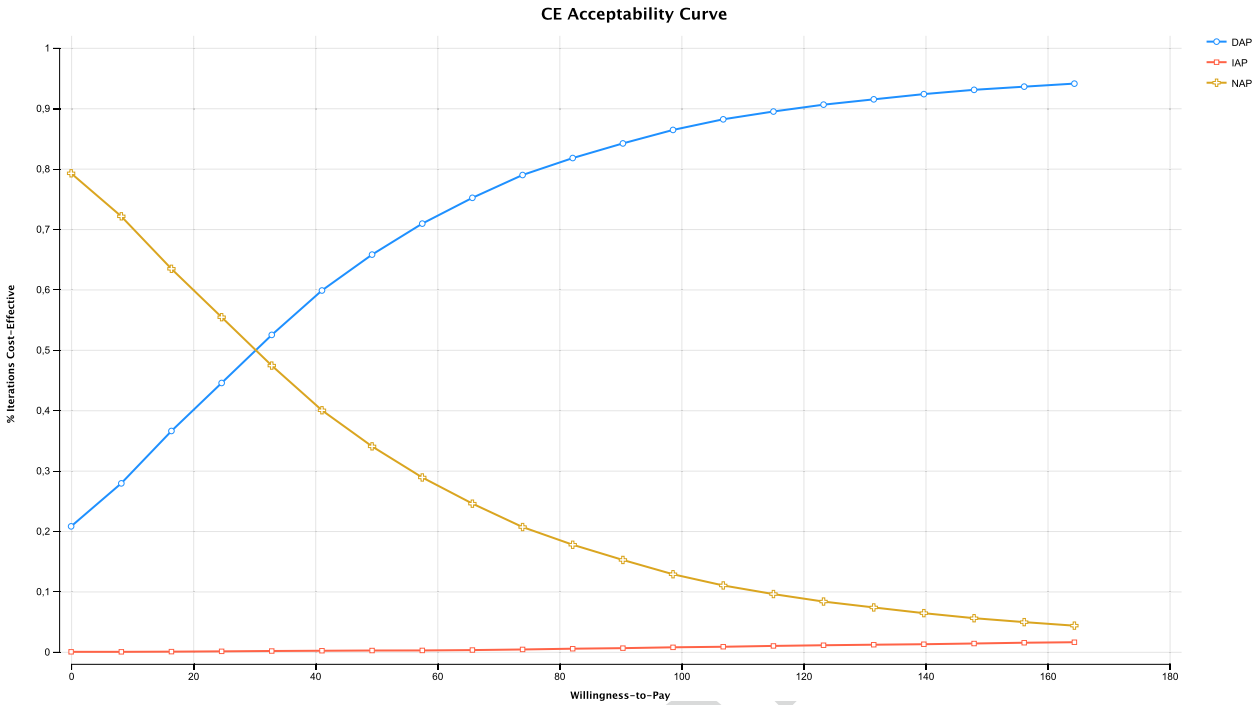

Fig. 4 Probabilistic sensitivity analysis: cost-effectiveness acceptability curve. DAP: delayed antibiotic prescription; IAP: immediate antibiotic prescription: NAP: no antibiotic prescription

Limitations and strengths

Our study has several possible limitations. First, we approximated health status utility using a VAS instead of measuring health status using standard gamble or time-trade off, or classifying health status using a questionnaire like the EuroQoL-5D [34]. Nevertheless, our findings can be considered reliable, as the QALDs were based on RCT data, and largely corroborate those of the meta-analysis by Oh [35]. Second, while the 30-day time horizon is sufficient for certain conditions, including RTIs, it is insufficient to assess the benefits of reduced antibiotic consumption in relation to reduced AMR. Third, we did not take into account private medical consultations, even though 12.6% of the Spanish population has private health insurance [36]. However, this limitation was likely to have had a similar impact on all three strategies. The trial was underpowered for two important cost drivers, namely, re-consultations and hospital admissions (included as complications), and wider individual-patient-data evidence [19] suggests that these are both higher with NAP compared to DAP; we therefore may have underestimated the cost-effectiveness of DAP. Fourth, the study was conducted in a pre-COVID-19 pandemic scenario, i.e., before the introduction of new rapid tests that could reduce diagnostic uncertainty. The cost of such tests were not considered but, as a fixed cost, it would not modify the results.

Our study also has some strengths. The main ones are that the study was based on a pragmatic RCT and, in analysing the cost-effectiveness of different antibiotic prescription strategies for children with RTIs, is the first such study performed outside North America. Our study, based on previous literature and a time horizon of 30 days, also considers AMR cost, a key issue not included in previous studies [20–23]. Finally, included also was the impact of non-healthcare direct and indirect costs in our study, reflecting a societal perspective.

Implications for practice and research

DAP is the most cost-effective strategy, although the difference with NAP is very small and the alternative IAP is a dominated strategy. For this reason, when panels consider the reduction of AMR a critical outcome, guideline panels are likely to recommend DAP strategies in those cases in which clinicians have doubts about whether it is necessary to administer an antibiotic to children with RTI.

Future studies should focus on more accurate analyses of the cost of AMR over a longer time period, and should consider the consequences of taking antibiotics not only in terms of costs, but also in terms of disutility of different health states, including re-consultations and complications.

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Conclusions

When clinicians are in doubt about whether an antibiotic is needed for children with RTIs attending PC centres, those treated with the DAP strategy will have slightly better efficiency outcomes than those treated with IAP because its costs are lower than those of IAP. DAP is also the most cost-effective strategy over a time horizon of 30 days if AMR is considered, despite higher short-term costs than NAP. However, if in the long term the costs of AMR are larger than estimated, NAP could also be an alternative strategy.

Abbreviations

AMR	Antimicrobial resistance
CREC	Clinical research ethics committee
DAP	Delayed antibiotic prescription
ED	Emergency department
IAP	Immediate antibiotic prescription
ICER	Incremental cost-effectiveness ratio
NAP	No antibiotic prescription
NMB	Net monetary benefit
PC	Primary care
QALD	Quality-adjusted life day
QALY	Quality-adjusted life year
RCT	Randomized clinical trial
RTI	Respiratory tract infection
VAS	Visual analogue scale

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Authors' contributions

Gemma Mas Dalmau (GMD): Conceptualization, Methodology, Data curation, Investigation, Writing – original draft, Project administration. María José Pérez Lacasta (MPL), Misericòrdia Carles Lavila (MCL): Conceptualization, Methodology, Formal analysis, Data curation, Writing – review and editing, Supervision. Pablo Alonso Coello (PAC): Conceptualization, Methodology, Writing – review and editing, Supervision, Funding acquisition. Pedro Gorrotxategi Gorrotxategi (PGG): Conceptualization, Methodology, Acquisition of data, Writing – review and editing. Emma Argüelles Prendes (EAP), Oscar Espinazo Ramos (OER), Teresa Valls Duran (TVD), María Encarnación Gonzalo Alonso (MGA), María Pilar Cortés Viana (MCV), Tatiana Menéndez Bada (TMB), Marta Esther Vázquez Fernández (MVF), Ana Isabel Pérez Hernández (APH): Acquisition of data, Writing – review and editing. Laura Muñoz Ortiz (LMO): Formal analysis, Writing – review and editing. Carmen Villanueva López (CVL): Conceptualization, Acquisition of data, Writing – review and editing. Paul Little (PL): Conceptualization, Writing – review and editing, Supervision. Mariam de la Poza Abad (MPA): Conceptualization, Methodology, Writing – review and editing, Funding acquisition.

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Availability of data and materials

Study data and materials not included in this article are available from the corresponding authors on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the IDIAPJGol Clinical Research Ethics Committee (CREC) (reference committee), CREC Consorci Sanitari del Maresme, CREC Hospital General Universitario Gregorio Marañón, CREC Euskadi, CREC Asturias, CREC Hospital Universitario de Burgos, CREC León, CREC Valladolid Área Oeste, CREC Área de salud de Segovia, CREC Aragón, CREC Hospital Virgen del Rocío, CREC Hospital Universitario de Guadalajara, CREC Corporativo de Atención Primaria en la Comunidad Valenciana, CREC Galicia, and by the Spanish Medicines Agency (AEMPS). All study procedures were in accordance with the ethical standards of the Declaration of Helsinki. All parents and included children aged 12 and older signed an informed consent form.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflicts of interest.

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5.3. ESTUDI 3. ESTUDI QUALITATIU SOBRE LES PERCEPCIONS, ACTITUDS I SATISFACCIÓ DELS PROFESSIONALS SANITARIS SOBRE LA UTILITZACIÓ D'ANTIBIÒTICS I LES DIFERENTS ESTRATÈGIES DE PRESCRIPCIÓ ANTIBIÒTICA DIFERIDA EN EL TRACTAMENT D' ADULTS AMB INFECCIONS RESPIRATÒRIES

5.3.1. RESUM DELS RESULTATS

Es van realitzar 4 GDs i 3 entrevistes semiestructurades individuals, amb un total de 26 participants, 25 metges i 1 infermera, amb una edat mitjana (DE) de 46.81 (8.56) anys, dels quals 13 (50%) treballaven en un centre d'AP en una àrea socioeconòmica mitjana-baixa i 12 (46.15%) havien participat prèviament en l'ACA-adults (22). Els GDs es van realitzar entre setembre de 2013 i juny de 2014 i les entrevistes individuals entre octubre i desembre del 2018.

Es van identificar 4 temes principals que van sorgir en els 4 GDs i les 3 entrevistes individuals: (1) Característiques de les visites per infeccions respiratòries; (2) Expectatives i adequació del tractament antibiòtic; (3) PDA, com i per a qui; i (4) Barreres en l'ACA-adults i la recerca a l'AP.

Característiques de les visites per infeccions respiratòries

La majoria de les infeccions respiratòries no complicades es van considerar banals i autolimitades. Tot i que es va considerar que les visites per aquest tipus d'infeccions requerien una inversió de temps per examinar, informar i educar els pacients, i per establir una relació de confiança. Tanmateix, aquesta inversió de temps sovint no era possible a causa de la càrrega de treball i l'estructura del sistema de salut. Les consultes per infeccions respiratòries van ser motivades principalment per l'autopercepció dels pacients sobre una pobre salut, ansietat i por a possibles complicacions. Aquests sentiments variaven depenent de les seves pròpies experiències prèvies o les dels seus coneguts. Es va considerar que l'educació en salut de la població en general era pobra.

Expectatives i adequació del tractament antibiòtic

Entre els participants hi va haver l'opinió generalitzada que la satisfacció del pacient era sovint més alta quan se li prescrivia un antibiòtic. Els pacients que acceptaven la no prescripció d'antibiòtics van ser aquells que s'havien recuperat prèviament sense antibiòtics, havien experimentat alguns efectes adversos dels antibiòtics o que, estaven més ben informats sobre

els antibiòtics. Es va reconèixer l'ús inadequat d' antibiòtics dins del sistema de salut. Aquest ús inadequat en l'AP es va atribuir principalment a la medicina defensiva.

PDA, com i per a qui

La PDA era utilitzada en casos de dubtes sobre l'etiologia. A més, la PDA s'implementava quan el seguiment no era possible, quan hi havia prou temps disponible per informar adequadament el pacient; i quan el pacient es negava a anar-se'n sense una recepta d'antibiòtic. Així com també, la PDA podia estar indicada en pacients específics, considerant, com el més important, la capacitat del pacient per comprendre l'estratègia. Evitar la necessitat d' una visita addicional es va considerar el principal avantatge de la PDA, tot i que el rang amb què aquest aspecte era considerat com un avantatge variava.

La principal preocupació va ser la incertesa respecte a l'ús adequat de l'estratègia PDA per part dels pacients, principalment perquè podrien fer servir l'antibiòtic immediatament. Si bé la PDA en recepció en comparació amb la PDA en mà va ser considerada per alguns com una millor estratègia perquè s'evita l'ús immediat, l'avantatge percebut de la PDA en mà va ser que evita un viatge addicional al centre de salut per part del pacient.

Barreres en el PDA-Adults i en la recerca a l'AP

La principal barrera percebuda tant pels participants de l'ACA com pels no participants va ser la falta de temps per realitzar el treball que implicava l'estudi. En relació amb la recerca en l'àmbit de l'AP, es va reconèixer que aquesta en comparació amb l' àmbit hospitalari era escassa, per la manca de temps i les pobres recompenses establertes.

5.3.2. PUBLICACIÓ DE L'ESTUDI 3

Mas-Dalmau G, Pequeño Saco S, de la Poza Abad M, Borrell Thió E, Besa Castellà M, Alsina Casalduero M, Cuixart Costa Ll, Liroz Navarro M, Calderón Gómez C, Martí J, Cruz Gómez I, Alonso-Coello P. Perceptions and attitudes regarding delayed antibiotic prescription for respiratory tract infections: a qualitative study. BMC Family Practice. 2023. Doi: 10.1186/s12875-023-02123-4. In press. Journal Impact Factor (2022): 2.9

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Perceptions and attitudes regarding delayed antibiotic prescription for respiratory tract infections: a qualitative study

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Abstract

Background Antibiotics are overprescribed for respiratory tract infections (RTIs). However, the decision to prescribe is often complex. Delayed antibiotic prescription (DAP), a strategy designed to promote more rational antibiotic use, is still not widely used. The aim of this study was to explore perceptions and attitudes in primary care professionals, regarding antibiotic use and different DAP strategies for uncomplicated RTIs.

Methods We conducted a qualitative study, using an inductive thematic approach to generate themes, based on focus group discussions and semi-structured interviews with professionals, recruited from 6 primary care centres (Barcelona metropolitan area, Spain).

Results 26 professionals (25 family physicians and one nurse) were included in four focus group discussions and three semi-structured interviews. Participants commented that RTIs were a main reason for consultation, motivated often by patient anxiety and fear of possible complications, and this was associated with the patients' poor health-related education. Acknowledging inappropriate antibiotic use in the health system, participants attributed this, mainly to defensive medicine strategies. DAP was used when in doubt about the aetiology, and considering factors related to patient-physician interactions. The main perceived advantage of DAP was that it could reduce the need for additional visits, while the main disadvantage was uncertainty regarding proper use by the patient.

Conclusions DAP was used by participants in cases of doubt, in specific situations, and for specific patient profiles. Weak points were detected in our primary care system and its users that affect the proper use of both antibiotics and DAP, namely, time pressure on professionals, poor patient health-related education, and the lack of a patient-physician relationship in some scenarios.

Keywords Qualitative research, Primary care, Professionals, Antibiotics, Delayed antibiotic prescription

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Introduction

Respiratory tract infections (RTIs), the most frequent infections encountered in primary care [1], are mostly self-limiting and are caused by viruses. While antibiotics may slightly modify course [2, 3], they tend to be overprescribed [4, 5]. Overuse of antibiotics is closely related with antimicrobial resistance [6–8], by now a major global public health challenge [9] that entails an increased risk of adverse effects for patients [10] and increased beliefs of the need to consult for similar episodes [11, 12]. In a context of optimal use of antibiotics, the decision to prescribe is complex, as, in some cases, symptoms are unclear; furthermore, the decision also depends on factors related to patient-physician interactions [4, 13], such as pressures from the patient [14, 15] and the patient-physician relationship [15].

One approach to reducing inappropriate antibiotic use for RTIs is delayed antibiotic prescription (DAP) [16], a strategy designed to promote a more rational antibiotic use in situations of uncertainty, regarding the need of immediate antibiotic prescription (IAP). DAP consists of the patient only using the antibiotic prescription if the RTI has not improved or has worsened, some days after consultation. A recent systematic review [17] comparing DAP, IAP, and no antibiotic prescription (NAP), reported that RTI symptom severity was similar for the 3 strategies, that symptom duration was slightly shorter for IAP versus DAP, and that re-visit and complication rates were lower and patient satisfaction was higher for DAP versus NAP.

DAP is still not widely deployed by professionals, as reported by several qualitative studies that have investigated views and experiences of DAP for RTIs among professionals in northern Europe [13, 18, 19], United States [18], Australia [20–22], and New Zealand [23]. While a study conducted by our group suggests that under 50% of primary care professionals in Spain use the DAP strategy [24], to our knowledge, no qualitative research evidence is available regarding this issue in Spain. Our objective was, therefore, to explore perceptions and attitudes of professionals regarding use of antibiotics and of different DAP strategies for noncomplicated RTIs.

Methods

Study design

Qualitative study using focus group discussions (FGDs) and semi-structured interviews [25–27], performed in primary care centres in the Barcelona metropolitan area (Spain).

Participants and recruitment

Family physicians were recruited from six primary care centres, five of which had previously participated in the DAP-Trial [11]. This trial, conducted with adults with uncomplicated RTIs in a primary care setting, assessed the efficacy and safety of IAP versus NAP, and versus two DAP strategies: a delayed patient-led strategy (the patients receives the prescription, with instructions to only use it if the RTI worsens or fails to improve), and a delayed collection strategy (the patient collects their prescription from the primary care centre if they think they need it).

Sampling was purposive, with participants selected according to a strategy in which sample design was based on a theoretical construct [25, 27]. The criteria to define professional profiles that reflected possibly different discourses, were as follows: (a) the professional's previous participation in the DAP-Trial (yes/no); and (b) the socioeconomic level of the professional's primary care centre's catchment population (medium-low/medium-high). Socioeconomic level was taken as a proxy for the education level of patients [28], as previous studies have shown that professionals do not consider DAP to be appropriate for less educated patients [21, 23]. For this reason, professionals were selected according to the deprivation index of the primary care centre's catchment area [29]. The sample was demographically as heterogeneous as possible in terms of gender (women/men) and age (junior: <45 years/ senior: ≥45 years).

Candidate participants for this study were recruited by the DAP-Trial centre coordinators. A sample size of 24–36 participants was estimated as necessary (4 FGDs based on 6–9 participants); however, the final number of included participants was determined once data saturation was reached.

Data collection

The study was conducted in two phases: first, focus group discussions, aimed at fostering interaction between participants [25–27]; and individual semi-structured interviews afterwards [25, 27]. In phase I, the participants completed a questionnaire about sociodemographic data and use of DAP strategy in their clinical practice.

Focus group discussions

FGDs were profiled according to sampling criteria as follows: FGD1, DAP-Trial participants and medium-low socioeconomic area; FGD2, DAP-Trial participants and medium-high socioeconomic area; FGD3, DAP-Trial non-participants and medium-low socioeconomic area; FGD4, DAP-Trial non-participants and medium-high socioeconomic area. In relation to FGD2, not enough family physicians were recruited. Thus, one nurse participating in the DAP-Trial was included. Even though her role with the antibiotics was different, we considered that her opinion could also be relevant because in many centres, the nurses carry out triage consultations. Similarly, their educational work and their experience in the

trial was deemed relevant. A script was prepared for this study (**Appendix 1**) that was sufficiently flexible for participants to suggest new topics. FGDs, run with a moderator and an observer, were conducted in a meeting room in the coordinating centre (Hospital de la Santa Creu i Sant Pau (HSCSP) in Barcelona, Spain). All FGDs were digitally audiorecorded, and recordings were transcribed verbatim. Notes taken by the moderator and observer were also used, to check and complement the transcriptions' data.

Individual semi-structured interviews

Semi-structured interviews were guided by a specifically designed script for this study (**Appendix 2**). They were carried out in order to further explore key issues that emerged in the FGDs. Interviews were conducted in the primary care centres where the participants worked with professionals drawn from the FGDs. The same researcher who moderated all FGDs also conducted the semi-structured interviews.

Data analysis

The transcriptions were cross-checked against the digital recordings and inductive thematic analysis was performed as described by Braun and Clarke [30]. The analysis was conducted by 3 researchers. Two of them independently analysed the transcription of FGD1 and agreed a preliminary coding frame. The analysis of the other transcriptions was conducted by one researcher and a second researcher reviewed the coding. The discrepancies about emergent themes and codes were resolved by consensus between the researchers. We used ATLAS.ti (version 8) software for data coding and analysis. Quotations from the FGDs and interviews were translated from Catalan or Spanish to English. Investigator triangulation and search for negative cases were undertaken to improve rigour of the analysis [31].

Table 1 Sociodemographic characteristics of study participants (N = 26)

Participant characteristics	Frequency (%)
Professional profile	
Family physician	25 (96.15%)
Nurse	1 (3.85%)
Gender	
Woman	19 (73.08%)
Man	7 (26.92%)
Age	
Junior	13 (50%)
Senior	13 (50%)
Socioeconomic level of the centre's population	
Medium-Low	13 (50%)
Medium-High	13 (50%)
Participant in the DAP-Trial	
Yes	12 (46.15%)
No	14 (53.85%)
Use of DAP strategy (even if only occasionally)	
Yes	19 (73.08%)
No	7 (26.92%)

Results

We conducted 4 FGDs and 3 individual interviews, with a total of 26 participants, 25 physicians and 1 nurse, with a mean (SD) age of 46.81 (8.56) years, 13 (50%) worked in a primary care centre in a medium-low socioeconomic area and 12 (46.15%) previously participated in the DAP-Trial (Table 1).

The FGDs were conducted between September 2013 and June 2014. Mean duration was 90 min, except for FGD2, which lasted 60 min. Note that 2 physicians in FGD1 and 1 physician in FGD2 belonged in primary care centres with a different socioeconomic level from the rest of participants in their groups. The semi-structured interviews were conducted between October and December 2018 and lasted approximately 60 min.

We identified 4 main themes arising in the 4 FGDs and the 3 interviews: (1) Characteristics of RTI visits; (2) Expectations and adequacy of antibiotic treatment; (3) DAP, how and for whom; and (4) DAP-Trial and primary care research barriers. Example quotes are shown in Tables 2 and 3.

Characteristics of RTI visits

The concept of RTI

Most uncomplicated RTIs were considered banal and self-limiting. Physicians commented that, with some patients, once informed that the infection was caused by a virus, they perceived this as the physician's incapacity to determine the diagnosis or as not having any disease. RTIs were one of the main reasons for scheduled and unscheduled visits in winter, and patients tended to consult at very early RTI stages seeking a rapid cure. Some patients reconsulted every year and several times for each episode, and this despite previous experiences and having received appropriate information.

Despite RTIs being considered mostly banal, visits required a time investment in examining, informing, and educating patients, and in establishing a relationship of trust (if not previously established). However, this time investment was often not possible due to work loads and the structure of the healthcare system. RTI consultations were mainly motivated by patient self-perceptions of poor health, anxiety, and a fear of possible complications. These feelings varied depended on their own or acquaintances' previous experiences and were often attributed to hearsay. According to some participants from centres with a medium-low socioeconomic level, poor health-related education was linked to a low socioeconomic

Table 2 Illustrative quotes:*Characteristics of RTI's visits* and *Expectations and adequacy of antibiotic treatment*

Major theme	*Subtheme*	*Quotations*
Characteristics of RTI's visits	*The concept of RTI*	*It is one of the main reasons for the consultations we get, and they involve many hours and many visits to address the reasons for consultation, most of which are trivial, and wouldn't require them to come, but they all come…here.* (Professional(P)3, DAP-Trial participant, medium-high socioeconomic area) *(…) I mean apparently it does not seem to be a serious or very complicated disease most of the times, but in daily practice, it is quite demanding.* (P13, DAP-Trial non-participant, medium-low socioeconomic area) *And then they say to you "oh, well, the virus again—when you don't know what I've got, I've always got a virus". That has been said to me.* (P25, DAP-Trial non-participant, medium-high socioeconomic area)
	RTI visits	*Sometimes I don't know, because they come so often with early symptoms, and one doesn't know what's going to happen after 24 hours, right? There are people who come, let's say, in the "prodromal stage" of the disease, right?, and you think "well, I don't know".* (P2, DAP-Trial participant, medium-low socioeconomic are)) *They are congested with an upper airway cold, but then "if it goes down to my chest", things get very complicated. Well, I don't know, sometimes they have a history of pneumonia or more serious problems, and then this…* (P13, DAP-Trial non-participant, medium-low socioeconomic area) *Colds, as you say, and gastroenteritis, these used to be resolved at home, and now people go to the doctor.* (P9, DAP-Trial participant, medium-high socioeconomic area) *Yes, I'd say we do secondary education, right?, and the potential complications. But at a primary prevention level, well, yes, more healthcare education should be conducted at the healthcare level as well as from mass media, other institutions, right?… I don't know… in adult day care, at schools or… In order to improve self-care and knowing that with an — apparently unimportant— cold, people with no other illnesses or complications, they shouldn't first go to the doctor or the healthcare centre.* (P4, DAP-Trial participant, medium-low socioeconomic area) *… since they are going to solve it for me, I don't need to try to be more self-sufficient.* (P4, DAP-Trial participant, medium-low socioeconomic area)
Expectations and adequacy of antibiotic treatment	*Physician-indicated treatment*	*In a patient with an uncomplicated acute infection, if this patient has no risk factors and is not very old, then a minimal examination, and depending on the symptoms, then the treatment… at most, a symptomatic treatment with paracetamol and a mucolytic if they have a lot of mucus; or if they have sneezing and congestion symptoms, an antihistamine, and so on…* (P1, DAP-Trial participant, medium-high socioeconomic area) *Supposedly at least a viral presentation and the treatment…it should be with paracetamol.* (P13, DAP-Trial non-participant, medium-low socioeconomic area)
	Inappropriate antibiotic use	*Also with regard to the clinicians, there may have been a bit of defensive medicine, right?, In order to play it safe, we prescribe antibiotics so they won't come back, or to satisfy the patient, or, I don't know, this has been going on for a long time too.* (P14, DAP-Trial non-participant, medium-low socioeconomic area) *I believe that it is quite rational now, compared to 10 years ago. For instance, I believe that now we prescribe perhaps 10 times less antibiotics. In my opinion, I don't know what the statistics say, but I think we prescribe antibiotics much less often now than 10 or 15 years ago.* (P19, DAP-Trial non-participant, medium-low socioeconomic area) *(…) And then, we often visit this type of patient profile in the unscheduled visits where not even the same doctor visits them. So the credibility of the professional here counts for a lot. For me, it's much easier to work with my usual patients than when I visit with someone else.* (P23, DAP-Trial non-participant, medium-high socioeconomic area) *The mindset in England or Germany is not the same as here, where since I was a child I have had the feeling that they are used to taking antibiotics relatively often. It's not their fault either, but also maybe there hasn't been a good education. They come in a second time, this second visit you give it [the antibiotic] them so they won't come back, I don't know, sometimes we are all a little guilty.* (P20, DAP-Trial non-participant, medium-high socioeconomic area)
	Patient self-medication	*Many times they say, "no, I'm already taking paracetamol, aren't I?", then, —"then continue, very well"— "but I'm not cured" —"wait… wait a few days, and you'll see, right?"* (P23, DAP-Trial non-participant, medium-high socioeconomic area) *A minority [has already started antibiotic treatment]. Pills left over from the last time, or from their grandmother.* (P11, DAP-Trial participant, medium-high socioeconomic area)

status, while other participants considered that health knowledge among the general population had decreased from previous generations. It was considered that more education was needed, via primary care centres, the media, and schools.

Consultation often reflected the patient's age, with young patients consulting because they were not used to being sick, and elderly patients consulting because they were concerned about their comorbidities. Another reason for consultation were requests for sick leave from work. Some participants were of the opinion that healthcare human resources were misused when patients consulted for mild cases of RTIs, with this misuse attributed to a lack of responsibility for self-care by patients. It was suggested that there was a need for patient empowerment, and also that access to rapid tests would be useful visit aid.

Expectations and adequacy of antibiotic treatment

Physician-indicated treatment

Some patients expected a drug prescription to feel reassured or considered antibiotics to be an effective and fast-acting cure. Some patients felt that they were not being treated properly when recommended symptomatic

Table 3 Illustrative quotes: *DAP, how and for whom*; and *DAP-Trial and primary care research barriers*

Main theme	Subtheme	Quotations
DAP, how and for whom	*Context*	*Yes, because [the DAP] is something we use when it's not entirely clear to us whether the presentation is going to resolve easily. When you have the slightest suspicion, a medical sixth sense that tells you, "hmm, this could get complicated", or you're not sure about a tonsillitis and you say, "well, look, it's quite likely that, with so much pain, so much fever, in 48 hours, you'll have an abscess or have terrible pus plaques." And you are not very sure. Basically, that's it. An uncertainty that it may be something viral that will get complicated or that is already a bacterial infection.* (P10, DAP-Trial participant, medium-high socioeconomic area)
		I have done it before the weekend. If they come in on a Monday, then you know it's Monday, it's fine because there is a lot of accessibility. I've done it more often on Thursdays, Fridays, thinking "where will they go on Saturday, Sunday?". Before a public holiday or Easter holidays. When I've done it, I've done it more often in those situations. (P22, DAP-Trial non-participant, medium-high socioeconomic area)
		There are also times you use it as a tool not to prescribe immediately. In other words, you think they shouldn't take it, the patient, you know they do not agree, so… and then you can use it in such a way, that a possibility, in the long run, maybe, is if they see that they are getting better, they won't take it, and they don't take it. (P4, DAP-Trial participant, medium-low socioeconomic area)
		… I believe it is more often in a situation of a quick unscheduled visit (…). Because you probably will not see this patient again, another professional will visit them instead, you lose follow-up of them. It's 'right here, right now', another decision of the moment. If this happens with your patient, it's easier to say "if you are not feeling well, come back in a few days and I will examine you again". (P4, DAP-Trial participant, medium-low socioeconomic area)
	Patient profiles	*That they really understand that they understand, or that one knows how to explain it to them, and they understand it (…)* (P13, DAP-Trial non-participant, medium-low socioeconomic area)
		Those of us who have been working for a long time now, when we know the patient. Because, of course, when you've been working for a long time, you know if they are a compliant patient, if they are a multi-frequenter patient, if they are…… You know these things. If you think they are compliant and will do well, then that is also a criterion. If they are multi-frequenters, they'll still come back after two days if they don't get better, even with the DAP, that can also influence whether you do it or not. I mean, those are criteria that you can also consider. (P9, DAP-Trial participant, medium-high socioeconomic area)
		It is the profile of the people. I think that perhaps the population that could benefit most is the young population, who can understand it. But this population rarely comes to see us. And then, when you have to educate a patient with whom you aren't too close, because the confidence your patients have in you is different. And then, we often visit with this type of patient profile in the unscheduled visits, where not even the same doctor visits them. So the credibility of the professional here counts a lot. For me, it is much easier to work with my usual patients than when I visit with someone else. (P23, DAP-Trial non-participant, medium-high socioeconomic area)
		In short, DAP is probably very suitable for patients who do not want antibiotics. This kind will wait 24 or 48 h. In other words, they are aware of not taking antibiotics. On the other hand, with those convinced of taking them, it doesn't matter if you ask them to wait. (P26, DAP-Trial non-participant, medium-high socioeconomic area)
		The problem is that you still have a doubt, right?, with the patient who doesn't agree, who's not sure… or if one thinks or this person is a hypochondriac, that once I give them a DAP, they will accept it, and will surely go directly to buy an antibiotic. Because I don't leave the prescriptions at the reception desk, I give them in person. And then you doubt, right? (P7, DAP-Trial participant, medium-low socioeconomic area)

Table 3 (continued)

Main theme	Subtheme	Quotations
	DAP advantages and disadvantages	*Let's see, advantages… You could say the number of visits, maybe, but I don't care. In other words, if the patient is not feeling well, it's fine that they come back and visit me again. This is the advantage I can think of.* (P15, DAP-Trial non-participant, medium-low socioeconomic area) *(…) I think they find this option safer for them, don't they? [they think,] "OK, you now think it is not necessary, but you let me this second option in case I get worse…"* (P4, DAP-Trial participant, medium-low socioeconomic area) (…) *Anyway, I use it and I use it also for that reason (…) they are no longer in distress thinking "I feel terrible", and it also gives them the chance to say, "well, maybe I don't need it, the antibiotic, right?" And therefore, well, I don't know, it's useful, it's useful. And the patient, from what I see, leaves satisfied.* (P4, DAP-Trial participant, medium-low socioeconomic area) *(…) what's most important to me: you give them a little independence and self-management of their own health. And actually the only thing you are doing differently is knowing that they must take the antibiotic if it happens to them or not, I mean, if you explain it to them, they are able to do it themselves. Not everyone, though.* (P3: DAP-Trial participant, medium-high socioeconomic area) *The problem is that you still have a doubt, right? With the patient who doesn't agree, who's not sure, or if one thinks that this person is a hypochondriac, that once I give them a DAP, they will accept it, and will surely go directly to buy an antibiotic. Because I don't leave the prescriptions at the reception desk, I give them in person. And then you doubt, right? You don't know if they've taken it or not, if you're actually making a good….* (P7, DAP-Trial participant, medium-low socioeconomic area) *So, of course, if I don't know how it is going to progress… without re-examining them, sometimes I'd rather be the one to decide when and how, than giving this to the patient.* (P25, DAP-Trial non-participant, medium-high socioeconomic area) *You have to think about it a lot and be really sure what you mustn't give them [antibiotics], what you can give them, what you have to explain to them well… Putting time aside, it's the act of thinking, it's much easier to click, click, click, antibiotic, and goodbye. I mean, a DAP involves extra efforts from the clinician, apart from explaining and so on, even if you have a person on the other side of the desk who understands it perfectly, it implies thinking about it, saying, "Come on, let's do it" and explaining it to them. I mean, I'm sure there are more DAPs at 3 pm than at 7 pm.* (P3, DAP-Trial participant, medium-high socioeconomic area)
	Patient-led DAP versus DAP collection	*The thing is, both as a professional and user of the system, I don't think I would like the second option [DAP prescription collection] at all, because actually, if I'm fine, I won't need it and I wouldn't go get it; but if I'm ill and I really need to go get the antibiotic, it would mean the fever continues —it hasn't decreased—, it would probably be a bacterial infection and I'm being forced to leave my house again or have to find someone to come with me . I mean, I find that when people are feeling bad, they are the ones to lose out in this case.* (P23, DAP-Trial non-participant, medium-high socioeconomic area) *If you leave it at the reception desk, the patient has to make an effort. Then, "this person may not come to collect it", but they won't schedule a visit either. This would be the ideal strategy, because they don't come to the office, but they also don't start taking it straight away, right?* (P14, DAP-Trial non-participant, medium-low socioeconomic area)
	Improvement proposals	*There could also be incentives for clinicians. Right? Make it a way to consider prescriptions, just as we have others, well, it could be one more.* (P4, DAP-Trial participant, medium-low socioeconomic area)
DAP-Trial and primary care research barriers	*DAP-Trial*	*(…) I found it very rewarding and interesting, partly because of what you see of an investment in the future, as promoting a rational use of drugs, of antibiotics, and for me it was very rewarding.* (P12, DAP-Trial participant, medium-low socioeconomic area) *Yes, because it's useful. It's a strategy… well, I didn't know either, I learned to apply it as a result of the study we did last year. Did you apply it before?* (P10, DAP-Trial participant, medium-high socioeconomic area) *Well, for me the field work was very tedious. There were a lot of people who could have been included, but there was very little time, and that limited one a lot to include patients. On the other hand, I think I liked the study, because it was conducted in the primary care setting, in a real-world situation. Everything I was against in reporting the field work, I was in favour of after with the results, how they came out. But anyway, I really thought it was very tedious and that one lost interest in doing it because of what it meant if…* (P4, DAP-Trial participant, medium-low socioeconomic area)

Table 3 (continued)

Main theme	Subtheme	Quotations
	Primary care research	*"(…) that most of the research is conducted at the hospital level, but at the primary care level or with conditions that we only see in the primary care setting, such as upper RTIs, little has been done (…)* (P9, DAP-Trial participant, medium-high socioeconomic area) *"Hmmm, I think, firstly, that if you are working full-time as a healthcare provider, it is very complicated, because with our visiting hours, our timetable is almost full, and we don't have much time left for anything else (…)* (P9, DAP-Trial participant, medium-high socioeconomic area) *It seems to me that perhaps now the only benefit —well, at least in the ICS [Catalan healthcare service]— that you can get is that, as an activity, it is valuable for your professional career. Well, I'm just saying this to try to see some personal benefit. The only thing I can think of right now. But apart from that…* (P2, DAP-Trial participant, medium-low socioeconomic area) I don't know, if it is an interesting study for primary care and so interesting, then I think that the organization could collaborate with the schedules, or —I don't know—, somehow saying, "if you do this, you will have fewer patients every day", because it is harmful for patients who are waiting on you. Because you are feeling bad, thinking "now I will spend half an hour with this person, and I am already running 15 minutes late, or half an hour, add another half an hour and it will be an hour", and the poor people there who had an appointment, you are also feeling bad about that, and so are they… it is also harming the healthcare service. I mean if the organization committed… (P9, DAP-Trial participant, medium-high socioeconomic area)

medication (e.g., analgesics, antihistamines, mucolytics, and antitussives) while other patients even explicitly expressed dissatisfaction that antibiotics were not prescribed. There was a general opinion that the patient's satisfaction was often greater when they were prescribed an antibiotic. Patients who accepted the non-prescription of antibiotics were those who had previously recovered without antibiotics, had experienced some adverse effects of antibiotics, or who were better informed about antibiotics, such as pregnant women.

Inappropriate antibiotic use

Inappropriate use of antibiotics in the healthcare system was acknowledged. This inappropriate use in primary care was attributed mainly to defensive medicine based on low-cost drugs, most especially when there were time pressures or when there was no patient-physician relationship (e.g., unscheduled visits). Another reason was the presentation of some antibiotics does not fit with prescription patterns, meaning that patients typically have medication left over. Some participants suggested that this may be due to potential financial interests from pharmaceutical industry.

Despite recognizing the inappropriate use of antibiotics, there was a generalized opinion that primary care professionals make every effort to use them rationally, and even a trend in both hospital and primary care settings towards prescribing fewer antibiotics. This was attributed to better training and incentives for professionals, although such strategies were still considered to be insufficient. The trend to reduce antibiotic use was considered not to occur in the private health sector. In the opinion of the participants, inappropriate use of antibiotics was due to a range of opinions regarding both indication and choice of antibiotics. Private health sector physicians tended to prescribe more antibiotics and they are more often non-generic and expensive than public health sector physicians. Finally, it was acknowledged that doubts existed regarding the use of antibiotics because the criteria were always not clear.

Patient self-medication

When patients visited, they had often already started symptomatic medication, and a typical recommendation was to follow the same treatment for a few more days. Occasionally, patients had already taken an antibiotic, typically left over from a previous prescription.

DAP, how and for whom

Context

DAP was used in cases of doubts regarding aetiology, and was mainly used for pharyngitis in adults, and for acute middle-ear infection in paediatric patients. Taking into account information obtained in the patient-physician interaction, DAP was typically deployed in the following circumstances: before a weekend, travel, or an event; in unscheduled visits without follow-up; when enough time was available to appropriately inform the patient; and when the patient refused to leave without an antibiotic prescription even if not clinically indicated.

Patient profiles

DAP may be indicated for specific patients, considering, most importantly, the patient's capacity to understand the strategy. Candidates were also patients who were considered trustworthy, those with greater common sense (they probably would not use the antibiotics immediately), those with a relationship of trust with their physician, and those with chronic conditions who were knowledgeable about their pathology.

There was no consensus as to whether it was more difficult to implement DAP in young people who probably

did not have a physician-patient relationship, or in older people with comorbidities or cognitive difficulties. It was agreed that DAP would not be indicated for patients experiencing anxiety, frequent healthcare users, or patients who insist on an antibiotic prescription.

DAP advantages and disadvantages

Avoiding the need for a further visit was considered the main advantage of DAP, although the extent of the advantage was perceived to vary. A second advantage was that the DAP strategy generally satisfied both patient and physician. DAP also meant that patients had a safety net, in that they had the prescription if the condition deteriorated or failed to improve. DAP also represented an opportunity to educate patients that antibiotics are not always needed for RTIs and empowered them with greater decision-making autonomy. Finally, DAP as an alternative was useful when pursuing more rational use of antibiotics.

The main concern was uncertainty regarding patients' proper use of the DAP strategy, mainly that they might use the antibiotic immediately. Some participants proposed that the prescription should not be available until a date recommended by physician. Related to this uncertainty, some physicians who did not use DAP stated that they preferred to take responsibility for the final clinical decision, despite the possibility of an additional visit. Two other physicians who did not use DAP considered that the patient had to be properly informed prior to being offered DAP and one physician considered that, with DAP, there was a possibility of antibiotics being prescribed despite not being indicated.

Some physicians who used DAP confirmed that it required a greater investment in time and effort, mainly in assessing whether the patient was a suitable candidate and then issuing instructions for use of the prescription. Possible professional responsibility in the event of a complication was expressed as a concern regarding the DAP strategy by one physician who used it.

Patient-led DAP versus DAP collection

While DAP collection rather than patient-led DAP was considered by some to be a better strategy because immediate use was avoided, a recognized advantage of patient-led DAP was that it avoided a return visit by the patient.

Improvement proposals

It was proposed that DAP use should be rewarded with incentives. It was also pointed out that deployment of DAP required more time and would need the health system's educational role to be enhanced. Another proposal was to involve nurses and pharmacies in deployment of the DAP strategy.

DAP-Trial and primary care research barriers

DAP-Trial

While some advantages to carrying out the DAP-Trial were commented, the main focus was on barriers. The main barrier perceived by both DAP-Trial participants and non-participants was the lack of time for the work implied by research. Perceived barriers by the DAP-Trial non-participants were the lack of suitable candidate patients and the disruption implied by DAP inclusion in routine practice. Perceived barriers by the DAP-Trial participants were the lack of support and a lack of agreement with recommendations to patients allocated to the DAP strategies. Some DAP-Trial participants found the study useful in making them more aware of and familiar with DAP, and interesting in that the study was implemented independently of the pharmaceutical industry. Also expressed was a feeling of belongingness, resulting from the follow-up emails periodically sent by the coordinating centre.

Primary care research

It was recognized that research in the primary care compared to the hospital setting was scant, with a lack of time and poor rewards stated as the main barriers. Proposed in addition to involving nurses and residents in research, were incentives such as reducing work burdens and healthcare pressures, and the provision of financial rewards and additional holidays.

Discussion

Main findings

We identified a vicious circle between poor health-related education in patients with RTIs and time pressures in primary care centres. Time-consuming RTI consultations of poorly educated patients feeling anxious and fearful of possible complications, led to healthcare pressures that constrained physicians in terms of educating patients.

Physicians generally acknowledged inappropriate use of antibiotics in the health system, but also considered that they made every effort to prescribe them rationally, attributing inappropriate use to defensive medicine with low-cost drugs, based on a perceived trade-off between short-term negative consequences of non-prescription (i.e., complications) and long-term negative consequences of prescription (antimicrobial resistance).

DAP was therefore deployed in cases of doubt, in specific situations, and to specific patient profiles. The main advantage of DAP was considered to be the reduction in additional visits, while the main disadvantage was perceived to be uncertainty as to proper patient use. Regarding the DAP-Trial and primary care research, a lack of time was considered to be the main barrier to research in primary care settings. We did not find major differences between DAP-Trial participants and non-participants

possibly because most of them used DAP in their practice.

Results in context

The decision to prescribe antibiotics for some RTIs depends not only on medical factors but also on patient-physician interaction factors [4, 13]. The results of our study corroborate previous studies in that the DAP strategy was considered useful for this kind of complex decision-making scenario [13, 18–23, 32].

Our study participants deployed DAP in cases of uncertainty and, as in previous studies, in specific situations, e.g., before the weekend or holidays [13, 19–21, 23, 32], as a negotiation strategy when patients insisted on antibiotics [13, 18–22, 32], and for certain patient profiles [13, 19–23, 32]. The main characteristics of DAP candidates that emerged in our study, consistent with previous studies, were patients capable of understanding the strategy [21, 23, 32], patients considered trustworthy [20, 32] and having common sense [32]. The patient-physician relationship was another key aspect to consider in deploying DAP, according to the results of our study. An issue that did not emerge in our study, unlike other studies, was that DAP was considered to strengthen this relationship [19–21, 23].

DAP was used by our study participants in apparently contradictory situations: (a) for patients who demanded antibiotics and refused to leave without a prescription, and for patients who were trusted not to immediately use the prescription (as in Hoye et al. [32] and Sargent et al. [21]; and (b) for patients consulting in unscheduled visits, in which the patient-physician relationship considered fundamental to this strategy was lacking. These apparently contradictory deployments of DAP, highlight the complexity of physician decision-making regarding antibiotic prescription.

DAP strategy advantages and disadvantages, in our study as in previous studies, are associated with the fact that DAP is a more patient-centred approach [18, 23]. Thus, while DAP provides the patient with a safety net [13, 18–22] since the prescription can be used if needed [32], and also empowers the patient by making them responsible for the final decision [18–21, 32], control is lost by the physician [13, 19, 20, 23].

Our study identified some important health system barriers to appropriate antibiotic use and DAP deployment, primarily the lack of a patient-physician relationship in unscheduled visits, poor patient health-related education, and the lack of professional time. These latter issues could be simultaneously addressed by nurses and pharmacists becoming more involved in educating patients regarding RTIs and their treatment. DAP was perceived, as in previous studies, as a golden opportunity for educating people about antibiotics [20, 21, 23, 32].

Limitations and strengths

The main limitation of our study is that the participants mostly came from primary care centres participating in the DAP-Trial, and most used DAP in their clinical practice. While the advantages of DAP may therefore be considered to be overestimated, our results are nonetheless consistent with the extant literature. A second limitation is that our study did not include participants from rural settings, although Fletcher et al. [22] found no differences between rural-urban contexts in their study. A third limitation is that, due to the few professionals participating in the DAP-Trial, two FGDs were not homogeneous in terms of the socioeconomic level of the centre's population. Furthermore, a nurse who participated in the DAP-Trial was included in a FGD. Including this participant granted the feasibility of one of the groups. The researchers involved in conducting and analysing the FGD assessed that the dynamics were not negatively affected, and, indeed, the nurse's contributions were particularly enriching.

A major strength of our study is that it included professionals who had deployed DAP and so were well aware of the positive and negative aspects of DAP. A second strength is that, as far as we are aware, this is the first qualitative study of professionals and DAP conducted in a country in southern Europe, where antibiotic use is comparatively higher than in northern Europe [6]. Finally, our study complements several other studies published by our group [11, 17, 24, 33] aimed at raising awareness and improving implementation of the DAP strategy.

Implications for practice and research

Our findings highlight the fact that time pressures, poor health-related education of patients, and the lack of a patient-physician relationship in unscheduled visits were important barriers to optimal antibiotic use and to deployment of the DAP strategy in primary care. Policymakers may therefore consider strategies, such as the following to overcome these challenges: (i) the provision of RTI health-related education and self-care, and the encouragement of proper use of healthcare services supported by primary care nurses and pharmacists; (ii) improved access to rapid streptococcal testing; and (iii) reorganization of physician agendas so that RTI consultations are attended by the referring physician whenever possible.

Another implication of our findings is that they point to a lack of consensus about some of the criteria to be considered by physicians in deploying the DAP strategy. This suggests that clinical guidelines on RTI management in primary care need to better specify criteria for deployment of DAP, including patient and contextual factors which should be considered when using DAP strategies, as well as the standardization of prescription use

recommendations for patients. Finally, the poor health-related education of patients was one of the main themes that emerged in this study. A recent systematic review showed that educational interventions were one of the most efficacious and safe strategies for optimal antibiotic prescribing for RTIs [16]. Given the need for further studies to evaluate RTI educational interventions for patients, our group is conducting a multicentre factorial trial of two educational interventions, targeting both parents and professionals.

Conclusions

DAP was used by participants in cases of doubt, in specific situations, and for specific patient profiles. Weak points were detected in our primary care system and in its users that affect the proper use of both antibiotics and DAP, namely, time pressures on professionals, poor patient health-related education, and the lack of a patient-physician relationship in certain scenarios. Proposed to overcome these challenges are educational interventions regarding RTIs and optimal use of healthcare resources and the formulation of better DAP-related recommendations in guidelines.

List of Abbreviations

DAP	Delayed antibiotic prescription
FGD	Focus group discussion
IAP	Immediate antibiotic prescription
NAP	No antibiotic prescription
RTI	Respiratory tract infection

Supplementary Information

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Supplementary Material 1

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Authors' contributions

CrediT authorship contribution statement. GMD: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data Curation, Writing-Original Draft, Visualization, Project administration and Funding acquisition. SPS: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data Curation, Writing-Review & Editing, Visualization, Project administration. MPA: Conceptualization, Methodology, Resources and Writing-Review & Editing, project administration. EBT, MBC, MAC, MLN and LCC: Conceptualization, Methodology, Resources and Writing-Review & Editing. CCG, JM and ICG: Methodology, Formal analysis and Writing-Review & Editing. PAC: Conceptualization, Methodology, Formal analysis, Investigation, Writing-Review & Editing, Visualization, Supervision, Project administration, and Funding acquisition. The authors have all read and approved the final manuscript.

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Data Availability

The data will be made available to researchers who provide a methodologically sound proposal for use. Proposals should be submitted to the corresponding author.

Declarations

Ethics approval and consent to participate

The ethics committee of the Jordi Gol i Gurina Foundation (Barcelona, Spain) approved the study. The study was conducted in compliance with the principles of the Declaration of Helsinki [34]. Informed consent was obtained from all the participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Publisher's Note

6. DISCUSSIÓ

6. DISCUSSIÓ

6.1. PRINCIPALS RESULTATS

L'ACA sobre la PDA en nens és l'estudi major fins l'actualitat, fora del nord d'Europa, per avaluar l'efecte d'aquesta estratègia, en la durada i severitat dels símptomes en IRAs no complicades, en població pediàtrica. La durada moderada i greu dels símptomes en la PDA, va ser lleugerament més gran que en la PIA i la NPA, i la gravetat més gran per a qualsevol símptoma va ser similar per als tres estratègies. L'ús d'antibiòtics va ser significativament menor en els braços PDA i NPA que en el braç PIA, i la medicació no antibiòtica va ser significativament més alta en els braços PDA i NPA. Les complicacions, les visites no programades a l'AP i les visites hospitalàries d'urgències van ser similars per a les 3 estratègies i, de la mateixa manera, la satisfacció va ser molt alta. El braç PIA va experimentar més efectes adversos gastrointestinals que els braços PDA i NPA.

En l'estudi cost-efectivitat, la PDA va ser l'estratègia més cost-efectiva per als nens de 2 a 14 anys que van consultar per una IRAs a l'AP, i els pediatres tenien dubtes raonables sobre la necessitat de prescriure un antibiòtic. La NPA va ser menys costosa però menys efectiva que la PDA, tot i que la diferència va ser molt petita (0.12 QALD). L'ICER de la PDA en comparació amb la NPA va ser de 28.84 euros per QALD guanyat. L'anàlisi de sensibilitat probabilística va mostrar que la PDA era més rendible que la NPA en el 81.75% de les iteracions de Monte Carlo, amb 82.2 euros com a valor de disposició a pagar. La PIA va ser l'estratègia dominada ja que era més costosa i va ser tan efectiva com la PDA. L'anàlisi de sensibilitat determinista va mostrar que el temps perdut de treball dels pares i les visites a l'AP, van ser els costos amb més impacte en els valors d'ICER. La inclusió del cost de les RAM en l'anàlisi, en un interval de 30 dies, no va modificar els resultats.

En l'estudi qualitatiu, es va identificar un cercle viciós entre la pobre educació en salut dels pacients, que comporta que consultin per IRAs no complicades, i les pressions de temps que tenen els professionals dels centres d'AP que limiten poder dedicar-se a fer educació per la salut. Els metges generalment van reconèixer l'ús inapropiat d'antibiòtics en el sistema de salut, però també van considerar que es feia l'esforç per prescriure'ls racionalment. L'ús inapropiat d'aquests

fàrmacs el van associar a una medicina defensiva amb medicaments de baix cost, basat en una compensació entre les conseqüències negatives a curt termini de la no prescripció (és a dir, complicacions) i les conseqüències negatives a llarg termini de la prescripció (les RAM).

Per tant, la PDA es va implementar en casos de dubte, en situacions específiques i en perfils de pacients específics. El principal avantatge considerat de la PDA va ser la reducció de les visites addicionals a l'AP, mentre que el principal desavantatge percebut va ser la incertesa sobre l'ús adequat de la recepta per part del pacient. Pel que fa a l'ACA-adults i a la recerca en l'àmbit de l'AP, es va considerar que la manca de temps era la principal barrera. No es van trobar diferències importants entre els participants i no participants, possiblement perquè la majoria d'ells utilitzaven la PDA en la seva pràctica.

6.2. RESULTATS EN EL CONTEXT DEL CONEIXEMENT ACTUAL

6.2.1. EFICÀCIA DE LA PRESCRIPCIÓ ANTIBIÒTICA DIFERIDA EN NENS AMB INFECCIONS RESPIRATÒRIES ATESOS A L'ATENCIÓ PRIMÀRIA

Els resultats del nostre estudi van ser inclosos en un metanàlisis posterior de dades individuals de pacients que comparava la PDA, la PIA i la NPA en IRAs, tant en adults com en nens (58). El nostre estudi coincideix amb els resultats del metanàlisi, en què la durada dels símptomes va ser lleugerament major per la PDA que per la PIA i que no es van trobar diferències en les complicacions entre la PDA i la NPA.

En canvi, en el nostre estudi, la severitat dels símptomes va ser lleugerament major en la PDA en comparació a les altres dues estratègies, tot i que sense diferències estadísticament significatives, mentre que en el metanàlisi va ser similar entre les tres estratègies. Així com també, en el nostre estudi no vam trobar diferències en les reconsultes a l'AP i en la satisfacció entre la PDA i la NPA i en el metanàlisi, es va concloure que per la PDA en comparació amb la NPA, les reconsultes a l'AP eren menors i la satisfacció major.

L'ús dels antibiòtics en el nostre estudi va ser menor en les estratègies PDA i NPA en comparació amb la PIA, com en una revisió Cochrane prèvia (33). No obstant això, el baix ús d'antibiòtics observat en els assajos clínics s'ha de considerar amb precaució; ja que l' ús real pot no reflectir-

se, perquè, a diferència dels estudis observacionals, els participants en l'estudi reben assessorament estructurat i, per tant, solen estar més motivats que en entorns de rutina (34). Així mateix, el nostre estudi va trobar una reducció significativa en els esdeveniments adversos gastrointestinals per a PDA i NPA en comparació amb PIA, corroborant estudis previs que han avaluat la PDA per a IRAs en nens (35,36).

Les nostres troballes són similars a les de un altre assaig clínic sobre la PDA en població adulta a Espanya, realitzat pel nostre grup (22) En aquest estudi, la durada dels símptomes moderats i greus va ser més alta per a la PDA que per a la PIA però menor per la NPA, mentre que en el nostre estudi en nens, la durada dels símptomes va ser lleugerament major per a la PDA que per a la PIA o la NPA. Pel que fa a l'ús d'antibiòtics, les troballes per a l'ACA sobre la PDA en nens van ser més favorables que en adults: el 32.6% dels adults en comparació amb 25.3% dels nens assignats a la PDA van finalment prendre antibiòtics.

El menor ús d'antibiòtics en el nostre estudi pediàtric, en comparació amb l'estudi en adults, pot estar relacionat amb dos factors: més preocupació dels pares pels efectes adversos dels antibiòtics i que les consultes mèdiques són per episodis més lleus. Pel que fa al primer factor, l'evidència mostra que els pares són cautelosos sobre l'ús d'antibiòtics per a les infeccions respiratòries en nens, per les preocupacions sobre els seus efectes adversos (60) i les experiències passades (61), mentre que els adults tendeixen a no recordar les conseqüències greus del tractament amb antibiòtics (61) Pel que fa referència al segon factor, les famílies van visitar al metge 3.5 dies abans que els adults, i els episodis eren més lleus (el valor mitjà de la puntuació sobre la màxima severitat per a qualsevol símptoma va ser dos punts menor per als nens que per als adults). Les raons d'una visita mèdica més precoç podrien ser per temors sobre la possibilitat d'empitjorament o complicacions importants en els nens, o diferències en les percepcions sobre l'equació risc-benefici dels antibiòtics (61).

6.2.2. ANÀLISI COST-EFECTIVITAT DE LA PRESCRIPCIÓ ANTIBIÒTICA DIFERIDA EN INFECCIONS RESPIRATÒRIES EN NENS ATESOS A L'ATENCIÓ PRIMÀRIA

Dos estudis previs (40,41) van avaluar la relació cost-efectivitat de diferents estratègies de prescripció d'antibiòtics, incloent la PDA. La PIA en el nostre estudi va ser més costosa que la

PDA, com en els estudis de Coco et al.(40) i Shaikh et al. (41), els quals també van adoptar una perspectiva social. No obstant això, en el nostre estudi, la diferència de cost entre la PIA i la PDA (8.78 euros) va ser menor que els 22.9 dòlars estatunidencs (PIA amb 7-10 dies d'amoxicil·lina en comparació amb la PDA) per a l'estudi de Coco et al., i 36.37 dòlars estatunidencs (PIA amb amoxicil·lina en comparació amb la PDA) per a l'estudi de Shaikh et al.

El guany incremental en QALDs entre estratègies va ser molt petit en el nostre estudi, coincidint també amb els resultats dels dos estudis esmentats anteriorment. No obstant això, en aquests estudis, la PIA va ser l'estratègia més cost-efectiva, mentre que en el nostre estudi, la PDA va ser l'estratègia més cost-efectiva. El nostre guany incremental en QALDs per a la PDA en comparació amb la PIA va ser d'1.44 hores, en comparació amb la PDA de 8.6 hores a l'estudi Shaikh et al., i 3.5 hores a l'estudi de Coco et al. Una possible explicació per a les diferències podria ser que els nostres valors de desutilitat per a l'estat de salut dels nens assignats a l'atzar a la PDA, basats en els valors d' EVA informats pels pares, van ser més baixos que en els estudis anteriors.

Altres dos estudis han avaluat la relació cost-efectivitat de diferents estratègies de prescripció d'antibiòtics, però sense incloure l'opció de la PDA (42,43). Sun et al., (43) en un estudi que també es va basar en una perspectiva social, van aplicar l'enfocament d'espera vigilant tal i com recomanen les guies de l'Acadèmia Americana de Pediatria, és a dir, es considera la prescripció antibiòtica només després d'esperar si els símptomes s'autoresolen. Basant-nos en què l'espera vigilant podria considerar-se una estratègia similar a la PDA, la nostra troballa que la PDA va ser l'estratègia més cost-efectiva corrobora els resultats de Sun et al. (23) en què van trobar que l'espera vigilant era l' estratègia més cost-efectiva. Gaboury et al. (42) van avaluar la relació cost-efectivitat de diferents estratègies de prescripció d'antibiòtics, sense incloure la PDA. Aquests autors, en canvi, van reportar un resultat que coincideix amb Coco et al. (40) i Shaikh et al. (41), en què la PIA va ser més cost-efectiva que l'espera vigilant. No obstant això, en l'estudi de Gaboury et al., i en contrast amb el nostre estudi i els de Coco et al. i Shaikh et al. (adoptant una perspectiva social), l'estratègia de l'espera vigilant en comparació amb la PIA amb amoxicil·lina va ser més costosa.

Tenint en compte el cost de les RAM, en certa mesura, els nostres resultats coincideixen amb l'estudi d'Oppong et al. (53), que va avaluar la relació cost-efectivitat de l'amoxicil·lina en comparació amb el placebo per a adults amb infeccions respiratòries de vies baixes, que van consultar en centres d'AP. Aquest estudi va observar que l'estratègia dominant no va canviar quan es va incloure el cost de les RAM (per a les dades europees però no per a les dades d'altres regions). No obstant, l'amoxicil·lina va ser l'estratègia dominant per a aquestes dades europees, mentre que la PDA va ser l'estratègia més cost-efectiva en el nostre estudi. L'estudi d' Oppong et al. però no va adoptar, com nosaltres, una perspectiva social.

No obstant això, en les comparacions entre les nostres troballes i les dels estudis esmentats anteriorment, les similituds i diferències s'han d' interpretar amb cautela, tant per la varietat de mètodes utilitzats com perquè aquests estudis s'han dut a terme als Estats Units o Canadà amb diferents models de sistemes de salut i costos d'assistència sanitària.

6.2.3. PERSPECTIVES I ACTITUDS SOBRE ELS ANTIBIÒTICS I LA PRECSRIPCIÓ ANTIBIÒTICA DIFERIDA ENTRE ELS PROFESSIONALS SANITARIS

La decisió de prescriure antibiòtics per a algunes infeccions respiratòries depèn no només de factors mèdics sinó també, de factors en la interacció metge-pacient (10,62). Els resultats del nostre estudi corroboren els estudis previs, en el sentit que l'estratègia PDA va ser considerada d'utilitat per als professionals sanitaris en aquest tipus d'escenaris complexos, en la presa de decisions (43–45,61–65).

Els participants del nostre estudi utilitzaven la PDA en casos d'incertesa i, com en estudis anteriors, en situacions específiques, com per exemple, abans del cap de setmana o dies festius (45,46,62–65), com a estratègia de negociació quan els pacients insistien en els antibiòtics (44,46,62–66), i per a certs perfils de pacients (45,46,62–66). Les principals característiques dels pacients candidats a la PDA que van sorgir en el nostre estudi, i consistents amb els estudis previs, van ser: pacients capaços de comprendre l'estratègia (45,46,63), pacients considerats confiables (46,65) i amb sentit comú (46). La relació metge-pacient va ser un altre aspecte clau a considerar en la implementació de la PDA, segons els resultats del nostre estudi. Una qüestió

que no va sorgir, a diferència d'altres estudis, va ser que es va considerar que la PDA enfortia aquesta relació (45,63–65).

La PDA va ser utilitzada pels participants del nostre estudi en situacions aparentment contradictòries: (a) per a pacients que demanaven antibiòtics i es negaven a marxar sense recepta, i per a pacients en els quals es confiava que no utilitzarien immediatament la recepta com en l'estudi de Høye et al. (46) i Sargent et al. (63); i (b) per als pacients que consultaven en visites no programades, en les quals faltava la relació metge-pacient, considerada fonamental per a aquesta estratègia. Aquests escenaris aparentment contradictoris en la utilització de la PDA ressalten la complexitat de la presa de decisions del metge pel que fa a la prescripció d'antibiòtics.

Els avantatges i desavantatges de l'estratègia PDA, en el nostre estudi com en estudis anteriors, estan associats amb el fet que la PDA comporta un enfocament més centrat en el pacient (44,45). Per tant, mentre que la PDA proporciona al pacient una xarxa de seguretat (44,62–66) ja que la recepta la pot utilitzar si ho necessita (46), i d'aquesta manera, empoderant al pacient, fent-lo responsable de la decisió final (44,46,63–65), fet que també comporta la pèrdua de control en la presa de decisions per part del metge (45,62,64,65).

El nostre estudi va identificar algunes barreres importants del sistema de salut per a l'ús apropiat dels antibiòtics i de la utilització de la PDA, principalment: la falta d'una relació metge-pacient en visites no programades, la pobre educació en salut dels pacients i la falta de temps dels professionals. Aquests últims problemes podrien ser abordats simultàniament per infermeres i farmacèutics que es podrien implicar encara més en l'educació els pacients sobre les IRA i el seu tractament. Així mateix, la DAP va ser percebuda, com en estudis anteriors, com una oportunitat d'or per educar les persones sobre els antibiòtics (45,46,63,65).

6.3. FORTALESES I LIMITACIONS

Assaig clínic aleatoritzat

Les troballes de l'ACA s'han de considerar amb algunes limitacions. Una primera limitació va ser el disseny obert de l'estudi, amb resultats informats per les famílies (67). No obstant això, per reduir el possible efecte placebo causat per la naturalesa oberta de l'estudi, totes les famílies van rebre informació estructurada sobre les malalties respiratòries i l'ús de medicaments no

antibiòtics. La segona limitació es relaciona amb els resultats inferits per a la bronquitis aguda i la rinosinusitis, ja que el 85% dels nens inclosos tenien otitis mitjana aguda o faringitis.

No obstant això, els punts forts de l'estudi són el seu disseny pragmàtic i el fet de ser el més gran mai realitzat sobre la PDA en nens al sud d'Europa, en un país amb una alta taxa d'ús d'antibiòtics.

Anàlisi cost-efectivitat

L'estudi cost-efectivitat també té algunes possibles limitacions. La primera és que aproximem la utilitat de l'estat de salut utilitzant un EVA en lloc de mesurar l'estat de salut utilitzant el *standard gamble* o el *time-trade off* , o classificar l'estat de salut utilitzant un qüestionari com el EuroQoL-5D (68). No obstant això, les nostres troballes poden considerar-se fiables, ja que els QALDs es van fonamentar en dades de l'ACA, i corroboren en gran mesura les del metanàlisi de Oh et al. (69). En segon lloc, si bé l'horitzó temporal de 30 dies és suficient per a determinades afeccions, incloses les IRAs, no és suficient per avaluar els beneficis de la reducció del consum d'antibiòtics en relació amb la reducció de les RAMs. En tercer lloc, no es van tenir en compte les consultes mèdiques privades, tot i que el 12.6% de la població espanyola té assegurança mèdica privada (70). Tanmateix, era probable que aquesta limitació hagués tingut un impacte similar en les tres estratègies. L'assaig va tenir poc poder estadístic per a dos factors de costos importants, com ho són les reconsultes i els ingressos hospitalaris (inclosos com a complicacions), i l'evidència més àmplia de dades de pacients individuals (58) suggereix que tots dos són majors amb la NPA, en comparació amb la PDA; per tant, és possible que hàgim subestimat la relació cost-efectivitat de la PDA. En quart lloc, l'estudi es va realitzar en un escenari pre-pandèmia COVID-19, és a dir, abans de la introducció de noves proves ràpides que podrien reduir la incertesa diagnòstica. No es va considerar el cost d'aquestes proves en l'estudi però, al tractar-se d'un cost fix, no modificaria els resultats.

El nostre estudi cost-efectivitat també té vàries fortaleses. Les principals són que l'estudi es va basar en un ACA pragmàtic i, en analitzar la relació cost-efectivitat de diferents estratègies de prescripció d'antibiòtics per a nens amb IRAs, i és el primer estudi d'aquest tipus realitzat fora d'Amèrica del Nord. El nostre estudi, basat en literatura prèvia i un horitzó temporal de 30 dies, també considera el cost de les RAMs, un tema clau no inclòs en els estudis anteriors (40–43).

Finalment, també es va incloure l'impacte dels costos directes i indirectes no sanitaris en el nostre estudi, la qual cosa reflecteix una perspectiva social.

Estudi qualitatiu

La principal limitació de l'estudi qualitatiu va ser que els participants procedien majoritàriament de centres d'AP participants en l'ACA-adults, i la majoria utilitzava la PDA en la seva pràctica clínica. Si bé els avantatges de la PDA es podrien considerar sobreestimats, els nostres resultats són, però, consistents amb la literatura existent. Una segona limitació és que el nostre estudi no va incloure participants d'entorns rurals, tot i que Fletcher et al. (66) no van trobar diferències entre els contextos rurals-urbans en el seu estudi. Una tercera limitació és que, a causa dels pocs professionals que van participar en l'ACA-adults, dos grups de discussió no van ser homogenis pel que fa al nivell socioeconòmic de la població del centre i una infermera que va participar en l'ACA-adults va ser inclosa en un GD. Incloure aquesta participant va permetre la viabilitat d' un dels grups. A més, els investigadors involucrats en la realització i anàlisi del GD van avaluar que la dinàmica no es va veure afectada negativament i les contribucions de la infermera van ser particularment enriquidores.

Una fortalesa important del nostre estudi va ser que incloure professionals que havien implementat la PDA i, per tant, eren molt conscients dels aspectes positius i negatius de la PDA. Una segona fortalesa és que, fins on sabem, aquest és el primer estudi qualitatiu de professionals i PDA realitzat en un país del sud d'Europa, on l'ús d'antibiòtics és comparativament més elevat que al nord d'Europa (23).

Finalment, els tres estudis complementen diversos altres estudis publicats pel nostre grup (22,47,58) destinat a millorar la implementació de l'estratègia de la PDA.

6.4. IMPLICACIONS

6.4.1. IMPLICACIONS PER A LA PRÀCTICA

L'assaig clínic realitzat ha demostrat que la PDA és una estratègia eficaç i segura per reduir el tractament antibiòtic inadequat de les IRAs no complicades en nens, quan el metge té dubtes raonables respecte a la indicació. Per tant, la PDA és una estratègia útil per abordar el problema de salut pública de les RAM (29). No obstant això, la NPA continua sent l'estratègia recomanada

quan està clar que els antibiòtics no estan indicats, com en la majoria de les bronquitis agudes (71).

Suggerim que els resultats d'aquest assaig clínic permetran fer recomanacions sobre la PDA en nens amb IRAs, atès que fins ara no hi ha pautes que estableixin distincions segons els grups d'edat (72). No obstant això, es necessiten estudis addicionals que explorin els perfils de nens per als quals la PDA no seria apropiada, així com estudis que avaluïn les intervencions educatives en relació amb la PDA per a metges, pares i nens (73).

La PDA és l'estratègia més cost-efectiva, encara que la diferència amb la NPA és molt petita i l'alternativa de la PIA és una estratègia dominada. Per aquest motiu, quan els panells de les guies de pràctica clínica consideren la reducció de les RAM, és probable que recomanin estratègies de PDA en aquells casos en què els metges tinguin dubtes sobre si és necessari administrar un antibiòtic en nens amb IRAs.

Les troballes del nostre estudi qualitatiu ressalten el fet que les pressions de temps, la pobre educació en salut dels pacients i la falta d'una relació metge-pacient en les visites no programades, van ser barreres importants per a l'ús òptim d'antibiòtics i per al desplegament de l'estratègia PDA en adults amb IRAs. Per tant, els responsables de les polítiques poden considerar les següents estratègies, per superar aquests desafiaments: (i) la provisió d'educació als pacients relacionada amb la salut i l'autocura de les IRAs, i el foment de l'ús adequat dels serveis de salut, contant amb el suport de les infermeres d'AP i farmacèutics; (ii) millor accés a proves ràpides d'estreptococs; i (iii) reorganització de les agendes dels metges perquè les consultes de les IRAs siguin ateses pel metge responsable, sempre que sigui possible.

Una altra implicació de les nostres troballes en el nostre estudi qualitatiu, és que apunten a una falta de consens sobre alguns dels criteris que han de considerar els metges en implementar l'estratègia PDA. Això suggereix que les guies clíniques sobre el maneig de les IRAs en l'AP han d'especificar millor els criteris per al desplegament de la PDA, inclosos els factors contextuals i del pacient que s'han de considerar en usar estratègies de PDA, així com l'estandardització de les recomanacions d' ús de prescripció per als pacients.

6.4.2. IMPLICACIONS PER A LA RECERCA

Estudis addicionals són necessaris que explorin els perfils de nens per als quals la PDA no seria apropiada, així com estudis que avaluïn les intervencions educatives relacionades amb la PDA per a metges, pares i nens amb IRAs no complicades (73).

Els futurs estudis econòmics s'han de centrar en anàlisis més precises del cost de les RAM durant un període de temps més llarg, i han de considerar les conseqüències de prendre antibiòtics no només en termes de costos, sinó també en termes de desutilitat de diferents estats de salut, incloses les reconsultes i les complicacions.

Finalment, la pobre educació relacionada amb la salut dels pacients va ser un dels principals temes que van sorgir en l'estudi qualitatiu. Com la revisió sistemàtica de Mc Donagh et al (73) va mostrar que les intervencions educatives van ser una de les estratègies més eficaces i segures per a la prescripció òptima d'antibiòtics per a les IRAs, i proposa estudis que combinin les diferents estratègies de reducció de les prescripcions antibiòtiques, com la PDA i les intervencions educatives (73).

7. CONCLUSIONS

7. CONCLUSIONS

- La PDA és una estratègia d'utilitat en nens amb IRAs no complicades, atesos a l'atenció primària, quan el pediatra té dubtes de la necessitat d'antibiòtic.

- La durada i severitat dels símptomes ens els nens amb IRAs no complicades que van ser assignats a la PDA van ser similars a aquells aleatoritzats a la PIA i la NPA.

- La PDA en comparació amb la PIA va donar lloc a una reducció considerable de l'ús d'antibiòtics i dels efectes adversos gastrointestinals associats amb el consum d'antibiòtics.

- Els nens tractats amb la PDA van tenir resultats d'eficiència lleugerament millors que els tractats amb la PIA perquè els seus costos van ser més baixos.

- La PDA va ser també l'estratègia més cost-efectiva en un horitzó temporal de 30 dies si es consideren les RAM, tot i els costos a curt termini més alts en comparació amb la NPA.

- La PDA en adults amb IRAs no complicades atesos a AP, era utilitzada pels metges de família en casos de dubte i considerant factors del context i del perfil del pacient.

- Es van detectar punts febles del nostre sistema d'AP i dels seus usuaris que afecten l'ús adequat tant dels antibiòtics com de la PDA, com les pressions de temps que tenen els professionals, la pobre educació en salut dels pacients i la falta d'una relació metge-pacient en certs escenaris.

- Per tal de superar les debilitats identificades, es proposen: intervencions educatives respecte a les IRAs, als antibiòtics i l'ús òptim dels recursos d'atenció sanitària així com, la millora de la formulació de les recomanacions relacionades amb PDA en les guies.

8. REFERÈNCIES

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9. ANNEXOS

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9.1. ABREVIATURES

ACA: Assaig Clínic Aleatoritzat

AP: Atenció Primària

EVA: Escala Analògica Visual

GD: Grup de discussió

IRA: Infecció Respiratòria Aguda

NPA: No Prescripció Antibiòtica

PDA: Prescripció Diferida d'Antibiòtics

PIA: Prescripció Immediata d'Antibiòtics

RAM: Resistències Antimicrobianes

9.2. PUBLICACIONS COMPLEMENTÀRIES

Delayed antibiotic prescribing for respiratory tract infections: individual patient data meta-analysis

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ABSTRACT

OBJECTIVE

To assess the overall effect of delayed antibiotic prescribing on average symptom severity for patients with respiratory tract infections in the community, and to identify any factors modifying this effect.

DESIGN

Systematic review and individual patient data meta-analysis.

DATA SOURCES

Cochrane Central Register of Controlled Trials, Ovid Medline, Ovid Embase, EBSCO CINAHL Plus, and Web of Science.

ELIGIBILITY CRITERIA FOR STUDY SELECTION

Randomised controlled trials and observational cohort studies in a community setting that allowed comparison between delayed versus no antibiotic prescribing, and delayed versus immediate antibiotic prescribing.

MAIN OUTCOME MEASURES

The primary outcome was the average symptom severity two to four days after the initial consultation measured on a seven item scale (ranging from normal to as bad as could be). Secondary outcomes were duration of illness after the initial consultation, complications resulting in admission to hospital or death, reconsultation with the same or worsening illness, and patient satisfaction rated on a Likert scale.

RESULTS

Data were obtained from nine randomised controlled trials and four observational studies, totalling 55 682 patients. No difference was found in follow-up symptom severity (seven point scale) for delayed versus immediate antibiotics (adjusted mean difference −0.003, 95% confidence interval −0.12 to 0.11) or delayed versus no antibiotics (0.02, −0.11 to 0.15). Symptom duration was slightly longer in those given delayed versus immediate antibiotics (11.4 *v* 10.9 days), but was similar for delayed versus no antibiotics. Complications resulting in hospital admission or death were lower with delayed versus no antibiotics (odds ratio 0.62, 95% confidence interval 0.30 to 1.27) and delayed versus immediate antibiotics (0.78, 0.53 to 1.13). A significant reduction in reconsultation rates (odds ratio 0.72, 95% confidence interval 0.60 to 0.87) and an increase in patient satisfaction (adjusted mean difference 0.09, 0.06 to 0.11) were observed in delayed versus no antibiotics. The effect of delayed versus immediate antibiotics and delayed versus no antibiotics was not modified by previous duration of illness, fever, comorbidity, or severity of symptoms. Children younger than 5 years had a slightly higher follow-up symptom severity with delayed antibiotics than with immediate antibiotics (adjusted mean difference 0.10, 95% confidence interval 0.03 to 0.18), but no increased severity was found in the older age group.

CONCLUSIONS

Delayed antibiotic prescribing is a safe and effective strategy for most patients, including those in higher risk subgroups. Delayed prescribing was associated with similar symptom duration as no antibiotic prescribing and is unlikely to lead to poorer symptom control than immediate antibiotic prescribing. Delayed prescribing could reduce reconsultation rates and is unlikely to be associated with an increase in symptoms or illness duration, except in young children.

STUDY REGISTRATION

PROSPERO CRD42018079400.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Clinical trials have suggested that delayed prescribing for respiratory tract infections is probably safe and effective for most patients

These clinical trials have been underpowered to look at subgroups or harms, and might be subject to selection bias

WHAT THIS STUDY ADDS

Individual patient data from randomised controlled trials and observational studies were used to investigate the effectiveness of delayed antibiotic prescribing (compared with no antibiotics or immediate antibiotic prescribing), overall and for subgroups such as children and those with comorbidities

Delayed prescribing was associated with similar symptom severity and duration as no antibiotics, but patient satisfaction was higher and reconsultation rates were lower; the effectiveness did not differ for any of the high risk subgroups

Delayed prescribing is unlikely to lead to poorer symptom control than immediate prescribing; older age was associated with increasing benefit on symptom severity two to four days after consultation

Introduction

Antimicrobial resistance is an important public health concern.[1 2] The burden of antimicrobial resistance has increased substantially in recent years,[3] and resistance to second and third line antibiotics is predicted to increase by 70% by 2030 if effective public health measures are not implemented.[4]

Reducing unnecessary and inappropriate use of antibiotics is crucial to reduce antimicrobial resistance, particularly in primary care where antibiotics are most prescribed.[2 5] However, antibiotics are commonly used to treat acute respiratory tract infections, despite studies showing that antibiotics have, at best, modest effects.[6-9] Guidelines recommend that the fewest number of antibiotic courses should be prescribed for the shortest period possible.[10 11] However, in the United Kingdom and internationally, antibiotics are still being overprescribed.[12-16] Delayed antibiotic prescribing is a useful strategy that can be used to help reduce antibiotic use, especially during consultations when patients expect to receive an antibiotic prescription.[6] A Cochrane review of 10 trials found that delayed prescribing was as effective as immediate prescribing in terms of clinical outcomes for cough and cold, but less effective for reducing fever, pain, and malaise in some studies, and with lower antibiotic use.[9] However, the review noted a high level of heterogeneity between studies that made combining them in a traditional meta-analysis difficult, and did not allow sufficient power for the examination of subgroups of participants or complications.

These problems can be addressed in part by evidence synthesis using raw individual level data from relevant studies.[17 18] Therefore, we conducted a collaborative individual patient data (IPD) meta-analysis of randomised controlled trials (RCTs) and observational cohort studies to determine the clinical effectiveness of a delayed prescribing strategy on outcomes for respiratory tract infection, overall and for key subgroups of people.

Methods

Protocol and registration

The systematic review and IPD meta-analysis were performed according to the published study protocol that was registered with PROSPERO (CRD42018079400) and was reported in line with PRISMA-IPD (preferred reporting items for systematic reviews and meta-analysis of individual participant data).[19 20]

Eligibility criteria

We included all observational cohort studies and RCTs in a community setting that had a delayed antibiotic prescribing strategy (prescribed an antibiotic but advised the patient not to start taking the course unless their condition deteriorated or failed to improve after a set period), or a watchful waiting approach (observation for a set period to allow spontaneous symptom resolution before antibiotic prescription). Included studies also had a comparator group (no antibiotic prescription or immediate prescription). We excluded studies on antibiotic prescribing that were not RCTs or observational cohorts (eg, cross sectional, case-control, or survey studies), and studies on patients in hospital.

Study identification and selection

Two researchers (HH and TB) searched the Cochrane Central Register of Controlled Trials, Ovid Medline, Ovid Embase, EBSCO CINAHL Plus, and Web of Science to identify eligible quantitative studies (observational cohort studies and RCTs). For observational studies, these searches were undertaken from inception to 23 October 2017. For RCTs, we updated the searches undertaken in the most recent Cochrane review, and searched from 26 May 2017 to 9 November 2017. We searched the International Standard Randomised Controlled Trial Number Registry, performed additional searches through Google, reviewed reference lists of identified papers, and contacted collaborators to identify any additional relevant studies. No language restrictions were reported. The full search strategy is available in the protocol.[19] Searches were rerun on 8 October 2020 but no additional eligible studies were identified.

Two reviewers (HH and TB) independently screened titles and abstracts to determine inclusion criteria. Both reviewers independently assessed the full text of potentially relevant studies and determined eligibility. Discrepancies were resolved through discussion with a third reviewer (BS).

Data collection processes

IPD were requested from the chief investigator for each eligible trial and observational study, initially by email and if no response was received after two emails by letter or telephone call. Once data had been received from the original authors, a complete database of all study data was prepared in Stata (version 15).[21] TB and HH performed internal consistency checks against the published data to ensure the published analysis could be replicated. While the protocol contained a provision to contact study authors about any discrepancies, this did not prove necessary.

Data relating to the general characteristics of the study were extracted, such as study design, country, setting, type of respiratory tract infection, average age, and funding source. We requested all the variables that had been collected in the individual studies from the authors and received the full datasets. These variables were used in the observational studies to calculate the propensity score.

The IPD dataset included baseline data on prescribing strategy, age (0-4, 5-15, 16-65, and >65 years), fever at baseline consultation (greater than or less than 37.5ºC), previous duration of illness (above or below the median for each study), baseline severity of symptoms (average severity across all symptoms being above or below the median of each study), sex, smoking status (smoker or non-smoker), and lung disease (asthma, coronary obstructive pulmonary disease, or any other lung disease). Patients were classified as having a comorbidity if they had any of the chronic conditions (eg, heart disease, diabetes) for which data were collected in the original study. Follow-up data included symptom diaries (if collected)

or days of illness determined by telephone interview, complications resulting in admission to hospital or death, reconsultation with same or worsening illness, and patient satisfaction.

Risk of bias assessment for included studies

Two reviewers (HH and BS; TB and BS) independently assessed the risk of bias of each included study. RCTs were assessed using the Cochrane risk of bias tool for allocation bias (random sequence generation, allocation concealment, baseline imbalance), departures from intended interventions (participant and study personnel blinding, deviations from intended interventions, and analysis in groups to which they were randomised), attrition bias and appropriate methods to account for missing data, detection bias (blinding of outcome assessors), and selective outcome reporting.[22] RCTs were considered to have a high risk of bias if scored as such in more than one of the six domains.

We assessed observational cohort studies using the ROBINS-I (risk of bias in non-randomised studies of interventions) tool for bias due to confounding, selection bias, bias due to deviations from intended intervention, and bias due to missing data and selective reporting.[23] Observational cohort studies were considered to have a high risk of bias if judged to be at serious or critical risk of bias in at least one of the domains.

Specification of outcome measures

The primary outcome of interest was the average symptom severity two to four days after the initial consultation. Symptom severity was measured on a seven item scale (0-6: normal, very little problem, slight problem, moderately bad, bad, very bad, as bad as could be).[24] Secondary outcomes were duration of illness after the initial consultation, complications resulting in admission to hospital or death, reconsultation with the same or worsening illness, and patient satisfaction rated on a Likert scale. Reconsultation and complications (defined as hospital admission or death) were defined as binary outcomes (yes or no). Patient satisfaction data were rescaled to a four point scale to allow comparison across studies.[25]

Synthesis methods

Study and patient level characteristics were described for all studies that contributed IPD. We performed a one stage IPD meta-analysis to obtain summary estimates and 95% confidence intervals for delayed antibiotic prescribing (compared with no antibiotic prescribing or immediate antibiotic prescribing) for each outcome measure.[18 26] The one stage approach combines all the data in a single meta-analysis based on a suitable regression model, with a random effect to account for individual studies. We used a linear regression to model the severity of symptoms and patient satisfaction, a count model to assess the duration of illness, and a logistic regression model to assess complications and reconsultation. All models controlled for baseline severity of illness, age, and condition (acute sore throat, cough or chest infection, otalgia or otitis media, or upper respiratory tract infection), and study type (RCT or observational). All participants were included as randomised and the primary analysis was of complete cases (without imputation for missing data).[27]

We used inverse probability weighting by propensity score analysis to adjust for baseline factor imbalance on measured covariates (such as age, sex, comorbid health conditions, and signs and symptoms at baseline consultation) in observational studies.[28-30] Propensity scores based on covariates associated with any of the outcomes were derived for each observational study. We checked balance by using standardised mean differences and the appendix figures show the results. Propensity scores were also calculated for the RCTs by using the probability of randomised intervention given baseline covariates.[31] An inverse probability of treatment weighting regression was carried out for the combined observational and RCT data to obtain a pooled estimate of treatment effect. We assessed heterogeneity across studies with the I^2 statistic (tested by Higgins I^2 test).[22] Substantial statistical heterogeneity was considered to be present if the I^2 statistic was greater than 50% and reasons for heterogeneity were explored.[22]

We repeated each model after including an interaction term between antibiotic prescribing strategy and subgroup characteristic to obtain summary estimates of the subgroup effects (interactions) of interest, which compared differential effects of interventions across the outcomes. The prespecified subgroups of interest were previous duration of illness (above or below median for the condition), age (<16, 16-64, >65 years), fever at baseline consultation (>37.5°C), comorbid conditions including lung comorbidity (such as asthma or chronic obstructive pulmonary disease), and severity of symptoms at baseline consultation.

We conducted several sensitivity analyses. All analyses were repeated using a two stage approach: IPD for each study were first analysed separately and then meta-analysed by using random effects models.[18] We performed a two stage meta-analysis of extracted study level data from RCTs that did not contribute to the IPD to obtain summary estimates of effects of delayed antibiotic prescribing that combined IPD and non-IPD RCT studies, and to assess IPD availability bias.[32] This process was not possible for observational studies because papers did not control consistently for the same confounding factors. Further sensitivity analyses included repeating the analyses after excluding studies with high risk of bias, and repeating subgroup analyses with age, fever, and baseline severity treated as continuous variables. All meta-analyses were undertaken with Stata software (version 15)[21] and statistical significance was considered at the 5% level.

Certainty of evidence per outcome

We used the five GRADE (grading of recommendations assessment, development and evaluation) considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of the evidence for our analysis of the primary outcomes.[33]

Patient and public involvement

Two patient and public involvement team members (JB and KS) were involved in determining the research question, defining outcome measures, study design, and implementation. They attended all study meetings and are coauthors on this publication. We also shared our research findings with a patient and public involvement panel, allowing them to feedback to us their interpretation of the evidence and how general practitioners might more effectively communicate this information to patients. In the absence of published minimum clinically important differences for the outcomes considered in this study, it was particularly helpful to discuss their interpretation as to whether the differences observed represented a meaningful change. This feedback helped to inform our interpretation of the findings.

Results

Study selection and IPD obtained

We sought IPD from 22 eligible studies (14 RCTs and eight observational studies), totalling 59 705 participants (fig 1).[6 34-49] IPD were obtained from 13 studies (nine RCTs, four observational studies; table 1), totalling 55 682 participants. We were unable to obtain data from nine eligible studies because of no response (n=6), researchers moving on (n=2), or no response after initial agreement (n=1).[50-58]

Study characteristics

Each study included between 129 and 28 856 participants (median 557, interquartile range 316-2690). Participants belonged to a delayed antibiotic prescription group and an immediate or no antibiotic prescription group. Studies were conducted in the UK, the United States, New Zealand, Spain, and one study used data from multiple European studies. Most studies

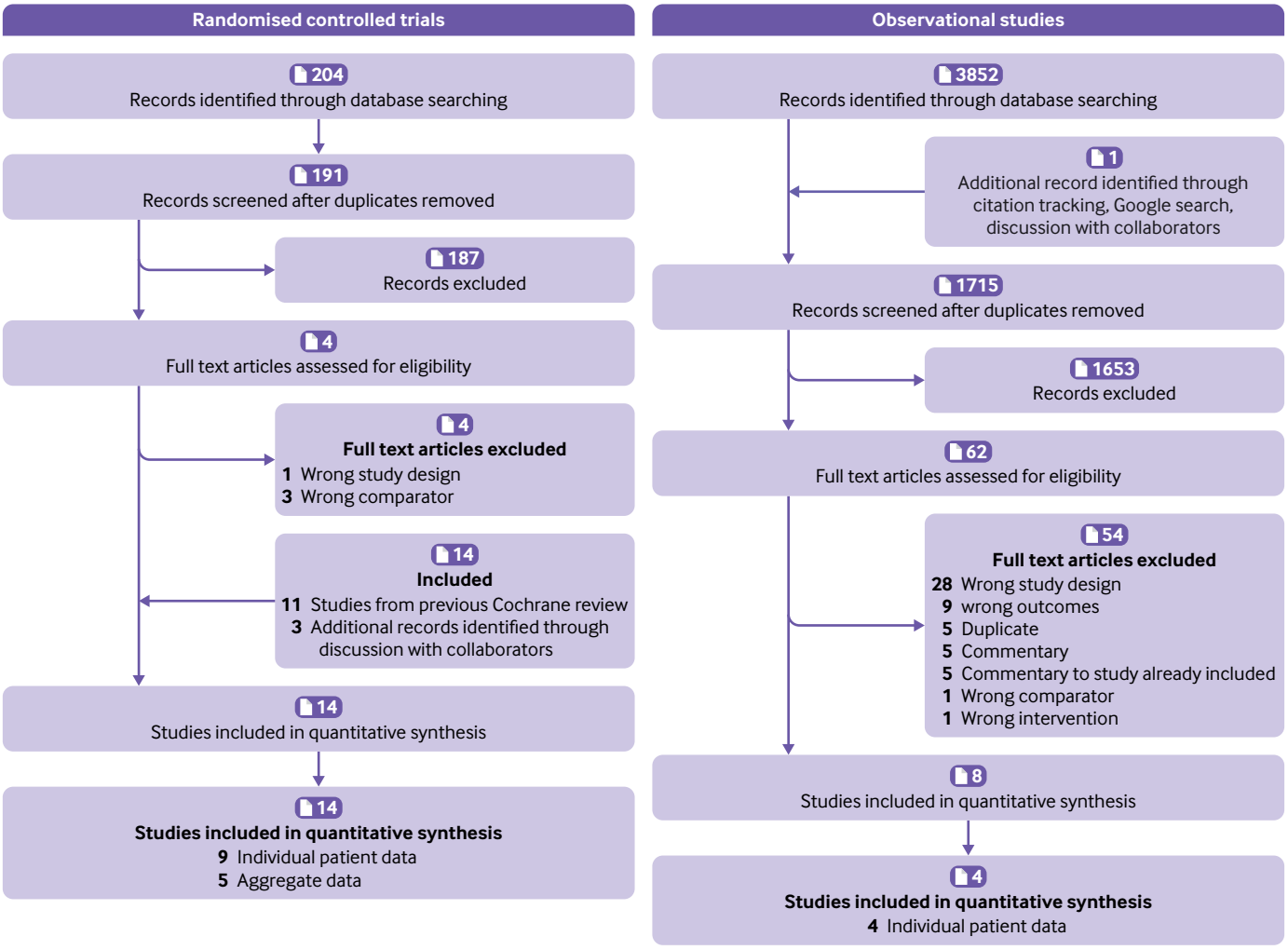

Fig 1 | PRISMA (preferred reporting items for systematic reviews and meta-analysis) flowchart for randomised controlled trials and observational studies on delayed antibiotic prescribing

Table 1 | Characteristics of included studies

Reference	Country and setting	No and age of participants*	Condition	Intervention and comparison group	Type of delay	Outcome					Funding source
						SS	SD	R	C	PS	
Randomised controlled trials											
Little 1997	UK, primary care	716; 25.3 (17.0)	Sore throat	None, immediate, delayed	Prescription to be filled if symptoms did not start to settle after 3 days	+	+	+	+	–	Wessex NHS
Little 2001	UK, primary care	315; 5.0 (2.8)	Acute otitis media	None, immediate, delayed	Prescription collected after 72 hours if child still not improving	+	+	+	+	+	NHS R&D
Arroll 2002	New Zealand, primary care	129; 25.6 (23.0)	Common cold	Immediate, delayed	Prescription to be filled after 3 days if symptoms fail to improve	–	+	–	–	+	NZ Health Research Council
McCormick 2005	USA, paediatric clinic	223; 2.7 (2.7)	Acute otitis media	None, delayed	No antibiotics unless returning with acute ear symptoms within 30 days	+	+	+	+	+	US National Institutes of Health
Little 2005	UK, primary care	807; 39 (20.8)	Lower respiratory tract infection	None, immediate, delayed	Prescription to be filled if symptoms not resolved after 4 days	+	+	+	+	–	Medical Research Council
Chao 2008	USA, paediatric emergency department	232; 5.1 (2.4)	Acute otitis media	None, delayed	Advised to fill prescription if symptoms did not resolve in 2-3 days	–	+	+	–	+	NR
Little 2014	UK, primary care	889; 31.0 (21.2)	Acute respiratory tract infection	None, delayed	Four types: recontact, postdated, collection, patient led	+	+	+	+	+	National Institute for Health Research
De La Poza Abad 2016	Spain, primary care	405; 44.9 (16.6)	Acute respiratory tract infection	None, immediate, delayed	Collection or patient led if symptoms did not start to improve after a few days	+	+	+	+	+	Spanish Ministry of Health
Mas-Dalmau 2021	Spain, primary care	437; 6.3 (3.1)	Acute respiratory tract infection	None, immediate, delayed	Collection or patient led if symptoms did not start to improve after a few days	+	+	+	+	+	Spanish Ministry of Health
Observational cohort studies											
Butler, Francis et al 2012	13 European countries, primary care network	2690; 47.8 (16.3)	Cough or lower respiratory tract infection	None, immediate, delayed	Advised to fill if symptoms did not start to improve after 2-7 days	+	+	+	+	+	European Commission; National Institute for Health Research; Research Foundation-Flanders
Little 2013	UK, primary care	12 626; 34.0 (14.6)	Sore throat	None, immediate, delayed	Patient led	+	+	+	+	–	Medical Research Council; National Institute for Health Research
Little 2017	UK, primary care	28 856; 51.7 (17.9)	Acute lower respiratory tract infection	None, immediate, delayed	Advised to fill if symptoms did not start to improve; median advised delay=3 days	–	–	+	+	–	National Institute for Health Research
Hay 2016	UK, primary care	8320; 3.9 (3.7)	Acute cough and respiratory tract infection	None, immediate, delayed	Advised to fill if symptoms did not start to improve; median advised delay=3 days	+	+	+	+	–	National Institute for Health Research
Studies for which individual patient data unavailable											
Pichichero 1987	USA, paediatric clinic	114; 7.5 (2.6); 7.8 (2.3)	Sore throat	Immediate, delayed	No detail	+	+	+	–	–	RobertWood Johnson Foundation, Eli Lilly & Co, and Elmwood Paediatric Research fund
Gerber 1990	USA, paediatric clinic	113; NR	Sore throat	Immediate, delayed	No detail	+	–	–	–	–	NR
El-Daher 1991	Jordan, paediatric clinic	229; 7.8 (0.23); 8.3 (0.24)	Sore throat	Immediate, delayed	No detail	+	–	–	–	–	Biochemie GmbH and Jordan University of Science and Technology
Dowell 2001	UK, primary care	191; 41.6	Cough	Immediate, delayed	Patient to pick up prescription after 1 week of delay	–	+	+	–	+	Royal College of General Practitioners
Spiro 2006	USA, emergency department	283; 3.2	Acute otitis media	Immediate, delayed	No detail	–	+	–	–	–	US National Institutes of Health and Yale University School of Medicine
Siegel 2003	USA, paediatric clinic	194; 5	Acute otitis media	Immediate, delayed	To be filled only if symptoms did not improve within 2 days	–	–	–	–	–	Whitehall-Robins Healthcare
Marchetti 2005	Italy, primary care	1672; 4.8	Acute otitis media	Immediate, delayed	No detail	–	–	–	–	–	NR
Fischer 2009	USA, emergency department	144; NR	Acute otitis media	Immediate, delayed	To be filled only if symptoms did not improve within 2 days	–	–	–	–	–	NR
Kavanagh 2011	Ireland, primary care	120; 47.6 (16.3); 48 (17.8)	Acute cough or sore throat	Immediate, delayed	No detail	–	–	+	–	+	WestREN, MSD

C=complication; NR=nor reported; PS=patient satisfaction; R=reconsultation; SD=symptom duration; SS=symptom severity.
*Mean (standard deviation).

were conducted in primary care settings (n=11/13). Other settings included a paediatric emergency department (n=1) and paediatric clinic (n=1). Mean age of study participants ranged from 2.7 to 51.7 years. Six, four, and three studies examined all age groups, adult populations only, and paediatric populations only, respectively. One study focused on the common cold, two studies each assessed sore throat and cough, three focused on acute otitis media, and seven included more than one respiratory tract infection. Eleven out of 13 studies (84.6%) reported symptom severity and complication outcomes, 12 studies (92.3%) reported data on symptom duration and reconsultation, and eight studies (61.5%) reported patient satisfaction. Length of follow-up was 28-30 days.

Eligible studies that did not contribute IPD data (five trials and four observational studies) were generally smaller, based on younger populations, and had a higher proportion focused on acute otitis media and sore throat than IPD studies (table 2). Aggregate data were available for 930 patients from five RCTs that did not contribute IPD.

The mean age of IPD study participants was 38.7 years (table 3). Patients in the delayed antibiotics group were younger than those prescribed immediate antibiotics. A lower proportion of patients in the delayed antibiotic group had high baseline severity, longer previous duration of illness, fever at baseline, or lung disease compared with those in the immediate antibiotics group (table 3).

IPD integrity and risk of bias

For all included IPD, we were able to replicate aggregate results that were reported in each of the associated publications. Each individual study contributing IPD was deemed low or moderate risk of bias (fig 2), except for two RCTs that were judged to be high risk of bias on two domains. We also assessed the risk of bias of studies that did not contribute IPD. These studies were judged to have potentially high (n=6) or unclear (n=2) risk of bias (fig 2), and were more likely to be at risk of selection bias but also more likely to have been low risk of bias with respect to blinding.

Table 2 | Comparison of included and excluded study characteristics in individual patient data (IPD)

	No (%) of studies	
Eligible study characteristics	**Included in IPD**	**Excluded from IPD**
Population source		
Primary care	11 (84.6)	3 (33.3)
Emergency department	1 (7.7)	2 (22.2)
Paediatric office (USA)	1 (7.7)	4 (44.4)
Condition		
Common cold	1 (7.7)	0 (0.0)
Acute otitis media	3 (23.1)	4 (44.4)
Sore throat	2 (15.4)	4 (44.4)
Cough	2 (15.4)	2 (22.2)
Respiratory tract infection	7 (53.8)	0 (0.0)
Antibiotic group		
None	12 (92.3)	2 (22.2)
Immediate	11 (84.6)	7 (77.8)
Delayed	12 (92.3)	7 (77.8)

Mean symptom severity two to four days after consultation

One stage random effects IPD meta-analysis of individual RCTs and observational studies combined found that, overall, there was no significant difference in symptom severity between delayed antibiotics and no antibiotics (mean difference on seven point scale −0.003, 95% confidence interval −0.12 to 0.11; seven studies, 3907 participants; table 4, fig 3). No significant difference was found in symptom severity between delayed and immediate antibiotics (0.02, −0.11 to 0.15; eight studies, 3752 participants; table 4, fig 3). Consistent results were obtained using a two stage approach.

Subgroup effects

None of the prespecified subgroup variables modified the effectiveness of delayed antibiotic prescribing relative to no antibiotics (table 5). We found a significant overall interaction effect of age on the effectiveness of delayed relative to immediate antibiotic prescribing (mean difference −0.10, 95% confidence interval −0.17 to −0.03). Children younger than 5 years had a slightly higher follow-up symptom severity score two to four days after consultation with delayed versus immediate antibiotics (0.10, 0.03 to 0.18), whereas no significant difference was found in severity between delayed and immediate antibiotics for other age groups (table 5).

Secondary outcomes

Time to symptom resolution was longer with delayed (11.4 days) than immediate antibiotics (10.9 days; hazard ratio 1.04, 95% confidence interval 1.01 to 1.08). Reconsultation rates were lower with delayed (13%) than with no antibiotics (17%; odds ratio 0.72, 95% confidence interval 0.60 to 0.87), but were not statistically significantly different for delayed (16%) versus immediate antibiotics (22%; odds ratio 0.95, 95% confidence interval 0.74 to 1.22). Complications resulting in hospital admission or death were lower with delayed than with no antibiotics (odds ratio 0.62, 95% confidence interval 0.30 to 1.27) and lower in delayed than immediate antibiotics (0.78, 0.53 to 1.13), but neither result was statistically significant. Patient satisfaction was higher with delayed (3.04 points) than no antibiotics (2.96), but by a small difference (mean difference 0.09, 95% confidence interval 0.06 to 0.11; table 4).

Quality of evidence across studies

Based on GRADE, the overall quality of the evidence for all outcomes in the IPD dataset was judged as moderate, apart from patient satisfaction which was low. Table 6 provides a full evidence profile. Two RCTs were deemed higher risk because of lack of blinding and allocation concealment, which lowered the rating for risk of bias to serious. However, consistent effects across RCTs suggest results are likely to be unbiased. Observational studies were considered high quality

Table 3 | Summary statistics for IPD database. Values are numbers (%) unless stated otherwise

	Combined					RCTs					Observational studies				
Characteristics	No of studies	No of participants	No antibiotics (n=19 360)	Immediate (n=28 129)	Delayed (n=8193)	No of studies	No of participants	No antibiotics (n=985)	Immediate (n=1082)	Delayed (n=1745)	No of studies	No of participants	No antibiotics (n=18 375)	Immediate (n=27 047)	Delayed (n=6448)
Age, years (mean (SD))	13	55 644	31.6 (23.4)	44.1 (22.3)	37.0 (22.4)	9	3779	27.2 (21.9)	23.4 (22.4)	24.2 (21.2)	4	51 865	31.8 (23.4)	44.9 (21.9)	40.4 (21.4)
Sex	12	54 848	—	—	—	8	2992	—	—	—	4	51 856	—	—	—
Male	—	—	7714 (40.4)	11 302 (40.6)	3047 (38.5)	—	—	281 (39.7)	352 (43.0)	621 (42.4)	—	—	7433 (40.5)	10 950 (40.5)	2426 (37.6)
Female	—	—	11 363 (59.6)	16 557 (59.4)	4865 (61.5)	—	—	427 (60.3)	466 (67.0)	845 (67.6)	—	—	10 936 (59.5)	16 091 (59.5)	4020 (62.4)
Condition	13	55 682	—	—	—	9	3812	—	—	—	4	51 870	—	—	—
Cough	4	—	14 067 (72.7)	21 497 (76.4)	5031 (61.4)	1	—	273 (27.7)	262 (24.2)	271 (15.5)	3	—	13 794 (75.1)	21 235 (78.5)	4760 (73.8)
Sore throat	2	—	4813 (24.9)	6058 (21.5)	1926 (23.5)	1	—	232 (23.6)	246 (22.7)	238 (13.6)	1	—	4581 (24.9)	5812 (21.5)	1688 (26.2)
RTI	4	—	364 (1.9)	311 (1.1)	846 (10.3)	4	—	364 (40.0)	311 (28.7)	846 (48.5)	—	—	—	—	—
Otitis media	3	—	116 (0.6)	263 (0.9)	390 (4.8)	3	—	116 (11.8)	263 (24.3)	390 (22.3)	—	—	—	—	—
Baseline severity average score, 0-4 (median (IQR))	13	54 956	0.7 (0.4-1.1)	0.9 (0.6-1.2)	0.8 (0.5-1.2)	8	3125	1.5 (0.75-2.0)	1.5 (0.75-2.1)	1.2 (0.8-1.8)	4	51 831	0.7 (0.4-1.0)	0.8 (0.6-1.2)	0.8 (0.5-1.1)
Below median	—	—	14 387 (75.2)	18 048 (64.7)	5616 (70.8)	—	—	400 (51.3)	490 (57.2)	895 (60.1)	—	—	13 987 (76.2)	17 558 (65.0)	4721 (73.2)
Median and above	—	—	4750 (24.8)	9837 (35.3)	2318 (29.2)	—	—	380 (48.7)	367 (42.8)	593 (39.9)	—	—	4370 (23.8)	9470 (35.0)	1725 (26.8)
Previous duration illness	11	54 462	—	—	—	6	2700	—	—	—	4	51 762	—	—	—
Below median	—	—	7794 (40.9)	10 388 (37.5)	3565 (46.3)	—	—	381 (52.0)	403 (57.4)	683 (53.9)	—	—	7413 (40.5)	9985 (37.0)	2882 (44.8)
Median and above	—	—	11 260 (59.1)	17 318 (62.5)	4137 (53.7)	—	—	351 (48.0)	299 (42.6)	583 (46.1)	—	—	10 909 (59.5)	17 019 (63.0)	3554 (55.2)
Fever at baseline	12	53 761	—	—	—	8	2896	—	—	—	4	50 865	—	—	—
No	—	—	11 169 (59.4)	13 472 (49.3)	4483 (58.8)	—	—	604 (79.7)	668 (81.7)	1002 (82.1)	—	—	10 565 (58.6)	12 804 (48.3)	3381 (53.7)
Yes	—	—	7634 (40.6)	13 865 (50.7)	3138 (41.2)	—	—	154 (20.3)	150 (18.3)	218 (17.9)	—	—	7480 (41.5)	13 715 (51.7)	2920 (46.3)
Any lung disease	11	47 504	—	—	—	7	2389	—	—	—	4	45 115	—	—	—
No	—	—	11 719 (80.1)	19 177 (74.2)	5618 (80.1)	—	—	514 (88.9)	560 (88.9)	1036 (87.7)	—	—	11 205 (79.7)	18 617 (73.8)	4582 (78.5)
Yes	—	—	2914 (19.9)	6679 (25.8)	1397 (19.9)	—	—	64 (11.1)	70 (11.1)	145 (12.3)	—	—	2850 (20.3)	6609 (26.2)	1252 (21.5)
Follow-up symptom severity score, 0-6 (median (IQR))	9	7074	1.8 (1-3)	2.03 (1.2-3.5)	2 (1.1-3.3)	6	2148	2.4 (1.4-3.8)	2.0 (0.8-3.0)	2.0 (1.0-3.0)	3	4926	1.7 (1.0-2.8)	2.1 (1.2-3.7)	2.0 (1.2-3.9)
Symptom duration, days (median (IQR))	11	8607	10 (5-28)	9 (4-28)	7 (3-12)	8	2918	5 (2-11)	6 (3-10)	6 (3-10)	3	5689	13 (6-28)	13 (5-28)	9 (4-28)
Reconsultation	11	54 105	—	—	—	8	2840	—	—	—	4	51 265	—	—	—
No	—	—	15 632 (83.2)	21 483 (77.3)	6433 (85.4)	—	—	556 (72.8)	678 (71.2)	842 (74.9)	—	—	15 076 (83.7)	20 805 (77.5)	5591 (87.2)
Yes	—	—	3155 (16.8)	6302 (22.7)	1100 (14.6)	—	—	208 (27.2)	274 (28.8)	282 (25.1)	—	—	2947 (16.4)	6028 (22.5)	818 (12.8)
Patient satisfaction score, 1-4 (median (IQR))	8	4584	4 (3-4)	4 (3-4)	3.2 (2.7-4)	—	2100	4 (2.7-4)	4 (3-4)	3.2 (2.7-4)	—	2484	3 (3-4)	4 (3-4)	4 (3-4)

IPD=individual patient data; IQR=interquartile range; RCT=randomised controlled trial; RTI=respiratory tract infection; SD=standard deviation.

and achieved balance on potential covariates, but were downrated because residual confounding could not be ruled out.

Sensitivity analyses

One stage versus two stage IPD analysis—consistent results were observed for analyses using a two stage approach. We found no significant difference in symptom severity between delayed and no antibiotics (mean difference 0.04, 95% confidence interval −0.12 to 0.20) or between delayed and immediate antibiotics (0.06, −0.05 to 0.17).

Exploring heterogeneity—additional sensitivity analyses explored the effect of heterogeneity across studies. For symptom severity analyses, heterogeneity was found within the RCTs (I^2=65%), and also between observational studies and RCTs (P<0.005, I^2=68%), for delayed versus no antibiotics. The forest plots clearly showed that the results for Little (2014) were different from the other included studies, perhaps because it was the only study to test several delayed strategies in a single trial. When data from the Little study were excluded from the analyses, the heterogeneity within the RCTs was reduced (I^2=0%), and also the overall heterogeneity between observational studies and RCTs was reduced (P=0.25, I^2=0%). The results remained consistent with the main analysis (no significant difference in treatment effect). We did not observe any important variability for analyses that explored delayed versus immediate antibiotic comparison (heterogeneity between observational studies and RCTs; P=0.02, I^2=24%).

Subgroup analyses with continuous variables—when we replaced dichotomised variables with a continuous variable for each subgroup, the subgroup results did not change. One exception was that patients with lower baseline severity had lower follow-up symptom severity with delayed versus immediate antibiotics (mean difference −0.27, 95% confidence interval −0.34 to −0.19).

Fig 2 | Risk of bias for randomised controlled trials (using the Cochrane risk of bias tool) and observation studies (risk of bias in non-randomised studies of interventions (ROBINS-I) tool). Bold studies contributed to individual patient data

Table 4 | Effect of antibiotic prescribing strategy on all clinical outcomes in one stage random effects IPD meta-analysis. Values are means (95% confidence intervals) unless stated otherwise

	Delayed *v* no antibiotics					Delayed *v* immediate antibiotics				
Outcome	No of participants (none)	No of participants (delayed)	No antibiotics	Delayed	Adjusted* estimate (95% CI)	No of participants (immediate)	No of participants (delayed)	Immediate	Delayed	Adjusted* estimate (95% CI)
Follow-up symptom severity score on days 2-4										
RCT+OS	2716	1192	2.499 (1.44 to 3.56)	2.496 (1.47 to 3.52)	−0.003 (−0.12 to 0.11)	2699	1053	2.68 (1.26 to 4.11)	2.70 (1.36 to 4.05)	0.02 (−0.11 to 0.15)
RCT	484	815	2.77 (1.13 to 4.11)	2.86 (1.6 to 4.06)	0.09 (−0.10 to 0.28)	606	674	2.29 (0.66 to 3.93)	2.40 (0.78 to 4.03)	0.11 (−0.004 to 0.22)
OS	2232	377	2.22 (1.86 to 2.59)	2.12 (1.74 to 2.50)	−0.10 (−0.12 to −0.08)†	2093	379	2.75 (2.24 to 3.26)	2.63 (2.05 to 3.20)	−0.12 (−0.33 to 0.07)
Time to complete symptom resolution (days)										
RCT+OS	3091	1123	11.5 (6.4 to 16.6)	11.6 (6.4 to 16.6)	1.00 (0.82 to 1.23)‡	3275	1442	10.9 (6.3 to 15.6)	11.4 (6.8 to 15.9)	1.04 (1.01 to 1.08)†‡
RCT	540	647	9.42 (4.22 to 14.62)	9.88 (4.37 to 15.38)	1.04 (0.95 to 1.13)	876	962	9.94 (7.17 to 12.70)	11.37 (8.19 to 14.54)	1.14 (1.06 to 1.22)†
OS	2551	476	15.1 (14.8 to 15.4)	15.5 (15.2 to 15.8)	0.98 (0.94 to 1.01)	2399	480	11.96 (5.90 to 18.03)	12.37 (6.40 to 18.35)	1.02 (0.97 to 1.07)‡
Duration of moderately severe or severe symptoms (days)										
RCT+OS	2997	1251	6.2 (5.0 to 7.5)	6.3 (5.0 to 7.5)	1.01 (0.91 to 1.12)	2744	902	5.8 (4.5 to 7.2)	6.4 (5.3 to 7.6)	1.08 (1.01 to 1.17)†
RCT	447	775	6.88 (4.21 to 9.56)	6.81 (4.16 to 9.46)	1.04 (0.94 to 1.15)	347	426	6.36 (5.85 to 6.86)	7.48 (6.94 to 8.02)	1.18 (1.06 to 1.31)†‡
OS	2550	476	6.59 (5.45 to 6.74)	6.74 (6.60 to 6.87)	0.97 (0.93 to 1.01)	2397	476	5.36 (4.02 to 6.70)	5.94 (4.86 to 7.02)	1.05 (0.96 to 1.16)‡
Reconsultation (%, 95% CI)										
RCT+OS	16232	5901	17 (4 to 58)	13 (2 to 52)	0.72 (0.60 to 0.87)†	22430	6157	22 (4 to 58)	16 (3 to 59)	0.95 (0.74 to 1.22)
RCT	509	611	25 (15 to 22)	21 (10 to 31)	0.92 (0.67 to 1.26)	796	865	25 (5 to 41)	24 (8 to 41)	1.29 (0.84 to 1.99)
OS	15723	5290	16 (4 to 60)	12 (2 to 54)	0.54 (0.49 to 0.60)†	21634	5292	22 (4 to 58)	15 (3 to 59)	0.70 (0.66 to 0.75)†
Complication (hospital admission or death; %, 95% CI)										
RCT+OS	16364	5827	0.6 (0.03 to 14)	0.4 (0.02 to 11)	0.62 (0.30 to 1.27)	22371	6017	0.8 (0.1 to 5)	0.6 (0.1 to 4)	0.78 (0.53 to 1.13)
RCT	431	530	0.6 (0.02 to 14)	2.09 (0.01 to 22)	0.35 (0.07 to 1.92)	650	719	0.9 (0.3 to 5)	1.0 (0.3 to 4)	1.25 (0.38 to 4.16)
OS	15933	5297	0.6 (0.01 to 3.7)	0.4 (0.01 to 2.2)	0.64 (0.28 to 1.43)	21721	5298	0.7 (0.3 to 1.7)	0.6 (0.2 to 1.6)	0.22 (0.19 to 0.27)†
Patient satisfaction score										
RCT+OS	1434	674	2.96 (2.55 to 3.36)	3.04 (2.64 to 3.44)	0.09 (0.06 to 0.11)†	1743	805	2.99 (2.33 to 3.64)	2.87 (2.25 to 3.49)	−0.12 (−0.26 to 0.03)
RCT	433	520	3.17 (2.82 to 3.51)	3.26 (2.92 to 3.60)	0.06 (−0.03 to 0.16)	563	649	3.20 (2.33 to 4.06)	3.07 (2.22 to 3.92)	−0.13 (−0.31 to 0.05)
OS	1001	154	2.77 (2.15 to 3.39)	2.85 (2.25 to 3.46)	0.10 (−0.03 to 0.23)	1180	156	2.88 (2.07 to 3.69)	2.77 (2.01 to 3.52)	−0.06 (−0.18 to 0.06)

Adjusted estimate=coefficient, odds ratio, or relative risk; IPD=individual patient data; OS=observational study; RCT=randomised controlled trial.
*Adjusted for baseline severity, age, and condition.
†Statistically significant result. The number of observations for each outcome varies as not all studies collected data on all outcomes; analyses used all available data for each outcome.
‡Estimated using fixed study specific effects and random treatment effect due to convergence difficulties.

Including data from studies that did not provide IPD—we carried out a further sensitivity analysis that included aggregate data from published estimates of studies that did not provide IPD. This sensitivity analysis compared the effect of immediate antibiotic prescribing with delayed antibiotic prescribing. We observed a stronger effect favouring immediate antibiotics for symptom severity (mean difference 0.95, 95% confidence interval 0.71 to 1.18) when including aggregate data, particularly the 1991 study by El-Daher, compared with IPD only analysis (0.09, −0.01 to 0.18; fig 4).

Patient and public involvement

We approached our patient and public involvement panel of 10 people with a history of respiratory tract infections to discuss these results as they emerged. They agreed that the results were reassuring and did not suggest a meaningful benefit to taking antibiotics. They suggested that the way in which delayed prescribing is communicated to patients is important. They felt that some patients might not easily assess and gauge the severity or nature of their symptoms and would need clear guidance to determine whether they needed to take antibiotics. Almost all contributors emphasised that general practitioners need to

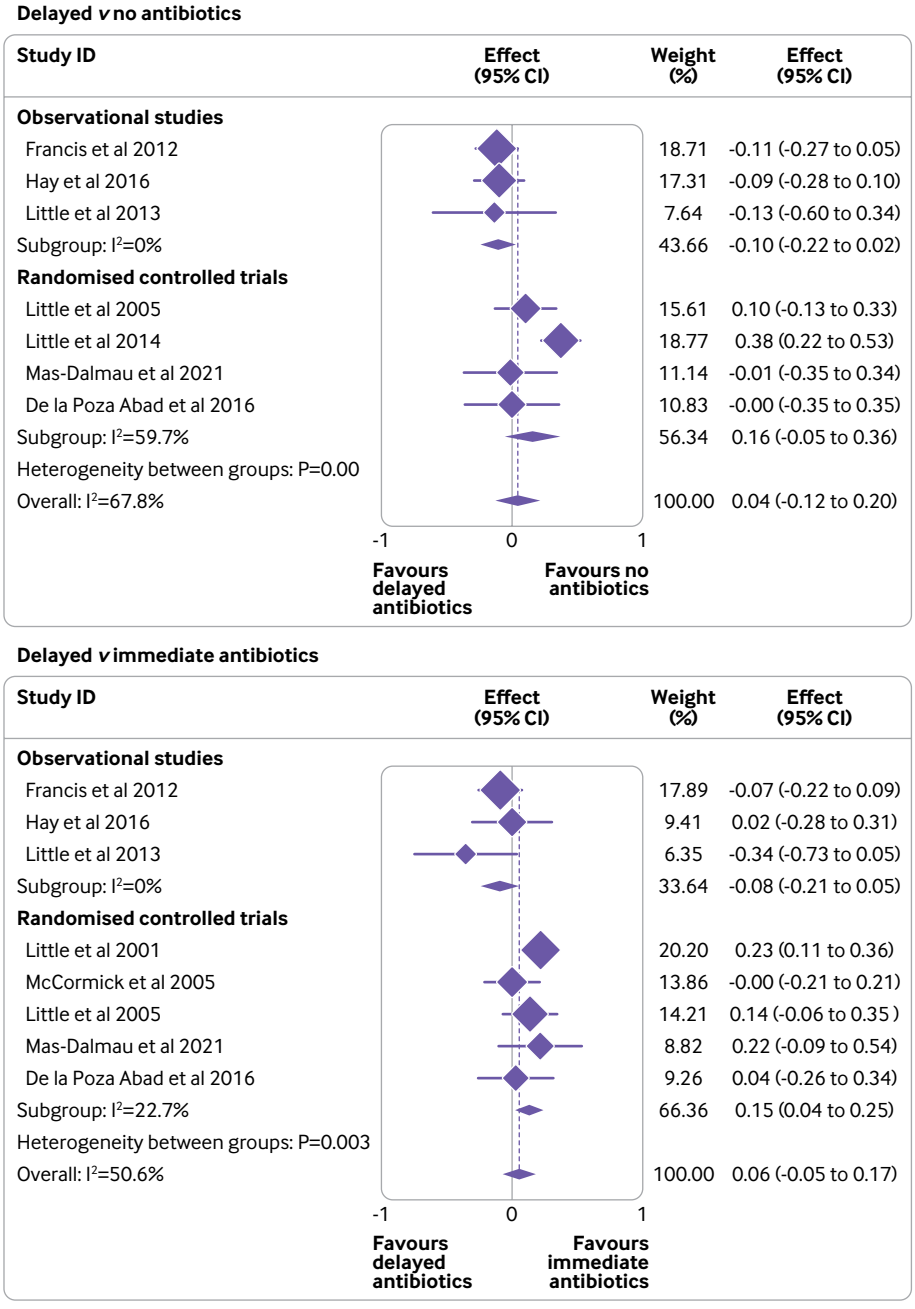

Fig 3 | Unadjusted association between treatment group and symptom severity two to four days after consultation for delayed versus no antibiotics, and delayed versus immediate antibiotics. Weights are from random effects model

Table 5 | Effect of antibiotic prescribing strategy subgroup variable interactions on mean symptom severity score two to four days after consultation for delayed versus no antibiotics, and delayed versus immediate antibiotics

Subgroup	No of studies	No of participants	Interaction (95% CI)	P	Adjusted* mean difference (95% CI)
Delayed *v* no antibiotics					
Previous duration					
Median and above	6	1835			0.008 (−0.21 to 0.23)
Below median		1589	0.05 (−0.23 to 0.34)	0.70	0.03 (−0.22 to 0.28)
Age (years)					
0-4	9	749			−0.20 (−0.24 to −0.15)
5-15		637			0.12 (0.07 to 0.16)
16-64		2153			−0.03 (−0.14 to 0.08)
>65		368	0.11 (−0.02 to 0.24)	0.11	0.07 (−0.36 to 0.51)
Fever					
≥37.5°C	8	1436			−0.03 (−0.15 to 0.09)
<37.5°C		2211	0.01 (−0.16 to 0.18)	0.88	−0.02 (−0.19 to 0.16)
Comorbidity					
Any lung disease	9	438			0.15 (−0.12 to 0.42)
No lung disease		2598	0.14 (−0.05 to 0.34)	0.15	−0.01 (−0.15 to 0.13)
Baseline severity					
Median and above	9	1972			−0.09 (−0.31 to 0.13)
Below median		1935	−0.05 (−0.28 to 0.19)	0.69	−0.14 (−0.33 to 0.04)
Delayed *v* immediate antibiotics					
Previous duration					
Median and above	6	1516	−0.07 (−0.41 to 0.27)	0.68	−0.04 (−0.38 to 0.29)
Below median		1526			0.02 (−0.17 to 0.21)
Age (years)					
0-4	9	729			0.10 (0.03 to 0.18)
5-15		548	−0.10 (−0.17 to −0.03)	0.005†	0.09 (−0.11 to 0.30)
16-64		2107			−0.09 (−0.27 to 0.09)
>65		366			−0.19 (−0.62 to 0.25)
Fever					
≥37.5°C	8	1765	−0.05 (−0.32 to 0.23)	0.80	−0.01 (−0.42 to 0.40)
<37.5°C		1662			0.03 (−0.06 to 0.11)
Comorbidity					
Any lung disease	9	483	0.01 (−0.16 to 0.19)	0.87	0.13 (−0.27 to 0.53)
No lung disease		2554			0.12 (−0.14 to 0.38)
Baseline severity					
Median and above	9	2286	0.35 (−0.23 to 0.93)	0.24	0.10 (−0.57 to 0.77)
Below median		1466			−0.27 (−0.34 to −0.19)

*Adjusted for baseline severity, age, and condition.
†Statistically significant interaction term.

be better at explaining the self-limiting nature of respiratory tract infections and the harmful effects of inappropriate use of antibiotics, using examples or pictures where necessary to relate to people and ensure a clear, simple, and effective message is delivered to patients. Qualitative studies of patients support these observations of our patient and public involvement collaborators.[59]

Discussion

We used individual level data from 13 RCTs and observational cohort studies (55 682 patients) to assess the clinical effectiveness of delayed antibiotic prescribing in patients with respiratory tract infections in the community setting. Overall, our findings suggest delayed antibiotic prescribing is just as effective as no antibiotics for all clinical outcomes, but increased patient satisfaction and reduced reconsultation and complication rates. The reasons for reduced reconsultation rates are unclear, but one suggestion is that if a prescription is delayed, by the time the antibiotic course has finished, symptoms will have had more time to settle and so reconsultation is less likely; or it could be that secondary opportunistic bacterial infections that start later after an initial viral illness are more effectively managed by the later start of a delayed prescription. The second suggestion is supported by findings from the large GRACE trial; one of the groups that reported beneficial effects for antibiotics were people for whom evidence was found of coinfection with viruses and bacterial pathogens.[60]

Delayed antibiotics resulted in longer duration of symptoms than immediate antibiotics, but were as effective for the remaining clinical outcomes. The literature suggests that delayed prescribing could also reduce antibiotic use by patients compared with immediate antibiotics by 23-75%.[48 61 62] Consistent results were obtained in subgroups often considered to be at higher risk, which suggests that delayed prescribing is unlikely to lead to poorer symptom control than immediate antibiotics. In children younger than 5 years and in those with higher symptom scores at baseline, we found statistically significant differences in the symptom severity scores two to four days after consultation. However, the mean differences were only 0.11 points higher on a scale from 0 to 6 (the

Table 6 | Evidence profiles based on GRADE (grading of recommendations assessment, development and evaluation) assessment

No of studies	Study design	Certainty assessment					No of participants		Adjusted* estimate (95% CI)	Quality	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No antibiotics	Delayed antibiotics			
Delayed *v* no antibiotics											
Symptom severity											
4	RCT	Serious†	Not serious‡	Not serious	Not serious§	None	484	815	0.09 (−0.10 to 0.28)	Moderate	Critical
3	OS	Serious¶	Not serious	Not serious	Not serious**	None	2231	377	−0.10 (−0.12 to −0.08)	Low	Critical
7	RCT+OS	Serious	Not serious	Not serious	Not serious§	None	2715	1192	−0.003 (−0.12 to 0.11)	Moderate	Critical
Time to complete symptom resolution (days)											
5	RCT	Serious†	Not serious‡	Not serious	Not serious§	None	540	647	1.04 (0.95 to 1.13)	Moderate	Important
3	OS	Serious¶	Not serious	Not serious	Not serious**	None	2551	476	0.98 (0.94 to 1.01)	Low	Important
8	RCT+OS	Serious	Not serious	Not serious	Not serious§	None	3091	1123	1.00 (0.82 to 1.23)	Moderate	Important
Reconsultation (%)											
5	RCT	Serious†	Not serious‡	Not serious	Not serious§	None	509	611	0.92 (0.67 to 1.26)	Moderate	Important
4	OS	Serious¶	Not serious	Not serious	Not serious**	None	15 723	5290	0.54 (0.49 to 0.60)	Low	Important
9	RCT+OS	Serious	Not serious	Not serious	Not serious§	None	16 232	5901	0.72 (0.60 to 0.87)	Moderate	Important
Complication (hospital admission or death; %)											
6	RCT	Serious†	Not serious‡	Not serious	Not serious§	None	431	530	0.35 (0.07 to 1.92)	Moderate	Important
4	OS	Serious¶	Not serious	Not serious	Not serious**	None	15 933	5297	0.60 (0.28 to 1.43)	Low	Important
10	RCT+OS	Serious	Not serious	Not serious	Not serious§	None	16 364	5827	0.62 (0.30 to 1.27)	Moderate	Important
Patient satisfaction score											
5	RCT	Serious†	Not serious‡	Not serious	Not serious§	None	433	520	0.06 (−0.03 to 0.16)	Moderate	Important
1	OS	Serious¶	NA	Not serious	Not serious**	None	1001	154	0.10 (−0.03 to 0.23)	Low	Important
6	RCT+OS	Serious	Not serious	Not serious	Not serious§	None	1434	674	0.09 (0.06 to 0.11)	Moderate	Important
Delayed *v* immediate antibiotics											
Symptom severity											
5	RCT	Serious†	Not serious	Not serious	Not serious	None	606	674	0.11 (−0.004 to 0.22)	Moderate	Critical
3	OS	Serious	Not serious	Not serious	Not serious	None	2093	377	−0.12 (−0.33 to 0.07)	Low	Critical
8	RCT+OS	Serious	Not serious	Not serious	Not serious	None	2699	1053	0.02 (−0.11 to 0.15)	Moderate	Critical
Time to complete symptom resolution (days)											
7	RCT	Serious	Serious‡	Not serious	Not serious	None	876	962	1.14 (1.06 to 1.22)	Low	Important
3	OS	Serious	Not serious	Not serious	Not serious	None	2399	480	1.02 (0.97 to 1.07)	Low	Important
10	RCT+OS	Serious	Not serious	Not serious	Not serious	None	3275	1442	1.04 (1.01 to 1.08)	Low	Important
Reconsultation (%)											
6	RCT	Serious	Not serious	Not serious	Not serious††	None	796	865	1.29 (0.84 to 1.99)	Moderate	Important
4	OS	Serious	Serious‡	Not serious	Not serious	None	21 634	5292	0.70 (0.66 to 0.75)	Low	Important
10	RCT+OS	Serious	Not serious	Not serious	Not serious	None	22 430	6157	0.95 (0.74 to 1.22)	Moderate	Important
Complication (hospital admission or death; %)											
3	RCT	Serious	Not serious	Not serious	Not serious††	None	650	719	1.25 (0.38 to 4.16)	Moderate	Important
4	OS	Serious	Not serious	Not serious	Not serious	None	21 721	5298	0.22 (0.19 to 0.27)	Low	Important
7	RCT+OS	Serious	Not serious	Not serious	Not serious	None	22 371	6017	0.78 (0.53 to 1.13)	Moderate	Important
Patient satisfaction score											
5	RCT	Serious	Serious‡	Not serious	Not serious	None	563	649	−0.13 (−0.31 to 0.05)	Low	Important
1	OS	Serious	NA	Not serious	Not serious	None	1180	156	−0.06 (−0.18 to 0.05)	Low	Important
6	RCT+OS	Serious	Serious	Not serious	Not serious	None	1743	805	−0.12 (−0.26 to 0.03)	Low	Important

Adjusted estimate=adjusted coefficient, odds ratio, or relative risk; NA=not applicable; OS=observational studies; RCT=randomised controlled trials.
*Adjusted for baseline severity, age, and condition.
†Most RCTs here were not blinded. However, results were not considered biased because similar evidence obtained for blinded studies and observational studies.
‡Statistical but not important heterogeneity.
§Confidence intervals exclude important benefits and harms.
¶Balance achieved for key covariates but residual confounding is still possible.
**Large enough sample size and the 95% confidence interval excludes no effect.
††Wide confidence intervals but not downgraded because overall same conclusion.

equivalent of 1 in 10 participants rating symptoms one point different; for example, as moderately bad rather than a slight problem). This finding suggests that while the effect might be statistically significant, these differences are not clinically significant, and our patient and public involvement panel did not feel that they were likely to be meaningful to patients.

Strengths and limitations

This large study examined the clinical effectiveness of the delayed antibiotic prescribing strategy. Strengths include the ability to control for baseline severity, to assess the quality of the studies based on the full dataset, to explore heterogeneity across studies, and to include results obtained from RCTs and observational studies. Selection bias associated with trials can limit perceived external validity, therefore a strength of this study was the ability to include observational data. Therefore, the external validity was improved and the impact of delayed antibiotic prescribing could be assessed in a clinical trial and a real world setting.[63]

The studies included in the IPD comprised 93% of the population from all eligible studies. The observational studies that did not provide data tended to be smaller studies. The trials for which IPD were not available but that were included in a sensitivity analysis were older studies (dating from 1991 or earlier). Therefore, the difference between the results of the primary analysis

and the sensitivity analysis might be because the trials that did provide IPD are more likely to be relevant to modern patient populations. This difference might also be partly due to eligible trials that did not contribute IPD being based on younger populations, as highlighted in our subgroup analyses which showed that children younger than 5 years might benefit more from immediate antibiotics; however, this is unlikely because the size of the interaction was statistically significant but not clinically important. The studies that were included with aggregate data only were also at high risk of selection, attrition, and other biases. In particular, the study by El-Daher favoured immediate antibiotics over delayed antibiotics. The Cochrane review on this topic suggests that the El-Daher study was one of the less methodologically sound of the included studies. However, the El-Daher study is also the only one undertaken in a lower income setting[9] and it is not clear whether the results of the IPD would generalise to that population. The illness spectrum in a lower income setting might be different, and the previous probability of more serious infection could be higher as could the risk of complications. Different organisms might be more prevalent and underlying comorbid conditions (such as tuberculosis) could lead to a different outcome. Delayed access to reassessment or secondary care in the event of deterioration might also be an important factor.[64] Further research is needed in low to middle income countries to determine whether delayed antibiotic prescribing would be a safe and effective strategy in such settings.

A further limitation relates to the statistical power. Not all outcomes were collected in all studies. Symptom severity data were not collected for all studies, or were only collected for a subset of participants in some studies, resulting in a smaller sample size for the outcome analysis. This outcome was based on diary data and those who completed and returned diaries might not be representative of all study participants, which could also impact generalisability. However, previously published estimates from included studies suggest that those who completed diaries had broadly similar characteristics to all recruited participants.[65 66] Power was also low for the comparisons involving complications because this outcome is extremely rare, even in a dataset as large as the one we compiled. However, this extensive dataset enabled us to include large numbers of participants when analysing outcomes—even the smallest comparison contained 2108 participants—and the rarity of severe complications should be reassuring.

Delayed prescribing is one of several strategies that might help to safely reduce inappropriate antibiotic prescribing and consumption. Other strategies, such as point of care diagnostic testing, patient decision aids, and specific training for health professionals, might also be helpful alone or in combination with delayed prescribing.[67 68] However, none of the studies included in our IPD evaluated these strategies, which means we can only draw conclusions about delayed prescribing when used in isolation rather than in combination with other approaches that might be deployed in a primary care setting.

Looking across all the outcomes we included, we found a tendency for the treatment effect estimates from observational studies to be in the opposite direction from those of RCTs. This finding could be because of residual confounding (eg, use of other, or known or unmeasured covariates such as patient presence and compliance) in observational studies, differences in how delayed prescribing is implemented in real life versus RCTs, and varying time periods. However, the overall heterogeneity estimates for the combined RCT and observational study analyses were not high or could be explained by individual studies at higher risk

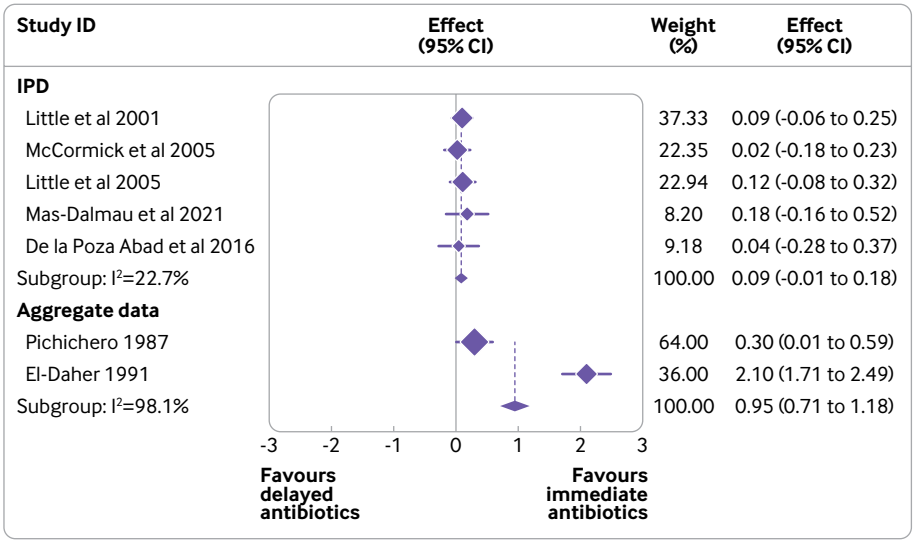

Fig 4 | Difference in mean symptom severity two to four days after consultation; aggregate meta-analysis including studies that did not provide individual patient data (IPD)

of bias. We recognise that our pooled effect estimates were influenced by observational studies because these contributed large numbers of individual participants to the overall pooled dataset. The magnitude of the pooled treatment effect needs to be interpreted with caution because, while propensity scores were used to control for measured confounding, there might still be residual confounding from unmeasured confounders.

Conclusions and implications

Delayed prescribing appears to be a safe and effective antibiotic strategy for most patients, including those in higher risk subgroups. Compared with a no prescription approach, delayed prescribing probably reduces reconsultation rates, and therefore the workload of general practitioners, with slightly higher levels of patient satisfaction. Compared with immediate antibiotics, delayed prescribing does not result in higher complication rates (if anything, they are lower) and it does not significantly decrease patient satisfaction. Delayed prescribing could be used as a standalone interventional approach, but it might also be a way of resolving mismatched expectations between clinician and patient.

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Data sharing: The IPD database can be shared subject to the approval of the study collaborators.

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination to participants and related patient and public communities: The findings of the study were disseminated to all members of the patient and public involvement panel at the time of our discussion with them as reported in this paper. No members asked for further disseminated information.

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Supplementary information: appendix figures

BMC Family Practice

RESEARCH ARTICLE Open Access

Use of delayed antibiotic prescription in primary care: a cross-sectional study

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Abstract

Background: One of several strategies developed to reduce inappropriate antibiotic use in situations where the indication is not clear is delayed antibiotic prescription (DAP), defined as an antibiotic prescription issued for the patient to take only in case of feeling worse or not feeling better several days after the visit. We conducted a survey to identify DAP use in Spanish primary care settings.

Methods: We surveyed 23 healthcare centers located in 4 autonomous regions where a randomized controlled trial (RCT) on DAP was underway. The primary variable was use of DAP. Categorical and quantitative variables were analyzed by means of the chi-squared test and non-parametric tests, respectively.

Results: The survey was sent to 375 healthcare professionals, 215 of whom responded (57.3% response rate), with 46% of these respondents declaring that they had used DAP in routine practice before the RCT started (66.6% afterwards), mostly (91.5%) for respiratory tract infections (RTIs), followed by urinary infections (45.1%). Regarding DAP use for RTIs, the most frequent conditions were pharyngotonsillitis (88.7%), acute bronchitis (62.7%), mild chronic obstructive pulmonary disease exacerbations (59.9%), sinusitis (51.4%), and acute otitis media (45.1%). Most respondents considered that DAP reduced emergency visits (85.4%), scheduled visits (79%) and inappropriate antibiotic use (73.7%) and most also perceived patients to be generally satisfied with the DAP approach (75.6%). Having participated or not in the DAP RCT (74.1% versus 46.2%; $p < 0.001$), having previously used or not used DAP (86.8% versus 44.2%; $p < 0.001$), and being a physician versus being a nurse (81.8% versus 18.2%; $p < 0.001$) were factors that reflected significantly higher rates of DAP use.

Conclusions: The majority of primary healthcare professionals in Spain do not use DAP. Those who use DAP believe that it reduces primary care visits and inappropriate antibiotic use, while maintaining patient satisfaction. Given the limited use of DAP in our setting, and given that its use is mainly limited to RTIs, DAP has considerable potential in terms of its implementation in routine practice.

Keywords: Delayed antibiotic prescription, Primary care, Survey, Infectious disease

Background

Infectious diseases are among the most common reasons for visits to primary care centers. Approximately 70% are respiratory tract infections (RTIs), most frequently, rhinitis, pharyngitis, and acute bronchitis [1]. Most RTIs are self-limiting, with recent reviews suggesting that —except in the case of an underlying comorbidity— antibiotics offer little or no clinical benefit [2, 3]. Inappropriate prescription of antibiotics —as well as implying a cost for national health systems and fostering a false belief that antibiotics are always beneficial— has serious consequences for patients' health, including the risk of adverse effects and antimicrobial resistance [4]. In recent years, the World Health Organization (WHO) has prioritized the problem of antimicrobial resistance in its agenda [5].

Several strategies have been developed to reduce inappropriate use of antibiotics. One of them is delayed antibiotic prescription (DAP), whereby the prescription is issued for the patient to take only in the event of feeling worse or not feeling better several days after the visit. DAP has been widely studied and applied in English-speaking countries [6],

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and is especially recommended as a potential strategy for treating acute uncomplicated RTIs [7]. DAP has also been shown to be effective in uncomplicated urinary tract infections [8] and in acute infective conjunctivitis [9], with better results when DAP is implemented in conjunction with appropriate and structured advice for the patient [10].

In Spain there is little information about the use of DAP. Llor et al. [11] conducted an observational study that showed that DAP resulted in reduced antibiotic use. More recently, our research group published results for a multicenter randomized controlled trial (RCT) of DAP [12] that confirmed reduced antibiotic use, similar satisfaction levels with other antibiotic strategies, and no increase in adverse effects or re-visits [13]. Since no information on use of DAP is available for our setting, despite its effectiveness in treating acute uncomplicated RTIs, we conducted a survey in primary care healthcare centers in Spain.

Methods

Design

Multicenter cross-sectional survey.

Study population

Healthcare staff from 23 Spanish health centers where an RCT on DAP was being conducted [12]. The healthcare centers were located in the 4 Spanish Autonomous Regions of Catalonia, Navarra, Madrid, and the Basque Country. Included were all healthcare professionals employed in those centers regardless of whether or not they were participating in the RCT.

The selected participants were those authorized to prescribe treatments, namely, primary care physicians, medical residents and registered nurses. Nurses were taken into account, given that in Spain they are authorized to attend to initial emergency cases in primary care centers [14]. We defined respondents as all individuals who returned a filled-in questionnaire.

Survey development

We developed the questionnaire based on a review of the scientific literature. Using a combination of descriptors and free-text terms (Additional file 1), we conducted a search in MEDLINE (via PubMed, from inception until March 2012) to identify studies of DAP.

We piloted the questionnaire with 6 healthcare professionals (2 primary care physicians, 2 nurses and 2 epidemiologists) and evaluated its sensitivity. The final questionnaire included 22 items grouped into 5 sections (Additional file 2): (1) sociodemographic data; (2) clinical scenarios; (3) awareness of and participation in the DAP RCT; (4) use of DAP; and (5) perceptions of DAP. Referring to the clinical scenarios, with the aim of assessing use of DAP in routine practice, the respondents were asked about 2 cases of uncomplicated RTIs posing clinical uncertainty regarding the prescription of antibiotics, namely, pharyngotonsillitis and chronic obstructive pulmonary disease (COPD) exacerbation. An online tool was used to run the survey and to collect responses, and 3 reminders were sent by email at 2-week intervals following initial contact.

Analysis

The data were analyzed descriptively, with absolute frequencies and proportions calculated for categorical variables, and means and standard deviations (or median and range when normality criteria were not fulfilled) calculated for quantitative variables. Groups of categorical variables were compared using the chi-squared test, and groups of quantitative variables using analysis of variance (ANOVA) for unpaired data or non-parametric tests (Mann-Whitney).

Differences in DAP use by disease and by healthcare professional characteristics (age, occupation, and RCT participation) were analyzed by comparing proportions using the chi-squared test. Responses to open questions were analyzed and coded according to the most frequent topics. Statistical significance was set to $p < 0.05$ and data were analyzed using SPSS version 24.0 (IBM-SPSS).

Results

A total of 375 healthcare professionals received the questionnaire, of whom 37.7% were participating in the RCT; 215 individuals replied to the questionnaire (response rate 56%). The mean age of respondents was 46.2 (10.1 SD) years, 72.6% ($n = 156$) were family physicians, and 74.4% ($n = 160$) were women. Respondent characteristics are described in Table 1.

Of the total respondents ($n = 215$), 46% ($n = 99$) had used DAP in routine practice before the DAP RCT (37.8% of physicians and 15.3% of nurses; $p = 0.013$), and 66.6% ($n = 143$) used DAP in routine practice during the DAP RCT (69.2% of physicians and 20.3% of nurses; $p < 0.001$). Regarding how DAP was applied, 76.3% ($n = 106$) of patients received DAP directly, 15.1% ($n = 21$) collected the prescription from reception, 7.2% ($n = 10$) were referred to their physician, and other strategies were used for 1.4% ($n = 2$) of patients.

DAP was used mainly for acute RTIs (n = 143; 91.5%), followed, at a distance, by urinary infections (45.1%), dental infections (36.6%), skin infections (23.9%), eye infections (14.8%), digestive infections (5.6%), and other infections (7%) (Fig. 1). Regarding DAP use for RTIs, the most frequent conditions were pharyngotonsillitis (88.7%), acute bronchitis (62.7%), mild COPD exacerbations (59.9%), sinusitis (51.4%), and acute otitis media (45.1%) (Fig. 2). Regarding prescription strategies for patients with pharyngotonsillitis, 50.2% received no antibiotic prescription, 3.3% immediate antibiotic prescription, and 30.7% received DAP (19.1% directly and 11.6% at reception). As for mild COPD exacerbations, 0 and 84.7% received no and immediate antibiotic prescriptions, respectively, and 4.2% received DAP (directly in all cases).

Table 1 Descriptive characteristics of delayed antibiotic prescription (DAP) survey respondents

		Number	Percent
Profession	Physician	156	72.6%
	Nurse	59	27.4%
Participating center	Catalonia	115	53.5%
	Madrid	72	33.5%
	Navarra	23	10.7%
	Basque Country	5	2.3%
Teaching center	Yes	146	67.4%
	No	70	32.6%
Rapid diagnostic techniques[a]	Multistix urine test strip	194	90.2%
	Reactive Strep-A	39	18.1%
	Reactive PCR	22	10.2%
	Other	15	7%
Used DAP before RCT	Yes	99	46%
	No	57	26.5%
Used DAP during RCT	Yes	143	66.6%
	No	16	7.4%
DAP type (for DAP users)	Direct (patient-led)	106	76.3%
	Collection from reception	21	15.1%
	Referral to physician	10	7.2%
	Other	2	1.4%

[a]Multistix urine test strip (in diagnosis of urine infection), Rapid antigen detection test (Group A streptococcal in pharyngitis) and C-reactive protein (in assessing etiological diagnosis of acute respiratory infection)

Strongly agree/agree responses from the survey participants (Fig. 3) were as follows: DAP reduces the number of primary-care emergency visits (85.4%; $n = 134$); DAP reduces the number of scheduled visits (79%; $n = 124$); DAP is a good strategy to optimize the use of available resources (85.2%; $n = 133$); DAP reduces inappropriate antibiotic use (73.7%; $n = 115$); patients were satisfied with DAP (75.6%; $n = 118$); and DAP can change patients' perceptions about the need for antibiotics for certain infections (68.8%; $n = 108$).

Professionals who had already used DAP in routine practice had a consistently more favorable perspective on DAP, as these strongly agreed/agreed more frequently than those who had not used DAP, as follows: DAP reduces the number of primary-care emergency visits (93.6% versus 80%; $p < 0.001$); DAP is a good strategy to optimize the use of available resources (95.1% versus 78.9%; $p < 0.001$); DAP reduces inappropriate antibiotic use (86.9% versus 65.2%; $p < 0.001$)); patients were satisfied

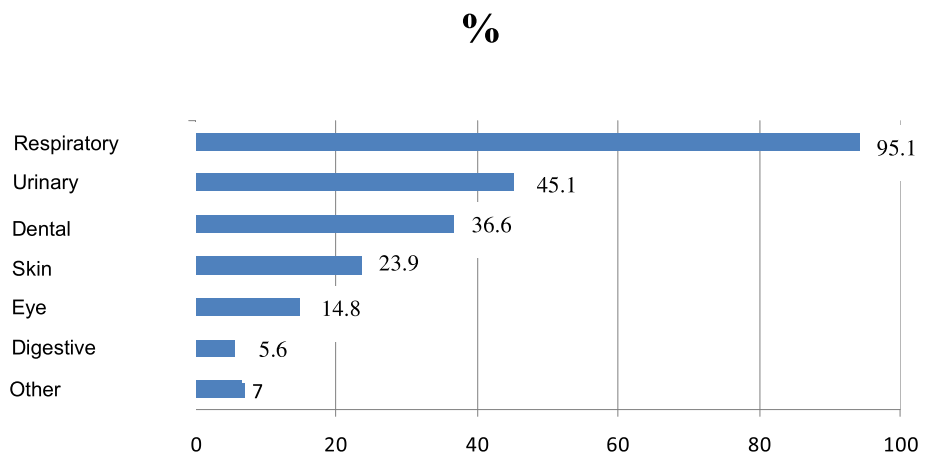
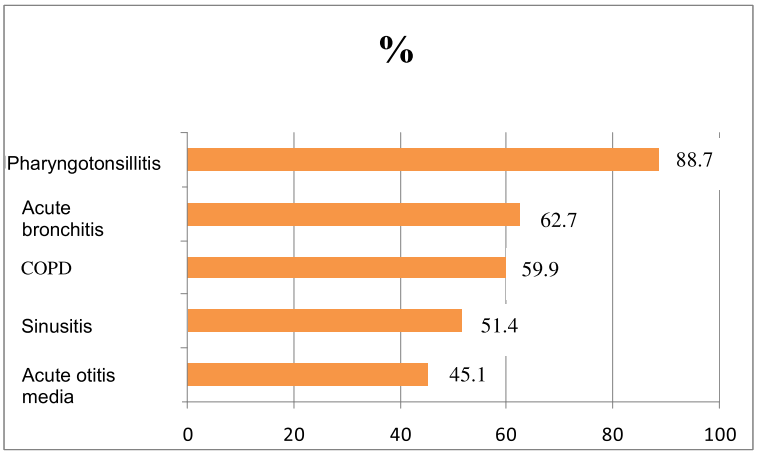


Fig. 1 Delayed antibiotic prescription use by infection type



COPD: chronic obstructive pulmonary disease.

Fig. 2 Delayed antibiotic prescription use by respiratory disease

with DAP (91.8% versus 65.3%; $p < 0.001$); and DAP can change patients' perceptions about the need for antibiotics for certain infections (87.1% versus 56.9%; $p < 0.001$). Differences were only non-significant for DAP reducing the number of scheduled visits (80.7% versus 77.9%; $p = 0.131$).

Factors that reflected significantly higher rates of DAP use were as follows: participation versus non-participation in the DAP RCT (74.1% versus 46.2%; $p < 0.001$), having previously used versus not having previously used DAP (86.8% versus 44.2%; $p < 0.001$), and being a physician versus being a nurse (81.8% versus 18.2%; $p < 0.001$). No significant differences in DAP use were observed in relation to the following factors: having rapid diagnostic techniques available; age (mean 46.7 versus 46.4 years; $p = 0.796$); work experience (mean 21.8 versus 21.71 years; $p = 0.929$); and employment in a teaching center versus a non-teaching center (69.2% versus 65%; $p = 0.561$).

Discussion

Main findings

Our study shows that an important proportion of primary healthcare professionals make no use of DAP strategies for the treatment of acute uncomplicated RTIs. DAP, when used, was most frequently used for pharyngotonsillitis and least frequently used for otitis and sinusitis. Professionals who became aware of DAP during the RCT started to implement a DAP strategy in their own routine clinical practice.

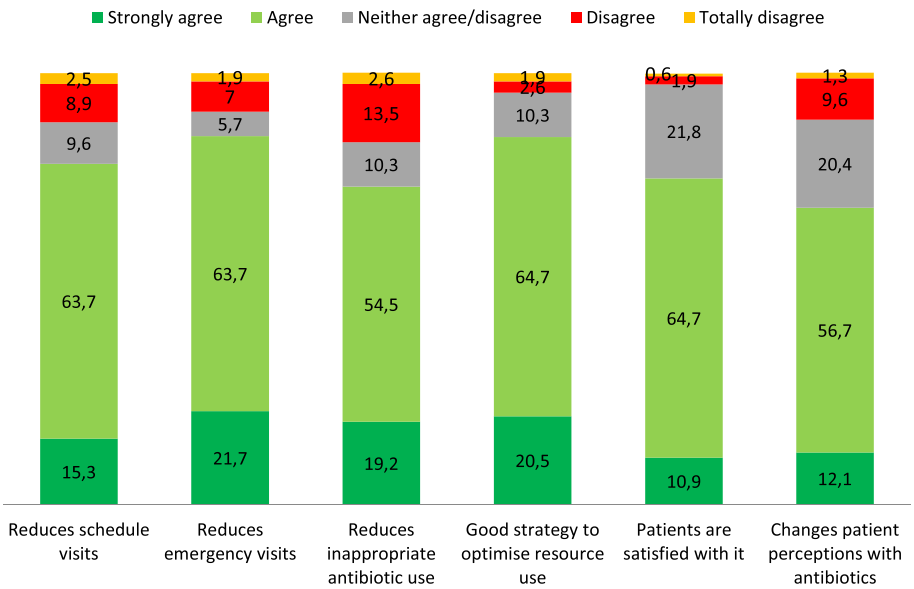


Fig. 3 Healthcare professional perceptions of delayed antibiotic prescription

Most of the respondents considered DAP to reduce the number of primary-care emergency visits (85.4%), the number of scheduled visits (79%), and inappropriate antibiotic use (73.7%), and most also considered that patients were broadly satisfied with DAP (75.6%). Use of DAP was not affected by the fact of having rapid diagnostic techniques available, age, work experience or the fact of being employed in a teaching versus a non-teaching center.

Our results in the context of previous research

The level of use of DAP as documented in our study (46%) is lower than in northern European countries; a Norwegian study [15], for instance, reported that almost 70% of family physicians considered DAP to be a feasible strategy for treating uncomplicated RTIs. According to that study, sinusitis was the infection for which DAP was most used, contrasting with our study, in which DAP was most frequently used for pharyngotonsillitis.

Although our results show lower use of DAP in Spain than in English-speaking countries, noteworthy is the fact its use led to more positive perceptions of DAP. This finding resonates with results from other countries with a lengthy DAP track record [16]. Note, however, that a qualitative study conducted in the UK showed that DAP was not considered to be a feasible strategy by physicians, as these felt uncomfortable giving patients clinical responsibilities, and only used it for uncertain diagnoses or to avoid conflict with patients [17]. This would indicate that it is important to determine the baseline situation of a country before designing, disseminating, and implementing DAP strategies in routine practice. This was done, for instance, in Australia [18], where, in an effort to combat high antibiotic prescription rates, strategies, including DAP, were designed and implemented to reduce inappropriate antibiotic use.

Spain continues to have a particularly high rate of antibiotic prescription [19]; moreover, the latest update on antibiotic use published by the European Center for Disease Prevention and Control —referring to the period 2010–2014— pointed to an increasing trend in the European Union in general [20]. High antibiotic prescription rates not only represent an economic burden but are also a serious public health problem, since overuse of antibiotics is the main cause of antimicrobial resistance. The latest data for the European Union confirm that a growing number of patients are infected by resistant bacteria [21].

Patients are not generally aware of the serious implications of antimicrobial resistance, nor are they aware that they too can contribute to the solution [22]. Although the association between antibiotic prescription and antimicrobial resistance is well documented, studies show that reduced antibiotic prescription at the primary care level can help reduce antibiotic resistance [23]. Evidence-based strategies are needed to reduce inappropriate antibiotic use in primary care settings, and DAP is one such strategy that has been shown to be highly effective [6, 13]. The absence of information on DAP use in Spain motivated us to conduct this study.

Limitations and strengths

The main limitation of our study was the low response rate to the survey despite several reminders. Another limitation was that we exclusively surveyed professionals from healthcare centers where the DAP RCT was conducted. Thus, since some non-participants in that RCT may have become aware of DAP through word-of-mouth, our results on DAP use may be overestimated. Nonetheless, this fact merely strengthens our conclusions.

The main strengths of our study are that, as far as we know, this is the first Spanish multicenter survey (23 participating centers) exploring use of DAP among healthcare professionals, and evaluating predictive factors regarding DAP use. Another potential strength is that we also included nurses in the survey; given that they prescribe symptomatic treatment and participate in DAP procedures.

Implications for practice and research

The current level of use of DAP by healthcare staff in Spain suggests that much needs to be done to make this strategy known among primary care health professionals. Healthcare policymakers should also be made aware of DAP as a potentially effective way to improve decision-making regarding antibiotics and to rationalize their prescription and use in primary care settings. It is also important to foster awareness of DAP as a potential treatment strategy among patients. In order to achieve this we should make known to the GP both the results obtained in other countries, and the excellent results that were obtained in our own country without forgetting beforehand to address the barriers that we could find for Implement the DAP in the usual GP practice as well as the barriers that patients can offer to accept them. Further studies of optimal strategies for implementing DAP in primary care, both in Spain and elsewhere. Thus qualitative research is necessary, which will reveal the barriers that we can find for its implementation by both sides, professionals and patients. As well as it will also provide us with information about the perspectives of the patients and how they receive the DAP and how they use. In this way our group are conducting a qualitative research study in parallel to assess these items, with groups of both professionals and patients.

Conclusions

Most primary care professionals in Spain still do not use DAP in routine practice. Once professionals become aware of and use DAP, they report that this strategy reduces primary care scheduled and emergency visits and inappropriate antibiotic use, while maintaining patient satisfaction. These findings, combined with positive efficacy and safety results from clinical studies of DAP, highlight the need to actively implement this strategy in primary care.

Additional files

Additional file 1: Search strategy. Search strategy in MEDLINE (via PubMed) from inception up to March 2012. (PDF 12 kb)

Additional file 2: Delayed antibiotic prescription (DAP) questionnaire. This is a survey aimed at understanding perceptions and attitudes of primary care professionals to antibiotic prescription for uncomplicated infections. (PDF 35 kb)

Abbreviations
COPD: Chronic obstructive pulmonary disease; DAP: Delayed antibiotic prescription; RCT: Randomized controlled trial; RTI: Respiratory tract infection

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Availability of data and materials
All data generated or analyzed in this study are included in this published article and its additional files.

Authors' contributions
MPA, PAC, and GMD designed the study and were responsible for conducting the study. All other authors (MPA, PAC, GMD and LMG and CL) critically commented on the study design. MPA and IG analyzed the data. MPA, GMD, LMG, CL, and PAC interpreted the data. MPA wrote the first draft of the manuscript. All authors critically read and approved the final version.

Ethics approval and consent to participate
Given that the questionnaire was completed by medical professionals who had been previously informed, by completing the questionnaire it was considered that their informed consent had been given.
The protocol was approved by the Clinical Research Ethics Committee of the Jordi Gol University Institute for Primary Care Research (IDIAP).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Publisher's Note

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Original Investigation

Prescription Strategies in Acute Uncomplicated Respiratory Infections
A Randomized Clinical Trial

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IMPORTANCE Delayed antibiotic prescription helps to reduce antibiotic use with reasonable symptom control. There are different strategies of delayed prescription, but it is not yet clear which one is the most effective.

OBJECTIVE To determine the efficacy and safety of 2 delayed strategies in acute, uncomplicated respiratory infections.

DESIGN, SETTING, AND PARTICIPANTS We recruited 405 adults with acute, uncomplicated respiratory infections from 23 primary care centers in Spain to participate in a pragmatic, open-label, randomized clinical trial.

INTERVENTIONS Patients were randomized to 1 of 4 potential prescription strategies: (1) a delayed patient-led prescription strategy; (2) a delayed prescription collection strategy requiring patients to collect their prescription from the primary care center; (3) an immediate prescription strategy; or (4) a no antibiotic strategy. Delayed prescription strategies consist of prescribing an antibiotic to take only if the symptoms worsen or if there is no improvement several days after the medical visit.

MAIN OUTCOMES AND MEASURES The primary outcomes were the duration of symptoms and severity of symptoms. Each symptom was scored using a 6-point Likert scale (scores of 3 or 4 were considered moderate; 5 or 6, severe). Secondary outcomes included antibiotic use, patient satisfaction, and patients' beliefs in the effectiveness of antibiotics.

RESULTS A total of 405 patients were recruited, 398 of whom were included in the analysis; 136 patients (34.2%) were men; mean (SD) age, 45 (17) years. The mean severity of symptoms ranged from 1.8 to 3.5 points on the Likert scale, and mean (SD) duration of symptoms described on first visit was 6 (6) days. The mean (SD) general health status on first visit was 54 (20) based on a scale with 0 indicating worst health status; 100, best status. Overall, 314 patients (80.1%) were nonsmokers, and 372 patients (93.5%) did not have a respiratory comorbidity. The presence of symptoms on first visit was similar among the 4 groups. The mean (SD) duration of severe symptoms was 3.6 (3.3) days for the immediate prescription group and 4.7 (3.6) days for the no prescription group. The median (interquartile range [IQR]) of severe symptoms was 3 (1-4) days for the prescription collection group and 3 (2-6) days for the patient-led prescription group. The median (IQR) of the maximum severity for any symptom was 5 (3-5) for the immediate prescription group and the prescription collection group; 5 (4-5) for the patient-led prescription group; and 5 (4-6) for the no prescription group. Patients randomized to the no prescription strategy or to either of the delayed strategies used fewer antibiotics and less frequently believed in antibiotic effectiveness. Satisfaction was similar across groups.

CONCLUSIONS AND RELEVANCE Delayed strategies were associated with slightly greater but clinically similar symptom burden and duration and also with substantially reduced antibiotic use when compared with an immediate strategy.

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Invited Commentary

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Respiratory diseases are one of the most common reasons for consultation with family physicians, the most frequent being rhinitis, pharyngitis, and acute bronchitis.[1] Most respiratory infections are self-limiting, and recent systematic reviews have suggested that antibiotics modify the course of most of these infections only slightly.[2-8] Nevertheless, in the United States, about 60% of patients with a sore throat and 71% of patients with acute uncomplicated bronchitis still receive an antibiotic prescription.[9,10] Overprescription of antibiotics not only increases resistance to these drugs[11,12] but also strains resources, places patients at risk of adverse effects, and increases the number of future consultations for similar episodes.[13-15] In primary care, the availability of diagnostic procedures is generally limited, contributing to diagnostic uncertainty and driving antibiotic prescription even when there is no clear indication of bacterial infection. Antibiotics are also often prescribed because physicians and patients are concerned about the risk of complications and because many patients still expect an antibiotic prescription,[16] an expectation that may be overestimated by physicians.[17]

In cases of uncertainty, when it is difficult to determine whether an infection is caused by a virus or bacteria, the delayed antibiotic prescribing strategy can be a valuable tool to avoid unnecessary antibiotic use. This approach consists of prescribing an antibiotic to take only if the symptoms worsen or if there is no improvement several days after the medical visit. This strategy has been evaluated mainly in acute, uncomplicated respiratory infections.[18] Systematic reviews have suggested that delayed antibiotic strategies could result in poorer symptom control than immediate use of antibiotics.[19-21] Nevertheless, in the largest clinical trial published to date for acute uncomplicated respiratory infections in primary care, Little et al[16] found little difference in symptom control in the short term between delayed antibiotic strategies and no prescription. In a recent British study[22] in patients with sore throat, complications were found in only 1.4% of patients, with the risk of complications being no higher in the delayed antibiotic group than in the immediate antibiotic group.

The use of delayed prescription varies widely from country to country. In the United Kingdom, more than 50% of all prescriptions for acute, uncomplicated respiratory infections are delayed,[23] while in Southern Europe this strategy is not commonly used. No evidence is available for the United States. In addition, most studies on delayed antibiotic strategies have been carried out in the United Kingdom and Scandinavian countries, where the consumption of antibiotics is lower than in Southern Europe or the United States.[24] A previous study[25] in Spain evaluated delayed prescribing in primary care and found a reduction of antibiotic prescribing but did not include clinical outcomes. Therefore, we designed our study to determine the effectiveness of 2 delayed antibiotic strategies compared with immediate antibiotic prescription or no offer of antibiotics.

Methods

Study Design and Participants

We performed a pragmatic, randomized, multicenter, clinical trial (trial protocol available in Supplement 1), the methodology of which has been published elsewhere.[26] Competitive recruitment was performed in 23 primary care centers in 4 regions in Spain from December 2009 to July 2012. Eligible patients were older than 18 years and had 1 of the following acute, uncomplicated respiratory infections: acute pharyngitis, rhinosinusitis, acute bronchitis, or exacerbation of mild-to-moderate chronic obstructive pulmonary disease (COPD) (eAppendix 1 in Supplement 2). In all cases, the physician had reasonable doubt as to whether to treat with an antibiotic. The study was approved by the ethics committee of the Jordi Gol i Gurina Foundation (Barcelona, Spain) and by the clinical research ethics committees in each healthcare area. Approval was also obtained from the Spanish Agency of Medicines and Health Products. Written informed consent was obtained from all participants.

Interventions

Patients were randomized to 1 of 4 strategies, two of which—the patient-led prescription strategy and the prescription collection strategy—were delayed prescription strategies. Patients randomized to the patient-led prescription strategy were given an antibiotic at first consultation, and patients randomized to the prescription collection strategy could collect the antibiotic at their primary care reception desk 3 days after the first consultation.

Patients allocated to the delayed antibiotic strategies received the same instructions from the physician. They were told it was normal to feel worse over the first few days after the visit. If they felt substantially worse in the first few days, however, they were recommended to consider taking the antibiotics or to return to the physician if they considered it necessary. If they noted no improvement after 5 days (in cases of pharyngitis) or after 10 days (in cases of other infections), they were also instructed to consider taking the antibiotics.

Patients randomized to the immediate prescription strategy received an antibiotic at first visit and were instructed to start the medication on the same day, and patients randomized to the no prescription strategy were not offered antibiotics.

Patients allocated to the immediate prescription strategy or to the no prescription strategy were told it was normal to feel worse over the first few days after the visit. However, they were instructed to consider reconsultation if they felt they should see their physician or if there was no improvement after 5 days (in cases of pharyngitis) or after 10 days (in cases of other infections).

In all 4 prescription strategy groups, the choice of antibiotic was made by the physician.

Randomization and Masking

Physicians randomized patients centrally using an electronic online platform. Randomization was performed using per-

muted block sizes of 4 and stratified by type of infection. Neither patients nor health professionals were blinded.

Outcomes

The primary outcome measure was the duration and severity of symptoms. Patients filled out a daily questionnaire for a maximum of 30 days.[27] Each symptom was scored using a 6-point Likert scale. Symptoms scoring 3 or 4 were considered moderate, and those scoring 5 or 6 were considered severe. We included common symptoms such as fever, discomfort or general pain, cough, difficulty sleeping, changes in everyday life in all patients, and specific symptoms according to the condition. Our secondary outcomes were antibiotic use, satisfaction with health care, belief in the effectiveness of antibiotics, and absenteeism (absence from work or doing their daily activities). We also determined the risk of complications (eg, pneumonia, abscesses, or cellulitis) and the need for unscheduled health care (eAppendix 2 in Supplement 2).

Procedures

All family physicians received training before recruitment began. Family physicians personally informed the patients during consultation at the primary care centers, using a structured script about: (1) the expected duration and the self-limiting natural history of the corresponding respiratory infection; (2) the marginal benefits and potential adverse effects of antibiotics; and (3) the study purpose and procedure. This information was also provided to patients in writing. After signing the consent form, those who agreed to participate were randomized to 1 of the 4 prescription strategies. All patients received recommendations according to the strategy assigned that included advice about nonantibiotic medication use. They also received a diary with a validated symptom questionnaire to be filled out daily.[27] Baseline data were collected by the family physician and/or a nurse. A central telephone follow up was conducted on days 2, 7, 15, and 22 if symptoms persisted. All patients were visited 30 days after randomization at their surgery.

Statistical Analyses

Sample Size Calculation

We calculated a sample size of 150 patients per arm (600 patients) considering a mean (SD) of 12 (6) days as the average duration of an acute uncomplicated respiratory infection without treatment.[27] We considered a difference of 2 days in the duration of symptoms in the immediate antibiotic strategy, compared with a delayed strategy, as a clinically relevant result. For our statistical analyses, we used an α error of 5% (α = .05) and a power of 80% (β = 0.2).

Main Analyses

Characteristics of the study population were described using frequencies for categorical variables, and mean (SD) for quantitative variables. To compare the included strategies, we used a χ^2 test or Fisher exact test for categorical variables and analysis of variance (ANOVA) for continuous variables. To compare the duration of symptoms across strategies, we used a negative binomial regression model per symptom with symptom duration (ie, number of days with the symptom) as the dependent variable and both the prescription strategy and antibiotic consumption as independent variables. For severity of symptoms, we used an ordered logistic regression model per symptom with severity of symptom as the dependent variable and both the prescription strategy and antibiotic consumption as independent variables. Both regression models were adjusted by reported antibiotic consumption. Intention-to-treat guided all the analyses. The level of significance was 5% (α = .05). We used STATA statistical software version 13.1 (StataCorp) for all statistical analyses.

Results

Characteristics of the Study Participants

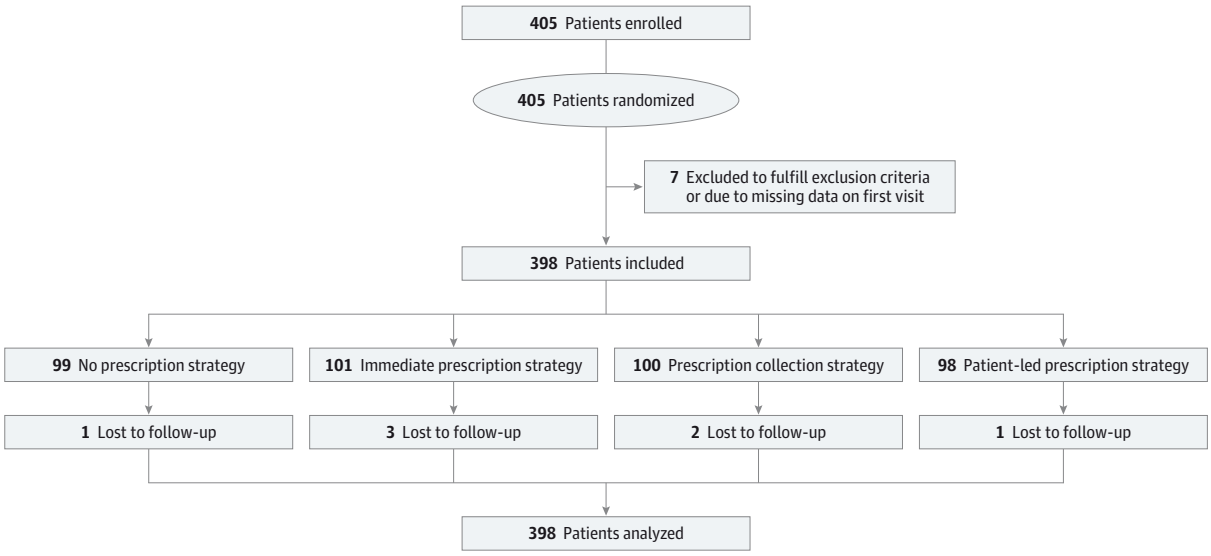
A total of 405 patients were recruited, 398 of whom were included in the analysis (**Figure**). Overall, 136 patients (34.2%) were men, mean (SD) age was 45 (17) years, and 265 patients (72%) had at least a secondary education level. The most common infection was pharyngitis (n = 184; 46.2%), followed by acute bronchitis (n = 128; 32.2%). Mean severity of symptoms ranged from 1.8 to 3.5 points on a Likert scale from 0 to 6, and the mean (SD) duration of symptoms described on the first visit was 6 (6) days. The mean (SD) general health status at the first visit was 54 (20), with 0 corresponding to the worst health status and 100 to the best status. Most patients were nonsmokers (n = 314; 80.1%) and did not have respiratory comorbidity (n = 372; 93.5%) (**Table 1**). The presence of symptoms at the first visit was similar among the 4 groups (**Table 2**).

Primary Outcomes

The mean (SD) duration of severe symptoms was 3.6 (3.3) days for the immediate prescription group and 4.7 (3.6) days for the no prescription group (P = .002). The median (IQR) duration of severe symptoms was 3 (1-4) days for the prescription collection group and 3 (2-6) days for the patient-led prescription group. Patients randomized to the immediate prescription strategy showed shorter durations of severe symptoms, ranging from 0.4 days less than the prescription collection strategy to 1.5 days less than the patient-led prescription strategy. The duration of moderate symptoms was mean (SD) 4.7 (4.0) days for the immediate prescription group; 5.2 (4.3) days for the prescription collection group; 6.0 (5.5) days for the patient-led prescription group; and 6.5 (5.2) days for the no prescription group (P < .001). The duration of moderate symptoms was significantly shorter for the prescription collection group than for the no prescription group (P = .008) (**Table 3**).

The duration of common symptoms (ie, fever, discomfort, cough, difficulty sleeping, and difficulty performing daily activities) in the immediate prescription group compared with the no prescription group was shorter for 3 out of 5 symptoms (P < .05 for all). For the immediate prescription group compared with the prescription collection and patient-led prescription groups, the duration was significantly different for only discomfort or general pain (prescription collection strategy, P = .003; patient-led prescription strategy, P = .05). Compared with the no prescription group, the duration of 2 com-

Figure. Patient Randomization Flowchart



Flowchart following the randomization of patients to different prescription strategies to final analysis.

mon symptoms was shorter for the patient-led prescription group and shorter for 1 symptom in the prescription collection group ($P < .05$ for all) (Table 3).

The maximum severity for any symptom was median (interquartile range [IQR]) 5 (3-5) points for the immediate prescription group; 5 (3-5) points for the prescription collection

Table 1. Baseline Patient Characteristics[a]

Characteristic	Prescription Strategy, No. (%)				
	Immediate (n = 101)	Collection (n = 100)	Patient-Led (n = 98)	No Prescription (n = 99)	Total (n = 398)
Men	39 (38.6)	29 (29.0)	33 (33.7)	35 (35.3)	136 (34.2)
Age, mean (SD), y	48 (17)	42 (17)	45 (17)	45 (16)	45 (17)
Educational level					
Primary or less	26 (28.3)	19 (21.1)	32 (34.8)	26 (27.7)	103 (28.0)
Secondary	32 (34.8)	42 (46.7)	35 (38.0)	33 (35.1)	142 (38.6)
Higher	34 (36.9)	29 (32.2)	25 (27.2)	35 (37.2)	123 (33.4)
Respiratory comorbidity[b]	7 (6.9)	5 (5.0)	4 (4.1)	10 (10.1)	26 (6.5)
Smoking status					
Nonsmoker	53 (54.1)	50 (50.5)	61 (62.2)	51 (52.6)	215 (54.8)
Smoker	22 (22.4)	25 (25.3)	11 (11.2)	20 (20.6)	78 (19.9)
Former smoker	23 (23.5)	24 (24.2)	26 (26.5)	26 (26.8)	99 (25.3)
Uncomplicated acute respiratory infection					
Rhinosinusitis	20 (19.8)	20 (20.0)	19 (19.4)	19 (19.2)	78 (19.6)
Pharyngitis	47 (46.5)	46 (46.0)	45 (45.9)	46 (46.5)	184 (46.2)
Acute bronchitis	32 (31.7)	32 (32.0)	32 (32.7)	32 (32.3)	128 (32.2)
Exacerbation of mild-to-moderate COPD	2 (2.0)	2 (2.0)	2 (2.0)	2 (2.0)	8 (2.0)
Severity of symptoms, mean (SD)[c]					
Fever	2.2 (1.8)	1.8 (1.7)	2.0 (1.9)	2.2 (1.8)	2.0 (1.8)
Discomfort or general pain	2.8 (1.7)	3.0 (1.6)	2.9 (1.8)	3.5 (1.6)	3.0 (1.7)
Cough	2.4 (2.0)	2.5 (2.0)	2.6 (2.0)	2.9 (2.1)	2.6 (2.0)
Difficulty sleeping	2.1 (1.9)	2.2 (2.1)	2.0 (2.1)	2.4 (1.9)	2.2 (2.0)
Changes in everyday life	2.3 (1.9)	1.9 (2.0)	2.1 (1.9)	2.4 (2.0)	2.2 (2.0)
Days with symptoms prior to the visit, mean (SD)	6 (6)	5 (5)	6 (7)	6 (8)	6 (6)
General health status, mean (SD)[d]	53 (21)	55 (20)	56 (19)	53 (19)	54 (20)

Abbreviation: COPD, chronic obstructive pulmonary disease.

[a] Data presented are the frequency (percentage) or mean (SD).

[b] Only cardiovascular comorbidity ($P = .12$) and diabetes ($P = .19$).

[c] Score based on a Likert scale from 0 (no problem) to 6 (as bad as it could be), and common symptoms are characteristic of the 4 pathologies studied (rhinosinusitis, pharyngitis, acute bronchitis, and exacerbation of mild-to-moderate COPD).

[d] Score based on a visual analog scale from 0 (worst health status) to 100 (best health status) on first visit.

Table 2. Presence of Patient Symptoms on First Visit[a]

Characteristic	Prescription Strategy, No. (%)				Overall *P* Value
	Immediate (n = 101)	Collection (n = 100)	Patient-Led (n = 98)	No Prescription (n = 99)	
Moderate symptoms (3 or 4)[b]	80 (93.0)	76 (89.4)	88 (97.8)	80 (92.0)	.13
Severe symptoms (5 or 6)[b]	47 (54.7)	45 (52.9)	47 (52.2)	53 (60.9)	.65
Common symptoms[c]					
Fever	66 (65.4)	63 (63.0)	64 (65.3)	67 (67.7)	.92
Discomfort or general pain	90 (89.1)	92 (92.0)	87 (88.8)	85 (85.9)	.59
Cough	77 (76.2)	82 (82.0)	78 (80.0)	83 (83.8)	.56
Difficulty sleeping	72 (71.3)	67 (67.0)	61 (62.2)	68 (68.7)	.58
Changes in everyday life	77 (76.2)	67 (67.0)	71 (72.5)	69 (69.7)	.51
Rhinosinusitis					
Spontaneous facial pain	12 (13.5)	12 (13.2)	13 (14.3)	13 (14.8)	.99
Facial pain on touch	12 (13.5)	13 (14.3)	11 (12.1)	13 (14.8)	.96
Pharyngitis					
Swallowing difficulties	46 (48.4)	41 (45.1)	38 (40.0)	31 (33.0)[d]	.16
Rhinosinusitis and pharyngitis					
Headache	58 (59.2)	51 (52.6)	52 (54.2)	48 (50.5)	.66
Nasal mucosity	50 (51.0)	49 (50.5)	53 (55.2)	51 (53.7)	.90
Sore throat	57 (58.2)	59 (60.8)	50 (52.1)	52 (54.7)	.63
Acute bronchitis and exacerbation of mild-to-moderate COPD					
Expectoration or phlegm	28 (31.5)	28. (31.8)	28 (30.4)	31 (34.1)	.96
Breathlessness	22 (24.7)	26 (29.6)	29 (31.5)	29 (31.9)	.70
Chest pain on breathing	25 (28.1)	17 (19.3)	21 (22.8)	23 (25.3)	.57
Chest noises on breathing	26 (29.2)	23 (26.1)	19 (20.7)	22 (24.2)	.60

Abbreviation: COPD, chronic obstructive pulmonary disease.

[a] Data presented are the frequency (percentage) of patients with symptoms. Statistical significance was calculated by adjusting a negative binomial regression model per symptom, with the number of days with the symptom as dependent variable and both strategy and antibiotic consumption as independent variables.

[b] Score based on a Likert scale from 0 (no problem) to 6 (as bad as it could be).

[c] Common symptoms are characteristic of the 4 pathologies studied (rhinosinusitis, pharyngitis, acute bronchitis, and exacerbation of mild-to-moderate COPD).

[d] *P* = .03 compared with the immediate prescription strategy.

group; 5 (4-5) points for the patient-led prescription group; and 5 (4-6) points for the no prescription group (*P* = .009). The severity of the specific symptoms and general health statuses was similar among the 4 strategies (**Table 4**).

Secondary Outcomes

In the immediate prescription group, 92 patients (91.1%) used antibiotics, compared with 12 patients (12.1%) in the no prescription group, 23 patients (23.0%) in the prescription collection group, and 32 patients (32.6%) in the patient-led prescription group. No differences were observed for complications, adverse effects, or the need for unscheduled care among the strategy groups, and no differences were observed in the perception of general health statuses assessed at 30 days. The majority of patients that collected the antibiotic reported that they finally took them (**Table 5**).

Rates of absenteeism were lower in the delayed strategy groups (prescription collection, 18 patients [21.4%]; patient-led prescription, 23 patients [25.8%]) than in the immediate prescription group (28 patients [33.3%]) and the no prescription group (33 patients [39.8%]) (*P* = .05). Patient satisfaction was high and similar among the 4 groups (*P* = .14). Belief that antibiotics had no effect or were not very effective was higher for patients in the 2 delayed antibiotic strategies (prescription collection, 12 patients [15.6%]; patient-led prescription, 16 patients [19.0%]) and the no antibiotic strategy (15 patients [19.7%]) than the immediate prescription strategy (7 patients [8.2%]) (*P* = .02). Finally, more patients randomized to the immediate prescription strategy (n = 72 [85.7%]) reported that they would return to their physician for a similar episode than patients in the no prescription (n = 59 [70.2%]), prescription collection (n = 58 [69.1%]), and patient-led prescription strategies (n = 60 [69.0%]) (*P* = .06).

Discussion

To our knowledge, this is the largest study to date outside Northern Europe to evaluate the effect of 2 delayed antibiotic strategies in acute, uncomplicated respiratory infections on symptom control. We found that the delayed strategy groups had slightly greater symptom burden and duration than the immediate prescription group, although the differences were not clinically relevant. Delayed prescription and no prescription strategies notably reduced antibiotic use compared with the immediate prescription group.

Our results are comparable with a previous Cochrane systematic review[21] and a recent trial by Little et al[16] studying delayed prescription in acute uncomplicated respiratory infections. With respect to the duration of symptoms, the Cochrane review of 3157 patients with respiratory infections reported that the duration of symptoms in the delayed antibiotic strategy groups was similar to that in the immediate prescription approach, particularly in those with a sore throat and acute otitis media.[21,22] This was consistent with our study, which showed that the duration of severe symptoms was quite similar in the immediate prescription group and in the 2 delayed prescription groups.

Table 3. Duration of Patient Symptoms After First Visit[a]

Characteristic	Duration of Symptoms per Prescription Strategy, d, Mean (SD)				Overall *P* Value
	Immediate	Collection	Patient-Led	No Prescription	
Any until disappearance	11.7 (8.4)	12.3 (7.3)	13.1 (8.5)	14.4 (8.1)[b]	.02
Moderate (3 or 4)[c]	4.7 (4.0)	5.2 (4.3)[b,d]	6.0 (5.5)[b]	6.5 (5.2)[b]	<.001
Severe (5 or 6)[c]	3.6 (3.3)	4.0 (4.2)[b]	5.1 (6.3)[b]	4.7 (3.6)[b]	.002
Common symptoms					
Fever	3.7 (4.2)	3.8 (3.2)[d]	3.8 (3.7)[d]	5.4 (6.3)[b]	.004
Discomfort or general pain	6.7 (5.7)	8.7 (7.0)[b]	7.9 (7.1)[b,d]	10.2 (7.1)[b]	.002
Cough	10.0 (6.6)	9.6 (6.7)	11.1 (8.0)	12.3 (8.1)[b]	.03
Difficulty sleeping	6.0 (6.2)	6.5 (5.2)	8.3 (7.1)	7.6 (6.2)	.11
Changes in everyday life	6.4 (6.4)	6.6 (5.5)	6.9 (6.3)	8.4 (6.6)	.14
Rhinosinusitis					
Spontaneous facial pain	7.1 (6.6)	5.4 (3.6)	6.1 (5.5)	8.6 (7.7)	.48
Facial pain on touch	7.6 (5.2)	11.6 (9.7)	9.0 (9.7)	9.2 (8.4)	.15
Pharyngitis					
Swallowing difficulties	5.1 (3.8)	6.1 (4.3)	5.6 (3.1)	6.8 (4.9)	.71
Rhinosinusitis and pharyngitis					
Headache	4.1 (3.8)	7.0 (5.9)[b]	6.3 (6.1)	9.0 (8.0)[b]	.03
Nasal mucosity	8.3 (7.2)	10.1 (7.8)	9.8 (7.5)	11.0 (7.4)	.47
Sore throat	5.9 (4.7)	7.0 (4.7)	6.7 (4.6)	8.1 (6.3)	.22
Acute bronchitis and exacerbation of mild-to-moderate COPD					
Expectoration or phlegm	12.1 (8.7)	13.1 (8.2)	14.6 (9.5)	13.4 (7.6)	.88
Breathlessness	11.8 (9.1)	6.7 (5.6)	9.7 (9.0)	10.3 (6.7)	.43
Chest pain on breathing	7.5 (6.4)	5.5 (3.4)	9.2 (8.4)	9.6 (6.9)	.22
Chest noises on breathing	7.2 (4.8)	5.3 (5.3)	11.9 (10.2)	10.9 (8.4)	.24

Abbreviation: COPD, chronic obstructive pulmonary disease.

[a] Data presented are mean (SD) of the number of days with symptoms. Only patients who had symptoms for 1 or more days were included. Statistical significance was calculated by adjusting a negative binomial regression model per symptom, with the number of days with the symptom as dependent variable and both prescription strategy and antibiotic use as independent variables.

[b] $P < .05$ compared with the immediate prescription strategy.

[c] Score based on a Likert scale from 0 (no problem) to 6 (as bad as it could be).

[d] $P < .05$ compared with the no prescription strategy.

In their trial, Little et al[16] found minimal differences in symptom severity. The authors compared the effectiveness of 4 delayed antibiotic strategies (recontact for a prescription, post-dated prescription, prescription collection, and patient-

Table 4. Severity of Patient Symptoms After First Visit[a]

Characteristic	Prescription Strategy, Median (IQR)				Overall *P* Value
	Immediate	Collection	Patient-Led	No Prescription	
Maximum severity of any symptom[b]	5 (3-5)	5 (3-5)[c]	5 (4-5)[c,d]	5 (4-6)[d]	.009
Common symptoms					
Fever	2 (2-3)	2 (1-3)	2 (1-3)	2 (1-3)	.49
Discomfort or general pain	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-4)	.54
Cough	2 (1-3)	2 (1-3)	2 (1-3)	3 (1-4)	.30
Difficulty sleeping	2 (1-4)	2 (1-3)	2 (1-4)	2 (1-3)	.54
Changes in everyday life	2 (1-3)	2 (1-3)[c]	2 (1-4)[c]	3 (1-4)[d]	.03
Rhinosinusitis					
Spontaneous facial pain	2 (1-3)	3 (2-3)	3 (2-4)	2 (1-4)	.33
Facial pain on touch	1 (1-2)	3 (3-4)	3 (2-4)	3 (1-5)	.08
Pharyngitis					
Swallowing difficulties	3 (2-4)	2 (1-4)	2 (1-4)	3 (1-4)	.41
Rhinosinusitis and pharyngitis					
Headache	2 (1-3)	2 (2-4)	3 (2-3)	2 (1-4)	.75
Nasal mucosity	2 (1-4)	2 (1-4)	3 (1-3)	3 (1-4)	.30
Sore throat	3 (2-4)	2 (1-4)	3 (2-4)	3 (2-4)	.49
Acute bronchitis and exacerbation of mild-to-moderate COPD					
Breathlessness	1 (1-2)	1 (1-2)	2 (1-2)	2 (1-3)	.46
Chest pain on breathing	2 (1-3)	1 (1-2)	2 (1-4)	2 (1-3)	.10
Chest noises on breathing	2 (1-3)	1 (1-2)[c]	2 (1-3)	2 (1-4)	.05

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

[a] Only patients with symptoms for 1 or more days were included. Statistical significance was calculated by adjusting an ordered logistic regression model per symptom, with severity of symptom as the dependent variable and both prescription strategy and antibiotic use as independent variables.

[b] Scores based on a Likert scale from 0 (no problem) to 6 (as bad as it could be).

[c] $P < .05$ compared with the no prescription strategy.

[d] $P < .05$ compared with the immediate prescription strategy.

Table 5. Secondary Outcomes

Characteristic	Prescription Strategy								
	Immediate (n = 101)	Collection (n = 100)	*P* Value[a]	Patient-Led (n = 98)	*P* Value[a]	No Prescription (n = 98)	*P* Value[a]	Total (n = 398)	Overall *P* Value
Antibiotic collected, No. (%)	90 (89.1)	26 (26.0)	<.001	34 (34.7)	<.001	NA	NA	150 (50.2)	<.001
Antibiotic used, No. (%)	92 (91.1)	23 (23.0)	<.001	32 (32.6)	<.001	12 (12.1)		159 (39.9)	<.001
Nonantibiotic medication use, No. (%)	75 (74.3)	75 (75.0)	.90	79 (80.6)	.29	81 (81.8)	.20	310 (77.9)	.46
Need for unscheduled health care, No. (%)	4 (4.0)	4 (4.0)		6 (6.1)		6 (6.1)		20 (5.0)	.84
General health status, mean (SD)[b]	95 (90-100)	91 (85-100)	.86	95 (90-100)	.98	95 (90-100)	.77	95 (90-100)	.87
Adverse effects, No. (%)	1 (1.0)	0		1 (1.0)		3 (3.0)		5 (1.3)	.27
Referral to the emergency department, No. (%)	0	0		1 (1.0)		1 (1.0)		2 (0.5)	.37

Abbreviation: NA, not applicable.

[a] Immediate antibiotic strategy was the reference category.

[b] Score based on a visual analog scale from 0 (worst health status) to 100 (best health status).

led prescription) with no antibiotics in patients with acute uncomplicated respiratory infections. However, the study did not include an immediate antibiotic randomization strategy. Our findings are concurrent with their results.

The Cochrane review[21] raised debate about whether a no prescription strategy is more suitable than a delayed strategy because it results in lower antibiotic use.[21] In line with these results, our study showed that the delayed prescription groups also reported a lower antibiotic use. Just over one-tenth of patients not initially prescribed antibiotics ended up using them, as opposed to 23.0% (n = 23) of patients randomized to the prescription collection strategy. Conversely, the use of antibiotics in the immediate antibiotic group was very high as expected (n = 92 [91.1%]).

Although still unclear, several patterns in the delayed prescription approach seem to be emerging. Earlier studies[21] comparing delayed prescription strategies showed variability in antibiotic use rates, with higher use in patient-led strategies than in the prescription collection strategies. Later studies,[16] like our own, show a similar pattern. The hassle of having to return to a clinic for a prescription likely plays a role in this difference. The low use of antibiotics observed in clinical trials should be considered with caution because they may not reflect real use. As opposed to observational studies, research participants receive structured advice and are typically more motivated than in usual practice.[25]

The Cochrane review[21] did not find any evidence that delayed antibiotics are safer or more harmful than a no antibiotic approach, but as in our study, this outcome was underpowered.[16] With respect to patient satisfaction in the Cochrane review, immediate antibiotics had slightly higher levels of patient satisfaction than delayed antibiotics, although the clinical significance was marginal (92% vs 87%, respectively).[21] Our results did not reveal any significant differences between groups.

Limitations and Strengths of Our Study

The first limitation of our study is that we did not achieve the target sample size. This was mainly because we ran out of funding since recruitment was slow as a result of clinicians' time limitations.[28] Despite the smaller sample size, however, the variability observed in the duration of symptoms was 2.8 instead of 6 standard deviations, which was lower than expected. With these new data our study was overpowered. Second, most patients had pharyngitis and bronchitis, limiting the inferences for patients with rhinosinusitis or exacerbation of mild-to-moderate COPD. Third, it could be argued that the open nature of the study may have caused a placebo effect favoring antibiotics. However, this effect was minimized by the similar structured information all patients received about the self-limiting nature of respiratory infections and the advice about nonantibiotic medication use. Furthermore, the open design allowed us to study the perceptions of patients in a situation similarly to usual practice.[29]

The strengths of our study are its pragmatic design and that our study, as far as we know, is the largest trial to assess delayed prescription strategies outside Northern Europe by directly comparing delayed prescription strategies with an immediate prescription arm in a randomized fashion.

Implications for Practice and Research

Delayed prescription strategies are a useful approach to management in patients with acute uncomplicated respiratory infections. When patients or physicians are concerned about the risk of complications, or when patients expect to be prescribed antibiotics, a delayed antibiotic strategy may be particularly helpful compared with a no prescription strategy. Delayed prescription strategies show high potential for clinical benefit not only in Spain but in other countries, including the United States, where antibiotic use is often inappropriate.[9,10]

Further studies are required to identify subgroups in which delayed prescription strategies may be most useful. Likewise, delayed strategies should be evaluated in larger populations that include older patients, participants with a lower educational level, exacerbations of mild-moderate COPD, or acute sinusitis and otitis. Finally, more qualitative research is called for to better understand the contextual use of delayed prescription strategies.

Conclusions

In this pragmatic, open-label, randomized trial of antibiotic treatment strategy for acute, uncomplicated respiratory infections, delayed strategies were associated with slightly greater, but clinically similar, symptom burden and duration, as well as substantially reduced antibiotic use when compared with an immediate prescription strategy. In case of uncertainty, delayed strategies should become standard practice as they reduce antibiotic use and patient belief in antibiotic effectiveness.

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